

From

Global Health, Department of Public Health Sciences
Karolinska Institutet, Stockholm, Sweden

ANTIBIOTIC USE & RESISTANCE
Patterns, Perceptions, Policy and the Price to Pay

Sujith John Chandy



**Karolinska
Institutet**

Stockholm 2014

The cover depicts a jigsaw puzzle view of antibiotic use and resistance. Many throughout the world have contributed in putting the numerous pieces together so as to get a better picture. Here is my small contribution by forming four pieces. These pieces and the pictures in each, represent the four constituent papers in this thesis, patterns of antibiotic use through surveillance, perceptions of key stakeholders such as doctors, pharmacists and the public, the cost and health consequences due to resistance, and the impact of policy guidelines. The P's (piece) in this thesis – patterns, perceptions, policy and the price to pay are important pieces of this puzzle. At the core is antibiotic use represented as Rx and a microscopic background image of bacteria representing the resistance potential. It is hoped that this thesis has contributed to the efforts to provide evidence to improve antibiotic use and move a step closer in the 'puzzle' of antibiotic resistance.

All previously published papers were reproduced with permission from the publisher.

Published by Karolinska Institutet, Stockholm, Sweden

Printed by Atta.45 Tryckeri AB, Karlsrogatan 2, 170 65 Solna, Stockholm, Sweden

© Sujith John Chandy, 2014

ISBN 978-91-7549-559-0



Karolinska Institutet

Global Health, Department of Public Health Sciences, Karolinska Institutet

ANTIBIOTIC USE & RESISTANCE Patterns, Perceptions, Policy and the Price to Pay

Academic Dissertation
for the degree of Doctor of Philosophy (PhD) at Karolinska Institutet.

The public defence: Karolinska Hall, Floor 2, Widerströmska Huset, Tomtebodavägen 18A,
Karolinska Institutet, Stockholm, Sweden

1 pm, Wednesday, 4th June, 2014

by

Sujith John Chandy

Supervisor:

Professor Cecilia Stålsby Lundborg
Global Health
Department of Public Health Sciences
Karolinska Institutet, Stockholm

Co-Supervisor:

Professor Kurien Thomas
Department of Medicine
Christian Medical College, Vellore

Mentor

Professor Denise H Fleming
Department of Pharmacology
& Clinical Pharmacology
Christian Medical College, Vellore

Chair:

Dr. Senia Rosales-Klintz
Global Health
Department of Public Health Sciences,
Karolinska Institutet, Stockholm

Opponent:

Professor Krisantha Weerasuriya
Medicines Access and Rational Use
Essential Medicines and Pharmaceutical Policies
World Health Organization, Geneva

Examination board:

Professor Katarina Hjelm,
Institutionen för Samhälls-och Välfärdsstudier (ISV)
Linköping University, Sweden

Professor Johan Fastbom
Geriatric Pharmacology
Dept of Neurobiology Care Sciences & Society
Karolinska Institutet, Stockholm

Professor Johan Giesecke
Chief Scientist
Head of the Office of the Chief Scientist
European Centre for Disease Prevention & Control
ECDC, Stockholm

Stockholm 2014

ABSTRACT

Background: Antibiotic resistance is a major health challenge especially in low and middle income countries such as India. Inappropriate antibiotic use is one important factor contributing to resistance. Strategies to improve use would help contain resistance. In order to develop strategies that are feasible and appropriate, knowledge is needed about patterns and perceptions of antibiotic use, the consequences of resistance and impact of policy guidelines. Current knowledge and evidence is limited in India.

Aim: To improve knowledge on the patterns and perceptions of antibiotic use in the community, the consequences of resistance in individual patients, and the impact of policy guidelines on hospital antibiotic use, so as to identify potential interventional targets, generate key messages and subsequently develop appropriate strategies towards improving use and containing resistance. The specific objectives were:

1. To determine patterns of antibiotic use through a surveillance system in the community and challenges faced while developing the system. (I)
2. To ascertain the perceptions of stakeholders in antibiotic use and resistance and highlight the challenges to changing practice. (II)
3. To assess the impact of antibiotic resistance on cost burden and health consequences in patients with suspected sepsis. (III)
4. To determine patterns of inpatient antibiotic use over a decade and evaluate the impact of policy guidelines and modes of dissemination on antibiotic use. (IV)

Methods: The first two studies (Paper I & II) for this thesis were done in urban and rural areas of Vellore district, south India and the two other studies (Paper III & IV) at Christian Medical College, Vellore (CMC), a not for profit, university teaching hospital with 2140 beds. Surveillance of antibiotic use patterns (prescriptions and dispensations) in thirty community healthcare facilities for 2 years was conducted with a repeated cross-sectional design (I). A qualitative study with eight focus group discussions among doctors, pharmacists and public explored perceptions about resistance, antibiotic use practices, factors driving use, and strategies for appropriate use (II). A one year observational study on inpatients with a preliminary diagnosis of suspected sepsis and a positive blood culture report analysed costs and health consequences in two groups, 'resistant' and 'susceptible' based on susceptibility of causative bacteria to the empiric antibiotic given (III). A time series segmented regression analysis of antibiotic use across a decade revealed the patterns of use over time segments and the impact of differing modes of policy guideline development and implementation (IV).

Findings: Surveillance in community healthcare facilities (I) revealed that among 52,788 patients, 40.9% were prescribed or dispensed antibiotics (antibiotic encounters). There were significant differences among facilities types and areas. Fluoroquinolones and penicillins were widely used, co-trimoxazole more in rural hospitals and cephalosporins in urban private hospitals. 41.1% of antibiotics were for respiratory infections. Focus group discussions (II) revealed that the public had limited awareness of infection, antibiotics and resistance and wanted quick relief through antibiotics. Doctors prescribed antibiotics for perceived patient

expectations and quick recovery. Business concerns promoted antibiotic sales by pharmacists. Improving public awareness, provider communication, diagnostic support, and strict regulatory implementation were suggested strategies. Among 220 patients admitted into the hospital with suspected sepsis (III), the median difference between 'resistant' and 'susceptible' groups in overall costs, antibiotic costs and pharmacy costs was Rs. 41,993 ($p = 0.001$), 8,315 ($p < 0.001$) and 21,492 ($p < 0.001$) respectively. Length of stay, intensive care admissions, complications and mortality were significantly higher in 'resistant' group by 3 days ($p = 0.027$), 23% ($p < 0.001$), 19% ($p = 0.006$) and 10% ($p = 0.011$). The overall antibiotic use in the hospital (IV), expressed in DDD per 100 bed days, increased monthly during Segments 1 (0.95), 2 (0.21) and 3 (0.31), stabilized in Segment 4 (0.05) and declined in Segment 5 (-0.37). Pairwise segmented regression adjusted for seasonality showed a drop in antibiotic use of 0.401 (SE=0.089; $p < 0.001$) for Segment 5 (guidelines booklet and online intranet guidelines) compared to Segment 4 (guidelines booklet alone).

Conclusion: The level of antibiotic use is significant in the community, especially for respiratory infections and fluoroquinolone use. Patterns of antibiotic use varied among healthcare facilities and stakeholders. Knowledge and understanding of resistance was limited. Patient demand and competitive pressures were some of the main challenges expressed in changing practice. Antibiotic resistance had significant impact on cost and health consequences in patients. Containment of rising inpatient antibiotic use was possible with guideline dissemination through intranet computer network.

LIST OF PUBLICATIONS

- I. Chandy SJ, Thomas K, Mathai E, Antonisamy B, Holloway KA, Stalsby Lundborg C. Patterns of antibiotic use in the community and challenges of antibiotic surveillance in a lower-middle-income country setting: a repeated cross-sectional study in Vellore, south India. *J Antimicrob Chemother.* 2013 Jan;68(1):229-36. PMID: 22945913
- II. Chandy SJ, Mathai E, Thomas K, Faruqui AR, Holloway K, Stalsby Lundborg C. Antibiotic Use and Resistance: perceptions and ethical challenges among doctors, pharmacists and the public in Vellore, South India. *Indian J Medical Ethics.* 2013 Jan-Mar;10(1):20-27. PMID: 23439193
- III. Chandy SJ, Naik GS, Balaji V, Jeyaseelan V, Thomas K, Stalsby Lundborg C. High Cost Burden and Health Consequences of Antibiotic Resistance – The Price to Pay. Resubmitted after revision.
- IV. Chandy SJ, Naik GS, Charles R, Jeyaseelan V, Naumova EN, Thomas K, Stalsby Lundborg C. The Impact of Policy Guidelines on Hospital Antibiotic Use over a Decade: A Segmented Time Series Analysis. *PLoS One.* 2014 Mar 19;9(3):e92206. doi:10.1371/journal.pone.0092206. PMID:24647339

These papers will be referred to in the text by their Roman numerals (I-IV).

Published papers were reproduced with permission from the publisher.

ABBREVIATIONS

AIDS – Acquired Immunodeficiency Syndrome
AMR – Antimicrobial Resistance
ASHA – Accredited Social Health Activist
ASPIC – Antibiotic Stewardship Prevention of Infection and Control
AYUSH – Ayurveda, Unani, Siddha, Homeopathy
BPL – Below Poverty Line
CDC – Centers for Disease Control and Prevention
CDSCO – Central Drugs Standard Control Organization
CHC – Community Health Centre
CI – Confidence Interval
DDD – Defined Daily Dose
DTC – Drugs and Therapeutics Committee
ESBL – Extended Spectrum Beta-Lactamases
EU – European Union
FGD – Focus Group Discussion
GDP – Gross Domestic Product
GNB – Gram Negative Bacteria
GP – General Practitioner
GPB – Gram Positive Bacteria
HAI – Hospital Acquired Infections
HIC – High Income Countries
HIS – Hospital Information Systems
HICC – Hospital Infection Control Committee
HIV – Human Immunodeficiency Virus
HPLC – High Performance Liquid Chromatography
HSEP – Higher Socioeconomic Public
ICU – Intensive Care Unit
ISM – Indian Systems of Medicine
IT – Information Technology
LMIC – Low and Middle Income Countries
LSEP – Lower Socioeconomic Public
MDR – Multi-Drug Resistance
MRSA – Methicillin Resistant *Staphylococcus aureus*
NDM-1 – New Delhi Metallo-beta-lactamase-1
NLEM – National List of Essential Medicines
NFGNB – Non Fermenting Gram Negative Bacteria
NGO – Non Governmental Organization
NRHM – National Rural Health Mission
OOP – Out Of Pocket
OPD – Outpatient Department
OTC – Over The Counter
PHC – Primary Health Centre
POC – Point Of Care
RDT – Rapid Diagnostic Testing
RMP – Registered Medical Practitioner
SC – Sub-Centre
STG – Standard Treatment Guidelines
USD – United States Dollar

DEFINITIONS

Antibiotics (Antibacterial agents): chemical substances that are either natural, semi-synthetic or synthetic that kill or inhibit the growth of bacterial microorganisms.

Antimicrobials: chemical substances or drugs that kill or inhibit the growth of a variety of microorganisms like bacteria, viruses, fungi, and parasites.

Antibiotic resistance: the result of bacteria changing in ways that reduce or eliminate the effectiveness of drugs, chemicals, or other agents that cure or prevent infections

Antibiotic encounter: prescription or dispensation to patient containing at least one antibiotic

Antibiotic use: prescription or dispensation of an antibiotic. For the purpose of this thesis, it does not include administration or consumption.

Defined Daily Dose (DDD): assumed average maintenance dose per day for a medicine used for its main indication in adults

Empiric therapy: the initiation of treatment prior to determination of a firm diagnosis.

Microbiota: the microorganisms of a particular site, habitat or region.

Multidrug resistance: acquired non-susceptibility to at least one agent in three or more antimicrobial categories

Pharmacy Shops: chemist or community pharmacy where medicines and other items are sold

Selection density: the total amount of antibiotic exposed to a geographically defined number of individuals in a setting

PREFACE

Life is a journey and the paths trodden are often unknown. Having a purpose in life allows you to choose the paths. The chosen direction then becomes much more meaningful and fruitful.

My life journey has trodden various paths over the years. As a child, I fondly remember sitting in the verandah on my grandfather's lap listening to his humorous stories as the monsoon rain came pelting down in Kerala, my home state in India. I remember with fondness the scooter rides with my parents and their encouragement to learn music even at a very early age. The path suddenly turned to the West when I was five, and for six subsequent years along with my parents, I experienced the cold and rainy conditions of northern England and the warm ambience of primary school education there. My return to India was a tough time, getting used to the hot and humid conditions again and the hard churn of Indian school education. Fortunately, I was able to study in Corpus Christi School (now known as Pallikoodam). The school encouraged me to think freely, have an enquiring mind and gave me the opportunity to do dramatics, sports and music. I was also given the responsibility as School Captain in my later years. Most importantly, my parents and the school taught me how to help people in need. I still remember visiting the slum areas, building a nursery school for the children there and teaching at the nursery regularly.

As the time came to leave school, I was in a dilemma. Which path should I take next? I had various interests and therefore I applied in good colleges for economics, architecture, statistics and medicine. I did not realize that the picture would get more confusing as I gained admission for all these programmes. The path that I took though was the hardest at that time, medicine. The journey through that hard path was made meaningful through the excellent medical education I got at Christian Medical College, Vellore. The training received through my teachers, the rich diversity of patients and diseases in the hospital, the college campus and student life, were all wonderful and enriching experiences. There I learnt a rational and ethical approach to medicine. I was taught to look at medicine holistically through the lives of patients rather than as disease entities. The college taught me to put community over self and this has stayed with me in my interactions with various people over the years. After graduation, I spent a couple of years in a small rural hospital where I learnt that health care in the real world is far from the academic world in knowledge, attitude and practice. However I tried my best to put in place the things I learnt. This was also the time that I got married and there was a loving person to accompany me on my journey.

Again came a crossroads in life, my postgraduate education. I was interested in community medicine at one point and also psychiatry, but ultimately I settled for pharmacology. Besides the interest in medicines and how they work, pharmacology gave me the chance to interact with students as a teacher. After completing my Doctor of Medicine (MD) specialization at the Department of Pharmacology and Clinical Pharmacology, CMC Vellore, I spent the initial years mainly teaching. I enjoyed this time greatly, interacting with students not just in

the subject, but also through various campus activities in music, drama, sports and chapel at my alma mater. I also started assisting the clinical pharmacology unit at hospital. This gave me the chance to work on various aspects of medicines such as medicines safety and medicine use. At that time, I also had the opportunity to integrate pharmacology with public health through a major research project in the community. Those days, I remember coining the term 'social pharmacology' for this integration. This was also the time when my interest in antibiotics and their use developed.

Within a few years, I had to take another path, this time a hard and perilous one. The administration at CMC Vellore requested me to take up the Headship of the Pharmacy department. I responded to this institutional need at a rather early age in addition to my teaching, research and clinical responsibilities. The pharmacy department was one of the largest departments of the hospital, contributing significantly to the financial base of the institution and assisting the work of the entire hospital. This path gave me the chance to put in place policies and approaches that could positively impact the lives and health of the patients. I was also able to practice social pharmacology by improving affordability through differential pricing systems for poor, enhancing the quality of medicines by putting in place a rigorous selection system with checks, providing availability through a proper purchase and inventory system and enhancing access by opening multiple outlets for dispensing.

It was a few years into this intense time, that I was called to embark on another steep path through the opening of a once in a life time opportunity - to be a part of the doctoral programme at Karolinska Institutet. My supervisor's encouragement and the support through the Erasmus scholarship gave me the courage and conviction to walk this path. I have been able to walk this path following the footsteps of many others at Global Health (IHCAR). It has been a truly great learning environment, putting in place the rigors and discipline of research, public health and education, all intertwined in one. The support of my supervisors, teachers and colleagues at both Karolinska Institutet and CMC Vellore has been outstanding. Most importantly, I was able to walk this path and help the cause of social pharmacology by being involved in the area of antibiotic use and resistance, a cause close to my heart. I truly believe that antibiotics are great gifts to mankind, a resource more precious than gold. Unfortunately, we have misused this gift through inappropriate antibiotic use. Mankind is therefore beginning to experience the terrible consequences. I have walked along with my co-investigators, colleagues, and fellow travelers in the movement to improve use.

Life has therefore been a journey, but a journey with many paths. The path that I am currently on is not the beginning and definitely not the end. It has indeed been a long walk. I have learnt over these many walks, and meeting people from various walks of life that it is how you walk and not where you walk to that is important. The journey is more important than the destination. This has been true with the PhD programme also. The knowledge, skills and attitude of learning through research has been most valuable. I thank everyone who has guided and encouraged me to walk this path.

CONTENTS

Abstract

List of Publications

Abbreviations

Definitions

Preface

Contents

1 Background.....1

- 1.1 A brief introduction
- 1.2 Antibiotic resistance
- 1.3 Antibiotic use
- 1.4 Strategies to counter resistance
- 1.5 Profile of India
- 1.6 Rationale for studies

2 Aim and Objectives.....20

3 Methods.....21

- 3.1 A summary of methods
- 3.2 Study design
- 3.3 Study setting
- 3.4 Sampling, participants and data collection
- 3.5 Analysis
- 3.6 Ethical permission

4 Main Findings.....31

- 4.1 Understanding of infections, antibiotics and resistance in community
- 4.2 Antibiotic use in community healthcare facilities
- 4.3 Antibiotic use in a teaching hospital facility
- 4.4 Practices and factors in antibiotic use in the community
- 4.5 Strategy in the hospital
- 4.6 Strategies in the community

5 Discussion.....45

- 5.1 Understanding of infections, antibiotics and resistance
- 5.2 Antibiotic use in community healthcare facilities
 - 5.2.1 *Level and patterns of antibiotic use*

5.2.2	<i>Symptoms prompting antibiotic use</i>	
5.2.3	<i>Surveillance through antibiotic encounters in patients</i>	
5.2.4	<i>Surveillance through antibiotic sales records</i>	
5.2.5	<i>Challenges in surveillance</i>	
5.3	Antibiotic use in a teaching hospital facility	
5.3.1	<i>Patterns of use among antibiotic groups across the decade</i>	
5.4	Practices, factors and challenges in antibiotic use in community	
5.4.1	<i>Antibiotic use practices</i>	
5.4.2	<i>Factors promoting antibiotic use</i>	
5.4.3	<i>Challenges and ethical dilemmas</i>	
5.5	Strategy in the hospital	
5.5.1	<i>Impact of policy guidelines on overall antibiotic use</i>	
5.5.2	<i>Impact of policy guidelines with online intranet access on antibiotic use</i>	
5.6	Strategies in the community	
5.6.1	<i>A key message - the price to pay</i>	
5.6.2	<i>The cost burden attributable to antibiotic resistance</i>	
5.6.3	<i>Health consequences attributable to antibiotic resistance</i>	
5.6.4	<i>Strategies suggested by stakeholders for appropriate antibiotic use</i>	
5.6.5	<i>Other strategies based on findings from surveillance</i>	
5.7	Methodological considerations	
6	Conclusions	65
7	Actions, implications and future research	67
8	Acknowledgements	70
9	References	72
10	Appendices	89

1. BACKGROUND

1.1 A brief introduction

For those who live in challenging circumstances, especially in low and middle income countries (LMIC), life can be a struggle. The struggle becomes intense when various external and internal factors influence life. One factor that often affects us in these circumstances is infection. Bacteria have co-existed with mankind, but some of them cause infection. The discovery of antibiotics has helped humans fight against infections. This precious discovery has been inappropriately used over the years. Bacteria have overcome many antibiotics through the phenomenon of resistance. Many antibiotics have therefore become ineffective. This rising problem of resistance and ineffective antibiotics has affected the world in a subtle manner, as opposed to terrorism, HIV and climate change which feature prominently in mass media. Antibiotic resistance has the potential to affect each and every one of us. This is the danger that we are facing - a post-antibiotic era.

Can we stop this rising problem and if so, how? That is something that has vexed researchers the world over. The multi-factorial nature and multiple stakeholders involved in antibiotic use and resistance diminish the chance of a one stop solution. The spread and severity of infections, the existing practices of health professionals and patterns of antibiotic use, the perceptions of stakeholders in the community, affordability and other economic issues, all play a part in influencing antibiotic use in humans. Unless these factors are understood properly, it would be difficult to develop sustainable and feasible interventional strategies to improve appropriate use. There are existing strategies, but often limited to the hospital. The main strategy in place in hospitals is antibiotic policy guidelines and it would be important to evaluate their impact in containing antibiotic use. This strategy could be contextualized for the community to aid health professionals in antibiotic use. By studying existing usage patterns and practices, these guidelines can be focused on the key areas of misuse. It would be important to develop other strategies also, especially for the public. That is why determining perceptions about antibiotics, resistance and infections and identifying factors leading to antibiotic use become important in developing the right strategy. Most importantly, key messages need to be developed and determining the economic burden and health consequence in patients would serve as a very important message in the battle against inappropriate antibiotic use.

The need to provide such an evidence base so that feasible strategies could be developed to improve antibiotic use at hospital and community levels have led to the doctoral studies and resulting papers. It is hoped that this thesis would encourage researchers in India and other LMIC to do similar studies with a similar purpose and thereby preserve effective antibiotics.

1.2 Antibiotic Resistance

1.2.1 The phenomenon of resistance

Microorganisms have lived together with humans since the beginning. Nevertheless, infections caused by microorganisms have been a threat to mankind. Over the last century, the discovery of antimicrobial agents, particularly antibacterial agents (hereafter referred to as antibiotics), have altered the relationship between humans and bacteria. Frequent use of antibiotics have reduced the susceptible strains of bacteria, and increased the resistant variants, thereby leading to the phenomenon of antibiotic resistance.

Bacterial resistance has been defined by the Centres for Disease Control and Prevention (CDC) as ‘the result of bacteria changing in ways that reduce or eliminate the effectiveness of drugs, chemicals, or other agents to cure or prevent infections’ [1]. Resistant bacteria are able to block the action of antibiotics. Treatment therefore becomes ineffective and infections continue with possibilities of complications and spread. The evolution of resistant strains is thus mainly a natural phenomenon that happens when bacteria are exposed to antibiotics. Resistant traits can be exchanged between bacteria also.

Drug-resistant strains initially appeared in hospitals, where most antibiotics were being used. Soon after introduction of penicillin in 1940’s, penicillin-resistant *Staphylococcus aureus* emerged in hospitals in London [2]. After the discovery of streptomycin, resistance in *Mycobacterium tuberculosis* soon emerged [3]. In the 1950s and 1960s, multi-drug resistance was noticed in enteric bacteria such as *Escherichia coli* [4]. In the 1970s, *Haemophilus influenzae* emerged with resistance to ampicillin, chloramphenicol and tetracycline [5-7]. The rising resistance over the years has meant that few antibiotics remain truly effective.

The mechanisms by which antibiotic resistance occur in bacteria are varied. They include antibiotic detoxification, target protection and substitution, and block of intracellular antibiotic accumulation [8]. Two broad points need to be considered in the resistance phenomenon. Firstly, the antibiotic which inhibits the susceptible and selects the resistant bacteria, and secondly, the genetic resistance determinant in bacteria selected by the antibiotic. Antibiotic resistance occurs when these two converge in the host leading to disease complications. Under continuous antibiotic selection, resistance genes spread to other hosts and environment. They are transferred among various taxonomic and ecological groups such as plasmids, integrons, bacteriophages, or transposons [8]. Plasmids can serve as a scaffold. On this, arrays of antibiotic resistance genes can be assembled by transposition and site-specific recombination mechanisms such as integron gene cassettes. These genes are usually directed at a single family or antibiotic type. However, multiple genes carrying single drug resistance traits can be present in the same organism. Plasmids and transposons usually mediate high-level resistance. Low-level resistance in bacteria can be transformed to high-level resistance through sequential mutations in chromosomes [9].

If usage of a particular antibiotic is widespread, susceptible strains will be at a disadvantage as compared to resistant strains. This imbalance can generate a larger pool of resistance in the environment. If the antibiotic is not widely used, the impact is often felt more at an individual level with less serious consequences. The selected resistant strains will be suppressed by the drug-susceptible bacteria [10]. However, each individual is potentially a generator of resistant bacteria that moves into the environment.

Increasing the density of antibiotic usage can increase resistance selection [8,10]. This 'selection density' is based on the total antibiotic used in a geographic setting with a specific population. Selective pressure also reflects the number of individuals who are promoting resistant bacteria in a particular setting and the residual number of susceptible but surviving bacteria. Selection density and pressure makes antibiotics a unique group. Individual use affects resistance and therefore community use. They are therefore truly societal medicines.

1.2.2 The global resistance situation

Antibiotic resistance has reached a crisis level in the world and especially so with the emergence of multidrug resistance (MDR) [11]. Community and hospital MDR strains of *Staphylococcus aureus*, *Enterococcus faecium*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, *Escherichia coli*, *Salmonella enteritidis*, *Shigella flexneri*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* are widely prevalent [12].

Among Gram-positive bacteria, *S. aureus* has been associated prominently with resistance. 40–60% of nosocomial *S. aureus* strains in USA were methicillin-resistant (MRSA) [13]. A steadily increasing proportion of MRSA is becoming resistant to vancomycin [14] and even to newly developed medicines such as dalfopristin/quinopristin and linezolid [15]. Among the Gram-negative bacteria and especially in hospitals, *P. aeruginosa* and *A. baumannii* have been a problem due to MDR. Extended spectrum beta-lactamases (ESBL) have been another grave problem, especially in the last decade. ESBL in Enterobacteriaceae such as *Enterobacter* and *Klebsiella*, have destroyed the later generations of penicillin and cephalosporins [16].

Hospital patients have been the major casualty of resistance. However, the community has not escaped resistance. MRSA strains differing from hospital strains have emerged in communities with resistance to beta-lactam antibiotics [17]. Strains of *E. coli* have become resistant to fluoroquinolones with the emergence of ESBL [18]. In Southeast Asia and China, 70% of *E. coli* are resistant to fluoroquinolones [19]. Pneumococcal resistance to penicillin, macrolides and tetracyclines are common in many areas [20]. This has affected the treatment of pneumonia and otitis media. Similarly, strains of *Neisseria gonorrhoeae* have become resistant to penicillins, tetracyclines and fluoroquinolones [21].

In recent years, antibiotic resistance has been in the news with reported cases in 2010 of New Delhi metallo-beta-lactamase-1 (NDM-1) producing *Enterobacteriaceae* [22]. This phenomenon has been reported from continents across the world [23-25]. Another carbapenemase, OXA-48 has reared its head in countries in Africa and Europe [26-27].

1.2.3 The antibiotic resistance situation in India

Antibiotic resistance is also a problem in LMIC such as India. Researchers working in the area of antibiotic resistance have been recommending appropriate use of antibiotics for a long time. These attempts largely remained in the background until the NDM article appeared [22] and became frontline news in the media. Overall, antibiotic resistance in both gram positive and gram negative bacteria appears to have become widespread.

Among the Gram positive bacteria, MRSA appears to be widely prevalent. In a study looking at 12 intensive care units (ICU) in seven Indian cities, 88% of *S. aureus* strains were MRSA among 476 hospital-acquired infections [28]. This problem is not isolated to ICUs or inpatients. A study done in paediatric outpatients in central India found that the prevalence of nasal carriage of *S. aureus* was 6.3% of which 16.3% were MRSA [29]. In a study on north Indian children, Group-A beta-hemolytic streptococci from throat swabs showed upto 25% resistance to macrolides, tetracycline and cotrimoxazole [30].

The problem of resistance among Gram negative bacteria appears equally problematic. The multicentric study in ICUs found that of the hospital acquired infections caused by *Pseudomonas spp.*, 65% was resistant to ceftazidime, 43% to piperacillin-tazobactam, 29% resistant to ciprofloxacin, and 42% to imipenem [28]. In a study on 265 *Acinetobacter spp.* isolates, 80% resistance to later generation cephalosporins, quinolones and aminoglycosides was noted [31]. A study of *K. pneumoniae* isolates from samples of urine and pus found that 25% were ESBL producers [32]. A study done in Vellore, south India found that 42% of commensal *E. coli* had resistance with higher resistance rates in infecting strains [33].

Overall the situation appears to be grim. The consequences could be catastrophic to India where high population, urbanization, inadequate health infrastructure and rising costs make a potentially explosive situation.

1.2.4 The consequences of antibiotic resistance

The pan-global use of antibiotics has favoured the growth of resistant strains. Confinement to a specific environment is improbable due to movement of vehicles such as people, animals, water and wind [34]. Resistant bacteria developing in vegetables, fruits, animals and water sources have used the food chain and environment to gain access to humans [35-37]. This problem has been compounded when commensal bacteria transfer their resistance genes to pathogenic bacteria in the same environment. This has led to the creation of ‘superbugs’ that are multidrug resistant [11,12]. These superbugs have been responsible for serious infectious diseases for which most antibiotics are ineffective. This in essence is the consequence to humans.

