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Antimicrobial stewardship managed by clinical pharmacists reduced antibiotic use and drug resistance in a Chinese hospital, 2010–2016: a hospital population-based retrospective study

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ABSTRACT

Objectives: "National Special Stewardship in the Clinical Use of Antibiotics" was put forward in July, 2011 in China. We aimed to retrospectively analyze and evaluate impacts of antimicrobial stewardship (AMS) managed by clinical pharmacists on antibiotic utilization, prophylaxis, and antimicrobial resistance.

Design: This was a retrospective observational study of trends in antibiotic use (2010–2016)

and antimicrobial resistance (2011–2016) in the context of AMS.

Setting: Beijing Chaoyang Hospital, Affiliate of Capital University of Medical Sciences in China, a 1400-bed tertiary hospital.

Data and participants: Antibiotic prescriptions involving all outpatients and inpatients during 2010–2016. Bacterial resistance data were from all inpatients during 2011–2016.

Interventions: Multi-aspect intervention measures were implemented by clinical pharmacists, such as formulating the activity program and performance management, advising on antibacterial prescriptions, and training doctors.

Outcome measures: The proportion of antibiotic prescriptions among outpatients and inpatients, intensity of consumption (defined daily dose (DDD)/100 bed-days), antibiotic prophylaxis in type I incision operations, and resistance rates of *Escherichia coli*, *Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* were retrospectively analyzed.

Results: The proportion of antibiotic prescriptions decreased to 13.21% in outpatients and 34.65% in inpatients, and the intensity of consumption dropped to 37.38 DDD/100 bed-days. The proportion of antibiotic prophylaxis was reduced to 18.93%. The proportion of rational timing of the initial dose reached 96.74%, and the proportion of rational duration rose to 42.63%. Time series analysis demonstrated significant increases in the resistance rates of *E. coli* and *K. pneumoniae* to carbapenems whereas the resistance rates of *E. coli* and *P. aeruginosa* to fluoroquinolones decreased; the incidence rate of MRSA also decreased. The intensity of consumption of antibiotics was partly positively correlated with changes in resistance rate.

Conclusions: Antimicrobial stewardship had an important role not in only reducing antibiotics use and surgical antibiotic prophylaxis but also in reducing antimicrobial resistance.

Strengths and limitations of this study

- Our study described the entire process of AMS, from management of antibiotics use to monitoring of antimicrobial resistance, by demonstrating effective results and identifying existing problems.
- In this study, we aimed to demonstrate the correlation between antibiotics use (carbapenems and fluoroquinolones) and the antimicrobial resistance rate of common nosocomial pathogens (the three most frequently isolated bacteria in our hospital: *E. coli*, *K. pneumoniae*, and *P. aeruginosa*).
- The findings of our study may indicate some potential directions for controlling the prevalence of CRE and MRSA.
- We compared our data with those of CHINET (the Chinese antimicrobial resistance surveillance network), which will help colleagues around the world to understand the current situation of bacterial resistance in China.
- Owing to space limitations, we did not discuss the economic changes of antibiotics use; this will be investigated in the future.

INTRODUCTION

In 2004, the first Guidelines for the Clinical Use of Antibiotics (Guidelines for short) was issued by the National Health and Family Planning Commission (NHFPC, originally called the Ministry of Health) of the People's Republic of China, describing the characteristics of all types of antibiotics and how to properly use them in the treatment and prevention of infectious diseases; the Guidelines were updated in 2015. Regretfully, not all medical staff knew about the Guidelines or their significance. Today, antimicrobial resistance is one of the greatest threats to global health. There are four main factors contributing to the development and spread of antimicrobial resistance: inappropriate use of antibiotics in the

community and hospitals, misuse of antibiotics in the management of food-producing animals and in agriculture, and the presence of resistant bacteria in the environment. The former three factors could aggravate the last one.[1] Chinese data from the Ministry of Health National Antibacterial Resistance Surveillance Net (MOHNARIN) showed that antimicrobial resistance has been rising steadily each year.[2] Hospital pharmacists should improve the rational use of antibiotics as much as possible, to help in controlling antimicrobial resistance.

On World Health Day 2011, the World Health Organization (WHO) began to take measures to combat the spread of antimicrobial resistance and strongly recommended governments to implement antimicrobial stewardship (AMS).[3] China acted immediately. In 2011, the NHFPC of China put forward "National Special Stewardship in the Clinical Use of Antibiotics",[4] the historically strictest management of antibiotics up to that date. The NHFPC set many goals for the use of clinical antibiotics, including restriction of antibiotic use in outpatients and inpatients and restricted antibiotic prophylactic use in clean operations, to promote rational antibiotics use and control antimicrobial resistance. These goals are described in detail below. This special stewardship policy mainly covered secondary and tertiary public hospitals and took effect on July 1, 2011. After that date, these hospitals were required to report data of antibiotics use to the government every month.

In recent years, some studies have reported that AMS has had positive effects on controlling antibiotic-resistant pathogens, rational use of antibiotics, and cost savings,[5, 6]highlighting the importance of AMS. After many years of hard work, the status of antibiotics use has improved substantially at our hospital.

The aim of this study was to evaluate the effective impact of AMS on antibiotics use and antimicrobial resistance trends, to share our successful management experience, and to identify existing problems. To our knowledge, few studies[7, 8] have analyzed the correlation between antibiotics usage (defined daily dose, DDD) and multidrug-resistant organisms

(bacterial isolation rate), and these studies have mainly focused on critically ill patients, such as those in intensive care units. In this study, we sought to demonstrate the correlation between antibacterial usage and the antimicrobial resistance rate of common nosocomial pathogens, using data from all inpatients in our hospital.

METHODS

Study design

According to the requirements of the national policy, "Special Stewardship in the Clinical Use of Antibiotics" was a 3-year plan (2011–2013). In April of 2014, the NHFPC issued a Notice Regarding Implementing Stewardship of Antibacterial Use in the Clinic;[9] its aim was to continuously maintain the positive effects gained during the previous 3 years. Accordingly, in our retrospective study, phases were divided into three stages, as follows. Stage 1: baseline phase (July 2010 to June 2011); stage 2: intervention phase (July 2011 to December 2013); and stage 3: stability phase (January 2014 to December 2016).

Patient and public involvement

The patients were not involved or recruited in this study. The Ethics Committee of Beijing Chaoyang Hospital agreed exemption applications of informed consent. The antibiotics utilization data was extracted directly from the Hospital Information System (HIS) and electronic medical records of all hospitalized patients (2010-2016). The bacterial resistance data from all inpatients (2011-2016) was provided by the Department of Infectious Diseases and Clinical Microbiology.

Ethics statement

This study was approved by the Ethics Committee of Beijing Chaoyang Hospital Affiliate of Capital University of Medical Sciences.

Multi-aspect intervention measures

Organization construction

To implement the program "National Special Stewardship in the Clinical Use of Antibiotics", an AMS group was set up in our hospital, which was attached to the Drug and Therapeutics Committee (DTC). The AMS group was composed of administrators, clinicians, infectious disease physicians, pharmacists, microbiologists, and information staff, and included a leadership group and expert group. The leadership group was responsible for work deployment and supervision whereas the expert group was responsible for technical guidance, training doctors on rational use of antibiotics, carrying out all tasks of AMS, and so on. As expected, the medical department led AMS in many hospitals in China, but in our hospital, the pharmacy department was the leading department, for the following reasons. (1) The pharmacy department in our hospital was not only a technical section but also a functional section. The pharmacy director was responsible for medication use. (2) There were many clinical pharmacists, such as infectious disease pharmacists who had sufficient knowledge and clinical experience to manage AMS. (3) The clinical pharmacists were working in the clinical departments every day, so they could give their professional advice regarding antibiotics use directly to doctors.

Formulating the activity program and administrative intervention

The AMS group formulated the activity program of stewardship and some regulations on antibiotic use were issued, as follows. (1) Antibiotic classification management system. All antibiotics were classified as non-restricted, restricted, and special grade antibiotics. Physicians with different professional titles were matched to the corresponding grade of antibiotic prescribing privileges. (2) Management system of antibiotic prescribing privileges. In May of 2012, the Regulations on Clinical Applications of Antibiotics were issued by the NHFPC, which took effect on August, 1, 2012. These were the first valid regulations on antibiotics in China.[10] The Regulations required that physicians would not be given antibiotic

prescribing privileges until they passed an exam, after completing training in the use of antibiotics. This prescribing privilege restriction was embedded into the Hospital Information System (HIS). (3) Regulation of perioperative prophylactic antibiotics use in clean operations, in which the choice of antibiotics, dose, timing of the initial dose, and duration of antibiotic prophylaxis were described.

According to the requirements of the national antibiotic stewardship program,[4] the AMS group established the goals for antibiotic application in the hospital (Table 1).

Table 1 Goals of clinical antibiotic use established by the NHFPC in 2011

Antibiotic outcome measures	Goals
1. Proportion of inpatients receiving antibiotics	≤ 60%
2. Proportion of outpatients receiving antibiotics	≤ 20%
3. Intensity of inpatients' antibiotic consumption	≤ 40 DDD/100 bed-days
4. Proportion of antibiotic prophylaxis in patients receiving type I incision operations/clean operations	≤ 30%
5. Timing of initial dose of preoperative antibiotic prophylaxis	Within 0.5–2 h before surgical incision
6. Duration of antibiotic prophylaxis in patients receiving type I incision operations/clean operations	Within 24 h after the end of operation

Performance management

Every year, the directors of clinical departments were asked by the director of the hospital to sign responsibility agreements for antibiotic use. Hospital leaders and the pharmacy director, together with clinical pharmacists, established or updated the performance appraisal system for antibiotic use, which indicated the circumstances to be rewarded or punished. For example, if clinical departments did not accomplish their goals, the directors would be fined 1000–3000 RMB, and doctors would be fined 300–500 RMB. If the clinical

departments accomplished their goals, the directors would be rewarded with 1000–5000 RMB and doctors with 300–1000 RMB, which were greater than the amounts of fines.

Antibiotic prescription evaluation and training

Retrospective rationality evaluation of antibiotic prescriptions for outpatients, emergency room patients, and inpatients was performed monthly by clinical pharmacists. Irrational prescriptions would be flagged in the Antibacterial Monitoring Report published by the pharmacy department each month; this report was made available to all medical staff. According to the frequency and severity of irrational prescriptions, some doctors would be fined.

Clinical pharmacists were responsible for training the medical staff on rational use of antibiotics. If necessary, pharmacists would go to the clinical departments to give lectures.

Multiple cooperation

Antibiotics data monitoring could not be implemented without the support of the information department. At the start of AMS at our hospital, data extraction modules were embedded into the HIS after discussions between clinical pharmacists and information personnel. Later, an automatic prescription screening system was also included in the HIS, which could intercept irrational prescriptions, such as repeated use or unreasonable combinations. Furthermore, clinical pharmacists took part in the Core Expert Meeting of Antibacterial Application held by the Infection Management Office, to discuss usage problems with carbapenems and glycopeptides. If irrational use was confirmed by the experts, the relevant physician would be penalized 1–2 points (1 point corresponded to a 100 RMB fine).

Data collection and outcome measures

Antibiotic outcome measures are shown in Table 1 (see“Antibiotic outcome measures”). The antibiotic utilization data was collected directly from the HIS. Antibiotic consumption

was standardized according to the Anatomical Therapeutic Chemical (ATC) classification system and the DDD was used as a measuring unit, as recommended by the WHO Collaborating Center for Drug Statistics Methodology.[11] The intensity of inpatients' antibiotic consumption was expressed as DDD per 100 bed-days. Information of type I incision operations was extracted from patients' electronic medical records. The outcome measures of antimicrobial resistance included the resistance rates of *Escherichia coli*, *Klebsiella pneumonia,* and *Pseudomonas aeruginosa* and incidence rate of methicillin-resistant *Staphylococcus aureus* (MRSA) in our hospital. The bacteriological data were obtained from the clinical microbiology laboratory. We analyzed the correlation between antibiotic consumption and antimicrobial resistance.

Statistical analysis

Segmented regression analysis of interrupted time series was used to analyze the monthly data of antibiotic utilization, which were divided into three stages (the baseline phase, intervention phase, and stability phase), to illustrate the effect of AMS. The statistical model in this study was as follows.[12]

$$Y_t = \beta_0 + \beta_1 \times time_t + \beta_2 \times intervention_t + \beta_3 \times time\ after\ intervention_t + \beta_4 \times stability_t + \beta_5 \times time\ after\ stability_t + e_t$$

In this model, Y_t was the average monthly value of the outcome measure at month t; β_0 estimates the level change in the outcome during the baseline phase; β_1 estimates the trend change during the baseline phase; β_2 estimates the level change during the intervention phase; β_3 estimates the trend change during the intervention phase; β_4 estimates the level change during the stability phase; and β_5 estimates the trend change during the stability phase. The parameter level was the value of a time series at the beginning of a given time series; the parameter trend was the rate of change in an outcome measure; *time* was a

continuous variable indicating time in months at time *t* starting from the baseline phase (time 0); *intervention* was an indicator for time *t* occurring before (*intervention* = 0) or after (*intervention* = 1) the multi-aspect intervention, which started at month 13 (July 2011); *time after intervention* was a continuous variable counting the months after the intervention; *stability* was an indicator for time *t* occurring before (*stability* = 0) or after stability (*stability* = 1), which started at month 43 (January 2014); *time after stability* was a continuous variable counting the months after stability. The error term, e_t, represented variation unexplained by the segmented regression model.

Comparisons of the average monthly values of outcome measures for antibiotic use during the three phases were conducted using the Bonferroni test. Box charts were plotted for data visualization, with error bars representing standard deviations.

In addition, a time series analysis model (autoregressive integrated moving average, ARIMA)[8] was used to analyze the trends in annual antibiotic use, antimicrobial resistance trends, and incidence trend of MRSA from 2011 to 2016. The β value indicated the variation of dependent variables when independent variables changed one unit at uniform time intervals. Pearson correlation coefficients were used to examine the relationships between antimicrobial resistance, the incidence rate of MRSA, and antibiotic use.

All statistics were performed using SAS, version 9.3 (SAS Institute, Cary, NC, USA). All reported *P* values were two-sided, with $P < 0.05$ considered statistically significant.

