Antimicrobial Resistance Associated with Infectious Diseases

Sanjeev Saini, Nivedita Thass, Jyoti Kayesth, and Welile Sikhondze

Contents

S. Saini (✉) · N. Thass · J. Kayesth · W. Sikhondze
Infectious Diseases Detection and Surveillance, ICF, Delhi, India
e-mail: sanjeev.saini@icf.com; jyoti.kayesth@icf.com

M. P. Mothadaka et al. (eds.), *Handbook on Antimicrobial Resistance*,
https://doi.org/10.1007/978-981-19-9279-7_49

Abstract

The silent pandemic of antimicrobial resistance (AMR) has been a lethal enemy of mankind for years. Unfortunately, humans have themselves been responsible for the troublesome and worsening trends of AMR. The lack of sanitation and hygiene, lack of awareness among the public, inadequate infection prevention, and control policies in hospitals, indiscriminate antimicrobial use in humans, animals, as well as the environment, and irresponsible disposal of these antibiotics into the environment have made matters worse. Our armamentarium against these pathogens is diminishing gradually with hardly any antibiotics left to treat the patients. Thus, the World Health Organization recently developed the significance pathogen list to rank the development of drugs for the most common but difficult-to-treat pathogens across the world. Carbapenem-unresponsive; *Klebsiella* spp., *Escherichia coli*, *Pseudomonas aeruginosa,* and *Acinetobacter baumannii*, MRSA, and VRE are some of the organisms on the list. Although research is ongoing to discover new molecules to fight these superbugs and cure the infections caused by them, the current pressing main concern is to rectify our practices by following judicious use and proper disposal of antibiotics, working toward the strategic priorities of creating awareness, strictly complying with infection prevention and control protocols along with integration and collaboration among all the sectors (human, animal, environment, research) as identified under the country's accomplishment strategy on fight against drug-unresponsive superbugs (NAP-AMR) in India.

Keywords

Resistance · NAP AMR · WHO Priority pathogens · Antibiotics · Infection

1 Introduction

The antibiotic unresponsiveness is a health problem across the globe and a major challenge to public well-being. Worldwide hazard of superbugs in humans and animals has resulted in contagious infections becoming the vital ground for diseases (Dhingra et al., 2020). As we enter the post-antibiotic era, the rapidly developing resistance among human pathogens and limited newer antimicrobials is interfering with the inhibition and cure of transmissible maladies (CDC, 2019). AMR has not only been responsible for causing lethal infections, overuse of antimicrobials, treatment failures, as well as increased morbidity and mortality in patients but also it has been associated with the requirement of extended hospital care, thus, leading to an unnecessary economic burden (Dadgostar, 2019). AMR is a rapidly spreading

silent global pandemic prevalent across high- and middle-income-income countries (Hay et al., 2018).

2 Global Scenario

A study to estimate the liability of drug-unaffected diseases throughout the world was conducted in 2019, together with an assessment of pathogen–drug (88) groups, which observed a near five million mortalities, of which 1.27 million deaths per annum were attributed to antimicrobial resistance (Laxminarayan et al., 2020). A research study commissioned by the UK government predicted that at the advent of 2050 AMR will burden the global economy with a hundred trillion USD and could be responsible for ten million human mortalities per annum (O'Neill, 2016).

The average length of hospital stays for a patient infected with a multidrug-resistant pathogen is around 13 days and contributes to an additional eight million hospital days, which is approximately US$29,000 per patient every year (Majumder et al., 2020).

At the same time, infectious diseases due to multidrug-resistant organisms (MDROs) are now the major contributors to mortalities among the pediatric age group. Most reported pathogens associated with high mortality rates in this age group are drug-resistant infections, such as extended-spectrum beta-lactamase (ESBL)-generating microbes and ailments associated with methicillin-resistant Staphylococcus aureus (MRSA) (Kayange et al., 2010).

In concordance with a global opinion that antimicrobial resistance is a risk to public well-being, a plan of action at global level (GAP) was formulated by the Assembly of World Health (WHA) in May 2014 (WHO, 2014). Furthermore, the WHA appeals its member states to draft their National Action Plans in such a way that they are in alignment with the GAP-AMR by May 2017. To strengthen the fight against AMR, a strong commitment by global leaders was endorsed at a meeting on AMR at the UNGA on September 21, 2016. In alignment with the 2016 announcement of the UN, the system of Conscience of Antimicrobial Resistance Accountability (CARA), was an initiative propelled to supervise the steps taken by countries to conserve the potency of antibiotics (Gelband, 2016).

3 Infectious Diseases and AMR

3.1 Indian Scenario

The disease burden owing to highly prevalent infectious diseases in India today is indicated by the simple mortality rate of 417 per 100,000 persons. Pneumonia alone accounts for nearly 25% of pediatric deaths (approximately 410,000 deaths) in India annually. As per the country's Accomplishment Strategy on Antimicrobial Obduracy 2017, the frequency of occurrence of pathogens immune to drugs in India is accelerating at a frightening pace. Infections of MRSA rose from 29% to 45%

during the period from 2008 to 2014 in a span of 6 years, among which 65% and 42% of pseudomonads were obdurate to ceftazidime and imipenem, respectively. While 51% of *Klebsiella* spp. were unresponsive to carbapenems (National Centre for Disease Control & World Health Organization, 2017; Taneja & Sharma, 2019).

Indiscriminate application of drugs in other sectors, namely, veterinary and agriculture, contributed massively to the problem of AMR as highlighted by the report of MoHFW. The worldwide intake of drugs in faunal feed in 2010 is assessed at 63.15×10^3 tons, and India at 3% is ranked the fourth highest antimicrobial-employing nation in the world. The continuous trend of unfettered consumption of antimicrobials in the food and animal sectors in India could lead to a twofold escalation by 2030 (National Centre for Disease Control & World Health Organization, 2017).

One of the major challenges in our fight against AMR remains low in report and deficiency of adequate data from economically underprivileged nations (Antimicrobial Resistance Collaborators, 2022). Research to understand the drug resistance mechanisms, better diagnostic methods, and vigilant AMR surveillance in hospitals will play a key role in curbing the morbidity and mortality rates due to infectious diseases.

3.2 Diagnosing Antimicrobial Resistance

Rapid and accurate laboratory methods to detect antimicrobial resistance among pathogens are indispensable in regulating and monitoring the development of resistance and ensuring effective treatments.

In most settings, approximately 50% of infectious disease cases are started on empirical antibiotics as the causative organism is identified late due to a lack of rapid and sensitive antimicrobial susceptibility testing (Vasala et al., 2020).

Despite the availability of effective diagnostic methods, clinicians still opt for empirical treatment, especially in outpatient departments, resulting in the overuse of antimicrobials (Li et al., 2016).

However, in practical experience across Indian hospitals, most of the rapid diagnostic methods are unaffordable for the public and not available for use in clinics and hospitals. The standalone labs take at least 1–2 days to release the required reports. Hence, empirical antibiotics are unavoidable in Outpatient Department (OPD) patients mostly. The cost of these diagnostics is, thus, a hindrance and a challenge to be resolved.

