

Fall 2015

# Tracing the Human Healthcare Roots of Antibiotic Resistance in India: Causes, Challenges, and Promising Solutions

Kelsey Matteson

*SIT Graduate Institute - Study Abroad*

Follow this and additional works at: [https://digitalcollections.sit.edu/isp\\_collection](https://digitalcollections.sit.edu/isp_collection)



Part of the [Chemicals and Drugs Commons](#), and the [Medical Pharmacology Commons](#)

---

## Recommended Citation

Matteson, Kelsey, "Tracing the Human Healthcare Roots of Antibiotic Resistance in India: Causes, Challenges, and Promising Solutions" (2015). *Independent Study Project (ISP) Collection*. 2218.

[https://digitalcollections.sit.edu/isp\\_collection/2218](https://digitalcollections.sit.edu/isp_collection/2218)

This Unpublished Paper is brought to you for free and open access by the SIT Study Abroad at SIT Digital Collections. It has been accepted for inclusion in Independent Study Project (ISP) Collection by an authorized administrator of SIT Digital Collections. For more information, please contact [digitalcollections@sit.edu](mailto:digitalcollections@sit.edu).

# Tracing the Human Healthcare Roots of Antibiotic Resistance in India: Causes, Challenges, and Promising Solutions

New Delhi, India

Kelsey Matteson

Academic Director: Dr. Azim Khan

Project Advisor: Dr. Sumanth Gandra

SIT Study Abroad

India: Public Health, Policy Advocacy, and Community

Fall 2015

## Table of Contents

I.	Acknowledgements	pg. 3
II.	Abstract	pg. 4
III.	Introduction	pg. 5
	- Study Objectives	pg. 6
	- Research Questions	pg. 7
	- Fieldwork Methods	pg. 7
V.	Background	pg. 8
	- State and Burden of Resistance	pg. 10
VI.	Causes of Antibiotic Resistance in India	pg. 13
	- Role of the Pharmaceutical Company	pg. 13
	- Role of the Medical Prescriber	pg. 14
	- Role of the Patient	pg. 17
	- Role of the Pharmacist	pg. 18
VII.	Challenges and Solutions	pg. 19
VIII.	Conclusion	pg. 37
IX.	Project Limitations	pg. 39
X.	Recommendations for Further Study	pg. 40
XI.	Bibliography	pg. 41

## Acknowledgements

I am immensely grateful to so many of the wonderful people that have helped me during my research period. A million thanks to Dr. Sumanth Gandra for going above and beyond as my advisor, patiently answering any questions I had, and searching for opportunities for me. The work that CDDEP does is amazing and inspiring, and I feel very lucky to have had the opportunity to visit there and talk with its staff. Thank you to my SIT advisors, Azim ji and Abid ji, for sharing their extensive knowledge and much-needed guidance. To Bhavna ji, Goutam ji, and Archana ji: I am so grateful for the warmth, love, and encouragement you all provided over the last four months, which helped make Delhi my second home. Thank you so much to my Delhi host family, for welcoming into your home for three months, and helping me to learn and grow. I am forever grateful to my family at home for their unconditional love, endless patience, and needed support. And, of course, much is owed to all of the wonderful doctors, researchers, and public health workers who I was lucky enough to talk to and observe with while researching this project. I feel extremely privileged to have learned from so many individuals with extensive knowledge and expertise.

## Abstract

The rapid development of biological defense mechanisms by bacteria, or antibiotic resistance, is a dangerously progressing public health concern worldwide. The spread of antibiotic resistant pathogens are not only a threat to the security of healthcare facilities and the stability of modern medicine across the globe, but this phenomenon also creates a particular burden on countries with a high prevalence of infectious disease such as India. This study attempts to explore India's unique human healthcare causes of the emergence and spread of antibiotic resistance, comprehend the obstacles that have created roadblocks to change, and outline possible solutions to overcome these challenges. The study was conducted under the advisement of the New Delhi Center for Disease Dynamics, Economics, and Policy. The main field methods were observation and interviews with doctors, microbiologists, researchers, and public health workers in India; attendance at public lectures and medical conferences; and a review of secondary literature sources. The findings indicate that the causes of antibiotic resistance are multi-faceted, occur at all stages of healthcare delivery, and include the actions and attitudes of many stakeholders, including patients, medical professionals, pharmacists, and drug companies. Findings also detail possible challenges for implementing solutions, such as the absence of comprehensive data, a lack of awareness by the general public and medical communities, an overburdened health system fueled by a scarcity of resources, and delays in the innovation of diagnostic tools and alternative therapies.

## Introduction

Evolution is the most powerful natural force; it has sculpted and melded every piece of life on this planet. In a race between man's capacity to engineer modern medicine and the biological drive to survive and reproduce, evolution will always win out; one can't outsmart the forces that shaped its own creation. Antimicrobial resistance (AMR) is the pinnacle of the competition between man's inventions and evolutionary ingenuity, and it is this struggle which provides one of the most pressing global health crises of the 21<sup>st</sup> century.

When Alexander Fleming identified penicillin in 1929, it was considered one of the greatest medical achievements in human history and was thought to be the end of death by infectious disease (Raghunath 2008). Although the development of antibiotics was a major victory in the treatment of communicable disease, it also prompted a biological "arms race" between microorganisms and medical technology (WHO 2014). The microorganisms of particular concern here are bacteria, as their increasing ability to survive even the most intense disinfectants and newest generations of antibiotics has been widely documented by global organizations such as the CDC and the WHO and constitute the largest potential threat to public health (CDC 2015). Almost all advanced procedures of modern medicine - from surgery to chemotherapy to basic sterilization - are extremely dependent on our supply of antimicrobials remaining effective. As one representative of the Indian Medical Research Council explained in a lecture on AMR, a post-antibiotic world, in which pan-resistant microorganisms are everywhere and antibiotics are no longer effective, would threaten medical advances by "forcing us to recede to the dark ages, where people will die of simple infections and medical surgeries and procedures will be impossible to perform" due to an inability to disinfect tools, sanitize

healthcare facilities, or treat post-operative infection (Lecture Speaker 2, 17 November 2015).

Identifying and controlling the factors which have contributed to the emergence and spread of AMR is a highest priority for the security of global health.

### Study Objectives

The goal of the study was to explore the human healthcare causes of the spread and emergence of antibiotic resistance specific to India. It looks at the interventions currently being pursued in India and perceptions of obstacles to implementing these solutions by a few medical professionals, researchers, and public health workers. Although antimicrobial resistance encompasses a diversity of microorganisms, including viruses, fungi, and protozoa, this study primarily focuses on bacterial antibiotic resistance as this is estimated by the CDC to have the highest potential cost to public health, and is of particular concern in Indian healthcare. The study focuses specifically on human healthcare causes of AMR, and does not address in-depth agricultural or environmental factors. The study intends to understand the sources of this public health problem in an Indian-specific context, gain insight into practical obstacles from the perspectives of various experts, and seek knowledge about realistic and feasible steps to putting preventive measures in place. When discussing factors contributing to AMR, the study does not intend to associate blame with any of the mentioned stakeholders, nor does it mean to imply by its specificity that India is the only contributor to the problem. Resistance is a worldwide phenomenon, and many developed nations are far higher contributors to the global burden. Instead, it is believed by the researcher that India has high potential for being a global force for positive change in this area, and will hopefully only benefit from more information compiled and

awareness spread. Hopefully, this study will contribute a small piece of insight in order to pave the way for further, more extensive efforts.

### **Research Questions**

The main question that the study seeks to answer is: what are the human healthcare causes of antibiotic-resistant infections in India and how can these problems be addressed? What practices in Indian healthcare facilities and pharmacies contribute to the emergence and spread of resistant bacteria? What promising research is currently being pursued by the government, public health organizations, and individual hospitals concerning AMR in India? Have any preventive measures been effective so far and, if so, how can these solutions be implemented on a larger scale? What are some of the cultural, economic, and political factors that create obstacles for implementing preventive measures and stewardship programs?

### **Field Methods**

Field methods include interviews, observation in hospitals and at CDDEP, scientific journal articles, one public lecture and panel discussion, “Rational Uses of Antibiotics” at AIIMS medical college and one medical conference “Antimicrobials: Access and Sustainable Effectiveness” at India Habitat Centre. The researcher collaborated with the New Delhi Center of Disease Dynamics, Economics, and Policies (CDDEP) and was advised by an infectious disease specialist and epidemiologist, Dr. Sumanth Gandra, who is a research fellow at CDDEP. Through this advising under CDDEP, the researcher was connected to Indian experts on AMR for interviews, had access to studies and research published by CDDEP, and was able to talk with and observe doctors and researchers studying AMR and global antibiotic usage. Nine individuals



were personally interviewed by the researcher either by phone or in-person, two of whom were interviewed on multiple occasions. Interviews were semi-structured, and therefore varied depending on the area of expertise and responses of the interviewee, but primarily asked for experiences with and opinions on India-specific causes, challenges, and promising solutions. As secondary sources were primarily used to obtain any statistical data, interviews were instead utilized to gain insight into the practical realities and experiences of those working in various aspects of healthcare that could not be obtained from literature review alone. All interviewees were fully informed of the goals of the study and informed consent was obtained. Varying levels of identification are used for interviewees in respect for their wishes concerning anonymity.

