ANTIMICROBIAL RESISTANCE: An Emerging Public Health Challenge



ANTIMICROBIAL RESISTANCE

Antimicrobial resistance (AMR) occurs when microbes evolve and become resistant to the antimicrobial drugs.¹ In other words, the microbes develop or acquire a way to prevent the drug from effectively killing them or controlling their growth. AMR is the broader term for resistance in different types of microorganisms and encompasses resistance to antibacterial (antibiotics), antiviral, antiparasitic and antifungal drugs. As an example, when antibiotics are given to a patient having a bacterial infection, they kill most of the bacteria in the human body. But it is likely that there are a few bacteria which are resistant or acquire resistance to that drug. These bacteria then multiply, along with the resistant gene and over a period of time, the antibiotic is unable to act upon the resistant bacteria. Microbes that develop antimicrobial resistance are sometimes also known as superbugs.²

According to the World Health Organization, AMR occurs when bacteria, viruses, fungi and parasites change over time and no longer respond to medicines making infections harder to treat and increasing the risk of disease spread, severe illness and death. As a result, the medicines become ineffective and infections persist in the body, increasing the risk of spread to others.

AMR poses a global public health challenge and also threatens our ability to treat infectious diseases. Resistance to first-line drugs also increases health care costs, since infections last longer (more days at the hospital) and become more expensive to treat.⁴ The threat of AMR is especially urgent with respect to antibiotic resistance in bacteria. Over several decades, bacteria causing common or severe infections have developed resistance of









varying degree to each new antibiotic brought to the market.⁵ Faced with this reality, it is imperative to take necessary steps to avert a developing global crisis in health care.

WHAT CAUSES AMR?

Although AMR is a natural process in microbes, it is facilitated by the inappropriate use of antimicrobial drugs. The more we use drugs such as antibiotics, the more the chances that the microbes become resistant to them.⁶ The global antibiotics market was valued at USD 44 billion in 2019 and is expected to account for USD 56.5 billion by 2027.⁷ This indirectly means that the present antimicrobial drugs will not work when we need them in the future because the microbes may have acquired resistance due to the excessive use of drugs.

The major factors responsible for AMR can be listed as follows⁸

- Extensive and inappropriate usage of antimicrobials in both human and veterinary applications
- Over-the-counter availability of these drugs, rising selfmedication and pill popping habits across the globe
- Untreated effluent discharge from industries and healthcare facilities
- Perception that these drugs are capable of treating common infections such as cough or cold, thus leading to their increased consumption

Although AMR is most often associated with the misuse and abuse of antimicrobials in healthcare, research has highlighted that environmental exposures play an equally important role.⁵ Pharmaceutical industries and hospitals discharging antibiotic-laden wastewaters (especially in the countries which are major producers of the drug raw materials such as India and China) into the water bodies is the most important yet an overlooked cause of AMR. Fish and livestock operations routinely use large quantities of antibiotics for actual disease treatment as well as indiscriminately for disease prevention and growth promotion through incorporation in the feed.

WHY AMR IS A SERIOUS THREAT?

According to the World Health Organization (WHO), almost 7 lakh people worldwide die every year from AMR.¹⁰ In the US itself, more than 2.8 million people are annually affected by antibiotic-resistant infections, with greater than 35000 deaths.¹¹ It has been estimated that AMR might cause more deaths than cancer i.e. close to 10 million by 2050.¹²

The medicines that were once an effective treatment for diseases have now become ineffective, leading to their reduced ability to successfully treat infections, increased mortality, more severe or prolonged illnesses, production losses in agriculture, reduced

consumption has increased by 65% between 2000 and 2015

It is important

to highlight

antibiotic

that the global

FIGURE 2.

Different routes of antibiotic resistance spread⁹



livelihoods and food security.¹³ Resistance in bacteria linked to numerous common infections (e.g. urinary tract infections, gonorrhoea, etc.) has been observed. Chloramphenicol is no longer a preferred choice for treatment of patients with antibiotic-resistant bacterial infections.¹⁴

With AMR on the rise, we stand to lose the immense ground we have gained in the last century. This includes: 1) the fight against life-threatening infectious diseases such as pneumonia, tuberculosis, HIV and malaria 2) the battle against cancer where antibiotics are crucial in helping chemotherapy patients avoid and fight infection and 3) huge advances in the surgical procedures such as organ transplants and caesarean sections, which have now become routine and relatively low-risk, thanks to our ability to effectively avoid or treat acute infections with antibiotics.

AMR has increasingly become a serious threat in recent times because excessive use of antimicrobials has increased the rate at which resistance is developing and spreading. Moreover, there is a lack of novel drugs to challenge these superbugs. This means that we are facing a growing enemy with a largely depleted armoury.

