Discussion on the Challenges Surrounding Anti-microbial Resistance, Using Relevant Case-study Examples

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ARTICLE INFO	ABSTRACT

The advent of antimicrobial drugs has made a huge contribution to human society, but their commodity nature has given rise to behaviors such as abuse and overuse, leading to the emergence of resistance to antimicrobial drugs and other hazards. Nowadays, the structure of interests formed by various stakeholders in the market circulation of antimicrobial agents has become unbalanced, and government intervention as a breakthrough still faces many challenges. This paper discusses the AMR challenges of government intervention under the interest structure in the context of case studies in the Global North and the Global South areas from the point of view of human health in terms of stagnant R & D processes for novel antimicrobial drugs, a profit-oriented neoliberal atmosphere that mismatches production trends of antimicrobial drugs with market demand, the prevalence of private institutions lacking effective regulation, incomplete government interventions, and the difficulty of pursuing the WHO strategic plan on antimicrobial resistance, etc.

1. Introduction

Since the advent of antimicrobial drugs, they have not only made great contributions to human society but also brought serious hazards such as drug resistance which was defined by WHO as a phenomenon that 'bacteria, viruses, fungi, and parasites change over time and no longer respond to medicines' [1]. With the spread of drug resistance over all the world, a post-antibiotic era in which there are no medicines available will emerge as it has become increasingly difficult and costly to treat infections and antimicrobial tend to be less effective. According to a 2016 estimate by a UK economist O'Neill, the number of deaths caused by drug resistance will exceed 10 million by 2050 if effective actions are not taken. Meanwhile, the World Bank and the Food and Agriculture Organisation of the United Nations (FAO) forecast in their research that in 2050, there would be a 1.1% to 3.8% decrease in the annual global GDP [2]. The WHO has declared antimicrobial resistance to be one of the top ten global public health threats to humanity with the misuse and overuse of antimicrobial drugs being one of the primary drivers [1].

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Ultimately, antimicrobial circulate in the market as a unique commodity. According to the nature of the product, the use of antimicrobial drugs is divided into six stages, including development, manufacturing, purchase, operation, provision, and consumption [3]. In this process, an interest structure is formed through the checks and balances between the various stakeholders at each link. However, the imbalance of interests and the absence of outside intervention in advance lead to market failure, antimicrobial proliferation, and uncontrolled drug resistance (Figure 1). Necessarily, a breakthrough is supposed to be government intervention.

As a result, this article aims to discuss the challenges of AMR in state intervention under the interest structure only from the point of view of human health (other areas of use including food-production, agricultural, aquaculture and so on). The first section describes the current issues of state involvement in the changing dynamics of interest relations at national and international levels through the six aspects mentioned above, and contrasts them by referring to case studies in the Global North and the Global South areas. The second section summarises the limitations of the paper including the problems of government interference itself. Last but not least, based on the challenges identified, several recommendations are made to tackle AMR in the context of national interventions.
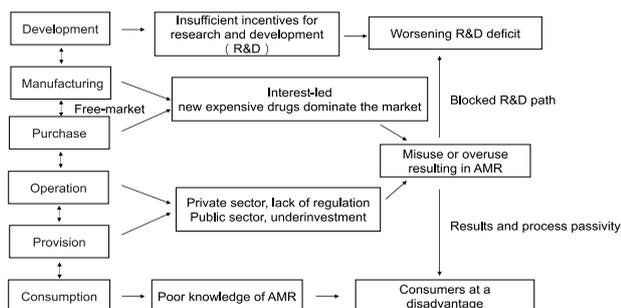
Figure 1. The Relationship Between Imbalance of Interests and AMR.

Modified after [3].

2. Challenges

2.1 Development Stage

At the international level, there is no explicit division of labour in each country. The rapid growth of anti-microbial resistance levels in countries including Brazil, Russia, India, China, and South Africa (BRICS) accounted for three-quarters of a 36% increase in the consumption of antimicrobials in 71 countries from 2000 to 2010 [4]. Although a report has shown that the British government

recently confirmed a financial examination of economic issues pertaining to antimicrobial resistance and a strategy to promote and facilitate the development and production of new generations of antimicrobials, the situation remains critical. In the 1990s, almost 20 companies were active in antimicrobial development around the world. At present, only GlaxoSmithKline and AstraZeneca are still among the world's pharmaceutical firms with antimicrobial testing programs [5,6].

