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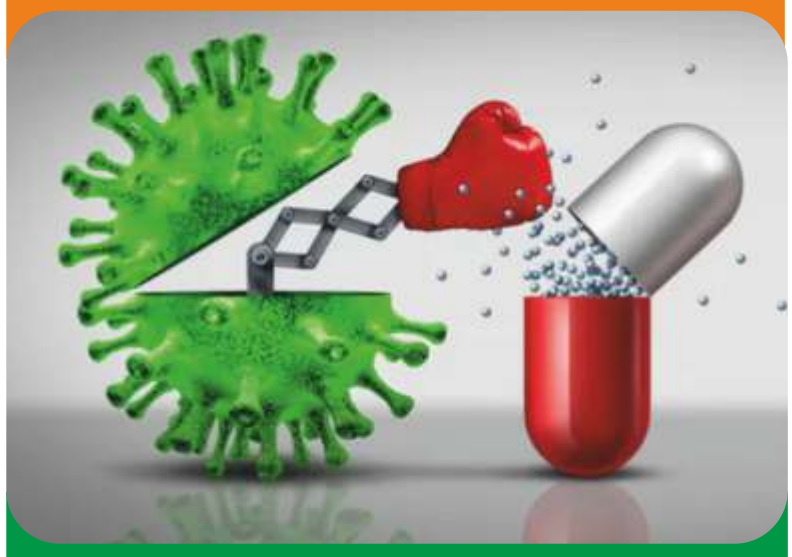

Way forward to challenges of Antibiotic resistance in India

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Review:

Frontiers in Antimicrobial agents: Way forward to challenges of Antibiotic resistance in India

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Contents **Page No.**

Introduction

Antimicrobial resistance (AMR) is a critical public health problem, which can shake the foundation of modern health-care.[1] Infections caused by drug-resistant organisms could lead to increased mortality and prolonged duration of hospitalization, causing a huge financial burden to the affected persons, health-care systems, and hinder the goals of sustainable development.[2]

Understanding the gravity of the situation and the threat posed by AMR on health-care, the World Health Assembly (WHA) adopted the Global Action Plan (GAP) on AMR in 2015.[3] Following this, many countries have formulated their own National action plans (NAPs). The Indian Ministry of Health and Family Welfare published the National Action Plan for containing AMR in April 2017. [4] It was submitted at the 70th WHA in Geneva in May 2017. This 5 year NAP on AMR (2017–2021) outlines the priorities and implementation strategies for curbing AMR in India. [4]

Antimicrobial resistance (AMR) occurs when microbes (i.e., bacteria, viruses, fungi, and parasites) develop mechanisms to evade antimicrobials (i.e., antibiotics, antivirals, antifungals, and antiparasitics) rendering them ineffective. A recent report from the WHO found that due to AMR, our armamentarium of effective antimicrobials is declining rapidly. [5]

Just like all living organisms, microbes are evolving for survival. AMR has existed even before the first antibiotic was discovered. AMR commonly develops due to selective pressure applied by antibiotic use, through genetic mutations or acquisition of genetic material through plasmid transfer from a resistant bacterium.[6]

AMR has been identified as a global health threat with serious health, political, and economic implications.[7] The progress made in modern medicine is under serious threat because of the emergence of AMR. Annual deaths due to AMR are anticipated to rise to 10 million worldwide by 2050.[7] This public health problem is receiving growing attention globally. Several countries are facing the emergence of bacteria that are completely resistant to available antibiotics and countries are preparing country-specific action plan for AMR based on the global action plan of the WHO.[8]

Random use of Antibiotics: Probable reasons

Studies have shown that resistance to antibiotics is directly linked to their usage.[9] It would therefore be important to briefly review the patterns of antibiotic use. In 2010, India recorded a staggering 12.9 billion units of antibiotic consumption, which was the highest among all the countries.[10] In addition, an increased consumption rate of carbapenems, lincosamides, glycopeptides, linezolid, and daptomycin has been reported in one study.[11] The reasons leading to such situations are multiple, as explained here under: [12-17]

a) Easy access to medicines over-the-counter in medical stores (chemist/pharmacy outlets);

b) Self-medication through hearsay or information gathered from the internet or upon the advice of the shop-keeper;

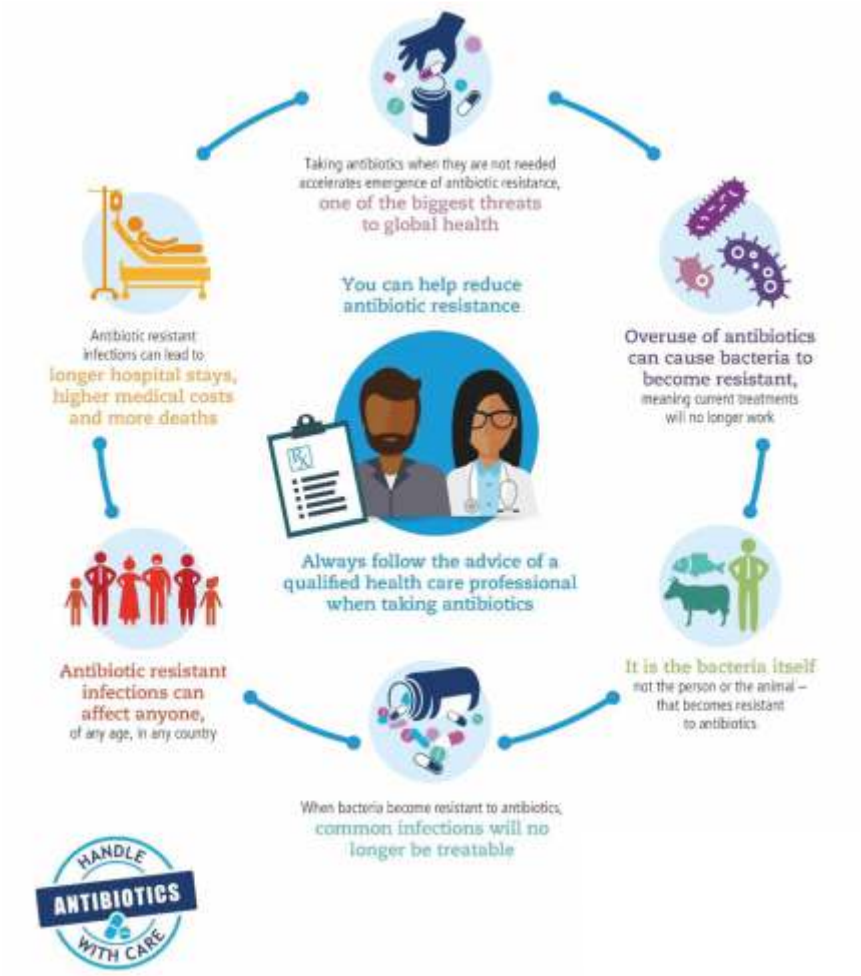
c) Non-availability and non-utilization of the laboratory service for cultures and antibiotic susceptibility testing;

