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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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 utilisation, 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=17 766 637) and inpatients (n=376 627) during 2010–2016. Bacterial resistance data were from all inpatients (n=350 699) during 2011–2016.

Interventions Multiaspect intervention measures were implemented by clinical pharmacists (13 persons), for example, formulating the activity programme 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 analysed.

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 also decreased, whereas the resistance rates of E. coli and K. pneumoniae to carbapenems increased. The antibiotic use was partly positively correlated with AMR.

Strengths and limitations of this study

- Our study described the entire process of antimicrobial stewardship, from management of antibiotic use to antimicrobial resistance (AMR) monitoring.
- Time series analysis, a better tool, was applied to analyse the change trends in antibiotic utilisation and AMR.
- By exploring the correlation between antibiotic use and AMR, this study may indicate some potential directions for controlling the prevalence of carbapenem-resistant Enterobacteriaceae and methicillin-resistant Staphylococcus aureus.

This was a retrospective observational study without simultaneous control group, the bias could not be well controlled; the evaluation of prophylactic antibiotic use by different clinical pharmacists might have individual differences.

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.

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. Regrettfully, 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 showed that AMR has been rising steadily each year.2

In 2001, 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, AMS 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 1 July 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 studies7–11 that analysed 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 behaviours 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 2014, the NHFPC issued a notice regarding implementing stewardship of antibacterial use in the clinic12; 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 utilisation data were 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) were 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**

Because the patient’s privacy was not violated in the study, so the Ethics Committee agreed exemption applications of informed consent.

**Multiaspect intervention measures**

**Organisation construction**

To implement the programme ‘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 a technical and 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 programme and administrative intervention

The AMS group formulated the activity programme 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 2012, the Regulations on Clinical Applications of Antibiotics were issued by the NHFPC, which took effect on 1 August 2012. These were the first valid regulations on antibiotics in China. 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 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 programme, the AMS group established the goals for antibiotic application in the hospital (table 1).

**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 penalised. For example, if clinical departments did not accomplish their goals, the directors would be fined ¥1000–3000, and doctors would be fined ¥300–500. If the clinical departments accomplished their goals, the directors would be rewarded with ¥1000–5000 and doctors with ¥300–1000, which were greater than the amounts of fines.

### Data collection and outcome measures

Antibiotic outcome measures are shown in table 1. The antibiotic utilisation data were collected directly from the HIS. Antibiotic consumption was standardised 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. The intensity of inpatients’ antibiotic consumption was expressed as DDD/100 bed-days. Information regarding type I incision operations was obtained from the clinical microbiology laboratory. We

### 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 did not 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 penalised ¥100–200 fine.

#### Table 1

| 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 hours before surgical incision |
| 6. Duration of antibiotic prophylaxis in patients receiving type I incision operations/clean operations | Within 24 hours after the end of operation |

DDD, defined daily dose; NHFPC, National Health and Family Planning Commission.

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Wang H, et al. BMJ Open 2019;9:e026072. doi:10.1136/bmjopen-2018-026072
analysed the correlation between antibiotic consumption and AMR.

**Statistical analysis**

Segmented regression analysis of interrupted time series was used to analyse the monthly data of antibiotic utilisation, 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:

\[ Y_t = \beta_0 + \beta_1 \times \text{time}_t + \beta_2 \times \text{intervention}_t + \beta_3 \times \text{time after intervention}_t + \beta_4 \times \text{stability}_t + \beta_5 \times \text{time after stability}_t + \epsilon_t \]

In this model, \( Y_t \) is the average monthly value of the outcome measure at month \( t \); \( \beta_0 \) estimates the level change in the outcome during the baseline phase; \( \beta_1 \) estimates the trend change during the baseline phase; \( \beta_2 \) estimates the level change during the intervention phase; \( \beta_3 \) estimates the trend change during the intervention phase; \( \beta_4 \) estimates the level change during the stability phase and \( \beta_5 \) estimates the trend change during the stability phase. The parameter \( \text{time} \) 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; \( \text{intervention} \) was an indicator for time \( t \) occurring before (\( \text{intervention}=0 \)) or after (\( \text{intervention}=1 \)) the multiaspect intervention, which started at month 13 (July 2011); \( \text{time after intervention} \) was a continuous variable counting the months after the intervention; \( \text{stability} \) was an indicator for time \( t \) occurring before (\( \text{stability}=0 \)) or after stability (\( \text{stability}=1 \)), which started at month 43 (January 2014); \( \text{time after stability} \) was a continuous variable counting the months after stability. The error term, \( \epsilon_t \), 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 visualisation, with error bars representing SD.

In addition, a time series analysis model (autoregressive integrated moving average) was used to analyse the trends in annual antibiotic use, AMR trends and incidence trend of MRSA from 2011 to 2016. The \( \beta \) value indicated the variation of dependent variables when independent variables changed one unit at uniform time intervals. Pearson’s 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, V.9.3 (SAS Institute, Cary, North Carolina, USA). All reported \( p \) values were two-sided, with \( p<0.05 \) considered to be statistically significant.

**RESULTS**

**Change trends in antibiotic utilisation 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, B.
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 show 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 shows 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 $\beta_0$ value for the intensity of consumption (0.70; p<0.001) implied a gradually increasing trend; this still met national standards.

