MULTI-DRUG RESISTANCE AS A THREAT TO HUMANKIND

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CERTIFICATE

It is hereby certified that the dissertation entitled "**MULTI-DRUG RESISTANCE AS A THREAT TO HUMANKIND**" has been carried out entirely by Twinkle Sipani, student of SEM VI, B.Sc. (Gen) in the Department of Botany, MUC Women's College, Burdwan University, Purba Bardhaman under my supervision. It is further certified that the candidate has fulfilled all the conditions necessary for the partial fulfilment of her B.Sc. (Gen) degree achievement under this University and this work has not been submitted anywhere for any other degree to the best of my knowledge.

Dr. Pritam Chattopadhyay

Place: Purba Burdwan

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SUMMARY

The world of science faces a significant issue as a result of the multidrug resistance to common medications, demanding the creation of innovative antibiotic medicines. Due to consumers' extensive exposure to antimicrobial medications during the coronavirus (COVID-19) epidemic, the issue of multidrug resistance will only worsen over time. Re-examining the phenomenon of resistance to multiple medications in order to develop efficient antibacterial medications is therefore urgently required. As a consequence, this dissertation provides insight into the multidrug crisis that poses a danger to people. It draws attention to the issue, its importance, and possible solutions to deal with microbial resistance. The dissertation is distinctive since it covers the root causes of multi-drug resistance, how it is classified, and its mechanism of action. Globally, the danger to the general population posed by diverse microbiological species (infectious agents) susceptibility to multiple antibiotics is growing at an alarming rate. It leads to an ineffective microbiological reactivity to normal therapy, which results in extended sickness, increased healthcare costs, and a significant risk of mortality. This absence of microbiological responsiveness to conventional therapy is caused by the rapid emergence of novel mechanisms of resistance and decline in the effectiveness of addressing prevalent viral illnesses. As a result, there are elevated incidences of multidrug resistance (MDR) and higher rates of death and morbidity. Nearly all effective infectious agents (such as bacteria, fungi, viruses, and parasites) are commonly referred to as "super bugs." Despite the fact that the growth of MDR is naturally occurring, improper antibiotic use, unsanitary living situations, improper handling of food, and subpar measures to prevent and control infections all are contributing to its appearance and its propagation. There is a dire requirement for innovative strategies to treat illnesses brought about by bacterial strains that are becoming more and more drug-resistant.

This dissertation has explored a number of strategies, including recent advancements in efflux pump inhibitors; novel strategies including interfering with the bacterial response to antibiotic presence by targeting bacterial signalling pathways. Early diagnosis of a viral infection's cause, which aids in choosing the best approach to treatment, is one strategy to avoid the careless abuse of antibiotics. Antimicrobial agents are frequently prescribed by clinicians in India for the treatment of viral illnesses. Quick testing can prevent antibiotic overuse at the point of service by identifying the precise bacteria and the medication to which they are most sensitive. The COVID-19 pandemic served as an example of the manner in

which soon people may be provided with swift tests for illness. Similar to this, research is required to diagnose AMR in order to build precise and economical detection techniques and uncover the proper biomarkers to find infections that are multi-drug resistant. Such work might be funded by organisations like ICMR and BIRAC.

Numerous individuals died from drug-resistant superbugs in 2019 than from HIV/AIDS or malaria combined, and the U.N. predicts that this figure may rise to ten million by 2050. MDR is growing, and the usage of emergency antibiotics such as cephalosporins is surging in India, the world's biggest customer of antibiotics. In 2040, the nation is expected to be hit by more than 1.6 million cases of transmissible illnesses that are resistant to several drugs, which is a considerable increase from any other nation. The signs are clear, yet it seems like our existing strategies to stop the propagation of superbugs are insufficient.

1. INTRODUCTION

Multi Drug Resistance (MDR) has ever since been increasingly threatening to human beings, hence has great importance in medicine and for the researchers trying to find a way to handle it. It has been a significant source of concern as one of the leading reasons of antibiotic failure over the world. MDR can be defined as the resistance or insensitivity of a microorganism developed to the administered antibiotics (having different structure and molecular targets) which were earlier sensitive to it (Singh, 2013). These microorganisms show resistance to the antibiotics thus rendering the treatment ineffective and hence the infection keeps spreading making it impossibly hard to cure it. Microbes include all types of fungi, viruses, parasites and bacteria. Bacterial infections are responsible for one in every eight global deaths (Rogers and Katwyk, 2023).

The inefficient measures to cure an infection, unhygienic surroundings, and unregulated use of antimicrobial drugs are responsible for the global rise of MDR. Also, since the recent pandemic the use of antibiotics has been huge. In addition to saving patients' lives, antibiotics have been instrumental in accomplishing major developments in both surgery and medicine. They have effectively treated diseases that can occur in patients receiving chemotherapy, the ones with chronic diseases such as end-stage kidney disease, diabetes, or rheumatoid arthritis, or those who have undergone complicated procedures such as organ transplants, joint replacements, or cardiac surgery (Gould and Bal, 2013). Antibiotics have also contributed to increased longevity by altering the course of infections caused by bacteria. They have reduced the number of casualties resulting from food-borne and other poverty-related infections in developing countries where sanitation is still deficient (Rossolini et al., 2014).

Sir Alexander Fleming's 1928 discovery of penicillin is what developed into the current era of antibiotics (Sengupta et al., 2013). Since then, Antibiotics have changed contemporary medicine and saved millions of lives. Antibiotics were originally prescribed to treat serious infections in the 1940s (Antibiotic resistance threats in the United States, 2013). Penicillin proved effective in treating bacterial illnesses among soldiers during World War II. But soon penicillin resistance became a significant clinical problem threatening many of the previous decade's advancements by the 1950s.In response to this new beta-lactam antibiotics were found, manufactured, and disseminated, restoring trust. However, the first instance of

methicillin-resistant *Staphylococcus aureus* (MRSA) was detected within the same decade, in the United Kingdom in 1962 and in the United States in 1968 (Sengupta et al., 2013).

In order to combat methicillin resistance in both *S. aureus* and coagulase-negative staphylococci, vancomycin was first made available in clinical settings. Because it was so difficult to establish vancomycin resistance, it was thought unlikely to occur in a clinical environment. But unfortunately, Vancomycin resistance cases were also documented. To address the issue of antibiotic resistance, the pharmaceutical industry introduced a large number of new antibiotics from the late 1960s through the early 1980s. However, beyond that point, the supply chain for new antibiotics stopped and significantly fewer new medications were introduced. As a result, bacterial infections returned in 2015, many decades after the first patients were treated with antibiotics.