### **Background**

Antimicrobial resistance (AMR) is the process by which pathogenic microorganisms evolve defense mechanisms to become impervious to the medications which were once used to cure or prevent them (WHO 2015). Antibiotics work by two major approaches: either by killing the bacteria itself, or by inhibiting the cell's reproduction (Aminov 2010). There are dozens of different types of antibiotics currently in use in the world today, all of which inhibit varying bacterial cell processes essential to its life or reproduction (Tenover 2006). Each category of antibiotic targets bacterial cells differently, and therefore, are specifically targeted and designed to treat only certain types of bacterial infections. When antibiotics are used, particularly when they are used unnecessarily or in the wrong dose or duration, it increases the selective pressure in a population of bacteria, causing vulnerable microorganisms to die and allowing the stronger, more evolved bacteria to survive and reproduce.

Bacteria are extremely well-adapted to quickly develop resistance. They multiply at astonishingly fast rates, can develop resistant strains through a single base pair mutation and are able to pass on resistant genes through a variety of unique mechanisms, such as horizontal gene transfer (Davies and Davies 2010). After the cycle of antimicrobial use and bacterial adaptation is completed a certain number of times, eventually the only bacterial population that remains is adapted to be completely impervious to the medicines attempting to target it (Tenover 2006). Antimicrobial-resistant microorganisms eventually stop responding to the classes of antibiotics that were once used to treat them. Corresponding infections become more difficult to treat, requiring costly or toxic drugs and more extensive care, and can possibly become incurable with any medication (Davies and Davies 2010).

A certain amount of bacterial evolution is inevitable and natural - it has been happening since the beginning of life itself (Lecture Speaker 1, 17 November 2015). Antibiotic resistance therefore has always existed, but has become a critical problem during the last 30 years, as the rate of the emergence and spread of resistant bacteria has obscenely accelerated due to antimicrobial misuses (WHO 2015). Without imprudent practices in human medicine, population dynamics would keep the proportion of resistant organisms low enough so it would not interfere with clinical outcomes (Lecture Speaker 1, 17 November 2015). However, misuse of antimicrobials has caused the evolutionary process of selective pressure to increase exponentially and, as a result, antibiotics continually become ineffective as resistant pathogenic microorganisms continue to spread and reproduce (Raghunath 2008; CDC 2015).

### **The State and Burden of Antimicrobial Resistance in India**

It may seem that in a healthcare infrastructure like India's, which suffers from an imbalance of resources and a lack of financial support, that practices intended to control antibiotic misuse are extraneous or unnecessary. One doctor at a rural, public hospital shed light on this conflict of priority: "[Antibiotic resistance] is not something many doctors in India will recognize as an issue. With so many different problems [facing] patients and doctors in rural, [impoverished] areas, anything not immediate is put on the back burner. Doctors will say they don't have time to confirm a diagnosis or the resources to run tests" (Interview 1, 14 October 2015).

First, it is essential to understand that, although the burden is often difficult to see in the short-term, antibiotic resistance carries profound and often devastating consequences. The progression of AMR is not something that merely harms individual patients or even individual hospitals. Resistant bacteria are exceptional at spreading and traveling at highly accelerated rates, through water supplies, food, and person-to-person transmission. Regional studies have been conducted over the last five years in India which reveal the alarming prevalence of these resistant bacteria. It is estimated that 95% of adults in India carry bacteria that are resistant to  $\beta$ -lactam antibiotics (Shaikha 2015).  $\beta$ -lactam resistant enterobacteriaeae has been reported in 70-90% of Indian tertiary level hospitals (Ghafur et al. 2012). Research has revealed rapidly accelerating rates of Methicillin-resistant *Staphylococcus aureus* (MRSA) infections and last-resort, Carbapenems-resistant *klebsiella pneumonia* in Indian healthcare facilities (Coghlan 2015). Cases of entirely pan-resistant infections in tertiary-level hospitals and the widespread presence of antibiotic resistant bacteria in major city water supplies, such as New Delhi, have also been documented (Kumar et al. 2013).

The burden of resistant infections in India is deep and multi-faceted. Resistant infections can have double the mortality rate of their drug-susceptible counterparts. Methicillin-resistant *Staphylococcus aureus* (MRSA) infections, for example, kill at a rate 64% higher than susceptible staph (WHO 2015). Resistance elongates the duration of illness and the intensity of care required so that AMR-resistant infections are able to spread to a larger number of people. Multi-drug or pan-resistant infections are most likely to emerge and become epidemic in areas where infectious disease is widespread and sanitation is low (CDC 2015). Socioeconomically poor areas with high infection rates, such as urban slums, are most at risk for severe outbreaks of these dangerous infections as well as the least equipped to handle such a crisis and the most likely to have high mortality rates for nosocomial infections. Rural areas routinely fall victim to AMR infections, and unlike in urban areas, those affected are often not able to afford or access the best care or the newest generation of powerful antibiotics. The World Health Organization and the Center for Disease Control estimate at least 2 million deaths every year directly as a result of resistant infections (WHO 2015).

The financial burdens of antibiotic misuse and resistant infections take a toll on every level of society. With over 600 million people living in poverty in India, the inappropriate use of antibiotics is a massive waste of scarce resources on expensive drugs that are not indicated or insufficiently dosed (Shrinivasan 2010; Saradamma et al. 2000). When a patient has a multidrug-resistant infection, they require prolonged treatment with powerful, late-generation antibiotics which are often more costly and more dangerous, with serious side effects and a higher chance of mortality (Kumar et al. 2013). The intensive care and prolonged stay not only affect patient outcomes and quality of life, but also increase the cost of healthcare for both individuals and

country expenditure overall (Times of India 2014; Boucher 2009). A nationwide analysis of the financial burden of resistance in India has not yet been published, but comparatively, the direct calculated annual burden of resistant infections in the UK is £1 billion and over \$20 billion in the US (Plowman et al. 2001; APUA 2014).

And that's nothing compared to the threats that are slowly but surely emerging: the spread of antibiotic resistance has devastating, long-term consequences in hospitals and health centers. India is the first country to report resistance to colistin, a nephrotoxic and neurotoxic antibiotic reserved for only last-resort treatment. Colistin-resistant bacteria has been detected in Delhi hospitals at a rate of 4-5%, with corresponding infections often deemed as pan-resistant and untreatable (Shrivastava 2014). With the widespread presence of pan-resistant pathogens, hospital-acquired or post-operative infections can become deadly (CDC 2014). As the problem increases in severity, the safety of treatments such as organ transplants, cancer chemotherapy, or major surgery will be heavily compromised without effective antimicrobials to disinfect tools, sanitize operating rooms, or treat post-operative infections. According to a study by CDDEP, "up to half of infections after surgery and over a quarter of infections after chemotherapy are caused by organisms already resistant to standard prophylactic antibiotics" (Teillant et al. 2015). CDDEP estimated that a "30% reduction in the efficacy of preventive antibiotics given routinely before, during, or after these procedures could result in 120,000 more infections and 6,300 infection-related deaths every year" (Teillant et al. 2015). With nothing available to fight resistant pathogens, these microorganisms would rapidly spread to other hospitals, throughout the community, and across the country (Kumar et al. 2013). The major infectious diseases that we

have spent a century combatting would risk becoming uncontrollable and would derail India's progress in reaching human health targets set by WHO and the UN.

Enforcing stricter medicine protocols and implementing surveillance programs are not extraneous costs, but economically and medically responsible choices necessary for a sustainable future of medicine. Early prevention, especially in the form of antibiotic stewardship programs, is a relatively inexpensive option. Considering the severity of the consequences of inaction, particularly in overburdened, rural, or low-socioeconomic areas, this is a necessary step which could prevent the costly medical disaster of a post-antibiotic society in the near future (WHO 2015).

## Causes of Antibiotic Resistance in India

### **Role of the Pharmaceutical Company**

For the first few decades after penicillin was discovered and mass-produced, pharmaceutical companies developed new antimicrobials with regularity, replacing them as frequently as their old brands became ineffective due to resistance. However, during the last 30 years, as life spans have increased and chronic conditions like diabetes and heart disease have become the focus for medical innovation, big pharmaceutical companies have brought the research and development of new antimicrobials, particularly gram-negative antibiotics, to a startlingly halt (Boucher et al. 2009). No new classes of antibiotics have been discovered and produced since 1987 (Knapton 2015). One epidemiologist explained this change as follows: "For pharmaceutical companies there is simply not enough return on their investment to continue to develop new antimicrobials. They are only taken by a patient for a short, temporary period,

bacterial infections are curable, and after a while they become ineffective due to the development of resistance” (Interview 4, 1 December 2015).

