IJARASEM

ISSN: 2395-7852

International Journal of Advanced Research in Arts, Science, Engineering & Management

INTERNATIONAL STANDARD SERIAL NUMBER INDIA

निस्केयर NISCAIR

+91 9940572462 +91 9940572462 ijarasem@gmail.com www.ijarasem.com

International Journal of Advanced Research in Arts, Science, Engineering & Management (IJARASEM)

| ISSN: 2395-7852 | www.ijarasem.com | Bimonthly, Peer Reviewed & Referred Journal|

| Volume 4, Issue 3, May 2017 |

Antimicrobial Resistance (AMR) –A Global Health and Development Threat

[1]Dr. Chandresh Pareek & [2] Narendra Nirwan

[1]Associate Professor in Chemistry, S.D. Govt. College, Beawar, Rajasthan, India

[2]S.D. Govt. College, Beawar, Rajasthan, India

ABSTRACT: Antimicrobial resistance (AMR) is a global health and development threat. It requires urgent multisectoral action in order to achieve the Sustainable Development Goals (SDGs).WHO has declared that AMR is one of the top 10 global public health threats facing humanity.Misuse and overuse of antimicrobials are the main drivers in the development of drug-resistant pathogens.Lack of clean water and sanitation and inadequate infection prevention and control promotes the spread of microbes, some of which can be resistant to antimicrobial treatment.The cost of AMR to the economy is significant. In addition to death and disability, prolonged illness results in longer hospital stays, the need for more expensive medicines and financial challenges for those impacted.Without effective antimicrobials, the success of modern medicine in treating infections, including during major surgery and cancer chemotherapy, would be at increased risk.

KEYWORDS: AMR, health, sustainable, pathogens, economy, infections, chemotherapy, risk

I. INTRODUCTION

Antimicrobials – including antibiotics, antivirals, antifungals and antiparasitics – are medicines used to prevent and treat infections in humans, animals and plants.Antimicrobial Resistance (AMR) occurs when bacteria, viruses, fungi and parasites change over time and no longer respond to medicines making infections harder to treat and increasing the risk of disease spread, severe illness and death.[1] As a result of drug resistance, antibiotics and other antimicrobial medicines become ineffective and infections become increasingly difficult or impossible to treat.The emergence and spread of drug-resistant pathogens that have acquired new resistance mechanisms, leading to antimicrobial resistance, continues to threaten our ability to treat common infections. Especially alarming is the rapid global spread of multi- and pan-resistant bacteria (also known as "superbugs")[2] that cause infections that are not treatable with existing antimicrobial medicines such as antibiotics.The clinical pipeline of new antimicrobials is dry. In 2014 WHO identified 32 antibiotics in clinical development that address the WHO list of priority pathogens, of which only six were classified as innovative. Furthermore, a lack of access to quality antimicrobials remains a major issue.[3] Antibiotic shortages are affecting countries of all levels of development and especially in health- care systems.Antibiotics are becoming increasingly ineffective as drug-resistance spreads globally leading to more difficult to treat infections and death.[4] New antibacterials are urgently needed – for example, to treat carbapenem-resistant gram-negative bacterial infections as identified in the WHO priority pathogen list. However, if people do not change the way antibiotics are used now, these new antibiotics will suffer the same fate as the current ones and become ineffective.[5]

The cost of AMR to national economies and their health systems is significant as it affects productivity of patients or their caretakers through prolonged hospital stays and the need for more expensive and intensive care[6]. Without effective tools for the prevention and adequate treatment of drug-resistant infections and improved access to existing and new quality-assured antimicrobials, the number of people for whom treatment is failing or who die of infections will increase. Medical procedures, such as surgery, including caesarean sections or hip replacements, cancer chemotherapy, and organ transplantation, will become more risky.AMR occurs naturally over time, usually through genetic changes[7]. Antimicrobial resistant organisms are found in people, animals, food, plants and the environment (in water, soil and air). They can spread from person to person or between people and animals, including from food of animal origin. The main drivers of antimicrobial resistance include the misuse and overuse of antimicrobials; lack of access to clean water, sanitation and hygiene[8] (WASH) for both humans and animals; poor infection and disease prevention and control in health-care facilities and farms; poor access to quality, affordable medicines, vaccines and diagnostics; lack of awareness and knowledge; and lack of enforcement of legislation.[9]

