[Indian J Chest Dis Allied Sci 2016;58:157-159]

Editorial

Antimicrobial Resistance: Challenges and the Way Forward

Over the past few decades antimicrobial resistance (AMR) has increased rapidly worldwide and emerged as an urgent public health threat. AMR has been estimated to cause 700,000 deaths annually which is projected to increase to 10 million by the year 2050, surpassing major non-communicable diseases as a causes of mortality.[1] In the current scenario of a rising AMR and the lack of new drugs to combat infection, there exists a possibility of a return to the pre-antibiotic era. The World Health Organization (WHO) notes that without effective antibiotics "the success of major surgery and cancer chemotherapy would be compromised". In response to this grave threat, the United Nations General Assembly took up the issue in September 2016. This has lead, for the first time, to heads of state committing to a broad approach to tackling the problem of AMR. The WHO along with the Food and Agriculture Organization of the United Nations and the World Organization for Animal Health developed a Global Action Plan on AMR in 2015, which all member nations reaffirmed their commitment to addressing the issue of AMR.[2]

The development of AMR is a natural phenomenon which occurs with or without exposure to antimicrobials. Even the use of metal and nitrogen fertilisers has been shown to affect AMR of soil microbiota. However, it is antibiotic pressure that drives the selection of resistant mutants and their spread. Therefore, it is the use and misuse of antimicrobials that must be checked. Contrary to popular perception, reversibility of AMR is a complex process influenced by many factors. While reducing antibiotic pressure can reduce resistance rates to some extent, many studies have failed to show such an effect at the individual or population level.[3] Moreover, the control of multi-drug resistance (MDR) would require many classes of antimicrobials to be withdrawn, which is not feasible. Therefore, the focus of any strategy to curb AMR must be multi-pronged.

A significant part of the problem is the over-the-counter (OTC) availability of antimicrobials in our country leading to rampant misuse of these drugs. Another factor in a low-income country like India is the lack of regulation of the quality of available antibiotics. The extent of this problem is unknown but may contribute greatly to AMR due to inadequate dosages. The transmission of resistant microbes from animals to humans is well established, however, the use of antibiotics as growth promoters in animal husbandry continues unchecked. In 2015, plasmid mediated colistin resistance was reported from China and has since been identified around the world. While resistance to colistin has been reported previously, there are grave epidemiological implications due to the plasmid mediated nature of resistance by the mcr-1 (colistin resistance mechanism) gene. This gene was first identified in *Escherichia coli* from food animals, highlighting the importance of control of antibiotic use in animal husbandry. The WHO has established a list of antimicrobials essential for human use which are to be avoided in non-human interventions[4] though compliance is not mandatory. On the part of treating doctors, the most important aspect is the rational prescription of drugs and their combinations. With infections by MDR organisms on the rise, a large percentage of in-patients receive combination therapy. Though due to differing mechanisms and pharmacokinetics some antimicrobial combinations are justified, these must only be used as empirical therapy. Once the organism and its antimicrobial susceptibility are known, there are strong arguments in favour of de-escalation of therapy to a single effective drug. Despite the intuitive appeal of combination therapy, most studies find no mortality benefit. There is also insufficient evidence that combination therapy reduces the development of resistance. One notable exception to this is the use of combination therapy for *Mycobacterium tuberculosis* which has significantly decreased the rate of development of rifampicin resistance.[3] However, the significantly different microbiological characteristics of mycobacteria make it difficult to extrapolate such results to common bacterial pathogens.

India is the world's largest consumer of antibiotics, partly due to a high burden of bacterial disease and partly due to the OTC availability of antimicrobials. We also face a very high burden of infections by resistant organisms. As per the Global Antibiotic Resistance Partnership report (2015), methicillin-resistant *Staphylococcus aureus* (MRSA) infections are increasing in India while these decline in most of the western world. Resistance rates in *Klebsiella pneumoniae* and *E. coli* have also shown a sharp increase.[5] At our hospital, we have observed an increase in resistance rates to various classes of antimicrobials every year. As an illustration, this year resistance among Gram-negative pathogens has increased in comparison to 2015 with respect to carbapenems (*Acinetobacter* spp 89% *versus* 80%, *Klebsiella* spp 80% *versus* 72%, *E.* coli 75% *versus* 62%, and *P. aeruginosa* 27% *versus* 16%), fluoroquinolones (*Acinetobacter* spp 88% *versus* 73%, *Klebsiella* spp 79% *versus* 72%, *E. coli* 88% *versus* 85%, and *P. aeruginosa* 31% *versus* 20%), aminoglycosides (*Acinetobacter* spp 88% *versus* 86%, *Klebsiella* spp 74%

versus 72%, *E. coli* 52% *versus* 38%, and *P. aeruginosa* 22% *versus* 12%), and most markedly to tigecycline (*Acinetobacter* spp 66% *versus* 15%, *Klebsiella* spp 28% *versus* 6% and *E. coli* 3% *versus* 2%) among others. This rather dramatic increase in tigecycline resistance is probably due to increased usage as other classes of antibiotics have become ineffective. Another reserve drug seeing wide usage is colistin. Though there is a looming threat of pan-resistant organisms, colistin resistance is not yet a significant problem in India. Till date, we have identified only two *K. pneumoniae* isolates resistant to colistin, neither of which harbored the mcr-1 gene.

