



## Antimicrobial Resistance: A Global Dilemma

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### ABSTRACT

Antimicrobial resistance is one of the most serious global health threats of our time. It causes huge obstacles in controlling infectious diseases. The world health organization explains the major problem is that it creates bacteria with high rates of resistance that can't be fought easily to overcome common infections. It has become progressively serious as certain microbes have reached at a verge of no reasonable antimicrobial which brings about them not having the option to be dealt with. This shows the importance of further research required in the field of antimicrobial resistance as it poses a threat to global health.

**Key words:** Antimicrobial, Bacteria, Health, Microbes, Resistance, Threat.

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### INTRODUCTION

AMR is a situation in which multiple microbes including bacteria, fungi, viruses, and parasites can exist and flourish in the presence of antimicrobials that have been shown to be potent against these virulent microorganisms in the past. AMR patterns that have been reported includes: Multi Drug-Resistant (MDR), Extensively Drug-Resistant (XDR), and Pan Drug Resistant (PDR). XDR is microbial resistance to at least one agent in all but two or fewer antimicrobial categories, whereas MDR is the acquired resistance of microbes to at least one agent in three or more antimicrobial groups. Ultimately, when microbial resistance is developed in every single antimicrobial group, the term PDR is used in this regard [1]. AMR is the direct consequence of inappropriate consumption of antibiotics, high burden of virulent diseases, poor or inadequate

infection prevention, loss of infection control, poor quality medications and the prescription of antibiotics when they are actually not needed for the treatment, inadequate knowledge about AMR, incorrect diagnosis of pathologies, lack of awareness and deficiency in terms of proper diagnostic tools and their application "it is known that the treatment of bacterial infections is highly problematic and creates access for the microorganisms to develop resistance" [2].

Additionally, the spontaneous evolution of microbes, bacterial mutation and transfer of resistant genes *via* horizontal gene transmission dominantly contributes to AMR [3].

The antibiotic era revolutionized the treatment of infectious diseases worldwide, although with much success in developed countries [4].

Antimicrobials have made a remarkable contribution in the history of mankind by saving millions of people. "Antimicrobials have reduced the death rate due to infectious diseases for the past 70 years" [5].

They also make it possible for surgeons to operate in difficult anatomical landmarks, make it possible to transplant organs, and give

oncologists high doses of chemotherapeutic agents for cancer, thereby increasing cure rates and life expectancy [6]. "Emergence of AMR in microorganisms is a natural phenomenon, yet AMR selection has been driven by anti-microbial exposure in health care" [7].

It is a matter of serious concern that antibiotics are no more effective against infectious diseases, it depicts, dark future in the domain of public health. Thus, "More than 25,000 deaths have been recorded annually in Europe due to AMR and around 1.5 billion euro additionally were spent to combat against the consequences caused by these infections.

Despite taking certain actions to solve the problem and to handle this global concern, the trend of global AMR shows no sign of slowing down. "The fact that infectious diseases can no longer be treated with antibiotics depicts an unknown future in health care".

Whole society needs to put their output and practical efforts to cope up with this challenge [8].

#### **Antimicrobial resistance global faceted phenomena**

Microorganisms continue to develop resistance to both new and conventional treatment methods; furthermore, this, joined with the outrageous decrease in antibiotic research has just expanded the size of AMR and its effects on worldwide medical services expenses and results [9].

Italy has the most elevated predominance of AMR among European nations. Infections caused by multidrug-resistant microorganisms are linked to an increased risk of complications, a higher rate of hospitalization, higher healthcare costs, decreased productivity, and increased mortality [10].

#### **Increase rate of infections**

Antimicrobials prevent bacteria from colonizing during treatment and even weeks after the normal microbiota have been restored. During this time, people are more likely to become infected with intestinal pathogens, which mean that a greater percentage of subjects will become infected upon exposure to the pathogen [11, 12].

#### **Mechanisms of AMR and alternative approaches to overcome AMR**

Anti-Microbial Resistance (AMR) rates have been steadily rising globally; one practical

solution to combat AMR is the creation of potent antimicrobial agents. Following are the mechanisms of development of AMR

#### **Barriers to Target Access**

Reduced permeability of the bacterial membrane can prevent an antibiotic from reaching its target. Hydrophilic anti-microbial can diffuse inside the cell of bacteria by the porin proteins which are available in the external film. OmpC and OmpF of *E. coli* are normal instances of the major porins tracked down in most Enterobacteriaceae. Resistant procedures gained by microorganisms include the downregulation for articulation of porin proteins, or the replacement of major porins with more-specific film channels.

