Editorial

The burgeoning challenge of antimicrobial resistance

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The discovery of penicillin by Fleming[1] revolutionized mankind's fight against communicable diseases. By 1940s, this drug was available for clinical use. Since then penicillin and many other antimicrobial agents that were discovered subsequently have saved millions of lives all over the world. So huge was the initial impact of antimicrobial agents that many people erroneously started believing that "time has come to close the chapter of communicable diseases". Unfortunately, they had not comprehended the versatility of microorganisms and the array of survival mechanisms developed by them over several millennia of their existence.

While the successful clinical use of penicillin[2] is widely known and lauded, detection of resistance to penicillin in 1940 itself[3] was ignored by the global community. Facilitated by the continuous and indiscriminate use of antimicrobials in health, veterinary and industrial sectors, the microorganisms slowly and steadily started developing resistance to several antimicrobial agents giving rise to multidrug resistant organisms. Antimicrobial resistance (AMR) is now proclaimed as the most important challenge being faced by humanity in its fight against infectious diseases. The emergence and spread of resistance in several microorganisms have rendered the management of many infectious diseases difficult. Failure to discover new antimicrobial agents has further hampered the war against infectious agents.

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Antimicrobial resistance is now no longer a local problem. It has international ramifications. In the modern era of travel and trade, resistant organisms rapidly cross the man-made boundaries through humans or the food chain. The emerging threat of resistance in malaria, tuberculosis (TB) and the human immunodeficiency virus (HIV)/AIDS is a huge impediment to achievement of the Millennium Development Goals (MDGs) by 2015[4].

This special issue of the Regional Health Forum provides ample evidence to demonstrate that AMR is a burgeoning and hugely neglected problem in the WHO South-East Asia (SEA) Region. The problem is assuming serious proportions in all Member States. The overview of the status of resistance in various microorganisms in Bangladesh[5], Nepal[6] and Sri Lanka[7] indicates the extent of the problem and its implications for care of patients and public health.

Bhatia et al.[8] have discussed the problem of resistance to first-line antiTB drugs, which has become a concern for national TB control programmes. It is estimated that around 180 000 cases of multidrug-resistant (MDR)-TB occur annually in this Region with more than 80% of these being in Bangladesh, India, Indonesia, Myanmar and Thailand[9]. The drugs needed to treat MDR-TB are over 100 times more expensive than the first-line drugs used to treat non-resistant forms[9].

The generic antiretroviral (ART) drugs available in the Region are contributing greatly towards improving the survival rate of patients worldwide and in rendering HIV a chronic but a manageable condition. A large number of

patients from India have been followed up by Balakrishna et al.[10] to elaborate the intricacies of ART therapy. Although the response to ART drugs is excellent when these are delivered at health facilities, there also are reports of emergence of resistance, which are a serious cause of concern.

Resistant malaria has already become a major issue for the population of 400 million living in areas that expose them to the high risk of contracting it. Artemisinin-based combination therapies (ACT) have recently been introduced in virtually all countries in which malaria is endemic. However, surveillance data from the Thai Ministry of Public Health indicate that clinical failures of artemisinin-based therapies exist on the Thai-Cambodian border, whereas efficacy with artesunate-mefloquine along the western borders of Thailand remains high[11, 12].

There has been a substantial change in the antimicrobial susceptibility of *Neisseria gonorrhoeae*. Thirty years back, gonorrhoea used to respond effectively to penicillin. Now the resistance to penicillin, tetracyclines and fluoroquinolones is widespread across the Region[13].

Pentavalent antimonials have been successfully used for treatment of kala-azar since the last six decades. Since the 1970s, however, their conventional dosages have failed to achieve the desired results with 60% unresponsiveness being reported with the WHO regimen in Bihar, India. The newer oral drug, miltefosine is a potent antileishmanial drug with a longer half-life, but requires rational use in affected areas[14].

