

# THE ACTIONS OF CHINA IN CONTAINING ANTIMICROBIAL RESISTANCE

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Bacterial resistance is a serious problem in China. In 2011, the Chinese government began a three-year special campaign for rational antibiotic use centred on the “Administrative Regulations for the Clinical Use of Antibiotics”, which integrated successful domestic and international experiences and defined all aspects of antibiotic use in hospitals. The regulations outline the roles, responsibilities and liabilities of health administrative authorities, medical institutions, hospital task forces and all categories of health-care professionals in detail. It also proposed antibiotic stewardship as a basic management concept and asked medical institutions to build professional teams, implement staff training, and establish and improve the technological systems supporting rational antibiotics use. Some indicators were defined and targets set for institutions. Surveillance from tertiary hospitals between 2010 and 2012 showed that the proportion of outpatients receiving prescriptions for antibiotics decreased from 22% to 14.7%, and that of inpatients decreased from 68.9% to 54%, and the use of antibiotic prophylaxis in surgical procedures decreased from 95% to 44.6%. Massive governmental effort and regulatory support could improve antibiotic use in a large country like China in a relatively short time.

Bacterial resistance is a serious problem in China (1). Surveillance data show that the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in clinical isolates in tertiary hospitals is approximately 50% and that more than 80% of *S. aureus*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes* were resistant to macrolides and clindamycin. Among Gram-negative bacteria, approximately 70% of *Escherichia coli* isolates were resistant to ciprofloxacin and approximately 60% were resistant to third-generation cephalosporins. Glucose nonfermenting Gram-negative bacteria such as *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Stenotrophomonas maltophilia*, and *Burkholderia* spp. were the second most frequent clinical isolates. Carbapenem-resistance was seen in 20%–35% of *P. aeruginosa* and in more than 50% of *Acinetobacter baumannii*. Although China is a vast country with large regional differences in socioeconomic development, there were no significant differences in bacterial resistance among the various geographical regions (1, 2). Bacterial resistance has created a serious socioeconomic burden throughout China (3), and the prevalence of resistant strains of several

bacteria with public health importance continues to increase or remain at high levels (Fig. 1).

Antibiotics have been the most frequently used medicines in Chinese health-care facilities, and account for approximately 20% of all drug sales by general hospitals. Inappropriate use of antibiotics has also been very common in health-care settings. The overall proportion of outpatients prescribed antibiotics in 2002–2012 was 50.3%, and was 47.1%, 49.2% and 53.4% in tertiary, secondary and primary care institutions, respectively (4). Surveillance data from 15 tertiary hospitals in four central cities in China in 2007 indicated that 49.1% of nonsurgical and 94.6% of surgical inpatients received antibiotic therapy or prophylaxis (5). The situation in rural clinics was even more serious. In those settings, 48.4% of prescriptions for outpatients in western China in 2008 were for antibiotics, and the prescribing physicians preferred broad spectrum and newly marketed agents, such as cephalosporins or fluoroquinolones (6). Such extensive use of broad spectrum antibiotics is likely to accelerate the development of bacterial resistance (7).