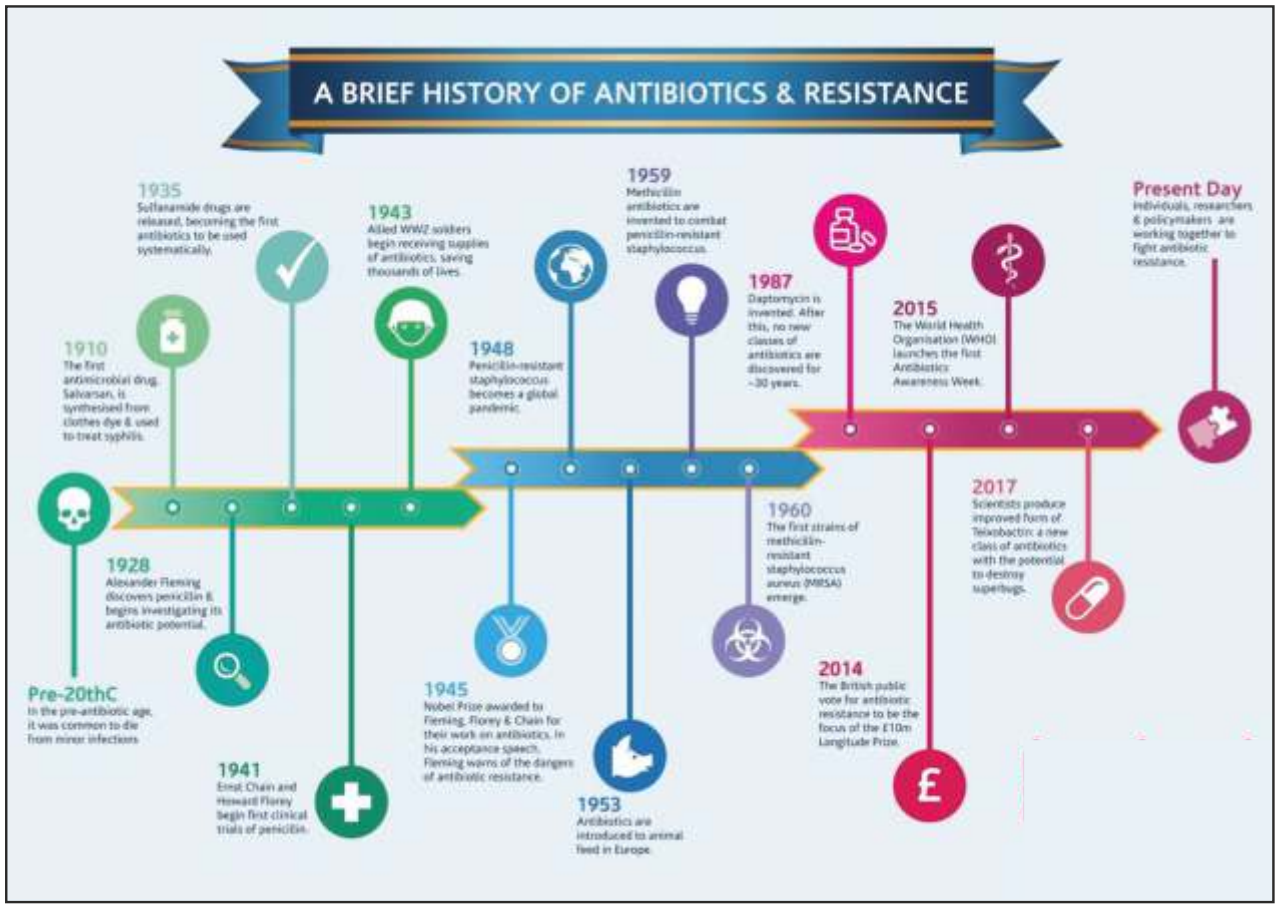
d) Varying approach of treating doctors – owing to the anxiety of missing a bacterial infection or covering for secondary bacterial infection, lack of up-to-date knowledge on the current revised guidelines and algorithms for antibiotic usage;

e) Empirical but incorrect use of antibiotics, simultaneous use of more than a single antibiotic when actually not necessary, not de-escalating when possible, inefficiency in the review of the response to antibiotics;

f) Regulatory issues – Lack of strict implementation of policies (such as schedule H1) and control by the regulatory authorities;

Misusing and overusing **ANTIBIOTICS** puts us all at risk





g) Varied perceptions such as perceived demand and expectations among key stakeholders and ethical challenges among healthcare professionals;

h) Unethical commercial practices to promote the sale of antibiotics in large quantities; and

i) Use of antibiotics by other non-medical and informal healthcare providers.

Not only misuse and overuse, but underuse due to lack of access is common in India. Lack of access to good quality, affordable antibiotics leads to significant mortality (especially in children), and hence, there is an urgent need to maximize access and limit excess antibiotic use.[18] Besides the healthcare sector, antibiotics are also used in livestock such as in animal husbandry, fisheries, and agricultural sectors for therapeutic purposes as well as growth promotion.[19]

Environmental pollution by means of pharmaceutical waste, waste from livestock, and hospitals is another dimension contributing to the crisis of antibiotic resistance.[20]

• Antimicrobial Resistance (AMR) Drivers -

Chereau et al[21], in their evaluation of risk assessment for AMR, have shown that while AMR originating from environmental sources may be contributing a low proportion in developed countries, it poses a moderate to high-risk in developing countries of South East Asia including India due to several cofactors associated with the overall event. Let us discuss the following AMR drivers in detail –

A) Excess use or misuse of antimicrobial agents

a) AMR contributed by antimicrobial use in humans:

• India ranks first among all countries of the world in total consumption of antibiotics for human use. A total of 12.9 × 109 units of antibiotics with 10.7 units per individual were consumed in India in 2010 alone[(22)].

• There was a 23 per cent increase in the volume of antibiotic retail sale from 2000 to 2010[(22)]. The rate of consumption is feared to be on a rise ever since. These figures, though threatening, are not surprising for India where antibiotics are used day in and day out[(23,24)].