- World is not developing new antibiotics with the pace resistant microbes are evolving
- Discovery, development, manufacture and marketing of new antimicrobials has significantly slowed down in the past 20 years
- Only 1 out of 15 antibiotics from early-stage research reaches clinical application for patients²

INDIA-A HOTSPOT OF AMR

FIGURE 3.

AMR in India came into limelight earlier in 2010 with the determination of superbugs carrying the New Delhi metallo-lactamase (NDM-1) gene, igniting much needed discussion and action on AMR at the global and national level.¹⁵ AMR control in India is challenging because it is the largest consumer of antimicrobials globally,¹⁶ with easy access to non-prescribed medications for both human health and livestock. The key drivers of the emergence of AMR in India are:¹⁷

- High burden of infectious diseases
- Unregulated access to antibiotics
- Financial incentives for healthcare providers to prescribe antibiotics
- Rising incomes
- Limited public health response to AMR
- India has one of the largest burdens of drugresistant pathogens worldwide, including the highest burden of multidrug-resistant tuberculosis¹⁵
- >56,000 newborn babies in India die each year due to infections from bacteria that are resistant to first-line antibiotics
- 2 million deaths are projected to occur in India due to AMR by 2050
- For every 1000 persons/year, at least 412 prescriptions of patients contain antibiotics

India has some of the highest antibiotic resistance rates among bacteria that commonly cause infections in the community and healthcare facilities. In 2012, India also overtook the United States as the highest consumer of a class of new antibiotics known as oxazolidinones, which are prescribed as a last resort when more commonly used antibiotics are not effective.¹⁸

Globally, India is the third largest producer of pharmaceuticals by volume,¹⁹ thus the manufacturing industries also contribute to India's rising AMR burden. India has at least 40 antibiotic API manufacturers and at least 250 antibiotic formulation companies manufacturing at least one antibiotic for

Different consequences of AMR					
Serious infections such as pneumonia or tuberculosis could be difficult to treat		Many routine medical procedures could be very risky to perform		1 in 4 infections in long-term acute care settings are caused by AMR	
Minor infections and injuries could become life- threatening	Travel can become too risky, impacting global trade		By 2050, global GDP could fall by 3.8% and 28.3 million people could fall into extreme poverty		Estimated 10 million annual deaths by 2050

Knowing the thin line between use and abuse

Some over-used antibiotics and the conditions they are taken for



human use, as per data from CIMS INDIA, April–July 2017 edition.²⁰ Multiple antimicrobials and antibiotics have been detected in the Indian rivers such as Musi River in Hyderabad,^{21,22} Yamuna in Delhi^{23,24} and Ganga in the Northern states²⁵. In fact, ciprofloxacin (an antibiotic) was detected in Musi river, Hyderabad with highest concentration up to 5000 μ g/L.²¹ A study has also revealed that river Ganga acts as a reservoir of microbes with antibiotic-resistance genes.²⁶

GLOBAL INITIATIVES AGAINST AMR

AMR has been recognized as a One Health issue encompassing humans, animals, agriculture and the environment. The tripartite of WHO, Food and Agriculture Organization of the United Nations (FAO) and the World Organization for Animal Health (OIE) has highlighted the importance of containment of AMR spread.

The WHO has long established the necessity of an improved and coordinated global effort to contain AMR. In 2001, the **WHO Global Strategy for Containment of Antimicrobial Resistance** provided a framework of interventions to slow the emergence and reduce the spread of resistant microbes.²⁷ In 2012, WHO published **The Evolving Threat of Antimicrobial Resistance** – **Options for Action** proposing a combination of interventions to deal with the AMR threat.²⁸

This publication was a result of an international consultation started in 2008 involving over 50 international AMR experts. Highlighting the importance of AMR surveillance, WHO published the first **Global report on surveillance of AMR** in April 2014.²⁹ This report was based on the data collected for the first time from national and international surveillance networks, showing the extent of this phenomenon in several parts of the world and also the presence of large gaps in the existing surveillance.

Several countries came up with national action plans to tackle AMR. In 2014, Canada came up with a federal action plan on AMR and use in Canada. The action plan maps out a coordinated, collaborative federal approach to respond to the AMR threat.³⁰ Japan also developed a national action plan (2016-2020) on AMR, which is structured around goals in the following six areas: [1] Public awareness and education, [2] Surveillance and monitoring, [3] Infection prevention and control, [4] Appropriate use of antimicrobials, [5] Research and development and [6] International cooperation.³¹ Building on the 2011 action plan, EU built a new One Health action plan against AMR in 2017.32 This plan will support the EU and its member states in delivering innovative, effective and sustainable responses to AMR, strategically reinforce the research agenda on AMR and enable the EU to actively promote global action and play a leading role in the fight against AMR.

