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**Lessons from diagnosis-prescribing and antibiotic
resistance surveillance in Ujjain, India:**

The lull before the storm

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Institutet**

Stockholm 2012

Cover photo depicts the conversation between Lord Krishna and the Pandava prince, Arjun that took place in middle of a battlefield before the start of the war described in the epic Mahabharatha. With armies standing on both sides ready for battle, Arjun a great archer refused to fight due to moral dilemma of fighting his own cousins. The context of the Gita is Lord Krishna's reply to Arjun. Ratna MG, Ujjain made the painting which belongs to my father.

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ABSTRACT

Background: The evolution of antibiotic resistance is a global public health crisis building over decades. In this build-up antibiotic use has been the main driver for antibiotic resistance. To develop context-specific interventions, effective surveillance of antibiotic use and resistance are needed in countries like India, which have witnessed a rapid rise in resistance recently and where the need for effective antibiotics is high.

Aim: The main aim of this thesis is to increase the knowledge regarding antibiotic prescribing patterns and prevalence of resistance in an Indian setting, so as to identify targets for interventions aimed to improve clinical practice for common infections.

Methods: This thesis includes five cross-sectional studies. Paper I and paper II describes the patterns of antibiotic prescribing for outpatients with suspected infectious aetiology and among admitted patients, respectively. The defined daily doses (DDDs) were calculated per 1000 patients per diagnosis considered in paper I. Focus of infection specific DDDs were calculated per 100 patient days in paper II. In paper III, prescriptions for children with diarrhoea were analysed for adherence to treatment guidelines and factors associated with adherence were explored. In paper IV healthy children were screened for nasal carriage of *S. aureus* to identify factors associated with nasal carriage and to describe the resistance patterns. Paper V describes the antibiotic susceptibility pattern of pathogens isolated from patients with suspected infections. Antibiotic susceptibility testing was performed by Kirby-Bauer disk-diffusion method. All the studies were done using structured, pilot tested questionnaires.

Results: Overall antibiotic prescribing was 66.3%, 3732 out of 5623 outpatients (Paper I) and 92%, 5531 out of 6026 admitted patients (Paper II). Quinolones were the most frequently prescribed antibiotic group among outpatients and third generation cephalosporins among the admitted patients (Paper I and II). For diarrhoea in children only 6 out of 843 prescriptions adhered completely to treatment guidelines. Oral rehydration solution (ORS) was prescribed for 58%, ORS with zinc for 22% and antibiotics for 71% of the cases (Paper III). The prevalence of nasal carriage of *S. aureus* was 98 out of 1562 i.e. 6.3% (95% confidence interval [CI] 5.1-7.5). Of these, 16.3% were methicillin-resistant *S. aureus* (MRSA). Overcrowding was associated with nasal carriage of *S. aureus* (Paper IV). Among pathogens (n=716) isolated from admitted patients (n=2568), Gram-negative pathogens predominated (62%). Extended-spectrum β -lactamase (ESBL) production in *E. coli* isolates (n=149) was 69% (95% CI 61.6–76.6) and in *K. pneumoniae* isolates (n=107), 41% (95% CI 31.6–50.5). MRSA constituted 30% of all *S. aureus* isolates (n=221).

Conclusions: The targets identified for interventions were: high antibiotic prescribing rates for diarrhoea (Paper I, II and III) and upper respiratory tract infection (Paper I). Other targets include, longer than recommended duration of prophylaxis (86% of 1846 patients) and lack of distinction between prophylaxis and therapy among surgical patients, irrational antibiotic prescribing in gastroenteritis, overuse of quinolones and lack of use of penicillin in pneumonia, overuse of quinolones and lack of use of doxycycline and macrolides in genital infections, and overreliance on antibiotics in treating skin and soft tissue infections (Paper II). The high rate of antibiotic prescribing among admitted patients together with the high rates of ESBL producing pathogens shows urgent need to curb antibiotic use when there is no indication for it (Paper V).

Key words: antibiotic prescribing, antibiotic resistance, patients, surveillance, defined daily dose, foci of infection, adherence, diarrhoea treatment guidelines, nasal carriage, *S. aureus*, extended-spectrum β -lactamase, pathogens, India.

LIST OF PUBLICATIONS

- I. **Pathak A**, Mahadik K, Dhaneria SP, Sharma A, Eriksson B, Stålsby Lundborg C. *Antibiotic prescribing in outpatients: Hospital and seasonal variations in Ujjain, India*. **Scand J Infect Dis**. 2011 Jul, 43(6-7): 479-88.
- II. **Pathak A**, Mahadik K, Dhaneria SP, Sharma A, Eriksson B and Stålsby Lundborg C: *Surveillance of antibiotic consumption using “focus of infection” approach in Ujjain, India* (Submitted)
- III. Pathak D, **Pathak A**, Marrone G, Diwan V, Stålsby Lundborg C. *Adherence to treatment guidelines for acute diarrhoea in children up to 12 years in Ujjain, India-a cross-sectional prescription analysis*. **BMC Infect Dis**. 2011 Jan 28; 11:32.
- IV. **Pathak A**, Marothi Y, Iyer RV, Singh B, Sharma M, Eriksson B, Macaden R, Stålsby Lundborg C: *Nasal carriage and antimicrobial susceptibility of Staphylococcus aureus in healthy preschool children in Ujjain, India*. **BMC Pediatr**. 2010 Dec 29; 10:100.
- V. **Pathak A**, Marothi Y, Kekre V, Mahadik K, Macaden R and Stålsby Lundborg C: *High prevalence of extended-spectrum β -lactamase producing pathogens: Results of a surveillance study in 2 hospitals, Ujjain, India*. **Infect and Drug Resist**. 2012, 5:65-73

The papers will be referred in the text by their roman numerals I-V.

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LIST OF ABBREVIATIONS

AST	Antimicrobial Susceptibility Testing
ATC	Anatomical Therapeutic Chemical
ATCC	American Type Culture Collection
AYUSH	Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy
CLSI	The Clinical and Laboratory Standards Institute
DDD	Defined Daily Dose
ECDC	The European Centre for Disease Prevention and Control
ESBL	Extended Spectrum Beta-lactamase
IDSA	Infectious Diseases Society of America
HAI	Healthcare-Associated Infections
MDR	Multidrug-Resistant
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
MSSA	Methicillin-sensitive <i>Staphylococcus aureus</i>
ORS	Oral Rehydration Solution
ORT	Oral Rehydration Therapy
STG	Standard Treatment Guidelines
UNICEF	The United Nations Children's Fund
WHO	The World Health Organization

DEFINITIONS

1. Acute watery diarrhoea: is defined as “three or more watery stools in a 24-hour period without blood, a loose stool being one that would take the shape of the container.” (WHO 1996)
2. Antimicrobials: Class of substances that can destroy or inhibit the growth of pathogenic groups of microorganisms, including bacteria, viruses, parasites, and fungi.
3. Antibiotic: Class of substances that can kill or inhibit the growth of some groups of microorganisms. In this thesis antibiotics refer to chemicals active against bacteria. Originally antibiotics were derived from natural sources (e.g., penicillin from molds), but many currently used antibiotics are semi-synthetic and modified with additions of man-made chemical components.
4. Antibiotic resistance: there is no consensus definition of bacterial resistance to antibiotics. The European Society of Clinical Microbiology and Infectious Disease Committee for Antibiotic Susceptibility Testing (EUCAST) defines antibiotic resistance as “microbiological resistant bacteria that possess any resistance mechanism demonstrated either phenotypically or genotypically”. In this thesis phenotypic demonstration of resistance by disk diffusion test is used. ('EUCAST Definitive Document E.Def 1.2, May 2000: Terminology relating to methods for the determination of susceptibility of bacteria to antimicrobial agents' 2000).
5. Defined Daily Dose (DDD): as defined by the World Health Organization Collaborating Centre for Drug Statistics Methodology, Oslo- The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (World Health Organization Collaborating Centre for Drug Statistics Methodology 2010)
6. Empirical therapy: Is a medical term referring to the initiation of treatment prior to determination of a firm diagnosis.

PREFACE

“You can’t cross the sea merely by standing and staring at the water”

My life has always been inspired by these words of Rabindranath Tagore. I therefore decided to leave my state of Madhya Pradesh (MP) in pursuit of better education and did my under graduation from TN Medical College & BYL Nair Municipal Hospital, Mumbai. Paediatrics fascinated me from day one of my Paediatrics ward posting in second year of MBBS. But before I could start my post-graduation in Paediatrics we were required to work as medical officer at a rural peripheral health centre (PHC). I went to a tribal PHC in Dhule, Maharashtra in the year 1998-99. This was my first brush with public health.

I always wanted to work in my hometown and so when I completed my post-graduation I moved back to Ujjain, MP in 2004. I started working at Department of Paediatrics, RD Gardi Medical College then as a senior resident and continue to work, now as associate professor. I realized that despite having adequate clinical competency I lacked the necessary research competencies. But, having inherited some “research genes” from my father, an accomplished entomologist, I volunteered to work with Prof. Cecilia when we first met in 2004. We did our first pilot study on antibiotic use in 2005, and that was just the beginning.

A carrier in research is difficult for clinicians like me in India mainly because the lure for private clinical practice is usually too much to resist. In spite of that, I took the plunge in 2007, registered as a PhD student in 2009, and never looked back since. The PhD journey has given me opportunities, which are hard to find in India. I have tried to utilize them as much as possible. Now, a public health prospective enriches my experience with every individual patient I look after and vice-versa. I think the PhD training has transformed a Paediatrician into “a pharmacoepidemiologist, an infection-control physician and a budding microbiologist”. But the skill I cherish the most is the working knowledge of “Stata”.

The implications of my research and also the dilemma I faced during this PhD work is reflected in the photograph on the cover page of this thesis. It is about the conversation between Lord Krishna and the Pandava prince, Arjun that took place in middle of a battlefield before the start of the war described in the epic Mahabharatha. With armies standing on both sides ready for battle, Arjun a great archer refused to fight due to moral dilemma of fighting his own cousins. The context of the Gita is Lord Krishna’s reply to Arjun. In many ways, this reflects my own dilemma: how to criticise my own colleagues when I am one of them. But, I think that I have been quite critical of my colleagues. According to me, the painting is also a reflection of the current scenario in India with respect to antibiotic resistance, giving us a glimpse of the havoc awaiting us“the lull before the storm”!

1 BACKGROUND

1.1 ANTIBIOTIC RESISTANCE: A GLOBAL PUBLIC HEALTH CHALLENGE

Antibiotics are considered an important element in the armamentarium of modern medicine. When antibiotics are used to treat diseases caused by bacteria, most of the bacteria are killed but a few surviving bacteria can respond by becoming resistant to the antibiotic used. This response is a natural adaptation for survival by the bacteria. Thus, the effective lifespan of antibiotics is limited. Many patients throughout the world suffer harm due to antibiotic resistance because bacterial infections are not susceptible any more to antibiotics used to treat them (WHO 2012a).

When Fleming discovered penicillin he had observed that some bacteria are inherently resistant and some sensitive (Fleming 1929). He forewarned the effects of “indiscriminate use” in his Nobel lecture where he noted that initially sensitive bacteria could become resistant, especially if exposed to low doses of antibiotics ('Sir Alexander Fleming - Nobel Lecture') but the scientific community continued to ignore this advice. By the 1980s, it was believed that man had already learnt all there is to know about antibiotic resistant bacteria, which translated to a reduction in funding for research in this area. The field of antibiotic use and bacterial resistance was considered “old fashioned”, thus drastically reducing the number of scientists working in the field. The last two decades however, have seen a resurgence of interest in the field of antibiotic use and resistance and can be described as the ‘dawning’ of awareness of the antimicrobial resistance problem especially in resource-rich countries. The insurance companies in the United States in particular recognized this problem due to the increasing costs associated with treating resistant organisms (Alvan et al. 2011, Barbosa and Levy 2000, Boucher et al. 2009, Cars et al. 2008). Today the topic of antibiotic resistance is in the forefront, because of the increasing realisation that we lack even the basic knowledge about the mechanisms of resistance. Extensive work has been done and is going on in the field but still many questions, particularly related to horizontal gene transfer among environmental and pathogenic bacteria, remain unanswered (Alvan et al. 2011, Barbosa and Levy 2000, Boucher et al. 2009, Cars et al. 2008, French 2010, Grundmann et al. 2011, Johnsen et al. 2009). There is insufficient information about the conditions and factors that lead to the mobilization, selection and movement of resistant bacteria or resistant genes into and between animal and human populations (Alvan et al. 2011). It is important to answer these questions because horizontal gene transfer maintains the acquired gene pool of resistance in a community.

1.1.1 A problem building up over decades

Very few countries had the foresight to implement preventive programmes and policies to reduce inappropriate antibiotic use and improve hygiene (Grundmann et al. 2011). Even in countries with preventive programmes and policies in place antibiotic resistant bacteria can be imported and persist in the environment, especially in farm animals (Grundmann et al. 2011, Johnsen et al. 2009). Antibiotic resistance is thus a global public health challenge of paramount importance (Alvan et al. 2011, Cars et al. 2008, French 2010, WHO 2012a). The evolution of antibiotic resistance threatens the success of medical interventions at all levels of health-care and in countries at all economic levels (Alvan et al. 2011, Cars et al. 2008, French 2010, Shanmugam 2011, WHO 2012a). This evolution has been building up

over decades, so today many common infections, which were easily treatable, are becoming difficult to treat (WHO 2012a).

1.1.2 Consequences of antibiotic resistance

Estimates from Europe suggest that excess deaths due to resistant bacterial hospital associated infections exceed 25,000 annually (ECDC 2010). The number of extra hospital days was estimated to be 2.5 million (ECDC 2010). The expenditure associated with these infections in terms of extra hospital costs and productivity losses exceed €1.5 billion each year (ECDC 2010). Similar estimates from the low-and middle-income countries are found wanting, primarily due to lack of surveillance systems to gather such information.

In many healthcare settings, especially in the low and middle-income settings, antibiotics are prescribed empirically. Empiric therapy refers to the initiation of treatment prior to conformation of a firm diagnosis. At individual level therefore, antibiotic resistance can lead to treatment failure due to wrong choice of empirical antibiotics. Failure of initial antibiotic therapy leads the treating physician to prescribe alternative antibiotics, often labelled as “second-line” or “third-line” antibiotics. These antibiotics differ from hospital to hospital and from one region of the world to another. But, generally failure of initial antibiotic therapy leads to prescribing of more costly and many times more toxic alternatives (Boucher et al. 2009). In hospitalised patients antibiotic resistance leads to prolonged hospitalisation and is associated with increased risk of mortality and morbidity in the infected patient (Kollef et al. 1999). In case of sepsis the increased mortality is not always related to increased virulence of the resistant bacteria but often due to inappropriate initial choice of antibiotics for initiating treatment of clinical sepsis. An inappropriate initial choice leaves the patient essentially unprotected for a period of time, which is critical for survival (Kollef et al. 1999, Ibrahim et al. 2000). The impact of antibiotic resistance, at the hospital level includes, increased risk of cross-infection of resistant health care associated infections (HAI). A high HAI rate is a “bad reputation” for the concerned hospital (Goff 2011). An increased actual or perceived risk of HAI by the physicians in a health-care setting leads to a shift in practice to more broad-spectrum empiric therapy leading to “empiric spiralism” (Kim and Gallis 1989) i.e. a perceived need to prescribe more broad-spectrum antibiotic cover to address the concern about increasing prevalence of resistant bacteria. At the societal level, there is increased burden of care and increased physical and psychological costs of leave-of-absence (Sarkar and Gould 2006, Goff 2011). The consequence of antibiotic resistance is therefore an increased cost of care for the individual, hospital and society (Pile 2011). The increased cost of care is usually borne by the patient as out-of-pocket expenditure in countries like India (De Costa et al. 2009).

1.1.3 Recent global concerns regarding antibiotic resistance

The global concerns on antibiotic use and resistance are reflected by the call for concerted action from all quarters and increased availability of reports dealing with this matter (Ferech et al. 2006, Goossens et al. 2005, Coenen et al. 2009, Cars et al. 2008). During the last decade, antimicrobial resistance has moved steadily to a more and more prominent position in the global public health agenda (WHO 2012a). The World Health Organization (WHO) in the year 2011 celebrated the World Health Day on the 7th April, with the slogan “Antimicrobial resistance: no action today, no cure tomorrow” (WHO 2011). A six-point policy package was introduced and countries were called upon to (1) commit to a comprehensive, financed national plan with accountability and civil society engagement, (2) strengthen surveillance and laboratory capacity, (3) ensure uninterrupted access to

essential medicines of assured quality, (4) regulate and promote rational use of medicines in animal husbandry and to ensure proper patient care, (5) enhance infection prevention and control, and (6) foster innovations and research and development of new tools (WHO 2011).

Another recent concern is the apparent shift of resistance burden from Gram-positive pathogens to Gram-negative pathogens. This shift is of a concern because there is an empty pipeline of new or effective treatment options for the emerging Gram-negative infections (Brussels et al. 2011, WHO 2012a). The recent spread of *Enterobacteriaceae* with resistance to carbapenem conferred by New Delhi metallo- β -lactamase 1 (NDM-1) received extensive media coverage for two reasons: the bacteria carrying the *bla*(NDM-1) gene are resistant to all antibiotics except tigecycline and colistin, and they are rapidly transmitted across national borders (Kumarasamy et al. 2010).

Transfer of resistant genes or bacteria from the environment or food to humans is also of major concern (WHO 2012a). Antibiotic use in animals can account for up-to 50% of the total antibiotic production in the world (WHO 2012a). Antibiotics in animals can be used for a wide variety of non-therapeutic purposes that include growth promotion (Marshall and Levy 2011). Antibiotic resistance has been shown in the gut bacteria of the animals fed antibiotics and also food products made from animals that have received antibiotics. This resistance can spread to other animals and humans directly by contact and indirectly via the food chain, water, air, and manured and sludge-fertilized soils (Marshall and Levy 2011). The role of presence of antibiotics and antibiotic resistance genes in the hospital wastewater is also of major concern for spread of bacteria in the environment (Diwan et al. 2010, Diwan et al. 2012).

