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Review Article

Multidrug Resistance – A Burning Issue of Modern World

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ABSTRACT

Globally, current position in the clinical world shows constant increase in the resistance among pathogenic bacteria for the available range of antibiotics. It has become a major threat and challenge for health care system to treat patients efficiently. Not only it is associated with high morbidity and mortality, it also raises a challenge of dramatic increase in number of strains that are resistant to multiple types of antibiotics. The aim of this review is to explore the timeline of antibiotics discovery, its societal impact, grade of usage, mechanism of development of resistance by microbes and probable solutions to combat the problem. This article reiterates about optimal usage of antimicrobial agents to reduce the chances of acquiring multi drug resistance.

Keywords: *antibiotics, Microbes, Antimicrobial resistance, Multidrug resistance.*

INTRODUCTION

Antibiotics**,** also known as an antibacterial agent, are medications that destroy or slow down the growth of bacteria. Basically, they are cytotoxic or cytostatic in nature towards the micro-organisms. They include a range of powerful drugs and are used to treat various diseases caused by bacteria. Antibiotics normally act in concert with an organism's immune system to eliminate an infection. Antibacterial mechanisms implicate the inhibition or regulation of enzymes involved in cell wall biosynthesis, nucleic acid metabolism and repair, or protein synthesis. (levy & Marshall, 2004) Antibiotics are used as a medicine against bacterial infections because of their cost-effectiveness and powerful outcomes. Yet, several studies have provided direct information that the frequent epidemic use of antibiotics has led to the development of multidrug-resistant microbial strains. Sometimes they also emerge due to poor infection control practice; multidrug-resistant microbial strains have ability to penetrate easily in patients and the environment. (Akova, 2016).

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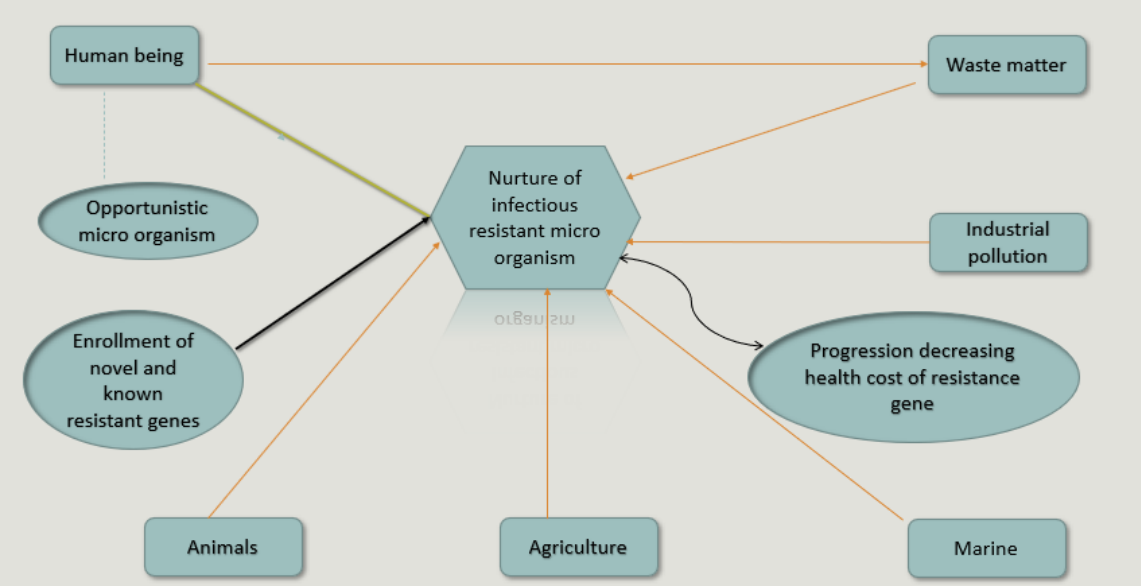

Figure 1: Schematic representation of spread of antibiotic resistance in the environment

Penicillin was the first naturally occurring antibiotic drug discovered by Sir Alexander Fleming in 1928 AD and used therapeutically since 20th century till date. The discovery of wonder drug Penicillin had changed the medical world leading to increase R & D in pharmaceutical companies. They began to screen large variety of other sources and natural products from where new range of antibiotics can be discovered. (Aminov, 2010; & Davies & Davies, 2010).