RESULTS

Change trends in antibiotics utilization rate and intensity

Changes in the proportion of antibiotic prescriptions in outpatients and inpatients during the baseline, intervention, and stability phases are shown in Figure 1A, 1B, 1C and 1D. The associated parameters of time series analysis are summarized in Table 2. The proportion of

antibiotic prescriptions in outpatients and inpatients declined by 0.33% ($P < 0.05$) and by 0.59% ($P < 0.05$) each month during the intervention stage, respectively. Bonferroni tests (Figure 1B) showed that the proportion of antibiotic prescriptions in outpatients was reduced from 19.38% during the baseline phase to 13.21% during the stability phase ($P < 0.05$). The proportion of antibiotic prescriptions among inpatients decreased significantly from 64.34% during the baseline phase to 34.65% during the stability phase ($P < 0.05$) (Figure 1D). Figure 1E and Table 2 showed that the intensity of inpatient antibiotic consumption decreased significantly by 6.46 DDD/100 bed-days ($P < 0.001$) per month during the first year of the intervention stage. Figure 1F showed the intensity of consumption dropped from the baseline phase to the stability phase (102.46 vs. 37.38 DDD/100 bed-days; $P < 0.05$). All the outcomes mentioned above met the national standards. In the stability phase, the $\beta 5$ value for the intensity of consumption (0.70; $P < 0.001$) implied a gradually increasing trend; this still met national standards.

Table 2 Time series analysis of change trends in antibiotic utilization

Antibiotic outcome measures	***β1*-trend (baseline)**	***β2*-level (intervention)**	***β3*-trend (intervention)**	***β4*-level (stability)**	***β5*-trend (stability)**
Proportion-O	−0.01 (0.04)	0.55 (0.83)	−0.33 (0.12)*	0.48 (0.85)	−0.19 (0.14)
Proportion-I	−0.25 (0.10)*	−5.03 (2.22)*	−0.59 (0.29)*	3.61 (2.23)	−0.66 (0.74)
Intensity-I	−0.04 (0.04)	−7.44 (3.62)*	−6.46 (0.56)***	4.20 (1.45)**	0.70 (0.19)***
Proportion-type I	−0.10 (0.04)*	−7.26 (2.92)*	−5.71 (0.61)***	−0.18 (1.44)	−0.12 (0.12)
Timing-type I	−0.01 (0.07)	0.64 (1.72)	1.18 (0.59)*	1.63 (2.00)	−0.17 (0.24)
Duration-type I	0.28 (0.06)***	8.78 (2.15)**	0.10 (0.27)	5.35 (1.44)***	−1.19 (0.19)***

Outcomes of antibiotic utilization included proportion of antibiotic prescriptions in outpatients (Proportion-O), inpatients (Proportion-I), and intensity of consumption in inpatients (Intensity-I). Outcomes of antibiotic prophylaxis included proportion of prophylaxis (Proportion-type I), proportion of

rational timing (Timing-type I), and proportion of rational duration (Duration-type I). Parameters of *β1–β5* were expressed as mean (SE), which represented the changes in level and trend.

*$P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Change trends of antibiotic prophylaxis in type I incision operations

The proportion of antibiotic prophylaxis in patients undergoing type I incision operations was significantly reduced by 5.71% ($P < 0.001$) monthly during the first year of the intervention phase (Figure 2A, Table 2), decreasing from 98.94% during the baseline phase to 18.93% during the stability phase ($P < 0.05$) (Figure 2B). The proportion of rational timing of the initial dose increased by 1.18% ($P < 0.05$) each month during the intervention stage (Figure 2C, Table 2), also increasing from 71.11% during the baseline phase to 96.74% during the stability phase ($P < 0.05$) (Figure 2D). These two outcomes all eventually reached national standards. Although the proportion of rational duration of antibiotic prophylaxis showed an increasing trend during the intervention phase (0.10; $P < 0.05$), the difference was not statistically significant (Figure 2E, Table 2). However, in the stability phase, this showed a decreasing trend (−1.19; $P < 0.001$), which did not meet the national standard (≥ 90%). Figure 2F showed the proportion of rational duration, increasing from 2.84% during the baseline phase to 42.63% during the stability phase ($P < 0.05$).

Trends in resistance rates for common gram-negative bacilli and incidence rate of MRSA, 2011–2016

Time series analysis demonstrated a significant increase in the resistance rates of *E. coli* to carbapenems during 2011–2016 ($P < 0.05$). The β value indicated that the resistance rates of *E. coli* to imipenem and meropenem increased by 0.27% and 0.22% each year, respectively. However, the resistance rates of *E.coli* to levofloxacin and ciprofloxacin

significantly decreased by 1.62% and 1.40% each year, respectively ($P < 0.01$ and $P < 0.001$) (Table 3).

Table 3 Trend changes in antimicrobial resistance of *E.coli* to carbapenems and fluoroquinolones from 2011 to 2016

Antibiotic	Resistance rate (%), by year						Time series analysis		
	2011	2012	2013	2014	2015	2016	Trend	*β*	*P*
Imipenem	0	0	0.1	0.4	0.5	1.5	Increasing	0.2657	0.0239
Meropenem	0	0	0	0.3	0.3	1.3	Increasing	0.2200	0.0471
Levofloxacin	61.3	61.3	59.1	57.7	55.5	53.9	Decreasing	−1.6191	0.0013
Ciprofloxacin	64.3	64.3	61.2	61.4	58.7	58.2	Decreasing	−1.4038	0.0002

Time series analysis demonstrated a significant increase in the resistance rates of *K. pneumoniae* to carbapenems ($P < 0.05$). The β value indicated that the resistance rates of *K. pneumoniae* to imipenem and meropenem increased by 1.29% and 1.14% each year, respectively. The resistance rates of *K. pneumoniae* to fluoroquinolones (FQs) remained stable (Table 4).

Table 4 Trend changes in antimicrobial resistance of *K. pneumoniae* to carbapenems and fluoroquinolones from 2011 to 2016

Antibiotic	Resistance rate (%), by year						Time series analysis		
	2011	2012	2013	2014	2015	2016	Trend	*β*	*P*
Imipenem	2.0	1.5	1	4.8	7.1	6.9	Increasing	1.2937	0.049
Meropenem	1.8	1.5	1	4.1	6.2	6.4	Increasing	1.1381	0.047
Levofloxacin	27.9	27.9	18.4	12.9	14.6	15.2	Stable	−3.0218	0.0973
Ciprofloxacin	28.9	28.9	20.2	15.5	17.0	19.0	Stable	−2.4467	0.1643

Time series analysis showed a significant decrease in the resistance rates of *P.*

aeruginosa to FQs ($P < 0.05$ and $P < 0.01$). The β value indicated that the resistance rate of *P. aeruginosa* to levofloxacin and ciprofloxacin decreased by 4.78% and 2.27% each year, respectively. Resistance rates of *P. aeruginosa* to carbapenems remained stable (Table 5).

Table 5 Trend changes in antimicrobial resistance of *P. aeruginosa* to carbapenems and fluoroquinolones from 2011 to 2016

Antibiotic	Resistance rate (%), by year						Time series analysis		
	2011	2012	2013	2014	2015	2016	Trend	β	*P*
Imipenem	23.1	20.9	15.2	16.5	15.3	15.8	Stable	−1.4811	0.1008
Meropenem	18.2	16.2	10.1	12.9	11.4	11.4	Stable	−1.2977	0.1140
Levofloxacin	28.1	28.1	20.5	10.0	10.1	8.1	Decreasing	−4.7833	0.0137
Ciprofloxacin	18.2	18.2	13.5	11.6	10.5	7.5	Decreasing	−2.2677	0.0011

Our study shows that the incidence rate of nosocomial MRSA decreased significantly by 5.26% each year, declining from 68.0% (2011) to 37.5% (2016) ($P < 0.001$) (Supplementary Table S1).

Correlation between antibiotic consumption and antimicrobial resistance

Because carbapenems and FQs are often used for nosocomial infection, we focused on evaluating the impact of use of these drugs on antimicrobial resistance. We found that the intensity of consumption of imipenem/cilastatin significantly increased from 0.59 to 1.36 DDD/100 bed-days ($P < 0.01$). However, the intensity of consumption of FQs significantly decreased each year ($P < 0.01$ and $P < 0.05$), respectively (Supplementary Table S2).

Increased consumption of imipenem/cilastatin was correlated with the prevalence of imipenem-resistant *E. coli*, ($r = 0.8651$, $P < 0.05$). Similarly, decreased consumption of FQs

was associated with the decreased resistance rate of *E. coli* to levofloxacin and ciprofloxacin (r = 0.8954 and r = 0.8950, respectively; $P < 0.05$) (Table 6).

Table 6 Correlation between antibiotic intensity of consumption and resistance rates of *E. coli*, *K. pneumoniae*, *P. aeruginosa*, and incidence rate of MRSA

Antibiotics	*E. coli*		*K. pneumoniae*		*P. aeruginosa*		MRSA	
	r	*p*	r	*p*	r	*p*	r	*p*
Imipenem/cilastatin	0.8651	0.0261	0.9050	0.0131	−0.7477	0.0875	−0.9611	0.0022
Meropenem	0.3252	0.5295	0.4095	0.4201	0.3672	0.4739	0.0012	0.9982
Levofloxacin	0.8954	0.0158	0.7523	0.0844	0.8954	0.0159	0.9450	0.0045
Ciprofloxacin	0.8950	0.0160	0.9209	0.0091	0.9282	0.0075	0.8883	0.0180

Antibiotics refer to intensity of consumption (DDD/100 bed-days); bacteria (*E. coli*, *K. pneumoniae*, and *P. aeruginosa*) refer to their resistance rates (%) to antibiotics; MRSA refers to incidence rate of MRSA (%).

r: correlation coefficient.

There was a relationship between the increased resistance rate of *K. pneumoniae* to imipenem/cilastatin and increased intensity of consumption of imipenem/cilastatin (r = 0.9050, $P < 0.05$). Although time series analysis showed a stable trend in the resistance rate of *K. pneumoniae* to ciprofloxacin (Table 4), there was still a significantly positive correlation between the prevalence of ciprofloxacin-resistant *K. pneumoniae* and use of ciprofloxacin (r = 0.9209, $P < 0.01$) (Table 6).

Table 6 indicates that the resistance rate of *P. aeruginosa* to FQs was correlated with the consumption of FQs (r = 0.8954, $P < 0.05$ for levofloxacin and r = 0.9282, $P < 0.01$ for ciprofloxacin).

The incidence rate of MRSA was positively correlated with the consumption of FQs (r = 0.9450, $P < 0.01$ for levofloxacin and r = 0.8883, $P < 0.05$ for ciprofloxacin). However, we found that the incidence rate of MRSA was negatively correlated with the consumption of

imipenem/cilastatin (r = - 0.9611, $P < 0.01$) (Table 6).

DISCUSSION

The global mortality attributable to antimicrobial resistance is estimated to reach 10 million annually by 2050, which would make it one of the leading causes of death, with an economic impact of up to 100 trillion US dollars (USD).[13] Therefore, many countries worldwide have implemented AMS, with many achieving positive effects in the rational use of antibiotics and health care cost savings.[14-18]

The implementation of AMS in our hospital is managed by clinical pharmacists and supported by the DTC. After many years of AMS, the proportion of antibiotic prescriptions decreased to 13.21% among outpatients and 34.65% among inpatients. The intensity of antibiotic consumption was reduced to 37.38 DDD/100 bed-days. These outcomes are similar to the study by Bao *et al*. [10] Regarding antibiotic prophylaxis in type I incision operations, the proportion of antibiotic prophylaxis decreased to 18.93% and the proportion of rational timing of the initial dose increased to 96.74%. Only the proportion of rational duration of antibiotic prophylaxis (42.63%) did not reach the national standard, for the following reasons. First, coronary artery bypass graft (CABG) surgery belongs to type I incision operations, according to the Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery,[19] the duration of prophylaxis for cardiothoracic procedures is up to 48 hours, with no supporting evidence. Chinese Guidelines suggest prophylactic duration be no more than 48 hours. But CABG involves important viscera, in which the consequences of infection would be severe. Therefore, doctors hesitate to stop antibiotics within 48 hours after surgery. Second, in orthopedic surgeries, such as open reduction and plate or screw internal fixation of fractures in consideration of implants, doctors also hesitate to stop antibiotics within 24 hours after surgery. Third, the difficult doctor–patient relationships in China make physicians hesitant

about premature discontinuation of antibiotics.

The aim of AMS is to limit the prevalence of antimicrobial resistance. The results showed that with decreased intensity of FQ consumption, the resistance rates of *E. coli* and *P. aeruginosa* to FQs and incidence rate of MRSA showed decreasing trends, and they were positively correlated. This implies that controlling the use of FQs might limit the prevalence of antimicrobial resistance as well as limit the emergence of MRSA; the latter is consistent with previous studies.[20,21] Other studies[22-25] have reported that a reduction in second/third-generation cephalosporins and clindamycin contributes to a reduction in both incidence rate of MRSA and prevalence density of MRSA bacteremia. In our study, we also found that the incidence rate of MRSA was negatively correlated with imipenem/cilastatin use, which was difficult to explain. To our knowledge, few studies have obtained results similar to ours. Lai *et al*. reported[26] a significant correlation between increased use of linezolid and teicoplanin and decreased prevalence of MRSA. Therefore, we theorize that the reduced use of non-special grade antibiotics (such as FQs and others) leads to a compensatory increased use of carbapenems; however, this negative correlation requires further exploration. In addition, we found the resistance rate of *E. coli* and *K. pneumoniae* to carbapenems showed an increasing trend, meaning that carbapenem-resistant Enterobacteriaceae (CRE) could pose a serious threat. On March 3, 2017, the NHFPC issued a Notice Regarding Further Reinforcement in Management of Clinical Application of Antibacterial to Control Bacteria Resistance, which required medical institutions to gather, archive, and analyze patient information with respect to the use of carbapenems, to help control the prevalence of CRE.[27]

CHINET surveillance of antimicrobial resistance in China reported the resistance trends from 2005 to 2014, using data from 19 hospitals.[28] In our hospital, the resistance rates of *E. coli*, *K. pneumoniae*, and *P. aeruginosa* to imipenem/cilastatin and meropenem in 2014 (0.4% and 0.9%, 4.8% and 4.1%, 16.5% and 12.9%, respectively) were significantly lower than

those reported by CHINET (0.9% and 1.0%, 10.5% and 13.4%, 26.6% and 24.3%, respectively). This proved that AMS in our hospital played an important role in the control of antimicrobial resistance.

