Review Article

Antimicrobial resistance: Causes and impact on public health in developed and developing countries

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ABSTRACT

Antibiotic-resistance (AR) has become an alarming issue, posing threats to public health in terms of mortality and economic loss. The drivers of AR include environmental contamination from varied sources, ultimately making its way into our drinking water and food. Other factors include reckless use of antibiotics by the uneducated health workers, unhygienic situation of the hospitals, overconsumption and careless discharge of medicines by the general populace, injudicious use of antibiotics in the livestock, and indiscriminate disposal of untreated pharmaceutical wastes into the municipal water have caused several health hazards, such as "AR in infants," respiratory disorders, and cancer. Furthermore, the sewage treatment process itself augments the antimicrobial resistance crisis. Hence, it is an alarming issue which must be taken care at the global level as well as the national level.

KEY WORDS: Antimicrobial Resistance; Antibiotic-resistance; Drivers; Alarming Issue; Hospitals; General Populace; Pharmaceutical Wastes; Infants; Global; National; Health Hazards

INTRODUCTION

The effective antibiotics treatment which has relieved men and animals from disease prognosis is now under threat. The unprecedented arrival of "superbugs" and antimicrobial resistance (AMR) is a burning issue of the present times, as it has escalated the morbidity rates to 700,000 per year in India. By 2050, another 10 million people are projected to face death due to AMR alone.[1] Hence, the mortality rates due to AMR alone are more than cancer and road accidents together.[2] Furthermore, AMR plays a pivotal role in reducing the gross domestic product by 2–3.5%, with a decline in livestock by 3–8%, costing USD 100 trillion to the world.[3] Not only India, but the threatening situation is prevailing throughout the world, though India is the worst victim of the situation, as she was the largest consumer of antibiotics until 2010.[4,5] Hence, our Government of India has sanctioned projects like the National Action Plan[1] to check the alarming AMR crisis, though more projects are needed to be sanctioned to eliminate the crisis situation. As AMR is known to enhance the mortality rates in across the world, the World Health Organization has announced AMR as an urgent priority area.[6] World leaders are also concerned and sincere efforts are being made to eradicate the common enemy at the earliest.

As for the containment and eradication of AMR, joint efforts by the medical professionals, health workers, environmentalists, and agriculturists are highly solicited. Hence, each of the contributors to crisis, including environmental sector, medical sector, pharmaceutical industries, and agricultural sector, must be given due weightage.[1]

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PATHWAYS OF ANTIBIOTIC-RESISTANCE GENES (ARG_S) AND BACTERIA LEADING TO ENVIRONMENTAL CONTAMINATIONS

ARG and AR bacteria (ARB) contaminate the air and water soil through various sources such as hospitals, pharmaceutical industries, livestock, aquaculture, and by means of anthropogenic activities.

Due to infected patients and nosocomial infections, ARGs and ARBs occur in the air-flow systems of the hospitals and also in the effluent water from the hospitals.[7-10] It is thus observed that the hospitals contribute to 33% of the ARBs.[10,11]

Pharmaceutical industries too, serve as an important bank for the ARBs and the ARGs. Improper discharge of partially or untreated pharmaceutical industries' wastewater and expired drugs adds the ARBs and the ARGs to the municipal sewage.[12]

General populace too, adds the moieties to the municipal sewage by means of urination, stools, or by other anthropogenic activities including the discharge of expired medicines through the washroom basin.[10,13]

In the water treatment plants, although the biological and physicochemical processes reduce the pathogenic load, remove nitrogen and phosphorus, yet the ARBs and the ARGs are not reduced, amplifying the AR crisis.[10,14,15] To add to the problem, during floods as the municipal sewage contaminate the surface water and groundwater (in India), the moieties find their ways into the water we use. Furthermore, the air adjoining the treatment plants also carries aerosols containing the ARBs and ARGs.[10,16]

As antibiotic injections are administered to the cattle and poultry for profuse growth, their manure carrying the dangerous ARBs[17,18] is applied to the agricultural fields as fertilizers. Hence, the soil gets contaminated and agricultural run-off contaminated the surface and groundwater.[10,19,20]

Aquaculture contributes to the crisis as antibiotics are directly added to the pens and due to evolution, the ARBs and ARGs are often evident in the open waters and sediments.[10,21,22]

