

Editorials

Antibiotic resistance: Some thoughts

The introduction of penicillin into therapeutics revolutionized medical practice. Successive discoveries of newer antibiotics, of different types and classes, and their chemical modification enabled the medical profession to conquer most infectious diseases. The topic has been reviewed elsewhere.¹ Successes of the mid-twentieth century generated a feeling that the ultimate control of infections was at hand.² The euphoria has now been shown to be misplaced. Studies of patterns of antibiotic resistance in large hospitals that maintain regular records reveal that multi-resistance is rampant. In the case of Gram-negative bacilli (GNB), polymixin/colistin are the only antibiotics that have retained a uniformly good level of sensitivity, apart from the very new agents such as tigecycline.³ In fact, the prevalence of antibiotic resistance has prompted the use of these agents (polymixin/colistin) in extreme cases with often satisfactory results and the realization that earlier fear of their high toxicity was exaggerated.⁴ Resistance to even this class of antibiotics is now present; one such case was quoted in an editorial.⁵ As a result, we are facing 'an epidemic of antibiotic-resistant infections'.⁶ This has generated numerous reports of impending doom in the print and electronic media on the subject.⁷

Antibiotic resistance was recognized soon after the therapeutic use of penicillin. Barber⁸ demonstrated *in vitro* that even a novel antibiotic could generate antibiotic resistance. She showed that resistance to methicillin, the then recently introduced semi-synthetic penicillin, could be generated in the laboratory. It has been shown that even pre-antibiotic era strains or strains from locales where clinical antibiotic usage was absent showed resistant strains in environmental and commensal flora. D'Costa *et al.* studied samples of permafrost core and showed that 'antibiotic resistance genes predate our use of antibiotics'.⁹ They could produce evidence for the existence of antibiotic-resistant genes (including those conferring vancomycin resistance) in bacteria that had remained frozen for around 30 000 years. The evolution of community-associated methicillin-resistant *Staphylococcus aureus* (CAMRSA)¹⁰ and its subsequent spread have shown the proclivity of resistant clones to proliferate and dominate.¹¹ Similarly, fluoroquinolone resistance has progressed from adaptation to chromosomal resistance and, now, to transmissible resistance.^{12,13} No wonder, antibiotic resistance emerges and builds up in antibiotic-charged environments that offer a selective advantage to the carriers of resistance factors. There is, however, considerable variation in the rate of acquisition of clinically important resistance. While some organisms (e.g. *Streptococcus pyogenes*) have remained sensitive in the antibiotic era, others (e.g. *S. pneumoniae*) have taken a longer time and yet others have quickly become resistant (e.g. *Shigellae*, *Klebsiella*, *Pseudomonas*, etc.). Environmental non-fermenters have also shown such ability and emerged as problematic agents in critical environments.¹⁴ A common community infection such as gonorrhoea is affected by developing antibiotic resistance. The changing susceptibility pattern of *Neisseria gonorrhoeae* has decreased the options for oral antibiotic treatment.¹⁵ This has resulted in 'a post-antibiotic era', a situation caused by the clash of decreasing effective antibiotic resources with burgeoning bacterial antimicrobial resistance. Livermore¹⁴ examines this and presents an optimistic scene in the case of Gram-

positive bacteria but a gloomier picture in the case of GNB. The decreasing interest of the pharmaceutical industry in the 'non-profitable' endeavour of antibiotic development has stimulated the establishment of global funding mechanisms, particularly for developing drugs for infections which are widely prevalent and are public health problems, such as malaria, tuberculosis, etc. The British Society for Antimicrobial Chemotherapy has initiated a campaign to induce State action in this field.¹⁶

The identification in Sweden of a new metallo-beta-lactamase (MBL) in the clinical cultures of a patient treated in India (last in New Delhi) and its designation as New Delhi metallo-beta-lactamase-1 (NDM-1) ignited community awareness and also hurt national pride.^{17,18} Since that time, NDM-1-bearing GNB have been identified the world over except (at present!) in Central and South America. While the Indian subcontinent is linked with a substantial proportion of infections by NDM-1-bearing GNB, other areas of endemicity too have been identified.¹⁹

The link to travel in the Indian subcontinent in infected cases, even in the absence of a history of prior hospitalization, and evidence of asymptomatic gut carriage prompted a study on environmental dissemination of NDM-1-bearing bacteria. This study, funded by the European Union and done by non-Indians, collected 171 swabs of environmental seepage (100 ml per swab) and 50 tap water samples (15 ml per tap) from sites within a 12 km radius in central New Delhi. Seventy sewage samples from Cardiff Waste Water Treatment Works served as controls and all the laboratory work was done in Cardiff. It showed that NDM-1 'is widely disseminated in New Delhi and has spread into key enteric pathogens' while, as expected, none of the Cardiff samples yielded GNB-carrying NDM-1.²⁰ The study was done in the immediate post-monsoon period when the study area would have had a mixing of environmental waters and occasional breaching of tap water pipes. The result would probably have been different if the study had been done in winter. In any case, the study would have had greater force if it had been planned properly. In view of the comments on 'medical tourism' in the earlier paper,²¹ the motive(s) of this study is questionable. Unpublished observations, in the late 1970s and early 1980s, from environmental sources in the Pune area on plasmid-mediated co-trimoxazole resistance showed that a similar situation prevailed there. Molecular techniques were not used in those days. The New Delhi environmental study of Walsh *et al.*²⁰ related to an area with a similar level of environmental sanitation. These results, though more convincing because of the modern technology used, were not surprising.

Based on the environment study, grave implications have been forecast for residents of New Delhi. Considering the wide dissemination of NDM-1-bearing organisms *ab initio*²¹ and the lack of evidence of an increase in difficult-to-treat infections since the time NDM-1 started circulating, it is doubtful if the prophecy would be fulfilled. Nevertheless, it has to be conceded that the emergence of MBLs has changed the scene of antibiotic therapy for serious GNB infections.⁶ Obviously, in resource-constrained situations, systemic infections caused by NDM-1-bearing GNB would be untreatable and accompanied by high mortality. The media has contributed to the hype by projecting estimates, based on dubious data, of 100 million carriers nationwide.

The NDM-1 controversy, however, has had a positive fallout. There has been an upsurge of interest in antibiotic resistance in medical administrative and research establishments. Efforts are being made to initiate laboratory networks and do a detailed study of antibiotic resistance in a variety of pathogens. It is hoped that in due course these efforts would enable the Indian healthcare community to gauge the extent of the problem and devise control measures. The mechanisms for studying specific programme-related organisms such as *Mycobacterium tuberculosis*, malarial parasites, *Leishmania donovani* are already in place and yielding useful information.²²

The reasons for a general high level of antibiotic resistance are many. These include a high level of antibiotic stress that free-living organisms are facing in the milieu of antibiotic over usage in human and veterinary practice. The use of 'human use' antibiotics in animal husbandry and poor hospital waste management are other drivers of the phenomenon. The complete elimination of an antibiotic from the environment does decrease the level of phenotypic resistance to the antibiotic but resistance genes continue

to circulate at low levels. This is evident from the variation in chloramphenicol resistance in *Salmonella typhi* consequent to the practically universal discontinuation of the therapeutic use of the antibiotic.²³ This is the *raison d'être* for the formulation of antibiotic policies at institutional, regional and national levels. The experience of The Netherlands in controlling rising levels of methicillin resistance in *Staphylococcus aureus* is a good example.²⁴ Of course, India is not The Netherlands, but, there is a target to reach! This would involve education of healthcare professionals as well as the public, control of pharmaceutical industry and trade, particularly control of over-the-counter sales.

It is clear that the basis of antibiotic resistance is embedded in prokaryote genomes. The rise to clinically important levels requires these factors to move between strains, species, genera and rarely across orders. This can only be restrained by the modalities that come under the comprehensive head 'infection control'. Above all, it would be necessary to have a competent laboratory infrastructure that detects, tracks and analyses changes in antibiotic susceptibility. The challenge is immense and requires great commitment. *Are we up to it?* We must be if we are not to lose our valuable antibiotic resources.

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