Conventional susceptibility testing requires the growth of organisms on culture media, followed by the identification of the organism and susceptibility testing by disc diffusion or automated systems like VITEK (Biomerieux, France) and Phoenix (Becton Dickinson, USA). The former is time-consuming, and by the time the report is available, empirical therapy is already started. Another system popularly known as Matrix Assisted Laser Desorption/Ionization Time of Flight MALDI-ToF is presently employed in some labs for the identification of organisms. Susceptibility testing using this technique is still being researched and not widely done yet.

Rapid molecular methods can guide effective treatment strategies even at the initial stage of the disease. There is no dearth of upcoming molecular methods available today such as nucleic acid amplification technology (NAAT), micro- and nanoparticles, microarrays, electrochemical methods, and mass spectrometry. However, only a few systems so far have been approved by the USFDA. These methods also help distinguish viral infections from bacterial infections, thereby reducing the chances of unnecessary antibiotic use in patients. These diagnostics can also identify colonizers, where the organism has been isolated by the laboratory but may not be pathogenic. Such cases are of critical importance in the hospital setting since these may not require treatment, thus reducing antibiotic overuse (Burnham et al., 2017).

3.3 Gaps in Diagnosing AMR

The currently available rapid tests for detecting AMR are mostly genotypic methods, that is, they identify certain resistance genes for a particular drug–pathogen combination. Although less time-consuming, their major drawback is the unavailability of screening outputs of proneness to drugs, which is indispensable for curing regimes (Burnham et al., 2017). Contrastingly, conventional tests are based on phenotypic methods that provide both susceptibility and resistance patterns as well as reproducible results. The conventional technology is time-consuming and has inadequate clinical predictive value as it does not consider host response, biofilm formation, or bioavailability at the tissue level, etc. (Doern & Brecher, 2011).

Despite the utility of rapid tests, culture correlation is indispensable. Polymerase Chain Reaction PCR detects a variety of genetic material in the specimen. When multiple organisms are detected along with multiple resistance genes, the automated molecular systems are unable to distinguish the source of the gene and, hence, a correlation with culture is recommended even by systems like Biofire Film array (Biomerieux, France).

Antimicrobial resistance is a natural phenomenon. The reckless and inconsiderate employment of drugs resulted in the evolution and transmission of superbugs that are immune to most classes of drugs (bacteria, viruses, parasites, and fungi). Other factors that have facilitated the proliferation of drug-resistant strains globally include nonadherence to infection control practices, inadequate sanitary conditions, misuse of antimicrobials in the veterinary sector, and inappropriate food handling (Hay et al., 2018).

4 Factors Contributing to AMR

The rising issue of AMR has highlighted that it is a multifaceted problem and has made us realize the significance of intersectoral collaboration: human health, animal health, food and hygiene, and environmental health in our fight against AMR. The rates of resistance have been rising disproportionately across these sectors and necessitate research in the field of AMR. The lack of standardized surveillance

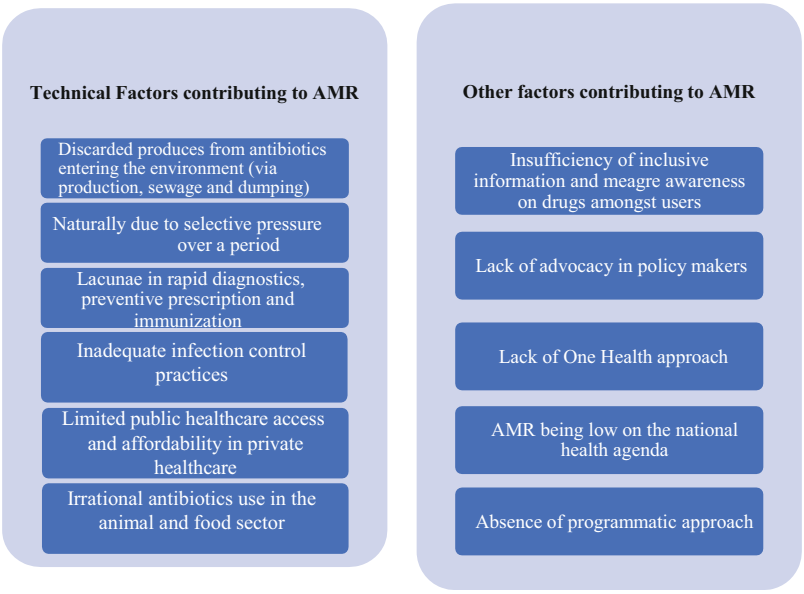

Fig. 1 Factors contributing to antimicrobial resistance

data makes gauging the extent and scope of AMR difficult (Taneja & Sharma, 2019). Some of the factors contributing to AMR are given below and are depicted in Fig. 1.

4.1 Antimicrobial Resistance Is a Natural Phenomenon

It takes place due to the selective pressure over a period when a particular antibiotic is in use. The strains that carry the resistance gene survive and replicate, thus resulting in the emergence of multidrug-resistant microbes. Numerous additional factors have contributed to the rapid acquisition of resistance by pathogens globally, and some are listed below.

4.2 Antibiotic Misuse/Overuse

Owing to inadequate regulatory systems to monitor antibiotic use, self-medication and ease in accessibility in buying drugs have exacerbated the spread of obduracy to drugs. The lack of antibiotic stewardship programs in India has enabled resistance to develop among the microbes (National Centre for Disease Control & World Health Organization, 2017; Prestinaci et al., 2015). Moreover, the pandemic of COVID-19 also fueled the immeasurable application of drugs for the last 2 years, increasing the rates of AMR globally. Despite the guidelines given by health authorities the world

over, including WHO, which discouraged the use of antibiotics for mild cases of COVID-19, the irrational and unsupervised use of antibiotics continued during the pandemic. This has only worsened the silent pandemic of AMR in the last 2 years by increasing the rates of hospitalizations and the emergence of drug-resistant pathogens (Majumder et al., 2020).

4.3 Inadequate Infection Control Practices

Lack of awareness and well-trained staff, infrastructure, and extraordinary workload, all have contributed to poor infection control practices. This directly leads to the nosocomial transmission of drug-resistant pathogens.

4.4 Environmental Pollution

The wastes generated from antimicrobials enter into the environment through manufacture, sewage, and disposal. Out of all Gram-negative bacteria isolated from the two important rivers of India, Ganges and Yamuna, 17.4% were ESBL producers, and all the *E. coli* totaling to a number of 283 isolated from the Cauvery River of Karnataka a south Indian state, were resistant to the third-generation cephalosporin (Taneja & Sharma, 2019). However, when discussing the AMR among humans, the effect of resistance genes present in environmental bacteria is rarely considered. The horizontal transfer of environmental resistance genes into pathogens causes infectious diseases and leads to treatment failures that will be given emphasis on the environmental aspect of AMR. The need of the hour is to fill the evidence gap that will enable policymakers and environmental regulators to deliver environmental protection from AMR (Taneja & Sharma, 2019).

4.5 Poor Diagnostics

As discussed earlier, due to the unavailability of good diagnostics there is a lack of early identification and diagnosis of pathogens and their susceptibility profile. This interferes with the initiation of appropriate antimicrobial therapy and forces physicians to initiate empirical treatment using broad-spectrum antimicrobials.