Two eminent scientists namely Alexander Fleming and Paul Ehrlich were famous for being a torchbearer of modern "antibiotic era". Antibiotics acts like a boon to the long-term suffering peoples against various syndromes, they can cease the infectious disease which is been caused by dangerous pathogenic microorganisms. (Aminov, 2010; & Davies & Davies, 2010) Novel antibiotics classes have been discovered in the golden era between the period from the 1950s to 1970s. Antibiotics are magical drugs that help fight against range of infections and can save life of millions of people globally when used properly. (Zaman et al., 2017).

From several decades antimicrobial drugs have been utilized worldwide. Observation in different regions of the world such as Africa, some parts of America, Eastern Mediterranean Region, Europe, South-East Asia, and Western Pacific Region has shown that pathogenic microorganisms have developed and mutated immensely over the years and there are a rising number of antibiotic-resistant microbes allowing themselves to resist the inhibitory effects of these drugs. Almost all the capable microbial pathogens like bacteria, fungi, virus, and parasite have developed high levels of microbial resistance with high morbidity and mortality rate and, hence, are known as "super bugs". (Laxminarayan et al., 2013; & Coates et al., 2002).

Multidrug resistant infections are correlated with weaker clinical results and higher cost of therapy than other infections and there is deep concern about the rise of pan-resistant strains (pathogens resistant to all available antibiotics) which will make some infections untreatable. MDR is particularly challenging as resistance to different antibiotics inclines rigorously on the same strains. An opportunistic connection between resistance with diverse range of drugs have been found in multiple species like *Streptococcus pneumoniae, Staphylococcus aureus, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae and Mycobacterium tuberculosis*. Considering this scenario, it can be predicted that the occurrence of MDR strains is much more than expected from the occurrence of resistance from randomly distributed population. (lehtinen et al., 2019).

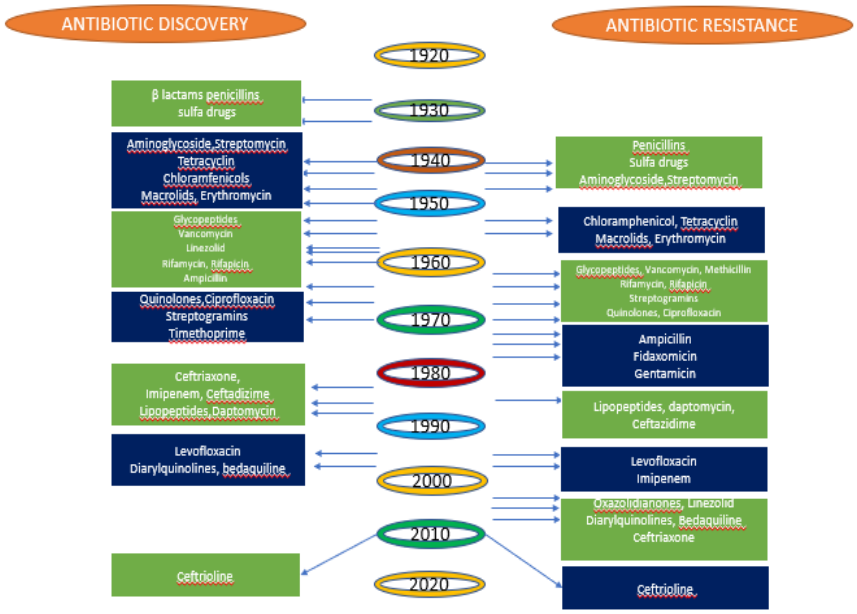

Figure 2: Timeline showing antibiotic discovery and resistance pattern

Multi Drug Resistance:

MDR stands for Multi Drug Resistance suggesting development of high levels of resistance among microbial strains, in spite of administration of proper dosages of medicines for a particular interval of time. This medical collapse is due to not only the antimicrobial resistance but also because of the concealed immune function, increased rate of drug metabolism. Pathogens determination by standard treatments, points out diverse types of antimicrobial drug resistance which is an increasing crisis in therapeutic world (Loeffler & Stevens 2003).

Multi Drug Resistance (MDR) can be broadly classified into three major types.

1) Primary resistance
2) Secondary resistance
3) Clinical resistance

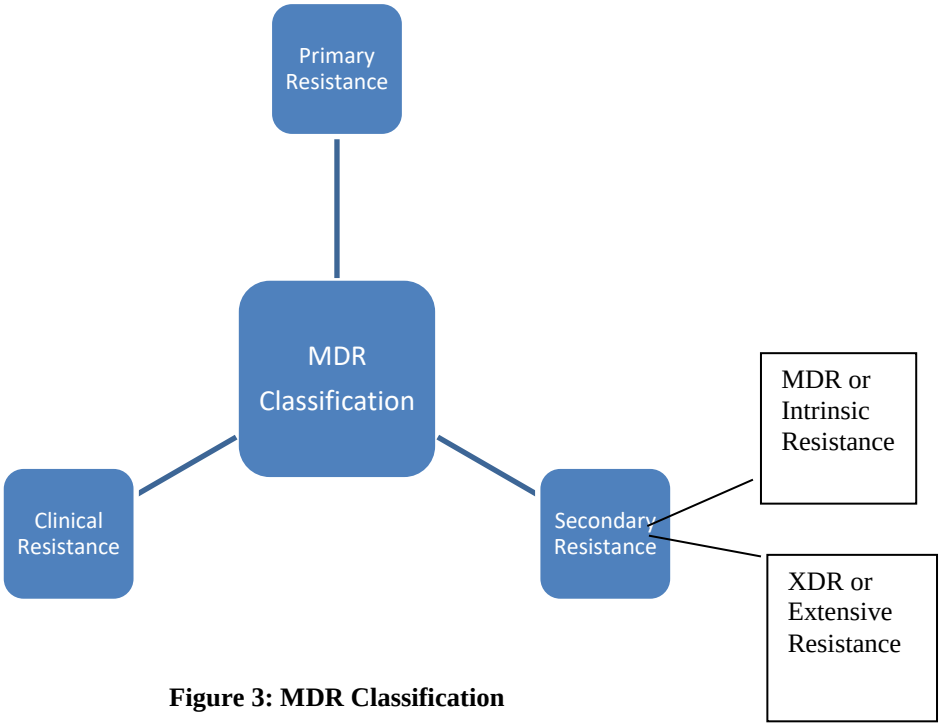

Figure 3: MDR Classification

Primary Resistance

When drug resistance is expressed in a patient who has never received the antibiotic drug of interest earlier or received less than one month of therapy, it is termed as primary (initial) resistance. Person to person spreading of drug resistant organism can cause Primary Resistance. (Khalilzadeh et al., 2006).

Secondary Resistance

It is also known as "acquired resistance".

- Pathogens are generally susceptible to drug but then become resistant to the specific drug during course of treatment because of idiopathic reason. (Khalilzadeh et al., 2006; & lee et al., 2013).
- It is further sub classified as follows -
- (i) Intrinsic resistance: it is the type of resistance in which the resistance of all microorganisms of a single species to some well-known first-line antibiotics, which are utilized to cure disorder based on the medical confirmation of the patient. for example, *Mycobacterium tuberculosis* resistant to rifampicin and isoniazid or Candida spp. resistant to fluconazole treatment.
- (ii) Extensive resistance: it is the type of resistance in which the organisms have ability to endure the resistance of at least one or two most effectual antibiotics. It is also called as XDR (Extremely Drug Resistant); this emerged to arise in patients after they have undergone a therapy with first line drugs, for example, XDR-TB resistant against fluoroquinolone. (Khalilzadeh et al., 2006; lee et al., 2013; marks et al., 2014; & Maranan et al., 1997).

