Perspective

Combating Antimicrobial Resistance

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Sri Lankan Journal of Infectious Diseases 2016 Vol.6 (2):72-82

DOI: http://dx.doi.org/10.4038/sljid.v6i2.8119

Abstract

Antimicrobial Resistance (AMR) is a key global health challenge. While numerous strategies have been put forward by different organizations to combat this problem, identification of locally relevant issues that drive resistance and addressing them would be the key to success.

Keywords : Antimicrobial resistance, AMR, Sri Lanka

Antimicrobial resistance (AMR) is recognized as one of the key global health concerns. At the 69th World Health Summit held in Geneva in May 2016, all member countries pledged to implement programmes to combat AMR. Although antimicrobials brought hope to a world plagued by infectious diseases, the emergence of resistance with the currently established mechanisms of action was inevitable following the introduction of almost all antibiotics. The introduction of sulfonamides, one of the earliest antimicrobial agents introduced in the late 1930s was followed by the demonstration of resistance. Penicillin, discovered in the late 1920s was available for use in hospitals in the early 1940s. However, almost immediately, as early as 1942, penicillin resistance in *Staphylococcus aureus* was recognized.[1,2,3]

Increasing antimicrobial resistance to currently available antibiotics is compounded by a reduction in the number of new antibiotics being licensed for clinical use.[4] This led to the U.S Food and Drug Administration (FDA) to launch the Qualified Infectious Diseases Product (QIDP) framework in 2012, as an incentive to motivate researchers and pharmaceutical industry to develop and trial new antibiotics.[5]

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Received 2nd August 2016 and revised version accepted 25th October 2016

Antimicrobial resistance (AMR) has now become one of the key threats faced globally by health care systems. Virtually no part of the world has been spared.[6] AMR is a natural phenomenon, well exemplified by the finding of resistant genes in bacteria even prior to the given antibiotic coming into the market.[7] However, practices by humans has driven AMR to heights that would have been unachievable only through natural selection

While some bacteria are intrinsically resistant to certain antibiotics, many acquire resistance through mechanisms involving mutations or horizontal gene transfer. Mobile genetic elements (MGEs) such as plasmids and transposons are instrumental in transferring resistance genes horizontally. As these MGEs could carry genes responsible for more than one resistance mechanism, many of the resistant bacteria become resistance to more than one class of drugs.[8] Therefore, multi-drug resistance (MDR), commonly defined as an isolate being resistant to three or more classes of antibiotics normally sensitive to the given group of organisms, is currently a common phenomenon.[9]

What are the costs of AMR?

Infections with resistant organisms are associated with increased mortality and morbidity. Numerous studies on different organisms have consistently demonstrated this finding. Additionally, there is an increase in cost, attributed directly to treatment, prolonged hospitalization and indirectly, to the loss of labour force occurring as a result of the increased mortality and morbidity.[10] According to the Centers for Disease Control and Prevention (CDC), Atlanta, infections with antibiotic resistance organisms were estimated to cost an additional $20 billion a year in health care costs and $8 million on additional hospitalization associated costs in the United States alone.[11]

What drives AMR?

AMR occurs both in health care settings and the community. Practices in both settings facilitate the emergence and spread of resistant bacteria.

In health care settings, taking a hospital as an example, inappropriate prescription of antibiotics, improper usage of antimicrobials including wrong dosage and timing of administration and lack of antibiotic stewardship programmes are some of the many reasons that promote the emergence of resistance.[12,13] Close proximity of patients in overcrowded inpatient and outpatient settings and the inability to carry out appropriate infection control practices due to lack of facilities and/or non-compliance with IC

protocols are some factors that contribute to the spread of antimicrobial resistance.[12,13]

In the community, the use of antibiotics in animal husbandry, food production and agriculture are often cited as drivers of AMR.[14] Additionally, behavioral practices of people in the community are known to drive resistance. These include practices by individuals in relation to antimicrobial use, such as not completing a course of antibiotics, use of antibiotics bought for another illness or given to someone else and over-the counter issuing of antibiotics by pharmacists without prescriptions. Patient perceptions, satisfaction and understanding on antibiotic use is recognized to influence a physician's prescription of such drugs.[15,16]

Wider socio-economic factors are also known to influence the emergence of resistance. For example, use of substandard drugs is known to contribute to the emergence of resistance.[17] Political instability and corruption was also found to be correlated with the prevalence of AMR.[18]

What is the situation in Sri Lanka?

AMR is a key challenge faced by the health care sector of Sri Lanka for the past few years. A perusal of abstracts published in the Bulletin of the Sri Lanka College of Microbiologists (SLCM) from 2013 to 2016 provides ample evidence of this.

