Journal of Infection and Public Health 16 (2023) 467–473

Contents lists available at ScienceDirect

Journal of Infection and Public Health

journal homepage: www.elsevier.com/locate/jiph

Original article

Impact of the cefazolin shortage on the selection and cost of parenteral antibiotics during the supply disruption period in Japan: A controlled interrupted time series analysis

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A R T I C L E I N F O

Article history:
Received 21 November 2022
Received in revised form 24 January 2023
Accepted 29 January 2023

Keywords:
Cefazolin shortage
Supply disruption
Controlled interrupted time series

A B S T R A C T

Background: A serious shortage of cefazolin (CEZ) occurred in Japan in 2019. We compared the impact of the CEZ shortage on the selection of parenteral antibiotics at affected and non-affected hospitals.
Methods: The data were extracted from a nationwide Japanese administrative database and included all hospitalized cases between April 2016 and December 2020. We defined 'hospitals with shortage' as those hospitals with a statistically significant decrease in the use of CEZ during the supply disruption period compared to the same months of the previous year; other hospitals as 'hospitals without shortage'. We determined the proportion of each selected parenteral antibiotic use to the sum of all selected antibiotic use in the two groups of hospitals during the supply disruption period and during the same months of the previous year. A controlled interrupted time series (CITS) analysis was conducted to estimate the impact of the CEZ shortage on each antibiotic use and the cost of all parenteral antibiotics per patient day in hospitals with shortage as compared to those without shortage.
Results: In the hospitals with shortage, the proportion of CEZ use to the sum of all selected antibiotics decreased (23.5–11.1%). The decrease in CEZ use was mainly offset by the use of ceftriaxone, ceftriaxone, and ampicillin/sulbactam. The CITS analysis showed a statistically significant increase in the use of broader-spectrum beta-lactams and clindamycin during the supply disruption period (flomoxef up 58.1%, cefotiam up 63.1%, cefmetazole up 14.5%, ceftriaxone up 13.9%, and clindamycin up 20.1%). The analysis showed no statistically significant change in the cost of all parenteral antibiotics per patient day.
Conclusions: During the CEZ supply disruption, there was a statistically significant increase in the use of broader-spectrum beta-lactams and clindamycin in hospitals with shortage compared with those without shortage.

Introduction

The availability and supply of antibiotics are constantly under threat, and antibiotic shortages have been a growing problem in healthcare worldwide [1,2]. In 1998, the United States experienced a severe shortage of intravenous penicillin G due to a voluntary recall of a penicillin product marketed by a large manufacturer [3]. From 2001–2013, 148 antibiotics were in shortage in the U.S [4]. In Europe, a survey of 38 countries revealed that antimicrobial agents were the most frequently reported type of medicine to be in shortage [5]. Antibiotic shortages can lead to the use of a broader spectrum of more expensive, less effective, and more toxic alternatives [6]. Antibiotic resistance organisms are also more likely to evolve due to the use of broad-spectrum antibiotics [7]. As an example, the association between increased usage of high-risk antibiotics and nosocomial *Clostridioides difficile* infections was revealed in piperacillin/tazobactam shortages [8].

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https://doi.org/10.1016/j.jiph.2023.01.021
1876-0341/

