



# SITUATION ANALYSIS

## Antibiotic Use and Resistance in India



Global Antibiotic Resistance Partnership-India National Working Group

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## Table of Contents

<b>Foreword</b>	iii
<b>Executive Summary</b>	v
<i>Lack of Access and Overuse of Antibiotics in India</i>	v
<i>Poor Surveillance and Increasing Resistance to Antibiotics</i>	vii
<i>Antibiotic Use in Animal Husbandry</i>	vii
<i>Policy Responses</i>	viii
<b>Part 1: GARP—The Global Antibiotic Resistance Partnership</b>	1
<i>Policy Development to Slow the Spread of Antibiotic Resistance</i>	1
<b>Part 2: Health and Economic Situation in India</b>	3
<i>Health Indicators</i>	3
<i>Healthcare Indicators</i>	3
<i>Access to Primary Care</i>	3
<i>Access to Drugs</i>	6
<i>Health Expenditures</i>	9
<b>Part 3: Antibiotic Resistance and Use</b>	11
<i>Hospital-Acquired Infections</i>	11
<i>Gram-Negative Bacteria</i>	12
<i>Gram-Positive Bacteria</i>	14
<i>Antibiotic Resistance in Animals</i>	17
<i>Surveillance of Antibiotic Resistance</i>	18
<i>Antibiotic Use</i>	21
<i>Government Regulation and the Supply Chain for Antibiotics</i>	29
<b>Part 4: Interventions to be Considered</b>	37
<i>Vaccines for Antibiotic-Treatable Diseases</i>	38
<i>Infection Control Interventions</i>	44
<i>Educational Interventions</i>	45
<i>Standard Treatment Guidelines</i>	47
<i>Guidelines and Checklists</i>	48
<i>Major Drivers of Antibiotic Resistance: Current Indications</i>	48
<b>Part 5: Next Steps for GARP</b>	55
<i>Current Research and Next Steps for GARP-India</i>	55
<i>Final Products for GARP</i>	56
<b>1st Global Forum on Bacterial Infections</b>	57
<b>Appendix 1: Basic Health and Economic Indicators for India</b>	58
<b>Appendix 2: Healthcare in Urban Slums in India</b>	61
<b>References</b>	62

## Foreword

**A**ntibiotic resistance is a stark reality across the globe, including in India. The challenges associated with controlling antibiotic resistance, particularly in India, are many and multifaceted. On one hand, antibiotics are necessary in many life-threatening cases. On the other hand, overuse of antibiotics can be disastrous in the long run. Hence, judicious use of antibiotics is required, but acceptable strategies to achieve this goal and to address the challenges must be devised and communicated.

Molecular-based detection of the drug resistance of indicator microorganisms is a challenge, as is monitoring their circulation in hospitals and in the community. An approach that integrates surveillance for drug resistant organisms in animals and humans is also a current need.

Another major challenge is the absence of a good monitoring or surveillance system for prescriptions. A rigid surveillance system for community- and hospital-based prescribing is the first step towards determining the magnitude of the problem and instituting appropriate remedial measures. Such a system would provide a window on the underlying trends in prescribing practices.

Prescription monitoring is indeed difficult, considering the vast Indian subcontinent. One feasible approach is to provide incentives to pharmacists to keep records of prescriptions dispensed and discourage their practice of dispensing antibiotics without prescriptions (especially common in suburban and rural areas) or out-of-date prescriptions. Changing the behaviour of pharmacists will be pivotal for the success of any campaign against misuse or abuse of antibiotics. They need to feel that they are part of the health system, rather than simply another business. Programs to educate the pharmacists in the critical area of drug dispensing need to be designed and implemented.

Another important issue related to drug dispensing is that many pharmacies are not owned or run by qualified pharmacists. The number of pharmacies licensed to a single pharmacist, yet run by unqualified personnel, has mushroomed. This has aggravated the problem of malpractice in drug dispensing, where the only goal is financial gains, and needs to be addressed legally.

Once a good surveillance system is in place, a national board should monitor all prescriptions. When this is in place, it should focus on physicians who inappropriately use antibiotics. As with pharmacists, changing prescribing habits is no easy task. Sustained efforts will be required to educate and re-educate physicians about the long-term consequences of antibiotic overuse. Here, technical issues need to be highlighted so that the physicians understand and appreciate the message.

Exacerbating this problem is the stagnation of the pharmaceutical industry in the development of new antibiotics. The lack of antimicrobial advances has led to the introduction of only one new class of antibiotics—the oxazolidinones—in the past three decades. One would think that knowing that the antibiotic armamentarium is on the verge of exhaustion would convince physicians to think twice before prescribing antibiotics.

While addressing the immediate concerns regarding antibiotic resistance should remain a priority, long-term goals should also be kept in mind. These include formulating strategies and incentives to kick-start new antimicrobial research and development by the pharmaceutical industry. Instituting effective public-private-partnerships may be crucial to initiate and sustain a strong antimicrobial drug pipeline over the long term. Again, all the foregoing efforts should occur simultaneously, in order to check misuse, abuse, or overuse of antibiotics.

Initiatives, such as the Global Antibiotic Resistance Partnership (GARP), should stimulate critical thinking and take the issue forward, so that the challenges are adequately addressed and, eventually, stabilization or even reversal of the antibiotic resistance pattern occurs—first regionally, then globally.

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## Executive Summary

The infectious disease burden in India is among the highest in the world. A large amount of antibiotics are consumed in fighting infections, some of them saving lives, but every use adding to antibiotic resistance in bacteria. Antibiotic use is increasing steadily (table 1), particularly certain antibiotic classes (beta-lactam antibacterials), most notably in the more prosperous states. Resistance follows in lock-step.

As a marker of disease burden, more than 5 million Indian children under the age of five years get pneumonia or sepsis, and 215,000 children die annually from infections from two bacterial pathogens, *Streptococcus pneumoniae* (*S. pneumoniae*) and *Haemophilus influenzae type b* (Hib)—both of which can be prevented with vaccines. Indian mortality rates are high, although not as high as some African countries and Afghanistan. Because India is so populous, it contributes more cases of infection and deaths to the global total than any other country. Preventing even a portion of these cases and deaths would be a boon to public health. The concomitant reduction in antibiotic demand would translate directly to considerably less antibiotic use and slower growth of antibiotic resistance.

### Lack of Access and Overuse of Antibiotics in India

As is the case with other resources, antibiotic effectiveness can be ‘used up’. When this happens, people will be forced to pay more for new drugs that replace inexpensive standard antibiotics or they will forego treatment because they cannot afford it. The eventual loss of current antibiotics is inevitable, but it can happen more quickly (years) or more slowly (decades), depending upon actions taken now. The Global Antibiotic Resistance Partnership (GARP) is developing policy alternatives to manage antibiotic effectiveness to the greatest benefit of the people in India Kenya, South Africa, and Viet Nam. This situation analysis is a preliminary report, designed to support in-depth policy evaluation that will result in final policy recommendations to address both lack of access to antibiotics and unnecessary use of antibiotics in India

A common response to slowing antibiotic resistance is to look for ways to limit antibiotic use, for example, by enforcing ‘prescription only’ laws for antibiotic sales. In Delhi, no prescription was presented for one-fifth of the antibiotics purchased recently. Yet, the situation is not so simple. In India, one is confronted with evidence of both overuse and underuse. In 2005–2006, a large portion of infant and childhood deaths from pneumonia would not have occurred if the children had been properly treated with antibiotics. Medical advice was sought for just under one-third of children with symptoms of pneumonia, and only about 13 percent of them were treated with an antibiotic. Not surprisingly, access is related to socioeconomic status, although the reasons may not be directly financial—low education levels, lack of nearby healthcare facilities, and few available medical practitioners also contribute.

Drug prices in India are generally low because of competition among generic manufacturers, although some analysts believe that the government should mandate lower prices for essential drugs because their cost may still be prohibitive for some. If access to antibiotics without prescriptions were cut off by govern-

**Table 1. Outpatient antibiotic purchases from retail outlets in India**

Year	2005	2006	2007	2008	2009
Antibiotic purchases in crore rupees (INR)	3,763	4,484	5,075	5,886	6,414

Notes: One crore equals 100 lakhs, equals 10 million

Source: Personal communication of IMS Health Information and Consulting Services-India data from Burzin Bharuch (Pfizer) to Ramanan Laxminarayan on July 30, 2009.

ment-mandated reforms, would more people go untreated and die? Despite a wealth of research in India, this question cannot be answered.

Antibiotics are also overused in treating patients with coughs and colds that do not require antibiotic treatment—which wastes their effectiveness. This practice is common among people who seek healthcare from a doctor or other practitioner, not just those purchasing antibiotics without prescriptions. Studies from India have uncovered an array of possible reasons for this overuse, similar to other countries:

- Lack of microbiology facilities
- Doctors prescribing antibiotics to any patients with a fever, taking it as a sign of bacterial infection
- Patient expectations
- Desire of pharmacists and some doctors to make a profit from drug sales
- The public’s lack of knowledge about the (in)appropriate use of antibiotics

If it were just a matter of spending money ineffectively, that is a waste, but indiscriminate use of antibiotics begets resistance. Regardless whether antibiotic treatment is appropriate, the bacteria inhabiting the gut and other parts of the body are affected by antibiotics and will evolve genetic material coding for resistance that they pass on to other—even unrelated—bacteria. Stopping use of certain antibiotics can reverse some trends, but in other cases, even after a drug has not been used for years, the common bacteria remain resistant.

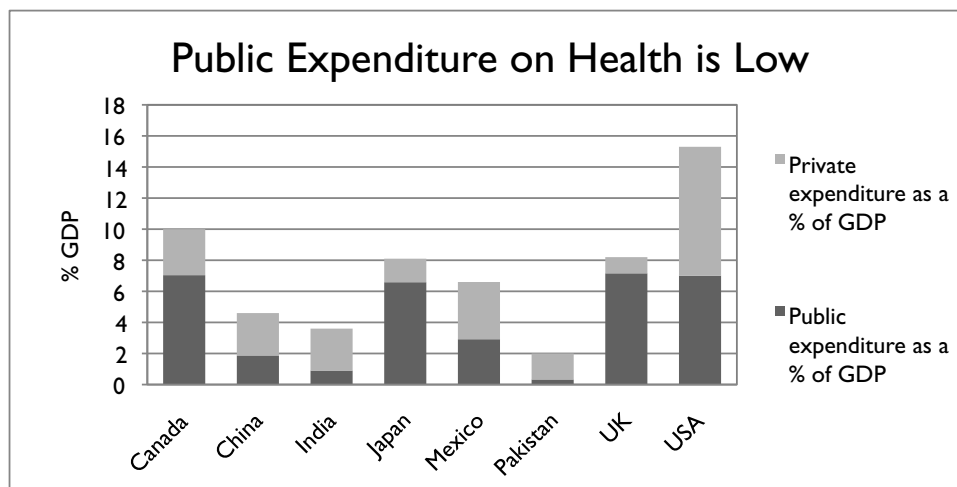
Access to antibiotic treatment is difficult to define, but it plays an important role in people’s healthcare decisions, including decisions about antibiotics. For some, the only realistic access to healthcare is through a pharmacy or shop because there are not enough public facilities to provide care for everyone. Where public healthcare facilities do exist, the buildings may be crumbling, equipment may not work, and the clinic may be out of drugs because of inconsistent supply from the government. Care and drugs may also cost more than the official rates because extra payments are required in many cases. It should be no surprise that 80 percent of healthcare visits are to private sector practitioners, many of whom are poorly trained and unlicensed.

Patients who do go to hospitals often arrive with serious infections, but in many places in India microbiology services are limited or non-existent. In this situation, the infecting organism cannot be identified nor can its antibiotic resistance profile be determined (if the infection is bacterial). Common treatment (particularly in private hospitals) is with an advanced, broad-spectrum antibiotic, which begins to erode the effectiveness of these drugs. Better matching of pathogens with antibiotics could avert some of this loss.

Who pays for antibiotics, vaccines, and healthcare in general is important. In India, spending on healthcare is 4–5 percent of gross domestic product (GDP), but the lion’s share—80 percent—is out-of-pocket spending, mostly for medicine. The government pays about 20 percent (1:4), but in most industrialized countries, spending is 6–8 percent or more of GDP (roughly 1:3, public to private expenses, respectively), meaning that other governments pay a much larger proportion (figure 1). This affects public and private decisions about what to buy and what not to buy. Even for an intervention that is relatively cost-effective—or even cost-saving—such as many vaccines, shifting costs from the private to the public sector may not be an immediately attractive option. The economics of such policies are usually not fully worked out, and nowhere in the world is the cost of antibiotic resistance factored in.

India is gradually improving access to healthcare for a greater proportion of its population by filling in some of the gaps in service. If it also shifted the balance so that government pays a somewhat larger share and if out-of-pocket expenditures decrease, people would be more likely to take advantage of available

**Figure 1. Public/Private Spending on Healthcare in India and Other Countries**



Source: WHO (2009).

health services. Recognizing that such change may not happen for years, policies on antibiotic use still can make progress under current conditions.

## Poor Surveillance and Increasing Resistance to Antibiotics

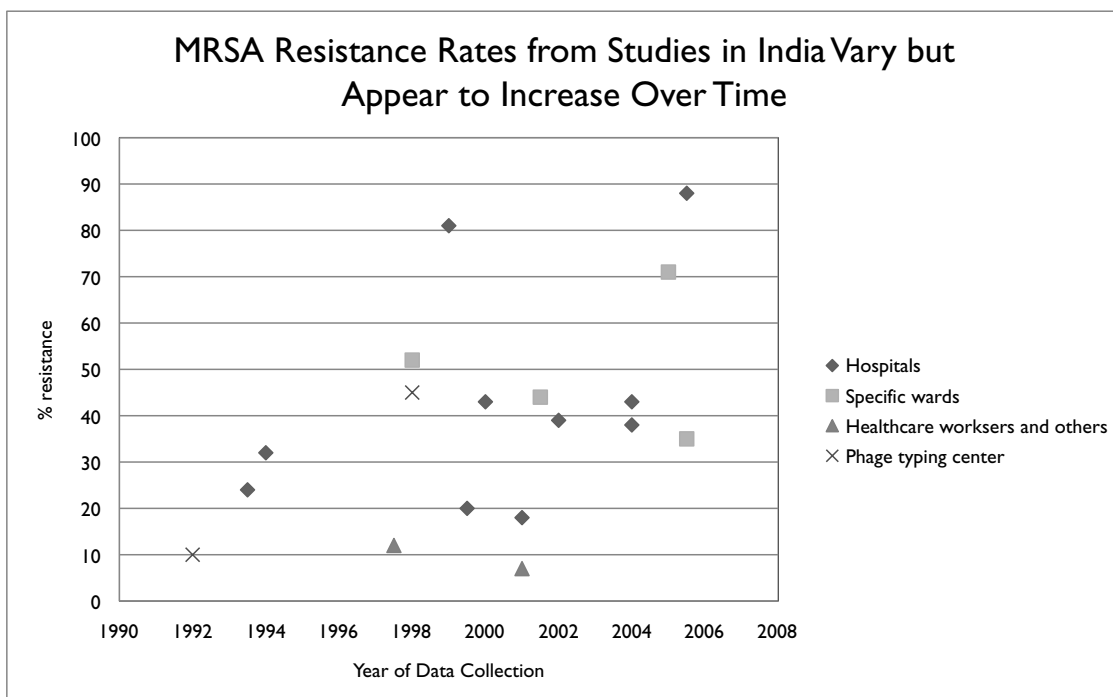
Surveillance for antibiotic resistance is a low priority—lower even than microbiology services for patient care—in most low- and middle-income countries, and India is no exception. The Invasive Bacterial Infection Surveillance (IBIS) project has produced valuable information, but is limited in scope. Evidence of high and increasing resistance levels is sparse and generally biased upward because samples are tested only when patients fail to respond to common treatments. Still, the levels of consumption, the cautionary data contained in this report, and experience elsewhere in the world leave no doubt that antibiotic resistance is rising (figure 2) and will become an ever-greater problem in India, as it has in other countries.

## Antibiotic Use in Animal Husbandry

Surprisingly little is known about the use of antibiotics in animal husbandry in India. Many drugs commonly used for people are also used for farm animals to treat illnesses and probably curb contagion. Whether antibiotics are also added to feed to promote growth (as in the United States, but no longer in Europe) is not well known. No government regulations exist to control antibiotic use in domestic animals in India. The precise impact of agricultural antibiotic use on resistance levels in the general population is not known anywhere, but the evidence points to a link. As with human use, reducing demand, for example, by improving sanitation and limiting use to instances where antibiotics can be effective are options that deserve to be explored.



**Figure 2. MRSA (Methicillin-Resistant *Staphylococcus aureus*) Resistance Rates in India**



Source: Data from all studies described in the section on MRSA in India, excluding those that did not specify when data was collected.

## Policy Responses

India could introduce various policies based on interventions that have proven effective in other countries, aimed at hospitals, clinics and other facilities, and communities. High on the list would be adoption of two infant vaccines, recommended by the World Health Organization (WHO), to prevent *H. influenzae type b* (Hib) and *S. pneumoniae*, which cause most of the infant deaths from pneumonia. Proven hospital infection-control measures (as simple as increasing the rate of hand washing by doctors and nurses) are not systematically employed. Other measures, such as public and professional education, about antibiotics are more country and context specific. Small-scale programs have been tried in India and elsewhere to encourage more rational antibiotic use and once further developed, these will likely be implemented more widely. Although India has successfully deployed economic incentives for better healthcare (e.g., promoting childbirth in hospitals), such innovations have yet to be developed for antibiotics.

The final GARP-India report (to be released in 2011) will consider all available options, each analysed in light of the information presented in this situation analysis and other pertinent factors.

## Part I: GARP—The Global Antibiotic Resistance Partnership

The global problem of antimicrobial resistance is particularly pressing in developing countries where the infectious disease burden is high and cost constrains the replacement of older antibiotics with newer, more expensive ones. Gastrointestinal, respiratory, sexually transmitted, and nosocomial infections are leading causes of disease and death in the developing world, and management of all these conditions has been critically compromised by the appearance and rapid spread of antibiotic-resistant bacteria.

‘Drug pressure’ is the single most important factor in the evolution of drug resistance in bacteria. Simply put, this means that the more antibiotics are used, the more likely resistant strains are to emerge and become common—the sensitive ones are killed and the few that are resistant genetically take over. The reasons for drug pressure are multifactorial. Although drug resistance is primarily a medical problem, the factors that influence the spread of resistance are ecological, epidemiological, cultural, social and economic. Patients, physicians, veterinarians and healthcare facilities and retailers—from large pharmacies to local drug sellers—have little motivation (economic or otherwise) to acknowledge the negative impact of their use of antibiotics on others (especially in the future). Standard responses, such as increased surveillance and public information campaigns about the hazards of drug resistance, are a necessary component of an overall policy response, but may have limited impact alone. In order to work, policy solutions must alter the incentives for patients, physicians and others in the healthcare system so that individual interests are aligned with society’s interests. Evaluating policy solutions involves understanding infectious diseases in populations. Research to design focused, context-specific policy solutions that are likely to have a significant impact on resistance is a first step. Translating these policy solutions into policy action is the second.

Antibiotic resistance does not top any list of national problems nor should proposed strategies drain resources from more pressing concerns. Done correctly, controlling antibiotic resistance should be either cost-neutral or, in fact, be one of

the few health interventions that actually saves money in the long term. Some initial investment will be required, however.

### Policy Development to Slow the Spread of Antibiotic Resistance

Starting from the premise that antibiotic use eventually leads to resistance, it follows that higher levels of use lead to earlier and quicker spread of resistant bacteria and that less usage means a slower spread. With less antibiotic use, antibiotic effectiveness is maintained for a longer period. Every use is not equal when it comes to the development and spread of resistant bacteria. However, this premise is generally true and it may not much matter whether a person takes an antibiotic for a bacterial infection (for which an antibiotic might be appropriate) or a viral or other infection (where an antibiotic is usually ineffective). One might argue that if antibiotics were kept on the shelf and never used, resistance would never develop. But, the aim of antibiotic policies is to maximize the benefit from each antibiotic, not keep it effective forever.

Two basic approaches are available to slow the spread of antibiotic resistance (and maintain effectiveness). First is better targeting of antibiotics to those people (and animals) who can benefit from them. This means not giving antibiotics to people (and animals) with non-bacterial illnesses. Not treating people who cannot benefit matters more because everyone has bacteria living in and on them. Resistance can develop in commensal bacteria—which are not causing illness—in the gut, on the skin, in the nose, or elsewhere because these non-pathogenic bacteria can pass resistance genes on to bacteria that cause disease.

Targeting the use of antibiotics is not easy. Diagnostic tests are not readily available when people get sick, whereas antibiotics are. Despite laws and regulations on the books, restricting antibiotic treatment to people with a prescription may not be enforceable in many countries, including India.

Steps to change this may be part of the solution, but it will not come quickly. The flip side is that, for some sick people, unregulated access is the only access to help.

Second, these policies should also include measures to reduce the need for antibiotics by reducing the incidence of infection. The most obvious way to do this is by vaccinating against the organisms that cause antibiotic-treatable disease. Vaccines against Hib and *S. pneumoniae*, which cause pneumonia, are good examples. Surprisingly, vaccines against other types of organisms—for example, rotavirus, which causes many cases of childhood diarrhoea—can also reduce antibiotic use. Even though rotavirus itself cannot be treated successfully with antibiotics, they are prescribed for the diarrhoea it causes in India and in other countries: a rotavirus vaccine would reduce this use. By far, the most important benefit of any vaccination is to prevent disease, but the benefit in terms of saving antibiotics is often overlooked.

Infection can be reduced in other ways, too. Hospitals around the world are notorious as places where bacteria thrive and are transmitted patient to patient, often by unsuspecting healthcare workers. The crowded conditions in many public hospitals, including those in India, are prime territory for bacteria. Patients with weakened immune systems—from disease or age—are more easily infected, but even healthy patients in the hospital for surgery (e.g., due to an accident) often end up infected. Even worse, many of the bacteria found in hospitals are resistant to a range of antibiotics, starting a nightmarish cycle of ever-longer and often difficult treatments. Fortunately, the infection rate in hospitals can be reduced with low technology and relatively inexpensive measures. The most difficult part of controlling hospital infection—which is no small matter—is changing the behaviour of healthcare personnel, including doctors. Infection control will not make hospitals less crowded (except by shortening the stay of people who do not become infected), but it can make them safer.

From this brief introduction, it is clear that measures to protect antibiotic effectiveness cannot simply be appropriated from other settings without considering the specific conditions in

the healthcare system, the socioeconomics of the population, the strength and reach of the central government and peripheral authorities and even geography.

This report begins with basic information about India. Consideration of this backdrop is important when specific policies are discussed. The feasibility, cost, and likelihood of success depend largely on the societal factors described here, and the choice of what to concentrate on first will be informed by them.

## Part 2: Health and Economic Situation in India

A combination of communicable and non-communicable diseases—tuberculosis, diarrheal diseases, cardiovascular diseases, and chronic respiratory diseases—are major contributors to mortality in India (figure 3). The severity of each disease varies from region to region. Specifically, infectious diseases tend to make up a larger proportion of the disease burden in the less-developed states (Jha et al. 2007). Thus, some states, especially in southern India, are at more advanced stages of the epidemiological transition that results from widespread access to medical care including antibiotics and vaccines.

### Health Indicators

Reliable estimates of mortality by cause have recently been made available as a result of the 'Million Death Study' conducted by the Office of the Registrar General, India (ORGI), and the Centre for Global Health Research (CGHR). This study uses a verbal autopsy system\* to sample deaths from households across India (CGHR 2003). According to phase 1 of this study, based on 113,692 deaths collected between 2001 and 2003 in India, 8 percent were from diarrheal diseases, 6 percent were from tuberculosis, 6 percent from respiratory infections, 4 percent from other infectious and parasitic diseases, 3 percent from malaria, 2 percent from fevers of unknown origin, and 0.5 percent from HIV/AIDS (CGHR 2003).\*\*

### Healthcare Indicators

The percent of children who are fully immunized—defined as having received a BCG injection

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\*Verbal autopsy is a method of ascertaining probable causes of a death based on an interview with primary caregivers about the signs, symptoms and circumstances preceding that death' (Baiden et al., 2007).

\*\*Background information on health indicators in India is presented in more detail in appendix I.

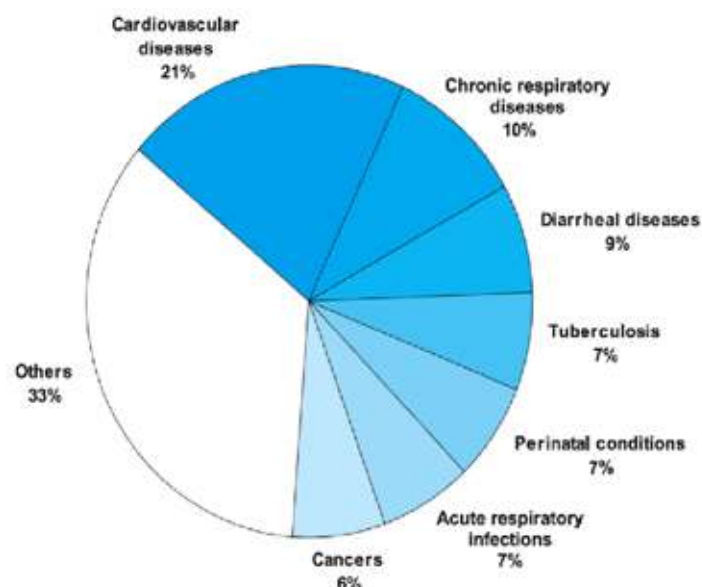
(Bacillus Calmette-Guérin vaccine for tuberculosis); three doses each of DPT (diphtheria, pertussis, tetanus) and polio vaccines; and one measles vaccine—was 44 percent among children 12–23 months in India's third National Family Health Survey (NFHS-3) in 2005–2006, although it was less than 33 percent in some states (IIPS et al. 2007). Rural-urban disparities exist as well, with 58 percent childhood vaccine coverage in urban areas and 39 percent in rural areas. Overall immunization coverage has increased from 36 percent in NFHS-1 (1992–1993), but only slightly since NFHS-2 (1998–1999), when it was 42 percent (IIPS 2007).