4.6 Irrational Antibiotics Use in the Animal and Food Sector

The absence of stringent rules in the application of drugs in farmed animals and cattle results in the indiscriminate use as growth promoters and for disease treatment, making these animals another reservoir of resistance genes. Since 2006, Europe has excluded the application of drugs as growth supporters, but the United States and several other countries continue to have this unrestricted practice (Prestinaci et al.,

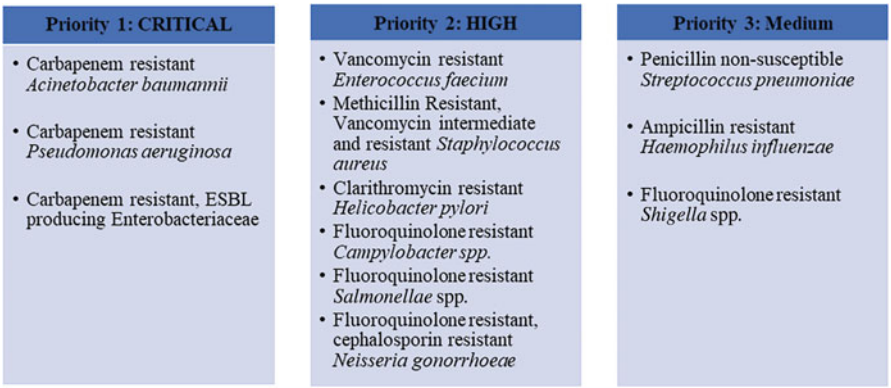

Fig. 2 WHO list of priority pathogens

2015). Establishing better infection control measures and surveillance networks to monitor resistance in both sectors, that is, animal and agriculture sectors, is essential.

Since infectious diseases are caused by superbugs are the primary reason for death all over the world, the WHO documented drug obdurate "priority pathogens" in 2017 (WHO, 2017) (Fig. 2), which includes 12 genera of microbes that are most commonly being reported across the globe and are recognized as public health threats. The CDC of the United States in 2019 authenticated AMR microbes categorized into three groups. There are a total of eight microbes on this list; most of these are also on the WHO list (CDC, 2019).

As per the WHO published worldwide information on AMR surveillance, the increasing rates of antimicrobial resistance among malarial parasites, human immunodeficiency virus, and MDR/XDR *Mycobacterium tuberculosis* are being reported worldwide, especially from China, India, and the Russian Federation cannot be ignored and public health strategies to fight antimicrobial resistance should also include these (WHO, 2014).

5 WHO Priority Pathogens

5.1 Carbapenem-Resistant *Acinetobacter baumannii* (CRAB)

The Problem Statement Among drug-resistant nosocomial microbes, CRAB is the main cause of maximum rate of demises. Various studies across the world have reported carbapenem unresponsiveness amounts to very high levels to an extent of 90%, and the death frequency allied to CRAB infections is approximately 60% (Isler et al., 2019). The biofilm-forming capacity of this organism in biomedical relevant devices leading to its persistence in hospital settings and its formidable drug resistance profile are the reasons behind frequent nosocomial outbreaks caused by CRAB (Rosales-Reyes et al., 2017). CRAB mostly affects most vulnerable patients

in ICU settings and is concomitant to life-threatening infections like ventilator-associated pneumonia and bacteremia (Isler et al., 2019).

Mechanism of Resistance Studies have shown various mechanisms for this resistance pattern of CRAB, (a) loss of outer membrane porins expression, (b) horizontal transfer of some resistance factors like OXA-23; NDM carbapenemases and aminoglycoside-altering enzymes; (c) they intrinsically express some β-lactamases; AmpC cephalosporinases, carbapenemases, and β-lactamases of OXA kind; (d) they form "resistance island" made of multiple mobile resistance gene elements; and (e) isoform of efflux pumps, viz., AbeABC, AbeFGH, etc. (Wong et al., 2017).

Treatment Selections: Widely drug-obdurate CRAB infections are commonly treated using tigecycline, polymyxin, and sulbactam. Tigecycline, although used widely against CRAB infections, is not effective against bloodstream infections due to its pharmacokinetic property of achieving low plasma levels. However, increasing cases of resistance to this drug are being reported globally, thus discouraging the use of tigecycline (Taccone et al., 2006). Minocycline too has shown good clinical efficacy in infections due to CRAB (Wong et al., 2017). Sulbactam also has intrinsic activity against CRAB, so sulbactam-containing regimens can be a treatment option. Its use is again limited due to high rates of resistance being reported worldwide (Viehman et al., 2014). Amikacin also carries anti-CRAB activity, but being nephrotoxic its use for systemic infections is not recommended. In vitro susceptibility tests showed that polymyxins have potent activity against *A. baumannii* strains, but clinical efficacy is unreliable due to the absence of susceptibility breakpoints, no therapeutic window, and their nephrotoxic and neurotoxic nature (Isler et al., 2019). Hence, there is an urgent need for alternative therapeutic options against CRAB.

Research is ongoing to find newer antimicrobials to treat such multidrug-resistant isolates of *Acinetobacter baumannii*. Until then, the need is to judiciously use the available antimicrobials and keep resistance rates under check. The need of the hour is a multidisciplinary approach, involving strict infection control practices, antimicrobial stewardship, and increased awareness among healthcare providers and patients (Wong et al., 2017).

5.2 Carbapenem-Resistant Enterobacteriaceae (CRE)

The Problem Statement In recent years, carbapenem-resistant Enterobacteriaceae (CRE) has been identified as one of the main reasons for epidemics and management failures of both nosocomial and community-acquired infections (Elshamy & Aboshanab, 2020).

With CRE demonstrating unresponsiveness to key classes of antibiotics, for example, fluoroquinolones β-lactams and aminoglycosides, the last resort for

treatment are polymyxins. In some cases, aminoglycosides and tigecycline have shown some efficacy (Elshamy & Aboshanab, 2020).

A US study reported a prevalence rate of colonized CRE ranging from 3% to 30.4%; meanwhile, in Asia, it ranged from 13% to 22.7% (Jean et al., 2022). The European Antimicrobial Resistance Surveillance Network (EARS-Net) described considerable variability across EEA/EU countries. The carbapenem resistance in *K. pneumoniae* aggressive isolates was observed to be ranging from 0% to 65% in 2017 (ECDC, 2018).

A national report from the surveillance network in China reported the prevalence of *K. pneumoniae* isolates unresponsiveness to meropenem and imipenem enhanced from 2.9% to 24.0% and 3.0%, to 20.9%, respectively, between the years 2005 and 2017 (Ding et al., 2019).

Indian studies have shown that the CRE prevalence rate varies from 13% in south India to 31% in western India. There may be varying factors influencing this prevalence. The density of the population in India, the ability of the organisms to spread through the intestinal flora of healthy carriers, the lack of adequate public health infrastructure, and the lack of antimicrobial stewardship (AMS) policies are a few of them. The lack of an Antimicrobial Stewardship Programme (AMSP) is related to nonjudicious application of drugs in healthcare settings, thus leading to selection pressure for resistant strains. These strains are eventually transmitted in the hospital, as well as the community, through various routes due to poor infection control practices (Modi et al., 2021). The surveillance data of the Indian Council of Medical Research (ICMR) Antimicrobials has shown a steady fall in Imipenem susceptibility among *E. coli* isolates (86% in 2016 to 63% in 2019), which in 2020 slightly improved to 72%. *Klebsiella pneumonia*-susceptible isolates plunged from 65% to 45% during the period 2016–2020 (ICMR, 2020).