II. DISCUSSION

For common bacterial infections, including urinary tract infections, sepsis, sexually transmitted infections, and some forms of diarrhoea, high rates of resistance against antibiotics frequently used to treat these infections have been observed world-wide, indicating that we are running out of effective antibiotics. For example, the rate of resistance to ciprofloxacin, an antibiotic commonly used to treat urinary tract infections, varied from 8.4% to 92.9% for *Escherichia coli* and from 4.1% to 79.4% for *Klebsiella pneumoniae* in countries reporting to the Global Antimicrobial Resistance and Use Surveillance System (GLASS)[10] .*Klebsiella pneumoniae* are common intestinal bacteria that can cause life-threatening infections. Resistance in *K. pneumoniae* to last resort treatment (carbapenem antibiotics) has spread to all regions of the world. *K. pneumoniae* is a major cause of hospital-acquired infections such as pneumonia, bloodstream infections, and infections in newborns and intensive-care unit patients. In some countries, carbapenem antibiotics do not work in more than half of the patients treated for *K. pneumoniae* infections[11] due to resistance.Resistance to fluoroquinolone antibiotics in *E. coli*, used for the treatment of urinary tract infections, is widespread.[12] There are countries in many parts of the world where this treatment is now ineffective in more than half of patients.Colistin is the only last resort treatment for life-threatening infections caused by carbapenem resistant Enterobacteriaceae (i.e. *E.coli, Klebsiella*, etc). [13]Bacteria resistant to colistin have also been detected in several countries and regions, causing infections for which there is no effective antibiotic treatment at present.The bacteria *Staphylococcus aureus* are part of our skin flora and arealso a common cause of infections both in the community and in health-care facilities. People with methicillin-resistant *Staphylococcus aureus* (MRSA) infections are 64% more likely to die than people with drug-sensitive infections.In 2014, a new AMR indicator was included in the SDG monitoring framework.[14] This indicator monitors the frequency of bloodstream infections due to two specific drug resistant pathogens: methicillin-resistant *Staphylococcus aureus* (MRSA); and *E. coli* resistant to third generation cephalosporins (3GC). In 2014, 25 countries, territories and areas provided data to GLASS on blood-stream infections due to MRSA and 49 countries provided data on bloodstream infections due to *E.coli*.[15] While the data are still not nationally representative, the median rate observed for methicillin-resistant *S. aureus* was 12.11% (IQR 6.4–26.4) and that for *E. coli* resistant to third generation cephalosporins was 36.0% (IQR 15.2–63.0). Widespread resistance in highly variable strains of *N. gonorrhoeae* has compromised the management and control of gonorrhoea. Resistance has rapidly emerged to sulphonamides, penicillins, tetracyclines, macrolides, fluoroquinolones, and early generation cephalosporins. Currently, in most countries, the injectable extended-spectrum cephalosporin (ESC) ceftriaxone is the only remaining empiric monotherapy for gonorrhoea. [16]

Antibiotic resistant Mycobacterium tuberculosis strains are threatening progress in containing the global tuberculosis epidemic. WHO estimates that, in 2015, there were about half a million new cases of rifampicin-resistant TB (RR-TB) identified globally, of which the vast majority have multi-drug resistant TB (MDR-TB), a form of tuberculosis that is resistant to the two most powerful anti-TB drugs. Only one-third of the approximately half a million people who developed MDR/RR-TB in 2015 were detected and reported. MDR-TB requires treatment courses that are longer, less effective and far more expensive than those for non-resistant TB. Less than 60% of those treated for MDR/RR-TB are successfully cured.In 2015, an estimated 3.4% of new TB cases and 18% of previously treated cases had MDR-TB/ RR-TB and the emergence of resistance to new 'last resort' TB drugs to treat drug resistant TB poses a major threat.[17]