A serious shortage of cefazolin (CEZ) occurred in Japan in March 2019 due to manufacturing issues at the site of a key supplier. On February 28, 2019, a major pharmaceutical company (hereinafter 'the affected company'), whose share of the Japanese CEZ market was roughly 60%, announced the cessation of its CEZ production [9]. The company's supply of CEZ was suspended due to a contamination of foreign substances at its Italian factory and the unavailability of the raw materials for CEZ production in China [10]. CEZ is a first-generation cephalosporin and is used to treat infectious diseases due to methicillin-susceptible *Staphylococcus aureus* and surgical prophylaxis. Because of its spectrum for common bacteria and low probability of inducing antibiotic resistance, CEZ is included in the 'Access' group of antibiotics (meaning countries should always maintain availability) in the WHO Model Lists of Essential Medicines [11]. CEZ is the second most used parenteral antibiotic following ceftriaxone and is the most used antibiotic among inpatients in Japan [12]. A list of alternative antibiotics to CEZ was published by the Japanese Ministry of Health, Labour and Welfare [13]. Although there have been a few small-scale studies on the impact of the CEZ shortage [14–16] and a few studies using sales databases [17], few large-scale studies are available [18]. Furthermore, the impact of the CEZ shortage might well depend on the share of CEZ supplied by the affected company [19]. We sought to compare the proportion of each parenteral antibiotic use before and during the supply disruption period and investigate the impact of the CEZ shortage on the prescription pattern and cost of parenteral antibiotic use for inpatients in hospitals classified by their susceptibility to the CEZ supply disruption. We also investigate the relationship between the share of CEZ supplied by the affected company to each hospital before the supply disruption and CEZ uses during the shortage.

Material and methods

Data source

The Diagnosis Procedure Combination (DPC) database of a research group funded by Japan's Ministry of Health, Labour and Welfare (MHLW) was used for the study. The database contains DPC data from approximately 1200 hospitals nationwide in 2016 [20]. The DPC/per-diem payment system (PDPS) was developed as a payment system for inpatients in the acute phase of illness and provides survey data to the MHLW for the purpose of standardizing and improving the quality of medical care for hospitalized patients [21]. The DPC data consists of several data files, including files related to the payment and discharge summaries for the survey. Form 1 in the DPC data contains the discharge summaries, which include the International Classification of Diseases 10th Revision (ICD-10) codes classified as the main diagnosis, the trigger diagnosis, the most and second-most medical-resource-intensive diagnoses, up to 10 comorbidities, and up to 10 complications for each hospitalization. Form 1 also includes the following patient details: age, sex, date of admission, date of discharge, and surgery type. Form 3 contains information on the hospital, such as the number of beds and the qualifications for application of special fees. Files E and F contain information related to medical services and medications, including medical fees, date of provision, and number/quantity of each service/medication.

Study population and study subjects

The study included inpatient cases discharged between April 1, 2016, and December 31, 2020, in hospitals that provided DPC data every month between April 1, 2016, and March 31, 2021, and had monthly uses of CEZ that were not zero before the supply disruption period. We defined the supply disruption period as March to November 2019 [22]. We used days of therapy (DOT) per 100 patient days (PD) (DOT/100PD) as our indicator of antibiotics use; one DOT represents the administration of one agent on a given day, regardless of the dosage and the number of administrations [23].

The included hospitals were divided into two groups: 'hospitals with shortage' and 'hospitals without shortage'. Hospitals with a statistically significant decrease in the use of parenteral CEZ during the supply disruption period compared to the same months of the previous year were designated as 'hospitals with shortage'; hospitals in which there was no significant decrease were designated as 'hospitals without shortage'. The latter served as the control group in the study. We used a chi-squared test to determine whether there was a statistically significant decrease in the proportion of patient days showing CEZ use (using the DOT scale) between the supply disruption period and the same months of the previous year for each hospital.

Descriptive statistics

A number of characteristics were included for the hospitals in each of the two categories: the median (IQR) number and/or proportion of general beds, hospitals eligible for additional fees for higher-level infection prevention measures, teaching hospitals, patient-days using antibiotics to all patient-days, and patient-days performing surgery under general anesthesia to all patient-days. These variables, except for the number of general beds, were described for three time periods: before the supply disruption period (April 2016 to February 2019), during the supply disruption period (March to November 2019), and after the resumption of supply (December 2019 to December 2020). The requirement for an additional fee for higher-level infection prevention includes having an antimicrobial stewardship team, prevention of nosocomial infections, providing training related to nosocomial infection control, and holding conferences on nosocomial infection control with local medical institutions. The percentage change in DOT/100PD of CEZ during the supply disruption period from the same months of the previous year (March and November 2018) was also determined for each classification of the CEZ share of the affected company. The share at each of the hospitals was classified as either Low (< 33%), Medium (33–66%), or High (> 66%).