One particularly harmful trend in Indian pharmaceuticals is the production of fixed-combination antibiotics (FDCs), where two or more antibiotics are combined and administered as one pill (CDMU 2010). For pharmaceutical companies, these combinations are an easy way to sell two medicines when one (or even none) may be needed for the patient, significantly increasing profits (Gautum and Saha 2008). According to one microbiologist interviewed, many of these fixed-combination antibiotics are irrational combinations, with little to no evidence indicating their effectiveness (Interview 9, 4 December 2015). Literature suggests that many FDCs can have toxic effects, have a higher risk of adverse drug effects, and contribute to the occurrence and severity of in-patient antibiotic-resistant infections (Hirsch et al. 1960). More than 100 drug combinations which are not approved in any developed country are currently being marketed in India (CDMU 2010). Despite the overwhelming evidence that most brands are unnecessary or even harmful, fixed-dose combination antibiotics are still widely administered for surgical prophylaxis and in basic antimicrobial therapies (Gautum and Saha 2008).

### **Role of the Medical Prescriber**

In sheer volume, India is the highest consumer of antibiotics in the world, with 12.9 billion units being consumed in 2010 alone (Ganguly 2011). The use of antibiotics in India doubled in the five years between 2006 and 2011, with a particular increase in sales of new-generation, powerful antibiotics such as carbapenems, linezolid, daptomycin, and tigecyclin, which are intended to be reserved as clinical last-resorts to the most severely virulent and

resistant infections (DNA 2011; Ganguly 2011). What is distressing about these high rates of drug consumption is that instead of being indicative of expanded access to medicine, most increases in the sale of antibiotics are for conditions that are not treated by them, such as viral or fungal infections. One doctor from the All India Institute of Medical Sciences (AIIMS) explained, “As high as 50% of antibiotics are used for something that is not treated by antimicrobials. In many hospitals and practices in India, antibiotics are routinely prescribed for every fever, cough, or diarrhea case, even when there is no indication of a bacterial infection” (Lecture Speaker 2, 17 November 2015). In regional studies, depending on the area, 45 to 80% of patients with symptoms of acute respiratory infections and diarrhea were given an antibiotic, even though these are more commonly attributable to viral infections for which these medicines are ineffective (Kumar et al. 2008).

Over-prescription and misuse have deep roots which extend in many different directions. First, it begins with a lack of knowledge about the role of antimicrobials and a misperception of antibiotics as an inexhaustible resource, by both medical professionals and lay people. According to one hospital director, “In India, patients - even doctors sometimes - assume that antibiotics are pills that cure everything. They will take them immediately when they start to get sick, whether or not they [have a bacterial infection]” (Interview 2, 16 October 2015). In a 2015 study of patient perceptions, a large proportion of individuals assumed that any time they felt particularly ill or had been sick longer than they expected to be, antibiotics would help (Wellcome Trust 2015). The majority of individuals surveyed had never heard of antimicrobial resistance, were skeptical of the concept when it was explained to them, and didn’t believe their use of antibiotics was excessive. Misconceptions often lead to patients either demanding



antibiotics from practitioners and switching doctors if they don't receive them or going to a pharmacist to obtain medication without consultation (Wellcome Trust 2015).

Second, it is essential to consider the context of the healthcare setting in India. The healthcare system is notoriously overburdened and underfunded in India, with a doctor to person ratio of 1:1700 and a staggeringly low 1.3% of the GDP expenditure spent on public health (Biswas 2014; World Bank 2015). One specialist described, "In Indian hospitals, infectious diseases are extremely common and create a huge burden on the system. It takes longer to explain to a patient the difference between viral and bacterial infection and why you're not prescribing them medicine than to just write a prescription. When you're seeing hundreds of patients a day, it's impossible to run tests and spend half an hour with everyone who comes in with a fever" (Interview 5, 23 November 2015).

Third, in many areas there is not only a lack of time, but a lack of resources. According to WHO recommended guidelines, except in the case of emergency interventions, antibiotics should not be prescribed for a patient until a bacterial infection is confirmed by cultures or blood tests. But to properly run bacterial cultures requires access to a microbiological lab, biological testing equipment, staff who are trained in the procedure, and money to fund the testing. In rural areas, there may be little to no access to such facilities or personnel. Outside of major cities, doctors often do not have access to the tests or lab needed to confirm a diagnosis of bacterial infections when ambiguous symptoms such as fever, sore throat, or diarrhea occur (Easton 2011). This leads to the use of "shotgun therapy": a person may or may not have a bacterial infection, so a doctor just prescribes an antibiotic anyway.

The lack of rapid diagnostic tests for bacterial infections is also a deterrent to testing. “If a patient is feeling sick and has travelled far or missed work to see a doctor, they don’t want to wait around for diagnostic testing to be done to confirm that they have a bacterial infection,” explains one physician (Interview 4, 12 November 2015). “They just want to be given medicine, even if it won’t help them or will make them sicker.”

### **Role of the Patient**

In large cities of India, like Mumbai, New Delhi, and Chennai, there is an epidemic of patient self-prescribing. Despite laws passed in 2011 to regulate antibiotics obtained without a prescription, it has been widely documented that, particularly in urban areas, antimicrobial agents are “readily available and can be purchased as a commodity without the advice or prescription of a physician or other trained health care provider” (Knobler 2003). A 2011 analysis by the Global Antibiotic Resistance Partnership (GARP) and the Public Health Foundation of India (PHFI) found that one-fifth of the antibiotics purchased recently in Delhi had been obtained without a prescription (Ganguly 2011). In various regional studies of Indian pharmacies, depending on the area, estimates range from 42-64% of antibiotics obtained without consultation with a doctor (Saradamma 2000).

When patients self-prescribe without medical consultation, they often take antibiotics when unnecessary, not finish the complete course, purchase the wrong type, or take an insufficient dose. A study of Delhi pharmacies found that 90% of antibiotic purchases were an incomplete dose, and the median number of pills purchased was three (Kotwani et al. 2012). Lack of adherence to the full course of antibiotics is a common and dangerous practice. Patients

will often stop taking medicine after the first few days, once they start feeling better. As a result, the bacteria causing the illness are not fully killed, and this breeds conditions for resistant bacteria to reproduce (Chan et al 2012). In some areas, these problems of noncompliance and self-medication are magnified because in developing countries, “significant amounts of the available antimicrobials are poorly manufactured, counterfeit, or have exceeded their effective lifetimes” (Knobler et al 2003).

### **Role of the Pharmacist**

The policies and education of pharmacists encourage the proliferation of inappropriate antibiotic consumption and enable self-medicating practices. According to one doctor at a private hospital, “The pharmacist plays a huge role in emerging resistance. They make money by selling as much medicine as possible and antibiotics are an easy drug to dispense unnecessarily” (Interview 7, 28 November 2015). Economic forces favor the growth of small drug shops in urban areas which compete for business and are enticed by the incentives of pharmaceutical companies to push their products for substantial compensation (Kamat and Nichter, 1998). These incentives encourage pharmacists to sell the newest brand-name medications while the drug patent is still valid, in order to turn over as large a profit as possible.

Speaking at a medical conference, one pharmacist and microbiologist attributed difficulties to the fact that “pharmacy practices and chemist shops in India are not held to high standards of regulation” and emphasized that education of most people working at a chemist shop is often “none or minimal” (Conference Speaker 1, 30 November 2015). Currently, there is no strict regulatory body or control for clinical pharmacy practice in India (Basak and Sathyanarayana

2010). To practice as a registered pharmacist, only a diploma in pharmacy is required, taking a little over two years, after which no further education or certification is needed. Many pharmacies operate without a registered pharmacist even employed (Basak and Sathyanarayana 2010). In a 2005 study of Indian pharmacies, 50% were found to function without a pharmacist on site, with the store owner or a relative dispensing drugs without any formal training (Basak 2009).

### Obstacles and Solutions

Strategies to tackle the emergence and spread of antibiotic resistance in India focus primarily on one of three areas: preventing and slowing the emergence of resistant bacterial genes, containing the spread of resistant pathogens, and producing innovations in diagnostics, monitoring, and alternative therapies. The following section overviews gaps in essential AMR knowledge, outlines some of the efforts that are currently being explored, describes possible solutions yet to be attempted, discusses the unique obstacles to implementation, and suggests routes for future research.

