Effects of Restrictive-prescribing Stewardship on Antibiotic Consumption in Primary Care in China: An Interrupted Time Series Analysis, 2012-2017

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Title

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Abstract

Background:The overuse of antibiotics has been a major public health problem worldwide, especially in low- and middle- income countries (LMIC). However, there are few policies specific to antibiotic stewardship in primary care and their effectiveness are still unclear. This study aimed to evaluate the effects of a restrictive-prescribing stewardship on antibiotic consumption in primary care so as to provideevidence-based suggestions for prudent use of antibiotics.

Methods:Monthly antibiotic consumption data were extracted from Hubei Medical Procurement Administrative Agency (HMPA) system from Sept 1, 2012, to Aug 31, 2017. Quality Indictors of European Surveillance of Antimicrobial Consumption (ESAC QIs) combined with Anatomical Therapeutic Chemical (ATC) classification codes and DDD per 1000 inhabitants per day (DID) methodologywere applied to measure antibiotic consumption. An interrupted time series analysis was performed to evaluate the effects of restrictive-prescribing stewardship on antibiotic consumption.

Results: Over the entire study period, a significant reduction (declined by 32.58%) was observed in total antibiotic consumption, which declined immediately after intervention (coefficient=-2.4518, P=0.005) and showed a downward trend (coefficient =-0.1193, P=0.017).Specifically,the use of penicillins, cephalosporins and macrolides/lincosamides/streptogramins showed declined trends after intervention (coefficient=-0.0553, P=0.035; coefficient=-0.0294, P=0.037; coefficient=-0.0182, P=0.003, respectively). An immediate decline was also found in the contribution of β-lactamase-sensitive penicillins of total antibiotic use (coefficient=-2.9126, P=0.001). However, an immediate increase in the contribution of third and fourth-generation cephalosporins (coefficient=5.0352, P=0.005) and an ascending trend in the contribution of fluoroquinolones (coefficient=0.0406, P=0.037) were observed after intervention. The stewardship led to an immediate increase in the ratio between broad- and narrow-spectrum antibiotic use (coefficient=1.8747, P=0.001) though they both had a significant downward trend (coefficient=-0.0423, P=0.017; coefficient=-0.0223, P=0.006, respectively). An immediate decline (coefficient=-1.9292, P=0.002) and an ascending trend (coefficient=-0.0815, P=0.018) were also found in the oral antibiotic use after intervention, but no significant changes were observed in the parenteral antibiotic use.

Conclusions:Restrictive-prescribing stewardship in primary care was effective in reducing total antibiotic consumption, especially use of penicillins, cephalosporins and macrolides/lincosamides/streptogramins. However, the intervention effects were mixed. Stronger administrative regulation focusing on specific antibiotics, such as the third and fourth-generation cephalosporins, fluoroquinolones, broad-spectrum antibiotics and parenteral antibiotics, is in urgent need in the future.

Keywords:antibiotic consumption; restrictive-prescribing stewardship; primary care; Quality Indictors of European Surveillance of Antimicrobial Consumption (ESAC QIs); interrupted time series analysis

1. Introduction

Antimicrobial resistance (AMR) has been increasingly concerned as a major public health problem worldwide, leading to longer hospital stays, higher medical costs and increased mortality [1; 2]. It was estimated that approximately 25,000 deaths in Europe, and 23,000 deaths in the USA were caused by AMR each year[3]. The health care costs resulted from antibiotic-resistant infections were as high as $20 billion and the lost productivity was estimated to be $35 billion per year in the US[4]. If no actions are taken, up to 10 million additional lives would be lost and the total economic burden would reach $100 trillion by 2050 [5].

The intensive use of antibiotics has been regarded as a main driver of AMR and the unnecessary use further worsened such situation [1; 6]. The global antibiotic consumption increased by 65%between 2000 and 2015, which was primarily driven by increased consumption in low- and middle-income countries (LMICs)[7]. It was reported that 30-50% of antibiotics prescribed were unnecessary or suboptimal [8]. It has been widely recognized that primary care should take main responsibilities because the most majority of antibiotic consumption tend to occur in primary care, which has been demonstrated by the fact that approximately half of patients attending primary care received at least one antibiotic in LMICs [9].

There are few policies specific to antibiotic stewardship in primary care and little is known about the practical effectiveness. Although previous studies have conducted some small-sale interventions to regulate antibiotic overuse in primary care, but the effects are mixed and confused. As examples, online evidence-based feedbacks effectively reduced antibiotic prescribing from 37.4% to 28.1%in patients with suspected respiratory tract infections (RTIs) attending primary care [10]. Similarly, a weekly prospective audit and feedback in three community facilities brought about a 25%

immediate reduction in all antibiotic prescriptions after conducting the antibiotic stewardship and a continuous 5% decrease over the entire intervention [11]. However, other studies showed inconsistent findings. A systematic review summarizing educational interventions to improve antibiotic prescribing showed that 62% of studies in primary care reported positive results for all measured outcomes, including total antibiotic prescription, prescribing attitudes and behaviors, and etc.; 30%reported partialresults that were not statistically significant and the remaining studies failed to report any significant improvements [12]. Further high-level evidence is needed to instructintervention strategies in regulating antibiotic consumption in primary care.