We determined the proportion of each selected parenteral antibiotic use to the sum of all selected antibiotics uses based on hospital classification during the supply disruption period and the same months of the previous year. We considered commonly used government-recommended CEZ alternatives, which included flomoxef (FOMX), cefotiam (CTM), cefmetazole (CMZ), ceftriaxone (CTRX), ampicillin/sulbactam (SBT/ABPC), clindamycin (CLDM), vancomycin (VCM), and levofloxacin (LVFX), and other frequently used broader-spectrum parenteral antibiotics, including piperacillin/tazobactam (TAZ/PIPC) and meropenem (MEPM)) [13,17]. We also presented the monthly use of each parenteral antibiotic on the DOT/100PD scale based on hospital classification.

Controlled interrupted time series analysis about parenteral antibiotic use

A controlled interrupted time series (CITS) analysis was used to estimate the effect of the CEZ shortage on each parenteral antibiotic use for inpatients in hospitals with shortage relative to hospitals without shortage, which served as the control [24]. We constructed CITS models with two change points assuming Poisson or quasi-Poisson distributions in consideration of the overdispersion of the data. The first change point was March 2019, when the CEZ supply disruption began; the second change point was November 2019, when the supply of CEZ resumed [22]. The outcome was defined as the sum of the monthly DOT/100PD of each parenteral antibiotic according to hospital classification. Seasonality was considered by including harmonic terms (sines and cosines).

The model used was shown in Appendix A. Our primary focus is the difference in first level changes between hospitals with shortage and hospitals without shortage.

Controlled interrupted time series analysis about the cost of parenteral antibiotics

We also conducted a CITS analysis to determine the impact of the CEZ shortage on the cost of parenteral antibiotics. Here, the outcome was the cost of all parenteral antibiotics per patient day. We defined the cost based on drug prices in the National Health Insurance Drug Price Standard. The model was shown in Appendix B.

All statistical analyses were performed with R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided p-value < 0.05 was considered statistically significant, and 95% confidence intervals (CI) were used for the outcomes.

Subgroup and sensitivity analyses

We first conducted the CITS analysis between two subgroups: hospitals that received 100% of their CEZ supply from the affected company from April 2018 to February 2019, and hospitals that received 0% of their CEZ supply from the affected company, which were treated as the control group. We then performed a sensitivity analysis to assess the consistency of the CITS analysis by changing the first change point to April 2019 in recognition of the time lag between the supply disruption by the company and the CEZ shortage in the hospitals.

Results

A total of 16,158,646 inpatient cases in 485 hospitals were included (Supplemental Fig. 1). Among these hospitals, 306 (63.1%, 11,248,929 inpatient cases) were hospitals with shortage and 179 (36.9%, 4909,717 inpatient cases) were hospitals without shortage.

Descriptive statistics

The characteristics of the two groups are shown in Table 1. The median number of general beds in hospitals with shortage was more than that in hospitals without shortage (361 vs 269.5). The other characteristics in the two hospital groups did not change substantially over time.

Supplemental Fig. 2 shows the percentage change from the corresponding months of the previous year in the DOT/100PD of CEZ by share of CEZ provided by the affected company. The median reduction in DOT/100PD using CEZ during the supply disruption period was greater (low −3.1%, medium −58.1%, high −81.6%) in hospitals whose share of CEZ from the affected company was higher.

We determined the proportion of each selected parenteral antibiotic use to the sum of all selected antibiotics by the two groups of hospitals during the supply disruption period and the same months of the previous year. In hospitals without shortage, the percentage of CEZ use to total antibiotics use showed no notable decrease during the supply disruption period compared to the previous year (22.9–23.4%) (Figure 1). In hospitals with shortage, the proportion of CEZ use decreased markedly (23.5–11.1%), with CTRX, CMZ, and SBT/ABPC serving as the main substitutes (Fig. 2). Supplemental Fig. 3 shows a plot of the monthly DOT/100PD in hospitals with a CEZ shortage and hospitals without a CEZ shortage. The monthly DOT/100PD of CEZ in hospitals with shortage decreased compared to hospitals without shortage and did not return to the same level as before the supply disruption period (Supplemental Fig. 4). Among the five most prescribed antibiotics excluding CEZ (SBT/ABPC,

Table 1
The characteristics of hospitals in each group.