DRIVERS OF AR ACROSS THE WORLD

There are various reasons for the development of AR in the world. In developing countries, the following is the factors for AR development:

a. Lack of monitoring of resistance development

Developing countries lack information on AR, for example, the data revealed[23] that out of 194 countries, only 129 had evidence on AR, of which only 22 countries had the complete data on all 9 infection – AR combinations, posing threat worldwide.[23-25]

b. Inferior quality of available antibiotics

Expired drugs in which the active ingredient is lacking are often sold at a cheaper rate in developing countries. Again, many developing countries lack quality assurance mechanisms to ensure the high quality of the pharmaceutical drugs, for example, a report from Nigeria in 2006 revealed that 25–40% of ampicillin/cloxacillin antibiotic formulations were of inferior quality.[25,26]

c. Clinical misuse of antibiotics

It is observed that the medical practitioners in private clinics often overprescribe antibiotics, more than the public sector, for example, a report from a study in Mumbai, India (2010), revealed that out of 63 different drugs prescribed by 106 private practitioners, only six drugs were appropriate for the tuberculosis patients.[25,27] Again, especially in the developing countries, physicians often prescribe drugs without diagnosing the disease at the molecular level.[25]

d. Easy accessibility of antibiotics

In many countries of Asia, Africa, and Latin America, antibiotics are readily available without prescription.[25,28] Again, self-medications and prescriptions given by unskilled health workers have contributed to the excessive use of antibiotics, for example, a report on antibiotics usage in Minya, Egypt, revealed that 81% of pharmacists prescribe antibiotics for cold.[25,29] Furthermore, illiteracy rates and unqualified pharmacists in especially rural areas, often aggravate the problem, for example, a study on rural Bangladesh, revealed that out of 2000 participants, 95% medications were from local pharmacies while 8% were from physicians.[25,28]

In developed nations, the following are the main reasons behind AR crisis:

a. Travelers from developing countries and economically compromised people of developed nations

Travelers from the developing countries often carry ARBs and ARGs to the developed nations.[3,25] Uninsured individuals and those belonging to below poverty line, get antibiotics from unreliable sources, even in countries like the United States.[25]

b. Self-medications

Self-medications and sharing of medications prescribed for other individuals pose a big threat.[25,30]

c. Inferior regulations on the usage of antibiotics in hospitals

Nosocomial infections, intimate interactions between patients, excessive use of antibiotics, improper hygiene, and sanitary conditions are the major causes behind drug-resistant bacterial infections.[25,31]

d. Excessive antibiotic administration in food-producing animals

A report by the Food and Drug Administration (FDA) on food-producing animals in 2013 revealed that the sale of

antibiotics increased by 26% from 2009 to 2015.[32] Hence, a huge amount of antibiotics is being administered in the animals and these enter our bodies through the meat and meat products. This can lead to outbreak of resistant diseases.[25,33]

e. Regulatory barriers and lack of antibiotics research

Finally, the lack of encouragement for antibiotics research and regulatory barriers has stopped the discovery of novel and potential drugs. As researchers lack economic incentives and pharmaceutical companies are reluctant to invest on antibiotics research, new drugs with innovative mechanisms are lacking. Furthermore, regulations of the FDA have barred the companies from such type of research.[25]

AR CRISIS: THE INDIAN SCENARIO

a. Reasons for high morbidity rates due to AR

AR crisis has caused high mortality rates in India. There are several mounting evidence and reason, which have contributed to this nuisance situation.

Until 2010, India was the world's largest consumer of antibiotics, as she consumed 10.7 units per person.[5,4] Over-prescribed antibiotics by the practitioners, poor hygiene and sanitary conditions in hospitals,[5,34] easy availability of antibiotics without proper prescription (often given by unskilled health workers),[25] high contamination of the soil, air and water due to discharge of untreated pharmaceutical wastes into the environment (no laws for the pharmaceutical companies to discharge their waste),[12] and antibiotic administration in food-producing animals[10,18] are the pivotal causes behind high AR in India.

b. Case Studies

i. In 2008, New Delhi metallo-β-lactamase (NDM) enzyme, first reported in New Delhi, India, is now evident worldwide[5,35]
ii. Between 2004 and 2007, *Escherichia coli* was isolated. It showed high resistance to antibiotics such as ampicillin (75%), nalidixic acid (73%), and co-trimoxazole (59%)[5,36]
iii. Again, *Salmonella typhi* isolates in India were found to be resistant to fluoroquinolones and the percentage of resistance enhanced from 8% in 2008 to 28% in 2014[5]
iv. While treating surgical infections related to Gram-negative bacteria, it was observed that the resistance to colistin was on rise, when it was used for the treatment[5,37]
v. Furthermore, 54.8% of methicillin-resistant *Staphylococcus aureus* (MRSA) were isolated from clinical samples.[5,4]

MULTIDRUG-RESISTANT (MDR) BACTERIA IN KOLKATA (WEST BENGAL) GANGA WATER

In the Ganges water of Kolkata, MDR bacteria and MDR genes are very much prevalent. MDR bacteria and MDR genes such as β-lactamases (blaTEM, blaCTX-M, blaOXA, and blaNDM-1), acetyl-, phospho-, and adenyl-transferases (aacC1/A2, aphA4, and aadA2) as well as mcr, tet, acr, and mexAB/CD/EF types drug efflux genes have been found in the water of the Ganges. Isolated superbugs from the Ganges water are also resistant to advanced drug derivatives such as imipenem, colistin, amikacin, linezolid, vancomycin, ceftriaxone, and lomefloxacin.[38]

Furthermore, studies conducted by Newcastle University (U.K) and IIT-Delhi in 2014 have shown that the superbugs are 60 times more during the months of pilgrimage (May and June) than at other times. Samples were taken from seven sites (Ganga water and sediments) along the Ganges, at different seasons, for this purpose of investigations.[39]

Thus, our Indian Government has sanctioned a project worth Rs. 9.3 crores, to check the AR throughout the entire stretch of the Ganga river.[39]

AR IN RIVER MAHANADI

E. coli isolates from river Mahanadi were found to be resistant to beta-lactam antibiotics, carboxypenicillin coupled with b-lactamase inhibitor, glycopeptides, carbapenems, macrolides, and until the fourth generation of fluoroquinolones cephalosporins. The isolates of *E. coli* also exhibited resistance against indigenously used antibiotics with multiple AR indices 0.51–0.90. This indicates a ferocious situation, posing an escalating danger to the public health.[40,41]

AR IN RIVER THAMES, LONDON

ARB are found in the river Thames (London, U.K) due to the dumping of sewage in the river. This has raised an alarm among the scientists of the University of Warwick that if the bacteria became very resistant, it could lead to untreatable infectious diseases.[42]

SEWAGE TREATMENT PROCESS AUGMENTS AR

Activated carbon added during the water treatment process drives AR transferability. Such AR is observed in MDR coliforms conferring resistance to ampicillin, sulfaguanidine penicillin, 2-sulfanilamide pyrimidine, tetracycline, chloramphenicol, neomycin, and streptomycin.[41,43] Hence, this kind of treatment process must be checked, to reduce the severity of the situation.

ANTIMICROBIALS BELOW MIC SPREAD AR

Susceptibility and resistance of microbes toward antibiotics are governed by measuring the minimum inhibitory concentration (MIC).[44] Studies conducted[45] have shown that antibiotics present below their MICs in nature often induce horizontal transfer causing the spread of AR. This shows that the presence of antimicrobial residues in nature is deleterious for the public health.

AR IN NEONATES

Newborn babies become victims to AR by acquiring the AR from the environment and mothers' milk. Environment has played the pivotal role in AR. Hence, in the gastrointestinal tract of the newborn babies up to 1 year age, several ARBs and ARGs are found. Representative ARGs including *tet*(M), *ermB*, *sul2*, and *bla*TEM were detected in the neonates. Furthermore, in this case, the ARBs carrying the ARG include *Enterococcus* spp., *Staphylococcus* spp., *Klebsiella* spp., *Streptococcus* spp., and *E. coli*/*Shigella* spp. Skin-related ARBs are also found in the mothers' milk.[46]

AR IN THE AGRICULTURAL SECTOR (LIVESTOCK)

Antibiotics are being profusely used in livestock, which include cattle, poultry, and aquaculture. Antibiotics are commonly administered into the animals for growth ("Feed efficiency") and disease prevention, that is, for nontherapeutic uses. They are also used for therapeutic uses, that is, to treat the diseases.[47]

AR in Cattle

Low-cost antibiotic residues such as ampicillin, tetracycline, gentamycin, and penicillin have been detected in milk samples, as per the study conducted by National Dairy Research Institute. Again, the use of beta-lactams and streptomycin has been found in milk samples, to treat the dairy cattle disease – mastitis.[48,49]

The frequent use of these antibiotics in cattle has been the drivers of AR in not only cattle but also men as he consumes the milk and meat of the cattle.