#### **Transformation in Antibiotic targets**

Antimicrobial resistance can be caused without affecting the target's function by morphological changes that reduce antibiotic binding efficiency. A solitary point transformation in the quality can bring about obstruction towards the given antibiotic [13].

#### **Adjustment (and Assurance) of Targets**

Post-translational change of targets is one more approach to accomplishing anti-microbial resistance without a mutational occasion happening in the genes encoding target particles.

#### **Direct antibiotic modification**

Microbes can likewise adjust the construction of antibiotics, making them inert. One of the mechanisms to inactivate microorganisms is through hydrolysis response. Until now, there are an assortment of enzymes, for example, carbapenemases, chloramphenicol acetyltransferases, which can corrupt or modify various classes of anti-microbial, for example, macrolides,  $\beta$ -lactams, aminoglycosides and phenicol's.

#### **Development and spread of antibiotic resistance in the environment**

The environment serves as both a vehicle for the spread of AMR microbes and a source of antimicrobial pollutants that have a negative impact on biodiversity and ecosystems (UNEP, 2022). Therefore, the same factors that alter microbial diversity and facilitate the development, transmission, and dissemination of AMR are linked to the triple planetary crisis of climate change, loss of biodiversity, and pollution (UNEP, 2022) [14].

**Consequences of AMR on Economy**

The time span of 15 years w.e.f 2000 to 2015 global use of antibiotics has elevated drastically at a rate of 65percent. The major reason being is the greater consumption of such drugs. The World Bank is highly concerned and issued a thorough report that if this phenomenon continues the global exports of antibiotics will substantially be reduced by 2050. Hence the unacceptable and unpleasant effects of AMR poses serious threats on labor incentive sectors and the effects will be more severe in long term [15-18].

Following Figure 1 clearly shows the economic consequences of AMR in the society at various levels.

**Ecology and evolution of AMR in bacterial communities**

The organization, design and connections inside microbial species are known to influence the Horizontal Gene Transfer (HGT) of antibiotic resistance. In Figure 2 Inter-species interactions are particularly those connections that influence the seriousness of diseases as well as modify the physiological reactions to antibiotics [20].

**Impact of Interspecies interaction**

The term "resistance" refers to a microorganism's capacity to grow in the presence of an antibiotic due to changes in the bacterial DNA caused by mutations or Horizontal Gene Transfer (HGT) [figure 3], which raise the microorganism's MIC (Minimum Inhibitory Concentration).

**Microbial biofilm control strategies**

Different arrangement of microorganisms in biofilms offer variable degree of antibiotic resistance and resultant severity and nature of microbial disease [Figure 4]. Almost everywhere, including medical implants, living tissues, water pipes and channels, hospital floors, food preservation units, and other biotic and abiotic surfaces, biofilms exhibit a variety of pathological manifestations [22].

**Use, Misuse and Overuse of antimicrobials**

Since the time of discovery of antibiotics scientists were very much concerned about the phenomenon of antibiotic resistance, they were well aware and well informed about the increased demand of antibiotics due to their efficacy in the treatment of infections. Apart from this, different