### **Surveillance of AMR**

An unavoidable part of the problem is that in many areas we don't have a thorough understanding of what the problem is. In a lecture on AMR and nosocomial infections, one medical researcher explained, "Most of the data [that] scientists have on the prevalence of drug-resistant infections was compiled in Western countries. We need to truly define the burden of infection in India in order to implement preventive measures, starting with surveillance that measures compliance as well as treatments, the type of antibiotics given, and the dosage"

(Lecture Speaker 3, 17 November 2015). In India, a huge obstacle to overcome is that “large parts of country do not have the technical infrastructure to generate useable data” about the prevalence of AMR infections (Raghunath 2008).

Strides have been made in surveillance during the last 5 years. The New Delhi CDDEP has processed and organized global data on the status of global antibiotic usage into a 2014 report and currently receives resistance data from routine microbiological testing of bacterial susceptibility to antibiotics from six different labs in various regions of India. An updated map of global antibiotic usage data and resistance data is available to the public on the CDDEP website (CDDEP 2015). The Indian Council of Medical Research (ICMR) has also taken a proactive approach to AMR surveillance. According to one ICMR researcher, “For the last two years, we have received data on bacterial resistance at four centers across India. We are hoping to add another ten centers of data collection in the next few years” (Conference Speaker 2, 30 November 2015).

Although this is an important contribution to our knowledge of the state and spread of resistance, it is also slightly skewed in representation, as data in India is collected primarily on a volunteer basis from urban hospitals with infection control programs already in place. State policies which require hospitals to collect and submit clinical and microbiological data about resistant and hospital-acquired infections could increase our understanding of the problem in rural and low-socioeconomic settings and may stimulate infection control measures.

---

## Public Awareness

Many experts interviewed emphasized the need for efforts to “increase public awareness of AMR through health campaigns and the media” (Interview 8, 1 December 2015). Initiatives to educate patients have the potential to increase understanding, improve rates of medication adherence, and deter self-medicating trends. Studies show that patients who have a basic understanding of antibiotics are much less likely to abuse them or request them unnecessarily from medical prescribers (Filipetto 2008).

There are promising indicators of the potential for education and public awareness campaigns on topics of antibiotics, drug resistance, and vaccination to effectively spread the message, particularly in urban populations. For one, health awareness campaigns have been underway in India for several years, and therefore can provide a model to build off of and learn from. Some have even been fairly successful, with Indian health communication campaigns on diseases such as leprosy, maternal health, and HIV/AIDS linked to health-proactive behavioral changes (Sood and Nambiar 2006). Three of the practicing doctors interviewed emphasized the country’s traditionally strong family and community presence in the care of those who are sick as a powerful force for positive change. When you pass memorable health knowledge on to one person in India, “you are likely also benefitting many others who are their family, friends, and neighbors” (Interview 7, 28 November 2015). According to one doctor, campaigns should be kept short, use a widely-viewed form of media such as television, and have a simple message that can be easily remembered (Interview 9, 4 December 2015). Small messages such as “not

every cold needs antibiotics” or “sharing antibiotics can do more harm than good” can spread widely and create a large impact.

### **Balancing National Contradictions in Access to Medicine**

Considering how widely they are misused and the high resulting potential for harm, it may seem at first that strict bans on the distribution of antimicrobials outside of hospitals are a simple solution. However, while overuse of antibiotics is a huge problem in urban and affluent areas of India, in rural areas, villagers suffer from a lack of access to any form of healthcare. For many, the cost of visiting a doctor is simply too high. For others, healthcare may be free or subsidized, but the quality of this care is severely lacking. Villagers may not have a hospital within a reasonable distance from their homes, or reliable transportation to get there. This diversity in the socioeconomics and culture of different regions in India is one of the main barriers in creating universal policies for the promotion of rational uses of antibiotics. A national policy which limits access to antibiotics without a prescription may be immensely helpful for combatting AMR in higher-income, urban areas, but for a rural villager, the idea of obtaining a prescription from a qualified physician may serve only as a further barrier to care. Proactivity in AMR policies is essential to preserve the resource of antibiotics, but it must be carefully balanced with consideration of the fact that “many individuals still die in rural areas from preventable and easily treatable infections due to a lack of access to life-saving drugs” (Conference Speaker 3, 30 November 2015).

The Chennai Declaration addresses these concerns through their idea of an “implementable antibiotic policy” instead of a “perfect policy” (Ghafur et al. 2013). The Chennai Declaration was

a document composed and published in 2013 by representatives from a variety of Indian medical societies describing the ideal steps for tackling AMR over the next five years. The document acknowledges that enforcing universal restrictions may not be immediately feasible, and that it is more realistic on certain issues to implement step-by-step changes over time and in a way that is sensitive to economic and political context (Ghafur et al. 2013). One viable route for regulating the sales of antibiotics is to begin by implementing stricter controls in large, urban cities, where access to a licensed physician is not as insurmountable a problem, and where the highest incidence of antibiotic misuse and the biggest contribution to AMR is occurring. In rural, low-socioeconomic areas, regulations on new-generation, last-line of defense antibiotics may be put in place, as treatment of a multi-drug resistant infection would require a doctor's consultation or hospitalization either way, but regulations on basic antibiotics needed to treat minor infections would be held off. In rural areas, a push to educate doctors on AMR, increase access to healthcare, improve community and hospital sanitation, and increase vaccination rates should be more immediate priorities which will both increase community health and indirectly decrease the antibiotic misuse and AMR progression.

### **Improve Hospital and Community Sanitation**

One way to both contain the spread of resistant pathogens and decrease the incidence of infection entirely is by improving sanitation in healthcare facilities. Studies by the Global Antibiotic Resistance Partnership (GARP) have revealed extremely high rates of hospital-acquired and resistant infections in many Indian hospitals and health centers. In certain ICUs, the rate of vancomycin-resistant enterococcus, a dangerous hospital infection, is five times the rate in the



rest of the world (India Medical Times 2011). Over 80% of samples taken in one hospital-based study found *Staphylococcus aureus* bacteria that was resistant to methicillin and other related antibiotics. GARP estimates that 30% of the 190,000 neonatal deaths in India each year due to sepsis are attributable to antibiotic resistant bacteria in hospital environments (India Medical Times 2011).

Director of CDDEP and vice president for research and policy at the Public Health Foundation of India, Dr. Ramanan Laxminarayan, explains in an article on nosocomial infections that most of these infections are easily preventable with simple measures, such as “frequent hand washing, use of isolation rooms for infected patients, increased availability and uptake of diagnostic tests, reminders to limit catheter use, and use of gloves and gowns” (India Medical Times 2011). Establishing infection control and stewardship committees which review prescription records and oversee hospital sanitation can be a big step to ensure sincere compliance and create accountability for following policies. However, these committees may also be met with uncooperative hospital staff and administrators. “The greatest challenge is to empower infection control committees and make hospital staff aware of their activities and recommendations,” adds Dr Ramanan Laxminarayan (India Medical Times 2011).

When the researcher completed a brief observership at a private hospital, it was noted that hundreds of patients were seen by the doctors in only a few hours, with multiple patients often being examined and diagnosed in the same room at the same time. Even at this private hospital, no sterilization of equipment or the room, use of gloves, or handwashing between patients was observed on the part of the doctors or nurses despite the fact that many of the

cases were contagious infections such as tuberculosis or pneumonia. These practices are also consistent with the researcher's brief observations of hygiene practices in several other hospitals and health centers in Rajasthan, Delhi, and Uttar Pradesh.

Hospital sanitation is perhaps the most perplexing contradiction of India's healthcare system. While India is definitely home to many top private hospitals with excellent infection control procedures, a huge number are still falling short in basic sanitary practices, even when they have adequate resources and a well-trained staff. When discussing the odd contradiction of well-educated and skilled medical professionals failing to consistently adhere to basic hygiene measures such as hand-washing and glove use, many of the experts interviewed referred to the mental disconnect between associating these small hygiene tasks with the resulting adverse outcomes. Educational and stewardship efforts may benefit from not only focusing on teaching hygiene guidelines, but also providing memorable evidence and imagery that truly connect the harm of dangerous infections with seemingly small lapses in infection control. In addition, developing national standard treatment and "infection control guidelines outside of those required for NABH accreditation" with a focus on resource-strapped and rural areas may provide more feasible targets for hospitals still struggling with these changes (Conference Speaker 2, 30 November 2015).

Creative solutions can also be used to motivate and implement infection control practices on the hospital level in resource-limited areas. At the Comprehensive Rural Health Project's Julia Hospital in Jamkhed, Maharashtra, they address the challenge of hospital sanitation in a rural, resource-limited community in an original but simple way. According to their model, "80% of

health problems can be prevented or managed” by laypeople, even in impoverished or illiterate communities (CRHP 2012). Therefore, when patients stay for prolonged periods in their hospital, the staff teaches the patient and his/ her family how to do basic tasks like changing the patient’s sheets, washing hands, and monitoring medication compliance. This approach has many benefits, explains the hospital’s director: “Involving the families in patient care lowers the required manpower and healthcare costs, empowers the patient and their family, and teaches valuable hygiene and health skills to villagers who will then often share them with their communities after they leave the hospital” (Interview 2, 16 October 2015). As a result of this method, healthcare costs are extremely low at Julia Hospital, and according to the director, there “has never been a case of hospital-acquired infection in over 40 years since it was founded” (Interview 2, 16 October 2015).

