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REVIEW ARTICLE

Scoping Report on Antibiotic resistance in India

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ABSTRACT

Antimicrobial resistance (AMR) is a cause for global concern due to the current and potential impact on global population health. However, in developing countries like India, recent hospital and some community based data showed increase in burden of antimicrobial resistance.AMR may create patient burden, and onward effects to healthcare system or society, occurs when procedures that utilise antimicrobials to reduce the risk of post-intervention adverse events (such as surgical procedures utilising prophylactic antibiotics) are performed less frequently due to AMR increasing the risk of adverse events. The present review describes that antimicrobial resistance in India and mechanism of AMR, factors affecting the AMR. Recent data from Google search, Medline and other sources were collected which was reviewed and analyzed by the authors. Hospital based studies showed higher and varied spectrum of resistance in different regions while there are limited number of community based studies at country level. The aims of the mapping exercise are to understand the current situation of AMR, with particular focus on ABR in India, and to identify the current research gaps to determine the future research priorities in India.

Keywords: Antimicrobial resistance (AMR), Patient, Hospital, India, Healthcare system

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CONTENTS

1. Introduction

Antimicrobial resistance (AMR) is a major public health problem globally. While all types of AMR are concerning, antibacterial resistance (ABR) is seen as currently posing the most serious health threat. Bacteria are present everywhere, including in every living being and in the soil, water, and air. With the interconnected ecosystems (humans, animals, the environment), the exchange of bacteria is continuous, and thus the ABR problem is no longer limited to medical science alone. It requires effective collaboration among several disciplines. Considering the complex nature of the ABR problem, no individual nation has the capacity to address this major public health problem independently. In response, the United Kingdom and India came together to fight against AMR in November 2016 with a new £13 million UK-India research program. The goal of this initiative was for the UK and India to conduct collaborative research across multiple disciplines to come up with comprehensive and creative solutions to overcome AMR. As the first step, the Department for Biotechnology (DBT), government of India, in partnership with Research Councils United Kingdom (RCUK) decided to undertake mapping of AMR research in India. The aims of the mapping exercise are to understand the current situation of AMR, with particular focus on ABR in India, and to identify the current research gaps to determine the future research priorities in India[1].

The discovery of antibiotics in the 1940s revolutionized medical care and had an enormous impact on human and animal health. The role of antibiotics expanded from treating serious infections to preventing infections in surgical patients, protecting cancer patients and promoting growth and preventing disease in livestock and other food animals. However, several bacterial organisms have become resistant to more than one antibiotic, and resistance to last-resort antibiotics is increasing. Declining antibiotic effectiveness has risen from being a minor problem to a major societal threat, regardless of a country's income or the sophistication of its healthcare system[2].

Causes of Antibiotics Resistance:

- Over prescribing of Antibiotics
- Patients not finishing their Treatment
- Over use of Antibiotics in livestock and fish farming
- Poor infection control in Hospitals and Clinics
- Lack of hygiene and poor sanitation
- Lack of new antibiotics being developed

2. Mechanisms of Antibiotic resistance

Emergence of resistance among the most important bacterial pathogens is recognized as a major public health threat affecting the humans worldwide[3].

Inactivate Drug:

A. Particularly to penicillins and cephalosporins
B. Cleavage by β – lactamases (penicillinases and cephalosporinases)
C. β-Lactamases produced by various organisms have different properties
Staphylococcal penicillinase: Inducible by penicillin and secreted into medium

Modify Drug Target in Bacteria:

A. Mutation in penicillin-binding proteins
B. Replace alanine with lactate in peptidoglycan
C. Mutation in catalase-peroxidase
D. Mutation in protein in 30s ribosomal subunits
E. Mutation in DNA gyrase
F. Mutation of RNA polymerase

Export of Drug from Bacteria:

Tetracyclines:

Failure of drug to reach an inhibitory concentration inside the bacteria. Due to plasmid – encoded processes that either reduce uptake of the drug or enhance its transport out of the cell.

Sulphonamides:

Resistance is mediated by 2 mechanisms: Plasmid-encoded transport system that actively exports the drug of the cell and chromosomal mutation in the gene coding for the target enzyme dihydropteroate synthetase, which reduces the affinity of the drug.