Relevant to antibiotic use, in 2005–2006, NFHS-3 found that 6 percent of children under five years had symptoms of acute respiratory infection in the previous two weeks; of these cases, 69 percent sought treatment and 13 percent received antibiotics. The survey also showed that, of 15 percent of children under five years who had a fever within the previous two weeks, 8 percent received an anti-malarial drug and 13 percent took an antibiotic. Nine percent of children under five years had diarrhoea in the previous two weeks, of which 60 percent went to a healthcare facility and 43 percent were treated with oral rehydration therapy or fluids (IIPS et al. 2007).

### Access to Primary Care

In rural areas, the government aims to run one community health centre (CHC) for every 100,000 people; one primary health centre (PHC) for every 30,000 people; and a subcentre for every 5,000 people in the plains and every 3,000 people in hilly, tribal, and desert areas (MoHFW 2006; WHO/SEARO 2007). However, in 2004, to reach these target ratios, about 7,000 CHCs and 12,000 PHCs needed to be constructed (Chow et al. 2007). Among existing PHCs, about 70 percent have inadequate infrastructure and 60 percent have inadequate equipment (Chow 2007, table 1). The National Rural Health Mission (NRHM) states that 6 percent of PHCs have no doctors, though the actual figure may be higher (NRHM 2005; Jha et al. 2007).

**Figure 3. Leading Causes of Death at all Ages in India, 2004**

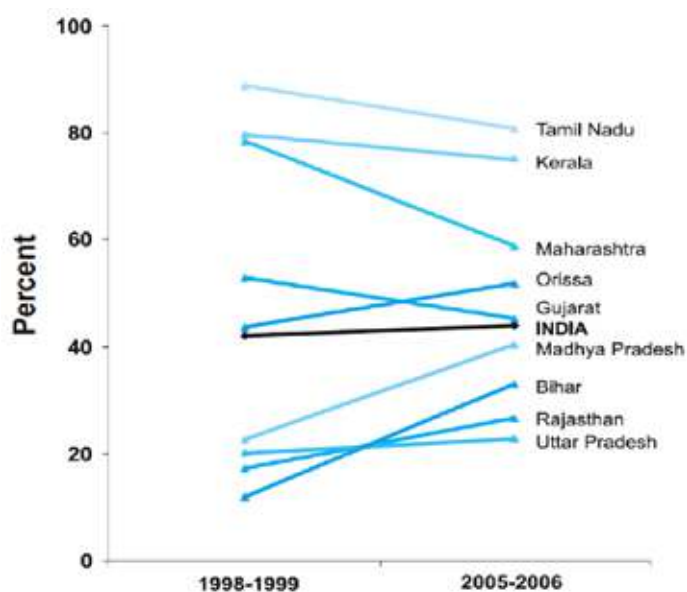


Source: Jha et al. (2007)

Subcentres employ one auxiliary nurse midwife (ANM) and one multipurpose worker (male). One lady health visitor (LHV) and one male health assistant from the PHCs supervise affiliated subcentres. The national government pays the salary

of ANMs and LHVs, rent and the cost of drugs and equipment. State governments pay the salaries of the male health workers. The Indian Public Health Standards (IPHS) are used to monitor the functioning of the subcentres. They review whether sub-

**Figure 4. Trends in Full Immunization Coverage**



Source: Jha et al. (2007)

**Table 2. Percentage of Inadequate Public Health Facilities, 2004**

	India	EAGA states	Other states
<b>District hospitals</b>			
Inadequate infrastructure	7.3	9.3	4.2
Inadequate equipment	15.9	15.5	16.7
<b>Community health centers</b>			
Inadequate infrastructure	37.2	46.8	29.9
Inadequate equipment	55.5	56.7	54.0
<b>Primary health centers</b>			
Inadequate infrastructure	68.2	85.1	39.1
Inadequate equipment	58.7	74.6	40.3
<b>Health subcenters</b>			
Without electricity	57.9	76.7	40.4
Without tap water	81.1	95.2	68.0
Without toilet	29.4	35.8	23.4

Figures are divided into those states that score lowest on development and health indicators (EAGA states are the Empowered Action Group (EAG), as designated by the Ministry of Health, and Assam) (Jha et al. 2007).

centres provide the specified basic services and what staff is employed. They also oversee the physical infrastructure; available equipment, drugs, and furniture; and the disease monitoring done by the subcentre. Subcentre labs are capable of basic blood and urine screens, such as haemoglobin estimations using test strips and urine tests for sugar and protein. The elementary set of drugs available for patients includes oral rehydration salts and co-trimoxazole. Gentamicin, ampicillin, and metronidazole are supposed to be available for use by ANMs and LHV's trained to attend childbirths (MoHFW 2006).

Due to the difference in standards of living between rural and urban areas, many doctors are averse to practicing in rural clinics. About three-fourths of doctors with a post-graduate medical degree live in urban areas, serving only 28 percent of the population (MoHFW/NRHM 2006). This means that rural posts are often filled by people without formal qualification in modern medicine.

Government support of public healthcare centres allows them to provide services at little or no cost. Public health facilities are supposed to dispense medicines prescribed by their doctors for free to families living below the poverty line, after they pay a small administrative fee (INR 2) for the

prescription (Gill 2009). The poverty line is defined differently in different states of India.

Although these services are supposed to be free, in practice, patients are frequently charged for them (Yip et al. 2008). A survey of patients at public health facilities found that free services were provided to most in Andhra Pradesh, while less than one-quarter of respondents in Uttar Pradesh, Bihar, and Rajasthan said that they had received medicine for free (Gill 2009). This disparity may be due to in part to higher socioeconomic levels in some states, as policies for proof of living below the poverty line differ from state to state. Variations in levels of accountability among states likely also contribute to these differences; there is evidence of some medical staff running for-profit clinics in public health facilities (Gill 2009).

In other cases, the perceived poor quality of public healthcare drives people to private practitioners, who may or may not be qualified (Bardhan 2008). The National Sample Survey in 1995–1996 found that more than 80 percent of outpatient visits in India were to private physicians. Many of these private practitioners are unqualified to practice allopathic (conventional Western) medicine. One study found that 6 percent of private medical practitioners held an undergraduate degree in

medicine (Bachelor of Medicine/Bachelor of Surgery [MBBS]). About 42 percent of private medical practitioners are trained in some form of alternative medicine, but they often prescribe allopathic drugs. Some practitioners have no recognized medical qualification at all (Kumar et al. 2007b).

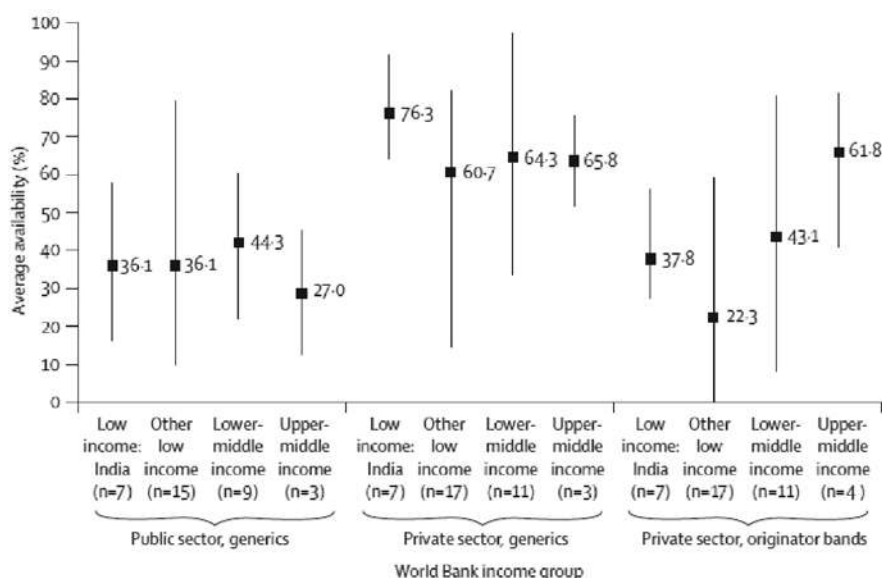
Many private medical practitioners run pharmacies without a license. They often repackage bulk drugs for patients and, while they keep records of what they sell, they dispense medicines without a prescription (Kumar et al. 2007b). Although it is expected that medical practitioners dispense drugs only to their own patients, they often supply medicines to others as well. Similar practices are found in nursing homes that operate unlicensed pharmacies. Only recently has the government taken steps to formally license medical practitioners and nursing homes (personal communication from G. P. Mohanta, Professor of Pharmacy at Annamalai University, to Alice Easton on June 23, 2010).

## Access to Drugs

Many medicines remain unavailable to the majority of Indians, as they are not always stocked in pharmacies. In 1999, an estimated 65 percent of Indians did not have reliable access to essential medicines, compared to 30 percent of people worldwide (personal communication from G. P. Mohanta, Professor of Pharmacy at Annamalai University, to Alice Easton on June 23, 2010). These figures came from surveys of local medicine experts in each country, who were asked to estimate the percentage of the population who have access to a minimum list of 20 essential medicines, which are continuously available and affordable at a health facility or medicine outlet within one hour's walk from the patients' home (WHO 2004).

The availability of 27 essential medicines in public sector facilities at 6 sites in 5 Indian states in 2004–2005 ranged from zero to 30 percent (Kotwani et al. 2007a). Availability was defined as the percentage of facilities with the medicines in stock on the day of the survey. A different price study in four areas of Rajasthan surveyed 27 medicines on the World Health Organization/Health Ac-

**Figure 5. Average Country-Level Mean Percentage Availability of Medicines, by World Bank Income Group**



Availability is measured according to a standardized WHO/Health Action International survey, and data are drawn from 45 such surveys in 36 countries. Indian survey results are reported separately.

Source: Cameron (2009).

**Table 3. Availability of Drugs in Public Sector Facilities in Five States of India**

Antibiotic	Haryana	Maharashtra	Chennai	West Bengal	Karnataka
Amoxicillin	73%	82%	100%	96%	46%
Ceftriaxone injection	20%	15%	30%	19%	85
Ciprofloxacin	80%	62%	55%	0%	83%
Co-trimoxazole suspension	7%	78%	45%	4%	29%

Source: Kotwani et al. (2007a).

tion International core list plus 9 locally important medicines. Availability was defined as above, and affordability was defined as the number of days the lowest-paid unskilled government worker must work to purchase standard treatment regimen for a common clinical condition (Kotwani et al. 2009b).

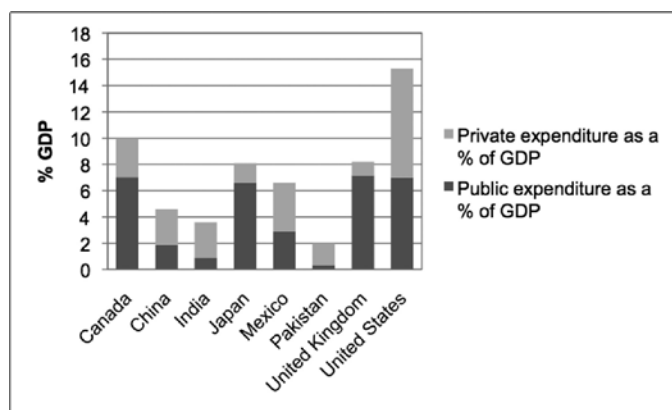
The study found that some drugs were more expensive in the public sector than in the private sector, that prices in the private sector did not depend on location, that there was little difference between generic and brand name drug prices, and that brand name drugs were not available in the public sector. In ‘cooperative’ pharmacies, the availability of generics was poor and usually the most popular brand (often the most expensive) of the essential medicines surveyed was available (Kotwani et al. 2009a). The lack of availability of essential medicines in Rajasthan was confirmed in another study that found inhalers for asthma treatment were not available at any of the public facilities surveyed except in the capital, Jaipur (Kotwani 2009).

A study in Rajasthan looked at two efforts to make drugs available at low cost, one by an NGO and the other by the government, and found that the initiatives focused too heavily on expensive non-essential drugs and did little to provide basic medicines at a low cost (Singh et al. 2008).

One reason that essential drugs may be unavailable at hospital pharmacies is the inconsistent supply of drugs from the government. This often forces hospitals to make expensive stopgap purchases from local pharmacies (Kotwani et al. 2007b).

Data from 45 surveys conducted by the WHO/Health Action International in 36 countries from 2001 to 2006 included 7 studies in India (2003–2005). They showed that the average availability of generic drugs in other countries was 36 percent, which was similar to their availability in the public sector in India (Cameron et al. 2009). Average availability of generic drugs in the private sector in India was 76 percent, in the same range as the average figure for low- or middle-income countries

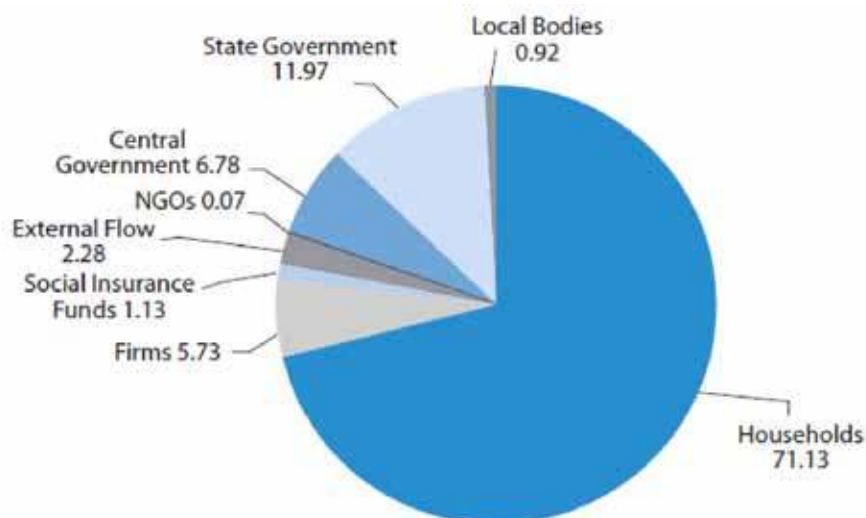
**Figure 6. Total Expenditure as a Percent of GDP by Private and Public Expenditure in Selected Countries**



Source: WHO (2009).



**Figure 7. Sources of Funds for Health Care in India, 2004–2005**

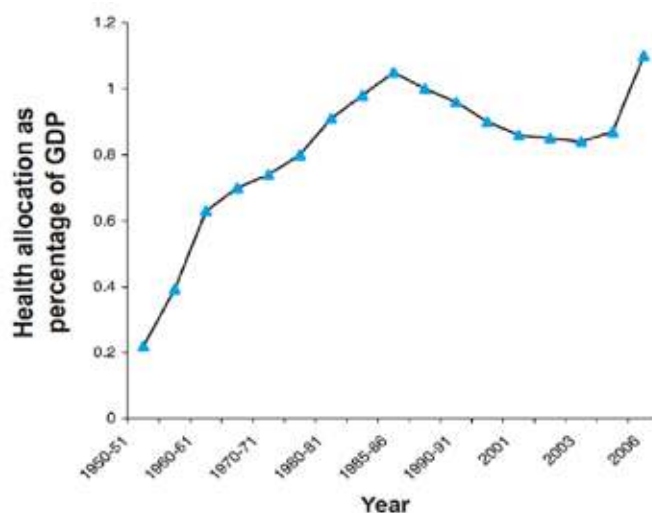


Source: Murthy et al. (2004–2005).

(Cameron et al. 2009, figure 3). (Availability was measured as the percentage of medicine outlets where a medicine was in stock on the day of the survey.) Four of 15 antibiotics in the sample (ciprofloxacin, amoxicillin, ceftriaxone, and co-trimoxazole) were available in at least 80 percent of the surveys (Cameron et al. 2009). The median availability of these four antibiotics in public sector facilities in five states of India (table 3) showed that only amoxicillin was widely available and the availability of co-trimoxazole suspension was very poor.

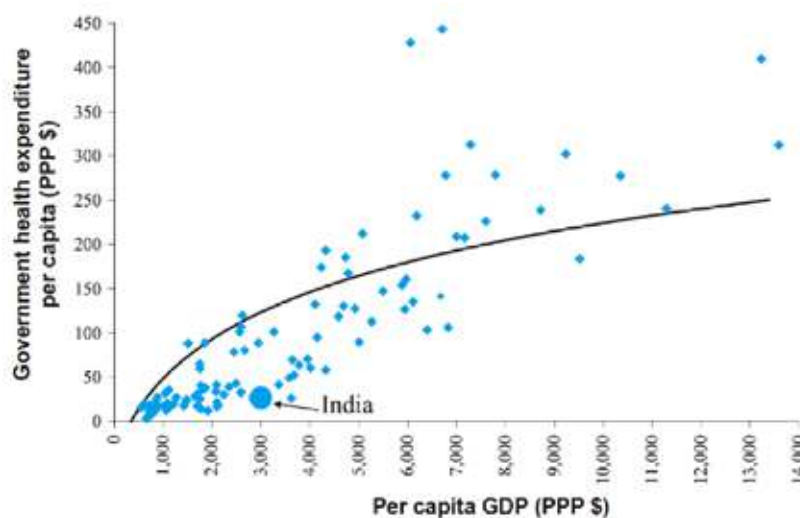
Drug prices are low in India, compared to both developed and developing countries (the reasons for this are discussed in the section, Government Regulation and Supply Chain of Antibiotics), and there are both government and private schemes to make drugs available. However, some studies indicate that even essential drugs are often unavailable in pharmacies, especially in the public sector. There are other non-price barriers to drugs in India. It may be difficult for patients to receive the correct drugs if there are few doctors serving their

**Figure 8. Health Spending as a Percentage of GDP in India, 1950–2007**



Source: Jha et al. (2007).

**Figure 9. Government Health Expenditure per Capita versus per Capita GDP in Countries with Low and Middle Development, Including India**



Source: Jha et al. (2007).

region (as discussed above), lines at clinics are long, or facilities and healthcare workers require extra fees before providing services. Although the situation varies across regions, many people in India have the perception that free or inexpensive services provided by government hospitals are substandard or may be withheld without outside payments to the provider (TII 2005). The government of India has launched a program, 'Jan Aushadhi', to open generic drug stores in every district of India and make essential medicines available at affordable prices. By September 2009, 20 generic drug stores had been opened in public facilities in Punjab and Rajasthan to provide government-subsidized free or cheap medicines to the population. However, these stores sell only a limited number of generic medicines, including antibiotics manufactured by five recently revived public-sector drug-manufacturing units. The Parliamentary Standing Committee on Health recently suggested that it should be made mandatory for the State governments to open the Jan Aushadhi outlets in all government hospitals (DWS 2010). Some stores report being supplied with a mix of drugs that do not correspond with demand, leaving them short of needed drugs, while other medicines languish on the shelves, which affects the stores' revenue stream (Deep 2009). There is also some doubt about the quality of the generic medicines sold at these pub-

lic facilities, leading doctors to write prescriptions to private pharmacies. Publicizing evidence on the quality of generic drugs and opening generic drug stores in the private sector could improve access to affordable medicines for the general public (Kotwani 2010).

## Health Expenditures

Overall, spending on healthcare is about 4–5 percent of GDP, but government expenditure constitutes only 28 percent of that amount (Murthy et al. 2004-05; WHO 2009), with private expenditures making up the rest, i.e., the ratio of public to private is about 1:3. Spending by the government on healthcare was less than 1 percent of GDP in the 1990s and is supposed to increase to 2 percent by 2012 (Jha et al. 2007); however, it is not currently on track to do so (MoHFW 2006). In contrast, in most high-income countries, 6–8 percent of GDP is spent on healthcare and the government to private contribution is the reverse of what it is in India, i.e., 3:1. In middle-income countries, on average, approximately equal amounts of public and private money are spent on healthcare, although this varies by country (figure 7). While most of the money spent on healthcare in India goes to private services, people in underprivileged and rural areas are

**Table 4. Percent Composition of Out-of-Pocket Expenditure in Inpatient Care**

	<b>Doctor's fees</b>	<b>Diagnostic tests</b>	<b>Bed</b>	<b>Blood, etc.</b>	<b>Medicine</b>	<b>Food</b>
Rural-public	4.16	11.92	4.36	66.49	3.75	9.33
Urban-public	4.64	15.12	5.84	62.32	4.57	7.52
Rural-private	25.84	9.37	16.57	40.43	2.86	4.91
Urban-private	27.32	10.84	16.56	37.77	4.43	3.09

Source: From the National Sample Survey Organization, as cited in Murthy et al. (2004–2005). The National Sample Survey collects continuous nation-wide data on socio-economic variables.

often dependent on public facilities for care, due to both location and price constraints (Chaudhury et al. 2005).

Out-of-pocket spending accounts for 80 percent of private funds spent on healthcare in India (Jha et al. 2007). Public health spending has been increasing over the last few years (Figure 8). However, public spending on health is still low in comparison to other countries with similar per capita GDP rates (Figure 9). In 2008, little over 2 percent of private health expenditure went towards insurance schemes (Murthy et al. 2004–2005). This means that uninsured families are often financially crippled by unexpected healthcare costs, in a coun-

try where millions live on the brink of destitution. Despite the personal expenses incurred, private healthcare is no guarantee of quality (Jha et al. 2007). The distribution of out-of-pocket costs varies by setting, but the majority of personal expenditure generally goes towards medicines (table 4).

In the state of Kerala, which has better access to healthcare than most states, a study using the 1995–1996 survey on healthcare by the National Sample Survey Organization found that 84 percent of people used allopathic medical services, though utilization of these services was lower among the very poor. Private care was sought in 77 percent of cases (Levesque et al. 2006).

## Part 3: Antibiotic Resistance and Use

Approximately 8 percent of deaths in India are from diarrhoeal diseases and 6 percent are from respiratory infections (CGHR 2003). The high disease burden caused by enteric and respiratory infections makes them important targets to improve the health of the public and to ensure appropriate antibiotic use.

### Hospital-Acquired Infections

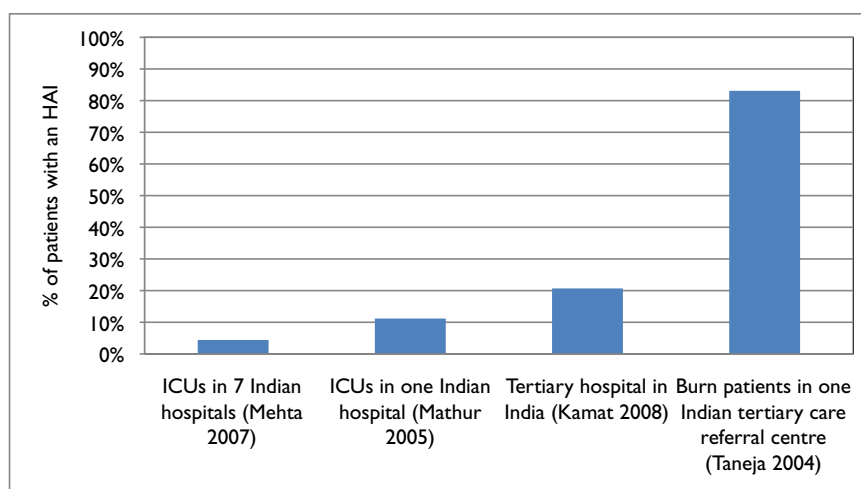
Some hospital-level data on infection rates hint at the burden of disease and causes of mortality due to specific bacterial infections acquired in hospitals in India. *Staphylococcus aureus* and *Pseudomonas aeruginosa* appear to be common causes of hospital-acquired infections (HAIs), along with a few other pathogens.

- A prospective study of 71 burn patients at Post Graduate Institute of Medical Education and Research in Chandigarh found that up to 59 patients (83 percent) had hospital-acquired infections: 35 percent of pathogens isolated from wounds and blood were *S. aureus*, 24 percent were *P. aeruginosa*, and 16 percent

were *β-hemolytic streptococci* (Taneja et al. 2004).

- A six-month study conducted in 2001 of the intensive care units (ICUs) in the All India Institute of Medical Sciences (AIIMS) in New Delhi, found that 140 of 1,253 patients (11 percent) had 152 hospital-acquired infections. *P. aeruginosa* made up 21 percent of isolates, 23 percent were *S. aureus*, 16 percent *Klebsiella spp.*, 15 percent *Acinetobacter baumannii* and 8 percent *Escherichia coli* (Mathur et al. 2005).
- A study by the International Nosocomial Infection Control Consortium (conducted in 12 ICUs in seven hospitals in seven Indian cities) followed 10,835 patients hospitalized for a total of 52,518 days. The observed patients acquired 476 infections in the hospital (4 percent), among which 46 percent were *Enterobacteriaceae*, 27 percent *Pseudomonas spp.*, 6 percent *Acinetobacter spp.*, 8 percent *Candida spp.*, and 3 percent *S. aureus* (Mehta et al. 2007a).

**Figure 10. Percent of Patients with Hospital-Acquired Infections, in Four Studies of Different Types of Hospitals in India**



- A study of 493 patients in a tertiary teaching hospital in Goa found that 103 people (21 percent) developed 169 infections (Kamat et al. 2008).

## Gram-Negative Bacteria

### *Escherichia coli*

*E. coli* causes a high proportion of infections in hospitals. In a primary healthcare centre in Srinagar, 90 percent of isolates were *E. coli* (Kadri et al. 2002). Similarly, in a primary and secondary rural healthcare setting in central India, 92 percent of 119 community-acquired isolates and 66 percent of 68 putative nosocomial isolates were *E. coli* (Chatterjee et al. 2009). These isolates were collected from urine samples of 356 consecutive symptomatic inpatients and outpatients with pyuria. In a tertiary care centre in Chandigarh, 64 percent of 602 outpatient isolates and 46 percent of 808 inpatient isolates were *E. coli* (Gupta et al. 2002).

A study that collected 45 urine samples each month for one year from the Christian Medical College in Vellore and a rural health clinic found that 42 percent of commensal *E. coli* from healthy asymptomatic pregnant women were resistant to at least one antibiotic, and 8 percent were resistant to ampicillin, co-trimoxazole, and nalidixic acid. Resistance rates were similar at the two sites. Strains causing infection were more likely to be antibiotic resistant than strains that were commensal (Mathai et al. 2008).

