**COMBATING ANTIMICROBIAL RESISTANCE – A ONE HEALTH APPROACH**

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**History and Concept:**

In the 19th century, Rudolf Virchow, MD, (1821-1902), the “Father of Pathology” stated that “between animal and human medicine there are no dividing lines–nor should there be.” It was Calvin W. Schwabe, DVM, MPH, ScD (1927-2006) who coined the term One Medicine in his textbook Veterinary Medicine and Human Health in 1965 following which the concept of One Health came.

The primary goal of One Health is to achieve optimal health and sustainability for humans, animals, and the environment all at the same time. Outbreaks of emerging infectious diseases, risks and benefits of companion animals, water and food security and safety, socioeconomic and cultural environments, **antimicrobial resistance**, environmental contamination, climate change, and biodiversity, habitat loss, and human encroachment into wildlife are some global challenges for the twenty-first century that should be addressed using this approach.(1),(2)

**Roderico H Ofrin,** WHO India’s representative, discussed the role played by WHO in tackling antimicrobial resistance in India **in an interview with DownToEarth.** Addressing this public health issue, he emphasized that it requires a collaborative, multi-sectoral and transdisciplinary ‘One Health’ approach at the local, regional, national, and global levels. The engagement of sectors outside human health — such as animal health, food, agriculture, and environment — had been a challenge that is slowly being addressed through the ‘One Health’ collaborations on AMR. To address the complex multi-factorial public health challenge of AMR, WHO India has been working with all health partners, including the India offices of the Food and Agriculture Organisation (FAO) and the United Nations Environment Programme (UNEP).

**Antimicrobial resistance (AMR)-A global threat:**

AMR is a complex, multifaceted problem that threatens human and animal health. As per Review on Antimicrobial Resistance, two important steps to reduce unnecessary use of antimicrobials in agriculture and their dissemination into the environment are – to improve global surveillance of drug resistance and to reduce antimicrobial consumption in humans and animals. In that review, it is also mentioned that if current trends continue, there might be up to 10 million annual AMR-related fatalities from a variety of infections by the year 2050. In the year 2016, the United Nations dedicated their 71st General to address the issue of AMR. The members of the house-made a resolution and emphasized that inappropriate use of antibiotics in human health, animal health, agriculture & livestock, food, and aquaculture as the main cause of AMR. Moreover, that resolution recognised AMR as an urgent issue that needed to be addressed with utmost urgency around the world. (3),(4)

One major challenge to combat AMR is understanding the true burden of resistance, particularly in locations where surveillance is minimal and data are not available. (5)Understanding the gravity of the problem, the World Health Assembly has adopted the Global Action Plan on AMR in the year 2015 as a part of the tripartite collaboration with World Health Organization, Food and Agricultural Organization, and World Organization for Animal Health. India’s National Action Plan (NAP) for AMR was released in April 2017 by the Union Ministry of Health and Family Welfare. The objectives of the NAP include improving awareness, enhancing surveillance measures, strengthening infection prevention and control, research and development, promoting investments, and collaborative activities to control AMR.(6)

**Threat of AMR spreading through Triad of environment, animals, man:**

The important One Health factors of global AMR distribution include intensive food production, globalization of food distribution, international travel (e.g., the spread of drug resistance genes), changing climate, increased population density or growth, and urbanization. The global burden of ABR is plausibly associated with excessive use of antibiotics in animals (food, pets, aquatic) and humans, antibiotics sold over the counter, increased international travel and trading, migratory birds, refugees, climate change, poor sanitation/hygiene, and the release of non-metabolized antibiotics or their residues into the environment.

 As per a review approximately 80% of marketed antibiotics in the USA are used either as growth supplements or to control animal infections. The global map of antibiotic use estimated the use of 63 151 tonnes of antibiotics in livestock in 2010. (7) In India, antibiotics are widely available without a prescription, resulting in indiscriminate use. In the absence of genuine drug laws and law enforcement, the distribution of counterfeit or inferior antibiotics by unscrupulous companies also contributes to growing resistance.

 Newer antimicrobials require more research and development. It is necessary to develop novel treatments while maintaining the efficacy of old ones. Furthermore, resistant microbes and genes proliferate widely throughout the environment and food chains. Coliform contamination of piped water in Asia is among the greatest in the world, with antibiotic resistance genes found in numerous of the region's drinking water supply systems. Antibiotics used indiscriminately in cattle and aquaculture for treatment and growth enhancement has accelerated the emergence and spread of foodborne antibiotic resistant pathogen.(9) The interdependence of human, animal, and environmental characteristics is crucial for the containment of AMR, according to the One Health concept. AMR surveillance only in hospital is not sufficient to contain antimicrobial resistance.