1.2 MEASURING ANTIBIOTIC USE AND RESISTANCE

1.2.1 Measuring antibiotic use

The antibiotic use data can be gathered at various healthcare levels or in the community, using different sources and methods (WHO 2012a). For health care, data could be gathered at primary care or hospital level and results presented as total use for the hospital using the purchased, prescribed, dispensed or administered data on antibiotics. Antibiotic use data could also be gathered at ward level or for outpatient clinics and admitted patients separately. Disease or symptom specific data could be more granular in identifying rationale antibiotic use, analysing adherence or compliance with standard treatment guidelines and to inform and evaluate resistance containment interventions. Point prevalence survey method as described by the European Surveillance of Antimicrobial Consumption (ESAC) is suitable for adapting to different health-care facilities (Zarb and Goossens 2011).

The various methods that can be used for antibiotic surveillance are: review of prescriptions, review of pharmacy sale or dispensing data, and drug purchase or procurement data (WHO 2012a). In places where the health system is weak, and there is no previously established surveillance system, WHO recommends measuring the following parameters: percentage of patients receiving antibiotics, pneumonia cases treated with recommended antibiotics, cases of upper respiratory tract infections

receiving antibiotics, and percentage of patients receiving antibiotics without prescriptions (WHO 2012a).

The antibiotic use can be reported as total use in grams, number of antibiotics constituting the 90% of the total drug utilised (DU90), financial cost for the patient or health care facility or total days of therapy, or by using prescribing indicators (Berrington 2010). The standardised measure of reporting antibiotic use information is by using the WHO Collaborating Centre for Drug Statistics Methodology, Anatomical Therapeutic Chemical (ATC) classification with Defined Daily Dose (DDD). By definition, the DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (WHO Collaborating Centre for Drug Statistics Methodology 2010).

The DDD is a unit of measurement and does not necessarily reflect the recommended or prescribed daily dose (Muller et al. 2006). The DDD reflects the global dosage irrespective of individual and population level genetic variations of drug metabolism. The DDD provides a fixed unit of measurement independent of drug cost, package size, and patient-specific dose ordered. To estimate antibiotic use, the total number of grams of each antibiotic used (purchased, dispensed, or administered) are summed during the period of interest and divided by the WHO-assigned DDD (WHO Collaborating Centre for Drug Statistics Methodology 2010). Expressing antibiotic use by DDDs, for example using the DDD per 1000 patient days, allows the researcher to compare the antibiotic use of one hospital with other hospitals', regardless of differences in formulary composition and antibiotic potency. The main advantage of the DDD methodology is that a researcher is able to assess trends in drug consumption and also to perform comparisons between population groups (WHO Collaborating Centre for Drug Statistics Methodology 2010). The other advantages are, the DDD methodology has a direct link to a widely accepted and used therapeutic classification system i.e. ATC/DDD classification system and the hierarchical structure of the ATC/DDD system that enables the aggregation of data at various healthcare levels. The WHO ATC/DDD system is also freely available. The ATC codes are alphanumeric and categorical and are thus easy to use. The main disadvantages are that the methodology is not suitable for children and patients with impaired renal function (Shetka et al. 2005). Also, in computation the alphanumeric nature of ATC codes is sometimes a complication.

1.2.2 Relationship between antibiotic use and resistance

Antibiotics have unfortunately been used excessively and inappropriately since the time of their discovery. The extent of antibiotic use is linked to resistance at an ecological level (Goossens et al. 2005) and more recently links between antibiotic prescribing and resistance at individual patient level have been shown (Costelloe et al. 2010). While antibiotics are the central element in selecting resistant bacteria they are not the only driving force for persistence of resistance (Barbosa and Levy 2000). Once bacteria acquire the elements responsible for resistance and stabilise them, resistance can be then transmitted horizontally within and between species (Blake et al. 2003). This makes the reversal of resistance very difficult to achieve (Johnsen et al. 2009). The persistence of glycopeptide-resistant enterococci in Norwegian and Danish poultry farms 12 years after the ban of the animal growth promoter avoparcin is an example (Johnsen et al. 2009). Thus, the need for surveillance of antibiotic prescribing to monitor and identify areas for improvement cannot be overemphasised.

1.2.3 Surveillance networks of antibiotic use and resistance at national, regional and global level

Surveillance involves systematic collection and analysis of health-related data to inform the health-care providers, administration and policy makers. An effective surveillance of antibiotic use should describe the pattern of antibiotic prescribing and “how” they are used, both by the patients and prescribers. The goal of antibiotic use surveillance is to provide the information, insights and tools needed to guide policy at local, national and global level (WHO 2012a).

At the national level Sweden is one of the most active and successful countries in the fight against antimicrobial resistance (Molstad et al. 2008). In Sweden, Strama (the Swedish Strategic Programme against Antibiotic Resistance) works for effective use of antibiotics. Other networks include, the Norwegian Surveillance for Antibiotic Drug Resistance (NORM) (Simonsen 2009), the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) (Bager 2000), the Dutch Working Party on Antibiotic Policy (Dutch acronym is SWAB) (Verbrugh 2003), Surveillance of Antibiotic Use and Resistance in Intensive Care (SARI) or Medical Antibiotic Use Surveillance and Evaluation (MABUSE) in Germany (de With et al. 2004), European Surveillance of Antimicrobial Consumption (ECDC, 2010) in Europe (Ansari et al. 2009, Zarb and Goossens 2011) and Intensive Care Antimicrobial Resistance Epidemiology (ICARE) in the United States (Fridkin et al. 1999).

At the European level the surveillance of antimicrobial resistance was conducted previously by the European Antimicrobial Resistance Surveillance System (EARSS), and is currently done by the European Antimicrobial Resistance Surveillance Network (EARS-Net). The network has played an important role to provide good quality data. The dissemination of EARS-Net data has increased the awareness of the problem of antimicrobial resistance not only in the scientific community but also at the public and the political level (ECDC 2010). The 2009 situation analysis report by EARS-Net contains data from 28 countries and analyses trends of resistance in many pathogenic bacteria (ECDC 2010). Data from Europe confirm a consistent rise in multidrug resistance and reveal a steady and significant decline of antimicrobial susceptibility in *Escherichia coli*. On the other hand a steady fall in the hospital prevalence of methicillin resistant *Staphylococcus aureus* (MRSA) has been reported (ECDC 2010). This fall has been achieved by active surveillance of carriers and patients in the hospitals and massive hand hygiene campaigns.

1.2.4 Need for antibiotic resistance surveillance systems in low and middle-income countries

Surveillance of antibiotic resistance is one of the most important components of an antibiotic stewardship programme. Antibiotic stewardship is commonly described as a programme that provides guidance for selection, dosing, route of administration and duration of antibiotic therapy and involves pharmacists, physicians and other healthcare providers (Griffith et al. 2012). Antibiotic stewardship is an obligation in European Union states and the United Kingdom but is a relatively new concept for Indian hospitals (Griffith et al. 2012).

WHO recognises laboratory-based surveillance of antibiotic resistance as a “fundamental priority” for the development of strategies to contain antibiotic resistance and to assess the impact of interventions especially in low and middle-income countries (WHO 2011). Action has been taken in response to the mounting crisis of antibiotic resistance, but most of the efforts have remained confined to resource-rich countries. Many of the existing surveillance networks continue to provide useful information (Gagliotti et al. 2011). There is however, no formal framework for collaboration among surveillance programmes worldwide. This lack of a global framework for collaborative surveillance of antibiotic resistance hinders rational discussions on antibiotic resistance patterns and also limits systematic comparison and evaluation of various intervention programmes (Grundmann et al. 2011). A standardized system for reporting antibiotic resistance needs to be established; such a system should rely on both public and private sector laboratories. In addition Health and Demographic Surveillance Sites (HDSS) have been suggested to obtain information from communities in resource limited settings at household level (Grundmann et al. 2011).

1.3 HEALTH SYSTEM IN INDIA

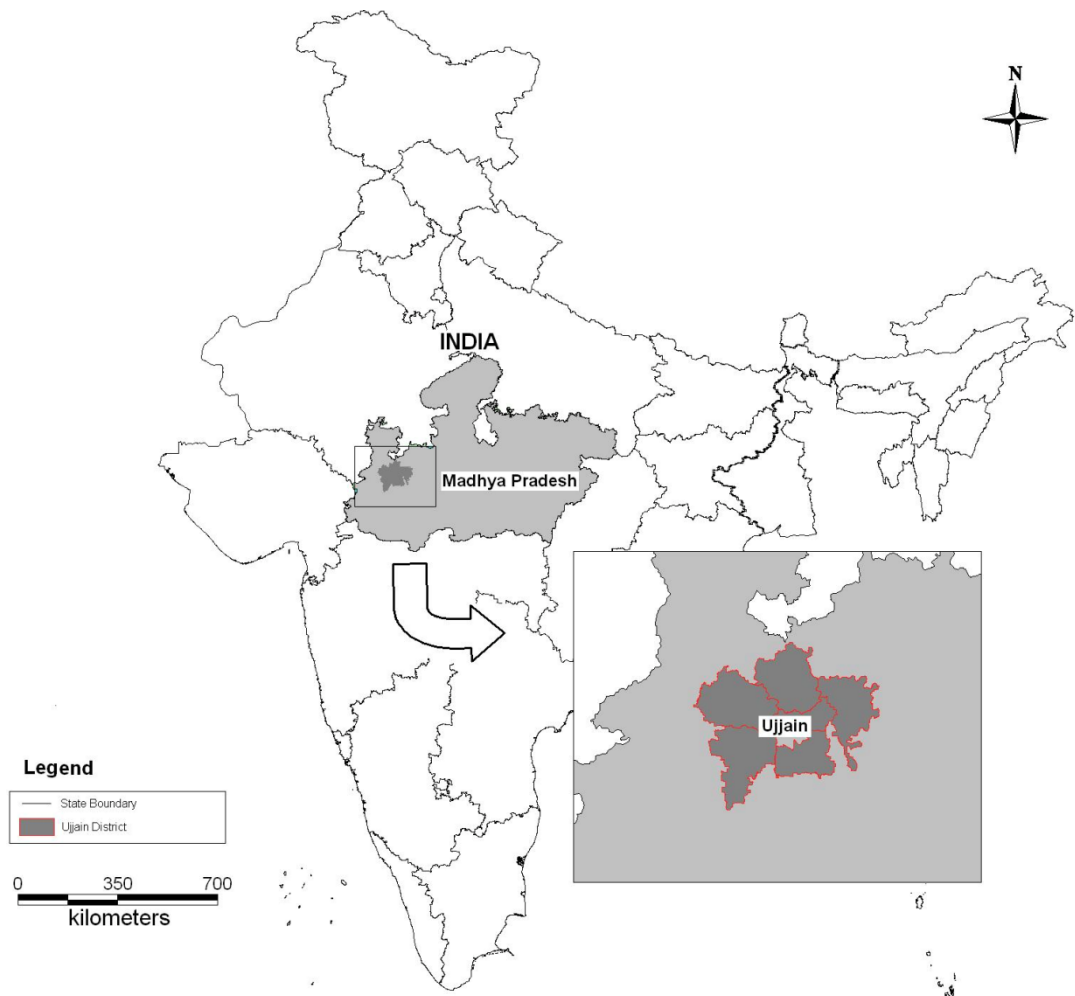


Figure 1.1 The map of India, Madhya Pradesh and Ujjain district

1.3.1 Public health care in India

India has 28 states and 7 union territories. States have their own elected governments. India has adopted a universal health care system, which is run by the states and union territories of India (WHO SEARO 2012).

Rural health services

India's primary health care system is based on the primary health center (PHC) and its sub centers. Each PHC (manned by a physician and health workers and auxiliary nurse midwives) caters to a population of about 30,000 in the plain areas and for a population of 20,000 in hilly, tribal and backward areas. Each sub-center provides health care to every 5000 population in general and for every 3000 in hilly, tribal and backward areas (WHO SEARO 2012).

Urban health services

Most Indian urban areas have secondary and tertiary facilities provided by the government. Most of the health care facilities in the government hospitals are either free or highly subsidized (WHO SEARO 2012).

1.3.2 Inadequacies of public health services in India

The performance of the primary public health care in India has been poor. Main reasons for poor performance have been pointed out in a world bank report (Radwan, 2005) and include: lack of flexibility of public-health structure and administration- resulting in ineffective response to the needs of a specific geographical area, lack of accountability- resulting in absentee doctors and staff, limited staff salaries, informal payments to obtain admission to a hospital, to obtain a bed or to obtain or deliver a drug, inability to fill vacancies, lack of public health management capacity among administrators or doctors, political interference with allocation of resources, poor infrastructure of the health centers and the hospitals and little or no community participation.

1.3.3 Private health care in India

India has one of the most highly privatized health care systems in the world in terms of finance and delivery (Sengupta and Nundy 2005). In the year 2005 it was estimated that private health care facilities accounted for 82% of outpatient visits, 58% of inpatient expenditure, and 40% of births in institutions (Sengupta and Nundy 2005). India ranks among the top 20 of the world's countries in its private spending, at 4.2% of GDP (GOI 2002). According to World Bank estimates in year 2008, 74.3% of the health care expenditure was out-of-pocket. As a result, more than 40% of all patients admitted to hospital have to borrow money or sell assets to cover expenses, and 25% of farmers are driven below the poverty line by the costs of their medical care (GOI 2002).

1.3.4 Other systems of medicine

Many people in India seek health-care from Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy (AYUSH) systems of medicine (<http://www.indianmedicine.nic.in/>). These systems run parallel to the allopathic system of medicine.

1.3.5 Demographic characteristics of India, Madhya Pradesh and Ujjain

Madhya Pradesh, in its present form, came into existence on November 1, 2000 following its bifurcation to create a new state of Chhattisgarh ('Department of Tourism, Government of Madhya Pradesh' 2012). The state is marked with a complex social structure, a predominantly agrarian economy. As pointed out in the Table 1.1 below, Madhya Pradesh is one of the worst performing states in terms of health indicators in India.

Table 1.1 Comparison of selected demographic indicators for India, Madhya Pradesh and Ujjain

Indicator	India	Madhya Pradesh	Ujjain
^a Population	1.21 billion (more than 1/6 th of the world population) ^b	6% of population of India, 72.6 million (almost equal to population of Germany) ^b	1.98 million
^c Sex ratio (total)	940	930	954
^c Crude birth rate	20.97	25	24.4
^c Crude death rate	7.48 deaths/1000 mid-year population	8 deaths/1000 mid-year population	6.4 deaths/1000 mid-year population
^c Life expectancy (at birth)	65	58 (lowest in India)	
^c Infant mortality rate/1000 live births	49.14	67 (highest in India)	59
^d Maternal mortality ratio	230 (150-350)	310	268
^a Population density/km	384	236	264
^a Literacy rate			
Male	82.14	80.53	73.5
Female	65.46	60.20	61.2

a <http://censusindia.gov.in/2011-prov-results> (provisional results of Census of India 2011)

b State of World Population, 2010

c Figures are estimates from Annual Health Survey 2010-11

d Data refers to estimates done in 2008. Figures in bracket for India are interagency estimates as reported by WHO (<http://apps.who.int/nha/database/StandardReport>)

1.4 THE PROBLEM OF ANTIMICROBIAL RESISTANCE IN INDIA

Rapid evolution of bacterial resistance in India (Kumarasamy et al. 2010) might be the result of a complex interaction of several factors. These include: higher burden of infectious disease, treatment uncertainty, lack of treatment guidelines, inadequate access to standard laboratory facilities, self medication, prescription based on availability, government support to pharmaceutical industries, market forces, qualification of the prescriber, lax law enforcement, fragmented public health system, poor population-wide health coverage, inadequate adherence to universal hygiene and infection control measures, and low population-wide education level (Kamat and Nichter 1998, Lakshmi 2008, Sahoo et al. 2010, Shanmugam 2011, Varghese et al. 2010).

In this thesis I will mainly discuss antibiotic prescribing with respect to clinical practice. The following are examples of the pressures and constraints under which physicians prescribe drugs:

- Prescribing with good intention: Physicians are most often motivated to give the best possible treatment often disregarding cost or spectrum of activity of the chosen antibiotic (Fishman and Polk 2010).
- Lack of access to diagnostics especially near-patient diagnostics and lack of treatment guidelines forces physicians to choose empirical antibiotic therapy based on experience (Hulscher et al. 2010).
- The marketing pressures of the pharmaceutical industry and other financial incentives for prescribing can influence the choice of antibiotics prescribed (or any other drug) (Jack 2011).
- “The fear of failure” of empirical antibiotic therapy is often quoted as a reason, which is further fuelled by the pharmaceutical industry through their biased presentation of drug information (Hulscher et al. 2010, Kunin et al. 1973).
- “The newer the better” is another myth in prescribing that increases patient costs and resistance (Avorn and Solomon 2000).
- “The more the better” is a myth that arises from a mistaken belief that if the effective dose of a particular drug is rather small, then a larger dose and prolonged treatment should definitely be better. The pharmacokinetics and pharmacodynamics of most antibiotics are complex and require extra effort on the part of physicians to understand them (Fishman and Polk 2010, Owens and Shorr 2009).
- Shorter patient consultation time and busy practice is associated with greater antibiotic prescribing (Gjelstad et al. 2011).
- There are often limited opportunities for continuing professional development for physicians, especially in low and middle-income countries (Adkoli et al. 2009, Vati and Walia 2001).
- Empiric spiralism, as explained earlier (Kim and Gallis 1989).
- Lack of innovation by the pharmaceutical industry in approach to treatment of infections in general and development of new antibiotics in particular has resulted in an empty pipeline of antibiotics against multi-drug resistant bacteria (Boucher et al. 2009).