In order to alleviate the global crisis of AMR and the shortage of antimicrobial drugs, the key point of the 2014 Commission chaired by the former Goldman Sachs economist Jim O'Neill was to stimulate antimicrobial researches and innovations with active incentives [7]. Nevertheless, hurdles or obstacles remain [8]. Firstly, in terms of incentives, pharmaceutical companies are gradually abandoning antimicrobial research teams in favour of fields that may not be 'easier' to explore but certainly have better economic returns as the process of discovery is time-consuming and expensive [5]. For example, compared with less than 50 antimicrobial products, almost 800 new drugs were produced in 2014 in the field of oncology [6]. Secondly, the financial assistance offered may be overdue or the determination of the appropriate amount of bonus could be difficult and eventually, all risks are borne by governments or other investors [9].

As for the current regional policies such as the Generating Antibiotics Incentives Now (GAIN) Act in the USA, and the Innovative Medicines Initiative (IMI) in Europe, the economic stimulus packages are inadequate and burdensome, even though initiatives have been suggested to boost the production channels for new antimicrobials [5,9]. For instance, the GAIN Act does not address antimicrobial stewardship measures [10]. Without the effective management of new antimicrobials, they are mostly used as a last resort therapy, which is impossible to obtain benefits for market exclusivity [11]. In the absence of sufficient usage of new antimicrobials, consequently, the effective life of new antimicrobials was shortened, and the reward impact of the GAIN Act was decreased due to the resistance condition aggravated by the abuse of antimicrobials [8]. Only if push and pull strategies operate together in the drug development environment will the best incentives be accomplished.

2.2 Manufacturing and Purchase Stages

With regard to AMR, different political parties have their respective positions. Three types of welfare states are recognized, including liberalism, social democracy, and nationalism, among which neo-liberalism is characterized by the highest level of commodified services that

are extremely distinctive and wide in scope and advocates less interference from the state. Therefore, interfering in strategies to minimize AMR in a neoliberal environment faces many challenges.

Although the role of the free market is emphasised in the neoliberal theory, the absence of external intervention is likely to cause severe consequences in the case of antimicrobial resistance as with the initial commercialisation of penicillin and many other antimicrobial compounds. In the 1940s, a vast number of pharmaceutical companies participated in the development of antimicrobials and the price of unpatented medications such as penicillin plummeted as funding grew. With the great demand for penicillin daily products, such as toothpaste, makeup, and other forms of consumer necessities, pharmaceutical firms have expanded the market under the guise that penicillin could not only cure bacterial infections but also benefit healthy people by preserving the efficacy of removing daily germs. After successfully inventing and patenting new antimicrobials, they increased their investment in the pharmaceutical industry and raised the price of these antimicrobials, as well as their manufacturing volumes regardless of the need. As a consequence, in the 1960s, many needless medications emerged in the market, resulting in a pattern that lasted until antimicrobial research programmes dried up in the 1980s when the pharmaceutical industry turned its focus to other more lucrative drugs [12].

Neoliberalism probably provides the overarching philosophy for the analysis of these economic developments in relation to AMR, affecting the restricted or counter-productive role of governments in facilitating actions that effectively regulate AMR [12].

Furthermore, the relationship between the industry output and the market demand is not completely exploited in neo-liberalism to tailor production according to changes in the market demand. One successful case is the ban on the use of antimicrobials on cattle by Namibia after its European consumers refuse to eat food-borne meat antimicrobials. It is a rare example of Namibia's prompt modification of its approach to market demand so as to sustain its sales market and reduce its AMR [13].

2.3 Operation and Provision Stages

Based on their ownership, major stakeholders in operation and provision stages can be divided into two categories, namely the public and private health sectors. What needs to be made clear is that private clinics and doctors act as operators and providers in the private system, while in the public system, the government acts as an operator and the public health sector as a provider.