Some limitations of this study should be noted. First, this study only represented the experience of a single medical institution. Second, because AMS has been ongoing for many years, several different clinical pharmacists have successively participated in the evaluation of prophylactic antibiotic use; therefore, the evaluation results might be affected slightly by individual differences.

CONCLUSION

This study demonstrated that AMS managed by clinical pharmacists has an important role in reducing and optimizing antibiotic use and controlling antimicrobial resistance. The findings of our study indicate some directions to pursue in controlling the prevalence of CRE and MRSA. Antimicrobial resistance is rising worldwide, so continual effort regarding AMS is critical not only in large hospitals but also in primary or community hospitals.

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Contributors LHL was the leader of AMS and responsible for supervising the work, work plan, and manuscript review. HGW was responsible for carrying out AMS and collecting, analyzing, and reporting data; she wrote this manuscript and made some amendments after review. HW was responsible for statistical analysis and wrote the analysis method in the manuscript. XJY, HZ, BYL, GC, ZKY, YW, XLC,YYZ, RZ, ZHW, HY were all involved in

the different aspects of data collection. PW and CXY provided the bacterial resistance data. All authors were involved in data verification.

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Competing interests None declared.

Patient consent Not required.

Ethics approval Beijing Chaoyang Hospital Ethics Committee.

Data sharing statement We state that if our manuscript is accepted and published, we would be pleased to share our data with readers to improve the rational use of antibiotics.

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Figure legends:

Figure 1. Changes in proportion of antibiotic prescriptions and intensity of

consumption.

Time series curves of each monthly value of antibiotic prescribing proportions, plotted for outpatients (A) and inpatients (C). Each monthly value of intensity of antibiotic consumption was plotted for inpatients (E). The Bonferroni test was conducted to compare these data in three stages, for antibiotic prescribing proportion among outpatients (B) and inpatients (D), and intensity of antibiotic consumption (F). Stage 1, Stage 2, and Stage 3 on the x-axis represent the baseline phase, intervention phase, and stability phase, respectively.

Figure 2. Changes in antibiotic prophylaxis in type I incision operations.

Time series curves of each monthly value of antibiotic prophylaxis were plotted for proportion of prophylaxis (A), proportion of rational timing (C), and proportion of rational duration (E). These data in three stages were compared by Bonferroni test (B, D, and F). Stage 1, Stage 2, and Stage 3 on the x-axis represent the baseline phase, intervention phase, and stability phase, respectively.

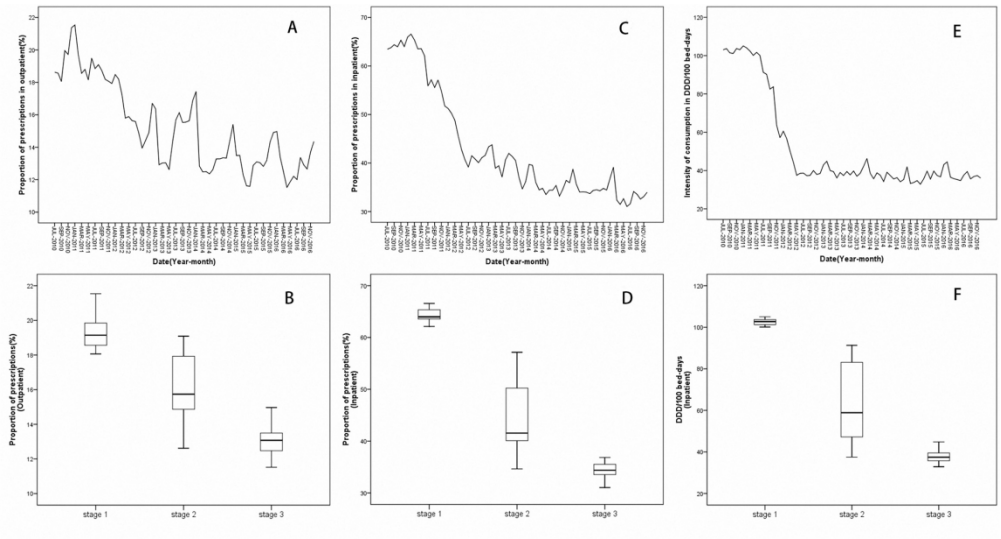

Figure 1. Changes in proportion of antibiotic prescriptions and intensity of consumption.
Time series curves of each monthly value of antibiotic prescribing proportions, plotted for outpatients (A) and inpatients (C). Each monthly value of intensity of antibiotic consumption was plotted for inpatients (E). The Bonferroni test was conducted to compare these data in three stages, for antibiotic prescribing proportion among outpatients (B) and inpatients (D), and intensity of antibiotic consumption (F). Stage 1, Stage 2, and Stage 3 on the x-axis represent the baseline phase, intervention phase, and stability phase, respectively.

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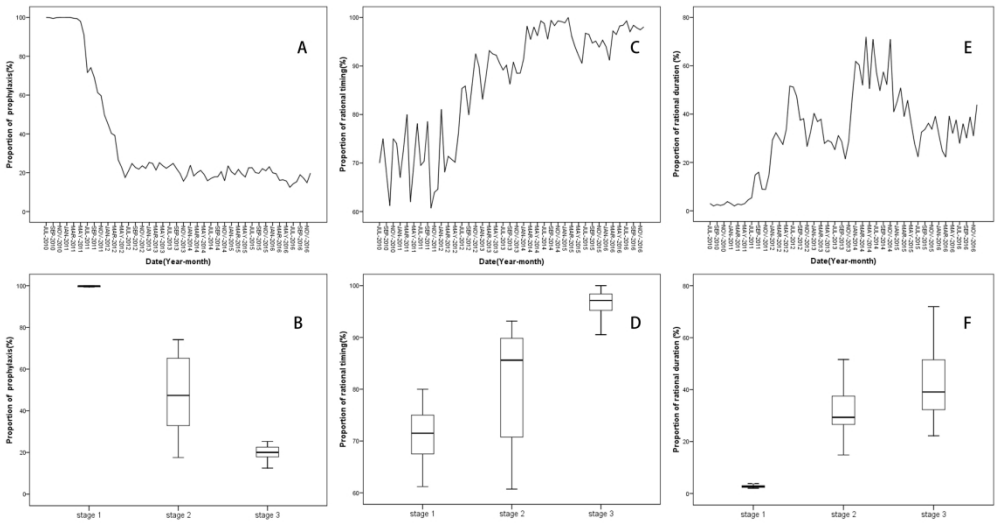

Figure 2. Changes in antibiotic prophylaxis in type I incision operations.
Time series curves of each monthly value of antibiotic prophylaxis were plotted for proportion of prophylaxis (A), proportion of rational timing (C), and proportion of rational duration (E). These data in three stages were compared by Bonferroni test (B, D, and F). Stage 1, Stage 2, and Stage 3 on the x-axis represent the baseline phase, intervention phase, and stability phase, respectively.

546x292mm (144 x 144 DPI)

Supplementary materials

Table S1 Trend changes in incidence rate of methicillin-resistant *Staphylococcus aureus* from 2011 to 2016

	By year						Time series analysis		
	2011	**2012**	**2013**	**2014**	**2015**	**2016**	**Trend**	***β***	***P***
Incidence rate (%)	68.0	60.3	58.3	49.8	51.5	37.5	Decreasing	−5.2565	0.0007

Table S2 Usage trend changes of carbapenems and fluoroquinolones from 2011 to 2016

Antibiotic	**Antibiotic consumption (DDD/100 bed-days) by year**						**Time series analysis**		
	2011	**2012**	**2013**	**2014**	**2015**	**2016**	**Trend**	***β***	***P***
Imipenem/cilastatin	0.59	0.71	0.79	1.17	1.16	1.36	Increasing	0.1599	0.0013
Meropenem	0.86	0.34	0.29	0.38	0.66	0.69	Stable	−0.0116	0.9193
Levofloxacin	11.18	9.70	10.64	7.74	7.71	6.35	Decreasing	−0.9292	0.0033
Ciprofloxacin	6.17	4.12	2.49	0.91	0.66	0.45	Decreasing	−1.1811	0.0461

DDD, defined daily dose.

STROBE Statement—checklist of items that should be included in reports of observational studies

Our research met all the items of STROBE statement.

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-5
Objectives	3	State specific objectives, including any prespecified hypotheses	3-5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2,4,5,8,9
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Not Applicable for this study. This study was a retrospective observational study,please See P5,8-10
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-10
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	1,2
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-10
		(*b*) Describe any methods used to examine subgroups and interactions	8-10
		(*c*) Explain how missing data were addressed	None
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Not Applicable for this study
		(*e*) Describe any sensitivity analyses	8-10

Continued on next page

Results			**Page number**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	2-3
		(b) Give reasons for non-participation at each stage	Applicable for this study
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Applicable for this study
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Applicable for this study
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Applicable for this study
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	19-21
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	4,22
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-22
Generalisability	21	Discuss the generalisability (external validity) of the study results	20-22
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	None

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Impact of antimicrobial stewardship managed by clinical pharmacists on antibiotic use and drug resistance in a Chinese hospital, 2010–2016: a retrospective observational study

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Impact of antimicrobial stewardship managed by clinical pharmacists on antibiotic use and drug resistance in a Chinese hospital, 2010–2016: a retrospective observational study

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Word count: 4121

ABSTRACT

Objectives: "National Special Stewardship in the Clinical Use of Antibiotics" was put forward in July, 2011 in China. We aimed to retrospectively evaluate the impact of antimicrobial stewardship (AMS) managed by clinical pharmacists on antibiotic utilization, prophylaxis and antimicrobial resistance (AMR).

Design: This was a retrospective observational study of trends in antibiotic use and AMR in

the context of AMS.

Setting: Beijing Chaoyang Hospital, a 1400-bed tertiary hospital, in China.

Data and participants: Antibiotic prescriptions from 820 doctors included all outpatients (N=17766637) and inpatients (N=376627) during 2010–2016. Bacterial resistance data were from all inpatients (N=350699) during 2011–2016.

Interventions: Multi-aspect intervention measures were implemented by clinical pharmacists (13persons), e.g. formulating the activity program and performance management, advising on antibacterial prescriptions and training.

Outcome measures: The proportion of antibiotic prescriptions among outpatients and inpatients, intensity of consumption in defined daily dose (DDD)/100 bed-days, antibiotic prophylaxis in type I incision operations, and resistance rates of *Escherichia coli*, *Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* were retrospectively analyzed.

Results: The proportion of antibiotic prescriptions decreased in outpatients (from 19.38% to 13.21%) and in inpatients (from 64.34% to 34.65%), the intensity of consumption dropped from 102.46 to 37.38 DDD/100 bed-days. The proportion of antibiotic prophylaxis decreased from 98.94% to 18.93%. The proportion of rational timing of initial dose increased from 71.11% to 96.74%, the proportion of rational duration rose from 2.84% to 42.63%. Time series analysis demonstrated the resistance rates of *E. coli* and *P. aeruginosa* to fluoroquinolones decreased, the incidence rate of methicillin-resistant *Staphylococcus aureus* (MRSA) also decreased; whereas the resistance rates of *E. coli* and *K. pneumoniae* to carbapenems increased. The antibiotic use was partly positively correlated with AMR.

Conclusions: AMS had an important role in reducing antibiotic use and surgical antibiotic prophylaxis. The AMR was positively correlated with antibiotic consumption to some extent.

Strengths and limitations of this study

- Our study described the entire process of AMS, from management of antibiotic use to AMR monitoring.
- Time series analysis, a better tool, was applied to analyze the change trends in antibiotic utilization and AMR.
- By exploring the correlation between antibiotic use and AMR， this study may indicate some potential directions for controlling the prevalence of CRE and MRSA.
- This was a retrospective observational study without simultaneous control group, the bias couldn't be well controlled; the evaluation of prophylactic antibiotic use by different clinical pharmacists might have individual differences.

INTRODUCTION

In 2004, the first Guidelines for the Clinical Use of Antibiotics (Guidelines for short) was issued by the National Health and Family Planning Commission (NHFPC, originally called the Ministry of Health) of the People's Republic of China, describing the characteristics of all types of antibiotics and appropriate use in treatment and prevention of infectious diseases; the Guidelines were updated in 2015. Regretfully, not all medical staff knew about the Guidelines or their significance. Today, antimicrobial resistance (AMR) is one of the greatest threats to global health. There are four main factors contributing to the spread of AMR: inappropriate use of antibiotics in the community and in hospitals, misuse of antibiotics in animal production and agriculture, and the presence of resistant bacteria in the environment. The former three factors could aggravate the last one.[1] Chinese data from the Ministry of Health National Antibacterial Resistance Surveillance Net (MOHNARIN) showed that AMR has been rising steadily each year.[2]

In 2001 the World Health Organization (WHO) began to take measures to combat the spread of AMR and strongly recommended governments to implement antimicrobial

stewardship (AMS).[3]On World Health Day 2011, AMR was also selected as the theme. In response to AMR, in 2011 the NHFPC of China put forward "National Special Stewardship in the Clinical Use of Antibiotics",[4] the historically strictest management of antibiotics up to that date. The NHFPC set many goals for the clinical use of antibiotics, including restriction of antibiotic use in outpatients and inpatients and restriction of antibiotic prophylactic use in clean operations, to promote rational antibiotic use and control AMR. These goals are described in detail below. This special stewardship policy mainly covered secondary and tertiary public hospitals and took effect on July 1, 2011. After that date, these hospitals were required to report data of antibiotic use to the government every month.

In recent years, some studies have reported that AMS had positive effects on controlling antibiotic-resistant pathogens, rational use of antibiotics, and cost savings,[5,6] highlighting the importance of AMS. There were also some studies [7-11]that analyzed the correlation between antibiotic use and AMR, although these all demonstrated the effectiveness of AMS, but the studied population, antibiotic and pathogen are different, and the results of correlation between antibiotic use and AMR were not exactly the same.

