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Pharmaceutical Sciences **Review Article……!!!**

ALARMING TRENDS OF ANTIBIOTIC RESISTANCE IN INDIA: A REVIEW

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ABSTRACT

Antibiotic resistance may be defined as resistance of microorganism towards antimicrobial agents due to evolution by natural selection. The current trends of antimicrobial resistance in India are quiet pusillanimous. However, many initiatives have been taken towards eliminating this problem. A literature review was performed to review the current trends of resistance in India due to use and misuse of antimicrobials. Various research and review articles were studied to reach the overall results. Data from various researches performed in different hospitals regarding different bacterial strains and the antimicrobial agents to which they were resistant was also studied. Data on antimicrobial resistant strains was collected from research and review articles. Overall resistance trends in India were thus compiled. A complete literature survey was performed to arrive at the conclusions.

INTRODUCTION:

Antibiotic resistance is an alarming problem all over the world. Newer types of antibiotic resistance can cross international boundaries and spread between continents with ease. World health leaders describe antibiotic-resistant microorganisms as “nightmare bacteria” which means “pose a catastrophic threat” to people in every country in the world.[1] AMR results in decreased efficacy of antibacterial, anti-parasitic, antiviral and antifungal drugs, thus making the treatment of patients difficult, costly, or even impossible. The development of AMR is a natural phenomenon in microorganisms, and is accelerated by the selective pressure exerted by use and misuse of antimicrobial agents in humans as well as animals. WHO since many years has promoted the global monitoring of AMR and taken steps to raise awareness of the impending public health crisis it will cause. Among wide range of WHO initiatives, in 2001 the Global strategy for containment of antimicrobial resistance was published.[2] The prevalence of drug resistance limits the therapeutic options for treatment of infections, and contributes to the global specter of a post-antimicrobial era in which some of the most effective tools in the physician‘s desk including antibiotics, anti-tuberculosis and anti-malarial drug lose their effectiveness. [3-10]

WORLDWIDE TRENDS OF ANTIBIOTIC RESISTANCE

The recent worldwide estimates of global antibiotic resistance, published by the World Health Organization (WHO) in 2014, list *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus* as the three agents of greatest concern which are associated with both hospital- and community-acquired infections. In five of the six WHO regions, some countries reported *E. coli* resistance of more than 50% to fluoroquinolones and third-generation cephalosporins. *Klebsilla pneumoniae* resistance rates to third-generation cephalosporins are above 30% in most WHO member countries and exceed 60% in some regions (WHO 2014). MRSA resistance rates exceed 20% in all WHO regions and are above 80% in some regions (WHO 2014). *Streptococcus pneumoniae*, *nontyphoidal Salmonella*, *Shigella* and *Neisseria gonorrhoeae* were also identified as community-acquired infections of great global concern. High rates of resistance to first- and second-line drugs are already increasing reliability on last-resort drugs, such as carbapenems (WHO 2014). This report provides an overview of the best available data on antibiotic resistance rates worldwide, drawing from Resistance Map.[11]

