# **Review Article**

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# **Antimicrobial resistance: the next BIG pandemic**

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# **ABSTRACT**

Pandemics have indefinitely threatened the resilience of health systems worldwide. Based on the costs inflicted by some of the deadliest pandemics in human history, economists have projected that global pandemics could cost over USD 6 trillion and generate an annual estimated loss of over USD 60 billion. While the global health community is tirelessly trying to curb the burden of premature mortality from several old and new forms of pathogens, it is now faced with the silently emerging antimicrobial resistance (AMR) pandemic that could endanger some of the most significant advances in modern medicine. Owing to rampant antibiotic consumption in India, the article shows why the country may become the 'AMR capital of the world'. It shows how health systems may be strengthened both at the national and international levels to reduce premature mortality and morbidity attributable to AMR and pandemics.

Keywords: Antimicrobial resistance, Pandemics, Health systems, Premature mortality, Public health, Surveillance

### INTRODUCTION

Time and again, outbreak of pandemics has strained health systems and challenged their resilience globally. Although the world has collectively battled some of the worst pandemics in history and prevented their recurrence - like the 'Black Death' which claimed the lives of 50 million Europeans from 1346 to 1353 and the 'Spanish Flu' of 1918 which killed nearly 40 million people worldwide - emergence and re-emergence of a host of viruses such as Ebola, Zika, Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS) and H1N1 in the last two decades are symptoms of new threats that confront the global health community.<sup>1,2</sup> Owing to disproportionately growing population, poor sanitation and insufficient allocation of resources to healthcare, the burden of infectious diseases and the risk of epidemic outbreaks continue to remain high for developing countries. For instance, Africa and Southeast Asia together accounted for 51 percent of the global death toll (estimated at 284,000) from H1N1

pandemic of 2009.<sup>3</sup> Similarly, from March 2014 to December 2015, Ebola risked the lives of 28,616 people in West African countries and claimed 11,310 lives. Further, although international wars against HIV/AIDS and TB were waged decades ago, 36.7 million people continued to live with HIV in 2015 and an estimated 25.6 million of them lived in Sub-Saharan Africa.<sup>4,5</sup> Tuberculosis- one of the leading causes of death worldwide - afflicted 10.4 million people, predominantly in low-and middle-income countries (LMICs) in 2015.<sup>6</sup> It is worthwhile to highlight that India contributes disproportionately to the global HIV and TB burden. In 2015, for instance, 2.9 million people were living with HIV and an additional 2.8 million with TB in India alone.<sup>7</sup>

Although it is difficult to arrive at accurate numbers to justify the economic loss of every pandemic outbreak, rough estimations are available. For instance, in 2008, the World Bank estimated that a severe influenza epidemic could severely cripple the global economy by leading to

an approximate loss of USD 3 trillion, which is equivalent to 4.8 percent of global GDP.8 It is important to note that costs associated with a pandemic eruption are not only limited to direct loss of labour productivity and the burden on healthcare resources - magnified economic losses can actually be the result of an adverse indirect effect of pandemics on global supply chains and tourism. For instance, while Ebola infected only 0.2 percent of the population of Liberia, 0.25 percent of the population of Sierra Leone and less than 0.05 population of Guinea, it led to an aggregate cumulative loss of more than 10 percent of their GDP in 2014 and 2015. Behavioural changes resulting from epidemic fear were also evident in the SARS outbreak of 2003. Even though the virus infected only 8,000 people and killed less than 800, economic losses were estimated in excess of USD 40 billion.9 Further, according to modelled estimates provided by the Commission on a Global Health Risk Framework for the Future, global pandemics could cost over USD 6 trillion and generate an expected loss of over USD 60 billion per year. 10 Thus, pandemics can deeply undermine the fiscal situation of economies, particularly of the developing world, and cause an irreversible damage to their growth prospects.

