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# Need for the Implementation of Antibiotic Policy in India: An Overview

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## ABSTRACT

World health organization accepted that antimicrobial resistance is a natural phenomenon, there is an urgent need for comprehensive national plans, based on a multi-sectorial approach and with sustainable financing to fight antimicrobial resistance globally. AMR continues to pose a significant public health problem in terms of mortality and economic loss. Studies related to antimicrobial drugs usage, determining factors and development of antimicrobial drug resistance, provincial discrepancy and interventional strategies is a big challenge for any developing country. This review article aims to highlight the importance of Antibiotic policy and its implementation in every health care system to make physicians, general practitioners, and other stakeholders aware of the issue of AMR and its factors and what can be done. Scoping review was done using ScienceDirect, Web of Science, EconLit, and PubMed. To discuss some of the challenges in the implementation of policies in India such as varied discernments about antibiotic use and AMR among key stakeholders, inappropriate antibiotic use and to achieve the aim of this review was performed by collecting around 80 published articles from 1999 to 2020. Initial suitable antibiotic treatment has been shown to reduce mortality, the span of stay in ICU and hospital. Early correct antibiotic chosen have also served to the reduction in antimicrobial costs. The hospitals which are having antibiotic policy shown decreased morbidity and mortality due to antibiotic-resistant infections. In developing countries, antimicrobial stewardship programs are emerging up, which will help to develop antibiotic policies for management of infections in various settings. This article focuses on the current status and implementation of antibiotic policy in Indian healthcare settings like the primary, secondary and tertiary hospital to combat antimicrobial resistance.

**Key Words:** Antimicrobial resistance, Antibiotic policy, Antibiotics, Antimicrobial Stewardship Program, Developing Country, Indian Healthcare

## INTRODUCTION

Antimicrobial resistance is a unique community health problem especially in developing countries where comparatively easy availability and higher consumption of medicines have led to the disproportionately higher prevalence of inappropriate use of antibiotics and greater levels of resistance compared to developed countries<sup>1-3</sup> Supervision of frequent and lethal bacterial infections has been significantly compromised by the appearance and quick increase of antibiotic-resistant bacteria. The Global Antibiotic Resistance Partnership (GARP) was started to begin the practice of developing actionable policy recommendations relevant to low- and middle-income countries.<sup>4,5</sup> Auta et al.,<sup>6</sup> recently demonstrated that obtaining antibiotics without restrictions is possible in many countries through prescriptions at com-

munity pharmacies. In their meta-analysis on the effects of the unregulated sale of antibiotics conducted during 2000-2017, the authors represented data suggesting that the largely pooled proportion of antibiotics sold with no a prescription had reached 72%. Proportions are high even in partially developed countries such as Mexico, where a ban on the sale of antibiotics without a prescription was instituted only nine years ago.<sup>7</sup> Every time an antibiotic is used - whether appropriately or not, in human beings or animals- the probability of the development and spread of antibiotic-resistant bacteria is increased.<sup>8,9</sup> In the evolution of drug resistance in bacteria 'Drug selection pressure' becomes the single most important factor. The reasons for selection of drug are multifactorial and involve both human and animal use. While antibiotic resistance is first and foremost a medical problem, the factors that control the spread of resistance are epidemiological,

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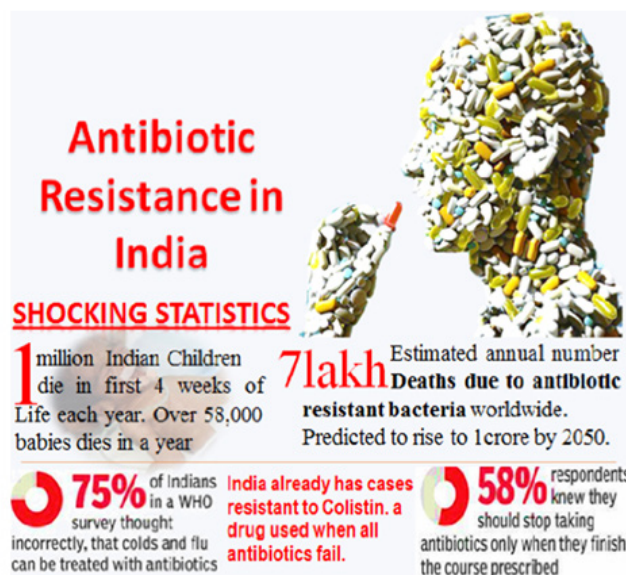
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social, cultural, ecological and economic. Physicians, veterinarians, patients, retailers and healthcare facilities - from huge pharmacies to limited drug sellers - have little enthusiasm (economic or otherwise) to recognize the consequences of their use of antibiotics on others, especially on future generations.<sup>5</sup> The microbial infection burden in India is among the highest in the world.<sup>10</sup> Accordingly, antibiotics will perform a perilous role in limiting morbidity and mortality in the nation. As an indicator of disease burden, pneumonia causes an estimated 410,000 deaths in India each year.<sup>11</sup> It is the number-one destroyer of children health.<sup>12</sup> Many of these leads to deaths which occur as patients do not have access to life-saving antibiotics when and where these are needed. At the other extreme, antimicrobial drugs are used in circumstances where these drugs cannot be expected to recover the patient's condition, mainly as a treatment for the frequent cold and unsophisticated cases of diarrhoea (which are appropriately treated with oral rehydration therapy).<sup>5</sup> The crude infectious disease mortality rate in India today is 5169.5 per 100,000 persons (according to Global Burden of Disease (GBD) study, carried out by Institute for Health Metrics and Evaluation, the USA from 1990 to 2017) and is twice the rate prevailing in the United States when antibiotics were introduced (roughly 200 per 100,000 persons).<sup>13</sup>