A study of 181 *E. coli* isolates from 2,655 pus and urine samples from a tertiary care hospital in Aligarh, the Jawaharlal Nehru Medical College, found that 2–4 percent of samples were susceptible to ampicillin, 2–11 percent was susceptible to co-trimoxazole, and 45–60 percent were susceptible to amikacin (Shahid et al. 2008).

A third *E. coli* study, which measured resistance in rural school children in Tamil Nadu, found that 63 percent of 119 stool samples were resistant to at least one antibiotic, and 32 percent were resistant to more than one. Antibiotic use in a poultry farm may have influenced prevalence in one of the

villages in the study. A study of gram-negative bacterial resistance to cephalosporins found that *E. coli* resistance was lowest to a second-generation cephalosporin, followed by a fourth-generation cephalosporin (Kaul et al. 2007).

### *Salmonella*

*Salmonella* infections cause diarrhoea (often bloody diarrhoea), which normally lasts 3–5 days, but can lead to sepsis in weak patients. It can be contracted by consuming contaminated foods, such as undercooked eggs and unpasteurized milk; having contact with excrement and polluted water; and handling reptiles. Cooking food at high temperatures can kill this pathogen. Most *Salmonella* serotypes can infect several species, including humans, and it can survive for weeks on non-biological surfaces.

From 1996–1999, 105 sporadic isolates of *S. paratyphi* from hospitals in and around New Delhi were collected and tested for susceptibility to antibiotics. The study found increasing drug resistance and that 32 percent of strains were resistant to ciprofloxacin, the drug of choice for treating this disease in India (Chandel et al. 2000).

Of 93 children admitted to a hospital in New Delhi with typhoid fever and positive blood culture for *S. typhi*, 67 percent had multidrug resistant typhoid fever. Sensitivity was below 35 percent for ampicillin, co-trimoxazole, chloramphenicol and amoxicillin, and less than 80 percent for norfloxacin, ciprofloxacin and cefotaxime. Sensitivity was greater than 90 percent for amikacin, gentamicin, ofloxacin and ceftriaxone (Kumar et al. 2007a).

### *Gonorrhoeae*

*Neisseria gonorrhoeae* is a sexually transmitted infection. In women, it is sometimes asymptomatic and usually mild, although symptoms include off-cycle bleeding and irregular urination. Symptoms in males include penile discharge and painful urination. Left untreated, this infection can cause pain, fever and sterility, and attack joints and the heart.

Of 45 isolates of *N. gonorrhoeae*, high levels of resistance were found to ciprofloxacin (78 percent), tetracycline (51 percent), and penicillin (47

percent). While all isolates were sensitive to ceftriaxone, 22 percent were  $\beta$ -lactamase producers. The samples were collected at clinics for sexually transmitted infections between July 2002 and July 2003 from consecutive male patients with suspected acute gonococcal urethritis (Sethi et al. 2006).

### *Acinetobacter*

*Acinetobacter* is usually nonvirulent in healthy people, although it commonly causes nosocomial infections of the skin and wounds, bacteraemia and meningitis. It can also cause pneumonia, usually in patients on respiratory support. New patterns of resistance are emerging, but it has always been innately resistant to some antibiotic classes. *A. baumannii* can survive for weeks on dry surfaces.

A study at St. John's Medical College and Hospital in Bangalore tested 150 *Acinetobacter* isolates from clinical samples collected between March 2003 and March 2004. Most were resistant to antibiotics, including third-generation cephalosporins, but sensitive to carbapenems and cefoperazone-sulbactam. Extended-spectrum  $\beta$ -lactamases (ESBL)\* were detected in 28 percent of isolates, and 36 percent of isolates were resistant to ciprofloxacin (Sinha et al. 2007).

In a second study, 265 *Acinetobacter spp.* isolates were tested with 14 antibiotics. More than 80 percent resistance to second- and third-generation cephalosporins, aminoglycosides, and quinolones was recorded. Thirty percent of the strains were resistant to cefoperazone/sulbactam. Resistance to meropenem was observed in 6 percent of *Acinetobacter spp.*, while 8 percent of the isolates showed intermediate resistance detected by minimum inhibitory concentration. All carbapenem-resistant intermediate strains were also resistant to other antibiotics (more than 10) tested by the disc-diffusion method (Gaur et al. 2008).

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\*Extended-spectrum  $\beta$ -lactamases are 'enzymes that mediate resistance to extended-spectrum (third generation) cephalosporins (e.g., ceftazidime, cefotaxime, and ceftriaxone) and monobactams (e.g., aztreonam), but do not affect cephamycins (e.g., cefoxitin and cefotetan) or carbapenems (e.g., meropenem or imipenem)' (CDC 2010b). They deactivate antibiotics with a beta-lactam molecular ring by cleaving it.

### *Pseudomonas aeruginosa*

*P. aeruginosa* is commonly found in soil, water, and biofilms, and living as plankton. Few infections are found in humans outside of hospitals. However, this organism is often fatal when it infects compromised tissues, causing urinary tract infections or systemic infections in immunocompromised patients with burns, cancer, and AIDS in hospitals.

Of 42 isolates from burn patients, 96 percent were multidrug resistant and 71 percent were resistant to five or more antibiotics. Resistance was especially high to tobramycin and amikacin (Shahid et al. 2005).

Another hospital study of aerobic gram-negative bacilli in lower respiratory tract specimens from ICU patients in a neurocare centre found that 5 percent of *P. aeruginosa* samples were multidrug resistant (Kumari et al. 2007).

A large study of 10,835 patients in seven hospitals in Indian cities, between 2004 and 2007, found that 27 percent of 476 hospital-acquired infections were caused by *Pseudomonas spp.* Of these, 29 percent were resistant to ciprofloxacin, 65 percent were resistant to ceftazidime, 42 percent to imipenem and 43 percent to piperacillin-tazobactam (Mehta et al. 2007a).

### *Vibrio cholerae*

Patients with *V. cholerae* infections are often asymptomatic, but those afflicted with cholera (the disease) exhibit watery diarrhoea and vomiting. Cholera patients can rapidly become dehydrated if they do not consume sufficient amounts of an oral rehydration solution and can die soon after the onset of disease. The organism affects the small intestine and is transmitted by contaminated food and water. Antibiotics can shorten the duration of sickness, and doxycycline is the first line treatment in areas where resistance has not yet emerged.

The emergence of fluoroquinolone resistance in India in 1996 was worrying because *V. cholerae* was already highly resistant to several other antibiotics, including ampicillin, furazolidone, neomycin and streptomycin (Mukhopadhyay et al. 1998). Surveillance in a rural hospital from 1990 to 2005 showed that for the *O1* strain of *V. cholerae*, resis-

tance to tetracycline ranged from 2 to 17 percent; resistance to nalidixic acid was between zero and 45 percent until 2003, when it shot up to 78 percent; chloramphenicol resistance ranged from 8 to 69 percent; and co-trimoxazole resistance ranged from 29 to 65 percent (Narang et al. 2008).

### *Klebsiella pneumoniae*

*K. pneumoniae* is found in the soil and usually causes disease in immunocompromised patients, the elderly, diabetics, and hospital patients. It can cause urinary tract infections and pneumonia. It is usually transmitted through contact with contaminated medical instruments or faeces.

*K. pneumoniae* resistance to second-, third-, and fourth-generation cephalosporins increased slightly during 2004 and then fell by half at the beginning of 2005, for reasons that are not clear. Resistance rates were generally 25–55 percent (Kaul et al. 2007).

A study of 61 *K. pneumoniae* isolates from 2,655 pus and urine samples from Jawaharlal Nehru Medical College in Aligarh, a tertiary care hospital, found that among the isolates from urine, 64 percent were susceptible to tobramycin, 54 percent were susceptible to amikacin, 32 percent to cefotaxime, and 14 percent to ceftriaxone. Similar patterns were found from pus samples. Twenty-five percent were ESBL producers (Shahid et al. 2008).

## Gram-Positive Bacteria

### *Staphylococcus aureus*

The most recognizable antibiotic resistant bacterium worldwide is methicillin-resistant *Staphylococcus aureus* (MRSA). First discovered in 1961, MRSA has become a common problem, not only in hospitals, but also more recently in communities. MRSA strains are often resistant to a range of antibiotics, and methicillin resistance is used as a marker for resistance to beta-lactam antibiotics, including penicillins. Hints of growing resistance to vancomycin have been noted recently, which is especially worrying because vancomycin is frequently the drug of last resort for treating MRSA. There are no reliable estimates of MRSA prevalence in India as a whole, but there are a number of point

estimates from hospitals across the country. These studies represent different regional and hospital ward populations.

Many people carry *S. aureus* asymptotically, but when symptoms develop, they are usually boils on the skin. MRSA can also cause invasive infections, including bloodstream and surgical wound infections.

*S. aureus* causes a range of problems, from minor skin infections to pneumonia, bacteraemia, sepsis, and meningitis. Infections are especially common in surgical wound sites. The organism is often found as a commensal on the bodies of healthy humans and can survive for days and months on dry surfaces, depending on the strain. It can be spread through contact, such as sheets and athletic equipment used by infected patients. Penicillin used to be the first-line drug to treat MRSA, but is now useless in most regions due to resistance.

Not surprisingly, a number of published papers on antibiotic resistance focus on MRSA. This literature is summarized here, although a coherent picture is difficult to draw from this body of work.

### Antibiotic-resistant *S. aureus* in hospitals in India

A number of studies have reported resistance to a variety of antibiotics in *S. aureus* samples from hospitals in India. Many of the studies are small and focus on population subsets, making it difficult to form a comprehensive picture of the antibiotic sensitivity or resistance status of this bacterium, and difficult to compare across time and location.

In 1993–1994, a study at Christian Medical College in Vellore tested pus or blood samples from patients, isolated 1,382 strains of *S. aureus*, and found that 24 percent were MRSA (Pulimood et al. 1996). Among the MRSA strains, resistance to gentamicin, norfloxacin, ciprofloxacin, co-trimoxazole, and netilmicin was higher than 75 percent for each; and resistance to amikacin, ofloxacin, and rifampicin was above 25 percent (intermediate). A smaller study published in 1997 found that 20 percent of 120 consecutively collected strains of *S. aureus* studied at the Jawaharlal Institute of Postgraduate Medical Education and Research in Pondicherry were MRSA (Shankar et al. 1997). Of 696 samples

collected in 1999 from the Choithram Hospital and Research Centre in Indore, MRSA levels are unknown, but 81 percent were resistant to oxacillin. Of these, there was no resistance to vancomycin and resistance to netilmicin was low (Verma et al. 2000). Samples collected from 1999–2000 in the Indira Gandhi Medical College in Nagpur yielded 230 *S. aureus* isolates, of which 20 percent were MRSA (Tahnkiwale et al. 2002). Of these MRSA strains, high resistance was noted to penicillin, co-trimoxazole, and chloramphenicol. Resistance to ciprofloxacin was 33 percent and resistance to gentamicin was 7 percent.

Samples collected after 2000 document higher rates of resistance. Of 100 strains from clinical samples at Jaya Jagadguru Murugharajendra Medical College in Davangere, in Karnataka, 43 percent were MRSA (Hanumanthappa et al. 2003). Of 549 *S. aureus* strains from the Institute of Medical Sciences at Banaras Hindu University, 55 percent were MRSA. More than 80 percent of MRSA strains were resistant to penicillin, co-trimoxazole, ciprofloxacin, gentamicin, erythromycin, and tetracycline, but all were susceptible to vancomycin (Anupurba et al. 2003). Of 1,059 *S. aureus* strains from pus samples of soft-tissue infections in various wards at AIIMS (New Delhi), 39 percent were MRSA (Mohanty et al. 2004). Of 116 patients with *S. aureus* infections at the Karnataka Institute of Medical Sciences in the smaller city of Hubli, only 18 percent carried MRSA strains. Of these, 62 percent were susceptible to clindamycin, a marker for community-acquired status; these strains were more susceptible to drugs (Krishna et al. 2004).

A study in Chennai found 31 percent MRSA among 805 *S. aureus* strains from the Sri Ramachandra Medical College and Research Institute (Anbumani et al. 2006). Among these, high resistance was found to gentamicin, co-trimoxazole, and erythromycin. Intermediate resistance was found to ciprofloxacin, and all strains were sensitive to vancomycin (Anbumani et al. 2006).

In 2008, a study from the microbiology department at the Post Graduate Institute of Medical Sciences in Rohtak found that 54 percent of 628 *S. aureus* strains from inpatients and outpatients were MRSA (Deep et al. 2008). Another study found that 38 percent of 783 strains from various clinical

isolates were MRSA, in the Sit Sundar Lal Hospital of Banaras Hindu University. Among the MRSA strains, high resistance was detected to norfloxacin, ciprofloxacin, penicillin, co-trimoxazole, chloramphenicol, and tetracycline. Resistance levels were intermediate for gentamicin, amikacin, and netilmicin (Tiwari et al. 2008).

Most of the studies that included tests for vancomycin resistance found that it was either very low or non-existent; however, one study from the Sher-i-Kashmir Institute of Medical Sciences found that 22 of 120 MRSA strains from clinical samples had intermediate sensitivity to vancomycin, although none was fully resistant (Assadullah et al. 2003).

A few studies have looked at resistance rates in multiple hospitals. One early study found that 32 percent of 739 *Staphylococci* strains were MRSA (Mehta et al. 1996). This study included hospitals in New Delhi, Mumbai, and Bangalore. Sixty-six percent of MRSA strains were resistant to ciprofloxacin, 22 percent were resistant to rifampicin, and all were sensitive to vancomycin.

Another publication looked at 12 ICUs in seven Indian cities and found that among 476 hospital-acquired infections in 10,835 patients, 88 percent of *S. aureus* strains were MRSA (Mehta et al. 2007a). A third multihospital study found a 43 percent-MRSA rate in 2,314 *S. aureus* strains from various hospitals around Coimbatore (Murugan et al. 2008). MRSA strains showed high levels of resistance to penicillin, co-trimoxazole, chloramphenicol, and ampicillin, and 64 percent resistance to gentamicin.

#### Studies of infections in specific hospital wards and ICUs

Some studies analyse high-risk populations, such as people in surgical or burn wards in hospitals. In the orthopaedic and burn units of Lok Nayak Hospital in New Delhi, 52 percent of 450 patients in 1998 carried MRSA (Vidhani et al. 2001). In the Assam Medical College Hospital, 313 *S. aureus* strains from people with diseases related to staph infections were studied and 53 percent were found to be MRSA (Majumder et al. 2001).



In a more recent study, 34 percent of 498 patients from medicine and surgery wards of the Goa Medical College Hospital were found to have hospital-acquired infections, and 71 percent of *S. aureus* strains were MRSA (Kamat et al. 2008). Among 2,080 pus samples from patients with surgical wound infections at AIIMS in New Delhi, 44 percent of *S. aureus* strains were MRSA (Tyagi et al. 2008). These MRSA strains were susceptible to vancomycin and rifampicin. Several hours outside Delhi, in the wards of Maharaja Agrasen Medical College Hospital in Agroha in Haryana, 35 percent of 800 *S. aureus* isolates were MRSA (Arora et al. 2008). Of these MRSA strains, intermediate resistance was noted to gentamicin, ciprofloxacin, and chloramphenicol. No resistance to vancomycin was detected and 2 percent of strains were resistant to rifampicin (Arora et al. 2008).

#### *S. aureus* in healthcare workers and others

Healthy carriers of *S. aureus* can become infected with this resistant pathogen in hospital settings, and healthcare workers who carry it (most of whom probably acquired it within the hospital) can transmit to patients. A study of 724 nasal swabs from healthcare workers in the Institute of Cardiovascular Diseases in Chennai, in 1997–1998, found that 18 percent carried *S. aureus*, of which 12 percent was MRSA (Verghese et al. 1999). Of 150 healthcare workers from operating theatres in Guru Tegh Bahadur Hospital in Delhi, 56 were colonized with *S. aureus*, of which 7 percent was MRSA (Goyal et al. 2002). In a mixed study of healthy parents and clinic volunteers in a baby clinic, 94 of 319 nasal swabs led to *S. aureus* isolates, 17 of which were resistant to oxacillin (Saxena et al. 2003).

#### Mixed groups

Some studies look at multiple groups, such as one that tested carriers and patients for MRSA. Of 850 *S. aureus* strains found in 750 patients and healthcare workers between 2000 and 2003 in Jawaharlal Nehru Medical College of Aligarh Muslim University, 35 percent were MRSA (Dar et al. 2006). Of 7,172 clinical samples and 1,725 healthy people screened in Tamil Nadu, 906 *S. aureus* strains were isolated. Of these, 31 percent of clinical samples and 38 percent of carrier samples were MRSA (Rajadurai et al. 2006).

#### National Staphylococcal Phage Typing Centre

A study of 7,574 *S. aureus* strains received between 1992 and 1998 at the National Staphylococcal Phage Typing Centre in New Delhi found that MRSA climbed from 10 percent in 1992 to 45 percent in 1998 (Mehndiratta et al. 2001). Samples were submitted from hospitals in a way that would not make them representative of a specific population, but this study is still important because of the large sample size and long study duration.

#### Summary

MRSA rates in various studies from India range from nearly zero to nearly 100 percent. This could mean that there is wide geographical variation in MRSA prevalence. It also may be due to the heterogeneity of the sources of biological samples, ranging from healthy people to patients in ICUs. Surveillance is notably lacking. The National Staphylococcal Phage Typing Centre is showing an upward trend over time, but as its sample is not representative of the country, it cannot provide an estimate of MRSA prevalence either in India or in Indian hospitals.

In Europe, *S. aureus* resistance to oxacillin ranged from over 50 percent in Romania to less than 1 percent in Norway and Sweden in 2006. Most Mediterranean countries and the United Kingdom had MRSA rates between 25 and 50 percent, similar to those found in India (Gould 2008).

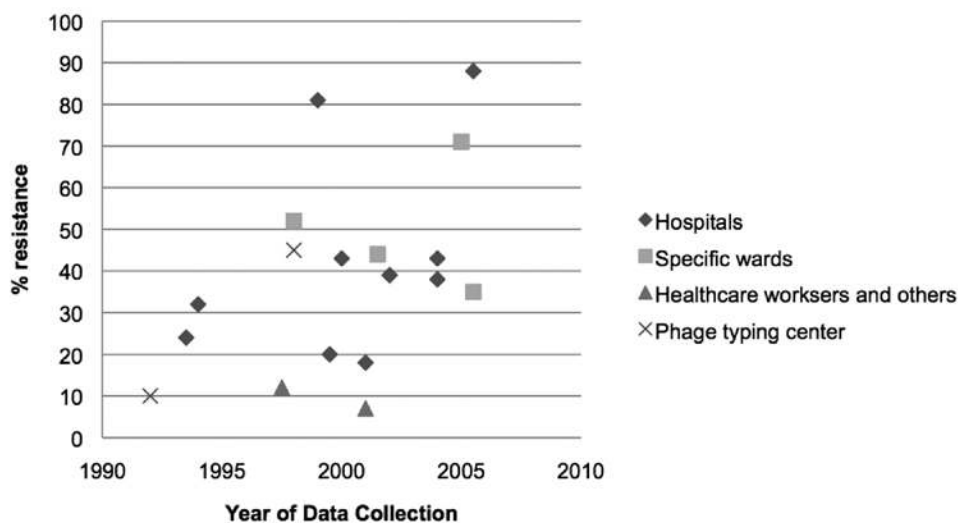
#### *Streptococci*

*Streptococci* strains can cause streptococcal pharyngitis (strep throat), meningitis, pneumonia and necrotizing fasciitis.

A 10-year retrospective study, in which the etiological agent of community-acquired acute bacterial meningitis could be identified for 284 cases, found *S. pneumoniae* to be the most common cause. No penicillin resistance was detected (Mani et al. 2007).

The South Asian Pneumococcal Alliance has undertaken antimicrobial surveillance of invasive pneumococcal diseases in India, Nepal, and Sri Lanka since 1993. Over this period, the study noted very high levels of resistance to co-trimoxazole, but low levels of penicillin resistance. Intermediate

**Figure II. MRSA Resistance Rates by Year and Study Setting**



resistance to co-trimoxazole was less than 10 percent in several tertiary teaching hospitals in India. However, at least 80 percent of clones in Sri Lanka are resistant (Thomas 2007).

*Group-A beta-haemolytic streptococci* isolated from throat swabs of 435 north Indian children showed 10–25 percent resistance to macrolides, tetracycline and co-trimoxazole, but all isolates were sensitive to penicillin G and chloramphenicol. The children in this sample were attending the paediatric outpatient department at Chhatrapati Shahuji Maharaj Medical University for acute pharyngo-tonsillitis and had not received an antibiotic in the prior week (Jain et al. 2008).

In two rural areas near Madurai, Tamil Nadu, 87 percent of 323 isolates from infants were not susceptible to one or more antibiotics. At 81 percent, resistance was particularly high to co-trimoxazole, which may be due to over-the-counter use of this cheap and widely available oral antibiotic in infants. These figures on these infants were drawn from a larger study population in a trial of vitamin A supplementation in newborns (Coles et al. 2002).

### Enterococci

Some *Enterococcus* species are commensal in human intestines, but others can cause urinary tract infections, bacteraemia, and meningitis. Many

strains are inherently resistant to beta-lactam antibiotics.

Researchers at a communicable diseases hospital in Chennai tested 40 stool specimens and found no vancomycin-resistant *enterococci* and a low recovery rate of high-level aminoglycoside-resistant *enterococci* (Sekar et al. 2008).

### Antibiotic Resistance in Animals

A number of studies have examined antibiotic resistance levels among bacteria found in livestock, poultry and seafood. *Salmonella* infection is an important public health concern, as it is easily transmitted to humans through contaminated food products (e.g., eggs, seafood, and poultry), as well as through direct contact with infected livestock (CDC 2010a).

Other studies have examined antibiotic resistance among *Salmonella* isolated from animals in India. Suresh and colleagues (2006) tested the prevalence and antibiotic-resistance patterns of *Salmonella* in eggs in South India (Suresh et al. 2006). *Salmonella* bacteria were found in 7.7 percent of 492 eggs tested. The bacteria were then tested for susceptibility to 10 common antibiotics, and 100 percent of strains were found to be resis-

tant to four different antimicrobials: ampicillin, neomycin, polymyxin-B, and tetracycline.

Kumar et al. (2009) studied *Salmonella* strains from seafood in Cochin to test for resistance to antibiotics commonly used in veterinary and human medicine (Kumar et al. 2009). Fifty percent of strains were found to be resistant to sulfamethizol and 39 percent were resistant to carbenicillin. Resistance to multiple drugs was prevalent, with 39 percent of strains resistant to both sulfamethizol and carbenicillin, and 14 percent resistant to sulfamethizol, carbenicillin, and oxytetracycline. Additionally, two studies examined antibiotic resistance of *Salmonella* isolates taken from equids in India. Singh and colleagues (2007) examined *Salmonella* isolates from horses, donkeys, and mules kept either on equine farms or by low-income individuals (Singh et al. 2007). Nearly all isolates were resistant to three or more antibiotics, with 91 percent resistant to sulfamethoxazole, 71 percent to tetracycline, and 68 percent to doxycycline. Singh and colleagues (2009) examined 111 isolates from equids and found that all were resistant to at least one antibiotic, and 89 percent were multidrug resistant (Singh et al. 2007). High levels of resistance were even found to antibiotics not used for the horse family.

Other bacterial infections of both human and animal health concern are *enterococci* and *E. coli*. Singh (2009) examined antibiotic resistance among 267 strains of *enterococci* isolated from horses (and related animals) in North India (Singh 2009). Vancomycin resistance was found in 80.2 percent of strains, and 99.3 percent were resistant to five or more antimicrobials. Levels of resistance to individual antibiotics were extremely high: cefdinir (96.5 percent), oxacillin (90.6 percent), cefotaxime (89.1 percent), ampicillin (88.4 percent), cloxacillin (88.4 percent), and cotrimazine (87.3 percent). Additionally, all strains isolated from foals with diarrhoea were resistant to at least 14 antibiotics. Antibiotic resistance to *E. coli* serogroup O157 in cattle stool in West Bengal was also examined (Manna et al. 2006). Ten of the 14 strains tested were resistant to at least one antimicrobial, and eight strains were multidrug resistant. *E. coli* resistance was high to the most frequently used antibiotics in the region: oxytetracycline, gentamicin, co-trimoxazole, and ampicillin. Another study

examined antimicrobial resistance of shiga toxin-producing *E. coli* isolated from calves with diarrhoea in Gujarat (Arya et al. 2008). Of 41 strains tested, 100 percent were resistant to three or more antibiotics, and 49 percent were resistant to at least eight of the 11 antibiotics tested.

These studies highlight the growing threat of antibiotic resistance to both animal and human health in India. Careful surveillance of antibiotic use and resistance patterns could aid in the development of antimicrobial guidelines to improve appropriate use and delay the spread of resistance to animals and humans.

## Surveillance of Antibiotic Resistance

There has not been a concerted effort to monitor antibiotic resistance nationally in India, except on a small scale by the Indian Council of Medical Research (ICMR) and some private agencies on a pilot basis. A recent study analysed 7,482 urine samples from antenatal women with no recent history of antibiotic use or complicated UTI attending Sir Ganga Ram Hospital, New Delhi, and residing within 10km of the hospital during the study period (November 2003 to December 2005 and November 2007 to November 2008), who had no history of recent antimicrobial use or complicated urinary tract infection (Wattal et al. 2009). A WHO study, using *E. coli* as the indicator organism at four sites and respiratory pathogens at one site, found high levels of resistance (Holloway et al. 2009). The results of this study are shown below (table 5).

## Invasive Bacterial Infection Surveillance

The Invasive Bacterial Infection Surveillance (IBIS) project has focused on invasive *S. pneumoniae* and *H. influenzae*. Phase 1 (1993–1998) was funded by the United States Agency for International Development (USAID) through the Indian Clinical Epidemiology Network (IndiaCLEN). It operated in tertiary teaching hospitals in Vellore, New Delhi, Mumbai, Lucknow, Trivandrum, and Chennai. Phase 2 (1998–2003) was funded by WHO's Global Alliance on Vaccines and Immunizations (GAVI), through PneumoADIP as a South Asian

**Table 5. Percentage of Antimicrobial Resistance in *E. coli* at Four Sites**

	<b>Brits, and Durban, South Africa</b>	<b>Vellore, India</b>	<b>Mumbai, India</b>	<b>Delhi, India</b>
Drug	Commensal and pathogen	Commensal/ pathogen	Commensal	Commensal/ pathogen
Ampicillin	65.6	18.2/52.3	41.7	51.5/84.6
Co-trimoxazole	51.9	24.2/45.5	41.6	55.6/65.0
Cefalexin/ cefuroxime*	59.7	2.1/15.9	13.1	28.4/49.8
Gentamicin	6.1	2.1/13.6	2.5	30.1/29.5
Tetracycline		23/40.9	57.9	78.4/77.3
Nalidixic acid		24.8/61.4	58.2	64.1/77.1
Ciprofloxacin	1.9	3.5/31.8	19.9	33.6/58.7
Nitrofurantoin	5.7	1.5	25	20.2

\*Cefuroxime was only tested in Britain; cefalexin was not tested there.

Source: Holloway et al. (2009).

Pneumococcal Alliance (SAPNA) study, with five sites in India, two in Nepal, and one in Sri Lanka.

The first IBIS report on patients with clinical symptoms of pneumonia, meningitis or septicaemia included 5,798 patients with suspected or proven invasive *S. pneumoniae* infections and 314 bacterial isolates collected over three years. The study found that penicillin resistance in *S. pneumoniae* was not yet a major issue in India, although an upward trend in resistance was worrying (IBIS et al. 1999), especially the high resistance to co-trimoxazole (figure 12). It also found that *H. influenzae* is increasingly resistant to ampicillin, chloramphenicol, erythromycin, and co-trimoxazole, but sensitive to cefotaxime (Steinhoff et. al 2002). The fact that both *H. influenzae* and *pneumococcus* were highly resistant to co-trimoxazole, the recommended drug for treatment in the Acute Respiratory Infection-Pneumonia Control program, also caused particular concern (Thomas 2003).

From 2004 to 2008, GAVI funded only one IBIS centre and reference laboratory in India, plus two sites in Nepal and one in Sri Lanka. In 2008, Johns Hopkins University (Baltimore, MD, USA) provided interim funding for surveillance of meningitis in children. The WHO South-East Asia Regional Office (SEARO) is currently funding one centre at the Christian Medical College (CMC) in Vellore for surveillance of all invasive pneumococcal disease,

as well as reference laboratories in Nepal and Sri Lanka (personal communication from Dr. Kurien Thomas, Christian Medical College, to Alice Easton, August 12, 2010b). The group is hopeful that ICMR or WHO will take on the responsibility of funding a larger set of sites in the future.

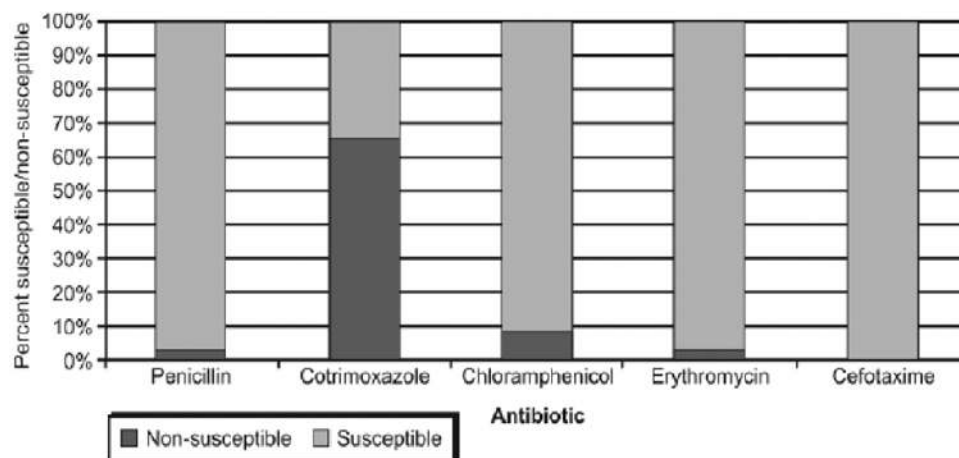
The IBIS study found that the 7-valent vaccine currently in use would provide coverage for only half of the infections with invasive serotypes in Indian children, whereas a proposed 11- or 13-valent pneumococcal vaccine would provide more than 80 percent coverage. It also noted that the 23-valent adult vaccine covered more than 80 percent of infection serotypes in Indian adults (figure 13) (Thomas 2003; Thomas 2007).

### Integrated Disease Surveillance Project

The Ministry of Health and Family Welfare initiated the Integrated Disease Surveillance Project (IDSP) in 1998 with funding from the World Bank. The National Institute of Communicable Diseases in New Delhi was identified as the coordinating national agency.

IDSP is a decentralized, district-based surveillance system for selected high-priority diseases that are easily recognizable in primary health care settings, including both communicable and non-communicable diseases (Suresh 2008). Where

**Figure 12. Antimicrobial Resistance in *S. pneumoniae***



Source: Thomas (2007).

fully operational, the system tracks and follows up reports of outbreaks, and reports and tracks weekly data from hospitals around India, including infectious disease hospitals (IDSP 2008a). The project's goals are to promote surveillance in major hospitals and among health workers who are exposed to a range of bacteria; build capacity for data collection, analysis, and interpretation; promote and establish appropriate testing practices at all levels of care; create quality-assured data; and connect partners through information technology (Suresh 2008).

The project will integrate both active and passive reporting from the public health system and private sector through a phased rollout. The laboratory-based report, including antimicrobial surveillance, will be generated from microbiological data gathered at district hospitals in the country. IDSP had identified state reference laboratories and disease-specific regional reference laboratories for monitoring antimicrobial resistance.

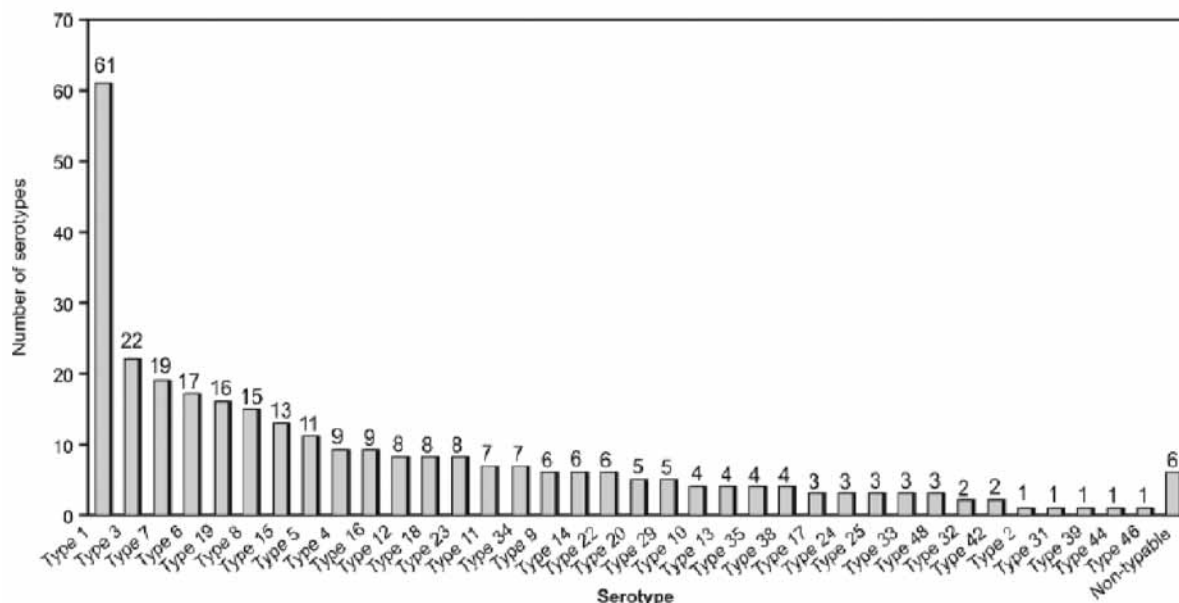
Cases are marked as suspected by health workers, presumptive by clinicians, and laboratory confirmed by clinical laboratory staff (State Surveillance Unit 2008). Certain diseases identified for tracking must be reported to the District Public Health Laboratory each week for collection for ISDP. Private laboratories are included in the scheme following an accreditation process. District laboratories are supposed to confirm 1 percent of results from peripheral labs, although they are cur-

rently not able to fulfil their function completely. State laboratories or networks of laboratories, in turn, provide quality control for district hospitals, train staff, and investigate outbreaks (WHO-India 2007). The project also includes a call centre and follows up reports of outbreaks received through this medium as well (IDSP 2008a).

The project was approved in 2004 with a US\$ 68 million budget. The grant was due to expire in 2010, but was extended for another two years. IDSP is currently active in Andhra Pradesh, Gujarat, Haryana, Jharkhand, Karnataka, Madhya Pradesh, Maharashtra and Tamil Nadu (Isalkar 2009). Currently it is reportedly working well in some states, but requires additional inputs at the national level to improve quality of output. No analysed data have yet been issued by the project. Different states are at different stages of implementing the system:

- In the state of Mizoram, the project began in government hospitals, as there were no medical colleges. Because many villages in the state are remote and isolated and the health workers based there are overburdened already, a system has been set up to pay special messengers to deliver data on a weekly basis (IDSP 2008a). Most important infectious diseases were surveyed in 2007–2008, and the state plans to survey

**Figure 13. Frequency of *S. pneumoniae* Serotypes in Adults**



Source: Thomas (2007).

road traffic accidents, air and water quality, nutrition, blindness, cancer and substance abuse in the future (Mizoram Health & Family Welfare).

- In Madhya Pradesh, all required reference laboratories have been established, and the system has identified a number of outbreaks. These laboratories can identify the causative agents of many bacterial infections, and the antimicrobial sensitivity of some organisms (State Surveillance Unit 2008).
- In Uttaranchal, IDSP has focused on upgrading facilities to the level required to participate in surveillance (Department of M.H. and F.W.).

## Antibiotic Use

Antibiotic use appears to be increasing steadily over time, with pronounced growth in beta-lactam antibacterials and overall use in some states, such as Uttar Pradesh and Maharashtra (figures 14 and 15).

In addition to the national and state data from IMS Health Information and Consulting Services-India, several small studies have examined the use of antibiotics in a single locality. For example, a study of prescribing practices in five districts of Tamil Nadu showed that amoxicillin was prescribed the most—in 21 percent of prescriptions containing antibiotics, followed by ciprofloxacin at 18 percent and co-trimoxazole at 11 percent (Sivagnanam et al. 2004).

## Sources of Antibiotics

Antibiotics are widely available in India to people, regardless who writes the prescriptions for them. Prescriptions from nonallopathic doctors are honoured, as are previously-used or outdated prescriptions; antibiotics are even dispensed with no prescription at all. About three-quarters of patients who ask pharmacists for antibiotics without a prescription ask for drugs they took previously on a physician's recommendation. Laws against dispensing antibiotics without a prescription are generally not enforced (Dua et al. 1994). Antibiotics are also available outside of pharmacies in some areas of India from traditional healers and other unlicensed prescribers, who dispense antibiotics to their clients directly (Radyowijati et al. 2002).

**Figure 14. Implementation Stage of IDSP in Indian States**

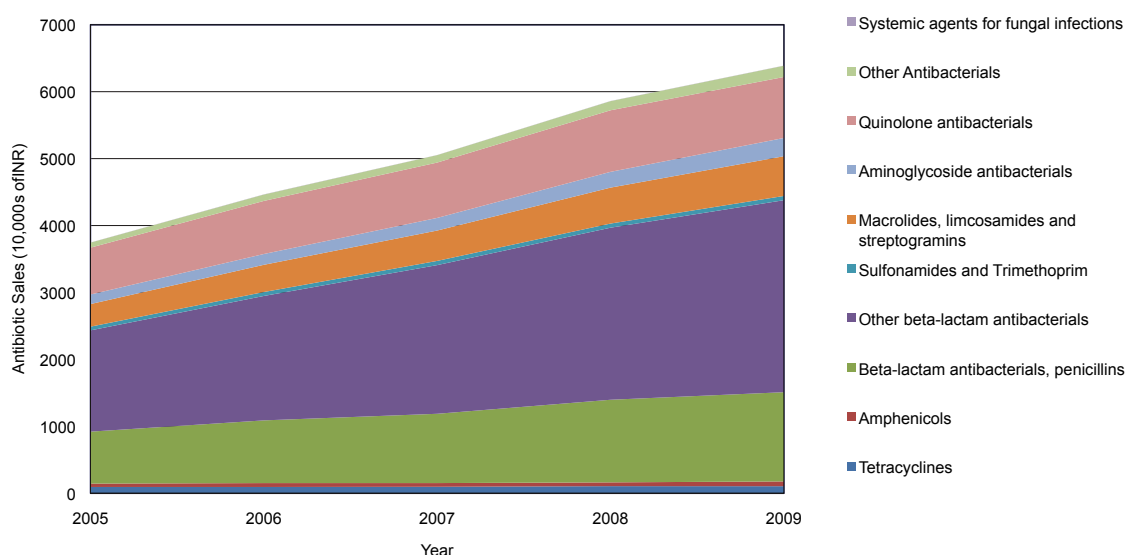


Source: Personal communication from Dr. Kurien Thomas, Christian Medical College, to Alice Easton on April 2, 2010b.

When doctors in a hospital prescribe antibiotics, the medicines are often available at an attached pharmacy. A study of prescriptions from public and private facilities in Bhopal district, Madhya Pradesh, found that 75 percent of drugs in these prescriptions were dispensed at an attached facil-

ity (De Costa et al. 2008). This often means that doctors will prescribe only those drugs that they know are available in the attached pharmacy. If the pharmacy stocks essential drugs, doctors are able to avoid prescribing unnecessarily expensive brand name drugs. On the other hand, if the phar-

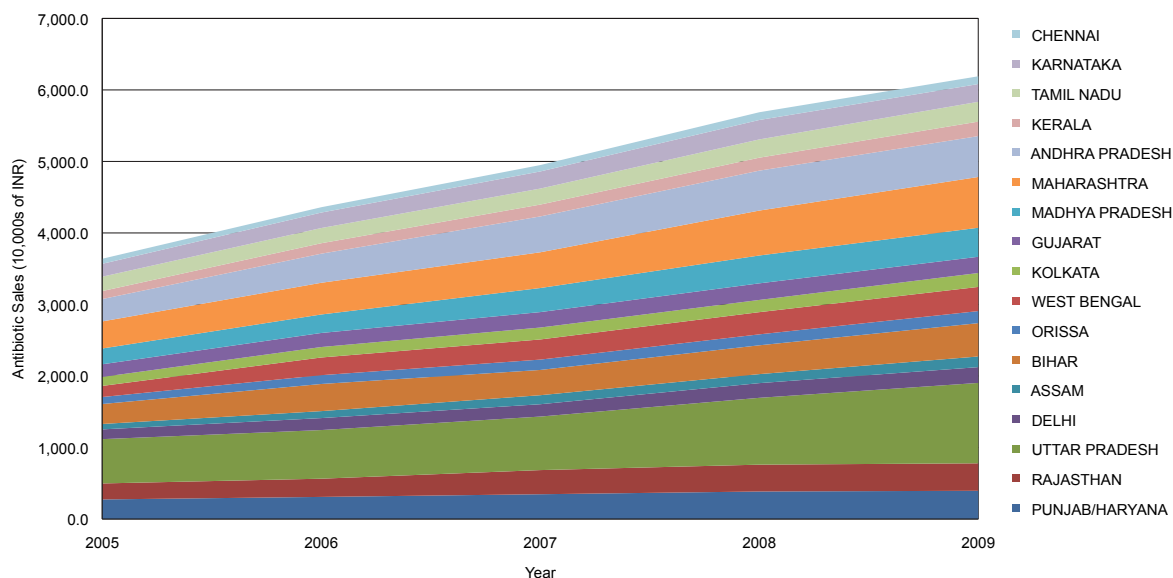
**Figure 15. Antibiotic Sales in India by Type**



Units of Antibiotic sold by type. The most commonly sold antibiotics are penicillins and other beta-lactam antibacterials.

Source: Personal communication of IMS Health Information and Consulting Services-India data from Burzin Bharuch (Pfizer) to Ramanan Laxminarayan on July 30, 2009.

**Figure 16. Antibiotic Sales in India by State, 2005–2009**



*Uttar Pradesh consumes the largest volume of antibiotics of any state.*

*Source: Personal communication of IMS Health Information and Consulting Services-India data from Burzin Bharuch (Pfizer) to Ramanan Laxminarayan on July 30, 2009.*

macy tends to purchase those drugs that are the most profitable, rather than those that are most necessary for the area, this can contribute to irrational prescribing.

### Antibiotic Prescribing Practices

A few hospital- and city-based studies of antibiotic use suggest that drugs are often prescribed in irrational\*\* or inappropriate ways in India. Some studies on antibiotic use have used indicators, such as the average number of drugs prescribed per encounter and the frequency with which fixed-dose combinations are prescribed. If many drugs are prescribed per encounter, doctors may be prescribing unnecessary and excessive drugs; a low number, however, does not give any information about the appropriateness of prescribing. Fixed-dose combinations can be proper for many conditions, but the perception is that many doctors prescribe them inappropriately. Other studies have

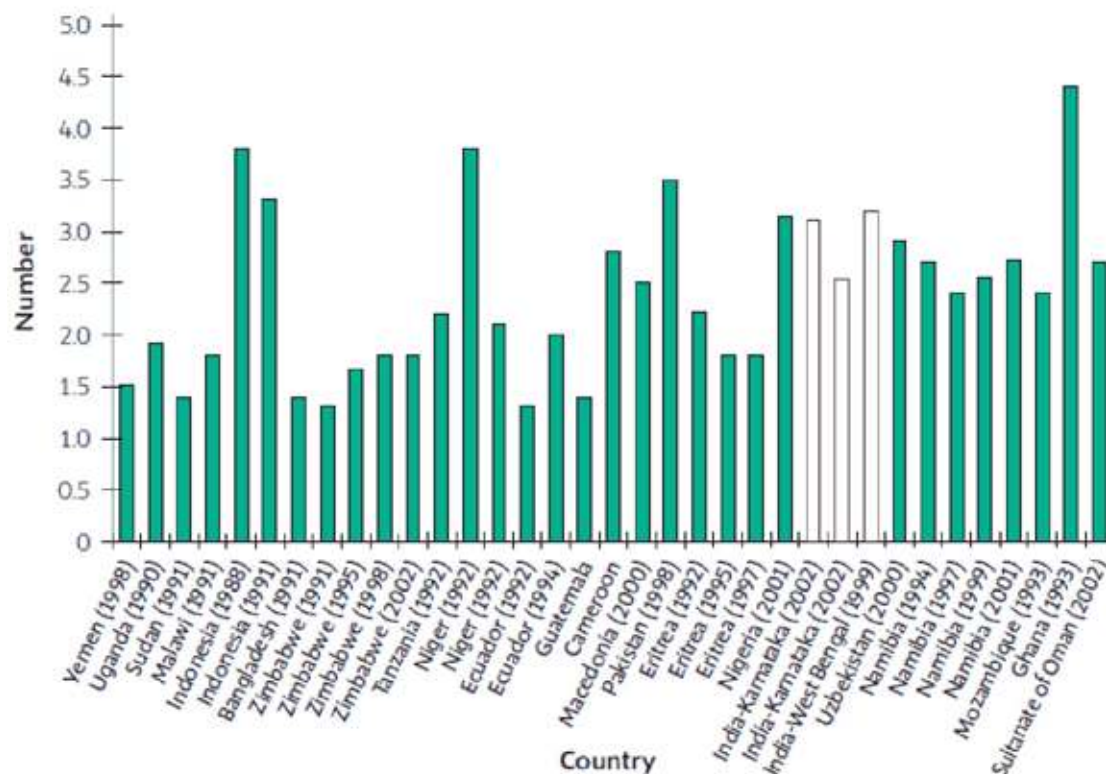
\*\* Irrational prescriptions are defined as those that are prescribed at an incorrect dose, frequency, or duration; that are redundant; or that should not be prescribed at the same time due to potential interactions (Kshirsagar et al. 1998).

examined prescriptions to determine the type and frequency of other errors. Figures 17, 18 and 19 show the outcomes of studies that look at selected indicators of rational prescribing. The relative merits of these indicators are debatable.

A study done at Christian Medical College in Vellore looked at 87 consecutive cases in a tertiary hospital and 98 cases in a primary care hospital. It found that cultures were tested for drug resistance in 80 percent of tertiary-care cases, but in more than half of these cases, multiple doses of antibiotics had already been started. Furthermore, the choice of antibiotic did not always correlate with the sensitivity report (Thomas et al. 1996). The authors of the study concluded that an ongoing peer audit was necessary to improve prescribing practices. However, another study (from a community healthcare program of the Christian Medical College in Vellore) found that, over 3 months, all prescribed drugs in 2,756 prescriptions were on WHO's essential drug list. The number of drugs prescribed for each patient ranged from one to seven, the most commonly prescribed drugs included vitamins, antibiotics and anti-inflammatories (Kuruvilla et al. 1994).



**Figure 17. Number of Medicines per Prescription**



Source: WHO (2004).

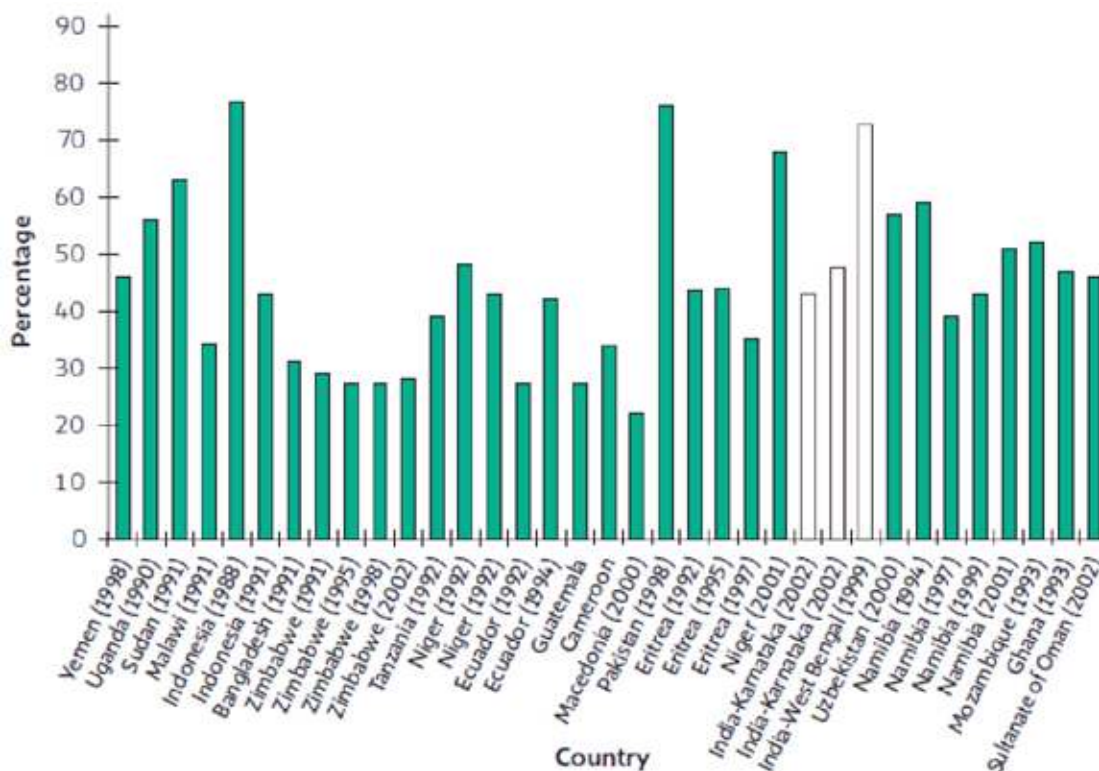
Analysis of 562 prescriptions for upper respiratory infections in children from 2002–2003 in an outpatient department in Gangtok showed that 2.37 drugs were prescribed per encounter, 59 percent of medicines prescribed were fixed-dose combination, and 31 percent were antimicrobials. Fixed-dose combinations can be appropriate treatments, but some fear that many on the Indian market are irrational combinations. The study authors concluded that treatment of upper respiratory infections in this hospital was not standardized and was often irrational (Das et al. 2006).

Two studies in Pune found also high levels of irrational prescribing. One, based on 1,105 prescriptions collected in 1996 from doctors who were unaware that their prescriptions were being audited, found that 30 percent of prescriptions were irrational and that fixed-dose combinations were very common (Kshirsagar et al. 1998). The second study from Pune evaluated 100 prescriptions from 10 pharmacies between July 2000 and January 2001, and found that the average number of drugs per prescription was 2.7 and that antibiotics

were prescribed in 30 percent of encounters. The authors worried that too many drugs were prescribed per encounter and that fixed-dose combinations, vitamins, and nonessential drugs were too common (Mhetre et al. 2003). Similar results were seen at LN Hospital, one of biggest public tertiary care facilities in Delhi. Prescription auditing of 350 outpatients showed that the average number of drugs per encounter was 2.75 and that antibiotics were prescribed to 29 percent of patients (Gupta et al. 1998).

A study at the Post Graduate Institute of Medical Education and Research (PGIMER) in Chandigarh found that over-prescription of drugs was a major problem in its ICU. The mean number of all drugs prescribed to patients admitted to the ICU was 5.3, starting with 12.9 drugs on the first day and increasing to 22.2 during the entire stay (Biswal et al. 2006). The authors concluded that drug costs, and antibiotic costs in particular, had a major impact on the cost of therapy in the ICU (Biswal et al. 2006).