There are a number of other potential implications. Due to reduced effectiveness of antibiotics, patients may remain infectious longer, thereby increasing the spread of resistant

bacteria. If the infections are caused by resistant bacteria, there will be a failure of standard treatment [15,18]. This may result in prolongation of infection, possible complications and a greater risk of mortality. Besides individuals, this may have implications for national policies and health programmes. Other implications are in particular groups of patients. Immuno-compromised patients, those in transplantation programmes and cancer chemotherapy are at risk of infections. The effectiveness of antibiotics in such patients is crucial to the success of overall treatment.

Cost implications at individual and aggregate levels are also important to consider. Infections caused by resistant bacteria are often resistant to first line of therapy. This leads to a loss of valuable time and complications. The second line of therapy maybe costlier and the treatment of complications may add to the financial burden. This economic burden will extend to the family, and depending on the source of support, to hospital and government budgets.

There are larger epidemiological and political concerns. Antibiotic resistance can hamper control of infectious diseases. This could lead to serious outbreaks of infections, especially in crowded populations and areas where hygiene is poor. Multilateral trade pacts and tourism have led to a situation where people and food products travel widely between countries. The risk of quick transfer of superbugs through these vehicles is important to consider [22]. The lack of new antibiotics on the horizon and the lethargy of pharmaceutical companies in researching and developing newer classes may complicate this already perilous scenario [38].

1.3 Antibiotic use

1.3.1 Rational use of medicines

The appropriate use of medicines by healthcare providers such as doctors, pharmacists, and nurses, is essential in optimizing care. A rational approach would include: identifying the patient's problems and focussing on an appropriate indication; choosing safe, effective and affordable treatment; selecting appropriate medicines, dose and duration for that indication; improving the patient's understanding of disease and medication through adequate communication; evaluation of treatment response [39]. The patient's tolerability and adverse effect profile should also be taken into consideration and monitored.

Unfortunately, many of these criteria are not met in practice due to differing reasons and circumstances. This then becomes inappropriate use. The systems, structures and factors influencing medicine use are complex and vary from country to country. Medicines may be produced locally or imported, thus bringing into play price, availability and quality issues. Counterfeits and substandard medicines are other problems to be considered. Medicine use occurs at multiple levels of healthcare facilities such as hospitals, clinics, private practitioners, pharmacy shops or even over the counter (OTC). In India, there are many alternate systems of medicine whose practitioners may prescribe allopathic medicines and also untrained practitioners who may prescribe without enough knowledge. The end user is

another key stakeholder. In many countries such as India, there could be a wide spectrum of knowledge, beliefs and attitudes among the public. Appropriate prescribing therefore becomes rather complex, but paradoxically, its need becomes crucial for optimal health and treatment.

Inappropriate use of medicines could have various consequences, for the individual, the society, health systems and even the economy. A compromise in the quality or choice of medicines, dose or duration may lead to increased morbidity and mortality. In a scenario where stock is limited or medicines budget constrained, unnecessary use could lead to reduced availability of vital medicines and possibly increased costs. Inappropriate medication with little communication between patient and health provider may increase the risk of adverse effects. In the case of antibiotics, it's not just adverse effects, but the emergence of antibiotic resistance.

1.3.2 Antibiotics and inappropriate use

The problem of inappropriate use is amplified in the case of antibiotics due to their use in agriculture and livestock besides humans. In livestock and food industries, antibiotics are often used as growth promoters and for prevention of infections [35]. The manure from the animals that may contain antibiotic residue and resistant bacteria is often applied to crop fields. Agricultural use of antibiotics is leading to contamination of soil and water sources [36]. The food industry is using antibiotics as preservatives [37]. All this could impact microbiota in the ecosystem thereby disrupting environmental cycling of organic matter. Inappropriate use in these industries has contributed to selection of antibiotic resistant bacteria in the environment thus posing a danger to humans also.

In humans, antibiotics are often prescribed or dispensed inappropriately for symptoms such as cough, sore throat, diarrhoea and fever, often suggestive of non-bacterial infections [40]. Factors which may contribute to this include lack of knowledgeable healthcare providers, non-qualified health providers, prescription habit, lack of medicines information, minimal consultation and dispensation time, non-availability of medicines, limited diagnostic support, and economic incentives. Access to affordable health care is often limited in India. The public may therefore self medicate and purchase antibiotics directly from pharmacy shops (community pharmacy).

The lack of understanding about appropriate use of antibiotics is not only limited to LMIC. Studies in HIC have revealed perceptions and behaviours that are not compatible with rational use. In USA, 45% of individuals who took antibiotics within a year thought that antibiotics could kill viruses [41]. Most patients, who asked for an antibiotic from a healthcare provider, were granted such a prescription. In UK, very few patients were willing to expect less antibiotic prescriptions [42]. Another study in Sweden revealed that although general practitioners (GPs) thought that restricting antibiotics would help preserve effectiveness, they felt that it was time consuming [43]. By and large, the global perception

towards antibiotic resistance and willingness to move towards appropriate antibiotic use appears to be poor.

1.3.3 Antibiotic use in India

In India, antibiotics are widely available to people with or without prescriptions. Prescriptions can be given by doctors who are registered medical practitioners (RMP) [44]. A significant number of patients who request for antibiotics in pharmacy shops, ask for antibiotics they took previously [44]. There are laws against dispensing antibiotics without prescriptions, but are not enforced [45]. Antibiotics as a group fall under Schedule H of the Drugs and Cosmetics Act 1940. Recently in an attempt to restrict antibiotic use, 46 medicines were separated by the national drug regulatory body, the Central Drugs Standard Control Organization (CDSCO) and notified under H1 [45]. Schedule H1 allows these medicines to be sold only on prescription by RMPs. The sale records are to be kept in a separate register for three years giving the prescriber details, patient name, name of antibiotic and quantity sold. These medicines should be labelled with the symbol Rx in red and in a box with red border with ‘Schedule H1 Drug – Warning: It is dangerous to take this preparation except in accordance with medical advice; Not to be sold by retail without the prescription of a Registered Medical Practitioner.’

It is yet to be seen whether Schedule H1 will have real impact in containing antibiotic use. Even during the Schedule H period, studies showed that antibiotics were often prescribed. In a study in central India, 80% of the inpatients were prescribed antibiotics with a high number of combinations [46]. A study on upper respiratory infections in children revealed that 31% of prescriptions were antimicrobials and 59% of medicines were fixed-dose combinations [47]. A study done in outpatient clinics revealed that 66% were prescribed antibiotics, of which quinolones were the most frequently prescribed [48]. Another study done in patients in primary and secondary health care facilities showed that 69% were prescribed antibiotics [40]. Two third of all antibiotics prescribed were cotrimoxazole and penicillins. More than 40% of private sector prescriptions were quinolones and cephalosporins. These few studies reveal that inappropriate antibiotic prescribing is relatively high in India.

1.3.4 Promoters for antibiotic use

The motivation to prescribe, dispense or consume antibiotics can be affected by various factors. It is therefore important to focus on specific factors that may influence use.

One study found that the more educated private practitioners prescribed lesser antibiotics. They would prescribe an antibiotic if they felt that the patient has bacterial infection [49]. In a study of physicians, patient satisfaction was a motivating factor for prescribing antibiotics in 29% [50]. Self medication is another factor to be considered. A study on mothers who fell ill during a one year period found that 16% of the time no action was taken. However 25% of the time, the illness was self-medicated [51].

Knowledge and perceptions of pharmacists are also important. A study in Tanzania revealed that drug-sellers in private drugstores had practical knowledge of antibiotics and some idea of resistance issues. However, 24% felt that antibiotics could be given for viral diseases [52]. Financial incentives for pharmacists may also play a part. A study in India found that rather than viewing themselves as health professionals, pharmacists viewed themselves as businessmen [44]. This often translates to profit as the main motive. In a country with lax regulations, patients visiting pharmacy shops directly could be higher. This could translate to more antibiotics being given. The influence of the pharmaceutical industry is also a factor that could influence both pharmacists and doctors to use more antibiotics. Overall there were very few studies in India looking at factors and perceptions of stakeholders.

1.3.5 Relationship between antibiotic use and resistance

The use of antibiotics has exerted selective pressure on susceptible bacteria thereby favouring the survival of resistant strains [53]. Among the various reasons for rise of resistance, individual and aggregate use of antibiotics are contributing factors [54, 55]. A meta-analysis provided strong evidence at the level of individual patients having urinary, respiratory and skin infections, of an association between antibiotic prescribing in primary care and antibiotic resistance [54]. Effects were strongest in the weeks after prescription but were detectable for a year. Another important finding was that the greater the number of antibiotic courses or the longer the duration of the course in the previous 12 months, the greater the likelihood of resistant bacteria being isolated from that patient.

Individual prescribing may also have consequences for the community. The residual effect could be an important driver for high levels of resistance in the community. This was evidenced through a study on amoxicillin prescribing for respiratory infections in children [56] This study also revealed that a transient effect of antibiotic use on carriage of resistant organisms by individuals could have impact on levels of resistance in the population.

Another study looked at the association between community prescribing and antibiotic resistance with a special focus on bias and confounding. It concluded that community antibiotic prescribing was associated with higher prevalence of colonization as well as infection with drug-resistant strains [57]. A recent systematic review and meta-analysis of 243 studies showed a positive association between resistance and antibiotic consumption in the community [58]. This meta-analysis supported the conclusion of Costelloe's study [54], that individual antibiotic prescribing was associated with antibiotic resistance.

Various antibiotic stewardship programmes have also demonstrated relationships between reduction in antibiotic use and decreasing resistance. A computer-generated intervention was designed to contain the use of fluoroquinolone antibiotics in a hospital. There was a 34% reduction in fluoroquinolone use. Correspondingly, nosocomial MRSA infection rate decreased drastically from 1.37 to 0.63 episodes per 1,000 patient-days [59]. Another study showed that cephalosporin reduction reduced the number of patients with MDR bacteria from 32% to 10.8% [60]. Though the causal relationship is still open to debate, most studies show

that there is an association between antibiotic use and subsequent development of resistance at both individual and community levels. It then becomes important to improve antibiotic prescribing at the individual level and reduce overall antibiotic consumption at the community and country levels [58].

1.4 Strategies to counter resistance

Until the discovery of antibiotics, infections were the major contributors to mortality and morbidity. Antibiotics changed this dramatically. Jawetz's opinion about antimicrobial chemotherapy in 1956, reads: "on the whole, the position of antimicrobial agents in medical therapy is highly satisfactory. The majority of bacterial infections can be cured simply, effectively, and cheaply. The mortality and morbidity from bacterial diseases have fallen so low that they are no longer among the important unsolved problems of medicine." [61]. Jawetz did not realize at that time the capacity of bacteria to adapt to new circumstances. The awareness about antibiotic resistance has grown since then, but the urgency and willingness to tackle the problem has been seen only in certain quarters.

To combat antibiotic resistance, interventional strategies need to be sustainable and comprehensive as outlined in the World Health Organization (WHO) policy package to combat resistance [62]. Though this thesis primarily focuses on human use, it is important to tackle non-human use also and a host of other factors. The sections below describe some of the strategies which have been attempted to counter various factors with varying degrees of success.

1.4.1 Strategies in veterinary and agriculture fields

Antibiotics including classes used for human diseases have been used for livestock and agriculture from the time of penicillin [63]. In 1990s, the growth-promoting antibiotic avoparcin (glycopeptides) was shown to be associated with the selection of vancomycin-resistant *Enterococcus faecium* [64]. In the European Union (EU), avoparcin was banned to preserve vancomycin's utility. This is one instance of good regulatory intervention that helped preserve a vital live saving antibiotic. Among countries, Sweden was one of the first that took a lead in banning antibiotics as growth promoters. If one needs to preserve antibiotics for humans, antibiotic use needs to be reduced in agriculture and livestock. Reduction of food intake or contact with environment may restrict entry of resistance genes into humans. In reality, this is difficult to do.

New strategies to manage infectious diseases in the animal husbandry industry have been therefore attempted such as the use of prebiotics, probiotics and enzymes [65]. Preventive measures include improving hygiene and overcrowding, and the use of vaccines [66]. Alternatives to antibiotic growth promoters, such as bacteriophages, bacteriocins and antimicrobial peptides have been tried [67].

Reducing antibiotic use in agriculture maybe more difficult. Policies may need to be changed in many countries so that medically important antibiotics are restricted. Research and development into antibiotic classes solely for agriculture with little chance of resistance gene transmission could be another way forward.

1.4.2 Strategies in industry and regulation

Most of the antibiotics used currently were discovered earlier than 1960s. The pharmaceutical industry has moved to chronic medications resulting in very few new antibiotic classes such as oxazolidinones (2000), cyclic lipopeptides (2003), and pleuromutilins (2007) [68]. New strategies have therefore been mooted recently which give a fresh political and business impetus for research and development (R&D) on new antibiotics. These include tax subsidies, financial incentives, clinical trial requirement modification, and enhancement of collaboration between industry and academia [69]. In addition, it is important to recognize that new antibiotics developed to meet public health needs may capture the market and justify the investment [70]. Recent initiatives have been launched to develop new antibiotics [71]. These initiatives may help in providing life saving antibiotics. However, regulation and application of ethical guidelines may be needed to curb the aggressive marketing of antibiotics by the pharmaceutical industry.

Countries differ in regulations for the use of antibiotics. Some countries have good laws that are implemented well. There are countries that have good laws, but poor implementation. There are also countries with limited laws in this area. As antibiotic use and resistance are global problems with global implications, it may be important to have a core set of basic principles and baseline regulations that are standard, uniform and harmonized for all countries. The policymakers in each country need to believe in these principles and ensure implementation at the grassroots level. The regulations should cover use of antibiotics in all fields such as aquaculture, livestock and agriculture as well as humans.

1.4.3 Strategies through hygiene, disinfection and diagnostics

Hospital acquired infections are often due to MDR pathogens. Endogenous flora of patients is one source of MDR pathogens. An alternate source is from health workers [72]. One of the key strategies has been to focus on hygiene habits of healthcare workers and hospital disinfection protocols. Organizations such as WHO and CDC have developed hand hygiene guidelines [73]. The evidence that hospital acquired infection (HAI) rates can reduce with hand hygiene compliance is well known [74]. Although many healthcare workers have embraced these guidelines, there are concerns about daily compliance at work [75]. Complex factors involving knowledge, attitudes and beliefs point to the difficulties of behavioural change [76].

Antibiotics are prescribed by physicians with varying expertise and laboratory support. Confirming bacterial aetiology in patients is a difficult task especially if the diagnostic support is not conducive. Having the availability of microbiological information is important

for appropriate therapeutic choice. Many physicians do not have access to this and for those who do, quality assurance is a problem. Rapid diagnostic tests (RDTs) and Point of care (POC) tests may give physicians the required confidence in avoiding antibiotics if there is no bacterial infection. This may decrease inappropriate prescribing. The decrease in time for the result as compared to standard microbiological tests will be a great advantage especially in outpatient and serious infections [77]. An example is of patients presenting with sore throat which is mainly viral in origin [78]. Group A streptococcal rapid test is an RDT that could be used in this situation since clinical features alone may not distinguish between viral and bacterial pharyngitis. The introduction of this test in areas such as paediatric emergency unit has reduced antibiotic prescriptions [79].

The use of RDT in clinical practice will be a feasible strategy in managing pathogens that are currently undetected or detected late with microbiological approaches. Further strategies in POC tests may lead to diagnostic techniques such as panel testing. These panels would hopefully be capable of testing suspected pathogens in an individual patient.

1.4.4 Strategies through education

Antibiotic use is a contributing factor for antibiotic resistance. The knowledge of the healthcare provider regarding infection and treatment is an important factor in use. For appropriate antibiotic prescribing, doctors should have a basic understanding of microbial disease aspects, epidemiology, immunological factors, and pharmacokinetics and pharmacodynamics of antibiotics. It is best that adequate knowledge and the correct approach are imparted at the student level itself so that future doctors do not imbibe wrong habits and attitude. Optimal antibiotic prescribing could be possible if students are given adequate knowledge, as well as the right approach [80].

Other healthcare providers such as pharmacists and nurses also need to be trained. Education must involve not just the approach to treatment but also the approach in managing patient demands and other ethical issues. Health care professionals must give patients clear information about antibiotics, its benefits and limitations and also about antibiotic resistance. In many countries the shortage of human resources limits consulting time with patients. Continuing education is essential due to changing resistance patterns and antibiotic choice.

The public also need awareness and education. This can be directly from providers, but other strategies are also available. Adult learning is possible, but teaching the schoolchildren will allow habits to be set properly during the formative years. In addition, children can impart this knowledge to their parents also. Basic knowledge on antibiotic use, its indications and other features have been imparted through schools programmes [81]. Public education through campaigns, posters and media with positive and key messages is another strategy that has been employed in HIC [82]. Its impact in LMIC needs evaluation.

1.4.5 Strategies through antibiotic stewardship

Antibiotic stewardship programmes have been instituted in many hospitals of HIC. The purpose has been to improve appropriate use of antibiotics, enhance clinical outcomes and safety, and most importantly to contain antibiotic resistance [83]. The effort needed for these programmes are quite intense. They need to involve a large number of personnel such as microbiologists, infectious disease specialists, pharmacists, nurses and many others with relevant experience in their respective fields. The effort taken appears to be well worth it. These programmes have the potential to contain the spread of resistance [84].

For these programmes to be successful, some vital components needed are educational, pharmaceutical and clinical interventions. Educational interventions include some of the strategies mentioned in the previous section. Pharmaceutical interventions include the development of standard treatment guidelines (STG), understanding of pharmacokinetic and pharmacodynamic properties of antibiotics, awareness of optimal dosing of antibiotics, formulary restriction and preauthorization. Formulary restriction and preauthorization has been particularly effective in reducing antibiotic use [85]. Clinical interventions include development of protocols for de-escalation, instituting audit review and feedback mechanisms, clinical decision support and antibiotic heterogeneity (cycling and mixing).

It would be useful to replicate stewardship programmes in all countries and at every level of hospital. The nature of the hospital, motives of service and other factors may influence the success in various countries. Another point is that antibiotic stewardship by its very nature focuses on hospitals. It would be good to transfer some components into the field so that stewardship in the community is also promoted.

1.5 Profile of India

1.5.1 Demographic profile

India gained independence in 1947 and had a slow growth until the 1980s. The economic liberalization in early 1990's provided a development impetus. Manufacturing growth, the rise of the middle class, and significant development in information technology (IT), have all contributed to development. Having the world's second largest population has also been a contributing factor. However, much of India's population is below the poverty line (BPL), having been left behind in its rapid growth. Health, education, economics, society, the environment and many other facets are being affected due to this. The country is still therefore categorized as belonging to Lower Middle Income Countries [86]. Based on the Indian census in 2011, almost 70% of the population live in rural areas (Table 1.1) and 30% are agricultural labourers [87,88]. The population density is 382 persons per square kilometre. 30.9% of the population lies in the age group between 0-14 years while only 7.5% are above 60 years. The birth rate is 21.8 per 1000 population, death rate is 7.1 per 1000

population and infant mortality rate is 44 per 1000 live births. Life expectancy for males is 67.3 years and for females is 69.6 years [87,88].

Table 1.1 Demographic Profile of India, Tamil Nadu state and Vellore district (Census 2011 [87,89])

		India (%)	Tamil Nadu (%)	Vellore district (%)
Population	Persons	1,210,569,573 (100)	72,147,030 (100)	3,936,331 (100)
	Rural	833,463,448 (68.8)	37,229,590 (51.6)	2,234,344 (56.8)
	Urban	377,106,125 (31.2)	34,917,440 (48.4)	1,701,987 (43.2)
	Male	623,121,843 (51.5)	36,137,975 (50.1)	1,961,688 (49.8)
	Female	587,447,730 (48.5)	36,009,055 (49.9)	1,974,643 (50.2)
Literacy	Persons	763,498,517 (73.0)	51,837,507 (80.1)	2,773,928 (79.2)
Child population	0-6 years	164,478,150 (13.6)	7,423,832 (10.3)	432,550 (11.0)
Workers ^a	Total	481,743,311 (39.8)	32,884,681 (45.6)	1,689,330 (42.9)
	Agricultural labourers	144,329,833 (30.0)	9,606,547 (29.2)	391,955 (23.2)

^a Workers include cultivators, agricultural labourers, household industry and others

India has 35 states of which Tamil Nadu is in the southern part. Its capital is Chennai. The state is known for its manufacturing industry, especially as a car manufacturing hub. It has 32 districts of which Vellore district is in the northern part of the state [89]. The district capital is Vellore city.

1.5.2 Health profile

Socioeconomic indicators such as education, poverty, employment and earning affect health in India. Though there are wide disparities between various states, the overall socioeconomic profile appears to be improving based on the latest census and other government estimates [87, 90]. According to the Planning Commission estimates using the Tendulkar Methodology with a mixed reference period, 21.9% of persons were below the poverty line (BPL) [90].

India is afflicted by a combination of communicable and non-communicable diseases. Among the communicable diseases, acute respiratory infections accounted for the maximum number of cases in 2012 (2597 per 100,000 population) [88]. Diarrhoeal diseases followed in distant second place (959 per 100,000 population). Both these infections may lead to unnecessary use of antibiotics since viruses are often responsible for symptoms suggestive of upper respiratory and diarrhoeal infections [40]. Tuberculosis, enteric fever, malaria and pneumonia are also among the top communicable diseases in India.

Among communicable diseases, pulmonary infections including tuberculosis, acute respiratory infections and pneumonias were the leading causes for mortality [88]. Other reliable estimates of mortality are from the Million Death Study which was done with a verbal autopsy system to sample premature deaths due to any cause from households across India [91]. According to this study, the mortality in the cases studied was from diarrheal diseases (8%), tuberculosis (6%), respiratory infections (6%), other infectious and parasitic diseases (4%), malaria (3%), fevers of unknown origin (2%) and HIV (0.5%).

Morbidity due to non-communicable diseases was second to communicable diseases [88]. Coronary heart disease, diabetes mellitus, blindness, mental disease and accidents featured in the top five non-communicable diseases. Reproductive and child health district surveys in 2012 revealed that only 49.8% of mothers received antenatal checkups, 47% of deliveries were in hospitals and only 54% of all children received the vaccinations required [88].

The human resources for healthcare are improving, but struggling with such a large and growing population. The population served by different types of healthcare personnel are 569 per trained nurse, 1312 per allopathic doctor, 1915 per pharmacist, 1922 per doctor practicing ayurveda, unani, siddha or homeopathy (AYUSH), and 9993 per dental surgeon [88].

1.5.3 Access to Health Care

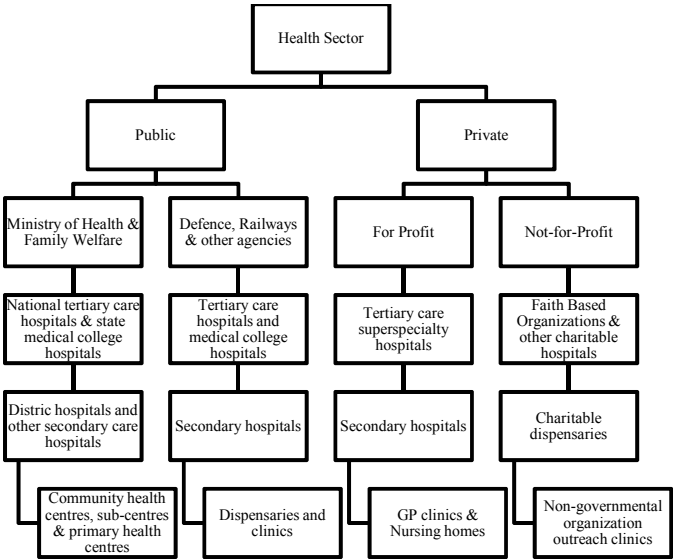


Figure 1.1 Healthcare structure (allopathic) in India

The healthcare infrastructure is also struggling to rise to the challenge of a growing India. Healthcare facilities in India are in both public and private sector (Figure 1.1). This figure represents the allopathic health system and does not include the Indian Systems of Medicine (ISM). After independence in 1947, the public sector healthcare facilities were the main hubs for accessing healthcare. Post liberalization in the 1990's, the number of private sector facilities and private teaching hospitals have dramatically increased. In 2012, there were 23,916 hospitals in the country with 622,628 beds [88]. For a population of 1.2 billion, the human resource and infrastructural status is still inadequate.

The government's norm for health infrastructure has been one Community Health Centre (CHC) for 120,000 people, one Primary Health Centre (PHC) for every 30,000 and a sub-centre (SC) for every 5000 [92]. The numbers of health facilities have fallen short and so has the infrastructure and equipment in each facility. In 2012, there was a shortage of 3044 CHCs (40%), 7954 PHCs (26%) and 4376 SCs (23%) across the country [93]. Not having adequate number of facilities affect access to healthcare and also puts stress on existing facilities. Many health professionals are used to urban life due to their family background or place of study. Standards of living could also be different between rural and urban areas. Many medical graduates therefore live and work in urban areas. This leaves a void in rural areas that is filled by practitioners from ISM or often by non-qualified practitioners.

The gap in publicly funded health is partly due to the PHCs and CHCs being financed by state governments that do not have the fiscal capacity to match the central government. These health facilities therefore often operate on minimum output. Other contributing factors include a lack of uniformity, fluctuating political commitment, minimal discipline in key routines at ground level, and a lack of integration with other support services. There have been some successes however. The National Rural Health Mission (NHRM) has helped improve the number of functional PHCs operating 24 hours a day and throughout the week [92]. The introduction of accredited social health activist (ASHA) in each village has helped. Some states have had significant improvements in health services due to these efforts [92].

Government support of public healthcare facilities allows services at little or no cost. In reality however, patients are sometimes charged for various services [94]. This may affect healthcare access and health itself. Poor infrastructure and resources, staff inadequacies and a perceived lack of quality in government health facilities often drive people to private health facilities and practitioners [95]. Some estimates suggest that 70-80% of the population are seeking healthcare from the private sector including not-for-profit healthcare facilities [95]. Affordability is often a barrier to healthcare access in for-profit private healthcare facilities.

1.5.4 Expenditures for health

Overall spending on health in India is upto 5% of the Gross Domestic Product (GDP) which has crossed 1.8 trillion US dollars [96]. In HIC the usual amount spent on healthcare is between 6-8% of GDP of which average public expenditure is thrice private. In India public

health spending accounts for less than 25% of aggregate expenditure [96]. Central government budget allocations for health are only 1.3% of total budget. The state government budgets have declined from 7.0% to 5.5.% of total budget [92, 96].

Currently India is undergoing a rapid commercialization of private medical practice often leading to higher costs. Expenses towards health are often met by out of pocket (OOP) expenditure for private healthcare. Those who are forced to seek such help inspite of affordability issues may experience financial consequences. Uninsured families could be financially crippled or forced to take loans. Services provided by private sector are largely ambulatory care. There may be variations in cost, pricing, and quality of services. Upto 75% of medical expenditure is spent on privately provided care. Households spend upto 10% of annual consumption expenses in meeting health care needs [97]. Insurance schemes are another option for bearing the burden of OOP. In 2012, 22 agencies provided health insurance, but only 14 million people were covered through these private schemes [88]. There could be significant cost escalation when backed by a third party payer system. The purchase of medicines is one key area that may be affected in such a situation.

1.5.5 The medicines situation

India has been a significant player in pharmaceutical manufacturing of generic medicines and is often called ‘the pharmacy of the world’. A wide spectrum of price exists between various generic brands, but on the whole cheaper than innovator brands. Many inexpensive generic medicines are not stocked in pharmacy shops possibly due to lower profit margins. This could be one of the reasons for some medicines being unavailable in rural areas of India. A study done in public sector facilities in several Indian states revealed that the availability of certain essential medicines ranged from zero to 30% [98]. This is a paradox considering the number of generics and formulations manufactured in India. A wide spectrum of formulations also may lead to variable quality of medicines.

India does have a National List of Essential Medicines (NLEM). The first NLEM was developed in 1996 and revised in 2003 and later in 2011. NLEM 2011 has 348 medicines and 653 formulations and dosage forms [99]. The world health survey report in 2011 reveals that access to medicines in LMIC is between 75 to 80% [100]. The Indian situation in reality is far worse as revealed in an earlier survey [98]. A lack of essential medicines in public sector pharmacies may force patients to buy from private sector pharmacy shops and contribute to OTC sales of medicines.