**Figure 1:** Shows the alarming statistics of antibiotic usage in India.

According to the centre for disease dynamics, economics & policy (CDDEP), one million Indian children die in the first 4 weeks of life each year, of these deaths 1,90,000 are caused by a bacterial infection, sepsis that surpass the bloodstream. Out of these deaths 58,319 (over 30%), deaths are due to antibiotic resistance. India already reported having resistance towards Colistin, an antimicrobial drug used when all other antibiotics fail.

Indian Council of Medical Research (ICMR) in recent times identified antimicrobial-resistant organisms in the digestive tracts of two out of every three healthy persons (67%) that it tested, pointing to a quick broaden of antimicrobial resistance in the Indian population. A mix of underprivileged community health systems and hospital infection, high rates of infectious disease, and irrational use of antibiotics is impending together to increase the prevalence of resistant pathogens and is increasing the burden of untreatable neonatal sepsis and health-care-associated infections.<sup>14</sup> The answer to the current approach to antibiotic resistance is to protect the efficiency of the drugs currently available by antibiotic stewardship and to capitalize on hospital infection-control practices, to limit the spread of resistance. Hence there is an urgent need to implement the antibiotic policy at all levels of Indian health care system. The principal aim of the hospital antibiotic policy is to diminish the morbidity and mortality due to antimicrobial-resistant infection, and to preserve the effectiveness of antimicrobial agents in the treatment and prevention of communicable diseases. Such policies are supposed to assist in reducing the spread of antimicrobial resistance, get better public health directly, benefit the population and lessen stress on the healthcare system. Lastly, ever-increasing the types and reporting of childhood vaccines presented by the government would decrease the disease burden extremely and spare antibiotics.

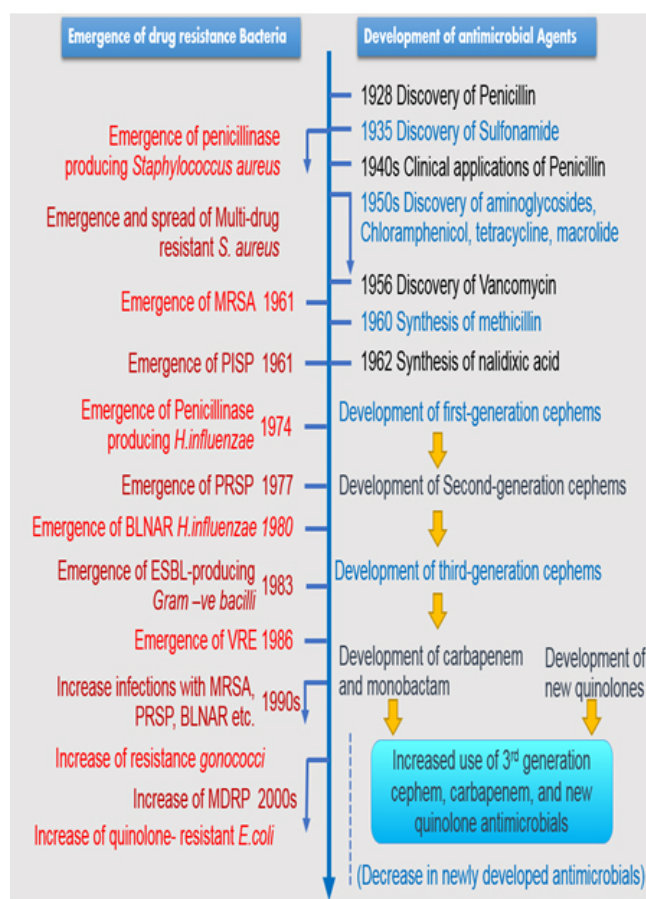
## THE RISE OF ANTIBIOTIC RESISTANCE

The resistance to penicillin was noticed even earlier the widespread use of penicillin started. Abraham and Chain showed that *E. coli* cell extract could destroy the antimicrobial activity of penicillin by enzymatic action.<sup>15</sup> Sir Alexander Fleming, also, had cautioned about the development of antibiotic resistance due to the overuse of antibiotic, as early as 1945, stating:

*"I would like to sound one note of warning. It is not difficult to make microbes resistant to penicillin in the laboratory, and the same thing has occasionally happened in the body. The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant."*

Sir Alexander Fleming: Nobel Lecture, December 11, 1945.

His cautioning has, unfortunately, turned out to be right. With the wide use of antibiotics, pathogens, which were previously sensitive to antibiotics, now started emerging resistance to many classes of antibiotics. The timeline for the development of antibiotics and antibiotic resistance is represented in Figure 2,<sup>16</sup> it indicates the increase in the antimicrobial drug resistance as the development of antimicrobial drug progressed and which may result in "Post antibiotic era" in 7-10 years from now.