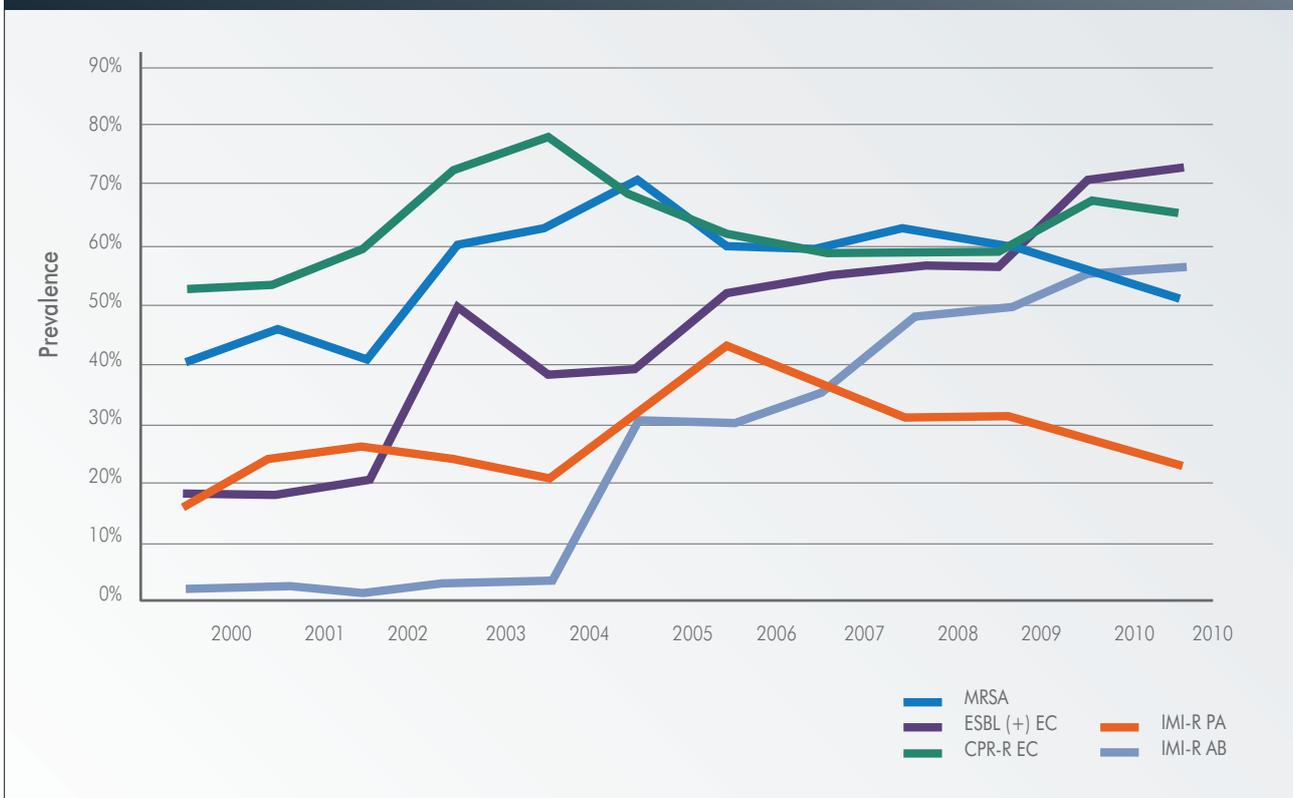
Table 1: Content and purposes of the national antibiotics stewardship system in China