AllMS Hospital’s Trauma Center has been testing a software, ASHAIN, which monitors infection control procedures, medical devices, and the duration and dosage of antibiotics. Studies have found that use of ASHAIN helps to reduce infection rates by up to 50% merely by creating a system of accountability and surveillance (Bhalla 2012). In addition, use of the software makes it easier for subtle infection trends to be tracked and monitored, so the source of the infection can be eliminated, rather than merely continuing to treat the aftermath. The widespread implementation of infection control software could be a useful and low-cost tool for combatting nosocomial infections and irrational antibiotic use (Bhalla 2012).

---

## Antimicrobial Stewardship

As an addition to standard infection control teams, in a recent years, a few major hospitals in India have begun piloting antimicrobial stewardship programs which specifically target the incidence of resistant infections, address poor diagnostic practices, and encourage the optimal use of antimicrobials (ASBN 2013). These antimicrobial stewardship teams work by creating a network of cooperation, implementing a team which oversees routine monitoring and surveillance of prescribing policies, pharmacy operations, and patient and prescriber education (ASBN 2013). They also may assist busy practitioners in accessing the proper antibiotic type, dose, and duration for cases of infection and provide informational resources for staff and medical professionals.

Apollo Hospital in Chennai was one of the first Indian hospitals to successfully implement such a program in their tertiary level oncology center. A study was conducted to analyze the impact of antibiotic stewardship activities- such as handwashing monitoring, strict isolation procedures for immunocompromised patients, AMR education for junior medical practitioners, infection protocol education for patient families and visitors, and consultation with an infection control committee- on the prevalence of carbapenem-resistant Enterobacteriaceae. The study found a significant decrease in the use of higher level antibiotics and in the prevalence of three different strains of resistant bacteria in only two years (Ghafur et al. 2012). Explains one specialist: “The effectiveness of the Chennai program, especially considering that it was conducted in an oncology ward, where patients are at high risk for severe infections, means that these policies are very capable of being implemented in other hospitals in India. What really

makes a difference is the level of education of the staff about antimicrobial resistance and the cooperation of the hospital community” (Interview 5. 23 November 2015).

One of the private hospitals that the researcher visited also had a strong, independent antibiotic stewardship program. Their program was headed by a review board, led by a physician who was interested in antimicrobial conservation. The review board oversaw the hospital’s antimicrobial prescriptions and advocated for awareness and rational use. The program placed a hospital ban on the use of irrational drug combinations and restrictions on certain high-end, last resort antibiotics, which required consultation and sign off by another doctor. The program also made information on infectious strains and corresponding antibiotics readily available to all doctors and encouraged the recording of infection data and monitoring of patients on more than two antibiotics.

Over the last two years, the Antibiotic Stewardship Network in India, based in Ujjain, Madhya Pradesh, has begun setting up a network of Indian healthcare workers dedicated to AMR accountability throughout the country and offering informational classes on AMR stewardship (ABSN 2013). National programs to connect representatives from different hospitals have the benefit of being able to collaborate data on a large scale, implement widespread accountability, and share resources and innovation.

### **Diagnostics**

Improvements in diagnostics have the potential to create a large, sustainable change in antimicrobial resistance. Currently, clinicians generally prescribe antibiotics empirically; when a patient comes in with symptoms of infection such as fever, cough, or diarrhea, clinicians will

prescribe a broad spectrum antibiotic without running any diagnostic tests (Murdoch et al. 2012). This practice has the benefits of saving time, but it is often inappropriate and ineffective, resulting in unnecessary or pathogen non-specific treatment (Braykov and Laxminarayan 2014). When asked about empiric prescribing, medical professionals commonly cite a lack of time or testing resources to run diagnostic tests, and pressure to be completely certain of results before turning a patient away without a prescription.

Unfortunately, many of the symptoms of bacterial and viral infections are identical, and no highly sensitive, universal clinical prediction rules for distinguishing the etiology of the infection currently exist (Murdoch et al. 2012). Classic tests for determining the pathogenic strain of infection include bacterial cultures, susceptibility tests, gram stains, blood tests, PCR, and enzyme-linked immunosorbent assay (ELISA). However, testing is not quick enough to be clinically useful, with the standard process of culture and susceptibility testing generally takes 24-48 hours (Maltezou 2008).

One possibility is the development of rapid diagnostic tests to identify infectious pathogens right at the point of care. A two-year study on the effects of a rapid antigen detection test (RADT), which can identify certain bacterial strains and their level of susceptibility, on antibiotic prescribing found that antibiotic prescription was reduced by 61% using the RADT compared with typical empirical management of patients (Maltezou 2008). A 2011 study in Israel developed a chemiluminescence-based blood test which distinguished between viral and bacterial infection in blood samples in less than two hours and with over 90% accuracy (Prilutsky et al. 2011).

Rapid, point-of-care diagnostic tests for viral and bacterial pathogens have the potential to improve the quality of infection care and decrease the spread of resistance and are worthy of priority in medical development and research. However, it is also important to acknowledge the practical limitations of these tests. First, although the last five years have brought promising innovations in quick and effective tests, all rapid diagnostic tests currently on the market or in development have limitations in their accuracy (Maltezou 2008). Even if a rapid diagnostic test is 90% accurate, the slight chance it is wrong still creates a liability for the doctor and therefore hesitation to rely on the test's results. Second, antibiotics in India are widely available and extremely inexpensive. According to one doctor, "In order for a rapid diagnostic test to be useful in India, it would have to be not only fast and accurate, but also less expensive than generic antibiotics" (Interview 4, 24 November 2015). The reality is that most patients do not want to pay for a test when they can just receive a treatment. Finally, many of the practicing doctors interviewed mentioned that medical professionals are "habituated to their diagnostic methods" (Interview 7, 28 November 2015). For a physician to change their practicing methods after decades without feeling confident in the reliability, expense, or usefulness of the test would be an unrealistic request for many. In order to prompt medical professionals to make a substantial change in their practice, the proper tools, resources, and motivation need to be provided to make that transition as smooth as possible.

For areas where rapid diagnostic tests are not available, a more feasible first step may be to improve empirical diagnostic and prescribing practices. In a study by CDDEP of empiric methods in hospitals, a third of patients receiving antimicrobial medications had no symptoms or tests which indicated an infection. Few patients had diagnostic tests conducted to determine the

source of infection tests. For those who did and had the tests show up as negative for bacterial infection, only 22 percent had their medication stopped or the spectrum narrowed (Braykov and Laxminarayan 2014). Even where rapid diagnostic tests are not readily available, doctors should be encouraged to narrow broad-spectrum treatment when an infection is identified or cease antibiotic administration upon negative test results. Appropriate antimicrobial de-escalation is an important component of antimicrobial stewardship which can minimize overuse in in-patient care.

### **Attitude and Priority**

In discussing AMR with doctors and researchers, one step that was mentioned almost universally was the need for an attitude change regarding antibiotics and resistance by doctors, the government, and the general public. “To make any change in medicine,” explains one doctor and researcher, “it requires first a change in attitude and a sense of cooperation. You can instill and enforce policies, you can improve access to [the required tools], and you can secure proper funding, but if doctors and patients don’t view resistance as important, the problem will continue to get worse.” (Speaker 5, November 23). This prompts the question at the base of all AMR interventions: how do we motivate stakeholders to authentically change imprudent practices?

Large, private hospitals in major cities are prompted to strive for strictly enforced stewardship practices and infection control programs in order to achieve hospital accreditation, maintain a good reputation, and secure funding. A regulatory committee that oversees prescriptions is a mandatory requirement for any hospital seeking accreditation from the



National Accreditation Board for Hospitals & Healthcare (NABH) (IBNS 2015). Accreditation and a good reputation are valued in order to encourage patients to choose their hospital for medical tourism and surgical procedures, which are huge income-generators for many large, private, urban hospitals. For these hospitals, a further step toward accountability may be a state requirement for them to publicly release annual data on resistance, nosocomial infections, and antibiotic prescriptions.

