Review Article

Antimicrobial resistance: Call for rational antibiotics practice in India

Shivani Chandra[1], P. P. R. Prithvi[1], K. Srija[1], Shalini Jauhari[2], Alka Grover[1]

[1]Amity Institute of Biotechnology, Amity University, Noida, Uttar Pradesh, [2]Starex University, Gurugram, Haryana, India

Abstract

It is a well-known fact that microorganisms are developing resistance to antimicrobial drugs present in the market that is known as antimicrobial resistance (AMR). This resistance in microbes is a great matter of concern among the scientific fraternity. This review article focuses on antibiotics and their respective resistant microbes, factors that cause resistance among microbes, and consequences of AMR at global as well as Indian scenario. This article would be a helpful resource in nutshell for making the ground for discovery of new antibiotics that will be more effective toward microbes.

Keywords: Antimicrobial resistance, antibiotics, antimicrobial resistance

Introduction

Day by day the medicines we know are becoming less effective because of the ability of microorganisms to resist the effects of the medications that were once used to kill them [Table 1]. This ability of the microorganisms is known as antimicrobial resistance (AMR) [Graph 1].[1] Because of this, the medications have become ineffective and the microorganisms persist for a longer time in the body, and the risk of the spread of the infections and diseases increases and threatens our ability to cure even the common infections. This may result in prolonged illness, disability, and even death [Graph 2]. And without effective antimicrobials, medical procedures and major surgeries also become very risky. In addition, AMR increases the cost of healthcare as stays in the hospitals will be longer and more intensive care will be required. The global health threats of AMR rose to a crescendo and is putting the gains of the Millennium Development Goals and Sustainable Development Goals at peril.[2]

Address for correspondence: Dr. Alka Grover, Assistant Professor, Amity Institute of Biotechnology, Amity University, Noida - 201 313, Uttar Pradesh, India.
E-mail: agrover@amity.edu

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Centers for Disease Control and Prevention (CDC), USA categorized antibiotic-resistant bacteria into three levels [Table 2]:

Concerning: Bacteria belonging to this classification have the threat of antibiotic resistance as "low." There may or may not be multiple options of therapeutics for the infections of bacterial resistance. These bacteria usually cause severe illness. To monitor these categorical threats, outbreak responses or rapid incidents are required.

Serious: These are significant threats. For various reasons like low or declining domestic incidences or reasonable availability of therapeutic agents, they may not be considered urgent but on a long run, the threats will worsen to turn urgent due to the lack of prevention activities and public health monitoring.

Urgent: The antibiotic resistance threats belonging to this category result in high consequences. Significant risks across various criteria have been attached to these bacteria. These might have the potential to be widespread due to lack of public attention that may identify infections and limit transmission.[16]

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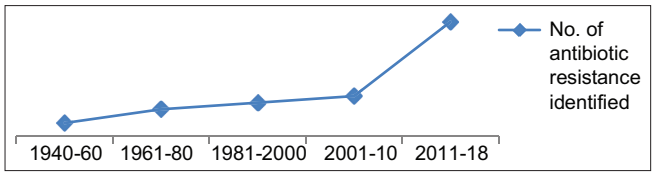


Graph 1: The number of microorganisms becoming antibiotic resistant is on a rise

Factors that Cause AMR

- Increase in AMR is linked with the amount of the antibiotic prescribed, number of doses missed, and inappropriate and unnecessary prescribing of antibiotics which happen maybe because sometimes patients insist physicians for antibiotics and the physicians prescribe them as they do not have time to explain why they are not needed[23,24]
- Lower antibiotic concentrations[25] and longer duration of treatment[26] contribute to the increase of AMR
- Underlying diseases in the healthcare setup such as mechanical ventilation and poor hygiene by hospital staff have also been associated with the spread of resistant organisms[27]
- AMR raise the crescendo when counterfeit medications with subtherapeutic concentrations of antibiotics are used[28]
- Some of the pharmaceutical companies release large amounts of antibiotics in the form of waste due to inappropriate wastewater treatment which eventually increases AMR[29]
- Antibacterial components[30] and antiseptics[31] may also be contributing to AMR
- Inappropriate use of antibiotics in animal husbandries is also found to be an underlying contributor to the emergence and spread of antibiotic-resistant microbes[32]
- Resistance toward antibiotics sometimes is also natural. These genes that gain resistance are called as environmental resistomes. These genes may be transferrable from non-pathogenic to pathogenic microbomes which may lead to antibiotic resistance[33]
- It has been found that heavy metals and other pollutants may also be contributing toward this global public health hazard.[34]