• While the lack of adequate knowledge regarding the rational use of antibiotics including fixed-drug combinations was found among medical practitioners[(25)], the wide availability of illegitimate antimicrobials[(26)] shows inadequacy in the working of health authorities.

• According to a review by Kelesidis and Falagas[(27)], India was the leading country in manufacture and usage of substandard and counterfeited antimicrobial agents where as many as 39 per cent of the tested agents were found substandard. Approximately half of the consumed antibiotic is eliminated unchanged from the body via faeces and urine.

• The practice of defecating in the open, as prevalent in India for decades[(28)], causes seeping of antibiotics or their residues into the environment via soil and water. With nearly 35 per cent population being exposed to faeces-contaminated drinking water[(29)], this part of environment contributes significantly to development of AMR.

b) AMR contributed by antimicrobial use in animals

• India is an important producer of food animals for the global market in the form of meat, meat products and farmed seafood and a rise by 312 per cent in this market is expected by 2030[(30)].

• Antimicrobial agents are widely used to prevent diseases in these farmed animals and to increase productivity [(31)].

• India is the world's fourth largest consumer of antimicrobials for animal use, after China, USA and Brazil.[(22)] Bayesian projections show that at this pace, India will contribute to the largest relative increase in antimicrobial consumption for use in livestock between 2010 and 2030 [(30)].

• Antibiotic residues have been reported from

food animal products in India like chicken meat and milk[32,33]. Since there are no data available to represent the national picture, future studies investigating the same are urgently required.

• The International Food Safety and Quality Network standards have laid down strict regulations for the use of antimicrobials in food animals[34,35]. Though this has curtailed excess use of antimicrobial agents in animal products for export, no such guidelines are currently in effect for domestic consumption of animal products in India. Even the Food Safety and Standard Regulations did not encompass use of antimicrobial agents in poultry till early 2017 [32]

c) AMR contributed by biocides

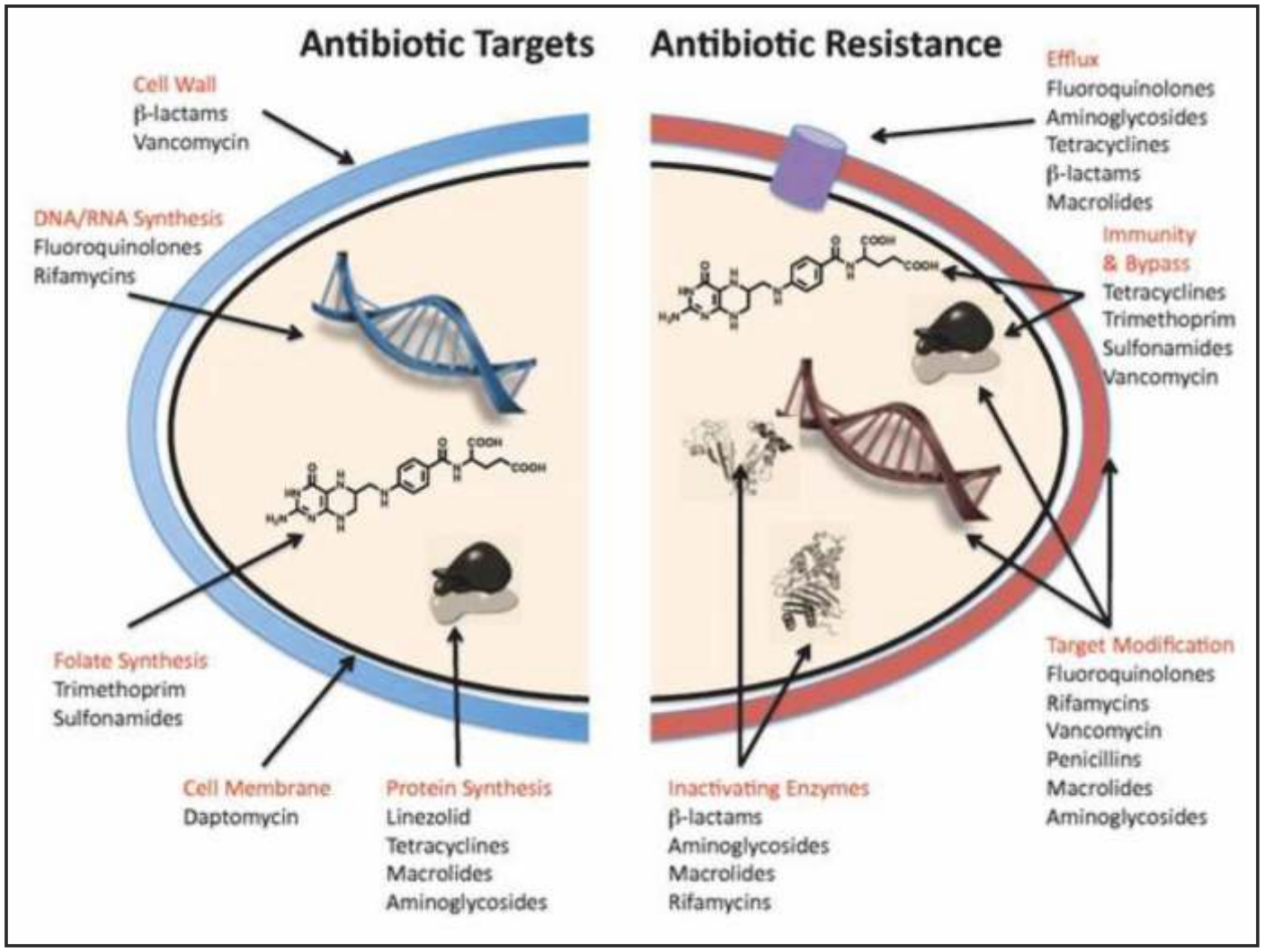
• Biocide is an umbrella term encompassing agents directed to kill the offending pathogen or microbe. It includes insecticides, pesticides, fertilizers and disinfectants[36].