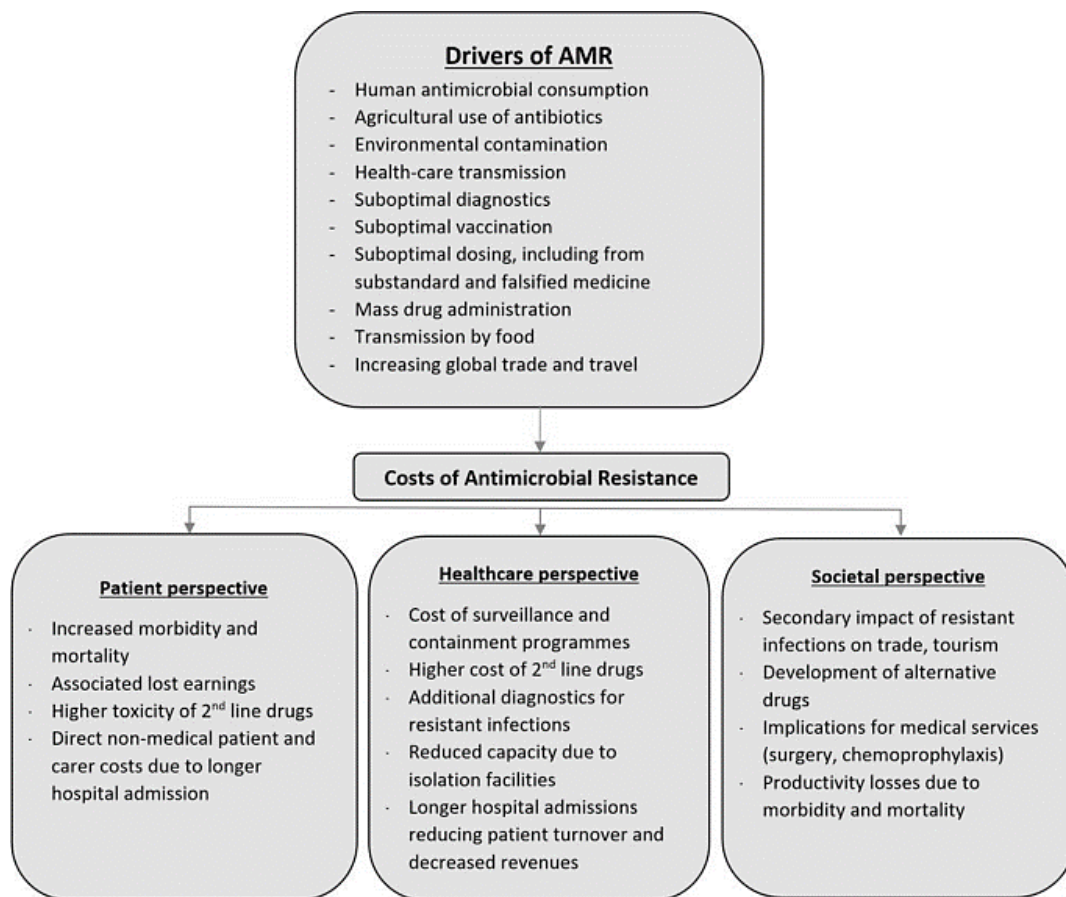


Figure 1: Accelerating factors of AMR and its consequences on different sectors of society [19].

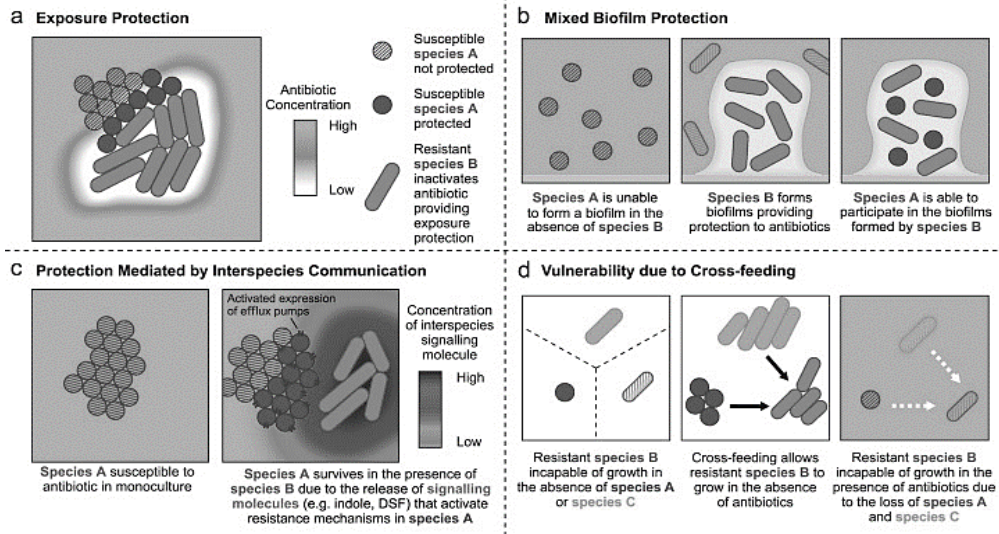


Figure 2: Mechanisms responsible for modification and evolution of bacteria.