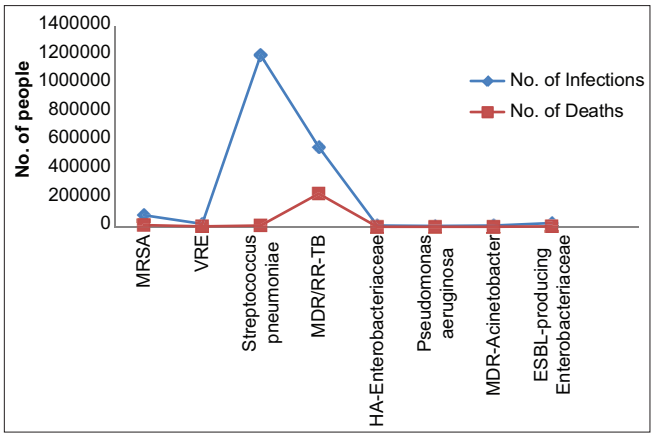
Global Overview of Antimicrobial Resistance

In U.S., at least 2 million people are infected with antibiotic-resistant bacteria, and at least 23,000 people die as a result every year [Table 3].[35] In the E.U., 33000 deaths due to antibiotic-resistant bacteria are reported every year.[6]

To combat AMR, new drugs are being made or combinations of already existing drugs are being used [Table 4].[37]

Indian Scenario

India also carries the burden of AMR, including the highest number of MDR-TB.[43] Antimicrobial-resistant microbes have also been found in various animals other than humans like cows, buffaloes, fishes, shrimps, shellfishes, crabs, etc., Even natural resources like water bodies are not safe as antimicrobial-resistant



Graph 2: The approximate number of infections and deaths caused by certain antibiotic-resistant microorganisms

bacteria and their genes have also been found in some of the water sources of India.[44]

In India, resistance toward fluoroquinolones, carbapenem, and colistin is found to be high among Gram-negative and Gram-positive bacteria [Table 5]. High resistance toward even the newer antimicrobials like carbapenems and faropenem has been reported.[45] Studies have reported high resistance toward fluoroquinolones and cephalosporinsins (third generation) pathogens such as *Salmonella typhi*, *Shigella*, *Pseudomonas*, and *Acinetobacter*.

It has been estimated that more than 50,000 newborns will die from sepsis due to pathogens being resistant to first-line antimicrobials. It is thought that neonates and elderly will be affected worse. It is estimated that more than two million deaths will occur in India due to AMR by the year 2050.[46] About 29% of isolated *S. aureus* in 2008 were methicillin resistant which by 2014, has reached 47%.[47] In addition, since 2011 MDR-yeast has also been reported in India. In another study conducted in 2015, researchers found AMR among *Enterobacter cloacae* and *Morganella morganii* in people residing in Burail, a semi-urban community in Chandigarh.[48] Around 17% to 75% of the *Vibrio cholera*e have been found to be resistant toward tetracycline.[44] Between 2004 and 2007, *E. coli* samples showed 73%, 59%, and 75% of rate of resistance to naladixic acid, co-trimoxazole, and ampicillin, respectively.[49] Also from 2008 to 2013, resistance of *E. coli* to cephalosporins (third generation) has increased from 70% to 83%, whereas resistance of fluoroquinolone has increased from 78% to 85%, and carbapenems resistance increased from 10% to 13%.[50]

From 2008 to 2014, the rate of resistance toward fluoroquinolones in *S. typhi* was found to be increased from 8% to 28%. In addition, *S. typhi* are becoming nalidixic acid resistant as use of other quinolones is increasing. But in 2014, the rate of *S. typhi* resistance toward ampicillin and co trimoxazole was found to be decreasing. 11% of the *Enterococcus faecium* isolates were found to be vancomycin resistant.[46] From 2002 to 2009, *K. pneumonia*