To combat antibiotic resistance in India two major and important initiatives have been taken. The first being Antibiotic Stewardship, Prevention of Infection and Control (ASPIC) programme which was initiated in 2012 by the Indian Council of Medical Research (ICMR) to contain the problems of resistance and infections.[6] Antimicrobial stewardship (AMS) is a multidisciplinary programme with interventions and strategies to encourage appropriate use of antibiotics. Stewardship programmes aim to restrict inappropriate use of antibiotics, thereby combating the emergence of resistance. This can be achieved by optimising the dose, route and duration of treatment for best outcomes and to minimise the adverse effects. It also aims at reducing the cost so that it is affordable and more widely accessible.

ASPIC was designed to bring together faculty from clinical pharmacology, microbiology and other disciplines to collaborate on initiating and improving antibiotic stewardship and concurrently curbing hospital infections through feasible infection control practices. This programme involves conducting training workshops every year wherein 20 centres from all over the country participate. Topics pertaining to the above areas are discussed in addition to planning a project which helps to improve AMS and infection control practices in the various centres. It is hoped that this programme will empower hospitals and institutions throughout the country to improve AMS and infection control and ultimately contain AMR.

The second important initiative is the Chennai Declaration.[7] A joint meeting of Medical Societies in India was held in 2012 at the 2nd Annual Conference of the Clinical Infectious Disease Society in Chennai to develop a road map to tackle the challenge of AMR.[7] The Chennai Declaration is a major step towards AMS policy in India. Its aim is to initiate efforts to formulate a policy to control the rising trend of AMR with following objectives: (i) to regulate over-the-counter sale of antibiotics; (ii) in-hospital antibiotic usage monitoring; (iii) audit and feedback; (iv) initiate measures to step up microbiology laboratory facilities; and (v) national AMR surveillance system.

The control of infectious diseases must be made a priority in our country. First and foremost, we require a system for collection and reporting of data at the national level to drive policy. A consensus on the use of guidelines must be reached for comparable reporting of resistance data. Recent reports indicate that resistance to some antibiotics is decreasing, such as co-trimoxazole against *Salmonella typhi*.[8] The availability of national data on such trends is essential for development of updated treatment guidelines. Further, sustainable business models must be adopted to encourage pharmaceutical companies to invest in the development of new antimicrobials. No new classes of antibiotics have been discovered since 1984, and there are very few drugs in the pipeline. In the past six years, the US Food and Drug Administration (USFDA) has only approved six new antimicrobials.[9] The O'Neill report, commissioned by the United Kingdom government, has made several recommendations for potential business models which must be considered, appropriately modified and adopted.[1] Appropriate use of new drugs is also essential. Drugs like bedaquiline and new fluoroquinolones have been reserved for MDR tuberculosis and must be conserved to maintain their efficacy. On the policy level, environmental contamination by antimicrobials must be checked and appropriate safeguards put in place. Schedule H1 containing 24 drugs has been in effect since 2014 to curb OTC sales of powerful antimicrobials, however, its implementation is sporadic at best and must be improved.[10]

The implementation of AMS in all hospitals and community health-care facilities is of utmost importance. The various components of AMS such as evaluation of educational activities, prescription practices, quantitative and qualitative antimicrobial use indicators, newer diagnostic tools, antimicrobial resistance patterns and health-care expenditure need to be assessed at regular intervals. Finally, health-care professionals must step up to the challenge of managing this growing problem by prescribing antimicrobials rationally, with the current scenario of rising resistance in mind.

Malini Shariff
Member, Editorial Board and
Head and
Aditi
Department of Microbiology
Vallabhbhai Patel Chest Institute
University of Delhi, Delhi
E-mail: malini.shariff@gmail.com

References

1. O'Neill J. *Tackling drug resistant infections globally: final report and recommendations*. May 2016. *Available at URL*: https://amr-review.org/. Accessed on November 2, 2016.
2. World Health Organization. *Global Action Plan on Antimicrobial Resistance*. 2015. WHA68/2015/REC/1, Annex 3. Accessed on November 2, 2016.
3. Holmes AH, Moore LSP, Sundsfjord A, Steinbakk M, Regmi S, Karkey A, *et al*. Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet* 2015;387):176–87.
4. World Health Organization. WHO list of critically important antimicrobials (CIA), 3rd revision. 2011. *Available at URL*: http://www.who.int/foodsafety/publications/antimicrobials-third/en. Accessed on November 2, 2016.
5. Center for Disease Dynamics, Economics and Policy. *State of the World's Antibiotics, 2015*. 2015. CDDEP: Washington, D.C.
6. Chandy SJ, Michael JS, Veeraraghavan B, Abraham OC, Bachhav SS, Kshirsagar NA. ICMR program on antibiotic stewardship, prevention of infection and control (ASPIC). *Indian J Med Res* 2014;139:226–30.
7. Chennai Declaration Team. The Chennai Declaration: Recommendations of a roadmap to tackle the challenge of antimicrobial resistance. A Joint Meeting of Medical Societies of India. *Indian J Cancer* 2012;49:84–94.
8. Laxminarayan R, Chaudhury RR. Antibiotic resistance in India: drivers and opportunities for action. *PLoS Med* 2016;13:e1001974.
9. Chaudhary AS. A review of global initiatives to fight antibiotic resistance and recent antibiotics' discovery. *Acta Pharm Sin B* 2016;6:552–6.
10. Department of Health, Ministry of Health and Family Welfare of GoI. Drugs and Cosmetics (2nd amendment) Rules, 2006. The Gazette of India (extraordinary) 2006 Part-II, section 3, sub-section (i) vide G.S.R. 160(E). Accessed on November 2, 2016.