Sir Alexander Fleming who was awarded noble prize for discovery of penicillin mentioned the issue of antibiotic misuse in 1945 and warned when he predicted that "the public will demand [the drug and] ...then will begin an era... of abuses.″ he also said that “the time may come when penicillin can be bought by anyone in the shops,” and “then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to nonlethal quantities of the drug make them resistant”. This occasion arrived within a century of his forecast. Antibiotic usage undoubtedly promotes the emergence of resistance. Study data has shown a link between the use of antibiotics and the establishment and spread of resistant bacterial species (**GARDP**). Genes in bacteria can be acquired from closely related people or transferred from distant relatives through mobile genetic elements like plasmids. Through this process of horizontal gene transfer (HGT), antibiotic resistance may spread between several bacterial species. Additionally, resistance can evolve on its own through mutation. Drug-sensitive rivals are eliminated by antibiotics, leaving drug-resistant bacteria to proliferate through natural selection. Despite cautions against abuse, antibiotics are prescribed excessively all across the world.

Antibiotics are often used as cattle growth promoters in both developed and developing nations. Around eighty percent of antibiotics marketed in the US are believed to be used on animals, largely to aid in growth and avoid illnesses. Antimicrobial treatments for cattle are thought to increase their general health, resulting in greater yields and better-quality produce (Michael et al., 2014). Humans acquire these antibiotics that are used in cattle when they eat the cattle as food. Farm animals initially transferred resistant bacteria to people more than 35 years ago, when significant levels of resistance to antibiotics were discovered in the gut of both livestock and farmers. Molecular detection methods have recently proven that

resistant bacteria in agricultural animals reach consumers via meat products. This is accomplished with the following series of events:

1) Antibiotic administration to animals that produce food eliminates or hinders vulnerable bacteria, enabling resistant bacteria to evolve;

2) Resistant bacteria are passed on to consumers through the food; and

3) These bacteria are capable of causing illnesses in humans, which can lead to negative health outcomes (Antibiotic resistance threats in the United States, 2013).

Because of our careless use of antibiotics, microorganisms such as bacteria, viruses, fungi, have developed resistance to frequently used antimicrobials. Worryingly, these microorganisms are changing quicker than we can develop medications to combat them. Our antimicrobial stockpile is depleting, while drug resistant microorganisms evolve and take over the planet. MDR is a developing public health problem that requires a multifaceted approach to be solved.

Multidrug resistance is connected with high death rates and high healthcare costs, and it has a considerable impact on the antibiotic's effectiveness. MDR complicates disease control by increasing the chance of resistant microorganisms spreading, lowering the effectiveness of therapy and, as a result, increasing the course of infection in the patient. MDR has also increased the expense of therapy since microorganisms have developed resistance to readily affordable medications, demanding the adoption of more expensive remedies. The rate of effectiveness of modern treatments such as transplantation of organs and treatment of cancer has greatly contributed to the development of MDR (Fishbain and Peleg, 2014).

While mankind is recovering from the severe stage of the COVID-19 pandemic, the extremely dangerous but concealed MDR pandemic is, sadly, here to stay. The majority of nations recognized COVID-19 as a clear and present risk in 2020, pushing governments, including India's, to react swiftly and precisely. Rapidly escalating MDR rates necessitate a multi-sectoral, worldwide and nationwide reaction. India is the world's capital of MDR, making it an emergent epidemic that requires quick response from decision-makers and the community of scientists (Chakravortty, 2023). Pneumonia, that needs to be cured by antibiotics, was a major contributing factor in many of the fatalities among COVID-19 hospitalized patients. Potent antibiotics are needed to treat these bacterial illnesses, but as MDR rises, these drugs are becoming harder to come by. In essence, protecting the few remaining powerful antibiotics is essential to reacting to any epidemic. It is for this reason that the probable repeal of policies that will decrease MDR and better protect the efficacy of

antibiotics is so worrisome (Rogers and Katwyk, 2023). All of this makes MDR significant, and it is a problem on which humans must have a high priority if antibiotic use is to remain successful in the future. As a result, given the rising challenges to humanity, this issue has been chosen for my research.

2. HISTORY

A major influence on human history has been caused by pandemics. They have brought about significant wrongful deaths, social unrest, economic instability, and political change. They have also sparked the creation of new medicines and scientific breakthroughs like the development of vaccinations and antibiotics. They have also emphasised the importance of global solidarity and cooperation in solving health concerns on a global scale (Taylor, 2021).

Pandemics have been a recurrent topic throughout history (Morens et al., 2020). The Plague of Athens in 430 BC was the first recorded pandemic, killing one-third of the city's inhabitants. The most well-known pandemic was the 14th-century Black Death, which killed an estimated 75-200 million people in Eurasia. The 1918-1919 Spanish flu pandemic affected an estimated 500 million individuals globally and killed between 50 and 100 million. More recently, we've witnessed the HIV/AIDS pandemic, which has killed over 32 million people since the 1980s, as well as the COVID-19 epidemic, which has killed millions of people globally since it began in 2019 (Sharma et al., 2022).

Table 1: Modern Flu Pandemics (Sharma et al., 2022)

S. No.	Pandemic	Year	Catastrophe
1	Black Death	14th century	75,000,000 deaths
2	Cholera	18th century	Every year 1,300,000 to 4,000,000 people are infected around the world, killing 21,000 to 143,000 people
3	Third plague pandemic	19th century	12,000,000 – 15,000,000 deaths
4	Spanish Influenza	1918–1920	500,000,000 people were affected
5	Asian Influenza	1957–1958	2,000,000 deaths globally
6	Hong Kong Influenza	1968–1969	1,000,000 death worldwide
7	Russian Influenza A (H1N1)	1977	–
8	HIV/AIDS pandemic	First detected in 1981 and it was a pandemic by late 20th century	Approximately 35,000,000 deaths
9	Severe Acute Respiratory Syndrome (SARS)	2002	8422 cases and 916 fatalities
10	Swine Flu pandemic (H1N1 Influenza)	2009–2010	151,700 to 575,400 deaths
11	Ebola epidemic	2014–2016	28,600 reported cases and 11,325 deaths
12	Covid-19 Pandemic	2019–present day	169,118,995 reported cases and 3,519,175 deaths

3. PANDEMICS, DISEASES AND ANTIBIOTICS RESISTANCE

While pandemics have always existed, breakthroughs in science and medicine have helped us to understand and battle them. Antibiotics have been frequently used during pandemics to treat secondary bacterial infections that emerged due to a compromised immune system. During the 1918 Spanish flu pandemic, for example, many deaths were caused by secondary bacterial illnesses such as pneumonia (????). Because antibiotics were unavailable at the time, many of these infections proved fatal. Antibiotics were found in the early twentieth century and have since been a pillar of contemporary medicine. Antibiotics were utilized to treat secondary bacterial infections that occurred in critically unwell patients during the COVID-19 pandemic. However, antibiotic overuse and misuse have resulted in the creation of antibiotic-resistant bacteria, which posed as a severe hazard during the pandemics (Manyi-Loh et al., 2018). Antibiotic-resistant illnesses have proved more difficult to treat and are associated with a higher fatality rate. During the COVID-19 pandemic, for example, there were concerns about antibiotic usage in some nations, which lead to the emergence of antibiotic-resistant diseases. Antibiotic resistance is more than just a problem for specific diseases. It is also a public health issue in general. When bacteria become resistant to antibiotics, it can make disease control more challenging. For example, if a person develops an antibiotic-resistant bacterial illness, they can transfer the infection to others. This may give rise to outbreaks of diseases that are hard to contain (Chedid et al., 2021). Table number two contains some MDR bacteria, as well as the diseases linked with them, which according to WHO investigations are very frequently occurring (Tanwar et al., 2014).