Furthermore, with the emergence of ESBL-producing Enterobacteriaceae around the year 2000, carbapenems were increasingly being used as a treatment option. Overuse of this class of antibiotics quickly resulted in the spread of carbapenemase-producing isolates of Enterobacteriaceae globally at an alarming rate (Elshamy & Aboshanab, 2020).

Mechanism of Resistance The resistance to carbapenems among Enterobacteriaceae is based on three main mechanisms: (a) enzymatic hydrolysis of carbapenems by carbapenemases. Carbapenemase enzymes are categorized into three key categories established on their molecular configuration: Ambler Classes A, B, and D. Class A carbapenemases are utmost shared and include *Klebsiella pneumoniae* carbapenemase (KPC) and imipenem-hydrolyzing beta-lactamase (IML). Class B metallo-beta-lactamases (MBL), namely, New Delhi Metallo-beta-lactamase (NDM), imipenem-unresponsive *Pseudomonas* (IMP), and Verona integron-encrypted metallo-lactamase (VIM), whereas oxacillin-hydrolyzing carbapenemase (OXA)) enzymes comprise class D carbapenemases. (b) Isoform of efflux pumps that drive away carbapenems from the cells of bacteria, and (c) lessening the outer membrane penetrability by creation of beta-lactamases

(AmpC) in amalgamating with modifications in cell membrane of bacteria through mutations of porin (Sheu et al., 2019).

Among the carbapenems, isolates continue to show susceptibility to meropenem and imipenem; however, the susceptibility of the organism toward ertapenem is dreadful. This is most likely due to the presence of AmpC/ESBL and altered porins (Codjoe & Donkor, 2017).

Detection of carbapenemases can be done by phenotypic as well as genotypic methods. There are various methods for phenotypic detection, namely, automatic methods or disc diffusion, modified Hodge test, and discerning agar and tests of combined effect such as double disc tests. These approaches can help in detecting the carbapenem unresponsiveness but may not necessarily indicate the mechanism in effect. Tests for molecular identification of genes related to carbapenemase include PCR, LAMP, MLST, MLE electrophoresis, and DNA fingerprinting methods, namely, AFLP and PFGE (Codjoe & Donkor, 2017; Elshamy & Aboshanab, 2020).

Treatment Options The recent surge in cases of CRE infections across the globe is a cause of concern. Until a few years back, only polymyxins and aminoglycosides formed a major part of our armamentarium against these pathogens (Doi, 2019). Few other agents have been recently introduced. For instance, ceftazidime/avibactam which has been reported to be active against KPC and OXA-48 producers plazomicin, and eravacycline, the next-generation antibiotics from the aminoglycosides and tetracycline group, respectively, contained CRE in laboratory conditions (Sheu et al., 2019). Other possible emerging therapeutic options are ceftolozane, meropenem, imipenem in combination with tazobactam, vaborbactam, cilastatin-relebactam, and cefiderocol, respectively, being employed (Doi, 2019). However, studies are being carried out to assess the efficacy of these antimicrobials against lethal infections.

Timely identification and differentiation between clinical pathogens and carriers are of critical importance in tackling CRE cases. Rational use of antibiotics and active screening of carriers accompanied by better infection prevention practices and improved surveillance network will be vital in curbing CRE infection rates.

5.3 Carbapenem-Resistant *Pseudomonas aeruginosa* (CRPA)

The Problem Statement *Pseudomonas aeruginosa,* a major opportunistic microbe, is concomitant to hospital outbreaks and most nosocomial ailments. This pathogen is commonly allied with pneumonia, bacteremia, and infections of skin, soft tissue, and urinary tract, particularly among immunocompromised groups. It can form biofilms and continue to survive on various exteriors such as medical equipment; it is resistant to most disinfectants and easily transmitted from patient to patient. It is intrinsically resistant to multiple antibiotics and acquires genes encoding resistance determinants (Losito et al., 2022).

As per 2020 EARS-Net data, out of all *P. aeruginosa* isolates, 30.1% were unresponsive to a minimum of one set of drugs, viz., fluoroquinolones, ceftazidime, piperacillin-tazobactam, etc., and further unresponsiveness to carbapenem was reported in 17.8% of isolates (ECDPC, 2020) As per ICMR for 2020, the prevalence of CRPA in India is around 30–40% (ICMR, 2020).

Mechanism of Resistance Carbapenem resistance in *P. aeruginosa* develops due to multiple factors, including the attainment of movable genes encrypting carbapenemases, such as the metallo-β-lactamases (MBLs), KPC, increased expression of the chromosomal cephalosporinase AmpC, porin loss due to mutations of OprD gene, overexpression of MexA-MexB-OprM efflux pump, and/or penicillin-binding protein alterations (Xu et al., 2020).

Due to changes in the porin expression, carbapenem resistance was first reported in *Pseudomonas aeruginosa* in the mid-1980s. In comparison, meropenem is less prone to developing porin-mediated resistance mechanism as it passes more swiftly through the OprD porin; however, upregulation of efflux pumps can lead to meropenem resistance. On the other hand, ertapenem has little or no activity against *Pseudomonas aeruginosa* (Doi, 2019).

Treatment Options Ceftolozane–tazobactam and ceftazidime–avibactam have good safety profiles and are efficient in treating carbapenem-resistant *Pseudomonas aeruginosa*. However, in contemporary period, intermittent circumstances of unresponsiveness were recorded for these antibiotics (Nichols et al., 2016; Teo et al., 2021). Ceftolozane–tazobactam-non-susceptible isolates can be treated using imipenem–cilastatin–relebactam, another novel drug combination. Cefiderocol is another effective option with excellent in vitro activity and stability, especially in cases with more complex mechanisms of resistance (Losito et al., 2022).

In view of inadequate opportunities for managing CRPA ailments, monitoring and controlling the spread of genes that cause resistance to these drugs through strict stewardship of drugs and stringent resistor procedures for nosocomial infections is the need of the hour.

5.4 Vancomycin-Resistant *Enterococci* (VRE)

The Problem Statement During the late 1970s, *Enterococci* were first identified as a common nosocomial pathogen due to overuse of third-generation cephalosporins to which enterococci are intrinsically obdurate (Cetinkaya et al., 2000). As per the National Healthcare Safety Network data from 2011 to 2014, *Enterococci* was the second most common organism causing healthcare-associated infections. *E. faecalis* isolation rate was 7.4%; however, vancomycin resistance reportedly is more common among *E. faecium* strains. From 2011 to 2014, approximately 83.8% of isolates causing CLABSI and 86.2% of isolates causing CAUTI were found to be vancomycin-resistant *E. faecium* strains (Levitus et al., 2022). The studies in India revealed that that the rate of VRE in *E. faecalis* is far less (2.8%), whereas it was

higher in *E. faecium* (22.7%) (ICMR, 2020). Studies from Europe have reported a substantial proliferation in the incidence of vancomycin-resistant *Enterococcus faecium* isolated from bloodstream infections (2015: 10.5% vs. 2019: 18.3%) (Correa-Martínez et al., 2022). Often vancomycin-sensitive strains isolated from patients do not respond to the treatment because of inducible resistance genes, *VanA* and *VanB*. Such isolates should be re-cultured in a few days to review the susceptibility (Levitus et al., 2022).

