The impacts of Chinese drug volume-based procurement policy on the volume and expenditure of antibiotic drugs

Ying Yang
Wuhan University
Lei Chen
Wuhan University
Xinfeng Ke
Wuhan University
Zongfu Mao (zfmao@whu.edu.cn)
Wuhan University
Bo Zheng
Peking University First Hospital

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Abstract

Background: In 2019, Chinese government implemented the first round of National Centralized Drug Procurement (NCDP) pilot (so-called "4+7" policy) in mainland China, in which an oral antibiotic agent (cefuroxime axetil) was included. Given the current condition of the irrational use of antibiotics in China, this study aims to evaluate the potential effect of the "4+7" policy on antibiotic use.

Methods: This study used drug purchasing order data from the Centralized Drug Procurement Survey in Shenzhen 2019, covering 24 months from January 2018 to December 2019. Oral antibiotic drugs related to "4+7" policy were selected as study samples, including cefuroxime axetil and its alternative drugs. Segmented linear regression analysis with interrupted time series was adopted to examine the effect of "4+7" policy on the volume and expenditure of antibiotic drugs.

Results: Compared with April to December 2018, the total volume and expenditures of cefuroxime axetil and its alternative antibiotic drugs from April to December 2019 increased 41.8% and 18.1%, respectively. The results of segmented linear regression showed that the volume of cefuroxime axetil products significantly increased 161.16 thousand DDDs after "4+7" policy (95% CI: 59.43 to 262.90, p-value = 0.004). For the alternative drugs of cefuroxime axetil, the volume and expenditures significantly increased 273.65 thousand DDDs (95% CI: 90.17 to 457.12, p-value = 0.006) and 3471.66 thousand RMB (95% CI: 1529.70 to 5413.62, p-value = 0.001), respectively.

Conclusion: This study provides evidence that the implementation of "4+7" volume-based procurement policy was associated with significant increases in the volume and expenditure of cefuroxime axetil and its alternative drugs. The increase in antibiotic use after the policy needs special attention and vigilance.

Background

The overuse and misuse of antibiotics stimulated the more rapid emergence of antibiotic resistant bacteria and antibiotic resistant genes, reducing their therapeutic potential against human and animal pathogens [1,2]. The rising of antibiotic resistant levels, in combination with a lack of new effective antibiotics, increases the morbidity and mortality of infectious diseases, as well as driving inflation related to healthcare costs [3]. World Health Organization (WHO) characterized antimicrobial resistance as a global public health crisis that must be managed with the utmost urgency [4].

China is one of the world's largest producers and consumers of antibiotics [5]. 92,700 tonnes of antibiotics (inclusive of 36 antibiotics) were consumed in China in 2013, which is estimated exceed usage in the UK and much of northern Europe (normalized by the defined daily dose), by a factor of six [6]. Globally, 76% of the overall increase in antibiotic consumption between 2000 and 2010 was attributable to BRICS countries (Brazil, Russia, India, China, and South Africa) [7]. In BRICS countries, up to 57% of the increase of antibiotic use in the hospital sector was attributable to China [7]. Yin et al. [8] systematically reviewed the condition of antibiotic utilization in China by using the data of 556,435 outpatient encounters, and reported an overall percentage of 50.3% for outpatients prescribed antibiotics, of which, 74.0% were prescribed one antibiotic, 23.3% were prescribed two antibiotics and 2.0% were prescribed three or more antibiotics. A national survey showed that 52.9% of the patients visiting primary care institutions in China were prescribed antibiotics, but only 39.4% of those who received antibiotics needed them based on their clinical condition [9]. Generally, China has a high prescription use of antibiotics for both inpatients and outpatients [10]. As a result of antibiotic misuse, China has the highest level of antibiotic resistance and the most rapid growth of antibiotic resistance globally [11,12]. Besides, the direct cost associated with the overuse of antibiotics in China is estimated to be around 2.91 to 13.93 billion yuan ($0.42 to 2.02 billion USD) per year [13]. Therefore, the overuse of antibiotics is an important issue that needs to be vigilant in China.