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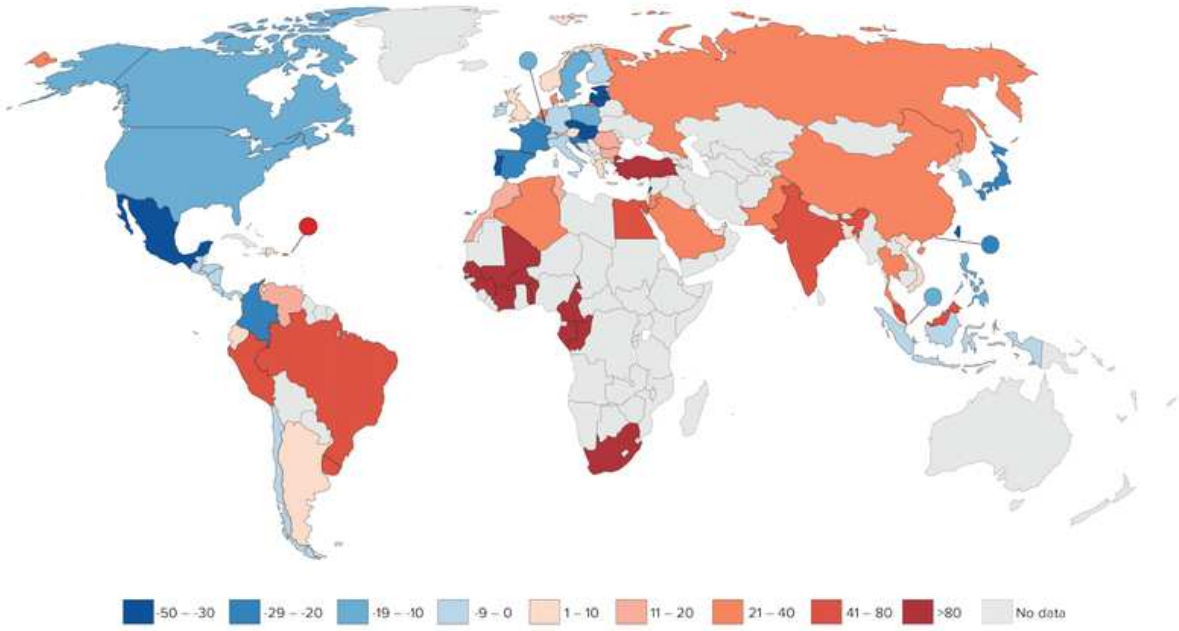

Figure 1: Percentage change in antibiotic consumption per capita, 2000-2010.

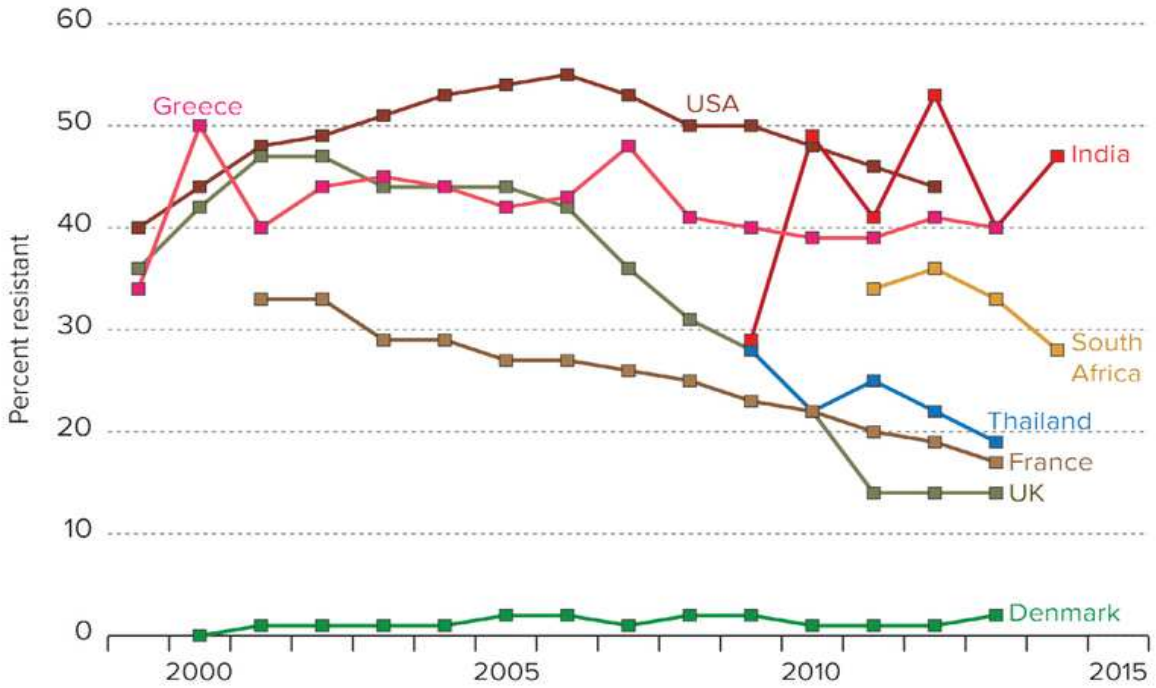

Figure 2: Percentage of *Staphylococcus aureus* isolates that are methicillin-resistant (MRSA) in selected countries, 1999-2014.