	Hospitals without shortage (n = 179)			Hospitals with shortage (n = 306)		
	before the supply disruption period	during the supply disruption period	after the resumption of supply	before the supply disruption period	during the supply disruption period	after the resumption of supply
The number of general beds, median (IQR)	269.5 (175–417.5)			361 (226.25–521.75)		
Hospitals eligible for additional fees for higher-level infection prevention measures, n (%)	125 (69.8)	125 (69.8)	126 (70.4)	251 (82.0)	252 (82.4)	254 (83.0)
Teaching hospitals, n (%)	99 (55.3)	101 (56.4)	101 (56.4)	217 (70.9)	215 (70.3)	215 (70.3)
The proportion of patient-days using antimicrobials to all patient-days, median (IQR)	62.1 (58.6–65.8)	63.4 (59.2–66.5)	62.4 (58.6–65.8)	63.1 (59.8–66.0)	62.8 (58.3–65.8)	62.3 (58.4–65.8)
The proportion of patient-days performing surgery under general anesthesia to all patient-days, median (IQR)	15.8 (10.4–22.5)	16.8 (11.6–23.4)	17.7 (12.0–24.7)	17.2 (12.5–22.8)	17.4 (12.2–23.2)	18.3 (12.9–24.4)

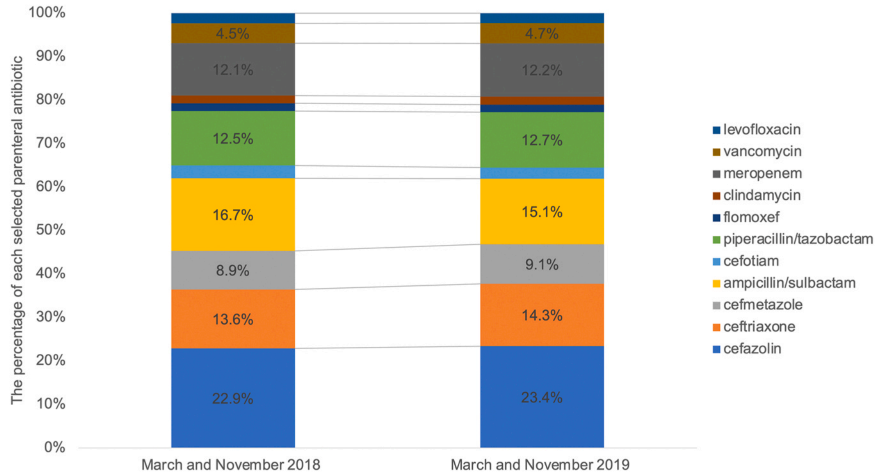

Fig. 1. The proportion of each selected parenteral antibiotic use to the sum of all selected antibiotics use in hospitals without shortage during the supply disruption period relative to the same months of the previous year (March and November 2018).

MEPM, CTRX, TAZ/PIPC, CMZ), the monthly DOT/100PD of CMZ, CTRX, and SBT/ABPC in hospitals with shortage increased compared to hospitals without shortage during the supply disruption period (Supplemental Figure 5).

Controlled interrupted time series analysis about parenteral antibiotic use

The results of the CITS analyses of selected antibiotics are shown in Table 2. We constructed the CITS models assuming quasi-Poisson distributions because of the overdispersion of the data. The CITS analysis showed a statistically significant decrease (−37.3%; 95% CI −45.9 to −27.3) in monthly DOT/100PD of CEZ in hospitals with shortage compared with the control group (Fig. 3). Among government-recommended alternatives, the monthly DOT/100PD of broader-spectrum beta-lactams (FMOX, CTM, CMZ, CTRX) and CLDM showed a significant increase after the first change point (Supplemental Figure 6). In contrast, DOT/100PD of SBT/ABPC, VCM, LVFX, TAZ/PIPC, and MEPM showed no significant change (Supplemental Figure 6).