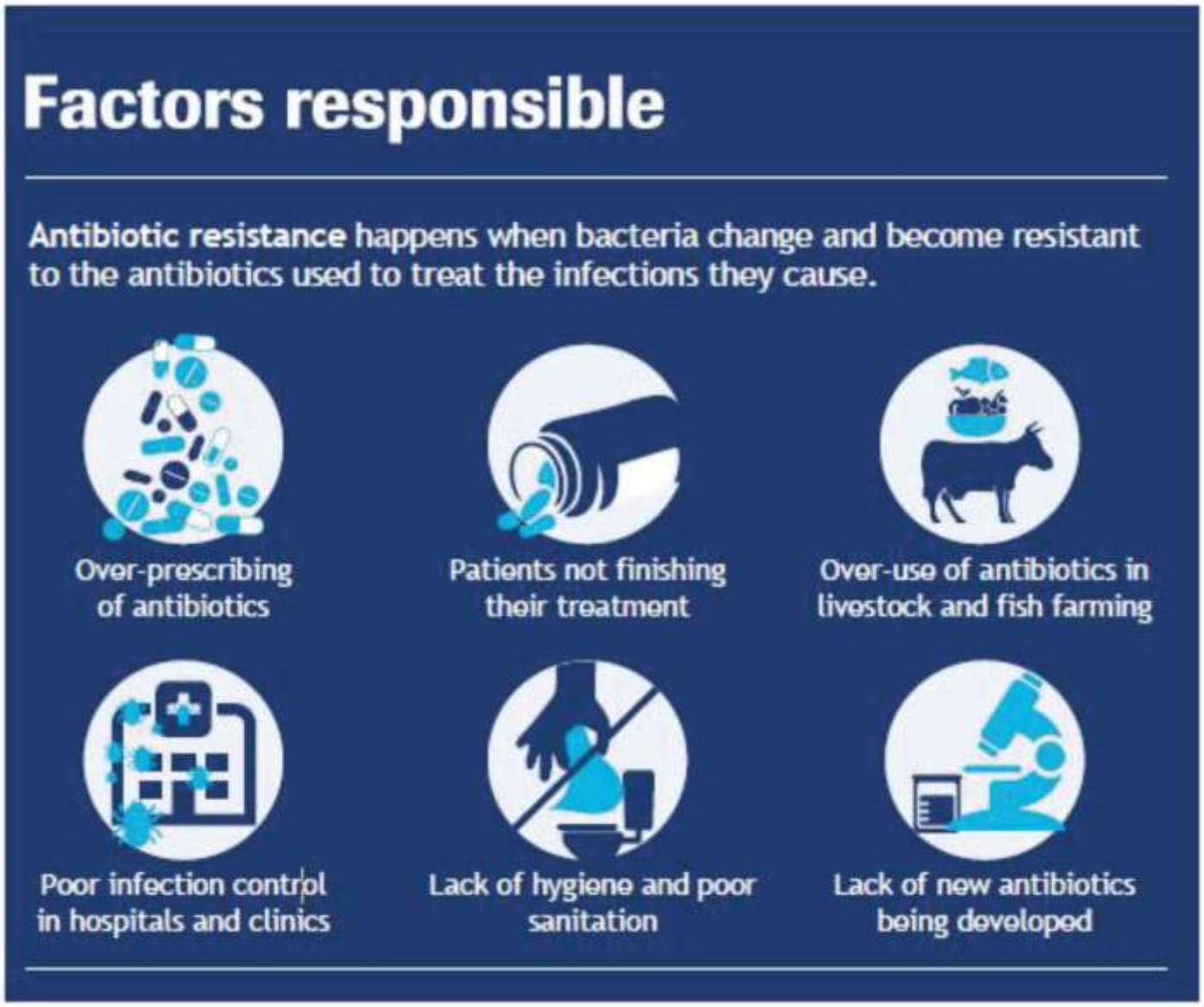
• Sub-lethal concentrations of biocides can increase the pool of resistant organisms in the environment [37].

• Use of nitrogen-based fertilizers has shown to alter the soil content selecting out vanA gene and thus contributing to clinical vancomycin resistance[38].

• Another important aspect is the sharing of resistance mechanisms between biocides and antimicrobial agents, thus facilitating their co-selection. Resistance of S. aureus to biocide benzalkonium chloride confers eight-fold higher tolerance to oxacillin due to the co-location of both the resistant genes on the plasmid[39].

• The global biocide market showed a 40 per cent growth between 1992 and 2007[36] and although the data regarding biocide consumption in India are largely lacking but it is feared to be high in magnitude.





• The European Commission[40] has incorporated the assessment of AMR generated by biocides and has also formulated regulation for use and disposal of biocides. Biocides as a route of AMR, however, have not been listed in the NAP on AMR of India and prospective studies analyzing the contribution of biocides towards AMR in Indian context should be undertaken.

B) Contaminated water as a source of AMR

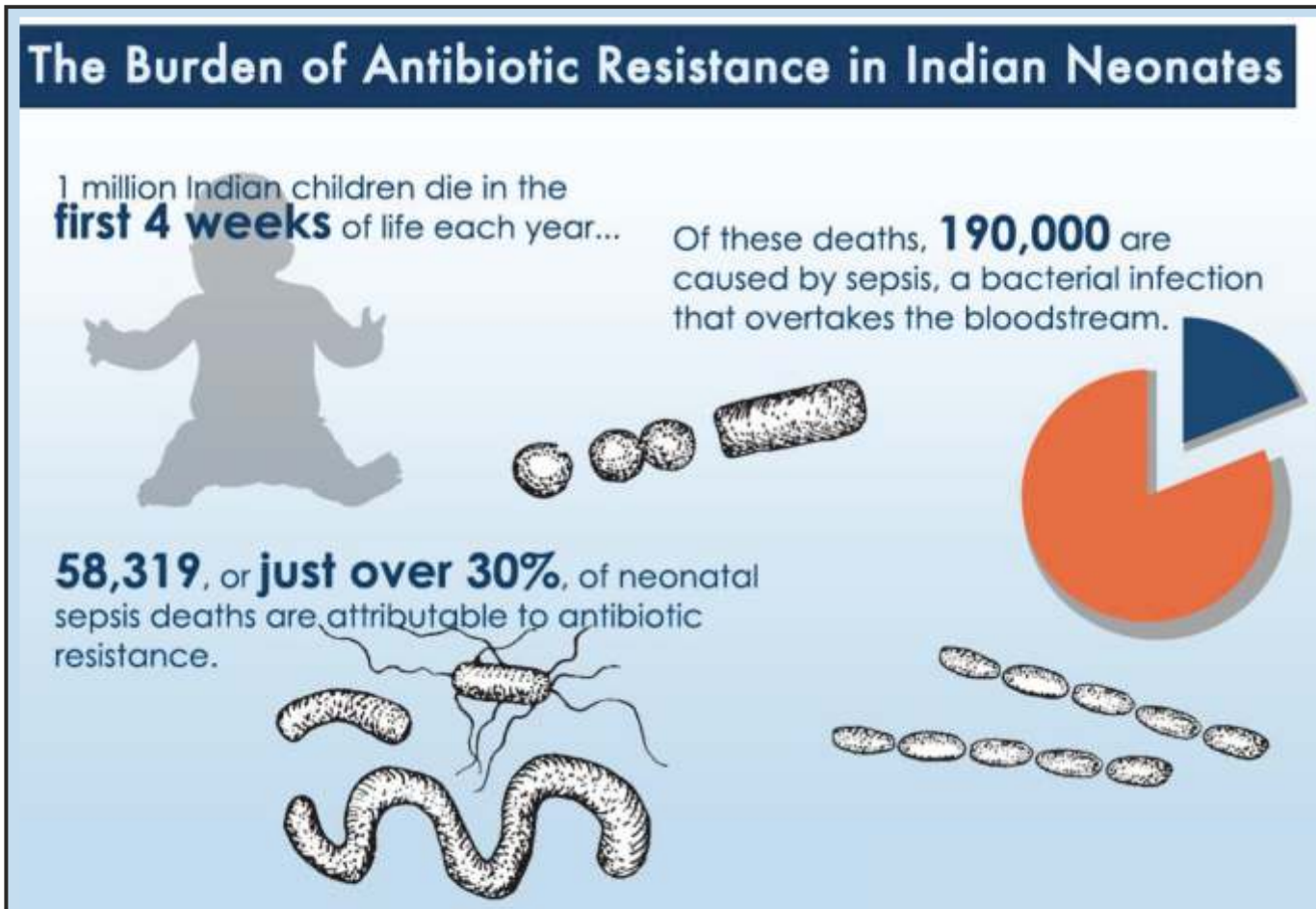
a) Pharmaceutical waste water –

• India is one of the leading producers of pharmaceuticals in the world[41]. In the effluent of one of the Indian pharmaceutical plants, the levels of ciprofloxacin were found to be 28 and 31 mg/l on two consecutive days[42]. Extrapolating these figures to the total volume of effluent generated, several kilograms of antibiotic are being released in to the waste water every day.

• Antimicrobial classes such as fluoro-quinolones and sulphonamides produce stable residues while beta-lactam group of drugs degrade relatively faster from the environment. While the former constitute an ever-growing pool of AMR, the latter indicates recent contamination of wastewater[43]. Both the types of drugs are widely present in the wastewaters of Indian pharmaceutical companies which pollute the neighbouring rivers, ponds and sea coasts[30,44].

• Lübbert et al[45] found antibiotic residues from 28 environmental sampling sites in the sewers of industrial area in Hyderabad, India.

• Wastewater is generated by every pharmaceutical company of the world, but as



per the risk assessment[21], the adequate treatment of this wastewater in developed countries decreases the overall associated risk while the lack of optimal wastewater treatment increases its overall risk in India.

• The high cost associated with regular monitoring of antimicrobial levels in pharmaceutical waste water makes it a low-priority objective for India[46].

• With the antibiotic factories in India and China being the largest contributors in global rise of AMR[47], a strict vigilance on the effluent produced is needed.

b) Municipal waste water:

• With 30-90 per cent fraction of all antimicrobials being excreted unchanged via human faeces and urine, municipal waste water becomes an important dumping ground of resistant organisms or genes.

• It is estimated that only 20-30 per cent of municipal waste water is treated in treatment plants and that too is not effective enough to eliminate the resistant organisms[46]. This potentially 'AMR-rich' municipal waste water is discharged into the nearby water bodies.

• Antibiotic-resistant genes even to high-end antibiotics were detected in Mutha river flowing through Pune, India, with 30 times higher concentration in the sediments near the city, originating from domestic and municipal sewage waste[48].

• While isolation of enterococci, a normal commensal of human gut, was possible from river sources at several places, the rate of vancomycin-resistant enterococci ranged between 22 and 100 per cent from banks of Indian river Gomti[49].

c) Hospital effluent:

• Hospitals and all other healthcare facilities are important sources of generation of antimicrobial waste indirectly via patient secretions or directly as unused discarded

medicines.

• Mutiyar and Mittal[50] have reported the worrisome extent to which residues of fluoroquinilones, sulphonamides and tinidazoles were recovered from one of the hospital effluents in India.

• Since hospitals are the places with highest level of antimicrobial consumption, their effluent waters are expected to be the richest source of resistant bacteria and their genes.

• The concentrations of antimicrobials from effluent plants of Indian hospitals were high enough to cause genotoxic alterations and modify bacterial strains[51]).

• It has been shown that 80-85 per cent of antimicrobial residues can be effectively removed if hospital effluent undergoes proper treatment before final disposa[52]l.

Unfortunately, <45% of healthcare facilities in India have adequate waste water treatment systems in place.[53]

C) Other sources of AMR

a) Livestock discard:

• Animal excreta can contaminate the environment directly with resistant organisms or indirectly with antimicrobials[54].

• In a study from Netherlands[55], more than one-third of the samples collected from faeces of pig and cattle contained more than one antibiotic or its residue, with three different antibiotics recovered from pig faeces and eight different antibiotics from cattle faeces.

• Although no such studies have been conducted in India, one can speculate the situation to be worse as overcrowded shelter houses and improper disposal of animal waste and carcasses are rampant among Indian livestock farms.

• A definite link was observed between consumption of antibiotic in animals and development of resistance in humans[56].

b) Agricultural manure and sludge:

• While manure is the natural or synthetic growth-promoter for crops, sludge is the undissolved slurry that is generated from biological treatment of waste water and is rich in micro-organisms and undegraded pharmaceuticals[57]. Owing to different sources of generation, the antimicrobial content of both is different.

• While manure has abundance of drugs like oxytetracycline, doxycycline and sulphadiazine[55], sludge mainly contains drugs that are less water-soluble like ofloxacin, ciprofloxacin, norfloxacin and trimethoprim[58].

• The 'resistome' or the collection of genes capable of conferring resistance has been found to persist long after the manure or sludge is decomposed[59,60].

• In absence of Indian data, the magnitude of problem can be inferred from a study in China[61], wherein 156 new antimicrobial resistant genes and mobile genetic elements were identified in the composted manure and sludge.

c) Heavy metals:

• Metals can have similar mechanisms of resistance, structurally or functionally, as that of antimicrobials like decreased membrane permeability, efflux pumps, target alterations, intracellular sequestration and the presence on the same plasmid[62].

• Also bacteria carrying metal resistance genes are more likely to harbour drug-resistance genes[39].