The above given *Staphylococcus aureus, Enterococcus faecium, Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumannii,* and *Enterobacter species* (ESKAPE pathogens) are responsible for the majority of infections worldwide, having high rates of drug resistance, and have been linked to several life-threatening diseases (Levin et al., 1999). Other MDR microorganisms include *E. coli, Streptococcus pneumonia (S. Chang et al., 2003)*, *Mycobacterium tuberculosis*, *Cryptococcus neoformans*, Human immunodeficiency virus (HIV), Influenza virus, Hepatitis B virus (HBV), *Plasmodia spp.,*

Table 2: Common MDR microorganisms and diseases (Tanwar et al., 2014)

Name of microorganisms	Associated diseases	Drug resistance
Staphylococcus aureus	Systemic, skin, bone, and lung infections	Penicillin, Methicillin, and Vancomycin
Escherichia coli	Systemic infection and urinary tract infections (UTI)	Cephalosporins, fluoroquinolones, penicillin, erythromycin, amoxicillin
Klebsiella pneumoniae	Systemic infection, UTI, pneumonia, abdominal infection, pyogenic liver abscess, and meningitis	Cephalosporins carbapenems, aminoglycoside, quinolones, tetracycline, and colistin
Streptococcus pneumoniae	Pneumonia, otitis, and meningitis	B-lactams, fluoroquinolones, macrolides, lincomycin, tetracyclines, and trimethoprim-sulfamethoxazole
Mycobacterium tuberculosis	Tuberculosis (TB)	Rifampicin, isoniazid, and fluoroquinolone
Cryptococcus neoformans	Cryptococcal meningitis	Fluconazole, Flucytosine
HIV	AIDS	Antiretroviral drugs
Influenza virus	Respiratory infections	Adamantane derivatives and neuraminidase inhibitors
HBV	Hepatitis B (Liver infection which can lead from cirrhosis to liver cancer)	Lamivudine, nucleos(t)ide analogues (NUCs)
Plasmodia spp.	Malaria	Chloroquine, artemisinin, and atovaquone
Leishmania spp.	Leishmaniasis	Pentavalentantimonials, Diamidine, Miltefosine, Paromomycin, Amphotericin B, Ketoconazole, Allopurinol
Entamoeba	Amoebiasis	Metronidazole, Trifluoromethionine
Trichomonasvaginalis	Trichomoniasis	Nitroimidazoles, Trifluoromethionine

Leishmania spp., *Trichomonasvaginalis*, and others that are resistant to drugs such as cephalosporin, macrolides, rifampicin, isoniazid, fluoroquinolone, fluconazole, antiretroviral drugs, adamantane derivatives, neuraminidase inhibitors, lamivudine, chloroquine, artemisinin, atovaquone, pentavalentantimonials, miltefosine, paromomycin, amphotericin B, and nitroimidazoles, respectively (Berkow and Lockhart, 2017). When these microorganisms are treated with the conventional methods of therapy, they cause severe diseases such as hepatitis B, UTIs, pneumonia, otitis, tuberculosis, trichomoniasis (Tanwar et al., 2014).

4. CLASSIFICATIONS OF MDR

In spite of receiving sufficient drug doses over a prolonged duration, the persistence of pathogenic microorganisms suggests the formation of drug resistance. The survival of these bacteria is based not solely on their resistance to specific medications, but also on poor drug bioavailability, rapid drug metabolism, and weak host immunity. However, the continued existence of bacteria even after extensive standard therapies sheds a spotlight on various types of resistance. They are namely primary, secondary, and clinical resistance (Tanwar et al., 2014).

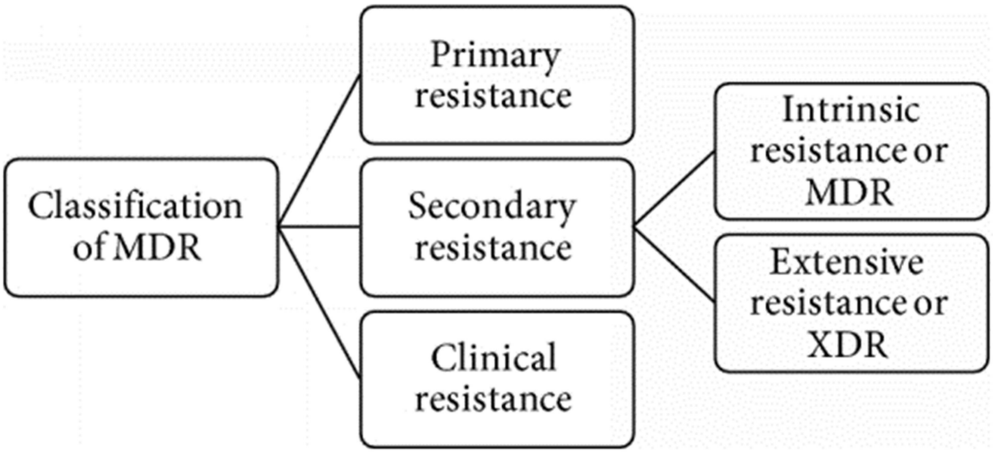

Figure 1: Classification of MDR. (Tanwar et al., 2014)

Primary Resistance: Primary resistance occurs when organisms develop tolerance to a variety of medications despite having no previous contact with the drug of interest (Gottesman et al., 2004). Alteration in drug metabolism or drugs target evolution can lead to this resistance metabolism is primarily concerned with absorption, elimination, and purification (Zahreddine and Borden, 2013). Absorption is mainly influenced by the chemical composition of the drug and the receptors used in its intake. Hence changes in these receptors cause the resistance. Additionally, a number of membrane transporters that increase drug efflux are to blame for the formation of resistance. Furthermore, modifications in the drug targets, such as changes to the site of binding, and drug deactivation by modifying metabolic pathways help the resistance (Khalilzadeh et al., 2006). Clinically isolated strains of *M. tuberculosis,* for instance, exhibited primary resistance to rifampicin, isoniazid, streptomycin,

and ethambutol (Song et al., 2019). Mutation in the rpoB gene of the RNA polymerase and the katG, inhA, ahpC, and kasA genes, respectively, are linked to rifampicin and isoniazid resistance (Abraham et al., 2020).

Secondary Resistance: This concept, sometimes known as "acquired resistance," refers to resilience that develops in an organism after interaction with the drug. It is further subdivided as follows**.**

I. **Intrinsic resistance:** It denotes to the apparent insensitivity by all bacteria, pathogen or viruses of a single species to a particular common first-line medications used for the treatment of illnesses depending on the individual's medical records. It is additionally referred to as Multidrug Resistance (MDR), for instance, *Mycobacterium tuberculosis* to rifampicin and isoniazid or *Candida spp*. to fluconazole.

II. **Extensive resistance**: It refers to a microorganism's potential to survive the hindering impact of at least one or two of the most potent antimicrobial medications. This, also known as XDR, appeared in individuals following treatment with first-line medicines, such as XDR-TB resistance to fluoroquinolone (Tanwar et al., 2014).