Introduction of antibiotics in treatment radically changed the preconditions for the evolution and spread of resistance by providing unprecedented selection pressures, especially on members of the microbiota of humans and domestic animals, but also in environments heavily polluted with antibiotics. This selection pressure has promoted the mobilization and horizontal transfer of a large range of antibiotic resistance genes (ARGs) to many bacterial species, particularly to those causing disease. The development of antibiotic resistance is a natural phenomenon that is encoded by the ARGs of microorganisms and is the product of billions of years of evolution. Bacteria in the environment already carry ARGs that aid in the development of resistance to newly approved antibiotics long before the first clinical use of the antibiotics. The three key components of AMR are antibiotics, antibiotic-resistant bacteria (ARB), and antibiotic resistance genes (ARGs), all of which are considered emergent pollutants. The three key components of AMR are antibiotics, antibiotic-resistant bacteria (ARB), and antibiotic resistance genes (ARGs), all of which are considered emergent pollutants. The three key components of AMR are antibiotics, antibiotic-resistant bacteria (ARB), and antibiotic resistance genes (ARGs), all of which are considered emergent pollutants.

The environment is now widely recognised for its role in the rise and global spread of antibiotic resistance due to the extensive presence of antibiotics, antibiotic resistant bacteria, antimicrobial resistant genes (ARGs). The pooling and proliferation of ARGs through aquatic environment and their transfer to clinically relevant bacteria is well documented, with several studies linking clinical isolates of multidrug-resistant pathogens to environmental water bodies and continued emergence of new highly resistant bacteria. Antibiotic resistance genes (ARGs) have been recognized as emerging pollutants that are widely distributed and accumulated in most of aquatic environment.

Majority of publications have focused on the inappropriate use of antimicrobial drugs for human and animal health, AMR caused by the environment has mostly gone unnoticed so far. What complicates matters is that, among the determinants of AMR, the contribution of the environment differs greatly across different geographical locations of the world.

Escherichia coli, the most common Gram-negative bacteria, has developed different resistance mechanisms, making treating infections difficult. Colistin is considered a last-resort drug in the treatment of infections caused by E. coli. Plasmid-mediated mobile-colistin-resistant (mcr) genes in E. coli are considered a major public-health threat. Humans, chickens, and pigs being the main reservoirs for E. coli, a meta analysis published in 2022 highlights about the findings in two groups; community-based which involved isolates from healthy humans, chickens, or pigs, and clinical studies which involved only hospital, outpatient, or laboratory isolates. Prevalence of mcr-mediated colistin-resistant E. coli (mcrMCRE) was 6.51% as reported in 54 countries on five continents; Asia reported the major diversity of mcr-variants (eight of nine, except mcr-2). Worldwide, chickens and pigs proved to be the principal reservoir of mcr with an estimated prevalence of 15.8% and 14.9%, respectively. Healthy humans and clinical isolates showed a lower prevalence with 7.4% and 4.2% respectively. This knowledge can be used to reduce the incidence of zoonotic transmission by implementing the appropriate control programs.(8)

In the year 2010 a study was conducted in New Delhi and Cardiff. In the study, 171 seepage samples and 50 tap water samples from New Delhi and 70 sewage effluent samples from Cardiff Wastewater Treatment Works were collected. blaNDM-1 was detected in two of 50 drinking-water samples and 51 of 171 seepage samples from New Delhi; the gene was not found in any sample from Cardiff. Bacteria with blaNDM-1 were grown from 12 of 171 seepage samples and two of 50 tap water samples, and included 11 species in which NDM-1 has not previously been reported, including *Shigella boydii* and *Vibrio cholerae*. In this study it is found that there is presence of NDM-1 β-lactamase-producing bacteria in environmental samples in New Delhi (10).

In 2015, India was one of the top antibiotic consumers, with a defined daily dosage (DDD) of 4,950 per 1,000 population. By 2030, therapeutic and nontherapeutic use of antibiotics in veterinary animals is projected to increase by 18%. Antibiotics, ARBs, and ARGs in solid and liquid waste enter the environment through many mechanisms. Domestic, hospital, and pharmaceutical industry wastewater, as well as solid/liquid waste generated by veterinary and food animals, are key sources of antibiotics, ARB, and ARG.