These motivators, however, do not apply to rural Community Health Centers (CHCs) and government-funded district hospitals, where it can be a challenge to prompt them to notice or admit to a problem, let alone voluntarily submit data about hospital-acquired or resistant infections or implement preventive measures. Government-funded hospitals and CHCs present a challenge, as they have no obvious incentive to track or release data about their burden of AMR or enforce stringent infection control procedures. When asked how to motivate rural district hospitals to promote AMR stewardship, one medical researcher explained, “It has to start with private hospitals and move down. Recently, a few private hospitals in India like AIIMS have implemented infection control and stewardship programs, and have published research. The more attention [is drawn to the problem,] the more the Health Ministry will regard resistance as a priority and state governments may require district hospitals to implement programs to receive funding” (Interview 6, 24 November 2015).

Additionally, now that research exists which shows how cost-effective antimicrobial stewardship is for hospitals, it creates an incentive for hospital administrators to develop plans and enforce these policies. According to a doctor with the Indian Institute of Health

Management Research (IIHMR), around 50% of patients in India fail to take medicines properly (Speaker 2; IBNS 2015). Pharmaceutical management in hospitals can be one of the most cost effective measures for appropriate use of scarce health care resources, making it a desirable course to pursue for hospital administrators and state governments. Medication management through a functional Drug and Therapeutics Committee (DTC) can provide a place for cooperative efforts to promote more efficient and rational medicine use.

China has implemented a promising stewardship and drug regulation reform during the last nine years which has been shown to significantly reduce antibiotic over-prescribing and cut excessive retail sales of antimicrobials (Xiao et al. 2013). The Chinese Ministry of Health has introduced mandatory policy changes in gradual steps for the conservation of antimicrobials, setting targets for antimicrobial conservation, organizing task forces and supervisory drug committees, developing strict inspections, and investigating hospital management staff who continue to violate conservation policies. Policies placed the responsibility of overuse on hospital staff and medical prescribers; hospitals that failed to meet targets could be downgraded to a lower level, and medical staff who seriously violate the regulations could lose their accreditation to prescribe antibacterial agents or have their professional qualification revoked. China's Ministry of Health also attempted to implement changes in the next generation of physicians, holding national medical education programs on the appropriate use of antibiotics (Xiao et al. 2013). If such a program were attempted in India, changes would have to be made to adjust for cultural and political differences, but China's policies suggest the role of assignment of responsibility and strict enforcement to motivate substantial behavioral changes in healthcare.

## Changes in Medical Education

A long-term step in tackling AMR is to emphasize positive infection control practices, diagnostic methods, and rational antibiotic use in the education of the next generation of pharmacists and medical professionals. Three physicians I talked with mentioned as a contributing roadblock that medical and pharmacological schools did not incorporate mechanisms of antimicrobial resistance, evaluations of the rationality of drug combinations, or extensive infection control discussions into the curriculum (Interviews 2, 4, and 7, November 2015). The Chennai Declaration recommends specific changes in medical education, including offering Post-MD/DNB specialization in infectious diseases at more post-graduate centers, requiring compulsory training in infection control for post-grads in all specialties, and the incorporation of one-week trainings in antibiotic stewardship and infection control during the last three years of medical school, as provided by The Medical Council of India (Ghafur et al. 2013).

## Vaccination

Widespread vaccination against common viral and bacterial infections would be a powerful measure to reduce both the need for and misuse of antibiotics through indirect and direct pathways. Vaccination against major viral pathogens is strongly linked with decreased antibiotic use, because a large portion of drug misuse is caused by the unnecessary administration of antibiotics for viral infections. As a result of this correlation, explains one epidemiologist, “achieving universal vaccination in developing countries would alone be a huge step forward in decreasing disease rates and unnecessary antibiotic use” (Interview 8, 1 December 2015).

Vaccines for bacterial pathogens prevent the incidence and spread of infection, establish herd immunity in a population, and reduce the need for antimicrobial therapy (Mishra et al. 2012). Although efforts by the National Immunization Programme have improved Indian vaccination rates in recent years, there are currently major gaps in the types of vaccines subsidized and there remains a huge inequity in care, with coverage in states ranging from 25 to 88% (Khera et al. 2011). Even for the vaccines that are labeled as essential and subsidized by the government, many rural areas do not have realistic access to care due to social and economic factors, such as a lack of knowledge, inaccessibility of transport, or the absence of high-quality and proximate medical centers.

*Streptococcus pneumoniae* and *Haemophilus influenzae* type B, for example, is a leading cause of bacterial pneumonia, meningitis and sepsis in children, is prone to developing drug resistance, and affects 43 million under-five children in India every year (Malik and Taneja 2013). A very effective vaccine has been developed to protect against most strains of pneumococcal; however, “the price makes it inaccessible for most individuals in rural areas” (Conference 3, 30 November 2015). Attempts to lobby for free or subsidized vaccines against major childhood infections such as pneumococcal are necessary to both combat India’s high rates of childhood mortality and to conserve the effectiveness of its treatment. According to estimates by the Public Health Foundation of India, 11.4 million days of antibiotic consumption in under-five children could be avoided annually if universal pneumococcal conjugate vaccination was achieved (Laxminarayan, Matsoso, et al. 2015). Additionally, the expansion and improvement of programs designed to close the rural coverage gap, such as ASHA health workers who deliver

basic healthcare directly to rural villages, or NGOs which facilitate medical transportation and provide education, could help obtain universal vaccination (Vashishtha 2012).

### **Innovation: New Antibiotics and Alternative Therapies**

In a 2013 survey of the largest companies, only five new antibiotics were under development, none of which were designed with new mechanisms of action, instead treating infections by the same increasingly ineffective methods as current antibiotics (Singh 2013). Considering the limitations on profit for big pharma, explained one public health worker, “government incentives can help encourage companies to continue research and production of innovative classes of antibiotics” (Interview 6, 24 November 2015). New antibiotics, of course, are a short-term solution, and less cost-efficient than efforts to conserve existing antimicrobials, but serve important purposes, as they will buy time before resistance becomes a mass crisis and can provide treatment options for those with multi- and pan-resistant infections. The Generating Antibiotics Incentives Now (GAIN) Act, a US bill passed in 2012, hopes to give incentives to pharmaceutical companies to continue to generate new medicines to fight life-threatening resistant infections (Singh 2013). The GAIN Act would make the testing and approval of new antibiotics an FDA first-priority and give market-exclusivity to drug companies for five years. Similar pushes for Indian pharmaceutical companies could be an important first step, especially, explains one researcher, if it was “accompanied by policies to streamline clinical trial and approval processes and provide research and development tax credits. Drug development is a huge investment and financial risk, anything to ease that risk provides motivation to pharmaceutical companies” (Interview 4, 1 December 2015).

Non-conventional alternative therapies to antibiotics are promising, long-term solutions. Some of these alternative approaches include the administration of antibodies which bind to and inactivate pathogens, the use of probiotics as alternative prophylaxis, bacteriophage therapy, or viruses which naturally destroy bacteria, immune system stimulation, and lifetime immunity bacterial vaccines (Allen et al. 2014). Partnerships between academic researchers and drug companies can be formed to get life-saving medicines and alternative therapies on the market safer and more efficiently (So et al. 2011). According to one doctor, “there is a lot of great scientific research that never makes it to trials or production because of funding constraints.” By combining their resources and developing a partnership, public and private sectors can overcome market limitations to pursue the development of original new drugs.

### **Conclusion**

This project sought to comprehend the human healthcare causes, challenges, and solutions of antibiotic resistance in India. The study was conducted over a 25-day period, primarily in the cities of New Delhi and Gurgaon in Northern India. Information was collected through the use of scientific literature, interviews with doctors and researchers, attendance at medical lectures, and observation at several hospitals and the Center for Disease Dynamics, Economics, and Policy. Though limited in its scope, the study indicates that the roots of the emergence and spread of resistance are a combination of actions by many stakeholders, including patients, medical professionals, hospital administrators, pharmacists, and pharmaceutical companies. Human healthcare causes of the emergence and spread of antibiotic resistance in India include imprudent practices by pharmaceutical companies, insufficient drug

regulation and policy enforcement, poor hospital sanitation, unchecked urban drug access and correspondingly high rates of patient self-medication, and rampant antimicrobial misuse.

The future of modern medicine is heavily dependent upon maintaining the effectiveness and availability of antimicrobials as a shared and limited resource. The spread of antibiotic resistance, therefore, is severe threat to human health security worldwide. India has the potential to be a global force for change by tackling AMR head-on with comprehensive surveillance and action plans at the national and state level. Considering India's substantial cultural, economic, and political diversity, efforts to address AMR in India must carefully balance access, conservation, and innovation. Major obstacles to addressing AMR in India include an absence of comprehensive and representative data, a lack of awareness of the issue by both the general public and medical community, an overburdened health system fueled by a scarcity of resources and qualified staff, health access discrepancies between rural and urban communities, attitude and priorities of hospitals and policy makers, disconnect between ideal policy and realistic follow-through, and delays in the innovation of diagnostic tools and alternative therapies. In order to be effective, strategies for change must be realistic, attentive to contextual realities, specifically defined, incentivized for stakeholders, and implemented on as regional a level as possible. As misunderstanding and a lack of awareness is the foundation of antibiotic misuse, all measures should be instated alongside easily understandable and readily available information and explanations. Any policy changes or conservation efforts need to incorporate a system of monitoring and feedback by an empowered regulatory body in order to assure compliance. Potential routes for combatting AMR include expanded surveillance, promotion of education and awareness for medical professionals and the public, antimicrobial stewardship

programs, strengthened sanitation and infection control measures in hospitals, and research into the development of improved diagnostics and alternative therapies.