The last two decades have witnessed the tremendous expansion of the private health care sector, especially in South Asia where 80% of patients were expected to receive treatment in private hospitals and in India where 93% of health facilities were provided in private sectors [14]. Despite services provided by private sectors for individuals whose needs cannot be met by public organisations, there is a lack of effective regulation in private sectors when compared with the public health sector, especially in Low- and Middle-Income Countries (LMICs), which constitutes a severe threat of AMR [15]. Firstly, differences in the quality of clinics have widened gaps in access to health services [16]. In most South Asian countries such as Pakistan and Bangladesh, few structures or tools are available for tracking and controlling private sectors, leading to the fact that active institutions are operated by untrained providers [14]. Secondly, it is a normal phenomenon that untrained or inexperienced individuals run pharmacies because of the limited control over the qualification for the sale of specific types of drugs, which directly leads to misdiagnosis, confusion, or inadequacy. Thirdly, commercial companies prefer to store a vaster array of antimicrobials than municipal hospitals without the desire to indiscriminately administer or prescribe them. In addition, the sale of antimicrobials on the internet as a form of online privatisation is the same case. One survey showed that without prescriptions of antimicrobials, a third of the 138 separate vendors listed as antimicrobials suppliers were selling them. Fourthly, doctors with the lowest credentials were found to have the lowest fees in general. However, they saw the largest number of vulnerable patients at the risk of infectious diseases, including Tuberculosis (TB), HIV, and Malaria [14]. Fifthly, the poor quality of medicines and the profit margins between various clinics intensify the pressure for options, leading to a flood of substandard and spurious medicines into the market. According to the statistics, the annual sales of falsified and adulterated pharmaceuticals in Peru and Columbia were about $66 million and $60 million, respectively [15]. In accordance with the above five points, it can be concluded that private organisations lacking monitoring and management systems are more likely to have issues in the diagnostic process that may form an anti-microbial resistance vicious circle (Figure 2).

The public health care sector faces multiple challenges caused by the local political structure, economic status, and social patterns. First and foremost, universal health promotion strategies, namely Infection Prevention and Control Interventions (IPCIs) proposed by WHO, have gained success in some domains in LMICs. For example, washing hands with soap in Karachi, Pakistan has not only halved diarrhea and acute respiratory infections but also decreased the occurrence of pustules that would require

antimicrobials by 30% [15]. However, the implementation of such strategies remains difficult as there is a frequent lack of access to even simple mechanisms, as well as a poor empirical base to justify their incorporation into such healthcare contexts [17]. Furthermore, government investment in infrastructure is far from being adequate. In spite of the importance of water and water-related devices for alleviating the transmission of AMR bacteria, basic clean water, sanitation, and hygiene facilities are not well-established in parts of developing countries to cut off AMR's environmental transmission pathways [18,19]. For example, open defecation is still occurring in many heavily populated areas such as India. More industrialised countries such as the United States and the UK are facing ageing facilities and the demand for more sophisticated and sustainable water treatment technologies [18].

2.4 Consumption Stage

In order to reduce AMR, WHO presented an international action plan in 2015, one of the strategic objectives of which is 'to improve awareness and understanding of antimicrobial resistance', and steps have been taken by several nations, such as the European Antibiotic Awareness Day campaigns [20,21]. However, surveys (Table 1) of the public's knowledge and perceptions about AMR from four typical countries (Sweden, USA, Japan, Nigeria) revealed that there were still many obstacles in the consumption process of antimicrobials in both the Global North and the Global South areas. Despite the limitations of the surveys due to the sample size and respondent bias, they still have a reference value.

At first, consumers had poor knowledge of the appropriate use of general antibiotics.

They did not know when antibiotics should be used. In Japan, for example, only 22% of respondents recognised that antibacterial medications could not kill viruses and 45.5% of them obtained antibiotics due to the cold [22]. In the United States, almost 40% of respondents felt that antibiotics were the best way to treat cold symptoms and the proportion was 13.4% in Sweden where AMR was low [23,24].

They did not know how to choose the right antibiotics. According to the Nigerian report, people tended to purchase and use the same antibiotics that had cured their previous diseases [25].

They did not know how to use antibiotics correctly. For example, about 26.1% of Nigerian participants avoided taking antibiotics when they felt better instead of taking all them as instructed [25]. Also, 23.6% of Japanese participants reported the halt or adjustment of their antibiotic doses on their own [22].

Next, storing antibiotics were more common in developed countries with a 31% storage rate in Nigeria compared to 12% in Japan [22,25]. Preserving antibiotics could be a temptation of self-use (e.g., self-treatment, avoidance of flu) but improper storage and expired antibiotics may lead to allergic reactions and increase the possibility of sharing them with others.