3. Antibiotic resistance situation in India

Healthcare delivery in India:

Healthcare services in India are delivered by both public and private sector. The public healthcare system is a three-tier structure, divided into primary, secondary, and tertiary care services. All services at public facilities, including preventive care, diagnostic services, and outpatient and inpatient hospital care, are delivered free of charge. Medications that are part of the essential drug list, including antimicrobials, are free, while other prescription drugs are purchased from private pharmacies. Although public healthcare services are available to all citizens, poor quality of services and severe shortages of staff and supplies force individuals to seek private care. There was a steady decrease in the use of public hospitalization services between 1995 and 2014 in both urban and rural areas. In India, the total number of doctors, nurses, and midwives is 11.9 per 10,000 population, which is half the World Health Organization (WHO) benchmark of 25.4 workers per 10 000 population[4,5].

Resistance rates in humans by bacterium:

India has some of the highest antibiotic resistance rates among bacteria that commonly cause infections in the community and healthcare facilities. A recent national-scale laboratorybased study and data from the newly established Indian Council of Medical Research (ICMR) AMR surveillance network1 showed high levels of resistance to first-line and broad-spectrum antibiotics among various bacteria isolated from bloodstream infections. Resistance to the broadspectrum antibiotics fluoroquinolones and third-generation cephalosporin was more than 70% in *Acinetobacter baumannii*, *Escherichia coli*, and *Klebsiella pneumoniae*, and more than 50% in *Pseudomonas aeruginosa*. The proportion of resistance to the carbapenem class of antibiotics, considered to be one of the lastresort agents, was very high among these four gram-negative bacteria. Approximately 70% of A. baumannii, 57% of K. pneumoniae, more than 40% of P. aeruginosa, and more

than 10% of E. coli were carbapenem resistant. Unfortunately, resistance to colistin, which is the last-resort antibiotic in human medicine, also emerged in these four organisms[6]. A high proportion of antibiotic resistance was also observed in *Neisseria gonorrhoeae*, which is a major cause of sexually transmitted infection.

One study in the regional reference laboratory comparing the antibiotic resistance of N. gonorrhoeae between 2002–2006 and 2007–2012 showed that ciprofloxacin resistance increased from 78% to 89.7% and azithromycin resistance increased from 0.8% to 1.5%. Although resistance to ceftriaxone was not detected, decreased susceptibility to ceftriaxone was observed, and this percentage increased from 0.8% in 2002–2006 to 1.5% in 2007–2012[7,8].

Carbapenemases:

The carbapenem class of antibiotics is one of the last-resort antibiotics to treat serious gram-negative infections in humans. Carbapenemases are beta-lactamase enzymes produced by bacteria and are capable of neutralizing various classes of antibiotics, including penicillins, cephalosporins, monobactams, and carbapenems, making them ineffective when administered. Infections arising from carbapenemaseproducing bacteria are difficult to treat, as there are limited therapeutic options, and treatment options vary by individual carbapenemases. In India, New Delhi metallo-beta-lactamase-1 (NDM-1), or blaNDM-1, has been the predominant gene encoding for carabpenem resistance in Enterobacteriaceae, and blaKPC is not frequently detected.

Colistin resistance:

Colistin is considered to be the lastresort antibiotic in human medicine. With increasing use of colistin for treatment of carbapenem-resistant gram-negative bacterial infections, colistin resistance has emerged in India. In a single center study, bloodstream infections due to dual carbapenem- and colistin-resistant K. pneumoniae were associated with 69.3% mortality among Indian patients. However, the presence of plasmid mediated colistin resistance genes mcr-1 and mcr-2 was not detected frequently. So far, only one study has reported the presence of the mcr-1 gene in *E. coli* isolated from the urine sample of a hospitalized patient[9].

Neonatal infections due to antibiotic-resistant bacteria:

Antibiotic-resistant bacterial infections are increasingly reported among neonates. A review of bloodstream infections among neonates and children between 2000 and 2015 in India showed that the most common pathogens isolated were *S. aureus and Klebsiella species*. Among the S. aureus isolates, 50% were *methicillinresistant S. aureus* (MRSA), and 63% of Klebsiella species were thirdgeneration cephalosporin resistant. In a recent prospective cohort study conducted between 2011 and 2014 in three neonatal intensive care units (NICUs) in New Delhi, *Acinetobacter species* and *Klebsiella* species were found to be the two most frequent organisms isolated in neonatal sepsis cases. In this study, 82% of the Acinetobacter species and 54% of the Klebsiella species were MDR, defined as resistant to three or more antibiotic classes. However, the most concerning issue is that 78% of Acinetobacter species and 35% of the Klebsiella species were carbapenem resistant[10].