### Limitations of the Study

The scope of this study was limited on the basis of time, resources, and connections. First, finding individuals who were both knowledgeable about the topic, and willing to discuss it was a considerable challenge. Initially, the researcher intended to gain perspectives on antimicrobial resistance from a larger diversity of individuals, including the general public and rural health professionals. However, after attempting to question laypeople and non-expert, rural physicians, it became clear that this was not a well-known problem in the Indian general public and these sessions only produced confusion and misunderstanding on the part of the interviewee. Therefore, it was decided that the most prudent course for hearing perspectives on AMR would be to talk with experts working to combat this issue, either as a researcher, public health worker, or medical professional.

In addition to the obstacle of finding individuals who had a strong understanding of AMR, the researcher also faced difficulty in finding experts who were willing to openly discuss the problem. After a 2009 study on the “superbug” New Delhi metallo- $\beta$ -lactamase 1 (NDM-1) created negative media and serious consequences for many involved, antimicrobial resistance became a sensitive and somewhat stigmatized topic for many doctors, scientists, and hospital workers in India (Yong et al. 2009). There is an inherent margin of error from the fact that the researcher could only talk to individuals who already prioritized antibiotic resistance. A hospital worker or physician who does not follow stringent policies regarding infection control and



prudence when prescribing antibiotics, for example, is unlikely to consent to having a student researching AMR observe or interview them.

Additional limitations were mostly due to practical restraints of time and travel. The research period was less than four weeks, and therefore restricted in the amount of field work that could be conducted. Without access to a lab or scientific testing equipment, the researcher was unable to perform any original scientific field work first hand, and therefore had to heavily rely on peer-reviewed journal articles for data on resistance and infections. Additionally, although some observation and cited studies took place in more rural hospitals, this study is mostly skewed toward urban areas because of restraints in travel and accommodation.

### **Suggestions for Future Research**

Interesting topics for future ISP health research may include the following. First, looking at perceptions and perspectives of pharmacists in India on antibiotic resistance and how they affect antibiotic dispersal rates. Second, obtaining qualitative data on the knowledge and awareness of antibiotic resistance by rural doctors or the general public in India. Third, an examination of pilot antimicrobial stewardship and infection control programs in government-funded or rural hospitals. Finally, a study comparing the effectiveness and outcomes of different methods for educating medical professionals and laypeople about antibiotic resistance would be useful for future health education campaigns.

## Bibliography

### Primary Sources

Interview 1. In-person interview. Physician. Public Hospital. 14 October 2015.

Interview 2. In-person interview. Hospital Head. 16 October 2015.

Interview 3. Phone interview. AMR researcher. 11 November 2015.

Interview 4. In-person interview. Physician and epidemiologist. Interviews conducted on multiple occasions. 12, 16, 24 November 2015. 1 December 2015.

Interview 5. Phone Interview. Oncologist and AMR researcher. 23 November 2015.

Interview 6. Phone Interview. Public Health Worker. Interviews conducted on multiple occasions. 23 and 24 November 2015.

Interview 7. In-person interview. Doctor. Private Hospital. 28 November 2015.

Interview 8. Phone interview. Epidemiologist and global health worker. 1 December 2015.

Interview 9. In-person interview. Microbiologist and hospital administrator. 4 December 2015.

Lecture Speaker 1. Professor and Medical Researcher. Public Lecture and Panel Discussion:

“Encouraging Rational Uses of Antibiotics.” AllMS Medical College. 17 November 2015.

Lecture Speaker 2. Doctor and AMR Researcher. Public Lecture and Panel Discussion:

“Encouraging Rational Uses of Antibiotics.” AllMS Medical College. 17 November 2015.

Lecture Speaker 3. Doctor and Infection Control Researcher. Public Lecture and Panel Discussion: "Encouraging Rational Uses of Antibiotics." AIIMS Medical College. 17 November 2015.

Conference Speaker 1. Pharmacist and microbiologist. Medical Conference: "Antimicrobials: access and sustainable effectiveness." India Habitat Centre. 30 November 2015.

Conference Speaker 2. ICMR Doctor and Researcher. Medical Conference: "Antimicrobials: access and sustainable effectiveness." India Habitat Centre. 30 November 2015.

Conference Speaker 3. Public Health Official and Medical Researcher. Medical Conference: "Antimicrobials: access and sustainable effectiveness." India Habitat Centre. 30 November 2015.

Bhalla, Jaya Shroff. Software salve on hospital infections. Hindustan Times. New Delhi. April 2012.

Center for Disease Control. About Antibiotic Resistance. [Cdc.gov/drugresistance/index.html](http://Cdc.gov/drugresistance/index.html). 2015.

DNA India. Government holds antibiotic policy, not to restrict access to drugs. New Delhi, India. 3 October 2011.

Easton, Alice. The fight for and against antibiotics. The Hindu Business Line. 7 November 2011.

Knapton, Sarah. Drug companies to blame for antibiotic resistance, says pharmaceutical boss. The Telegraph. January 2105.

Shrinivasan, Rukmini. 55% of India's population poor: Report. Times of India. 15 July 2010.

Shrivastava, Roli. New worry: Resistance to 'last antibiotic' surfaces in India. The Times of India. 28 December 2014.

Singh, Anoop. GAIN Act Gives Pharmaceutical Companies Incentive To Make First New Antibiotics In 15 Years: Antibiotic Resistance Fight Continues. Medical Daily. June 2013.

World Bank. Health expenditure, public (% of GDP). World Health Organization Global Health Expenditure database. 2015.

World Health Organization. Antimicrobial Resistance Fact Sheet.

<http://www.who.int/mediacentre/factsheets/fs194/en>. April 2015.

World Health Organization. Antimicrobial resistance: global report on surveillance 2014.

<http://data.worldbank.org/indicator/SH.XPD.PUBL.ZS>. 30 April 2014.

### Secondary Sources

Allen, Heather K. ; Trachsel, Julian ; Looft, Torey ; Casey, Thomas A. Finding alternatives to antibiotics. Annals of the New York Academy of Sciences. Vol.13231(1), pp.91-100. 2014.

Aminov RI. A Brief History of the Antibiotic Era: Lessons Learned and Challenges for the Future. Frontiers in Microbiology: 1:134. 2010.

APUA: Alliance for the Prudent Use of Antibiotics. The Cost of Resistance.

[Tufts.edu/med/apua/about\\_issue/about-the-issue---the-cost-of-resistance.shtml](http://Tufts.edu/med/apua/about_issue/about-the-issue---the-cost-of-resistance.shtml). 2014.

Arnold SR, Straus SE. Interventions to improve antibiotic prescribing practices in ambulatory care. Cochrane Database of Systematic Reviews Issue 4. 2005.

Basak, S. C., & Sathyanarayana, D. Community Pharmacy Practice in India: Past, Present and Future. *Southern Med Review*, 2(1), 11–14. 2009.

Basak, S. C., & Sathyanarayana, D. Pharmacy Education in India. *American Journal of Pharmaceutical Education*, 74(4), 68. 2010.

Boucher, Helen. Talbot, George. Bradley, Thomas. Edwards, John. Gilbert, David. Rice, Louis. CDDEP. Resistance Map. <http://resistancemap.cddep.org/resmap/c/in/India>. 2015.

Braykov, N. Laxminarayan, R. Assessment of empirical antibiotic therapy optimisation in six hospitals: an observational cohort study. *The Lancet Journal of Infectious Disease*. Volume 14. December 2014.

Community Development Medicinal Unit (CDMU). Fixed-dose combination in India, inception – marketing – a study. Health Action International Asia Pacific. Kolkata. December 2010.

Comprehensive Rural Health Project (CRHP). Jamkhed.org. 2012.

Chan, Y. Fan, M. Fok, C. Lok, Z. Ni, M. Sin, C. Wong, K. Wong, S. Yeung, R. Yeung, T. Chow, W.

Lam, T. Schooling, C. Antibiotics nonadherence and knowledge in a community with the world's leading prevalence of antibiotics resistance: Implications for public health intervention. *American Journal of Infection Control*, Volume 40 n. 2, p. 113-117. 2012.