ANTIBIOTIC USE IN INDIA

Antibiotic use is a major driver of resistance. In 2010, India was the world's largest consumer of antibiotics for human health at 12.9 x 109 units (10.7 units per person). The next largest consumers

were China at 10.0 x109 units (7.5 units per person) and the US at 6.8 x109 units (22.0 units per person). Globally, the overall 76% increase of antibiotic consumption between 2000 and 2010 was attributable to BRICS countries, i.e., Brazil, Russia, India, China, and South Africa.[11] In BRICS countries, 23% of the increase in the retail antibiotic sales volume was attributable to India, and up to 57% of the increase in the hospital sector was attributable to China. Overall, ampicillin and co-trimoxazole use is declining in India (Fig. 3), while quinolone consumption is high and increasing in India. Rates of carbapenem use per capita are low com- pared to other antibiotics in 2000 but had risen to over 10 million standard units by 2010. Antibiotics continue to be prescribed or sold for diarrheal diseases and upper respiratory infections for which they have limited value.[12-13]

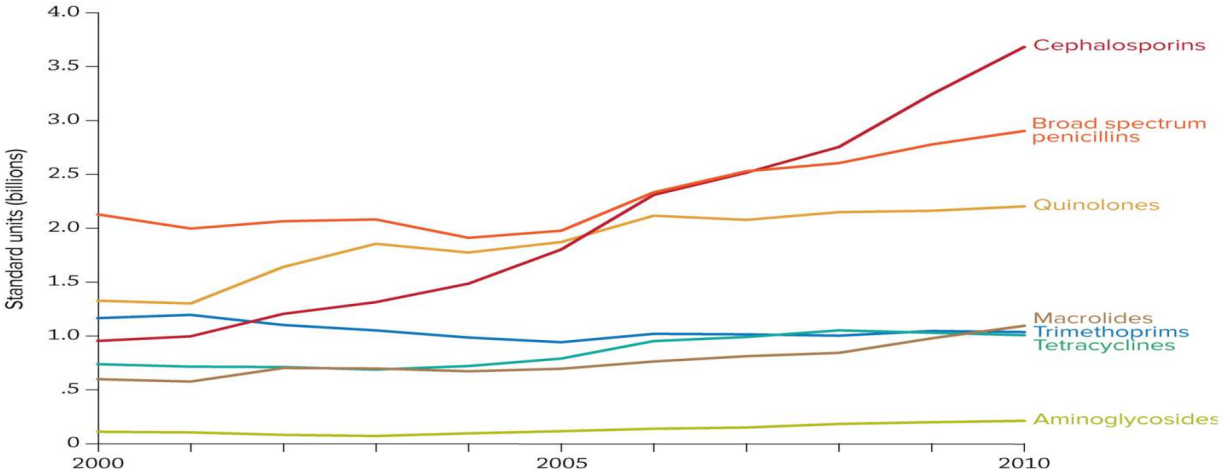

Figure 3: Trends in antibiotic consumption in India, 2000–2010.