Table 1: Some of the recent occurrences of antimicrobial-resistant microbes and the antimicrobials they are resistant to

Microorganism	Antimicrobial Resistance toward	Year
Staphylococcus	Penicillin	1940
Shigella	Tetracycline	1959
Staphylococcus	Methicillin	1962
Pneumococcus	Penicillin	1965
Streptococcus	Erythromycin	1968
Enterococcus	Gentamicin	1979
Enterobacteriaceae	Ceftazidime	1987
Enterococcus	Vancomycin	1988
Pneumococcus	Levofloxacin	1996
Enterobacteriaceae	Imipenem	1998
Extensively drug-resistant tuberculosis (XDR-TB)	Isoniazid, Rifampicin, Fluoroquinolones, and many more of the three second-line injectable drugs.[3]	2000[1]
Staphylococcus	Linezolid	2001
Staphylococcus	Vancomycin	2002
Pan-Drug Resistant (PDR)- *Acinetobactor*	All Cephalosporins and inhibitor combinations, Fluroquinolones, Aminoglycosides, Carbapenems, Polymyxins.[4]	2004/05[1]
PDR-Pseudomonas	Penicillins, Cephalosporins, Carbapenems, Monobactams, Quinolones, Aminoglycosides, and Polymyxins.[5]	2004/05
Escherichia coli	Third-generation cephalosporin-resistant	2007[6]
Neisseria gonorrhoeae	Ceftriaxone	2009
Klebseilla pneumoniae	Carbapenem, Colistin	2009[7]
Staphylococcus	Ceftraroline	2011[1]
Neisseria gonorrhoeae	Azithromycin	2011[8]
Multi-Drug Resistant Tuberculosis (MDR-TB)	Rifamycin, Isoniazid, Pyrazinamide	2012[9]
Salmonella paratyphi	Ampicillin, Cefotaxime, Ceftazidime, Ceftriaxone, Nalidixic acid, Aztreonam, Trimethoprim/sulfamethoxazole	2013[10]
Escherichia coli	Carbapenem	2015[6]
Enterococcus faecalis	Vancomycin	2015[6]
Plasmodium falciparum	Artemisinin-based combination therapies (ACTs)	2016[11]
Salmonella typhi	Fluoroquinolones, Ampicillin, Chloramphenicol, Trimethoprim-sulfamethoxazole, Third-generation cephalosporins	2016[12]
New Delhi metallo-beta-lactamase (NDM) type carbapenemase-producing organisms (CPOs)	β-lactam antibiotics[13]	2017[14]
Clostridium difficile	Aminoglycosides, Lincomycin, Tetracyclines, Erythromycin, Clindamycin, Penicillins, Cephalosporins, Fluoroquinolones[15]	2017[14]

associated carbapenem resistance has significantly increased from 2% to 52%. In addition, the fluoroquinolone resistance had increased from 57% to 73%. However, the resistance rate of *K.* pneumoniae isolates toward cephalosporins (third generation) had decreased from 90% to 80%.[50]

A study found that 48% of the bacteria (Gram-negative) in the milk of buffalo and cow in West Bengal were detected to be extended spectrum beta lactamase (ESBL)producers and in Gujarat, 47.5% were oxytetracycline resistant.[51] Also among the bacteria (Gram-positive) isolated from the same milk samples, 2.4% of *S. aureus* in West Bengal were vancomycin resistant,[52] while in Karnataka, 21.4% *S. aureus* were MRSA.[53] In Maharashtra, 48% of the Enterobacteriaceae isolated from the fish gut of Tilapia were producing ESBL.[54] The rate of ESBL-producing Enterobacteriaceae in Odisha, Madhya Pradesh, and Punjab was found to be 9.4%, 33.5%, and 87%, respectively.[55] In Kerala, *Vibrio cholera* and *Vibrio parahaemolyticus* found in shrimps, crabs, and shellfish were found to be totally resistant to ampicillin, ceftazidime resistance also ranged from 67% to 96% but were found to be susceptible to chloramphenicol.[56] Another study showed the presence of MDR *Salmonella* species in Bihar and West Bengal being resistant to ciprofloxacin, gentamicin, and tetracycline.[55]