Controlled interrupted time series analysis about the cost of parenteral antibiotics

The CITS analysis showed no statistically significant change (1.9%; 95% CI −5.3 to 9.6) in the cost of parenteral antibiotics per patient-day in hospitals with shortage compared with the control group (Fig. 4).

Subgroup and sensitivity analyses

The results of the subgroup and sensitivity analyses are shown in Supplemental Tables 1 and 2, and Supplemental Figures 7 and 8. The CITS analysis of the subgroup and sensitivity analyses showed nearly the same trends as the results of the main analyses, except for a statistically significant increase in the DOT/100PD of SBT/ABPC (16.1%; 95% CI 3.3–30.4) in the sensitivity analysis by changing the first change point to April 2019.

Discussion

This study used a nationwide administrative database to analyze the impact of the 2019 CEZ shortage on the selection and cost of

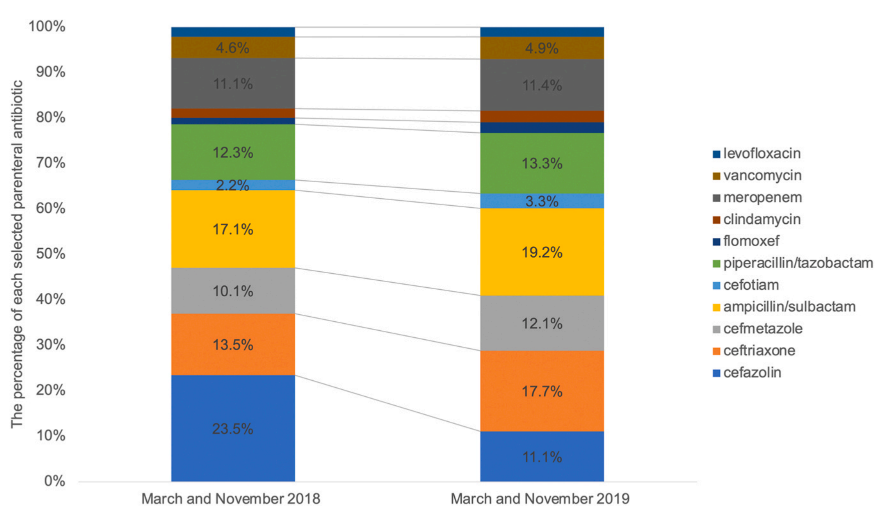

Fig. 2. The proportion of each selected parenteral antibiotic use to the sum of all selected antibiotics use in hospitals with shortage during the supply disruption period relative to the same months of the previous year (March and November 2018).

Table 2
Controlled interrupted time-series analysis for use of each parenteral antibiotic.

	Type of parenteral antibiotics	Intercept	First level change (%)	(95% CI)	P value
Cephalosporin	Cefazolin	5.09	-37.3	(−45.9 to −27.3)	< 0.001
	Flomoxef	0.61	58.1	(37.2–82.1)	< 0.001
	Cefotiam	0.93	63.1	(46.5–81.6)	< 0.001
	Cefmetazole	1.67	14.5	(9.0–20.3)	< 0.001
	Ceftriaxone	2.89	13.9	(2.6–26.5)	0.016
Penicillin	Ampicillin/sulbactam	3.79	10.9	(−1.4 to 24.7)	0.089
	Piperacillin/tazobactam	2.44	2.4	(−5.3 to 10.6)	0.557
Others	Clindamycin	0.44	20.1	(6.7–35.2)	0.003
	Vancomycin	0.98	-1.5	(−7.7 to 5.0)	0.635
	Levofloxacin	0.58	-4.6	(−14.2 to 6.1)	0.388
	Meropenem	2.88	-0.7	(−7.7 to 6.8)	0.857