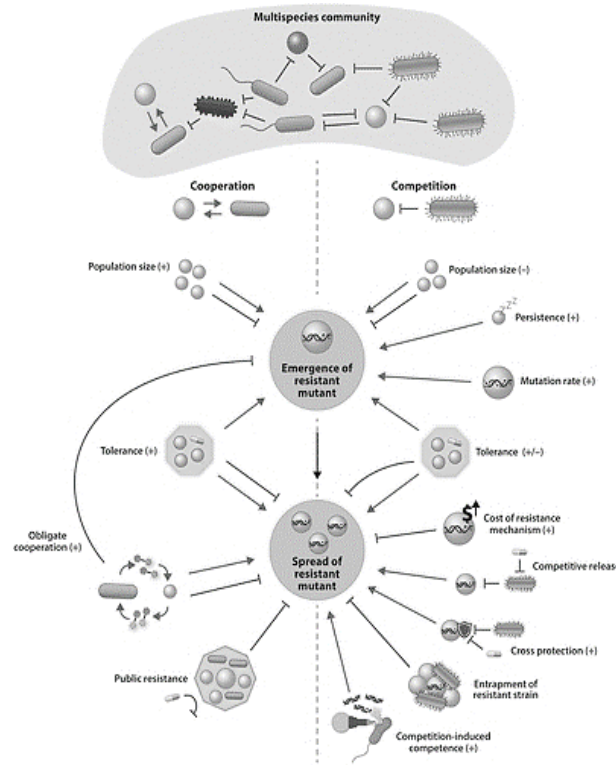


Figure 3: Emergence and spread antimicrobial resistant gene variant [21].

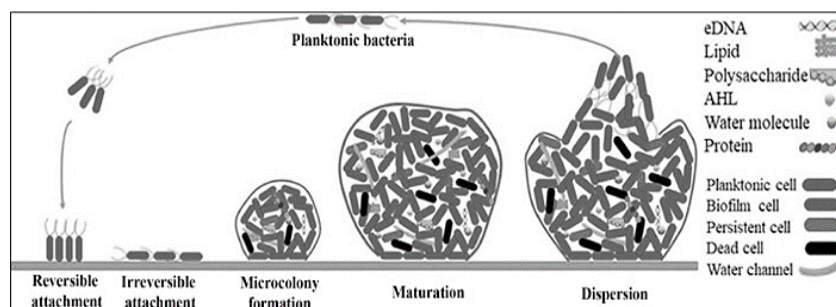


Figure 4: Evolution pattern of bacteria responsible for AMR.



surveys across the world indicate that excessive and unnecessary use of antibiotics is the leading cause of antibiotic resistance.

**Awareness regarding antimicrobial resistance in dentistry**

Prescriptions for oral health care are included in the major part of human antibiotic utilization in primary care. It has been revealed that dentists prescribe approximately 10% of antibiotics to humans, but this rate can differ by country. Sudan and collaborators conducted a retrospective cohort study in the United States [Figure 5]. Using retrospective insurance data, they examined the suitability of antibiotic prescriptions for dental prophylaxis and found that more than 80% of the prescriptions were deemed unnecessary [23].

**Link between antibiotic resistance and persistence**

Antibiotic producers may be able to limit the competition from other antibiotic-sensitive microorganisms in their immediate environment thanks to antibiotic production. These Antibiotic Resistance (ABR) genes are transmitted to subsequent generations and may eventually be horizontally transferred to other nearby bacteria.

Expanding quantities of microscopic organisms are becoming impervious to various antimicrobial as of now being used coming about in multi-drug-resistant (MDR) microorganisms [Figure 6]. Diseases by antibiotic-resistant microbes are answerable for around 700,000 deaths each year overall and assessed to be reason for 10 million deaths each year by 2050 [24].

**Role of health professionals**

Physicians play a pivotal role in this era of crisis by irrational use of antimicrobials.

"Antimicrobial stewardship program plays a significant role to rationalize the use of antimicrobials in health care settings".

Antimicrobial stewardship projects can assist in decreasing improper prescription and broad-spectrum use of antimicrobials, in this way working on clinical results for the populace in general, decreasing the rise of antimicrobial resistance and thereby saving medical care assets. Drug specialists have a significant role in the stewardship group and play an important part in handling antimicrobial resistance [25].

**Auditing of antimicrobials**

Government should also emphasize strict policies in the health care universities to update and educate health professionals regarding modern research occurring in this domain.

Following [Table 1] clearly shows the over the counter available antibiotics in Pakistan and their prices [26].