The aim of this study was to evaluate the impact of AMS on antibiotic use and AMR trends, to share our successful management experience, and to identify existing problems. In addition, because the doctors' prescription behaviors and antibiotic variety are different in each country or region, so is the status of AMR, therefore we sought to demonstrate the correlation between antibiotic use and antimicrobial resistance rate of common nosocomial pathogens, using data from all inpatients in our hospital.

METHODS

Study design

According to the requirements of the national policy, " Special Stewardship in the Clinical Use of Antibiotics " was a 3-year plan (2011–2013). In April of 2014, the NHFPC

issued a Notice Regarding Implementing Stewardship of Antibacterial Use in the Clinic;[12]its aim was to continuously maintain the positive effects gained during the previous 3 years. Accordingly, in our retrospective study, phases were divided into three stages, as follows. Stage 1: baseline phase (July 2010 to June 2011); stage 2: intervention phase (July 2011 to December 2013); and stage 3: stability phase (January 2014 to December 2016).

Patient and public involvement

The antibiotic utilization data was extracted directly from the Hospital Information System (HIS) and electronic medical records of all patients (2010-2016). The patient's personal information was hidden. The bacterial resistance data from all inpatients (2011-2016) was provided by the Department of Infectious Diseases and Clinical Microbiology. Clinical sample sources included blood, cerebrospinal fluid, pleural effusion, ascites, urine and sputum, etc. Duplicate isolates, defined as the isolates of the same species that showed the same susceptibility results at the same site for each patient in different days, were excluded, only the first isolated strain was included in the study (excluding isolates of surveillance cultures).

Ethics statement

This study was approved by the Ethics Committee of Beijing Chaoyang Hospital (Approval Number: 2017-11-28-3). Because the patient's privacy was not violated in the study, so the Ethics Committee agreed exemption applications of informed consent.

Multi-aspect intervention measures

Organization construction

To implement the program “National Special Stewardship in the Clinical Use of Antibiotics”, an AMS group was set up in our hospital, which was attached to the Drug and Therapeutics Committee (DTC). The AMS group was composed of administrators, clinicians, infectious disease physicians, pharmacists, microbiologists, and information staff, and

included a leadership group and expert group. The leadership group was responsible for work deployment and supervision whereas the expert group was responsible for technical guidance, participation in consultations, training doctors on rational use of antibiotics and implementation of AMS monitoring (such as data collection and report, prescription review and feedback, AMR monitoring, etc). Generally the medical department led AMS in many hospitals in China, but in our hospital, the pharmacy department was the leading department, for the following reasons. (1) The pharmacy department in our hospital is not only a technical section but also a functional section. The pharmacy director is responsible for medication use. (2) There are many clinical pharmacists, such as infectious disease pharmacists who have sufficient knowledge and clinical experience to manage AMS. (3) Clinical pharmacists work in the clinical departments every day, so they could give their professional advice regarding antibiotic use directly to doctors.

Formulating the activity program and administrative intervention

The AMS group formulated the activity program of stewardship and some regulations on antibiotic use were issued, as follows. (1) Antibiotic classification management system. All antibiotics were classified as non-restricted, restricted, and special grade antibiotics. Physicians with different professional titles were matched to the corresponding grade of antibiotic prescribing privileges. (2) Management system of antibiotic prescribing privileges. In May of 2012, the Regulations on Clinical Applications of Antibiotics were issued by the NHFPC, which took effect on August, 1, 2012. These were the first valid regulations on antibiotics in China.[13]The regulations required that physicians would not be given antibiotic prescribing privileges until they passed an exam, after completing training on rational use of antibiotics. This prescribing privilege restriction was embedded into the Hospital Information System (HIS). (3) Regulation of perioperative prophylactic antibiotic use in clean operations, in which the choice of antibiotics, dose, timing of the initial dose, and duration of antibiotic

prophylaxis were described.

According to the requirements of the national antibiotic stewardship program,[4] the AMS group established the goals for antibiotic application in the hospital (Table 1).

Table 1 Goals of clinical antibiotic use established by the NHFPC in 2011

Antibiotic outcome measures	Goals
1. Proportion of inpatients receiving antibiotics	≤ 60%
2. Proportion of outpatients receiving antibiotics	≤ 20%
3. Intensity of inpatients' antibiotic consumption	≤ 40 DDD/100 bed-days
4. Proportion of antibiotic prophylaxis in patients receiving type I incision operations/clean operations	≤ 30%
5. Timing of initial dose of preoperative antibiotic prophylaxis	Within 0.5–2 h before surgical incision
6. Duration of antibiotic prophylaxis in patients receiving type I incision operations/clean operations	Within 24 h after the end of operation

Performance management

Every year, the directors of clinical departments were asked by the director of the hospital to sign responsibility agreements for antibiotic use. Hospital leaders and the pharmacy director, together with clinical pharmacists, established or updated the performance appraisal system for antibiotic use, which indicated the circumstances to be rewarded or penalized. For example, if clinical departments did not accomplish their goals, the directors would be fined 1000–3000CNY, and doctors would be fined 300–500CNY. If the clinical departments accomplished their goals, the directors would be rewarded with 1000–5000 CNY and doctors with 300–1000 CNY, which were greater than the amounts of fines.

Antibiotic prescription evaluation and training

Retrospective rationality evaluation of antibiotic prescriptions for outpatients,

emergency room patients, and inpatients was performed monthly by clinical pharmacists. For example, some doctors used moxifloxacin to treat urinary tract infections, which didn't conform to the recommendation of guideline and medicine specification; the combination of imipenem/cilastatin and metronidazole was unsuitable, the latter was unnecessary. Clinical pharmacists would contact the doctors to modify the prescriptions. Inappropriate prescriptions would be flagged in the Antibacterial Monitoring Report published by the pharmacy department each month; this report was made available to all medical staff. According to the frequency and severity of inappropriate prescriptions, some doctors would be fined.

Clinical pharmacists were responsible for training the medical staff on rational use of antibiotics. Training was conducted every 6 months in two forms. (1) Clinical pharmacists gave lessons to the medical staff in the lecture hall, they need to complete an exam after class. (2) Clinical pharmacists and the medical department jointly made online learning and exam, medical staff was required to finish it. If necessary, pharmacists would go to the clinical departments to give lectures.

Multiple cooperation

Antibiotics data monitoring could not be implemented without the support of the information department. At the start of AMS at our hospital, data extraction modules were embedded into the HIS after discussions between clinical pharmacists and information personnel. Later, an automatic prescription screening system was also included in the HIS, which could intercept inappropriate prescriptions, such as repeated use or unreasonable combinations. Furthermore, clinical pharmacists took part in the Core Expert Meeting of Antibacterial Application held by the Infection Management Office, to discuss usage problems with carbapenems and glycopeptides. If inappropriate use was confirmed by the experts, the relevant physician would be penalized 100–200CNY fine.

Data collection and outcome measures

Antibiotic outcome measures are shown in Table 1(see "Antibiotic outcome measures"). The antibiotic utilization data was collected directly from the HIS. Antibiotic consumption was standardized according to the Anatomical Therapeutic Chemical (ATC) classification system and the DDD was used as a measuring unit, as recommended by the WHO Collaborating Center for Drug Statistics Methodology.[14]The intensity of inpatients' antibiotic consumption was expressed as DDD per 100 bed-days. Information of type I incision operations was extracted from inpatients' electronic medical records. The outcome measures of AMR included the resistance rates of *Escherichia coli*, *Klebsiella pneumonia,* and *Pseudomonas aeruginosa* and incidence rate of methicillin-resistant *Staphylococcus aureus* (MRSA) in our hospital. The bacteriological data were obtained from the clinical microbiology laboratory. We analyzed the correlation between antibiotic consumption and AMR.

Statistical analysis

Segmented regression analysis of interrupted time series was used to analyze the monthly data of antibiotic utilization, which were divided into three stages (the baseline phase, intervention phase, and stability phase), to illustrate the effect of AMS. The statistical model in this study was as follows.[15]

$$Y_t = \beta_0 + \beta_1 \times time_t + \beta_2 \times intervention_t + \beta_3 \times time\ after\ intervention_t + \beta_4 \times stability_t + \beta_5 \times time\ after\ stability_t + e_t$$

In this model, Y_t was the average monthly value of the outcome measure at month t; β_0 estimates the level change in the outcome during the baseline phase; β_1 estimates the trend change during the baseline phase; β_2 estimates the level change during the intervention phase; β_3 estimates the trend change during the intervention phase; β_4 estimates the level

change during the stability phase; and β_5 estimates the trend change during the stability phase. The parameter level was the value of a time series at the beginning of a given time series; the parameter trend was the rate of change in an outcome measure; *time* was a continuous variable indicating time in months at time *t* starting from the baseline phase (time 0); *intervention* was an indicator for time *t* occurring before (*intervention*=0) or after (*intervention*=1) the multi-aspect intervention, which started at month 13 (July 2011); *time after intervention* was a continuous variable counting the months after the intervention; *stability* was an indicator for time *t* occurring before (*stability*=0) or after stability (*stability*=1), which started at month 43 (January 2014); *time after stability* was a continuous variable counting the months after stability. The error term, e_t, represented variation unexplained by the segmented regression model.

Comparisons of the average monthly values of outcome measures for antibiotic use during the three phases were conducted using the Bonferroni test. Box charts were plotted for data visualization, with error bars representing standard deviations.

In addition, a time series analysis model (autoregressive integrated moving average, ARIMA)[8]was used to analyze the trends in annual antibiotic use, AMR trends, and incidence trend of MRSA from 2011 to 2016. The β value indicated the variation of dependent variables when independent variables changed one unit at uniform time intervals. Pearson correlation coefficients were used to examine the relationships between antimicrobial resistance rate, the incidence rate of MRSA, and antibiotic use.

All statistics were performed using SAS, version 9.3 (SAS Institute, Cary, NC, USA). All reported *P* values were two-sided, with $P<0.05$ considered statistically significant.

RESULTS

Change trends in antibiotic utilization rate and intensity

Changes in the proportion of antibiotic prescriptions in outpatients and inpatients during the baseline, intervention, and stability phases are shown in Figure 1A, 1B, 1C and 1D.The associated parameters of time series analysis are summarized in Table 2.The proportion of antibiotic prescriptions in outpatients and inpatients declined by 0.33% (P<0.05) and by 0.59% (P<0.05) each month during the intervention stage, respectively. Bonferroni tests (Figure 1B) showed that the proportion of antibiotic prescriptions in outpatients was reduced from 19.38% during the baseline phase to 13.21% during the stability phase (P<0.05).The proportion of antibiotic prescriptions among inpatients decreased significantly from 64.34% during the baseline phase to 34.65% during the stability phase (P<0.05) (Figure 1D). Figure 1E and Table 2 showed that the intensity of inpatients' antibiotic consumption decreased significantly by 6.46 DDD/100 bed-days (P<0.001) per month during the first year of the intervention stage. Figure 1F showed the intensity of consumption dropped from the baseline phase to the stability phase (102.46 vs. 37.38 DDD/100 bed-days; P<0.05). All the outcomes mentioned above met the national standards. In the stability phase, the $\beta 5$ value for the intensity of consumption (0.70; P<0.001) implied a gradually increasing trend; this still met national standards.

Table 2 Time series analysis of change trends in antibiotic utilization

Antibiotic outcome measures	***β1*-trend (baseline)**	***β2*-level (intervention)**	***β3*-trend (intervention)**	***β4*-level (stability)**	***β5*-trend (stability)**
Proportion-O	−0.01 (0.04)	0.55 (0.83)	−0.33 (0.12)*	0.48 (0.85)	−0.19 (0.14)
Proportion-I	−0.25 (0.10)*	−5.03 (2.22)*	−0.59 (0.29)*	3.61 (2.23)	−0.66 (0.74)
Intensity-I	−0.04 (0.04)	−7.44 (3.62)*	−6.46 (0.56)***	4.20 (1.45)**	0.70 (0.19)***
Proportion-type I	−0.10 (0.04)*	−7.26 (2.92)*	−5.71 (0.61)***	−0.18 (1.44)	−0.12 (0.12)
Timing-type I	−0.01 (0.07)	0.64 (1.72)	1.18 (0.59)*	1.63 (2.00)	−0.17 (0.24)

Duration-type I	0.28 (0.06)***	8.78 (2.15)**	0.10 (0.27)	5.35 (1.44)***	−1.19 (0.19)***

Outcomes of antibiotic utilization included proportion of antibiotic prescriptions in outpatients (Proportion-O), inpatients (Proportion-I), and intensity of consumption in inpatients (Intensity-I). Outcomes of antibiotic prophylaxis included proportion of prophylaxis (Proportion-type I), proportion of rational timing (Timing-type I),and proportion of rational duration(Duration-type I). Parameters of *β1–β5* were expressed as mean (SE), which represented the changes in level and trend.

*P< 0.05； ** P< 0.01； *** P< 0.001.

Change trends of antibiotic prophylaxis in type I incision operations

The proportion of antibiotic prophylaxis in patients undergoing type I incision operations was significantly reduced by 5.71% (P<0.001) monthly during the first year of the intervention phase (Figure 2A, Table 2), decreasing from 98.94% during the baseline phase to 18.93% during the stability phase (P<0.05) (Figure 2B). The proportion of rational timing of the initial dose increased by 1.18% (P<0.05) each month during the intervention stage (Figure 2C, Table2), also increasing from 71.11% during the baseline phase to 96.74% during the stability phase (P<0.05) (Figure 2D).These two outcomes all eventually reached national standards. Although the proportion of rational duration of antibiotic prophylaxis showed an increasing trend during the intervention phase (0.10; P<0.05), the difference was not statistically significant (Figure 2E,Table 2). However, in the stability phase, this showed a decreasing trend (−1.19; P<0.001), which did not meet the national standard (≥ 90%). Figure 2F showed the proportion of rational duration, increasing from 2.84% during the baseline phase to 42.63% during the stability phase (P<0.05).

Trends in resistance rates for common gram-negative bacilli and incidence rate of MRSA, 2011–2016

Time series analysis demonstrated a significant increase in the resistance rates of *E. coli* to carbapenems during 2011–2016 ($P<0.05$).The β value indicated that the resistance rates of *E. coli* to imipenem and meropenem increased by 0.27% and 0.22% each year, respectively. However, the resistance rates of *E.coli* to levofloxacin and ciprofloxacin significantly decreased by 1.62% and 1.40% each year, respectively ($P<0.01$ and $P<0.001$) (Table 3).