In January 2019, the General Office of the State Council of the People's Republic of China issued the National Centralized Drug Procurement (NCDP) policy, aiming at deepening the health system reform and improving the mechanism for the formation of drug prices [14]. In the first round of NCDP pilot, 11 cities were selected as pilot cities to carry out drug volume-based purchasing, including 4 municipalities (Beijing, Tianjin, Shanghai, and Chongqing) and 7 key cities (Shenyang, Dalian, Xiamen, Guangzhou, Shenzhen, Chengdu, and Xi'an) in mainland China. Therefore, the first round of NCDP is also known as the "4+7" pilot or "4+7" policy in mainland China. The highlight of the "4+7" policy lies in the implementation of "volume-based procurement", which refers to that the tenderee (government representative) clarifies the procurement volume (60-70% of the total annual drug use of all public medical institutions in pilot cities) when conducting tendering, and the tenderers (pharmaceutical companies) quote according to this specific procurement volume. "4+7" policy successfully tendered 25 drug varieties, and most of whom are drugs for chronic diseases such as hypertension, diabetes, and hyperlipidemia [15]. The average price of 25 selected drugs dropped 52%, with a maximum drop of 96%. It is worth noting that, an oral antibiotic drug, i.e. *cefuroxime axetil* was included in the 25 drugs. According to the bidding results, cefuroxime axetil tablets (250mg*12 tablets/box) manufactured by Chengdu Brilliant Pharmaceutical Co. Ltd won the bidding at a price of 6.16 yuan/box, which dropped 52.5% when compared with the average price in the past three years.

According to the characteristics of the "4+7" policy, the clinical use of the bid winning antibiotic drug is constrained by the "contracted procurement volume", that is, the hospitals are required to complete their reported annual procurement volume. The usage of winning cefuroxime axetil was included in the performance evaluation of hospitals, clinical departments, and even doctors. Therefore, we proposed that there might be potential risk for the overuse of antibiotic drugs related to cefuroxime axetil after the implementation of "4+7" policy. However, no qualitative evidence clarified this issue. However, there was no relevant research clarified the impact of volume-based procurement on the utilization of antibiotic drugs. It is urgent to provide quantitative evidence regarding this issue.

Given the shortage of existing evidence, we conducted this exploratory study to quantitatively evaluate the effect of "4+7" policy on the utilization and expenditures of antibiotic drugs, considering the case of cefuroxime axetil and its alternative drugs.

Methods

Data sources

This study used data from Centralized Drug Procurement Survey in Shenzhen 2019 (CDPS-SZ 2019). In China, the CDPS-SZ 2019 was organized and conducted by the Global Health Institute of Wuhan University between December 2019 and January 2020. The survey aimed to evaluate the effect of drug-related policies in Shenzhen, and collected monthly drug purchase order data between 2017 and 2019. In the CDPS-SZ 2019 database, each purchase order record included purchase date, generic name, dosage form, specification, pharmaceutical manufacturer, price per unit, purchase volume, purchase expenditures, etc. A general database containing 963,127 monthly aggregated purchase order records was established, involving 1079 drug varieties (by generic name), 346 medical institutions, 857 pharmaceutical manufacturers. The total purchase expenditures reached 20.87 billion RMB.

This study aims to examine the effect of "4+7" policy on the utilization of policy-related oral antibiotic agents. Thus, we included samples with the following criteria: (a) the medication covered cefuroxime axetil and its alternative drugs, (b) the time period is between January 2018 and December 2019, and (c) the medical institutions purchasing drugs were from Shenzhen. Finally, 9577 purchase order records of 30 drug varieties (by generic name) were extracted, involving 70 medical institutions, 30 pharmaceutical manufacturers.

Outcome measures

This study assessed the effect of "4+7" policy on both volume and expenditures of antibacterial agents. Expenditure data was reported in Chinese yuan, i.e. RMB. Volume was measured using Defined Daily Dose (DDD), a measurement developed by WHO to compare drug consumptions. DDD refers to the average maintenance dose per day for a drug used for its main indication in adults. In this study, DDD value of each medication is determined according to the *Guidelines for ATC classification and DDD assignment 2020* [16]. DDD equivalence per package (DPP) of medicines was calculated in DDD units (DPP = unit strength × pack size/DDD) [17]. The total volume for each group of procured medicines (DDDs) was estimated as the summed DPPs of all-inclusive products.

$$DDDs = \sum_{i=1}^{n} (DPP_i \times N_i)$$

Where, N_i represents the number of packages of a certain product (i) delivered to the medical institutions.

Statistical analysis

Descriptive statistics were used. We first described the volume and expenditures of included medications in the same period before (April to December 2018) and after (April to December 2019) the implementation of "4+7" policy. Then, we created graphical displays of the monthly procurement volume and expenditures of each study medication in order to observe and describe patterns over time from January 2018 to December 2019.