**Figure 2:** Orientation of development of antimicrobial agents and emergence of drugresistant.<sup>14</sup>

**MECHANISMS OF RESISTANCE**

Pathogenic microorganisms are becoming resistant by the mutations of pre-existing Deoxyribonucleic acid (DNA) or by the procurement of DNA comprehending antibiotic resistance genes. These resistance genes converse ranges of different antibiotic resistance mechanisms to the pathogens. Table 1 represents the diverse classes of antimicrobial agents along with their mode of action and the mechanism of resistance by microorganisms clearly shows the resistance to antibiotics can be caused by four general mechanisms (inactivation, alteration of the target, circumvention of the target pathway or efflux of the antibiotic) and an organism can develop resistance by mutating existing genes, or by acquiring new genes from other strains or species.

**Table 1: Modes of action and the mechanisms of resistance of different Classes of Antibiotics**

Antibiotic class	Representative Antibiotics	Mode of action	Mechanism of Resistance
β-Lactams	Penicillins Cephalosporins Cefotaxime Carbapenems	Inhibition of cell-wall Synthesis	Enzymatic degradation of the drug, Drug binding proteins.

**Table 1: (Continued)**

Antibiotic class	Representative Antibiotics	Mode of action	Mechanism of Resistance
Aminoglycosides	Streptomycin Gentamycin Tobramycin Amikacin	Inhibition of protein Synthesis	Enzymatic modification, efflux, ribosomal mutations, 16S rRNA methylation.
Quinolones	Ciprofloxacin Ofloxacin Norfloxacin	Ciprofloxacin, Ofloxacin, Norfloxacin	Efflux, modification of target by mutations, protection of target.
Glycopeptides	Vancomycin	Inhibition of cell-wall Synthesis	Altered cell walls, drug Modification
Tetracyclines	Tetracycline	Inhibition of Translation	Efflux, modification of ribosomal proteins.
Macrolides	Azithromycin Erythromycin	Inhibition of protein Synthesis	Enzymatic modification, efflux, ribosomal mutations, 16S rRNA methylation.
Sulfonamides	Sulfamethoxazole Trimethoprim CoTrimoxazole	Inhibition of Folic acid synthesis	Modification of target

- 1) Modification of the antibiotic: The resistance can be achieved by shifting the drug molecule so that it is no more effective. This kind of resistance is observed in the case of β-lactams, macrolides and chloramphenicol. The β-lactam antibiotics are antibiotics that contain a beta-lactam ring in their molecular structure. This includes penicillin derivatives, carbapenems, cephalosporins, carbacephems, and monobactams are one of the most commonly prescribed drug classes with numerous clinical indications. The intact β-lactam ring is necessary for the action of penicillins. Bacteria produce a heterogeneous group of enzymes called β-lactamases, which cleave the β-lactam ring and inactivate the drug, thus, conferring resistance.<sup>15</sup> Chloramphenicol resistance is usually due to inactivation of the antibiotic by chloramphenicol acetyl-transferase,<sup>18</sup> while resistance to aminoglycosides is widespread, with more than 50 aminoglycoside-modifying enzymes being discovered.<sup>19</sup>
- 2) Resistance by influx–efflux systems: Microorganisms have dissimilar arrangements for transport of small molecules crosswise the cell membrane. If the antibiotic does not stay in the cell, then it would not have any adverse effect. The antibiotics are flushed out of the cells by efflux pumps thus, conferring resistance.



Resistance to fluoroquinolones and tetracyclines is commonly observed by efflux mechanism.<sup>17,20</sup>

- 3) Modification of the target site: If the target site is altered, it means that antibiotic cannot affect. The alterations in the antibiotic target sites can be carried out by mutation e.g., the mutation in DNA gyrase for resistance against quinolones, or enzyme modification of the target site e.g., methylation of an adenine residue in 23S rRNA making it insensitive to macrolides or by replacing targets e.g., ribosomal protection proteins conferring resistance to tetracyclines.<sup>17,20,21</sup>

There are other mechanisms of resistance such as overproduction of the target gene (dihydrofolate reductase overproduction for sulfonamide resistance), target protection (qnr genes for quinolone resistance), or production of other proteins which bind to the drug and prevents the original target (penicillin-binding proteins), but the above-discussed mechanisms are the major basic mechanisms of resistance widely encountered in pathogens.<sup>17,20,21</sup>