In its endeavour to reduce premature mortality and resulting economic losses from pandemics, the global health fraternity is now faced with the silently emerging AMR pandemic. Diminishing antimicrobial effectiveness has the potential to imperil even the most important medical advances and reverse the gains achieved in treating infections, managing chronic diseases and surgical/post-surgical care. AMR is a formidable problem for developed and developing countries alike. Based on broad estimates, deaths from antimicrobial resistant infections are projected to increase from current toll of 700,000 to 10 million every year by 2050. In addition to the costs associated with loss of human lives, AMR can result in a loss of 2-3.5 percent of global GDP, which could amount to USD 100 trillion by 2050. 11-13 Irrational use of antimicrobial drugs in human beings and livestock, over-the-counter (OTC) availability of drugs without prescription, lack of adherence to specified treatment regimen and poor hygiene in health care facilities are major factors that contribute to development of resistance in pathogens, which render antimicrobial drugs ineffective.

# THE GROWING SEVERITY OF PROBLEM IN INDIA

In the Indian context, AMR gained policy traction after formulation of the National Policy for Containment of AMR in India in 2011. 14 The policy ambitiously planned to capture the incidence of 'use and misuse of antibiotics in the country' through creation of national surveillance system for antibiotic resistance, mechanism of monitoring prescription audits, diagnostic tools for AMR monitoring, regulatory provision for monitoring use of antibiotics in human, veterinary and industrial sectors and

identification of specific intervention measures for rational use of antibiotics and antibiotic policies in hospitals. The AMR policy can most convincingly trace its existence to the NDM-1 enzyme (New Delhi Metallobeta-lactamase-1), which was first diagnosed in a Swedish patient (of Indian origin) in 2008 who reportedly acquired the bug after undergoing surgery in a Delhibased hospital. As the enzyme can make bacteria resistant, many antibiotics which were administered to the patient for treating post-surgical infections were rendered ineffective.

Several more instances of AMR have since been reported in the country although the total burden is difficult to evaluate. Present statistics are primarily confined to neonates and the aged population who are more susceptible to infections and resilient microbes which can make treatment ineffective. For instance, a recent Lancet study estimated that 56,254 neonatal deaths in India were caused by antibiotic resistant sepsis every year. 15 As antibiotic consumption is the most important factor for making bacteria resistant against the most powerful class of antibiotics, India is at a severely high risk of becoming the 'AMR capital of the world'. In 2010, Indians emerged as the largest consumer of antibiotics in the world. 16 Moreover, per capita consumption of last resort antibiotics such as carbapenem increased to over 10 million standard units by 2010.<sup>17</sup> In addition to the rampant use of powerful antibiotics, India is faced with perennial public health concerns like inadequate access to and poorly implemented infection-control measures in hospitals. For instance, results of a pointprevalence study conducted in a large 1800-bed tertiary care hospital in India showed an overall hospital-acquired infection (HAI) prevalence of 7 percent. <sup>18</sup> Another study estimated the rate to be 8.78 percent for a tertiary care facility in India.19

In cognizance of the increasingly growing antibiotic consumption in India, the Central Drugs Standard Control Organization (CDSCO) introduced Schedule H1 drugs in 2014. Drugs included in Schedule H1 can now only be sold by a registered medical practitioner who is also mandated to maintain a record of his sold drugs and retain that record for at least 3 years.<sup>20</sup> However, many important antibiotics are still kept out of the Schedule H1 purview. OTC sale of these 'excluded' drugs is expected to increase rapidly, more importantly to compensate for the restricted sales of Schedule H1 drugs. Further, availability of fixed-dose combination (FDC) of drugs and/or loose antimicrobials - without medical/clinician supervision - is aggravating the AMR problem in India. By exposing patients to an increased risk of drug reaction, irrational FDCs have the potential to rapidly produce resistant strains in pathogens.<sup>21</sup>

Another crucial factor that is contributing to the rising AMR incidence is the injudicious use of antibiotics in agriculture and livestock for increasing productivity of agricultural/livestock output. India, like many developing

countries, lacks regulatory mechanisms for antibiotic use in livestock and agriculture, as a result of which antimicrobial residues have often been found in agricultural produce, chicken, meat and milk in several parts of the country. <sup>22-24</sup> Rising demand of hybrid, high-value agricultural commodities and animal food products is further expected to stimulate antibiotic use in the environment and add to the growing AMR prevalence.