Interrupted time-series (ITS) analysis was applied to assess the effect of "4+7" policy on purchase volume and expenditures of Cefuroxime Axetil and related medications. ITS is a commonly used approach for evaluating changes in longitudinal series following a quasi-experimental intervention occurring at a fixed point in time, such as the date of implementing "4+7" policy, i.e. 1 April 2019 in Shenzhen. We constructed interrupted time series using drug procurement data in Shenzhen from January 2018 to December 2019. The time unit was set to 1 month and the intervention time point was set to April 2019, making 24 time points available for analysis, including 15 points before the intervention and 9 points thereafter. To estimate the effect of the intervention on the outcome variables, the following segmented linear regression model was developed [18]:

$$Y_t = \beta_0 + \beta_1 \times time_t + \beta_2 \times intervention_t + \beta_3 \times time\ after\ intervention_t \\ + \beta_4 \times cold + \varepsilon_t$$

Where, Y_t is the independent outcome variable (volume or expenditures) in month t; *time* is a continuous variable indicating time in months at time t from the start of the observation period; *intervention* is an indicator for time t occurring before (*intervention* = 0) or after (*intervention* = 1) "4+7" policy, which was implemented at month 15 in the series; and *time after intervention* is a continuous variable indicating months passed since the intervention (time prior to the intervention is coded 0). Besides, we set a dummy variable *cold* to control the extreme value of antibiotic use during the Spring Festival holiday, which is “wild data points” in this study [18]. It is when the Spring Festival that is the coldest time of the year in China, and common seasonal illness (cold) prevalence. The possibility of antibiotics overuse rises to treat fever and other associated symptoms [19-21]. The variable *cold* is assigned the value 1 in December and January of each year and 0 otherwise.

In this model, β_0 estimates the baseline level of the independent variable at the beginning of the observation period. β_1 estimates the linear trend during the preintervention period where time t is an integer variable indicating the time in months at time t from the beginning of the study period. β_2 estimates the change in the outcome immediately following the intervention. β_3 estimates the change in trend in the outcome measures after the intervention compared with the monthly trend before the intervention. B_4 estimates the "coldest weather" effect. ε_t is an estimate of the random error at time t. Durbin-Watson test was performed to test the presence of first-order auto-correlation (a value around 2 indicates no sign of auto-correlation). If auto-correlation is detected, the Prais-Winsten method was applied to estimate the regression. Stata version 16.0 was used to perform the ITS analysis.

Results

Descriptive statistics

A total of 30 drug varieties (by generic name) were included in this study. The total purchase volume was 29.33 million DDDs, and the total purchase expenditure was 266.83 million RMB. Of those, the volume and expenditures of cefuroxime axetil were 6.39 million DDDs and 12.74 million RMB, respectively.

Table 1 demonstrates the change of volume and expenditures of antibiotic medications included in this study during the same period before (April to December 2018) and after (April to December 2019) the implementation of "4+7" policy. Compared with April to December 2018, the purchase volume of cefuroxime axetil during April to December 2019 increased by 92.9%, and the purchase expenditures decreased by 18.9%. Of which, the volume and expenditures of winning products increased by 182.9% and 102.4%, respectively; those of non-winning products decreased by 70.3% and 74.1%, respectively. From April to December 2019, the volume and expenditures of cefuroxime axetil's alternative medication increased by 30.2% and 20.1%, respectively, when compared with those from April to December 2018. Besides, the overall volume of all included antibiotics in this study rose 41.8% and the expenditures rose 18.8%.

ITS analysis

Changes of winning and non-winning products

The monthly trends of volume and expenditures of winning and non-winning cefuroxime axetil products are displayed in **Figure 1**. **Table 2** and **Table 3** show the results of the segmented regression analysis of winning and non-winning products. For volume, winning products significantly increased 185.07 thousand DDDs after "4+7" policy (95% *CI*: 80.13 to 290.02, *p*-value = 0.002). The trend of volume decreased by 0.82 thousand DDDs per month but with no statistically significant (*p*-value = 0.920). Non-winning products decreased by 26.35 thousand DDDs (*p*-value = 0.096) and the trend of volume decreased by 4.27 thousand DDDs per month (*p*-value = 0.091), but no significant differences were observed. As for expenditures, winning products significantly increased 158.92 thousand RMB after "4+7" policy (95% *CI*: 57.34 to 260.50, *p*-value = 0.004).

Changes of cefuroxime axetil and alternative drugs

The monthly trends of volume and expenditures of cefuroxime axetil and its alternative drugs are displayed in **Figure 2**. **Table 4** and **Table 5** show the results of the segmented regression analysis of cefuroxime axetil and its alternative drugs. For volume, cefuroxime axetil significantly increased 161.16 thousand DDDs after "4+7" policy (95% *CI*: 59.43 to 262.90, *p*-value = 0.004). The trend of cefuroxime axetil's volume decreased by 5.41 thousand DDDs per month but with no statistically significant (*p*-value = 0.480). The alternatives drugs of cefuroxime axetil significantly increased by 273.65 thousand DDDs after "4+7" policy (95% *CI*: 90.17 to 457.12, *p*-value = 0.006). The trend of alternatives drugs' volume significantly decreased by 47.57 thousand DDDs per month (95% *CI*: -74.59 to -20.25, *p*-value = 0.002). The total volume of selected antibiotic drugs significantly increased 436.31 thousand DDDs after "4+7" policy (95% *CI*: 190.81 to 681.81, *p*-value = 0.001). The trend of volume significantly decreased by 54.09 thousand DDDs per month (95% *CI*: 90.31 to 17.88, *p*-value = 0.006).