Antimicrobial-resistant microbes have been found in water sources too. All of the samples of *E. coli* isolated from Kaveri in Karnataka were found to be resistant toward cephalosporins (third generation).[57] The ground and surface water used for drinking along with recreational purposes in central India, Kashmir, Sikkim, and Hyderabad have been reported with 17%, 7%, 50%, and 100% rate of third-generation resistant *E. coli,* respectively.[57,-60] The rate of cephalosporin (third generation) resistant *E. coli* in domestic water alone, waste along with hospital effluent, and hospital effluent alone was found to be 25%, 70%, and 95%, respectively.[61] The ESBL producers were 17.4% among bacteria (Gram-negative) isolated from Yamuna and Ganga.[62]

Table 2: Categorization of antibiotic-resistant bacteria into three levels by Center for Disease Control and Prevention (CDC), USA.[16]

Category	Microorganisms	Antimicrobial Resistance toward
Concerning Threats	Vancomycin-resistant *Staphylococcus aureus*	Vancomycin
	Erythromycin-resistant Group A *Streptococcus*	Erythromycin
	Clindamycin-resistant Group B *Streptococcus*	Clindamycin
Serious Threats	Multidrug-resistant *Acinetobacter*	All cephalosporins and inhibitor combinations, Fluoroquinolones, Aminoglycosides[4]
	Drug-resistant *Campylobacter*	Fluoroquinolones[17]
	Fluconazole-resistant *Candida*	Fluconazole
	Vancomycin-resistant *Enterococci* (VRE)	Vancomycin
	Multidrug-resistant *Pseudomonas aeruginosa*	Imipenem, Ceftazidime, Ciprofloxacin, Tobramycin[18]
	Drug-resistant *Salmonella typhimurium*	Ampicillin, Trimethoprim-sulfamethoxazole, Chloramphenicol, Fluoroquinolones, Ceftriaxone, Azithromycin[19]
	Drug-resistant *Shigella*	Sulphonamides, Tetracycline, Chloramphenicol, Ampicillin, Co-Trimoxazole[20]
	Methicillin-resistant *Staphylococcus aureus* (MRSA)	Methicillin
	Drug-resistant *Streptococcus pneumonia*	Penicillin, Erythromycin, Trimethoprim-sulfamethoxazole, Tetracycline, Chloramphenicol, Fluoroquinolones[21]
Urgent Threats	*Clostridium difficile*	Aminoglycosides, Lincomycin, Tetracyclines, Erythromycin, Clindamycin, Penicillins, Cephalosporins, Fluoroquinolones[15]
	Carbapenem-resistant Enterobacteriaceae (CRE)	Carbapenem
	Drug-resistant *Neisseria gonorrhoeae*[16]	Sulfonamides, Penicillins, Cephalosporins, Tetracyclines, Macrolides, Fluoroquinolones[22]

Table 3: Deaths attributable to AMR by 2050

Continent	Number of deaths
Asia	4,730,000
Africa	4,150,000
Europe	390,000
North America	317,000
Oceania	22,000
South America	392,000[36]

Measures Taken to Overcome AMR

Some of the approaches for combating AMR are:

- Educating people about AMR.
- Educating people about the rational use of antimicrobials.
- Control of substandard and counterfeit antimicrobials.
- Inducements such as developing new vaccines and drugs.
- Usage of alcohol-based hand cleansers for hands.[63]
- 72 h after the symptoms resolve, antibiotics can be safely stopped.[64]
- Usage of antibiotics with short course along with regular reevaluation with the doctor is necessary. The course must be stopped if no signs of clinical infection are seen as most of the time individuals do not complete the full course.
- Increasing awareness among the nurses and other health care providers is necessary as they are in direct contact with the patients and eventually being responsible for infection spread or control of AMR.[65]
- The standards of drug advertising and promotions should be followed by pharmaceutical companies. Moreover, action toward pharmaceutical companies that encourage inappropriate use of antimicrobials should be taken.[66]
- Minimized antimicrobial usage in animals, improved sanitization along with the regulated provision of probiotics or supplements in vaccination and feed to control common animal diseases need to be administered.[67]
- Collective national and international academic networks are necessary to identify new categories of antibiotics along with diagnostic technologies.
- Providing incentives for the development of new antimicrobials to pharmaceutical companies.[66]