Table 3 Trend changes in antimicrobial resistance of *E.coli* to carbapenems and fluoroquinolones from 2011 to 2016

Antibiotic	Resistance rate(%), by year						Time series analysis		
	2011	2012	2013	2014	2015	2016	Trend	β	*P*
Imipenem	0	0	0.1	0.4	0.5	1.5	Increasing	0.2657	0.0239
Meropenem	0	0	0	0.3	0.3	1.3	Increasing	0.2200	0.0471
Levofloxacin	61.3	61.3	59.1	57.7	55.5	53.9	Decreasing	−1.6191	0.0013
Ciprofloxacin	64.3	64.3	61.2	61.4	58.7	58.2	Decreasing	−1.4038	0.0002

Time series analysis demonstrated a significant increase in the resistance rates of *K. pneumoniae* to carbapenems ($P<0.05$).The β value indicated that the resistance rates of *K.pneumoniae* to imipenem and meropenem increased by 1.29% and 1.14% each year, respectively. The resistance rates of *K.pneumoniae* to fluoroquinolones (FQs) remained stable (Table 4).

Table 4 Trend changes in antimicrobial resistance of *K. pneumoniae* to carbapenems and fluoroquinolones from 2011 to 2016

Antibiotic	Resistance rate(%), by year						Time series analysis		
	2011	2012	2013	2014	2015	2016	Trend	β	*P*
Imipenem	2.0	1.5	1	4.8	7.1	6.9	Increasing	1.2937	0.049
Meropenem	1.8	1.5	1	4.1	6.2	6.4	Increasing	1.1381	0.047

Levofloxacin	27.9	27.9	18.4	12.9	14.6	15.2	Stable	−3.0218	0.0973
Ciprofloxacin	28.9	28.9	20.2	15.5	17.0	19.0	Stable	−2.4467	0.1643

Time series analysis showed a significant decrease in the resistance rates of *P. aeruginosa* to FQs ($P<0.05$ and $P<0.01$).The β value indicated that the resistance rate of *P. aeruginosa* to levofloxacin and ciprofloxacin decreased by 4.78% and 2.27% each year, respectively. Resistance rates of *P. aeruginosa* to carbapenems remained stable (Table 5).

Table 5 Trend changes in antimicrobial resistance of *P. aeruginosa* to carbapenems and fluoroquinolones from 2011 to 2016

Antibiotic	**Resistance rate(%), by year**						**Time series analysis**		
	2011	**2012**	**2013**	**2014**	**2015**	**2016**	**Trend**	***β***	***P***
Imipenem	23.1	20.9	15.2	16.5	15.3	15.8	Stable	−1.4811	0.1008
Meropenem	18.2	16.2	10.1	12.9	11.4	11.4	Stable	−1.2977	0.1140
Levofloxacin	28.1	28.1	20.5	10.0	10.1	8.1	Decreasing	−4.7833	0.0137
Ciprofloxacin	18.2	18.2	13.5	11.6	10.5	7.5	Decreasing	−2.2677	0.0011

Our study showed that the incidence rate of nosocomial MRSA decreased significantly by 5.26% each year, declining from 68.0% (2011) to 37.5% (2016) ($P<0.001$) (Supplementary Table S1).

Correlation between antibiotic consumption and AMR

Because carbapenems and FQs are often used for nosocomial infection, we focused on evaluating the impact of use of these drugs on AMR. We found that the intensity of consumption of imipenem/cilastatin significantly increased from 0.59 to 1.36 DDD/100 bed-days ($P<0.01$). However, the intensity of consumption of FQs significantly decreased

each year (P<0.01 and P<0.05), respectively (Supplementary Table S2).

Increased consumption of imipenem/cilastatin was correlated with the prevalence of imipenem-resistant *E. coli*, (r=0.8651, P<0.05). Similarly, decreased consumption of FQs was associated with the decreased resistance rate of *E.coli* to levofloxacin and ciprofloxacin (r=0.8954 and r=0.8950, respectively; P <0.05)(Table 6).

Table 6 Correlation between antibiotic intensity of consumption and resistance rates of *E. coli*, *K. pneumoniae*, *P. aeruginosa*, and incidence rate of MRSA

Antibiotics	***E. coli***		***K. pneumoniae***		***P. aeruginosa***		**MRSA**	
	r	***p***	**r**	***p***	**r**	***p***	**r**	***p***
Imipenem/cilastatin	0.8651	0.0261	0.9050	0.0131	−0.7477	0.0875	−0.9611	0.0022
Meropenem	0.3252	0.5295	0.4095	0.4201	0.3672	0.4739	0.0012	0.9982
Levofloxacin	0.8954	0.0158	0.7523	0.0844	0.8954	0.0159	0.9450	0.0045
Ciprofloxacin	0.8950	0.0160	0.9209	0.0091	0.9282	0.0075	0.8883	0.0180

Antibiotics refer to intensity of consumption (DDD/100 bed-days); bacteria (*E. coli*, *K. pneumoniae*, and *P. aeruginosa*) refer to their resistance rates (%) to antibiotics; MRSA refers to incidence rate of MRSA (%).

r: correlation coefficient.

There was a relationship between the increased resistance rate of *K.pneumoniae* to imipenem/cilastatin and increased intensity of consumption of imipenem/cilastatin (r=0.9050, P <0.05). Although time series analysis showed a stable trend in the resistance rate of *K.pneumoniae* to ciprofloxacin (Table 4), there was still a significantly positive correlation between the prevalence of ciprofloxacin-resistant *K.pneumoniae* and use of ciprofloxacin (r=0.9209, P <0.01)(Table 6).

Table6 indicated that the resistance rate of *P.aeruginosa* to FQs was correlated with the consumption of FQs(r=0.8954, P<0.05 for levofloxacin and r=0.9282, P<0.01 for ciprofloxacin).

The incidence rate of MRSA was positively correlated with the consumption of FQs(r=0.9450, P <0.01 for levofloxacin and r=0.8883, P <0.05 for ciprofloxacin). However, we found that the incidence rate of MRSA was negatively correlated with the consumption of imipenem/cilastatin (r= - 0.9611, P <0.01) (Table 6).

DISCUSSION

The global mortality attributable to AMR is estimated to reach 10 million annually by 2050, which would make it one of the leading causes of death, with an economic impact of up to 100 trillion US dollars (USD).[16]Therefore, many countries worldwide have implemented AMS, with many positive effects in the rational use of antibiotics and health care cost savings.[17-21]

The implementation of AMS in our hospital is managed by clinical pharmacists and supported by the DTC, while multiple sectors participate in it. AMS includes a multifaceted approach to combat the spread of AMR. Except the regular management strategy, our hospital established the reward and punishment mechanism aiming to arouse the doctor's attention to the rational use of antibiotics. After many years of AMS, the proportion of antibiotic prescriptions decreased to 13.21% among outpatients and 34.65% among inpatients. The intensity of antibiotic consumption was reduced to 37.38 DDD/100 bed-days. These outcomes are similar to the study by Bao *et al*.[15]Regarding antibiotic prophylaxis in type I incision operations, the proportion of antibiotic prophylaxis decreased to 18.93% and the proportion of rational timing of the initial dose increased to 96.74%. Only the proportion of rational duration of antibiotic prophylaxis (42.63%) did not reach the national standard, for the following reasons. First, coronary artery bypass graft (CABG) surgery belongs to type I incision operations, according to the Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery,[22]the duration of prophylaxis for cardiothoracic procedures is up to 48

hours, with no supporting evidence. Chinese Guidelines suggest prophylactic duration be no more than 48 hours. But CABG involves important viscera, in which the consequences of infection would be severe. Therefore, doctors hesitate to stop antibiotics within 48 hours after surgery. Second, in orthopedic surgeries, such as open reduction and plate or screw internal fixation of fractures, in consideration of implants doctors also hesitate to stop antibiotics within 24 hours after surgery. Third, the difficult doctor-patient relationships in China make physicians hesitant about premature discontinuation of antibiotics.

The aim of AMS is to limit the prevalence of AMR. The results showed that with decreased intensity of FQ consumption, the resistance rates of *E. coli* and *P.aeruginosa* to FQs and incidence rate of MRSA showed decreasing trends, and they were positively correlated. This implied that controlling the use of FQs might limit the prevalence of AMR as well as limit the emergence of MRSA; the latter is consistent with previous studies.[23,24]Other studies[25-28]have reported that a reduction in second/third-generation cephalosporins and clindamycin contributed to a reduction in both incidence rate of MRSA and prevalence density of MRSA bacteremia. In our study, we also found that the incidence rate of MRSA was negatively correlated with imipenem/cilastatin use, which was difficult to explain. To our knowledge, few studies have obtained results similar to ours. Lai *et al*. reported[29]a significant correlation between increased use of linezolid and teicoplanin and decreased prevalence of MRSA. Therefore, we theorize that the reduced use of non-special grade antibiotics (such as FQs and others) leads to a compensatory increased use of carbapenems; however, this negative correlation requires further exploration. In addition, we found the resistance rate of *E. coli* and *K.pneumoniae* to carbapenems showed an increasing trend, meaning that carbapenem-resistant Enterobacteriaceae (CRE) could pose a serious threat. On March 3, 2017, the NHFPC issued a Notice Regarding Further Reinforcement in Management of Clinical Application of Antibacterial to Control Bacteria Resistance, which required medical

institutions to gather, archive, and analyze patient information with respect to the use of carbapenems, to help control the prevalence of CRE.[30]

CHINET surveillance of AMR in China reported the resistance trends from 2005 to 2014, using data from 19 hospitals.[31]In our hospital, the resistance rates of *E. coli*, *K.pneumoniae*, and *P.aeruginosa* to imipenem/cilastatin and meropenem in 2014 (0.4% and 0.9%, 4.8% and 4.1%, 16.5% and 12.9%, respectively) were significantly lower than those reported by CHINET (0.9% and 1.0%, 10.5% and 13.4%, 26.6% and 24.3%, respectively). This proved that AMS in our hospital played an important role in control of AMR.

Some limitations of this study should be noted. First, this was a retrospective observational study without simultaneous control group, the bias couldn't be well controlled, it was less convincing than a prospective, controlled study design. So the favorable results obtained can not be attributed solely to the pharmacist intervention, which were affected by many factors. Second, because AMS has been ongoing for many years, several different clinical pharmacists have successively participated in the evaluation of prophylactic antibiotic use; therefore, the evaluation results might be affected slightly by individual differences.

CONCLUSION

This study demonstrated that AMS in our hospital could reduce and optimize antibiotic use, declining bacterial resistance to FQs was associated with its reduced consumption. Clinical pharmacists played an important role in improving the rational use of antibiotics, however, hospital infection prevention and control measures, national policy guidance all contributed to it. The findings of our study indicate some directions to pursue in controlling the prevalence of CRE and MRSA. AMR is rising worldwide, so continual effort regarding AMS is critical not only in large hospitals but also in primary or community hospitals.

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Contributors LHL was the leader of AMS and responsible for supervising the work, work plan, and manuscript review. HGW was responsible for carrying out AMS and collecting, analyzing, and reporting data; she wrote this manuscript and made some amendments after review. HW was responsible for statistical analysis and wrote the analysis method in the manuscript. XJY, HZ, BYL, GC, ZKY, YW, XLC,YYZ, RZ, ZHW, HY were all involved in the different aspects of data collection. PW and CXY provided the bacterial resistance data. All authors were involved in data verification.

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Competing interests None declared.

Patient consent Not required.

Ethics approval Beijing Chaoyang Hospital Ethics Committee.

Data sharing statement No additional unpublished data are available.

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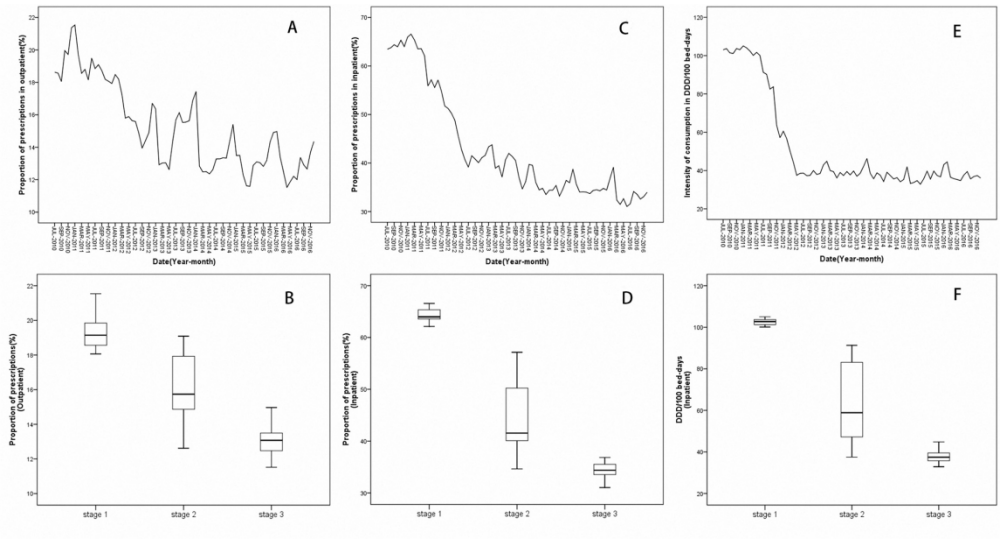
Figure legends:

Figure 1. Changes in proportion of antibiotic prescriptions and intensity of consumption.

Time series curves of each monthly value of antibiotic prescribing proportions, plotted for outpatients (A) and inpatients (C). Each monthly value of intensity of antibiotic consumption was plotted for inpatients (E). The Bonferroni test was conducted to compare these data in three stages, for antibiotic prescribing proportion among outpatients (B) and inpatients (D), and intensity of antibiotic consumption (F). Stage 1, Stage 2, and Stage 3 on the x-axis represent the baseline phase, intervention phase, and stability phase, respectively.

Figure 2. Changes in antibiotic prophylaxis in type I incision operations.

Time series curves of each monthly value of antibiotic prophylaxis were plotted for proportion of prophylaxis (A), proportion of rational timing (C), and proportion of rational duration (E). These data in three stages were compared by Bonferroni test (B, D, and F). Stage 1, Stage 2, and Stage 3 on the x-axis represent the baseline phase, intervention phase, and stability phase, respectively.