There are various antibiotics available in the NLEM 2011, but only 21 in total. Many of the antibiotics in the list are inexpensive, but may be ineffective due to antibiotic resistance. The ever changing pattern of resistance would necessitate a periodic review of antibiotics in the list. The essential list has been revised only twice in the last 18 years. The NLEM 2011 is only a small part of the many antibiotics and formulations including fixed dose combinations flooding the Indian market. The chance of inappropriate use remains very high due to availability of OTC antibiotics.

1.6 Rationale for studies

1.6.1 Overall rationale

Bacterial infections are still a significant cause of mortality in the world [101]. Antibiotics have been a major factor in successfully treating these infections. Access to effective antibiotics can no longer be taken for granted, due to the emergence of bacterial resistance throughout the world [102,103], including India [104,105]. The problem is complex. Very few novel antibiotics are on the horizon. There has been a major shift in the focus of research and development to non-communicable diseases. A new antibiotic if developed would not solve the problem. It would be important to reverse the ecological imbalance between susceptible and resistant bacteria. If susceptible microbiota were to be restored, there could be a chance to contain antibiotic resistance. For this there needs to be appropriate use of antibiotics.

A multiplicity of factors may influence use of antibiotics such as knowledge and expectations of patients and healthcare providers, economic factors, the health system and processes, as well as the impact of policies and regulatory environments. Many of these factors and how much they influence antibiotic use are well known in many HIC (section 1.2.2 and 1.3.2). However, in LMIC such as India, there is a significant knowledge gap in these areas and comparatively very few studies (section 1.2.3 and 1.3.3). It is important to garner evidence in the local context since challenges, ground realities influencing antibiotic use and the consequences due to resistance may be quite different to HIC. Improving knowledge in these areas could help in planning appropriate interventions. For this purpose, studies were planned to monitor the patterns of antibiotic use in community healthcare facilities by developing a surveillance system, ascertain the perceptions and factors influencing antibiotic use among stakeholders in the community, assess the cost burden and health consequences of antibiotic resistance and determine the impact of existing strategies such as policy guidelines on antibiotic use and patterns over a period of time. This thesis with its constituent papers has therefore been compiled with this overall rationale.

1.6.2 The need to determine patterns of antibiotic use through a surveillance system in the community (I)

Studies show that individual and aggregate antibiotic use are factors contributing to resistance [54,55]. The few studies done in India revealed that antibiotic containing prescriptions varied from 26% [106], to as high as 80% [40]. In 2001, WHO published the WHO Global Strategy for Containment of Antimicrobial Resistance [107]. This document urged development of strategies to optimize antibiotic use. This was also advocated by other organizations and leading experts in this area [108].

Before developing strategies however, it is important to monitor the level and patterns of antibiotic use in the community. Unfortunately, there is a paucity of such information in

LMIC such as India due to a lack of drug registries and permanent databases. Therefore the first step was to develop a monitoring system through surveillance in the local setting. This system could help identify the types of healthcare facilities driving antibiotic use and monitor changing antibiotic patterns and even be used to assess the impact of future interventions. The challenges in setting up the system could also be documented. This was important to determine feasibility for replication of such a system in other settings in LMIC.

1.6.3 The need to ascertain perceptions of stakeholders, determine factors that influence and highlight the challenges in antibiotic use (II)

There are often variations in antibiotic therapy for many infections [109]. This could be due to various factors that influence antibiotic prescribing, dispensing and consumption. In LMIC such as India, these factors are often different to HIC. Poor access to health facilities, the practice of selling OTC antibiotics, and affordability issues are realities of life in India. Perceptions and practices of healthcare providers and consumers may be different to HIC.

The 58th World Health Assembly (WHA) had urged states “to minimize the development and spread of antimicrobial resistance, in particular by promotion of the rational use of antimicrobial agents by providers and consumers” [110]. Determining the factors and reasons for inappropriate use and ascertaining the perceptions of doctors, pharmacists and the public about antibiotic use and resistance would be important to prepare feasible and appropriate interventional strategies in the local context. Such studies in non-metropolitan areas of India have been few [50,111]. A qualitative study using focus group discussions was therefore done to ascertain perceptions of these stakeholders about antibiotic use and resistance and highlight some of the ethical issues and challenges in changing practice. This could help to prepare appropriate strategies and strengthen policies to improve use of antibiotics.

1.6.4 The need to assess the impact of antibiotic resistance on cost burden and health consequences in patients (III)

The problem of antibiotic resistance has led to older generation antibiotics becoming less effective against certain bacteria [112]. Newer antibiotics are significantly costlier [113]. The burden and impact on patients need assessment especially in LMIC such as India where a significant part of the population is below the poverty line [97]. In India, a steady deterioration of services in government healthcare facilities has been experienced by patients [114, 115]. People who continue to utilize these facilities often do so due to lack of choice, affordability or access to other facilities. The other problem is that budget constraints necessitate stocks of cheap, older generation antibiotics [40]. These may not be effective due to antibiotic resistance. Many patients have therefore now turned to the private health sector [115]. This shift may have increased costs at an individual level. It is estimated that medicines account for 72% of out-of-pocket health expenses in families [97].

This situation is potentially catastrophic for families if a member develops a serious bacterial infection such as sepsis. If causative bacteria are resistant to initial empiric antibiotics chosen

by physicians, there could be a valuable loss of time and grave health consequences. The change to a more effective antibiotic and treatment of complications is likely to increase expenditure. Assessing the incremental burden of cost and health consequences due to antibiotic resistance may provide a key message to all stakeholders including policy makers and public. This is especially so in LMIC where economic constraints for the individual and the government are key emotive issues.

1.6.5 The need to evaluate the impact of existing strategies such as antibiotic policy guidelines on containing antibiotic use (IV)

One of the main strategies to improve rational use in hospitals has been antibiotic stewardship and the development of policy guidelines [116]. Another purpose of antibiotic stewardship is to contain antibiotic use. Containment is important as increased environmental pressure contributes to bacterial resistance [117]. Many studies evaluating stewardship have looked at how policy interventions have improved antibiotic treatment and most have been from HIC [118]. Evidence has been limited in LMIC where treatment practices, economics and regulatory environment are vastly different to HIC. Very few studies have evaluated whether policy guidelines contain antibiotic use. This paper helps in bridging this gap.

Computerized data on medicine use is not available in most hospitals in India. However, it has been available since 2002 at Christian Medical College, Vellore, in the institution where the study (IV) was conducted. This facilitated a detailed analysis of patterns of antibiotic use and trends over a ten year period. During this time, there were various time segments in which different modes of guideline development and implementation took place. This paper therefore used the opportunity to compare different modes of guideline implementation and dissemination and see which was effective in containment. The findings would be useful for policy makers and hospitals managements in LMIC to decide about the usefulness of antibiotic policy guidelines in hospitals for containing antibiotic use.

2. AIM AND OBJECTIVES

Aim

To improve knowledge on the patterns and perceptions of antibiotic use in the community, the consequences of resistance in individual patients, and the impact of policy guidelines on hospital antibiotic use, so as to identify potential interventional targets, generate key messages and subsequently develop appropriate strategies towards improving use and containing resistance.

Objectives

1. To determine patterns of antibiotic use through a surveillance system in the community and challenges faced while developing the system. (I)
2. To ascertain the perceptions of stakeholders about antibiotic use and resistance and highlight the challenges to changing practice. (II)
3. To assess the impact of antibiotic resistance on cost burden and health consequences in patients with suspected sepsis. (III)
4. To determine patterns of inpatient antibiotic use over a decade and evaluate the impact of policy guidelines and modes of dissemination on antibiotic use. (IV)

3. METHODS

3.1 A summary of methods

Table 3.1 A summary of methods

Paper	Focus	Design	Setting	Sample	Participants	Analysis
I	Level of antibiotic use, patterns & challenges of surveillance	Repeated cross sectional	Vellore city and KV Kuppam rural block	52788 patients with 21600 antibiotic encounters over two years	Patients attending hospitals, GP clinics, pharmacy shops	Descriptive statistics and chi-square test of proportions
II	Perceptions and factors influencing antibiotic use and challenges	Focus group discussion (FGD)	Vellore city and KV Kuppam rural block	Eight FGDs within one year	FGDs with doctors, pharmacists and public	Content analysis with predefined themes
III	Cost burden and health consequences of antibiotic resistance	Observational study presenting costs and health consequences	Not-for-profit tertiary care teaching hospital	220 inpatients over one year	Patients with suspected sepsis & bacteremia on empirical antibiotic	Descriptive statistics, Mann Whitney U test & Fisher's exact test
IV	Impact of policy guidelines and implementation modes on antibiotic use	Segmented time series	Not-for-profit tertiary care teaching hospital	122 monthly data points over 10 years	Antibiotic use in inpatients as DDD per 100 bed days	Regression analysis models adapted for segmented time series

3.2 Study Design

To fulfil the aim and objectives, four studies were conducted and the constituent papers included as part of the thesis. The study designs for these four papers consisted of both quantitative and qualitative methods.

Paper I – Repeated cross sectional design over two years to determine patterns of antibiotic use.

Repeated data collection was done monthly at different types of healthcare facilities; hospitals, private general practitioner (GP) clinics and pharmacy shops. This ensured regular surveillance of antibiotic use and aided monitoring of factors such as seasonality.

Paper II – Eight focus group discussions to ascertain perceptions of stakeholders.

Focus group discussion (FGD) was the selected methodology for ascertaining perceptions of stakeholders on antibiotic use, resistance and factors influencing use. The FGD method

helped elicit various views, attitudes and practices among stakeholders. It also helped to generate discussion on various points as well as counter-points, and encouraged group dynamism and interactions. It brought to the fore reasons for inappropriate antibiotic use, provided rich information and group perspectives through interaction between individuals.

Paper III - An observational study over one year presenting costs and health consequences in patients with a preliminary diagnosis of suspected sepsis and confirmed bacteremia.

Those receiving empirical antibiotics were categorized into two groups: (i) the 'resistant' group - all patients in whom the susceptibility report documented resistance of causative bacteria to the empirical antibiotic and (ii) the 'susceptible' group - all patients in whom the report documented susceptibility of causative bacteria to the empirical antibiotic. Costs and health consequences were compared between the two groups.

Paper IV - A segmented time series design determining antibiotic use over ten years and evaluating impact of antibiotic policy guidelines.

This time series compared trends in antibiotic use in five adjacent time segments based on modes of guideline dissemination: Segment 1 - Baseline prior to antibiotic guidelines development; Segment 2 - During preparation of guidelines and booklet dissemination; Segment 3 - Dormant period with no guidelines dissemination; Segment 4 - Booklet dissemination of revised guidelines; Segment 5 - Booklet dissemination of revised guidelines with intranet access.

3.3 Study setting

The study area was Vellore district, in the state of Tamil Nadu, south India (Figure 3.1). This district has an area of 6075 sq.km and a population of 3.9 million people according to the last census in 2011 [89]. The overall literacy in the district is 79.2%. The male and female populations are approximately similar in number. Of the population, 56.8% live in rural areas [89]. Agriculture is the primary occupation. The main religion is Hinduism. Vellore district is known for its agriculture and leather industry [119].

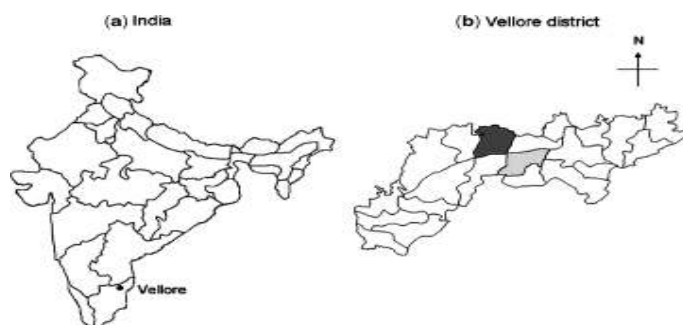


Figure 3.1 Maps showing (a) Location of Vellore in Tamil Nadu state of India (b) Vellore district highlighting KV Kuppam block (rural area–dark grey) and Vellore city (urban area–light grey)

The setting of Paper I and II was in Vellore city (urban area) and KV Kuppam Block (rural area) of Vellore district. Vellore municipal corporation is the district headquarters and had a population of 185,895 in 2011 [89]. Vellore lies between the IT majors (Chennai & Bangalore) and major pilgrim centres (Tirupathi and Thiruvannamalai). It has a medical college, a district hospital, private hospitals and numerous private GP clinics and pharmacy shops. Kilvayattanankuppam commonly referred to as KV Kuppam is a rural block in the district. The number of healthcare facilities is fewer than in the urban area. The block has one not-for-profit private hospital, PHCs, private GP clinics and pharmacy shops. Patients in both rural and urban areas access healthcare mainly through allopathic facilities. ISM such as Ayurveda, Unani, Siddha and Homeopathy (AYUSH) and naturopathy are practiced through individual practitioners rather than facilities.

There are various differences in the demographic profile between Vellore district, Tamil Nadu state and India as a country (Table 1.1). Though each district in India has differing profiles, Vellore district has many demographic indices similar to both state and the country. This district was chosen for the studies due to the proximity to the Christian Medical College, Vellore, the willingness of district authorities to give permission for monitoring use and the support received by the local associations of healthcare providers. This was important in setting up the surveillance (monitoring) system and ascertaining perceptions from various stakeholders.

The setting of Paper III and IV was in Christian Medical College Hospital, Vellore. This is a not-for-profit tertiary care teaching hospital. This hospital caters to patients from various socioeconomic strata and many parts of the country. It has 2140 beds and more than 6000 outpatients per day [120]. It has outreach facilities for primary care, secondary care clinical departments and also super (higher) speciality departments. In relation to medicines and antibiotic use, the hospital has a Drugs and Therapeutics Committee (DTC). New antibiotics are introduced into the pharmacy through the formulary subcommittee after review and discussion. The hospital has an Antibiotic Policy Committee responsible for guidelines formation. The Hospital Infection Control Committee (HICC) consisting of members from various departments is responsible for hygiene, prevention of infection and control.

There are three departments directly related to antibiotic use within the hospital. The microbiology department operates the quality assessment program in India for microbiological laboratories under the umbrella of Indian Association of Medical Microbiologists. The clinical pharmacology unit conducts pharmacoepidemiological studies, therapeutic drug monitoring and is a national pharmacovigilance centre. The unit conducts content testing of antibiotics and other medicines using high performance liquid chromatography (HPLC). The pharmacy department has a purchase and stores division, numerous dispensing outlets, the drug information and education division and also a manufacturing unit. It has over 200 staff and deals with over 8000 prescriptions per day.

This hospital was selected for these studies since the hospital had a diverse group of patients from all over India with various socioeconomic backgrounds and a wide spectrum of infections. The hospital also had a computer system with online investigations, accounting and pharmacy database that allowed for comprehensive data collection in Paper III and IV.

3.4 Sampling, participants and data collection

3.4.1 Paper I

In India, the public has access to antibiotics through healthcare facilities such as hospitals, GP clinics and pharmacy shops (chemist or community pharmacy). Determining the level and type of antibiotics used in each facility type would help in developing appropriate interventions for each. All three types of facility were included in the surveillance. Facilities in rural and urban areas were identified through lists available from medical and pharmacy associations and selected based on feasibility.

A total of 30 healthcare facilities were selected from both rural and urban areas. These facilities included 10 hospitals, 10 private GP clinics and 10 pharmacy shops. In each facility, 30 antibiotic encounters (prescriptions or dispensations containing antibiotic) were observed for one day per month [121]. This amounted to a total of 900 antibiotic encounters per month. This was observed on a monthly basis for 2 years. In total, 21,600 prescriptions antibiotic encounters were included from 52,788 patients interviewed. Antibiotic encounters in pharmacy shops were with and without prescriptions (over the counter).

Surveillance data on antibiotic use was collected through a structured interview process with the patient. The questionnaire had been pretested and checked for face validity (Appendix 1). The prescriptions and dispensations of patients exiting each facility were reviewed until 30 antibiotic encounters for that month were noted. This was the numerator for each facility. The total number of patients interviewed in each facility to reach 30 antibiotic encounters was the denominator. Data collected from each facility included: (i) The number of encounters with a specific antibiotic converted into a percentage (percent encounter) (ii) The type of antibiotics used which was then grouped (iii) Dose and quantity of the antibiotic prescribed or dispensed. This enabled the calculation of number of Defined Daily Dose (DDD) for specific antibiotics and groups [122]. Data on indications for antibiotic use was studied by observing the prescription for any written symptoms and if absent, by asking the patient about their reason for visiting the health facility. These symptoms were then systemically grouped.

An alternate methodology was also undertaken by collecting data on bulk antibiotic use to determine feasibility of such a method. This was done by reviewing sale records of specific antibiotics in facilities. Such records were however available only in pharmacy shops and rural hospitals. Data was therefore collected from only these facilities for this methodology. The number of patients visiting the facility during the period was the denominator.

3.4.2 Paper II

The main stakeholders involved in human antibiotic use are healthcare providers such as doctors and pharmacists and the consumers, the public (Table 3.2). A total of eight focus groups were formed for FGD and chosen to represent these stakeholders. These included two groups each (urban and rural) from among doctors, pharmacists, higher socioeconomic public (HSEP) and lower socioeconomic public (LSEP). HSEP consisted of teachers and housewives. LSEP consisted of relatives of patients attending hospitals catering to the poor. There were six to eight participants in each group.

Table 3.2 Socio-demographic description of focus groups

Group	Area	Group name	Qualification*/Occupation	Participant numbers	Age range
1	Urban	Doctors	4 MBBS, 2 MD	6	33-63
2	Rural	Doctors	6 MBBS	6	29-54
3	Urban	Pharmacists	3 B.Pharm, 3 D.Pharm	6	23-55
4	Rural	Pharmacists	6 D.Pharm	6	21-66
5	Urban	Public – HSEP	Teachers, Housewives	6	30-53
6	Rural	Public – HSEP	Teachers, Housewives	8	35-60
7	Urban	Public– LSEP	Relatives of patients	8	19-65
8	Rural	Public– LSEP	Relatives of patients	7	24-66

*MBBS: Bachelor of Medicine, Bachelor of Surgery, MD: Doctor of Medicine, B.Pharm: Bachelor of Pharmacy, DPharm: Diploma in Pharmacy

Participant recruitment was through purposive sampling to obtain a diversity of opinion. Healthcare providers were doctors working as private practice GPs or in hospitals, and pharmacists owning or working in pharmacy shops. Invitations for an open meeting were given to these stakeholders through their respective associations. From those that came, participants were chosen based on interest and willingness to commit time for the FGD. Consumers were public and represented the society from different strata. Invitations were given through community forums, schools and health facility notice boards to attend a public meeting. Those who expressed interest and could commit time for the FGD were included.

As part of the preparation for the study, the moderators underwent training in moderating FGDs from a social scientist. They moderated pilot groups for standardisation of technique. Before starting the FGD, each group was requested to choose either Tamil (the local language) or English as the medium for discussion. The FGDs were arranged at convenient times and venues accessible to participants. The study purpose, process and confidentiality issues were then discussed. Written informed consent was obtained. After introductions, the moderator reiterated the objectives of the discussion.

A semi-structured discussion guide with predefined themes (Appendix 2) was used to ascertain the required information, maintain uniformity and data comparison, as well as for continuity of discussion. The overall themes explored were: (i) awareness and knowledge of infections and antibiotics; (ii) knowledge and understanding of resistance; (iii) patterns, and practices in antibiotic use, and treatment preferences between healthcare providers; (iv) reasons, pressures and incentives for antibiotic use; (v) strategies to encourage appropriate antibiotic use. Each group continued discussions for up to two hours until all themes were covered and no new information generated. A sociogram was maintained. Notes and audio recordings of each discussion aided in collecting data comprehensively, increased transparency of process, and allowed for an audit trail.

3.4.3 Paper III

Participants were included into the study based on the following criteria: (i) adult patients who were admitted into medical wards with a preliminary diagnosis of suspected sepsis from January 1st 2010 to December 31st 2010 (ii) patients who were prescribed an empiric antibiotic and (iii) the availability of a blood culture report that identified causative bacteria with antibiotic susceptibility profile.

As part of the normal diagnostic work up, patients admitted with a preliminary diagnosis of suspected sepsis had 5 to 8 ml of blood collected aseptically. Bed side inoculation was done in Bact-Alert bottles. Aerobic bottles containing Trypticase soy broth was used. Bact-Alert bottles were loaded in the BacT/ALERT®3D system until a positive signal was detected and characterized further using the Vitek®2 system [123]. Samples were ruled negative if no signal was detected after five days of incubation. Bacterial resistance was assessed by antibiotic susceptibility testing performed on isolates by the Kirby-Bauer disk diffusion method at the microbiology department. This department operates the quality assessment programme for microbiological laboratories in India under the umbrella of Indian Association of Medical Microbiologists. The susceptibility breakpoints for each antibiotic were defined according to Clinical Laboratory Standards Institute (CLSI) guidelines [124].

In patients who fulfilled the inclusion criteria, the two main parameters assessed were overall costs and health consequences attributable to the impact of antibiotic resistance. Various categories of cost incurred by the patients were documented. These included costs of antibiotic, the total cost of pharmacy items (medicines and consumable items), laboratory costs (investigations) and ward costs (all other costs incurred while in the ward). Overall costs included pharmacy (including antibiotics), ward and investigation costs. Hospital electronic accounting records and the pharmacy database were used to calculate these costs. The main health consequences assessed were length of stay in hospital, admission to intensive care unit (ICU), complications and mortality. This information was collected from patient charts and electronic records. Data access and availability was good due to the comprehensive data filing in patient charts, electronic records and the pharmacy database.

Triangulation through these sources was done to maintain accuracy. The data collected was documented in a proforma (Appendix 3).

3.4.4 Paper IV

This study had no direct participation of patients. Aggregate data of antibiotic use by patients was determined on a monthly basis over a period of 10 years and segmented based on the time periods of antibiotic policy guideline implementation. There were three major phases with guideline development and dissemination during the study period between July 2002 and August 2012: one in 2005 (A), the second in 2009 (B), and the third in 2011 (C). Based on this, the study period was divided into:

Segment 1: July 2002 to February 2004 - This period was before preparation began for the 2005 policy guidelines.

Segment 2: March 2004 to December 2005 – During this period, the Antibiotic Policy Committee with active participation of clinical departments and pharmacy and microbiology departments initiated preparation for a comprehensive antibiotic policy in March 2004. The preparation phase included weekly meetings and active discussion of proposed guidelines. Guidelines were finalized and distributed from January 2005 as a small booklet. Active dissemination continued till December 2005. Segment 2 was therefore taken as a period which included both preparation and dissemination.

Segment 3: January 2006 to December 2008 – This was a dormant period with no active guideline dissemination.

Segment 4: January 2009 to December 2010 – The guidelines were revised and published as a booklet in January 2009 and disseminated till end of 2010. Unlike the guidelines in Segment 2, there was no sustained preparatory phase with all clinical departments.

Segment 5: January 2011 to August 2012 - In January 2011, revised guidelines were published and distributed as a booklet. It was also made available through the intranet computer network accessible in every ward, outpatient room and office of the hospital.

Data collection was by calculating the antibiotic use in inpatients using the hospital pharmacy computer system. Consumption was calculated as DDD (Defined Daily Dose) normalized for 100 bed days [122]. DDD per 100 bed days is an important indicator of inpatient antibiotic use and an objective measure of assessing changes in use due to interventions. Calculation of number of DDDs was by documenting the dose and quantity of the antibiotic purchased. Inpatients do not receive antibiotics from sources outside the hospital. Antibiotic use within the hospital was captured comprehensively. Bed days were calculated using the monthly hospitals admission data and the bed occupancy rate from the medical records department.

Each antibiotic was calculated separately and coded as per DDD/ATC (Anatomical, Therapeutic and Chemical) Index [122]. Individual antibiotics were then categorized and DDD estimated for nine antibiotic groups: J01A – Tetracyclines, J01B – Amphenicols, J01C - Beta-lactam antibacterials, J01D - Other Beta-lactam antibacterials, J01E – Sulfonamides and trimethoprim, J01F Macrolides and Lincosamides, J01G - Aminoglycosides, J01M –

Quinolones and J01X - Other antibacterials. With this categorization, it was possible to determine antibiotic group trends and patterns. The overall antibiotic DDD per 100 bed days for the entire antibiotic spectrum (J01) was also calculated monthly. This formed the main basis of the time series from July 2002 to August 2012.

3.5 Analysis

3.5.1 Paper I

Locally developed FoxPro data entry software was used for capturing antibiotic use data. Double entry was performed to check and minimize errors. Data was exported into SPSS (Statistical Package for the Social Sciences) for descriptive statistics and chi-square test of proportions.

The DDD of a specific antibiotic encountered for 100 patients was calculated as below:

1. Total dose of the specific antibiotic in grams per patient = Unit strength x number of units per day x number of days.
2. Number of DDD of specific antibiotic per patient = Total dose of specific antibiotic (in grams) per patient divided by the DDD for that specific antibiotic.
3. DDD of the specific antibiotic encountered per 100 patients per period = Sum of DDDs per patient per period x 100 divided by total number of patient encounters during the period.

Antibiotic use was expressed as percentage of encounters with specific antibiotic, and converted to DDD of specific antibiotic use per 100 patients. The above method from individual facilities in both urban and rural areas was the primary mode of analysis. Comparison of antibiotic encounters between facility types and between urban and rural areas was analysed for significance. Comparison of p values was also done among facility types for specific antibiotic group encounters. For the alternate method of bulk use, analysis was by calculating DDD of a specific antibiotic per 100 patients attending each facility per month.

3.5.2 Paper II

For the FGD, transcription and translation of each was done verbatim. FGDs conducted in the vernacular language Tamil were translated into English. Reliability was confirmed through back-translation. A validated method involving content analysis with predefined themes was used in this study [125]. Transcripts were colour coded to ensure that relevant data were ascribed to specific stakeholder groups. Tone and nonverbal communication was assessed through field notes.

Study group members reviewed transcripts individually, met to compare segments of transcribed text, and reached consensus about their interpretation. Meaning units were coded, categorized and grouped under the relevant predefined themes and then verified. Patterns, regularities and trends relating to the predefined themes were noted. Data was summarised with salient features and quotations under each predefined theme. Quotations were chosen

which best represented the opinions of stakeholders. The challenges and ethical issues raised within the themes were highlighted. Follow-up meetings with participants were also held to present and discuss the main findings. These meetings helped in prioritizing some of the feasible interventional strategies suggested by stakeholders.

3.5.3 Paper III

Patients with a preliminary diagnosis of suspected sepsis and receiving empirical antibiotics were categorized into two groups: (i) the ‘resistant’ group - patients in whom the susceptibility report documented resistance of causative bacteria to the empirical antibiotic and (ii) the ‘susceptible’ group - patients in whom the report documented susceptibility of causative bacteria to the empirical antibiotic. Empiric choices in the guidelines for suspected infections were based on antibiograms in the hospital. Empiric antibiotics were retained or changed based on the susceptibility report and clinical response. The antibiotics used were documented and coded based on ATC (Anatomical, Therapeutic and Chemical) Index [124].

The overall and categorized costs incurred by patients were compared between the two groups. Costs were compared using Mann-Whitney U test and presented as median costs and their respective IQR (inter-quartile range). The median differences between the groups and their 95% Bootstrap confidence interval (CI) were calculated using R version 2.15.1 [126]. Besides costs, the other comparative analysis conducted was on health consequences in the two groups. Length of stay was analysed using Mann Whitney U test. The proportion of patients having complications, patients with ICU admissions and mortality in each group were compared using Fisher’s exact test. $p < 0.05$ was considered significant.

3.5.4 Paper IV

A segmented time series design was used to assess the impact of guidelines on antibiotic use across different segments. Each of the five segments in our study had a minimum of 20 monthly time points. Monthly DDD values were plotted using a standard time series plot and calendar plots to better depict monthly and seasonal variation in overall and specific antibiotic groups. The average values of DDD per hundred bed days were estimated for each segment and each antibiotic group. For exploratory purposes, we estimated the linear trend for each segment (Model 1) and examined the effect of seasonality on the segment trend for each outcome of interest (Model 2).

The models were formulated as:

$$Y_i = \beta_0 + \beta_1 time_i, \text{ (Model 1)}$$

$$Y_i = \beta_0 + \beta_1 time_i + \beta_2 \sin\left(\frac{2\pi time_i}{12}\right) + \beta_3 \cos\left(\frac{2\pi time_i}{12}\right), \text{ (Model 2)}$$

where Y_i – are monthly values for overall DDD or DDD values in specific i -segments. This exploratory analysis was performed to characterize the trend (β_1) for each segment individually and correct for a potential seasonality effect (β_2 and β_3) [127,128]. Exploratory analysis was conducted for each antibiotic group. For Models 1 and 2, the results were presented as values with corresponding confidence intervals (CI) for start and end dates for each segment.

