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NOVEL ANTIBIOTICS DISCOVERY AND DRUG RESISTANCE REVISITED

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ABSTRACT: Drug resistance in bacterial strains has often been detected in the last two decades and is increasing yearly. Novel survival mechanisms and over-the-counter antibiotic availability (OTC) complicated this issue, especially in relation to the Asian continent. Resistance to drug/antibiotic is multifactorial *viz*, plasmid encoding drug resistance, pumping the drug out by pumping mechanism from the bacterial cell, degradation of antibiotic by using enzymes such as β-lactamases, carbapenemase and others. Bacterial drug resistance is a global threat, and the discovery of novel antibiotics to address this challenge has not kept pace. Critical appraisal and drug development timelines in clinical phases made the task costly and tedious. Global pharmaceutical companies have withdrawn their attention, and only a limited number of companies are doing research and development in this field. The present review discusses the current scenario worldwide and introduces one health plan's role in terms of the discovery of novel drugs and increased drug resistance.

INTRODUCTION: Superbugs are drug-resistant pathogenic bacterial strains that cannot be treated with traditional antibiotics due to their unique drug escape mechanisms [1-2]. These emerging drug-resistant bacterial strains are a major threat for humanity. World health organization (WHO) has declared antibacterial resistance or antimicrobial resistance one of the top ten global public health threats facing humanity [2, 3]. Now the question arises in each scientist/researcher's mind: how is the drug resistance coming in these bacterial strains? What are the causes behind this? How to address this challenge? Let's try to figure it out.

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Drug Resistance in Bacteria is Multifactorial: Antibiotic resistance comes up naturally, but overuse/misuse of antibiotics in humans, animals and agriculture fastens this process. Many infections are difficult to treat due to the ineffectiveness of antibiotics nowadays. Penicillin discoverer Alexander Fleming (1945) said that the resistance in pathogenic bacterial strains could come up if exposed to low/nonlethal concentrations of drugs.

Industrialization and competition between pharmaceutical industries (research and development unit) to make more profit ended up with large number of antibiotics generation by generation in a comprehensive manner with improper collaboration and tie-ups at global level. Excessive use of chemical pesticides in agriculture, overuse of antibiotics by rural people and availability of over-the-counter (OTC) antibiotics in developing countries leads to complicate the

condition. Thus, most of the pathogenic bacterial strains became drug-resistant year by year [4-8].

The Interplay of Many Factors influences the use of Antimicrobials in Animal and Plant Production: Burden of diseases that are otherwise preventable through modification of environmental hygiene, nutrition, husbandry and other management practices, Limited access to animal and plant health experts, as well as limitations in training and support for these experts. The use of antimicrobials as growth and production promoters in animals, Lack of regulation and oversight of the use of antimicrobial drugs, over-the-counter or internet sales that make antimicrobial drugs readily available on the patient's doorstep.

Availability and use of substandard and falsified antimicrobials, Lack of awareness regarding good practices, leading to excessive or inappropriate use, anthropological, sociocultural, political and economic factors [8] that pose barriers good practices as shown in **Fig. 1.**