In terms of expenditures, the alternatives drugs of cefuroxime axetil significantly increased 3471.66 thousand RMB after "4+7" policy (95% *CI*: 1529.70 to 5413.62, *p*-value = 0.001). The trend of alternatives drugs' expenditures significantly decreased by 658.52 thousand RMB per month (95% *CI*: -944.20 to -372.83, *p*-value <0.001). The total expenditures of selected antibiotic drugs significantly increased 3437.80 thousand RMB after "4+7" policy (95% *CI*: 1324.56 to 5551.05, *p*-value = 0.003). The trend expenditures significantly decreased by 680.44 thousand RMB per month (95% *CI*: -991.63 to -369.25, *p*-value <0.001).

Discussion

In this study, using the drug purchase order data of medical institutions in Shenzhen between January 2018 and December 2019, we analyzed the impact of "4+7" volume-based procurement policy on the utilization and expenditures of cefuroxime axetil and its related antibiotic drugs by conducting interruption time series analysis. The present findings might provide references for promoting the rational use of antibiotic agents, as well as the implementation and adjustment of NCDP policy in the following rounds.

This study found that the purchase volume and expenditures of winning cefuroxime axetil products significantly increased in Shenzhen after the implementation of "4+7" policy, with an increment of 182.9% and 102.4%, respectively. The finding is generally consistent with the results of all 25 winning drugs regarding the total purchase volumes and expenditures [22]. It is suggested that after a price cut of 52.5% for the bid winning products, the medication accessibility was improved for patients, and the medication demand was greatly released [23]. This fully reflects the notable effect of the 4+7 policy in reducing the drug burden of the public. However, the results of segmented linear regression showed no significant difference in the monthly trend of the volume and expenditures of the winning cefuroxime axetil product before and after "4+7" policy. On the one hand, it indicated that the effect of "4+7" policy might be insufficient for failing to change the prescription behavior of doctors, so it does not change the changing trend of antibiotic use. On the other hand, it may be related to the short post-intervention time period applied in this study (only 9 months after the intervention), thus is deficiencies in trend analysis. In the future, it is necessary for follow-up research to explore this problem. In the future, it might make sense to conduct continuous tracking analysis and to explore the long-term trend of policy impact.

Compared with April to December 2018, the volume and expenditures of non-winning cefuroxime axetil products from April to December 2019 decreased by 70.3% and 74.1%, respectively. However, the results of segmented linear regression indicated no statically significant difference in the change of volume or expenditure for non-winning products, whether in level change or in trend change. In terms of the original intention of policy design, the NCDP policy hopes that the bid winning drugs under substantial price cut will replace the non-winning drugs as much as possible, so as to archive the goal of reducing drug costs and relieve the overall drug burden of patients [24,25]. From this point of view, the original intention of this policy may have not been fully achieved.

In this study, the total volume of all cefuroxime axetil products significantly increased after the intervention, with an increase of 92.9% compared with the same period in 2018. More importantly, the results of segmented linear regression showed that the volume and expenditures of cefuroxime axetil's alternative drugs increased significantly after "4+7" policy, which increased by 31.2% and 21.0%, respectively. Overall, significant increasements were also observed in the total volume and expenditures of all included antibiotic agents in this study, with an increment of 41.8% for volume and 18.8% for expenditures. These findings suggested that the risk of overuse of antibiotics might be exacerbated after the "4+7" volume-based procurement. Li et al [26] found that patients' average drug costs had not been brought down by the price reduction after in implementation of bidding procurement of antimicrobial drugs in Hubei, China. Liu et al.'s survey [27] on 5 county-level public hospitals in Anhui, China reported that the daily drug costs (DDDc) of antibacterial drugs decreased after the implementation of centralized bidding system, while the volumes and expenditures were still increasing. These findings are generally in line with our results in this study, indicating that price cut alone could not effectively curb the increasing trend of antibiotic drugs whether in volume or in expenditures. More importantly, it is necessary to change doctors' behaviors regarding the prescription of antibiotics [19], so as to promote the rational use of antibiotics and control the growth of drug expenditures.