In order to adjust for interruption implied by Models 1 and 2, a pair-wise segmented regression adjusted for seasonality was performed that facilitated identification of the changes in two consecutive segments [129].

$$Y_i = \beta_0 + \beta_1 time + \beta_2 \sin\left(\frac{2\pi time}{12}\right) + \beta_3 \cos\left(\frac{2\pi time}{12}\right) + \beta_4 time_i + \beta_5 time_{i+1} \quad (\text{Model 3})$$

where Y_i – are monthly values for overall DDD or DDD values for antibiotic groups in two adjacent i - and $i+1$ -segments; $time_i$ – is a month sequence (in reverse order) for i -segment; $time_{i+1}$ – is a month sequence for $i+1$ -segment; $time$ – is a month sequence for two adjacent segments to adjust for seasonality. The difference between regression parameters β_4 and β_5 indicates changes in segment-specific trends. By assuming the expected normality of point estimates obtained via the Ordinary Least Squares (OLS) fitting procedure, the uncertainty measures for these regression parameters allow to directly compare trends in individual segments and to interpret the significance of standard z-test to infer the changes in adjacent segments [129]. For example, if one segment demonstrates no significant change while another segment shows a significant change, a difference between two segments can be inferred by proxy. Furthermore, non-overlapping 95% CI for β_4 and β_5 indicate high likelihood for a significant difference between two segments. For Model 3, the results were presented as predicted values for the start of the i -segment, start and end of the $i+1$ -segment, and p -values indicating the standard z-test for a linear trend against $H_0: \beta = 0$, for i -segment and $i+1$ -segments, respectively. For all models, the quality of fit was assessed by the R^2 values. Model diagnostics showed no significant autocorrelation of residuals.

3.6 Ethical permission

The Institutional Review Board of the Christian Medical College, Vellore approved all the four studies constituting the four papers for this thesis with the following reference numbers: IRB EC 9/02 (Paper I), IRB EC 8/04 (Paper II), IRB (EC)-ER-5-10-03-2010 (Paper III), and IRB (EC)-ER-4-10-03-2010 (Paper IV).

4. MAIN FINDINGS

In this section, the main findings of the four constituent papers have been integrated under various themes to illustrate the evidence base. In each theme title, the papers have been referred to by their Roman numerals.

4.1 Understanding of infections, antibiotics and resistance in community (II)

The FGD with various stakeholders revealed the following:

Doctors were well versed with infections and antibiotics, but wanted updates through continuing education. Doctors were somewhat knowledgeable about resistance, its consequences and its relationship to antibiotic misuse.

"Every time we give new antibiotics, the organisms mould accordingly." Rural doctor

Pharmacists had some knowledge of antibiotics, but limited awareness of course duration.

"Amoxicillin, 6 tablets is to be taken [for full course]." Rural pharmacist

Urban pharmacists had some knowledge of resistance. Rural pharmacists had little concern.

"Patient's resistance power towards diseases will decrease. After sometime, no antibiotic will work." Urban pharmacist

"Not come across such patients; these are things for doctors" Rural pharmacist

Awareness was generally poor among LSEP about infections, their causes, and treatment.

They were able to physically identify some antibiotics but could not mention any names.

"If we take Metacin [paracetamol], fever comes down. But this tablet [antibiotic displayed] is better than Metacin." Rural LSEP

HSEP had basic knowledge about infections, could name some antibiotics, and felt that infections needed antibiotics.

"My understanding of antibiotic is that it stops bacteria growing in body...I think amoxicillin is for throat infection." Urban HSEP

Overall the public had limited awareness of antibiotic resistance.

"Sometimes, resistance happens to us. We go back to doctor with same problem. Then doctor changes medicines." Rural LSEP

Urban HSEP had some understanding of antibiotic resistance compared with rural HSEP.

"They don't complete the course. From my little knowledge, this creates resistance." Urban HSEP

Overall, the public appeared to have limited knowledge and understanding of infections, antibiotics and resistance. Among the healthcare providers, doctors had greater knowledge, but both doctors and pharmacists expressed need for updates in these areas.

4.2 Antibiotic use in community healthcare facilities (I)

4.2.1 Antibiotic use in rural and urban healthcare facilities (I)

Over a period of two years (Phase A and B), a total of 52,788 patients were observed through surveillance and 21,600 antibiotic encounters (40.9%) were obtained (Table 4.1).

Table 4.1 Antibiotic encounters in health provider facilities

	Phase A		Phase B		Phase A and B	
	Patients observed	Antibiotic encounters (%)	Patients observed	Antibiotic encounters (%)	Patients observed	Antibiotic encounters (%)
<i>Urban</i>						
Pharmacy shops	4554	1800 (39.5)	5000	1800 (36.0)	9554	3600 (37.7) ^a
Hospitals	4195	1800 (42.9)	4665	1800 (38.6)	8860	3600 (40.6) ^a
GP clinics	4634	1800 (38.8)	3971	1800 (45.3)	8605	3600 (41.8) ^a
Urban Total	13383	5400 (40.3)	13636	5400 (39.6)	27019	10800(40.0) ^b
<i>Rural</i>						
Pharmacy shops	5091	1800 (35.4)	5314	1800 (33.9)	10405	3600 (34.6) ^a
Hospitals	3935	1800 (45.7)	3937	1800 (45.7)	7872	3600 (45.7) ^a
GP clinics	3721	1800 (48.4)	3771	1800 (47.7)	7492	3600 (48.1) ^a
Rural Total	12747	5400 (42.4)	13,022	5400 (41.4)	25,769	10,800 (41.9) ^b
Urban and Rural facilities	26130	10800 (41.3)	26658	10800 (40.5)	52788	21600 (40.9)

^aComparison of antibiotic encounters among facility types: $p < 0.001$

^bComparison of antibiotic encounters among urban and rural areas: $p < 0.01$

Specific antibiotic use was expressed as percent encounters containing that specific antibiotic in a particular facility type within the urban or rural areas.

Table 4.2 Antibiotic group encounters in rural and urban facility types

Antibiotic Groups	Urban Area			Rural Area		
	Pharmacy Shops ^a	Hospitals ^a	GP Clinics ^a	Pharmacy Shops ^a	Hospitals ^a	GP Clinics ^a
	% (n=3600)	% (n=3600)	% (n=3600)	% (n=3600)	% (n=3600)	% (n=3600)
Aminoglycosides	0.8	3.6	7.3	1.4	1.3	0.7
Amphenicols	2.6	1.7	0.5	1.4	3.3	1.5
BLR penicillins	4.9	5.8	6.1	11.3	0.2	13.9
BLS penicillins	0.3	16.3	3.9	0.5	8.5	0.4
Cephalosporins	21.8	25.2	10.9	7.6	0.1	8.1
ES penicillins	26.9	16.6	12.9	27.3	15.7	30.0
Fluoroquinolones	27.2	20.0	43.6	34.3	5.9	33.7
Macrolides	7.4	2.9	6.1	4.1	1.1	4.9
SXT	3.8	2.1	1.4	3.5	56.9	2.9
Tetracyclines	4.3	5.8	7.3	8.6	7.0	3.9
All groups	100	100	100	100	100	100

BLR - Beta lactamase resistant, BLS - Beta lactamase sensitive, ES – Extended spectrum,
SXT – Sulfamethoxazole and trimethoprim (co-trimoxazole)

^a Comparison of specific antibiotic group encounters among facility types: $p < 0.01$

Variations in antibiotic encounters were present between facility types and geographical areas (Table 4.2). Antibiotic encounters with fluoroquinolones were generally high especially in private GP facilities. Extended spectrum penicillins (ESP) were highly used in pharmacy shops and rural GP facilities. Urban hospitals and pharmacy shops used more cephalosporins. Rural hospitals used mainly co-trimoxazole.

4.2.2 Antibiotic use for specific symptoms (I)

The symptom groups for which antibiotics were given and the main antibiotics used are mentioned in Table 4.3. Fever and upper respiratory infections are the main symptoms for use of antibiotics for which ciprofloxacin and amoxicillin respectively, were the most commonly used.

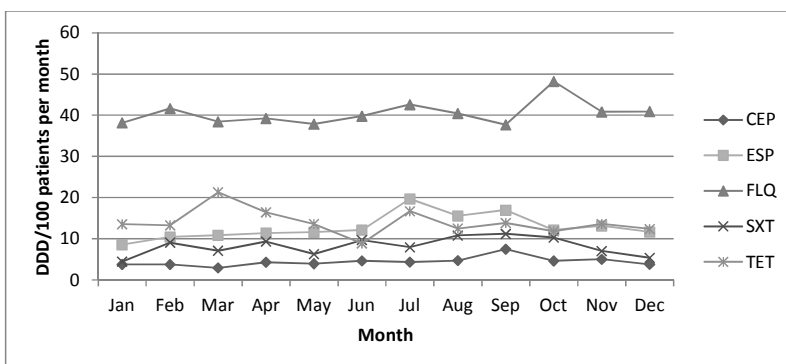
Table 4.3 Top three antibiotics for patients' symptoms

Symptom group	Patient encounters (n=10800)	Most common antibiotic	Antibiotic encounters (%)	Second most common antibiotic	Antibiotic encounters (%)	Third most common antibiotic	Antibiotic encounters (%)
Bronchial	292	AMX	97 (33)	SXT	63 (22)	DOX	40 (14)
Cardiovascular	435	PEN	404 (93)	AMP	7 (2)	SXT	6 (2)
Dental	353	AMX	150 (42)	TET	42 (12)	DOX	35 (10)
Ear and Eye	243	AMX	52 (21)	SXT	38 (16)	CIP	32 (13)
Fever	2292	CIP	737 (32)	AMX	364 (16)	SXT	184 (8)
Fever and Cough	332	AMX	96 (29)	CIP	70 (21)	SXT	35 (11)
Gastrointestinal	705	NOR	300 (43)	SXT	143 (20)	CIP	93 (13)
Gynaecological	185	DOX	114 (62)	CIP	15 (8)	SXT	15 (8)
Lower Respiratory	1241	AMX	424 (34)	OFX	114 (9)	CIP	93 (7)
Musculoskeletal	187	CIP	43 (23)	OFX	36 (19)	AMX	28 (15)
Surgery related	340	CTX	85 (25)	SXT	73 (21)	CIP	53 (16)
Skin Soft tissue	568	AMX	80 (14)	CIP	76 (13)	SXT	62 (11)
Urinary	516	NOR	195 (38)	CIP	73 (14)	DOX	58 (11)
Upper Respiratory	2132	AMX	652 (31)	SXT	161 (8)	RXM	158 (7)
Wound	979	LEX	176 (18)	AMX	134 (14)	AMP	126 (13)

AMX – amoxicillin, AMP – ampicillin, CIP – ciprofloxacin, CTX – cefotaxime, DOX – doxycycline, LEX – cephalexin, NOR – norfloxacin, OFX – ofloxacin, PEN – penicillin, RXM – roxithromycin, SXT – sulfamethoxazole and trimethoprim

4.2.3 Surveillance using antibiotic encounters and sales records (I)

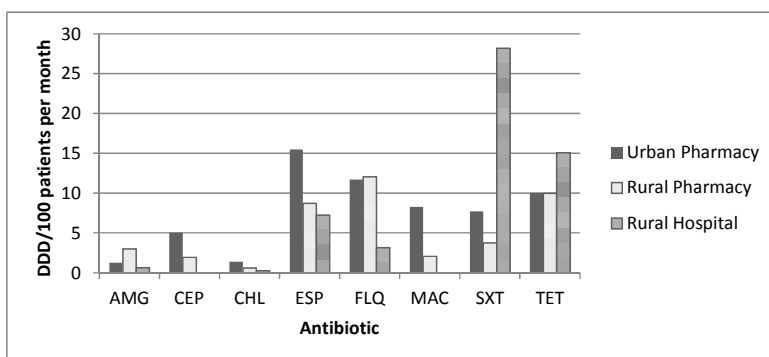
An example of a graph generated through surveillance is shown in Figure 4.1. These graphs represent monthly antibiotic encounters over a period and can use either percent encounters or be converted to DDD per 100 patients as is shown in this figure. This kind of graph can be generated for specific facility types in rural or urban areas and for any period.



CEP – Cephalosporins, ESP – Extended Spectrum Penicillins, FLQ – Fluoroquinolones, TET – Tetracyclines, SXT – Sulfamethoxazole and trimethoprim

Figure 4.1 Antibiotic Encounters in all facilities as DDD/100 patients per month

Among all healthcare facilities, fluoroquinolones were the most commonly used antibiotic group. There is an overall consistency in levels of most antibiotics through the year. An alternative methodology to measure bulk antibiotic use was to collect the sales data for specific antibiotics from pharmacy shops and rural hospitals (Figure 4.2).



AMG – Aminoglycosides, CEP – Cephalosporins, CHL – Chloramphenicol, ESP – Extended Spectrum Penicillins, FLQ – Fluoroquinolones, MAC – Macrolides, SXT – Sulfamethoxazole and trimethoprim, TET – Tetracyclines

Figure 4.2 Antibiotic sales in facilities measured as DDD/100 patients per month

Co-trimoxazole and tetracyclines use was very high in rural hospitals. Urban pharmacy shops used a lot of extended spectrum penicillins (ESP) whereas rural pharmacy shops used fluoroquinolones the most.

4.3 Antibiotic use in a teaching hospital facility (IV)

4.3.1 Antibiotic use across the decade (IV)

Table 4.4 summarizes antibiotic use in the teaching hospital in specific segments across the decade. Individual antibiotic groups were arranged in descending order based on average monthly DDD per 100 bed days at the beginning of the study period (Segment 1).

Table 4.4 Average monthly DDD/100 bed days for individual segments with standard deviation (SD) for overall and individual antibiotic groups

Antibiotic groups*	DDD/100 bed days (SD)				
Segments	1	2	3	4	5
J01	65.83 (6.67)	72.17 (3.15)	82.68 (4.63)	87.88 (4.37)	84.02 (3.90)
J01C	19.12 (2.33)	20.45 (1.47)	25.51 (2.63)	26.40 (1.68)	28.56 (1.79)
J01D	18.16 (2.12)	20.48 (1.19)	21.91 (1.72)	22.95 (0.91)	19.51 (2.18)
J01M	11.26 (1.58)	11.23 (1.03)	12.12 (1.11)	12.71 (1.00)	12.03 (1.13)
J01G	7.98 (0.75)	8.12 (0.61)	7.85 (0.64)	7.40 (0.48)	5.88 (0.46)
J01X	3.91 (0.44)	5.27 (0.75)	6.72 (0.75)	7.75 (0.72)	7.78 (0.70)
J01E	1.90 (0.27)	2.12 (0.28)	2.18 (0.56)	2.74 (0.49)	2.84 (0.45)
J01A	1.69 (0.43)	1.87 (0.46)	3.14 (1.00)	3.71 (1.24)	3.08 (1.13)
J01F	0.96 (0.41)	1.71 (0.44)	2.46 (0.66)	3.60 (0.80)	4.10 (0.66)
J01B	0.84 (0.17)	0.91(0.18)	0.78 (0.10)	0.62 (0.08)	0.54 (0.06)

*J01 - Overall, J01C - Beta-Lactam Antibacterials, J01D - Other Beta-Lactam Antibacterials, J01M - Quinolones, J01G-Aminoglycosides, J01X - Other Antibacterials, J01E - Sulfonamides and Trimethoprim, J01A - Tetracyclines, J01F - Macrolides and Lincosamides, J01B - Amphenicols

4.3.2 Patterns of use among antibiotic groups (IV)

To facilitate visualization of trends and seasonal patterns across antibiotic groups, a compact version of monthly DDD per 100 bed days for individual antibiotic groups is shown using calendar plots (Figure 4.3). Trends, seasonality, and spikes in individual antibiotic groups across the five segments indicate the importance of seasonal variations in analysis.

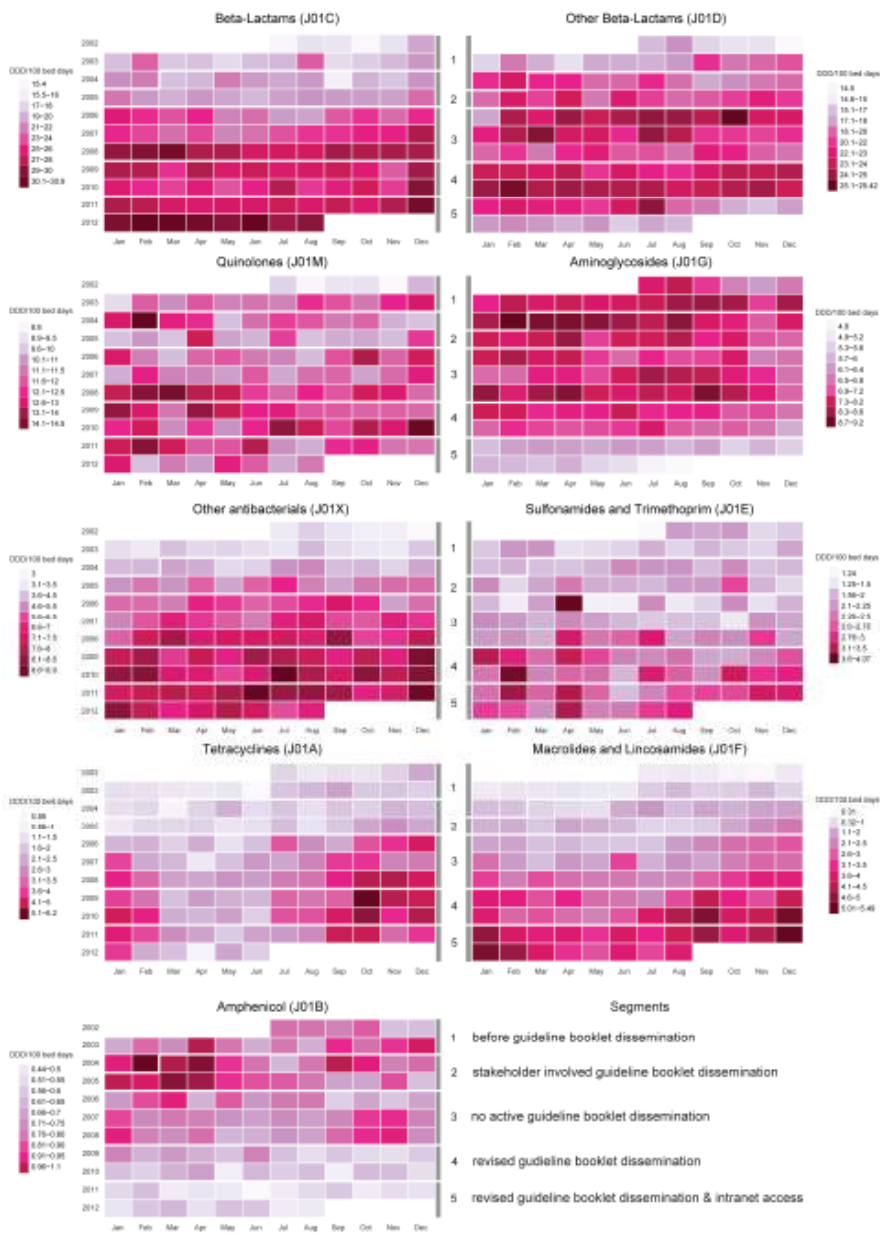


Figure 4.3 Calendar plot showing seasonal patterns and trends in use for nine antibiotic groups.

4.4 Practices and factors in antibiotic use in the community (II)

4.4.1 Antibiotic use practices (II)

Doctors made various observations in FGD about the way antibiotics were used. They were of the opinion that common inexpensive antibiotics were prescribed in government hospitals, and costlier newer antibiotics in private practice. The full course was not prescribed since patients could not afford it or would stop the antibiotic after getting relief. Many patients visited quacks (unqualified practitioners) and pharmacy shops directly for antibiotics.

"Nobody completes the course. If you write 20, they take five." Urban doctor

"Quacks come on bicycles in mornings and afternoons, see patients for five rupees and give medicines." Rural doctor

Pharmacists initially denied dispensing antibiotics without prescription. On further probing, they admitted that they dispense medicines which they think are appropriate if patients approach. Amoxicillin, co-trimoxazole and combination antibiotics were dispensed for colds and symptoms suggestive of viral infection. Often inadequate doses were dispensed.

"We are giving antibiotics to more than 75% of patients. Even for common cold, we prescribe two tablets of Septran [co-trimoxazole]" Rural pharmacist

"We give antibiotics for only one day...If doctors write 250mg of erythromycin for children, we ask parents to buy half the dose" Urban pharmacist

LSEP generally visited allopathic doctors only if they felt that the condition was serious enough to warrant a visit. Long distances in rural areas and non-availability of doctors during the nights, and doctor fees and investigation charges in urban areas were mentioned as reasons for self-medication and visiting pharmacy shops. Antibiotics were given for common symptoms such as cold, fever and body ache and stopped once symptoms subsided. Patients said doctors did not explain about the medicines to them.

"When they prescribe costly tablets, say for 100 rupees, we buy only half." – 'Rural LSEP'

"If I have money I go to hospital. If not, I get medicine from pharmacy shop. If I get better, I stop and keep for future use" – 'Urban LSEP'

HSEP visited doctors for illnesses requiring diagnosis, but visited pharmacy shops for immediate needs, to save time and get antibiotics for a faster recovery.

"If I know about the illness and feel I can manage, I go to pharmacy shop. If I have a doubt, I go to doctor." Rural HSEP

"To see a doctor, we take leave, stand in queue. Finally doctor will prescribe, possibly the same drug. So we go to pharmacy shop." Urban HSEP

Public groups mentioned visiting ISM practitioners. Adverse effects with allopathic medicines, previous positive experiences and perceived advantages of ISM encouraged use.

"For dysentery we have separate native treatment. Allopathic medicines have side effects." Rural HSEP

"Wherever they get chicken pox, they go to Alanthur [native medicine centre]. If they go there, they recover." Rural LSEP

4.4.2 Factors promoting antibiotic use (II)

In the FGDs, doctors initially blamed unqualified practitioners and pharmacy shops for high antibiotic use claiming that antibiotics were given without proper diagnosis and prescription. *"Quacks provide 40% [percentage of antibiotics used], medical shops 30%, doctors 30%"* Rural doctor

Doctors admitted to high antibiotic prescribing on detailed probing, attributing this to: (i) inadequate diagnostic facilities; (ii) lack of antibiotic guidelines; (iii) difficulty in observing patient progress; (iv) poor intensive care facilities in rural areas; (v) patient demand for quick relief, and (vi) perceived patient expectation.

"If we ask for investigations on first day, patient never turns up again. We immediately give antibiotics and watch for two days. Nobody bothers about diagnosis, only symptom relief." Urban, doctor

"We are compelled to give drugs. Sometimes they dictate to us! They have pre-conceived ideas." Urban doctor

Doctors also admitted that pharmaceutical companies put pressure by introducing newer brands. Decisions and antibiotic choice were influenced by incentives.

"Even reputed companies offer compliments. If you prescribe more, they offer air conditioned car or free tickets." "Of late, we are forced to try new antibiotics" Urban doctor

Pharmacists initially blamed doctors for high antibiotic prescriptions due to industry pressure, but admitted to receiving various incentives from companies to achieve sale targets.

"Usually company representatives approach doctors. Certain companies give us extra strips of tablets as gifts." Rural pharmacist

On detailed probing pharmacists admitted to selling antibiotics, stating that this was necessary because of: (i) patient demand; (ii) a belief that cure is through antibiotics; (iii) competition from other pharmacy shops, and (iv) antibiotic sales promoting business.

"We cannot avoid antibiotics at time of necessity." Rural pharmacist

"Nobody likes to lose business. We give whatever they ask. Competition, location of shops, license issues...everything has become commercialized" Urban pharmacist

4.5 Strategy in the hospital (IV)

The main existing interventional strategy in the teaching hospital facility for improving antibiotic use has been antibiotic policy guidelines. The following sections illustrate their impact on containing antibiotic use over a decade.

4.5.1 Antibiotic use trends with various modes of antibiotic guideline dissemination (IV)

The time series of monthly values for overall antibiotic use as DDD per 100 bed days are shown in Figure 4.4. Vertical lines separate individual segments and delineate general trends.

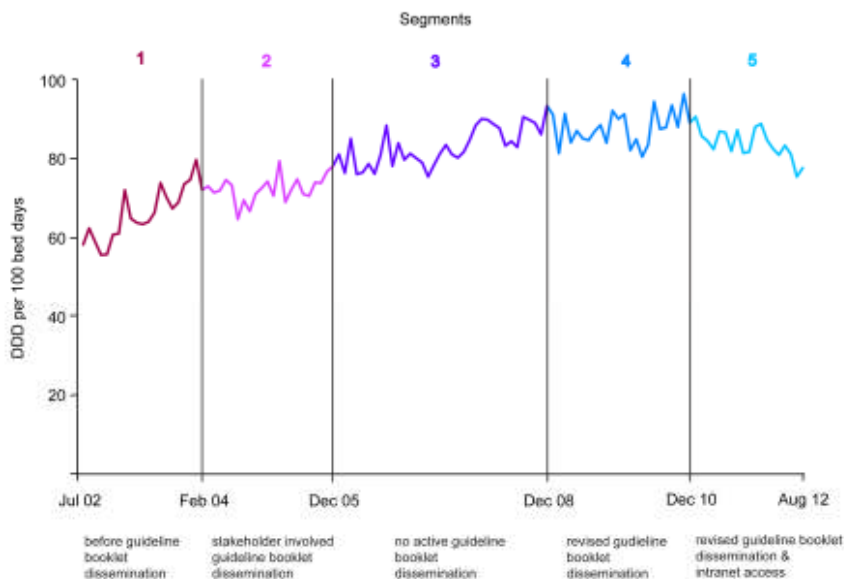


Figure 4.4 Time series of monthly overall antibiotic use over ten years with segments demarcated by vertical lines.

Antibiotic use showed a rising trend in Segments 1, 2 and 3, stabilized during Segment 4 and declined in Segment 5.

4.5.2 Segments comparison with and without seasonality (IV)

To demonstrate the trend for overall antibiotic use with and without adjusting for seasonality, the results of the two regression models are presented in Table 4.5. The results include values for monthly rate (slope with standard error, *p*-values and quality of fit) and predicted values of DDD per 100 bed days for the start of the segment. The seasonality adjustment for overall antibiotic use was critical for Segments 1, 2, and 4. Model 2 improved quality of fit and better predicted DDD/100 bed days due to adjustment for seasonality.

In Model 2, a significant increase of approximately 20 DDD per 100 bed days was observed in the first segment at a rate of 0.95 (SE=0.18). Segment 3 also showed a significant rise in trend at a rate of 0.31 (*p* < 0.001). Only Segment 5 showed a significant decrease in use at a rate of 0.37 (SE=0.11) with a reduction of over 10 DDD per 100 bed days.

Table 4.5 Exploratory analysis of trends in individual segments without (Model 1) and with (Model 2) adjustment for seasonality for overall antibiotic use (DDD/100 bed days).

Segment	Model 1		Model 2	
	Slope (SE), <i>p</i> -value*; R ² **	Predicted values with CI for start/end dates	Slope (SE), <i>p</i> -value*; R ² **	Predicted values with CI for start/end dates
1	0.97(0.16), <0.001; 0.63	56.68 (52.98 - 60.38) 75.16 (71.46 - 78.86)	0.95 (0.18), <0.001; 0.65	56.88 (52.67 - 61.08) 75.99 (71.79 - 80.20)
2	0.13(0.10), 0.211; 0.11	70.79 (68.37 - 73.21) 73.53 (71.11 - 75.95)	0.21 (0.08), 0.025; 0.78	71.80 (69.57 - 74.03) 73.57 (71.34 - 75.81)
3	0.30 (0.07), <0.001; 0.49	77.44 (74.71 - 80.17) 87.90 (85.16 - 90.63)	0.31(0.06), <0.001; 0.49	79.04 (76.21 - 81.86) 89.60 (86.78 - 92.42)
4	0.10 (0.13), 0.418; 0.03	86.67 (83.35 - 89.98) 89.06 (85.74 - 92.37)	0.05 (0.10), 0.644; 0.61	89.33 (86.24 - 92.42) 91.13 (88.04 - 94.22)
5	-0.46 (0.14), 0.004; 0.78	88.33 (85.26 - 91.40) 79.70 (76.60 - 82.74)	-0.37 (0.11), 0.004; 0.59	89.68 (87.09 - 92.26) 78.86 (76.28 - 81.45)

* *p*-values below 0.05 are italicized

** R²- values that increase in the seasonally adjusted Model 2 are shown in bold

4.5.3 The impact of antibiotic guidelines comparing adjacent segments (IV)

To compare the trends in adjacent segments, a pair-wise segmented regression adjusted for seasonal variation (Model 3) is presented in Table 4.6.