India

In 2013, surveillance networks of AMR were started by the Indian Council of Medical Research and in 2014, the National Centre for Disease Control also started an AMR surveillance network to know the approximate extent of AMR. In 2015, these two organizations along with CDC started assessing the already existing IPC practices in India to formulate new guidelines for preventing hospital-acquired infections.[68] The National Health Policy, 2017 calls for a rapid standardization of guidelines soliciting antibiotic use and limiting the use of antibiotics. In addition, OTC (over the counter) medications, banning or restricting the use of antibiotics as growth promoters in animal livestock, and pharmacovigilance including prescription audits inclusive of antibiotic usage in the hospital and community should be taken care of.[69] Other policies that were created to deal with AMR are as follows.

Table 4: Drugs that work and do not work on certain antibiotic-resistant microorganisms

Microorganism	Antibiotics that do not work	Antibiotics that work
MRSA	B-lactam antibiotics	Vancomycin, Teicoplanin, Daptomycin, Linezolid[38]
VRE	Vancomycin	Linezolid, Dalfopristin, Daptomycin, Tigecycline, Telavancin[39]
Streptococcus pneumoniae	Penicillin, Erythromycin, Trimethoprim-sulfamethoxazole[21]	PCV7, PCV13[40]
XDR-TB	Isoniazid, Rifampicin, Fluoroquinolones, and any of the three second-line injectable drugs	Fewer treatment options are available, and the drugs available are much less effective[3]
CRE	All or nearly all available antibiotics	Aminoglycosides, Polymyxins, Tigecycline, Fosfomycin, and Temocillin have been used with some success[41]
Pseudomonas aeruginosa	Aminoglycosides, Imipenem, Ceftazidime, Ciprofloxacin, Tobramycin	Polymyxins, β-lactam antibiotics, Carbapenems[18]
ESBL-producing Enterobacteriaceae	Penicillins, First-, second-, and third-generation cephalosporins, and Aztreonam	Carbapenem, Clavulanic acid[42]
Cephalosporin-resistant *Neisseria gonorrhoeae*	Cephalosporin, Fluoroquinolones, Tetracyclines, Penicillins, Macrolides	Extended Spectrum Cephalosporins (ESCs like-Cefixime, Ceftriaxone), Spectinomycin, Azithromycin.[22]
MDR-*Acinetobacter baumannii*	All penicillins and cephalosporins (including inhibitor combinations), Fluoroquinolones, Aminoglycosides	Colistin, Tigecycline[4]
Non-Typhoidal *Salmonella*	Ampicillin, Chloramphenicol, Co-trimoxazole, Sulphonamides, Tetracycline	Ciprofloxacin, Cefotaxime, Ceftriaxone, Cefoperazone, Aztreonam, Azithromycin[19]

Table 5: AMR microorganisms found in India and the antimicrobials they are resistant to

AMR Microorganisms	Antibiotic Resistance Toward
Escherichia coli	Third-generation Cephalosporins, Fluoroquinolones, Carbapenem, Ampicillin, Naladixic acid, Co-trimoxazole.[49,50]
Salmonella species	Ciprofloxacin, Gentamicin, Tetracycline, Ceftriaxone, Co-trimoxazole, Ampicillin, Nalidixic acid, Fluoroquinolones, Third Generation Cephalosporins. [46,55]
Vibrio cholera	Ampicillin, Tetracycline, Chloramphenicol, Ceftazidime.[44,56]
Vibrio parahaemolyticus	Ampicillin, Chloramphenicol, Ceftazidime.[56]
Staphylococcus aureus	Vancomycin, Methicillin.[47,52]
Shigella species	Ceftriaxone, Co-trimoxazole, Third Generation Cephalosporins, Fluoroquinolones, Azithromycin, Chloramphenicol, Ampicillin, Nalidixic acid[20]
Enterococcus faecium	Vancomycin[46]
Klebsiella pneumoniae	Carbapenem, Fluoroquinolones, Third-generation Cephalosporins.[50]
Acinetobacter baumannii	Fluoroquinolones, Third Generation Cephalosporins.[46]
Pseudomonas aeruginosa[44]	Fluoroquinolones, Third Generation Cephalosporins.[46]

