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Global Threat of Bacterial Antimicrobial Resistance

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Antimicrobial resistance (AMR) is one of the most serious health threats worldwide. Infections from antimicrobial resistant bacteria are now very common as some of these pathogens have shown resistance to multiple types or classes of antimicrobial agents. This has been a very difficult problem the global healthcare sector has to grapple with over the years.

According to World Health Organization in 2019, the total annual deaths due to drug resistance was 4.95 million deaths, out of these, 1.27 million deaths were due to AMR bacteria, which is even more than those from Human immunodeficiency virus (HIV). The WHO lists AMR among ten threats to global health.The economic impact of AMR is enormous as it is estimated at 1.1% of gross domestic product (GDP) reduction, which is projected to exceed US$ one trillion annually across the world. The AMR cost could cost from $300 billion to over $1 trillion annually by 2050 worldwide.

It is a fact, although unknown to many, that the first hospital use of drug that would be named as antibiotic, was the so called pyocyanate prepared by Rudolf Emmerich and Oscar Low, two German physicians, in 1899 from *Paeudomonas aeruginosa*. However, the accidental discovery of penicillin by Alexander Fleming in 1928 was an event that re-defined treatment of infectious diseases, but was short-lived as it was soon discovered that microbial pathogens amplified their armamaterium to dwarf this very high hope.

Drug companies were very interested in Alexander Flemming's discovery and started making penicillin for commercial purposes, which was widely used for treating soldiers with battle wounds and pneumonia during World War II. From mid- to late 1940s, it became widely accessible for the general public use. However, in the 1930s, the first commercially available antibacterial agent called Prontosil, a sulfonamide was developed by a German biochemist called Gerhard Domagk. In 1945, penicillin was introduced on a large scale in the treatment of bacterial infections, especially through the work of Howard Florey and Ernst Chain, who efficiently purified penicillin and scaled-up production.

The introduction of penicillin marked the beginning of the' golden era of antibiotics' classes for use in medicine, when antibiotics were discovered and introduced to the market between 1940 -1962. Each class contained several antibiotics which were discovered and modified versions of earlier types. Today, very few novel antibiotics are being developed while antimicrobial resistant bacteria that survive antimicrobial treatment are on the increase. These bacteria render most antibiotics ineffective or useless, which has further complicated this global health burden.

The time-line of the discovery of different classes of antibiotics in clinical use, otherwise known as "the discovery void' refers to the period from 1987 until today, as the last antibiotic class was introduced for treatment of infectious diseases in 1987.

Bacteria use several mechanisms of drug resistance, some of the major ones of which include: 1) Drug inactivation using bacterial enzymes, 2) structural modification of drug's target site by mutation, 3) reduction of drug intake through lowering of bacterial cell permeability, 4) drug efflux outside the bacterial cell membrane etc.

The AMR crisis due to increasing global incidence of infectious diseases is affecting the human population. This thus threatens human and animal health, and welfare for food and nutrition security, the environment, economic development as well as equity within societies.

Some causes of antibiotic resistance include: 1) over or under-prescription , 2) patients' inability to complete antibiotic course, 3) overuse of antibiotics in livestock and fish farming, 4) poor sanitation and hygiene, 5) poor access to quality drugs, 6) poor infection and disease prevention and control in healthcare facilities, 7) lack of access to clean water, sanitation, and hygiene (WASH) for both human and animals, 8) self medication and 9) non-application of one health as a preventive strategy.

World Health Organization categorised antibiotic resistant bacteria into 3 groups, as mainly critical, high and medium priority; critical group include *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and members of the family Enterobacteriaceae, aetiological agents of pneumonia and blood stream infections, the high and medium priority group include drug resistant bacteria like *Salmonella* that causes common infections like gastroenteritis, diarrhoea, food poisoning and *Neisseria gonorrhoeae*, a sexually transmitted pathogen.

The prevalence of drug resistance limits therapeutic options for the treatment of infectious diseases, thus contribute to the specter of "post-antibiotic era" in which most antibiotics are already ineffective.

The consequences of multiple drug resistance is the emergence of the superbugs, which are strains of bacteria, parasites, fungi, and viruses, that are resistant to most of the antibiotics and other medications used in the treatment of their infections. Superbug refers to bacteria which infections cannot be treated with two or more antibiotics. Examples of superbugs include drug resistant bacteria that cause pneumonia, complicated urinary tract infections (cUTI), skin infections etc. Infections by superbugs can however be successfully treated, although, they are much more challenging to treat and manage. A few examples are methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant Enterbacteriaceae (CRE), vancomycin-resistant *Enterococcus* (VRE), multi-drug resistant *Pseudomonas aeruginosa* (MRPA) and multi-drug resistant *Eshcerichia coli* (MREC).

The loss of efficacy by antibiotics surely undermines man's ability to fight and win the battle against infectious diseases and manage complications among vulnerable patients especially those undergoing chemotherapy, invasive treatment procedures, surgery and organ transplantation.

Various options are applied in the treatment of antimicrobial resistant bacterial infections such as combinatorial drug approaches, antimicrobial polymeric bio-material products, bio- nanotechnology approach, among others.

Therapy against superbugs particularly employ two major methods: 1) pathogen-directed therapeutics approach which decreases bacterial toxicity by alteriing their virulence factors and 2) the host-directed therapeutics approach which limits the superbug by modulating immune cells, enhance host cells' functions and effectively modify disease pathology. Where the first line and second line antibiotic treatment options are limited by resistance or are unavailable, healthcare providers are compelled to use toxic antibiotics in the treatment of patients, which often result in high treatment cost, definitely less effective treatment characterised by high mortality, longer hospital stay, delayed recuperation and long term disability.

Conerted efforts are required to fight the spread of AMR, some of which are : 1) prevent infections from occurring and preventing resistant bacteria from spreading, 2) minimise the use of broad spectrum antibiotics and promoting the use of narrow spectrum an-

tibiotics, 3) tracking drug resistant bacteria, 4) promoting development of new antibiotics, 5) building on the foundation of proven public health strategies, 6) immunization, 7) infection prevention and control, 8) protecting food supply, antibiotic stewardship and 9) minimizing person-to-person transmission or spread of infections, by screening, diligent treatment and education.

Preventive measures must be taken to minimise the menace of AMR, through rational use of antimicrobial drugs whenever necessary. Healthcare professionals should endeavour to promote drug safety awareness. The proper use of disinfectant must be practiced by both patients and health-workers, so as prevent nosocomial spread of multiple drug resistant bacteria.

In the global attempt at mitigating AMR, nearly 43 new antibiotics are in clinical development by the top 50 pharmaceutical companies with significant antibacterial properties against life-threatening infections, 18 of which have shown potential action against drug resistant Gram negatives and 10 others against *Neisseria gonorrhoeae*.

While attempts must be made to search for the best treatment strategies against super bugs, as resistance can easily be developed against new and novel antibiotics in the nearest future, rational antibiotic use and proper hygiene practices among patients and health-workers should be compulsory.