1.5 RATIONALE OF THE STUDIES

1.5.1 Drug utilisation studies with focus on antibiotic use from India

In India little is known about antibiotics prescribing for a given clinical diagnosis. Drug utilisation studies done in India show that antibiotics are one of the most frequently prescribed drug groups (Sivaraman et al. 2009, Patel et al. 2005, Jhaj et al. 2001, Dineshkumar et al. 1995, Biswas et al. 2000, Karande et al. 2005), but there are surprisingly few published studies of antibiotic prescribing done in India using the WHO ATC/DDD methodology (Holloway et al. 2011, Kotwani et al. 2009, Kotwani et al. 2010, Sharma and Barman 2010, Wattal et al. 2005). The primary reason for the lack of such studies is the fact that in most health care facilities antibiotic use data is not collected at all. At pharmacy level there can be sales without prescription thus limiting the accuracy of the data. The standardised method of reporting for outpatient antibiotic use suggested by the WHO ATC/DDD methodology is DDD per 1000 inhabitants per year. This type of reporting is not possible currently as most health-care set-ups in India have no defined population to which they cater. Patients often travel to distant hospitals and purchase prescribed medications from pharmacies close to where they reside. Lack of a computerised tracking system makes DDD per 1000 inhabitants a redundant concept for countries like India. In view of the paucity of studies and the methodological challenge two surveillance studies were planned adapting the WHO, ATC/DDD methodology to suit the local context. One study was planned among outpatients (Paper I) and other among admitted patients (Paper II).

1.5.2 Adherence to treatment guidelines for diarrhoea

WHO and UNICEF, since 2004 recommend that all children with acute diarrhoea be given zinc in some form for 10 to 14 days during and after diarrhoea (10 milligrams per day for infants younger than 6 months and 20 milligrams per day for those older than 6 months) (UNICEF and WHO 2004). The Indian Academy of Paediatrics also has recommendations on ORS and zinc use since 2004 (Bhatnagar et al. 2004), which were re-endorsed in 2006 (Bhatnagar et al. 2007). Later in 2007, the Government of India recommended use of zinc for acute diarrhoea. The National Rural Health Mission included ORS and zinc in the list of drugs to be made available to the sub centres (Bhatnagar et al. 2010). In spite of this only about 34% of the children with diarrhoea are prescribed ORS and only about 1% children are prescribed zinc (Gitanjali and Weerasuriya 2011). Improving the case management of diarrhoea can be considered as one of the few “low hanging” fruits for reducing child mortality, as the two most important interventions, i.e. ORS and zinc use, can be scaled up using a massive public health campaign, and with minimal funding (Sabot et al. 2012). However, there has been no reported follow up on adherence to treatment guidelines in India. So, a study on prescriptions for diarrhoea among children in Ujjain, India, to determine factors associated with adherence to treatment guidelines by the prescribing physicians was planned (Paper III).

1.5.3 Importance of surveillance of antibiotic resistance among commensal and pathogenic bacteria

There is a serious lack of surveillance initiatives in resource-constrained settings, where the burden of infections requiring effective antibiotics is higher (Ashley et al. 2011, WHO 2005a). In India there is no systematic surveillance of antimicrobial resistance at national or

regional level. The National Centre for Disease Control, under the Director General of Health Services, Ministry of Health and Family Welfare, Government of India, published *The National Policy for Containment of Antimicrobial Resistance, India* (The National Policy for Containment of Antimicrobial Resistance, India 2011). However, the policy lacks a solid evidence base from studies done in India. The main constraint for generation of evidence-base for policy is lack of laboratory capacity in many parts of India and many low and middle-income countries (WHO 2011). In view of the paucity of studies from India, two surveillance studies, one on nasal carriage of commensal *S. aureus* in children below five years of age (Paper IV) and the other on bacterial pathogens isolated from the patients with suspected infections (Paper V) were planned.

2 AIMS AND RESEARCH QUESTIONS

2.1 AIMS

The main aim of the thesis is to increase the knowledge regarding antibiotic prescribing patterns and prevalence of resistance using two hospitals in Ujjain, India as examples. The knowledge and methods will be used to identify targets for intervention to improve clinical practice with regards to antibiotic prescribing in this and similar settings.

2.2 RESEARCH QUESTIONS

Diagnosis prescribing

- What is the pattern of prescribing for common infections in outpatient clinics of the two hospitals?
- What is the pattern of prescribing for common infections in admitted patients of the two hospitals?

Adherence to prescribing guidelines

- What is the adherence to treatment guidelines by health-care providers in city of Ujjain for diarrhoea in children?

Resistant bacteria

- What is the prevalence of nasal carriage of *S. aureus* in healthy children below five years and what is the antibiotic sensitivity of *S. aureus* isolates?
- What is the prevalence of, and antibiotic sensitivity of, pathogenic bacteria among patients with suspected infections in the two hospitals?

3 PATIENTS AND METHODS

3.1 STUDY DESIGN

All the five studies of the thesis were cross-sectional using quantitative methods. The first two studies were conducted to understand the prescribing pattern for common infections or infectious disease complaints in outpatient clinics (Paper I) and the prescribing patterns for common infections using “foci of infection” approach among admitted patients (Paper II) in the two hospitals in Ujjain, India. Another of the studies (Paper III) was performed to estimate the adherence to treatment guidelines for acute diarrhoea, a common infection among children. Paper IV and V were microbiological studies. The study in Paper IV was performed to estimate the prevalence of nasal carriage of *S. aureus*, its resistance pattern and factors associated with nasal carriage in children below five years of age. The Paper V was done to define the magnitude of resistance among pathogenic bacteria isolated from patients with suspected infections. For papers I, II, IV and V the data was collected repeatedly over 15 months, from November 2007 to February 2009. Data was first collected at the teaching hospital (CRGH) and then at the non-teaching hospital (UCTH), for 45 days in each hospital. To allow time for appropriate data management a period of 15 days was introduced between the two hospitals and the two seasons. Data was thus collected four times for 45 days each in the two hospitals. For paper III data was collected from 1st June to 14th August 2009.

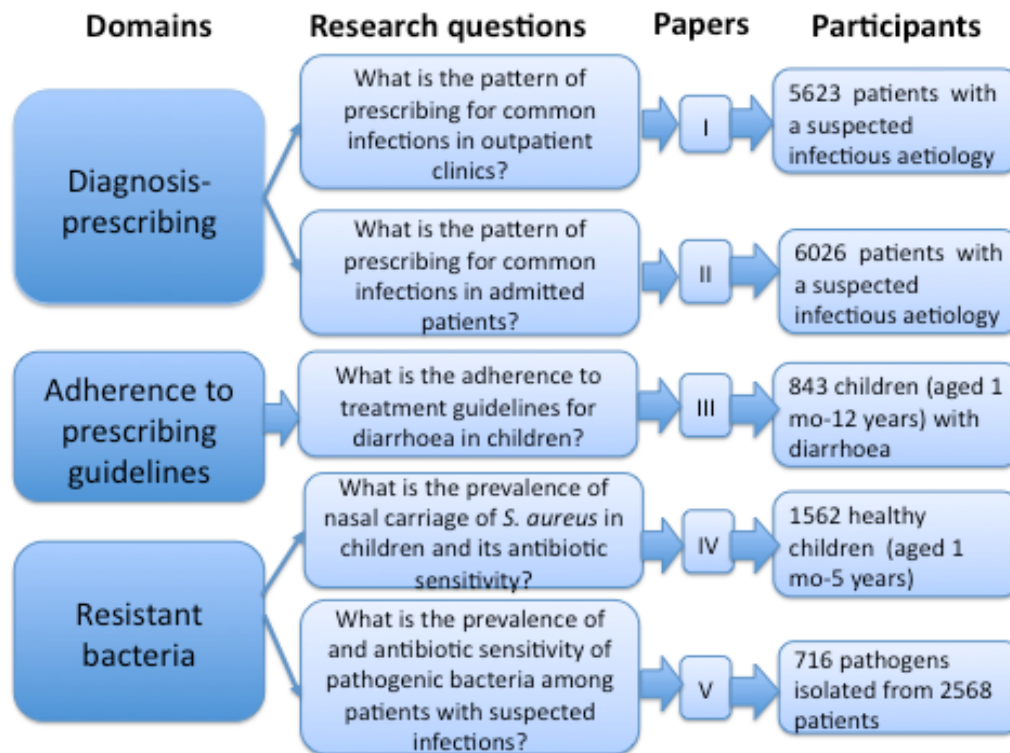


Figure 3.1: Overview of research questions and overall research framework for the thesis.

3.2 STUDY SETTINGS

3.2.1 Ujjain and the study settings

Ujjain district is situated in the western part of state of Madhya Pradesh, India. This region is popularly known as Malwa, with agriculture as the main source of income. The district has an area of 6,091 sq. km. with a population of about 1.98 million. Ujjain city is the administrative centre of Ujjain District with a population of about 700,000 inhabitants (Census of India 2011).

Health care infrastructure in Ujjain

The district chief medical and health officer controls the public health care in Ujjain district. There is one district hospital located in Ujjain city. There are two community health centres, one in a rural area and one in an urban area. A network of 20 primary health centres and 175 sub-centres caters to the rural population. In urban areas, there are five civil dispensaries serving the same purpose as primary health centres in rural areas. There are four hospitals, one Ayurvedic medical college hospital and four post-partum centres in Ujjain district (Deshpande et al. 2004).

Apart from the above public health infrastructure there are five large private hospitals (having at least 100 beds), including one teaching hospital attached to Ruxmaniben Deepchand Gardi Medical College. In Ujjain district, there are around 300 qualified doctors working in different health care facilities. Many of the practitioners in government hospitals are allowed to work in private clinics outside of their official hours of work. Practitioners from other formal systems of medicine mainly, Ayurveda and Homeopathy (around 110 in number) and informal health-care providers (around 800 in number) outnumber the allopathic practitioners. Most (82%) of the informal health-care providers are based in the rural areas (De Costa et al. 2009, Deshpande et al. 2004). The health-care workers trained in AYUSH are not allowed to prescribe allopathic medicines but many of them do so.

Private Pharmacies in Ujjain District

Since most of the health care in India is sought in private health care facilities, it is expected that most drugs are dispensed by the private pharmacies. Private pharmacies are privately owned pharmacies that sell the drugs for profit. In a mapping study using the geographic information system a total of 475 private pharmacies were identified in the Ujjain district (Sabde et al. 2011). Three-quarter of the pharmacies were in urban areas, concentrated around physician practices. In rural areas, private pharmacies were located along the main roads. It was found that medicines were sold to 39% of the clients without prescription. The mapping study also showed that only 11.5% of the pharmacy staff had any formal pharmacist qualification (Sabde et al. 2011).

The specific study hospitals

The specific settings of the studies were two hospitals (Paper I, II, IV and V), namely the V.D. Gardi Charitable Trust Hospital (UCTH or non-teaching hospital) and the Chandrikaben Rashmikant Gardi Hospital (CRGH or teaching hospital). The non-teaching

hospital is a 350 bedded hospital located in the city of Ujjain while the 570 bedded, teaching hospital is located about six km from Ujjain city in a village called Surasa. Both the hospitals are run and managed by Ujjain Charitable Trust Hospital and Research Centre, a non-profit organisation. In both the hospitals qualified allopathic doctors provide services. In the non-teaching hospital health care workers provide paid services but the hospital is run on a break-even basis. The consultants in the non-teaching hospital are allowed to work in private clinics outside of their working hours. The teaching hospital is completely charitable and there is no charge for services. Academic professionals manage the healthcare services in the teaching hospital. The consultants in this hospital have an institutional hospital-based practice and are not allowed to work in private practice. Both hospitals cater predominantly to a rural population from the villages surrounding Ujjain city. In both hospitals, most admissions (91%) in medical and intensive care units are emergency admissions, whereas in the surgical units, both elective and emergency admissions are equally common. Treatment guidelines for infectious diseases have not been implemented in either hospital.

The above two hospitals in Ujjain were selected as primary sites for all studies (Paper I, II, IV and V) as most people seek health care in similar private settings because of the inadequacies of the primary public health care in India as discussed earlier. I work in both of the above hospitals.

In paper III the settings were five large (more than 100 bedded) hospitals and 17 large (based on sales) pharmacies in the city of Ujjain.

3.3 SAMPLING AND DATA COLLECTION METHODS

3.3.1 Pilot studies

Since these were the first studies undertaken in the area, we had very little or no information on the basic data required for sample size calculations. Pilot studies were carried out to calculate the sample size, test the data collection instruments, and to train the consultants (Paper I, II and V), the resident medical officers (Paper II and III), and the study assistants (Paper III and IV). The pilot studies were done in both the teaching and the non-teaching hospital. The time and the duration of the pilot studies varied for each study. A pilot study was done for one month in March 2007 among outpatients in two hospitals (Paper I and IV), on 100 patients each in two hospitals in March and May 2007 among admitted patients (Paper II and V) and for two weeks in May 2009 among 25 children with diarrhoea (Paper III).

3.3.2 Sample size

Sample size calculations were made using the data from the pilot studies (Paper I, II and III). For studies in paper IV and V we decided to include all patients detected to be culture positive.

The primary outcome in Papers I and II was antibiotic prescribing rate. The antibiotic prescribing rate was 60 to 80% for Paper I and 80 to 90% for Paper II in the respective pilot studies. For sample size calculation the lower limit of antibiotic prescribing rate was used to get the maximum sample size. Thus, using the antibiotic prescribing rate of 60% in

Paper I and 80% in Paper II and requesting 80% power to detect a difference of 10 percentage points for single comparison (the two hospitals in Paper I and “foci of infection or antibiotic prophylaxis” in Paper II) in a statistical test for comparison of two proportions at 5% significance level, the sample size was 376 for each comparison in study I and 108 for each comparison in study II. Since, we had 15 foci of infection to be compared the minimum sample size was $15 \times 108 \times 2 = 3240$ patients in study in Paper II.

For Paper III the primary outcome for sample size calculation was prescribing rate for oral rehydration solution (ORS). The estimated rate of ORS prescribing was 50%, which was assumed as the basic percentage of prescribing of ORS. Thus, requesting a 95% confidence interval for the proportion (0.5) with width no higher than 15%, the minimum sample size needed was 170. A design effect of “4” was used to adjust for clustering of the data from healthcare facility and the prescribers. The estimated figure of “4” is considered a reasonable estimate of design effect in such studies (Rowe et al. 2002). Thus, considering the design effect of “4”, gave a minimum sample size of $170 \times 4 = 680$ cases with diarrhoea.

3.3.3 Study Participants

3.3.3.1 Paper I

Consecutive patients suspected to have an infectious aetiology (children from the age of 1 month to 5 years and adults 18 years and above) seen by specialist consultants from Departments of Paediatrics, Medicine, Chest medicine, Emergency care, Obstetrics and Gynaecology and Surgery (in teaching hospital only) participated in the study. The consultant of the concerned specialty suspected the infectious aetiology and made the final diagnosis. No external validation of the diagnosis was done. The study was undertaken during the outpatient clinics between 9:00 AM and 4:00 PM on weekdays, except Sundays and public holidays. A total of 62 consultants out of the available 70 participated voluntarily in the data collection, which covered 80% of the first consultations for infectious disease complaints. The remaining consultations were done outside of the routine working hours, on holidays and were not covered for logistic reasons.

3.3.3.2 Paper II

All patients for whom the admitting consultant suspected an infectious aetiology at the time of admission or during the hospital stay and were started on antibiotic therapy, or who were given antibiotic prophylaxis were included in the study. Patients admitted for infectious aetiologies, requiring anti-infective agents other than antibiotics, and patients diagnosed and treated for tuberculosis, were not included. Ninety-six percent of the available physicians (n=72) from the neonatal intensive care unit; general medicine, including the medicine intensive care unit; general surgery; obstetrics and gynaecology; ear, nose, and throat; and orthopaedics of the two hospitals participated voluntarily in the study.

3.3.3.3 Paper III

Children (aged one month to 12 years) with prescriptions for current episode of diarrhoea, who were either a) admitted for acute diarrhoea in one of the five participating hospitals in Ujjain city or b) the prescription for acute diarrhoea was honoured in one of the seventeen participating pharmacies in Ujjain city. A paediatrician, a qualified medical professional (including the AYUSH practitioners) or the informal health care providers could have

written the prescription included in the study. The study included prescriptions from 86% of the practising paediatricians (n=34) in the city of Ujjain at the time of the study. In the participating hospitals the resident medical officers collected data and in the pharmacies the pharmacy assistants collected data.

3.3.3.4 Paper IV

The children aged from 1 month to 59 months visiting the paediatric outpatient clinics of the two hospitals for routine immunisation were screened for their health status by a paediatrician. Healthy children were recruited in the study to identify nasal carriage of *S. aureus* and its antibiotic sensitivity. A structured questionnaire was filled to explore factors associated with nasal carriage of *S. aureus*.

3.3.3.5 Paper V

Patients admitted with suspected infections (Paper II) and for whom the admitting consultant sent clinically relevant samples for bacterial culture were included in the study. Information from non-duplicate, consecutive, bacterial isolates (except for anaerobic bacteria and Mycobacteria) from the clinical samples (urine, pus or pus swabs, blood or broncho-alveolar lavage fluid) was presented in the study.

3.3.4 Data collection procedure (form)

Data collection was done on pre-designed; pilot-tested structured questionnaires (Paper I-V). For actual questionnaires see Annexure I-V. The forms contained diagnosis or symptoms (Paper I) or codes for “foci of infection” which were based on the anatomical system or sub-system (Paper II). Details of current diarrhoeal episode, its duration, associated symptoms and signs, and drugs prescribed for treating the child (1 month to 12 years) was included in data collection form (Paper III). Details of epidemiological factors suspected to be associated with nasal carriage of *S. aureus* in healthy children (1 month to 5 years) were included (Paper IV). Details of clinical site of infection and the corresponding samples sent for bacterial culture from admitted patients with suspected infections were included in the structured questionnaires (Paper V).

The form used in Paper I has been adapted from similar studies done in Sweden (Andre et al. 2002, Andre et al. 2008, Lundborg et al. 2002). The form used in study II has been adapted from point prevalence studies of Strama and the European Surveillance of Antibiotic resistance (ESAC) (Ansari et al. 2009, Molstad et al. 2008).

Demographic details of the patients varied according to the study and were tailored from the feedback and results of the pilot studies. Details of diagnostics done (Paper I, II, III and V) were not included and assessment of severity of illness (Paper I, II and III) was not carried out due to non-feasibility of data collection over the long period of time planned for the study.