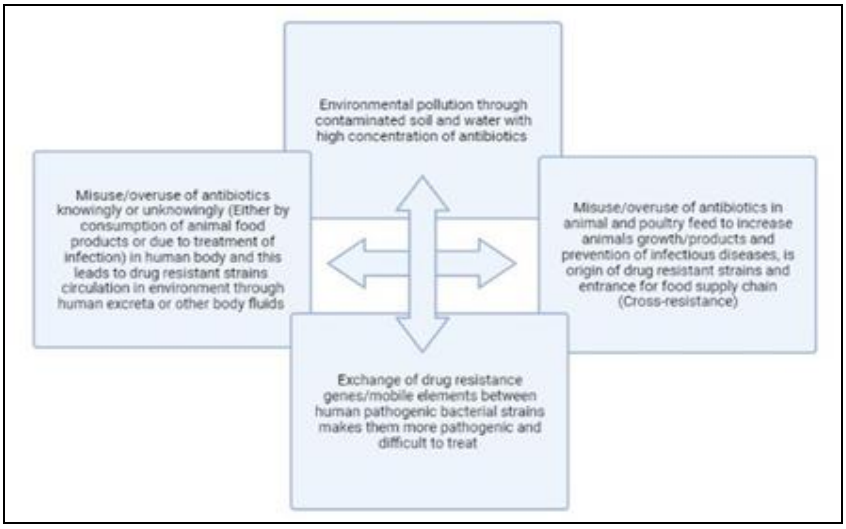

FIG. 1: INTERCONNECTED SUPPLY CHAIN FOR BACTERIAL DRUG RESISTANCE

Drug resistance is seen in almost all bacterial strains/superbugs, including *Mycobacterium* species. Severe infections include complicated urinary tract infections, hospital and ventilator acquired pneumonia, multidrug resistance tuberculosis, acute bacterial skin and skin structure infections (ABSSSI), multidrug resistance *Neisseria gonorrhoeae* and *Clostridium difficile* infections are becoming difficult to treat due to antibiotic resistance [9, 10]. The common mechanism of antibiotic resistance in bacterial strains is shown in **Fig. 2.**

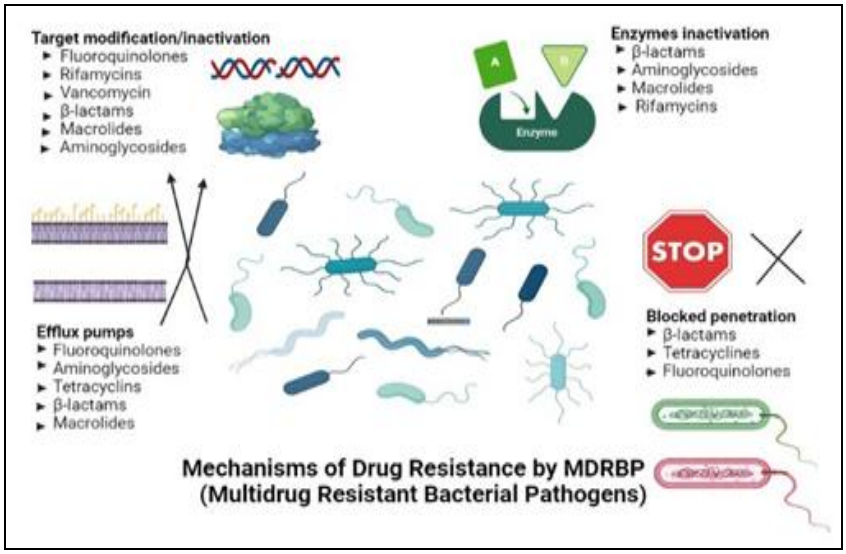

FIG. 2: DIVERSE MECHANISMS OF DRUG RESISTANCE BY MULTIDRUG-RESISTANT BACTERIAL PATHOGENS

Carbapenemase producing carbapenem resistant *Enterobacteriaceae/Enterobacterales* (CRE) is a threat to public health due to their unique mechanisms of drug resistance and one of the important groups, as shown in **Fig. 3.** The major mechanisms by which these superbugs become resistant are enzyme production, efflux pumps and porin mutations.

Out of these, enzyme production was the main mechanism seen in these superbugs. The novel groups/strains such as MBL, (New Delhi metallo-β-lactamase), OXA-48 and KPC (*K. pneumoniae* carbapenemase-producing) were identified and reported plasmid/gene encoded drug resistance time by time and were considered as major public threat worldwide [11-25].