Research has shown that VRE isolates are capable of surviving on surfaces like countertops for up to 7 days and can be recovered from bedrails, telephone handpieces, or stethoscope diaphragms for up to 24 hours or more. It can stay in the hands of healthcare workers for around 60 minutes after inoculation. Further surveys have found that as many as 26–41% of healthcare workers were VRE carriers (Levitus et al., 2022; Cetinkaya et al., 2000).

The hazards associated with VRE colonization are observed to be high among the patients who are hospitalized, especially the ones who are being treated in intensive care units, have co-morbid conditions, and have undergone invasive procedures (Davis et al., 2020).

Mechanism of Resistance The foremost mode of glycopeptide unresponsiveness, for instance, vancomycin in Enterococci is due to replacement of D-alanine-D-alanine, to D-alanine-D-lactate or D-alanine-D-serine that ultimately alters the peptidoglycan synthesis pathway. This is coded by genotypes identified alphabetically as *VanA* to *VanG*. Of these, *VanA* and *VanB* genotypes are plasmid coded and by far the most common (Ahmed & Baptiste, 2018; Levitus et al., 2022).

Treatment Options Intrinsic resistance to multiple antibiotics and the inducible resistance gene have made treatment options for VRE very scarce. Over the past decade, linezolid, daptomycin, quinupristin–dalfopristin, and tigecycline application substantially enhanced as an ultimate solution in the management of VRE isolates (Ahmed & Baptiste, 2018).

The increased prevalence of VRE in hospitals worldwide points to the lack of appropriate infection control programs surveillance systems and inefficient antibiotic stewardship. Active improvement in these aspects is a critical step toward curbing the further rise of VRE.

5.5 Drug-Resistant *Neisseria*

The Problem Statement Among the sexually transmitted diseases, *Neisseria gonorrhoeae* ranks second with considerably high morbidity (St. Cyr et al., 2020).

In the United States, annual drug-resistant *N. gonorrhoeae* infections are approximately 550,000 and 1.14 million new cases every year as documented in the CDC report of 2019 (CDC, 2021). Studies across Europe have reported high cefixime-resistant *N. gonorrhea*; Slovakia, Austria, Poland, Germany, Belgium, Luxembourg, and Croatia at 3.6%, 4.2%, 5.2%, 6.4%, 8.1%, 10%, and 11.1%, respectively

(Młynarczyk-Bonikowska et al., 2019). The data seems to be scarce from economically underprivileged nations. However, the WHO worldwide AMR assessment for *Neisseria gonorrhea* during the years 2017–18 showed that less than 5% isolates had been reported as having decreased susceptibility or resistance to ceftriaxone (Unemo et al., 2021).

The majority of cases of *N. gonorrhoeae* are asymptomatic and can be missed; therefore, routine screening for prompt diagnosis and effective treatment is of significance. Cases that are missed and left untreated often lead to complications such as sterility in females, ectopic pregnancies, and pelvic inflammatory infections (Kueakulpattana et al., 2021).

Mechanism of Action The increasing trend of *Neisseria gonorrhoeae* being reported unresponsive to ceftriaxone and cefixime that come under the category of extended spectrum of cephalosporins (ESC), is a cause of grave concern. The characteristic feature of *Neisseria* genus is to receive DNA of chromosomes through the process of transformation from the other *Neisseria* triggering number of mutations in its chromosomal genes. The resistance mechanisms seen in *N. gonorrhoeae* isolates are alterations in the chromosomal area of penA gene (encrypting the PBP2 protein's transpeptidase sphere), which has contributed the furthermost to the expansion of chromosomal unresponsiveness or condensed vulnerability to ESC group of bacteria. Other mechanisms involve overexpression of efflux pumps like MtrCDE membrane pump proteins (Młynarczyk-Bonikowska et al., 2019).

In the past decade, NAAT (molecular methods) has become the test of choice for the diagnosis of gonorrhea. Conventional culture methods are not used that often, and this presents a major challenge when dealing with emerging drug resistance because the existing amplifications processing of screening with nucleic acids will not facilitate susceptibility to drugs. Furthermore, the lack of standard or established breakpoints and different sampling strategies across countries has resulted in skewed epidemiological and resistance rates; therefore, comparison of data like epidemiological patterns cannot be done effectively (Costa-Lourenço et al., 2017). Thus, the need of the hour is enhanced molecular diagnostics that can guide antibiotic therapy by providing antimicrobial-susceptibility patterns. Novel know-hows such as WGS methods that can detect the drug-resistant isolates can help in resolving this issue (Cristillo et al., 2019).

5.6 Methicillin-Resistant *Staphylococcus aureus* (MRSA)

The Problem Statement *Staphylococcus aureus* is one of the commonly encountered organisms in hospital settings. In the past few decades, a more notorious form of MRSA has developed. The first case reports of MRSA came in 1961 from the United Kingdom (Jevons, 1961). It is a superbug with a multitude of virulence characters and the capability to obtain obduracy to most drugs, namely, β-lactams viz., penicillins, chloramphenicol, cephalosporins, tetracyclines, quinophthalones, aminoglycosides, sulfonamides, etc. Thus, it is frequently associated with treatment failures and fatal infections in patients (Guo et al., 2020; Lakhundi & Zhang, 2018).

Over the years, two types of MRSA have emerged, namely, community-acquired MRSA and hospital-acquired MRSA. Although they evolve from a single bacterium, they have a distinct genetic reservoir and so differ widely in terms of resistance patterns, the population affected, toxins, virulence factors, and resistance genes. The wide spectrum of infections caused by MRSA ranges from mild diseases related to skin and soft tissue to lethal illnesses, namely, infective endocarditis, osteomyelitis, bacteremia, etc. Studies have shown that mortality due to systemic MRSA infections can be as high as 60% (Guo et al., 2020).

In India, the pervasiveness of MRSA in nosocomial and community settings is high and varies between 40% and 70% (ICMR, 2020; NCDC, 2021). The CDC report of 2019–2020 showed an enhancement of 15% bacteremia associated with MRSA picked up from hospital sources (CDC, 2021).

Mechanism of Resistance The evolution of MRSA is due to the existence of the mecA exogenous gene, which is integral to staphylococcal cassette chromosome SCCmec that produces a transpeptidase PB2a, which in turn alters the affinity of the organism toward beta-lactam class of antibiotics. This penicillin-binding protein is one of the unique and medically relevant chromosome-mediated drug resistances that occurs via phage transduction. Based on antibiotic susceptibility testing guidelines, a *Staphylococcus aureus* isolate found resistant to oxacillin is called MRSA (Lakhundi & Zhang, 2018).

Treatment Options Vancomycin is the ideal drug for the medication for MRSA (Brown and Brown, 2021; ICMR, 2019). But many cases of vancomycin treatment failure and the emergence of strains, namely, VRSA, VISA, and Hetero-VRSA, are being reported worldwide (Guo et al., 2020).