**One health initiative on the problem of antimicrobial resistance**

In order to adopt the one Health perspective on antibiotic resistance, we must examine the concept's history and origins as well as the context in which health and political actors have adopted it as a strategy to combat antibiotic resistance and its economic and societal effects. This marked the fourth time in its history that the United Nations has put a health issue on its agenda, marking a turning point in the process

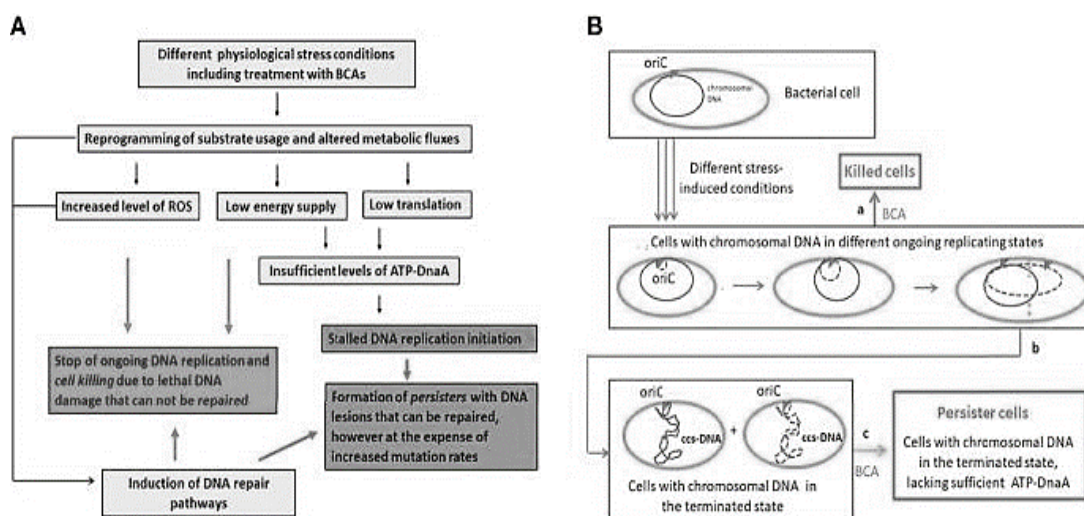


Figure 5: Pattern of bacteria killing and associated factors.

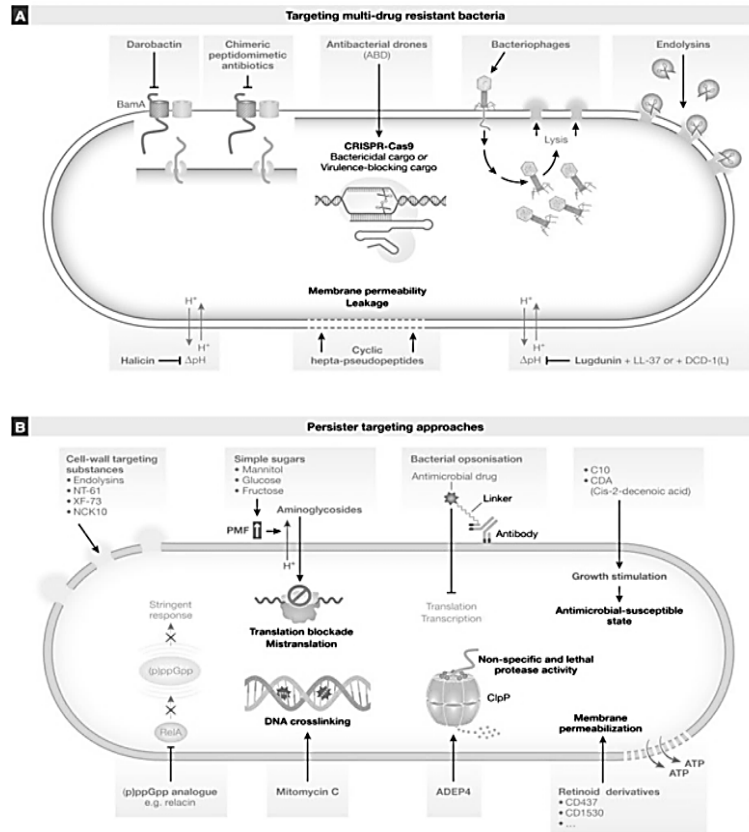


Figure 6: Illustration showing targeting approaches against multi drug resistant bacteria.

Table 1: Individual middle value for overviewed anti-infection agents in Pakistan.