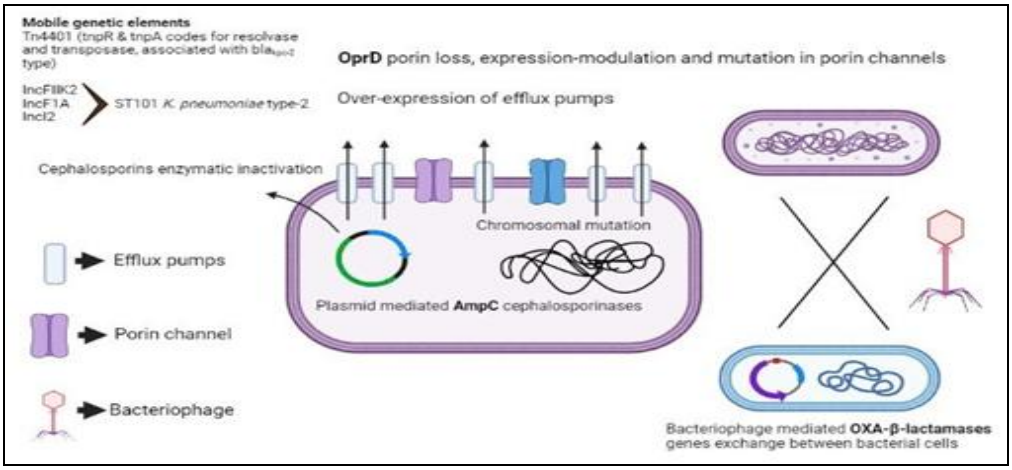

FIG. 3: MECHANISMS OF CARBAPENEMASE-PRODUCING CARBAPENEM-RESISTANT *ENTEROBACTERIACEAE*

Novel Drugs: Novel class of antimicrobial agents has a higher potential to sort out drug resistance than the existing class of antibiotics. However, the current industry pipeline shows a marked gap, denoted as a discovery void. If we look into the causes, we will find multiple factors for this situation. The major challenge faced by all multinational big pharma companies is that the process of novel drug development is tedious, complicated, and costly. Moreover, the discovery task of research and development within a timeline until final approval by FDA is cumbersome [15, 16]. Due to instability, most novel molecules cannot pass phase II or phase III. Thus, the big pharma companies are in secured and lose interest due to failure and attrition of the novel drug. Perhaps the novel drug discovery demands more patience and innovative/smarter ways to handle and address this problem because there is still plenty of room to discover new antibiotics. A detailed list of new antibiotics discovered in the latest years is shown in **Table 1.** WHO and CDC brainstormed and decided on a new concept called a one-health approach. These global organizations decided on one health issue. They declared that the one health approach would be sustainable and comprehensive if novel/new molecules were developed with extended-spectrum against these multidrug-resistant bacterial strains [1-7, 17-21].

Since, antibiotic resistance is one of the issues chosen under one health program. Therefore, these global organizations must come out with a concrete plan in this direction and appreciate the efforts of big pharma companies and the challenging tasks for new antibiotic/molecule discovery.

TABLE 1: LIST OF NOVEL ANTIBIOTICS DISCOVERED IN RECENT YEARS AND THEIR PHASES OF CLINICAL DEVELOPMENT

Diseases caused by drug-resistant pathogens	Drug/Compound	Mechanism of action	Class and substituent
Multi drug-resistant *Neisseria gonorrhoeae*	Zoliflodacin (Phase III in 2019, developed by Entasis Therapeutics with Global Antibiotic Research Development Program)	Inhibition of type II bacterial topoisomerase by binding to unique site	Pyrimidinetrione spirocyclic pharmacophore[15-20] (New benzisoxazole scaffold) (4-methyl-1,3-oxazolidin-2-one in position 3 of benzisoxazole ring)