ANTIBIOTIC RESISTANCE IN INDIA:

The crude infectious disease mortality rate in India today is 416.75 per 100,000 persons (author calculations based on World Bank data and the Global Burden of Disease, 1990 and is twice the rate prevailing in the United States when antibiotics were introduced (roughly 200 per 100,000 persons).[14-15] New Delhi data of resistance showed that, *Metallo-β-lactamase* (NDM) enzymes resistance first reported in 2008, are now found worldwide.[16] Multi-resistant *Enterobacteriaceae* due to the production of extended spectrum β-lactamases (ESBL) have become quite common in India. [17-18] In addition, different studies in South India highlighted the drug resistance pattern like multidrug resistant extended-spectrum β-Lactamase producing *Klebsiella pneumonia*, ciprofloxacin resistant s*almonella enteric* serovar *typhi*, emergence of vancomycin-intermediate resistant *staphylococci*, fluoroquinolone resistance among *salmonella* enteric serovar p*aratyphi A, pseudomonas aeruginosa* and *acinetobacter, and baumannii* resistant to ceftazidime, cefepime and ciprofloxacin.[19-23]

Surgical site infections are a problem and are predominantly related to gram-negative pathogens. A recent study from Mumbai reported a 1.6% rate of surgical site infections, with 66% caused by gram-negative bacilli (GNB) because of antibiotic resistance. This study also showed, 0.02-5.2% rate of surgical site infections, in year 2009, in one of tertiary-care hospital, New Delhi.[24] Resistance to fluoroquinolones among invasive *salmonella typhi* isolates in India has increased from 8% in 2008 to 28% in 2014. However, resistance in 2014 to two older antibiotics—ampicillin (5%), and cotrimoxazole (4%) is decreasing, possibly because of a decrease in consumption of these two drugs, and is much lower than rates of resistance to fluoroquinolones. Resistance to nalidixic acid in *S. typhi* is increasing (resistance is about 20%–30%) because of widespread use of other quinolones (not because of nalidixic acid use). Among *enterococcus faecium* isolates, 11% were vancomycin resistant.[12] In India, 10% of *E. coli* isolates were resistant to carbapenems in 2008, increasing to 13% in 2013. For *K. pneumoniae*, 29% were resistant in 2008, increasing to 57% in 2014 (CDDEP). Carbapenem resistance among *K. pneumoniae* increased from 2% in 2002 to 52% in 2009.[25] In India, *E. coli* resistance in pregnant women and schoolchildren to at least one antibiotic exceeded 40 and 60 percent, respectively. High levels of resistance were detected in *N. gonorrhoeae* isolates: although all were sensitive to ceftriaxone, nearly one-fourth were beta-lactamase producers. Resistance in *K. pneumoniae* to second, third, and fourth generation cephalosporins was in the 25 to 55 range in 2004–2005.[26]

Table.1: **Antibiotic resistance rates in India**

LOCATION (year published)	**Isolates**	**Organism**	**Resistance rates**
MVIDH. Delhi(2007) Kolkata (2007)	9858 stool samples 284 clinical isolates	*V. Cholera* *Metallo-beta-lactamase* (MBL) producing bacteria	96% to furazolidone, cotrimoxazole and nalidixic acid 43.3% were resistant to atleast seven antibiotics (ampicillin, amoxicillin, cephalexin, ciprofloxacin, cotrimoxazole, erythromycin, gentamycin)
Lucknow (2007)	2995 blood samples	*Klebsiella spp.*	ESBL producing Klebsiellaspp. Were 98.28% resistant to ampicillin, ticarcillin, piperacillin. Monobactam and cephalosporin resistance was also higher(>60%)
Puducherry (2008)	261 clinical isolates	*Staphylococcus isolates*	72.34 % of staphylococcus aureus were resistant to oxacillin
Nagpur (2009)	1300 nasopharyngeal swabs from school children	MRSA	4.16 % multiple drug resistance
CMS Vellore, various centres across	176 clinical specimens	*P. aeruginosa*	Among the 61% *P. aeruginosa* isolates , resistance to carbapenem was 42.6 %