As per a study done in South India STP (Sewage treatment plant) is one of the most important interfaces of environmental contamination with antimicrobial resistant bacteria. Hospital wastewater inflows considerably enhanced the prevalence of antimicrobial-resistant E. coli in South Indian STPs, whereas treatment techniques and sampling seasons had no effect. (12) Wastewater from hospital must be treated before releasing into main stream to prevent the contamination of environment with antimicrobial-resistant bacteria.

**Steps being taken to counter the threat of AMR:**

Existing traditional wastewater treatment technologies, such as the activated sludge process (ASP), do not assure that antibiotics, ARBs, and ARGs are completely removed from wastewater. Similarly, the created sludge finds its way to agricultural land, where it eventually spreads resistance in the ecosystem. Once introduced into the ecosystem, these pollutants are difficult to remove. In 2017, India's AMR action plan regulated antibiotic use for humans and animals, as well as addressed AMR transmission from all possible sources and containment.

Agriculture, livestock, fisheries waste water

Pharmaceutical industrial waste water

Hospital waste water

**ENVIRONMENT**

Community -Humans and animals

**Key sources of antibiotics, ARB, and ARG contamination the environment.**

The Indian government implemented a discharge regulation for 121 antibiotics in the effluents of bulk drug production businesses, formulation industries, and common effluent treatment plants (CETP) handling pharmaceutical wastewater in 2020. (11)

It has been over six years since the National Action Plan for Anti-microbial Resistance (NAP-AMR) was rolled out across India, in line with the Global Action Plan for Anti-microbial Resistance (GAP-AMR). Major AMR stakeholders are Ministries of Health and Family Welfare, Agriculture and farmer’s welfare, Environment Forest and climate change, and the ongoing AMR surveillance by INSAR, NCDC and ICMR networks are playing pivotal roles. Different states have been at various stages of development of the State Action Plan for Anti-microbial Resistance. Three states (Kerala, Madhya Pradesh and Delhi) have come out with their state action plan and are implementing it.

1.State Action Plan to Combat Antimicrobial Resistance in Delhi (SAP-CARD)

2.Madhya Pradesh State Action Plan for Containment of Antimicrobial Resistance

3.Kerala Antimicrobial Resistance Strategic Plan

Health being a state subject, the focus of action should also include development of State Action Plans for Containment of Antimicrobial Resistance or SAPCAR in all states and Union territories (UTs) of India. WHO India has supported the Union Ministry of Health and Family Welfare (MoHFW) in the development and implementation of SAPCAR in Kerala, Madhya Pradesh and Delhi. Using the experience from these states, other states and Union territories are trying to develop their state action plans on AMR The WHO Country Office for India has supported the MoHFW in establishing the governance mechanisms on AMR — the Intersectoral Coordination Committee, Technical Advisory Group and the Core Working Group on AMR.

In addition to the development of the National Action Plan on AMR, Delhi Declaration on AMR, SAPCAR in three states, WHO also convened the First Regional Workshop on Developing SAPCAR for the southern states and UTs in 2020, in collaboration with MoHFW and the government of Kerala. The surveillance of AMR is a critical priority for benchmarking its status, monitoring the impact of interventions and in prioritising effective evidence-based actions.

WHO India has helped to establish three state-level AMR surveillance networks in Maharashtra, Kerala and Delhi, and more state networks are planned in the future. WHO India is also supporting a ‘One Health’ AMR pilot project in the Krishna district of Andhra Pradesh in collaboration with MoHFW, the government of Andhra Pradesh and the Netherlands government. Despite the achievements, challenges are there for AMR containment. These include: Changing and competing health and development priorities, engagement, and ownership of 'One Health' AMR stakeholders, investing in AMR activities within government budgets, strengthening the implementation of existing policies and regulations, as well as monitoring and evaluation, and a lack of dedicated human resources and systems to address the AMR agenda. Recently Bihar has launched State Action Plan for containment of Antimicrobial Resistance for the state of Bihar.

Awareness and advocacy through strong community engagement is the need of the hour. Enhanced surveillance and strategies based on evidence must be implemented. Strick vigilance over use of antimicrobials in human, animal, poultry sector is utmost important. Treatment of wastewater discharges from pharmaceutical industries, healthcare industries.

**Future perspectives:**

The concept of One health emphasises the need for a more integrative effort by all the major stakeholders since AMR enters our food chain stealthily and affects each one of us directly or indirectly. AMR in the food chain not only reduces overall productivity, health risks, food insecurity, higher healthcare costs, as altering the climate. An intersectoral approach would be the best way to mitigate this menace of AMR. The farm-to-plate continuum should thus adopt a holistic One Health approach that considers not only the problem itself but also all factors associated with this menace of AMR.

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