Clostridium difficile infection (CDI)	Ridinilazole (Discovered by Summit Therapeutics)	Inhibits the cell division of the bacterium by binding to minor groove of DNA (Antibiotic exposure leads to altered genes expression of cell division)	Bis-benzimidazoles class[10-20] (Double benzimidazole each one bonded by pyridinic ring)
Clostridium difficile infection (CDI)	Bezlotoxumab (Approved by FDA in 2016, name Zinplava in United States)	Intravenous administration, stops the toxin B formation and prevent recurrent CDI in adults. (A human monoclonal antibody directed against toxin B, based on phase-III data, FDA approved in 2016)	Glusosyl transferase activity[10-20]
Community-acquired pneumonia (CAP) caused by MRSA, Gram-positive bacteria and some Gram-negative bacteria	Omadacycline	Inhibits bacterial protein synthesis by binding to 30S subunit of bacterial ribosomes	Tetracycline class [20-25]
Complicated urinary tract infections (cUTIs)	Vabomere (Approved by FDA in 2017 is a combination of varobactam and meropenem for intravenous administration)	Vaborbactam is a cyclic boronic acid pharmacophore β-lactamase inhibitor that elicits potent inhibition of *Klebsiella pneumoniae* carbapenemase enzymes (KPC) and other amber class A and C enzymes such as serine β-lactamases that confer resistance to commonly used antibiotics such as carbapenems	Carbapenem and β-lactamase inhibitor[20-25]
Complicated intra-abdominal infections (cIAI) in adult patients	Eravacycline (Fully synthetic fluorocycline, developed by Tetraphase Pharmaceuticals and approved by EMA and FDA in 2018, marketed under the name of Xerava)	The mechanism of action of eravacycline is to reversible bind 30S subunit of bacterial ribosome and block the entry of molecules of the aminoacyl-tRNA complex	Eravacycline also contains tetracycline pharmacophore with changes in C7 (addition of fluorine atom) and C9 (addition of a pyrrolidine acetamide group) position of ring D[20-25]
Acute bacterial skin and skin structure infections (ABSSSI)	Delafloxacin developed by Melinta Therapeutics, approved by FDA in 2017, marketed under the name Baxdela	Mechanism of action of delafloxacin includes binding to both DNA gyrase and topoisomerase with equal affinity and reduces the resistance	Delafloxacin differs from other fluoroquiniolones in the absence of basic group in position C7 and on position C8, a chlorine atom is added. Thus, increases activity and stability due to an electron-attractor group on the aromatic ring and improves polarity of compound[1-15]
Complicated urinary tract infections (cUTIs) /pyelonephritis in adults	Plazomycin developed by Achaogen and approved by FDA in 2018 with brand name Zemdri	Mechanism of action of plazomycin includes irreversible binding to ribosomal site consisting of three proteins of subunit 50S and other proteins of 30S subunit, block the ribosome on starting codon and stops the protein synthesis	Plazomycin is a new aminoglycoside, derived from modification of sisomicin. Plazomycin belongs to the group of 2-deoxystreptamines, the aminocyclitol is substituted in positions 1', 4' and 6' thus more potent against KPC Enterobacteria[12-24]
Hospital acquired bacterial pneumonia (HABP), Ventilator associated bacterial pneumonia (VABP) and complicated urinary tract	Cefiderocol is part of the siderophore cephalosporins, new class of drugs, approved by FDA in 2019 and by EMA in 2020.	The siderophore group of these molecules seizes iron from the external environment. The iron-siderophore antibiotic complex binds to the iron transporter outside the bacterial membrane	The structure of cefiderocol is similar like cefepime. A fourth generation cephalosporin, both have a pyrrolydinic group bound to the chain in C3, which results in quaternary

infections		and actively transported inside the bacterial cell, bypasses the pathogens defense systems and improves the penetration of antibiotic (Trojan horse strategy)	ammonium. Zwitterions allows them to penetrate better in Gram positive and Gram-negative bacteria. Carboxylic acid in the C7 side-chain improves the permeability of cefiderocol in the outer membrane[1-25]
Multi drug resistant pulmonary tuberculosis	Pretomanid is the first antitubercular bicyclic nitroimidazooxazine approved by FDA in 2019, developed and registered by TB alliance, a nonprofit organization in South Africa. The suffix preto came from the city Pretoria, where the drug was developed. Drug received marketing approval in a combination regimen with bedaquiline and linezolid	Pretomanid mechanism of action includes the inhibition of biosynthesis of mycobacterium proteins and lipids under aerobic conditions especially blocking transformation of hydroximicolic acid into ketomycolate with subsequent accumulation of hydroxymycolic acid and depletion of ketomycolates. Moreover, blocking the cellular respiratory processes of mycobacterium in anaerobic environment	The presence of a nitro group in position 2 of the imidazole ring, the lipophilic tail in position 6 of the oxazinic ring, and the rigidity of the bicyclic system are crucial for antitubercular activity[1-25]

WHO Guidelines and Preventive Measures to Sort out the Problem: World Health Organization (WHO) adopted the global action plan to address the antibiotic resistance problem with five strategic objectives: to improve awareness and understanding of antimicrobial resistance; to strengthen knowledge through surveillance and research; to reduce the incidence of infection; to optimize the use of antimicrobial agents; and develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions [1-7].

United Nations Food and Agriculture Organization (UNFAO) Policy and Guidelines: UNFAO plays a role in aquatic and terrestrial livestock health and production, crop production, natural resource management and food safety. An important area for FAO's work is to identify and address the critical information gaps on the subject. Moreover, FAO is working closely with key partners such as the World Organization for Animal Health (OIE), the World Health Organization (WHO) and others in a global response to the threat of antimicrobial resistance [1-7].