Multi-drug resistant *Acinetobacter* spp. are a major problem in the clinical arena. A study conducted at the National Hospital of Sri Lanka (NHSL) between June and August 2014 showed that almost all *Acinetobacter* spp. and 25% of the coliforms responsible for Ventilator Associated Pneumonias (VAP) were multi-drug resistant. Additionally, all the coliform isolates obtained from the study samples were resistant to the tested 3rd generation cephalosporins.[19] Similarly, 70% of clinically significant *Acinetobacter* spp. isolates (n=30) identified at Teaching Hospital, Anuradhapura between 1st August to 31st October 2009 were resistant to two or more antimicrobial agents, and were stated as being MDR by the authors. The intermediate/resistant rate for cefotaxime in the given study was 90%, while that for ceftazidime and imipenem were 73.3% and 70% respectively. Cefoperazone-sulbactam resistance was demonstrated in 53%. None of the isolates were resistant to colistin.[20]

Extended spectrum β lactamase (ESBL) producing enterobacteriaceae continue to be present in both the community and health care settings. An analysis of bacterial pathogens causing post-operative wound infections among patients who had undergone

abdominal surgery in the first quarter of 2012 at a tertiary care unit in the Southern Province of Sri Lanka identified a surgical site infection (SSI) rate of 5.97%. The ESBL producer rate among the coliforms isolated from the SSIs were given as 62.5%.[21]

Carbapenem resistant enterobacteriaceae (CRE) are also emerging in the country. The prevalence of carbapenamase producers among coliforms obtained from blood cultures and respiratory specimens received at the NHSL and North Colombo Teaching Hospital between Jan to April 2012 were 7.9% and 0% respectively.[22,23]

Along with the emergence of Gram negative resistance, resistance in Gram positive bacteria continue to pose a challenge in Sri Lanka. Analysis of MRSA isolates obtained from a private hospital in Sri Lanka between April 2013 to November 2014 identified an MRSA proportion of 42% (n=156).[24] Interestingly, of these MRSA, the majority (59%), had antibiograms compatible with community acquired MRSA as the isolates were sensitive to non-β lactam drugs. This indicates the possibility that AMR has crossed over from health care settings into the community in Sri Lanka.

In relation to urinary isolates, the potentially community onset isolates were found to have a more favorable sensitivity profile than those potentially originating from a health care setting. Analysis of urine culture isolates sent to the national laboratory based surveillance programme of the SLCM for the year 2014 showed that the cefotaxime susceptibility rate for urinary isolates obtained from adults attending the out-patient treatment units were 63.4% while the rate was 39.5% for adult inward patients. Meropenem susceptibility rates for the two groups were 100% and 87.9% while the co-amoxyclav susceptibility rates were 54% and 34.1%.[25,26]. Data for oral antiseptics and antibiotics was not stated.

Available data from private sector hospitals show that they are similarly affected. A study conducted at a private healthcare institution in the Western province reported a 26% prevalence of ESBL producers among 386 enterobacteriaceae isolates obtained from 75 urine, 3 sterile body fluid, 10 wound and ulcer swabs and 7 high vaginal swabs.[27]

Isolates such as *Salmonella spp.*, which predominantly originate in the community, also show high levels of resistance. *Salmonella spp*. analyzed at the National Reference laboratory of the Medical Research Institute in the year 2013 had a 66.6% ciprofloxacin resistance.[28]

Although legal provisions exist to regulate the use of antibiotics in animal husbandry, antibiotics continue to be used in animal feed as well as for treatment of infections.[29] This has led to the high rates of colonization of farm animals with resistant organisms.[30] A study looking at the presence of multi resistant enteric organisms among food animals in Colombo district identified a 50% rate of resistance to multiple drugs with majority of these (48%) being from poultry. Most resistant isolates had been obtained from poultry as compared to swine or cattle.[31]

There is more than sufficient evidence to say that AMR is an immense challenge faced by the health care sector of Sri Lanka. What can we do about it?

Different global institutions have come-up with conceptual frame works on which local bodies can build up programmes to combat AMR in a locally relevant manner. For example, the core actions identified by the CDC, Atlanta in preventing antimicrobial resistance are as follows.[32]

1) preventing infections, preventing the spread of resistance
2) tracking the status of antibiotic resistance
3) improving antibiotic prescribing and stewardship
4) developing new drugs and diagnostic tests.

Awareness about AMR among health care workers and the public need to be improved for the successful implementation of any programme launched to prevent the further emergence and spread of AMR. Education of both the public and health care professionals about the current situation in relation to antibiotic resistance in Sri Lanka is urgently required. Feedback obtained by one of the author's following a newly introduced lecture on AMR to third year medical students identified that the commonest learning point was that only the given lecture made them aware of the issue of AMR. This highlights the possible lack of awareness among health professionals.