Previous antibiotic stewardship programs in China mainly focus on secondary and tertiary hospitals, which have achieved significant improvements [13]. However, very few detailed or targeted policies are specific to antibiotic consumption in primary care, leading to a relatively poor regulation efficiency on them. For instance, an increasing trend was observed in the overall antibiotic consumption in urban primary healthcare centers in Shandong province of China, revealing an urgent need for strengthened regulation on antibiotic use in primary care [14]. Therefore, it is necessary to evaluate theintervention effectson antibiotic use in primary care, especially on some specific antibiotics, so as to supplement more targeted evidence.

A restrictive-prescribing stewardship with specified administrative regulation was issued in 2014 in Hubei province of China, aiming at further promote prudent use of antibiotics[15]. This administrative regulation put forward detailed restriction specific to antibiotic prescribing in primary care, featured as concretely restricting the type, dose, form, route of administration on antibiotics.This study aimed to evaluate the effects of this restrictive-prescribing stewardship on antibiotic consumption in primary care, especially with advantage of an internationally comparable methodology of

Quality Indictors of European Surveillance of Antimicrobial Consumption (ESAC QIs)[16]. The findings will fill the gaps in literature, especially supplementing comparable evidence on the antibiotic stewardship in primary care, so asto further promote prudent use of antibiotics in primary care.

2. Methods

2.1 Settings and data sources

This study was conducted in Hubei province, central China. Hubei has a population of over 61 million and covers an area of 185,900 km^2. Its per capita gross domestic product (GDP) is 60198.68 yuan ($8915.95 USD), ranking in the middle range of all provinces. The disposable income for rural residents and urban residents is 13,812.09 yuan ($2,059.38 USD) and 31,889.42 yuan ($4,754.71 USD) respectively (2017).There are 36,323 healthcare institutions in Hubei, among which 34,742 are primary care institutions, including state-owned community or township centers[17].

Data used in this study were extracted from the Hubei Medical Procurement Administrative Agency (HMPA) system, which provided a specialized and reliable source on the medicine consumption, including antibiotics[18]. The database is targeted for primary care institutions, and monthly procurement data are recorded and updated. According to the requirements of HMPA, primary care institutions are allowed to stock and dispense medicines listed in the Essential Medicines List (EML) from its procurement platform, except for few supplementary medicines, e.g. emergency medicine. All the valid procurement records of antibiotics between September 2012 and August 2017 (except for few blank procurement records) were collected for our study.

2.2 Study design

A restrictive-prescribing stewardship specific to antibiotics in primary care was developed in November 2014 and formally implemented since December 2014 in Hubei Province. The core objective of this policy was to strengthen the prudent use of antibiotics. Restrict regulation on the antibiotic type, dose, form and route of administration were primary measures of this restrictive-prescribing stewardship.To better guarantee the implementation effects, local health commission were required to take responsibilities for the stewardship, supervision and evaluation on this program. The local healthcare institutions were also demanded to manage the antibiotic procurement, storage, usage, supervision and feedback[15].

2.3 Measurement of antibiotic consumption

The Anatomical Therapeutic Chemical (ATC) classification codes were used to categorize medicines, and procurement records of J01 (antibiotics for systemic use) were extracted for the purpose of this study[19]. Defined daily dose (DDD) was used to measure the volume of antibiotics according to the WHO Collaborating Centre for Drug Statistics Methodology[20]. DDD equivalence per package (DPP) was expressed in DDD units [(unit strength × pack size)/DDD]. The summed DPPs of all-inclusive products formed the total volume for each group of antibiotic consumption (DDDs). To strengthen the comparability of antibiotic use, the DDD per 1000 inhabitants per day (DID) was eventually transformed to calculate antibiotic consumption.

To provide drug-specific insight in measuringantibiotic consumption and trigger action to improve antibiotic use, quality indictors (QIs) proposed by European Surveillance of Antimicrobial Consumption (ESAC) were used to measure antibiotic use, which has become an internationally comparable methodology[16; 21]. In this study, 10 ESAC QIs were selected into analysis and the remaining 2 ESAC QIs were not included because they were not suitable for the statistical methodology in this study.In addition, 4 local QIs were developedafter considering the policy context in

China (Table 1).

[Table 1 could be cited here]

2.4 Statistical analysis

Regular, evenly spaced intervals are appropriate for a segmented regression analysis to evaluate the effect of intervention[22]. In this research, monthly antibiotic consumptionfrom Sept 1, 2012, to Aug 31, 2017 was applied as analytical unites.