Director Generals (2018) of FAO, WHO and OIE agreed to strengthen their long-standing partnership with a strong focus on tackling antimicrobial resistance. These three organizations share the responsibilities for coordinating global activities and tackling antimicrobial resistance through a "One Health" approach, which considers animals, humans and ecosystems simultaneously as shown in **Fig. 4.**

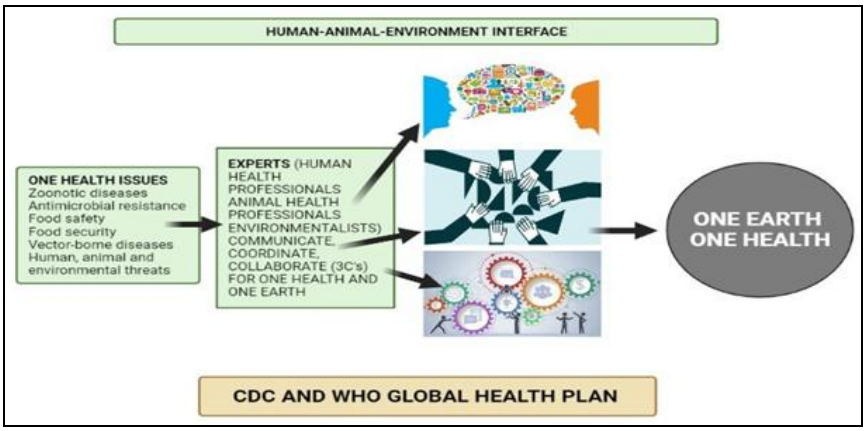

FIG. 4: CDC AND WHO GLOBAL HEALTH PLAN

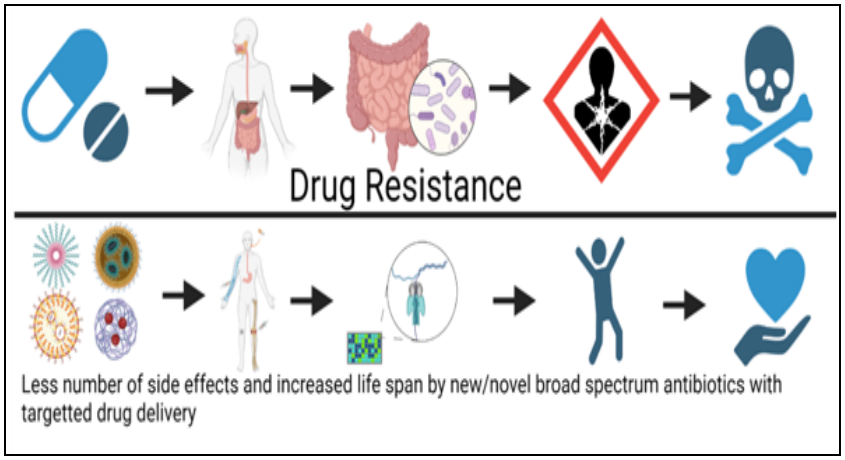

FIG. 5: TARGETED DRUG DELIVERY BY NANOMEDICINE-BASED DRUGS

Nanomedicine is the Future: The bio-film-forming potential of drug-resistant bacterial strains makes them more difficult to treat. Destruction of bio-film leads to susceptibility of bacterial cells and is an innovative way to treat complicated abdominal infections, as shown in **Fig. 5.** Various researchers are studying the polymeric nanoparticles to combat severe infections. Results of nano-antibiotic formulations in therapeutics were impressive and probably are the future. Moreover, it has been reported that the chemical-physical properties and bioavailability of antibiotics increases at a nano scale. So, drug penetration and bacterial cell susceptibility are quite high. Latest examples include inhalation formulations of liposomal ciprofloxacin (Phase I, II, and III) and liposomal amikacin formulation for the treatment of complicated *Pseudomonas aeruginosa* infections (Phase III) in patients with cystic fibrosis [37-42].

CONCLUSION: The sky is the limit as far as novel drug development research progress is concerned. Shared interest and collaboration at the global level will give more insight and probably facilitate the decision-making process. Novel antibiotic discovery is just the beginning. Nanomedicine and the combined use of antibiotics will be key role players in treating complicated bacterial infections worldwide. One health approach will also provide new hope and makes a difference in moving forward with significant outcomes.

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