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Time series curves of each monthly value of antibiotic prescribing proportions, plotted for outpatients (A) and inpatients (C). Each monthly value of intensity of antibiotic consumption was plotted for inpatients (E). The Bonferroni test was conducted to compare these data in three stages, for antibiotic prescribing proportion among outpatients (B) and inpatients (D), and intensity of antibiotic consumption (F). Stage 1, Stage 2, and Stage 3 on the x-axis represent the baseline phase, intervention phase, and stability phase, respectively.

388x207mm (144 x 144 DPI)

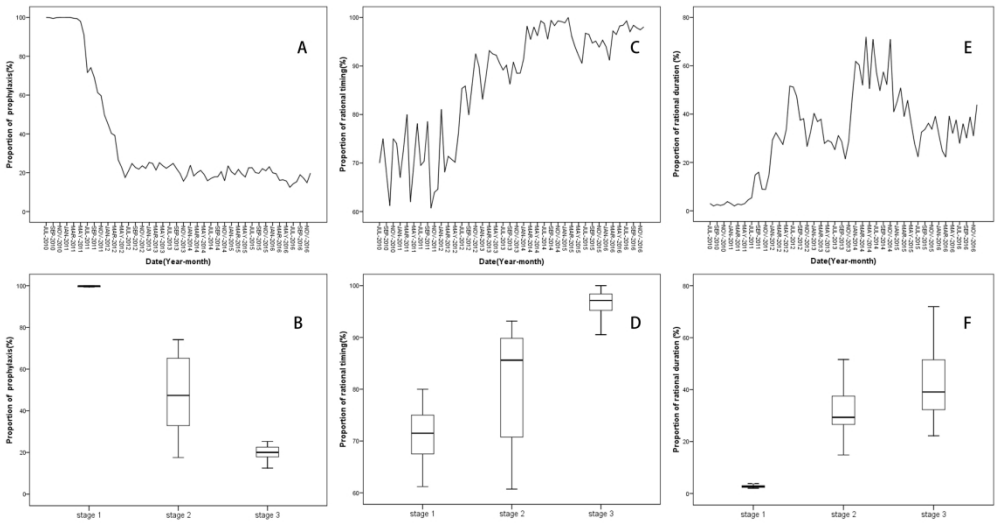

Figure 2. Changes in antibiotic prophylaxis in type I incision operations.
Time series curves of each monthly value of antibiotic prophylaxis were plotted for proportion of prophylaxis (A), proportion of rational timing (C), and proportion of rational duration (E). These data in three stages were compared by Bonferroni test (B, D, and F). Stage 1, Stage 2, and Stage 3 on the x-axis represent the baseline phase, intervention phase, and stability phase, respectively.

546x292mm (144 x 144 DPI)

Supplementary materials

Table S1 Trend changes in incidence rate of methicillin-resistant *Staphylococcus aureus* from 2011 to 2016

	By year						Time series analysis		
	2011	**2012**	**2013**	**2014**	**2015**	**2016**	**Trend**	***β***	***P***
Incidence rate (%)	68.0	60.3	58.3	49.8	51.5	37.5	Decreasing	−5.2565	0.0007

Table S2 Usage trend changes of carbapenems and fluoroquinolones from 2011 to 2016

Antibiotic	**Antibiotic consumption (DDD/100 bed-days) by year**						**Time series analysis**		
	2011	**2012**	**2013**	**2014**	**2015**	**2016**	**Trend**	***β***	***P***
Imipenem/cilastatin	0.59	0.71	0.79	1.17	1.16	1.36	Increasing	0.1599	0.0013
Meropenem	0.86	0.34	0.29	0.38	0.66	0.69	Stable	−0.0116	0.9193
Levofloxacin	11.18	9.70	10.64	7.74	7.71	6.35	Decreasing	−0.9292	0.0033
Ciprofloxacin	6.17	4.12	2.49	0.91	0.66	0.45	Decreasing	−1.1811	0.0461

DDD, defined daily dose.

STROBE Statement—checklist of items that should be included in reports of observational studies

Our research met all the items of STROBE statement.

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-5
Objectives	3	State specific objectives, including any prespecified hypotheses	3-5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2,4,5,8,9
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Not Applicable for this study. This study was a retrospective observational study,please See P5,8-10
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-10
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	1,2
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-10
		(*b*) Describe any methods used to examine subgroups and interactions	8-10
		(*c*) Explain how missing data were addressed	None
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Not Applicable for this study
		(*e*) Describe any sensitivity analyses	8-10

Continued on next page

Results			**Page number**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	2-3
		(b) Give reasons for non-participation at each stage	Applicable for this study
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Applicable for this study
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Applicable for this study
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Applicable for this study
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	19-21
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	4,22
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-22
Generalisability	21	Discuss the generalisability (external validity) of the study results	20-22
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	None

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Impact of antimicrobial stewardship managed by clinical pharmacists on antibiotic use and drug resistance in a Chinese hospital, 2010–2016: a retrospective observational study

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Impact of antimicrobial stewardship managed by clinical pharmacists on antibiotic use and drug resistance in a Chinese hospital, 2010–2016: a retrospective observational study

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Word count: 4121

ABSTRACT

Objectives: "National Special Stewardship in the Clinical Use of Antibiotics" was put forward in July, 2011 in China. We aimed to retrospectively evaluate the impact of antimicrobial stewardship (AMS) managed by clinical pharmacists on antibiotic utilization, prophylaxis and antimicrobial resistance (AMR).

Design: This was a retrospective observational study of trends in antibiotic use and AMR in

the context of AMS.

Setting: Beijing Chaoyang Hospital, a 1400-bed tertiary hospital, in China.

Data and participants: Antibiotic prescriptions from 820 doctors included all outpatients (N=17766637) and inpatients (N=376627) during 2010–2016. Bacterial resistance data were from all inpatients (N=350699) during 2011–2016.

Interventions: Multi-aspect intervention measures were implemented by clinical pharmacists (13persons), e.g. formulating the activity program and performance management, advising on antibacterial prescriptions and training.

Outcome measures: The proportion of antibiotic prescriptions among outpatients and inpatients, intensity of consumption in defined daily dose (DDD)/100 bed-days, antibiotic prophylaxis in type I incision operations, and resistance rates of *Escherichia coli*, *Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* were retrospectively analyzed.

Results: The proportion of antibiotic prescriptions decreased in outpatients (from 19.38% to 13.21%) and in inpatients (from 64.34% to 34.65%), the intensity of consumption dropped from 102.46 to 37.38 DDD/100 bed-days. The proportion of antibiotic prophylaxis decreased from 98.94% to 18.93%. The proportion of rational timing of initial dose increased from 71.11% to 96.74%, the proportion of rational duration rose from 2.84% to 42.63%. Time series analysis demonstrated the resistance rates of *E. coli* and *P. aeruginosa* to fluoroquinolones decreased, the incidence rate of methicillin-resistant *Staphylococcus aureus* (MRSA) also decreased; whereas the resistance rates of *E. coli* and *K. pneumoniae* to carbapenems increased. The antibiotic use was partly positively correlated with AMR.

Conclusions: AMS had an important role in reducing antibiotic use and surgical antibiotic prophylaxis. The AMR was positively correlated with antibiotic consumption to some extent.

Strengths and limitations of this study

- Our study described the entire process of AMS, from management of antibiotic use to AMR monitoring.
- Time series analysis, a better tool, was applied to analyze the change trends in antibiotic utilization and AMR.
- By exploring the correlation between antibiotic use and AMR， this study may indicate some potential directions for controlling the prevalence of CRE and MRSA.
- This was a retrospective observational study without simultaneous control group, the bias couldn't be well controlled; the evaluation of prophylactic antibiotic use by different clinical pharmacists might have individual differences.

INTRODUCTION

In 2004, the first Guidelines for the Clinical Use of Antibiotics (Guidelines for short) was issued by the National Health and Family Planning Commission (NHFPC, originally called the Ministry of Health) of the People's Republic of China, describing the characteristics of all types of antibiotics and appropriate use in treatment and prevention of infectious diseases; the Guidelines were updated in 2015. Regretfully, not all medical staff knew about the Guidelines or their significance. Today, antimicrobial resistance (AMR) is one of the greatest threats to global health. There are four main factors contributing to the spread of AMR: inappropriate use of antibiotics in the community and in hospitals, misuse of antibiotics in animal production and agriculture, and the presence of resistant bacteria in the environment. The former three factors could aggravate the last one.[1] Chinese data from the Ministry of Health National Antibacterial Resistance Surveillance Net (MOHNARIN) showed that AMR has been rising steadily each year.[2]

In 2001 the World Health Organization (WHO) began to take measures to combat the spread of AMR and strongly recommended governments to implement antimicrobial

stewardship (AMS).[3]On World Health Day 2011, AMR was also selected as the theme. In response to AMR, in 2011 the NHFPC of China put forward "National Special Stewardship in the Clinical Use of Antibiotics",[4] the historically strictest management of antibiotics up to that date. The NHFPC set many goals for the clinical use of antibiotics, including restriction of antibiotic use in outpatients and inpatients and restriction of antibiotic prophylactic use in clean operations, to promote rational antibiotic use and control AMR. These goals are described in detail below. This special stewardship policy mainly covered secondary and tertiary public hospitals and took effect on July 1, 2011. After that date, these hospitals were required to report data of antibiotic use to the government every month.

In recent years, some studies have reported that AMS had positive effects on controlling antibiotic-resistant pathogens, rational use of antibiotics, and cost savings,[5,6] highlighting the importance of AMS. There were also some studies [7-11]that analyzed the correlation between antibiotic use and AMR, although these all demonstrated the effectiveness of AMS, but the studied population, antibiotic and pathogen are different, and the results of correlation between antibiotic use and AMR were not exactly the same.

The aim of this study was to evaluate the impact of AMS on antibiotic use and AMR trends, to share our successful management experience, and to identify existing problems. In addition, because the doctors' prescription behaviors and antibiotic variety are different in each country or region, so is the status of AMR, therefore we sought to demonstrate the correlation between antibiotic use and antimicrobial resistance rate of common nosocomial pathogens, using data from all inpatients in our hospital.

METHODS

Study design

According to the requirements of the national policy, " Special Stewardship in the Clinical Use of Antibiotics " was a 3-year plan (2011–2013). In April of 2014, the NHFPC

issued a Notice Regarding Implementing Stewardship of Antibacterial Use in the Clinic;[12]its aim was to continuously maintain the positive effects gained during the previous 3 years. Accordingly, in our retrospective study, phases were divided into three stages, as follows. Stage 1: baseline phase (July 2010 to June 2011); stage 2: intervention phase (July 2011 to December 2013); and stage 3: stability phase (January 2014 to December 2016).

Patient and public involvement

The antibiotic utilization data was extracted directly from the Hospital Information System (HIS) and electronic medical records of all patients (2010-2016). The patient's personal information was hidden. The bacterial resistance data from all inpatients (2011-2016) was provided by the Department of Infectious Diseases and Clinical Microbiology. Clinical sample sources included blood, cerebrospinal fluid, pleural effusion, ascites, urine and sputum, etc. Duplicate isolates, defined as the isolates of the same species that showed the same susceptibility results at the same site for each patient in different days, were excluded, only the first isolated strain was included in the study (excluding isolates of surveillance cultures).

Ethics statement

This study was approved by the Ethics Committee of Beijing Chaoyang Hospital (Approval Number: 2017-11-28-3). Because the patient's privacy was not violated in the study, so the Ethics Committee agreed exemption applications of informed consent.

Multi-aspect intervention measures

Organization construction

To implement the program “National Special Stewardship in the Clinical Use of Antibiotics”, an AMS group was set up in our hospital, which was attached to the Drug and Therapeutics Committee (DTC). The AMS group was composed of administrators, clinicians, infectious disease physicians, pharmacists, microbiologists, and information staff, and

included a leadership group and expert group. The leadership group was responsible for work deployment and supervision whereas the expert group was responsible for technical guidance, participation in consultations, training doctors on rational use of antibiotics and implementation of AMS monitoring (such as data collection and report, prescription review and feedback, AMR monitoring, etc). Generally the medical department led AMS in many hospitals in China, but in our hospital, the pharmacy department was the leading department, for the following reasons. (1) The pharmacy department in our hospital is not only a technical section but also a functional section. The pharmacy director is responsible for medication use. (2) There are many clinical pharmacists, such as infectious disease pharmacists who have sufficient knowledge and clinical experience to manage AMS. (3) Clinical pharmacists work in the clinical departments every day, so they could give their professional advice regarding antibiotic use directly to doctors.

Formulating the activity program and administrative intervention

The AMS group formulated the activity program of stewardship and some regulations on antibiotic use were issued, as follows. (1) Antibiotic classification management system. All antibiotics were classified as non-restricted, restricted, and special grade antibiotics. Physicians with different professional titles were matched to the corresponding grade of antibiotic prescribing privileges. (2) Management system of antibiotic prescribing privileges. In May of 2012, the Regulations on Clinical Applications of Antibiotics were issued by the NHFPC, which took effect on August, 1, 2012. These were the first valid regulations on antibiotics in China.[13]The regulations required that physicians would not be given antibiotic prescribing privileges until they passed an exam, after completing training on rational use of antibiotics. This prescribing privilege restriction was embedded into the Hospital Information System (HIS). (3) Regulation of perioperative prophylactic antibiotic use in clean operations, in which the choice of antibiotics, dose, timing of the initial dose, and duration of antibiotic

prophylaxis were described.

According to the requirements of the national antibiotic stewardship program,[4] the AMS group established the goals for antibiotic application in the hospital (Table 1).

Table 1 Goals of clinical antibiotic use established by the NHFPC in 2011

Antibiotic outcome measures	Goals
1. Proportion of inpatients receiving antibiotics	≤ 60%
2. Proportion of outpatients receiving antibiotics	≤ 20%
3. Intensity of inpatients' antibiotic consumption	≤ 40 DDD/100 bed-days
4. Proportion of antibiotic prophylaxis in patients receiving type I incision operations/clean operations	≤ 30%
5. Timing of initial dose of preoperative antibiotic prophylaxis	Within 0.5–2 h before surgical incision
6. Duration of antibiotic prophylaxis in patients receiving type I incision operations/clean operations	Within 24 h after the end of operation

Performance management

Every year, the directors of clinical departments were asked by the director of the hospital to sign responsibility agreements for antibiotic use. Hospital leaders and the pharmacy director, together with clinical pharmacists, established or updated the performance appraisal system for antibiotic use, which indicated the circumstances to be rewarded or penalized. For example, if clinical departments did not accomplish their goals, the directors would be fined 1000–3000CNY, and doctors would be fined 300–500CNY. If the clinical departments accomplished their goals, the directors would be rewarded with 1000–5000 CNY and doctors with 300–1000 CNY, which were greater than the amounts of fines.