To estimate the effect of restrictive prescribing stewardship on antibiotic use, the following segmented linear regression model was applied [23]:

$$Y_t = \beta_0 + \beta_1 * Time_t + \beta_2 * Intervention_t + \beta_3 * Time\ \ after\ \ intervention_t + \beta_4 * \sin(2\Pi Time_t\ /12)\ + \beta_5 * \cos(2\Pi Time_t\ /12)\,\varepsilon_t$$

As two key parameters in the segmented linear regression, level and trend define each segment of a time series. The level is the value of the series at the beginning of a given time interval, while the trend is the rate of change of the intervention measure.

Here, Y_t is the average number of antibiotic use in montht; Time is a continuous variable indicating time in months at time t from the start of observation; intervention is an indicator for $Time_t$occurring before (intervention=0) or after (intervention=1) the cap, which was implemented at month 28 (December, 2014) in the series; and $Time\ \ after\ \ intervention_t$is a continuous variable counting the number of months after the intervention at time t, coded 0 before the cap and added by 1 continuously after the cap. The coefficients $\beta_0$and $\beta_1$respectively estimate the baseline level of outcome at time zero, and the change that occurs with each month before the intervention;β_2 and β_3 respectively estimate the level change in the average monthly number of antibiotic use immediately after the intervention, and the trend change of indicators after the cap, compared with the monthly trend before the cap; The sum of $\beta_1 + \beta_3$ is the post intervention slope. $\beta_4$and β_5 were used to adjust for a potential seasonality effect [24]. The error termε_t represents the random variable not explained by the model at time t.

The Durbin-Watson test was used to check for autocorrelation.

All statistical analyses above were performed using STATA version 12.0 (STATA Corp, College Station, TX, USA) and P<0.05 was considered statistically significant.

3. Results

3.1 Overallantibiotic consumptionover the entire study period

Over the entire study period,the total antibiotic consumption (J01) in primary care in Hubei province declined from 11.02 DID to 7.43 DID(declined by 32.58%). For penicillins (J01C) and cephalosporins (J01D), the consumption respectively decreased from 5.01 DID to 2.64 DID (declined by 52.69%) and 3.08 DID to 2.54 DID (declined by 17.53%). For quinolones (J01M) and macrolides/lincosamides/streptogramines(J01F), the consumption declined from 1.05 DID to 0.71 DID (declined by 32.38%) and 1.03 DID to 0.82 DID (declined by 20.39%) respectively (Fig.1).

[Figure 1 could be cited here]

The relative contributions of ß-lactamse-sentitivepenicillins (J01CE) of total antibiotic use declined from 7.78% to 4.12% (declined by 3.66%). However, the relative contributions of penicillins with ß-lactamase inhibitors (J01CR), third and fourth generation cephalosporins (J01DD/DE) and fluoroquinolones (J01MA)of total antibiotic use respectively increased from 3.08% to 6.19%, 14.43% to 18.13%, and 9.51% to 9.56% (increased by 3.11%, 3.70% and 0.05%, respectively)(Fig.2).

[Figure 2 could be cited here]

The consumption of broad-spectrum antibioticsand narrow-spectrum antibiotics respectively declined from 3.82 DID to 3.20 DID (declined by 16.23%) and 1.51 DID to 0.68 DID (declined by 54.97%). However, the ratio between broad- and narrow-spectrum antibiotic consumption increased from 2.51 to 5.09(Fig.3).

[Figure 3 could be cited here]

The consumption of oral antibiotics and parenteral antibiotics respectively declined from 5.84 DID to 3.33 DID (declined by 42.98%), and 5.18 DID to 4.09 DID (21.04%). The average decline of oral antibiotic consumption was greater than that of parenteral antibiotics over the entire study period (Fig.4).

[Figure 4 could be cited here]

3.2 Effects of restrictive-prescribing stewardship on antibiotic consumption

Before implementing restrictive-prescribing stewardship, the consumption of total antibiotics(J01) showed an ascending trend that was not statistically significant (coefficient=0.0237, P=0.554), while the consumption declined immediately after intervention (coefficient=-2.4518, P=0.005) and had a significant downward trend (coefficient=-0.1193,P=0.017).The consumption of penicillins (J01C), macrolides/lincosamides/streptogramins (J01F), quinolones (J01M) declined immediately after intervention (coefficient=-1.9109, P<0.001; coefficient=-0.2248, P=0.030; coefficient=-0.2019, P=0.019, respectively), and the consumption of penicillins (J01C), cephalosporins (J01D) and macrolides/lincosamides/streptogramins (J01F) showed declined trends after intervention (coefficient=-0.0553, P=0.035; coefficient=-0.0294, P=0.037; coefficient=-0.0182, P=0.003, respectively).

The restrictive-prescribing stewardship was associated with an immediate decline in the contribution of β-lactamase-sensitive penicillins (J01CE) of total antibiotic use (coefficient=-2.9126, P=0.001). However, an immediate increase was observed in the contribution of third and fourth-generation cephalosporins (J01DD/DE) of total antibiotic use(coefficient=5.0352, P=0.005), and an ascending trend was found in the contribution of fluoroquinolones (J01MA) of total antibiotic use (coefficient=0.0406, P=0.037) after intervention.