### ANTIMICROBIAL RESISTANCE IN INDIA

Development of penicillin-resistant *Streptococcus pneumoniae* (PRSP), methicillin-resistant *Staphylococcus aureus* (MRSA), multidrug-resistant *Pseudomonas aeruginosa*, vancomycin-resistant *Enterococcus* (VRE) and multidrug-resistant *Mycobacterium tuberculosis* has led to difficulties in the treatment of infections caused by this pathogens.<sup>22</sup> According to 'scoping report on antimicrobial resistance in India (2017),<sup>23</sup> under the tutelage of Government of India, among the Gram-negative bacteria, above 70% isolates of *Escherichia coli*, *Acinetobacter baumannii* and *Klebsiella pneumoniae* and approximately 50% of *Pseudomonas aeruginosa* were resistant to fluoroquinolones and 3<sup>rd</sup> generation cephalosporins. While the resistance to the drug combination of piperacillin-tazobactam was still below 35% for *E. coli* and *P. aeruginosa*, the existence of multiple resistance genes including carbapenemases leads to 65% *K. pneumoniae* resistant.<sup>23,24</sup> Increasing rates of carbapenem resistance, 71% for *A. baumannii* led to the frequent use of colistin as the last

resort antimicrobial.<sup>23</sup> The percentage of resistance among *Salmonella Typhi* was 28% and *Shigella species* was 82%, respectively, for ciprofloxacin, 0.6% and 12% for ceftriaxone and 2.3% and 80% for co-trimoxazole. For *Vibrio cholerae*, resistance rates to tetracycline varied from 17 to 75% in different parts of the country.<sup>23,24</sup> Recently, high mortality rates are detected due to multidrug-resistant bacterial infections. Each year, around 410,000 people die in India from infection with multidrug-resistant.<sup>11</sup>

The drug susceptibility study results of various laboratories in India disclose an increasing trend of development of resistance to commonly used antibiotics in pathogens like *Salmonella*, *Shigella*, *Vibrio cholerae*, *Staphylococcus aureus*, *Neisseria gonorrhoeae*, *N. meningitidis*, *Klebsiella*, *Mycobacterium tuberculosis*, HIV (human immunodeficiency virus), *plasmidium* and others.<sup>25</sup> New resistance mechanisms, such as the Metallo beta-lactamase NDM-1 (New Delhi Metallo beta-lactamase 1), have developed among several gram-negative bacilli. This can render powerful antibiotics ineffective, which are often used as the last line of defence against multi-resistant strains of bacteria.<sup>3</sup> Table 2 shows the various studies on antimicrobial resistance in India. Due to the Extended-spectrum beta-lactamases (ESBL), multidrug-resistant *entero bacteriaceae*, have become very frequent in India. Besides, different studies in South India highlighted the resistance pattern like Ciprofloxacin resistant *Salmonella enteric serovar Typhi*, multidrug-resistant Extended-Spectrum  $\beta$ -Lactamase Producing *Klebsiella pneumoniae*, fluoroquinolone resistance among *Salmonella enteric serovar Paratyphi A*, the emergence of vancomycin-intermediate *staphylococci*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* resistant to ceftazidime, cefepime and ciprofloxacin. The resistance to colistin has also developed in India. Although the percentage of colistin resistance was below one, high mortality of 70% was associated with colistin-resistant *K. pneumoniae*. Amongst the Gram-positive organisms, 42.6% of *Staphylococcus aureus* were methicillin-resistant and 10.5% of *Enterococcus faecium* were vancomycin-resistant.<sup>26,27</sup>

**Table 2: Antibiotic resistance rates of various organisms in India during Last two decades**

S. No	Type, number and Location of Isolates	Name of the microorganism	Resistance rate %	Author and Year Reported
1	338 Urinary isolates @ Armed Force Medical College (AFMC), Pune	<i>E. coli</i> <i>Proteus spp</i> <i>K. pneumoniae</i>	81% to Ampicillin, 23% to Cefotaxime 89% to Ampicillin, 82% to Ofloxacin 100% to Sulphamethoxazole & Trimethoprim.	RN Mishra et al. (1999) <sup>28</sup>
2	63 sputum isolates @ Christian Medical College Hospital (CMCH), Vellore	<i>Mycobacterium tuberculosis</i>	49% to Isoniazid, 35% to Rifampicin, 25% to Streptomycin.	Kenneth A et al. (2000) <sup>29</sup>

Table 2: (Continued)

S. No	Type, number and Location of Isolates	Name of the microorganism	Resistance rate %	Author and Year Reported
3	Single isolate @ CMCH, Vellore	<i>S. pneumoniae</i>	First confirmed isolate resistant to cefotaxime & erythromycin	MK Lalitha et al. (2002) <sup>39</sup>
4	30 Burn skin swab isolates @ Aligarh	<i>P. aeruginosa</i>	83.3% Multidrug-Resistant 56.7% to Amikacin	Shahid M et al (2003) <sup>31</sup>
5	1175 clinical isolates @AFMC, Pune	<i>Acinetobacter species</i>	69.7% Multidrug-Resistant, 77% to Sulphamethoxazole & Trimethoprim, 80% to Ampicillin 75% to Nalidixic Acid	K Lahiri et al. (2004) <sup>32</sup>
6	158 clinical isolates @Kolkata	<i>Aeromonascaviae</i>	53% to Nalidixic Acid & 30% to Ciprofloxacin	Sinha S et al. (2004) <sup>33</sup>
7	Clinical isolates collected between 1995-2001 @ New Delhi	<i>Staphylococcus aureus</i> <i>Escherichia coli</i> <i>Pseudomonas aeruginosa</i>	Increased from 55% (1995) to 90% for Penicillin, Increased from 55% (1995) to 82% (2001) for Amoxycylav, Increased from 20% (1995) to 49% (2001) for Amikacin	Wattal C et al. (2005) <sup>34</sup>
8	Clinical Isolates @Sant Parmanand Hospital, Delhi	<i>Escherichia coli</i> <i>Klebsiellaspp</i> <i>Pseudomonas.</i>	40% to Ceftriaxone 57% to Amoxicillin 63% to Amoxicillin	Subhash et al. (2006) <sup>35</sup>
9	61 isolates During the cholera epidemic @ Hubli	<i>Vibrio cholerae</i>	56% to Norfloxacin 47% to Ciprofloxacin	Krishna et al. (2006) <sup>36</sup>
10	9858 clinical isolates @ Delhi	<i>V.cholera</i>	96% to Furazolidone, Cotrimoxazole & Nalidixic Acid	Sharma NC et al. (2007) <sup>37</sup>
11	284 clinical isolates @ Kolkata	<i>metallo-beta-lactamase(MBL) producing bacteria</i>	43.3% to 7 Antibiotics (Ampicillin, Amoxicillin, Cephalexin, Ciprofloxacin, Cotrimoxazole, Erythromycin & Gentamycin)	Arora RS et al. (2007) <sup>38</sup>
12	2995 clinical isolates @ Lucknow	<i>Klebsiella spp.</i>	98% to Ampicillin, Ticarcillin & Piperacillin	Jain A et al. (2007) <sup>39</sup>
13	261 clinical isolates @ Pudukcherry	<i>Staphylococcus spp.</i>	72% to Oxacillin	Menezes GA et al. (2008) <sup>40</sup>
14	1300 isolates from nasopharyngeal swabs @ Nagpur	<i>MR-S.aureus</i>	4.16% to Methicillin	Chande CA et al. (2009) <sup>41</sup>
15	61 isolates from 176 clinical specimens @CMC, Vellore	<i>P. aeruginosa</i>	42.6% to Carbapenem	Manoharan A et al. (2010) <sup>42</sup>
16	83 clinical isolates @Mangalore	Community associated <i>MR-S. aureus</i>	93% to Penicillin & 31% to Erythromycin	Shenoy MS et al. (2010) <sup>43</sup>
17	180 clinical isolates @ Mangalore	<i>Enterococcal strains</i>	17 - 43% to Aminoglycosides	Adhikari L (2010) <sup>44</sup>
18	3984 clinical isolates @ AIIMS, Delhi	<i>Pseudomonas spp.</i> <i>Acinetobacter spp.</i> <i>Klebsiella Spp.</i> <i>E. Coli</i> <i>Enterobacter spp.</i>	50% to Carbapenems 66% to Aminoglycosides 76% to Fluoroquinolones 88% to third generation Cephalosporins	Behera B et al. (2011) <sup>45</sup>
19	3984 clinical isolates @ AIIMS, Delhi	Gram Positive <i>S.aureus</i> <i>staphylococci</i>	66% to Betalactamase inhibitor combinations 85% to Methicillin	Behera B et al. (2011) <sup>45</sup>
20	337 blood culture isolates @ Pondicherry	<i>Salmonella Typhi</i>	22% Multidrug Resistant 78% Nalidixic Acid Resistant	Menezes et al. (2012) <sup>46</sup>

Table 2: (Continued)

S. No	Type, number and Location of Isolates	Name of the microorganism	Resistance rate %	Author and Year Reported
21	1140 blood culture isolates @ NICU, Delhi	<i>Klebsiella spp.</i> <i>S aureus and</i> <i>E. coli</i>	72% to Ceftriaxone 63% to Meropenem 70% to Ciprofloxacin	Jyoti B et al. (2013) <sup>47</sup>
22	3771 blood culture isolates @ tertiary care hospital, North India	<i>E. coli</i> <i>Klebsiella spp.</i> <i>S. aureus</i> <i>Enterococcus spp.</i>	MDR, 96% to Ampicillin, MDR, 95% to Ceftazidime 100% to Penicillin 84% to Gentamicin <sub>120</sub>	Chand Wattal et al. (2014) <sup>48</sup>
23	92 isolates from circulating clones in Bangalore	<i>Staphylococcus aureus</i> (SA)	54% to Erythromycin 71% to Ciprofloxacin	C. Bouchiat et al. (2015) <sup>49</sup>
24	7131 blood culture isolates @Delhi Neonatal Infection Study	<i>Acinetobacter spp</i> <i>Klebsiella spp</i> <i>E coli</i>	High rates of multidrug resistance (40–81%) Emerging resistance to Colistin is observed (1%)	Agrawal R et al. (2016) <sup>50</sup>
25	18695 clinical isolates @27 states (including two UTs)	<i>Escherichia coli</i> <i>Enterococcus faecium</i>	85% to Fluoroquinolones 3% to Colistin 97% to Ampicillin 32% to Vancomycin	Gandra S et al. (2016) <sup>51</sup>
26	77 clinical isolates @ J.N. Medical College, Aligarh	<i>Staphylococcus aureus</i> <i>P. aeruginosa</i>	83% to Clindamycin 75% to Ofloxacin 79% to Cefepime 81% to Ofloxacin	Gupta R et al. (2017) <sup>52</sup>
27	1103 clinical isolates @ tertiary-care hospital in Eastern India	<i>Klebsiella pneumoniae</i>	45% Extensively drug-resistant 28% Pandrug-resistant 16% to Colistin 52% to Tigecycline	Mohapatra DP et al. (2018) <sup>53</sup>
28.	2499 clinical isolates @ multi-speciality ICU, Ludhiana	<i>Klebsiella spp</i> <i>Acinetobacter spp.</i>	9% to Colistin 60% to Cefoperazone 3% to Colistin	Sodhi K et al. (2019) <sup>26</sup>
29.	60 clinical isolates ocular infection @ Eye Institute, Bhubaneswar	<i>Serratia</i> <i>Marcescens</i> <i>Burkholderiacepacia</i>	13% to Colistin 11% to Colistin	Mitra S et al. (2020) <sup>27</sup>

