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Viewpoint

Integrated antimicrobial resistance management strategy: A way forward to mitigate antimicrobial resistance crisis

Antimicrobial resistance (AMR) has emerged as major global health crisis. Multidrug-resistant microbes are evolving faster than earlier anticipated and more rapidly than the drug discovery process, with a resultant danger that antimicrobials can stop functioning against the very microbes against which these were found efficacious earlier[1]. One of the solutions for this is developing alternative/supplementary therapies to antimicrobials[2], such as vaccines, antibodies, pattern recognition receptors, probiotics, bacteriophages, peptides, phytochemicals, metals and antimicrobial enzymes. However, a clinical therapeutic approach alone to mitigate the AMR crisis may not offer a failproof solution as resistance development has many more origins, precursors and, triggers than just the clinical use of antibiotics as prophylactic and therapeutic agents for humans and animals[3,4]. The general refrain, currently, is that inappropriate use of antibiotics is the raison d'etre for resistance development in bacteria.

SARS-CoV-2 pandemic has underscored the fact that when no therapy is available (*e.g.*, say antibiotics are not functioning against a target bacterial pathogen), it is the integration of the non-therapeutic preventive measures that will save the situation. Imagine a situation where face masks, hand sanitization and social distancing would not have worked. The utility of these have underlined the importance of a physical barrier[5], chemical disinfection, as well as socio-behavioural change, and their integration with whatever therapeutic aspects that were implemented in solving the SARS-CoV-2 crisis. Another aspect that was brought out by the SARS-CoV-2 pandemic is that every location has different strategic epidemiological aspects, and the situation has to be tackled according to location-specific contexts.

There are several stimuli besides human and animal prophylactic and therapeutic use that have a direct and/or indirect impact in modulating the levels of AMR, with their origin being in several diverse niches, such as infection control strategies, general and particularly healthcare infrastructure, pharmaceutical industry, pharmacists and their regulation, various environmental compartments-their contexts and characteristics, socio-behavioural contexts, legislation policies and their implementation, resources and resource allocation, culture, level of literacy, behavioural motivation skills of communicators, civil society organizations, *etc*[6]. For a long-lasting success of AMR control, all/several of these need to be simultaneously targeted for implementation, to bring out the desired results, keeping in mind that these may need to be location specific[7]. Thus, it can be said that Integrated AMR Management Strategy (iARMS) involves integrating all possible prophylactic and curative components from human, animal and environmental domains simultaneously to obtain control of AMR.

Some examples are given here to show how diverse factors directly or indirectly influence resistance generation. A study on modelling found that healthcare infrastructure and surface transport infrastructure are the determinants of antibiotic consumption for India[8] and thus it derives from it that these probably also determine the resistance levels at various locations, antibiotic consumption directly being correlated to resistance levels. Therefore, it emerges that to avoid the AMR pandemic, appropriate management of healthcare and surface transport infrastructure will help ameliorate the situation. For instance, we recently witnessed how healthcare infrastructure, transport and travel impacted the spread and control of SARS-CoV-2. Antibiotic residues resulting from antibiotic use in healthcare settings[9] and the ones released from antibiotic manufacturing industries spread in environment, and wherever the effluent spreads (*e.g.* particularly in receiving water bodies and thereafter to soils)[10], these generate and spread resistant bacteria. Anthropogenic events such as holy mass bathing in rivers (and events like 'Kumbh Mela') create pools of resistant bacteria at the locations where these occur[11].

For this, inexpensive solutions need to be generated and research and development about them should be a matter of routine. For example, for the decontamination of antibiotic residues and disinfection of resistant bacteria in wastewaters and natural waters, the current techniques are inadequate, which entails the search of new technologies. One such example from India is solar photocatalytic decontamination of antibiotics and disinfection of multidrug-resistant bacterial pathogens from polluted waters using inexpensive nanomaterials from Fe, kaolinite clay instead of expensive metals such as gold (Ag), silver (Au), platinum (Pt), using the free, abundant solar energy as the energy source, which can bring down the costs several folds[12,13].

Behaviour modification strategies aimed at changing prescriber and consumer behaviour[14] also need to be integrated into the AMR containment efforts. While the government organizations do their job of AMR containment, concurrently civil society organizations can engage in organising campaigns through voluntary efforts that can in turn generate awareness about antibiotic misuse, storage and disposal[6]. In one such nationwide effort in India that combined physical events with digital propaganda on mobile phones and community radio stations (CRS) spread all over India, with the broadcast of messages in 11 local languages, an estimated audience of >5 million could be reached without any specific cost to the exchequer or to the non-profit organization; the Indian Initiative for Management of AMR[15,16]. CRS are helpful tools for spreading such messages as these belong to the local community, their agenda being local development goals for health, nutrition, education, *etc*. Thus, the target community has emotional ownership towards CRS and therefore also to its contents.

In the context of AMR, 'One health' should be looked at as a 'study and interpretation of an integrated paradigm of antimicrobial and AMR dynamics and epidemiology that encompasses human and biodiversity health and ecosystem health including socio-behavioural health that informs on processes leading to occurrence and recurrence of infectious agents and their resistance and dissemination and extinction in organic and inorganic habitats and environment for the development of AMR strategies'[17]. Thus, an integrated approach is required because all/several of these domains are interdependent and/or complementary to each other and carry similar resistant patterns. For example, when commensal coliform isolates from stool samples from children aged 1-3 yr and their environment consisting of common source water, drinking water, household animals and waste-water were studied for antibiotic susceptibility and plasmid-encoded resistance genes in a rural community in Central India, the isolates from all of these showed a similar pattern of resistance, co-resistance and resistance genes[18]. With our present knowledge of the occurrence of horizontal gene transfer, it is obvious that efforts should be directed towards integrated management of AMR.

In the context of India (and possibly in the context of Global One health as well) the importance of AYUSH[19] (Ayurveda, Yoga, Unani, Siddha, Homeopathy) therapies should not be ignored. Herbal medicines have been part of therapies involved in AYUSH. There is, however, a need to identify and endorse these by conducting appropriate clinical trials similar to allopathic medicines and integrating these into AMR management strategies.

The World Health Organization has declared a list of critical high priority groups of pathogens (ESKAPE: *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter* spp.) that have developed a high degree of resistance to antibiotics used against them and need urgent combatant therapies[20]. A beginning can be made in this context by developing models of integrated AMR management strategies-iARMS-for the ESKAPE pathogens integrating all types of containment approaches. It may be possible first to develop a general model as there could be many common features to the model and then develop within it more targeted areas for a specific pathogen.

***Conflicts of Interest*:** None.

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