Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/mjafi

Contemporary Issue

Antimicrobial resistance: A public health challenge

Brig A.K. Jindal, ^{a,*}, Maj Kapil Pandya ^b, Maj I.D. Khan ^c^a Commandant, Military Hospital Nasirabad, C/O 56 APO, India^b DADH, HQ 17 Mtn Div, C/O 99 APO, India^c Graded Specialist (Microbiology), Command Hospital (Eastern Command), Kolkata, India

ARTICLE INFO

Article history:

Received 10 January 2014

Accepted 17 April 2014

Available online 4 August 2014

Keywords:

Antimicrobial resistance (AMR)

Public health

Microorganisms

Health care expenditure

ABSTRACT

Antimicrobial resistance has become a global concern. Though an evolutionary phenomenon, it is promulgated by faulty human behaviours. It is a growing concern ever since first reported in 1940s. Today, a plethora of newer generation antimicrobials have become ineffective against previously susceptible organisms. This is a huge challenge for health care managers all across the globe, compounded by the “discovery void” in the field of development of new antibiotics. If proper steps are not taken presently, the lurking fear of reaching a therapeutic dead end will become a reality. This paper aims at describing the pandemic of AMR from a public health perspective and suggesting strategies to deal with it in an effective and collaborative manner.

© 2014, Armed Forces Medical Services (AFMS). All rights reserved.

Introduction

Antimicrobial resistance (AMR) is defined as resistance of microorganisms to an antimicrobial against which they were originally sensitive. Though a natural evolutionary phenomenon, it is accelerated by the misuse of antimicrobial medicines and poor infection control practices. Newer and newer antibiotics have been challenged with the threat of resistance over past few decades. The global spread of AMR is lubricated by increased mobility of patients or carriers and hence, that of the resistant bugs. AMR is a major threat to the gains made in public health with a potential of even reversing such gains. It affects a myriad of stakeholders such as individual patients, healthcare providers, pharmaceutical industry and society at large. A concentrated effort at all levels of health care is the need of the hour to tackle the menace of AMR.

A growing concern

Resistance to sulphonamides and penicillin was reported as early as 1940s followed by resistance to other antimicrobials subsequently. Today, almost all major infectious diseases of public health concern are faced with the scourge of AMR.

The WHO estimates that in 2011, out of the total 12 million TB cases worldwide, 630,000 were MDR. Extensively drug-resistant TB has been identified in 84 countries.¹ As the world contemplates on dealing with resistance to antimalarials such as chloroquine and sulfadoxine–pyrimethamine, *Plasmodium falciparum*'s resistance to artemisinin derivatives is already knocking on the doors in South East Asia.

The incidence of hospital-acquired infections caused by highly resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) or multidrug-resistant Gram-negative bacteria is steadily rising all over the world. *Shigella* is showing

* Corresponding author. Tel.: +91 9672394133.

E-mail address: akj4902@rediffmail.com (A.K. Jindal).<http://dx.doi.org/10.1016/j.mjafi.2014.04.011>

0377-1237/© 2014, Armed Forces Medical Services (AFMS). All rights reserved.

a widespread resistance to Ciprofloxacin, the only antibiotic currently recommended by WHO for treating infections by it. For gonorrhoea oral cephalosporins are reckoned as “last-line” of defense, against which resistance is increasing worldwide. By 2012, virtually all circulating Influenza A viruses in humans were resistant to amantadine and rimantadine.¹

The “Plasmid encoding carbapenem resistant metallo beta lactamase”, known as the New Delhi superbug, was detected in December 2009 in a Swedish patient in India. Within a few months, it was reported from many countries. Apart from the above, Vancomycin Resistant Enterococci (VRE), Extended Spectrum Beta Lactamase (ESBL) producing Enterobacteriaceae, Carbapenem resistant *Klebsiella* (CRK), pan drug resistant (PDR) *Pseudomonas* and *Acinetobacter*, antifungal resistant fungi and antiviral resistant viruses are playing a havoc in treatment facilities around the world, causing deaths and delaying healing.

Antibiotics are inseparable from medical procedures such as heart surgery, diabetes related chronic infections, post organ transplantation, aggressive immune-modulating therapy for auto-immune diseases such as rheumatoid arthritis, as well as for several malignancies. With changing lifestyles and ageing populations, chronic diseases which are currently treated through surgery, are ought to rise that would be impossible without effective antibiotics.

Suggested cause of this pandemic

In India, studies suggest that antibiotics are often prescribed in irrational ways such as incorrect indication, dose, frequency, or duration. Overprescribing and overuse are seen in all settings: public and private hospitals.² Literature reveals that 45–80% of patients with symptoms of acute respiratory infections and diarrhoea are likely to receive an antibiotic when the cause is viral.^{3,4}

Antibiotics are also over-used in agriculture, livestock rearing and fishing industry. Resistant bacteria can be transferred to humans through contact with livestock, through the food chain, and through wastewater from these operations, as well as wastewater from hospitals and pharmaceutical plants.

The phenomenon is also affected by the misconceptions, that antibiotics are a panacea for all infections, among physicians as well as in the general populace.

Key public health issues relating to AMR

AMR hampers the control of infectious diseases

AMR delays treatment, rendering patients infectious for longer time, increasing the risk of spreading resistant microorganisms to others. From the public health perspective, the patient acts as a reservoir of infection for a longer period thus putting at risk more members of community and health care workers. The longer duration of illness and treatment increases health-care costs and the economic burden to families and societies. A 2010 study in Vellore compared the overall cost in patients when empirical antibiotic therapy is effective (causative bacteria being susceptible) compared with those in whom it was ineffective (bacterial resistance to the empirical

antibiotic). The median cost of treatment in the ‘susceptible’ group was Rs. 8437 while that for the ‘resistant’ group was Rs. 13,652. Apart from this direct increase in cost of higher antibiotics, associated expenses like longer ICU stay, repeated Lab culture and sensitivity tests and ward charges put even more financial burden on the patients or the health care system. Overall, an individual had to spend around Rs. 20,959 more if he/she belonged to the ‘resistant’ group.⁵

As of August 2013, an Indian agricultural worker (majority of national workforce) earns a daily wage of Rs. 224 as per Labor Bureau, Govt of India. A difference of Rs. 20,959/- per patient in overall cost between resistant and susceptible groups therefore translates to approximately 90 days of income. According to WHO, the death rate for patients with serious infections treated in hospitals is about twice that in patients with infections caused by non-resistant bacteria.

AMR threatens a return to the pre-antibiotic era

Many infectious diseases risk becoming untreatable and uncontrollable, which could derail the progress made towards reaching the targets of the health-related United Nations Millennium Development Goals set for 2015. A report from WHO SEARO shows that shortly after the emergence of multi-drug resistant *Salmonella typhi* in this region, death rates approaching 10% were reported, close to 12.8% of the pre-antibiotic era.¹

We now face a dramatic challenge resulting from two combined problems. First, microorganisms are becoming extremely resistant to existing antibiotics. Resistance can be combined with virulence, acting as a potentially deadly duo, as observed in the recent large epidemic outbreak of *Escherichia coli* O104:H4 in Europe in 2011. Second, the antibiotic pipeline has become extremely dry, especially for Gram-negative bacteria. The fear of clinicians facing a therapeutic dead end in the treatment of several bacterial infections might soon become a reality. This worrisome situation will lead us back to the pre-antibiotic era of the 1930s and early 1940s.

No new antibiotic discoveries

Our present generation antibiotics are the result of scientific discoveries that happened decades ago. A timeline of dates of discovery of distinct classes of antibiotics (and not those of market introduction) illustrates that there have been no successful discoveries of new classes of antibiotics since 1987.⁶ A major reason for the same may be that chronic illness medications like those for hypertension and diabetes form more lucrative business propositions for the pharmaceutical companies as compared to newer antibiotics, because of their prolonged usage in a given patient and no issues of resistance. Also, smaller pharmaceutical companies cannot afford the cost of meeting complex requirements for clinical trials involving antibiotics. This compromises the development of many promising new agents.

AMR poses a significant challenge to Primary Health Care

Majority of the Indian population, especially in the rural areas and urban slums, is dependent on grass root Government

healthcare services for primary care. Most of the antimicrobials available in the Sub Centres and Primary Health Centres are essentially first generation drugs. The curative component of the entire Primary Health Care system can collapse if AMR is not dealt with in a systematic manner.⁷

The road ahead

Although development of resistance in a microorganism is natural, its amplification and spread is through faulty practices by humans. The underlying factors that accelerate the emergence and spread of AMR have been identified as inappropriate use of antimicrobial medicines, including in animal husbandry, lack of a comprehensive and coordinated response, weak or absent antimicrobial resistance surveillance and monitoring systems, inadequate systems to ensure quality and uninterrupted supply of medicines, and poor infection control practices. In light of these, there have been national and international efforts to halt or slow the progress of resistance. The WHO aptly selected the theme for World Health Day 2011 as “Antimicrobial resistance: No action today, no cure tomorrow”.⁸

Activities at global level

The coordinated fight against AMR can be said to have begun in the late 1990s and 2000, when the WHO convened a series of consultative groups, expert workshops, and consensus meetings to assess the situation and came out with The Global Strategy 2001 for AMR. The thrust areas suggested were education to patients, prescribers and dispensers at all levels, better implementation of existing infection control programmes, monitoring the activities of pharmaceutical companies within hospitals, phasing out the use of antimicrobials for growth promotion in animals and plants if they are also used for treatment of humans and encourage cooperation between industry, government bodies and academic institutions in the search for new drugs and vaccines.¹

Activities at national level

India is signatory to the “Jaipur Declaration on Anti Microbial Resistance – 2011” for the SEAR. Even though the Govt of India has formulated the National Policy for Containment of Antimicrobial Resistance in India in 2011, there is ample scope for improving our health systems to reduce AMR.

The authors feel that inadequate control on over-the-counter sale of antimicrobials, their inappropriate use by clinicians and lack of coordination in resistance surveillance are the main road-blocks in our country. A three pronged approach to tackle this menace can be looked into.