The results of segmented linear regression also found that monthly trend of the volume and expenditures of cefuroxime axetil's alternative drugs significantly decreased by 54.09 thousand DDDs per month and 680.44 thousand RMB per month, respectively. Besides, the monthly trend of total volume and expenditures for all included antibiotic drugs in this study also significantly slowed down. On the one hand, it might reflect the effectiveness of a series of supporting policies issued by the Chinese government regarding drug use monitoring in medical institutions on the management of antibiotic use [28]. On the other hand, this result might be related to the short post-intervention time period used in this study, thus is deficiencies in trend analysis. Following studies are needed to focus on a longer post-intervention time period and control possible confounding factors, such as policies that might affect the use of antibiotic drugs, so as to further analyze the long-term effect of volume-based procurement policy on antibiotic use.

Overall, the increase in the volume and expenditures of bid winning products is a common phenomenon for most kinds of drugs under "4+7" policy [22,29]. This is so-called "bypass effect" and very common in pharmaceutical policies [30,31], that is, the expenditure of the drugs with price cuts was steady or decease, but the use of drugs without price cuts substantially increased. For antibiotic drugs, their overuse is of great hazard [32]. Thus, we believe there is a certain possibility that antibiotic drugs might not be suitable for involving in volume-based procurement policy. In the future, it is necessary to furtherly improve the contents of the DCNP policy, such as standardizing the formulation criteria of drug procurement catalogue. In addition, policy supporting measures for NCDP policy should be implemented, such as promoting the adoption of prescriptions audit on policy-related antibiotic drugs.

Several potential limitations should be mentioned regarding the present study. Firstly, in terms of evaluating policy effect, the two groups of ITS has more advantages than the single group ITS by setting a control group [33]. However, we failed to set a control group in this study, thus it is difficult to observe and control other factors that may affect the results. Secondly, considering the policy intervention time point and the stability of baseline data, this study only included the data for 24 months. The follow-up periods were short from the date when the policy was implemented with only 9 time points after the intervention, which may be insufficient in trend analysis.

Conclusion

This study provides evidence that the implementation of "4+7" volume-based procurement policy was associated with significant increases in the volume and expenditure of cefuroxime axetil and its alternative drugs. Given the increasing antibiotic resistance in China, the rising of antibiotic use after the policy needs special attention and vigilance. For the improvement of DCNP policy, it might make great sense to standardizing the formulation criteria of drug procurement catalogue and to promote the adoption of prescriptions audit on policy-related drugs.

Abbreviations

WHO: World Health Organization; BRICS countries: Brazil, Russia, India, China, and South Africa; NCDP: National Centralized Drug Procurement; CDPS-SZ: Centralized Drug Procurement Survey in Shenzhen; DDD: Defined Daily Dose; DPP: DDD equivalence per package; ITS: Interrupted time-series; *CI*: Confidence interval; DDDc: Daily Drug Costs.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Faculty of Medical Sciences, Wuhan University (IRB number: 2019YF2050). In this project, no actual human participants were recruited, and no consent to participant was necessary.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated or analysed during the current study are not publicly available due confidentiality policies but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ZM and BZ designed the study. YY and LC collected data. YY, LC, and XK analyzed and interpreted the data. YY, LC and XK drafted the manuscript. ZM and BZ supervised the study and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Authors' information

[1]School of Health Sciences, Wuhan University, 115# Donghu Road, Wuhan 430071, China. [2]Global Health Institute, Wuhan University, 115# Donghu Road, Wuhan 430071, China. [3]Institute of Clinical Pharmacology, Peking University First Hospital, No. 8 Xishiku Street, Xicheng District, Beijing 100034, China.

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Tables

Table 1. Purchase volume and expenditures of included antibacterial agents in April to December 2018 and April to December 2019.

Categories	Volume (million DDDs)			Expenditures (million RMB)		
	Apr. to Dec. 2018	Apr. to Dec. 2019	Relative change (%)	Apr. to Dec. 2018	Apr. to Dec. 2019	Relative change (%)
Cefuroxime Axetil	1.75	3.38	92.9	5.19	4.21	-18.9
Winning products	1.13	3.20	182.9	1.62	3.29	102.4
Non-winning products	0.62	0.18	-70.3	3.56	0.92	-74.1
Alternatives	7.71	10.04	30.2	87.49	105.89	21.0
Total	9.47	13.42	41.8	92.67	110.09	18.8

Table 2. Results of the segmented linear regression models for the volume of winning and non-winning products.