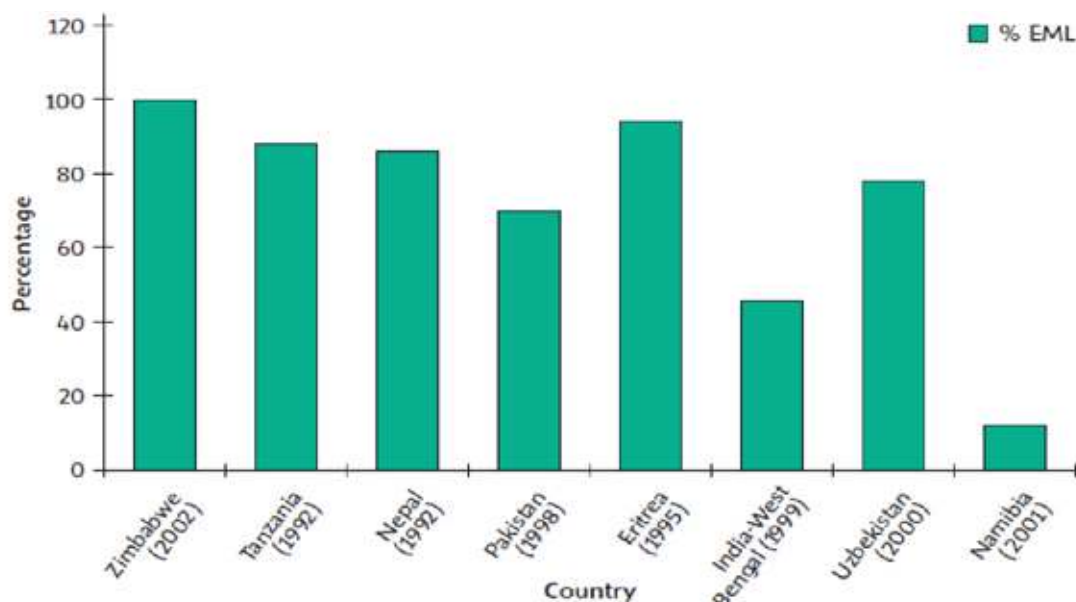
**Figure 18. The Percentage of Patients Receiving Antibiotics in 35 Studies**



Of the three studies from India in the graph, two show normal rates, compared to other developing countries, and one shows the third-highest rate of any of the 35 studies shown here.

Source: WHO (2004).

**Figure 19. The Percentage of Essential Medicines Prescribed**



Source: WHO (2004).

Another study at PGIMER in Chandigarh analysed 550 prescriptions from patients receiving antimicrobial drugs in the departments of internal medicine, surgery, urology and paediatrics. Prescription of a single antimicrobial was most frequently observed in surgery, urology, and internal medicine, while two antimicrobials most frequently were given to patients in paediatrics (Sharma et al. 1998). This study found that in 'all the departments, quinolones, aminoglycosides, cephalosporins and penicillins were frequently prescribed, among which amikacin, ciprofloxacin, cefotaxime, and cloxacillin were the most preferred drugs, with a general tendency of prescribing newer antimicrobials', often in the absence of microbiological data (Sharma et al. 1998, 533).

In addition to the studies on prescriptions in hospitals, one survey asked 700 surgeons from India at a conference in 2003 about their prescribing habits. Results from the 650 surgeons who responded showed that they prescribed antibiotics for longer than recommended by standard surgical guidelines (Kulkarni et al. 2005).

Some results of hospital studies are harder to interpret. Over 1,000 prescriptions were collected from the nine rural PHCs and 17 urban civil dispensaries in Bhopal district, Madhya Pradesh. On average, 2.76 drugs were prescribed to each patient, although this was higher in rural areas. Antibiotics were prescribed in 64 percent of consultations, and 67 percent of drugs prescribed were from a list of 20 essential drugs created for the study in the absence of a local essential drug list. Eighty-seven percent of patients knew the dosage schedule (De Costa et al. 2008). The authors concluded that antibiotic use was high; however, it is difficult to determine what the ideal levels of antibiotic prescription are for this area, so this data serve largely as a baseline.

In contrast, some studies show appropriate prescribing in the absence of awareness of standard treatment guidelines or an essential drug list. Another study from PGIMER in Kolkata followed 176 neonates over six months in 2005. WHO guidelines for the rational use of drugs were largely followed, and 89 percent of prescribed drugs were on the essential medicines list, despite a lack of

awareness about these guidelines or the list (Chatterjee et al. 2007).

In a study of prescriptions, which included interviews with parents of 500 patients at the Lokmanya Tilak Municipal Medical College and General Hospital in Mumbai, antibiotics were dispensed in about 40 percent of encounters and injection use was very low. Most of the drugs prescribed conformed to a model list, although no copy of India's essential drugs list was available (Karande et al. 2005). This is taken as an indication that efficacious, safe and cost-effective drugs are being prescribed, although other drugs not on the list may also have these qualities.

Given the range of outcomes in prescribing studies across India, it is important to assess the motivations behind prescribing practices. The studies of doctor- or hospital-related factors that influence prescribing raise interesting questions, but cannot tell us why doctors overprescribe antibiotics. One study found that patient and doctor factors explained 25 percent of prescribing behaviour, specifically that Indian-trained doctors prescribed more antibiotics than U.K.-trained doctors (Gill et al. 2001). Similarly, a study of 403 prescriptions by 40 private practitioners in Chennai found that more-educated doctors prescribed fewer antibiotics (Bharathiraja et al. 2005). Based on 2,440 prescriptions collected in urban, rural, government and private healthcare centres in Uttar Pradesh, antibiotics were prescribed to 82 percent of people presenting with a cold, diarrhoea, or fever. There were more prescriptions written in private and rural hospitals, and for younger and wealthier (higher socioeconomic status) patients (Kumar et al. 2008). Surprisingly, the survey of surgeons discussed above found that the presence of a hospital infection control committee had no impact on the prescribing behaviour of the surgeons (Kulkarni et al. 2005).

## Defined Daily Doses per Bed Days

Defined daily doses (DDDs) of antibiotics prescribed per 100 bed-days are a good measure of antibiotic use, since they are reasonably comparable across different facilities and countries. While few studies in India have published DDDs of antibiotics per 100 bed-days, initial data from Indian

hospitals appear high in comparison to figures found in other low- and middle-income countries (GARP-India inaugural meeting, India Habitat Center, New Delhi, August 25-26).

A WHO study in Delhi, Mumbai, and Vellore interviewed people exiting pharmacies to calculate the DDDs per 100 patients visiting the pharmacies. DDDs were calculated by type of antibiotic and revealed that about 120 DDDs were prescribed for each 100 patients (WHO 2009). Since this figure is somewhat different from DDDs per 100 bed-days of patients at hospitals, it cannot be compared directly.

In 2002, the total antimicrobial prescription rate in a hospital in neighbouring Nepal was 108.5 DDD per 100 bed-days (Shankar et al. 2003), 124.6 DDD per 100 bed-days in a Brazilian hospital (de Castro et al. 2002), and 32.9 DDDs per 100 bed-days in a hospital in Croatia after the implementation of a hospital antibiotic policy (Vlahovic-Palcevski et al. 2000). In Serbia, antimicrobial prescription rates of around 25–30 DDDs per 100 patient days were observed between 1997 and 1999 (Jankovic et al. 2001). Another study (2003–2004) from the same hospital in Nepal looked at DDDs per 100 bed-days by antibiotic class and found that 7.76 DDDs of fluoroquinolones per 100 bed-days were prescribed (Shankar et al. 2007).

Rates are lower in developed countries as well. A study of 26 departments in six Israeli hospitals found that DDDs per 100 bed-days ranged from 115 to 49, showing great variability between departments (Shalit et al. 2008). A literature review found that antibiotic use in different hospitals ranged from 0.10 DDD to 323 DDDs per 100 bed-days (Kuster et al. 2008). However, this review concluded that much of the variability in outcomes from the studies reviewed was due to differences in definitions and methodology, rather than real differences in prescribing, which makes comparisons difficult (Kuster et al. 2008).

## Incentives for Antibiotic Use

On the path from illness to treatment, many different factors influence whether or not an antibiotic will be used. The first step is when a sick individual decides how to seek treatment. A study

that followed 421 mothers in Karnataka for one year found that 16 percent of the time no action was taken. (The authors speculated that this result might be because women perceived their ailment as normal, a result of diet, or too taboo to discuss.) For 25 percent, the women self-medicated their illness (which included getting pharmacists' recommendations for treatment). The others sought medical consultations (Bhatia et al. 2001).

Patients who go straight to a pharmacy or consult a medical professional may be prescribed antibiotics for a range of reasons. Doctors may be motivated to prescribe an antibiotic if they feel (or determine from cultures) that the patient has a bacterial infection. Uncertainty about the cause of an ailment, especially upper respiratory infections and diarrhoea, often leads doctors to prescribe antibiotics (Kotwani et al. 2010). When microbiology facilities are not available, doctors may prescribe antibiotics to most patients with a fever, taking it as a sign of bacterial infection (Sivagnanam et al. 2004; Bharathiraja et al. 2005). Increasing the use of microbiology labs, either by building new ones or outsourcing cultures when facilities are not available on-site, could cut the number of prescriptions for antibiotics to patients suffering from viral fever. This presupposes that doctors base or at least modify their prescriptions according to lab results.

Some resistance to greater use of microbiology facilities may also come from patients. They may not want to spend their time and money to undergo tests for what they may feel is a small problem (Kotwani et al. 2010). The ability of low-cost solutions to reduce improper use of antibiotics should be examined.

Patient demands can drive both doctors and pharmacists to prescribe antibiotics. In a study of 285 physicians in Tamil Nadu, 29 percent listed patient satisfaction as a motivating factor behind antibiotic prescription (Sivagnanam et al. 2004). Focus group discussions also concluded that doctors feel pressured to prescribe antibiotics because patients may be upset if they are prescribed an over-the-counter drug (like paracetamol), particularly after they have paid for a consultation or waited in long lines (Kotwani et al. 2010). However, contrary to popular belief, the study in Uttar Pradesh men-

tioned above found that patient requests for antibiotics were rare (Kumar et al. 2008). The availability of medicines in a primary care centre's stock of drugs, the ability of patients to afford particular drugs, and physician concerns about counterfeit generic drugs can also affect what antibiotics are prescribed (Dua et al. 1994; Biswal et al. 2006). Factors contributing to antibiotic prescribing and dispensing behaviours are shown in figures 20 and 21, respectively.

Patients also skip the medical consultation and go directly to pharmacies with their demands. In a review of antibiotic use in Kerala (Saradamma et al. 2000), the authors found that about 0.4 percent of people self-medicate with antibiotics during any two-week period. People often decide to self-medicate because they think public clinics are understocked or they simply try medicines to see if they work, in lieu of or before consulting a doctor. More broadly, 69 percent of households in Kerala had at least one member who had used a pharmaceutical product during the prior two weeks. Almost 11 percent of medicines used were antibiotics and 18 percent of antibiotics were bought without a prescription.

In India, patients may decide that they can be cured more quickly and easily by asking a pharmacist for a specific drug or for advice, than by attending a medical clinic. Patient demand for specific name-brand drugs convinced a pharmacy in South India to stock more than 25 brands of co-trimoxazole (Nichter et al. 1994). The high incidence of patients demanding to receive antibiotics directly can have a large impact on antibiotic use rates.

Among 600 families in Jammu city, chosen by stratified sampling, self-medication with any drug was higher in adults who had not completed the 12th standard (final year of secondary school), but antibiotic use was higher in more educated families. Both groups showed little knowledge of the proper dosage and possible side effects of the drugs they bought (Sharma et al. 2005). The study in Kerala, mentioned above, also found that self-medication was more common among lower socioeconomic classes (Saradamma et al. 2000). The exact impact of socioeconomic class on self-medication with antibiotics is not clear, but may be important. Studies examining this relationship

should look at both overall and antibiotic-only purchasing, and differentiate between patients purchasing drugs for themselves or for others.

Finally, financial incentives for pharmacists can drive up antibiotic sales. Antibiotics make up 20 percent of pharmacy sales, meaning that fluctuations in antibiotic purchasing can have a major impact on income (Dua et al. 1994). A study in India found that pharmacists viewed their profession as a business, rather than as a part of the healthcare system (Dua et al. 1994). This means that the profit motive is perhaps stronger than their incentive to advise a patient that a requested antibiotic is unnecessary. Pharmacists are only one small part of the picture and, even if they do not prescribe antibiotics for every patient, resistant bacteria can flow into their region from elsewhere. Of course, many pharmacists may be unaware of the impact of antibiotic use on resistance.

## Pharmaceutical Company Influence

There are several ways that pharmaceutical manufacturers influence how pharmacists and doctors recommend medicines to patients, but this has not been well studied in India. A few examples that have been documented include 'buy some, get some free' schemes by pharmaceutical companies to encourage pharmacies to stock specific medicines. Some pharmacists may recommend products purchased via such schemes because they stand to make a large profit, especially when the drug is not popular or well-known enough to be asked for by name (Kamat et al. 1998). In some cases, retailers may be given cash incentives to sell the products of a specific company (Kamat et al. 1998).

Medical representatives (also known as detail men or women), who visit healthcare providers, may also promote one drug over another for reasons other than health benefits. A study of the quality of written prescriptions at public and private pharmacies found that private practitioners were more likely to prescribe brand-name products, be they vitamins, antibiotics, or other medicines. The authors hypothesized that private pharmacists 'were more likely to prescribe branded medicines because they were more likely to be influenced by pharmaceutical company marketing' (Patel et al. 2005, 9). The whole area of pharmaceutical influ-

ence could provide much useful information in India and help to understand the drivers of antibiotic use. Currently, little such information is available.

## Antibiotic Use in Animals

Veterinarians and the livestock and aquaculture industries also use many of the antibiotics used to treat humans. Veterinarians and livestock keepers treat (and prevent) infections with antimicrobial drugs, such as diarrhoeal diseases in cattle (Manna et al. 2006) and may use them more controversially to enhance growth in poultry, dairy, meat, and seafood production (Khachatourians 1998). Currently, no government regulations cover the use of antibiotics for domestic animals in India (Singh et al. 2009). Lack of regulation and monitoring of antimicrobials contribute to their overuse, and the subsequent development of antibiotic-resistant infections in animals, which can be passed from animals to humans, should be a growing public health concern (Kuehn 2007). Cattle farming are a common livelihood in many parts of India and a large proportion of the population maintains close contact with livestock, putting them at risk of acquiring resistant infections from their animals (Arya et al. 2008). Levels of antibiotic usage in animals are not readily available.

## Government Regulation and the Supply Chain for Antibiotics

India's patent and price control laws have made Indian drugs some of the cheapest in the world. However, studies indicate that essential drug availability is low, especially in the public sector, and laws prohibiting over-the-counter sales of prescription-only antibiotics and counterfeit drugs have not been entirely successful.

### Patents

India's Patent Act of 1970 allowed processes, but not substances, to be patented for seven years after drug development. This meant that companies could use 'reverse engineering' to understand the original brand's formulation and then develop

a process to manufacture the same substance. Generic drugs became very cheap in India as a result.

India joined the World Trade Organization (WTO) in 1995, making it difficult to keep this loose patent regime in place. In 2005, patent laws were amended to allow product patents, although this does not apply to drugs developed prior to that year. Drugs can qualify for patents if they are either a new invention or a significant improvement on an existing drug that was invented after 1995.

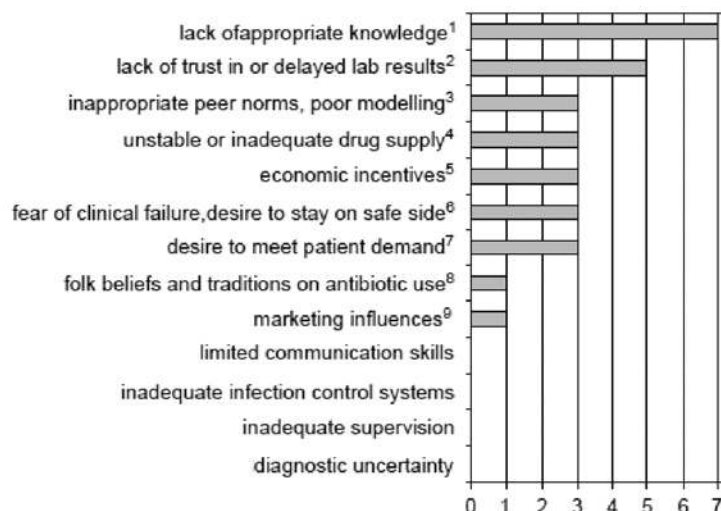
### Prices

Drug prices in India are among the lowest in the world (Gross et al. 2002; Cameron et al. 2009). A study of public sector facilities at six sites in five Indian states, between 2004 and 2005 (mentioned previously), found that the procurement prices of medicines in the public sector was 0.27–0.48 times the international reference price (Kotwani et al. 2007a). However, price variations were found across regions, and the majority of people in the study had to buy drugs in the private sector because availability was so poor in the public sector (Kotwani et al. 2007a).

Brand-name drugs, as well as generics, tend to be inexpensive in India, with only a 6 percent difference between them (figure 21). In the WHO/HAI study (discussed previously), median prices of 30 core drugs were recorded (Cameron et al. 2009). However, the popularity of 'buy some, get some free' marketing schemes suggests that some prices can be lowered without unduly depriving manufacturers of profits (Kotwani et al. 2007b). These schemes benefit the retailer, but not the customer, since savings to the retailer do not result in discounts in the manufacturer's retail price (Kotwani et al. 2007b).

Part of the reason that drugs are inexpensive in India is that competitive generic producers dominate the market. Over 80 percent of drug products are generic and most have multiple manufacturers, which keep prices competitive (Nair 2006). However, product marketing, brand loyalty, and trade terms appear to have impeded market competition from lowering drug prices across the board. Many patients purchase expensive drugs if prescribed by

**Figure 20. Prescribing Determinants of Antibiotics**



These studies on prescribing-related determinants are derived from a meta-analysis of studies from low-income countries. The top determinants of irrational antibiotic prescribing are a lack of knowledge about their appropriate use and inability to access reliable lab results.

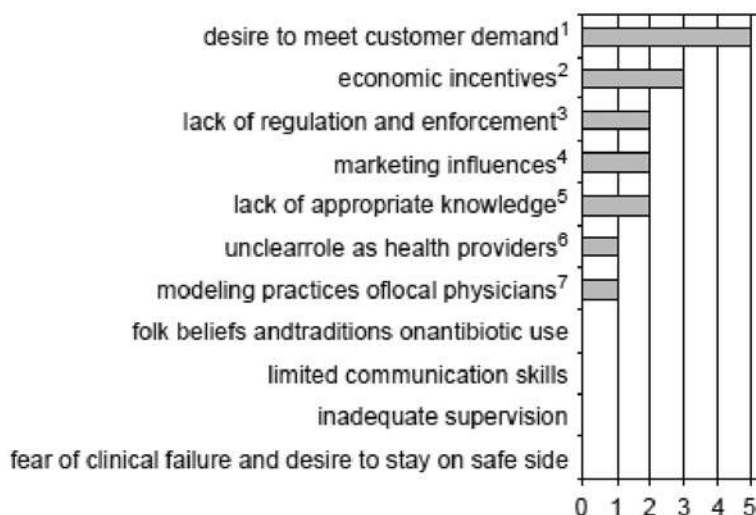
Source: Radyowijati et al. (2002).

their physician, even though cheaper equivalents are available (Kotwani et al. 2007b).

Government price controls contribute to low prices of some drugs in India. About 40 percent of the market consists of price-controlled drugs, for which the maximum retail price and local taxes cannot exceed twice the cost of production (Kumar

2008; OPPI 2008). Price controls covering most bulk drugs were first instituted in 1963. The number of drugs covered has decreased steadily since then, from 347 in 1979, to 142 in 1986, and finally to 74 in 1995. Some believe that this still leaves many new antibiotics out of reach of people living in poverty (Shrivastava 2006).

**Figure 21. Dispensing Determinants of Antibiotics**



These studies on dispensing determinants are derived from a meta-analysis of studies from low-income countries. The top reasons for antibiotic dispensing are a desire to meet consumer demand and economic incentives.

Source: (Radyowijati et al. (2002).

In 2002, changes to the criteria for price controls were proposed, but they were not implemented by the government due to decisions by the Karnataka High Court (Department of Chemicals and Petrochemicals 2005). Active pharmaceutical agents are selected for price controls if a manufacturer dominates a large proportion of the market. The decision to control prices of drugs does not depend on whether the medicines are considered essential (Kotwani et al. 2007b).

Procurement prices are thus fixed by the government for many essential drugs, but local purchases by public facilities, such as in the case of stock shortfalls, can result in variations in prices (Kotwani et al. 2007a). Local purchases are often necessitated by the inconsistent delivery of government-supplied drugs (Kotwani et al. 2007b).

Prices include a variety of mark-ups and taxes. The tax regime for pharmaceutical products is multi-layered and at times confusing (Kotwani et al. 2007b). For price-controlled drugs, wholesalers are allowed to have mark-ups of 8 percent, and retailers are allowed 16 percent. For other drugs,

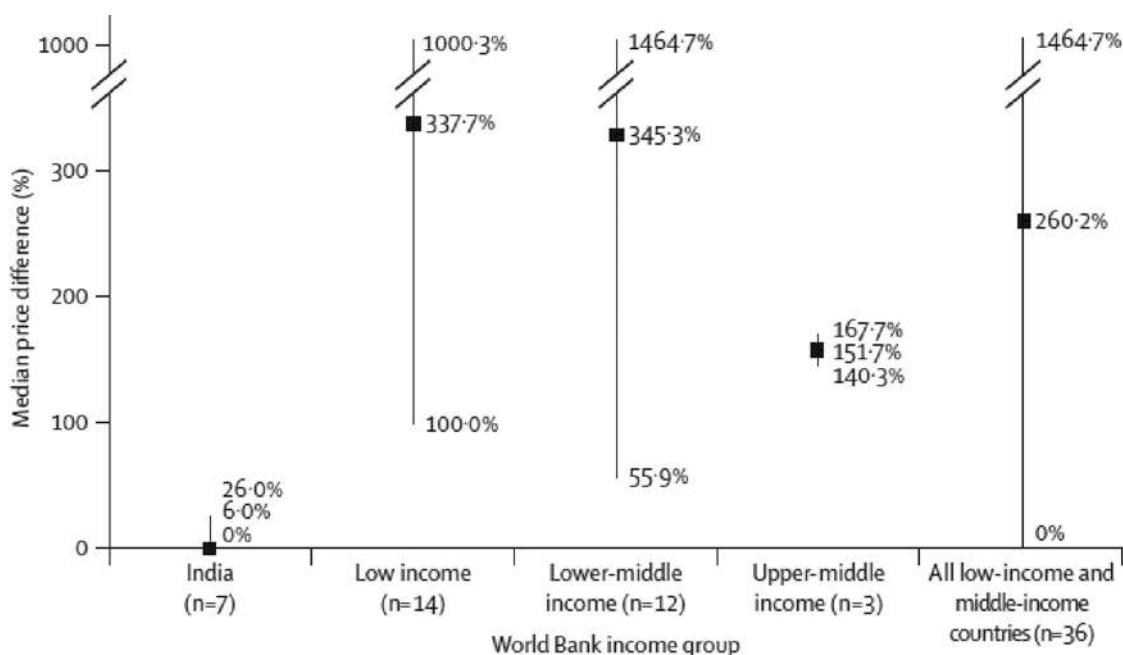
these are not set, but tend to be around 10 percent and 20 percent, respectively, for brand-name medicines. Mark-ups tend to be much higher for off-brand, non-scheduled medicines (Kotwani et al. 2007b). Tertiary hospitals often pay around 10 percent to the distributor, which covers delivery and other costs (Kotwani et al. 2007b).

## Production

The Indian pharmaceutical market was US\$ \$6.2 billion in 2006 (US Census Bureau, Economist Intelligence Unit, Cygnus Research, in (CII 2008)). Between 1996 and 2006, pharmaceutical sales increased 9 percent each year, compared to 7 percent growth in the global pharmaceutical market (Perlitz 2008).

Limited patent protection in India has encouraged high levels of generic drug production domestically. One-fifth of generic drugs sold globally are from India, whereas only about 2 percent of all new brand name drugs come from India. India exported € 3 billion in 2006, up from € 650 million in 1996 (figures cited verbatim from reference), which was

**Figure 22. Median Price Differences between Name Brands and Lowest-Priced Generics for Matched Pairs of Medicines in the Private Sector, by World Bank Income Group**



Source: Cameron et al. (2009).



largely driven by the demand for generics in the United States, Europe and Japan (Perlitz 2008). In total, India exports two-thirds of the drugs it makes (Steinbrook 2007). In 2002, imports made up only 4 percent of the market (Gross et al. 2002).

Exports of cheap generics are expected to decline as patent regulations in India normalize with those of other countries. However, India is likely to remain a major player in pharmaceuticals because research and development has grown in recent years as Indian companies ally with global corporations and hold numerous clinical trials (Gross et al. 2007).

## Procurement

Most drugs are obtained through either government or private outlets, as pharmacies run by non-governmental organisations (NGOs) are scarce and largely faith-based (Kotwani et al. 2007b).

## Public Sector

PHC and CHC pharmacists submit a list of required medicines (called an indent) to the medical officer in charge, who forwards it to either the block chief medical health officer or directly to the central drug store run by the district medical health office. Here, the district chief medical health officer is responsible for supplying drugs to CHCs and PHCs (Gill 2009). Each state's PHCs and CHCs have a quarterly budget, against which they order medicines using the indents. Despite complaints of

irregular deliveries, most CHCs and PHCs receive at least one drug shipment each month. In emergencies, public health facilities can purchase drugs on the open market as well. Because of these emergency purchases, public sector drug prices can vary from location to location, despite government regulation of bulk purchase prices (Kotwani et al. 2007a).

## Tamil Nadu model

The Tamil Nadu Medical Services Corporation Ltd. (TNMSC) was set up in 1994 as a government company in the wake of a spurious drug scam. Before TNMSC, public hospitals sourced drugs on their own. TNMSC's goals were to provide drugs efficiently, cheaply, and consistently. It created a list of 276 items following WHO guidelines, instituted strict quality control of these products, and carefully selected bidders to produce them.

The Tamil Nadu government only made purchases after first conducting technical evaluations and then offering contracts to qualified suppliers with the lowest price bid. Eleven laboratories in the state test the quality of the first batch of each drug supplied and now conduct random checks as well. If a company fails a test and is blacklisted, it cannot provide supplies to the government for the next four years.