Antibiotic Resistance in Food Animals:

The use of antibiotics in food animals plays a major role in human health, as antibiotic-resistant bacteria can be transmitted between humans and animals through contact, in food products, and from the environment. The same antibiotics used to treat human infections are commonly used in animals, raising the concern about diminishing the effectiveness of these agents at the expense of human health. With a rise in incomes, there has been an increase in the demand for animalderived protein in India. From 2000to 2030, it is expected that poultry consumption will increase by 577% in India. Similarly, India is the largest producer of milk and second-largest producer of fish, and this production continues to increase (State of Indian Agriculture 2015–16). This is leading to intensive farming with increasing reliance on antibiotics in place of improving hygiene and sanitation. Although a limited number of studies were conducted in food animals, high levels of antibiotic-resistant bacteria were identified[11].

Antibiotic-resistant bacteria in poultry

In a recent study involving 18 poultry farms, 1,556 isolates of E. coli obtained from cloacal samples of 530 birds were tested for susceptibility to 11 antibiotics. Resistance profiles were significantly different between broiler and layer farms. Broiler farms were 2.2 times more likely to harbor resistant E. coli strains than layer farms. Increased prevalence of ESBLproducing strains was observed in broiler farms (87% compared with 42% in layers). Broiler chickens are bred for meat; they grow rapidly and live for less than eight weeks before they are slaughtered. The high resistance in broiler chickens indicates increased use of antibiotics either for growth promotion or for prophylaxis to prevent infection during their short lifespan. Two other studies showed that the proportion of ESBL-producing E. coli in poultry was 33.5% and 9.4%, respectively. Few studies examined for the presence and antibiotic susceptibility of Salmonella species in chicken meat samples and in samples from healthy chickens and their environment. In one study, the prevalence of Salmonella species in chicken meat samples was 7%, and they were 100% resistant to erythromycin but 100% sensitive to ciprofloxacin. In a second study, the prevalence of Salmonella species in chicken meat samples was 23.7%, and they were 100% resistant to ampicillin, moderately sensitive to ciprofloxacin, and highly sensitive to ceftriaxone. A study by Samanta et al. (2014) found that the prevalence of Salmonella species in healthy chickens and their environment was 6.1%, and they were 100% resistant to ciprofloxacin, gentamicin, and tetracycline. In another study, the prevalence of Salmonella species was 3.1%, and they were moderately resistant to various antibiotics[13,14].

Antibiotic Resistance in the Environment:

Antibiotic Resistance in the Environment With the interconnectedness of ecosystems, the role of the environment, particularly water, in the spread of antibiotic-resistant bacteria is increasingly gaining attention (Andremont and Walsh 2015). Antibiotic-resistant bacteria along with antibiotic residues are increasingly

contaminating the environment through ineffective industrial effluent and sewage management and subsequently recontaminating humans and animals through drinking water and food. The national water quality monitoring results from 1995 to 2011 indicate gradual degradation in water quality, with increasing bacterial contamination in critical water bodies across the country (CPCB 2013). Accordingly, published studies, although limited in number, indicate high levels of antibiotic-resistant bacteria and antibiotic resistance genes (ARGs) in various water bodies.

4. Factors Driving Antibiotic Resistance

Antibiotic consumption in humans:

Based on antibiotic sales data, in 2014, India was the highest consumer of antibiotics, followed by China and the United States. However, the per capita consumption of antibiotics in India is much lower than in several other highincome countries. Why are resistance rates high in India? Some possible reasons for the high ABR rates are discussed in this section[15].

High consumption of broad-spectrum antibiotics:

Broad-spectrum antibiotics are those that are effective against a wide range of disease causing bacteria, in contrast to narrow-spectrum antibiotics, which are effective against specific families of bacteria. Broad-spectrum antibiotics are generally prescribed empirically when there is a wide range of possible illnesses and a potentially serious illness would result if treatment were delayed. However, unnecessary use of broad-spectrum antibiotics leads to increased prevalence of MDR bacteria. From 2000 to 2015, cephalosporin and broadspectrum penicillin consumption increased rapidly, whereas narrowspectrum penicillin consumption was low and decreasing[16].

Use of broad-spectrum antibiotics, particularly third-generation cephalosporins, has increased considerably. Between 2000 and 2015, the proportion of third-generation cephalosporins among the total antibiotics increased significantly, while penicillin consumption remained constant and the use of fluoroquinolones decreased. This increased use of thirdgeneration cephalosporins is consistent with the high prevalence of thirdgeneration cephalosporin-resistant E. coli in India.