Table 4.6 Pair-wise segmented analysis as the estimated rate of change in monthly DDD /100 bed days for adjacent segments and predicted values for the start of the *i*-segment, start and end of the *i*+1-segment.

S*	Slopes (SE) for two adjacent <i>i</i> - segment and <i>i</i> +1-segments	Predicted values for the start of the <i>i</i> -segment, start and end of the <i>i</i> +1- segment	R ²	<i>p</i> value **
1	0.708 (0.120)	57.88, 74.23, 73.01	0.61	<0.001
2	0.010 (0.107)			0.926
2	0.265 (0.088)	71.32, 77.35, 89.39	0.73	0.004
3	0.362 (0.050)			<0.001
3	0.273 (0.046)	79.70, 89.58, 90.63	0.59	<0.001
4	0.036 (0.075)			0.629
4	0.067 (0.072)	89.15, 90.35, 79.31	0.55	0.357
5	-0.401(0.089)			<0.001

*S - Segment

***p*-values reflect the results of standard z-test for a linear trend for *i*-segment and *i*+1 segments, respectively;

p-values below 0.05 are italicized.

The modeling results confirm the observed significant increase in monthly DDD per 100 bed days in Segments 1 and 3 and a significant decline in Segment 5 resulting in the level decreasing to 79 DDD per 100 bed days similar to the beginning of Segment 3. There were no significant trends in Segments 2 and 4 ($p = 0.926$ and 0.629 respectively).

4.6 Strategies in the community (III, II)

4.6.1 A key message – the price to pay (III)

The following sections describe a key message through the findings of Paper III that assess cost burden and health consequences attributable to antibiotic resistance. Over one year, 33897 blood cultures were received by the microbiology laboratory from the entire hospital, of which 2264 had positive blood cultures with confirmed bacteremia. Among this, 409 blood cultures were from medical wards. Cultures that were duplicate, without susceptibility profile, and belonging to patients not having a preliminary diagnosis of suspected sepsis were eliminated. Finally, 220 patients who had a preliminary diagnosis of suspected sepsis, with confirmed bacteremia, and administration of empiric antibiotic, were included into the study. These patients were divided into two groups, ‘resistant’ and ‘susceptible’ based on susceptibility of causative bacteria to the empiric antibiotics administered (Table 4.7).

Table 4.7 Description of demographics, co-morbidities and bacteria cultured

n=220	Resistant group n=133	Susceptible group n=87	p value (sig if < 0.05)*
Mean age with SD	52 years (± 17.3)	53 years (± 17.2)	0.675
Gender			
Male	86 (65%)	58 (67%)	0.774
Female	47 (35%)	29 (33%)	
Co-morbidities			
Patients with co-morbidities	112 (84%)	76 (87%)	0.563
Patients with diabetes alone as co-morbidity	42 (32%)	33 (38%)	0.383
Mean Number of co-morbidities per patient with SD	2.1 (± 1.3)	2.3 (± 1.5)	0.234
Bacteria cultured			
Gram Negative Bacteria (GNB)	102 (77%)	66 (76%)	1.000
<i>Escherichia coli</i>	53	37	
<i>Klebsiella pneumoniae</i>	4	7	
NFGNB*	36	15	
<i>Enterobacter</i>	1	3	
Other GNB	5	4	
Mixed GNB	3	0	
Gram Positive Bacteria (GPB)	24 (18%)	18 (21%)	0.726
<i>Staphylococcus aureus</i>	17	8	
<i>Enterococcus</i>	4	4	
<i>Streptococcus pneumoniae</i>	3	4	
Group A beta haemolytic streptococcus	0	2	
Mixed GPB/GNB	7 (5%)	3 (3%)	

* Non Fermenting Gram Negative Bacteria including *Acinetobacter baumannii* and *Pseudomonas aeruginosa*.

+ Categorical variables were compared between groups by fisher’s exact test and continuous variables were compared using student’s t test

The ‘resistant’ and ‘susceptible’ groups were comparable and there was no significant difference in the main baseline parameters. The main co-morbidity was diabetes. Other co-morbidities were kidney disease, liver disease and other systems involvement.

4.6.2 The burden of cost and health consequences (III)

There was a significant difference in cost (Table 4.8) between ‘resistant’ and ‘susceptible’ groups in overall cost, antibiotic cost and total pharmacy cost. The overall median cost difference was 41,993 Rupees (700 US Dollars) [130].

Table 4.8 Comparison of direct costs between Resistant (R) and Susceptible (S) Groups (n = 220)

Cost in Rupees (Rs)/USD ^a	Resistant group n=133 Median cost Rs/USD (IQR ^b)	Susceptible group n=87 Median cost Rs/USD (IQR ^b)	R& S difference Median cost Rs/USD (Bootstrap 95% CI)	p value
Overall Cost	88686/1478 (36265 - 164850)	47380/790 (25847 - 8608)	41993/700 (16667 – 63848)	0.001
Antibiotic Cost	16734/279 (6722 - 27853)	8255/138 (3799 - 13560)	8315/139 (4953- 10859)	<0.001
Total Pharmacy Cost	39482/658 (20205 - 64431)	16309/272 (9359 - 36891)	21492/358 (8950-29001)	<0.001
Laboratory Investigation Cost	12235/204 (4452 - 22309)	8436/141 (4035 - 16278)	3710/62 (136-7033)	0.055
Ward cost	12425/207 (7543 - 20925)	10300/172 (7419 - 16090)	2060/34 (-286 – 4045)	0.108

^aOne US Dollar (USD) = 60 Rupees [130] ^bIQR – Inter Quartile Range

Intensive care admissions, complications and mortality were significantly higher in the ‘resistant’ group as compared to the ‘susceptible’ group (Table 4.9). The median length of hospital stay was also higher.

Table 4.9 Comparison of Health Consequences between Resistant (R) and Susceptible (S) Groups

Patients n=220	Resistant group n=133	Susceptible group n=87	Difference between R and S groups	p value
MLS ^a in days (IQR ^b)	14 (8.5 – 22.5)	11 (8 - 17)	3	0.027
ICU Admissions	59 (44%)	18 (21%)	23%	<0.001
Complications	75 (56%)	32 (37%)	19%	0.006
Mortality	16 (12%)	2 (2%)	10%	0.011

^aMLS – Median Length of Stay ^bIQR – Inter Quartile Range

Overall, the significant difference in both costs and health consequences provide a key message that there is a price to pay for antibiotic resistance.

4.6.3 Suggested strategies for appropriate antibiotic use (II)

Doctors in FGD suggested improving the awareness of public about infections to reduce antibiotic demand. Other strategies suggested were: (i) improved laboratory facilities to differentiate viral and bacterial infections; (ii) development of guidelines and continuing education; (iii) development of rational use module in the medical curriculum; and (iv) law enforcement for antibiotic sales by prescription and ban on unqualified health practitioners.

“For this, you have to enforce law, avoid free availability, check legal status of pharmacy shop and eradicate quacks!” Urban doctor

The pharmacists were more reticent, saying that doctors were primarily responsible for antibiotic use. They however suggested the following: (i) public awareness programmes through media; (ii) continuing education and inclusion of modules on rational use in their curriculum; and (iii) restriction of higher antibiotics through prescriptions.

“If doctors have intention, this problem can be reduced. Pharmacists are only like the arrow which has to be shot from the bow.” Urban pharmacist

“We have to bring change at every level. This can be telecast on TV or newspaper and awareness created.” Urban pharmacist

The public were concerned that awareness of resistance was poor in comparison to issues such as ‘AIDS’. They shared the view that the primary strategy should focus on improving awareness through mass education possibly starting at school level. Children could be receptive to new ideas and could influence parents. Other strategies suggested were: (i) more explanation by doctors about health and disease; (ii) better communication about antibiotics; (iii) improved awareness through self help, women’s groups and media; and (iv) implementation of laws for appropriate use of antibiotics.

“Awareness should start from schools. Teachers can spread awareness.” “Doctors should explain to patients the problems related with antibiotic use. Even uneducated will understand if explained properly.” Urban HSEP

5. DISCUSSION

In this section, the four constituent papers have been integrated under various themes for discussion. In each theme title, the papers have been referred to by their Roman numerals.

5.1 Understanding of infections, antibiotics and resistance (II)

Among doctors, understanding of antibiotic resistance was reasonable, but willingness to act on knowledge was low. This problem is not isolated to doctors in India. In other countries too, physicians often recognize antibiotic resistance as a national problem, but concerns about patient care and managing infections with antibiotics were higher priority [131]. Among pharmacists, there appeared to be less knowledge about resistance than doctors. For those who had some understanding, other factors such as the volume of antibiotic sales were priority. For both groups of providers, the need for continuing education was greatly felt.

Awareness among the public about infections, antibiotics and their indications was limited. This lack of knowledge and understanding prevents the public from taking ownership of their own health. This situation of limited awareness is present among other LMIC and some HIC too. A study from HIC revealed that people believe antibiotics cure colds, and have poor knowledge of treatment of bacterial and viral illnesses [132]. A study in a LMIC revealed a strong culture of self medication and some knowledge about antibiotics [133]. These findings suggest the urgent need for creating greater public awareness about health, illness, hygiene and antibiotic indications. Healthcare providers should adequately communicate with their patients, thereby improving treatment compliance and health outcomes. The public had poor understanding regarding antibiotic resistance. Media coverage of resistance and its implications is negligible in comparison to issues such as AIDS and smoking. There is an urgent need to improve awareness through various strategies at the community level.

5.2 Antibiotic use in community healthcare facilities (I)

5.2.1 Level and patterns of antibiotic use (I)

The burden of communicable disease in India according to the National Commission on Macroeconomics and Health is approximately 50% as compared to other disease categories [134]. Within the communicable diseases category, 10-15% of infections have bacterial aetiology and therefore truly need antibiotics. Comparing this to the 41% of patients (Table 4.1) who received antibiotic in our study (I), points to a significant overuse of antibiotics. Besides the potential implications for antibiotic resistance, policy makers should take note of the economic implications for governments, hospitals and individuals.

In India, the level of antibiotic use has differed based on region, 48% in Kerala to 82% in Uttar Pradesh [40]. Differences in setting, education of stakeholders, a spectrum of infections, and access to healthcare could be reasons for the wide range. This strengthens the argument for need for monitoring through surveillance systems to prioritize interventional strategies in regions with high use. Studies showing rural and urban comparisons are lacking and surveillance in various healthcare facilities is also important. In our study, urban facilities had similar antibiotic use, while in rural, GP clinics contributed to higher antibiotic use.

The other information generated by surveillance is antibiotic group patterns (Table 4.2). The high use of co-trimoxazole in rural hospitals is noteworthy. This is the main antibiotic stocked in budget constrained government PHCs due to its low cost. In our study, fluoroquinolone use was high except in rural hospitals. GPs used it most. Urban private hospitals and pharmacy shops contributed towards cephalosporins. Future interventional strategies could focus on the appropriate use of such antibiotic groups. Very few studies in India have identified patterns. In a study across three states, penicillins and co-trimoxazole were the most used antibiotics. 40% of private sector prescriptions were quinolones and cephalosporins [40]. Another study in central India also highlighted the use of ciprofloxacin and cephalosporins [135]. These studies have the disadvantage of being at specific time points but conform to our findings.

5.2.2 Symptoms prompting antibiotic use (I)

Determining the main symptoms that prompt doctors to prescribe certain antibiotics could point towards the disease conditions that would benefit from standard treatment guidelines. Fever and respiratory symptoms were the most common indications for antibiotic use (Table 4.3). This compares well with other studies in which acute respiratory infections were widely prescribed antibiotics such as amoxicillin [40,136]. Upper respiratory infections are commonly viral and therefore the need to avoid antibiotics could be a focus through educational interventions and guidelines. Ciprofloxacin was the favoured antibiotic for fever. This again is a questionable choice and raises the stakes for resistance. The high use of doxycycline for gynaecological conditions and use of cefotaxime as the most common antibiotic for surgical infections are further points to consider. Interventional strategies should focus on these indications with inappropriate antibiotic use, raise healthcare provider and patient awareness, and generate appropriate standard treatment guidelines (STG).

STGs have been developed in some states in India [137]. Its accessibility and distribution to facilities and personnel may not be optimal. In the STG of one state [137], the section on infectious diseases dwells on HIV, tuberculosis, vector borne diseases, protozoal diseases and others, but mentions common bacterial conditions in a sparse manner. In the section on fever, antibiotics are not mentioned. Fever was a common indication for antibiotic use as revealed in our surveillance. Antibiotic therapy is briefly mentioned in sections on specific system based disease conditions, but does not adequately deal with issues such as the high level of fluoroquinolone use. Future interventional strategies should consider these points while updating the guidelines, so as to improve local relevance and compliance.

5.2.3 Surveillance through antibiotic encounters in patients (I)

There are extensive surveillance systems to monitor antibiotic resistance and use in HIC [138, 139]. In India, surveillance networks for antibiotic resistance had been established for some years [140]. The efforts to develop antibiotic use monitoring through surveillance however has been limited. This could be due to the diversity of health systems in states, a lack of registers and pharmacy networks. Setting up surveillance in India has been challenging, but essential, in order to identify patterns and target healthcare providers.

The type of graphs generated with our surveillance system is represented in Figure 4.1. It was possible to generate different time periods, type of facility (hospitals, GPs, pharmacy shops) and setting (rural, urban). Surveillance graphs have the additional advantage that seasonal variation could be monitored. The example in this figure shows that fluoroquinolones were the most used throughout the year, with the highest in October. Monsoon rains in October could explain higher antibiotic use due to a possible increase in infections.

The information generated with percent antibiotic encounters can be converted to DDD per 100 patients (Figure 4.1). Calculation using DDD makes the data comparable with other studies in countries where prescription data and registries are available [139]. These studies often use number of inhabitants as denominator. In contrast, our study uses the number of patients exit interviewed to attain 30 antibiotic prescriptions as the denominator. In India, government facilities provide health coverage to specific geographical areas, but easy access to private health facilities encourages patients to visit different facilities and areas.

5.2.4 Surveillance through antibiotic sales records (I)

The primary method of surveillance in our study was the percent antibiotic encounter method. Daily visits to facilities and long periods spent in monitoring encounters made the method cumbersome and time consuming. An alternate method for surveillance by determining bulk use through antibiotic sales records in facilities was therefore attempted (Figure 4.2). Data was collected only from facilities with sales records such as pharmacy shops and rural hospitals that stocked and dispensed antibiotics directly to patients. Sales records were occasionally incomplete and therefore had to be supplemented with purchase records.

There were similar findings to the percent antibiotic encounter data such as high use of extended spectrum penicillins and fluoroquinolones in pharmacy shops and co-trimoxazole use in rural hospitals. The consumption of tetracycline group of antibiotics in rural hospitals was higher than in the percent encounter method. The high use of co-trimoxazole was prominent. Co-trimoxazole is rarely mentioned in the state STG inspite of its high use [137]. This is again an example of the advantage of surveillance in improving guidelines and making them more practical and relevant.

5.2.5 Challenges in surveillance (I)

There were various challenges while developing the surveillance system for monitoring antibiotic use. This included challenges in sampling, data collection and analysis. Some of these challenges may be unique to India, but many are probably relevant to other LMIC.

One major challenge was the process for sampling. In many HIC, health provider facilities cover fixed populations or inhabitants specific to geographical areas. In India, this may be so with governmental hospitals, but estimates suggest up to 80% of population access private facilities [141]. Patients cross geographical areas and access private facilities such as hospitals, GP clinics and pharmacy shops where antibiotics are prescribed or dispensed. Individual health facilities covering specific geographical populations as sampling units thus become difficult. A comprehensive and updated list of health provider facilities was difficult to obtain. After persistent attempts, lists were obtained from local bodies such as the pharmacy association or medical association. Facilities were then selected based on feasibility as many were reluctant to allow monitoring. Physicians were hesitant to give permission fearing an audit of their prescriptions. Another apprehension was whether it would delay patient consultations. Permission from pharmacy shops was even more difficult. Owners feared that data collectors standing nearby may inhibit potential customers. Fear of information being shared with regulatory authorities was also a likely reason.

Data collection and analysis also had challenges. Standardization of data collection technique involved substantial training time for data collectors. Some facilities such as government hospitals had huge numbers of patients. Estimating an accurate denominator was sometimes difficult. Illegible prescriptions contributed to the problem and so did unrecognizable brands. In pharmacy shops, observing all dispensations was difficult at peak times or if OTC. Bulk sales data collection in pharmacy shops was challenging since they did not have systematic filing systems or computers but only manual registers that were not always written or filed properly. Though quality and reliability of bulk sales data was an issue, less time and manpower was a significant advantage. In contrast, the percent encounter method needed two data collectors spending long periods in facilities, interaction with patients and close observation of prescriptions and dispensations. In countries with meticulous pharmacy records, bulk sales data would be more reliable and feasible for surveillance. However in LMIC, bulk sales data methodology would be difficult unless reliability is improved.

Determining the denominator for DDD calculation was difficult in both methods. Since patients had free access to any facility, the calculation of the population denominator became contentious. The denominator used was number of patients encountered rather than a fixed population in that area. Another departure was the use of DDD per 100 patients rather than 1000 inhabitants. This was necessary for better illustration and interpretation of graphs. Denominator calculation in the bulk sales method was even more challenging since it was difficult to estimate accurate numbers visiting a facility. The results of both methods were therefore difficult to compare with studies in HIC [139].

There were other difficulties. Recruiting data collectors and their training could be another difficult issue especially if surveillance needs to be developed in remote parts of the country. The other need was to have a software system for data entry and analysis. Since this was not readily available, it had to be developed and customized for our study. A common software system must be developed for widening surveillance keeping in mind feasibility issues. Costs and budgetary limits may be a significant issue if such surveillance systems are to be replicated or sustained in different parts of India and LMIC. The major cost in our study was salary for data collectors and data entry operators. If policy makers decide to establish a network of surveillance sites, a central data entry and analysis system could decrease the individual costs in sites.

5.3 Antibiotic use in a teaching hospital facility (IV)

5.3.1 Patterns of use among antibiotic groups across the decade (IV)

The patterns of use among individual antibiotic groups varied throughout the decade (Figure 4.3). The main highlights are discussed below:

Beta-lactam antibacterials (J01C): A rising trend was observed across all segments unlike other groups. This could be due to the increasing use of antibiotics such as piperacillin-tazobactam for MDR hospital acquired infections, especially in critical care settings [142]. Another contributing factor could have been the substitution of third and fourth generation cephalosporins with piperacillin-tazobactam due to the problem of ESBL.

Other Beta-lactam antibacterials (J01D): The initial segments showed a rising trend that could be explained by increased use due to MDR for other antibiotics. Cephalosporins and carbapenems were among the targeted antibiotic groups for containment in the policy introduced in Segment 5. This could explain the observed decline in Segment 5.

Quinolones (J01M): During the year, higher use was noticed in the colder months of January and February. Quinolones are commonly prescribed empirically for respiratory infections including community acquired pneumonia and exacerbations of chronic obstructive pulmonary disease (COPD) [143]. This may account for high quinolone use noted in earlier segments. Quinolone use was targeted for containment in Segment 5 and may explain the decline seen.

Aminoglycosides (J01G): A rapid decline in use was evident after Segment 3. Availability of newer antibiotics with gram negative spectrum and less adverse effects may have contributed.

Other anti-bacterials (J01X): There has been a rising trend in the use of glycopeptides and nitroimidazoles. Nitroimidazoles to cover anaerobic infections and use of glycopeptides to tackle rising incidence of MRSA may have been contributing factors [144].

Sulfonamides and trimethoprim (J01E): Rising trend in Segments 4 and 5 could be explained by additional indications like HIV associated opportunistic infections and the rise of multi-drug resistant malaria [145, 146].

Tetracyclines (J01A): Seasonal fluctuation was observed in the calendar plot. Scrub typhus is endemic in the study area and more seen in the rainy season and cooler months (October to February) [147]. Other rickettsial infections (undifferentiated acute febrile illness) that respond well to doxycycline may have also contributed.

Amphenicols (J01B): A rapid decline in use was evident. This decline was predictable after the emergence of widespread resistance especially among salmonella species [148]. The availability of safer and more efficacious alternatives may have contributed to this decline.

Macrolides and lincosamides (J01F): An overall rising trend with seasonal fluctuations was apparent. Macrolides, especially azithromycin, are frequently prescribed for respiratory infections that flare up during the cold months of the year [143]. The other reason for its popularity could be the convenient dosage schedule of once a day for three days.

Among the few studies in India, a study in intensive care showed that third generation cephalosporins and meropenem were frequently used [149]. Another study using the focus of infection approach reported high rates of fluoroquinolone and third generation cephalosporin prescriptions [135]. Our findings are similar to these patterns but with the added advantage of observing antibiotic use over a decade.

5.4 Practices, factors and challenges in antibiotic use in community (II)

5.4.1 Antibiotic use practices (II)

Though infections are widely prevalent in India, bacterial infections that need antibiotics form only a small proportion [150]. Healthcare providers in the FGD expressed the view that a significant section of the community was receiving antibiotics. Pharmacists said that they give antibiotics for upto 75% of patients who approached them. This should raise an alarm. The NLEM contains only 21 antibiotics and two combinations, co-trimoxazole and co-amoxiclav [99]. The Indian market has more than 10,000 formulations, many of which are irrational combinations [151]. This could lead to a wide use of antibiotics with varying brands, quality and price. There may be pressure to sell higher margin brands. Affordability is also a concern. Buying an antibiotic course for 100 rupees is approximately two days average daily earnings for a casual worker in India [152]. This factor may prevent patients from purchasing a complete course.

Purchasing antibiotics directly from pharmacy shops without prescription is another worrying practice. The main reason expressed through FGD by the public was to avoid spending extra

time and money for consulting doctors. Though excesses such as OTC antibiotic use have to be regulated, issues about access to doctors especially in rural areas and affordability of consultation fees and investigations should also be considered. Patient demand and lack of guidelines and updates were expressed by doctors and pharmacists. The knowledge of pharmacists about duration and dosing specifications is to a large extent limited. There is a need for continuing education. In India, many pharmacy shops are attended by untrained personnel and have only one qualified pharmacist. This could be a major factor leading to errors in dispensing of medicines. Guidelines and education will help prescribing and dispensing practice conform to scientific evidence and ethical norms.

Another issue of concern raised by doctors was that of unqualified practitioners (quacks) and ISM practitioners prescribing antibiotics to patients. Though regulation does exist that only qualified practitioners are allowed to prescribe medicines, stricter implementation of law is needed to encourage safe treatment and appropriate use. There is no doubt that quacks should not prescribe antibiotics. The debate by various nodal agencies continues about whether ISM practitioners should prescribe allopathic medicines [153]. Some have supported ISM practitioners being allowed to prescribe a limited category of medicines with special training.

5.4.2 Factors promoting antibiotic use (II)

Doctors felt the lack of diagnostic capacity in facilities justified prescribing antibiotics so as not to risk complications in patients having infections. Doctors also said that perceived patient expectation and patient demands were reasons for high antibiotic use. These factors appear to vary from country to country. GPs in the UK think prescribing antibiotics is part of their social responsibility [154]. In contrast, a Swedish study showed the public trusted doctors more when antibiotics were not prescribed [155].

Pharmacists were of the opinion that much of inappropriate use was due to doctors. Their perception that doctors receive incentives for antibiotic prescriptions was supported by a study from Orissa [156]. From the pharmacy viewpoint, OTC demand, business competition and incentives were factors contributing to antibiotic use. Many pharmacists viewed their profession as a business and not as a health facility service. This is in direct contrast to drug-sellers in private drugstores in Tanzania. They were perceived by patients to be quite knowledgeable and gave antibiotics with prescriptions or if bacterial infections were suspected [52]. Pharmacists in our study justified antibiotic use as supporting their business. This attitude will be difficult to change as there is a perception that livelihoods are at stake.

On similar lines, the fear among GPs of losing patients due to competition from rival facilities was mentioned as a factor. This pressure could be minimised by policies and systems that allocate patients to health provider registries based on geographical area. Patients could then visit allocated GP clinics and get medicines dispensed from adjacent pharmacy shops. This may improve communication between patients, doctors and pharmacists. In the UK and other HIC, patients are often assigned to GP groups [157].

5.4.3 Challenges and ethical dilemmas (II)

The perceptions and views expressed by all the stakeholders through the FGD raised various ethical dilemmas and challenges to changing practice of antibiotic use. Poor awareness about infections, antibiotics and resistance could minimize patients' participation in treatment decisions thereby compromising patient autonomy. On the other hand, the public enjoys autonomy to choose healthcare providers and in India there is access to OTC antibiotics from pharmacy shops and unqualified practitioners. This unfortunately creates a major risk to health also. This risk is compounded by other factors in LMIC such as variable quality of medicines [158], unsatisfactory storage conditions of antibiotics, potential medication errors, and a lack of diagnostic support in certain types of facilities. There is also the risk of adverse effects. A study on patients using fluoroquinolones revealed that ciprofloxacin had the highest proportion of cutaneous adverse effects among fluoroquinolones [159]. The incidence of such adverse effects can be reduced if unnecessary use is minimized.

The risks and benefits of prescribing antibiotics raise an ethical debate between access versus excess. Underuse of antibiotics due to poor access can prolong bacterial infections, increase potential for transmission and complications from untreated infection. This in turn raises the cost burden through hospitalization and wages lost. Giving antibiotics especially in critical situations such as sepsis will actually save lives (provided that antibiotics remain effective). Conversely, as expressed by stakeholders, antibiotics are often given on patient demand, for symptomatic relief and often for mild non-bacterial conditions. Using antibiotics in this way will not only lead to antibiotic resistance, but have financial implications. It may deplete government allocation for the medicines budget and possibly leading to denial of antibiotic therapy for patients with severe infections. Availability of better laboratory capacity can improve diagnosis and generate data on community resistance patterns that is essential for empiric antibiotic therapy. On the flip side, patient costs may increase and in private settings, there may be a tendency for doctors to investigate excessively. Inappropriate antibiotic use may also have other consequences. Antibiotics destroy normal protective bacteria in the gut (commensal flora) thereby allowing survival of pathogenic bacteria that may be resistant to many antibiotics [54]. Resistant bacteria may spread through unhygienic habits and conditions to others in the vicinity and community. The individual risk notwithstanding, high use of antibiotics may lead to rising community antibiotic resistance [58].

Justice demands that antibiotics be accessible and affordable, but balanced by appropriate evidence-based therapy. Justice is often compromised as revealed in the FGD. Competition between healthcare providers, business concerns, and the pervading influence of the pharmaceutical industry are powerful pressures. Lax implementation of policies and law does not help. Enforcing regulation to ensure antibiotics are sold only through prescriptions from qualified practitioners appears difficult to implement. The recent move by the government to implement Schedule H1 is a valiant effort [45]. This makes it compulsory for certain antibiotics to be sold with a prescription and the names and addresses of the patient are to be maintained in a register at the pharmacy shop. Unfortunately, this has already evoked a sharp reaction from the All India Chemists and Distributors Federation which has threatened a

strike [160]. Their rationale against Schedule H1 is that it would be impractical for pharmacy shops to maintain manual registers since they receive upto 400 patients a day. Based on earlier representations from trade bodies, there had been a relaxation of the number of medicines included in Schedule H1 from 91 to 46 [160]. This has led to a gradual dilution of the original draft rule and an ambience far from impending enforcement. However, the picture is not bleak for all medicines. The control of narcotic drugs for healthcare in India is a shining example of good regulation and implementation, balancing control and access [161]. Narcotics have specific indications and misuse potential and therefore cannot be compared to the diverse groups of antibiotics that are curative rather than palliative. The success in narcotics control does however raise the hope that discipline is possible, and that appropriate regulation balancing access and excess is not just a distant dream.

Pharmaceutical incentives, business concerns and competition had been talked about in the FGD. All these have a common thread, money. Tackling this would be extremely challenging, requiring a multipronged approach with the cooperation of all stakeholders. Cooperation would be the key, but also the greatest hurdle. It would need an embracement of professional values and etiquette by healthcare providers, development of relevant professional guidelines, and a refinement of existing laws to facilitate appropriate use. The step by the Medical Council of India to ban practitioners from taking free gifts and the subsequent move by the Central Board of Direct Taxes to charge income tax on pharmaceutical industry gifts are quite encouraging [162]. Practical implementation on the ground has been difficult due to various loopholes. The pharmaceutical industry also needs to play its part with a more scientific and humanitarian concern to true public service.

Ultimately, the ethical and philosophical dilemma one faces when confronted with issues in antibiotic use and resistance is that of individual versus society. Should autonomy and benefits to individuals get preference over risks to society and distributive justice? Antibiotics should be accessible and affordable, but individual antibiotic use must be appropriate and regulated. This balance is needed for preservation of antibiotics for the whole society.

5.5 Strategy in the hospital (IV)

5.5.1 Impact of policy guidelines on overall antibiotic use (IV)

There are multiple approaches in hospitals to contain antibiotic resistance, but two are commonly employed in many facilities. One approach is by prevention and control of infections through ensuring proper hygiene, disinfection and better diagnostic facilities [72,73]. The other approach is through antibiotic stewardship programmes [83]. One of the common interventional strategies used in such programmes is the implementation of antibiotic policy guidelines. Paper IV looked at the impact of policy guidelines during ten years of antibiotic use in a tertiary care hospital setting that has patients coming from all over India and beyond. During this period, antibiotic guidelines were prepared and disseminated in various modes and each had varying impact in respective segments (Figure 4.4).

The rising trend of antibiotic use seen in Segment 1 changed as guidelines were introduced at various periods across the decade. In Segment 2, a decline in trend in antibiotic use was seen though not statistically significant (Table 4.5 and 4.6). This period was characterized by efforts by the core antibiotic policy group and clinical departments as stakeholders to come together and jointly prepare a guidelines booklet. The participatory nature was a catalyst in encouraging clinicians to comply with the guidelines. This aspect may have led to a decline in slope as compared to Segment 1. The intense participatory nature and efforts required toward active dissemination could not be sustained beyond a period. Hence Segment 3 had no active dissemination of guidelines. This could explain the marked increase in trend and strengthens the argument for continuous exposure to guidelines and reinforcement. A revised guidelines booklet was actively disseminated in Segment 4. Carrying the booklet in every instance in a busy hospital setting and referring to guidelines was not always practical. Nevertheless there was stabilization in the trend of antibiotic use. This shows that booklet guidelines with active dissemination may help to contain but not reduce antibiotic use.

5.5.2 Impact of policy guidelines with online intranet access on antibiotic use (IV)

The antibiotic use trends and patterns of use changed during the ten year period. This was not the only thing that changed. Hospital capacity, infrastructure and capabilities also grew. One of the areas which witnessed remarkable changes was the increased presence of computers in all wards, outpatient rooms, department and other areas of the hospital. In addition, there was a great leap in technological capacity of the online intranet network and access throughout the hospital. Segment 5 was therefore marked by dissemination of policy guidelines not just through the booklet, but also through compute intranet network in all outpatient, departmental offices and ward computers.

During Segment 5, a significant decrease in overall antibiotic use was seen (Table 4.5 and 4.6). Intranet policy guidelines are possible in hospital facilities that have access to computers in wards, outpatient departments (OPDs), ICUs and other critical areas. Our hospital has such facilities making such a strategy feasible. This mode of policy dissemination has the advantage of widespread and instant dissemination of standard guidelines. In addition, it improves the ease and possibility of frequent updates. Easy access facilitates quick reviews by healthcare professionals anytime within the hospital. Feedback and query is also possible. This in turn facilitates vertical and horizontal interaction between stakeholders.

In LMICs, the number of hospitals with hospital information system (HIS) is growing. Unfortunately many do not have antibiotic policy guidelines let alone accessibility through the computer network. This strategy however should be explored by hospitals that have existing capacity. Hospital facilities that incorporate a similar mode of guideline dissemination may optimize their chances in containing antibiotic use as evidenced through this study. There is a lack of infrastructure in many government facilities and this may hinder implementation through this mode. However, bigger government hospitals do have computer networks and therefore the situation is hopeful. Another encouraging thought is that India and

other LMIC are rapidly developing their information technology (IT) networks. Mobile ‘apps’ (applications) could herald a new dawn for hospitals with no intranet network capacity. Most health professionals have mobile phones and this therefore could be an important tool. The IT potential should be used by health policy makers and governments to their advantage so as to effectively disseminate antibiotic guidelines.

Computer network applications for the purpose of guideline dissemination have been used in HIC. In the wake of an ESBL producing *Klebsiella pneumoniae* outbreak, a university hospital in Sweden implemented persuasive antibiotic policy guidelines that were made available on the local intranet [163]. There was significant containment in prescription of 3rd and 4th generation cephalosporins. Further increase in fluoroquinolone and carbapenem prescriptions was prevented. Computerized systems for medication reviews have been shown to support decision making by doctors and improve quality of medicines utilization in the elderly [164]. The same approach and tools could be imbibed for treating infections with antibiotics. Our study shows that, the developing nature of the country is no bar to using the power of IT, computers and applications for disseminating guidelines and other clinical support components.

5.6 Strategies in the community (III, II, I)

5.6.1 A key message - ‘the price to pay’ (III)

Different strategies have been recommended to improve antibiotic use and contain resistance [165]. Some of them have been focussed, whereas others had broad aims. Most of these strategies were developed and implemented in HIC. The cultural milieu, affordability, access to health and other factors are often different in LMIC. Another point to consider is that strategies have often focussed on hospitals [83,84] and less in the community [82]. For strategies in the community, it would be important to develop key messages to truly catch the attention of the target audience. The antibiotic resistance issue is rather complex and technical. As revealed in the perceptions through FGD, even healthcare providers do not have a proper understanding, let alone the public. Hence the message developed for the public should be understandable and most importantly, the message must be clear and compelling.

Antibiotic resistance is a phenomenon in which both health and wealth could be affected. This is especially so in LMIC such as India where state supported health care is on the wane and OOP expenditure for health care and medicine purchase is on the rise [97]. In India, infections still occupy a prominent place in the spectrum of ill-health [88,150] and resistance is a problem [22,34]. Effective antibiotics have thus become a precious resource especially in life and death situations such as severe bacterial infection. Having an infection with resistant bacteria in such a situation may affect both health and wealth. This is a potential message for the community. In Paper III, we therefore looked at patients admitted with a preliminary diagnosis of suspected sepsis and determined the cost burden and health consequences in

patients who were having an infection resistant to the empirical antibiotic (resistant group) in comparison to those susceptible (susceptible group).

5.6.2 The cost burden attributable to antibiotic resistance (III)

The median overall cost was significantly higher in the 'resistant' group as compared to the 'susceptible' group (Table 4.8). The average daily wage of a rural male casual worker in India is approximately Rs 95 (1.6 US Dollar) [166, 130]. The median difference amount of Rupees 41,993 (700 USD) incurred by patients in the 'resistant' group therefore equates to 442 days worth of wages being spent. This financial loss of more than one year wages attributable to antibiotic resistance would be catastrophic for the affected patient and family. Few studies have looked at direct cost for the individual patient due to a resistant infection and none in LMIC. In a study in HIC on cost attributable to acute resistant infections, extra cost burden was calculated at 21,018 dollars [167]. The higher cost of care in HIC makes it difficult to compare with the figures in our study. The burden in India however is compounded with the lack of health insurance and OOP expenditure. The national poverty line is Rs. 816 (14 USD) per capita per month in rural areas and Rs. 1000 (17 USD) per capita per month in urban areas [90]. The Government of India Planning Commission report in 2013 estimated that 21.9% of the Indian population was BPL [90]. For BPL patients, the extra cost due to an episode of severe bacterial infection would be insurmountable. Rising antibiotic resistance may further increase the 5% of Indian households that currently suffer catastrophic health expenditure [97].

A significant proportion of OOP expenditure for health in India is for medicines [97]. The antibiotic costs borne by patients in the 'resistant' group were significantly higher by Rs 8,315 (139 USD) than for patients in the 'susceptible' group (table 4.8). Pharmacy costs were again significantly more in the 'resistant' group. This shows that antibiotic resistance may lead to use of other medicines and consumables, thereby further adding to the cost.

5.6.3 Health consequences attributable to antibiotic resistance (III)

The health consequences that were assessed were length of stay, intensive care admission, complications and mortality (Table 4.9). Patients in the 'resistant' group had to stay an extra three days. A study done in HIC on patients with hospital acquired infections has reported a longer stay attributable to resistance [168]. Increasing bed stay not only has cost implications but may increase the risk of HAI. In hospitals where bed occupancy is saturated, increasing stay will potentially delay treatment to other patients waiting for admission.

A comparison of intensive care admissions between the groups showed 24% more admissions in the 'resistant' group (Table 4.9). If crucial beds in intensive care are occupied, life saving care may potentially be denied to other critical patients. The proportion of patients developing complications was 20% more in the 'resistant' group. Renal failure, respiratory failure and circulatory shock were some of the common complications. Many studies looking

at health consequences have focussed on length of stay and mortality [169]. Complications may have a cascading impact on costs and therefore needs to be included in assessments.

Mortality was more than five times higher in the 'resistant' group. The magnitude of difference is larger than in other studies. In a study with 1391 hospitalized patients in HIC, there were totally 70 deaths (5%) of which only half had a resistant organism [167]. The relatively higher mortality in our study is therefore a point to note for policy makers, healthcare providers and most importantly for the public. The message is not only clear, it's alarming. The burden of cost and health consequences attributable to antibiotic resistance as evidenced by this study is significant and all the more important due to the economic situation of many families in India. This key message needs to be disseminated to all stakeholders.

5.6.4 Strategies suggested by stakeholders for appropriate antibiotic use (II)

It would be important to develop various strategies in the community regarding antibiotic use and resistance in addition to the key message. Inappropriate use of antibiotics involves multiple stakeholders, different facilities, behavioural issues, cost considerations, as well the ever persistent bacteria that develop new ways of survival. Multipronged strategies are therefore essential. Strategies should also be contextualized. Strategies suggested by local stakeholders therefore assume great importance.

Healthcare providers in the FGD, both doctors and pharmacists, mentioned the need for changes in their respective curriculum to incorporate modules on rational use of medicines and antibiotics. They were of the opinion that emphasis should be given to good prescribing and dispensing practices so that these could be imbibed early in their careers. Continuing professional education was also suggested since once formal education is completed, there is very little update. Keeping abreast of newer antibiotics, evidence based changes in practice and changing resistance patterns would be crucial. Improving laboratory capacity was another important suggestion. Enhancing the quality of microbiological laboratories would be crucial. The entry of point of care (POC) tests and rapid diagnostic tests needs to be also considered. These tests could offer differentiation between viral and bacterial aetiology and avoid unnecessary prescription of antibiotics. However, various barriers may exist for widespread use of POC tests in LMIC such as affordability, sensitivity and cost-effectiveness [170].

Among various strategies mentioned in the FGD, one common point mentioned by all stakeholders was the relatively poor awareness about infections, antibiotics and resistance. One key suggestion was that of empowering the public through education and media. Different techniques have been used for raising awareness. An empowerment technique using leaflets and posters succeeded in improving awareness of antibiotics and generating relevant questions to doctors [171]. Stakeholders in our study supported the idea that school children, teachers, women's and self-help groups could be key partners in the process. Improved patient communication from healthcare providers about illness and antibiotics was another suggestion. Studies have shown that interventions for improving patient communication

reduced antibiotic prescription rates by 60% [171]. Communication initiatives to encourage behaviour change by using national mass media to target larger geographic areas such as communities and school districts may have a quick and wide impact, but may lack sustainability. It may be prudent to also use local media. Other modes of dissemination could include peer-education programmes in schools, pamphlet distribution at healthcare facilities and community events, posters on public transportation and other forms of advertisement with key messages [172].

Improving the awareness of school children in issues of antibiotic use and resistance could be a key strategy. If children gain the right knowledge, they may be able to practice some of the principles of hygiene and rational use of antibiotics from an early age. The e-Bug project in Europe is an innovative way to improve children's awareness [173]. This project uses teaching packs and a website to teach students about antibiotic use, microorganisms, infections, hygiene and vaccines. Another high school interventional program in Portugal on 15-17 year olds also proved to be successful in improving knowledge in such areas [174]. However what is not known is whether this changed attitude. Imbibing the right knowledge early is important as potentially harmful attitudes and practices maybe learnt over the developing years and become a habit. Background research for the e-Bug project in France revealed that such topics were best suited for curricula in Forms (Grades) four to six which includes children between nine and eleven years [175]. Another important aspect to consider is that students could be ideal partners in disseminating these messages to their friends, siblings, parents and even grandparents. Research in the elderly has shown that poor education is associated with taking multiple medicines and potential inappropriate use [176]. With the knowledge gained from school programmes, children could improve the medicine taking habits of their grandparents. Incorporating various aspects of medicine use in school curriculum would therefore be greatly beneficial.

Developing guidelines for antibiotic use, continuing education programmes, and rational use modules in healthcare curricula were other suggestions by healthcare providers in our study. All these could have overall and long term impact in the community by improving prescribing and dispensing practices.

5.6.5 Other strategies based on findings from surveillance (I)

The intention of surveillance in the community was not only to determine the level and patterns of antibiotic use, but also to identify inappropriate use in key facility types, symptom conditions, and among specific antibiotics, so that messages and interventional strategies could be focussed. These potential strategies are discussed below.

Development and dissemination of messages:

It was found from surveillance that fluoroquinolones, extended spectrum penicillins and cephalosporins were the most commonly used classes of antibiotics in the private sector and that they were often used for respiratory infections and diarrhoeas. The main message to the

community would be to not use these antibiotics for symptoms such as runny nose, common cold and simple diarrhoeas which are often caused by viruses. Messages given could vary according to prior knowledge and understanding of the audience but would include:

- (i) There is high use of antibiotics in symptoms such as runny nose, sore throat, cough and cold and simple diarrhoea.
- (ii) Antibiotics such as ciprofloxacin, amoxicillin and cephalixin are usually not indicated in these infections.
- (iii) The more antibiotics we use, the more resistance will develop. Therefore if we use antibiotics inappropriately, we are unnecessarily causing resistance.
- (iv) Resistance among bacteria means that the antibiotics will no longer work and we will have treatment failures, increased costs and complications.
- (v) Using unnecessary antibiotics may lead to unnecessary adverse effects.

These messages could be disseminated through various means, such as posters, pamphlets or through mass media:

(i) Using Posters and Pamphlets: Posters could be prepared with these simple messages in local language and also in English. These could be put up in places like waiting areas of hospitals, private clinics and public facilities like bus stations, railway stations, and main shopping areas. Short messages could be exhibited on buses and auto rickshaws. Pamphlets could be given to doctors and pharmacists to be distributed to their patients.

(ii) Mass media: Newspapers, magazines, radio and television could be engaged to increase awareness. Help from journalists could be obtained to write articles related to antibiotic use and its consequences in local newspapers. Another dissemination strategy is to telecast sub-captions on antibiotics prior to popular programmes. Television chat shows could also be an option to discuss cases about antibiotic misuse and resistance.

For the above messages, it could be useful to apply approaches that are frequently used in other fields such as social sciences and even the pharmaceutical industry. These approaches could help in developing and disseminating messages on antibiotic use and resistance to the public and specific groups of stakeholders. In social sciences, the 'Ps' of social marketing, product, place, price and promotion have been used to change the behaviour of another 'P', people [177]. Some of the principles include behaviour change as a benchmark, audience research, segmentation of target audiences, creating appealing and motivational interactions, and using a marketing mix coupled with good communication. The principles of social marketing are increasingly being applied to promote public health and also in the area of antibiotic use. An example of this is the inexpensive information campaign which targeted the communities in northern Italy. This along with a newsletter targeting healthcare providers significantly decreased total rates of antibiotic prescribing [178]. Buzz marketing is another approach which has been used in the area of antibiotic use and resistance [179]. This approach is commonly used in the pharmaceutical industry for promoting products, services and ideas. It works best for ideas that are memorable, where small changes in behaviour have big effects over time, and when patients perceive the benefit of the idea.

Interventional strategies:

Human behavior depends on time, place, person and many other factors. Culture, surroundings, circumstances, finance, the lack of basic necessities, social relations and stress may all affect beliefs about health and illness [180]. This in turn may affect health seeking behavior. Antibiotic use in humans is affected by behavior at all levels, from the initial decision of patients to seek a healthcare provider to the full completion of treatment. The behavior and factors affecting this can be at various levels. This includes individual (patient or healthcare provider), interpersonal (stakeholder interactions), facility (a number of healthcare levels including diagnosis and treatment), community (peer practices, beliefs, cultural issues) and policy (regulations and implementation). For strategies to be effective and sustainable it would be important to apply models or theories of behaviour change to the interventions that are to be developed [181]. There are various models that could be applied such as the educational model, stages of change theory, 'precede/proceed' model, social learning theory, and academic detailing, to name a few [181]. However, for optimal behavioural change in antibiotic use, one of the other models that could prove quite effective could be the 'mainstreaming' model. This has been used for gender mainstreaming with reasonable success [182]. To ensure that mainstreaming works, it should be a core part of planning. Various decisions of the society should be analyzed through the mainstreaming perspective and consequences that arise should be visible. Mainstreaming could be a game changer in modifying behavior at various levels of antibiotic use in the society.

It would be important to apply some of the principles espoused in these models and theories when developing the following interventional strategies:

- (i) Targeted programmes: These programmes could target various groups such as youth, mothers, social clubs, non-governmental organization (NGO) workers, health aids and school students. A team consisting of doctors, pharmacists and a research team member could visit the target group and give simple messages. At schools, besides giving messages, children could carry out a set of activities such as street theatre, competitions and poster development in their own community.
- (ii) Developing treatment algorithms for acute respiratory infections and diarrhoeas: Simple guidelines for management of acute respiratory infections and diarrhoeas could be developed by local GPs. They could make realistic protocols that can be followed and true to the clinical scenarios faced in everyday work. The research team can facilitate the process to ensure guidelines consistent with the main message and good practice. GPs should be encouraged to distribute this information freely among their peer group and get feedback about guidelines.
- (iii) Self monitoring and peer review of prescribing for doctors: An anonymous set of exiting patient interview forms showing prescribing practices can be presented in turn by different GPs. Compliance with guidelines, appropriateness and difficulties could be discussed. The

research team could ensure that no individual's prescribing practices could be identified by peers. Changes in behaviour could be assessed using a monitoring system for antibiotic use.

(iv) Self monitoring and peer review of dispensing for pharmacists: Pharmacists and local pharmacy shop owners could be asked to cooperate in a programme of simulated patient surveys whereby each month a random selection of pharmacy shops are visited and the pharmacist asked to sell a "strong medicine" for mild respiratory infection or diarrhoea. A standardised instrument could be developed. The research team should ensure anonymity. In this way, they will be able to discuss changing their own behaviour.

Implementation of such multipronged strategies involving all stakeholders is the need of the hour, and should be simultaneous, comprehensive and sustainable. The lives of people from various walks of life, spanning different age groups, and experiencing a variety of circumstances, are at stake due to antibiotic resistance [183].

Evaluating the impact of future interventions:

Change of prescribing or dispensing behaviour can be evaluated by surveillance of antibiotic use in respiratory infections and diarrhoeas. This can be done by measuring trends before, during, and after intervention with regard to: (i) percentage of patients receiving antibiotics; (ii) percentage of patients receiving fluoroquinolones; (iii) percentage of patients receiving inappropriate antibiotics for respiratory infections and diarrhoeas; and (iv) percentage of resistance of *E. coli* to specific antibiotics, particularly fluoroquinolones.

Extra information on behaviour could be gained from: (i) Dispensing behaviour of shop owners through simulated patient surveys enabling assessment of OTC antibiotic use; (ii) Prescribing behaviour of doctors through regular prescription audit and peer review; and (iii) Process information indicating the extent and quality of implementation of interventions.

5.7 Methodological Considerations

The studies for the four constituent papers in this thesis were based in one district in the state of Tamil Nadu in India. The demographic profile of Vellore district and the state of Tamil Nadu cannot represent the diversity of India. This is true of any state or district in India. The profile of Vellore district does however have various similarities with both the state and the country (Table 1.1). Ideally it would be important to get a more representative sample of the country. India is however a very diverse country with different languages, culture, race, caste, religion, socioeconomic status and beliefs. The feasibility of doing surveillance on a continuous basis in various regions may be unknown and difficult unless a start is made in one area. This start could then help other researchers and policy makers to use these methodologies in their own setting or nationally as the situation demands. These studies maybe therefore difficult to generalize, but transferability is possible. In addition, some of the

main findings and messages would be relevant for developing future interventional strategies in various parts of the country and other LMICs.

Discussing the various challenges and methodological considerations of each individual study would therefore be helpful:

5.7.1 Paper I

Paper I was unique in that there have been very few studies in LMIC that have determined patterns of antibiotic use over a two year period. The percent encounter method was a useful alternative to collect data in LMIC where registries on medicine prescriptions and sales hardly exist.

Documenting the various challenges of developing such a surveillance system may provide useful information for other researchers in LMIC. The selection of GP clinics and pharmacy shops were based on feasibility. Many GPs initially thought that this study was part of a government surveillance programme and were afraid of a possible inspection of their prescriptions from authorities. Pharmacists were reluctant to part with sales records for fear of tax audits. The actual process of data collection was challenging due to medicines often being prescribed on small pieces of paper. Accurately deciphering and identifying brand names in the midst of illegible handwriting was a challenge and often required cross verification. In pharmacy shops and government hospitals, documenting antibiotic encounters was quite difficult due to high patient turnover and crowded situations in front of pharmacy counters. For bulk use data, sales records were often not organized in a systematic manner. Hence a lot of time and effort was spent to maintain completeness and accuracy of data.

Data collection for such a large number of patients over a two year period resulted in a huge data set. It took a lot of time to develop customized software, data entry, and data verification. Data cleaning and sorting out the analytical issues also took time. The data collected was based on prescriptions, dispensations and bulk sales. Actual consumption and compliance by patients contributes to revealing the true antibiotic burden. This was not determined. This surveillance assessed only antibiotic encounters in humans. Antibiotic use in animal husbandry, agriculture and other industries should also be determined.

5.7.2 Paper II

There have been very few studies in LMIC regarding perceptions of stakeholders about antibiotic use and resistance. Additionally, Paper II uniquely highlights some of the ethical issues and challenges in changing practice raised through the various themes. The FGD methodology served its purpose in bringing out various views, attitudes, interactions, areas of consensus, and community practices. This was helpful since there were different stakeholders and various themes. Supplementation with in-depth interviews could have strengthened information on sensitive issues such as pharmaceutical industry incentives, possible commissions for antibiotic sales and regulatory loopholes.

Purposive sampling helped to select interested stakeholders. The public were stratified into HSEP and LSEP so that knowledge, attitudes and practices from two socioeconomic backgrounds could be explored. It also helped to maintain homogeneity for the smooth functioning of the FGDs. Participant numbers in groups were restricted for easier management and to provide participants more opportunities for expressing their views. A follow-up workshop was conducted where the findings were presented and the participants agreed to the authors' interpretation of their statements. This study included only three major stakeholders for human antibiotic use. Policy makers, regulators, ISM practitioners and representatives of the pharmaceutical industry would be important to include in further studies. In addition, it would be important to ascertain the perceptions of antibiotic users in agriculture, food and livestock industry to complete the picture.

5.7.3 Paper III

This paper looking at cost and health consequences of antibiotic resistance is one of the first studies assessing impact at an individual level. There have been various studies in HIC. The data generated was mainly direct costs, but gives crucial evidence on the huge impact of antibiotic resistance especially in severe bacterial infections. It also forms the basis for a future economic study, where indirect and intangible costs could be measured in addition to the quality of life. Hospitals in HICs have data pooled in electronic records and national registries. This makes it relatively easier to collect data and analyze larger numbers. The data for this study had to be sourced through multiple channels including accounts, pharmacy, clinical and laboratory departments. This was time consuming and involved triangulation to maintain accuracy.

This paper focuses on assessing cost burden. The value of the currency fluctuates and depreciation is a factor. However it is important to note that these fluctuations will affect both groups in the study, both 'resistant' and 'susceptible'. The difference in both groups is the real message. This study did not do a comparison for all infections in the hospital. Instead it focussed on severe bacterial infections where being resistant or susceptible to the antibiotic could be a major factor in health outcome. Patients with only a preliminary diagnosis by the physician of suspected sepsis were taken into the study. Patients may have had or later developed systemic inflammatory response syndrome [184]. Confirmed bacteremia was the main consideration while including patients into the study.

5.7.4 Paper IV

This paper is unique in that there have been few studies of this kind in LMIC looking at antibiotic use over ten years. The availability of a pharmacy database and the initiative to put in place antibiotic policy guidelines contributed was essential. Another unique point was the assessment of different modes of guideline dissemination.

The observed trends in antibiotic use across the decade could have been influenced by other factors due to changes in the hospital. Some of these factors include bed capacity, number of doctors, introduction of new laboratory tests, the input of antibiotic use audits and role of other health professionals such as clinical pharmacists. An important point is that inspite of these factors there was a rising trend for a greater part of the decade. Given the short period of time in Segment 5, the influence of other factors may not have had an impact in arresting the rising trend only within that segment since they could have potentially influenced the trend at various times across other segments. Also, our study spans all the antibiotic groups in the hospital formulary and these antibiotics are used for a variety of indications throughout the hospital, across several departments and for differing levels of severity. In most groups, the rising trend and subsequent decline in Segment 5 has been in a fairly uniform manner across the antibiotic group spectrum.

This paper has not assessed the rationality of antibiotic prescriptions and adherence of physicians to policy guidelines. We focused on containment of antibiotic use within the hospital. It would be important in the future to also study rationality in order to complete the picture. Linking antibiotic use data with resistance rates and clinical outcome such as mortality rates would give additional information.

6. CONCLUSIONS

This thesis and its constituent papers have been written to improve knowledge and provide an evidence base in a LMIC, so as to develop appropriate strategies in both community and hospitals for improving antibiotic use.

The key conclusions of this thesis are:

1. There is widespread use of antibiotics especially for respiratory infections in healthcare facilities in the community. Future interventions to contain antibiotic use should involve all types of facilities but strategies should be customized as there are variations in types of antibiotics used. Antibiotics from the fluoroquinolones and penicillins groups were widely used in most facilities, especially in GP clinics and pharmacy shops. Rural hospitals used huge quantities of co-trimoxazole. Urban private hospitals used a lot of cephalosporins. STG should stress on appropriate use of antibiotics and focus on specific indications for individual antibiotic groups.

2. Developing surveillance systems for monitoring of antibiotic use is possible in LMIC despite the challenges. The main challenges appear to be methodological issues such as sampling, denominator calculation and data management, as well as feasibility issues such as permissions, the effort needed for data collection and costs involved. It is hoped that policymakers in LMIC would be able to use the experiences presented in this paper to set up such surveillance systems. This would help in monitoring antibiotic use, planning appropriate strategies, as well as evaluating the impact of future interventions.

3. Perceptions of various stakeholders revealed that healthcare providers had a basic knowledge of antibiotics and infections, whereas the public had little awareness. Overall understanding of resistance and its consequences was limited. Antibiotic use for non-bacterial infections, inadequate dosages, incomplete courses, and antibiotic sales directly from pharmacy shops were observed to be common practices. Perceived patient expectation, need for quick relief, inadequate diagnostic facilities, competition and industry incentives were some of the challenges that contributed to inappropriate antibiotic use.

4. Antibiotic policy guidelines are an effective strategy that can contain antibiotic use in a LMIC hospital setting. The mode of implementation is critical to the effectiveness of policy as the formulation of the policy itself. The segment (time period) where guidelines were disseminated with intranet access showed a significant reduction in antibiotic use. In addition to guideline booklet dissemination by standard methods, computer networking and newer IT technologies such as mobile applications should be used to broaden the accessibility to healthcare personnel. This will bring additional value by improving flexibility for frequent updates, feedback and referrals.

5. There were significantly higher costs in patients infected with bacteria resistant to empiric antibiotics as compared to those infected with susceptible bacteria. Health consequences such as mortality, intensive care admissions, complications and hospital stay were all significantly higher. The message is clear and alarming. The economic and health burden of resistance can be devastating to patients, their families, and health budgets in LMIC. This message needs to be used in interventional strategies and disseminated to all stakeholders, the public, healthcare providers, hospital administrators, policy makers and regulators.

6. Suggested strategies by stakeholders in the community to contain antibiotic use and resistance dwelt on improving public awareness, better communication, improved diagnostic support, continuing education, and regulation enforcement. Empowering the public, curbing pharmaceutical industry incentives, and encouraging healthcare providers to have a scientific and professional approach, would address some of the major ethical challenges.