## CHALLENGES OF AMR IN INDIA

India has been raised as ‘the AMR capital of the world’.<sup>54</sup> Whereas, development of newer multi-drug resistant (MDR) organisms posture newer diagnostic and therapeutic challenges, while India is still striving to combat old enemies such as tuberculosis, malaria and cholera pathogens, which became more and more drug-resistant. Factors such as poverty, illiteracy, overcrowding and malnutrition additional compound the situation.<sup>55</sup> Lack of awareness about infectious diseases in the common people and inaccessibility to healthcare frequently prevent them from seeking medical guidance. This, often, leads to self-prescription of antibiotics without any expert knowledge about the dose and duration of treatment.<sup>56</sup> Patients who seek medical guidance, many end up consuming broad-spectrum high-end antibiotics due to lack of appropriate diagnostic modalities for identifying the pathogen and its drug susceptibility. Low doctor to patient and nurse to patient ratios along with lack of infection

prevention and control (IPC) guidelines favour the spread of MDR organisms in the hospital settings.<sup>13,55</sup> Easy accessibility of over the counter (OTC) drugs,<sup>57</sup> additional contributes to antimicrobial resistance. Also, the increase in the pharmaceutical segment has triggered a corresponding increase in the amount of waste generated by these firms. With the absence of firm controlling and legal actions, this waste reaches the water bodies and serves as a continuous source of AMR in the environment.<sup>13,58</sup> Another important challenge is the use of antimicrobial agents as pesticides and insecticides in the agriculture industry, while the evidence for the same is inadequate currently.<sup>59</sup>

## CONSEQUENCES OF RESISTANCE

Antibiotic resistance had a great impact on health and wealth consequences. Increase in the resistance results in a decrease in the patient outcome and increase in the cost of pharmacy.

According to most recent study resistance developed patients had an increase in intensive care admission and long duration of stay in hospitals. There is also an increase in the mortality rate of the patients admitted with antibiotic resistance. Bacterial resistance makes the therapeutic dilemma to clinicians.<sup>15</sup> However, the rules for controlling the sale of antibiotics worldwide, but particularly in developing countries, are weak, thus making it necessary to establish more rigorous preventive actions to control the side effects of infections that are resistant to antibiotics (usually unnecessarily prescribed) or even multi-drug-resistance (MDR).<sup>60</sup> MDR, defined as antimicrobial resistance to at least one agent across three or more antimicrobial categories, results from one of two mechanisms.<sup>61</sup> Multiple genes accumulated by bacteria, each coding for resistance to a single drug within a single cell,<sup>62</sup> and increased expression of genes that code for multi-drug efflux points.<sup>63,64</sup> The prevalence of MDR has been reported as ranging from 4% to 20%, with higher prevalence in nosocomial infections. MDR affects both Gram-positive and Gram-negative bacteria, but therapeutic options are more limited for the latter. MDR is a major global public health concern, magnified by antibiotic overuse and unwarranted prescribing antibiotics. The use of inappropriate empiric antimicrobials increases the risk of MDR and mortality.<sup>7</sup>

Antibacterial drugs have been misused in humans for several decades, thereby creating ways for selection and spread of drug-resistant bacteria. Consequently, antibacterial drugs have become less effective or even ineffective, resulting in an accelerating global health security emergency that is rapidly outpacing the availability treatment options. WHO reports identify *Staphylococcus aureus* resistance to beta-lactam antibacterial drug methicillin as an international concern.<sup>65</sup> Excess usage of antibiotics has expedited the development of methicillin resistance in *S. aureus* (MRSA). Risk of death in patients infected with MRSA is as high as 26.3%. Antibacterial resistance by MRSA also causes additional medical costs for antibacterial therapy, medical care and additional cost variable.<sup>66</sup> MRSA strains identified four decades ago have become more problematic due to the evolutionary mechanisms adapted by the bacteria to evade antibiotics which are supported by environmental changes which aid the bacterial spread beyond the restrictions of health care facilities. Virulence conferred by these factors rendered the bacterium dominant resulting in making significant changes in the choice of antibiotics for the management of community-acquired infections.<sup>67</sup>