The government improved packaging for drugs and logos were added to discourage misuse. It created a passbook system, rather than cash transactions, for purchasers to access drugs stored in 23

**Table 6. Price Trends for Selected Antibiotics, 1996–2005**

*Average price rounded to nearest whole rupee (Total number of manufacturers)*

Drug and Dosage (Pack)	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005*
Ofloxacin 200mg (4tab)	INR 94 (3)	INR 97 (4)	INR 96 (4)	INR 97 (5)	INR 94 (5)	INR 68 (20)	INR 39 (41)	INR 22 (55)	INR 20 (66)	INR 19 (60)
Ciprofloxacin 500mg (10tab)	INR 66 (63)	INR 69 (71)	INR 69 (80)	INR 63 (81)	INR 60 (80)	INR 60 (89)	INR 59 (104)	INR 58 (101)	INR 58 (79)	INR 57 (73)
Norfloxacin 400mg (10tab)	INR 42 (27)	INR 36 (28)	INR 34 (25)	INR 30 (28)	INR 29 (28)	INR 29 (30)	INR 26 (33)	INR 24 (29)	INR 25 (26)	INR 22 (27)
Pefloxacin 400mg (4tab)	INR 18 (16)	INR 18 (17)	INR 17 (16)	INR 17 (16)	INR 17 (15)	INR 17 (13)	INR 18 (15)	INR 18 (12)	INR 18 (10)	INR 18 (9)

\*2005 data are from the July-August Issue.

Source: Data are from the Indian Drug Review, Jan-Feb. issue each year, Mediworld Publication Group, New Delhi and was compiled by the National Institute of Pharmaceutical Education and Research (NIPER), Mohali-160062 India.

warehouses (Selvaraj 2009). This system was inspired by that used in banks to track inventory (Narayanan 2010). Supplier's stock district warehouses with enough medicines to last three months. Medicines can then be transferred between warehouses as necessary to keep all stocks above the minimum level. Hospitals also withdraw drugs from the warehouses, per their annual budgetary allocation (NIPER 2006). The new procurement system has eliminated drug shortages, facilitated savings of 32 percent in the first year, increased client satisfaction with drug quality and flexibility of the ordering system, and reduced the problem of expired drugs (Selvaraj 2009).

Although Tamil Nadu still has a large budget for drugs (INR 27 per capita versus INR 2–3 in Rajasthan and Uttar Pradesh in 2006–2007), TNMSC helped cut costs by 30 percent. The average cost of drugs for inpatients in Tamil Nadu decreased during the implementation of this program and is an order of magnitude less than in other states, such as Haryana, Himachal Pradesh and Rajasthan (Narayanan 2010). The NRHM review commission has advised the other state governments to follow the Tamil Nadu example (personal communication from G. P. Mohanta, Professor of Pharmacy at Annamalai University, to Alice Easton on June 23, 2010). So far, only Kerala has successfully copied the model, although other states have considered it and some have started setting up similar corporations (Narayanan 2010).

#### *Delhi model*

The Delhi model of centralized drug procurement is a much-copied method introduced by the Delhi Society for Promotion of Rational Use of Drugs and WHO in 1996. Prior to this, despite spending about one-third of the government's health budget on drugs, essential medicines were often unavailable in hospitals. Delhi's earlier decentralized system allowed the purchase of rarely used expensive drugs and generally suffered from poor management (NIPER 2006).

Currently, drugs are procured centrally for all state-run hospitals and at least 150 PHCs in Delhi. In the state hospitals, 90 percent of drugs are from the procurement list. Focusing on essential drugs for the procurement list, rather than expensive combinations, has dramatically decreased

drug costs for these hospitals. In order to be an approved supplier, drug companies must undergo quality control inspections (NIPER 2006).

In Delhi, the Medical Stores Organization (MSO) manages drug procurements for the state hospitals. Producers submitting technical bids to the MSO to supply generic drugs require a good manufacturing process certification, market presence for three years, and INR 100,000,000 annual turnover. Offers are given to the lowest bid made by an approved manufacturer. Only one bid (sometimes even none) is made for many generic drugs (Kotwani et al. 2007b). The government procurement committee buys proprietary medicines at a price discounted from the manufacturer's retail price, with a greater discount for non-scheduled medicines (Kotwani et al. 2007b).

#### *Private Sector*

In the private sector, manufacturers sell to wholesalers, who sell to retailers. There are more than 100,000 licensed retail chemists in India. In Delhi, wholesalers make daily deliveries, often in quick response to demands (Kotwani et al. 2007b). Manufacturing, wholesale and retail licenses can be held by the same company (Kotwani et al. 2007b).

#### *Essential Drug Lists*

Essential drug lists, meant to contain the costs of drugs needed to serve the main health needs of a community, aim to make drugs available at reasonable prices. The percent of all drugs sold that are not on these lists is often used as an indicator of whether unnecessary drugs are being prescribed.

India's National Essential Drug List was compiled in 1996 and amended in 2003, based on WHO's suggested list. The 2003 National List of Essential Medicines, currently in force, contains 354 drugs, including some categorized as complementary to other more basic drugs (Directorate General of Health Services 2003; Department of Chemicals and Petrochemicals 2005; Bhargava et al. 2006). However, many Indian states have developed their own essential drug lists. These lists are more important because most healthcare is the responsibility of the state governments. For example, Tamil Nadu has revised its list every two years since 1994, and this list is used to guide the

procurement and distribution process (personal communication from G. P. Mohanta, Professor of Pharmacy at Annamalai University, to Alice Easton on June 23, 2010).

We have found no evaluation of the impact of the essential medicines list in India. Studies in other countries have found that in areas where essential drug programs have been implemented, antibiotic use is less. They can bring order to drug procurement plans, and ensure that only drugs, which are useful in the country, are reimbursed, but merely making people aware of what drugs are on the list does not seem to have an impact (Lindtjorn 1987; Hogerzeil et al. 1989; Hogerzeil et al. 1993).

## Drug Control

The Central Drug Standards Control Organization is the primary national drug authority, in charge of drug standards, drug regulation, authorization of new drugs, drug import licenses and regulation of clinical research. It is headed by the Drug Controller General India (DGCI). State governments are responsible for licensing drug manufacturing and sales establishments, licensing drug testing laboratories, approving drug formulations, monitoring drug quality, inspecting and recalling drugs (Directorate General of Health Services 2010).

Approval is needed for all new drugs, drugs marketed at new dosages or for new purposes and new fixed-dose combinations (Gross et al. 2007). For drugs with new active ingredients to be marketed in India, full preclinical and clinical testing is necessary, including 'chemical and pharmaceutical information; animal pharmacology; animal toxicology; human clinical data from phases 1, 2 and 3; bioavailability and bioequivalence; and other special studies, such as appropriate information on status in other countries' (Gross et al. 2007, 1). Regulations can be relaxed at the early stages if the drugs have been marketed for some years in other countries, and phase 3 trials may not be required in India if there is an immediate need for the drug and ample foreign data on safety and efficacy exists (Gross et al. 2007).

Legally, drugs can only be prescribed by doctors for approved usages. Some activists have

sought to enforce these rules by bringing cases against doctors who prescribe drugs that are not in accordance with a patient's symptoms (Mudur 1996). However, some doctors have pressed for a relaxation of these regulations on an exception basis, allowing drugs to be prescribed for indications for which they have not been approved when doctors believe there is sufficient evidence in the literature to warrant their use (Mudur 2004).

The Drugs and Cosmetics Act and Rules of 1940 created a list of schedule H and schedule X drugs, which can be sold only with a prescription. Schedule H drugs include antibiotics and injections, and schedule X drugs are narcotics. An exception was made to these rules, which allows stores without a pharmacy or drug license to sell a few medicines classified as 'household remedies' in villages with a population less than 1,000 (OPPI 2008).

A registered medical practitioner must write prescriptions, and pharmacists must retain a copy of all schedule X prescriptions dispensed for two years. Schedule X prescriptions may not be dispensed more than once, unless the prescribing doctor has given directions that the drugs should be dispensed multiple times. Sellers must note their name, address, and the date of dispensing above the name of the prescriber on the prescription. Antibiotic medicines must be conspicuously labelled 'schedule H drug—Warning: To be sold by retail on the prescription of a Registered Medical Practitioner only' (MoHFW 2005).

Some states have gone further in regulating what drugs are prescribed, and how prescriptions are recorded. For example, doctors in government hospitals in Rajasthan have to keep carbon copies of their prescriptions for official records. The state government also recently advised doctors in government hospitals to prescribe generic drugs wherever possible (DWS 2010). However, a study by the Delhi Society for Promotion of Rational Use of Drugs (DSPRUD) found that 22 percent of 600 antibiotic purchases examined in Delhi were made without a prescription (Usha Gupta, Executive Vice President of DSPRUD, presentation at GARP Inaugural Meeting, PLACE, August 25-26, 2009). Pharmacists commonly prescribe antibiotics to patients who come to them directly complaining of diarrhoea or cold symptoms.

**Table 7. Antibiotics on the 2009 WHO List of Essential Medicines and 2003 Indian National List of Essential Medicines**

		16th WHO Model List of Essential Medicines, 2009	2003 National List of Essential Medicines
Beta-lactam medicines	Amoxicillin	X	X
	Amoxicillin + clavulanic acid	X	
	Ampicillin	X	X
	Benzathine benzylpenicillin	X	X
	Benzylpenicillin	X	X
	Cefalexin	X	
	Cefazolin	X	
	Cefixime	X	
	Cefotaxime	X*	X* (ST)
	Ceftazidime	X*	X* (ST)
	Ceftriaxone	X	X* (ST)
	Cloxacillin	X	X
	Imipenem + cilastatin	X*	
	Phenoxyethylpenicillin	X	
	Procaine benzylpenicillin	X	X
Other	Amikacin		X* (ST)
	Azithromycin	X	X* (ST)
	Cephalexin		X*
	Chloramphenicol	X	
	Clarithromycin		X* (ST)
	Clindamycin	X*	
	Ciprofloxacin hydrochloride	X	X
	Trimethoprim + sulphamethoxazole	X	X
	Doxycycline	X	X
	Erythromycin estolate	X	X
	Gentamicin	X	X
	Metronidazole	X	X
	Nalidixic Acid		X
	Nitrofurantoin	X	X
	Norfloxacin		X
	Spectinomycin	X	
	Roxithromycin		X* (ST)
	Sulphadiazine		X* (ST)
	Tetracycline		X
	Trimethoprim	X	
Vancomycin hydrochloride	X*	X* (T)	

Notes: Drugs marked with an asterisk are considered complementary. The WHO list defines complementary as needing specialized facilities or being less attractive from a cost-effectiveness standpoint; the Indian list defines it as drugs to be used in specific situations or if similar drugs are not available. Drugs marked 'T' are needed only in tertiary health care centres; those marked 'ST' are needed in both secondary and tertiary healthcare centres. All other drugs are needed in all primary, secondary and tertiary healthcare centres.

Additionally, prescription-only drugs are not publicly advertised under a voluntary agreement with the pharmaceutical industry (OPPI 2008). The Drugs and Magic Remedies Act control medicine advertisements.

## Drug Quality

Drug quality is compromised when active ingredients degrade due to poor storage conditions or age, or because they are outright counterfeits or contain less (or more) than the active ingredient as labelled. (This can be intentional or the result of poor manufacturing techniques.) Impure filler ingredients in drugs can also be hazardous to those who take them.

China and India hold the ignoble distinction of being the top producers of counterfeit drugs (Charatan 2001). Substandard drugs plague the Indian market, although the exact magnitude of the problem is disputed. Analysis by state regulatory authorities found that 0.5 percent of drugs were spurious and 10 percent were of low quality (Committee 2003). Other studies have estimated that 20–25 percent of drugs available in India are spurious, counterfeit, or substandard (Chakravarty et al. 2001; Mukerjee 2003). A more recent study took random samples of antimalarial, antibiotic (ciprofloxacin and erythromycin), and antimycobacterial (isoniazid and rifampicin) drugs from areas in and around Delhi and Chennai, and found that 12 percent of samples in Delhi and 5 percent in Chennai were substandard (Bate et al. 2009).

Many states do not have facilities to test the quality of drugs, making the collection of representative data difficult (Committee 2003). Governments and pharmaceutical companies are hesitant to report counterfeit drugs, lest it create panic among consumers (Gautam et al. 2009). The Organization of Pharmaceutical Producers of India (OPPI 2008) and Indian Pharmaceutical Alliance (IPA), both groups of manufacturers, have started initiatives to monitor counterfeit drug production within the industry (Gautam et al. 2009).

Drug quality can also be compromised if drugs are left in stock beyond their expiration date. Drugs at higher-level health centres are less likely to be expired, but many rural clinics dispense drugs that

are expired, especially in areas plagued by violence (Gill 2009).

An amendment in 2008 to the Drugs and Cosmetics Act of 1940 made sanctions for the manufacture and sale of substandard drugs significantly more severe. For example, the penalty for manufacture or sale of spurious drugs was previously five years to life in prison and at least a fine of INR 10,000. Under the 2008 amendment, the punishment is either 10 years to life and INR 1,000,000, or three times the value of the confiscated drugs, whichever is more. Proceeds from the fine will now be divided among the people who took the adulterated drugs or their relatives in case of their death. The penalty for not disclosing the name of a manufacturer producing substandard or adulterated drugs or withholding documents that proved such malfeasance was increased from INR 1,000 to INR 20,000. Penalties for repeat offenders who manufacture substandard medicines or produce medicines without a valid license were increased as well (Government of India 2008).

Even before their expiration dates, drugs may lose their effectiveness due to poor distribution and storage conditions. India has stringent requirements for good manufacturing practices, but no mandatory standards for good distribution and storage practices. There are currently no guidelines for maintaining medicines at safe temperatures in retail pharmacies, other than that they must have a refrigerator (personal communication from G. P. Mohanta, Professor of Pharmacy at Annamalai University, to Alice Easton on June 23, 2010).

## Part 4: Interventions to be Considered

This report has focused on understanding the current status of antibiotic use and antibiotic resistance in India. Much antibiotic use is therapeutic and some of it is life saving. Unfortunately, as is the case in every country, antibiotics are overused in various circumstances and by particular segments of the population. In hospitals, antibiotics are often substituted when better infection control is needed; in the community (particularly in affluent areas), they may be used frequently and inappropriately for colds, just in case they work.

The direct costs of antibiotic overuse are minimal, but the indirect costs—especially the costs of drug resistance—are rarely considered in India or any other country. That unchecked antibiotic use has a cost is becoming more apparent, particularly in hospitals. Second- and third-generation antibiotics are needed to cure staphylococcal and streptococcal infections, and the gram-negative bacteria often associated with surgery, are ever more difficult to treat effectively.

At the same time, a significant segment of the population appears to have limited or no access to antibiotic treatment. Pneumonia—largely bacterial—still kills more neonates and older infants than any other disease. With a simple antibiotic, most of these deaths can be prevented.

GARP is focused mainly on rationalizing antibiotic use, which in the United States and other wealthy countries has produced an overall reduction. However, increasing access to potentially life-saving antibiotics in low- and middle-income countries, where the availability of these drugs is not universal, must be considered explicitly by new policies.

Policymakers, who are faced with improving availability to save lives and curtailing use where these drugs are unnecessary—at the same time, must consider interventions that can slow the evolution and spread of resistance, which—almost by definition—is synonymous with decrease in use. Although with awareness of the potential adverse effects of access, modifications and policies could be put in place to avoid them. Unfortunately, the

evidence supporting interventions mostly comes from outside India; only a small proportion of these studies are from other low- and middle-income countries. As a result, the approaches emphasized generally do not include improving access.

Few studies in India assess the possible impact of various interventions to curb the emergence and spread of antibiotic resistance. Without baseline data against which to evaluate interventions, assessment of their relative efficacy and cost-effectiveness is problematic. Prioritizing policies according to their benefits and affordability is also difficult. Before recommending a series of interventions, it will be necessary to investigate the relative effectiveness of different strategies in the Indian context.

The main approaches that are applicable in India and countries with similar resources are:

- increased use of vaccines that reduce disease and, therefore, the demand for antibiotics;
- improved infection control, including using safety checklists during procedures and providing hospital staff with guidelines or feedback; and
- education and public awareness campaigns for providers and consumers.

Three additional approaches that might be useful in India, but would be more resource-intensive are:

- increasing the number and use of good-quality diagnostics to better target antibiotic use (The development of a range of rapid diagnostic tests [RDTs] that would not require a microbiology laboratory could be a huge boon, but such tests are not yet available. Although it is intuitively appealing, evidence of a positive ef-

fect from improved diagnostics on antibiotic prescribing patterns is currently lacking. An added benefit of better diagnosis, either with RDTs or enhanced laboratory capacity, is the potential for better surveillance of resistance trends.);

- addressing supply chain constraints and failures to improve the quality of drugs on the market, as well as access to trained prescribers and dispensers (Some patterns of use may relate directly to weaknesses in the drug supply chain or the accessibility of authorized prescribers—issues that are of much less concern in developed countries.); and
- using economic incentives, such as subsidies, to encourage better use of antibiotics (This strategy has been not been well developed in any country, but has great potential. Crafting interventions that create appropriate incentives and disincentives for purchasers and sellers will require in-depth understanding of the incentives that exist currently. Some of the short-term research ongoing in GARP countries should provide insights into current incentives.).

## Vaccines for Antibiotic-Treatable Diseases

Vaccines are arguably the most powerful health interventions for individuals and for society. At an individual level, they prevent disease—both the primary disease and its sequel. The vaccines in widespread use are very safe and are given routinely, not at the moment illness strikes. If most people in the population are immunized, even those who are not vaccinated may be protected through what is referred to as ‘herd immunity’. Once enough people are protected against a disease, those who are not vaccinated benefit from the pathogen’s inability to spread in the largely-immune population.

Overall, vaccines may reduce healthcare costs under many circumstances. In India, for example, because the government does not pay for most healthcare services, its costs may increase with vaccination, which is a public health measure, even though citizens’ out-of-pocket costs may decrease. In addition to the direct health benefits, vaccines reduce the use of antibiotics by reducing the need for them (promoting and enforcing appropriate use) or more broadly the demand for them (reducing both appropriate and inappropriate use).

## Opposition to Vaccination

Some activists and doctors in India claim that WHO has misrepresented some studies when promoting the *H. influenzae type b* (Hib) vaccine, and that deaths of children who received the vaccine have not been properly investigated (Mudur 2010). Some of these activists are part of the All India Drug Action network, which posted a letter to WHO on their blog discussing their concerns over the safety of the vaccine (Dabade et al. 2009). Jacob Puliyel, a paediatrician at St. Stephen’s Hospital in New Delhi; Mira Shiva, a public health and human rights activist; and Gopal Dabade, a health activist, have been some of the most vocal members of this group. There has also been opposition to other vaccinations, especially for polio, from Muslim clerics in India and abroad. On the other hand, popular film and sport personalities have starred in public service announcements encouraging people to get vaccinated (Balasubramanian 2006).

## Vaccine Production in India

Fifteen vaccine institutes were established in India during British rule, but vaccine development has accelerated in India over the last 60 years (Gogtay et al. 2009). India has gone from being largely dependent on imported vaccines to being self-sufficient and exporting vaccines that meet international standards (Gogtay et al. 2009). ICMR sets the rules for clinical trials in phases 1–4, and a network of monitoring centres keep track of any adverse effects following immunization, in an attempt to ensure good manufacturing practices within India (Gogtay et al. 2009).

The market for vaccines in India was estimated to be INR 30.53 billion in 2006–2007 (Cygnus

2008). The largest vaccine manufacturer in India is the Pune-based Serum Institute of India. This institute exports to 140 countries and supplies international agencies, such as WHO, the United Nations Children's Education Fund (UNICEF), and GAVI, the Global Alliance for Vaccines and Immunisation (BTJ-Forum 2009). In India, WHO first approached the Serum Institute to develop and manufacture an H1N1 (so-called 'swine flu') vaccine (CyberMedia 2010). The institute came out with an intranasal H1N1 vaccine in the summer of 2010 (Mascarenhas 2010). Some vaccine producers have received prequalification from the WHO (such as the Haffkine Bio-Pharmaceutical Corporation Ltd., a government of Maharashtra undertaking) for its bivalent oral polio vaccine in June 2010 and now supplies UNICEF (Correspondent 2010).

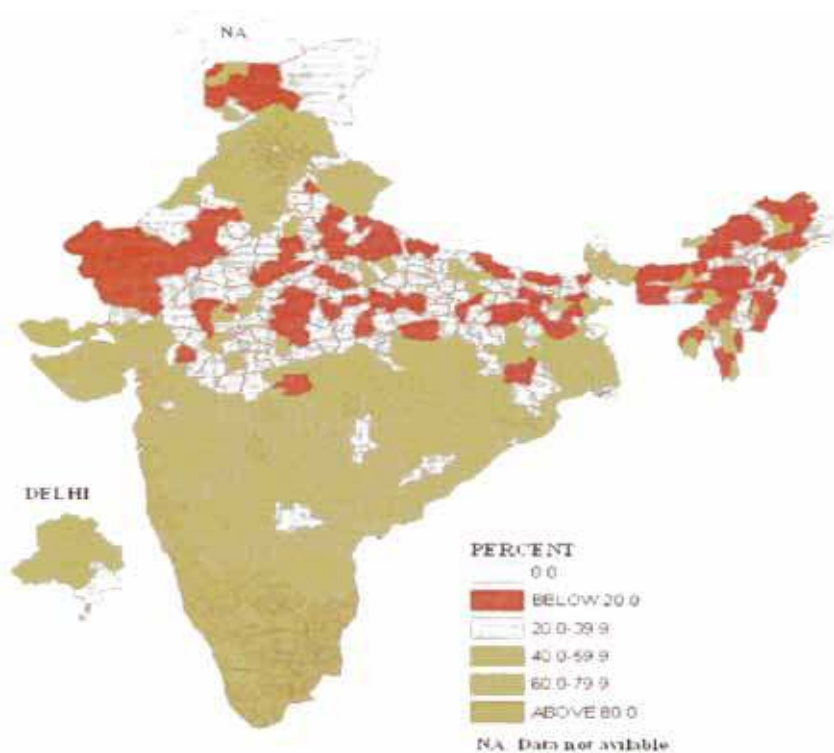
In 2009–2010, the Indian government enabled the Central Research Institute in Kasauli, Pasteur Institute of India in Coonoor, and Bacillus Calmette-Guérin (BCG) Vaccine Laboratory in Guindy to resume production of vaccines (SifyNews 2010). Vaccine production should also increase with the

newly built plant in Dholka, Gujarat, which is a collaboration between Novavax and other pharmaceutical companies. It will be able to produce 60 million doses of seasonal and pandemic flu vaccines each year, for use in India and other countries (Rand 2010).

### The Universal Immunization Program

The Universal Immunization Program (UIP) was launched in 1985 with the goal of covering all districts, immunizing 85 percent of infants and all pregnant women, and achieving self-sufficiency in vaccine production and cold-chain equipment by 1990 (Princeton 2004). The six diseases covered are diphtheria, pertussis, tetanus, poliomyelitis, measles and childhood tuberculosis (WHO-India 2008). The DPT vaccine combines the vaccines for diphtheria, pertussis and tetanus into a single formula and is administered three times, followed by a booster shot. The vaccines are available to all citizens free of cost. UIP now covers all districts and is aiming to vaccinate all infants (Princeton 2004). It

**Figure 23. Percentage of Children (12–23 Months) Receiving Full Vaccines**



Source: Sharma (2007).



**Table 8. Government Vaccination Schedule for India**

Disease	Doses	Booster	Method	Additional doses
Diphtheria, pertussis, tetanus	6 weeks, 10 weeks, 14 weeks	18–24 months, 4–6 years	Intramuscular injection	Diphtheria and tetanus only at 5 years, tetanus only at 10 years and 16 years
Polio	Birth (in institutional deliveries and endemic areas), 6 weeks, 10 weeks, and 14 weeks	15–18 months	Oral vaccine	
Measles	9 months			
Bacillus Calmette-Guérin (BCG) for TB	Birth			
Hepatitis B (in pilot areas)	6 weeks, 10 weeks, 14 weeks			

Source: (WHO 2011)

is one of the largest programs of its kind, in terms of vaccine usage and the number of people it reaches (WHO 2008).

Reported coverage rates from other sources for some vaccines exceed 100 percent, calling into question the reliability of these reports and making surveys, such as NFHS, very important (WHO 2004). The likelihood of a child being vaccinated depends on the child's gender, religion, birth order, location of residence, mother's education level and mother's exposure to information from mass media (Princeton 2004). Some states, such as Uttar

Pradesh, Rajasthan, Nagaland, Arunachal Pradesh, and Assam, have vaccination rates less than 33 percent (IIPS 2007). In Tamil Nadu, Kerala, and Goa, more than 75 percent of children are fully vaccinated.

Reporting on vaccination programs is currently limited to routine reports on the number of people immunized. A computer-based monitoring system will soon be implemented nationally and will include data on immunization, vaccine supply, the status of cold chain equipment, and adverse events following immunization (WHO-India 2008). A re-

**Table 9. Percent of Children (12–23 Months) Receiving Specific Vaccines**

	NFHS-1 1992–1993	NFHS-2 1998–1999	NFHS-3 2005–2006
BCG, measles, 3 doses each of polio and DPT	36 %	42 %	43.5 %
BCG			78.2 %
Polio			78.2 %
DPT			55.3 %
Measles			58.8 %
No vaccines received	30 %	14 %	

Notes: Complete vaccination remains low, largely due to low coverage of the DPT vaccine.

DPT = diphtheria, pertussis, tetanus.

Source: National Family Health Surveys (IIPS 1995, IIPS 2000, IIPS 2007).

cent study sampled several poorer states in India and found that the cold chain equipment was usually adequate, whereas injection safety and waste disposal techniques were substandard (WHO 2004).

### Vaccines against *S. pneumoniae* and *H. influenzae*

Introducing two other vaccines into the UIP—the pneumococcal conjugate vaccine (PCV), which prevents against *S. pneumoniae*, and the *H. influenzae type b* (Hib) vaccine—could greatly reduce the burden of pneumonia in India. This would result in a reduced need for antibiotics to treat pneumonia cases and save many lives (Levine et al. 2007).