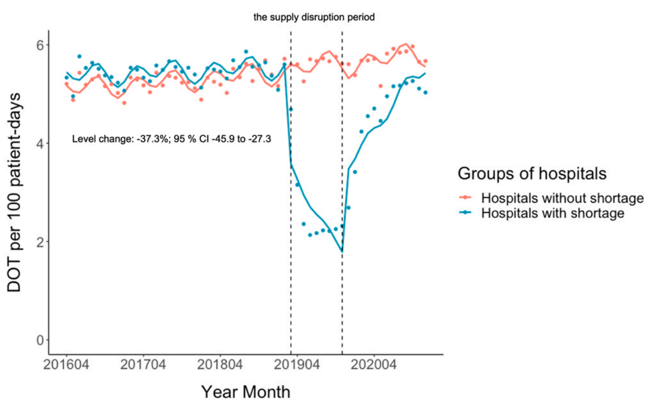

Fig. 3. Results of the controlled interrupted time series analysis for the monthly DOT/100PD of cefazolin between April 2016 and December 2020. Red lines indicate the predicted trend in hospitals without shortage based on the model; green lines indicate the predicted trend in hospitals with shortage. CI: Confidence Interval.

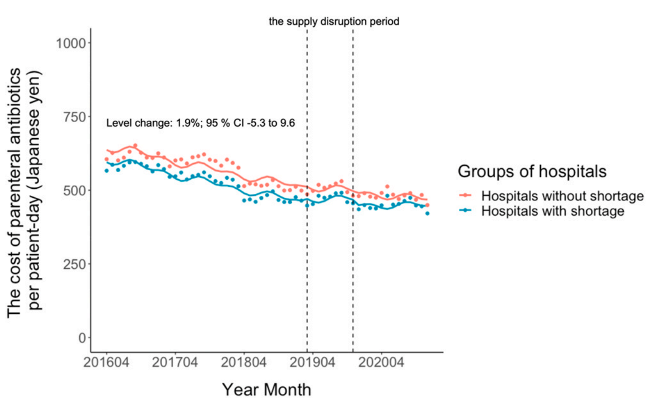

Fig. 4. Results of the controlled interrupted time series analysis of the cost of parenteral antibiotics per patient-day between April 2016 and December 2020. Red lines indicate the predicted trend in hospitals without shortage based on the model; green lines indicate the predicted trend in hospitals with shortage. CI: Confidence Interval.

parenteral antibiotics use. The main findings were as follows: During the supply disruption period, 1) there was a statistically significant decrease in CEZ use in 63.1% of the included hospitals (306/485), and the proportion of CEZ use in hospitals with shortage decreased from 23.5% to 11.1%, with CEZ being mainly replaced by CTRX, CMZ, and SBT/ABPC; 2) the use of broader-spectrum beta-lactams and clindamycin increased in hospitals with shortage compared to the control group; 3) no significant change was observed in the cost of parenteral antibiotics per patient-day in hospitals with shortage compared to the control group; 4) CEZ use decreased more in hospitals that had a higher share of CEZ being supplied by the affected company before the supply disruption period.

Appropriate antibiotic use as a part of antibiotic stewardship is important for improving patient outcomes [25]. Our results showed that many hospitals were affected by the CEZ supply disruption, and the use of broader-spectrum beta-lactams and SBT/ABPC increased in hospitals with shortage. These alternative antibiotics were used for both patients with infectious diseases and those undergoing surgery for the prevention of surgical site infection. This result is consistent with previous reports [14,16]. Second and third generation cephalosporins are listed in the 'Watch' group in Essential Medicines List of WHO because of the increased risk of *Clostridioides difficle* infection [26] and extended-spectrum beta-lactamase (ESBL) selection [27,28]. The results of our research imply broader-spectrum beta-lactams were used instead of CEZ during the supply disruption period, which would impact negatively on appropriate antibiotic use since these could promote antibiotic resistance. Another study has shown that the restriction of CEZ use because of shortage was associated with an improvement in bacterial susceptibility to CEZ [18]. Further study is needed regarding the impact of the CEZ shortage on *Clostridioides difficle* infection and extended-spectrum beta-lactamase (ESBL) selection.