Antibiotic prescription evaluation and training

Retrospective rationality evaluation of antibiotic prescriptions for outpatients,

emergency room patients, and inpatients was performed monthly by clinical pharmacists. For example, some doctors used moxifloxacin to treat urinary tract infections, which didn't conform to the recommendation of guideline and medicine specification; the combination of imipenem/cilastatin and metronidazole was unsuitable, the latter was unnecessary. Clinical pharmacists would contact the doctors to modify the prescriptions. Inappropriate prescriptions would be flagged in the Antibacterial Monitoring Report published by the pharmacy department each month; this report was made available to all medical staff. According to the frequency and severity of inappropriate prescriptions, some doctors would be fined.

Clinical pharmacists were responsible for training the medical staff on rational use of antibiotics. Training was conducted every 6 months in two forms. (1) Clinical pharmacists gave lessons to the medical staff in the lecture hall, they need to complete an exam after class. (2) Clinical pharmacists and the medical department jointly made online learning and exam, medical staff was required to finish it. If necessary, pharmacists would go to the clinical departments to give lectures.

Multiple cooperation

Antibiotics data monitoring could not be implemented without the support of the information department. At the start of AMS at our hospital, data extraction modules were embedded into the HIS after discussions between clinical pharmacists and information personnel. Later, an automatic prescription screening system was also included in the HIS, which could intercept inappropriate prescriptions, such as repeated use or unreasonable combinations. Furthermore, clinical pharmacists took part in the Core Expert Meeting of Antibacterial Application held by the Infection Management Office, to discuss usage problems with carbapenems and glycopeptides. If inappropriate use was confirmed by the experts, the relevant physician would be penalized 100–200CNY fine.

Data collection and outcome measures

Antibiotic outcome measures are shown in Table 1(see "Antibiotic outcome measures"). The antibiotic utilization data was collected directly from the HIS. Antibiotic consumption was standardized according to the Anatomical Therapeutic Chemical (ATC) classification system and the DDD was used as a measuring unit, as recommended by the WHO Collaborating Center for Drug Statistics Methodology.[14]The intensity of inpatients' antibiotic consumption was expressed as DDD per 100 bed-days. Information of type I incision operations was extracted from inpatients' electronic medical records. The outcome measures of AMR included the resistance rates of *Escherichia coli*, *Klebsiella pneumonia,* and *Pseudomonas aeruginosa* and incidence rate of methicillin-resistant *Staphylococcus aureus* (MRSA) in our hospital. The bacteriological data were obtained from the clinical microbiology laboratory. We analyzed the correlation between antibiotic consumption and AMR.

Statistical analysis

Segmented regression analysis of interrupted time series was used to analyze the monthly data of antibiotic utilization, which were divided into three stages (the baseline phase, intervention phase, and stability phase), to illustrate the effect of AMS. The statistical model in this study was as follows.[15]

$$Y_t = \beta_0 + \beta_1 \times time_t + \beta_2 \times intervention_t + \beta_3 \times time\ after\ intervention_t + \beta_4 \times stability_t + \beta_5 \times time\ after\ stability_t + e_t$$

In this model, Y_t was the average monthly value of the outcome measure at month t; β_0 estimates the level change in the outcome during the baseline phase; β_1 estimates the trend change during the baseline phase; β_2 estimates the level change during the intervention phase; β_3 estimates the trend change during the intervention phase; β_4 estimates the level

change during the stability phase; and β_5 estimates the trend change during the stability phase. The parameter level was the value of a time series at the beginning of a given time series; the parameter trend was the rate of change in an outcome measure; *time* was a continuous variable indicating time in months at time *t* starting from the baseline phase (time 0); *intervention* was an indicator for time *t* occurring before (*intervention*=0) or after (*intervention*=1) the multi-aspect intervention, which started at month 13 (July 2011); *time after intervention* was a continuous variable counting the months after the intervention; *stability* was an indicator for time *t* occurring before (*stability*=0) or after stability (*stability*=1), which started at month 43 (January 2014); *time after stability* was a continuous variable counting the months after stability. The error term, e_t, represented variation unexplained by the segmented regression model.

Comparisons of the average monthly values of outcome measures for antibiotic use during the three phases were conducted using the Bonferroni test. Box charts were plotted for data visualization, with error bars representing standard deviations.

In addition, a time series analysis model (autoregressive integrated moving average, ARIMA)[8]was used to analyze the trends in annual antibiotic use, AMR trends, and incidence trend of MRSA from 2011 to 2016. The β value indicated the variation of dependent variables when independent variables changed one unit at uniform time intervals. Pearson correlation coefficients were used to examine the relationships between antimicrobial resistance rate, the incidence rate of MRSA, and antibiotic use.

All statistics were performed using SAS, version 9.3 (SAS Institute, Cary, NC, USA). All reported *P* values were two-sided, with $P<0.05$ considered statistically significant.

RESULTS

Change trends in antibiotic utilization rate and intensity

Changes in the proportion of antibiotic prescriptions in outpatients and inpatients during the baseline, intervention, and stability phases are shown in Figure 1A, 1B, 1C and 1D.The associated parameters of time series analysis are summarized in Table 2.The proportion of antibiotic prescriptions in outpatients and inpatients declined by 0.33% (P<0.05) and by 0.59% (P<0.05) each month during the intervention stage, respectively. Bonferroni tests (Figure 1B) showed that the proportion of antibiotic prescriptions in outpatients was reduced from 19.38% during the baseline phase to 13.21% during the stability phase (P<0.05).The proportion of antibiotic prescriptions among inpatients decreased significantly from 64.34% during the baseline phase to 34.65% during the stability phase (P<0.05) (Figure 1D). Figure 1E and Table 2 showed that the intensity of inpatients' antibiotic consumption decreased significantly by 6.46 DDD/100 bed-days (P<0.001) per month during the first year of the intervention stage. Figure 1F showed the intensity of consumption dropped from the baseline phase to the stability phase (102.46 vs. 37.38 DDD/100 bed-days; P<0.05). All the outcomes mentioned above met the national standards. In the stability phase, the $\beta 5$ value for the intensity of consumption (0.70; P<0.001) implied a gradually increasing trend; this still met national standards.

Table 2 Time series analysis of change trends in antibiotic utilization

Antibiotic outcome measures	***β1*-trend (baseline)**	***β2*-level (intervention)**	***β3*-trend (intervention)**	***β4*-level (stability)**	***β5*-trend (stability)**
Proportion-O	−0.01 (0.04)	0.55 (0.83)	−0.33 (0.12)*	0.48 (0.85)	−0.19 (0.14)
Proportion-I	−0.25 (0.10)*	−5.03 (2.22)*	−0.59 (0.29)*	3.61 (2.23)	−0.66 (0.74)
Intensity-I	−0.04 (0.04)	−7.44 (3.62)*	−6.46 (0.56)***	4.20 (1.45)**	0.70 (0.19)***
Proportion-type I	−0.10 (0.04)*	−7.26 (2.92)*	−5.71 (0.61)***	−0.18 (1.44)	−0.12 (0.12)
Timing-type I	−0.01 (0.07)	0.64 (1.72)	1.18 (0.59)*	1.63 (2.00)	−0.17 (0.24)

Duration-type I	0.28 (0.06)***	8.78 (2.15)**	0.10 (0.27)	5.35 (1.44)***	−1.19 (0.19)***

Outcomes of antibiotic utilization included proportion of antibiotic prescriptions in outpatients (Proportion-O), inpatients (Proportion-I), and intensity of consumption in inpatients (Intensity-I). Outcomes of antibiotic prophylaxis included proportion of prophylaxis (Proportion-type I), proportion of rational timing (Timing-type I),and proportion of rational duration(Duration-type I). Parameters of *β1–β5* were expressed as mean (SE), which represented the changes in level and trend.

*P< 0.05； ** P< 0.01； *** P< 0.001.

Change trends of antibiotic prophylaxis in type I incision operations

The proportion of antibiotic prophylaxis in patients undergoing type I incision operations was significantly reduced by 5.71% (P<0.001) monthly during the first year of the intervention phase (Figure 2A, Table 2), decreasing from 98.94% during the baseline phase to 18.93% during the stability phase (P<0.05) (Figure 2B). The proportion of rational timing of the initial dose increased by 1.18% (P<0.05) each month during the intervention stage (Figure 2C, Table2), also increasing from 71.11% during the baseline phase to 96.74% during the stability phase (P<0.05) (Figure 2D).These two outcomes all eventually reached national standards. Although the proportion of rational duration of antibiotic prophylaxis showed an increasing trend during the intervention phase (0.10; P<0.05), the difference was not statistically significant (Figure 2E,Table 2). However, in the stability phase, this showed a decreasing trend (−1.19; P<0.001), which did not meet the national standard (≥ 90%). Figure 2F showed the proportion of rational duration, increasing from 2.84% during the baseline phase to 42.63% during the stability phase (P<0.05).

Trends in resistance rates for common gram-negative bacilli and incidence rate of MRSA, 2011–2016

Time series analysis demonstrated a significant increase in the resistance rates of *E. coli* to carbapenems during 2011–2016 ($P<0.05$).The β value indicated that the resistance rates of *E. coli* to imipenem and meropenem increased by 0.27% and 0.22% each year, respectively. However, the resistance rates of *E.coli* to levofloxacin and ciprofloxacin significantly decreased by 1.62% and 1.40% each year, respectively ($P<0.01$ and $P<0.001$) (Table 3).

Table 3 Trend changes in antimicrobial resistance of *E.coli* to carbapenems and fluoroquinolones from 2011 to 2016

Antibiotic	Resistance rate(%), by year						Time series analysis		
	2011	2012	2013	2014	2015	2016	Trend	β	*P*
Imipenem	0	0	0.1	0.4	0.5	1.5	Increasing	0.2657	0.0239
Meropenem	0	0	0	0.3	0.3	1.3	Increasing	0.2200	0.0471
Levofloxacin	61.3	61.3	59.1	57.7	55.5	53.9	Decreasing	−1.6191	0.0013
Ciprofloxacin	64.3	64.3	61.2	61.4	58.7	58.2	Decreasing	−1.4038	0.0002

Time series analysis demonstrated a significant increase in the resistance rates of *K. pneumoniae* to carbapenems ($P<0.05$).The β value indicated that the resistance rates of *K.pneumoniae* to imipenem and meropenem increased by 1.29% and 1.14% each year, respectively. The resistance rates of *K.pneumoniae* to fluoroquinolones (FQs) remained stable (Table 4).

Table 4 Trend changes in antimicrobial resistance of *K. pneumoniae* to carbapenems and fluoroquinolones from 2011 to 2016

Antibiotic	Resistance rate(%), by year						Time series analysis		
	2011	2012	2013	2014	2015	2016	Trend	β	*P*
Imipenem	2.0	1.5	1	4.8	7.1	6.9	Increasing	1.2937	0.049
Meropenem	1.8	1.5	1	4.1	6.2	6.4	Increasing	1.1381	0.047

Levofloxacin	27.9	27.9	18.4	12.9	14.6	15.2	Stable	−3.0218	0.0973
Ciprofloxacin	28.9	28.9	20.2	15.5	17.0	19.0	Stable	−2.4467	0.1643

Time series analysis showed a significant decrease in the resistance rates of *P. aeruginosa* to FQs ($P<0.05$ and $P<0.01$).The β value indicated that the resistance rate of *P. aeruginosa* to levofloxacin and ciprofloxacin decreased by 4.78% and 2.27% each year, respectively. Resistance rates of *P. aeruginosa* to carbapenems remained stable (Table 5).

Table 5 Trend changes in antimicrobial resistance of *P. aeruginosa* to carbapenems and fluoroquinolones from 2011 to 2016

Antibiotic	**Resistance rate(%), by year**						**Time series analysis**		
	2011	**2012**	**2013**	**2014**	**2015**	**2016**	**Trend**	***β***	***P***
Imipenem	23.1	20.9	15.2	16.5	15.3	15.8	Stable	−1.4811	0.1008
Meropenem	18.2	16.2	10.1	12.9	11.4	11.4	Stable	−1.2977	0.1140
Levofloxacin	28.1	28.1	20.5	10.0	10.1	8.1	Decreasing	−4.7833	0.0137
Ciprofloxacin	18.2	18.2	13.5	11.6	10.5	7.5	Decreasing	−2.2677	0.0011

Our study showed that the incidence rate of nosocomial MRSA decreased significantly by 5.26% each year, declining from 68.0% (2011) to 37.5% (2016) ($P<0.001$) (Supplementary Table S1).

Correlation between antibiotic consumption and AMR

Because carbapenems and FQs are often used for nosocomial infection, we focused on evaluating the impact of use of these drugs on AMR. We found that the intensity of consumption of imipenem/cilastatin significantly increased from 0.59 to 1.36 DDD/100 bed-days ($P<0.01$). However, the intensity of consumption of FQs significantly decreased

each year (P<0.01 and P<0.05), respectively (Supplementary Table S2).

Increased consumption of imipenem/cilastatin was correlated with the prevalence of imipenem-resistant *E. coli*, (r=0.8651, P<0.05). Similarly, decreased consumption of FQs was associated with the decreased resistance rate of *E.coli* to levofloxacin and ciprofloxacin (r=0.8954 and r=0.8950, respectively; P <0.05)(Table 6).

