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PERSPECTIVES FROM THE FIELD

Antimicrobial resistance in developing Asian countries: a challenge to global health security demanding tailored, local approaches

Rajesh Bhatia[1]

[1]Former Director Communicable Diseases, WHO Regional Office for South-East Asia, New Delhi, India

Abstract

Antimicrobial resistance (AMR) has been globally recognized as one of the largest and harshest challenges to global health security and economic development. Factors responsible for rising rates of AMR are well known. In developing countries, including India, antimicrobial agents are extensively and often irrationally used in human health, veterinary and fisheries sectors. The main reasons for such widespread usage are inadequate awareness, weak regulatory mechanisms, inadequate diagnostic services and a conducive environment. Possible avenues for rapid containment of AMR have been articulated. Huge resources, both financial and technical, are needed by developing countries. In the absence of these, innovative cost-effective approaches are needed. Universal health coverage and a One Health approach that brings together human health, animal health and environmental sectors may be considered by resource-limited countries. While universal health coverage, which is already high on national political agendas, can improve access to and rational use of antimicrobial agents, a one health approach may facilitate comprehensive and multipronged actions to contain antimicrobial resistance. These approaches need to be adopted in local contexts and implemented efficiently and effectively.

Despite rapid advances in medical innovations, the treatment of infectious diseases is becoming more difficult due to widespread emergence of antimicrobial resistance (AMR) in major pathogens, which makes antibiotics ineffective and results in treatment failure, prolonged illness, disability, greater risk of death and economic loss [1]. Furthermore, due to slowed development of new antimicrobials, very few antimicrobials are left to effectively treat infections caused by multidrug-resistant pathogens, and still fewer that are affordable in the developing world [2]. Containment of AMR is complex. Many developing countries may not be able to garner adequate resources to combat AMR. Clearly innovative approaches that are result-oriented and cost-effective are needed. Two of these approaches are described in this article.

Several studies in the current millennium have documented international spread of resistant pathogens originating from Asia [3,4]. An example is the swift spread of the New Delhi metallo-beta-lactamase-1 (NDM-1) producing Escherichia coli from India to the UK, Sweden, Austria, Belgium, France, Netherlands, Germany, the United States, Canada, Japan, China, Malaysia, Australia and Korea [3]. Colistin-resistant Enterobacteriaceae emerged in China in 2016 and spread rapidly to more than 30 countries [4].

The future implications of AMR are a serious risk to global health security. Immense gains of antimicrobial agents in the past eight decades may be negated by the emergence and spread of resistant malaria and common bacterial infections, including healthcare-associated infections, which account for high morbidity, mortality and economic loss in resource-limited countries with weak infection control practices [5]. Antimicrobial resistant pathogens currently cause about 700,000 deaths worldwide every year. If no serious action is initiated now, this number is estimated to rise to 10 million by 2050 [6], with most of these deaths in low income countries in Asia and Africa. It is estimated that by 2050, AMR will cause a global loss of US$100 trillion and a decrease of global gross domestic product by 3.5% [6]. Livestock production may decrease due to infections in food producing animals, thus impacting food security and disproportionately affecting the poor [7]. The past few years have seen immense global concern and political dialogue on combating AMR. In an unprecedented move in 2016, the United Nations General Assembly [8] deliberated on AMR and called for urgent implementation of global, coordinated efforts adopting a One Health approach to address AMR.

Few Asian countries have efficient surveillance systems to detect and monitor trends in antimicrobial resistance or antimicrobial use across human, animal and food production sectors. The Asian Network for Surveillance of Resistant Pathogens, with members spread over 14 countries (Saudi Arabia, Sri Lanka, India, China, South Korea, Japan, Hong Kong, Taiwan, Thailand, Vietnam, the Philippines, Malaysia, Singapore and Indonesia), has demonstrated increasing trends in AMR in these nations [10]. Thailand has estimated that antibiotic resistant pathogens are killing more than 38,000 people every year and an annual economic loss of US $1.3 billion [9].

Methicillin resistant Staphylococcus aureus (MRSA) is widely prevalent in almost all Asian countries. In China, Indonesia, Korea, Japan, Thailand and Vietnam

the rates of this pathogen exceed 50% in several health-care facilities [11]. The Indian Network for Surveillance of Antimicrobial Resistance found an MRSA prevalence rate of 41% [12]. The same Indian network detected resistance to nalidixic acid in 83% of the S. enterica serovar Typhi, and 93% of S. enterica serovar Paratyphi A strains [13].

More than 70% of bacteria were resistant to erythromycin in several countries, including Sri Lanka, India, China, South Korea, Japan, Hong Kong, Taiwan, Thailand, Vietnam, the Philippines, Malaysia, Singapore and Indonesia [14]. Carbapenem-resistance in Acinetobacter spp. and Pseudomonas aeruginosa are highly prevalent in Asian economies [15]. In Thailand, between 2000 and 2014, the prevalence of imipenem resistant P aeruginosa and Acinetobacter spp increased from 10% to 22% and from 14% to 65%, respectively [16]. NDM-producing Enterobacteriaceae that were first detected in India [17] have been frequently isolated from several geographical locations in India, Pakistan, Europe and Bangladesh [18,19,20].

Data from India during 1996-2008 reveals the alarming trend of swift increases in ciprofloxacin and penicillin resistance in Neisseria gonorrhoeae (Figure 1). Rising trends of resistance to several affordable antibiotics were observed. All the isolates were sensitive to spectinomycin except one strain in 2002. Of the total isolates analysed in this study [21], 23.3% were resistant to multiple antibiotics.

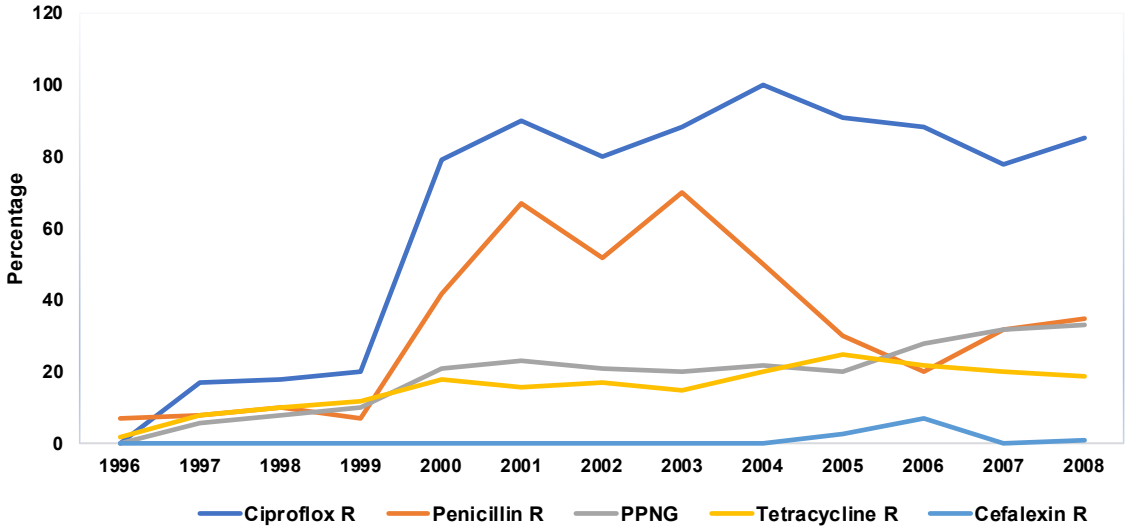
Access to diagnostic services to determine rational management and self-medication are serious issues for Asia. In China, 78% of hospital inpatients were treated with antibiotics in 2002 while only 3.8% of these had laboratory-based evidence of bacterial infections [22]. In Indonesia, antibiotics were prescribed for 84% of inpatients, of which only 21% had laboratory- evidence of bacterial infection [23]. Upper respiratory tract infections (URTI) accounted for almost half of the prescriptions for antibiotics, in spite of URTI being often of viral aetiology [24].

Contrary to common beliefs, more antibiotics are used in livestock production than in humans. It is estimated that in the USA, veterinary sector consumes almost 80% of all antibiotics [25]. In 2013, the global consumption of antimicrobials in food-producing animals was estimated at 131,109 tons and is projected to reach 200,235 tons by 2030 [26]. Between 2000 and 2015, antibiotic consumption in India doubled, making it the world's biggest consumer of antibiotics [27].