The use of TAZ/PIPC and MEPM did not increase during the supply disruption period in hospitals with shortage compared to the control group. These two drugs are important antibiotics against resistant bacteria such as *Pseudomonas aeruginosa* and ESBL-producing bacteria. Their frequent use could increase the risk of bacterial resistance to the two drugs [7,29,30]. A previous study reported that sales of TAZ/PIPC and MEPM increased during the CEZ supply disruption period [17]. Our study is based on hospital DPC data; therefore, our results reflect actual antibiotic usage more accurately than do sales data.

There was no significant change in the cost of parenteral antibiotics per patient day in hospitals with shortage compared to the control group. This might be because cefazolin [31] and its alternatives were relatively low-priced and the proportion of the cost of these antibiotics in the total of all parenteral antibiotics was small (data was not shown), which means that the replacement of cefazolin with the alternatives had only a minimal impact on the overall cost. The lack of commercial incentives results in pharmaceutical companies becoming dependent on overseas manufacturing, and thus can contribute to an antibiotic shortage in Japan [31]. Many other causes of antibiotic shortages exist, including inefficient forecasting systems, issues related to policy and regulatory processes, and a single source of active pharmaceutical ingredients and other essential materials [2]. Because efforts by individual hospitals or manufacturers alone are not capable of addressing these root causes of antibiotic shortages and related issues, the involvement of the national government in planning and regulation to ensure stable antibiotics access is needed. It is important to secure multiple sources of clinically important antibiotics and develop domestic production of antibiotic resources by offering financial incentives to manufacturers [32]. For national-level shortages, the government should improve the demand forecast of essential antibiotics, develop recommendations listing alternatives in case of shortage, and increase the stocks of critically important antibiotics [32].

Our study revealed that the higher the pre-shortage share of CEZ supplied by the affected pharmaceutical company, the greater was the reduction in the use of CEZ during the supply disruption period. Heavy reliance on a few manufacturers for the supply of antibiotics can lead to a critical shortage of drugs when the supply chain collapses for these manufacturers. Our results also suggested that the use of CEZ in hospitals with shortage has not returned to previous levels following the supply disruption period. One questionnaire survey showed that even in February 2020, 46% of the responding hospitals were experiencing a shortage of antibiotics, primarily CEZ and SBT/ABPC [33], suggesting that a CEZ shortage can have long-term effects at the individual hospital level.

We recognize that our study has several limitations. First, the study population was restricted to hospitals from the research group's database. However, considering the wide coverage in the database [20], the effect of this restriction may be minor. Second, the Coronavirus (COVID-19) pandemic may have affected inpatient characteristics and, consequently, the selection of parenteral antibiotics uses. However, our focus on the difference in first level change (March 2019) was not affected since the COVID-19 pandemic occurred after March 2020 [34]. Third, the influence of the CEZ supply disruption may have affected hospitals without shortage insofar as the disruption in the CEZ supply from the affected company had a likely impact on the CEZ supply from other companies and other antibiotics supplies. However, this influence would bias the result towards the model's null hypothesis; hence, if this influence existed, our results would be robust.

Despite these several limitations, our work provides important information on the impact of the CEZ shortage on the pattern and cost of parenteral antibiotic use in Japan. In conclusion, during the supply disruption in 2019, there was an increase in the use of broader-spectrum beta-lactams and clindamycin in hospitals with shortage compared to the control group.

CRediT authorship contribution statement

Hiroyuki Nagano: Conceptualization, Methodology, Software, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Jung-ho Shin:** Conceptualization, Software, Validation, Investigation, Data curation, Writing – review & editing. **Susumu Kunisawa:** Conceptualization, Validation, Investigation, Data curation, Resources, Writing – review & editing. **Kiyohide Fushimi:** Conceptualization, Data curation, Writing – review & editing. **Miki Nagao:** Conceptualization, Writing – review & editing. **Yuichi Imanaka:** Conceptualization, Validation, Investigation, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Funding

This study was supported by Health and Labour Sciences Research Grants (https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/hokabunya/kenkyujigyou/index.html) from the Ministry of Health, