Emergence and burden of antibiotic drug resistance: an endogenous cycle

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Antibiotic drug resistance is a global crisis today. The deleterious impact of this crisis is acting relatively in higher degrees in poor nations compared to developed countries in the world. Low economy and irrational perspective on medical practice are accelerating the development of drug resistance, leading the population in more economically challenged situations. This article discusses current situations, expresses opinions and views on the self-reinforcement process in the emergence and development of drug resistance.

Antibiotic drug resistance is one of the biggest threats today to our global health, economy and development. It is a worldwide issue both clinically and publicly[1]. The emergence and spread of resistant strains are occurring across continents, questioning the effectiveness of antibiotics which save millions of lives[2]. The new Global Antimicrobial Surveillance System (GLASS) initiated by World Health Organization (WHO) reveals the widespread occurrence of antibiotic resistance among 500,000 people with suspected bacterial infections across 22 countries[3]. A study by the European Center for Disease Control (ECDC) estimates that 33,000 people die every year due to antibiotic drug resistant bacteria[4]. According to a report by the United Nations, antibiotic drug-resistance can result in 10 million deaths each year globally by 2050, if there is no effort to control the resistance[5]. Deleterious effects of resistance are already manifesting themselves across the world. Studies predict that 300 million people may die due to resistance over the next 35 years and the world's GDP would decrease by 2–3.5% in 2050 (Figure 1). This shows that the globe can expect to suffer a loss between 60 and 100 trillion USD worth of economic output by 2050 from today. The threat of rising drug resistance is more frightful in poorer countries. Growing resistance to treatments for diseases, such as TB, malaria and HIV has more impact on lower-income nations[6]. Prolonged hospitalizations, expensive medication and specialized care are needed to treat patients with resistance which proves expensive compared to drug-susceptible infections. According to a study in New York City, USA, the expenditure of treating *methicillin-resistant Staphylococcus aureus* (MRSA) was almost 22% higher compared to treating methicillin-susceptible *S. aureus*

(MSSA); even the mortality rate had increased almost three times from 8% to 21% (ref. 7).

The widespread irrational use of antibiotics accelerates the process of drug resistance[8–10]. In India, more than 58,000 infants died in 2013 due to antibiotic-resistant bacterial infections. Moreover 40% of the world's antibiotics are consumed in India[11]. Selection pressure by extensive use of antibiotics accelerates the emergence and multiplication of resistant mutants[9,12,13]. As reported in the literature, irrational antibiotics consumption would eventually lead to expulsion of sensitive strains from the community and to procreation and propagation of resistant bacteria in the population[1]. India followed by China were the largest consumers of antibiotics between 2000 and 2010. BRICS countries (Brazil, Russia, India, China and South Africa) showed the highest drug consumption from 2000 to 2010, where 23% of the total increase in antibiotic consumption was attributable to India alone[14]. A recent report indicates that the global antibiotic consumption is increased by 65% between 2000 and

2015, from 2.1 to 34.8 billion daily defined dose (DDD), and the global increase was driven by increased consumption in lower middle-income countries (LMICs)[15] (Figure 2).

Self-medication is a common practice in developing and under-developed nations, that fuels the development of resistance over time[16–18]. Many developing countries allow the sale of over-the-counter (OTC) drugs, which is also a contributing factor to self-medication[19]. In a survey from Rajbari district, Bangladesh, approximately 100,000 antibiotics were dispensed without prescription in a month[20]. Another survey in Bangladesh revealed that 92% of medicines sold by pharmacies were without prescription[21]. Recent studies suggest that self-medication is highly prevalent in economically deprived communities[22,23]. In many developing nations, this becomes an easy and obvious choice, where proper health-care facilities are relatively expensive, especially in private settings. The most important factor that promotes self-medication is individual perceptions of healthcare practice. Avoiding the
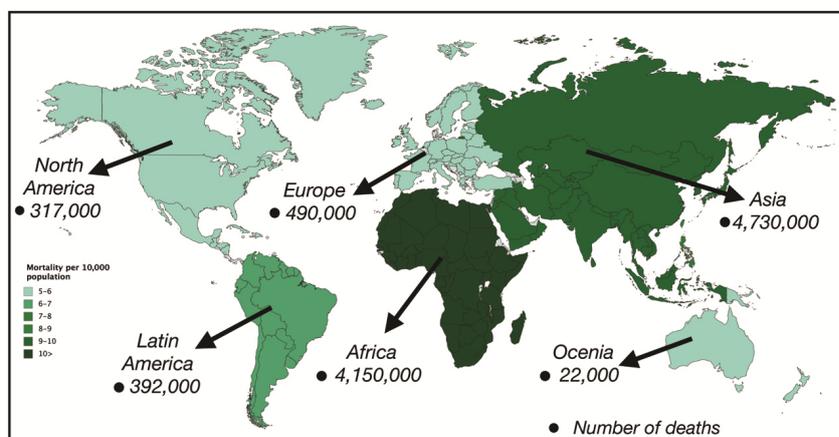