Clinical resistance: This is characterised as a microorganism's resistance to therapeutically acceptable doses of the treatment, which is related to treatment failure or the return of infections due to reduced host immune function, like in neutropenia. These organisms can be efficiently suppressed with medicine doses that are substantially higher compared to clinically acceptable levels or through a combination of therapies. for example, *S. aureus* is resistant to vancomycin and *A. baumanni*, is resistant to meropenem. The most prevalent source of meropenem resistance in *A. baumanni* is chromosomal AmpC gene overexpression; subsequently, vancomycin resistance in *S. aureus* is caused by a vanA gene cluster borne by the mobile genetic component Tn1546 obtained via vancomycin-resistant enterococcus (Sharma et al., 2022).

5. MECHANISM OF MDR

The insensitivity of a microorganism to an antimicrobial treatment as opposed to other samples of the identical species is referred to as resistance. Despite the commercialization of various new medications, the emergence of resistance amongst pathogenic organisms is growing, particularly in individuals who have had continuous exposure to drugs. Antimicrobial medicines usually work on microorganisms either by blocking a metabolic pathway such as nucleotide synthesis, which in turn inhibits DNA/RNA synthesis, additionally protein synthesis, and cell membrane disruption, or by competing with the starting material of any enzyme responsible for cell wall synthesis. Microbes have developed a plethora of methods to circumvent therapeutic efficacy and survive drug exposure. The four primary biochemistry techniques using which microbes gain antibiotic resistance are target alteration, drug inactivation or destruction by enzymes, reduced drug absorption by decreased permeability of the membrane, and drug efflux via efflux transporter. In both microbial and fungal species, the cell wall is critical for existence. As previously noted, medicines decrease cell wall formation by attaching to the peptidoglycan layer in bacteria or altering ergosterol synthesis (e.g., polyenes) in fungi, hence inhibiting cellular development and division. Microbes such as *K. pneumoniae*, undergo mutations in chromosomes or exchange of extrachromosomal DNA elements via pairing or transformation (horizontal gene transfer), which can result in changes in cell membrane composition (e.g., a decrease in the ergosterol material of the fungi plasma membrane), leading to reduced permeability and drug absorption into the cell. Changes in the composition of membranes (for example, -1,3-glucan and lipid content in fungal cell membrane) results in the absence of active target regions for medications (for example, echinocandins in fungi). Changes in the target's genes generate alterations in molecules and preserve the activity of cells by decreasing sensitivity to suppression. A different cause of MDR was discovered to be an increased expression of drug target enzymes causing target bypass because of alteration in specific pathways of metabolism (e.g., azoles and allylamines in fungi), which leads to the generation of different molecules of target and disruption of certain protein synthesis, that may affect drug entry into the target regions.

Random variation of the chromosomal bacterial genome often affects modifications of the targets. Changes in RNA polymerase and DNA gyrase, for instance, result in resistance to rifamycin and quinolones, respectively. Certain types of genetic transfer (conjugation,

transduction, or transformation) from different microbes may result in the formation of resistance in some cases (Tanwar et al., 2014). For example, in *S. aureus*, acquisition of the mecA genes encoding methicillin resistance and in enterococci, acquisition of the different van genes encoding glycopeptide resistance. Due to the variety of gene encoding, the formation of bacterial enzyme superfamilies is linked to another significant resistance mechanism. Hydrolysis of amide as well as ester bonds results in the deactivation or chemical destruction of antibiotics (such as the development of antibiotic resistance to β-lactams because of β-lactamases etc.). and the chemical modification of these substances through acetylation, phosphorylation, glycosylation, adenylation, and hydroxylation has additionally emerged as potential MDR-causing factors. Clinically isolated specimens of resistant varieties of various organisms have the capacity to oxidise or decrease antibiotic chemicals in order to inhibit contact with the appropriate targe. Antiviral medications often prevent reverse transcriptase function in DNA polymerase thus hindering the replication of viruses. Mutations that occur in antibiotic-resistant variants impact how the drug and the enzyme interact. Any structural alterations or altered substrate attachment to the viral polymerase can result in the emergence of resistance to the medication's inhibitory impact on the enzyme.

MDR in parasites has arisen as a major global health issue due to the absence of potent antiparasitic vaccinations and the sluggish development of new medications. Similar to bacteria or fungi, these parasites, like *Plasmodia spp*. and *Toxoplasma gondii*, are also subject to point mutations/substitutions that alter the targets of medicines, impacts calcium homeostasis in the ER, and eliminate medications (such as artemisinin, chloroquine, atovaquone, antifolate combination drugs, and atovaquone) from the cells (????). The most prevalent MDR mechanism is still the one driven by drug efflux pumps. MDR typically results from the excessive expression of genes encoding for ATP-binding cassette (ABC) transporter membrane proteins, also referred to as the multidrug efflux pumps that are in charge of the transfer or elimination of drugs from the cell, such as P-glycoprotein (Pgp), and it does so without interfering with cellular processes. In membranes or multidrug resistance proteins (MRP) of *Entamoeba spp*. and *Leishmania spp.*, the excessive expression of P-glycoprotein alters mobility and permeability, causing the drugs to exit the cell in an ATP-dependent manner and thus lowering their levels inside the cell. Cancer cells also make use of MDR, which restricts the administration of chemotherapy over an extended period of time. An understanding of the processes underlying chemoresistance, which can develop either at the start of therapy (innate) or during treatment, reveals that cancer cells overexpress specific multidrug resistance proteins (e.g., MRP and Pgp), which promote a rise in drug efflux by

inhibiting proper drugs diffusion, inducing DNA repair mechanisms, inhibiting apoptosis, changing drug targets, and changing cell membrane composition (Sharma et al., 2022).

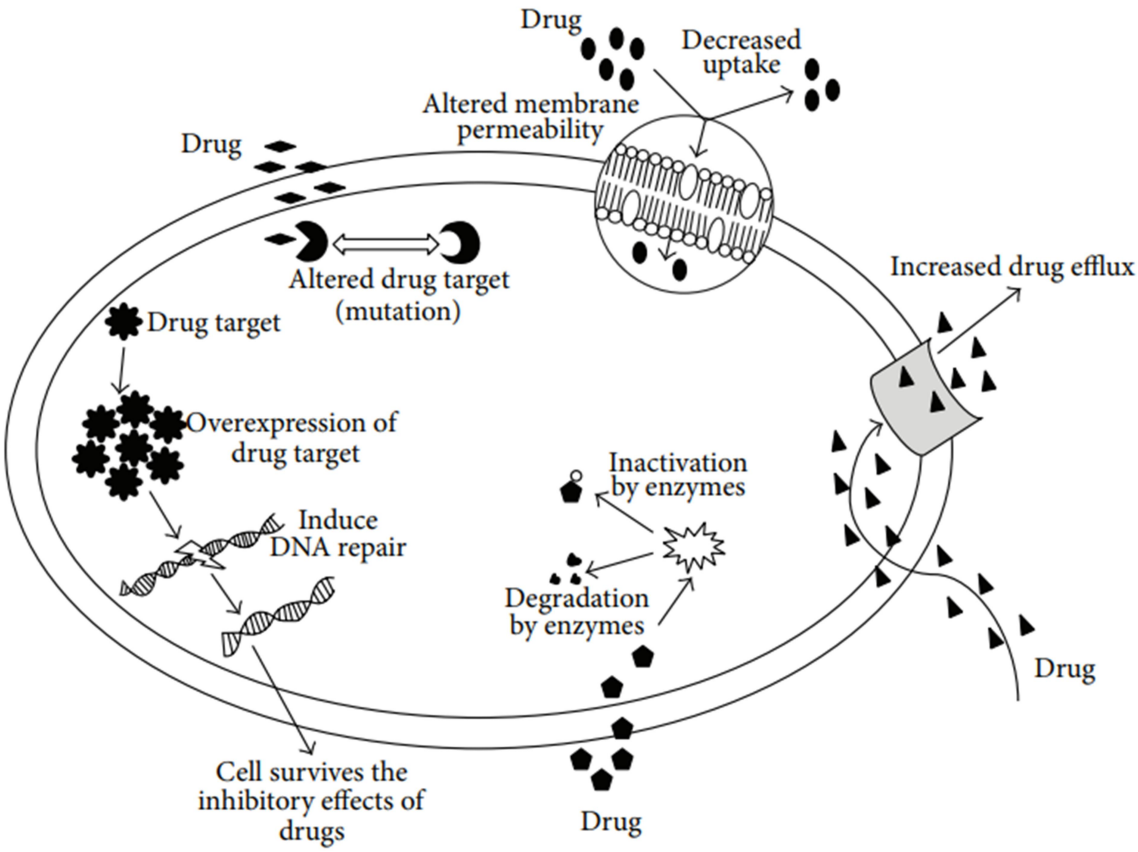

Figure 2: Mechanisms of MDR (Tanwar et al., 2014)

6. CAUSES OF MDR

The fast spread of resistant bacteria has been referred to by many healthcare bodies as a "crisis" or "nightmare scenario" that might have “catastrophic consequences”. In 2013, the CDC claimed that humanity has entered a "post-antibiotic era", and the World Health Organization (WHO) issued a severe warning about the antibiotic resistance situation in 2014. Some causes of MDR are as follows:

Inadequate Prescription: Drug misuse and excess use is one of the leading and main causes of MDR bacteria. When medications are given incorrectly or needlessly, bacteria that are resistant to antibiotics can emerge. For example, when antibiotics are prescribed for a viral illness, it will not be useful. This is because antibiotics only operate against bacterial diseases. Hence Antibiotic resistance may develop in bacteria gradually, leading to the emergence of MDR bacteria. Inadequate prescription of antibiotics is a big cause for the emergence of MDR bacteria. Such a case occurs when doctors prescribe antibiotics but they give it for incorrect duration or an incorrect amount. And when medications are not prescribed in the correct amount, it causes the growth of drug resistant bacteria. It's due to the bacteria not being subjected to sufficient amount of medication to eliminate them. In a comparable manner when medicines are not administered for the proper time frame, MDR bacteria might emerge. This is due to the possibility that the bacteria were not entirely eliminated, which could result in the creation of resistant to antibiotics microorganisms. Inadequately given medicines have unclear beneficial effects and subject individuals to potential antibiotic-related problems. Subinhibitory and subtherapeutic antibiotic doses can induce antibiotic resistance formation by promoting genetic modifications such as variations in the expression of genes, HGT, and mutations. Drug-induced alterations in gene expression can boost virulence, whereas higher mutations and HGT enhance resistance to antibiotics and propagation. Drugs at low concentrations have been demonstrated to aid in strain diversification in microorganisms like *Pseudomonas aeruginosa*. Piperacillin and/or tazobactam at levels below inhibitory have additionally been proved to cause extensive proteomic changes in *Bacteroides fragilis*.

According to antibiotic sales information, India was the largest consumer of antibiotics in 2014, succeeded by China and then the United States. However, per capita antibiotic consumption in India is substantially lower than in numerous nations with high

incomes (Laxminarayan et al., 2016). In addition, the use of antibiotics with a broad spectrum has resulted in significant resistance levels in India. Whenever there's an extensive variety of potential ailments and the possibility of serious sickness would follow if treatment was put off, broad-spectrum antibiotics are often recommended empirically. Nevertheless, the overuse of broad-spectrum antibiotics increases the incidence of antibiotic-resistant bacteria (Asensio et al., 2011). broad spectrum penicillin consumption and Third-generation cephalosporin consumption climbed fast between 2000 and 2015, while narrow spectrum penicillin usage was little and falling. Fluoroquinolone use likewise dropped. To begin, fluoroquinolones have been the cornerstone of treatment of bacterial dysentery and for enteric fever, however due to growing quinolone resistance, third-generation cephalosporins are being employed as basic treatment options for these two frequent illnesses (Taneja, 2007; Mukherjee et al., 2013).

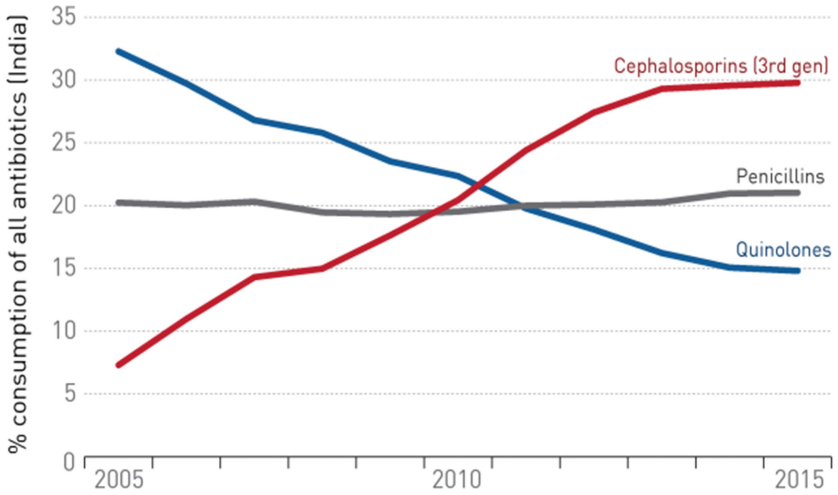

Figure 3: Percentage consumption of various antibiotics in India (Source: QuintilesIMS)

So, why do these healthcare practitioners feel the need to offer substandard prescriptions? The following is the answer to this question: The factors that contribute to inadequate prescriptions for antibiotics among professional physicians differ depending on if they work in the governmental or private sectors. Several variables have been linked to inappropriate prescribing of antibiotics among persons working in the private sector.