India accounts for 27 percent of the global number of pneumonia cases. UNICEF has estimated that 44 million cases occur each year in India (WHO/UNICEF 2006; Rudan et al. 2008; O'Brien et al. 2009), but this may be an overestimate. Although these estimates mean that every third child is affected by pneumonia, clinical experience suggests that the incidence is lower (Mathew 2009b). Regardless of the exact number of cases, there is a 'significant burden of pneumonia and meningitis among children in India' (Gupta et al. 2010, 649). Pneumonia causes an estimated 410,000 deaths in India each year (Mathew 2009b), and it is the number one killer of children (Levine et al. 2007). The uncertainty in incidence and fatality figures makes calculation of the case fatality rate difficult.

Hib is the leading cause of pneumonia in India, and bacterial strains resistant to all major antibiotics have been documented in the country (Kant 2009). India has the greatest number of Hib deaths of any country: 72,000 children under the age of five years die each year from infection (Watt et al. 2009). Annually, *S. pneumoniae* causes 6.6 million–22 million cases of pneumonia and leads to 142,000 deaths among children under five years (IAPCOI 2008; O'Brien et al. 2009).

The Hib vaccine has been found to be highly cost-effective, fits well within India's current UIP immunization schedule, and if added to the UIP could prevent over 70,000 child deaths per year (Kant 2009). In 2009, the National Technical Advisory Group on Immunizations (NTAGI) recom-

mended that the Hib vaccine be introduced into the UIP as soon as possible (Kant 2009). In addition, GAVI committed US\$ 165 million to introduce a pentavalent vaccine, consisting of DPT vaccines plus hepatitis B and Hib, initially in 11 states that currently perform well on health indicators, with eventual national coverage (Alliance 2009). In its first year of rollout, the vaccination program would cover 10 million children, approximately 40 percent of babies born each year. Despite this progress, the antivaccine lobby has submitted public interest litigation against this rollout, resulting in postponing the pentavalent vaccine's introduction (Professor O. Levine, Johns Hopkins Bloomberg School of Public Health, communication to Hellen Gelband, February 26, 2010), and putting production on hold while the Indian Institute of Medical Research re-examines the issue.

In addition to Hib, NTAGI also recommended that pneumococcal vaccines be included in the routine immunization program, beginning in one Indian state in 2010 and then introduced nationally (Professor O. Levine, Johns Hopkins Bloomberg School of Public Health, communication to Hellen Gelband, February 26, 2010). It has been estimated that the serotypes contained in the 7-valent PCV (pneumococcal conjugate vaccine) would cover 52 percent of severe cases in children under five years in India (IBIS et al. 1999; Kanungo et al. 2001). The available 10-valent vaccine might be more effective in India, but more reliable data on the disease burden incidence in India and the vaccine's cost-effectiveness might be necessary before there is the political will required to include it in the UIP (Lahariya 2008). Use in India of the newer 13-valent vaccine, licensed by the U.S. Food and Drug Administration in February 2010, would probably have even greater benefits, although its effectiveness still needs to be tested in India.

In 2007, GAVI contacted the government of India to assess its interest in introducing pneumococcal vaccines, which could be obtained by the government for US\$0.15–\$0.30 per dose (Levine et al. 2007). The Indian Academy of Paediatrics Committee on Immunization (IAPCOI) recommended that the government apply for GAVI support to establish a pneumococcal surveillance system and begin the process of including PCV in the routine immunization program (Singhal 2008). Despite the

recommendations by NTAGI and IAPCOI, introduction of PCV has not moved forward.

The PCV and Hib vaccines are designed to protect against the most prevalent serotypes of these bacteria, but other serotypes ('nonvaccine serotypes') do colonize and infect people. These strains do, to at least some extent (based on experience in Europe and North America), fill some of the niches left open by vaccine-prevented strains. Eventually, this 'serotype replacement' could result in a situation where bacterial infections are as common as they were before widespread use of the vaccine. An even worse scenario is if future strains tend to be more antibiotic resistant. This is one more indication that surveillance for bacterial strains and vaccine development needs to be constant as opposed to sporadic. Every country that has established these vaccinations has seen continuing success, and none has faced the worst-case scenario described above. The bacterial landscape is not the same in India as it is in the countries where it has been followed, however. A monitoring system that detects both serotype replacement and a changing ecology of serious respiratory infections is called for, along with new vaccination programs.

## Other New Vaccines and Existing Underused Vaccines

A number of other vaccines could play a role in preventing disease and death and reducing antibiotic use in India. The most prominent are discussed here.

### Rotavirus

Worldwide, rotavirus is the main cause of diarrhoea in pre-schoolers and causes 500,000 deaths annually (Pillscribe 2009). About 120,000 of these deaths are in India (Financial Express 2008). Vaccines against rotavirus have just become available in the last few years, with clinical trials and background studies still ongoing in some countries. Rotavirus vaccines have been available in much of the developed world since 2005, and subsequent studies verifying the efficacy of vaccines in developing countries, including India, led WHO to recommend that it be included in all national immunization programs (Pillscribe 2009).

Asian countries, including India, tend to have a large number of rotaviral strains due to the proximity of humans and livestock, making vaccine development difficult (Pillscribe 2009). Following a technology transfer from the U.S. National Institutes of Health in 2005, Bharat Biotech International, Biological E. Ltd., Shantha Biotechnics Ltd., and Serum Institute of India Ltd. obtained licenses to work on rotavirus vaccines (Pillscribe 2009). Bharat Biotech expects to launch one in India by 2011. Such a vaccine could save 100,000 children each year. Vaccines are already available in the market and are expected to be used widely in the private sector, but it may be some time before it is included in public vaccination schemes (Shankar 2010).

IAPCOI recognizes the large morbidity and mortality associated with rotavirus, but will not recommend its inclusion in a national immunization program until there are more data on the immunogenicity and efficacy of the vaccine from India (Singhal 2008). ICMR recently announced an upcoming series of projects to determine the burden of rotavirus diarrhoea in India, under the Indian Rotavirus Surveillance Network (Shankar 2010). This follows the completion of an ICMR project on a hospital-based rotavirus-strain surveillance network of four laboratories and ten hospitals around India. This study found that rotavirus was present in 39 percent of children under five years who both had acute gastroenteritis and had been hospitalized for rehydration (Shankar 2010).

It is true that rotavirus itself is not treatable with antibiotics, but in India, as in other countries, antibiotics (and antimotility drugs) are used routinely by mothers when their children have watery diarrhoea (not bloody diarrhoea, or dysentery, which is more serious and is caused by bacteria). Rotavirus vaccination would prevent a large number of cases of dehydrating diarrhoea—some of them fatal—and reduce what is largely inappropriate antibiotic use.

### Typhoid Vaccine

Typhoid fever, a serious disease caused by the bacterium *Salmonella enterica serovar Typhi* (*S. Typhi*), is most common where water supply and sanitation are poor. Infection comes from water or food

contaminated with the faeces of an infected person. Contaminated water and food are particularly challenging in slum areas of developing countries. The number of cases of typhoid fever that occur each year is not well known, but WHO estimates conservatively that there may be 21 million around the world. Ninety percent of cases are estimated to occur in Asia, mainly in poor countries, where 1–4 percent of patients die of the disease. In section 2, what is known about *S. Typhi* in India is reviewed, highlighting the elevated rates of multidrug resistant organisms. Besides preventing serious illness, typhoid vaccines could reduce drug pressure on *S. Typhi* bacteria, which already can be difficult to treat because of high and rising resistance levels. Two typhoid vaccines are available: one is an oral attenuated vaccine, requiring three or four doses; and the other is an injectable inactivated vaccine, requiring a single dose. However, it is largely travellers, not inhabitants of endemic areas, who use both vaccines. The vaccines are given after age two (because they have not yet been tested in younger children). Use in India would prevent disease and death, and reduce demand for antibiotics. In 2008, WHO recommended that countries consider vaccination against typhoid, in light of its high incidence, although not necessarily nationwide. According to WHO, the vaccine should be targeted to high-risk groups.

Typhoid fever could be controlled through ‘improved housing, water supply, sanitation, and food handling [but] in many typhoid- and cholera-endemic areas, these investments are expensive to implement and unlikely to occur in the near term’ (Whittington et al. 2009, 400). Indian public health programs have looked to vaccines to mitigate morbidity and mortality from typhoid fever under current conditions.

In India, typhoid was among the six diseases selected for inclusion in the Expanded Programme on Immunization, launched in India in 1978, following the eradication of smallpox in 1975. However, it was discontinued in 1985 (WHO-India 2008). A free vaccine against typhoid, paratyphoid A and B, and cholera was administered in Kolkata between the 1950s and 1980s, after which it was discontinued because of its side effects. A recent discussion determined that the disease burden of typhoid and levels of antibiotic resistance are not high enough

to warrant the vaccine’s reintroduction into the national immunization schedule (Mathew 2009b).

A new typhoid vaccine has prevented a fairly low 44 percent of cases in India (Sur et al. 2009) and has sparked new discussion over whether it should be given routinely in the country. This vaccine, the Vi capsular polysaccharide vaccine, is a subunit vaccine made from the *Ty2 Salmonella Typhi* strain. It is one of two typhoid vaccines recommended by WHO—the other being the one discussed above. The vaccine does not protect against *S. paratyphi*, which has been an increasingly major cause of typhoid fever (Schwartz 2009). However, it may still make a difference in a significant proportion and number of typhoid cases (Levine 2009). The typhoid Vi polysaccharide vaccine can be purchased in the private sector in some locations, but most people do not seek it out unless they need it for travel abroad or school (Whittington et al. 2009).

Some are also concerned that use of the Vi vaccine could select for virulent strains against which the vaccine provides no protection. However, such strains did not emerge as a major problem in Chile following the large-scale use of a Vi vaccine (Levine 2009).

### Influenza Vaccine

In India, the burden of seasonal influenza is low (Mathew 2009a) and high-risk groups have not been identified (Jameel 2010), so it is not clear that annual vaccination would improve health significantly. Vaccination against seasonal influenza would not be on the radar screen at all if not for a recent study in Bangladesh that had promising results. In that study, pregnant women were vaccinated. Influenza and other respiratory illnesses were significantly less frequent in mothers who received the flu vaccine and their infants than in the control group, who had been given pneumococcal vaccine to test the main hypothesis of the study (Zaman et al. 2008). This finding requires corroboration and examination in a variety of contexts throughout the subcontinent. If this study is accurate, vaccinating pregnant women could be an effective strategy to improve infant and maternal health, and save antibiotics—both those that would be used appropri-

ately to treat secondary infections and those used against the flu itself, an ineffective clinical measure.

## Infection Control Interventions

Several measures can be implemented in hospitals to reduce the spread of infections, such as hand washing, isolation rooms, and use of gloves, gowns, etc. Beyond hand hygiene, the most commonly advocated approach to hospital infection control (to date, largely in high-income countries) involves identifying and isolating hospital patients colonized or infected with certain bacteria (especially *S. aureus*) and treating them away from other patients. A systematic review of the efficacy of isolation found that, despite the limitations of existing research, there is evidence that interventions that include isolation measures can reduce transmission of MRSA (Cooper et al. 2003; Cooper et al. 2004). Given all the possible measures, the feasibility of establishing them will limit what is and is not a reasonable approach in a particular setting. A measure such as improved hand hygiene (assuming some deficiency) should be feasible in any hospital, but isolation may not be.

Studies on infection control in India are largely limited to components of multi-country studies organized by the International Nosocomial Infection Control Consortium. Two such studies look at the impact of 'outcome and process surveillance' on infection rates.

Outcome surveillance measures the rates of hospital-acquired infections, as well as their consequences, including mortality, extended hospital stays, attributable costs, and bacterial resistance. HAIs are often reported as infections per 1,000 patient days or device days. This information is required for comprehensive baseline studies and has been used by developed countries in planning effective infection control programs. These studies are especially useful in areas where there is a general perception, often unfounded, that HAI rates are low and compliance with hand hygiene recommendations is high. In these areas, outcome surveillance studies can make the concerned parties aware of the magnitude of the problem.

Process surveillance measures compliance with infection control practices. This includes proper catheter use, measures to prevent surgical site infections and antibiotic prophylaxis. Giving performance feedback to the personnel who were monitored usually follows surveillance. Process surveillance has been part of several successful infection control programs, which also included education and feedback. One study found that education alone did not have a long-term impact on infection control practices, whereas education plus process surveillance and performance feedback improved compliance in a sustainable way (Dubbert et al. 1990).

Two other studies focused on catheter-associated infections. The first investigated catheter-associated urinary tract infections in 42 ICUs in 11 developing countries, including India. The second study examined central vascular blood-stream infections in 71 ICUs in 12 developing countries, including India. In the two studies, hand-hygiene increased from 53 percent to 59 percent, and 51 percent to 61 percent, respectively; the number of catheter-associated infections per 1,000 catheter-days decreased significantly from 9 to 6, and from 14 to 10, respectively; and bacterial resistance rates decreased overall (Rosenthal et al. 2008b; Rosenthal et al. 2008c).

A third study evaluated the impact of hand-hygiene observation, education, performance monitoring and feedback, and peer support in 50 ICUs in 12 developing countries, including India. It found that hand-hygiene compliance increased from 37 to 59 percent among healthcare workers following this multipart intervention (Rosenthal et al. 2008a). A study of ventilator-associated pneumonia and mortality in an ICU in India found that the number of ventilator-associated pneumonia cases per 1,000 mechanical ventilator days decreased significantly from 26 to 11, following outcome surveillance and infection control measures (Mehta et al. 2007b). Finally, a study by the same group found that outcome and process surveillance plus education and feedback had a positive effect on device-associated infection rates in critical care patients in a private Indian hospital. Hand-washing rates increased from 64 to 92 percent, and device-associated infection rates decreased from 3.89 per 1,000

bed-days to 0.29 per 1,000 bed days (Chakravarthy et al. 2006).

## Infection Control Studies Outside India

This section evaluates studies in the developed and developing world on the impact of introducing such measures, as little evidence from the Indian setting is currently available. However, even when data from outside India are included, there is 'a lack of published studies exploring the implementation of comprehensive infection control advice and programs, including the minimal advice, which is designed specifically for resource-limited settings' (Zimmerman 2007, 499).

Many evaluations of infection control programs are difficult to interpret because they do not discuss '(1) what other infection control program components were in place; (2) whether there were policies or practices in place for basic infection prevention; (3) the financial cost of implementing individual program components; or (4) on what available infection control advice they may have been based' (Zimmerman 2007, 496).

- A before-and-after study of nurse-generated daily reminders to remove unnecessary catheters reduced catheter use, catheter-associated urinary tract infections, and the total length of hospitalization. The total cost per patient to the hospital was reduced by 58 percent (Apisarnthanarak et al. 2009).
- A study in Argentina found that the implementation of staff education, performance feedback and hand hygiene initiatives resulted in a decrease from 45.94 bloodstream infections per 1,000 intravascular device-days to 11.10 bloodstream infections per 1,000 intravascular device-days, and 47.55 HAIs per 1,000 bed-days to 27.93 HAIs per 1,000 bed-days. Training for this initiative was conducted in a well-funded urban facility, but barriers to implementation were still numerous and included a lack of resources,

infection control programs, awareness, and support (Rosenthal et al. 2003; Rosenthal et al. 2005).

- A study in an Indonesian paediatric intensive care unit found that literal adoption of unmodified guidelines published by the Centres for Disease Control (for the United States) was impossible because the facilities for hand washing were lacking and too expensive to procure, microbiology labs were unavailable, healthcare workers were uninformed, workplace hierarchies prevented change and the hospital administration was unsupportive (Rhinehart et al. 1991).

## Educational Interventions

Studies have noted that both physicians and pharmacists in India are interested in educational activities related to antibiotic use. However, evidence of the efficacy of educational interventions in India is lacking. Thus, the literature from other developing countries currently provides the best indication of what might work in India.

Of 319 medical practitioners in Tamil Nadu who participated in a self-administered questionnaire about their prescribing practices, 12 percent suggested that continuing medical education should be provided to keep them updated on antibiotic use guidelines and resistance rates. Six percent felt that patient awareness of antibiotics should be improved (Sivagnanam et al. 2004). An anthropological study of pharmacist-client relations in Mumbai found that pharmacy staff were enthusiastic about participating in in-service training as an opportunity to acquire a certificate and thereby increase their earning potential (Kamat et al. 1998).

## Education Campaigns: Pharmacies

In a lower-middle income country, such as India, where over-the-counter antibiotic sales are frequent, a logical target for interventions are re-

tail pharmacists. Indian pharmacists working in private retail pharmacies have been encouraged to attend continuing education programs, some of which are supported by the Pharmacy Council of India. The Maharashtra State Pharmacy Council has been conducting continuing professional development programmes for retail pharmacists. Pharmacy departments at universities, such as Annamalai University in Tamil Nadu, also organize programs regularly for hospital and community pharmacists (personal communication from G. P. Mohanta, Professor of Pharmacy at Annamalai University, to Alice Easton on June 23, 2010). A few studies have found that meeting with pharmacists can lead to a decrease in antibiotic prescribing.

In a randomized controlled trial in Indonesia and a before-and-after study in Kenya, one-on-one meetings with pharmacists and group sessions with attendants increased short-term sales of oral rehydration salts (ORS) and decreased sales of antidiarrhoeal drugs. The meetings sought to train staff, as well as give them the sense of being a health professional (Ross-Degnan et al. 1996). Outreach consisted of brief meetings between diarrhoea program educators and pharmacists, followed by a small group training session with pharmacy counter attendants. Impact was assessed using before-and-after comparison groups of pharmacies and their case management of surrogate patients posing as mothers of young children with simple, watery diarrhoea. Reported knowledge about dehydration and appropriate treatment after training was also measured. As previously discussed, the study found major discrepancies at the baseline between reported and observed behaviour. Although 66 percent of pharmacies reported selling ORS for cases of childhood diarrhoea, only 33 percent of surrogate patients actually received ORS during visits. After the training, sales of ORS by intervention pharmacies increased by an average of 30 percent, while other medicines, including antibiotics, declined by about 15 percent. There was also a significant increase in the number of pharmacies that discussed the importance of dehydration with clients ( $p < 0.05$ ).

Based on this study, it appears that face-to-face training of pharmacy attendants can result in short-term improvements in diarrhoea case management and reduction in antibiotic sales for un-

complicated infections. This indicates that, while knowledge and practice might diverge at baseline, training can positively change product sales in the direction of recommended treatment. Questions remain, however, about the long-term effectiveness of such models. More information is needed on the resources and incentives necessary to continue education activities and which actors to engage in designing and implementing similar programs (e.g., ORS manufacturers, healthcare NGOs, pharmaceutical researchers). Finally, research is inconclusive as to whether these results can be generalized to other health problems commonly treated with antibiotics, such as respiratory illness.

A study in Hanoi and Bangkok found that visits to pharmacies by inspectors, to discuss prescription laws and review practice, decreased illegal dispensing of steroids in both cities. It also decreased illegal sales of low-dose antibiotics from 90 percent to 69 percent, and increased the frequency with which pharmacy staff would ask questions and give advice to their customers in Hanoi (Chalker et al. 2005).

In resource-poor countries where the government cannot review pharmacies, professional associations can be called upon to provide periodic accreditation and continuing education for pharmacy staff.

## Education Campaigns: Hospitals

A number of studies have investigated the ability of in-service training for physicians to improve prescribing behaviour. Randomized, controlled trials have shown that seminars can improve prescribing patterns, although it is not clear how long their effects will last. In Zambia, 16 health centres were divided into two groups, one attending a seminar and the other group not. Afterwards, 5,685 patients' cards were analysed and it was found that the number of drugs per patient and frequency of antibiotic prescription was lower in the experimental group and non-pharmacological treatment was higher (Bexell 1996). Another randomized, controlled trial in Cuba showed that a refresher course on managing acute respiratory infections improved prescribing practices (Ochoa et al. 1996). However, a study using a survey of prescriptions, questionnaires and focus group discussions found

that the effect of training undertaken by the Ministry of Health in Ghana to improve malaria management was not sustained after a year (Ofori-Adjei et al. 1996). A review of studies on interventions to improve prescribing found that, in general, seminars did not have a long-term impact, perhaps because of a lack of follow-up (Le Grand et al. 1999).

Group discussions are a more interactive form of educational intervention. In Indonesia, they effectively reduced irrational injection use, although another randomised, controlled trial found that face-to-face interactive interventions did not have a greater impact on prescribing than seminar interventions (Santoso et al. 1996). However, a study of focus groups and interactive discussions in Iran found that indicators were similar in both groups and concluded that underlying factors must be considered more carefully (Garjani et al. 2006).

At the other end of the spectrum, disseminating written information to prescribers is inexpensive, but less personalized and less direct. A small randomised, controlled trial in Sri Lanka revealed a reduction in antibiotic prescription following the dissemination of drug information, but it was not statistically significant (Angunawela et al. 1991). In general, providing prescribers with bulletins and newsletters about rational drug use have not been effective (Le Grand et al. 1999).

An educational intervention incorporating several different methods improved prescribing behaviour in Mexico, although not in the long term (Perez-Cuevas et al. 1996). A review of interventions to improve professional practice in developing countries found that no educational intervention had proven to be more effective than others, but that in general mixed interventions with a focus on local involvement were the most successful. However, it also noted that no studies were able to show improvement in professional behaviour in the long term (Siddiqi et al. 2005).

Prescribing practices of 69 physicians in two primary health care units in Mexico were studied at the baseline. A training workshop was conducted for 36 physicians, which included analysis of the literature, discussion of a treatment algorithm for acute diarrhoea, and discussion of results from a previous phase of the study. Afterwards, a peer review committee was created to discuss treatment

behaviour of physicians. Evaluations were conducted at 2, 6, 12 and 18 months after the committee stopped functioning. It found a reduction in the use of antibiotics from 79 percent to 39 percent in the short term, and in the long term the prescribing algorithm was followed more closely in the experimental group (Gutierrez et al. 1994).

Another study examined the effect of an interactive educational workshop and peer review on prescribing practices for rhinopharyngitis. A quasi-experimental design split 119 physicians from family medical clinics and MoH health centres into intervention and control groups. The study found that the percent of patients receiving antibiotics decreased from 85 percent to 48 percent in the family clinics, and 69 percent to 49 percent in the MoH health centres.

These studies indicate that peer review may have a positive impact on the antibiotic prescribing habits of physicians. However, studies that separate the effect of feedback from other educational interventions are needed to determine the true cause of the recorded changes in prescribing behaviour.

## Standard Treatment Guidelines

Standard treatment guidelines (STG) have been formulated in many developing countries, but few have been evaluated for effectiveness (Le Grand et al. 1999). To the best of our knowledge, their impact has not been evaluated in the Indian context.

A before-and-after study in Fiji showed that the introduction of an STG reduced the use of antibiotics. On the other hand, a study in Uganda found that the introduction of a national STG and training did not decrease the number of antibiotics per prescription. However, compliance with STGs seemed to increase, with the most dramatic changes among untrained health workers (Naivalulevu 1990; Kafuko 1994).

More recently in Bangladesh, the 26 worst performing centres, of 60 studied, were split into three groups: one would receive an STG intervention, one that would receive an STG and audit intervention, and a control group. The STG intervention group showed a 7 percent decrease in antibiotic



use, once changes in the control group were adjusted for, and the STG plus audit group showed a 15 percent decrease (Chowdhury 2007).

Other studies found that the development and implementation of standard treatment guidelines had an impact on case management, although the impact of the guidelines cannot be separated from the training, audit and feedback that were also a part of these interventions (Wahlstrom 2003).

In 2007, National Standard Treatment Guidelines were developed for 35 conditions with high prevalence in India by the Armed Forces Medical College in association with the government of India and the WHO-India Country Office. Different guidelines were created for each of four different levels of care: 1) solo physicians, 2) health facilities with 6 to 10 beds, 3) facilities with 30 to 100 beds and 4) more than 100 beds (WHO India). This group of collaborators also estimated the cost of providing care as described in these guidelines.

For example, the standard treatment for enteric fever includes ciprofloxacin and ofloxacin as first-line drugs, even for resistant typhoid. The recommended second-line drugs are amoxicillin, trimethoprim/sulfamethoxazole, or chloramphenicol, although the guidelines note that widespread resistance to these drugs is reported in India. In cases of multidrug-resistant typhoid, cefixime or azithromycin can be used. Guidelines generally limit the more specialized drugs to larger facilities.

The Delhi Society for Rational Use of Drugs has developed and updated standard treatment guidelines (table 10), which are available from the government of India for HIV/AIDS, tuberculosis, malaria and other diseases that have specific national programs.

## Guidelines and Checklists

Another common approach, which is rising in profile, is the use of checklists and guidelines for standard hospital procedures. The biggest boost came from a trial conducted by the WHO patient-safety initiative in eight hospitals in different countries (including an urban charity hospital in New Delhi), which was published in 2009

in the *New England Journal of Medicine* (Haynes et al. 2009). The checklist—mainly oral confirmation of common-sense measures—was applied to surgery patients. Local investigators introduced operating-room staff to the checklist procedure, using a variable mix of lectures, written materials, and guidance. Infection-related outcomes included surgical site infection, pneumonia and death (from all causes). The proportion of patients with surgical site infections and deaths were approximately cut in half; pneumonia occurred in about as many patients before and after the intervention. At most study sites, infections and death decreased following implementation of the checklist. However, the results were not significant at the 5 percent level, at five of the eight hospitals studied, including the one in Delhi. Despite the promising results, concern remains that some of the improvement could have been due to the fact that staff knew an intervention was occurring (Haynes et al. 2009).

The WHO study is not the only one to report positive results with a checklist, for example, to reduce the incidence of *Clostridium difficile* (Abbett et al. 2009). But, even if guidelines and checklists promote good practice, they work only if followed. Adherence to guidelines can be stymied by several factors, including practitioners with insufficient knowledge about the efficacy of the practice, no awareness of the guideline itself, few resources and supplies, patient demands for a particular treatment, and poor motivation. In practice, infection control teams seem to make the difference between success and failure (Farr 2000; Larson et al. 2007), but whether they are necessary in all environments is unclear.

## Major Drivers of Antibiotic Resistance: Current Indications

Current indications suggest that a combination of behavioural factors and economic incentives motivate the prescribing, dispensing, and purchasing of antibiotics when they are inappropriate for treating a condition, in amounts inappropriate to the situation, or both. On the patient side, demand for fast eradication of symptoms, particularly with diarrhoea, leads to specific requests for antibiotics.