The stewardship also led to an immediate increase in the ratio between broad- and narrow-spectrum antibiotic use (coefficient=1.8747, P=0.001) though they both had a significant downward trend (coefficient=-0.0423, P=0.017; coefficient=-0.0223, P=0.006, respectively).

Finally, the stewardship was associated with an immediate decline in the consumption of oral antibiotics (coefficient=-1.9292, P=0.002) and a continuous downward trend (coefficient=-0.0815, P=0.018). However, no significant changes were found in the consumption of parenteral antibiotics after intervention (Table 2).

[Table 2 could be cited here]

4. Discussion

4.1 Summary of main findings

This study confirmed that the restrictive-prescribing stewardship achieved positive effects in declining total antibiotic use, especially the use of penicillins, cephalosporins and macrolides/lincosamides/streptogramins. However, the intervention effects on the consumption of some other antibiotics were mixed, which deserved more attention and discussion.

4.2 Strengths and limitations of the study

To the best of our knowledge, it was the first study that attempted to evaluate the effects of restrictive-prescribing stewardship on antibiotic consumption in primary care, with advantage of drug-specific quality indicators of ESAC (ESAC QIs) combined with an interrupted time series design and DID methodology.

There are several limitations in this study. First, not all antibiotics consumed in primary care institutions were included in this study. The data of non-prescribed antibiotic use (e.g. self-medication at home or over-the-counter) and prescriptions in private primary care facilities were difficult to access. Second, the data used in this study were procurement data instead of directly extracting from the actual medicine use in each institution. However, the procurement data were based on the current practical consumption, which was approximately equivalent to the actual medicine use.

4.3 Comparison with existing literature

This study confirmed that the restrictive-prescribing stewardship was associated with a significant reduction in total antibiotic consumption, especially the use of penicillins, cephalosporins and macrolides/lincosamides/streptogramins, which was consistent with some previous findings. Borde J Pet al.[25] found that the total antibiotic use declined by 11% after implementing anintensified antibiotic stewardship in community hospital in Germany, and the use of cephalosporins declined by 33%.Borde J P et al.[26]discovered that the use of macrolides/ clindamycin declined by 24.4% after intervention in a tertiary academic hospital.Regarding the use of penicillins, there were some different findings in other studies.For instance, Tavares M et al.[27]found that a significant increase was discovered in the use of penicillins, followed by a monthlydecrease in slope after implementing an audit and feedback antibiotic stewardship. It can be seen that the restrictive prescribing stewardship in this study achieved better intervention results than other studies, especially in regulating the use of penicillins.Regarding the consumption of quinolones, an immediate decline was observed after intervention but no significant effects were observed afterwards in this study, which was consistent with a study by McNulty C et al. [28]that the quinolone use in the intervention group was lower than that in the control group, but a slight increase was then observed though there was no statistical significance. Cheng AC et al.[29] found that educational initiatives made no substantial progress in reducing quinolone use in primary care in Australia, but a decline of 30% was achieved after introducing a narrowed list of indications forquinolones, which confirmed that a strongeradministrative regulation specific to antibiotic categories is necessary.

Judging from the relative contributions of total antibiotic use, an immediate decline was found in the contribution of β-lactamase-sensitive penicillins of total antibiotic use, while an immediate increase was observed in the contribution of third and fourth-generation cephalosporins and an ascending trend was found in the contribution of fluoroquinolones after intervention. Similar findings were discovered in previous studies. For instance, Ruiz J et al.[30] found that the consumption of β-lactamase-sensitive penicillins significantly declined by 34.50 DDD per 100 patients per day after implementing audit and feedback antimicrobial stewardship. Regarding the contribution of third and fourth-generation cephalosporins and fluoroquinolones of total antibiotic use, it has been recognized that the third generation cephalosporins and fluoroquinolones were frequently prescribed for common infections, which is usually difficult to largely reduce their prescriptions accounting fortotal antibiotics[31].Moreover, Jindai K et al. [32] discovered a significant initial reduction on fluoroquinolone prescribing rate but the reduction was not sustained later, which put forward requirement on sustainable strategies.

It is well-known that broad-spectrum antibiotics are prescibed instead of narrow-apecturm antibiotics in many cases [33]. Regulating the overuse of broad-spectrum antibiotics can make great significance in minimizing resistance for patients. This study revealed that restrictive-prescribing stewardship led to a significant downward trend in broad- and narrow-spectrum antibiotic use, but an immediate increase was observed in the ratio between them. Hernandez-Santiago V et al. [34]found that the broad-spectrum antibiotic prescription achieved a significant sustained reduction after introducing an intervention combing guidelines, education and feedback in Scotland.Kuyvenhoven M et al. [35] pointed out that a decrease of narrow-spectrum antibiotic use has been accompanied by an increase of broad-spectrum antibiotics in America. Aabenhus R et al.[36] also found that the consumption of broad-spectrum antibiotics increased while narrow-spectrum antibiotics declined in primary care in Denmark. These also demonstrated that the ratio between broad- and narrow-spectrum antibiotic use is difficult to decline as the consumption of broad-spectrum antibiotics over the last decades has always occupied a major proportion of total antibiotics and presented a dramatical increase[33].

