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VIEWPOINT IN
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Discovery of the deadly New Delhi metallo-beta-lactamase 1 superbug in the Arctic: The Indian context

Tanmayee JOSHI[1], Isha PATEL[2]

Affiliations:

[1] M.S., CU Shah College of Pharmacy, SNDT Women's University, Mumbai, India
[2] P.h.D. Department of Pharmacy Practice, Administration and Research, Marshall University School of Pharmacy (MUSOP), Marshall University, Huntington, United States.

Corresponding author:

Dr Isha Patel, Department of Pharmacy Practice, Administration and Research Marshall University School of Pharmacy (MUSOP) One John Marshall Drive Huntington, WV 25755.
E-mail: pateli@marshall.edu

Abstract

The overuse of antibiotics is the single most factor leading to antibiotic resistance worldwide. The antibiotic resistance crisis has been attributed to the overuse and misuse of these medicines. Antibiotic resistant-bacteria are found in people, animals, food, and the environment (water, soil and air). Resistant bacteria pass this resistant gene from one bacterium to another, thus making older antibiotics ineffective. A superbug gene blaNDM-1 (New Delhi metallo-beta-lactamase), which was found in New Delhi in 2008, has now spread to the Arctic. NDM-1 is the enzyme encoded by blaNDM-1 gene, which renders the bacteria *Klebsiella pneumoniae* resistant to wide range of beta lactam antibiotics. In 2010, India was the number one consumer of antibiotics in the world for treating humans. On one hand, the unabated use of antibiotics in India has been fuelled by rapid economic growth and rising incomes, but has not comparatively translated into improvements in sanitation and public health. Poor public health infrastructure, a high disease burden, and unregulated sales of antibiotics, in unison, have created ideal conditions for rise in bacterial resistant infections in India. This viewpoint focuses on the Indian government's actions and future measures needed to promote rationale use of antibiotics in humans and animals.

KEY WORDS: antimicrobial resistance; antibiotics; India; New Delhi metallo-beta-lactamase 1 superbug; public health.

INTRODUCTION

Antibiotic resistance is a worldwide problem. Antibiotic resistance can cross international boundaries and spread between continents with ease. World health leaders have described antibiotic resistant microorganisms as 'nightmare bacteria' responsible for catastrophic consequences among people in every country in the world. Superbugs are strains of bacteria that are resistant to several types of antibiotics. The overuse of antibiotics is the single most important factor leading to antibiotic resistance around the world. In most cases, antibiotic-resistant infections require prolonged and/or costlier treatments, result in extended hospital stays, additional doctor visits and healthcare use, as well as greater disability and death compared to infections that are easily treatable with antibiotics [1].

The rapid emergence of resistant bacteria is occurring worldwide, endangering the efficacy of antibiotics, that have transformed medicine and saved millions of lives. The antibiotic resistance crisis has been attributed to the overuse and misuse of these medications, combined with lack of new drug development by the pharmaceutical companies due to reduced economic incentives and challenging regulatory requirements [2]. The U.S. Centers for Disease Control and Prevention (CDC) has classified a number of bacteria presenting urgent, serious, and concerning threats, many of which are already responsible for placing a substantial clinical and financial burden on the health care system, patients, and their families. Coordinated efforts to implement new policies, renew research efforts, and pursue steps to manage the crisis are the need of the day [3].

DISCUSSION

Antibiotic resistant-bacteria survive exposure to antibiotics and continue to multiply in the body, potentially causing more harm and spreading to other animals or people. Antibiotic resistance occurs naturally over time, usually through genetic changes. However, the misuse and overuse of antimicrobials is accelerating this process over time. Antibiotic resistant-bacteria are found in people, animals, food, and the environment (water, soil and air). These bacteria can spread between

TAKE-HOME MESSAGE

In India, collaborative efforts between the healthcare professionals, patients and the government are needed to rigorously implement a national plan against antimicrobial resistance.

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people and animals, through food from animal origin, and from other people. Process of resistance generally occurs naturally. A few bacteria contain traits which enable them to survive in the presence of antibiotics. On the other hand, susceptible bacteria that lack those resistant traits get diminished, leaving only resistant bacteria behind. This allows for dramatic increase in bacterial resistant populations. Resistant bacteria pass this resistant gene from one bacterium to another, thus making older antibiotics ineffective [4, 5].

In bacteria, genes can be inherited from relatives or can be acquired from nonrelatives on mobile genetic elements such as plasmids. This horizontal gene transfer (HGT) allows antibiotic resistance to be transferred among different species of bacteria. Resistance can also occur spontaneously through mutation. Antibiotics remove drug-sensitive competitors, leaving behind resistant bacteria to reproduce as a result of natural selection [6]. Despite warnings regarding overuse, antibiotics are overprescribed worldwide [7].

Antibiotic resistance is present in every country. Times of India, had reported a superbug gene blaNDM-1 (New Delhi metallo-beta-lactamase), which was found in New Delhi, in 2008 and this has now spread to the Arctic. The gene was assumed to have spread through fecal matter of wildlife and human visitors. This finding has huge implications for global as well as Indian antibiotic resistance situation [8].

The New Delhi metallo beta-lactamase-1 (NDM-1) enzyme was named after New Delhi, the capital city of India, because it was first described by Yong et al. [8] in December 2009 in a Swedish national who fell ill with an antibiotic-resistant bacterial infection that he possibly acquired in India [9]. Presence of Antibiotic Resistant Genes (ARGs) lead to multidrug resistance in microbes. NDM-1 is the enzyme encoded by blaNDM-1 gene which renders the bacteria *Klebsiella pneumoniae* resistant to wide range of beta lactam antibiotics. Carbapenems are one of the classes of beta lactam antibiotics, which are used as last option to treat bacterial infections [10]. Undoubtedly, the impact of activity of NDM-1 is threatening as today we may not have potent and effective antibiotics to treat such patients. There is also the danger of spread of such infections due to poor disinfecting practices. Further, such episodes can cause a scare in the minds of people interested in foreign travel and medical tourism [9].

In 2010, India was the world's largest consumer of antibiotics for treating humans [11]. The scale-up in antibiotic use in India has been enabled by rapid economic growth and rising incomes, which have not translated into improvements in water, sanitation, and public health. Antibiotics continue to be prescribed or sold for diarrheal diseases and upper respiratory infections for which they have limited value. The main problem is that India lags on basic public health measures. Under the Swachh Bharat Abhiyan (Clean India Program), the government has undertaken measures to providing toilets and improving sewage systems, but these will take time to implement. Poor public health infrastructure, a high disease burden, and unregulated sales of antibiotics, in unison, create ideal conditions for rise in bacterial resistant infections in India. Waste water treatment plants serving antibiotic manufacturing facilities have been implicated in the transfer of resistance genes into human microbiota and pose a serious threat to antibiotic effectiveness given the size of India's pharmaceutical sector [11].

Schedule H1 was introduced on March 1, 2014; as an amendment to the Drugs and Cosmetics Rules of 1945. A total of 46 drugs were included under this schedule, also including certain 3rd and 4th generation antibiotics. Since the passage of the amendment, the sale of these drugs is restricted and there is a red box warning introduced on the label [11]. The Indian government has also introduced a National Action Plan on Antimicrobial Resistance (NAP-AMR) spanning from 2017 to 2022. The 'National Treatment Guidelines for Antimicrobial use in Infectious Diseases' has been released as a reference guide to promote rational use of antibiotics. The focus areas of the strategic priorities of

NAP-AMR include, improving awareness and understanding of anti-microbial resistance (AMR) utilizing information, education and communication based resources, reducing incidence of infection through effective infection prevention and control, and promoting investments for AMR activities. This action plan aims to promote rationale use of antibiotics in humans and animals. AMR surveillance is also the part of program, and Klebsiella is one of the species included in surveillance [12]. Considering the complex nature of the Indian health sector, coordination between public and private healthcare entities is a must. Major challenges for the implementation of the NAP-AMR plan include limited diagnostic services, high burden of TB, malaria, HIV, and patient affordability [13]. Surveillance of AMR is also part of the European Centre for Disease Prevention and Control (ECDC) which is complementary with WHO guidelines [14]. Spotty implementation, limited availability of trained physicians and pharmacists in rural areas, poverty, illiteracy, overcrowding and malnutrition further compound the situation [15, 16]. Lack of awareness about infectious diseases among the general masses and their inaccessibility to healthcare often preclude them from seeking medical advice. This, more often than not, leads to self-prescription of microbial agents without any professional knowledge regarding the dose and duration of treatment [16]. There also have been some positive implications of the AMR problem in India. India has seen the emergence of several start-ups, who have initiated research against multi-drug resistant bacteria and novel antibiotics. In 2018, a firm invented a novel topoisomaerase inhibitor, which has shown activity against many multi-drug resistant bacteria including Klebsiella [17]. Another start-up is working on developing therapies for multi-drug resistant hospital acquired infections, and has come up with molecules effective against MRSA (Methicillin-resistant *Staphylococcus aureus*) infections, which is currently under preclinical studies [18].

CONCLUSION

Antibiotic resistance is a global challenge as resistant microbes can spread easily through air, food, soil and water. In India, collaborative efforts between the healthcare professionals, patients and the government are needed to rigorously implement schedule H1, as well as a national antimicrobial plan. Tackling antibiotic resistance should involve efforts from all the stakeholders on multiple fronts such as, improving sanitation standards, access to cleaner toilets and hygiene training, and education related to use of antibiotics among community residents. Finally, national plans against AMR should take into consideration different causes specific to any country and differences between developed and developing countries, but should be coordinated in a global way, requiring action across all governments sectors and society [19].

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