Case studies of AR in cattle

1. Calves with diarrhea, carrying Shiga toxin-producing *E. coli*, manifested a very high level of AR in Gujarat and Kashmir Valley[50,51]
2. Cows suffering from mastitis have been observed to be co-infected with MDR bacteria, which showed resistance to antibiotics such as ampicillin, carbenicillin, and oxacillin[52,53]
3. Bovine and caprine milk samples have been detected with vancomycin-resistant *S. aureus*.[54]

AR in Poultry

ARB conferring a very high level of resistance has been isolated from poultry animals and seafoods. Recent studies have shown that broiler farms harbor more drug-resistant bacteria than layer farms.[49] Hence, this ARB ultimately find their ways into the human digestive system, thereby causing AR to humans.

Case studies of AR in poultry

1. *Staphylococcus* and *Pasteurella multocida* poultry isolates have shown 100% resistance[55]
2. *Salmonella* detected from egg samples conferred resistance to multiple groups of antibiotics[56,57]
3. *E. coli* and MDR are more prevalent in broiler farms (94%) than layer farms (60%)[55]
4. Extended-spectrum beta-lactamase producing *E. coli* was more prevalent among broiler chicken (87%) than layers (47%).[55]

AR in Aquaculture

In fish-breeding too, the antibiotics are directly administered in the pens, contaminating the water and open sediments. Hence, the resistant varieties are very much prevalent among the different varieties of aquaculture, causing deleterious effects in humans.

Case studies of antibiotic – resistance in aquaculture

1. In Mangalore, two-thirds of the fish and shellfish samples, contaminated with *Salmonella*, were found to be resistant to two antibiotics and one-fourth of the samples were resistant to three or more antibiotics[58]
2. In coastal Southern India, 90% of *Vibrio cholerae* isolates were resistant to ampicillin, penicillin, and streptomycin while two-thirds of the samples were detected to be resistant to bacitracin.[59]

WATER CONTAMINATION BY PHARMACEUTICAL INDUSTRIES

Contamination of water by pharmaceutical drugs is an upcoming burning issue across the globe, though India is still reluctant to act over the problem. Still, some researchers in India have investigated about the said contamination and evidences have been reported.

a. Laboratory – based quantification of pharmaceutical drugs in freshwater and wastewater samples

Specific extraction methods such as high-performance liquid chromatography (HPLC), HPLC coupled with mass spectrometry, and HPLC coupled with tandem mass spectrometry have detected the presence of pharmaceutical residues at concentrations of µg/L to ng/L, in various water samples.[12]

b. Detection of pharmaceutical residues in drinking water

Several research groups[60] have revealed the presence of pharmaceutical residues in freshwater samples in sufficient concentrations. Drugs such as norfloxacin, ciprofloxacin, metoprolol, and citalopram have been detected in the lakes, rivers, and wells of Hyderabad region of India.[12]

c. Consequences of pharmaceutical pollutants on water quality

The pharmaceutical residues in water have affected the pH, temperature and have raised the total dissolved solids, biochemical oxygen demand, and chemical oxygen demand in the industrial effluents of different parts of India including Mumbai and Bengaluru.[12]

d. Health hazards related to pharmaceutical water pollution

Water pollution through pharmaceutical residues causes various diseases directly such as respiratory disorders, cancers, reproductive problems, chronic depression, and congenital problems including mental retardation and physical abnormalities.[12] Especially the release of EDCs (endocrine-disrupting chemicals) has caused male sterility, birth defects, breast, and testicular cancer.[61] Genotoxic effects, such as DNA damage, have also been observed in individuals.[62,63] Recent studies have shown that countries such as India and China are promoting AR superbugs. These superbugs are known to enhance the morbidity rates by converting the curable illnesses such as gonorrhea, tuberculosis, and pneumococcal pneumonia into deadly ones.[64]

e. Impact of pharmaceutical water pollution on agriculture and livestock

Indirectly, pharmaceutical water pollution has caused a decline in crop productivity and has caused the morbidity of live stocks and fishes in huge numbers.[12]

Thus, detailed investigations pertaining to pharmaceutical water pollution are required to safeguard the health of mankind and all other biotic entities in nature.

CONCLUSION

As AMR crisis has become a dreadful issue, causing loss to life and property, immediate attention of all strata of the society, especially the State Government bodies and Indian Government, is highly solicited. It is a great challenge and to diminish this "common enemy," one health concept is put forth. According to this concept, an interrelatedness exists among human health, animal health, food, and environment.[1] Hence, professionals from all these sectors must join hands and create an "inhibition wall" against our "common enemy," i.e., AMR, to save our lives, making a better tomorrow.

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