• Although a few studies have addressed the effect of changing metal concentrations and toxicities in soil and water environment[63], there is not much information on its contribution to selection of resistant genes.

d) Aquaculture:

• With aquaculture becoming a fast growing industry in India and neighbouring countries, the injudicious use of antimicrobial agents to increase the productivity of farmed seafood can serve as an emerging source of environmental AMR.

• As described by Henriksson et al[64], the disturbing fact is that unlike soil and waste water which are geographically more confined, AMR in the aquatic environment has the

Priorities outlined in the National Action Plan for AMR in India. (77)

Priority	Main objective
Strategic priority 1	Improve awareness and understanding of AMR through effective communication, education, and training
Strategic priority 2	Strengthen knowledge and evidence through surveillance
Strategic priority 3	Reduce the incidence of infection through effective infection, prevention, and control
Strategic priority 4	Optimize the use of antimicrobial agents in all sectors
Strategic priority 5	Promote investments for AMR activities, research, and innovations
Strategic priority 6	Strengthen India's leadership on AMR by means of collaborations on AMR at international, national, and sub-national levels

Future Directions for India are as below[78]

Future directions for India

1. Promoting further research on the drivers of AMR with due importance to components other than antimicrobial use for human health alone
2. Framing of antibiotic stewardship plans for healthcare settings to monitor and ensure judicious use of antimicrobials, including all tiers of healthcare-primary health centres, secondary and tertiary hospitals
3. Strict vigilance and control over sale of antimicrobial agents. Prescription audit to bring down the over the counter (OTC) sale
4. Disciplinary control over the functioning of hospital effluent plants with periodic assessment and reporting of antimicrobial residue in the discharge
5. Regulation of waste water discharges from pharmaceutical companies with regular monitoring of antimicrobial residues in them along with provision of legislative support to punish offenders
6. Framing and implementing rules and regulations for the use of antimicrobial agents in food animals including farmed seafood
7. Improving agricultural practices by ensuring use of environment-friendly manure and fertilizers
8. Educating the masses at the community level regarding AMR and formulating educational bodies/non-governmental organizations for continued dissipation of information.

maximum propensity of international spread through international waters. Although the exact extent is yet not known, antimicrobial residues have been reported from aquaculture shrimps of India[65].

Antimicrobial Resistance: Indian scenario

Antimicrobial resistance is one of the major public health problems especially in developing countries where relatively easy availability and

higher consumption of medicines have lead to disproportionately higher incidence of inappropriate use of antibiotics and greater levels of resistance compared to developed countries.[66] In India the infectious disease burden is among the highest in the world and recent report showed the inappropriate and irrational use of antimicrobial agents against these diseases, which led to increase in development of antimicrobial resistance.[67] Besides, it has shown that health sector in India suffers from gross inadequacy of public finance which will result in the conditions favorable for development of drug resistance.[68] A recent study highlighted the importance of rationalizing antibiotic use to limit antibiotic resistance in India.[69] Antimicrobial resistance will result in difficulty in controlling the diseases in the community and ineffective delivery of the health care services.

Little is known regarding the epidemiological aspects of antimicrobial resistance in most of South East Asian countries.[70] Although many International agencies like World Health Organization, European Centre for Disease Control and World Health Assembly resolutions highlighted the antimicrobial resistance as a major public health issue, it will be a big challenge to tackle the problem for the policy makers and health care providers. World Health Organization has proposed regional strategy on antimicrobial resistance with the goal to minimize the morbidity and mortality due to antimicrobial resistant infection to preserve the effectiveness of antimicrobial agents in the treatment and prevention of microbial infections.[67] In the public health point of view, it is important to look for the existing situational analysis in Indian context, so that appropriate interventions can be initiated at community level to tackle the problem.

• Emergence of AMR in Milk –

Milk as a source of nutrition is especially important for infants and children, who need nutrient and energy rich foods for growth and cognitive development.

• The presence of antibiotic adulterants in milk can have a profound impact on the health of infants and children in regions already facing high rates of diarrheal disease and malnutrition. Numerous studies have shown a link between the gut microbiome, health status and disease [95],[96],[97].

• Antibiotic residues can negatively impact the microbiome of those consuming adulterated milk, resulting in dysbiosis, a change in microbiota associated with disease states[94, 98].

• *Bifidobacterium* spp. are a keystone species that play an important role in intestinal homeostasis and infant health. This bacterium is highly susceptible to antibiotics and exposure to antibiotic residues from food can greatly impact the microbial diversity of the gut microbiome resulting in reduced levels of *Bifidobacterium* and increases in *Proteobacteria*[99,100].

• Dysbiosis can last for years resulting in long-term health risks, especially in infants and children, such as stunted growth, compromised immune response, and recurring diarrheal disease[94].

• Presence of antimicrobial residues in milk has been reported from different parts of India, indicating wide antimicrobial use in food animal production in India.

• One of the most common clinical issues encountered in the dairy farms is mastitis and milk from cows and buffaloes, affected by the disease, have been shown to contain bacteria, with a wide spectrum of resistance against commonly used antibiotics. In some cases, multiple drug resistant bacteria have been seen to co-infect animals suffering from mastitis.(101)

• S. aureus is one among the leading causes of food-borne illnesses. Milk and dairy products are often contaminated with strains of S. aureus. Therefore, a survey report on occurrence of S. aureus in meat and dairy products indicated around 68.8% strains resistant to at least one antibiotic tested.

• Usually, S. aureus is present on the skin and mucosae of various animals, as well as

frequently associated with subclinical mastitis, which leads to its entry into milk chain.[102]

• Milk samples collected from several regions of Bihar were found to contain residues of tetracycline, oxytetracycline, sulfadimidine and sulfamethoxazole.[103] This indicates use of such antibiotics as growth promoters or for treatment of cows with infections.

Overall, however, there is little data on use of antimicrobials in dairy farms due to lack of maintenance of the antibiotic treatment records; low dependence on the veterinarian's advice; and administration of medicines by the owners themselves.

National Action Plan for Prevention of Antimicrobial Resistance

With 700,000 people losing battle to antimicrobial resistance (AMR) per year and another 10 million projected to die from it by 2050, AMR alone is killing more people than cancer and road traffic accidents combined together(71) . Economic projections suggest that by 2050, AMR would decrease gross domestic product (GDP) by 2-3.5 per cent with a fall in livestock by 3-8 per cent, costing USD100 trillion to the world (72) . The global rise of AMR has attracted the attention of World Health Organization (WHO) and several other stakeholders. With WHO announcing AMR as an urgent priority area[73] and several world leaders from Europe framing their Action Plans for the containment of AMR[74,75]. It is obvious that sincere efforts are being directed against this common enemy. India has also framed its National Action Plan (NAP) for AMR [76].

