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Control of antibiotic resistance in China must not be delayed: The current state of resistance and policy suggestions for the government, medical facilities, and patients

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Summary **Antibiotics are medicines used to prevent and treat bacterial infections. Antibiotic resistance occurs when bacteria change in response to the use of these medicines. Antibiotic resistance is rising to dangerously high levels in all parts of the world, leading to higher medical costs, prolonged hospital stays, and increased mortality. In the European Union alone, drug-resistant bacteria are estimated to cause 25,000 deaths and cost more than US$1.5 billion every year in healthcare expenses and productivity losses. The problems of antibiotic misuse and antibiotic resistance are quite serious in China. In 2015, results of a study by the State Key Laboratory of Organic Geochemistry, Guangzhou Institute of Geochemistry, Chinese Academy of Sciences indicated that the total antibiotic usage in China in 2013 was approximately 162,000 tons, including human use (48%) and use in animals (52%). This amount accounted for about half of the antibiotic usage worldwide. The per-capita use of antibiotics in China is more than 5 times that in Europe and the United States. These data mean that China is one of the world's leading countries with serious problems in terms of antibiotic misuse and antibiotic resistance. The current article analyzes the current state and harms of antibiotic misuse and causes of antibiotic resistance in China. The Government needs to pay close attention to the issue of antibiotic resistance in China and formulate a strategy at the national level. Thus, the following suggestions are offered: *i*) The Chinese Government should implement policies that promote antibiotic research and development; *ii*) Medical facilities in China should create multidisciplinary teams (MDTs) and encourage early action by MDTs to control the spread of multi-drug-resistant bacteria (MDRB); *iii*) An intervention in the form of health education should target patients and accompanying family members (AFM) in China. In other words, antibiotic resistance is not a personal problem but an urgent public health problem. Without urgent action, China is heading for a post-antibiotic era in which common infections and minor injuries can once again kill. Therefore, the aforementioned proposals have been offered with the hope that policy suggestions help to limit the phenomenon of antibiotic misuse and antibiotic resistance in China.**

Keywords: Antibiotic resistance, antibiotic misuse, China

1. Introduction

The early 20th century was a time of ground-breaking scientific progress. One major advance was the development of penicillin and other antibiotics that have prevented thousands and even millions of people from dying of bacterial infections. The ability to treat diseases played a key part in increasing life expectancy and improving human health, but diminished ability to combat infections may lead to an acceleration of antimicrobial resistance the 21st century (*1*).

Antibiotics are medicines that are used to prevent and treat bacterial infections. Antibiotic resistance occurs when bacteria change in response to the use

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of these medicines (*2*). Antimicrobial resistance has been detected in all parts of the world and is one of the greatest challenges to global public health today. Although antimicrobial resistance is a natural phenomenon, it is also being caused by misuse of antimicrobials, inadequate or inexistent programs for infection prevention and control (IPC), poor-quality medicines, limited laboratory capacity, inadequate surveillance, and insufficient regulation of the use of antimicrobials (*3*).

Antibiotic resistance is rising to dangerously high levels in all parts of the world. New mechanisms of resistance emerge and spread globally every day, threatening our ability to treat common infectious diseases. A growing list of infections – such as pneumonia, tuberculosis, blood poisoning, and gonorrhea – are becoming harder, and sometimes impossible, to treat as antibiotics become less effective (*4*). In addition, antibiotic resistance leads to higher medical costs, prolonged hospital stays, and increased mortality. In the European Union alone, drug-resistant bacteria are estimated to cause 25,000 deaths and cost more than US$1.5 billion every year in healthcare expenses and productivity losses (*5*).