Clinical Resistance

According to the above-stated types, medical resistance is explained as the condition in which the pathogens are repressed by a concentration of antibiotics that is related with a high therapeutic failure within an organism due to weaken host immune function. (Khalilzadeh et al., 2006) as per recent research it is depicted that there is a role of the Mobile Genetics Elements namely plasmids and transposons, both of which plays a key role in the growth and spreading of antimicrobial resistance among clinically related organisms. (Jose et al., 2015).

Mechanisms of developing MDR among Micro-organisms:

Antimicrobial drugs are generally designed for targeting metabolic pathway of the microbes, disrupting their nucleotide or protein synthesis leading to further disruption of cell membrane or inactivation of enzymes involved in cell wall synthesis. (Lehtinen et al., 2019) Gram positive and gram-negative bacteria had acquired different patterns of multidrug resistance, which leads to difficulty or even no treatment with traditionally available antimicrobial drugs in the market. (Maranan et al., 1997).

Antibiotics control antimicrobial growth by varied mechanisms. They attach to Binding Proteins acting at the transpeptidation stage of cell wall synthesis to obstruct peptidoglycan cross-linking. The beta-lactam antibiotics also activate autolysins, which break down the bacterial cell wall. (Maranan et al., 1997) Extensive study is going on in order to understand molecular mechanism of resistance to antibiotics involving investigations of different microbes at level of genetics and biochemistry depicting facts of its cellular functions. (Jose et al., 2016).

Naturally, bacteria can be intrinsically resistant to several antibiotics but by mutations in chromosomal genes and by horizontal gene transfer it can also acquire resistance to varied range of antibiotics. Bacterial species carry inherent structural or some specific functional characteristics and can develop intrinsic resistance for more than one antibiotic. For example, resistance in lipopeptide and daptomycin (approved for clinical use in 2003). Daptomycin is effective against Gram-positive bacteria but it is not effective against Gram-negative bacteria. This is because of the basic intrinsic difference in the structure of the cytoplasmic membrane of both types of bacteria. In case of Gram-negative bacterial species, the cytoplasmic membrane contains lower proportion of anionic phospholipids presence than in Gram-positive bacteria.

Anionic phospholipids diminishes the effectiveness of the Ca2+ mediated insertion of daptomycin into the cytoplasmic membrane which is required for its antibacterial activity. (Jessica et al., 2014).

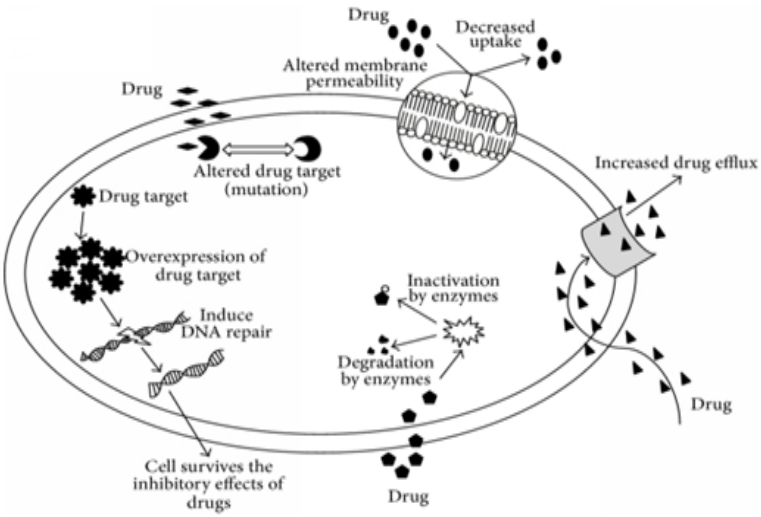

Figure 4: Pictorial representation of mechanism of acquiring multi drug resistance, adopted from reference no. 9