#### POSSIBLE SOLUTIONS

While the predominant focus of health systems has been on treatment of diseases, growing instances of AMR and pandemics emerging are an indication that comprehensive prevention strategies should be unanimously embraced by health systems. spearheading prevention-oriented initiatives, the global health community can play a distinguishing role in minimizing premature mortality and morbidity attributable to AMR and pandemics. This can be most reasonably done by adopting health strengthening measures that are not only confined to the health sector but go beyond to include the larger ecosystem, which inadvertently stimulates AMR and contributes to an increase in the incidence of pandemics. Following remedial measures are called for consideration:

#### Strengthening domestic public health surveillance

Where surveillance is weak, as in developing countries, it is difficult to estimate the scale of the problem. Lack of epidemiological data severely undermines development of clinical practices. This is particularly crucial in the immediate aftermath of a public health emergency as health agencies can duly act only when there is accurate and urgent availability of virological data. Since local populations are at the forefront of any health crisis, it is important for national governments to ensure:

- a. the establishment of an exhaustive surveillance mechanism that collects and evaluates public health information in near-to-real time;
- affordability and accessibility to adequate diagnostic services;
- c. that a robust transport and communication network is laid out so that laboratory samples are safely and promptly transported to appropriate laboratories;
- d. that skilled, competent public health cadre is constituted to work in emergency situations;
- the appointment of public health experts in core positions at national and sub-national levels to prioritize prevention.

# International health crises response measures

At the International front, nodal health agencies and non-health sectors can ensure:

- a. strengthening of regional/sub-regional emergency preparedness strategies for timely and effective execution in the advent of public health crises;
- formulating relevant contingency-related medical agreements which can gain quick legitimacy at the onset of a crisis;
- that the Central governments assume full-fledged responsibility in the event of a health crisis and work in close collaboration with state/regional governments;
- that an annual self-assessment of reforms, taking into account the recommended International Health Regulations (IHR) core capacities, is undertaken by member countries;
- e. strengthening of epidemiological/biomedical/socialscientific research and collaborations.

#### Accelerating drug discovery and innovation

Outbreak of pandemics and instances of AMR imply that the existing drugs are no longer effective. This problem is aggravated by the fact that the pace at which new drugs are discovered and become available for consumption has witnessed a rapid slowdown in the past decade. Even though drug development is considered to offer significant gains to society, high research and development (R&D) costs and imprecise estimation of potential market size are challenges that pharmaceutical companies are faced with. Unlike chronic diseases which require longer treatment and sustained expenses on management, antibacterial therapies are often prescribed for shorter durations, limiting the scope of returns on R&D costs. Further, new antimicrobial drugs can only be introduced once the existing ones become clinically ineffective. In view of these challenges, following measures may be taken into consideration:

- a. A global fund should be created to support scientific research for drug development and identification of alternative therapies. In order to reinvigorate innovations while ensuring that these are aligned with public health needs, public-private partnerships for product development may be considered.
- b. In order to make R&D in drug discovery economically viable, governments at national level need to ensure that developers have enough economic incentives to go through long processes of drug development. Measures like financial grants, tax incentives, advanced market commitment can go a long way in incentivising pharmaceutical companies to promote drug discovery.

# Reforms at the policy level

a. As AMR can be developed by more than one causal factor, it is important for national governments to work in collaboration with several ministries. For instance, in February 2017, Union Health Minister of

- India, Mr. JP Nadda, announced that ministries of agriculture, animal husbandry, pharmaceuticals and environment will work in tandem to design policies to curb the problem of AMR in the country.<sup>25</sup>
- b. Strong regulatory measures to overhaul delivery and procurement systems of anti-microbial drugs are required to enhance their shelf-life. For instance, implementing the concept of prescription-only sales for all groups of antibiotics, selling certain higher order drugs only at accredited drug dispensing units, etc.
- c. Rapidly growing incidence of HAIs inflicts a heavy cost in terms prolonged morbidity and hospital stays and increased risk of mortality. Implementing a certain standard of hygiene practices, adopting infection control protocols, training staff about the hazards of poor hygiene is recommended here.

#### Community-based approaches for tackling AMR

- a. Promoting rational and responsible use of drugs in individuals, agriculture and livestock so that efficacy of existing drugs is prolonged.
- b. Encouraging treatment adherence, averting suboptimum drug consumption practices like selfprescription, taking spare medicines from earlier prescribed doses, sharing leftover drugs with others, etc.

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