The problems of antibiotic misuse and antibiotic resistance are quite serious in China. Yang Zhiyin, the chairman of the behavioral medicine branch of the Chinese Medical Association, noted that about 200,000 people died due to adverse drug reactions, 40% of which were due to antibiotic misuse. In addition, antibiotic use per capita is about 138 grams in China but only 13 grams in the US. These data mean that China is one of the world's leading countries with a serious problem of antibiotic misuse (*6*). Without urgent action, China is heading for a post-antibiotic era in which common infections and minor injuries can once again kill. This article describes the current state of antibiotic resistance in China and it describes the international experience of the World Health Organization (WHO) in order to put forward policy suggestions for the Chinese Government, medical facilities, and patients and their family members.

2. Antibiotic resistance in China

The total use of antibiotics in China tends to be "unknown" because there is no authoritative source of data at the national level. In 2015, however, the results of a study by the State Key Laboratory of Organic Geochemistry, Guangzhou Institute of Geochemistry, Chinese Academy of Sciences indicated that the total antibiotic usage in China in 2013 was approximately 162,000 tons, including human use (48%) and use in animals (52%). This amount accounts for about half of the antibiotic usage worldwide. The per-capita usage of antibiotics in China is more than 5 times that in Europe and the United States (*7*). Thus, the Government needs to pay close attention to the issue of antibiotic resistance in China and formulate a strategy at the national level.

2.1. *Current state of antibiotic misuse in China*

2.1.1. *Irrational use in clinical settings*

Because of information asymmetry in medicine, physicians tend to be the indirect selectors and purchasers and of drugs, largely influencing the rational use of antibiotics through their prescribing behavior. However, irrational use of antibiotics in clinic settings is a major factor for antibiotic misuse in China. This phenomenon is apparent in the following three aspects.

i) *Incorrect drug selection*. Physicians cannot prescribe antibiotics "where indicated" since most physicians prescribe based on their own experiences, and a study has reported that pathogens are detected in inpatients at a rate of 16.5% (*8*). In addition, the commercialization of medicine has led some physicians to use expensive drugs out of self-interest. Some physicians tend to prescribe new or imported drugs to avoid complications, but these drugs may have difficulty producing the desired effect and they can more easily produce antibiotic resistance. In addition, a study found that 93.7% of all infusions given to outpatients were given to children and that 97.3% of all infusions given to children included antibiotics (*9*).

ii) *Incorrect drug dosing*. There are many phenomena and problems with incorrect dosage when antibiotics are used in clinical practice, such as irrational dosing, courses, and drug combinations. Data from the World Health Organization (WHO) indicated that antibiotic utilization was as high as 80% in inpatients and 95% in surgical departments, which far exceeded the international standards of 30% and 22-25% in the West (*10*). In addition, a retrospective study of antibiotic use in 1,688 patients indicated that antibiotic utilization was 74.76% (*11*). However, an antibiotic susceptibility test was performed for 6.09% of those patients, 38.04% of patients lacked definite symptoms or had mild symptoms, 31.31% of patients received more than two antibiotics, 9.09% of patients received antibiotics for a prolonged period, 8.08% of patients frequently received different antibiotics, and 7.40% of patients received an improper combination of antibiotics.

iii) *Poor monitoring of prophylaxis*. At present, antibiotics are too often used for perioperative prophylaxis in different departments of medical facilities. For insurance purposes, antibiotics have become an essential medicine in surgery. A study of 1,235 patients in a hospital in Guangdong found that the rate of antimicrobial use was 100% in Surgery, Gynecology, and Ophthalmology (*12*).

2.1.2. *Irrational antibiotic use by patients*

Patients are not merely a victim of antibiotic misuse

but are also responsible for the acceleration of antibiotic resistance. A WHO multi-country survey revealed widespread public misunderstanding about antibiotic resistance (*13*). One thousand and two online interviews of Chinese yielded the following findings: *i*) 57% of respondents reported taking antibiotics within the past 6 months; 74% say they were prescribed or provided the antibiotic by a doctor or nurse; 5% say they purchased them on the Internet, *ii*) More than half (53%) of respondents wrongly believed that they should stop taking antibiotics when they felt better, rather than taking the full course as directed, *iii*) 61% of respondents thought, incorrectly, that colds and flu can be treated by antibiotics, *iv*) Two-thirds (67%) of respondents were familiar with the term "antibiotic resistance" and three quarters (75%) said it is "one of the biggest problems in the world," and *v*) 83% of respondents said that farmers should give fewer antibiotics to animals – the highest proportion of any country in the survey.