Increasing faropenem consumption:

With the increasing prevalence of community-acquired and healthcareassociated third-generation cephalosporin-resistant bacterial infections, penem and carbapenem consumption increased in India. However, the consumption of faropenem , which is an oral penem, a broad-spectrum antibiotic, increased 150% between 2010 and 2014. In India, faropenem is approved for treatment of a variety of common infections, including respiratory tract, urinary tract, skin and soft tissue, and gynecological infections. The sharp increase in use of faropenem is of concern because of the potential for cross-resistance to carbapenems. At present, susceptibility testing against faropenem is not routinely performed in microbiology laboratories due to a lack of guidelines from the Clinical & Laboratory Standards Institute (CLSI) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST). There is currently a lack of understanding regarding the resistance situation and selection potential of faropenem with carbapenems[16].

Antibiotic fixed-dose combinations:

Antibiotic fixed-dose combinations (FDCs) are combinations of two or more active antibiotics in a single dosage form. Antibiotic FDCs should be prescribed when the combination has a proven advantage over single compounds administered separately in therapeutic effect, safety, or compliance. However, in India, antibiotic FDCs are heavily prescribed even without the knowledge of a proven advantage over single compounds. In 2012, about 15% of total drug sales were attributed to dual antiinfectives.2 Lack of diagnostic precision due to unavailability of diagnostic laboratory services has led to increased use of antibiotic FDCs in India. Injudicious use of antibiotic FDCs could lead to emergence of bacterial strains resistant to multiple antibiotics. Approximately 118 antibiotic FDCs are available in India. These FDCs include dual oral broad-spectrum antibiotics such as third-generation cephalosporins and last-resort antibiotics such as linezolid. The following are some of the common FDCs available in India: Azithromycin-cefixime,cefixime-ofloxacin, cefixime-levofloxacin, cefixime-linezolid, Azithromycin-levofloxacin[17].

5. Recommendations for Future Studies

This mapping exercise indicates that AMR research studies in India were of limited scope in all areas, including humans, animals, environment, and others. In humans, the majority were retrospective single-center surveillance-based studies examining the prevalence of phenotypic resistance and molecular characterization of resistance for various pathogens. Animal studies were confined to examining resistance profiles of bacteria isolated from food animals; studies examining the frequency of antibiotic use and reasons for use during animal rearing were absent. Similarly, environmental studies were confined to examining resistance profiles of bacteria or antibiotic resistance genes isolated from various water bodies.

Novel agent studies were limited to in vitro experiments, and none of them progressed to clinical evaluation. Studies concentrating on comprehensive understanding of molecular mechanisms of emerging resistance among various pathogens were lacking[18,19]. A limited number of studies focused on new diagnostics and interdisciplinary studies. Studies categorized as “one health” were merely surveillance studies looking at the resistance proportion in various bacteria isolated from humans, animals, and the environment. Studies examining the impact of various policies were also lacking. The following research in various categories is urgently needed in India:

Humans:

- Understanding transmission mechanisms by which antibiotic resistance spreads in hospitals and in the community

- Developing and studying the impact of various antimicrobial stewardship activities and infection control measures in healthcare facilities with varying resources and in the community
- Examining the impact of behavioral interventions on antibiotic use in healthcare settings and in the community
- Developing methods for communicating the issue of antibiotic resistance to the general public and healthcare workers and studying their impact on antibiotic use
- Focusing on the burden of antibiotic resistance in various groups (neonates, children, young adults, the elderly) in the community and in various levels of healthcare settings

Animals:

- Conducting large-scale studies on surveillance of antibiotic resistance in food animals
- Conducting large-scale studies on antibiotic use for various purposes (growth promotion, prophylaxis,Animals treatment) among food animals, especially in poultry
- Understanding the social aspects of antibiotic use in food animals and subsequent behavioral interventions à Studying variations in antibiotic use in different farming practices, such as industrial and backyard farming

Environment:

- Studying the extent of environmental antibiotic pollution through pharmaceutical industrial waste (wastewater, solid waste and air) in various parts of India
- Developing standards and detection tools for antibiotic residues in pharmaceutical industrial effluents
- Examining acquisition of antibiotic-resistant bacteria during religious mass gatherings in rivers
- Focusing on waste management to reduce the contamination of rivers during religious mass gatherings

6. Conclusion

The present review concluded that scoping report on various antibiotics study in india. In every year increasing the rate of antibiotic resistance, different kind of situations like over usage of antibiotics, improper sanitation and some other health problemsare produce the antibiotic resistance in humans.There is an urgent need to developand strengthen antimicrobial policy, standard treatment guidelines and national plan for containment of AMR in India.Information Education Communication activities with monitoring and evaluation of the existing health care delivery system for both health care providers and consumers to improve drug use, should be undertaken simultaneously.

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