3.3.5 Measuring antibiotic prescribing

Antibiotic prescribing data (Paper I and II) were collected at individual patient level and were grouped according to the suspected infectious aetiology. Each prescribed antibiotic was coded according to the World Health Organization (WHO) Collaborating Centre for

Drug Statistics Methodology, Anatomical Therapeutic Chemical (ATC) classification with Defined Daily Dose (DDD) 2009 (Methodology 2010) as defined in the ATC fifth level in J01 (antibacterial for systemic use). Imidazole group (P01AB) and netazoxanide (P01AX11) were also included. The DDDs were calculated per 1000 patients per diagnosis (DDD/TPD) (Paper I) and the focus-specific DDDs were calculated per hundred patient days (DDD/HPD) (Paper II).

3.3.6 Laboratory methods

3.3.6.1 Antibiotic susceptibility testing

Swabs from anterior nares were cultured within four hours of receipt in the microbiology laboratory on 5% sheep blood agar plates, incubated at $35 \pm 1^\circ\text{C}$ and examined for growth after 24-48 hours (Paper IV). The clinical samples were plated on blood agar and (or) MacConkey's agar medium (HiMedia Laboratories Pvt. Ltd, Mumbai, India) within four hours of receipt in the laboratory (Paper V).

The bacteria were identified by their typical colony morphology, results of Gram's staining and conventional microbiological methods (Murray PR 1999).

Antibiotic susceptibility testing (AST) was performed by Kirby-Bauer disk-diffusion method on Muller Hinton agar plates. The disk strengths (antibiotic concentrations) were as recommended by the Clinical and Laboratory Standards Institute (CLSI) at the time of the study (CLSI 2006). CLSI interpretive criteria for susceptibility and resistance were followed (CLSI 2006). AST quality control was performed using the following reference strains: *Escherichia coli* ATCC (American Type Culture Collection) 25922, *Klebsiella pneumoniae* ATCC 70063, *Pseudomonas aeruginosa* ATCC 27853, *Enterococcus faecalis* ATCC 29212 and *Staphylococcus aureus* ATCC 29213. For Gram-negative bacteria, the intermediate susceptible isolates were counted as resistant in calculations.

Extended-spectrum beta lactamase (ESBL) production was detected using the double-disk synergy test (Jarlier et al. 1988). Presence of ESBL was assayed using the following antibiotic disks: cefotaxime (30 μg), cefotaxime/clavulanic acid (30/10 μg), ceftazidime (30 μg) and ceftazidime/clavulanic acid (30/10 μg); (HiMedia Laboratories Pvt. Ltd, Mumbai, India). According to the CLSI criteria for ESBL detection, each isolate with an inhibition zone diameter of ≤ 22 mm for ceftazidime or ≤ 27 mm for cefotaxime was considered to be a potential ESBL producer or screen positive. A zone diameter increase of ≥ 5 mm for either antimicrobial agent when tested in combination with clavulanic acid versus when tested alone was considered as an ESBL-producing organism. *K. pneumoniae* ATCC 700603 (positive control) and *E. coli* ATCC 25922 (negative control) were used for quality control in the ESBL tests (Jarlier et al. 1988).

Inducible clindamycin resistance for *S. aureus* was detected by double disk-diffusion test (D test); performed by placing the clindamycin and erythromycin disks 15 mm apart (Fiebelkorn et al. 2003).

Multi-drug resistant (MDR) isolates were defined as those isolates having co-resistance to three or more antibiotic groups (Magiorakos et al. 2011).

3.4 DATA ANALYSIS

For all studies data were entered in Epidata software (Version 3.1, Epidata software Association, Odense, Denmark) and transferred to Stata version 10 (Stata Corp., College Station, TX, USA) for further analysis. The data was double entered and checked.

As presented in Figure 3.1 the five research questions of the thesis were investigated in five papers. The outcome in paper I was antibiotic prescribing calculated as DDD per TPD among patients with suspected infections attending outpatient clinics. Antibiotic prescribing among admitted patients calculated, as DDD per HPD was the outcome in paper II. The primary outcome in paper III was ORS prescribing rate. The secondary outcomes were (a) prescribing of “ORS together with zinc” and (b) “antibiotics”. For paper IV the outcome was prevalence of nasal carriage of *S. aureus* in children below five years of age and prevalence of antibiotic resistance among isolates of *S. aureus*. For paper V the outcome was prevalence of antibiotic resistance among pathogens cultured from admitted patients with suspected patients.

Descriptive statistics were presented as mean, median and (or) proportion (Paper I to V). Two-by-two tables were made to calculate crude odds ratio (OR) using Chi square test. The P-value smaller than 0.05 were taken to define statistical significance. The test of significance was two-sided. Odds ratios and their 95% confidence intervals (CI) were also computed (Paper I, III, IV and V).

Logistic regression models were fitted for studies in papers III and IV to determine the factors associated with the outcome (as defined above). In paper IV a given variable was entered in the final multivariate logistic model if the bivariate analysis yielded a P value less than 0.1. All the variables were adjusted for age and sex. A complete case series analysis was used. A post-hoc power calculation was done for the study in paper IV and was found to be 0.98.

In paper III two multivariate stepwise logistic regression models, one for each secondary outcome variable, were computed. The outcome variables were controlled for design effect due to intra cluster correlation (ICC). Covariates found significant in bivariate analysis using Chi-square test at a level of $P < 0.20$ were included in the model and removed using a backwards stepwise method (Wald test with removal level of significance of $P < 0.10$). Bonferroni correction was applied for OR's because of the double comparison of independent variables with two outcomes. A value of $P < 0.05$ was considered statistically significant in the final models.

3.5 ETHICAL CONSIDERATIONS

The ethics committee of R.D. Gardi Medical College has approved the overall proposal (approval number 41/2007). The ethics committee considered the Indian Council of Medical Research (ICMR) guidelines (icmr.nic.in/ethical_guidelines) before clearing the project. After explaining the purpose of the study informed consent of all participants was sought in local language (Hindi). The consent was obtained orally for studies presented in Papers I and III, while written informed consent was taken for studies presented in Papers II, IV and V. There was no change in the care offered to the patients who refused to participate in the study, however the refusal rates were very low (1.3% overall). All

information revealing personal identity has been kept confidential. The participating consultants were informed about culture results of each patient they were in charge of (Paper IV and V). The children that were found to be culture positive for *S. aureus* were counselled and were offered treatment with mupirocin cream for local application for seven days. The patients were not charged for cultures obtained during the study period. The potential future benefit of the project was explained to the patients, as the empirical antibiotic therapy needs to be guided by prevailing sensitivity patterns.

3.6 SUMMARY OF METHODS

Paper	I	II	III	IV	V
Research questions	What is the pattern of prescribing for common infections in outpatient clinics of the two hospitals?	What is the pattern of prescribing for common infections in admitted patients of the two hospitals?	What is the adherence to treatment guidelines for diarrhoea in children in the city of Ujjain?	What is the prevalence of nasal carriage of <i>S. aureus</i> in healthy children below five years and what is the antibiotic sensitivity of <i>S. aureus</i> isolates?	What is the prevalence of and antibiotic sensitivity of pathogenic bacteria among patients with suspected infections in the two hospitals?
Study setting	Outpatient clinics of two hospitals, the UCTH ¹ and CRGH ²	Admitted patients of two hospitals, the UCTH ¹ and CRGH ²	Five large hospitals ³ and 17 large pharmacies ⁴ in the city of Ujjain	Paediatric immunization clinics of two hospitals, the UCTH ¹ and CRGH ²	Admitted patients of two hospitals, the UCTH ¹ and CRGH ²
Design (Quantitative)	Cross-sectional with repeated data collection ⁵	Cross-sectional with repeated data collection ⁵	Cross-sectional	Cross-sectional	Cross-sectional
Study population	5623 consecutive out-patients with suspected infection, children (aged 1 month to 5 years) and adults	6026 consecutive admitted patients with suspected infection, children (aged 1 month to 12 years) and adults	843 children with diarrhoea (aged 1 month to 12 years)	1562 healthy children below five years of age	716 pathogens from 2568 patients with suspected infections (patients in paper II)
Data collection period	15 months from November 2007 to February 2009	15 months from November 2007 to February 2009	1 st June to 14 August 2009	15 months from November 2007 to February 2009	15 months from November 2007 to February 2009
Analysis	Descriptive statistics	Descriptive statistics	Logistic regression	Logistic regression	Descriptive statistics

¹V.D. Gardi Charitable Trust Hospital (non-teaching hospital), ² Chandrikaben Rashmikant Gardi Hospital (teaching hospital), ³ more than 100-bedded hospitals, ⁴ based on sales ⁵ Data were collected for duration of 45 days each, first in CRGH and then UCTH with a gap of 15 days between hospitals.

4 RESULTS AND MAIN LESSONS LEARNT

Many results of the five studies in this thesis can be considered important targets for intervention to improve clinical practice with regards to antibiotic prescribing. I have chosen to present the main results and lessons learned from the studies.

4.1 OVERALL ANTIBIOTIC PRESCRIBING

4.1.1 Paper I

Antibiotics were prescribed for 3732 patients out of 5623 outpatients with for various suspected infections, thus the overall antibiotic prescribing for outpatients was 66.3%. Most (98.7%) of the outpatient antibiotics were prescribed as oral formulations. The outpatients had a mean of 1.28 antibiotics prescribed. Antibiotic prescribing was less frequent by 11.3 percentage units in the teaching hospital compared to the non-teaching hospital. Antibiotic prescribing varied slightly with different seasons. Overall antibiotic prescribing was highest in summer, with a prescribing rate of 75%, in the outpatient clinics of non-teaching hospital but was highest in rainy season in the outpatient clinics of teaching hospital with a prescribing rate of 70%. There were differences in antibiotic prescribing rates between children and adult patients. Eighty six percent of the adults in the outpatient clinics of non-teaching hospitals and 79% of adults in the outpatient clinics of teaching hospital were prescribed antibiotics compared to a prescribing rate of 57% and 40% in the non-teaching and the teaching hospital's outpatient clinics respectively, for children up-to the age of 5 years.

4.1.2 Paper II

Among the 6026 admitted patients 5531 were prescribed antibiotics for one of the fifteen "foci of infection", thus the overall prescribing rate for admitted patients was 92%. Most (59%) patients were prescribed one antibiotic. A combination of two, three or four antibiotics was prescribed significantly more often in the teaching hospital. HAI was identified in 9% of all infections. The most common HAI recorded was skin and soft tissue infection due to surgical site infection. The mean length of stay in the teaching hospital was 7.8 days (95% CI 7.3-8.3 days) and that of non-teaching hospitals 4.2 days (95% CI 4.1-4.4 days).

4.1.3 Antibiotic prescribing for surgical prophylaxis (Paper II)

One third of all antibiotic prescribing among the admitted patients was for surgical prophylaxis. A total of 1846 patients i.e. 34% of 5531 patients that were prescribed antibiotics were given surgical prophylaxis. Among the patients that were given prophylaxis (n=1846), 86% (n=1593) received prophylaxis for duration more than one day and belonged to the surgical services like departments of general surgery, obstetrics and gynaecology, ear, nose and throat and orthopaedics.

4.2 PRESCRIBING FOR ACUTE DIARRHOEA

Diarrhoea is a common complaint for seeking healthcare in the settings and, in this study, also a common reason of antibiotic prescribing. In this thesis there is information on

prescribing for 1600 patients presenting with diarrhoea (525 Paper I, 232 Paper II, and 843 Paper III). Out of these 463 patients (29%) were admitted patients (232 Paper II and 231 Paper III). The main lessons learnt from the three studies (Paper I, II and III) were:

- a. Comparing antibiotic prescribing for diarrhoea between adults and children in the outpatient clinics of the teaching and the non-teaching hospital (Paper I), a higher proportion of adults (91%) compared with children (40%, aged 1 month to 5 years) were prescribed antibiotics, OR 3.8 (95% CI 2.8 to 5.2, $P < 0.001$).
- b. In the study done in pharmacies and hospitals of Ujjain city 71% of children with diarrhoea (aged 1 month-12 years) were prescribed antibiotics (Paper III).
- c. Facility level differences were seen with regards to antibiotic prescribing both in outpatient clinics (Paper I and III) and among admitted patients (Paper II and III). Antibiotics were prescribed less often in the teaching hospital outpatient clinics, OR 0.01 (95% CI 0.01-0.04, $P < 0.001$) (Paper III). Also, when the teaching and non-teaching hospitals were compared directly, the teaching hospital had less antibiotic prescribing, OR 0.35 (95% CI 0.22-0.52, $P < 0.001$) (Paper I).
- d. Overall in the two hospitals the nitroimidazole group (metronidazole, tinidazole and ornidazole) was the commonest group prescribed (Table 4.2 and Figure 4.1), most often in combination with co-trimoxazole (more commonly in the teaching hospital) and quinolones (more commonly in the non-teaching hospital) (Paper I).
- e. In the study conducted in Ujjain city the illogical fixed dose combination ofloxacin and ornidazole was the most frequent (22% of prescribed antibiotics) oral antibiotic prescribed (Paper III).
- f. Practitioners of alternate systems of medicine and informal health-care providers ($n=171$), prescribed antibiotics more often compared to paediatricians (OR 3.21 95% CI 1.19 to 8.65 $P=0.023$) (Paper III).
- g. The odds of prescribing antibiotics were significantly higher in the presence of fever (OR 3.32, 95% CI 1.82-6.07; $P < 0.001$), stomach pain (OR 7.25, 95% CI 1.81-28.94; $P=0.007$) and blood in stools (OR 9.93, 95% CI 3.65-27.01; $P < 0.001$) (Paper III).
- h. ORS alone was prescribed in 58% of the prescriptions, while ORS with zinc was prescribed in 22% of prescriptions (Paper III).
- i. Practitioners from 'non-paying' hospitals are more likely to prescribe ORS and zinc (OR 4.94, 95% CI 2.45-9.96, $P < 0.001$) and less likely to prescribe antibiotics (OR 0.01, 95% CI 0.01-0-04, $P < 0.001$) compared to practitioners from 'paying' hospitals (Paper III).

4.3 ANTIBIOTIC PRESCRIBING FOR PNEUMONIA

Among outpatients, 422 had presented with symptoms of pneumonia (Paper I) and 611 patients were admitted with clinical diagnosis of pneumonia (Paper II). The details of distribution of number of cases of pneumonia in the two hospitals and two studies are shown in the Table 4.1:

The following lessons were learnt:

- a. A total of 4466 DDD/TPD were prescribed for outpatients diagnosed with pneumonia (Paper I) and 357 DDD/HPD among admitted patients (Paper II).

- b. Among adult outpatients with pneumonia the quinolone group (Table 4.2 and Figure 4.1) was the most prescribed antibiotic with 1889 DDD/TPD (61% levofloxacin, 32% ciprofloxacin). Levofloxacin was prescribed much more often in the non-teaching hospital compared to teaching hospital (72% versus 18%) whereas ciprofloxacin was prescribed more often in the teaching hospital (Paper I).
- c. Levofloxacin was also the commonest antibiotic prescribed for upper respiratory tract infections in the non-teaching hospital (Paper I).

Table 4.1 Number of cases of pneumonia in the two hospitals and two studies in Ujjain, India

Study	Hospital	Number of cases of pneumonia		Total
		Adults (%)	Children (%)	
Paper I (Outpatient)	Non-teaching hospital	175 (64)	98 (36)	273
	Teaching hospital	68 (46)	81 (54) (Up-to 5 years of age)	149
Paper II (Admitted patients)	Non-teaching hospital	251 (66)	128 (34)	379
	Teaching hospital	180 (78)	52 (22) (Up-to 12 years of age)	232
				1033

- d. The tetracycline group (tetracycline and doxycycline) was prescribed more often in the teaching hospital both among outpatients (Table 4.2 and Figure 4.1) and admitted patients (Paper I and II).
- e. Co-trimoxazole was also prescribed more often in the teaching hospital (Paper I and II).
- f. In cases of pneumonia in the teaching hospital tetracyclines (69 DDD/HPD: 63% doxycycline and 37% tetracycline) were the most prescribed class, followed by quinolones (42 DDD/HPD: 94% ciprofloxacin, 5% levofloxacin), and penicillins with extended spectrum (41 DDD/HPD: 76% ampicillin with cloxacillin, 18% ampicillin, 6% amoxicillin), and 3rd generation cephalosporins (22 DDD/HPD: 66% cefotaxime, 24% ceftriaxone) (Paper II).
- g. In the non-teaching hospital 3rd generation cephalosporins (57 DDD/HPD-56% ceftriaxone with beta-lactamase inhibitor, 28% ceftriaxone, 12% cefotaxime), quinolones (32 DDD/HPD 68% ciprofloxacin, 22% levofloxacin) and co-amoxiclav were prescribed (Paper II).