	Coefficient	Standard Error	t	p-value	95% *CI*	
					Lower	Upper
Model 1, Winning products						
Secular trend, β_1	3.94	3.28	1.20	0.245	-2.92	10.80
Change in level, β_2	185.07	50.14	3.69	0.002	80.13	290.02
Change in trend, β_3	-0.82	8.01	-0.10	0.920	-17.58	15.95
Cold, β_4	73.25	31.36	2.34	0.031	7.61	138.89
Constant, β_0	87.74	30.10	2.92	0.009	24.75	150.73
Model 2, Non-winning products						
Secular trend, β_1	0.33	0.98	0.33	0.744	-1.73	2.38
Change in level, β_2	-26.35	15.03	-1.75	0.096	-57.81	5.11
Change in trend, β_3	-4.27	2.40	-1.78	0.091	-9.30	0.75
Cold, β_4	23.97	9.41	2.55	0.020	4.27	43.66
Constant, β_0	59.08	9.02	6.55	0.000	40.21	77.95

Model 1, $F = 25.18$, p-value < 0.001, $R^2 = 0.841$, Adjusted $R^2 = 0.808$; Model 2, $F = 13.02$, p-value < 0.001, $R^2 = 0.733$, Adjusted $R^2 = 0.676$.

Table 3. Results of the segmented linear regression models for the expenditures of winning and non-winning products.

	Coefficient	Standard Error	t	p-value	95% *CI*	
					Lower	Upper
Model 1, Winning products						
Secular trend, β_1	3.27	3.07	1.07	0.300	-3.15	9.70
Change in level, β_2	158.92	48.53	3.27	0.004	57.34	260.50
Change in trend, β_3	-2.66	7.47	-0.36	0.726	-18.29	12.97
Cold, β_4	94.59	32.36	2.92	0.009	26.85	162.33
Constant, β_0	143.04	27.78	5.15	0.000	84.90	201.19
Model 2, Non-winning products						
Secular trend, β_1	1.93	5.62	0.34	0.735	-9.84	13.70
Change in level, β_2	-176.39	86.10	-2.05	0.055	-356.61	3.82
Change in trend, β_3	-22.48	13.74	-1.64	0.118	-51.24	6.28
Cold, β_4	136.03	53.92	2.52	0.021	23.18	248.88
Constant, β_0	337.51	51.63	6.54	0.000	229.45	445.57

Model 1, $F = 20.02$, p-value < 0.001, $R^2 = 0.808$, Adjusted $R^2 = 0.768$; Model 2, $F = 14.17$, p-value < 0.001, $R^2 = 0.749$, Adjusted $R^2 = 0.696$.

Table 4. Results of the segmented linear regression models for the volume of Cefuroxime Axetil and its alternative agents.

	Coefficient	Standard Error	t	p-value	95% CI	
					Lower	Upper
Model 1, Cefuroxime Axetil						
Secular trend, β_1	4.12	3.09	1.33	0.199	-2.35	10.59
Change in level, β_2	161.16	48.61	3.32	0.004	59.43	262.90
Change in trend, β_3	-5.41	7.52	-0.72	0.480	-21.16	10.33
Cold, β_4	89.67	32.04	2.80	0.011	22.62	156.72
Constant, β_0	149.22	28.04	5.32	0.000	90.54	207.89
Model 2, Alternatives						
Secular trend, β_1	20.52	5.42	3.79	0.001	9.18	31.86
Change in level, β_2	273.65	87.66	3.12	0.006	90.17	457.12
Change in trend, β_3	-47.57	12.91	-3.69	0.002	-74.59	-20.55
Cold, β_4	313.94	65.63	4.78	0.000	176.56	451.31
Constant, β_0	634.46	47.66	13.31	0.000	534.70	734.22
Model 3, Total						
Secular trend, β_1	24.70	7.25	3.41	0.003	9.52	39.88
Change in level, β_2	436.31	117.29	3.72	0.001	190.81	681.81
Change in trend, β_3	-54.09	17.30	-3.13	0.006	-90.31	-17.88
Cold, β_4	385.09	87.21	4.42	0.000	202.55	567.63
Constant, β_0	786.20	63.89	12.30	0.000	652.47	919.94

Model 1, $F = 19.63$, p-value < 0.001, $R^2 = 0.805$, Adjusted $R^2 = 0.764$; Model 2, $F = 32.63$, p-value < 0.001, $R^2 = 0.873$, Adjusted $R^2 = 0.846$; Model 3, $F = 36.12$, p-value < 0.001, $R^2 = 0.884$, Adjusted $R^2 = 0.859$.

Table 5. Results of the segmented linear regression models for the expenditures of Cefuroxime Axetil and its alternative agents.