In cases where nephrotoxicity is a concern, teicoplanin can be an alternative to vancomycin. Other treatment options for MRSA include linezolid, daptomycin, ceftaroline, and combination therapies (Brown and Brown, 2021; ICMR, 2019). MRSA spread in hospital settings usually happens due to lack of infection prevention practices. Therefore, the implementation of infection-control steps such as hand hygiene compliance and adherence to contact precautions are imperative in the deterrence and governing of MRSA infections. Other critical steps to curb healthcare-associated MRSA infection rates are prompt isolation or cohort of patients in wards, regular screening of MRSA carriers, and identifying colonized healthcare workers through surveillance, decolonization of carriers using mupirocin and chlorhexidine body washes, and environmental decontamination, as almost 20% of populace are carriers of *S. aureus* on a long-term basis (Guo et al., 2020).

5.7 Clarithromycin-Resistant *Helicobacter pylori* (CRHP)

The Problem Statement *Helicobacter pylori* is responsible for communal protracted bacterial infection among humans, leading to 4.4 billion cases per year around the globe. A study done to find the prevalence of *H. pylori* reported a

prevalence rate ranging between 28% to 84% across populations (Saleem & Howden, 2020). The annual relapse hazard was 3.4% and 8.7% for high- and low-income category countries, respectively (Miftahussurur et al., 2019).

Since *H. pylori* has been the etiological agent associated with gastric adenocarcinomas, peptic ulcers chronic atrophic gastritis, and B-cell mucosa-associated lymphoid tissue (MALT) lymphomas, it is a lingering major problematic organism across the world, and hence, the need of the hour is complete suppression (Hu et al., 2017; Kocsmár et al., 2021; Saleem & Howden, 2020). However, transmission of drug obdurate strains has led to the failure of triple-drug treatment over the years. Although monoresistance to clarithromycin, amoxicillin, and metronidazole is reported, the most common and rapidly increasing resistance is reported to clarithromycin, and thus, clarithromycin-immuned *H. pylori* incorporated in the top preeminence pathogen group by the WHO (2017).

Mechanism of Resistance Clarithromycin is a bacteriostatic macrolide that acts by adhering to the 50S ribosomal subunit of *H. pylori* and inhibits production of proteins. The unresponsiveness to clarithromycin (Cla-res) in *H. pylori* takes place owing to topical transmutations of specific codons in the peptidyl transferase area of the 23S rRNA, lowering the affinity of the drug toward the bacterial ribosome. In these 23s mutant strains additionally, efflux pumps synergistically offer resistance by pushing the drug out of the cells (Kocsmár et al., 2021).

Treatment Options Recommended first-line treatment options include quadruple regimens either bismuth-based (two antibiotics, plus bismuth, and proton pump inhibitors) or concomitant/non-bismuth-based. However, the potential toxicity of bismuth as well as the scarcity of bismuth salts in a few countries has been a cause of concern (Goderska et al., 2017; Chey et al., 2017). Newer drug combinations are also being introduced like a highly effective rifabutin-centered blend, permitted lately by the USFDA. A potassium-competitive acid blocker vonoprazan has shown promising results as part of dual-/triple-combination regimens and is still under evaluation (Hu et al., 2017; Saleem & Howden, 2020). Of late, the treatment of *H. pylori*-related infections with probiotics, along with routine antimicrobial therapy, has garnered significant attention. It helps by facilitating eradication and improving tolerability for treatment-related side effects (Goderska et al., 2017).

The most frequently used screening methods in the identification of *H. pylori* are the tests of urea breath and the fecal antigen kind as they are noninvasive and have great accuracy and specificity. These tests can also be employed to make initial diagnosis as well as know the eradication status post-treatment; however, they do not provide the resistance profile of the organism. Invasive methods include endoscopy to obtain biopsy samples to test for urease activity, histopathology, and culture. The culture method can guide susceptibility-based therapy, avoids the use of unnecessary antibiotics, and is a good alternative in the present scenario of increasing resistance (Hu et al., 2017; Saleem & Howden, 2020).

5.8 Fluoroquinolone-Resistant *Salmonella* (FRS)

The Problem Statement *Salmonella* infection lingers to be a predominant apprehension of public health across the world and places an increased economic burden, especially in developing countries of South and Southeast Asia. *Salmonella* genus has over 2600 *Salmonella* serotypes, mostly belonging to *Salmonella enterica* subsp. *enterica*, which are responsible for the maximum number of infirmities in humans. Human Salmonellosis can present clinically as bacteremia, enteric fever, and gastroenteritis, and sometimes lead to extraintestinal problems and a lingering carrier state. Across the world, nearly 93.8×10^6 foodborne infections and 1.55×10^5 mortalities per annum are linked to nontyphoidal *Salmonella* (NTS) as one of the shared pathogens that is the root cause of bacterial enteritis (Gong et al., 2022). Typhoidal *Salmonella* is the leading cause of typhoid fever, accounting for approximately 21.7 million cases and 217,000 deaths every year (Cuypers et al., 2018). The incidence of culture-confirmed typhoid cases in India is around 377 per 100,000 population and case fatality rate of 1% (Veeraraghavan et al., 2021).

In order to term an isolate as Multidrug-resistant (MDR) *Salmonella*, there should be co-resistance to the first-line antibiotics ampicillin, chloramphenicol, and trimethoprim/sulfamethoxazole. The emergence of this strain led to the rampant use of fluoroquinolones. However, by 2010, this indiscriminate use of fluoroquinolones gave rise to complete fluoroquinolone-resistant isolates, including resistance to even the third-generation fluoroquinolone gatifloxacin, and subsequently causing treatment failures and various problems such as gastrointestinal bleeding, intestinal perforation, and less frequently encephalopathy and shock (Crump et al., 2015; Eng et al., 2015). Thus in 2017, the WHO included FQ-resistant *Salmonella* in the list of high-priority pathogens (WHO, 2017).

Mechanism of Resistance The fluoroquinolones unresponsiveness is due to transmutation at the quinolone unresponsive defining locations known as *"Quinolone Resistance-Determining Regions"* (*QRDRs*) of the gene gyrA, which decreases quinolone-binding affinity of topoisomerase enzymes, and by means of upregulation or downregulation and of chromosome-encoded porins or multidrug efflux pumps (Crump et al., 2015; Eng et al., 2015). The quinolone unresponsiveness occurring through plasmids is called "*Plasmid-Mediated Quinolone Resistance (PMQR)*" has also been observed via three genes: (i) *qnr* genes that encrypt topoisomerase-binding proteins responsible for causing a physical barrier for the drug; (ii) genes encoding a modifying enzyme that decreases FQ activity (the *aac (6′)-lb-cr* gene); and (iii) genes that encode quinolone efflux pumps (*oqxAB* and *qepA*) (Cuypers et al., 2018; Li et al., 2018).

Treatment Options Azithromycin and ceftriaxone have become the treatment of choice due to rapidly developing fluoroquinolone-resistant strains. Although the susceptibility for these two drugs is still good due to selective pressure, sporadic occurrence of ceftriaxone and azithromycin-unresponsive strains was recorded in the last few years (Veeraraghavan et al., 2021).

Limiting the use of fluoroquinolones, together with the judicious use of azithromycin and ceftriaxone, should be implemented strictly as we have very few treatment options for Salmonellosis (Li et al., 2018). Despite the dose recommendation for azithromycin being changed years ago, many clinicians are still prescribing suboptimal doses (NCDC, 2016; ICMR, 2019).