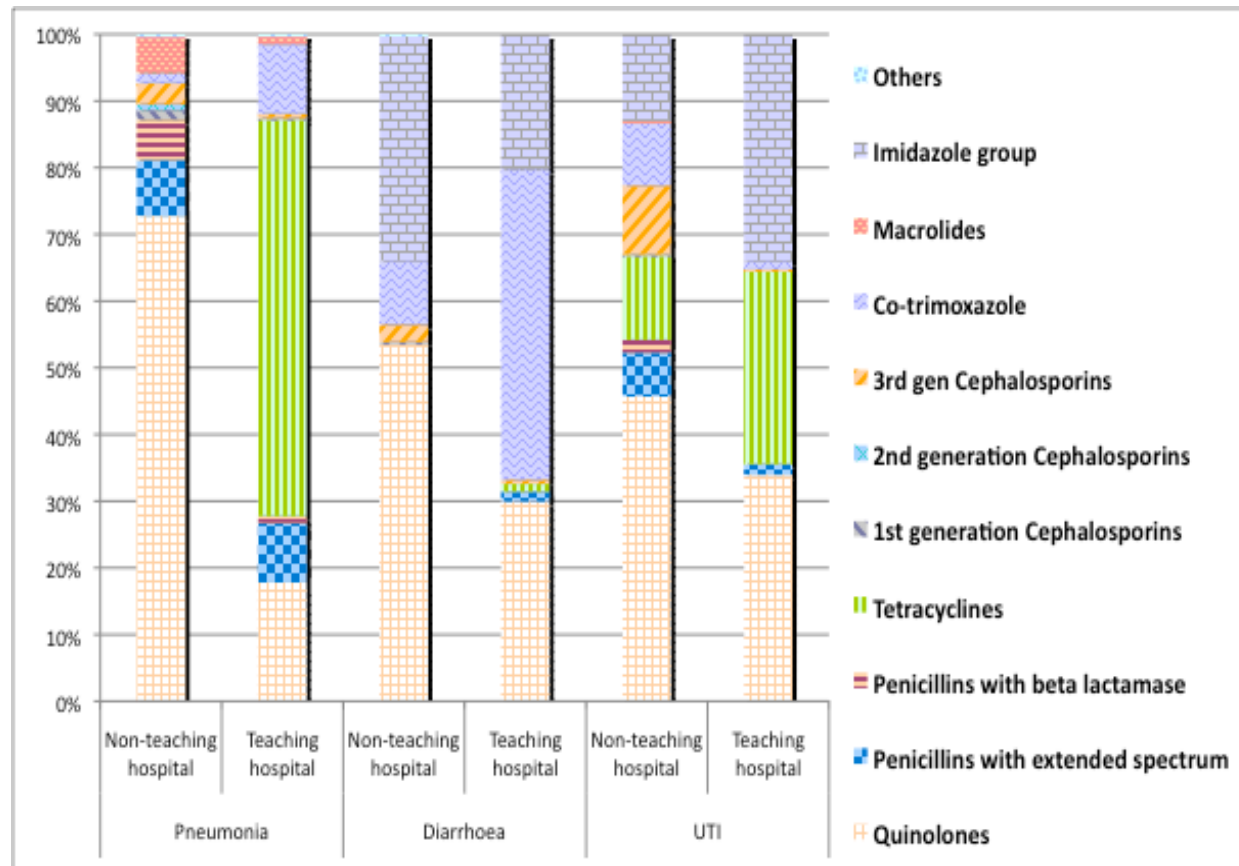


Figure 4.1- Relative distribution of defined daily doses per1000 patients per diagnosis (DDD/TPD) of the two hospitals for the diagnosis of pneumonia, diarrhoea and urinary tract infection (UTI) (Paper I)

Table 4.2 Distribution of defined daily doses of different classes antibiotics per 1000 patients per diagnosis (DDD/TPD) in the two hospitals for pneumonia, diarrhoea and urinary tract infection (UTI) in the two hospitals in Ujjain, India (Paper I)

Diagnosis	Hospital	Penicillins with extended spectrum	Penicillins with beta lactamase	Tetracyclines	1st generation Cephalosporins	2nd generation Cephalosporins	3rd gen Cephalosporins	Co-trimoxazole	Macrolides	Quinolones	Imidazole group	Others
Pneumonia	NTH	177	129	0	30	18	67	32	121	1544	1	2
	TH	218	24	1453	2	0	15	255	34	434	1	1
Diarrhoea	NTH	0	0	0	1.5	0	41	147	0	828	521	2
	TH	14	0	11	0	0	6	441	0	284	192	0
UTI	NTH	152	43	295	0.2	0	238	214	8	1051	299	0
	TH	118	0	2227	0	0	4	100	0	2596	2594	0

NTH-Non-teaching hospital

TH- Teaching hospital

4.4 ANTIBIOTIC PRESCRIBING FOR URINARY TRACT INFECTION AND PYELONEPHRITIS

The following lessons were learnt from outpatient antibiotic prescribing in urinary tract infection (UTI) (Paper I):

- a. In outpatient prescribing study 647 patients of suspected UTI were registered and antibiotics were prescribed for 622 (antibiotic prescribing rate 96%). A total of 9930 DDD/TPD of antibiotics were prescribed for UTI.
- b. The commonest antibiotic group prescribed was quinolones (3647 DDD/TPD). Norfloxacin was the commonest antibiotic prescribed in both the hospitals.
- c. Nitroimidazoles (2893 DDD/HPD- 94% metronidazole, 5% tinidazole) were prescribed along with quinolones.
- d. Tetracyclines (2522 DDD/HPD-74% doxycycline and 26% tetracycline) were also prescribed.
- e. Co-trimoxazole was prescribed to 22 patients (3.4% of the patients).
- f. Third generation cephalosporins (injectable antibiotics) were prescribed to outpatients only in the non-teaching hospital.

The following lessons were learnt from antibiotic prescribing among admitted patients with pyelonephritis (n=495) (Paper II):

- a. Both hospitals had a similar pattern of antibiotic prescribing in patients diagnosed with pyelonephritis.
- b. Quinolones (commonest antibiotic prescribed-ciprofloxacin) and third generation cephalosporins (commonest antibiotic prescribed-ceftriaxone) were the commonest groups prescribed in the two hospitals.
- c. Aminoglycosides (commonest antibiotic prescribed-amikacin) were prescribed in combination with quinolones or third generation cephalosporins in 50% of cases.

4.5 ANTIBIOTIC PRESCRIBING FOR VAGINAL DISCHARGE AND GENITAL INFECTIONS

Vaginal discharge as a complaint was responsible for almost half of the total adult female outpatient visits in the two hospitals. The following lessons were learnt:

- a. Vaginal discharge was reported in 1361 patients. An overall antibiotic prescribing rate of 72.2% was observed.
- b. A total of 21512 DDDs/TPD were prescribed (11632 nitroimidazoles, 9183 tetracyclines and 434 quinolones).
- c. Metronidazole with doxycycline was the commonest combination prescribed (94% of the total DDD/TDP) followed by ciprofloxacin, metronidazole and doxycycline combination (3% of the DDD/TPD). The above combination prescribing represents “syndromic management” of vaginal discharge.
- d. Macrolides were not frequently prescribed (110 DDD/TPD).
- e. The total duration of therapy was 7 days or less in 73% of the patients.

Among the admitted patients with genital infections (n=665; 409 patients admitted in non-teaching hospital and 256 in the teaching hospital) the following lessons were learnt (Paper II):

- a. A total of 272 DDD/HPD were prescribed in the teaching hospital compared to 289 DDD/HPD prescribed in the non-teaching hospital.
- b. Quinolones (ciprofloxacin or norfloxacin) were more frequently prescribed in the teaching hospital compared to the non-teaching hospital, where 3rd generation cephalosporins (cefotaxime or ceftriaxone) was the commonest group prescribed.
- c. Co-prescription of antibiotics was common (observed in one third of the patients) in both the hospitals. Commonest combination was ciprofloxacin and metronidazole in the teaching hospital and cefotaxime with metronidazole in the non-teaching hospital.
- d. Aminoglycosides (38 DDD/HPD; 13% of the total DDD/HPD for genital infections, in the teaching hospital, and 32 DDD/HPD; 12% of the total DDD/HPD for genital infections, in the non-teaching hospital) were also prescribed in combination with other antibiotic classes.
- e. Co-trimoxazole was prescribed only in the non-teaching hospital.
- f. Macrolides were not frequently prescribed (less than 3% of total DDD/HPD in both the hospitals)

4.6 ANTIBIOTIC PRESCRIBING FOR SKIN AND SOFT TISSUE INFECTIONS

- a. Most of the patients diagnosed as skin and soft tissue infections (SSTI) that were seen as outpatients (n=575) were prescribed antibiotics. The prescription rate was 99.2% for the diagnosis of cutaneous abscess, cellulitis or surgical site infections and 85.7% for pyoderma (Paper I).
- b. Among the outpatients co-trimoxazole was the commonest antibiotic prescribed (4032.5 DU/TPD) followed by the quinolone group (1873 DDD/TPD-67% ciprofloxacin) (Paper I).
- c. Among the admitted patients with SSTI (n=481) also co-trimoxazole was the commonest antibiotic prescribed (1361 DU/HPD in the teaching hospital versus 236 DU/HPD in the non-teaching hospital) (Paper II).
- d. In the teaching hospital aminoglycosides was the 2nd commonest class prescribed (58 HPD/HPD), most often in combination with other antibiotic groups.
- e. In the non-teaching hospital 3rd generation cephalosporins (92 DDD/HPD) were prescribed most often. Twenty percent of the 3rd generation cephalosporin DDD/HPD comprised of ceftazidime with sulbactam/tazobactam. These combinations were prescribed most often in patients with hospital associated SSI

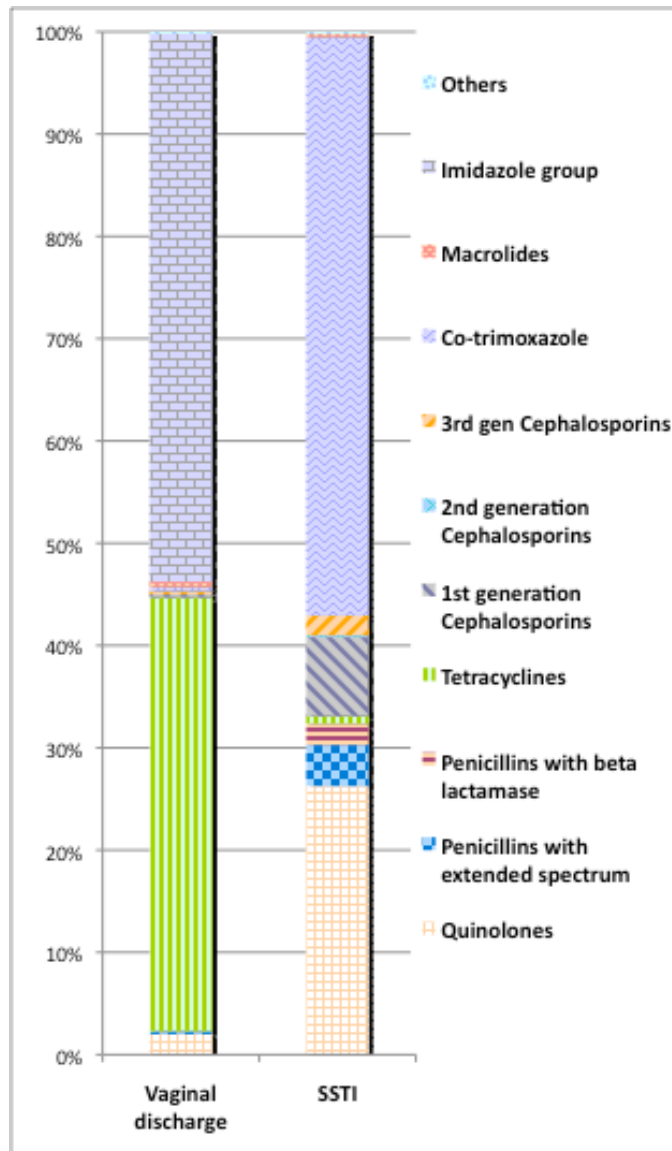


Figure 4.2-Relative distribution of defined daily doses per 1000 patients per diagnosis (DDD/TPD) of the two hospitals for the diagnosis of vaginal discharge (n=1361) and skin and soft tissue infection (n=575) (Paper I).

4.7 NASAL CARRIAGE AND ANTIBIOTIC SENSITIVITY OF *STAPHYLOCOCCUS AUREUS* IN HEALTHY CHILDREN BELOW FIVE YEARS (PAPER IV)

The following are the results of screening of healthy children up-to 5 years of age for nasal carriage of *S. aureus*:

- a. The study included 1,562 children up-to 5 years of age, 902 boys (58%) and 660 girls (42%). Thirty-nine percent of the children were between 1 and 6 months of age, 31% were between 25 and 59 months.
- b. Between 9 to 17% of children in the different age categories utilised *anganwadis*, which are Government of India run mother and child care services (pre-school), intended for children between 0 to 6 years of age.

- c. Antibiotic usage in the last 2 weeks was reported for 26% of children and 8.7% had a history of hospitalisation in the last 2 weeks.
- d. The prevalence of nasal carriage of *S. aureus* was 6.3% (95% CI 5.07- 7.47). Out of 98 *S. aureus* isolates 16.3% (95% CI 8.87-23.77) were MRSA.
- e. The factors significantly associated with nasal carriage of *S. aureus* were “child attending preschool” (OR 4.26, 95% CI 2.25-8.03; $P=0.007$) or “school” (OR 3.02, 95% CI 1.27-7.18; $P<0.001$) and “family size more than 10 members” (OR 2.76 95% CI 1.06-7.15; $P=0.03$).
- f. Among the MSSA isolates high proportion of resistance was noted to commonly used oral antibiotics: ampicillin (90%), co-amoxiclav (54%), co-trimoxazole (49%), ciprofloxacin (23%) and erythromycin (11%). No resistance was noted to vancomycin, linezolid or teicoplanin. Higher sensitivity was noted to clindamycin (94%), chloramphenicol (87.5%), doxycycline (82.7%), amikacin (81.3%) and erythromycin (76.6%).
- g. The MRSA isolates showed resistance to co-trimoxazole (75%), doxycycline (44%), ciprofloxacin (44%), levofloxacin (31%) and erythromycin (44%). Among the erythromycin resistant strains of MRSA 35% were clindamycin inducible.
- h. Out of 82 MSSA isolates four were MDR and out of 16 MRSA isolates three isolates (19%) were MDR. Among the seven MDR isolates three had received antibiotics during the last two weeks.

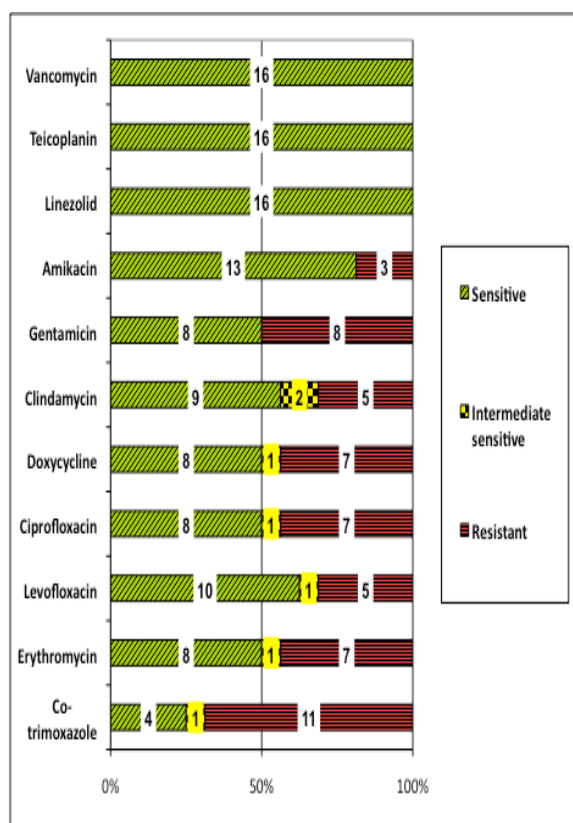


Figure 4.3-Antimicrobial susceptibility pattern of 16 isolates of MRSA isolated from anterior nares of healthy children below five years in Ujjain, India (Paper IV)

4.8 HIGH PREVALENCE OF EXTENDED-SPECTRUM BETA-LACTAMASE-PRODUCING PATHOGENS (PAPER V)

- Out of 2568 patients (median age 25 years (range 0 days to 92 years) admitted with suspected infectious aetiology 716 bacterial pathogens were isolated.
- Gram-negative infections predominated (62%). The isolated pathogens were *Escherichia coli* (n=149, 21%), *Pseudomonas aeruginosa* (n=127, 18%) and *Klebsiella pneumoniae* (n=107, 15%) and *Staphylococcus aureus* (n=221, 31%).
- The common diagnoses were: abscesses (56%), urinary tract infection (14%), blood stream infections (10%), pneumonia (10%), and vaginal infections (10%). The pathogens identified in the abscesses are shown in Table 4.3 and those identified in urinary tract infection and blood stream infections are shown in Table 4.4.
- Extended-spectrum β -lactamase (ESBL) production in *E. coli* isolates (n=149) was 69% (95% CI 61.6–76.6) and in *K. pneumoniae* isolates (n=107), 41% (95% CI 31.6–50.5). The antibiotic sensitivity pattern of the common pathogens is shown in Table 4.5. The extended-spectrum β -lactamase (ESBL) producing organisms showed high percentage of resistance to fluoroquinolones and β -lactams except for imipenem and piperacillin-tazobactam. *Salmonella typhi* remained sensitive to 3rd generation cephalosporins.
- The methicillin-resistant *Staphylococcus aureus* (MRSA) constituted 30% of all *S. aureus* isolates and showed resistance to ciprofloxacin (81%), co-trimoxazole (76%) and levofloxacin (60%).

Table 4.3 Details of site of infection and proportion of different bacteria (n=393) isolated from abscesses in two hospitals in Ujjain, India (Paper V).