Field	Time	Policies and actions	Main activities and goals
1. Talent team	2003	Set up infectious disease units in hospitals	<ul style="list-style-type: none"> <li>• Diagnosis and treatment of infectious diseases</li> <li>• Antibiotic stewardship and control of drug resistance</li> <li>• Dealing with emerging &amp; re-emerging infectious diseases</li> </ul>
	2007	Launch pilot programmes for clinical pharmacists	<ul style="list-style-type: none"> <li>• Consult on medicinal treatment</li> <li>• Prescription review and feedback</li> <li>• Therapeutic drug monitoring</li> <li>• Patient consultation of drug use</li> </ul>
	2008	Organize the Expert Committee of Drug Rational Use of the Ministry of Health	<ul style="list-style-type: none"> <li>• Counseling the government for drug rational use</li> <li>• Making recommendations and strategies for drug rational use</li> <li>• Investigation &amp; monitoring of drug use</li> <li>• Training &amp; education for rational drug use</li> </ul>
2. Legislation and policies	2002	Temporary Rules for Pharmaceutical Affairs in Health-care Institutions	<ul style="list-style-type: none"> <li>• Establishing clinical pharmacist system in health-care institutions</li> <li>• Setting up drug therapeutics committee (DTC) in hospitals</li> <li>• Regulating the full-procedure management of medicine in hospitals</li> <li>• Pharmacovigilance</li> </ul>
	2006	Administrative Regulations for Nosocomial Infections	<ul style="list-style-type: none"> <li>• Assigning responsibility of nosocomial infection control in each health-care sector</li> <li>• Monitoring, supervision and control strategies on control of nosocomial infection and antimicrobial resistance</li> <li>• Legal responsibility for violating the regulations</li> </ul>
	2007	Administrative Regulations for Prescription	<ul style="list-style-type: none"> <li>• Accrediting prescription rights for physicians</li> <li>• Standardizing prescription procedures</li> <li>• Monitoring and supervising prescriptions</li> <li>• Legal responsibility for violating the regulations</li> </ul>
	2012	Administrative Regulations for Clinical Use of Antibiotics (see also Table 2)	<ul style="list-style-type: none"> <li>• Assigning personal, institutional and governmental liability in antibiotic use</li> <li>• Strategies and support systems for rational use of antibiotics</li> <li>• Administrative penalties and legal responsibilities for violating the regulations</li> </ul>
3. Technological specification and guidance	2004	Principles for the clinical use of antimicrobials	<ul style="list-style-type: none"> <li>• Principles of antimicrobial rational use</li> <li>• Formulary restriction for antimicrobials</li> <li>• Pharmacological characteristics of primary antimicrobials and recommendations of antimicrobial therapies for common infections</li> </ul>
	2009	Notification on strengthening management of clinical use of antibiotics	<ul style="list-style-type: none"> <li>• Hierarchical management on antibiotics</li> <li>• Monitoring and alerts of drug-resistant bacteria</li> <li>• Antibiotic prophylaxis in surgical procedures</li> <li>• Benchmarking of fluoroquinolone use</li> <li>• Diagnosis and therapy of infections caused by the NDM-1-producing bacteria</li> </ul>
	2010	Guidance in diagnosis and therapy of pan-drug resistant <i>Enterobacteriaceae</i> infections	
	2011	Guidance for the prevention and control of multi-drug resistant bacterial infections	<ul style="list-style-type: none"> <li>• Strengthening measures to prevent and control MDR nosocomial infections</li> <li>• Monitoring MDR nosocomial infections</li> <li>• Rational use of antibiotics</li> <li>• National model formulary</li> </ul>
	2009, 2012	National formulary & National formulary (pediatric edition)	
	2009, 2012	National essential drug list (Elementary edition) & National essential drug list (2012 edition)	<ul style="list-style-type: none"> <li>• National essential drug lists containing 205 and 317 pharmaceuticals, respectively</li> </ul>
	2013	National guidelines for antimicrobial therapy	<ul style="list-style-type: none"> <li>• Empiric therapy for infectious diseases</li> <li>• Target therapy for microbial infections</li> <li>• Pharmacological characteristics and safety of antibiotics</li> <li>• Special points for antimicrobial therapy of pediatric infections</li> </ul>
4. Surveillance	2006	Surveillance network for the use of antibiotics in health-care institutions	<ul style="list-style-type: none"> <li>• The national monitoring network for antimicrobial use in hospitals (mainly in tertiary &amp; secondary hospitals)</li> </ul>
	2006	Ministry of Health National Antimicrobial Resistance Investigation Net (Mohnarin)	<ul style="list-style-type: none"> <li>• The national monitoring network for antibiotic resistance in hospitals (mainly in tertiary &amp; secondary hospitals)</li> </ul>
5. Education and training	2007	Training course for clinical pharmacists	<ul style="list-style-type: none"> <li>• There are more than 50 training sites, and more than 2,000 pharmacists have been trained to improve competency</li> </ul>

Table 1: Content and purposes of the national antibiotics stewardship system in China (continued)

Field	Time	Policies and actions	Main activities and goals
5. Education and training (continued)	2008	National training programme for clinicians in the rational use of antibiotics	Training 40,000 physicians in three years in basic theories and strategies of antibiotic use
	2009	Training programme for clinical microbiologists	Training 500 microbiologists from primary health-care institutions on theory and 100 microbiologists on site in practice during three years
	2010	Training course for physicians from primary health-care setting on the rational use of medicines	Training 20,000 physicians in five years on basic knowledge of rational antibiotic use

Figure 1: Resistance trends in the predominant antimicrobial-resistant bacteria in China from 2000 to 2011 (MRSA, Methicillin-resistant *Staphylococcus aureus*; ESBL (+) EC, extended-spectrum  $\beta$ -lactamase producing *Escherichia coli*; CPR-R EC, ciprofloxacin-resistant *Escherichia coli*; IMI-R PA, imipenem-resistant *Pseudomonas aeruginosa*; IMI-R AB, imipenem-resistant *Acinetobacter baumannii*).



### The national antibiotics stewardship system in China

The system includes five different fields, as shown in Table 1.