Through the development of era of Next Genome Sequencing (NGS), recent studies have led to the identification of many genes that are responsible for intrinsic as well as acquired resistance to antibiotics of different classes, including β-lactams, fluoroquinolones and aminoglycosides, chloramphenicol, glycopeptide, macrolide-lincosamide-streptogramin B, sulfonamide, tetracycline and trimethoprim.

β-lactam resistance gene: Since 1940, they are major antibiotics class in clinical use. From the beginning more than hundreds of β lactamases are developed so far. Resistance to penicillin leads to the identification of first two AMR genes namely, bla_{SHV-1} and bla_{TEM-1}. Shortly after another AMR gene CTX-M, bla_{OXA} (horizontal gene transfer), rare genes bla_{GES}, bla_{SFO}, bla_{TLA}, bla_{VES} are also been noted. Plasmid encoded genes namely AmpC, bla_{ACT}, bla_{MIR}, bla_{ACC}, bla_{LAT} are also found to be responsible for the drug resistance. (Bush & Jacoby, 2010).

Aminoglycoside resistance gene: aminoglycoside drugs were actively used from mid-1940 to 1980. During this period bacteria developed resistance against it by drug modification mechanism involving acetylation, adenylation and phosphorylation. (Krause et al., 2016) plasmid mediated resistance genes of aac, ant and aph families were also identified later on. Decrease use of this class of antibiotics slowed down the evolution procedure of development of resistance. the invention of 16S rRNA methylase from armA gene family that codes enzymes which is found to stop the drug to bind with 16S rRNA target. (Doi et al., 2016) It was also depicted that chromosomal resistance against this class is due to alteration in AcrAB-TolC and KpnEF efflux pump which modify the permeability. Another plasmid mediated Rmt family gene and NpmA were also noted playing role in acquiring resistance. (Padilla et al., 2010).

Quinolone resistance gene: Quinolone was widely used since 1960s, its use increased with the entry of first fluoroquinolones drug in the market with proven efficacy, this overuse led to the development of quinolone resistance. Quinolone resistance in gram negative bacteria developed by different mechanisms like target site gene mutation, modifying enzymes, modifying target protection proteins and increased production of MDR efflux pumps. (Naeem et al., 2016) First and major resistance mechanism which was elucidates was chromosomal mutations in the quinolone binding targets, DNA gyrase and

topoisomerase. Mutations in gyrA, parC, gyr B and parE genes are found to be more common. (Nam et al., 2013) Deficiency of OmpK36 is found to alter the cell permeability and over expression of multi drug resistance pump acrAB and plasmid mediated pump OqxAB also found to be responsible for quinolone resistance. (Wong et al., 2015).

Polymyxin resistance gene: This class of drugs upsets membrane integrity through dislocation of cations in the outer membrane by attachment with the negatively charged lipopolysaccharides which leads to the cell lysis. The changes in LPS is carried out by mutations in several core genes such as lpxM and its regulator ramA, phosphoethanolamine pmrC, by additional binding of amino arabinose pbgP. Additional mechanism found in the resistance are efflux pump AcrAb-TolC and KpnEF. Also, Plasmid mediated resistance was reported by identification of mcr-1 gene. (Clements et al., 2007).

Issues associated with Multi Drug Resistance:

Effectiveness of antimicrobial therapy is decreasing day by day leading to extended duration of infection in patient which is due to the possibility of increasing dispersion of pathogenic microorganisms. Since these Microbial Pathogens have become resistant to almost all existing antimicrobial drug available in the market it ultimately results into high mortality rates as well as expensive treatment. (Fishbain & peleg, 2010) Worldwide, TB is one of the top 10 causes of death and a total of 1.5 million people died from TB in 2018 (including 2,51,000 people with HIV co-infection). Multidrug-resistant TB (MDR-TB) remains a major public health crisis and a health security threat. WHO estimates that there were 4,84,000 new cases with resistance to rifampicin, which is the most effective first-line drug, of which 78% will have MDR-TB. (WHO, 2018).