Site of infection	<i>S. aureus</i> n=185	<i>P. aeruginosa</i> n=84	<i>K. pneumoniae</i> n=44	<i>E. coli</i> n=43	Others n=37
Skin and soft tissue infections (n=141)	118	12	6	2	3
Surgical site infections (n=54)	19	24	3	5	3
Post traumatic wound infections (n=38)	12	11	3	2	10
Burns (n=61)	12	20	16	7	6
Empyema (n=19)	8	4	2	3	2
Otitis media (with pus discharge) n=24	8	6	7	1	2
Breast abscesses (n=15)	8	4	2	1	0
Intra abdominal abscesses (n=40)	0	2	5	22	11

Table 4.4 Number of the pathogens identified from urinary tract infection (n=103) and from blood stream infections (n=75) in two hospitals in Ujjain, India (Paper V)

Site of Infection	Number of isolates
UTI^a	
<i>E. coli</i>	61
<i>K. pneumoniae</i>	25
<i>P. aeruginosa</i>	6
<i>Bacillus</i> spp.	3
Others	8
Total	103
BSI^b	
<i>S. typhi</i>	21
CoNS	20
<i>S. aureus</i>	10
<i>P. aeruginosa</i>	6
Others (including 8 isolates of <i>E.coli</i>)	18
Total	75

a UTI: Urinary Tract Infection; most (91%) samples were mid-stream clean catch and the rest urine from catheter

b BSI: Blood Stream infections; samples sent in cases of clinical sepsis

Table 4.5 Antibiotic susceptibility pattern of the three most prevalent causes of Gram-negative infections in a surveillance study in two hospitals, Ujjain, India (PaperV)

Antimicrobial class/agent tested	Activity by organism (number tested)		
	<i>E. coli</i> (149) R (%)	<i>P. aeruginosa</i> (127) R (%)	<i>K. pneumoniae</i> (107) R (%)
Penicillin			
Ampicillin	89	-	97
Amoxicillin/clavulanate	82	-	90
Piperacillin/tazobactam	15	17	21
Cephalosporins			
Cefuroxime	80	-	93
Ceftriaxone	72	-	79
Cefixime	79	-	96
Cefpodoxime	79	-	75
Ceftazidime	73	87	82
Other β lactum			
Imipenem	2	2	2
Quinolones			
Nalidixic acid	92	-	-
Ciprofloxacin	83	63	65
Norfloxacin	85	-	-
Ofloxacin	80	55	55
Gatifloxacin	79	64	53
Sparfloxacin	80	61	51
Aminoglycosides			
Gentamicin	59	69	69
Amikacin	33	38	32
Others			
Chloramphenicol	33	-	-
Tetracycline	92	-	-
Co-trimoxazole	83	76	94
Nitrofurantoin (tested in urine samples only)	12	-	-

R, resistant

5 DISCUSSION

5.1 OVERALL ANTIBIOTIC PRESCRIBING

In Paper I an overall antibiotic prescribing rate of 66% was documented in the outpatient diagnosis-prescribing study. In a study in Delhi using the exit interview methodology it was found that 39% of the patients attending public clinics and 43% of the patients attending private health-care facilities were prescribed antibiotics (Kotwani and Holloway 2011). However, that study was done among all patients attending outpatients and not specifically among patients suspected to have an infectious aetiology as in our study. Therefore, the proportion of patients receiving antibiotics is not strictly comparable. In another study done in secondary level hospitals in Maharashtra in outpatient attendees using the WHO core prescribing indicators, 35% of the prescriptions contained an antibiotic and 25% of the prescriptions contained an injection (Potharaju and Kabra 2011). In our outpatient clinics injectable antibiotics were prescribed to 1.2% of the patients. This low rate could be due to the fact that our study involved only antibiotics and not all drugs in a prescription. Also, our study was done with only the specialist practitioners and not all practitioners. A study done among the Paediatric outpatient clinics of a tertiary care set-up found a rate of 29% for antibiotic prescribing among all children attending outpatients (Dimri et al. 2009).

In contrast a study done in primary and secondary health-care facilities in Uttar Pradesh, India found a high prescribing rate (81.8%) of antibiotics (Kumar et al. 2008). That study also noted differences in antibiotic prescribing between health care facilities at different levels. Lower prescribing rates were found in government hospitals compared to the private hospitals. Practitioners doing speciality practice prescribed fewer antibiotics compared to general practitioners. In Paper I facility level differences in the antibiotic prescribing were found, with less prescribing (by 11 percent points) in the teaching hospital as compared to the non-teaching hospital. This could be due to better opportunities of continuous professional development for the teaching hospital staff. Also, it is possible that the physicians at the teaching hospitals face less pressure because of a policy of restricting the pharmaceutical company representatives. Similar effects of the policy of restricting the academic detailing by the pharmaceutical company representatives have been observed in European hospitals (Jack 2011). No comparison of antibiotic prescribing between teaching and non-teaching hospital have been published from India before. In Europe however, a lower prescribing rates in outpatients of teaching hospitals have been observed (Zarb and Goossens 2011).

Higher rates of antibiotic prescribing have been noted in the rural areas compared to the urban areas (Kumar et al. 2008). In our study however, the non-teaching hospital located in the urban setting had a higher prescribing rate of antibiotics compared to teaching hospital located in the rural setting (Paper I). The only earlier published study conducted in the province of Madhya Pradesh was done in primary health centres of Bhopal district and found that 63.5% of the prescriptions contained antibiotics (De Costa et al. 2008).

Seasonal variations in antibiotic prescribing have not been well studied in India. A study conducted in Delhi found very little seasonal variation in antibiotic prescribing, but observed slightly higher consumption of fluoroquinolones in winter (Kotwani et al. 2009). However, seasonal variation in outpatient antibiotic prescribing is well documented in studies from Europe (Ganestam et al. 2003, Abell et al. 1999, Adriaenssens et al. 2011). These studies show that antibiotic-prescribing peaks occur in Europe during the winter season and correlate well with the peaks of influenza season (Ganestam et al. 2003, Molstad et al. 2008). This may be due to more frequent diagnostic dilemmas of the physicians during the influenza season but nevertheless represents inappropriate antibiotic prescribing. The prescribing peaks were also more pronounced in countries with high overall rates of antibiotic prescribing (Goossens et al. 2005). In paper I, higher prescribing during summer in the non-teaching hospital and in the rainy season in the teaching hospital was observed. In the context of a high overall prescribing rate (66%) these peaks are less important, but nonetheless give us important information on the diagnostic uncertainties faced by the physicians in the study area. The variation in antibiotic prescribing according to seasons deserves to be studied in future studies on outpatient antibiotic prescribing in India.

In Paper II, 92% of the admitted patients with suspected bacterial infections were prescribed antibiotics. There is no similar published study from India using the WHO ATC/DDD methodology and “focus of infection” approach to study antibiotic prescribing. ESAC has carried out three point-prevalence surveys on hospital antibiotic use in Europe (Zarb and Goossens 2011). These surveys were carried out in the second quarter of the year 2006 (Ansari et al. 2009), 2008 (Amadeo et al. 2010) and 2009 (Zarb et al. 2011). Higher antibiotic prescribing rates among the admitted patients in the teaching hospital compared to the non-teaching hospital were observed in our study. This finding is consistent with three point-prevalence surveys conducted in Europe (Zarb and Goossens 2011) and one study in the United States (Pakyz et al. 2008). The differences in the antibiotic prescribing observed between the teaching and the non-teaching hospital can to some extent be explained by the differences in the case-mix.

5.2 SURGICAL PROPHYLAXIS AMONG ADMITTED PATIENTS

In paper II it was observed that about one third of all antibiotic prescribing was for surgical prophylaxis. The proportion of patients receiving surgical prophylaxis in our study (34%) was higher than that recorded by the ESAC surveys (13 to 15%) (Zarb and Goossens 2011). The problem of continued prophylaxis for duration of more than 24 hours is an area of concern. In our study 86% of the patients receiving surgical prophylaxis received it for more than 24 hours, which is inappropriate as most guidelines recommend surgical prophylaxis as a single dose sixty minutes before surgery (Dellinger et al. 1994). Surgical prophylaxis of inappropriate duration is also a problem in Europe, where between 53 to 69% patients received inappropriately long prophylaxis (Zarb and Goossens 2011). Lack of stop orders once the surgical prophylaxis is begun or the fears of high infection rate in the unit are the main reason cited for long prophylaxis (Zarb and Goossens 2011). So, antibiotics are being prescribed to compensate for a poor actual or perceived hygiene (environmental or hand hygiene). In a study on perceptions of hand hygiene done in our teaching hospital important motivational and infrastructure barriers were identified for

introducing hand hygiene practices (Joshi et al. 2012). The duration of surgical prophylaxis need to be reduced. Work is ongoing to identify possible methods for this.

5.3 DIARRHOEA

Pneumonia and diarrhoea are the two most common diseases associated with child deaths worldwide (Black et al. 2003). Diarrhoea also contributes to malnutrition, which is the commonest underlying cause of child deaths associated with infectious diseases (Black et al. 2003). Diarrhoea kills more than 650 children below the age of five years each day in India (Gitanjali and Weerasuriya 2011). The WHO launched the diarrhoeal disease control programme in 1980s, which included training of the community health workers in diarrhoeal case management and promotion of the use of oral rehydration salts (ORS) at the community level. Political and religious leaders, and celebrities endorsed the use of ORS in mass media campaigns (Santosham et al. 2010). The result was a steep worldwide fall in mortality due to diarrhoea by 75% from 1980s to 2008 (Santosham et al. 2010). Since then the mortality rates have remained stable and have not shown a sharp decline of previous two decades. The reduced osmolarity ORS has been shown to reduce stool output by 20%, vomiting by 30% and need for unscheduled intravenous fluids by 40% (Santosham et al. 2010). Zinc therapy has been shown to reduce the duration of acute diarrhoea by 12 hours and that of persistent diarrhoea by 16 hours. A child receiving zinc therapy during a diarrhoeal episode has a 29% lower relative risk of continuation of acute diarrhoea to the seventh day (Santosham et al. 2010). There is one-third reduction in the frequency of diarrhoea in the subsequent 2-3 months after a 14-day course of zinc. Community-based trials have demonstrated a 51% decrease in overall mortality due to diarrhoea attributable to zinc use alone.

In Paper I differences in antibiotic prescribing for diarrhoea between adults and children were found. Adults were close to four times more likely to be prescribed antibiotics as compared to children. This might be due to differences in training, knowledge and perceptions of physicians treating adults compared to paediatricians. The physicians treating adults also prescribed more combination therapy compared to paediatricians. The commonest combination prescribed for adults was ciprofloxacin with tinidazole. In Paper III 71% of the children with diarrhoea seeking care in the participating pharmacies and hospitals in Ujjain city were prescribed antibiotics. Illogical fixed dose combination therapy was also prescribed to children. One such combination, ofloxacin and ornidazole, was the commonest antibiotic prescribed and accounted for 22% of antibiotics prescribed to children. These fixed dose combinations are not only pharmacologically illogical, but are considered by some experts as unethical prescribing (Chakrabarti 2007). Antibiotic prescribing for diarrhoea is not only a waste of financial resources but exposes the patients to adverse drug effects and fuels antibiotic resistance by creating the gene pool of resistant organisms in the gut (Blake et al. 2003). The most effective policy (if implemented) to reduce diarrhoeal morbidity and mortality is promotion of a combination of low osmolarity ORS with zinc as an effective treatment without unnecessary antibiotic or drug use (Santosham et al. 2010). Unnecessary antibiotic use has been identified as a barrier to effective policy implementation to reduce diarrhoeal mortality and morbidity (Santosham et al. 2010).

The health care providers of alternative systems of medicine and informal health-care providers are three times more likely to prescribe antibiotics compared to the paediatricians (Paper III). There are insufficient efforts by policy makers to address the issue of awareness and knowledge of standard treatment guidelines among health care providers of alternate systems of medicine, informal health-care providers and also among the paediatricians. The present study demonstrates the need for continuous professional development programmes to improve case management of diarrhoea. Unfortunately, improvement of case management of diarrhoea is not a priority in many countries including India. Therefore, the clinical management of diarrhoea is unlikely to improve by simply introducing oral rehydration solution and zinc in treatment guidelines. Dissemination of the standard treatment guidelines by community based public health campaign with a renewed political will is urgently needed (Santosham et al. 2010).

5.4 PNEUMONIA

Community acquired pneumonia (CAP) is the third leading cause of all global deaths. Among children below five years of age pneumonia is the leading cause of death (Black et al. 2010, Wardlaw et al. 2006). It is estimated that 7.6 million children died before the age of 5 years in 2010 (Black and El Arifeen 2012). Throughout the world the majority of episodes of pneumonia are treated as outpatients (Mandell et al. 2007). In the resource rich countries most of the deaths as well as health-care expenditure due to pneumonia occurs in hospitalised patients, whereas in the low and middle-income countries most of the deaths occur in the community at household level. Lack of availability of health-care facilities and (or) effective antibiotics for treatment are equally responsible for mortality in resource-constrained settings (Mandell et al. 2007). The highest incidence of pneumonia is seen in children below 5 years of age and in adults older than 75 years and could be up-to five times higher in resource constrained settings as compared to resource-rich countries (Ruuskanen et al. 2011). The burden of CAP in the Asia-Pacific is underestimated because many episodes are not reported due to: self-treatment, availability of antibiotics over the counter, high cost and (or) lack of availability of diagnostics, lack of surveillance programmes and empiric antibiotic therapy (Song et al. 2011). In India Integrated Management of Childhood Illness (IMCI) provide guidelines for management of respiratory infections, diarrheal diseases, measles, malaria and malnutrition for community health care workers (Patwari and Raina 2002). IMCI is a strategy fostering holistic approach to child health and development, is built upon successful experiences gained from effective child health interventions like immunization, oral rehydration therapy, management of acute respiratory infections and improved infant feeding (Patwari and Raina 2002). However, a low concordance between physician and IMCI algorithmic diagnosis of pneumonia and other severe childhood illnesses has been shown in India (Jain et al. 2009).

5.4.1 Aetiology of community acquired pneumonia

Aetiology of pneumonia varies with age. Bacteria are the most common pathogens. They can be “typical” or “atypical” bacteria (Ramirez and Anzueto 2011). The common typical bacteria include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, group A streptococci and *Moraxella catarrhalis*. The atypical organisms cannot be stained by Gram’s stain and cannot be cultured on blood or sputum culture medium.

Atypical pathogens include *Legionella* spp., *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* (Ramirez and Anzueto 2011). In severely ill patients and neonates Gram-negative bacilli, especially *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* are common. Viruses are also well-recognised pathogens for CAP (Ramirez and Anzueto 2011).

5.4.2 Treatment of community acquired pneumonia

It is recommended that empiric therapy should be initiated based on age, most likely pathogen, local antimicrobial susceptibility pattern of the pathogens, and the severity of disease (Wardlaw et al. 2006, Ruuskanen et al. 2011, Song et al. 2011, Ramirez and Anzueto 2011). Early initiation of antibiotics is recommended for reducing mortality (Ramirez and Anzueto 2011). For empiric therapy in cases of non-severe pneumonia in children (aged less than 5 years) the WHO guidelines recommend oral amoxicillin in the dose of 40mg/kg/day, for 3 days in HIV non-endemic areas and for 5 days in HIV endemic areas (WHO 2012c). The Infectious Disease Society of America (IDSA) guidelines for outpatient treatment in a previously healthy adult with no co-morbidities recommend a macrolide (erythromycin, azithromycin or clarithromycin) or doxycycline (Mandell et al. 2007). A respiratory fluoroquinolone (moxifloxacin, gatifloxacin, levofloxacin or gemifloxacin) or a new macrolide (azithromycin or clarithromycin) is recommended in a patient with co-morbidities or if the patient has received an antibiotic in the previous three months (Mandell et al. 2007). In the admitted patients with pneumonia the empiric therapy includes a combination of a beta-lactam antibiotic (to cover typical bacteria) and a macrolide (to cover atypical bacteria) or monotherapy with a respiratory fluoroquinolone (as they have activity against both typical and atypical bacteria) (Mandell et al. 2007). However, in both the hospitals in our study settings at the time of the study standard treatment guidelines were not developed. The situation is the same for most of the health-care settings in the country. There is therefore a need for national guidelines in India for most common diseases, which could be adapted for local use in the secondary and tertiary level hospitals.

In outpatients with pneumonia a respiratory quinolone, levofloxacin, was prescribed in adults diagnosed with pneumonia, more often in the non-teaching hospital than in the teaching hospital (Paper I). However, levofloxacin was also the commonest antibiotic prescribed for self-limiting upper respiratory tract infection (in the same hospital). This is a reason for concern and has been identified as an area for intervention aimed to improvement of outpatient antibiotic prescribing. Doxycycline was prescribed in the adults diagnosed with pneumonia more often in the teaching hospital. Co-trimoxazole was prescribed most often in children with pneumonia in the teaching hospital. However, recent evidence does not support the use of co-trimoxazole due to a high rate of treatment failure in children with pneumonia (Mandell et al. 2007).

Among the admitted patients (Paper II) both in the teaching and the non-teaching hospital most patients were prescribed antibiotics in accordance with the IDSA guidelines. Doxycycline was prescribed most often in the teaching hospital and third-generation cephalosporins in the non-teaching hospital. Again, like in the outpatient study respiratory quinolones were prescribed more often in the non-teaching hospital.

5.5 URINARY TRACT INFECTIONS AND PYELONEPHRITIS

Urinary tract infection (UTI) is a pathogenic invasion of the urothelium with resultant inflammation, encompassing a spectrum of upper and lower urinary tract disease (Dielubanza and Schaeffer 2011). UTI is the most common extraintestinal infectious disease in women, with 50% of all women experiencing at least one episode in their lifetime in the United States (Foxman 2002). Most of the UTI are uncomplicated cystitis caused by *E. coli* (86%), *Staphylococcus saprophyticus* (4%), *Klebsiella* sp. (3%), *Proteus* sp. (3%) and others including the *Enterobacter*, *Citrobacter* and *Enterococcus* species (Colgan and Williams 2011). The estimated costs of health care visits for UTI in the US are \$ 1.6 billion per year (Foxman 2002).

By definition an acute uncomplicated cystitis normally means a UTI in a premenopausal, non-pregnant woman with no known urologic abnormalities (like stones, stents, catheters, neurogenic bladder or polycystic kidney disease) or co-morbidities (like diabetes mellitus). In contrast UTI in men are usually complicated (Dielubanza and Schaeffer 2011, Colgan and Williams 2011).

The diagnosis of UTI is usually made clinically based on history (Dielubanza and Schaeffer 2011). Classic symptoms are dysuria, frequency and urgency. Sometimes hematuria or supra-pubic discomfort can occur (Dielubanza and Schaeffer 2011, Colgan and Williams 2011). IDSA updated the guidelines for management of UTI in 2010 (Gupta et al. 2011). According to the guidelines no single antibiotic is considered best for treating uncomplicated UTI and the choice should be individualised. First line antibiotics suggested are: fosfomycin 3 gm single dose, nitrofurantoin for five days, or co-trimoxazole for three days. Second line antibiotics are: ciprofloxacin or extended-release ciprofloxacin, levofloxacin or ofloxacin (all for three days). Third line includes amoxicillin/clavulanate (7 days), cefdinir (10 days) or cefpodoxime (7 days). Beta-lactam antibiotics are not recommended as first-line therapy for acute uncomplicated cystitis if *E. coli* resistance in the area is above 20% (Gupta et al. 2011).

Most outpatients (more than 80%) in both hospitals were treated with norfloxacin (Paper I). The second commonest choice of antibiotic was inappropriate in both the hospitals, which was doxycycline in the teaching hospital and 3rd generation cephalosporins in the non-teaching hospital. High use of quinolones and absence of nitrofurantoin prescriptions is a cause of concern. Despite the fact that nitrofurantoin was the first oral drug introduced in the treatment of UTI more than 50 years ago it retains good activity against *E. coli* in our settings (Paper V) and elsewhere (Kashanian et al. 2008).