Challenges of AMR in India

• India has been referred to as 'the AMR capital of the world' [79]. While on one hand, emergence of newer multi-drug resistant (MDR) organisms pose newer diagnostic and therapeutic challenges, on the other hand India is still striving to combat old enemies such as tuberculosis, malaria and cholera pathogens, which are becoming more and more drug resistant. [80]

• Factors such as poverty, illiteracy, overcrowding and malnutrition further compound the situation[80].

• Lack of awareness about infectious diseases in the general masses and inaccessibility to healthcare often preclude them from seeking medical advice [81]. This, more often than not, leads to self-prescription of antimicrobial agents without any professional knowledge regarding the dose and duration of treatment[82].

• Among those who seek medical advice, many end up receiving broad-spectrum high-end antimicrobials owing to lack of proper diagnostic modalities for identifying the pathogen and its drug susceptibility.[80,83].

• Low doctor to patient and nurse to patient ratios along with lack of infection prevention and control (IPC) guidelines favour the spread of MDR organisms in the hospital settings[30,33].

• Easy availability of over-the-counter (OTC) drugs[84], further contributes to AMR.

• The rise in the pharmaceutical sector has caused parallel rise in the amount of waste generated from these companies. With the lack of strict supervisory and legal actions, this waste reaches the water bodies and serves as a continuous source of AMR in the environment[83,85].

• Another important challenge could be the use of antimicrobial agents as pesticides and insecticides in the agriculture industry, although the evidence for the same is currently lacking[86]. India has vast agricultural lands and farmers already face a lot of adversities at the hands of harsh weather, difficult terrain and natural calamities. They fall an easy prey to the lure of protecting their hard-earned field from pests and rodents by using antimicrobial agents without considering the future consequences.

This large reservoir of antimicrobial agents forms a favourable niche for th emergence of MDR pathogens who then drift into the water bodies with rains and floods. The paucity of data on the extent of AMR, especially in animals and environment, presents hurdles to framing and implementation of policies on the control of AMR.

Recent Developments

In the last decade, a large number of new initiatives have been launched by various agencies to contain this problem. These include-

• India Clen (Indian Clinical Epidemiology Network) which has generated some quality data on AMR in pathogens like pneumococcus, *H.influenzae* across the country;

• IIMAR (Indian Initiative for Management of Antibiotic Resistance) launched in March 2008, with WHO support, by a consortium of NGOs to promote prudent use of antimicrobials,

• INSAR (Indian Network for Surveillance of Antimicrobial Resistance) a network of 20 laboratories in the private as well as public sector across the country to generate quality data on AMR,

• Organizational meet of the ICMR expert group in December 2009 and an Indo-Swedish workshop held at New Delhi on 2 February 2010 to discuss a joint strategy for containment of AMR.[70]

• WHO has supported a few community-based surveillance studies to determine the antimicrobial resistance as well as use of antimicrobial agents and generated some baseline data on Antimicrobial use and resistance in five pilot sites in India (Delhi, Mumbai, Vellore) and South Africa (Durban, Brits) showed very high AMR rates to cotrimoxazole and amoxycillin (>70% for *H.influenzae*). Higher resistance was seen in pathogens compared to commensals. It was also observed that inexpensive older antibiotics (cotrimoxazole and tetracycline) were used more in public facilities and expensive newer ones (fluoroquinolines, cephalosporins) were used in private facilities.[87]

In India, several other initiatives are under way to address the problem.

• A national antibiotic policy is being prepared which highlights about the hospitals incorporating into their guidelines.

• The government is urging hospitals to get accredited with the National Accreditation Board for Hospitals and Health Care Providers which will result in practices relating to judicious use of antibiotics.[88]

• Though there are many interventional studies in developing countries,[89] very few studies have been conducted to improve the use of antimicrobials and evaluate the evidence of their effectiveness in India.[90-92] Before recommending a series of interventions, it will be necessary to investigate the relative effectiveness of different strategies in the Indian context.[93]

• Implementation and follow up of intervention research should be strengthened by health care planners, managers and practitioners to identify the most appropriate strategies to improve drug use and prevent the emergence of drug resistance.

Rational Antibiotic Use: The Key(104)

• Principles of rational antibiotic use –

Human antimicrobial misuse or overuse is one of the main drivers of AMR and in the presence of a dry antibiotic pipeline, it becomes imperative that we learn to use antibiotics judiciously and responsibly. In 2010, India was adjudicated to be the world's largest consumer of antibiotics and hence curbing injudicious use of antibiotics is a must.

A stewardship program implementing rational antibiotic use is mandatory to curb irrational

antibiotic use. Antimicrobial stewardship is defined as a set of coordinated interventions designed to measure and improve the appropriate use of antibiotics by promoting the selection of the optimal choice, dose, duration and route of the antibiotic which in turn lead to improved patient outcomes and decreased adverse effects.

• Steps of rational antibiotic use

Step 1: Making a clinical diagnosis is often not given enough importance leading us to most often stumble upon a diagnosis while sending multiple lab tests. A clinical diagnosis most often helps us to predict causative pathogens fitting in to a clinical syndrome which would tailor the correct antibiotic rather than blindly relying on fever, procalcitonin levels, WBC counts, cultures or radiology to make a diagnosis of infection.

Step 2: Limiting empiric antibiotic therapy to genuine seriously ill patients. Generally, empiric antibiotic therapy is ONLY recommended for a select group of patients after taking appropriate cultures - Febrile neutropenia - Severe sepsis and septic shock - Community acquired pneumonia - Ventilator associated pneumonia - Necrotizing fasciitis. Hence, it is important to start smart and then focus, i.e., evaluate if empiric therapy can be justified or de-escalated and then make a plan with regard to the duration of therapy.

Step 3: Know your bugs Approach includes –

a) Identify the clinical syndrome

b) Elucidate possible sources of infection

c) Predict possible microbial pathogens

d) Predict the local resistance pattern based on institutional antibiogram

Step 4: Choose the appropriate antibiotic –

a) Based on the spectrum of the antibiotic taking into account possible resistant patterns

b) Use the correct dose, route and duration

c) Ensure chosen antibiotic has adequate tissue penetration at the site of infection

d) Optimize PK-PD parameters according to co-morbidities

Step 5: De-escalation/modification –

a) Modify empiric broad spectrum antibiotics depending on culture and antimicrobial susceptibility reports and patient status

b) Stop polymyxins and glycopeptides if no carbapenem resistant organisms (CRO) or methicillin resistant Staphylococcus aureus (MRSA) identified on cultures

c) Avoid double or redundant gram negative or anaerobic coverage

d) Discontinue antibiotics if a non-infectious mimic identified

e) De-escalate combination therapy to a single agent

f) Change a broad spectrum antibiotic to a narrow spectrum one

g) Change IV to oral antibiotics

De-escalation is safe in all patients including febrile neutropenia and septic shock and reduces mortality and length of hospital stay.