Medicine Name	Type	MPR	25%tile	75%tile	Min	Max
Cap. Doxycycline 100 mg J01AA02	OB	4.33	4.33	4.33	3.75	4.34
	LPG	2.9	1.7	3.92	1.36	4.94
Cap. Ampicillin 500 mg J01CA01	OB	1.5	1.35	1.5	1.25	1.5
	LPG	NA	NA	NA	NA	NA
Cap. Amoxicillin 500 mg J01CA04	OB	2.6	2.6	2.61	2.48	2.61
	LPG	1.87	1.51	2.26	1.06	2.59
Inj. Benzyl penicillin 1MIU J01CE01	OB	NA	NA	NA	NA	NA
	LPG	1.79	1.66	1.82	1.28	1.92
Tab. Co-amoxiclav 625 mg J01CR04	OB	1.2	1.19	1.2	1.19	1.2
	LPG	1.1	1.08	1.11	0.86	1.17
Inj. Piperacillin + tazobactam 4500 mg J01CR05	OB	2.45	2.45	2.45	2.34	2.45
	LPG	2.07	2.07	2.07	2.34	2.45
Cap. Cefalexin 500 mg J01DB01	OB	1.94	1.92	1.95	1.92	1.99
	LPG	1.83	1.69	1.93	1.53	1.95
Inj. Cefotaxime 1 g J01DD01	OB	2.32	2.32	2.32	2.32	2.32
	LPG	1.47	0.88	1.96	0.86	2.01
Inj. Ceftriaxone 1 g inj J01DD04	OB	15.31	15.31	15.31	15.31	15.31
	LPG	6.38	6.04	6.38	4.78	8.66
Cap. Cefixime 400 mg J01DD08	OB	NA	NA	NA	NA	NA
	LPG	2.17	2.14	2.47	1.32	2.47
Inj. Meropenem 1 g J01DH02	OB	NA	NA	NA	NA	NA
	LPG	1.44	1.44	1.8	0.73	2.06
Tab. Sulfamethoxazole + trimethoprim 960 mg J01EE01	OB	0.74	0.73	1.48	0.71	1.5
	LPG	NA	NA	NA	NA	NA
Tab. Clarithromycin 500 mg J01FA09	OB	2.34	2.34	2.34	1.78	2.38
	LPG	1.55	1.27	1.55	1.16	1.58
Tab. Azithromycin 250 mg J01FA10	OB	NA	NA	NA	NA	NA
	LPG	1.98	1.7	2.14	1.55	3.29

Tab. Clindamycin 300 mg J01FF01	OB	2.5	2.5	2.54	2.49	3.33
	LPG	NA	NA	NA	NA	NA
	LPG	3.04	3.03	3.05	3.02	3.07
Inj. Amikacin 50 mg/ml J01GB06	OB	NA	NA	NA	NA	NA
	LPG	1.88	1.87	1.88	1.87	12.44
Tab. Ciprofloxacin 500 mg J01MA02	OB	12.42	12.34	12.45	12.15	12.45
	LPG	5.77	5.23	6.81	2.53	6.96
Inj. Vancomycin 500 mg J01XA01	OB	4.06	4.06	4.42	3.33	5.37
	LPG	3.73	3.54	4.06	3.42	4.06
Tab. Metronidazole 400 J01XD01	OB	1.21	1.21	1.23	1.15	1.41
	LPG	1.16	1.15	1.18	1.15	1.2

Cap Capsule, Tab Tablet, Inj Injection, MPR Median Price Ratio+

of raising awareness of the issue of antibiotic resistance and taking action. HIV/AIDS, Ebola, and other non-communicable diseases were the other three occasions. Antibiotic resistance reexamining as well as its extension concerning working and pertinence [27].

#### Threats of antibiotic resistance

There is no doubt that the marketing status of pharmaceutical companies contributed to a “replacement dynamics” to out-compete “older” drugs that could become inactive because of resistance. This strategy has strongly contributed to the notion of “the unbearable threat of resistance,” and in fact many international surveys on antibiotic resistance in the world were financed by pharmaceutical companies, mostly in order to demonstrate the “superiority” of their new drugs over the old ones. In parallel, the antibiotic “replacement strategy” was also increased by launching less-toxic drugs, sometimes overstating few and transient, or controllable, toxic events of the “older” one [28].

#### Crossroads of antibiotic resistance and biosynthesis:

The expanded event of antibiotic resistance in human microbes has raised worldwide concern as the anti-microbial consistently lose capacity in clinical and local area settings. Antibiotic marketing is still strong, even though antibiotic resistance is rising and private drug discovery programs are changing. The aminoglycoside plazomicin and the tetracyclines eravacycline, omadacycline, and sarecycline were among the four new antibiotics that the FDA approved in 2018 [29].