Firstly, regulations on the sale of over the counter antimicrobials does influence the consumption and therefore, the spread of resistance, as shown by several European studies.^{9,10} Levying fines on the dealers who indulge in such practices by the regulatory authorities is a long standing need.

Secondly, allopathic doctors as well as practitioners of other forms of healing must be encouraged to get involved in continuous education regarding the trends in AMR in their

areas. Establishing standard treatment guidelines for common infectious diseases will go a long way in achieving uniformity in treatment and reduction in newer generation drugs getting resistant.

Finally, in absence of a national programme for AMR surveillance, a hospital based sentinel surveillance system for monitoring resistance can be established across the country. There are a few examples of successful networking of laboratories carrying out antimicrobial sensitivity testing of gonococcus in the country with regional STD laboratory at Safdarjung Hospital in New Delhi being the referral laboratory. Networking of laboratories also exists in the national TB control programme, generating some useful data on drug resistance in TB in the country. Using software like the WHONET for AMR data management, designating a national focal point for AMR and using standardized techniques such as the modified Kirby Bauer Method for AST in these laboratories as per the WHO-recommended CLSI guidelines are other viable approaches to face the challenge of AMR surveillance.¹¹

Conclusion

Infections caused by resistant microorganisms often fail to respond to conventional treatment, resulting in prolonged illness, greater risk of death and higher costs. New resistance mechanisms have emerged, making the latest generation of antibiotics virtually ineffective.

Though there are definite policies and guidelines for appropriate use of antimicrobials in specific national health programmes such as for TB, AIDS and malaria, the same are not available for other diseases of public health importance like enteric fever, diarrhoeal diseases, respiratory infections, etc. Effective public health measures such as improved hygiene and sanitation, improving immunization coverage, rapid outbreak response, effective IEC, promoting AYUSH and other holistic systems of healing will reduce reliance on antimicrobials and break the chain of transmission of resistant microbes.

There is a need to identify the threat of AMR, develop concerted multipronged strategy, develop infrastructure and take coordinated and urgent steps to tackle this serious public health challenge.

Conflicts of interest

All authors have none to declare.

REFERENCES

1. World Health Organization. Anti Microbial Resistance [homepage on internet]; 2011 [cited Sep 2013]. Available from: http://www.who.int/topics/drug_resistance/en/.
2. Kotwani A, Roy CR, Holloway K. Prescribing antibiotics for acute respiratory tract infections by primary care physicians in New Delhi, India. In: *Conference Paper: From Adaptive Trials to Personalized Medicine: Providing Value for Decision Makers*. 15th

- International Society of Pharmacoeconomics and Outcomes Research Annual International Meeting*. May 15–19, 2010. Atlanta, GA, USA.
3. Smith R. The true cost of anti-microbial resistance. *BMJ*. 2013;346:f1493 [internet]. Available from: <http://www.bmj.com/content/346/bmj.f1493>. Accessed Jun 2013.
 4. Kumar R, Indira K, Rizvi A, Rizvi T, Jeyaseelan L. Antibiotic prescribing practices in primary and secondary health care facilities in Uttar Pradesh, India. *J Clin Pharm Ther*. 2008;33:625–634.
 5. Chandy SJ, Kurien T, Nalloor T, Balaji V, Christopher S, Lundborg CS. Economic burden and health consequences of antibiotic resistance in patients at a Tertiary Care Hospital, Vellore, South India. In: *Conference Paper: Informed Strategies, Effective Policies, Lasting Solutions*. 3rd International Conference for Improving Use of Medicines. Turkey: Antalya; Nov 14–18, 2011. Available at: http://www.inrud.org/icium/conferencematerials/538-chandy_c.pdf. Accessed Sep 2013.
 6. World Economic Forum. *Report on Global Risks*. Geneva: WEF; 2013. Available at: http://qfc.de/qfc.de/uploads/media/WEF_GlobalRisks_Report_2013Teil2.pdf. Accessed Sep 2013.
 7. Govt. of India. *National List of Essential Medicines of India*, 2011. New Delhi: Ministry of Health and Family Welfare, GOI.
 8. World Health Organization. *World Health Day 2011: Policy Briefs*. Geneva: WHO; 2011. Available at: <http://www.who.int/world-health-day/2011/policybriefs/en/index.html>. Accessed Nov 2012.
 9. Plachouras D, Kavatha D, Antoniadou A, et al. Dispensing of antibiotics without prescription in Greece, 2008: another link in the antibiotic resistance chain. *Euro Surveill*. 2010;15(7):19488 [internet]. [cited Aug 2013] Available at: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19488>.
 10. Goossens H, Ferech M, Vander SR, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet*. 2005;365(9459):579–587.
 11. World Health Organization, South East Asia Regional Office. *SEA Regional Strategy on Antimicrobial Resistance* [homepage on internet] 2010. Geneva: WHO; 2010 [cited Aug 2013]. Available at: http://www.searo.who.int/entity/antimicrobial_resistance/en/index.html.