Bacterial and fungal pathogens possess different resistance profiles as well as public hygiene quality also have a significant impact on the efficiency of antimicrobial drug (WHO, 2014; Fishbain et al., 2010). Spreading out of global employment and tourism lead to augmented possibility of MDR to disperse globally. (WHO, 2014) In supplement to the general risk factors of MDR bacteria transport, foreign patients looking for advanced medical care are more likely to carry MDR bacteria than locals. (Shmuel et al., 2018).

Antibiotic resistance has reached a point where, if immediate action is not taken, human medicine will enter a post antibiotic world and simple injuries could once again be life threatening. Now a days, there are disputes in fight of pathogens & acute ailment along with deficiency of efficient medicine and effectual hindrance will need the improvement of novel handling options with unconventional techniques together with alternative antimicrobial therapies. (Muhlen & Dersch, 2016).

Direct Adverse Outcomes Related to Resistance:

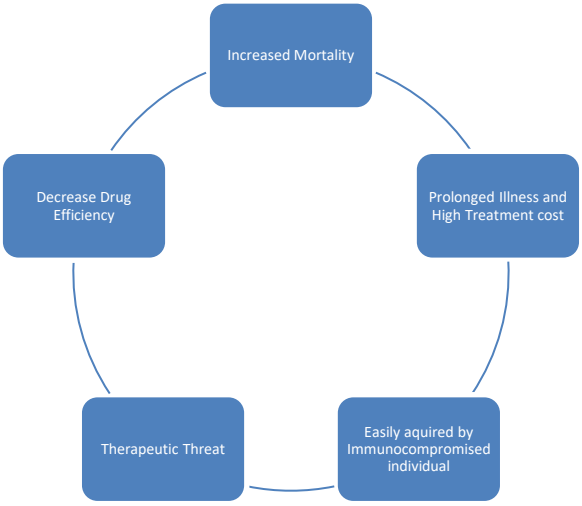

Figure 5: Issue related with MDR

Infections originated through resistant pathogens cause up to two-fold higher rates of adverse results proportionate to similar infections caused by vulnerable strains. (Eliopoulos et al., 2003) These adverse results may be medical (death or treatment failure) or financial (costs of care, length of stay) and imitated both therapy and interrupts leasing to the failure of antibiotic treatment to treat infections. The scale of these adverse outcomes will be more pronounced along with disease severity and virulent strain. (Friedman et al., 2016).

Reasons for Desiccation of Antibiotic Channel:

The main reason for desiccation of antibiotic channel is requirement of more funding and time duration for the discovery and improvement of new antibiotics. Pharmaceutical industries need to precedencize challenging plans for antimicrobial improvement, but instead it has an inferior precedence than further challenging medicines during selection process. In the late 1960s, contagious infection was considerable to be successed and changing to its persistent situation like cancer and cardiovascular disease. Antimicrobial drug treatment prescribed for an inadequate period makes them less profitable than further antibiotic prescribed for a year against persistent situation like hypertension and diabetes. (Powers, 2007:2010).

In market there is tough rivalry within the exiting antimicrobial drug. Whereas Multidrug resistance is a rising and burning issue, cheap generic antibiotics in the market are utilized as first line therapy because they are still effectual against most diseases. Newly synthesized antimicrobial drug may be used as a last alternative therapy, that is why consequentially doing lower transaction for Pharmaceutical industries. (Powers, 2007:2010).

Due to the chance of development of antibiotic resistance, newly synthesize antimicrobial drug can have limited existence. Alteration in regulatory process having created a "difficult situation". Regulators have been demanding demonstrations of the relative efficacy of new antibiotics *versus* those already registered within tighter statistical parameters. (Powers, 2007:2010).