India(2010)			
Puducherry (2010)	31 clinical samples	*K. Pneumoniae*	93.55 % multiple drug resistance and ESBL producer
Mangalore (2010)	83 CA-MRSA clinical isolates	Community associated methicillin resistant *staphylococcus aureus* strains CA-MRSA	92.8% were resistant to penicillin 31.32 % were resistant to erythromycin
Loknayak Hospital, New Delhi (2010)	83 isolates from OPD cases of pyoderma	CA-MRSA	9.6% multiple drug resistance
Mangalore (2010)	180 clinical samples	*Enterococcal strains*	16.67-42.86 % to aminoglycosides
Sikkim (2011)	291 clinical specimens 196 carrier screening nasal samples	MRSA	38.14 % in clinical specimens 20.92 % in nasal samples
Tertiary Trauma Centre of AIIMS, New Delhi (2011)	3,984 clinical specimens	Gram negative Pseudomonas *Acinetobactor Klebsiella E.coli Enterobacter* spp. Gram positive *S.aureus* Coagulase negative *staphylococci*	Overall resistance of gram negative organisms were 50% against carbapenems, 66% aminoglycosides, 76% fluoroquinolones, 88% third generation cephalosporins, 66% beta lactam beta-lactamase inhibitor combinations 58 methicillin resistant

DATA ON ANTIBIOTIC RESISTANT STRAINS

Methicillin-resistant *Staphylococcus aureus* (MRSA) -MRSA is a common pathogen for skin and soft tissue infections, severe bloodstream infections, and pneumonia. MRSA was once a predominantly hospital-acquired infection but in recent years it has been increasingly found in community-onset infections. In India, a steep increase in MRSA, from 29% of S. aureus isolates in 2009 to 47% in 2014, was recorded by a large private laboratory network.[10]

Extended-spectrum *Beta-lactamase* producers -Extended-spectrum beta-lactamases (ESBLs) are a family of enzymes, produced by gram-negative bacteria that confer resistance to some of the world's most widely prescribed. ESBLs can inactivate all penicillins and cephalosporins, including third-generation cephalosporins (e.g., ceftriaxone, cefotaxime, and ceftazidime) and monobactams (aztreonam). ESBL-producing enterobacteriaceae are of concern throughout Asia and are on the rise. In 2009 and 2010, 28% of all enterobacteriaceae from urinary tract infections in 11 countries were ESBL producers, and resistance to third and fourth generation cephalosporins ranged from 26 to 50% in those countries. ESBL-producing *E. coli* increased from 40 to 61% between 2002 and 2009 in one hospital in New Delhi.[9]

Carbapenem-resistant *Enterobacteriaceae* -Carbapenems are considered last-resort antibiotics, used for infections that are resistant to first, second and even third-line antibiotics. Infections with

carbapenem-resistant enterobacteriaceae (CRE) are increasingly reported from healthcare facilities, primarily in developed countries, but are also increasing in low and middle income countries. In India, 10% of *E. coli* isolates were resistant to carbapenems in 2008, increasing to 13% in 2013. For *K. pneumoniae,* 29% were resistant in 2008, increasing to 57% in 2014. Carbapenem resistance among *K. pneumoniae* increased from 2% in 2002 to 52% in 2009 in one tertiary care hospital in New Delhi.[15]

Antibiotic-resistant *Metallo-beta-lactamase*-1 - New Delhi metallo-beta-lactamase-1 (NDM-1) is a genetic element with multiple resistance genes which can be harbored by and transmitted between Gram-negative bacteria, originally identified in a Swedish patient returning from New Delhi, India, in 2008. NDM-1 is highly resistant to most antibiotics except polymyxins. *E.coli* and *Klebsiella spp*. carrying NDM-1 now account for the majority of carbapenem resistance in some countries from their original detection in 2008, NDM-1 carrying enterobacteriaceae have been identified in more than 70 countries in all regions. Initially, much of the global spread was attributed to travelers exposed through medical treatment or hospital stays in the Indian subcontinent and potentially the Balkans, but now, NDM-1 carrying organisms are being increasingly detected worldwide in cases unrelated to travel, suggesting local transmission. NDM-1 has also been identified in environmental samples from water sources in India, indicating that the gene is present in both community as well as hospital settings. [16]