Overuse of injections has become common concerns in many LMICs and may result in unexpected outcomes and resource wastage[37]. The restrictive-prescribing stewardship failed to make significant progress in regulating parenteral antibiotic use, though significant decline were found in the consumption of oral antibiotics. However, Hersh A L et al.[38] found a 24% decline in parenteral antibiotic use after implementing an outpatient parenteral antibiotic therapy (OPAT) stewardship program. The different intervention effects may attribute to whether the stewardship program was specific to parenteral antibiotics. The reason for the overuse of injections lies in a wide belief in many cultures that injection is a quite powerful method for health, so patients tend to prefer injections to oral medicines [39]. In addition, physicians are more likely to prescribe injections to satisfy patients' demand and earn a higher salary due to a more expensive price on injections [39].

4.4 Policy implications

It is a well-known fact that overuse of antibiotics is directly related to AMR and to an increase in morbidity and mortality [30]. Restrictive-prescribing stewardship could play an essential role in regulating overuse of antibiotics from the whole. However, regarding the use of antibiotics whose intervention effects were limited in this study, for instance, broad-spectrum antibiotics especially the third and fourth-generation cephalosporins, fluoroquinolones and etc.,a stronger antibiotic stewardship is needed. Future stewardship programs focusing on individual antibiotics combined with multi-faceted interventions should be strengthened to achieve sustainable improvement.

5. *Conclusion*

Restrictive-prescribing stewardship in primary care achieved significant effects in reducing total antibiotic consumption, especially use of penicillins, cephalosporins and macrolides/lincosamides/streptogramins. However, the effects on other antibiotics were mixed. Stronger administrative regulation is necessary to focus on drug-specific antibiotics, such as the third and fourth-generation cephalosporins, fluoroquinolones, broad-spectrum antibiotics and parenteral antibiotics. Future studies are warranted to explore the potential influencing factors of limited effects in those antibiotics and accordingly design a stronger and more targeted antibiotic stewardship strategy.

List of abbreviations

ATC: Anatomical Therapeutic Chemical classification

DID: DDD per 1000 inhabitants per day

ESAC QIs: Quality Indictors of European Surveillance of Antimicrobial Consumption

J01: antibiotics for systemic use

J01C: penicillins

J01D: cephalosporins

J01F: macrolides/lincosamides/streptogramins

J01M: quinolones

J01CE: ß-lactamse-sentitivepenicillins

J01CR: penicillins with ß-lactamase inhibitors

J01DD/DE: third and fourth generation cephalosporins

J01MA: fluoroquinolones

J01DC:second generationcephalosporins

J01FA01:erythromycin

J01DB:first generation cephalosporins

CI: confidence intervals

DW: Durbin-Watson

Declarations

Ethics approval and consent to participate

A prior abstract about part of the findings was submitted for the 2019 Lancet–CAMS Health Conference held in China, and it was accepted and printed on the conference brochure and posters[40]. However, the full manuscripthas never been submitted or published in the Lancet journal or elsewhere. According to the ethics and consent, we have cited the published abstract in this article.

Consent for publication

Consent for publication was obtained from each participant prior to the survey, and the formal fullmanuscriptwas also allowed for publication in other journals by the 2019 Lancet–CAMS Health Conference.

Availability of data and materials

The original data used in this study were extracted from the Hubei MedicalProcurement Administrative System(HMPAS), which is a publicly available platform.

Competing interests

The authors declare no conflict of interest.

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Authors' contributions

XW contributed to the study design, data analysis, and drafting of the manuscript. YT was involved in the conception and revision of the manuscript.CL and JL participated in the revision of the manuscript. YC participated in the extraction and interpretation of the data. XZ and YT made substantialcontributions to the conception, design, and revision of the manuscript. All authors have seen and approved the final version of this articlefor publication.

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Tables

Table 1. Quality indicators of measuring antibiotic consumption in this study

NO.	Quality indicators
ESAC QIs 1-5 are the use of relevant antibiotics (expressed in DID):	
1	*total use of J01*
2	*use of penicillins (J01C)*
3	*use of cephalosporins (J01D)*
4	*use of macrolides/lincosamides/streptogramins (J01F)*
5	*use of quinolones (J01M).*
ESAC QIs 6-9 are the relative contributions (% of total J01 use) of:	
6	*ß-lactamse-sentitivepenicillins (J01CE)*
7	*combinations of penicillins with ß-lactamase inhibitors (J01CR)*
8	*third and fourth generation cephalosporins (J01DD/DE)*
9	*fluoroquinolones (J01MA)*
ESAC QI 10 is the ratio between broad- and narrow-spectrum antibiotics:	
10	*(J01CR+J01DC+J01DD+J01F (minus J01FA01)/(J01CE+J01DB+J01FA01)*
QIs 11-14 are adapted according to the policy context in China (expressed in DID):	
11	*use of broad-spectrum antibiotics*
12	*use of narrow-spectrum antibiotics*
13	*use of oral antibiotics*
14	*use of parenteral antibiotic*