#### Combating AMR

The most important recommended strategies include rational use of antibiotics, regulation of antibiotic availability over the counter, improved hand hygiene, and improved infection prevention

and control. The need is for a comprehensive comprehension of the resistance mechanism and for new drug and vaccine innovation. In order to combat antimicrobial resistance, a regulatory strategy that is collaborative and multidisciplinary is required [30, 31].

The following are some of the strategies that have been suggested by the World Health Organization [32]. Brand-new networks that monitor antimicrobial use and AMR.

Worldwide methodology for controlling fake antimicrobials.

Financial incentives for vaccine and drug research and development.

A public board is needed to screen for the effects of anti-infection opposition and provide inter-sectoral co-appointment, as well as to strengthen existing programs to contain AMR. The goal of disease prevention and control measures is to stop the spread of germs, even healthy ones, inside medical offices and throughout the greater area. This might stop the spread of AMR and extra contaminations [33]. Infection control and

#### Prevention guidelines for healthcare facilities include

Forming a committee to control and prevent infections (IPC).

Good hand hygiene practice.

Reasonable use of antibiotics and accurate diagnosis and treatment of infections

Monitoring of antibiotic use and resistance to antibiotics.

Chipping away at antimicrobial quality and store organization.

Great microbial science rehearses.

At the nearby and public levels, an observation [Figure 7] organization of antimicrobial use and

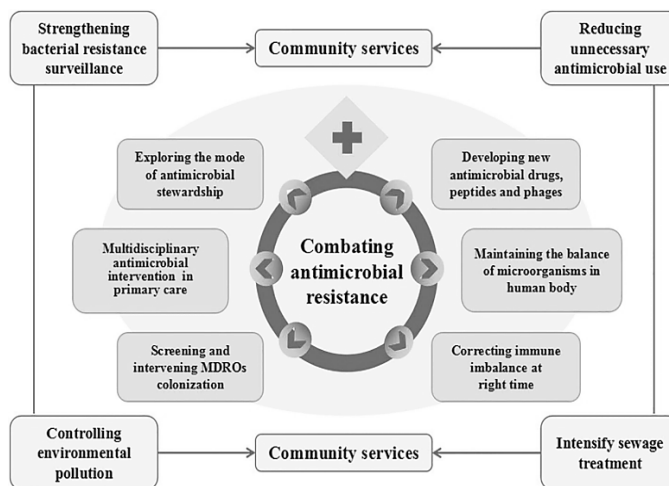


Figure 7: Steps taken to combat against antimicrobial resistance8.

Table 2: Newly discovered antimicrobial drugs after 2017.

Drug Name	Trade Name	Antibiotic Class	Administration		Indication(s)
				Route	
Cefiderocol	Fetroja (Shionogi)	Siderophore cephalosporin		iv	cUTI
Delafloxacin	Baxdela (Melinta)	Fluoroquinolone	iv; oral		ABSSSI; CAP
Eravacycline	Xerava (Tetraphase)	Tetracycline		iv	cIAI
Lascufloxacin	Lasvic (Kyorin Pharmaceutical)	Fluoroquinolone	iv; oral		CAP; otorhinolaryngological
Lefamulin	Xenleta (Nabriva)	Pleuromutilin	iv; oral		CAP
Levonadifloxacin Alalevonadifloxacin	Emrok/Emrok O (Wockhardt)	Fluoroquinolone	iv; oral		ABSSSI
Omadacycline	Nuzyra (Paratek)	Tetracycline	iv; oral		CAP (iv); ABSSSI (iv;oral)
Plazomicin	Zemdri (Achaogen)	Aminoglycoside		iv	cUTI
Pretomanid	PA-824 (TB Alliance)	Nitroimidazole		oral	XDR- and MDR-TB
Relebactam + imipenem/cilastatin	Recarbrio (MSD)	BLI + carbapenem/degradation inhibitor		iv	cUTI; cIAI; HAP/VAP
Vaborbactam + meropenem	Vabomere (Melinta)	BLI + carbapenem		iv	cUTI

ABSSSI: intense bacterial endlessly skin structure diseases; CAP: local area related pneumonia; cIAI: intra-abdominal infection that is complicated; cUTI: complicated infection of the urinary tract; HAP: clinic related pneumonia; iv: intravenous; MDR: multi-drug safe; VAP: pneumonia brought on by a ventilator; XDR: extensively resistant to drugs.

obstruction designs from drug stores, centers, clinics, the climate, horticulture, and creature cultivation should be laid out.