National Antimicrobial Resistance Policy, India

In 2011, national policy on AMR has been introduced. The objective of this policy is to increase awareness in the emergence of AMR and the factors influencing it. In addition, to establish programs such as antimicrobial rationalized usage and to provide incentives to develop new effective antimicrobial drugs, this policy came into act. This policy concentrates on three categories such as sentinel surveillance, point prevalence, and comprehensive surveillance. Some of the action plans included in the policy are as given below:[70]

- To establish surveillance system of AMR
- Prevention of infections along with respective control measures
- To increase awareness of rational antimicrobial use in all stakeholders.

National Action Plan on Antimicrobial Resistance (NAP-AMR)

The objective of NAP-AMR is to combat AMR and contribute to tackle this global health threat. This policy will help establish and strengthen governance mechanisms and volume of stakeholders to decrease the aftermath of AMR in India. The extent of NAP-AMR primarily emphasizes on resistance in bacteria.

The objectives of the NAP-AMR are:

1. To define the strategic priorities, key actions, outputs, responsibilities, and indicative timeline and budget to slow the emergence of AMR in India and strengthen the organizational and management structures to ensure intra- and inter-sectoral coordination with a One Health approach;
2. To combat AMR in India through better understanding and awareness of AMR, strengthened surveillance, prevention of emergence and spread of resistant bacteria through infection prevention and control, optimized use of antibiotics in all sectors, and enhanced investments for AMR activities, research, and innovations; and
3. To enable monitoring and evaluation (M and E) of the NAP-AMR implementation based on the M and E framework.

The NAP-AMR has outlined six strategic priorities to tackle this public health challenge and these are to be implemented over 2017–2021. The first 5 strategic priorities of NAP-AMR are aligned with the Global Action Plan on AMR and the sixth strategic priority highlights India's role in the containment of AMR at the international level and at subnational/state level to ensure action at the ground level. The focus areas of the six strategic priorities of NAP-AMR are:

1. Improve awareness and understanding of AMR through i) effective communication and IEC resources to raise awareness among all stakeholders, including policymakers, general public, and farmers, and ii) education and training to improve the knowledge and behavior of professionals.
2. Strengthen knowledge and evidence through surveillance by strengthening laboratories for evidence-informed policy-making in human, animal, food, and environment sectors. And by surveillance of AMR for evidence-informed policy-making in human, animal/food, and environment sectors.
3. Reduce the incidence of infection through effective infection prevention and control in- i) Healthcare to reduce the burden of infection, ii) Animal health/food to reduce the spread of AMR and antimicrobials through animals and food and, iii) Community and community environment to reduce the spread of AMR and antimicrobials in the community and environment.
4. Optimize the use of antimicrobial agents in health, animals, and food with the help of i) Regulations, access, and surveillance of antimicrobial use to ensure rational use without affecting access to antimicrobials, ii) Antimicrobial stewardship in healthcare to optimize the use of antimicrobials in humans, and iii) Animal health, agriculture to optimize the use of antimicrobials in animal and food sectors.
5. Promote investments for AMR activities, research, and innovations by i) New medicines and diagnostics to ensure availability of effective diagnostics and drugs to treat infections, ii) Innovations to develop alternative approaches to manage infectious diseases, and iii) Financing to ensure sustainable resources for containment of AMR.
6. Strengthen India's leadership on AMR with i) International collaborations to ensure India's contributions toward global efforts to contain AMR, ii) National collaborations to facilitate collaborations among vertical disease control programs and national stakeholders, and iii) State level collaborations to ensure action at the ground level against AMR.[71]

Conclusion

One of the most important statistics in the public health sector is that of AMR. The statistical overview of the drug-resistant microbes helps in enhancing people's knowledge along with helping with discovering new antimicrobials. Different policies give broad guidelines on how to combat the microbes from developing resistance. As mentioned in the review, microbes belonging to different generations which are classified on the basis of bacterial strains of a genus developing resistance are increased in both global and Indian scenario. Hence, to provide insight, this review holds great importance to the respective statistics.

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Conflicts of interest

There are no conflicts of interest.

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