Compared with the abrupt contests of HIV/AIDS, tuberculosis, malaria, pneumonia, and many other communicable diseases, the loss of antibiotics at some future time does not capture the same consideration. Resistance in contradiction of certain antibiotics is already at high levels in certain places in India (and around the world), but the problem has persisted largely unidentified because comparatively few studies

were available and countrywide observation was not being carried out. But the issue came to the fore in India when New Delhi Metallo- $\beta$ -lactamase-1 (NDM-1), first reported in 2009, made front-page news in 2010<sup>5</sup>. Briefly, NDM-1 is an enzyme produced by the gene blaNDM-1; it is named for New Delhi because the Swedish patient in whom it was first identified had undergone surgery in a New Delhi hospital.<sup>68</sup> NDM-1 may be the most widely known form of antibiotic resistance in India, but several studies in recent years have documented significant rates of resistance to a wide range of antibiotics. Many are of hospital-acquired Gram-negative infections with *Acinetobacter*, *Pseudomonas*, *Klebsiella*, *E. coli* and *gonorrhoeae*.<sup>69,70</sup>

Comparable studies on the rise of antimicrobial resistance in gram-positive and gram-negative bacteria are reported also from India. The resistance array varies widely reliant on the type of the geographical location and health care setting, availability of antibiotics in hospitals and over the counter, prescribing habits of treating clinicians coming from different streams of medicine like allopathy, ayurvedic, homoeopathy or quacks. The drug resistance has been reported to develop in a population to an antibiotic molecule following its improper and irrational use. Irrespective of whether NDM-1 turns out to impend patients' health in India, the attention focused on this pathogen has encouraged the Government to act on antibiotic resistance. As an outcome, a Ministry of Health and Family Welfare task force declared a new national anti-microbial policy.<sup>71</sup>

## ANTIBIOTIC POLICY

The terms antibiotic guidelines and policy are frequently used interchangeably and may be unclear to many health-care professionals. An antibiotic policy is a set of ideologies to guide the execution of prudent and rational antimicrobial prescribing in the healthcare system. Antibiotic guidelines are detailed endorsements for antibiotic treatment or prophylaxis for particular infections, diseases or syndromes.<sup>72</sup> The antibiotic policy is the set of approaches and events commenced to establish the antimicrobial treatment in the hospital and reach health outcomes for patients. The straightforward ideologies are to be direct evidence-based medicine, local epidemiology and liberty for prescribing physicians. An antibiotic policy is now more mandatory than ever for clinical, epidemiological and economic reasons. The Infection Committee is responsible for the antibiotics policy in hospitals.<sup>73</sup> The primary aim of the hospital antimicrobial policy is to diminish the morbidity and mortality due to antimicrobial-resistant infection, and to preserve the efficiency of antimicrobial agents in the treatment and deterrence of communicable diseases. The antibiotic policy is fundamentally for prophylaxis, definitive and empirical therapy. The policy shall include detailed endorsements for the treatment



of diverse high-risk/special groups such as immunocompromised hosts; community-associated infections and hospital-associated infections. It ought to similarly set the stages for recommending antibiotics; for instance, first-choice antibiotics can be prescribed by all doctors while restricted choice antibiotics can only be prescribed after consulting the antimicrobial team (AMT) representative or the head of the department. Reserve antibiotics, conversely, are prescribed only by designated experts.<sup>74</sup>

### ATTRIBUTES OF ANTIBIOTIC POLICY

The policy should be simple, clear, clinically appropriate, flexible and pertinent to day-to-day practice and accessible in user-friendly presentation such as a pocket guide, web-based form, etc. The recommended antibiotic should be effective against pathogens often seen in that locality.<sup>72</sup> Guidelines should be provided for optimal selection, dosage, route of administration, duration, and alternatives for allergy to first-line agents; and for adjusted dosage for patients with impaired liver or renal function. Recommendation for prophylactic use should specify procedures for which antibiotic are needed, optimal agents, dosage, timing, route and duration of administration so that adequate antibiotic concentrations are available at the time of bacterial contamination. Prophylaxis recommendation should mainly focus on clean as well as contaminated procedures. The prophylactic dose is recommended for a short duration, free of side-effects, and should be relatively cheap. Also, the antibiotics selected for prophylaxis should not be used therapeutically; as this may lead to the emergence of antimicrobial resistance.<sup>74</sup>

It will take substantial effort, time and resources to formulate antibiotic policies and guidelines from the scratch in this situation. It is worthwhile to go through the other guidelines that are pertinent to the local condition in the hospital setting or country and adapt accordingly. A multidisciplinary antibiotic administration team can be set up to engrave the antibiotic policy and guideline in hospital and the team includes surgeons, physicians, paediatricians, clinical microbiologists and pharmacists.<sup>43</sup> And the policy should recommend the principles of antimicrobial stewardship, antibiotics for general use, reserved and restricted antibiotics; replacements for antibiotic use in case of allergy, guidance for the route of administration like intravenous to oral switch etc. Further, the guideline should also provide information on the disease/syndrome e.g. pneumonia; type of clinical setting – inpatient units, outpatient clinics, ICU setting; when to switch from IV to oral and measures for the finding of infection/syndrome. The policy and guideline should be clear, simple, appropriate to day to day practice, relevant to local clinical conditions and available in suitable formats. The antibiotic guidelines and policy are alive documents and consequently should be revised at regular intervals. They should be modernized con-

ferring to current medical information, medical practice and local circumstances.<sup>75</sup>

### HOSPITAL VERSUS NATIONAL ANTIBIOTIC POLICY

Generally, the hospital antibiotic policy should concur or align with the national antibiotic policy except for a few changes as warranted by the local antimicrobial resistance profiles. If there is a wide variation from national to hospital, and hospital to hospital then the desired purpose is defeated i.e., to minimize the morbidity and mortality due to antimicrobial-resistant infections; to preserve the effectiveness of antimicrobial agents in the treatment and to prevent microbial infections.<sup>74</sup> A national antibiotic policy should address all relevant issues for antibiotic use, both in the community and the hospital, including veterinary and agricultural use.