First, clinicians may believe they are obligated to prescribe antibiotics because patients arrive with established beliefs and want immediate comfort (Chandy et al., 2013). Since patients spend out of money for treatments, clinicians may be concerned that when they

do not prescribe medicines and alternatively request testing for diagnosis, the patients won't come back, and so they are going to lose their patients (Chandy et al., 2013; Kotwani and Holloway, 2013). Second, the diagnosing ambiguity caused by the incapacity to conduct tests drives clinicians to administer broad spectrum antibiotics in order to avoid a clinical error. Third, drug companies put physicians and chemists on the hook to give patients fresh antibiotics in exchange for monetary rewards (Chandy et al., 2013; Kotwani and Holloway, 2013).

Public-sector clinicians need to treat a large number of people in a short amount of time. As a result, these doctors don't have sufficient time to persuade individuals against using antibiotics and ultimately administer them (Kotwani et al., 2010; Kotwani and Holloway, 2013). Second, microbiological diagnosis testing facilities are not available in public primary health care and supplementary care hospitals. Patients seeing public-sector clinicians are unable to pay for private-lab examinations, forcing clinicians to recommend antibiotics (Kotwani et al., 2010). Third, medication supplies in the public sector may be irregular, with a shortage for certain months and an overabundance in others, and medicines may be nearing expiration. Physicians in the public sector have to suggest antibiotics even if they aren't required by the patient in order to get rid of the drugs prior to their expiry (Kotwani et al., 2010). Although Some criteria apply to public as well as private medical services. One such aspect is the disparity in understanding among health care professionals about the MDR epidemic and even no education on this issue. Hence To avoid the growth of MDR bacteria, medical professionals must give drugs appropriately. This involves prescription antibiotics being used only when necessary and ensuring that the proper quantity and amount of time are given. Doctors should additionally consider the threats and advantages of prescription antibiotics and simply do so if the advantages outweigh the dangers.

Usage of antibiotics in animals for food and in agriculture: Antibiotics are commonly utilized as growth enhancers in cattle throughout nations that are developed and those that are developing. Approximately 80% of medicines supplied in the United States are utilized in livestock, mostly to boost production and infection prevention. Antimicrobial treatment of animals is supposed to contribute to their health as a whole, resulting in increased production and greater quality output. Humans eat this food and ingest antibiotics that are administered to animals. Farm livestock initially transferred antimicrobial-resistant microbes to people over thirty-five years back, after significant levels of drug resistance were identified in the

gut ecosystem of both livestock and workers. Antibiotic utilization in agriculture also has an impact on the environment. As much as 90 percent of drugs administered to animals are eliminated in urine and faeces, where they are widely disseminated via fertilizer, ground water, as well as runoff from the surface. Furthermore, in the western and southern United States, tetracyclines and streptomycin are applied on fruit trees in order to act as insecticides. Although this kind of usage contributes to a significantly lesser share of total usage of antibiotics, the geographical dispersion that results can be significant. This method likewise leads to the contact of environmental microbes to growth-inhibiting chemicals, affecting the ecological balance by raising the fraction of resistant vs vulnerable bacteria (Lee, 2015). Data on sales of antibiotic for livestock management is not obtainable from India. According to farm animals' population density, it is projected that India was the world's 5th largest antibiotics consumer in livestock (poultry, pigs, and cattle) in 2010 after China, the United States, Brazil, and Germany (Van Boeckel et al., 2015). The need for animal-based protein is rising as a result of shifting nutritional needs and wealth patterns; this is fueling the usage of antibiotics in livestock raised for consumption. Consequently, it is anticipated that India's use of antibiotics in the production of animals raised for consumption will increase by 312%, placing it as the world's 4th biggest user of antibiotics in livestock by 2030 (Van Boeckel et al., 2015). It is normal practice to utilize antibiotics to enhance development in chicken and other livestock used for food, although it is unclear how widely this is done.

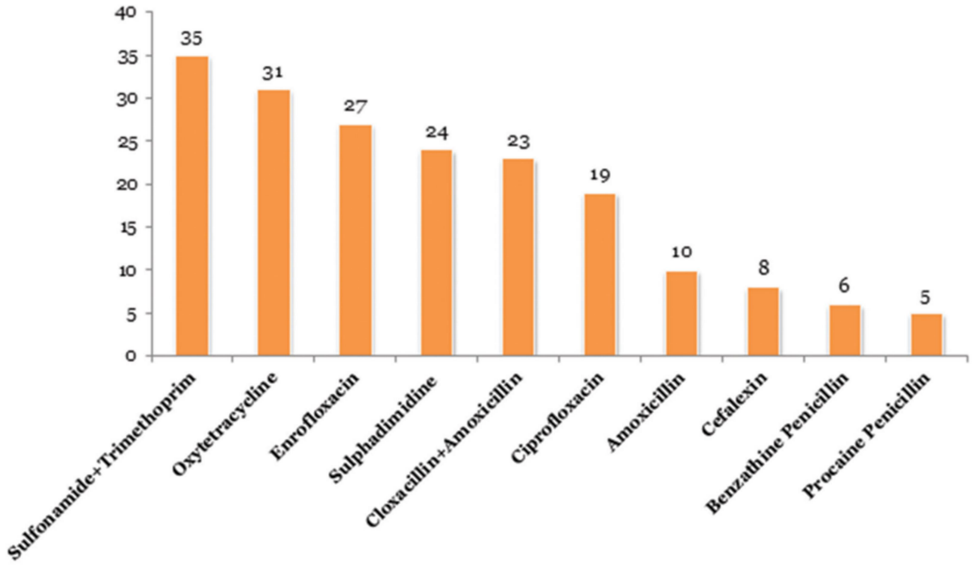

Figure 4: Number of formulation companies manufacturing various antibiotics for human use.

For encouraging growth Chickens are frequently given antibiotics that are critical to the well-being of humans, like colistin, tetracycline, doxycycline, and ciprofloxacin (Brower et al., 2017). In the latest research, which looked at traces of antibiotics in chicken meat intended for consumption by humans, it was discovered that 40% of the 70 samples of chicken meat examined did indeed have antimicrobial residues. Enrofloxacin (20%), ciprofloxacin (14.3%), doxycycline (14.3%), oxytetracycline (11.4%), and chlortetracycline (1.4%) were among the most prevalent antimicrobials found (Sahu and Saxena, 2014).

Parallel to this, erythromycin, sulphonamides, and chloramphenicol traces were found in a variety of shrimp specimens taken from important aquaculture operations in Andhra Pradesh, Karnataka, Kerala, and Tamil Nadu (Swapna et al., 2012). The administration of polymyxins (colistin) for enhancement of growth, prophylactic, and treatment purposes in poultry is an even more worrying issue because this family of medications is the last line of defence for treating life-threatening illnesses in humans. It is extremely pressing to forbid the application of drugs vitally crucial to humans for the promotion of growth in livestock due to the rise of plasmid-mediated resistance (mcr^{-1} gene) due to the use of polymyxins in livestock (Liu et al., 2016) and the possibility of transfer of this gene to human beings. Ironically there is just one firm that makes benzathine penicillin for human use, and at least six companies manufacture benzathine penicillin for animal use.