2.1.3. *Irrational antibiotic use in animal husbandry*

Annually, 97,000 tons of antibiotics are used in animal husbandry in China, accounting for 46.1% of all antibiotics used per year. Thirty percent of these antibiotics were used as feed supplements and 10% were used to treat diseases in livestock. A study has revealed that antibiotic metabolites are found in 50% of the animal foods and dairy products in Chinese supermarkets, including prohibited drugs such as chloramphenicol, tetracyclines, sulfonamides, and nitrofurans (*14*). In addition, a study by the East China University of Science and Technology in 2014 indicated that there are 68 antibiotics in surface water in China (*15*).

2.2. *Harms of antibiotic misuse in China*

2.2.1. *The creation of multi-drug resistant bacteria (MDRB)*

Antimicrobial resistance occurs when microorganisms such as bacteria, viruses, fungi, and parasites change in ways that render the medications used to cure the infections they cause ineffective. When the microorganisms become resistant to most antimicrobials, they are often referred to as "superbugs." This is a major concern because a resistant infection may kill, it can spread to others, and it imposes huge costs on individuals and society (*16*).

The 2015 *Report on Monitoring of Bacterial Drug Resistance* in China indicated that a total of 2,400,786 strains of bacteria were detected from October 2014 to September 2105 (*17*). These strains included 695,066 strains of Gram-positive bacteria (28.9%) and 1,705,720 strains of Gram-negative bacteria (71.1%). The top ten bacteria that were detected are listed in Figure 1.

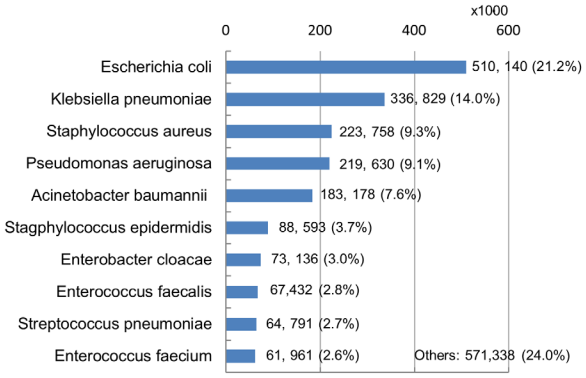

Figure 1. Bacterial drug resistance monitoring repott of China in 2015.

Antimicrobial resistance is the broader term for the resistance of different types of microorganisms to antibacterials, antivirals, antiparasitics, and antifungals. Antimicrobial resistance has become a leading public health problem. Ciprofloxacin was efficacious and caused few adverse reactions 20 years ago, but it is now inefficacious in more than 60% of patients (*18*). In addition, a study from UK has found that failure to find ways to cope with multi-drug resistant bacteria (MDRB) will result in the deaths of 10 million people and loss of US$ 100 trillion worldwide. Data have revealed that 80,000 people have died due to antimicrobial resistance in China (*19*). If this situation persists, it will lead to the death of 1 million people in China in 2050.

2.2.2. *Causing nosocomial infection (NI)*

A nosocomial infection (NI) is an "infection that is acquired in the hospital and becomes evident after hospital discharge" and that "was not present neither was incubating at the moment of patient admission at a hospital" (*20,21*). Several studies have investigated the mortality rate in patients developing a postoperative infection in General Surgery, and they noted a mortality rate of 7.5% in patients with a single-pathogen nosocomial infection and a mortality rate of 17.1% in patients with a multiple-pathogen mixed infection (*22*). The occurrence of an NI is a serious threat to the patient's health and also increases the burden of medical care on the patient's family (*23,24*).