III. RESULTS

Antiviral drug resistance is an increasing concern in immunocompromised patient populations, where ongoing viral replication and prolonged drug exposure lead to the selection of resistant strains. Resistance has developed to most antivirals including antiretroviral (ARV) drugs. All antiretroviral (ARV) drugs, including newer classes, are at risk of becoming partly or fully inactive because of the emergence of drug-resistant HIV (HIVDR). People receiving antiretroviral therapy can acquire HIVDR, and people can also be infected with HIV that is already drug resistant.[18] Levels of pretreatment HIVDR (PDR) to non-nucleoside reverse-transcriptase inhibitors (NNRTIs) among adults initiating first-line therapy exceeded 10% in the majority of the monitored countries in Africa, Asia and Latin America. The prevalence of PDR among infants is alarmingly high. In sub-Saharan Africa, over 50% of the infants newly diagnosed with HIV carry a virus that is resistant to NNRTI. Informed by these findings, latest WHO ARV guidelines now recommend the adoption of a new drug, dolutegravir, as the preferred first-line treatment for adults and children.[19] The use of this drug is particularly urgent in averting the negative effects of resistance to NNRTIs. Increasing levels of resistance have important economic implications since second- and third-line regimens are much more expensive than first-line drugs.[20] WHO's HIV drug resistance programme is monitoring the transmission and emergence of resistance to older and newer HIV drugs around the globe.The emergence of drug-resistant parasites poses one of the greatest threats to malaria control and results in increased malaria morbidity and mortality. Artemisinin-based combination

therapies (ACTs) are the recommended first-line treatment for uncomplicated *P. falciparum* malaria and are used by most malaria endemic countries.[21] ACTs are a combination of an artemisinin component and a partner drug. In the WHO Western Pacific Region and in the WHO South-East Asia Region, partial resistance to artemisinin and resistance to a number of the ACT partner drugs has been confirmed in Cambodia, Lao People's Democratic Republic, Myanmar, Thailand, and Viet Nam through studies conducted between 2001 and 2014. This makes selecting the right treatment more challenging and requires close monitoring. In the WHO Eastern Mediterranean Region, P. falciparum resistance to sulfadoxine-pyrimethamine led to artesunate-sulfadoxine-pyrimethamine failures in some countries, necessitating a change to another ACT. In Africa, evidence has recently been published showing emergence of mutations linked to partial artemisinin resistance in Rwanda. So far, ACTs that have been tested remain highly efficacious. However, further spread of resistance to artemisinin and ACT partner drugs could pose a major public health challenge and jeopardize important gains in malaria control.The prevalence of drug-resistant fungal infections is increasing and exasperating the already difficult treatment situation. [22]Many fungal infections have existing treatability issues such as toxicity especially for patients with other underlying infections (e.g. HIV). Drug-resistant Candida auris, one of the most common invasive fungal infections, is already widespread with increasing resistance reported to fluconazole, amphotericin B and voriconazole as well as emerging caspofungin resistance.This is leading to more difficult to treat fungal infections, treatment failures, longer hospital stays and much more expensive treatment options. WHO is undertaking a comprehensive review of fungal infections globally and will publish a list of fungal pathogens of public health importance, along with an analysis of the antifungal development pipeline. [23]