Typhoid and paratyphoid fever continue to be important causes of illness and death, particularly among children and adolescents in the SEA Region where this disease is associated with poor sanitation and unsafe food and water. Shortly after the emergence of MDR *S.* Typhi in this Region, case fatality rates approaching 10% (close to 12.8% recorded in pre-antibiotic era) were reported[15]. Rational use of some of the recommended drugs for typhoid fever can prolong the life of these drugs, especially chloramphenicol[16].

More than 50% isolates of *Staphylococcus aureus* in hospital settings are now methicillin resistant. The resistant strains are widely prevalent in developing as well as developed countries, and are creating major issues in the proper management of seriously ill patients in hospitals[17].

Multiresistant klebsiellae, *Pseudomonas* and *Acinetobacter* species have given a new dimension to the problem of hospital-associated infections. *A. baumannii* has become an important pathogen in intensive care units. In a study done in Thailand, the mortality rate for patients admitted due to imipenem-resistant *A. baumannii* was 52% as compared with 19% for those infected with the sensitive variant[18]. Kumthorn et al.[19] describe the growing problem of *A. baumanii* group in hospital settings in Thailand. It is likely that similar situations are prevalent in other countries too.

The presence of a drug-resistant gene, $bla_{\text{NDM-1}}$, in several members of the family *Enterbacteriaceae* has given rise to organisms that are resistant to a large number of commonly used antimicrobial agents. A reality check on these organisms and their recent emergence has been articulated by Rodrigues[20].

Antimicrobial resistance in viruses and fungi is making management of diseases caused by these microorganisms difficult. The recently detected resistance in influenza viruses[21] and fungi of medical importance[22] should draw researchers' special attention to this menace, which is now threatening the hitherto neglected organisms.

Antimicrobial resistance has several severe consequences. The patient remains sick for a longer period thus requiring prolonged treatment usually with expensive and at times toxic drugs. Not only there is greater morbidity and mortality but the burden on health system

also increases. The impact of modern technological and complex surgeries gets negated when the patient after successful intervention gets infected with resistant microorganisms. From the public health perspective, the patient acts as a reservoir of infection for a longer period thus putting at risk more members of the community and health-care workers. All these factors have a substantial effect on the economy, at both individual and societal levels. In fact, it is difficult to imagine effective newer surgical procedures, transplantations and prolonged chemotherapy for various cancers, care of the critically ill young and the old, or prolonged treatment of HIV-infected persons in the absence of measures aimed at effective containment of AMR[4].

The need for new antibiotics to address the emerging resistance in microorganisms cannot be overstated. There has been a near-empty antibiotic pipeline[23]. However, there is some light at the end of the tunnel with a few significant new global initiatives that are under way. Some antimicrobial agents are being developed and are awaiting approval of the Food and Drug Administration of the United States of America[24]. The European Commission recently sought proposals for new antibiotic research and development for multidrug-resistant Gram negative pathogens. This quickly led to the establishment of a joint EU-US Transatlantic Taskforce on Antimicrobial Resistance. The call by the Infectious Diseases Society of America for a 10x20 initiative viz., development of 10 new antibiotics by 2020[25], should trigger new research and development by the pharma companies.

We need to recognize that the problem of resistance is complex and encompasses biological, behavioural, technical, economic, regulatory and educational dimensions that require a comprehensive response. It requires ownership and active participation by several stakeholders, and a strategic approach with objectives that include establishment of a national alliance for prevention and control of antimicrobial resistance. The WHO Regional Office for South-East Asia has recently developed one such strategy[26]. It addresses four areas that need attention of national authorities; governance; regulatory mechanisms; building national capacity; and mobilizing active participation of communities.

Recognizing the emerging importance of this subject and to enhance its visibility for an early action, "antimicrobial resistance" is the theme of the World Health Day 2011. Far too long, antimicrobial resistance has been an unrecognized and neglected problem. The time to act is now.

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