**Pharmaceutical approaches on antimicrobial resistance**

In order to reduce antimicrobial resistance, new antibiotic compounds and Resistance Modifying Agents (RMAs) must be discovered quickly. Research focused on this is being done broadly from one side of the planet to the other. The World Health Organization (WHO) has received information that indicates that eleven new antibiotics [Table 2] have been granted approval to be sold between 2017 and 2020. The majority of these substances are derived from antibiotics. Nevertheless, it is essential to keep in mind that two of the mixtures, lefamulin and vaborbactam, have been identified as novel antibiotics.

ABSSSI: intense bacterial endlessly skin structure diseases; CAP: local area related pneumonia; cIAI: intra-abdominal infection that is complicated; cUTI: complicated infection of the urinary tract; HAP: clinic related pneumonia; iv: intravenous; MDR: multi-drug safe; VAP: pneumonia brought on by a ventilator; XDR: extensively resistant to drugs.

**Anti-infection Obstruction: The Perspective on One Health, One World**

To address well-being dangers at the human-creature climate interface, which are covered by the One Well-being idea, ABR requires a multidisciplinary, multi-spectral, and facilitated approach. In order to better comprehend the evolution or genetic relatedness of ABR in pathogens and vectors, hosts (humans and animals), and the environment that is associated with them, the concept of "One Health,



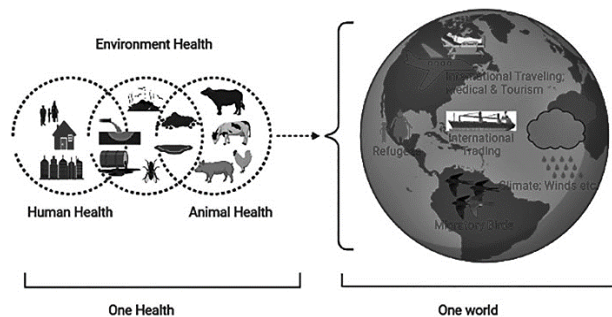


Figure 8: Illustration of one health one world initiative.

"One World" incorporates global molecular epidemiological aspects. Monetary elements like world exchanges, wars, expulsion, travel, human, and animal development are critical drivers of the overall dissipating of ABR [Figure 8].

#### FUTURE RECOMMENDATIONS

Health care practitioners should have sound knowledge about the diseases in which prescribing antibiotics should be crucial

Government should devise policies in order to prevent the selling and purchasing of over the counter antibiotics

Different advertisement campaigns should be launched in order to aware the people about the adverse effects and consequences of using excessive antibiotics

Thorough researches should be conducted in order to develop the vaccines that can protect humans against life threatening infections and ultimately their consequences

Combating antimicrobial resistance through prevention

Further researches should be conducted in order to develop new types of antibiotics that can be used independently or in combination with the old ones to fight multi drug resistant pathogens and overcome antimicrobial resistance.

More investments should be done in the domain of antibiotic resistance and antibiotic overuse to cope up with this global challenge.

Governments should intervene at national and international levels to combat Antimicrobial resistance.

Novel approaches based on reconceptualization of the nature of resistance, disease and prevention are needed.

Common people should be made aware to take antibiotics as prescribed and not to skip any doses in between [34].

#### CONCLUSION

In conclusion, antimicrobial resistance poses significant global threat to public health. It is imperative that we take concerned efforts to combat these phenomena through responsible antibiotic use, robust surveillance, development of new antibiotics and education of healthcare professionals and the public. Failure to address antimicrobial resistance could lead to dire consequences, making many common infections untreatable and undermining the foundations of modern medicine

Antimicrobials are the mainstays of present day medication and have considerably added to the advancement of medical services during the last half-century. Consequently, the changing patterns in AMR ought to be halted or it will hinder us to the dull periods of medicine. Anti-microbial resistance is a normally occurring mechanism however, battling AMR requires aggregate activity, political force, and strong multispectral coordinated effort and associations between all partners overall including legislative and non-legislative offices, scientists, suppliers, general wellbeing professionals, drug organizations, clinic organizations, policymakers, farming industry pioneers, and patient. Progressing instructive exercises ought to keep on refreshing the doctor's information and most recent reports on antimicrobials, which assists with diminishing the gamble of antimicrobial resistance which is an arising issue through the world.

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