Davies, J. and D. Davies, Origins and Evolution of Antibiotic Resistance. *Microbiology and Molecular Biology Reviews* : MMBR, 2010. 74(3): p. 417-433.

Filipetto FA, Modi DS, Weiss LB, Ciervo CA. Patient knowledge and perception of upper respiratory infections, antibiotic indications and resistance. Patient preference and adherence. 2:35-39. 2008.

Gautum, CS. Aditya, S. Irrational drug combinations: Need to sensitize undergraduates. Indian Journal of Pharmacology. Volume 38. Issue 3. Page 169-170. 2006.

Ghafur, Abdul. Vidyalakshmi, A Murali, Priyadarshini, Thirunarayan. Emergence of Pan-drug resistance amongst gram negative bacteria! The First case series from India . Journal of Microbiology and Infectious Diseases. 2014; 4 (3): 86-91 JMID doi: 10.5799/ahinjs.02.2014.03.0145

Ghafur A, Mathai D, Muruganathan A, Jayalal JA, Kant R, Chaudhary D, et al. "The Chennai Declaration" Recommendations of "A roadmap- to tackle the challenge of antimicrobial resistance" - A joint meeting of medical societies of India. Indian J Cancer. 2013.

Ghafur, A. Nagvekar, V. Thilakavathy, S. Chandra, K. Gopalakrishnan, R. Vidyalakshmi, PR. "Save Antibiotics, Save lives": an Indian success story of infection control through persuasive diplomacy. Antimicrobial Resistance and Infection Control 2012. 1:29 doi:10.1186/2047-2994-1-29.

Helen C. Maltezou. Vasilios Tsagris. Anastasia Antoniadou. Tabrini Galani. Constantinos Douros. Ioannis Katsarolis. Antonios Maragos. Vasilios Raftopoulos. Panagiota Biskini. Kyriaki Kanellakopoulou. Andreas Fretzayas. Theodoros Papadimitriou. Polyxeni Nicolaidou. Helen Giamarellou. Evaluation of a rapid antigen detection test in the diagnosis of streptococcal

pharyngitis in children and its impact on antibiotic prescription. *J. Antimicrob. Chemother.* 62 (6): 1407-1412. 2008. doi: 10.1093/jac/dkn376

Hirsch, Hans A. Maxwell Finland. Clare Wilcox. Joan Yarrows. Antibiotic Combinations — Antibacterial Action of Serum after Ingestion of Novobiocin or Tetracycline or Both. *N Engl J Med* 1960; 262:209-214.

IBNS. Approximately 50% patients in India fail to take medicines correctly – IIHMR University. November 6, 2015. Jaipur.

India Medical Times. Hospital-acquired infections high in India: a study.

[Indiamedicaltimes.com/2011/09/22/hospital-acquired-infections-high-in-india-study/](http://indiamedicaltimes.com/2011/09/22/hospital-acquired-infections-high-in-india-study/).

September 22, 2011.

V.R. Kamat, M. Nichter. Pharmacies, self-medication and pharmaceutical marketing in Bombay, India. *Social Science & Medicine*, 47, pp. 779–794. 1998.

Khera, Ajay. Gupta, Anuradha. Gogia, Hema. Rao, Sujatha. India's national immunization programme. [india-seminar.com/2012/631/631\\_ajay\\_khera\\_et\\_at.htm](http://india-seminar.com/2012/631/631_ajay_khera_et_at.htm). 2011.

Knobler SL, Lemon SM, Najafi M, et al., editors. *The Resistance Phenomenon in Microbes and Infectious Disease Vectors: Implications for Human Health and Strategies for Containment: Workshop Summary*. Washington (DC): National Academies Press (US); 2005.

Kotwani, A., Wattal, C., Joshi, P. C. and Holloway, K. Irrational use of antibiotics and role of the pharmacist: an insight from a qualitative study in New Delhi, India. *Journal of Clinical Pharmacy and Therapeutics*, 37: 308–312. 2012.

Kumar R, Indira K, Rizvi A, Rizvi T, Jeyaseelan L. Antibiotic prescribing practices in primary and secondary health care facilities in Uttar Pradesh, India. *J Clin Pharm Ther*: 33 : 625-34. 2008.

Kumarasamy, KK. M.A. Toleman, T.R. Walsh, J. Bagaria, F. Butt, R. Balakrishnan, U. Chaudhary, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. *Lancet Infectious Diseases*, 10 (9) pp. 597–602. 2010.

Malik A, Taneja D K. Conjugate pneumococcal vaccines: Need and choice in India. *Indian J Community Med* 2013;38:189-91

Murdoch, DR. O'Brien, KL. Amanda J. Driscoll, Ruth A. Karron, Niranjana Bhat, the Pneumonia Methods Working Group, the PERCH Core Team. Laboratory Methods for Determining Pneumonia Etiology in Children, *Clinical Infectious Diseases*. S146-S152. 2012.

Mishra, Ravi. Ernesto Oviedo-Orta, Prachi Prachi, Rino Rappuoli, Fabio Bagnoli. Vaccines and antibiotic resistance. *Current Opinion in Microbiology*. Volume 15, Issue 5. Pages 596–602. 2012.

Laxminarayan, R. Matsoso, P. Pant, S. Brower, C. Rottingen, JA. Klugman, K. Davies, S. Access to effective antimicrobials: a worldwide challenge. *The Lancet*. November 18, 2015.

Plowman R , Graves N, Griffin M A, Roberts J A, Swan A V, Cookson B and Taylor L. The rate and art of hospital acquired infections occurring in patients admitted to selected specialities of a District General hospital and the national burden imposed; *J. Hosp. Inf.* 47 198–209. 2001.



Prilutsky, Daria. Evgeni Shneider, Alex Shefer, Boris Rogachev, Leslie Lobel, Mark Last, and Robert S. Marks. Differentiation between Viral and Bacterial Acute Infections Using Chemiluminescent Signatures of Circulating Phagocytes. *Anal. Chem.*, 83 (11), pp 4258–4265. 26 April 2011.

Raghunath, D. Emerging antibiotic resistance in bacteria with special reference to India. *J. Bioscience*. 33 593–603. 2008.

Saradamma, Rema Divii. Higginbotham, Nick. Nichter, Mark. Social factors influencing the acquisition of antibiotics without prescription in Kerala State, south India. *Social Science & Medicine*. Volume 50, Issue 6, March 2000, Pages 891–903.

Scheld, Michael. Spellberg, Brad. Bartlett, Journal of Clinical Infectious Disease. (2009) 48 (1): 1-12. doi: 10.1086/595011

Shaikha, Sibghatulla. Jamale Fatimab. Shazi Shakilb. Syed Mohd. Danish Rizvia. Mohammad Amjad Kamal. Antibiotic resistance and extended spectrum beta-lactamases: Types, epidemiology and treatment. *Saudi Journal of Biological Sciences*. Volume 22, Issue 1, January 2015, Pages 90–101.

So, A.D. N. Guptaa, S.K. Brahmachari, I. Chopra, B. Munos, C. Nathan, K. Outtersson, J.P. Paccaud, D.J. Payne, R.W. Peeling, M. Spigelman, J. Weigelt. Towards new business models for R&D for novel antibiotics. *Drug Resistance Updates*. Volume 14, Issue 2. Pages 88–94. April 2011.

Sood S. Nambiar D. Comparative Cost-Effectiveness of the Components of a Behavior Change Communication Campaign on HIV/AIDS in North India. *Journal Of Health Communication*:11:143-162. 2006.

Tenover, Fred C. Mechanisms of antimicrobial resistance in bacteria. *American Journal of Infection Control*. Volume 34, Issue 5, Supplement. Pages S3–S10. June 2006.

Teillant, Aude. Gandra, Sumanth. Barter, Devra. Morgan, DJ. Laxminarayan, R. Potential burden of antibiotic resistance on surgery and cancer chemotherapy antibiotic prophylaxis in the USA: a literature review and modelling study. *The Lancet Infectious Diseases*. Volume 15, No. 12, p1429–1437, 15 October 2015.

Vashishtha, Vipin M. Status of Immunization and Need for Intensification of Routine Immunization in India. *Indian Pediatrics* 49: 357-361. 2012.

Xiao, Yonghong. Zhang, Jing. Zheng, Beiwen. Zhao, Lina. Li, Sujuan. Li, Lanjuan. Changes in Chinese Policies to Promote the Rational Use of Antibiotics. *PLOS Medicine*. November 2013. Volume 10, Issue 11.

Yong D, Toleman MA, Giske CG, Cho HS, Sundman K, Lee K, Walsh TR. "Characterization of a new metallo-beta-lactamase gene, bla(NDM-1), and a novel erythromycin esterase gene carried on a unique genetic structure in *Klebsiella pneumoniae* sequence type 14 from India". *Antimicrob Agents Chemother* 53 (12): 5046–5054. 2009.