Denmark was among the first countries to ban the use of antimicrobials for growth promotion in animal production

China have

taken measures to reduce the USE Of antimicrobials among hospital patients, with the decrease in rates from 67.3% in 2010 to 36.9% in 2017 The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) has raised nearly USD 1 billion to support clinical research into new antibiotics in a bid to tackle growing AMR.³³

In 2015, the Sixty-eight World Health Assembly endorsed a Global Action Plan (GAP) on AMR, calling for a dedicated global campaign to raise public awareness and understanding of antibiotic resistance.34 The GAP provides a framework for developing national action plans, including key actions (structured around the five strategic objectives) that the various stakeholders should take within 5-10 years to combat AMR. The plan emphasises the necessity of an integrated network at regional, national and global levels in a One Health approach, taking into consideration different sectors of human health, agriculture, veterinary medicine and environment. The WHO secretariat will support the development of standards and guidance on antimicrobial residues in food, animal feed and environment as per GAP.35

5 strategic objectives of the global action plan

- Information, education and training
- Surveillance, monitoring and record-keeping
- Reduction of infection
- Legislation and optimization of use of antimicrobial agents
- Sustainable investment for alternatives and reduced use

INDIA'S FIGHT AGAINST AMR

The Government of India notified a **National Policy for Containment of AMR in 2011.** Further, based on the GAP, the Indian Ministry of Health and Family Welfare (MoHFW) published the **National Action Plan for containing AMR** in April 2017, with the MoHFW as the nodal ministry and the National Centre for Disease Control (NCDC) as the key surveillance body. This 5-year action plan on AMR (2017–2021) outlines the priorities and implementation strategies for curbing AMR in India.³⁶

- Kerala, Andhra Pradesh, Uttar Pradesh, Himachal Pradesh and Orissa were identified as five nodal states to lead the National Action Plan implementation process
- India notified the Food Safety and Standards (contaminants, toxins and residues) Amendment Regulations 2018, relating to the tolerance limits of 43 antibiotics and other veterinary drugs in food products such as meat, poultry, fish, milk, etc.
- Indian Council of Agricultural Research (ICAR) also initiated the Indian Network for Fisheries and Animal Antimicrobial Resistance (INFAAR) with 18 labs at ICAR institutes
- New National Authority for Containment of Antimicrobial Resistance (NACA) was planned as a comprehensive body for AMR containment activities and a stakeholder in implementing the Action Plan

The Ministry of Health & Family Welfare (MoHFW) identified AMR as one of the top 10 priorities for the ministry's collaborative work with WHO

A significant victory was achieved in 2019 when MoHFW banned the use of Colistin, a last-resort antibiotic in fish and livestock industries

FIGURE 4. Priorities outlined in India's National Action Plan



Improve awareness and understanding of AMR through effective communication, education and training



Optimize the use of antimicrobial agents in health, animals and food









 On 23 January 2020 the Indian Ministry of Environment, Forest and Climate Change (MoEF&CC) notified an amendment to the Environment (Protection) Rules specific to the Bulk and Formulation viz. Pharmaceutical industry. The most important addition to the rules is the concentration values of 121 antibiotic residues in the treated effluent of any bulk drug and formulation industry as well as for Common Effluent Treatment Plant (CETP)³⁷

COVID-19 AND AMR

Microbes and infectious diseases do not care for national borders and what better example do we have than COVID-19. We saw how the world came to a standstill altogether due to a virus, that originated in one place but spread to most of the countries across the globe. As per the WHO, only a small percentage of COVID-19 patients need antibiotic treatment for subsequent bacterial infections and has issued guidelines not to provide antibiotic treatment to patients with mild COVID-19 illness. However, people are consuming high doses of antibiotics as a precautionary measure when they feel symptoms such as fever, cold and cough, without acknowledging that this could lead to AMR.³⁸ It is essential to consider that patients in countries that use high levels of antibiotics such as India may also now face further complications during co-infection by antibiotic- resistant bacteria. According to a study on hospitalized COVID-19 patients, out of 72% patients receiving antibiotics, 8% developed hospital-acquired bacterial or fungal co-infections.³⁹ Thus, bacterial co-infections have already been reported as a significant cause of morbidity and mortality during viral infections and having a significant impact in the context of COVID-19. During the 2009 H1N1 influenza pandemic, nearly 3 lakh lives were claimed around the world. Many of those deaths, i.e. 29-55% were actually caused by secondary bacterial pneumonia, according to the Center for Disease Control and Prevention.40 Thus, the indiscriminate use of antimicrobials to control the COVID-19 virus and co-infections may further lead to rise in AMR.

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WHAT CAN YOU DO

- Do not purchase antibiotics over the counter without doctor's prescription
- Do not consume antibiotics for common cold and other viral diseases
- Complete your antibiotic course as per your doctor's prescription. Follow all the instructions and dosage
- Never share your antibiotics with anyone
- Do not discard unused or expired antibiotics and other medicines in the municipal bin
- Ask your doctor or medical store to take back the unused or expired stock

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