According to the World Organisation for Animal Health (OIE), only 27% of its member countries collect quantitative data on antimicrobial use in livestock production [28]. Economic prosperity and population growth have increased demand for animal protein and have resulted in a substantial increase in per capita consumption of animal protein in many Asian countries in recent years [29]. Fish production systems have become more intensive to meet this growing demand [30]. China, India and Vietnam are currently the three largest producers of aquaculture products globally [31] and also large consumers of antibiotics. Most developing countries use antimicrobials as growth promoters to prevent, rather than to treat, infections in poultry and pig production systems [32,33]. The United Nations Food and Agriculture Organization (FAO) has determined that all classes of antimicrobials important for human medicine are used in animals in Southeast Asia [33]. Several European countries and Thailand have discontinued use of antibiotics as growth promoters without any adverse impact on food production [34,35].

Weak enforcement of regulations facilitates the availability of almost all antimicrobials 'over the counter' in all Asian countries. Self-medication and prescription for antibiotics by unauthorized health professionals is widely reported [36]. The quality of antimicrobials available in Asia is also questionable. An estimated 78% of all counterfeit drugs are manufactured in Asia and 44% are used also in Asia [37]. The magnitude of counterfeit drugs can be seen by the fact that global value of these drugs is estimated to be about $75 billion a year [37]. The counterfeit drugs usually carry suboptimal quantity of antimicrobials, thus giving an advantage to pathogens in their interaction with antimicrobial agent.

Figure 1. Trends in resistance to antibiotics for *Neisseria gonorroheae* in India 1996-2008 [21]



The health sectors in developing countries have been devising various strategies to combat AMR. Under the WHO Global Action Plan against AMR, more than 60 countries have developed their respective National Action Plans (NAP) [38]. However, implementation of these NAPs is difficult. It is neither technically nor financially feasible to have a stand-alone national AMR programme in many Asian countries. The NAPs in developing countries suffer from waning advocacy, inadequate availability of financial and technical resources, inadequate engagement from the private sector, and poor coordination and collaboration amongst different stakeholders [39]. Nevertheless, immediate actions can be initiated through a few other operational vehicles or platforms, including universal health coverage (UHC) and a One Health approach.

Innovative approaches

UHC means that all individuals and communities receive the health services they need without suffering financial hardship [40]. UHC provides expanded coverage in activities such as vaccination, preventative care and hygiene measures that reduce disease burden, thus bringing about a proportionate reduction of antimicrobial resistance [41]. All UN Member States have agreed to try to achieve UHC by 2030 [40]. UHC with appropriate amendments can support various AMR-specific and AMR-sensitive interventions. One of the components of the Global Action Plan on AMR is to improve access to affordable antibiotics, and UHC can facilitate implementation of this component efficiently [42]. Access to quality antibiotics and their rational use are common features of both UHC and Global Action Plan on AMR. AMR Programmes can also draw financial resources provided by international development partners for UHC.

One Health is a simple and powerful transdisciplinary approach, yet its implementation is complex and its adoption in Asia is slow. It must overcome currently practised and well-established silo approaches towards health in all countries wherein there is inadequate collaboration between all sectors that influence animal and human health. It is imperative to bring about a change in national narratives to zoonoses. This change can be catalysed by political leadership. Strong, continuous advocacy is important, especially by international development partners such as WHO, FAO and OIE through sharing of evidence-based outcomes, expected economic gains and global best practices. The Sustainable Development Goals offer a unique opportunity for advocacy, as well as an integrated methodology in which several sectors work together with a common objective of preserving efficacy of antimicrobial agents [43,44].

The framework for effective implementation of One Health would involve incorporation of political commitments, policy formulation, sustainable financing, programme development, knowledge sharing, institutional collaboration, capacity enhancement, engagement of civil society and active participation of the communities [41].

While AMR has increased, the discovery and development of new classes of antimicrobial medicines have drastically slowed because of the high cost of discovery and low return on investment. The inappropriate use of antibiotics in humans, animals and food production must be curbed. In human health, both prescribers and users must consider the potential risks of indiscriminate use of antimicrobial agents. In animal health, the use of antibiotics as growth promoters must be discontinued and replaced with good animal husbandry practices in Asia. The global battle against AMR must ensure engagement of Asian countries.

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