#### 1. The Talent Team: building the capacity for the rational use of antimicrobial agents.

##### Infectious disease units in hospitals

After the outbreak of SARS in 2003, the Ministry of Health (MoH) asked medical institutions around the country to establish infectious diseases units to take responsibility for treating a variety of infectious diseases, the prevention and control of antibacterial resistance, and managing emerging infectious diseases. Most tertiary and some secondary hospitals have established these units, but their

effectiveness needs to be strengthened because most infectious disease physicians are still interested in, and occupied by, the management of common communicable diseases, such as viral hepatitis, tuberculosis and AIDS (8).

##### Institutionalizing clinical pharmacists in hospitals

In 2002, the MoH issued "Temporary Rules for Pharmaceutical Affairs in Healthcare Institutions", which required medical institutions to implement systems and personnel, including clinical pharmacists. Since then, more than 50 clinical pharmacist training centres have been established around the country. By this time, all tertiary hospitals and more than 50% of secondary hospitals already had clinical pharmacists, who engaged in patient drug

Table 2: Content of the “Administrative Regulations for Clinical Use of Antibiotics

Subjects	Responsibility	Tasks	The manner of the work	Penalty for violation
<b>Ministry of Health (MoH)</b>	<ul style="list-style-type: none"> <li>National management of clinical use of antibiotics</li> </ul>	<ul style="list-style-type: none"> <li>Making policies</li> <li>Setting targets</li> <li>Supervising and inspecting</li> </ul>	<ul style="list-style-type: none"> <li>Making and issuing policies</li> <li>Periodically setting management targets</li> <li>Setting up national surveillance networks of antibacterial resistance and antibacterial use</li> <li>Punishing local subsidiaries or MoH-owned health-care institutions that violate laws or policies</li> </ul>	
<b>Local health administrative authorities</b>	<ul style="list-style-type: none"> <li>Implementing the regulations and policies of MoH</li> <li>Supervising the use of antibacterials in local health-care institutions</li> </ul>	<ul style="list-style-type: none"> <li>Specifying the policies of MoH</li> <li>Defining the antibiotic category list</li> <li>Supervising and inspecting</li> </ul>	<ul style="list-style-type: none"> <li>Formulating and issuing the antibiotic category list</li> <li>Supervising hospital antibiotic formularies</li> <li>Supervising and inspecting antibiotic use in health-care institutions</li> <li>Setting up the local surveillance networks</li> <li>Punishing local health institutions that violate laws and policies</li> </ul>	<ul style="list-style-type: none"> <li>MoH will punish its local subsidiaries that violate the law or policies or are guilty of nonfeasance with criticism, warnings, demotion, or dismissing staff</li> </ul>
<b>Health-care institutions</b>	<ul style="list-style-type: none"> <li>Practicing the rational use of antibiotics in institutions</li> </ul>	<ul style="list-style-type: none"> <li>Following the laws and policies issued by MoH</li> <li>Achieving the targets set by MoH</li> </ul>	<ul style="list-style-type: none"> <li>Formulary restriction of antibiotics and accrediting physician antibiotic prescribing rights</li> <li>Selection and procurement of antibiotics</li> <li>Development of information systems on the rational use of antibiotics</li> <li>Setting targets for clinical departments</li> <li>Review and feedback of antibiotic prescriptions</li> <li>Medical staff and patient education</li> <li>Posting antibiotic use and prescription review reports</li> <li>Removing financial incentives for antibiotic use</li> <li>Punishing personnel who violate policies</li> </ul>	<p>Health-care authorities will punish the institutions or its administrators failing to comply with regulations through:</p> <ul style="list-style-type: none"> <li>nonconformity to facility quality control</li> <li>lowering the academic grade of the institution</li> <li>warning or dismissing the administrative staff</li> </ul>
<b>Physicians</b>	<ul style="list-style-type: none"> <li>Following the rational use of antibiotics in daily practice</li> <li>Infectious disease physicians are members of hospital antibiotic management teams</li> </ul>	<ul style="list-style-type: none"> <li>Patient therapy with rational antibiotic use</li> </ul>	<ul style="list-style-type: none"> <li>Accredit prescription rights of antibiotics with different antibiotic indications</li> <li>Rational treatment of patients with infectious diseases</li> <li>Taking continuing medical education courses on rational use of antibiotics</li> </ul>	<p>People who violate policies will be punished by:</p> <ul style="list-style-type: none"> <li>economic penalties</li> <li>lowering the level of antibiotics prescription rights</li> <li>suspending antibiotic prescription rights</li> <li>suspending the career promotion</li> <li>revoking physician's license</li> <li>legal liability to severe outcome</li> </ul>
<b>Pharmacists</b>	<ul style="list-style-type: none"> <li>The management and review of the use of antibiotics</li> <li>Members of the hospital antibiotic management team</li> </ul>	<ul style="list-style-type: none"> <li>Antibiotic dispensing</li> <li>Antibiotic prescription review and feedback</li> </ul>	<ul style="list-style-type: none"> <li>Antibiotic dispensing</li> <li>Antibiotic use consultations</li> <li>Antibiotic prescription review and feedback</li> <li>Public education</li> </ul>	<p>Persons who violate policies will be punished by:</p> <ul style="list-style-type: none"> <li>economic penalties</li> <li>suspension of drug-dispensing qualification</li> <li>suspension of career promotions</li> <li>legal liability to severe outcome</li> </ul>
<b>Microbiologists</b>	<ul style="list-style-type: none"> <li>Pathogen isolation and resistance surveillance</li> <li>Members of the hospital antibiotic management team</li> </ul>	<ul style="list-style-type: none"> <li>Microbiological diagnosis of infections</li> <li>Drug-resistance surveillance</li> </ul>	<ul style="list-style-type: none"> <li>Pathogen isolation and susceptibility testing</li> <li>Antibiotic use consultations</li> <li>Participating in national or regional resistance surveillance</li> <li>Providing regular reporting on hospital-resistance surveillance</li> </ul>	<p>Person to violate policies will be punished by:</p> <ul style="list-style-type: none"> <li>economic penalties</li> <li>suspension of career promotions</li> <li>administrative penalties, such as criticism or warning</li> </ul>