IV. IMPLICATIONS

AMR is a complex problem that requires a united multisectoral approach. The One Health approach brings together multiple sectors and stakeholders engaged in human, terrestrial and aquatic animal and plant health, food and feed production and the environment to communicate and work together in the design and implementation of programmes, policies, legislation and research to attain better public health outcomes. Greater innovation and investment is required in operational research, and in research and development of new antimicrobial medicines, vaccines, and diagnostic tools especially those targeting the critical gram-negative bacteria such as carbapenem-resistant Enterobacteriaceae and *Acinetobacter baumannii*. The launch of the Antimicrobial Resistance Multi Partner Trust Fund (AMR MPTF), the Global Antibiotic Research & Development Partnership (GARDP), AMR Action Fund and other funds and initiatives could fill a major funding gap. Various governments are piloting reimbursement models including Sweden, Germany, the USA and the United Kingdom. More initiatives are needed to find lasting solutions.Globally, countries committed to the framework set out in the Global Action Plan[1] (GAP) 2015 on AMR during the 2015 World Health Assembly and committed to the development and implementation of multisectoral national action plans. It was subsequently endorsed by the Governing Bodies of the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE). To ensure global progress, countries need to ensure costing and implementation of national action plans across sectors to ensure sustainable progress. Prior to the endorsement of the GAP in 2015, global efforts to contain AMR included the WHO global strategy for containment of Antimicrobial Resistance developed in 2001 which provides a framework of interventions to slow the emergence and reduce the spread of AMR.The political declaration at the UN High Level Meeting on AMR, committed to by Heads of State at the United Nations General Assembly in New York in September 2016, confirmed a strong focus on a broad, coordinated approach that engages all including the human, animal, plant and environmental health sectors. WHO is working closely with FAO and OIE in a 'One Health' approach to promote best practices to reduce the levels of AMR and slow its development.[24]

The Interagency Coordination Group (IACG) on AMR was convened by the Secretary-General of the United Nations after the UN High-Level Meeting on Antimicrobial Resistance in 2016. The IACG brought together partners across the UN, international organizations and individuals with expertise across human, animal and plant health, as well as the food, animal feed, trade, development and environment sectors, to formulate a plan for the fight against antimicrobial resistance. The Interagency Coordination Group on AMR submitted its report " No time to wait: Securing the future from drug-resistant infections" to the UN Secretary-General in April 2014. Its recommendations are now being implemented. A tripartite joint secretariat (FAO, OIE and WHO) has been established and is hosted by WHO to drive multi-stakeholder engagement in AMR. The key governance structures agreed include the Global Leaders Group on AMR, which began its work in November 2015, the Independent Panel on Evidence for Action against AMR and the Multi-Stakeholder Partnership Platform, both of which are in the process of being established.[25]

| ISSN: 2395-7852 | www.ijarasem.com | Bimonthly, Peer Reviewed & Referred Journal|

| Volume 4, Issue 3, May 2017 |

V. CONCLUSIONS

WAAW was previously called World Antibiotic Awareness Week. Since 2015, it has been called World Antimicrobial Awareness Week. This reflects the broadened scope of WAAW to include all antimicrobials including antibiotics, antifungals, antiparasitics and antivirals. Held annually since 2015, WAAW is a global campaign that aims to raise awareness of antimicrobial resistance worldwide and encourage best practices among the general public, health workers and policy makers to slow the development and spread of drug-resistant infections. The Tripartite Executive Committee decided to set all future WAAW dates as 18 to 24 November. The overarching slogan used for the last 5 years was "Antibiotics: Handle with Care." This was changed to "Antimicrobials: Handle with Care" in 2015. WHO launched the Global Antimicrobial Resistance and Use Surveillance System (GLASS) in 2015 to continue filling knowledge gaps and to inform strategies at all levels. GLASS has been conceived to progressively incorporate data from surveillance of AMR in humans, surveillance of the use of antimicrobial medicines, AMR in the food chain and in the environment. GLASS provides a standardized approach to the collection, analysis, interpretation and sharing of data by countries, territories and areas, and monitors the status of existing and new national surveillance systems, with emphasis on representativeness and quality of data collection. Some WHO regions have established surveillance networks that provide technical support to countries and facilitate enrollment into GLASS. In 2016, to guide research and development into new antimicrobials, diagnostics and vaccines, WHO developed the WHO priority pathogens list. It will be updated in 2016. On an annual basis, WHO reviews the pre-clinical and clinical antibacterial pipelines to see how the pipeline is progressing with respect to the WHO priority pathogens list. A critical gap remains in research and development, in particular for antibacterial targeting of the gram-negative carbapenem resistant bacteria. Global Antibiotic Research and Development Partnership (GARDP). GARDP is a not-for-profit global partnership developing treatments for drug-resistant infections that pose the greatest threat to health. GARDP works across sectors to ensure equitable access to treatments and promote their responsible use.[25]