It is hoped that this thesis, the constituent papers, their findings and the messages highlighted, encourage stakeholders to refocus their attention on the dangers of resistance and tackle the problem through strategies to improve antibiotic use. These steps in turn will hopefully decrease the burden to the individual and improve health in the society. The autonomy to use antibiotics needs to be balanced against the risk of rising resistance and beneficial outcome with prudent antibiotic therapy. Interventional strategies need to emphasise the need for appropriate and ethical use of antibiotics. Stakeholders need to embrace these efforts and contribute to completing the 'jigsaw puzzle' of antibiotic resistance. If these measures are embraced wholeheartedly by the world, we could help preserve this precious resource and keep effective antibiotics available for use, not just for the present, but also for future generations. *'Antibiotics save us. Can we save antibiotics?'*

7 ACTIONS, IMPLICATIONS AND FUTURE RESEARCH

7.1 Actions

Based on the knowledge and inspiration gained through the doctoral work, courses, studies, constituent papers and thesis, a number of important activities and actions were undertaken with the aim of improving awareness of issues in antibiotic use and resistance. These include:

(i) Organization of school programmes on healthy living and antibiotic use

One of the main findings was that knowledge of the public with regard to infections, hygiene, antibiotic use and resistance was poor. School programmes were therefore organized. My primary task was to improve awareness and understanding about some of these issues as well as healthy living and medicine use. The target audience were students from Grade 4 to 7 and Grade 8 to 11 (two sessions), teachers and also parents. This was organized with the intention of encouraging the right attitude, habits and discipline in health for life. In addition, children would be ideal catalysts at home and society for improving awareness and changing the attitudes of elders. It is hoped that the school programme would continue in many more schools.

(ii) Contribution to development of a guidelines document

This document was entitled ‘Step-by-Step Approach for development and implementation of hospital antibiotic policy and standard treatment guidelines’ [185]. It focuses on the practical approach to developing a hospital antibiotic policy. Development of standard treatment guidelines and practical ways to implement them are also presented. The document also discusses various steps and information needed for developing antibiograms, policies and STGs. It also dwells on setting up surveillance programmes, strategies for controlling antibiotic resistance and HAI, and evaluating performance of such programmes.

(iii) Contribution to development of Standard Treatment Guidelines

The Standard Treatment Guidelines for Primary Healthcare Facilities (2012) was a book published by Social Initiatives for Growth and Networking (SIGN), Ranchi in collaboration with Community Development Medicines Unit (CDMU), Kolkata. This STG was developed with the aim of assisting care givers in remote health centers in making decisions about appropriate health care for specified clinical circumstances. Another aim of this book was to focus on essential medicines and rationalize medical practice especially in topics such as the treatment of infections.

(iv) Development of medicine policies and medicines information publication

Various medicines policies on purchase, storage, dispensing, medication safety and rational use were developed for a group of 14 hospitals across various islands of Indonesia in 2013. The focus in these policies was rational use of quality medicines with emphasis on antibiotics. A publication entitled MedUSER (Medicine Update, Safety, Ethics and Research), was developed on rational use of medicines with a special focus on antibiotic use. This was disseminated on a monthly basis to over 1000 healthcare professionals.

(v) Development and organization of the 'ASPIC' programme

Antibiotic stewardship, prevention of infection and control (ASPIC), was a programme for which my role was as principal investigator and main coordinator. This was initiated in 2012 by the Indian Council of Medical Research (ICMR) in collaboration with the Office of the National Chair of Clinical Pharmacology, ICMR, and the Christian Medical College, Vellore [186]. The purpose was to bring together faculty from clinical pharmacology, microbiology, and other disciplines, to train and collaborate on initiating and improving antibiotic stewardship, and concurrently curb hospital infections through feasible infection control practices. This programme involved the participation of 20 institutions per year throughout the country. The duration was one year with two contact sessions (workshops) and a research project. The programme was planned to provide training for participants to equip them with (a) skills and understanding required for infection prevention and control practice; (b) knowledge and skills required for development and implementation of antibiotic policy guidelines for rational use of antibiotics; and (c) ability to plan and conduct research projects in antibiotic policy, infection prevention and control practice.

7.2 Implications and future research

The various findings in the thesis and constituent papers have implications for the community, healthcare providers and policy makers as previously discussed. These implications and some of the strategies required need further research. The potential areas therefore for furthering research include:

(i) Improving public awareness through key messages about antibiotic use and resistance: This would be important since all key stakeholders conveyed their opinion that awareness in the community about infections, antibiotic use and resistance was poor. Various strategies may need to be developed such as school programmes and each would need to be evaluated. It would also be important to apply various principles of social marketing. The impact of these strategies could be determined through the surveillance system.

(ii) Determining the use of antibiotics in agriculture and animal husbandry: Bulk antibiotic use would have to be assessed in these areas by extending the surveillance system to these

areas. This research would be a challenge as stakeholders would be reluctant to part with information for fear of regulatory reprisals. Nevertheless, collecting this information through innovative research methods would be a priority.

(iii) Eliciting sensitive information on pharmaceutical incentives: This would be important since one of the major challenges in containing antibiotic use would be to reduce the influence of the pharmaceutical industry on GPs and pharmacy shops. For this, in-depth interviews with doctors, pharmacists and key representatives from the industry such as medical representatives would be needed and the evidence gained used for advocacy.

(iv) Assessing the impact of antibiotic resistance on indirect costs and quality of life: This would be important as the findings of our study focussed on direct costs and health consequences. Estimating indirect costs and quality of life would complete the picture, provide a strong message and support advocacy for urgent action among policy makers.

(v) Linking antibiotic use patterns to resistance patterns over the decade: This would be important to research in both the community and the hospital setting due to a paucity of such linkages in LMIC. The hospital setting has readily available resistance patterns and therefore the task would be to compare antibiotic use and resistance, and determine correlation. This could be done for specific antibiotic groups. Doing this in the community setting would require setting up parallel surveillance of both use and resistance.

(vi) Evaluating the impact of antibiotic policy guidelines on rational prescribing: Paper IV describes the impact on containing antibiotic use. It would be important to complement this by looking at how effective the policy has been in improving rational prescribing over the decade. In addition, it would be interesting to note how the different modes of dissemination affect rational prescribing.

(vii) Studying the application of theories of behavioural change in intervention studies: Various theories of behavioural change such as ‘antibiotic mainstreaming’ could help in developing effective interventional strategies. It would be important to research their impact in changing behaviour to improve antibiotic use especially in the LMIC context.

8. ACKNOWLEDGEMENTS

I would like to take this opportunity to thank two great institutions with a combined experience of more than 300 years, the many people who have been teachers, colleagues and friends throughout my life, and a much wider community from whom I learnt a great deal during the doctoral programme. I would like to sincerely thank:

The study participants – A special heartfelt appreciation to all those who participated both directly and indirectly in the various studies. Hopefully your lives and those around you would be positively impacted through the research done.

Cecilia Stålsby Lundborg, Professor, Global Health (IHCAR), Dept of Public Health Sciences and my supervisor - My heartfelt warmth, thanks and eternal gratitude for encouraging me to take up this PhD journey and being the guiding hand throughout. I have learnt a lot from you, not just academically, but through the many interactions and discussions we had. Your passion for researching the various issues in antibiotic use and resistance has been truly inspirational.

Kurien Thomas, Professor & Head, Dept of Medicine, Christian Medical College, Vellore and my co-supervisor – my appreciation and thankfulness for your wisdom and guidance throughout my work. I have admired your clarity, clinical application and wide knowledge and am thankful that this greatly helped me in all my work.

Denise H Fleming, Honorary Professor, Clinical Pharmacology, Christian Medical College, Vellore and my mentor – for your valuable advice and my heartfelt thanks to both Joe and Denny for their warmth and friendship.

Elisabeth Mathai, Kathleen Holloway, Girish Naik and all the Co-investigators – my thanks and deep appreciation for your sincere efforts, advice and collaborative support towards all the studies and the resulting papers.

The Global Health family

Lucie Laflamme, Professor & Head, Dept of Public Health Sciences - for the constant support and giving the opportunity to be associated with the department.

Marie Hasselberg, Associate Professor & Director of Doctoral Research Education – for the guidance and valuable advice in various steps of doctoral education.

Vinod Diwan, Professor – for the encouraging presence and creating an environment conducive to true learning.

Göran Tomson, Professor – for the inspiring words and providing an ambience of research.

Johan von Schreeb, Asli Kulane, Andreas Mårtensson, Gaetano Marrone – for their valuable inputs and advice during pre-registration and pre-defence seminars.

Other faculty at Global Health – for the inputs during my PhD programme at Global Health.

Gun-Britt Eriksson – for the warmth, friendship and support throughout my years at Stockholm, **Marita Larsson** – for the valuable support, **and other administrative support staff** – for the help and assistance in so many ways during the PhD programme.

Senia Rosales - for the sincere and valuable advice at various stages of the thesis preparation.

My other colleagues and friends in the research group ‘Medicines in the Health System

focussing antibiotics’ - Dr. Tamhankar, Megha, Vishal, Ashish, Krushna, Sandeep, Quynh Lien, Jennifer and many others – a wonderful group and lovely to work with sharing our passion in the area of antibiotic use.

Anita, Arun, Ayesha, Christine, Lin Hai, Meena, Wang Ying, and other colleagues and friends in Global Health – for their valued friendship.

The CMC Vellore family

The administration at Christian Medical College, Vellore – my gratefulness for the support and encouragement towards the PhD programme.

The colleagues at Dept of Pharmacology & Clinical Pharmacology, and Dept of Pharmacy – my appreciation for their support and cooperation in my work area.

The colleagues at other departments of CMC Vellore – faculty of Medicine, Microbiology, Pharmacy, Biostatistics, Rural Unit for Health and Social Affairs, and Low Cost Effective Care Unit and Research Office – for their collaborative support for the studies.

My teachers at Pallikoodam School, Kottayam and Christian Medical College, Vellore – for their role in moulding my learning skills and encouraging me at every point in my life.

Otto Cars of ReAct, Albert Peterson and Eva Ombaka of EPN, Ranjit Roy Chaudhury of DSPRUD, Ramanan Laxminarayan of CDDEP-GARP, Nilima Kshirsagar of ICMR, João Carapinha of BRICS Medicines Alliance and Sten Olsson of UMC - for their passion and work in medicines and antibiotic use and the opportunities to work together.

Friends – Lalit, Sujata, Doug, Jodi, Kamal, Birgitta, Mark Tatlow and many others for their valuable and sincere friendship during my stay in Stockholm

My family

Sheeba Chandy, my wife – for your loving support, friendship, encouragement and wise counsel both in my life and during this PhD period. My special thanks for shouldering the responsibility at home during the last many years in addition to your work as Professor.

Shaun Chandy, our son – for your loving nature and allowing me to be away from home during the PhD and for constantly enquiring about my progress with the thesis!

Sugu and Jaya Chandy, my parents – for your loving care through my life, nurturing my enquiring mind, encouraging me in education and music, and for inspiring me to help others.

Sunil Chandy, my brother – for your love and companionship.

Philip and Saramma Benjamin, my in-laws – for your love and constant support.

Financial support

The World Health Organization – for funding the studies for paper I and II.

The EMCEW (Erasmus Mundus External Co-operation Window) lot 15 India - for the scholarship support towards the PhD programme.

9. REFERENCES

1. Centers for Disease Control and Prevention(CDC), Atlanta. Antibiotic/Antimicrobial Resistance. Glossary.
Available: www.cdc.gov/drugresistance/glossary.htm. Accessed: 2 January 2014
2. Barber M, Rozwadowska-Dowzenko M. .Infection by penicillin-resistant *Staphylococci*. *Lancet*. 1948 Oct 23;2(6530): 641–4.
3. Crofton J, Mitchison, DA. Streptomycin resistance in pulmonary tuberculosis. *Br Med J*. 1948 Dec 11;2(4588):1009–15.
4. Watanabe T. Infective heredity of multidrug resistance in bacteria. *Bacteriol Rev*. 1963 Mar;27:87–115.
5. De Graaff J, Elwell LP, Falkow S. Molecular nature of two-beta-lactamase-specifying plasmids isolated from *Haemophilus influenzae* type b. *J Bacteriol*. 1976 Apr;126(1):439–46.
6. Marshall B, Roberts M, Smith A, Levy SB. Homogeneity of transferable tetracycline-resistance determinants in *Haemophilus* species. *J Infect Dis*. 1984 Jun;149(6):1028–9.
7. van Klingeren B, van Embden JD, Dessens-Kroon M. Plasmid-mediated chloramphenicol resistance in *Haemophilus influenzae*. *Antimicrob Agents Chemother*. 1997 Mar;11(3):383–7.
8. Bennett PM. Plasmid encoded antibiotic resistance: acquisition and transfer of antibiotic resistance genes in bacteria. *Br J Pharmacol*. 2008 Mar;153 Suppl 1:S347–57.
9. Schneiders T, Amyes SG, Levy SB. Role of AcrR and ramA in fluoroquinolone resistance in clinical *Klebsiella pneumoniae* isolates from Singapore. *Antimicrob Agents Chemother*. 2003 Sep;47(9):28317.
10. Alekshun MN, Levy SB. Regulation of chromosomally mediated multiple antibiotic resistance: the *mar* regulon. *Antimicrob Agents Chemother*. 1997 Oct;41(10):2067–75.
11. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect*. 2012 Mar;18(3):268–81.
12. de Kraker M, van de Sande-Bruinsma N. Trends in antimicrobial resistance in Europe: update of EARSS results. *Euro Surveill*. 2007 Mar 15;12(3):E070315.3.

13. Weinstein RA. Controlling antimicrobial resistance in hospitals: infection control and use of antibiotics. *Emerg Infect Dis*. 2001 Mar-Apr;7(2):188–92.
14. Fridkin SK. Vancomycin-intermediate and -resistant *Staphylococcus aureus*: what the infectious disease specialist needs to know. *Clin Infect Dis*. 2001 Jan;32(1):108–15.
15. Meka VG, Gold HS. Antimicrobial resistance to linezolid. *Clin Infect Dis*. 2004 Oct 1;39(7):1010–15.
16. Bradford PA. Extended-spectrum beta-lactamases in the 21st century: characterization, epidemiology and detection of this important resistance threat. *Clin Microbiol Rev*. 2001 Oct;14(4):933–51.
17. Vandenesch F, Naimi T, Enright MC, Lina G, Nimmo GR, Heffernan H, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* carrying Panton-Valentine leukocidin genes: worldwide emergence. *Emerg Infect Dis*. 2003 Aug;9(8):978–84.
18. Zervos MJ, Hershberger E, Nicolau DP, Ritchie DJ, Blackner LK, Coyle EA, et al. Relationship between fluoroquinolone use and changes in susceptibility to fluoroquinolones of selected pathogens in 10 United States teaching hospitals, 1991–2000. *Clin Infect Dis*. 2003 Dec 15;37(12):1643–8.
19. Wang H, Dzink-Fox JL, Chen M, Levy SB. Genetic characterization of highly fluoroquinolone-resistant clinical *Escherichia coli* strains from China: role of *acrR* mutations. *Antimicrob Agents Chemother*. 2001 May;45(5):1515–21.
20. Schrag SJ, McGee L, Whitney CG, Beall B, Craig AS, Choate ME, et al. Emergence of *Streptococcus pneumoniae* with very-high-level resistance to penicillin. *Antimicrob Agents Chemother*. 2004 Aug;48(8):3016–23.
21. Tanaka M, Nakayama H, Haraoka M, Saika T. Antimicrobial resistance of *Neisseria gonorrhoeae* and high prevalence of ciprofloxacin-resistant isolates in Japan, 1993 to 1998. *J Clin Microbiol*. 2000 Feb;38(2):521–5.
22. Kumarasamy KK, Toleman MA, Walsh TR, Bagaria J, Butt F, Balakrishnan R, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. *Lancet Infect Dis*. 2010 Sep;10(9):597–602.
23. Struelens MJ, Monnet DL, Magiorakos AP, Santos O'Connor F, Giesecke J, European NDM-1 Survey Participants. New Delhi metallo-beta-lactamase 1-producing Enterobacteriaceae: emergence and response in Europe. *Euro Surveill*. 2010 Nov 18;15(46):pii: 19716.

24. Mulvey MR, Grant JM, Plewes K, Roscoe D, Boyd DA. New Delhi metallo-beta-lactamase in *Klebsiella pneumoniae* and *Escherichia coli*, Canada. *Emerg Infect Dis*. 2011 Jan;17(1):103–6.
25. Chihara S, Okuzumi K, Yamamoto Y, Oikawa S, Hishinuma A. First case of New Delhi metallo-beta-lactamase 1-producing *Escherichia coli* infection in Japan. *Clin Infect Dis*. 2011 Jan 1;52(1):153–4.
26. Moquet O, Bouchiat C, Kinana A, Seck A, Arouna O, Bercion R, et al. Class D OXA-48 carbapenemase in multidrug-resistant enterobacteria, Senegal. *Emerg Infect Dis*. 2011 Jan;17(1):143–4.
27. Carrer A, Poirel L, Yilmaz M, Akan OA, Feriha C, Cuzon G, et al. Spread of OXA-48-encoding plasmid in Turkey and beyond. *Antimicrob Agents Chemother*. 2010 Mar;54(3):1369–73.
28. Mehta A, Rosenthal VD, Mehta Y, Chakravarthy M, Todi SK, Sen N, et al. Device-associated nosocomial infection rates in intensive care units of seven Indian cities. Findings of the International Nosocomial Infection Control Consortium. *J Hosp Infect*. 2007 Oct;67(2):168–74.
29. Pathak A, Marothi Y, Iyer RV, Singh B, Sharma M, Eriksson B, Macaden R, Lundborg CS. Nasal carriage and antimicrobial susceptibility of *Staphylococcus aureus* in healthy preschool children in Ujjain, India. *BMC Pediatr*. 2010 Dec 29;10:100.
30. Jain A, Shukla VK, Tiwari V, Kumar R. Antibiotic resistance pattern of group-a beta-hemolytic streptococci isolated from north Indian children. *Indian J Med Sci*. 2008 Oct;62(10):392–6.
31. Gaur A, Garg A, Prakash P, Anupurba S, Mohapatra TM. Observations on carbapenem resistance by minimum inhibitory concentration in nosocomial isolates of *Acinetobacter* species: An experience at a tertiary care hospital in north India. *J. Health Popul Nutr*. 2008 Jun;26(2):183–8.
32. Shahid M, Malik A, Akram M, Agrawal LM, Khan AU, Agrawal M. Prevalent phenotypes and antibiotic resistance in *Escherichia coli* and *Klebsiella pneumoniae* at an Indian tertiary care hospital: plasmid-mediated cefoxitin resistance. *Int J Infect Dis*. 2008 May;12(3):256–64.
33. Mathai E, Chandy S, Thomas K, Antoniswamy B, Joseph I, Mathai M, et al. Antimicrobial resistance surveillance among commensal *Escherichia coli* in rural and urban areas in Southern India. *Trop Med Int Health*. 2008 Jan;13(1):41–5.

34. Finley RL, Collignon P, Larsson DG, McEwen SA, Li XZ, Gaze WH, et al. The scourge of antibiotic resistance: the important role of the environment. *Clin Infect Dis*. 2013 Sep;57(5):704-10.
35. Casey JA, Curriero FC, Cosgrove SE, Nachman KE, Schwartz BS. High-density_livestock_operations, crop field application of manure, and risk of community-associated methicillin-resistant *Staphylococcus aureus* infection in Pennsylvania. *JAMA Intern Med*. 2013 Nov 25;173(21):1980-90.
36. Li YW, Wu XL, Mo CH, Tai YP, Huang XP, Xiang L. Investigation of sulfonamide, tetracycline, and quinolone antibiotics in vegetable farmland soil in the Pearl River Delta area, southern China. *J Agric Food Chem*. 2011 Jul13;59(13):7268-76.
37. European Food Safety Authority. The European Union Summary Report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in the European Union in 2009. *EFSA Journal*. 2011 9(7):2154[321pp.]. Available: <http://www.efsa.europa.eu/en/efsajournal/pub/2154.htm>. Accessed: 9 January 2014.
38. Butler MS, Blaskovich MA, Cooper MA. Antibiotics in the clinical pipeline in 2013. *J Antibiot (Tokyo)*. 2013 Oct;66(10):571-91.
39. World Health Organization, Geneva. WHO Policy Perspectives on Medicine. Promoting rational use of medicines: core components. 2002. Available: <http://apps.who.int/medicinedocs/pdf/h3011e/h3011e.pdf>. Accessed: 10 January 2014.
40. S KI, Chandy SJ, Jeyaseelan L, Kumar R, Suresh S. Antimicrobial prescription patterns for common acute infections in some rural and urban health facilities of India. *Indian J Med Res*. 2008 Aug;128(2):165-71.
41. Boyd S, Foster S. Patient behaviors and beliefs regarding antibiotic use: implications for clinical practice. 2006. Available: http://www.tufts.edu/med/apua/about_us/Poster1PatientBehaviorsandbeliefs.pdf. Accessed 11 January 2014.
42. Hawkins NJ, Wood F, Butler CC. Public attitudes towards bacterial resistance: a qualitative study. *J Antimicrob Chemother*. 2007 Jun;59(6):1155-60.
43. Björkman I, Erntell M, Röing M, Lundborg CS. Infectious disease management in primary care: perceptions of GPs. *BMC Fam Pract*. 2011 Jan 11;12:1.
44. Dua V, Kunin CM, White LV. The use of antimicrobial drugs in Nagpur, India. A window on medical care in a developing country. *Soc Sci Med*. 1994 Mar;38(5): 717-24.

45. Ministry of Health and Family Welfare 2013. Notification GSR 588E. New Delhi. Available: <http://www.cdsc.nic.in/writereaddata/588E30thAug2013.pdf>. Accessed on 21 January 2014.
46. Sharma M, Eriksson B, Marrone G, Dhaneria S, Lundborg CS. Antibiotic prescribing in two private sector hospitals; one teaching and one non-teaching: a cross-sectional study in Ujjain, India. *BMC Infect Dis*. 2012 Jul 12;12:155.
47. Das B, Sarkar C, Majumder AG. Medication use for pediatric upper respiratory tract infections. *Fundam Clin Pharmacol*. 2006 Aug ;20(4):385-90.
48. Pathak, A, Mahadik K, Dhaneria SP, Sharma A, Eriksson B, Lundborg CS. Antibiotic prescribing in outpatients: Hospital and seasonal variations in Ujjain, India. *Scand J Infect Dis*. 2011 Jul;43(6-7):479-88.
49. Bharathiraja R, Sridharan S, Chelliah LR, Suresh S, Senguttavan M. Factors affecting antibiotic prescribing pattern in paediatric practice. *Indian J Paediatr*. 2005 Oct;72(10):877-79.
50. Sivagnanam G, Thirumalaikolundusubramanian P, Mohanasundaram J, Raaj AA, Namasivayam K, Rajaram S. A survey on current attitude of practicing physicians upon usage of antimicrobial agents in southern part of India. *MedGenMed*. 2004 May 11;6(2):1.
51. Bhatia J, Cleland J. Health-care seeking and expenditure by young Indian mothers in the public and private sectors. *Health Policy Plan*. 2001 Mar;6(1):55-61.
52. Viberg N, Kalala W, Mujinja P, Tomson G, Lundborg CS. "Practical knowledge" and perceptions of antibiotics and antibiotic resistance among drugsellers in Tanzanian private drugstores. *BMC Infect Dis*. 2010 Sep 16;10:270.
53. Arason VA., Sigurdsson JA, Erlendsdottir H, Gudmundsson S, Kristinsson KG. *The role of antimicrobial use in the epidemiology of resistant pneumococci: A 10-year follow up*. *Microb Drug Resist*. 2006 Fall;12(3):169–76.
54. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay D. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and metanalysis. *BMJ*. 2010 May 18; 340: c2096.
55. Goossens H, Ferech M, Vander Stichele R, Elseviers M, ESAC Project Group. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet*. 2005 Feb 12-18; 365(9459):579-587.

56. Chung A, Perera R, Brueggemann AB, Elamin AE, Harnden A, Mayon-White R, et al. Effect of antibiotic prescribing on antibiotic resistance in individual children in primary care: prospective cohort study. *BMJ*. 2007 Sep1;335 (7617):429-34.
57. Steinke D, Davey P. Association between antibiotic resistance and community prescribing: A critical review of bias and confounding in published studies. *Clin Infect Dis*. 2001 Sep 15;33 Suppl 3:S193–205.
58. Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC Infect Dis*. 2014 Jan 9;14:13.
59. Madaras-Kelly KJ, Remington RE, Lewis PG, Stevens DL. Evaluation of an intervention designed to decrease the rate of nosocomial methicillin-resistant *Staphylococcus aureus* infection by encouraging decreased fluoroquinolone use. *Infect Control Hosp Epidemiol*. 2006 Feb;27(2):155–69.
60. Calil R, Marba ST, von Nowakowski A, Tresoldi AT. Reduction in colonization and nosocomial infection by multiresistant bacteria in a neonatal unit after institution of educational measures and restriction in the use of cephalosporins. *Am J Infect Control*. 2001 Jun;29(3):133–8.
61. Jawetz, E. Antimicrobial chemotherapy. *Annu Rev Microbiol*. 1956;10:85–114.
62. Leung E, Weil DE, Raviglione M, Nakatani H; World Health Organization World Health Day Antimicrobial Resistance Technical Working Group. The WHO policy package to combat antimicrobial resistance. *Bull World Health Organ*. 2011 May 1;89(5):390-2. doi: 10.2471/BLT.11.088435.
63. McEwen, S.A. Antibiotic use in animal agriculture: What have we learned and where are we going? *Anim Biotechnol*. 2006;17(2):239–250.
64. Bager F, Madsen M, Christensen J, Aarestrup FM. Avoparcin used as a growth promoter is associated with the occurrence of vancomycin-resistant *Enterococcus faecium* on Danish poultry and pig farms. *Pre Vet Med*. 1997 Jul;31(1-2):95–112.
65. Callaway TR, Edrington TS, Anderson RC, Harvey RB, Genovese KJ, Kennedy CN, et al. Probiotics, prebiotics and competitive exclusion for prophylaxis against bacterial disease. *Anim Health Res Rev*. 2008 Dec;9(2):217–25.
66. Potter A, Gerds V, Littel-van den Hurk Sv. Veterinary vaccines: Alternatives to antibiotics? *Anim Health Res Rev*. 2008 Dec;9(2):187–99.

67. Joerger RD. Alternatives to antibiotics: Bacteriocins, antimicrobial peptides and bacteriophages. *Poult Sci*. 2003 Apr;82(4):640–7.
68. Butler MS, Cooper MA. Screening strategies to identify new antibiotics. *Curr Drug Targets*. 2012 Mar;13(3):373–87.
69. Hogberg LD, Heddini A, Cars O. The global need for effective antibiotics: Challenges and recent advances. *Trends Pharmacol Sci*. 2010 Nov;31:509–15.
70. Monnet DL, Giesecke J. Public health need versus sales of antibacterial agents active against multidrug-resistant bacteria: a historical perspective. *J Antimicrob Chemother*. 2014 Apr;69(4):1151–3.
71. Infectious Diseases Society of America. The 10 × 20 initiative: Pursuing a global commitment to develop 10 new antibacterial drugs by 2020. *Clin Infect Dis*. 2010 Apr;50(8):1081–83.
72. Caron WP, Mousa SA. Prevention strategies for antimicrobial resistance: A systematic review of the literature. *Infect Drug Resist*. 2010;3:25–33.
73. Pittet D, Allegranzi B, Boyce J; World Health Organization World Alliance for Patient Safety First Global Patient Safety Challenge Core Group of Experts. The World Health Organization Guidelines on Hand Hygiene in Health Care and their consensus recommendations. *Infect Control Hosp Epidemiol*. 2009 Jul;30(7):611–622.
74. Allegranzi B, Pittet D. Role of hand hygiene in healthcare-associated infection prevention. *J Hosp Infect*. 2009 Dec;73(4):305–15.
75. Salama MF, Jamal WY, Mousa HA, Al-Abdulghani KA, Rotimi VO. The effect of hand hygiene compliance on hospital-acquired infections in an ICU setting in a Kuwaiti teaching hospital. *J Infect Public Health*. 2013 Feb;6(1):27–34.
76. Erasmus V, Brouwer W, van Beeck EF, Oenema A, Daha TJ, Richardus JH, et al. A qualitative exploration of reasons for poor hand hygiene among hospital workers: Lack of positive role models and of convincing evidence that hand hygiene prevents cross-infection. *Infect Control Hosp Epidemiol*. 2009 May;30(5):415–19.
77. Clerc O, Greub G. Routine use of point-of-care tests: usefulness and application in clinical microbiology. *Clin Microbiol Infect*. 2010 Aug; 16(8):1054–1061.
78. Bisno AL. Acute pharyngitis. *N Engl J Med*. 2001 Jan 18; 344(3):205–11.