The National Policy for Containment of Antimicrobial Resistance - India covers a range of topics, including curbing antibiotic use in animals, particularly those raised for human consumption; conducting infection surveillance in hospitals; improving hospital surveillance for monitoring antibiotic resistance; promoting rational drug use through education, monitoring, and supervision; researching new drugs; and developing and implementing a standard and more restrictive antibiotic policy. Under the new Schedule H1 (now called HX), which will regulate antibiotic use, selling antibiotics over the counter will be banned. Certain antibiotics, including carbapenems, will be available at only tertiary hospitals.<sup>71</sup>

### IMPLEMENTATION OF ANTIBIOTIC POLICIES

Antibiotic policy contributes to the optimization of antimicrobial therapy, ensuring the proper use (indication, dose and duration) and minimizing side effects.<sup>76</sup> An adoption of these kinds of policies leads to a reduction in the prevalence of antimicrobial resistance, costs and save lives.<sup>77</sup> In 2015 Center for Disease Control and Prevention (CDC) published a report about core elements of hospital antibiotic stewardship programs.<sup>78</sup> According to CDC “there is no single template to optimize antibiotic usage”. The medical decision is complex and the antibiotic implementation policies should be flexible. Therefore, there is a need for defined leadership and coordinated multidisciplinary approach.<sup>78</sup> For ideal decision making in prescribing antibiotics, doctors essentially have adequate information about infectious diseases, infecting microbes, and antimicrobials. So, the leader of the program should be infectious disease expert or infectious disease professional should co-direct the program with a clinical pharmacist. Thus, the key members of an antimicrobial stewardship team are constituted.<sup>79</sup> For antimicrobial resistance investigation a clinical microbiologist, and the computer support an information system specialist is also needed.<sup>80</sup>



The infectious diseases physician or a clinical pharmacist with infectious diseases training has to have interactions with the prescriber physicians. They should perform a prospective audit and a feedback system, serving to reduce the inappropriate use of antimicrobials.<sup>79,80</sup>

In India, National Centre For Disease Control, under Directorate General of Health Services, Ministry of Health & Family Welfare, has formulated National Treatment Guidelines for Antimicrobial Use in Infectious Diseases in the year 2016 to combat emerging Antimicrobial resistance in India<sup>71</sup>, and the implementation in the hospital level is lagging. As per data available from NABH assessor's conclave most accredited hospitals, though having a well written antibiotic policy on paper, are not compliant in practice. And so far, no hospital is maintaining a separate register for the use of antibiotics up to the mark. In a recent study antibiotics usage in an intensive care ICU are more expensive that has to be concerned and there is a need to follow the guidelines to be followed in using them which clearly states that the policies and guidelines for antibiotics used in the country are not efficient practice. India, with more than 20,000 hospitals, more than a billion population, wide cultural diversity, socio-economic disparity, and a large medical community of more than three-fourths of a million doctors, will find the resistance problem an issue very difficult to tackle. Hence the government, policymakers and stakeholders should initiate the strategies to reduce the economic burden on the patient by developing and implementing the antibiotic policies in Indian healthcare settings like the primary, secondary and tertiary hospital to combat Antimicrobial resistance. To implement antibiotic usage as per the developed policies in India the national Action plan of the government should develop information, educate the physicians and the patients and training should be given on the usage of policies.

## CONCLUSION

In summary, the choice of suitable antimicrobial depends on an understanding of the prospective pathogens and local vulnerability patterns. In selecting the right antibiotics, the properties of the antimicrobials; such as Pharmacokinetics and Pharmacodynamic (PK and PD) profiles, mechanism of action and strength, permissibility and safety, are all important factors.<sup>81</sup> Initial suitable antibiotic treatment has been shown to reduce mortality, the span of stay in ICU and hospital. Early correct antibiotic chooses have also served to the reduction in antimicrobial costs.<sup>82</sup>In this reverence, it is emphasized that infectious disease specialist service being a professional in the arena, plays a significant part in improving antimicrobial usage, by advising on the judicious use of antimicrobial agents and by developing evidence-based guidelines under the light of antibiotic implementation policies.<sup>83,84</sup> Therefore it is essential to develop Antibiotic policy

in every Indian health care system and implement it properly by educating and training the infectious disease specialist. All hospitals must have an infection control committee (ICC) and an antibiotic policy and should initiate or augment efforts towards implementation. Those hospitals with an existing ICC and an antibiotic policy should augment efforts to increase compliance with the policy. Hospitals without a policy must initiate efforts to formulate an ICC and an antibiotic policy. The Government of India and respective state governments should take initiative to develop the antibiotic policy at every public care hospital to decrease the morbidity and mortality due to antimicrobial-resistant infection, and to preserve the efficiency of antimicrobial agents in the treatment and prevention of communicable diseases.

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