2.2.3. *Difficulties of innovative drug research and development*

Although new antibiotics have emerged, antibiotic development lags behind the pace at which bacteria develop drug resistance; development of a new antibiotic takes 10 years while bacteria develop resistance in only 2 years (*25*). Since the 1980s, no new antibiotics have been discovered or synthesized except daptomycin. According to the WHO, there are some new antibiotics

Table 1. Steps at all levels of society to reduce the spread of drug resistance according to the WHO

Positions	Actions
General public	• Preventing infections by regularly washing hands, practicing good food hygiene, avoiding close contact with sick people and keeping vaccinations up to date. • Only using antibiotics when prescribed by a certified health professional. • Always taking the full prescription. • Never using left-over antibiotics. • Never sharing antibiotics with others.
Health workers and pharmacists	• Preventing infections by ensuring hands, instruments and environment are clean. • Keeping patients' vaccinations up to date. • When a bacterial infection is suspected, perform bacterial cultures and testing to confirm. • Only prescribing and dispensing antibiotics when they are truly needed. • Prescribing and dispensing the right antibiotic at the right dose for the right duration.
Policymakers	• Having a robust national action plan to tackle antibiotic resistance. • Improving surveillance of antibiotic-resistant infections. • Strengthening infection prevention and control measures. • Regulating and promoting the appropriate use of quality medicines. • Making information on the impact of antibiotic resistance available. • Rewarding the development of new treatment options, vaccines and diagnostics.
The agricultural sector	• Ensure that antibiotics given to animals - including food-producing and companion animals - are only used to treat infectious diseases and under veterinary supervision. • Vaccinate animals to reduce the need for antibiotics and develop alternatives to the use of antibiotics in plants. • Promote and apply good practices at all steps of production and processing of foods from animal and plant sources. • Adopt sustainable systems with improved hygiene, biosecurity and stress-free handling of animals. • Implement international standards for the responsible use of antibiotics, set out by OIE, FAO and WHO.
The healthcare industry	• Investing in new antibiotics, vaccines, and diagnostics.

in development, but none of these are expected to be effective against the most dangerous forms of antibiotic-resistant bacteria.

2.3. *Reasons for antibiotic misuse and antibiotic resistance in China*

2.3.1. *Inadequate government oversight and a lack of policy incentives for new drug research and development*

Although the Ministry of Health of China has issued standards and regulations stipulating limited use of antibiotics in medical facilities, the Government failed to control the sales of antibiotics, causing a "market boom" in antibiotics. Despite the serious state of research into new antibiotics, the Government has not legislated clear and definite incentives for new antibiotic research and development.

2.3.2. *Improper dosing by physicians*

Improper dosing by physicians in China is mainly due to: *i*) physicians relying on their own experiences, *ii*) a low level of expertise; *iii*) the need to protect at-risk patients, and *iv*) a dearth of clinical pharmacists. A study of drug selection by physicians indicated that 35% of physicians selected a drug based on their own experiences and 80% selected a drug without being sure of its type or whether its use was sanctioned by the government (*26*).

2.3.3. *Patient factors*

Many patients tend to misuse antibiotics by taking them on their own and failing to comply with instructions because of their lack of medical knowledge and misconceptions. A study found that 23% patients took medication on their own over the past year and 25.1% failed to follow a doctor's advice.

3. Policy suggestions for the Chinese Government

3.1. *International experience of the WHO*

In countries where antibiotics can be bought without a prescription, the emergence and spread of resistance is worse according to the WHO. Similarly, antibiotics are often over-prescribed by health workers and over-used by the public in countries without standard treatment guidelines.

Given the ease and frequency with which people now travel, antibiotic resistance is a global problem, requiring efforts from all nations. Antibiotic resistance is accelerated by the misuse and overuse of antibiotics, as well as poor infection prevention and control. Steps can be taken at all levels of society to reduce the impact and limit the spread of resistance (Table 1).