79. Ayanruoh S, Waseem M, Quee F, Humphrey A, Reynolds T. Impact of rapid streptococcal test on antibiotic use in a pediatric emergency department. *Pediatr Emerg Care*. 2009 Nov;25(11):748-50.
80. Pulcini C, Gyssens IC. How to educate prescribers in antimicrobial stewardship practices. *Virulence*. 2013 Feb 15;4(2):192–202.
81. Lecky DM, McNulty CA, Touboul P, Herotova TK, Benes J, Dellamonica P, et al. Evaluation of e-Bug, an educational pack, teaching about prudent antibiotic use and hygiene, in the Czech Republic, France and England. *J Antimicrob Chemother*. 2010 Dec;65(12):2674–84.
82. Huttner B, Goossens H, Verheij T, Harbarth S, CHAMP consortium. Characteristics and outcomes of public campaigns aimed at improving the use of antibiotics in outpatients in high-income countries. *Lancet Infect Dis*. 2010 Jan;10(1):17–31.
83. Owens RC Jr. Antimicrobial stewardship: Concepts and strategies in the 21st century. *Diagn Microbiol Infect Dis*. 2008 May;61(1):110–28.
84. Drew, R.H. Antimicrobial stewardship programs: How to start and steer a successful program. *J Manag Care Pharm*. 2009 Mar;15(2 Suppl):S18–S23.
85. Beardsley JR, Williamson JC, Johnson JW, Luther VP, Wrenn RH, Ohl CC. Show me the money: Long-term financial impact of an antimicrobial stewardship program. *Infect Control Hosp Epidemiol*. 2012 Apr;33(4):398–400.
86. The World Bank. Country and lending groups. 2014.
Available: http://data.worldbank.org/about/country-classifications/country-and-lending-groups#Lower_middle_income. Accessed: 12 February 2014.
87. Registrar General of India. Census of India 2011. Available:
<http://www.censusindia.gov.in/2011census/censusinfodashboard>. Accessed: 12 February 2014.
88. Ministry of Health and Family Welfare. Central Bureau of Health Intelligence. National Health Profile of India 2012. Available:
<http://www.cbhidghs.nic.in/index2.asp?slid=1256&sublinkid=1163>. Accessed: 14 February 2014.
89. Ministry of Home Affairs. Directorate of Census Operations – Tamil Nadu. Census 2011. Available: www.census.tn.nic.in/index.php?pca_2011.html. Accessed: 14 February 2014.

90. Government of India Planning Commission (2011) Press Notes on Poverty Estimates 2011-2012. Available: http://planningcommission.nic.in/news/pre_pov2307.pdf. Accessed 20 February 2014.
91. Office of Registrar General of India. Million Death Study. Report on Cause of Death in India 2001-2003. Available: www.cghr.org/wordpress/wp-content/uploads/Causes_of_death_2001-03.pdf. Accessed: 22 February 2014.
92. Ministry of Health and Family Welfare. National Health Mission 2013. Available: <http://nrhm.gov.in/> Accessed: 23 February 2014.
93. Rural Health Statistics 2012. Available: <http://nrhm.gov.in/images/pdf/publication/RHS-2012.pdf>. Accessed: 23 February 2014.
94. Yip W, Mahal A. Health Care Systems of China and India: Performance and future challenges. *Health Aff.* 2008 Aug;27(4):921–32.
95. Bardhan P. The state of health services in China and India: A larger context. *Health Aff.* 2008;27(4): 933-936.
96. Jha P, Laxminarayan R. Choosing Health: An entitlement for all Indians. 2009. Available: <http://cghr.org/wordpress/wp-content/uploads/2011/06/Choosing-Health-report-FINAL.pdf>. Accessed: 26 February 2014.
97. Shahrawat R, Rao KD. Insured yet vulnerable: out-of-pocket payments and India's poor. *Health Policy Plan.* 2012 May;27(3):213-21.
98. Kotwani A, Ewen M, Dey D, Iyer S, Lakshmi PK, Patel A, et al. Prices and availability of common medicines at six sites in India using a standard methodology. *Indian J Med Res.* 2007 May;125(5): 645-654.
99. Ministry of Health and Family Welfare, Government of India, National List of Essential Medicines of India. 2011. Available: <http://pharmaceuticals.gov.in/NLEM.pdf>. Accessed: 28 February 2014.
100. Wagner AK, Graves AJ, Reiss SK, Lecates R, Zhang F, Ross-Degnan. Access to care and medicines, burden of health care expenditures and risk protection: results from the World Health Survey. *Health Policy.* 2011 May;100(2-3):151-8.
101. World Health Organization, Geneva. Media Centre, Fact Sheets. The top ten causes of death in the world 2011. Available: <http://www.who.int/mediacentre/factsheets/fs310/en/> Accessed: 3 March 2014.

102. Gales AC, Jones RN, Turnidge J, Rennie R, Ramphal R. Characterization of *Pseudomonas aeruginosa* isolates: occurrence rates, antimicrobial susceptibility patterns and molecular typing in the SENTRY antimicrobial surveillance program, 1997-1999. *Clin Infect Dis*. 2001 May 15;32 Suppl 2:S146-55.
103. Hoa NQ, Trung NV, Larsson M, Eriksson B, Phuc HD, Chuc NT, Lundborg CS. Decreased *Streptococcus pneumoniae* susceptibility to oral antibiotics among children in rural Vietnam: a community study. *BMC Infect Dis*. 2010 Mar 31;10:85.
104. Kandle SK, Ghatole MP, Takpere AY, Hittinalli VB, Yemul VL. Bacteriophage typing and antibiotic sensitivity pattern of *Staphylococcus aureus* from clinical specimen in and around Solapur (South Maharashtra). *J Commun Dis*. 2003 Mar;35(1):17-23.
105. Jain D, Sinha S, Prasad KN, Pandey CM. *Campylobacter* species and drug resistance in a north Indian rural community. *Trans R Soc Trop Med Hyg*. 2005 Mar;99(3): 207-214.
106. Patel V, Vaidya R, Naik D, Borker P. Irrational Drug Use in India: A prescription survey from Goa. *J Postgrad Med*. 2005 Jan-Mar;51(1):9-12.
107. World Health Organization (WHO), Geneva. WHO Global Strategy for Containment of Antimicrobial Resistance. 2001. Available: http://whqlibdoc.who.int/hq/2001/WHO_CDS_CSR_DRS_2001.2.pdf. Accessed: 4 March 2014.
108. Cars O, Högberg LD, Murray M, Nordberg O, Sivaraman S, Lundborg CS, So AD, Tomson G. Meeting the challenge of antibiotic resistance. *BMJ*. 2008 Sep 18;337:a1438.
109. Mathai E, Thomas RJ, Chandy S, Mathai M, Bergstrom S. Antimicrobials for the treatment of urinary tract infection in pregnancy: practices in southern India. *Pharmacoepidemiol Drug Saf*. 2004 Sep;13(9):645-52.
110. World Health Organization (WHO), Geneva. *Improving the containment of antimicrobial resistance*. :World Health Assembly 58.27: 108,2005. Available: http://apps.who.int/gb/ebwha/pdf_files/WHA58-REC1/A58_2005_REC1-en.pdf. Accessed: 4 March 2014.
111. Sahoo KC, Tamhankar AJ, Johansson E, Lundborg CS. Antibiotic use, resistance development and environmental factors: a qualitative study among healthcare professionals in Orissa, India. *BMC Public Health*. 2010 Oct 21;10:629.
112. Karageorgopoulos DE, Falagas ME. New antibiotics: optimal use in current clinical practice. *Int J Antimicrob Agents*. 2009;34 Suppl 4:55-62.

113. Cameron A, Ewen M, Ross-Degnan D, Ball D, Laing R. Medicine prices, availability, and affordability in 36 developing and middle-income countries: a secondary analysis. *Lancet*. 2009 Jan 17;373(9659): 240-9.
114. Purohit BC. Inter-state disparities in health care and financial burden on the poor in India. *J Health Soc Policy*. 2004;18(3): 37-60.
115. Varatharajan D, Thankappan R, Jayapalan S. Assessing the performance of primary health centres under decentralized government in Kerala, India. *Health Policy Plan*. 2004 Jan;19(1):41-51.
116. Dellit TH, Owens RC, McGowan JE Jr, Gerding DN, Weinstein RA, Burke JP. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis*. 2007 Jan 15;44(2):159–77.
117. Goossens H. Antibiotic consumption and link to resistance. *Clin Microbiol Infect*. 2009 Apr;15 Suppl 3:12–5.
118. Davey P, Brown E, Charani E, Fenelon L, Gould IM, Holmes A, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev*. 2013 Apr 30;4:CD003543.
119. District Collectorate. District Profile. Available: <http://www.vellore.tn.nic.in/distprof.htm>. Accessed 14 February 2014.
120. Christian Medical College, Vellore. Supplement Book - CMCTYear2011.pdf (n.d.) 2011. Available: <http://www.cmch-vellore.edu/pdf/CMCTYear2011.pdf>. Accessed 14 February 2014.
121. World Health Organization, Geneva. WHO Department of Essential Drugs and Medicines Policy. Essential Medicines and Health Products Information Portal. How to investigate drug use in health facilities. 1993. Available: <http://apps.who.int/medicinedocs/en/d/Js2289e/> Accessed 14 February 2014.
122. WHO Collaborating Centre for Drug Statistics Methodology, Oslo, Norway. ATC Index With DDDs. 2014. Available: http://www.whocc.no/atc_ddd_index. Accessed 18 February, 2014.
123. Biomerieux. *BacT/ALERT*® 3D: Healthcare. 2009. Available: http://www.biomerieux-usa.com/servlet/srt/bio/usa/dynPage?doc=USA_PRD_LST_G_PRD_USA_6. Accessed 14 February 2014.

124. Clinical and Laboratory Standards Institute (CLSI). 2014. Available: clsi.org/standards. Accessed: 14 February 2014.
125. Krueger RA, Casey MA. Focus groups: a practical guide for applied Research. 3rd ed. Thousand Oaks, CA: Sage Publications. 2000. pp.320.
126. R Project. The R Project for Statistical Computing. 2011. Available: <http://www.r-project.org>. Accessed 20 February 2014.
127. Naumova EN, Jagai JS, Matyas B, DeMaria A Jr, MacNeill IB, Griffiths JK. Seasonality in six enterically transmitted diseases and ambient temperature. *Epidemiol Infect.* 2007 Feb;135(2):281–92.
128. Lofgren E, Fefferman N, Doshi M, Naumova EN. Assessing seasonal variation in multisource surveillance data: annual harmonic regression. *Intelligence and Security Informatics: Biosurveillance*. Springer. pp. 114–123. Available: http://link.springer.com/chapter/10.1007/978-3-540-72608-1_11. Accessed 22 February 2014.
129. Naumova EN, Must A, Laird NM. Tutorial in Biostatistics: Evaluating the impact of “critical periods” in longitudinal studies of growth using piecewise mixed effects models. *Int J Epidemiol.* 2001 Dec;30(6):1332–41.
130. XE (2014). XE Currency Converter Exchange Rate. Available: <http://www.xe.com/currencyconverter/convert/?Amount=1&From=USD&To=INR>. Accessed 31 March 2014.
131. Björkman I, Berg J, Röing M, Erntell M, Lundborg CS. Perceptions among Swedish hospital physicians on prescribing of antibiotics and antibiotic resistance. *Qual Saf Health Care.* 2010 Dec;19(6):e8.
132. André M, Vernby A, Berg J, Lundborg CS. A survey of public knowledge and awareness related to antibiotic use and resistance in Sweden. *J Antimicrob Chemother.* 2010 Jun;65(6):1292-6.
133. Hoa NQ, Ohman A, Lundborg CS, Chuc NT. Drug use and health-seeking behaviour for childhood illness in Vietnam-a qualitative study. *Health Policy.* 2007 Aug;82(3):320-9.
134. National Commission on Macroeconomics and Health. Burden of Disease in India. Available: [http://www.who.int/macrohealth/action/NCMH_Burden%20of%20disease_\(29%20Sep%202005\).pdf](http://www.who.int/macrohealth/action/NCMH_Burden%20of%20disease_(29%20Sep%202005).pdf). Accessed: 1 March 2014.

135. Pathak A, Mahadik K, Dhaneria SP, Sharma A, Eriksson B, Lundborg CS. Surveillance of antibiotic consumption using the "focus of infection" approach in 2 hospitals in Ujjain, India. *PLoS One*. 2012;7(6):e38641.
136. Hoa NQ, Larsson M, Kim Chuc NT, Eriksson B, Trung NV, Stalsby CL. Antibiotics and paediatric acute respiratory infections in rural Vietnam: Healthcare providers' knowledge, practical competence and reported practice. *Trop Med Int Health*. 2009 May;14(5):546-55.
137. Government of Tamil Nadu. Tamil Nadu Health Systems Project. Standard Treatment Guidelines. 2010. Available: <http://www.scribd.com/doc/25528109/Standard-Treatment-Guidelines>. Accessed: 2 March 2014.
138. de Kraker ME, Jarlier V, Monen JC, Heuer OE, van de Sande N, Grundmann H. The changing epidemiology of bacteraemias in Europe: trends from the European Antimicrobial Resistance Surveillance System. *Clin Microbiol Infect*. 2013 Sep;19(9):860-8.
139. Adriaenssens N, Coenen S, Versporten A, Muller A, Vankerckhoven V, Goossens H; ESAC Project Group. European Surveillance of Antimicrobial Consumption (ESAC): quality appraisal of antibiotic use in Europe. *J Antimicrob Chemother*. 2011 Dec;66 Suppl 6:vi71-77.
140. Invasive bacterial infection surveillance (IBIS) Group, International clinical epidemiology network (INCLEN). Prospective Multicentre Hospital Surveillance of *Streptococcus pneumoniae* disease in India. *Lancet*. 1999 Apr 10; 353(9160):1216-21.
141. Sengupta A, Nundy S. The private health sector in India. *BMJ*. 2005 Nov 19; 331(7526): 1157-8.
142. Kaul S, Brahmadathan KN, Jagannati M, Sudarsanam TD, Pitchamuthu K, Abraham OC, et al. One year trends in the gram-negative bacterial antibiotic susceptibility patterns in a medical intensive care unit in South India. *Indian J Med Microbiol*. 2007 Jul;25(3):230-5.
143. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007 Mar 1;44 Suppl 2: S27-72.
144. Joshi S, Ray P, Manchanda V, Bajaj J, Gautam V, Goswami P, et al. Methicillin resistant *Staphylococcus aureus* (MRSA) in India: Prevalence & susceptibility pattern. *Indian J Med Res*. 2013 Feb;137(2):363-9.
145. Kumar S, Wanchu A, Abeygunasekera N, Sharma A, Singh S, Varma S. Profile of Presentation of Human Immunodeficiency Virus Infection in North India, 2003-2007. *Indian J Community Med*. 2012 Jul;37(3):158-64.

146. Das A, Anvikar AR, Cator LJ, Dhiman RC, Eapen A, Mishra N, et al. Malaria in India: The Center for the Study of Complex Malaria in India. *Acta Trop*. 2012 Mar;121(3):267–73.
147. Mathai E, Rolain JM, Verghese GM, Abraham OC, Mathai D, Mathai M, et al. Outbreak of scrub typhus in southern India during the cooler months. *Ann N Y Acad Sci*. 2003 Jun;990: 359–64.
148. Kaurthe J (2013) Increasing Antimicrobial Resistance and Narrowing Therapeutics in Typhoidal Salmonellae. *J Clin Diagn Res*. 2013 Mar;7(3): 576–9.
149. Williams A, Mathai AS, Phillips AS. Antibiotic prescription patterns at admission into a tertiary level intensive care unit in Northern India. *J Pharm Bioallied Sci*. 2011 Oct;3(4): 531–536.
150. Government of India, Ministry of Health and Family Welfare. National Centre for Disease Control (NCDC). Integrated Diseases Surveillance Programme (IDSP). 2014. Available: <http://www.idsp.nic.in/> Accessed 3 March 2014.
151. Med India Network for Health. Brand names and generic equivalents with price details. 2014. Available: <http://www.medindia.net/drug-price/index.asp>. Accessed: 3 March 2014.
152. Government of India, Ministry of Labour and Employment. Annual report to the people on employment. 2010. Table 5: Average daily wages/earnings (Rs) across social groups in India, 2004-05. Available: http://www.dget.nic.in/publications/Report_to_People.pdf. Accessed: 3 March 2014.
153. Government of India, Planning Commission. Report of the Steering Committee on AYUSH for the 12th five year plan 2012-2017. Available: http://planningcommission.gov.in/aboutus/committee/strgrp12/st_ayush0903.pdf. Accessed: 3 March 2014.
154. Wood F, Simpson S, Butler CC. Socially responsible antibiotic choices in primary care: a qualitative study of GPs' decisions to prescribe broad-spectrum and fluoroquinolone antibiotics. *Fam Pract*. 2007 Oct;24(5):427-34.
155. André M, Vernby A, Berg J, Lundborg CS. A survey of public knowledge and awareness related to antibiotic use and resistance in Sweden. *J Antimicrob Chemother*. 2010 Jun;65(6):1292-6.
156. Sahoo KC, Tamhankar AJ, Johansson E, Lundborg CS. Antibiotic use, resistance development and environmental factors: a qualitative study among healthcare professionals in Orissa, India. *BMC Public Health*. 2010 Oct 21; 10: 629.

157. Department of Health, United Kingdom. Choice of GP practice: The Patient Choice Scheme. 2012 Available: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_133411.pdf. Accessed: 5 March 2014.
158. Bate R, Tren R, Mooney L, Hess K, Mitra B, Debroy B, et al. Pilot study of essential drug quality in two major cities in India. *PLoS One*. 2009 Jun 23;4(6):e6003.
159. Lapi F, Tuccori M, Motola D, Pugi A, Vietry M, Montanaro N et al. Safety profile of the fluoroquinolones: analysis of adverse drug reactions in relation to prescription data using four regional pharmacovigilance databases in Italy. *Drug Saf*. 2010 Sep 1;33(9):789-99.
160. The Hindu. New National. Special Correspondent. Pharmacists oppose sales record. 2014 March 23. Available: <http://www.thehindu.com/news/national/pharmacists-oppose-sales-record-rule/article5820428.ece>. Accessed: 23 March 2014.
161. Government of India. Narcotics Control Bureau. Narcotic Drugs and Psychotropic Substances Act. 1985. Available: <http://narcoticsindia.nic.in/NDPSACT.htm> Accessed: 23 March 2014.
162. Ministry of Finance, Income Tax Department. Circular No 5/2012. Inadmissibility of expenses incurred in providing freebies to medical practitioner by pharmaceutical and allied health sector industry. 2012. Available: <http://law.incometaxindia.gov.in/DIT/Circulars.aspx>. Accessed: 23 March 2014.
163. Tängdén T, Eriksson B-M, Melhus Å, Svennblad B, Cars O. Radical reduction of cephalosporin use at a tertiary hospital after educational antibiotic intervention during an outbreak of extended-spectrum β -lactamase-producing *Klebsiella pneumoniae*. *J Antimicrob Chemother*. 2011 May;66(5):1161–67.
164. Ulfvarson J, Rahmner PB, Fastbom J, Sjövikar S, Karlsson EA. Medication reviews with computerised expert support: evaluation of a method to improve the quality of drug utilisation in the elderly. *Int J Health Care Qual Assur*. 2010;23(6):571-82.
165. Davey P, Sneddon J, Nathwani D. Overview of strategies for overcoming the challenge of antimicrobial resistance. *Expert Rev Clin Pharmacol*. 2010 Sep;3(5):667-86.
166. Government of India, Ministry of Labour and Employment. Second Annual Report to the People on Employment. Table 4.5: Average Daily Wage Rates (in Rs.) across different population groups and types of works. 2011. Available: www.dget.nic.in/publications/annualreportemployment2011.pdf. Accessed: 25 March 2013.

167. Roberts RR, Hota B, Ahmad I, Scott RD 2nd, Foster SD, Abbasi F, et al. Hospital and societal costs of antimicrobial-resistant infections in a Chicago teaching hospital: implications for antibiotic stewardship. *Clin Infect Dis*. 2009 Oct 15;49(8):1175-84.
168. Mauldin PD, Salgado CD, Hansen IS, Durup DT, Bosso JA. Attributable hospital cost and length of stay associated with health care-associated infections caused by antibiotic-resistant gram-negative bacteria. *Antimicrob Agents Chemother*. 2010 Jan;54(1):109-15.
169. de Kraker ME, Davey PG, Grundmann H; BURDEN study group. Mortality and hospital stay associated with resistant *Staphylococcus aureus* and *Escherichia coli* bacteremia: estimating the burden of antibiotic resistance in Europe. *PLoS Med*. 2011 Oct;8(10):e1001104.
170. Pai NP, Vadnais C, Denkinger C, Engel N, Pai M. Point-of-Care Testing for Infectious Diseases: Diversity, Complexity, and Barriers in Low- And Middle-Income Countries. *PLoS Med*. 2012 Sept 04;9(9):e1001306.
171. Altiner A, Brockmann S, Sielk M, Wilm S, Wegscheider K, Abholz HH. Reducing antibiotic prescriptions for acute cough by motivating GPs to change their attitudes to communication and empowering patients: a cluster-randomized intervention study. *J Antimicrob Chemother*. 2007 Sep;60(3):638-44.
172. Lambert MF, Masters GA, Brent SL. Can mass media campaigns change antimicrobial prescribing? A regional evaluation study. *J Antimicrob Chemother*. 2007 Mar;59(3):537-43.
173. McNulty CA, Lecky DM, Farrell D, Kostkova P, Adriaenssens N, Koprivová Herotová T, et al. Overview of e-Bug: an antibiotic and hygiene educational resource for schools. *J Antimicrob Chemother*. 2011 Jun;66 Suppl 5:v3-12.
174. Fonseca MJ, Santos CL, Costa P, Lencastre L, Tavares F. Increasing awareness about antibiotic use and resistance: a hands-on project for high school students. *PLoS One*. 2012;7(9):e44699.
175. Touboul P, Dunais B, Urcun JM, Michard JL, Loarer C, Azanowsky JM, et al. The e-Bug project in France. *J Antimicrob Chemother*. 2011 Jun;66 Suppl 5:v67-70.
176. Haider SI, Johnell K, Weitoft GR, Thorslund M, Fastbom J. The influence of educational level on polypharmacy and inappropriate drug use: a register-based study of more than 600,000 older people. *J Am Geriatr Soc*. 2009 Jan;57(1):62-9.
177. Stead M, Hastings G, McDermott L. The meaning, effectiveness and future of social marketing. *Obes Rev*. 2007 Mar;8 Suppl 1:189-93.

178. Formoso G, Paltrinieri B, Marata AM, Gagliotti C, Pan A, Moro ML, et al. Feasibility and effectiveness of a low cost campaign on antibiotic prescribing in Italy: community level, controlled, non-randomised trial. *BMJ*. 2013 Sep 12;347:f5391.
179. Holdford DA. Using buzz marketing to promote ideas, services, and products. *J Am Pharm Assoc*. 2004 May-Jun;44(3):387-95; quiz 395-6.
180. Hjelm K, Bard K. Beliefs about health and illness in latin-american migrants with diabetes living in sweden. *Open Nurs J*. 2013 Apr 5;7:57-65. doi: 10.2174/1874434601307010057. Print 2013.
181. Stålsby Lundborg C, Tamhankar AJ. Understanding and changing human behavior - Antibiotic mainstreaming as an approach to facilitate modification of provider and consumer behavior. *Ups J Med Sci*. 2014 Apr 15.
182. Ravindran TK, Kelkar-Khambete A. Gender mainstreaming in health: looking back, looking forward. *Glob Public Health*. 2008;3Suppl 1:121-42.
183. Weerasuriya K, Stelling J, O'Brien TF. Containing antimicrobial resistance: a renewed effort. *Bull World Health Organ*. 2010 Dec 1;88(12):878. doi: 10.2471/BLT.10.084236.
184. Marik PE, Lipman J. The definition of septic shock: implications for treatment. *Crit Care Resusc*. 2007 Mar;9(1):101-3.
185. World Health Organization. Regional Office for South-East Asia, New Delhi. Step-by-Step Approach for development and implementation of hospital antibiotic policy and standard treatment guidelines. 2011. Available: www.searo.who.int/entity/world_health_day/.../whd-11_ha-policy.pdf. Accessed 26 March 2014.
186. Chandy SJ, Michael JS, Balaji V, Abraham OC, Bachav SS, Kshirsagar NA. ICMR Programme on Antibiotic Stewardship, Prevention of Infection and Control (ASPIC). *Indian J Med Res*. 2014 Feb;139:226-30.

10. APPENDICES

APPENDIX 1 – PROFORMA FOR ANTIBIOTIC USE SURVEILLANCE

INDIVIDUAL DRUG USE

AMUREC

Form No.

Geographical Area : ☐ 1 = Vellore Town 2 = K.V. Kuppam Block

Type of Health Facility : ☐ 1 = Medical Shop 2 = Hospital 3 = Private Practitioner

Unique Identifier of health facility :

Serial Number : Date :

Details of Prescription				
1.	Total Number of Drugs Prescribed			
2.	Patient given one or more injections		1. Yes 2. No	
3.	Patient given atleast 1 antibiotic		1. Yes 2. No	
4.	Patient given more than 1 antibiotic		1. Yes 2. No	
5.	Patient given antibiotic with prescription		1. Yes 2. No	
6.	Antimicrobial details	Prescribed		Dispensed
		mg strength	no. units	mg strength no. units
	Norfloxacin			
	Cotrimoxazole			
	Ampicillin			
	Amoxicillin			
	Augmentin			
	Gentamicin			
	Nitrofurantoin			
	Cephalexin			
	Cefuroxime			
	Cefotaxime			
	Tetracycline			
	Doxycycline			
	Nalidixic Acid			
	Chloramphenicol			
	Other-1			
	Other-2			
	Other-3			

Age in years Gender : ☐ 1 = Male 2 = Female

Main Symptoms : _____

Signature of Research Assistant : _____

Signature Co-investigator : _____

APPENDIX 2

FOCUS GROUP DISCUSSION GUIDE - Antibiotic Use and Resistance

I. Introduction

Welcome participant and introduce the research staff present.

- Explain general purpose of interview discussion and why participants were chosen.
- To maintain confidentiality
- Explain presence and purpose of recording equipment and introduce observers.
- Inform the time duration of discussion and need to allow all to participate.
- Invite participant to introduce himself

Objective: To elicit views and perception of participants about antibiotic use and resistance.

II. Discussion

Themes in our discussion with public groups:

- Awareness, knowledge of infections and antibiotics
- Patterns and practices in antibiotic use
- Treatment preferences between doctors, pharmacist, other practitioners
- Understanding of resistance and strategies for reducing antibiotic use

Themes in our discussion with doctor and pharmacist groups:

- Pattern and practices of antibiotic use in community
- Reasons, pressures and incentives for high antibiotic usage
- Knowledge and understanding of infections, antibiotics and resistance
- Possible ways and strategies for appropriate antibiotic use

III. Closing - *Closing remarks: Thank you for participating in this discussion.*

APPENDIX 3 PROFORMA FOR PHARMACOECONOMICS STUDY

Patient Study No:-

Hospital Number:-

Patient Initials:-

Age:- Sex:- Wards/Units:-

Date of Admission:- Date of Discharge:-

Date of Culture (reported):- No. of Days Hospitalized:-

Primary Diagnosis:- _____

- Co-morbidities:-
1. _____
 2. _____
 3. _____
 4. _____
 5. _____

Antibiotic Administration and Sensitivity (in order of purchase)

Sl No	Date of first administration	Antibiotic Name	Antibiotic dose	Qty	D-	E*/C*	Organisms found #		
1									
2									
3									
4									
5									
6									
7									
8									
9									
‘Minimum Cost’ Antibiotic									
1									
2									

Susceptibility Culture No.

*E- Empiric, C-Changeover
#S- Susceptible, R- Resistant, I-Intermediate
~D- Antibiotic Descalation

COST														
Bed/ Treatment/ Nursing/ Professional	Compressed air/ Oxygen/ Ventilator/ Postural Drainage/	ICU/ MHDU	Medicines	Blood bank/ Transfusion / Electrophoresis/ Red cell/ Blood products	Diet/ Exercise/ PMR	Surgery/ Operation fees/ Instruments/ Theatre/ Dialysis	Medical Records/ Registration/	Biopsies	Micro /Path/ Biochem/ Virology/Labs	Diagnostic Scans / Imaging	Others	Total cost	Total Pharmacy Cost	Cost of Antibiotic alone
														01. Enterococcus faecalis 02. NFGFB 03. E.coli 04. MRSA 05. MRSA, Staph aureus 06. Pseudomonas 07.B & Streptococcus Gp B 08. Klebsiella spp. 09. Enterobacter 10. Shigella sonnei 11. Enterobacter spp 12. Clostridium difficile 13.B & Streptococcus Gp A 14. Other - specify