therapy, therapeutic drug monitoring and patient medication counseling. They were also responsible for the management of rational drug use and prescription review (9–11).

#### Organizing the Expert Committee for Rational Drug Use

To strengthen the management of rational drug use, the MoH set up the Expert Committee for Drug Rational Use (ECDRU) in October 2008. The main task of the ECDRU is to develop national rational drug use strategies, objectives and work protocols, to develop proposals for the national implementation of rational drug use practices, to study and formulate the clinical rational drug use measures and standards, and to organize education and training for drug rational use (12).

## 2. Regulatory mechanisms: Issuing rules and regulations for the rational antibiotic use and control of antibiotic resistance

From 2002 onwards, the Chinese MoH issued the following regulatory file for promoting drug rational use:

- ▶ (Temporary) Rules for Pharmaceutical Affairs in Healthcare Institutions (13,14);
- ▶ Regulations for Nosocomial Infections (15);
- ▶ Administrative Regulations for Prescriptions (16);
- ▶ Administrative Regulations for Clinical Use of Antibiotics (17).

## 3. Technical specifications of antibiotic rational use

From 2004 onwards, the Chinese MoH issued the following

technical guidelines and principles for promoting antibacterial agent rational use:

- ▶ Principles for the clinical use of antimicrobials and its supplementary rules (18,19);
- ▶ Guidance for specific infections (20);
- ▶ National Formulary and National Formulary (Pediatric Edition) (21);
- ▶ National Essential Drugs List (2009 Elementary Edition and 2012 Edition) (22,23);
- ▶ National Guidelines for Antimicrobial Therapy (24).