Besides, the persistent absence of information by patients will produce an unfair interaction with doctors. As mentioned above, people could rely on professors who might be more susceptible to external factors such as pharmaceutical firms to prescribe profit-related or counterfeit drugs [26].
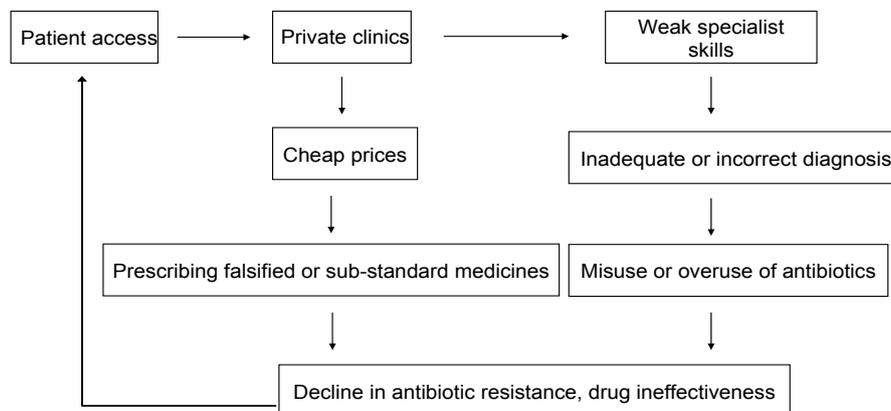

Figure 2. An Anti-microbial Resistance Vicious Circle

Table 1. Surveys from Four Countries of Public's Perceptions and Knowledge about AMR

Country	Swedish	America	Japan	Nigeria
Characteristics	Global North low AMR	Global North	Global North	Global South
Subjects of Survey	public	public	public	public
Number of participants	1426	215	3390	482
Agree that antibiotics cannot effectively fight against viruses (%) (right statement)	77%	70%	22%	
Agree that antibiotics can effectively fight against cold and flu (%) (wrong statement)	13%	less than 25%	three-quarter (75.4%)	44%
Store antibiotics (%)			12%	31%
Level of knowledge of the relevant terms	29.50% of interviewees are with accurate knowledge.		4 out of 10 interviewees had heard the term 'AMR'.	8.3% of interviewees are with accurate knowledge; 7.3% of interviewees had heard the term 'AMR'; 56.45% of interviewees had heard the term 'antibiotic resistance'; 46.9% of interviewees had heard the term 'drug resistance'; 17% of interviewees had heard the term 'AMR'.
Use over the counter (OTC) antibiotic drugs (%)			3%	2%
The most common source of information about AMR		Television and the Internet	TV news or newspapers (25.7%) doctors (19.1%).	doctors/nurses (50%) pharmacists (31.3%) specific campaigns (8.5%) media (9.8%)

3. Conclusions

This article has discussed the challenges of AMR in state intervention under interest structure from six perspectives (developing, manufacturing, purchasing, operating, providing, consuming) based on the use of antimicrobial drugs.

Owing to a lack of consistency in the government's external division of labor and inadequate domestic economic recovery measures, the research and development process of new antimicrobials has stagnated.

A free market between production and purchase was established in a neo-liberal atmosphere, and the principle of benefit was encouraged above all else. However, the AMR proved to be worse and worse without government interference, making clever use of the relationship between production trends and market demand.

In recent years, private clinics have become more prev-alent as a cornerstone of the operating phase, but the lack of effective government regulatory policies and institutions, particularly in countries with low and medium incomes, has led to a vicious circle of untrained or inexperienced providers mixing and creating AMR.

The government, as an operator, uses interventions such as policy implementation and the distribution by the public health sector of basic services such as vaccines and sanitation to minimize the spread of infectious diseases in public systems, but this remains difficult to do in the near term due to discrepancies between countries.

Countries have used social marketing ads to fulfill the WHO 2015 strategic plan to 'improve awareness and understanding of antimicrobial resistance', but a review of surveys from four typical countries reveals that there is still a long way to go to meet customers with AMR expertise.

In order to achieve checks and balances in the interests

of society as a whole, the government, as the most powerful mediator in the whole process, should limit the intentions of abusive subjects by fostering anti-abuse subjects and provide awareness and intelligence to support the acts of anti-abuse subjects by partially or completely opening up information channels.

It should be noted that this paper has been primarily concerned with the point of view of human health; what is needed in the future directions are cross-national studies involving strategic policy analysis of plants and animals to provide more possibilities for addressing anti-microbial resistance.

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