There is currently no available data on practices and beliefs among the community in Sri Lanka which contribute to the development and spread of resistance. Such studies are urgently needed. However, as the issue is very real and addressing it cannot be postponed, awareness programmes need to be launched immediately. When results from studies on the public and health care practices contributing to emergence of resistance become available, these programmes could be fine-tuned to suit local needs.

The Sri Lankan public health services provides a tremendous service in health promotion and prevention. The framework is well set with the community level health care teams including Public Health Midwives (PHMs) and Public Health Inspectors (PHIs). These officers could be aptly used in such programmes after initial training. As examples, the PHMs and PHIs can educate the public along with the Medical Officers of Health (MoHs) and the PHIs could be trained to monitor antimicrobial use in farms and antibiotic sales from pharmacies.

The changing socioeconomic conditions, internal and external migration and ageing population has increased the number of care or assisted homes in the country. Nursing homes are globally known to be places where resistance could spread easily.[33] Training the care takers of such institutions and making sure that private sector hospitals also follow basic infection prevention strategies need to be included as a part of the programmes designed to curb resistance in the country.

What practices need to be implemented at health care settings? The obvious answers would be implementation of treatment guidelines, strengthening infection control practices and introduction of antibiotic stewardship programmes.

Treatment guidelines have been introduced by the SLCM in collaboration with academic bodies representing various clinical specialties. The Ministry of Health and individual hospitals need to take initiatives to launch these in practice. In addition, individual hospital laboratories need to continuously monitor the data generated from their locale to fine tune treatment guidelines in accordance with local resistance patterns. With the ongoing implementation of computer based data entry systems to the laboratories and the monitoring systems in-place such as the WHO-NET and other surveillance programmes by the SLCM, this would not be a very difficult task.

Strengthening infection control practices in health care settings in Sri Lanka would be an uphill but achievable goal. Hand washing has been identified as the single most effective strategy to combat the spread of organisms in health care settings. However, compliance with hand hygiene procedures leave much to be desired. In a self-reported questionnaire based study conducted among 177 medical students attached to the Kotelawala Defense Academy, 85.88% had agreed that hand washing was the single most important practice to prevent hospital associated infections. However, only 34.46% students had known that the duration of hand washing was important.[34] A study

conducted to assess hand washing practices among health care workers at the North Colombo Teaching Hospital, identified that soap and single use towels were available in 95% and 80% of observed hand washing episodes. However, this study also found that it was only in 3.3% of all instances that all steps of the procedure was followed.[35]

Educating health care workers, implementation of audits, adding incentives to promote hand hygiene practices and making sure that the necessary infrastructure such as sinks, soap, alcohol hand rub, disposable single use towels are available should be the first step. Administrative back up is essential in achieving this.

Despite being an integral part of patient management in other countries, antibiotic stewardship programmes have not yet been routinely implemented in Sri Lanka. Steps need to be taken to initiate such programmes very rapidly with incorporation of a wide segment of the stakeholders.

Private sector health care providers need to be brought on-board into the national programmes. Most of the larger private sector hospital do have on-site laboratories. However a larger segment of the private sector health care providers, namely the independent general practitioners, do not have direct access to laboratories. The patient population consulting such doctors cannot normally afford culture testing offered by private sector laboratories. This in turn leads to the general practitioners to prescribe antibiotics without appropriate testing. This is an issue that needs to be addressed by the relevant authorities.

Sri Lanka has a diverse group of traditional medical practitioners. Plant materials have been used for generations by many such practitioners in treating infections. Numerous small scale studies have been conducted to identify the antimicrobial activity of such products with success. This field needs to be encouraged further to move into the possibility of discovering new classes of antibacterial agents. A dialogue between allopathic and traditional medical practitioners plus the scientific community is essential if such programmes are to successfully go ahead to product development stage.

Changes in the health care sector alone would not be sufficient to curb AMR in a country. Veterinary services and agricultural services need to be brought under one umbrella along with health services in a “one health” approach if AMR is to be successfully stalled. Political and administrative commitment is equally important.

With the increase in global travel, any AMR related issue affecting one country could affect the rest of the world in a matter of time. Therefore, each country should take steps to minimize the further emergence and spread of resistance. As discussed in the preceding sections, many of the measures to be taken are simple. However, implementation could be difficult in the pre-existing environmental and social contexts. Tackling AMR needs to be set as a priority among the health agenda of every government promptly, for time is running out.

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