Step 6: Stop antibiotics in the following clinical situations

a) Respiratory tract syndromes

• Viral pharyngitis

• Viral rhinosinusitis

• Viral bronchitis

• Non-infectious cardio-pulmonary syndromes misdiagnosed as pneumonia

b) Skin and Soft Tissue Infections

• Subcutaneous abscesses

• Lower extremity stasis dermatitis

c) Asymptomatic bacteriuria and pyuria including in catheterized patients

d) Microbial colonization and culture contamination

e) Low grade fever

Step 7: Reduce the duration of therapy Duration of therapy should be optimized to minimum possible to reduce selection pressure.

Step 8: Optimize PK-PD parameters

We cannot influence how a drug gets metabolized but we can influence drug

administration for maximum efficacy. Age and co-morbidities like renal failure, sepsis and burns also influence the outcomes of the patients. Overall, exposure of the infective agent to the unbound antibiotic drug fraction at the relevant effect site seems to be the most important factor. Optimizing Pk-PD parameters include loading doses when needed, therapeutic drug monitoring for toxicity and efficacy and optimization of drug infusion or administration.

Antimicrobial stewardship is a pressing need and is the only proven strategy to prevent human antimicrobial over use and abuse which is one of the main drivers of antimicrobial resistance.

8. Summary

• AMR has been identified as a global health threat with serious health, political, and economic implications. [7] The progress made in modern medicine is under serious threat because of the emergence of AMR. Annual deaths due to AMR are anticipated to rise to 10 million worldwide by 2050.[7]

• This public health problem is receiving growing attention globally. Several countries are facing the emergence of bacteria that are completely resistant to available antibiotics and countries are preparing country-specific action plan for AMR based on the global action plan of the WHO.[8]

• Studies have shown that resistance to antibiotics is directly linked to their usage. [9] In 2010, India recorded a staggering 12.9 billion units of antibiotic consumption, which was the highest among all the countries.[10]

• Not only misuse and overuse, but underuse due to lack of access is common in India. Lack of access to good quality, affordable antibiotics leads to significant mortality (especially in children), and hence, there is an urgent need to maximize access and limit excess antibiotic use.[18]

• Besides the healthcare sector, antibiotics are also used in livestock such as in animal husbandry, fisheries, and agricultural sectors for therapeutic purposes as well as growth promotion.[19]

• Environmental pollution by means of pharmaceutical waste, waste from livestock, and hospitals is another dimension contributing to the crisis of antibiotic resistance.

• In India the infectious disease burden is among the highest in the world and recent report showed the inappropriate and irrational use of antimicrobial agents against these diseases, which led to increase in development of antimicrobial resistance.[67]

• Besides, it has shown that health sector in India suffers from gross inadequacy of public finance which will result in the conditions favorable for development of drug resistance.[68]

• Presence of antimicrobial residues in milk has been reported from different parts of India, indicating wide antimicrobial use in food animal production in India.

• Antibiotic residues can negatively impact the microbiome of those consuming adulterated milk, resulting in dysbiosis, a change in microbiota associated with disease states [94,98].

• Milk samples collected from several regions of Bihar were found to contain residues of tetracycline, oxytetracycline, sulfadimidine and sulfamethoxazole.[103] This indicates use of such antibiotics as growth promoters or for treatment of cows with infections.

• With WHO announcing AMR as an urgent priority area[73] and several world leaders from Europe framing their Action Plans for the containment of AMR[74,75]. It is obvious that sincere efforts are being directed against this common enemy. India has also framed its National Action Plan (NAP) for AMR[76].

• India has been referred to as 'the AMR capital of the world'[79]. While on one hand, emergence of newer multi-drug resistant (MDR) organisms pose newer diagnostic and therapeutic challenges, on the other hand India is still

striving to combat old enemies such as tuberculosis, malaria and cholera pathogens, which are becoming more and more drug resistant.[80]

• Factors such as poverty, illiteracy, overcrowding and malnutrition further compound the situation[80].

• In the last decade, a large number of new initiatives have been launched by various agencies to contain this problem.

• Human antimicrobial misuse or overuse is one of the main drivers of AMR and in the presence of a dry antibiotic pipeline, it becomes imperative that we learn to use antibiotics judiciously and responsibly. In 2010, India was adjudicated to be the world's largest consumer of antibiotics and hence curbing injudicious use of antibiotics is a must. [104]

• Antimicrobial stewardship is a pressing need and is the only proven strategy to prevent human antimicrobial over use and abuse which is one of the main drivers of antimicrobial resistance. [104]

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Dear Doctor,

Antimicrobial resistance (AMR) is a critical public health problem, which can shake the foundation of modern health-care. Annual deaths due to AMR are anticipated to rise to 10 million worldwide by 2050. This public health problem is receiving growing attention globally. Several countries are facing the emergence of bacteria that are completely resistant to available antibiotics and countries are preparing country-specific action plan for AMR based on the global action plan of the WHO. Human antimicrobial misuse or overuse is one of the main drivers of AMR and in the presence of a dry antibiotic pipeline, it becomes imperative that we learn to use antibiotics judiciously and responsibly. In 2010, India was adjudicated to be the world's largest consumer of antibiotics and hence curbing injudicious use of antibiotics is a must.

It is indeed a pleasure to present to you this QMR issue by **Dr. S. B. Ganguly,** MD (Cal), FRCP (Glassgo). In this issue he is enlightening us on "Frontiers in Antimicrobial agents: Way forward to challenges of Antibiotic resistance in India".

I signoff by once again reminding you to continue sending your comments and suggestion regarding the QMR. Do write to me at rahul.badwaik@raptakos.com with your write ups, notes or tidbits on various topics of interest that can make for informative and interesting reading.

Dr. Rahul Badwaik
Vice President - Medical

Feedback form: October - December 2020
Frontiers in Antimicrobial agents:
Way forward to challenges of Antibiotic resistance in India

1. Your comments on this issue of Q.M.R.

   _____

   _____

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   _____

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