Acute pyelonephritis is an infection of the renal parenchyma and the renal pelvis (Ramakrishnan and Scheid 2005). It usually results from an ascending bacterial infection. Haematogenous acute pyelonephritis usually occurs in an immunosuppressed, chronically ill, and debilitated patient. Acute uncomplicated pyelonephritis is caused by typical pathogens (*E.coli*, *Stapylococcus saprophyticus*, *Proteus* and *Klebsiella* sp.) in an immunocompetent host with normal urinary tract anatomy and renal function (Ramakrishnan and Scheid 2005). *E. coli* causes more than 80% of the cases of acute pyelonephritis (Ramakrishnan and Scheid 2005). Women are five times more likely to be hospitalised with this condition but have a better prognosis compared to men

(Ramakrishnan and Scheid 2005). The spectrum of clinical presentation varies widely from mild presentation to frank sepsis (Ramakrishnan and Scheid 2005).

IDSA guidelines recommend the use of one of the following three initial intravenous therapies in adults: (a) a fluoroquinolone, (b) aminoglycoside with or without ampicillin, or (c) extended spectrum cephalosporin with or without aminoglycoside (Ramakrishnan and Scheid 2005). The recommended duration of therapy is 7 to 14 days. The antibiotic prescribing pattern in two hospitals for patients admitted with pyelonephritis was in accordance with IDSA guidelines (Paper II). Quinolones and 3rd generation cephalosporins were the commonest groups prescribed with an aminoglycoside added in 50% of the cases.

5.6 VAGINAL DISCHARGE AND GENITAL INFECTIONS

There is a very high unmet demand for treatment of obstetric and gynaecological disorders in India (Reddy et al. 2011). This demand may be even higher in our study settings due to skewed distribution of the health care providers in Ujjain district (Deshpande et al. 2004).

Vaginal discharge can be physiological (normal) or pathological (abnormal in terms of quantity, colour or odour) (Spence and Melville 2007). In our outpatient study (Paper I) the consultant gynaecologist decided if the vaginal discharge was normal or abnormal. Pathological vaginal discharge is usually caused by three conditions: bacterial vaginosis, vulvovaginal candidiasis or vaginal trichomoniasis (Spence and Melville 2007). Bacterial vaginosis and vulvovaginal candidiasis are thought to be caused by a disturbance of the normal vaginal flora and are not sexually transmitted. *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Trichomonas vaginalis* are sexually transmitted and can present with vaginal discharge but many women are asymptomatic (Spence and Melville 2007). The timing, colour, consistency, smell, and presence of itch are important in distinguishing between various infections, for example lack of itching makes candidiasis less likely and lack of odour makes a diagnosis of bacterial vaginosis less likely (Anderson et al. 2004). Inflammation on examination is associated with candidiasis. Pelvic pain, pelvic tenderness, and fever should be considered as red flags for pelvic inflammatory disease (Spence and Melville 2007, Anderson et al. 2004). However, definitive diagnosis requires microscopy. In view of the complexity of diagnostics required for accurate aetiological diagnosis, the WHO adopts a syndromic management approach (WHO 2005b). The syndromic management is based on identification of a group of symptoms and signs (syndromes) and provision of treatment for most organisms responsible for producing the syndrome (WHO 2005b). Syndromic management was followed in the treatment of vaginal discharge in outpatients in both teaching and non-teaching hospitals (Paper I).

In the outpatient prescribing study (Paper I) as shown in Figure 4.2, the most common antibiotic prescribed was doxycycline, which reflects syndromic management for *Chlamydia trachomatis*. A high prescribing rate of metronidazole was also documented, which reflects syndromic management for bacterial vaginosis and *Trichomonas vaginalis*. Thus, the choice of drugs for syndromic management of vaginal discharge was appropriate in the two hospitals. A relatively low prescribing rate for quinolones (norfloxacin) was also noted. This might be due to a perceived low prevalence of high-risk patients (and thus *N. gonorrhoea*) in the community. Ideally syndromic management should be adjusted

according to local prevalence of infections and their antibiotic sensitivity (Spence and Melville 2007). It is important to do such a prevalence study in the settings.

In Paper II the antibiotic prescribing pattern for admitted patients with vaginal infections especially the pelvic inflammatory disease were studied. The optimisation of therapy for hospitalised genital infections (especially pelvic inflammatory disease) must take into account the polymicrobial aetiology of the disease, the severity of the disease, and patient compliance with antibiotic use. The optimal treatment for patients admitted with genital infections requires an antibiotic with activity against *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Mycoplasma genitalium*. Because no single agent covers all of these organisms, combination therapy is recommended (Jaiyeoba et al. 2011).

In the teaching hospital, ciprofloxacin or norfloxacin were prescribed, often in combination with metronidazole. But ciprofloxacin can be associated with possible relapse as it is less effective against bacterial vaginosis-associated microorganisms. Also, quinolone resistance among *N. gonorrhoeae* isolates has been increasing in the Asia-Pacific region (Ashley et al. 2011). Third generation cephalosporins when added to the regimen increase the clearance rates and reduce relapse rates (Jaiyeoba et al. 2011). Third generation cephalosporins were used more often in the non-teaching hospital. However, aminoglycosides were overused among the admitted patients. Doxycycline, an effective treatment against the *Chlamydia trachomatis*, was sparsely used; also macrolides were prescribed less often for genital infections.

5.7 SKIN AND SOFT TISSUE INFECTIONS

Skin and soft tissue infections (SSTI) can be difficult to treat (Liu et al. 2011, Esposito et al. 2009). Severe SSTI are associated with high mortality and morbidity and substantial costs. For outpatient management of cellulitis with purulent discharge or a non-drainable abscess empiric therapy for MRSA is recommended (Liu et al. 2011). The choice for MRSA therapy includes one of the following: clindamycin, co-trimoxazole, a tetracycline (doxycycline or minocycline), or linezolid (Liu et al. 2011). The duration of therapy is 5 to 10 days and need to be individualised based on clinical response.

The cornerstone of treatment for cutaneous abscess and boils is incision and drainage (Liu et al. 2011). For cellulitis the treatment of choice is narrow spectrum penicillins. In our outpatient study (Paper I) the penicillin group prescriptions for SSTI were low. The high prescribing rate of co-trimoxazole in the same study reflects appropriate prescribing. This is because co-trimoxazole is an antibiotic that is effective against both methicillin sensitive *Staphylococcus aureus* and methicillin resistant *Staphylococcus aureus* (Liu et al. 2011, Esposito et al. 2009).

Among hospitalised patients with SSTI, antibiotic therapy should be initiated only if the patient fails to respond to incision and drainage or shows abscess with severe and extensive disease, rapidly progressive cellulitis, signs and symptoms of systemic disease, associated co-morbidities, immunosuppression, or an abscess in an area difficult to drain (face, neck, or hand) (Esposito et al. 2009). Thus, defining the severity of illness is central for deciding if antibiotics are needed at all, and the route of administration. Most of the admitted patients treated with antibiotics for SSTI in the two hospitals did not fulfill these criteria (Paper II). The most common choice of antibiotic among admitted patients was also co-trimoxazole, which appears appropriate. However, the relatively common use of quinolones and third-generation cephalosporins is not justified.

5.8 NASAL CARRIAGE OF *S. AUREUS* IN HEALTHY CHILDREN BELOW FIVE YEARS OF AGE

In the past decade there has been emergence of community-associated (CA) strains of methicillin-resistant *Staphylococcus aureus* (CA-MRSA) in community members with no previous risk factors for acquisition for MRSA (Kluka 2011). The classic risk factors for MRSA infections include hospital care, especially admission to intensive care units, extremes of age, immunocompromised patients, and antibiotic use in the recent past (Miller et al. 2009).

Nasal carriage in healthy children can account for increasing incidence of respiratory tract and deep-space neck infections caused by MRSA. This is because the *S. aureus* that reside in anterior nares of hosts serve as reservoirs for both the exogenous spread of the pathogen in the community and predispose the host to subsequent infections by endogenous spread (Sivaraman et al. 2009). Persistent nasal carriage (carriage for more than 6 months) is a risk factor for endogenous *S. aureus* infection (Kluytmans et al. 1997).

Studies on prevalence of nasal carriage and antibiotic susceptibility pattern of commensal *S. aureus* in Indian children are few (Ramana et al. 2009, Chatterjee et al. 2009) and have been done in children aged between 5 to 15 years of age. But, there is little knowledge about epidemiology of *S. aureus* in children below five years of age. Paper IV is the first study from India reporting *S. aureus* nasal carriage rate in healthy children below 5 years of age. The prevalence of *S. aureus* was 6.3% out of which 16.3% isolates were MRSA.

The prevalence of nasal carriage is age dependent (Kluka 2011, Miller et al. 2009, Sivaraman et al. 2009, Bogaert et al. 2004). The prevalence varied across different age groups in our study with lower prevalence in the first six months of life although these differences were not statistically significant. The change of colonisation prevalence is probably because of competition of the same niche (anterior nares) among many bacteria including *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. It has been demonstrated that as age increases the nasal carriage of *S. aureus* increases and that of other bacteria like *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* decreases (Bae et al. 2012). In a study among children, colonisation with *S. pneumoniae* was found to be protective for MRSA carriage (Lamaro-Cardoso et al. 2009).

In Paper IV the children attending school or preschool-*anganwadi* (Government of India run mother and child care services) or living in large family size with 10 or more members were shown to have significantly higher prevalence of carriage of *S. aureus*. All the above factors can be associated with poor hygiene and overcrowding. Poor hygiene and overcrowding have been identified as risk factors for carriage of *S. aureus* in other studies also (Chen et al. 2011, Sivaraman et al. 2009).

In our study (Paper IV) two of the four children carrying MDR isolates of methicillin susceptible *S. aureus* and one of the three children carrying MDR MRSA isolates had reported history of hospitalisation. Most of these children had received antibiotics in the last two weeks. The children carrying MRSA in our study could have acquired it during hospitalisation. MRSA is also a hospital-associated pathogen and so the risk of acquiring it

is higher in health care workers (Olsen et al. 2012a). High antibiotic prescribing pressure in the study area is reflected by the fact that 26% of children enrolled in our study had received an antibiotic in the previous two weeks.

The possibility of horizontal transfer of resistant genes from hospitalized patients to community members is also reflected in the susceptibility pattern of *S. aureus* isolates in our study. Early in the global epidemic of MRSA there was a clear distinction in susceptibility pattern of CA-MRSA and hospital associated MRSA (HA-MRSA). CA-MRSA isolates were susceptible to most antibiotics and typically highly susceptible to clindamycin (Aleksun and Levy 2006). The isolates in our study show high susceptibility to clindamycin but have high resistance to co-amoxiclav (Paper IV). This might represent a scenario of spread of resistant genes in the community from the hospitals due to poor hygiene measures.

5.9 HIGH PREVALENCE OF EXTENDED-SPECTRUM β -LACTAMASE PRODUCING PATHOGENS

Surveillance of antibiotic susceptibility is fundamental for an antibiotic stewardship programme. Thus, a surveillance system was set-up in the two hospitals in Ujjain with the aim to define the magnitude and pattern of resistance in the bacterial pathogens and also to provide locally applicable data to guide empiric therapy. This to our knowledge is the first surveillance study that has examined the antimicrobial susceptibilities of common pathogens from a rural resource-poor setting in central India. Previously reported studies have been done mostly in larger metropolitan cities (Subbalaxmi et al. 2010, Varghese et al. 2010). The most common pathogens identified were *S. aureus* (31%) followed by *E. coli* (21%), *P. aeruginosa* (18%), *K. pneumoniae* (15%). Thus, *E. coli*, *P. aeruginosa*, *K. pneumoniae* and *S. aureus* were responsible for 85% of the culture positive infections. The clinical diagnosis of abscesses, pneumonia and UTI were responsible for 80% of all the culture positive infections. A high rate of ESBL producing *E. coli* 69% (95% CI 61.6-76.6) and *K. pneumoniae* 41% (95% CI 31.6-50.5) were found. A similar pattern (Table 4.5) of bacterial isolates is noted from other resource-constrained countries (Ashley et al. 2011, Jean and Hsueh 2011) and India (Subbalaxmi et al. 2010, Varghese et al. 2010).

The resistance pattern for the two Gram-negative bacteria *E. coli* and *K. pneumoniae* showed that co-resistance for ciprofloxacin and ceftriaxone was 51.2%. This pattern might indicate to AmpC and cephalosporinase producing pathogens. Studies have already shown plasmid-borne and (or) chromosomally mediated AmpC β -lactamase producing pathogens are common in India (Bhattacharya 2011).

The *E. coli* isolates from UTI retain good sensitivity for nitrofurantoin (88%) but show high resistance to co-trimoxazole (83%). This has clinical implications for outpatient management of uncomplicated UTI as guidelines suggest using a fluoroquinolone, nitrofurantoin or fosfomycin, if co-trimoxazole resistance exceeds 20% among *E. coli* isolates (Mehnert-Kay 2005). Fosfomycin has been recently marketed in India but safety and efficacy in children less than 12 years is not established. Thus, nitrofurantoin in view of its good susceptibility should be the drug of choice for uncomplicated UTI in our settings.

SENTRY Antimicrobial Surveillance Program in Asia-Pacific also reported *S. aureus* as the commonest organism followed by *P. aeruginosa* and *E. coli*. (Bell et al. 2007, Biedenbach et al. 2007). The susceptibility rates found in the present study for *Pseudomonas* (13% for ceftazidime and 37% for ciprofloxacin) are similar to other studies from India (Bhattacharya 2011, Mayank et al. 2009).

5.10 METHODOLOGICAL CONSIDERATIONS

5.10.1 Main strengths

The WHO ATC/DDD methodology for quantifying antibiotic use was used. For DDD calculations the data of the actual prescribed antibiotic (Paper I) and the administered antibiotics (Paper II) was utilised. This type of data is much more informative than the pharmacy sales data where the link between the diagnosis and prescribing is mainly lacking even in countries with a computerised database. The link between diagnosis and prescribing that was established in both Papers I and II is the main strength of this thesis. The results produced by this type of methodology can be directly used for identifying areas in need for improving quality of antibiotic prescribing and designing context-specific interventions. The range of diagnoses and (or) symptoms that were studied in both the above papers have not been studied before from India. There is a great need for this type of information to design antibiotic-stewardship programmes in India and countries with similar health system.

In Paper III the adherence to treatment guidelines by the prescribers for diarrhoea in children were evaluated. The guidelines for rationale prescribing have been in place since the year 2004, but no formal evaluation of their adherence had been done before. We evaluated the adherence of the guidelines not only among the registered health care providers but documented the prescribing pattern of informal health care providers for the first time in India. Informal health care providers are usually the first point for seeking health-care in many rural areas of India, like in Ujjain district, since the qualified providers are geographically concentrated in urban areas (Deshpande et al. 2004). Thus, if we want to improve case management of diarrhoea we need to understand the prescribing patterns of the informal health-care providers.

In Paper IV the nasal carriage of *S. aureus* in children below five years of age was documented. There are widespread concerns of community spread of *S. aureus* and specifically the MRSA infections. An improved understanding of epidemiology and resistance mechanisms of community acquired MRSA is required for better designing preventive strategies to stop spread of resistance. Our study is the first from India documenting the nasal carriage of *S. aureus* in healthy children up to five years of age.

5.10.2 Attempts to minimise systematic errors

Pilot testing of questionnaires

All the questionnaires used for data collection in this thesis (Paper I-V) were pilot tested and revised. All the study assistants and the clinicians were trained for filling the questionnaires during the pilot studies. The protocols for the procedures of filling the questionnaires (Paper I-V), clinical specimen collection (Paper IV to V) and transport to the

microbiology laboratory (Paper IV to V) were defined and field-tested during pilot studies. The above procedures were carefully supervised during the data collection period to assure quality of the data.

Data entry

Data entry for Papers I and II was done by me. For the remaining papers, I supervised the data entry. The data were double entered and crosschecked for all studies.

Laboratory tests

Trained microbiologists did all the procedures in the laboratory. In the microbiology laboratory standard operating protocols were devised for all laboratory procedures in general and particularly for this study (Paper IV and V). The protocols were harmonised together with the colleagues from St. John's Medical College, Bangalore, a premier tertiary care medical college of India and also reference laboratory for a number of microorganisms. A proportion (10%) of all the samples were sent to Bangalore for re-checking the antibiotic sensitivity as an external quality assurance of our laboratory. Generally there was good (more than 98%) inter-institute co-relation of antibiograms. I did the collection of all the nasal swabs in paper IV.

5.10.3 Attempts to minimise biases

The paper I and II were diagnosis-prescribing surveys involving the physicians of the two hospitals, 62 in the Paper I and 72 in Paper II. Observational studies of this kind can involve two common biases. "Desirability bias" means that the physicians knowing that they are under observation report lower than actual antibiotic prescribing rates. This kind of bias is known as the expectancy effect. In our studies (Paper I and II) the data collection was repeated using the same questionnaire four times in each hospital (for a period of 45 days each) with the same physicians, thus possibly reducing the desirability bias in the two studies. In Paper III data was collected in the pharmacies and the prescribers were not directly observed. A second common bias in such surveys is the "self-selection bias" i.e. only the physicians with a high level of motivation self-select themselves to participate, but in our studies the participation rate was high, with 85% of all the available consultants participating in Paper I and 96% of all the available consultants in Paper II, thus limiting the self-selection bias.