### 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 (290%). Figure 2F shows 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 $\beta$ 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).

Time series analysis demonstrated a significant increase in the resistance rates of K. pneumoniae to carbapenems (p<0.05). The $\beta$ 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).

Time series analysis showed a significant decrease in the resistance rates of P. aeruginosa to FQs (p<0.05 and p<0.01). The $\beta$ 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).

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) (online 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).

### Table 2 Time series analysis of change trends in antibiotic utilisation

| Antibiotic outcome measures | $\beta_0$ trend (baseline) | $\beta_1$ level (intervention) | $\beta_2$ trend (intervention) | $\beta_3$ level (stability) | $\beta_4$ 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 utilisation 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 $\beta_1$−$\beta_5$ were expressed as mean (SE), which represented the changes in level and trend.

*P<0.05; **p<0.01; ***p<0.001.
However, the intensity of consumption of FQs significantly decreased each year ($p<0.01$ and $p<0.05$), respectively (online 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).

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 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 US$100 trillion. Therefore, many countries worldwide have implemented AMS, with many

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

| Antibiotic     | Resistance rate (%) | Time series analysis |
|----------------|---------------------|---------------------|
|                | 2011    | 2012    | 2013    | 2014    | 2015    | 2016    | Trend | $\beta$       | P value |
| 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 |
positive effects in the rational use of antibiotics and healthcare 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 for 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 is slightly different from the existing intervention model.

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. Other studies have reported that a reduction in second-generation/third-generation cephalosporins and clindamycin contributed to a reduction in both incidence rate of MRSA and prevalence density of MRSA bacteraemia. 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 a significant correlation between increased use of linezolid and teicoplanin and decreased prevalence of MRSA. Therefore, we theorise 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 2 March 2017, the NHFPC issued a notice regarding further reinforcement in management

| Table 4 | Trend changes in antimicrobial resistance of Klebsiella pneumoniae to carbapenems and fluoroquinolones from 2011 to 2016 |
|----------------------|---------------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| Antibiotic          | Resistance rate (%), by year    | 2011                | 2012                | 2013                | 2014                | 2015                | 2016                |
| Imipenem            | Increasing                      | 2.0                 | 1.5                 | 1                   | 4.8                 | 7.1                 | 6.9                 |
| Meropenem           | Increasing                      | 1.8                 | 1.5                 | 1                   | 4.1                 | 6.2                 | 6.4                 |
| Levofloxacin        | Stable                          | 27.9                | 27.9                | 18.4                | 12.9                | 14.6                | 15.2                |
| Ciprofloxacin       | Stable                          | 28.9                | 28.9                | 20.2                | 15.5                | 17.0                | 19.0                |
| Time series analysis| Trend                           | β                    | P value             | Trend                           | β                    | P value             | Trend                           | β                    | P value             |
|                     | Increasing                      | 1.2937              | 0.049               | Increasing                      | 1.1381              | 0.047               |
|                     | Stable                          | −3.0218             | 0.0973              | Stable                          | −2.4467             | 0.1643              |

| Table 5 | Trend changes in antimicrobial resistance of Pseudomonas aeruginosa to carbapenems and fluoroquinolones from 2011 to 2016 |
|----------------------|---------------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| Antibiotic          | Resistance rate (%), by year    | 2011                | 2012                | 2013                | 2014                | 2015                | 2016                |
| Imipenem            | Stable                          | 23.1                | 20.9                | 15.2                | 16.5                | 15.3                | 15.8                |
| Meropenem           | Stable                          | 18.2                | 16.2                | 10.1                | 12.9                | 11.4                | 11.4                |
| Levofloxacin        | Decreasing                      | 28.1                | 28.1                | 20.5                | 10.0                | 10.1                | 8.1                 |
| Ciprofloxacin       | Decreasing                      | 18.2                | 18.2                | 13.5                | 11.6                | 10.5                | 7.5                 |
| Time series analysis| Trend                           | β                    | P value             | Trend                           | β                    | P value             | Trend                           | β                    | P value             |
|                     | Stable                          | −1.4811             | 0.1008              | Stable                          | −1.2977             | 0.1140              |
|                     | Decreasing                      | −4.7833             | 0.0137              | Decreasing                      | −2.2677             | 0.0011              |

Wang H, et al. BMJ Open 2019;9:e026072. doi:10.1136/bmjopen-2018-026072
of clinical application of antibacterial to control bacteria resistance, which required medical institutions to gather, archive and analyse 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 could not be well controlled, it was less convincing than a prospective, controlled study design. So the favourable results obtained cannot 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 optimise 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. AMS is rising worldwide, so continual effort regarding AMS is critical in large hospitals and in primary or community hospitals.

Table 6 Correlation between antibiotic intensity of consumption and resistance rates of Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa and incidence rate of methicillin-resistant Staphylococcus aureus

| Antibiotics       | E. coli  | K. pneumoniae | P. aeruginosa | MRSA |
|-------------------|----------|---------------|---------------|------|
|                   | r        | P value       | r             | P value | r  | P value |
| 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.

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Data sharing statement The authors state that if their manuscript is accepted and published, they would be pleased to share the data with readers to improve the rational use of antibiotics.

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