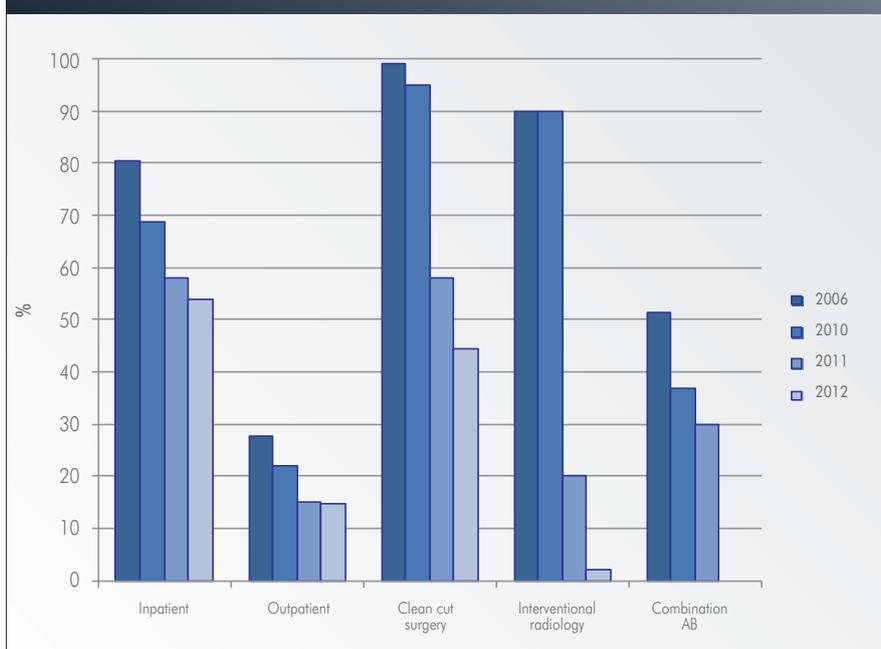
## 4. Antimicrobials consumption and bacterial resistance surveillance

In 2005, the MoH established hospital antibiotic consumption surveillance and bacterial resistance surveillance networks to link the prevalence of bacterial resistance to the rational use of antibacterials in medical institutions. Up to now, the member hospitals in the networks have expanded to more than 1,300, and include more than 800 tertiary hospitals and more than 500 secondary hospitals, and two-thirds of the provinces have networks that include all the tertiary and major county medical institutions (25, 26).

## 5. Education and training for rational antibiotic use

In recent years, national health administration authorities have led training programmes and continuing education courses in rational antibiotic use, including clinical pharmacist training, clinician antibiotic training and clinical microbiologist training for primary health-care practitioners that have enrolled more than 72,500 people in total.

Figure 2: Comparison of antibiotic prescription rates in various services before and after the special campaign



## National special campaigns to promote antibiotic rational use

In 2011, the MoH launched a three-year national campaign for antibiotic rational use in association with these health-care reforms. Considering international successes in fostering the rational use of antibiotics, the government used antibiotic formulary restriction as a core strategy, set management targets, conducted education and training and recommended rational antibiotic-use strategies to hospitals. The authorities then conducted

Textbox 1: Major strategies and targets of the annual special campaigns for rational antibiotic use from 2011 to 2013

### Step 1: Initiation (before May)

1. MoH issues protocol for the special campaign
2. MoH sets major targets and strategies:
  - a) Set up task force in health-care institutions (a professional working team: infectious disease physicians, clinical pharmacists and microbiologists);
  - b) Enforcing formulary restriction in health-care institutions;
  - c) Clinician training and antibiotic prescription rights accreditation in grades;
  - d) Building up electronic prescription systems in institutions;
  - e) Antibiotic resistance and utilization surveillance, prescription review;
  - f) Major targets for the campaign;
    - i. Antibacterial agents being stocked less than 50 or 35 in tertiary or secondary hospitals, respectively;
    - ii. Prescriptions with antibiotics for outpatients being < 20% ;
    - iii. Prescriptions with antibiotics for emergency patients being < 40%;
    - iv. Antibiotic-use rate for inpatients being < 60%;
    - v. Antibiotic prophylaxis use for surgical procedures being < 30%, and regimen rationality > 80%;
    - vi. Antibiotic utilizing intensity for inpatients being < 40DDD/100 patient days;
    - vii. Microbiological testing rate before antibacterial therapy being > 35% (in 2011) or > 50% (in 2012).

### Step 2: Implementation (the whole year)

1. Actions of local health administrative authorities:
  - a) Setting up directory for antimicrobial formulary restriction;
  - b) Formulating detailed rules for the campaign.
2. Actions in health-care institutions:
  - a) Setting up task force;
  - b) Conducting clinician training and antibiotic prescription rights accreditation in grade;
  - c) Setting antibiotic prescription privileges for each clinician in the prescription system;
  - d) Generating antibiotic formularies;
  - e) Setting up individual antibiotic target values for each clinical unit;
  - f) Professionals following antibiotics management strategy in daily work;
  - g) Carrying out supervision and monitoring of the use of antibiotics;
  - h) Antibiotic-resistance monitoring at institutions;
  - i) Antibiotic prescription review and feedback;
  - j) Penalizing clinicians and pharmacists for violating regulations.