**Table 10. Standard Treatment Guidelines Involving Antibiotics (WHO-India 2007)**

<b>Condition</b>	<b>Solo physician clinic</b>	<b>6–10 bed primary health centre</b>	<b>30–100 bed community health centre</b>	<b>100+ bed district hospital</b>
Amoebiasis	Metronidazole 800 mg, 2 x daily, orally for 7 days; and diloxanide furoate 500 mg, 3 x daily, orally for 10 days	Same as left	For amoebic liver abscess which has not responded to metronidazole therapy: oral chloroquin 250 mg tablet, 2 tablets, 2 x daily, for 2 days; 1 tablet, 2 x daily, for 19 days OR dihydroemetine (although this should be avoided). For intestinal amoebiasis which has not responded to metronidazole plus diloxanide therapy, add tetracycline 500 mg, 4 x daily, for 5 days	Same as left
Community-acquired pneumonia	Early treatment is essential: trimethoprim 80 mg + sulfamethoxazole 400 mg, 2 x daily OR amoxicillin 500 mg to 1 g, 3 x daily OR oral macrolides OR azithromycin 500mg, 1 x daily	Oral amoxicillin 500mg to 1 g, 3 x daily, plus erythromycin 500mg, 4 x daily OR azithromycin 500 mg, 2 x daily. Consider second-line antibiotics, fluoroquinolones (levofloxacin 500 mg 1 x daily)	First-line antibiotics: co-amoxiclav 1.2 g, 3 x daily, OR cefuroxime 1.5 g, 3 x daily OR cefotaxime 1 gm, 3 x daily OR ceftriaxone 2g, 1 x daily, plus erythromycin 500 mg, 4 x daily, IV or clarithromycin 500 mg, 2 x daily, IV. Second line: levofloxacin 500 mg, 1 x daily, IV.	Same as left

<b>Condition</b>	<b>Solo physician clinic</b>	<b>6–10 bed primary health centre</b>	<b>30–100 bed community health centre</b>	<b>100+ bed district hospital</b>
Acute Otitis Media	Uncomplicated: empirical antibiotic therapy with amoxicillin 500 mg, every 8 hours for 5-7 days OR oral amoxicillin/clavulanate potassium. For penicillin-allergic patients: erythromycin 500 mg, every 6 hours for 10 days	Same as left	Parenteral antibiotics: Injectable ampicillin and injectable gentamicin-cephalosporins OR injectable quinolones OR as guided by sensitivity tests	Same as left
Cholera	Oral rehydration salts started early	Same as left	In severe cases, antibiotics can reduce diarrhoea, but are not necessary in mild cases and will hasten the development of resistance. ciprofloxacin 500 mg, 2 x daily OR doxycycline 300 mg, single dose OR tetracycline 500 mg, every 6 hours for 48 hours or 2 gm single does	Same as left
Chronic otitis media, attico-antral disease	None indicated unless there is a complication, in which case parenteral broad spectrum antibiotics should be used	Same as left	Same as left	Same as left
Chronic otitis media, tubotympanic disease	Active stage: amoxicillin 500 mg capsule every 8 hours for 5-7 days. Second line: amoxicillin/clavulanate potassium, antibiotic ear drops	Same as left	Same as left	Same as left

Condition	Solo physician clinic	6–10 bed primary health centre	30–100 bed community health centre	100+ bed district hospital
Management of burns	<p>Broad spectrum antibiotics not indicated in the early post-burn period, as use will lead to colonization of the wound by resistant organisms. However, ceftazidime plus amikacin plus metronidazole can be used after 48 hours and after sensitivity tests</p>	Same as left	Same as left	Same as left
Dental caries	In case of acute pain, amoxicillin 30-40 mg/kg/day every 8 hours for 5 days	Same as left	According to culture and sensitivity test	In case of swelling or cellulite or abscess: amoxicillin 30-40 mg/kg/day every 8 hours for 5 days; tinidazole 500 mg every 12 hours for 5 days
Enteric fever (typhoid)	<p>First line--oral ciprofloxacin/ ofloxacin 7.5 mg/kg, 2 x daily for 5-7 days (choice even for multidrug resistant typhoid).            Second line--to which wide-spread resistance is reported in India: oral amoxicillin 25 mg/kg, 2 x daily for 10-14 days</p>	Same as left	<p>Second line--to which wide-spread resistance is reported in India: chloramphenicol IV 12.5 mg/kg, every 6 hours for 14-21 days; ampicillin IV 25 mg/kg, every 6 hours for 10-14 days; trimethoprim/sulphamethoxazole IV 4/20 mg/kg, every 12 hours for 14 days. In case of multidrug resistance: oral cefixime 5 mg/kg, 2 x daily for 7-14 days; oral azithromycin 10 mg/kg, 1 x daily for 7 days</p>	<p>In case of multidrug resistance or patient unable to take oral drugs: ceftriaxone IV 30 mg/kg, every 12 hours for 10-14 days. In case of peritonitis, IV antibiotics, such as trimethoprim/Sulphamethoxazole 4/20 mg/kg, 2 x daily for 10-14 days. In case of multidrug resistance: oral cefixime 5 mg/kg, 2 x daily for 7-14 days; oral azithromycin 10 mg/kg, 1 x daily for 7 days; ampicillin 1 x daily; gentamicin 5 mg/kg, 1 x daily; and metronidazole 500mg, 1 x daily will be required</p>

<b>Condition</b>	<b>Solo physician clinic</b>	<b>6–10 bed primary health centre</b>	<b>30–100 bed community health centre</b>	<b>100+ bed district hospital</b>
Periodontitis	Antibiotics if acute pain or swelling: ciprofloxacin 500 mg tablet, every 12 hours for 5 days; and tinidazole 500 mg tablet every 12 hours for 5 days	Same as left	Same as left	Ciprofloxacin 500 mg tablet every 12 hours for 5 days; and tinidazole 500 mg tablet, every 12 hours for 5 days
Trauma	For minor trauma, oral ciprofloxacin 500 mg, 2 x daily for 5 days. For major trauma, injectable or IV cefotaxime 1 gm, every 8 hours; injectable or IV gentamicin 80 mg; injectable or IV metronidazole 500 mg, every 8 hours	Same as left	Same as left	Same as left
Reproductive tract infections: urethral discharge/burning micturition in males	Oral cefixime 400 mg single dose; plus oral azithromycin 1 gm single dose under supervision. Advise to return after 7 days. If allergic to azithromycin, then erythromycin 500 mg, 4 x daily for 7 days	If symptoms persist, treat for trichomonas vaginalis: oral secnidazole 2 gm, single dose.	Treat pregnant partners for gonorrhoea and chlamydial infection: oral cefixime 400 mg, single dose OR ceftriazone 125 mg intramuscular injection; plus oral erythromycin 500 mg, 4 x daily for 7 days; OR oral amoxicillin 500 mg, 3 x daily for 7 days. Contraindications: quinolones like ofloxacin and ciprofloxacin, and doxycycline.	Same as left
Scrotal swelling	Oral cefixime 400 mg, 2 x daily for 7 days; plus oral doxycycline 100 mg, 2 x daily for 14 days		Pregnant partners: oral erythromycin base 500 mg, 4 x daily OR oral amoxicillin 500 mg, 3 x daily. Contraindications: erythromycin estolate	

<b>Condition</b>	<b>Solo physician clinic</b>	<b>6–10 bed primary health centre</b>	<b>30–100 bed community health centre</b>	<b>100 + bed district hospital</b>
Inguinal bubo	Oral doxycycline 100 mg capsule, 2 x daily for 21 days; plus oral azithromycin 1 gm tablet single dose OR oral ciprofloxacin 500 mg, 2 x daily for 3 days	Same as left	Pregnant partners and lactating women: oral erythromycin base 500 mg tablet, 4 x daily for 21 days; plus parenteral amino glycoside (gentamicin), contraindications.	Same as left
Vaginal discharge in females	Secnidazole 2 gm orally single dose OR Oral tinidazole 500 mg tablet 2 x daily for 5 days; candidiasis: oral fluconazole 150 mg tablet, single dose OR local clotrimazole 500mg vaginal pessary once.	Treat current partner only if no improvement after initial treatment. Cervical infection: oral cefixime 400 mg tablet, single dose plus oral azithromycin 1 gm tablet once.	Pregnant women with vaginitis: First trimester: local clotrimazole vaginal pessary/cream; metronidazole pessaries or cream for TV or BV. Second-third trimester: oral metronidazole tablet; oral secnidazole 2 gm, single dose or oral tinidazole 500 mg tablet, 2 x daily for 5 days.	Same as left
Lower abdominal pain in females	Mild/moderate pelvic inflammatory disease: oral cefixime 400 mg tablet, 2 x daily for 7 days plus oral metronidazole 400 mg tablet, 2 x daily for 14 days (N. gonorrhoeae, anaerobes); plus oral doxycycline 100 mg capsule, 3 x daily for 3-5 days (Chlamydia)	Same as left	Same as left	Same as left
Oral and anal sexually transmitted diseases	Depending on symptoms, can be treated as urethral discharge syndrome or genital ulcer syndrome	Same as left	Same as left	Same as left

Source: (WHO-India 2007)

The high cost of drugs relative to the incomes of most people suffering from infectious diseases results in purchases of partial doses, sharing drugs with others, or hoarding them for future use. Cost and time constraints also encourage patients to self-medicate familiar symptoms or diseases at retail pharmacies, rather than visiting a healthcare facility for a diagnosis and prescription. For clinicians and dispensers, the drivers stem from incomplete knowledge of either the correct usage of antibiotics or the exact cause of an infection, leading to misuse of antibiotics for viral disease or overuse of the right drug at the wrong dosage.

Empiric treatment in a setting that lacks information about the patterns of bacterial disease and their antibiotic susceptibilities is thus viewed as a major driver of resistance. Even where knowledge exists, however, irrational application of antibiotics persists. This could be the result of strong underlying beliefs about the power of antibiotics, pressure to meet client demand, financial rewards from the profitability of antibiotic sales in a facility, or the simple availability of antibiotics when other indicated treatments, such as oral rehydration salt packets for diarrhoea, are not present.

Hospital infection control practices in the country also vary widely and fail to prevent the spread of bacterial disease within some facilities. This leads to increased antibiotic use, which increases the selection pressure for resistance on bacteria.

Major drivers of antibiotic resistance in India have not been sufficiently investigated. However, existing studies from India are discussed in the section 'Incentive for Antibiotic Use' and 'Infection Control'.

## Part 5: Next Steps for GARP

The extent and consequences of antibiotic resistance in India, including the full burden of resistance on human health and the economic costs it places on society and individual patients, are largely unknown—as they are for every other country, both developed and developing. Research is hampered by institutional factors, leading to a number of information gaps.

First, without a systematic national surveillance system in place, data on levels of bacterial disease and drug resistance in common pathogens are limited and are drawn primarily from hospital-based studies. Isolates used for analysis in these reports are usually only available when a clinician orders a test, which can be infrequent and unpredictable. When clinicians do order cultures, it is typically late in the course of a disease and limited to higher-level referral care (district hospitals and above). Both situations lend themselves to a greater prevalence of complicated cases and elevated antibiotic exposure in the patient, likely biasing study results for resistance levels in various bacteria.

Second, without national standards for reporting data, comparing trends over time and between regions is difficult, and microbiology labs are ill-equipped for assessing the impact of resistance. Capital equipment may be lacking or in poor operational condition, and consumables may be of poor quality or available in insufficient quantities. Finally, information on the clinical outcomes of resistance is difficult to obtain and rarely collected. Without a coordinated and routine data-collection system in place, national risk assessments and the advancement of effective policies to address the threat to human health from antibiotic resistance will remain elusive.

Given the current scarcity of surveillance data, there is a need for more large meta-analytic studies on antibiotic resistance in India, as well as national standards for susceptibility testing (Lakshmi 2008). No central monitoring agency exists, unlike for *M. tuberculosis*, which is monitored by centres in Chennai, Bangalore and Agra (Raghunath 2008).

### Current Research and Next Steps for GARP-India

In the effort to develop an actionable policy agenda to improve antibiotic use and slow the emergence and spread of resistance, GARP-India and the National Working Group have endorsed and are supporting a number of research activities designed to fill key information gaps. One study, in collaboration with Sir Ganga Ram Hospital in New Delhi, seeks to evaluate the impact on prescribing practices by giving hospital-based physicians feedback on their antibiotic prescribing rates relative to those of their peers within the same hospital. Another, in collaboration with the Karuna Trust, seeks to measure the use of all types of antibiotics in a rural setting:

- by type of antibiotic dispensed,
- by month,
- by type of pharmacy (government- and NGO-run PHCs, Taluka (subdivision of a district) and district hospitals, and private retail pharmacies),
- by characterizing the relationship between prescriptions and antibiotics dispensed,
- by characterizing the concordance between the prescription and the acquired antibiotics,
- by comparing antibiotics prescribed and acquired to local treatment guidelines,
- by describing the demographics of people purchasing antibiotics, and
- by illustrating the degree to which different methods of collecting antibiotic use data reach similar conclusions.



The central objective of these studies is to derive critical information necessary to inform intervention approaches aimed at containing resistance. To the extent possible, the study results will aid the GARP-India National Working Group in comparing policy approaches and highlighting mechanisms that offer the greatest epidemiological impact. Data on antibiotic prices, profitability to the supplier, and affordability to the patient or consumer, coupled with information on the volumes of antibiotics stocked at various points of sale, will assist in evaluating economic incentives or disincentives related to antibiotic demand.

## Final Products for GARP

This situation analysis is a preliminary report that will serve as a jumping off point to discuss the policy alternatives for controlling antibiotic resistance in India. The GARP-India National Working Group that has been considering these issues and has produced this situation analysis will lead policy discussions among a wider circle, including all sectors. This will culminate in a final report, to be issued in spring 2011, which will recommend a set of policy options and directions, along with the analysis of expected consequences. We anticipate a GARP phase 2, during which steps necessary for policy implementation can be followed.

A global report will also be published, bringing together the lessons learned from all four GARP countries: India, Kenya, South Africa, and Vietnam. This will be released at the first 'Global Forum on Bacterial Infections: Balancing Treatment Access and Antibiotic Resistance', which will be held in New Delhi, October 3–5, 2011, at the India Habitat Centre.

# 1<sup>ST</sup> GLOBAL FORUM ON BACTERIAL INFECTIONS

## Balancing Treatment Access and Antibiotic Resistance

India Habitat Centre, New Delhi, India. 3-5 October 2011

A meeting for **researchers** to present new data on antibiotic access and resistance, and for **policymakers, clinicians, public health program managers and researchers** to **debate policy innovations in low- and middle-income countries** to address these critical questions:

### ANTIBIOTIC ACCESS

- How can we expand treatment access and minimize the spread of resistance?
- What interventions—in addition to vaccination—will reduce the need for antibiotics?
- What tools are best used to measure the burden of bacterial infections and the avertable burden of various interventions?
- What policies at all levels in the healthcare system will best achieve our goals?

### ANTIBIOTIC RESISTANCE

- What are the drivers and economics of antibiotic resistance in low-resource settings?
- What are the challenges to infection control programs to reduce hospital-acquired infections (HAIs)?
- How can surveillance and tracking be used to inform policies about resistance?

### PNEUMONIA

- How can we best support vaccine introductions for childhood bacterial pneumonias?
- Can we better use information on bacterial serotype distribution and serotype replacement to plan vaccination campaigns and develop new vaccines?

Release of Antibiotic Resistance National Policy Strategy reports from China, India, Kenya, South Africa and Vietnam.

**Early abstract submission deadline (discounts available): 15 April 2011.**

Preference will be given to early submissions.

**Early registration deadline: 15 July 2011.**

For more information, please visit [www.globalbacteria.org](http://www.globalbacteria.org)



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## Appendix I: Basic Health and Economic Indicators for India

In a little over 60 years since independence, India has become a global force. With the world's second largest population, its economy continues to grow at more than 7 percent per year (since 1997) in real terms. Demand for automobiles and other goods continue to rise. But, India is also home to the greatest number of people living on less than US\$ 1 per day, which is one-third of the 1.2 billion who live in the country. India, without doubt, is a country of strong contrasts.

The largely open-market economy is driven by the service sector, which accounts for more than half of its output and employs about one-third of workers. Just over half of the population is engaged in agriculture. In 2001 (the most recent data available), the majority of the population—72 percent—lived in rural areas (Office of the Registrar General and Census Commissioner 2001). For the

population as a whole, most of whom depend on public services, the physical and social infrastructure, including healthcare, are inadequate and require substantial investment if they are to improve living and learning, and healthcare.

Some indicators in India, such as the number of women who die in childbirth for each 1,000 live births, compare unfavourably with similar countries (Jha et al. 2007). Other indicators, such as rates of underweight and wasting children, have shown little decline in recent years (IIPS et al. 2007). In fact, the proportion of children in India who are underweight is nearly twice that found in sub-Saharan Africa (Arnold et al. 2009). On the other hand, infant mortality has declined steadily in both urban and rural areas since 1992 (IIPS 2007).

**Table A1. Population Statistics**

Variables	Statistics (year collected)*
Population growth rate	1.407% (2009)
Birth rate	21.72 births/1,000 population (2009)
Infant mortality rate	50.78 deaths/1,000 live births (2009)
Life expectancy at birth	66.09 years (2009)
Literacy	61% (2001)
Population with access to improved drinking water	89% (2006)
Access to improved sanitation (facilities that ensure hygienic separation of human excreta from human contact)	14% in 1996; 28% in 2006 (2006)

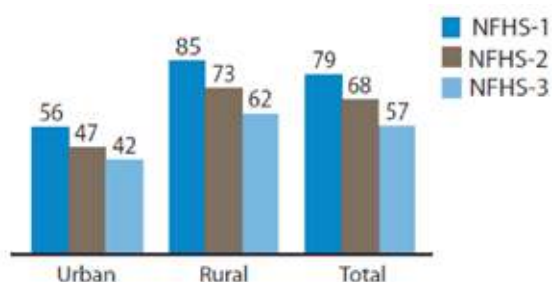
\*Source: CIA The World Factbook (2011)

**Table A2. Economic Statistics**

Variables	Statistics (year collected)*
GDP real growth rate	9% in 2007, 7.4% in 2008, 6.1% in 2009
GDP by sector	62.6% services, 20% industry, and 17.5% agriculture
GDP per capita (PPP) in 2009 USD	\$3,100 (2009)
Unemployment rate	9.5% (2009)
Population below poverty line	25% (2007)

\*Source: CIA The World Factbook (2011).

**Figure A1. Trends in the Number of Infant Deaths per 1000 Live Births in the Last 5 Years**

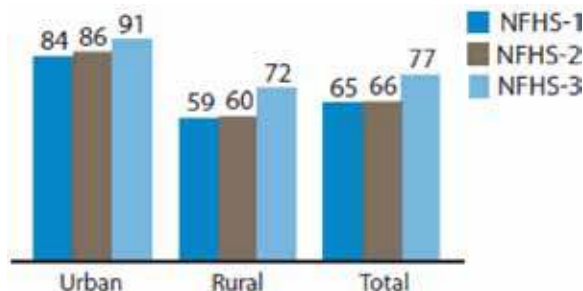


Source: IIPS (2007)

In most cases, summary statistics for health indicators mask great geographic variability. For example, a much smaller proportion of children are underweight in Kerala and Punjab, compared to the central Indian states (Arnold et al. 2009). On a smaller scale, underweight children are a much greater problem in rural areas and in slums, compared to the rest of India (Arnold et al. 2009).

In south India, 80 percent of babies are born in institutions, whereas in poorer states the figure is lower, near 25 percent (National Family Health

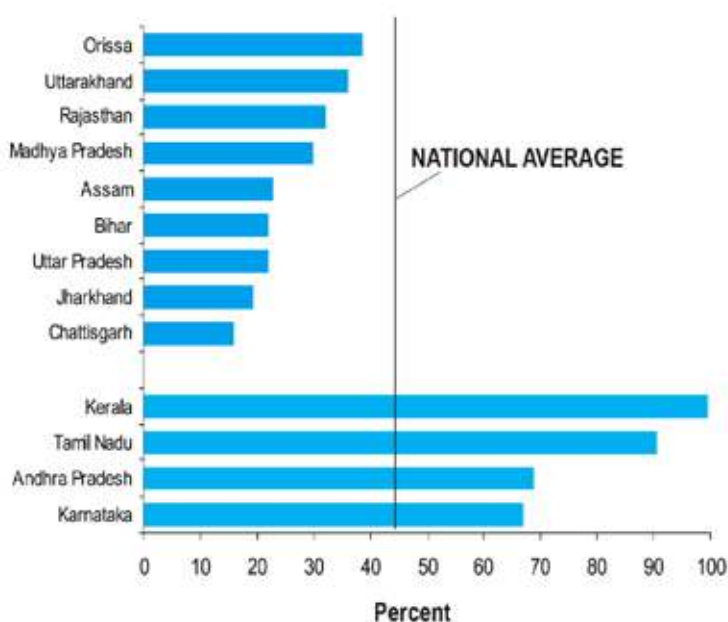
**Figure A3. Antenatal Care in 1992–1993 (NFHS-1), 1998–1999 (NFHS-2), and 2005–2006 (NFHS 3)**



Source: IIPS et al. (2007).

Survey 2006). This statistic is understood to represent access to delivery services and may in turn represent access to prenatal and antenatal care, instructions about breastfeeding and malnutrition, and appropriate responses to common childhood diseases, such as vaccinations. In 2005–2006, 31 percent of rural births in the last three years were in institutions, whereas the equivalent figure for urban areas was 69 percent (IIPS et al. 2007). Overall, institutional deliveries increased from 26 percent in NFHS-1 to 41 percent in NFHS-3. Use of antenatal care (figure A3) was 77 percent in 2005–

**Figure A2. Institutional Deliveries in Selected States, 2005–2006**



Source: Jha et al. (2007).

2006, up from 65 percent in NFHS-1 (IIPS 2007). These numbers mask great disparities between urban and rural areas, states, religions, and socioeconomic groups (IIPS 2007).

Perhaps as a result of improvements in access to care and advice during pregnancies, the maternal mortality ratio is estimated to have declined from 400 maternal deaths per 100,000 live births in 1997–2008 to 300 in 2001–2003 (Office of the Registrar General of India 2006). The National Rural Health Mission seeks to reduce this figure to 100 by 2012 (IIPS et al. 2007).

## Appendix 2: Healthcare in Urban Slums in India

Slums are ‘informal’ settlements that lack the civic infrastructure that elsewhere provides basic services, such as clean water and waste disposal, and the scaffolding of a healthcare system. It is no surprise that people who live in slums are at high risk for many diseases and have little means to do much about it. Somewhere between 40 and 62 million people lived in slums in and around Indian cities, per 2001 statistics (The Hindu 2003; IANS 2009). While slums are growing around the world, as many residents migrate to cities from rural areas, they also have a degree of permanence, with residents who are born and die in the same slum.

Unlicensed doctors, who call themselves ‘Bengali doctors’ in some parts of India, operate in and around slum communities in India. Of the 20 private practitioners in a Bombay slum, where more than 10,000 people lived in the mid-1990s, none had formal training in health (Emmel et al. 1996). This is true of almost all self-defined healthcare providers in slums. These individuals’ credentials may be only that they have worked as assistants—or even janitors—in hospitals or dispensaries (Joshi 2010).

Such private practitioners offer first-line medical care to slum dwellers. They are available, accessible, and affordable. Residents know them and are comfortable with them. Some practitioners provide care and medicines on credit. Patients know that the informal practitioners are not as qualified as doctors or nurses in government hospitals, but they may find them more humane and communicative, in contrast with the rude reception poor people often receive in government hospitals (Pande 2005).

Bengali doctors commonly dispense what, by law, are prescription-only medicines, including antibiotics. They may be injections, syrups or powders mixed with water. These drugs may have no labels, so that patients do not know what they are. The practitioners’ usually poor information about medicine means that they may prescribe the same things for most sicknesses. In other cases, patients may ask for medicines that they have heard about on television or through friends. People also self-

treat with leftover medicines to save money. In all of these cases, people may be taking drugs that will not speed their recovery and may be harmful. However, it is important to keep in mind that the greatest overuses of antibiotics are unlikely to be among poor communities, where the decision to use them means a significant cost to the patient.

Slums have their own patterns of health problems, which may not resemble the problems of the surrounding or nearby city. The lack of toilets and sewers, bathing units, garbage disposal, and drinking water (Pande 2005), plus crowded conditions and inadequate nutrition of a large proportion of inhabitants, makes them highly vulnerable to infections transmitted person-to-person and to water- and food-borne infections (Pande 2005). The dependence of slum communities on informal practitioners means that people often only reach hospitals when they are in the late stages of a disease that has not been effectively treated (Riley et al. 2007). This makes treatment more difficult, but also presents hospitals with conditions and infections that are not representative of the day-to-day level of illnesses in the slums (Riley et al. 2007). The types and extent of the health problems of slum populations are largely unknown because they have been so little studied. Bacterial infections that are resistant to common antibiotics—the focus of this report—may or may not yet be a problem.

The interventions that would make the greatest difference for infectious diseases and drug resistance would be clean water and proper sanitation, not those involving healthcare itself.

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## ABOUT CDDEP

The Center for Disease Dynamics, Economics & Policy (CDDEP) was founded with the objective of using research to support better decision-making in health policy. The CDDEP team employs a range of expertise—including economics, epidemiology, disease modeling, risk analysis, and statistics—to produce actionable, policy-oriented studies on malaria, antibiotic resistance, disease control priorities, environmental health, alcohol and tobacco, and various other diseases.

Many CDDEP projects are global in scope, spanning Africa, Asia, and North America. The strength of CDDEP derives from its researchers' experience in addressing country and region-specific health problems, as well as truly global challenges, while recognizing the circumstances in which the answers must fit. The outcomes of individual projects go beyond the usual models to inspire new strategies for analysis, and innovative approaches are shared through publications and presentations focusing specifically on methodology.

Founded in 2009 as a center of Resources for the Future, CDDEP is an independent non-profit organization. With headquarters in Washington D.C. and New Delhi, CDDEP currently employs full-time staff members in India, Kenya, and the United States, and relies on a distinguished team of academics and policy analysts around the world.

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