	Coefficient	Standard Error	t	p-value	95% *CI*	
					Lower	Upper
Model 1, Cefuroxime Axetil						
Secular trend, β_1	4.96	5.92	0.84	0.412	-7.43	17.35
Change in level, β_2	-28.45	93.99	-0.30	0.765	-225.17	168.27
Change in trend, β_3	-22.85	14.37	-1.59	0.128	-52.93	7.22
Cold, β_4	221.88	63.49	3.49	0.002	88.99	354.77
Constant, β_0	486.16	53.39	9.11	0.000	374.42	597.90
Model 2, Alternatives						
Secular trend, β_1	168.83	57.35	2.94	0.008	48.79	288.86
Change in level, β_2	3471.66	927.83	3.74	0.001	1529.70	5413.62
Change in trend, β_3	-658.52	136.49	-4.82	0.000	-944.20	-372.83
Cold, β_4	3630.32	697.27	5.21	0.000	2170.91	5089.72
Constant, β_0	7813.30	504.01	15.50	0.000	6758.39	8868.22
Model 3, Total						
Secular trend, β_1	173.62	62.41	2.78	0.012	43.00	304.24
Change in level, β_2	3437.80	1009.66	3.40	0.003	1324.56	5551.05
Change in trend, β_3	-680.44	148.68	-4.58	0.000	-991.63	-369.25
Cold, β_4	3839.38	755.78	5.08	0.000	2257.51	5421.26
Constant, β_0	8304.29	549.01	15.13	0.000	7155.20	9453.38

Model 1, $F = 5.04$, p-value = 0.006, $R^2 = 0.515$, Adjusted $R^2 = 0.413$; Model 2, $F = 26.85$, p-value < 0.001, $R^2 = 0.850$, Adjusted $R^2 = 0.818$; Model 3, $F = 23.22$, p-value < 0.001, $R^2 = 0.830$, Adjusted $R^2 = 0.795$.

Figures

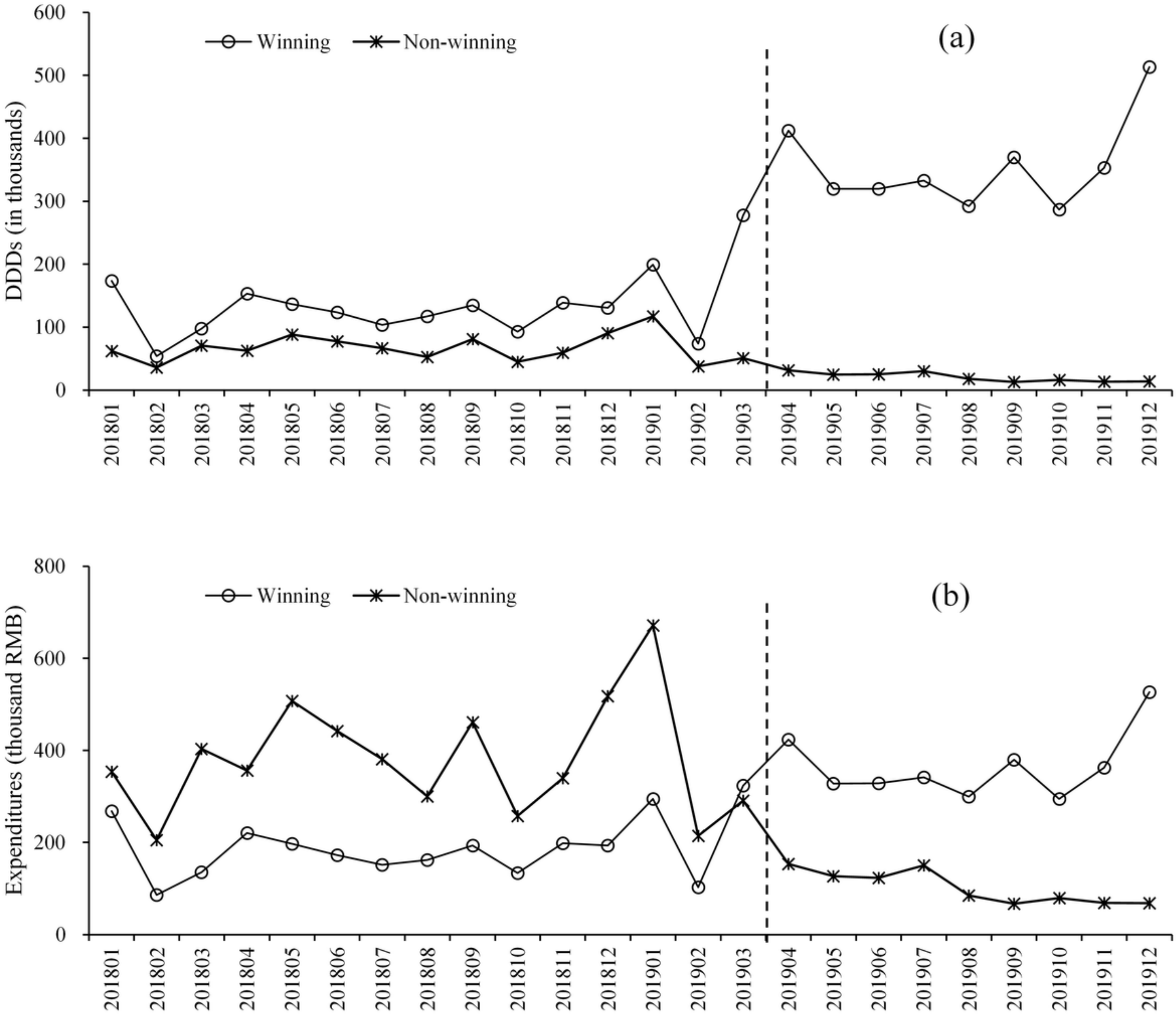

Figure 1

Trends of monthly drug purchase volume and expenditures for winning and non-winning products. (a) Volume (thousand DDDs); (b) Expenditures (thousand RMB).