Lack of diagnostic tests complicates the controlling of typhoid infection, and, furthermore, makes it problematic to differentiate these contagions the fibrile-associated infections. The mainstay of laboratory diagnosis for typhoid fever is microbiological confirmation by blood or bone marrow culture (Crump et al., 2015). However, this method lacks good sensitivity (ranging between 40% and 80%) (Eng et al., 2015). Antibiotics being used as growth promoters in animal feed, and their unregulated use in the veterinary field to treat various infections, have both been indirectly responsible for the development of drug unresponsiveness in *Salmonella* (Vercelli et al., 2022).

5.9 Fluoroquinolone-Unresponsive *Campylobacter jejuni*

The Problem Statement *Campylobacter jejuni* is a grim civic well-being hazard worldwide as a source of gastroenteritis. The rapid spread of fluoroquinolone-resistant strains has only added to the disease burden. *Campylobacter* is a commensal found in the gut flora of chicken and is transmitted to humans upon ingestion of uncooked/raw poultry (Sproston et al., 2018; Whelan et al., 2019). Despite the fact that it is highly invasive in human intestine, most diseases due to *Campylobacter* are self-limiting. However, due to the unsupervised use of fluoroquinolones to treat every undiagnosed cases of gastroenteritis in humans and rampant misuse of fluoroquinolones in poultry, the resistant isolates have been associated with abdominal and general ailments. The persistent sequelae in communities include serious diseases, namely, Guillain–Barré syndrome hemolytic uremic syndrome, Miller–Fisher syndrome, Reiter's syndrome, reactive arthritis, and septicemia (Sierra-Arguello et al., 2018; Whelan et al., 2019).

Campylobacteriosis affects an estimated 400 and 500 million individuals across the globe annually. Various studies have reported a high prevalence of fluoroquinolone-resistant *Campylobacter* isolates among humans and animals (Kaakoush et al., 2015). Studies indicate that in the United States and Canada, Europe and Africa, and Asia, the prevalence rates are 19–47%, 17–99%, and >80%, respectively (Khademi & Sahebkar, 2020).

Mechanism of Resistance Modifications in gyrA gene encrypting fragment of the GyrA subunit of DNA gyrase, which is one of the target bacterial enzymes of quinolones, lead to fluoroquinolone resistance among the *Campylobacter* strains. The other mechanism of resistance is reduced outer membrane permeability and efflux pump existence, CmeABC. CmeABC is a multidrug efflux pump responsible for antimicrobial resistance against fluoroquinolones and macrolides and works synergistically with the mutation in Gyr A mutations (Lin et al., 2002; Wieczorek & Osek, 2013).

Treatment Options Although not all cases of campylobacteriosis require antimicrobial therapy, only the immunocompromised with complications would need to be treated with antibiotics. Gentamicin and macrolides have been still found to be effective against *Campylobacter*-related ailments (Sproston et al., 2018). However, the rapid emergence of resistance to fluoroquinolones among *Campylobacter* strains led to its inclusion in the WHO priority list of pathogens.

Multiple studies have established the relationship between the misapplication of drugs in all animal sectors, especially fluoroquinolones being used as growth promoters among poultry, and an increase in the number of resistant isolates of *Campylobacter* in humans (Sierra-Arguello et al., 2018; Wieczorek & Osek, 2013).

As per a report by the CDC, the number of fluoroquinolone-resistant *C. jejuni* strains increased in the United States by 8.55% between the years 1997 and 2015 (CDC, 2018).

Some emerging pathogens like *Clostridioides difficile* and *Candida auris* have also become a foremost health hazard in the past few years; however, they are not yet incorporated into the WHO priority pathogen list. However, the CDC of the United States has categorized these as high-threat pathogens (CDC, 2019).

5.10 *Clostridiodes difficile*

Problem Statement *Clostridioides difficile* is the most frequently reported hospital-acquired intestinal infection globally (Peng et al., 2017). Nearly all pseudomembranous colitis-related ailments and approximately 15–25% of diarrheal drug-related infections are caused by this organism. This organism is responsible for the rates of demises to an extent of 17% and an even higher rate of 25% in immunocompromised elderly citizens (Dilnessa et al., 2022).

Inappropriate and prolonged use of broad-spectrum antibiotics like ampicillin, amoxicillin, cephalosporins, fluoroquinolones, and clindamycin leads to the disruption of human intestinal flora and the consequent proliferation of *C. difficile* (Leffler & Lamont, 2015). Hypervirulent strains of *C. difficile* are notorious and becoming a major nosocomial pathogen (Dilnessa et al., 2022). The molecular studies from the last decade have shown that hypervirulent drug-resistant strains ribotype (RT) 027 and 078 were responsible for major outbreaks across, Europe, North America, and South Africa (Harnvoravongchai et al., 2017). Numerous epidemics were recorded in Europe, North America, Oceania, and South Africa during the last decade (Borren et al., 2017), whereas outbreaks in Asia were linked to multidrug-resistant *C. difficile* PCR ribotypes 017 and 018. Other less common but reported to have multidrug-resistant activity are ribotypes 053 and 078 (Harnvoravongchai et al., 2017).

Although it has been established that *C. difficile* infection occurs due to antibiotic misuse, its spore-forming nature helps protect against the antibiotic activity and germinate, thereby leading to cases of relapse of *C. difficile* infection (CDI) post-treatment completion (Peng et al., 2017).

Mechanism of Resistance *C. difficile* develops drug resistance mainly by three mechanisms: suppression of the drugs, alteration of the target drug, and active efflux pump. Modification of the target drug occurs through methylation, protection, or some genetic mutation that leads to decreased binding affinity and limited target access. *C. difficile* could make antibiotics nonfunctional by degrading or modifying them via enzymatic degradation and modification. Furthermore, *C. difficile* has also been seen to modulate metabolic pathways to respond to antibiotics. Genome flexibility in *C. difficile* is due to the mobile genetic elements that comprise more than 10% of its genome. Mobile genetic elements contribute to its pathogenicity, virulence, and resistance mechanisms (Harnvoravongchai et al., 2017).

Treatment Options Presently, metronidazole, vancomycin, and fidaxomicin are effective drugs and are projected for managing primary and recurrent CDI. Because only a small number of antibiotics are available as treatment options for CDI, surveillance of circulating strains and their resistance profiles is critical to tackling this pathogen. Some alternatives are also available as treatment options, namely, tigecycline and rifampicin, out of which tigecycline had a lower resistance rate (Sholeh et al., 2020).

From the infection control perspective in the hospital, patients need to be isolated and put under contact precautions to avoid spread in the hospital. Moreover, the bacteria are resistant to commonly used hand sanitizers, and hence, handwashing with soap and water is recommended for all personnel involved in the care of these patients (Turner & Anderson, 2020).

Knowledge of circulating strains, their resistance mechanisms, strict monitoring of the broad-spectrum antibiotics use among hospitalized patients, and adherence to hospital infection control practices are indispensable practices toward curbing these infections.

5.11 *Candida auris*

The Problem Statement *C. auris* was isolated for the first time in Japan in 2009, with a specimen collected from a patient's ear suffering from external otitis media. Before that most cases of invasive candidiasis were caused by *Candida albicans,* but over the last decade, it has shifted to non-albicans *Candida*. The injudicious use of fluconazole to empirically treat cases of invasive candidiasis is responsible for the occurrence of drug-obdurate strains of *Candida auris*. The organism has been found to be associated *with various nosocomial* outbreaks and deep-seated infections in intensive care units of several hospitals. It exhibits resistance to multiple classes of antifungals (Garcia-Bustos et al., 2021; Du et al., 2020).

Therefore, this infection is often associated with treatment failures in the ICUs, especially among the immunocompromised group (Garcia-Bustos et al., 2021). Unlike other *Candida* spp. that colonize the gut, *C. auris* is postulated to primarily inhabit the skin and rarely the gut. Nearly most of its unique

characteristics, viz., high transmissibility, prolonged persistence in the healthcare settings despite the use of common disinfectants, ability to colonize patients indefinitely, and development of multidrug unresponsiveness to most classes of antifungals, made this organism a serious global health hazard. It has been seen to form dry biofilms that resist disinfectants and decontamination procedures done routinely in hospitals. For this reason, *C. auris* is a major concern from an infection prevention and control perspective (Du et al., 2020). In nosocomial conditions, *C. auris* most commonly causes diseases related to bloodstream. Deep-seated 30–60% infections due to *C. auris* are accountable for global mortalities (Du et al., 2020).

Mechanism of Resistance The primary ways of obduracy against triazoles are (i) overregulation that hinders expression of ERG11, (ii) alterations in the ERG11 gene that is responsible for antifungal character, and (iii) overregulation of efflux pumps (Frías-De-León et al., 2020). Data regarding the molecular mechanism responsible for resistance against AMB are still indistinguishable. Nonetheless, considering the mode of action of polyenes, alteration in the pathway of ergosterol through gene mutation in *ERG2*, *ERG3*, and *ERG6* has been assumed to be the most important possibility (Frías-De-León et al., 2020). Information on echinocandin unresponsiveness has also been reported due to mutations observed in *FKS1* and *FKS2* genes (Frías-De-León et al., 2020). More research studies are being carried out to discover and comprehend various means of unresponsiveness in this notorious organism.

Treatment Options *C. auris* isolates have shown a higher frequency of unresponsiveness to the most important and repeatedly employed antifungals in medical practice, namely, azoles and amphotericin B (ICMR, 2020), although resistance patterns differ between clades. Echinocandins are still the drugs of choice for this organism, despite drug-unresponsive strains gradually being discovered (ICMR, 2020). Some alternative therapies being researched are nitric oxide (NO) in nanoparticles, normal peptides, and phenolic compounds. Furthermore, reuse of old drugs like miltefosine and iodoquinol is also being explored (Frías-De-León et al., 2020). Early and timely diagnosis of fungal infections, along with susceptibility report-guided treatment and robust infection control practices, is needed to tackle *C. auris* infections in hospitals.

6 Initiatives in India for Containment of AMR

In the recent years, it has been acknowledged in India that AMR alleviation is a nation's main concern. India has announced various approaches, changing from instructive and responsiveness initiatives, infection governing regimes, reconnaissance agendas, and antimicrobial stewardship to govern the calamity of AMR (Fig. 3).

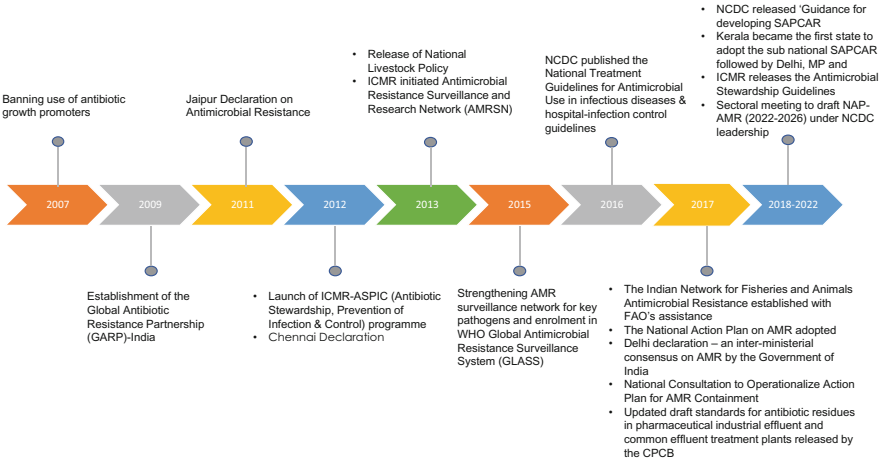

Fig. 3 Initiatives for containment of AMR in India

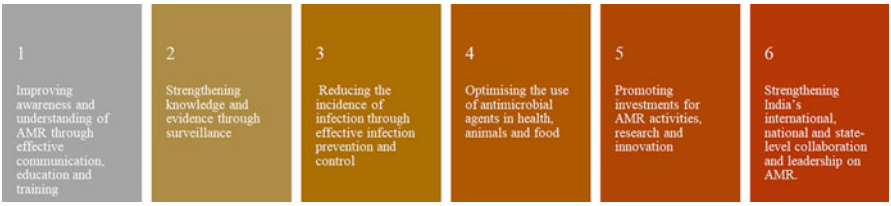

Fig. 4 Strategic priorities of NAP-AMR

6.1 National Action Plan (2017–2021)

NAP-AMR replicates the GAP of WHO and adheres to a One Health concept, including AMR in the perspective of animal, agriculture, environment, and human well-being sectors following the six premeditated primacies (Fig. 4).

Though the NAP-AMR efficaciously emulates WHO's Global Action Plan, inadequate multisectoral coordination, insufficient fiscal support across the nation, poor implementation, and pandemic of COVID-19 have hampered the progress.

6.2 Combating AMR: Concept of "*One Health*"

The concept of "*One Health"* is based on a combined strength of numerous disciplines that join together to make available elucidations for animal, environmental, and human well-being. In the process, the impediments to surpass are the contending benefits of manifold fiscal sectors and organizations mentioned above. Various stakeholders need to agree on key priorities for action, the best ways to monitor AMR and control infections, and the policies that should govern

Fig. 5 Key strategies for addressing AMR from the One Health approach

antimicrobial use. Some of the significant stratagems for tackling the menace of AMR from the "*One Health"* approach are shown in Fig. 5.

7 Conclusion

Though India has announced capable actions for undertaking AMR, there is a long way to go and necessitates noteworthy determinations from all interested parties. Vigorously augmented intersectoral coordination and public–private partnerships will help reinforce the nation's crusade on AMR. To fight drug obduracy menace, it is mandatory to back "One Health" system that includes animal, environment, human, and plant health. A collaborative effort from all sectors, including human, faunal, food, and environment, is obligatory to control the advent and transmission of multidrug-resistant "superbugs" as these pathogens add tremendous health and financial burden by increasing morbidity and mortality.

Acknowledgments The authors thank Moe Moore, Reeti Hobson, Ashima Jain Vidyarthi, Shreeparna Ghosh, and Rajesh Bhatia for their efforts in providing an insightful review and inputs to refine the chapter.

Disclaimer This chapter was created with funding from the USAID, Global Health, under the terms of the Infectious Disease Detection and Surveillance contract GS00Q14OADU119. Opinions stated are not essentially those of USAID or the US government.

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