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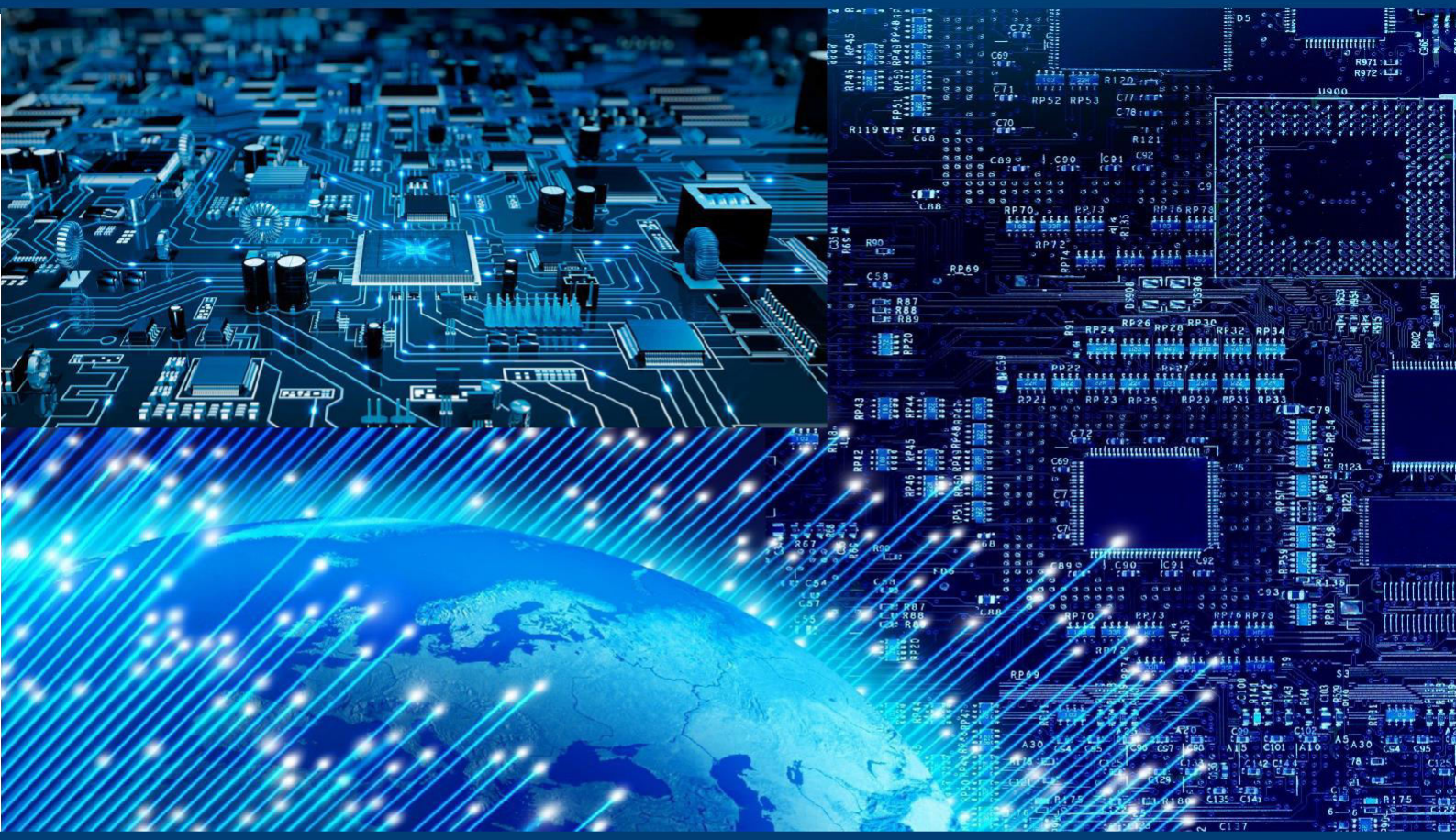

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| Mobile No: +91-9940572462 | Whatsapp: +91-9940572462 | ijarasem@gmail.com |