3.2. *Government: Policy incentives for new drug development*

The Government of China should adopt policy incentives to promote antibiotic research and development. A model could be the *Generating Antibiotic Incentives Now Act* (GAIN Act). In the US, the Senate examined and adopted the *Food and Drug Administration (FDA) Safety and Innovation Act*, which featured the GAIN Act to encourage pharmaceutical companies and biotechnology firms to research and development innovative antibiotics. The Act provides that qualified infectious disease products (QIDP) can qualify for incentives, which include *i*) fast-tracking in the research stage, *ii*) priority review in the approval stage, and *iii*) patent exclusivity for an additional five years post-marketing. In addition, the GAIN Act requires the FDA to release at least 3 guidelines on clinical research into antibacterials every year and timely updates. Using these incentives, the FDA has awarded 28 QIDP qualifications, and 4 have (Dalvanc, Sivextro, Orbactiv, and Zerbaxa) have been approved by FDA and are now publicly available (*27*).

In addition to the GAIN Act, the FDA relaxed the requirements for clinical trials of antibiotics but specified a narrow range in order to prevent their misuse. In addition, the US has also established a plan for antibiotic research and development, which means that the Government provides financing for companies and it established a fund for loans to small and medium-sized enterprises (*28*).

In the value chain of drug research and development, scientific, funding, and review obstacles can all influence innovation by pharmaceutical companies and research institutes, while policy incentives can mitigate the effects of those obstacles to some extent. Therefore, the Chinese Government should implement policies that promote antibiotic research and development.

3.3. *Medical facilities: A multidisciplinary team (MDT) model*

An MDT is a group composed of members from different healthcare professions with varied but complimentary experience, qualifications, and skills that contribute to the achievement of an organization's specific objectives. An MDT approach is usually used in cancer care and has been widely accepted throughout much of Europe and the US (*29*). An MDT improves coordination and communication among and decision-making by team members and could help to reduce NIs caused by MDRB.

A growing number of hospitals in China have created MDTs for diagnosis and management of care. However, most of these teams provide specific consultations, so they have difficulty serving all departments at the same time. If a patient has a disease that is treated by a different department, a transfer would cause increased bureaucracy and a financial burden for the patient. Hence, medical facilities in China should create MDTs and encourage early action by MDTs to control the spread of MDRB (*30*).

3.4. *Patients and accompanying family members (AFM): Intervention in the form of health education*

Due to insufficient nursing personnel, the ratio of doctors to nurses of China was 1:1.04 in 2014, which is far below the standard of developed countries (*31*). For the most part, nurses provide treatment, basic nursing, and perform administrative work in China, so they have difficulty meeting the emotional and livelihood needs of patients. The presence of family members accompanying patients (accompanying family members, or AFM) tends to be a phenomenon specific to China, and an intervention in the form of health education is a key factor for MDRB control in China (*32*).

Health education for inpatients and AFM should: *i*) Instruct patients in the correct way to cough, *ii*) encourage patients to become mobile as early as possible, *iii*) instruct the patient's family on turning the patient over and the correct way to tap the patient on the back, *iv*) instruct the patient in assisting with elimination, and *v*) encourage the patient to drink more water to replenish bodily fluids and prevent dry phlegm.

Given the current state of AFM in China, the following points should be observed. *i*) Rules and regulations should be devised to govern AFM, *ii*) a unified management system should be created for professional caregivers, and *iii*) one option for AFM could be to supplement the care provided by professional caregivers.

4. Conclusion

In summary, this article has described the accelerated development of antimicrobial resistance around the world. The problems of antibiotic misuse and antibiotic resistance are quite serious in China. The current state of resistance and its harms and the causes of antibiotic misuse in China have been described in detail. Policy suggestions for the Chinese Government, medical facilities, and patients and their family members have been offered in the hopes that these efforts will limit the phenomenon of antibiotic misuse and antibiotic resistance in China.

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