Few New Antibiotics Are Now Available: Pharmaceutical sector's research of new antibiotics, which had previously been successful in treating resistant germs, had competently frozen because of financial and regulatory constraints. 15 of the top 18 pharmaceutical corporations have exited the antibiotics market. Also, Alliances amongst pharmaceutical corporations have additionally decreased the amount and variety of study teams significantly. Antibiotics discovery in universities has been curtailed as a consequence of funding limitations caused by the financial crisis. Antibiotics production is no more regarded as an investment that is profitable in the pharmaceutical business. Antibiotics aren't as lucrative as medications that cure chronic illnesses such as diabetes, mental disorders, asthma, or gastric reflux since they are administered for a limited amount of time and are generally beneficial. According to an assessment of costs and benefits conducted by the Department of Health Economics in London, the NPV of a novel antibiotic is just around fifty million, opposed to roughly $1 billion for a medicine employed for the treatment of a neurological illness. Drug manufacturers like to put money in chronic illness treatments because these therapies prove to be more valuable. Another element contributing to antibiotic research's not-so-great

commercial attractiveness is antibiotics' cheap cost. In comparison to cancer chemotherapy, which can run into tens of thousands of dollars, modern antibiotics are normally marketed at an average of $1,000 to $3,000 for each treatment. Antibiotics' accessibility, convenience of administration, and low overall costs has contributed to a sense of low worth amongst suppliers and consumers in general (Lee, 2015). Furthermore, researchers in microbiology and infectious-disease professionals have advocated antibiotic caution. As a result, when a novel antibiotic is approved for use, doctors frequently save it for precisely the most severe patients out of anxiety about creating resistance to it, yet they proceed to give older medicines with equivalent effectiveness. As the end result, new antibiotics are frequently regarded as "last-line" treatments for severe infections (Lee, 2015). This method results in a decreased utilisation of novel antibiotics and a worse profit from investment. When novel substances are ultimately utilised, resistance is almost unavoidable. The Great Recession's financial instability has additionally had a hindering influence on antibiotics consumers. Although advanced nations with financially secure medical systems have implemented budget cuts, developing nations like India and China continue to struggle with a big populace who can't afford costly novel drugs. As an added problem, the majority of antibiotics are presently off copyright and are offered by generic medicine makers. As a consequence, everyone now has a supply of low-cost, generally efficient medications; nonetheless, most consumers demand each antibiotic to have their prices priced identically, including new medications aimed at multidrug-resistant (MDR) infections. Due to these issues, many huge pharmaceutical corporations are concerned about a possible absence of yield on their millions of dollars. Whilst the use of drugs such as cephalosporins, quinolones, and macrolides has expanded dramatically in nations with low or middle incomes, the pipeline of novel medicines is depleted. Insufficient financing in scientific research, clinical testing along with supply chain issues, and regulations have all hindered the creation of novel antibiotics. It is costly to create fresh antibiotics, and it generally requires several years for novel medicines to become readily accessible in countries with low to middle incomes. Like it did with Covaxin, India needs to stimulate in-house discovery of novel antibiotics by utilising public-private collaborations among pharmaceutical corporations and government research institutions. Government organisations that include the ICMR and CSIR, in addition to DBT and DST, might collaborate alongside outside organisations such as the Global Antibiotic Research Development Partnership (GARDP), the Wellcome Trust, and many more to advance antibacterial research and conduct exemplary clinical trials.

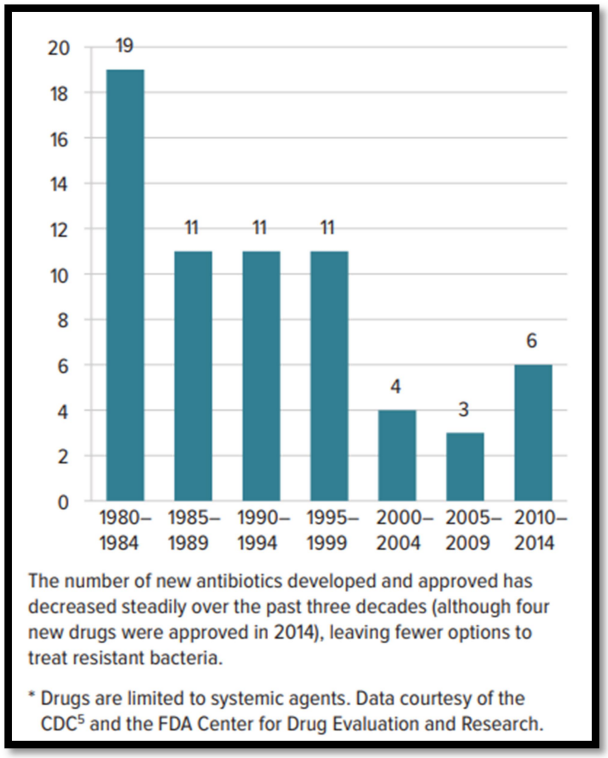

Figure 5: Number of new antibiotics developed (Lee, 2015)

In the Indian subcontinent, wherein private hospitals account for 80% of urban providers of healthcare, resource-constrained hospitals fail to get expensive antibiotics. Creative pricing methods, mass buying of these types of antibiotics, and secured buying agreements from facilities might not just decrease costs but additionally instil trust in the pharmaceutical firms who have committed in antimicrobial discovery. The implementation of comprehensive health care in India might enhance the availability of medicines for over one hundred million households by lowering the cost of medication for people and streamlining government spending through bulk buys. MDR is a growing epidemic, and India is the globe's MDR capital, requiring immediate response from governments & scientists alike.

7. REMEDIES FOR MDR

MDR growth is a challenging topic that has grown into a major global issue. Cooperation is required to reduce the growth and dissemination of MDR since diseases that were formerly preventable are growing into important causes of mortality in this day and age. Furthermore, concentrating on regions that are prone to antimicrobial usage through the introduction of antibiotic stewardship (described as concerted efforts meant to enhance and analyse the proper application of antimicrobials) is critical. Various antimicrobial stewardship programmes (ASPs) are now being implemented to maximise antibiotic therapy, decrease treatment-related costs, enhance clinical results and lower or stabilise MDR. Therapies using ASPs are made by either limiting the accessibility of specific antimicrobial medicines, referred to as "front-end," or by investigating broad range of antibiotic usage and subsequently reducing or eliminating use, known as "back-end". As a result, there exists a pressing requirement for global, regional, subregional, and national assistance and collaboration to assist the pursuit of future progress. While different medications and hypotheses were tested, the results were constant demonstrating a clear link between sensitivity and the development of antibiotic resistance. Significant attempts are now being made to develop techniques for eradicating tenacious microbe cells, which might possibly contribute to the development of resistance (Tanwar et al., 2014).