Antibiotic-resistant *Neisseria gonorrhoeae* - Gonorrhea is a sexually transmitted infection, mainly of the reproductive tract, caused by the bacterium *N. gonorrhoeae.* It has developed resistance to several former first-line antibiotics, including sulfonamides, penicillins, tetracyclines, and fluoroquinolones. Currently, treatments of choice are third- generation cephalosporins (parenteral ceftriaxone and oral cefixime), the last remaining option for single-drug treatment.[12]

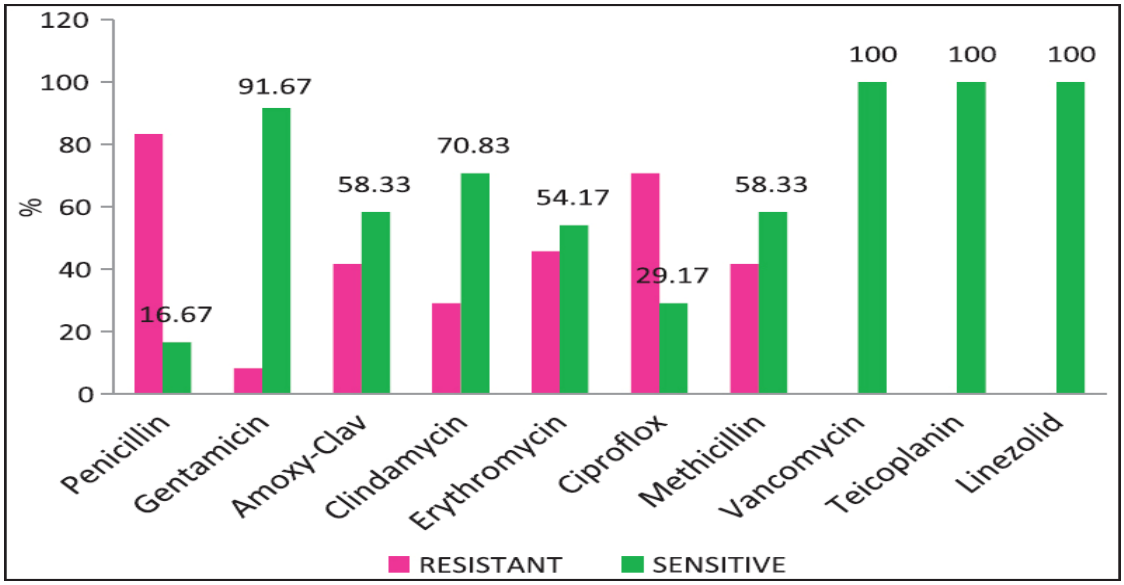

Figure 4: *Staphylococcus aureus* — susceptibility patterns

CONCLUSION

Illiteracy, cheap antibiotics available as over the counter drugs (OTC), compensation by pharmaceutical companies to the physicians for prescribing the antibiotic, etc. are all the major factors responsible for antibiotic resistance in India. Many organizations like World Health Organization, Antibiotic Resistance Partnership are doing efforts to combat this problem. The first important step to combat this alarming situation is implementation of Standard Treatment Guidelines (STGs) in all hospitals all over the country. Using limited amount of antibiotics and for their respective course will reduce the incidence of antibiotic resistance. Second step should be behavioral and social changes. Need of the hour is to maintain a clean and healthy environment to reduce the infections. Hospitals need to take care of sterilization and disinfection to reduce hospital acquired infections because most of the bacteria's transmitted through hospitals are resistant to antibiotics. Strict rules need to be laid down against the compensation given by pharmaceutical companies. Public awareness campaigns need to be set up to make the community aware about the drawbacks of over the counter use of antibiotics. India has become a hotbed for antibiotic resistance. Antibiotics are being sold on an alarming rate and so is the rate of antibiotic resistance. So need of the country is to prevent this threatening condition by a combined effort of all healthcare professionals.

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