Table 2. The segmented regression analysis of stewardship on antibiotic consumption

	Baseline level (95% CI)	Baseline trend (95% CI)	Level change after intervention (95% CI)	Trend change after intervention (95% CI)	DW
Use of relevant antibiotics (expressed in DID)					
J01	10.7777*** (9.51, 12.05)	0.0237 (-0.06, 0.10)	-2.4518** (-4.14, -0.76)	-0.1193* (-0.22, -0.02)	2.0572
J01C	4.8920*** (4.22, 5.56)	0.0124 (-0.03, 0.05)	-1.9109*** (-2.80, -1.02)	-0.0553* (-0.11, -0.00)	1.9703
J01D	3.1150*** (2.75, 3.48)	-0.0015 (-0.02, 0.02)	-0.0262 (-0.51 ,0.45)	-0.0294* (-0.06, -0.00)	2.2194

J01F	0.9053*** (0.75, 1.06)	0.0099* (0.00, 0.02)	-0.2248* (-0.43, -0.02)	-0.0182** (-0.03, -0.01)	1.9409
J01M	1.0594*** (0.93, 1.19)	-0.0005 (-0.01, 0.01)	-0.2019* (-0.37, -0.03)	-0.0077 (-0.02,0.00)	2.0270
Relative contributions (% of total J01 use)					
J01CE	7.2141*** (5.86, 8.57)	0.0271 (-0.06, 0.11)	-2.9126** (-4.55, -1.27)	-0.0825 (-0.19, 0.03)	2.0439
J01CR	2.6349*** (1.71, 3.56)	0.0312 (-0.03, 0.09)	1.2010 (-0.01, 2.41)	0.0618 (-0.01, 0.13)	1.9534
J01DD/DE	16.2036*** (13.55, 18.85)	-0.1312 (-0.30, 0.03)	5.0352** (1.55, 8.52)	0.1543(-0.05, 0.36)	1.9815
J01MA	9.7988*** (9.31, 10.29)	-0.0246 (-0.05, 0.01)	0.2156 (-0.42, 0.85)	0.0406* (0.00, 0.08)	1.8880
Use of Broad- and narrow-spectrum antibiotics (expressed in DID)					
Broad	3.6089*** (3.16, 4.06)	0.0148 (-0.01, 0.04)	-0.1212 (-0.72, 0.48)	-0.0423* (-0.08, -0.01)	2.2142
Narrow	1.4481*** (1.24, 1.65)	0.0055 (-0.01, 0.02)	-0.6449*** (-0.92, -0.37)	-0.0223** (-0.04, -0.01)	1.9398
Ratio between broad-narrow spectrum antibiotic use (ratio)					
broad /narrow	2.4977*** (1.65, 3.34)	0.0032 (-0.05, 0.06)	1.8747** (0.78, 2.97)	0.0500 (-0.02, 0.12)	1.9345
Use of oral and parenteral antibiotics (expressed in DID)					
Oral	5.6076*** (4.73, 6.48)	0.0221 (-0.03, 0.08)	-1.9292** (-3.09, -0.77)	-0.0815* (-0.15, -0.01)	1.9424
Parenteral	5.1721*** (4.63, 5.71)	0.0011 (-0.03, 0.03)	-0.5049 (-1.22, 0.21)	-0.0373 (-0.08, 0.00)	2.2052

Notes: *p<0.05; **p<0.01; ***p<0.001;

CI: confidence intervals; DW: Durbin-Watson

Figures

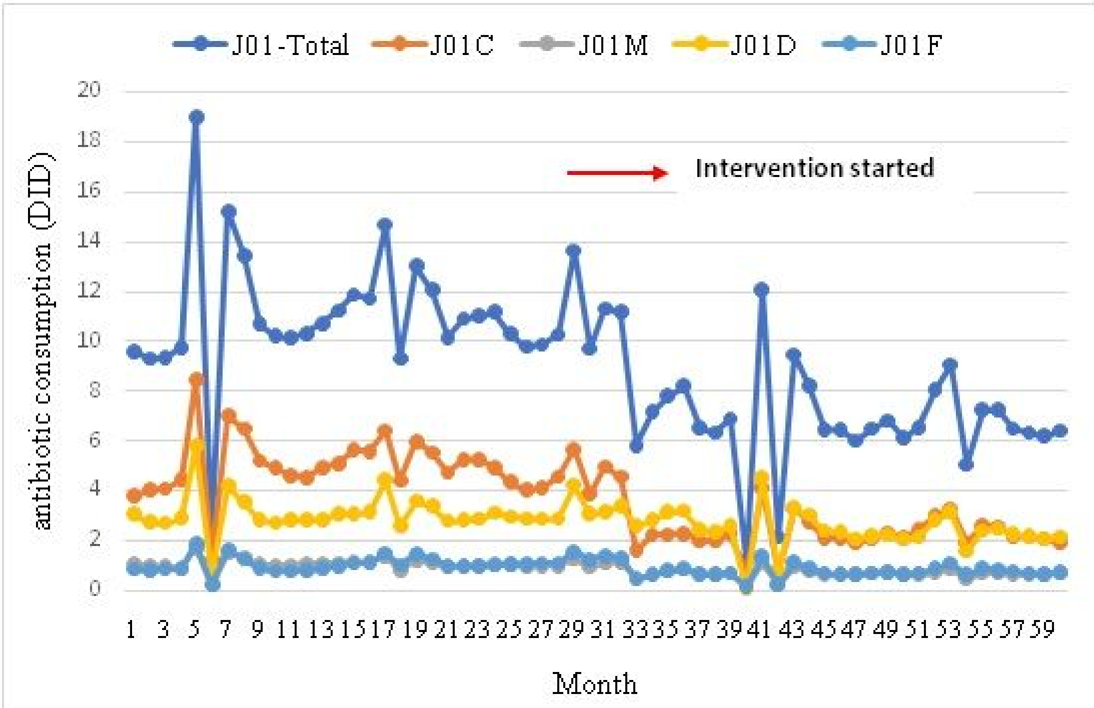

Figure 1

Monthly antibiotic consumption of J01 Total, J01C, J01M, J01D and J01F

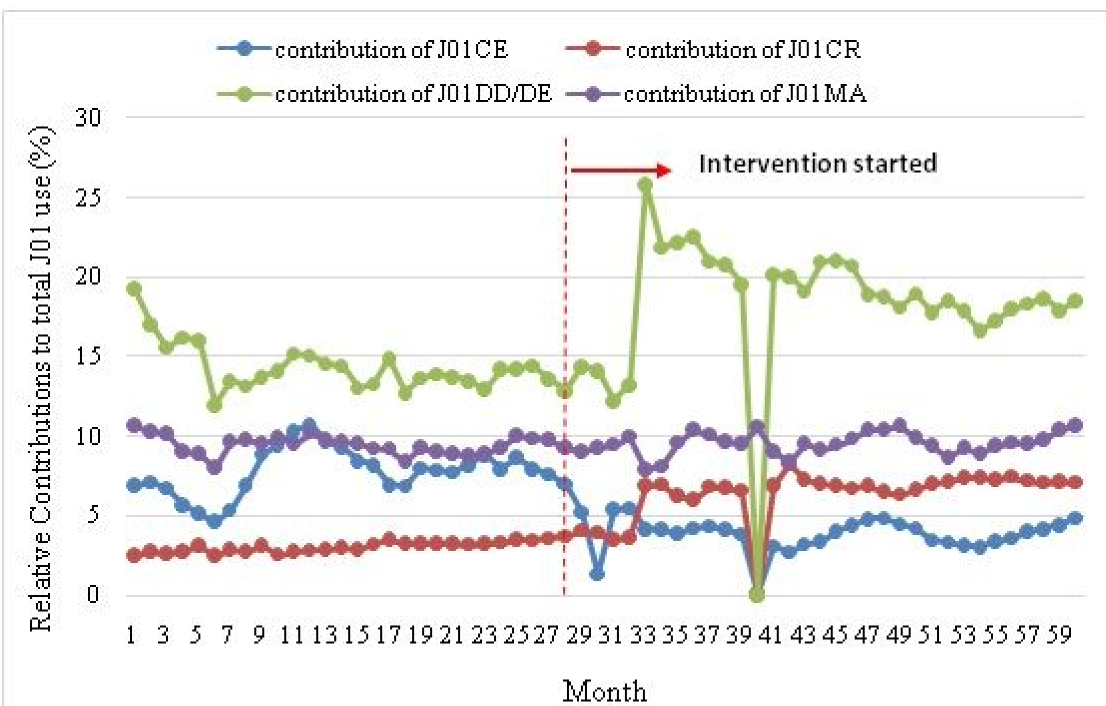

Figure 2

Monthly relative contributions of J01CE, J01CR, J01DD/DE, J01MA of total J01 use