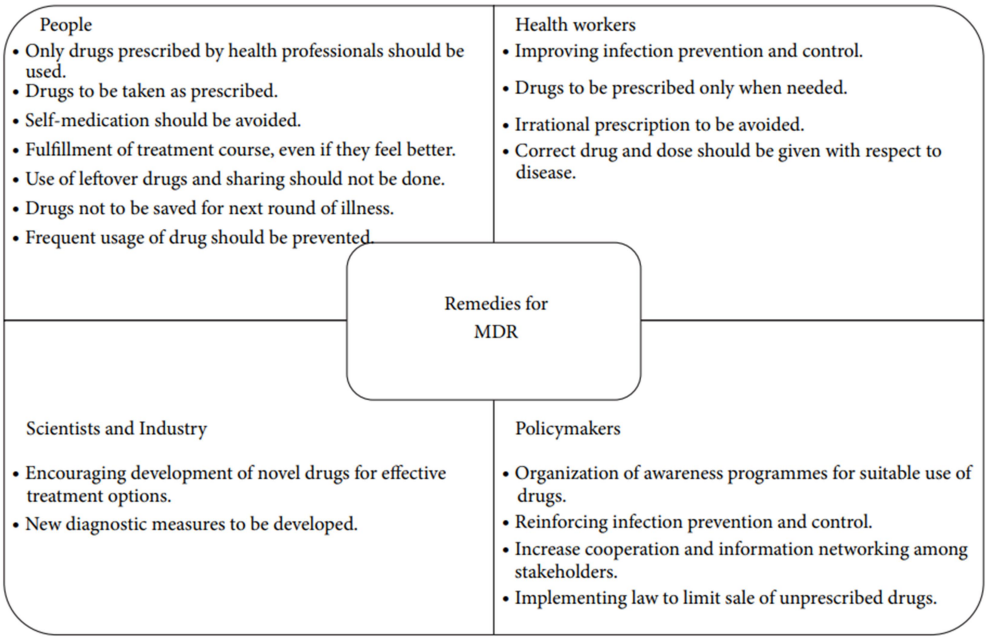

Figure 6: Remedies for MDR (Tanwar et al., 2014)

Resistance to antibiotics gets worse by antibiotic abuse and excessive use, and also by inadequate disease mitigation and management. At every level of the community, efforts can be made to decrease the effect and propagation of resistance.

BY INDIVIDUALS

People can take the following steps to stop the propagation of resistant infections (????):

a. solely take antibiotics as directed by a licenced medical expert.
b. When a health professional tells you that you do not require antibiotics, do not insist on getting them.
c. Consistently heed the advice of your healthcare provider when taking antibiotics.
d. Residue of Medicines must not ever be shared or used up.
e. Avoid direct contact with sick individuals, wash hands frequently, prepare food cleanly, and stay updated on your vaccines to avoid infections.
f. Prepare meals in a hygienic manner (keep clean, distinguish raw from prepared food, cook meals completely, maintain food at suitable temperatures, use hygienic water and raw ingredients), and select food items that have been manufactured minus the application of antibiotics to promote growth or to avoid disease in livestock that are in good health.

BY POLICY MAKERS

- Authorities can do the following to put an end to the propagation of resistance to antibiotics
- Ensure that a strong nationwide approach to combat resistance to antibiotics is in existence
- Boost antibiotic-resistant illness monitoring
- Upgrade the plans, regulations, and practises used to carry out preventive and control strategies
- Regulate and encourage the proper disposal of potent medications
- Spread awareness of the effects of antibiotic resistance (????)

BY HEALTHCARE PRACTITIONERS

Healthcare workers can take the following steps to stop and slow the advancement of resistant antibiotics:

- Prevent infections by keeping your hands, instruments, and surroundings clean (????)

- Follow the most recent recommendations for prescribing and dispensing antibiotics
- Inform surveillance teams about infections that are resistant to antibiotics
- Discuss the risks of improper usage, antibiotic resistance, and proper antibiotic use with your patients
- Discuss infection prevention with your patients, such as immunisation, washing their hands, and closing their mouth and nose when they sneeze.

BY HEALTHCARE INDUSTRY

The healthcare industry can take the following actions to stop and slow the growth of resistant bacteria:

- Making investments in the study and creation of fresh antibiotics, vaccines, diagnostics, and other instruments.

BY AGRICULTURE INDUSTRY

The agriculture industry may do the following to stop and slow the propagation of resistant infections:

- Only provide medicines to livestock under a veterinarian's guidance
- Avoid giving animals who are well antibiotics to promote development or forestall illness
- immunise animals to lessen their requirement for antibiotics and, when possible, employ substitutes to antibiotics
- Encourage and use best practises throughout the entire manufacturing and preparation of food derived from animals as well as plants
- Enhance the well-being of animals and biosecurity on farms to prevent diseases and increase hygiene (????).

8. CONCLUSION

India holds the chance to combat MDR and set an example for other developing nations thanks to its proven competence in pharmaceutical knowledge, expertise, and facilities as seen during the COVID-19 pandemic with the creation and roll-out of vaccines. Encouraging innovation and global collaboration are essential steps in this path. The nation needs to take action immediately because the impending MDR epidemic threatens countless lives. Multi drug Resistance is an international health crisis that is having a disproportionately negative impact on the lives and economies of people in middle-income countries and low-income countries. According to an analysis conducted by Global Research on MDR, 1.27 million fatalities were primarily related to MDR in 2019, and it was projected that 4.95 million individuals had at least one resistant to drugs infection. Arguably India's greatest public health issues, MDR is solely to blame for 30% of neonatal sepsis-related deaths there. In a lot of cases, they are the result of infections contracted in hospitals that are multidrug resistant (MDR). We could be held responsible for nearly thirty percent of the total COVID-19 deaths in the nation by failing to effectively manage the subsequent infections from bacteria brought about by MDR microorganisms. Drug-resistant bacteria are created by the healthcare community's, the overall public's, and producers' irrational usage of antibiotics. Inappropriate prevention of infection at healthcare facilities and hygiene problems in the neighbourhood are the reasons for the propagation of these infections. Undisputed facts include a sharp increase in serious chronic diseases and the emergence of resistant bacteria. Antimicrobial drug shortage forces ongoing research and development of novel medications. In order to regain supremacy over illnesses, multiple education initiatives that should assist with their proper usage have to be developed. MDR is an inevitable natural occurrence that poses a severe global threat to human health. To tackle the MDR, a worldwide cooperation effort is necessary. Pathogens frequently use a variety of strategies for resistance to endure unfavourable circumstances. A more thorough comprehension about the pathobiology of microorganisms will be cultivated thanks to advances in knowledge regarding the molecular pathways governing MDR, which should assist the discovery of innovative medicines to treat these stubborn infections. The enormous improvements in wellness which have been made possible by antibiotics are at danger due to rapidly growing resistant microorganisms. Because of the widespread abuse of these medications and a shortage of novel antimicrobial drugs being developed by drug manufacturers to tackle the issue, the situation is

international. Diseases that are resistant to antibiotics have a significant negative impact on the general public as well as the medical treatment systems in the United States. It is imperative to work together to enact new regulations, redouble research efforts, and explore crisis management strategies.

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Susan Rogers Van Katwyk is adjunct professor, School of Global Health, and managing director, AMR Policy Accelerator, York University, Canada. This information is paraphrased from The Conversation (2023)

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Y.K. Gupta is Principal Advisor India Strategy Development, Global Antibiotics Research and Development Partnership (GARDP). Subasree Srinivasan is Medical Director, Global Antibiotics Research and Development Partnership (GARDP), Geneva