### Step 3: Supervision and summary (September to December)

1. MoH supervises tertiary hospitals in central cities, and local health authorities supervise the others.
2. Composition of the supervision team (about five people): management staff, infectious disease physician, clinical microbiologist, clinical pharmacist and information specialist.
3. Focus of supervision;
  - a) Actions of task force for rational antibiotic use;
  - b) Measurement for promoting antibiotic rational use;
  - c) Implementation of formulary restriction;
  - d) Utilization of antibiotics in the institution;
  - e) Target values;
  - f) Technology support system: talents, surveillance and information system.
4. Reporting the results of supervision;
  - a) Feedback of the results to hospitals;
  - b) Medical institutions and their responsible persons with poor implementation or serious violation of regulation would be penalized;
  - c) Partial results will be available to the public.

supervisions and inspections to push the campaign forward by the end of each year, and any medical institutions and administrators, physicians and pharmacists who violated the regulations or failed to meet targets were penalized. The special campaign laid the foundation for establishing the sustainable development of rational antibiotics use and control of bacterial resistance control (see Textbox 1) (27, 28).

### Effects to date

Data from the hospital antibiotic consumption surveillance network in 2012 indicated that inappropriate use of antibiotics had significantly decreased (Fig. 2) (29). At the national level, the proportion of outpatients receiving antibiotic prescriptions dropped from 22% to 14.7% from 2010 to 2012. Similarly, the proportion of inpatients receiving antibiotics decreased from 68.9% to 54%, antibiotic prophylaxis in surgical procedures decreased from 95% to 44.6%, and combined antibiotic treatment with two or more agents decreased from 37% to 30%. The special campaign was obviously successful in both tertiary and secondary hospitals. A tertiary hospital in Hangzhou in eastern China reported that the prescription of antibiotics in emergency service patients, outpatients and inpatients declined from 58.4%, 39.6% and 68.9% to 46.3%, 22% and 39.2%, respectively. Inpatient antibiotic utilization intensity dropped from 65.6 DDD per 100 hospital days to 39.2 (30); the situation in

other regions of China was the same. A general hospital in Sichuan in western China witnessed decreases of 9.5% in hospital antibiotic sales, 15% in outpatient antibiotic prescriptions and 14.7% in inpatient antibiotic use. Inpatient antibiotic utilization intensity decreased by 44 DDD/100 patient days and antibiotic prophylaxis in surgical procedures decreased by 20.4% (31). The achievement in secondary hospitals was also exciting. A hospital in Shanghai reported that the inpatient antibiotic-use rate, antibiotic surgical prophylaxis and inpatient utilization intensity were 60.2%, 78.4% and 60 DDD/100 patient days in early 2011 and had fallen to 55.3%, 42.6% and 35 DDD/100 patient days, respectively, by September 2012 (32). Another county hospital in Guangzhou found that outpatient antibiotic prescriptions, inpatient antibiotic use and antibiotic surgical prophylaxis were 38.5%, 70.1%, and 80.1% in 2010 and 18.2%, 56.4%, and 29.9% in 2012, respectively (33).

### Summary

During past decades, the Chinese authorities have established a national antibiotic stewardship system, but the efficacy in promoting antimicrobial rational use was very weak because the rules, guidelines and surveillance were not mandatory. Inappropriate use of antibiotics in health-care institutions remained a common phenomenon. Beginning in 2011 with a new round of health-care reform in China, the

MoH issued new legislation and implemented a special campaign to promote the rational use of antibiotics. The new strategies included antibiotic formulary restriction in hospitals, setting up a task force, and law liability assignment. After three years, a substantial change has been observed in most of the hospitals; national and hospital surveillance data indicate that antibiotic use in health-care institutions has improved in quality and the quantity used has been reduced (33–38). Considering the conflict between hospital operating practices and insufficient governmental investment, additional new sustainable strategies for expanding the achievement of rational antibiotic use in China should still be explored (34). ●

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