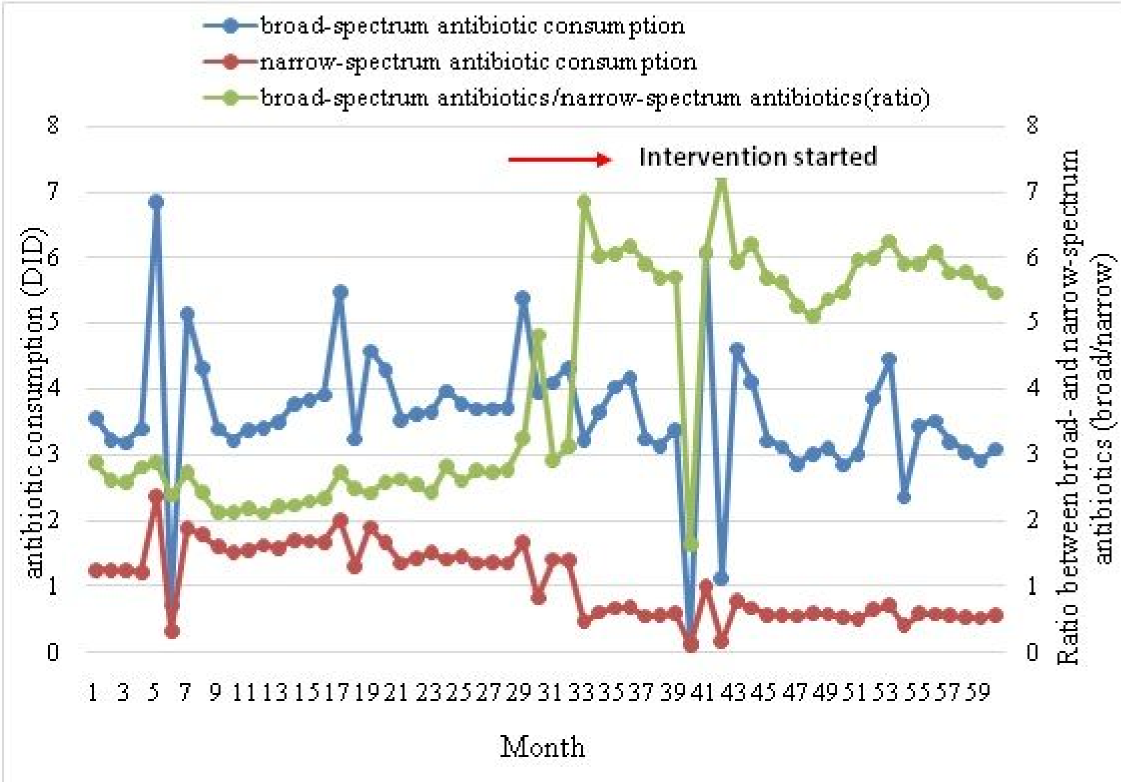

Figure 3

Monthly broad- and narrow-spectrum antibiotic consumption as well as the ratio between them

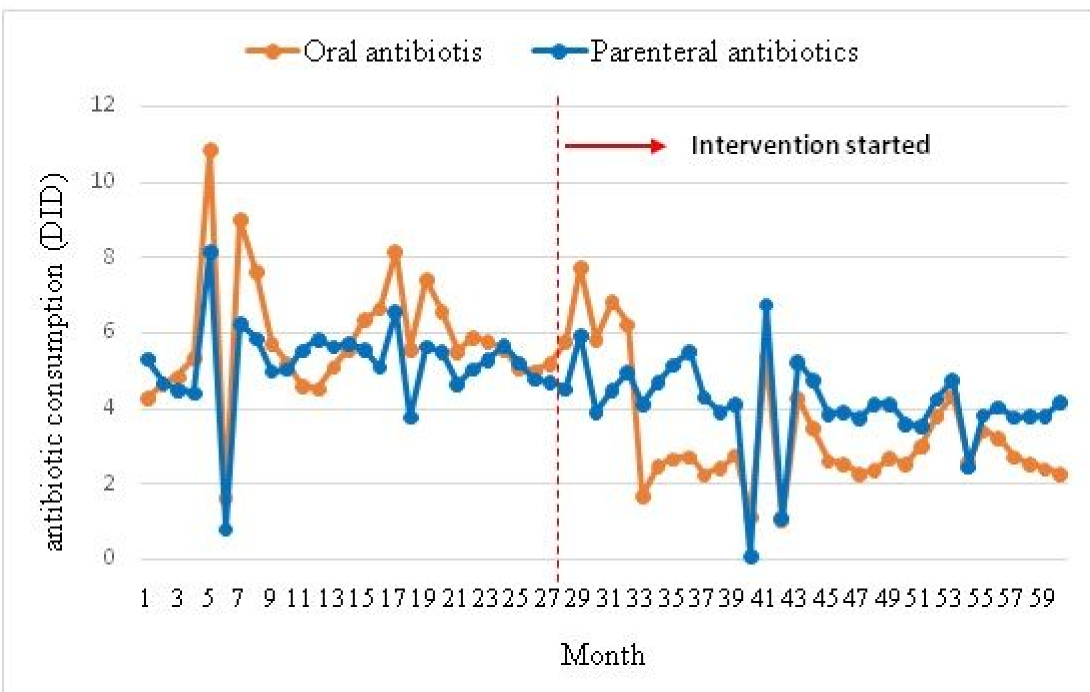

Figure 4

Monthly antibiotic consumption of oral and parenteral antibiotics