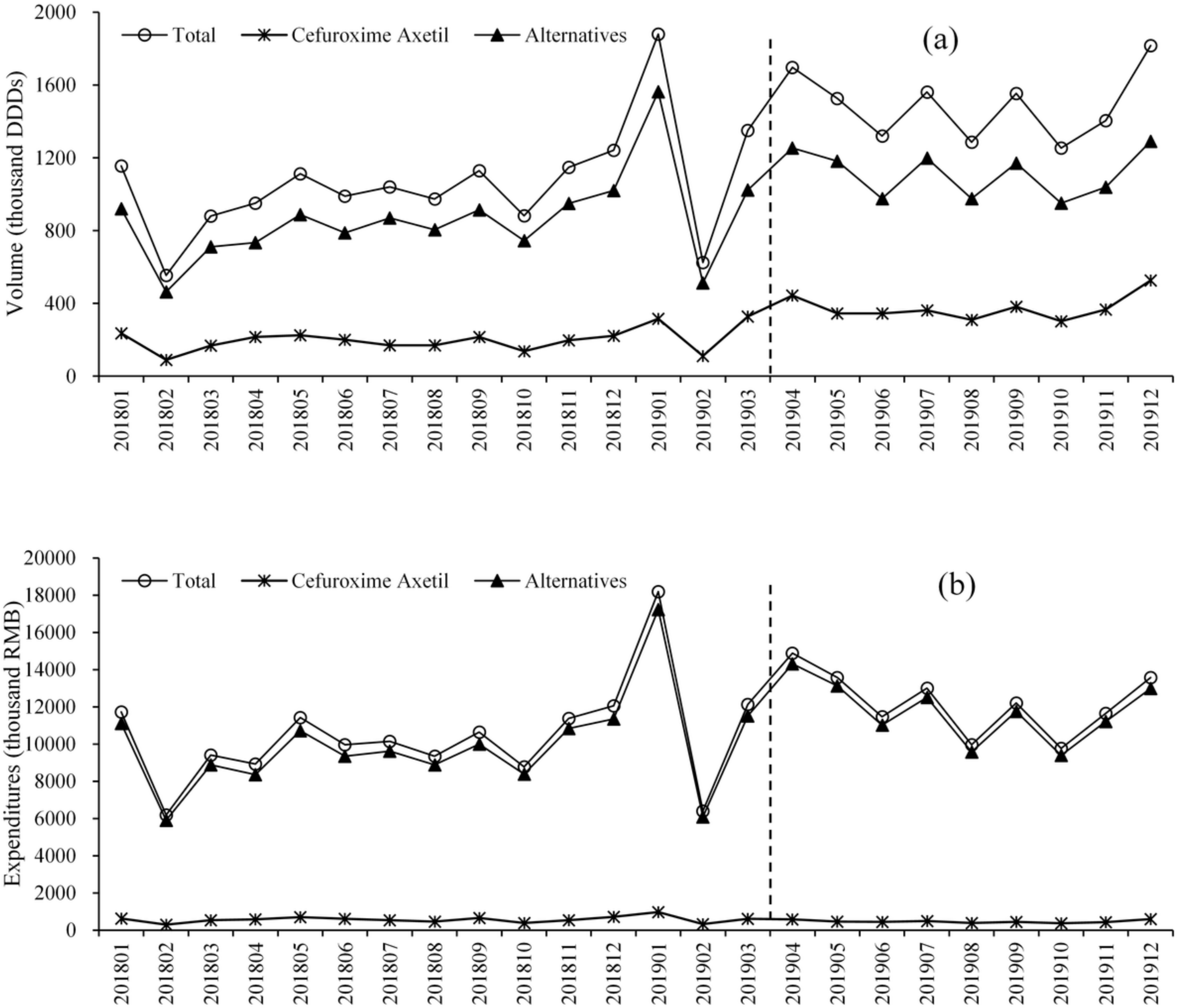

Figure 2

Trends of monthly drug purchase volume and expenditures for Cefuroxime Axetil and its Alternatives. (a) Volume (thousand DDDs); (b) Expenditures (thousand RMB).