5.10.4 Limitations

The studies have a few limitations. An external or independent assessment of the severity of disease was not done in any of the studies. The assessment of severity would have increased our workload further; we found it non-sustainable for long runs in our pilot studies. But, areas and diseases have been identified for which an assessment of severity of diseases will be done in future studies. The data could not be collected simultaneously in the two hospitals (Paper I and II) so the seasonal data are not strictly comparable. The WHO ATC/DDD methodology was used for presenting the prescribing data. The main limitation of the methodology is that the DDD definition does not allow for dose adaptation for children, so when used for presenting antibiotic use in children (Paper I and II) it underestimates the total antibiotic use. The design of the study in Paper II required high motivation of everybody involved in the study. The study design is very resource intensive

especially as the study was done over a long time period. The design is more suitable for doing short-term (1 to 2 weeks duration) studies as is shown by ESAC point prevalence studies (Zarb and Goossens 2011). In Paper II the focus was on the choice of antibiotics in the discussion, as this was the main outcome of the study. Other important aspects of rational antibiotic prescribing like duration of treatment and appropriateness of choice of formulations for example oral therapy versus intravenous and use of syrup or tablets is not discussed. In Paper III an unexpectedly high design effect was reported. Because of this high design effect association of some of the variables to prescribing might have been missed. In Paper IV data on factors associated with nasal carriage of *S. aureus* was collected using a structured questionnaire. Other factors associated with nasal carriage have been identified since the study was planned. The factors that increase risk of nasal carriage of *S. aureus* identified recently include: exposure to pets (Abdel-moein and Samir 2011), other family members having an infection with *S. aureus* or having nasal carriage of *S. aureus* (Olsen et al. 2012a). Low vitamin D levels have also been associated with increased risk for carriage of *S. aureus* (Olsen et al. 2012b). Drinking of hot coffee or tea has been shown to be protective for nasal carriage of MRSA (Matheson et al. 2011). In Paper IV healthy children reporting for immunisation were studied as a proxy for children in the community. Ideally a community-based design would have been better to identify factors associated with nasal carriage of *S. aureus* in healthy children. The genetic mechanisms of resistance (*mecA* gene in Paper IV and genetic mechanism of ESBL production in Paper V) have not been tested for the studies in the thesis.

6 CONCLUSIONS AND IMPLICATIONS

This thesis provides much needed information on antibiotic prescribing linked to the diagnosis of individual patients in an Indian setting. It also provides information on antimicrobial resistance among bacteria (both commensal and pathogens) from two hospitals in Ujjain, India. I believe that the findings can be useful for planning antibiotic stewardship programmes in other similar settings throughout the world. The thesis identified several key areas that call for interventions. These are:

- Outpatient antibiotic prescribing was found to be less frequent in the teaching hospital compared to the non-teaching hospital. Broad-spectrum antibiotics were prescribed more often in the non-teaching hospital irrespective of diagnosis and age group.
- High antibiotic prescribing rates were observed for self-limiting diseases like diarrhoea and upper respiratory tract infection.
- A high rate of quinolone prescribing in outpatients is a cause of concern and treatment guidelines are needed to define such use for common infections.
- The method for surveillance adapted for the outpatient diagnosis prescribing study appears suitable for busy outpatient settings like ours in India and might be tried in other low and middle-income countries.
- The targets identified for interventions in the surveillance study among admitted patients were: higher antibiotic prescribing in a teaching hospital compared with a non-teaching hospital, longer than recommended duration of prophylaxis and lack of distinction between prophylaxis and therapy among surgical patients, irrational antibiotic prescribing in gastroenteritis, overuse of quinolones and lack of use of penicillin in pneumonia, overuse of quinolones and lack of use of doxycycline and macrolides in genital infections, and overreliance on antibiotics in treating skin and soft tissue infections.
- Even the specialist paediatricians did not adhere to standard treatment guidelines for diarrhoea among children. So, developing guidelines alone is not enough. Research, advocacy, political commitment and public health campaigns are needed for implementing the guidelines along with training of healthcare workforce.
- Antimicrobial susceptibility testing and surveillance among the healthy individuals commensal bacteria also suggests importance of prudent antibiotic prescribing.
- High rate of antibiotic prescribing among admitted patients, especially of 3rd generation cephalosporins and quinolones together with high rates of ESBL producing pathogens, shows urgent need to curb antibiotic use when there is no indication for it. The therapeutic armament against the ESBL producing Gram-negative bacteria is very limited. Thus, to preserve the effectiveness of current antibiotics we urgently need antibiotic stewardship programmes. The situation is like “the lull before the storm”. The time to act is now!

7 FUTURE RESEARCH

- In this thesis targets for intervention with regards to improving antibiotic prescribing were indentified. An intervention programme focusing on hospital-associated infections is ongoing in the teaching hospital in Ujjain. Further interventions are planned for outpatient and inpatient prescribing based on the results of this thesis.
- An observational surveillance study should attempt to be more granular in determining subtle patterns that may leverage policy changes to improve laboratory detection methods. For example, since 2006, CLSI recommends E-test or other methods to assess vancomycin MICs for MRSA strains to better appreciate the gradations of drug susceptibility and resistance even within the "susceptible range." Further, molecular methods are needed to confirm and also to substantiate the results obtained from disc-diffusion methods. We are in the process of upgrading the microbiology laboratory to address the above-mentioned issues. The molecular microbiological work is ongoing at St Johns Research Institute, Bangalore, India.
- Development of context-specific guidelines and treatment algorithms are ongoing. These are to be based on local susceptibility data and epidemiological studies. For this, efforts to establish community based cohorts for collection of longitudinal data on antibiotic use and resistance are ongoing.
- Association between overcrowding and carriage of resistant bacteria in the normal flora is worthy of further studies.
- The role of near patient diagnostics has not been well studied in resource-limited settings. We need translational research in the area to bring down unindicted antibiotic prescribing. We are examining the role of near patient diagnostics in treatment algorithms for patients with fever.
- The duration of surgical prophylaxis need to be reduced. Work is ongoing to identify possible methods for this.

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APPENDICES

APPENDIX I: QUESTIONNAIRE USED IN STUDY I

“APRIAM”: Out-patient Antibiotic use

Date:..... Department: Paediatrics = 1..... Obgyn=2
Medicine=3.....

1. Name 2. O.P.D. No

3. Age.....

Please mark the appropriate option for the items below

4. Sex: Male =1..... Female = 2.....

5. Level of education:

Illiterate = 1..... Less than higher secondary = 2..... Higher secondary=3.....

More than higher secondary = 4.....

SYMPTOMS

6. Fever: Yes = 1..... No= 2.....

7. Duration of fever: 1-3 days=1..... 4-7 days=2..... >7 days=3.....

8. Respiratory Tract Infection: Upper respiratory tract infection = 1.....

Pneumonia/Lower Respiratory Tract infection =2

.....

9. Cough: Yes=1..... No=2.....

10. Productive:Yes=1..... No=2.....

11. Duration of productive cough; <7 days= 1..... 7-14 days=2.....
>14=3.....

12. Breathlessness: Yes=1..... No=2.....

13. Ear Discharge: Yes=1..... No=2.....

14. Pyoderma: Yes=1..... No=2.....

15. Urinary Tract Infection. Yes=1..... No=2.....

16a. Vaginal discharge: Yes=1..... No=2.....

17 Prophylaxis for OPD procedures Yes =1..... No=2.....

18. Diarrhoea

19a. Loose motions: Yes=1..... No=2..... 19b. Frequency _____/day

19c Duration _____Days

20. Bottle Feeding: Yes=1..... No=2.....
21. Blood in stools: Yes=1..... No=2.....
22. Other causes of diarrhea suspected (Eg enteric fever ,malaria or worm infestation)Yes=1..... No=2.....
23. Abscess/Wound discharge: Yes=1..... No=2.....
24. Osteomyelitis: Yes=1..... No=2.....

PREVIOUS HISTORY OF TREATMENT IN LAST 2 WEEKS

25. Any treatment in the last two weeks Yes=1..... No=2.....
26. Name of Antibiotic/s and other drugs previously receive Known= 1.....
Not Known =2.....
- 27a. Name of first Antibiotic received (if known)
- 27b. Duration of Treatment for first antibiotic received.....days
- 28a. Name of first Antibiotic received (if known)
- 28b. Duration of Treatment for first antibiotic received.....days

TREATMENT GIVEN

29. Antibiotic given Yes=1..... No=2.....
- 30a. Name of first Antibiotic (generic name).....
- 30b.Dose
- 30c.Duration of treatment in days.....
- 31a. Name of second Antibiotic (generic name).....
- 31b.Dose
- 31c.Duration of treatment in days.....
- 32a. Name of third Antibiotic (generic name).....
- 32b.Dose
- 32c.Duration of treatment in days.....
- 33a. Name of fourth Antibiotic (generic name).....
- 33b.Dose
- 33c.Duration of treatment in days.....
- 34a. Name of fifth Antibiotic (generic name).....
- 34b.Dose
- 34c.Duration of treatment in days.....

APPENDIX II: QUESTIONNAIRE USED IN DIAGNOSIS-PRESCRIBING STUDY AMONG ADMITTED PATIENTS IN PAPER II

APRIAM-ANTIBIOTIC USE

IPD Form

IPD No.: _____

Name of the patient: _____

Code No.

--	--	--	--	--	--	--

Age: _____

Sex- F / M

Hospital- UCTH / CRGH

Department: - Pediatrics- 1/ Medicine- 2/ Obs & Gyn- 3/ Surgery- 4/ Orthopedics- 5/ ENT- 6/ Ophthalmology- 7/

Chest & TB- 8/ Skin- 9/ Casualty-10/ PICU- 11/ Pvt. Ward- 12/ NICU- 13/ Other- 14/ ICU- 15

Ward: Male / Female / Both

Date of admission: -

Date of start of antibiotic:-

Date of discharge:-

Antibiotics continued after discharge: - Y / N

Date of completion of antibiotic:-

Name of the drug	Dose per admin (mg)	No.of doses per day	Route of Admin Oral / Parenteral / Rectal	Diagnosis Group (Code)	Immuno suppression Yes / No	Foreign Material Assoc Yes / No	Indication for therapy **** A / B 1 - 5 / C 1 - 3 / D	Relevant culture before therapy Yes / No	Indication for given therapy in records Yes / No	Assessment of given treatment

This form is to be filled by the resident doctor / consultant.

Signature of RMO / consultant: _____

**APPENDIX III: PRESCRIPTION ANALYSIS OF THE TREATMENT OF ACUTE DIARRHOEA
IN CHILDREN (UP-TO 12 YEARS) IN UJJAIN, INDIA (PAPER III)**

A Name of patient: _____
address _____

urban / rural ____

Sex: Male=1 / Female=2 ____ b1 Pharmacy code: __
b2 Hospital code: __

c Age __ years __ months __ days

d Date of prescription: __field1__field2____

e Patient currently : 1) Admitted in hospital 2) Out patient ____

f Doctor degree ____ : 1)MD2) DCH 3) MBBS 4)BAMS
5 BHMS 6) RMP7) other ____ (mention name)

g Years in practice : __

Diarrhoea History:

h Duration of diarrhea: __ days

i Blood in stools: Yes=1 No=2 __

j Fever: Yes=1 No=2 __

k If yes duration in days 1)1-3 days 2) 4-7 days 3) > 7 days ____

l Vomiting: yes=1 no=2 ____

m Pain in abdomen: yes =1 no=2 __

Treatment given:

n Antibiotics given: Yes =1 no=2 ____

n1 Name of antibiotic __

1. Ornidazole

2. Ofloxacin

3. Ornidazole+ofloxacin

4. Metronidazole

5. Metronidazole+ofloxacin

6. Satronidazole+ofloxacin

7. Metronidazole+nalidixic acid

8. Levofloxacin

9. Tinidazole+norfloxacin

10. Furazolidone

11. Netazoxanide

12. Netazoxanide+ofloxacin

13. Diloxanide furoate+metronidazole

14 Other _____(write name)

o Zinc supplements: Yes =1 no=2 __

o1 Name of Zinc supplement ___

1. Ascazin
2. Emzinc
3. Zinconia
4. Zinsy
5. Z&d
6. Zincolife
- 7 Other _____

p Pre- pro-biotic prescribed: Yes =1 No= 2 ___

p1 Name of Probiotic: ___

1. Econorm sacht.
2. Gnorm sacht.
3. Bioclin sacht
4. Re flora -r sacht
5. Re flora z sacht.
6. Bifilac sacht.
7. Sporolac sacht./tab
8. Sporolac plus sacht/tab
9. Lactofol junior tab
10. Cynobac tender. Tab
11. Biozora sacht./tab
12. Enuff xtra sacht./tab
13. Gastrolin sacht/tab
14. Flora sb sacht/tab
15. Cyfolac tab
16. Cyfolac jr. tab
17. Flora bc syr/tab
18. Neutrolin b syr/tab
19. Rinifol syr/tab
20. Other _____(write name)

q Racecadotril: Yes =1 no=2 ___

q1 name___

1. Zedott sacht/tab
2. Racedott sacht/tab
3. Re flora kid sacht
4. Enuff sacht/tab
5. Ad sacht/tab
6. Other _____(write name)

r O.R.S. : Yes =1 no=2___

r1 name___

1. Electral
2. Electrobion
3. Rebalanz
4. Zintra
5. Cosalyte
6. Ricetra
7. Relyte
8. Minerva

9. Other _____(write name)

s. Misc.drugs: Yes =1 no=2 ____

For fever ,pain, vomiting:

1. Paracetamol _

2. Ondasetron _

3. Ranitidine _

4. Dicyclomine _

5. Nimesulide _

6. Mefenamic acid _

7. Domperidone _

8. Other _____(write name)

Appendix IV: Form used for nasal carriage of *S. aureus*

R.D.Gardi Medical College, Surasa,Ujjain

APRIAM

For Commensal

Place: UCTH / CRGH

Dept.: _____

Perianal swab (PS) (1)

Anterior nares (AN) (2)

Name: _____

Date: -- / -- / --

Age: ____yrs ____months ____days

OPD No ____/____

Lab ID NO.--/-----

For children

Gender M (1) / F (2)

Breastfed Yes (1) No (0)

School Yes (1) No (0) Anganwadi Yes (1) No (0)

Family size ≤4 persons (1) 5-10 persons (2) >10 persons (3)

Education of parent : Illiterate (1) Primary (2) ≤ higher secondary (3)
 more than higher secondary (4)

Occupation of parent : Salaried (1) Self employed (2)

H/O Antibiotics received in last 2 wks Yes (1) No (0) Not known

(2)

H/O Hospitalization in last 2 wks Yes (1) No (0)

H/O Hospital visit in last 2 wks Yes (1) No (0)

For adults

Family size ≤4 persons (1) 5-10 persons (2) >10 persons (3)

Education : Illiterate (1) Primary (2) ≤ higher secondary (3)

more than higher secondary (4)

Occupation : Salaried (1) Self employed (2)

H/O Antibiotics received in last 2 wks Yes (1) No (0) Not known

(2)

H/O Hospitalization in last 2 wks Yes (1) No (0)

H/O Hospital visit in last 2 wks Yes (1) No (0)

जानकारी पत्रक स्वीकार नामा

मैं शपथ पूर्वक यह कथन करता/करती हूँ कि मैं बिना किसी मानसिक एवं आर्थिक दबाव में एवं अपने विवेक से स्वयं की राजी मर्जी से इस स्वयं सेवा की इस योजना/परियोजना में शामिल हुआ/हुई हूँ। इस संदर्भ में मुझे इस योजना/परियोजना की पूर्ण जानकारी एवं तरीके का ज्ञान पहले दिया गया है एवं मुझे नमूने एकत्र करने की कार्यविधि भी बताई गयी है जिससे मैं संतुष्ट हूँ। एवं यह समझता/समझती हूँ कि यह कार्य विज्ञान एवं मानवता के फायदे के लिए है।

मैं समझता/समझती हूँ कि मेरा सहयोग इस ज्ञान में स्वयंसेवी की तरह है और मैं किसी भी समय बिना कारण बताए इससे अलग हो सकता/सकती हूँ जो मेरे कानून व भयशजित हक को भी बरकरार रखती है।

हस्ताक्षर व अगूटे का निशान
विषय/कानूनी मान्य प्रतिनिधि

Appendix V: Form used for Pathogen study

R.D.Gardi Medical College, Surasa, Ujjain
APRIAM

For Pathogens

Place: UCTH / CRGH

Dept :

Date of collection

Lab ID NO.--/----

PUS (1) SPUTUM (2) WOUND SWAB (3) URINE (4)
 THROAT SWAB (5) VAGINAL SWAB (7) OTHERS (6)

Name : _____

Age ____yrs ____mths ____days

IPD NO/OPD No __/____

Gender M (1) / F (2)

Family size 4 persons (1) 5-10persons (2) >10 persons (3)

For children

Weight in kg: _____

Breast-fed Yes (1) No (0)

School Yes (1) No (0) Anganwadi Yes (1) No (0)

Occupation of parent Salaried (1) Self employed (2)

Education of parent: illiterate(1) Primary(2) higher secondary

(3)

more than higher secondary (4)

H/O Medication since last 2 wks Yes (1) No(0)

H/O Hospitalization since last 2 wks Yes (1) No(0)

H/O Hospital visit since last 2wks. Yes (1) No(0)

For adults

Education: illiterate(1) Primary(2) higher secondary (3)

more than higher secondary (4)

Occupation: Salaried (1) self employed (2)

H/O Medication since last 2 wks Yes (1) No(0)

H/O Hospitalization since last 2 wks Yes (1) No(0)

H/O Hospital visit since last 2wks Yes (1) No(0)

Provisional diagnosis:

जानकारी पत्रक स्वीकार नामा

मैं शपथ पूर्वक यह कथन करता/करती हूँ कि मैं बिना किसी मानसिक एवं आर्थिक दबाव में एवं अपने विवेक से स्वयं की राजी मर्जी से इस स्वयं सेवा की इस योजना/परियोजना में शामिल हुआ/हुई हूँ। इस संदर्भ में मुझे इस योजना/परियोजना की पूर्ण जानकारी एवं तरीके का ज्ञान पहले दिया गया है एवं मुझे नमूने एकत्र करने की कार्यविधि भी बताई गयी है जिससे मैं संतुष्ट हूँ। एवं यह समझता/समझती हूँ कि यह कार्य विज्ञान एवं मानवता के फायदे के लिए है।

मैं समझता/समझती हूँ कि मेरा सहयोग इस ज्ञान में स्वयंसेवी की तरह है और मैं किसी भी समय बिना कारण बताए इससे अलग हो सकता/सकती हूँ जो मेरे कानून व भयशजित हक को भी बरकरार रखती है।

हस्ताक्षर व अंगूठे का निशान
विषय/कानूनी मान्य प्रतिनिधि