Figure 1. Predicted annual number of deaths from drug resistance by 2050 (source: ref.
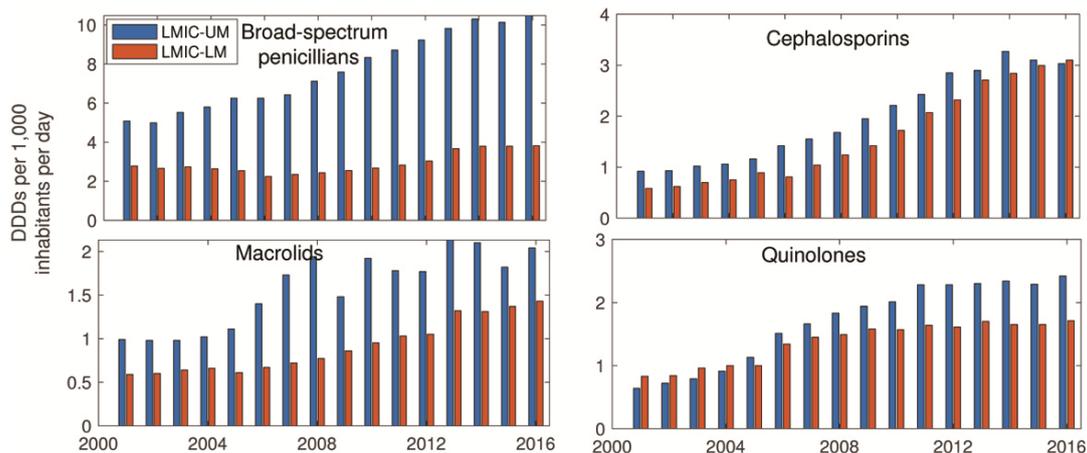
Figure 2. Antibiotic consumption rate for low-income and lower-middle-income countries (LMIC-LM) and upper-middle-income countries (LMIC-UM) during 2000–2015. IQVIA MIDAS, 2010–2015 (source: ref. 14).
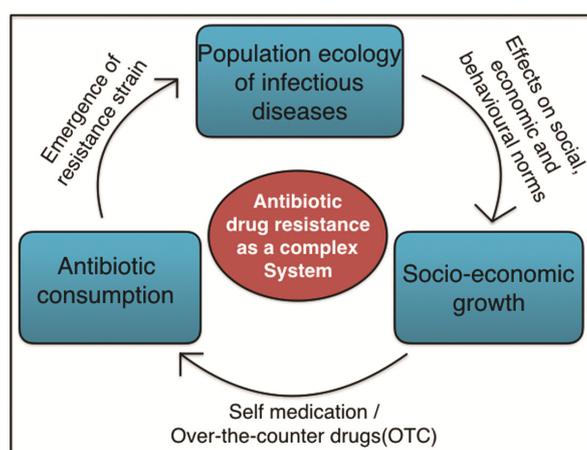

Figure 3. Antibiotic drug resistance as a self-reinforcing cycle driven by population ecology of infectious diseases, socio-economic growth and antibiotic consumption through self-medication and over-the-counter drugs.

expenditure of correct treatment, and collecting OTC medication without prescription seems to be more cost-effective and time-saving in such economically challenged nations[24]. Studies reported that 73% of the population in Punjab, India indulged in self-medication for the treatment of minor health problems[25,26].

The high economic burden from drug resistance pushes developing nations towards further poverty, which leads people to practice self-medication as an ineluctable choice. Although there are many factors behind the global burden of drug resistance today, this reinforcement interaction among self-medication, infections and socio-economic growth works as a cyclic process, contributing to the burden of resistance. This is, in fact, one of the reasons for significant economic

disparity between the developed and developing nations. We have developed a mathematical model using three components, viz. *socio-economic growth, population ecology of infectious diseases, and antibiotic misuse* to showcase how these interactions may fuel the proliferation of resistance in society[27]. The sum effect of poor economy, infection and self-medication produce interactions through positive feedbacks on each other, demonstrating the emergence of drug resistance as a self-cycle (Figure 3). Here we have explained how divergence in drug resistance among the different populations can lead to the growing disparity in the economy. Different studies indicate that the populations in LMICs indulge in self-medication. The present study model also exhibits a pattern showing negative

relationship of drug resistance with average income of the population. Lack of awareness and low education can also accelerate the emergence of resistant strains and impose a high economic burden cost as discussed in this study.

Several immediate actions are required to stop such inappropriate use of antibiotics to tackle this ever increasing burden of resistance. For example, rapid diagnostics at the point-of-care, introducing technology oriented surveillance programmes, increasing public awareness, and education regarding, and changing the habit of prescribing antibiotics irrespective of infection types need to be implemented in the health systems. The government must provide monetary aid by reducing the cost of diagnosis and treatment, as well as medicines for

middle- and low-income countries. More importantly, these actions and decisions should be taken without further delay, as this study suggests that it is difficult to reduce the burden once a resistant pathogen is established in the population. Such strategies can also bring back the economic prosperity of the developing nations. WHO and stakeholders from developed countries have already taken steps to tackle antibiotic drug resistance[28,29]. Coordinated efforts to implement new research on drugs and vaccines, new medical policies and preventive steps for developing nations are needed to combat this global crisis.

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