Table 6 Correlation between antibiotic intensity of consumption and resistance rates of *E. coli*, *K. pneumoniae*, *P. aeruginosa*, and incidence rate of MRSA

Antibiotics	***E. coli***		***K. pneumoniae***		***P. aeruginosa***		**MRSA**	
	r	***p***	**r**	***p***	**r**	***p***	**r**	***p***
Imipenem/cilastatin	0.8651	0.0261	0.9050	0.0131	−0.7477	0.0875	−0.9611	0.0022
Meropenem	0.3252	0.5295	0.4095	0.4201	0.3672	0.4739	0.0012	0.9982
Levofloxacin	0.8954	0.0158	0.7523	0.0844	0.8954	0.0159	0.9450	0.0045
Ciprofloxacin	0.8950	0.0160	0.9209	0.0091	0.9282	0.0075	0.8883	0.0180

Antibiotics refer to intensity of consumption (DDD/100 bed-days); bacteria (*E. coli*, *K. pneumoniae*, and *P. aeruginosa*) refer to their resistance rates (%) to antibiotics; MRSA refers to incidence rate of MRSA (%).

r: correlation coefficient.

There was a relationship between the increased resistance rate of *K.pneumoniae* to imipenem/cilastatin and increased intensity of consumption of imipenem/cilastatin (r=0.9050, P <0.05). Although time series analysis showed a stable trend in the resistance rate of *K.pneumoniae* to ciprofloxacin (Table 4), there was still a significantly positive correlation between the prevalence of ciprofloxacin-resistant *K.pneumoniae* and use of ciprofloxacin (r=0.9209, P <0.01)(Table 6).

Table6 indicated that the resistance rate of *P.aeruginosa* to FQs was correlated with the consumption of FQs(r=0.8954, P<0.05 for levofloxacin and r=0.9282, P<0.01 for ciprofloxacin).

The incidence rate of MRSA was positively correlated with the consumption of FQs(r=0.9450, P <0.01 for levofloxacin and r=0.8883, P <0.05 for ciprofloxacin). However, we found that the incidence rate of MRSA was negatively correlated with the consumption of imipenem/cilastatin (r= - 0.9611, P <0.01) (Table 6).

DISCUSSION

The global mortality attributable to AMR is estimated to reach 10 million annually by 2050, which would make it one of the leading causes of death, with an economic impact of up to 100 trillion US dollars (USD).[16]Therefore, many countries worldwide have implemented AMS, with many positive effects in the rational use of antibiotics and health care cost savings.[17-21]

The implementation of AMS in our hospital is managed by clinical pharmacists and supported by the DTC, while multiple sectors participate in it. AMS includes a multifaceted approach to combat the spread of AMR. Except the regular management strategy (such as multidisciplinary consultation, nosocomial infection control, prescription prospective audit, prescription evaluation and feedback, publicity and education, etc), our hospital established the reward and punishment mechanism aiming to arouse the doctor's attention to the rational use of antibiotics, which is slightly different from the existing intervention model and is unique among the published studies of AMS, but it reflects the current situation of some Chinese hospitals. After many years of AMS, the proportion of antibiotic prescriptions decreased to 13.21% among outpatients and 34.65% among inpatients. The intensity of antibiotic consumption was reduced to 37.38 DDD/100 bed-days. These outcomes are similar to the study by Bao *et al*.[15]Regarding antibiotic prophylaxis in type I incision operations, the proportion of antibiotic prophylaxis decreased to 18.93% and the proportion of rational timing of the initial dose increased to 96.74%. Only the proportion of rational duration of

antibiotic prophylaxis (42.63%) did not reach the national standard, for the following reasons. First, coronary artery bypass graft (CABG) surgery belongs to type I incision operations, according to the Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery,[22]the duration of prophylaxis for cardiothoracic procedures is up to 48 hours, with no supporting evidence. Chinese Guidelines suggest prophylactic duration be no more than 48 hours. But CABG involves important viscera, in which the consequences of infection would be severe. Therefore, doctors hesitate to stop antibiotics within 48 hours after surgery. Second, in orthopedic surgeries, such as open reduction and plate or screw internal fixation of fractures, in consideration of implants doctors also hesitate to stop antibiotics within 24 hours after surgery. Third, the difficult doctor-patient relationships in China make physicians hesitant about premature discontinuation of antibiotics.

The aim of AMS is to limit the prevalence of AMR. The results showed that with decreased intensity of FQ consumption, the resistance rates of *E. coli* and *P.aeruginosa* to FQs and incidence rate of MRSA showed decreasing trends, and they were positively correlated. This implied that controlling the use of FQs might limit the prevalence of AMR as well as limit the emergence of MRSA; the latter is consistent with previous studies.[23,24]Other studies[25-28]have reported that a reduction in second/third-generation cephalosporins and clindamycin contributed to a reduction in both incidence rate of MRSA and prevalence density of MRSA bacteremia. In our study, we also found that the incidence rate of MRSA was negatively correlated with imipenem/cilastatin use, which was difficult to explain. To our knowledge, few studies have obtained results similar to ours. Lai *et al*. reported[29]a significant correlation between increased use of linezolid and teicoplanin and decreased prevalence of MRSA. Therefore, we theorize that the reduced use of non-special grade antibiotics (such as FQs and others) leads to a compensatory increased use of carbapenems; however, this negative correlation requires further exploration. In addition, we found the resistance rate of

E. coli and *K.pneumoniae* to carbapenems showed an increasing trend, meaning that carbapenem-resistant Enterobacteriaceae (CRE) could pose a serious threat. On March 3, 2017, the NHFPC issued a Notice Regarding Further Reinforcement in Management of Clinical Application of Antibacterial to Control Bacteria Resistance, which required medical institutions to gather, archive, and analyze patient information with respect to the use of carbapenems, to help control the prevalence of CRE.[30]

CHINET surveillance of AMR in China reported the resistance trends from 2005 to 2014, using data from 19 hospitals.[31]In our hospital, the resistance rates of *E. coli*, *K.pneumoniae*, and *P.aeruginosa* to imipenem/cilastatin and meropenem in 2014 (0.4% and 0.9%, 4.8% and 4.1%, 16.5% and 12.9%, respectively) were significantly lower than those reported by CHINET (0.9% and 1.0%, 10.5% and 13.4%, 26.6% and 24.3%, respectively). This proved that AMS in our hospital played an important role in control of AMR.

Some limitations of this study should be noted. First, this was a retrospective observational study without simultaneous control group, the bias couldn't be well controlled, it was less convincing than a prospective, controlled study design. So the favorable results obtained can not be attributed solely to the pharmacist intervention, which were affected by many factors. Second, because AMS has been ongoing for many years, several different clinical pharmacists have successively participated in the evaluation of prophylactic antibiotic use; therefore, the evaluation results might be affected slightly by individual differences.

CONCLUSION

This study demonstrated that AMS in our hospital could reduce and optimize antibiotic use, declining bacterial resistance to FQs was associated with its reduced consumption. Clinical pharmacists played an important role in improving the rational use of antibiotics, however, hospital infection prevention and control measures, national policy guidance all

contributed to it. The findings of our study indicate some directions to pursue in controlling the prevalence of CRE and MRSA. AMR is rising worldwide, so continual effort regarding AMS is critical not only in large hospitals but also in primary or community hospitals.

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Contributors LHL was the leader of AMS and responsible for supervising the work, work plan, and manuscript review. HGW was responsible for carrying out AMS and collecting, analyzing, and reporting data; she wrote this manuscript and made some amendments after review. HW was responsible for statistical analysis and wrote the analysis method in the manuscript. XJY, HZ, BYL, GC, ZKY, YW, XLC,YYZ, RZ, ZHW, HY were all involved in the different aspects of data collection. PW and CXY provided the bacterial resistance data. All authors were involved in data verification.

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Competing interests None declared.

Patient consent Not required.

Ethics approval Beijing Chaoyang Hospital Ethics Committee.

Data sharing statement No additional unpublished data are available.

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Figure legends:

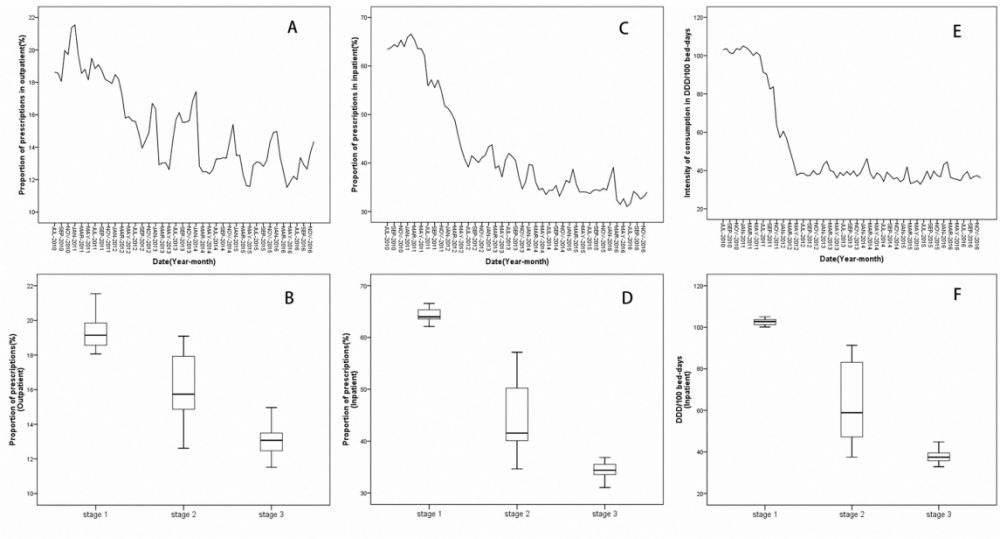
Figure 1. Changes in proportion of antibiotic prescriptions and intensity of consumption.

Time series curves of each monthly value of antibiotic prescribing proportions, plotted for outpatients (A) and inpatients (C). Each monthly value of intensity of antibiotic consumption was plotted for inpatients (E). The Bonferroni test was conducted to compare these data in

three stages, for antibiotic prescribing proportion among outpatients (B) and inpatients (D), and intensity of antibiotic consumption (F). Stage 1, Stage 2, and Stage 3 on the x-axis represent the baseline phase, intervention phase, and stability phase, respectively.

Figure 2. Changes in antibiotic prophylaxis in type I incision operations.

Time series curves of each monthly value of antibiotic prophylaxis were plotted for proportion of prophylaxis (A), proportion of rational timing (C), and proportion of rational duration (E). These data in three stages were compared by Bonferroni test (B, D, and F). Stage 1, Stage 2, and Stage 3 on the x-axis represent the baseline phase, intervention phase, and stability phase, respectively.



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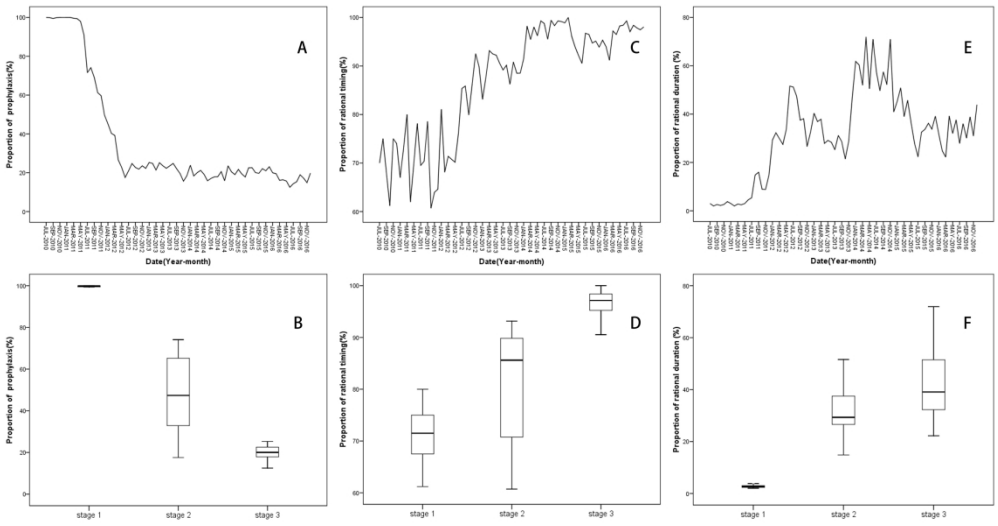

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Time series curves of each monthly value of antibiotic prophylaxis were plotted for proportion of prophylaxis (A), proportion of rational timing (C), and proportion of rational duration (E). These data in three stages were compared by Bonferroni test (B, D, and F). Stage 1, Stage 2, and Stage 3 on the x-axis represent the baseline phase, intervention phase, and stability phase, respectively.

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Supplementary materials

Table S1 Trend changes in incidence rate of methicillin-resistant *Staphylococcus aureus* from 2011 to 2016

	By year						Time series analysis		
	2011	**2012**	**2013**	**2014**	**2015**	**2016**	**Trend**	***β***	***P***
Incidence rate (%)	68.0	60.3	58.3	49.8	51.5	37.5	Decreasing	−5.2565	0.0007

Table S2 Usage trend changes of carbapenems and fluoroquinolones from 2011 to 2016

Antibiotic	**Antibiotic consumption (DDD/100 bed-days) by year**						**Time series analysis**		
	2011	**2012**	**2013**	**2014**	**2015**	**2016**	**Trend**	***β***	***P***
Imipenem/cilastatin	0.59	0.71	0.79	1.17	1.16	1.36	Increasing	0.1599	0.0013
Meropenem	0.86	0.34	0.29	0.38	0.66	0.69	Stable	−0.0116	0.9193
Levofloxacin	11.18	9.70	10.64	7.74	7.71	6.35	Decreasing	−0.9292	0.0033
Ciprofloxacin	6.17	4.12	2.49	0.91	0.66	0.45	Decreasing	−1.1811	0.0461

DDD, defined daily dose.

STROBE Statement—checklist of items that should be included in reports of observational studies

Our research met all the items of STROBE statement.

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-5
Objectives	3	State specific objectives, including any prespecified hypotheses	3-5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2,4,5,8,9
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Not Applicable for this study. This study was a retrospective observational study,please See P5,8-10
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-10
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	1,2
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-10
		(*b*) Describe any methods used to examine subgroups and interactions	8-10
		(*c*) Explain how missing data were addressed	None
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Not Applicable for this study
		(*e*) Describe any sensitivity analyses	8-10

Continued on next page

Results			**Page number**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	2-3
		(b) Give reasons for non-participation at each stage	Applicable for this study
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Applicable for this study
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Applicable for this study
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Applicable for this study
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	19-21
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	4,22
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-22
Generalisability	21	Discuss the generalisability (external validity) of the study results	20-22
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	None

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.