Remedies for MDR

MDR is enhanced by the mistreatment and overdose of antibiotics, with weak infection prevention and control. Actions need to be taken at all points of society to decrease the influence and restrict the spread of resistance. Updated epidemiological report on antimicrobial resistance will be helpful for selecting treatment strategies and for developing a powerful antimicrobial program in medical centers. (USFDA, 2019; & WHO 2018).

Most important solution as per antibiotic policy (Antibiotic Stewardship) and Chennai Declaration for AMR guideline is to go with discontinuation or alteration of the antibiotic in use.

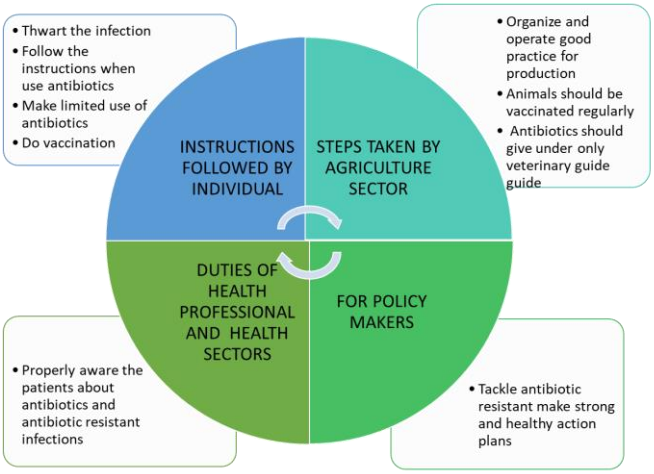

Figure 6: Suggested solutions for combatting MDR

Instructions to be followed by individual: Thwart infections by regularly washing hands, making food hygienically, evading close contact with ill people, and keep on vaccinations in advance. antibiotics to be used always as recommended by a certified health professional. As well as never ask for antibiotics if health worker says no need for it and never give out or utilize leftover antibiotics.

Steps to be taken by Agriculture sector: Organize and operate good practices for production and processing of foods from animal and plant sources. These animals should be vaccinated regularly to decrease the need for antibiotics and if needed than they should be given medications only under veterinary supervision. antibiotics should be never use as a growth stimulator. We must develop biosecurity on farms and stop infections by better sanitation and animal welfare.

Duties of Health professionals and health sectors: Health professionals should properly give advice to patients about how to take antibiotics accurately, antibiotic resistance and the risks of misuse. And should give out antibiotics only when they are required, as per existing guidelines. Make patients aware about cleanliness of hands, devices, and atmosphere to avoid the infections. Surveillance teams need to be Informed about antibiotic-resistant infections.

For policy makers: Persons who deals with this sector should make strong and healthy action plan to tackle antibiotic resistance. Also, standardization and policy to be made to promote the correct use and disposal of quality medicines.

Finance is to be provided to enhance the research and development of new antibiotics, vaccines, diagnostics and other tools. For example, Precision Medicine – it is a newer approach where greater understanding of the genotype is done through WGS (whole genome sequencing) and of the phenotype through interaction testing forming the basis for sensible combination therapy. Precision medicine increases quality and safety of drug. (Federico et al., 2020).

Maps of country specific MDR prevalence should be publicly available and routinely updated in order to provide better care for medical tourists and reduce the risk of bacterial transmission in the host countries. (Shmuel et al., 2018).

CONCLUSION

Research data suggest that multidrug-resistant organisms had evolved and spreaded globally at fast rate since past 50 years. The global increase of bacterial resistance is recognized as priority threat which need to be addressed urgently. Infections caused by multi drug resistant bacteria leads to two-fold higher rate of adverse outcome and associated with increased morbidity and mortality rates, as well as higher healthcare costs representing a growing public health threat. Thus, immediate action is needed to combat drug resistance.

Acknowledgments

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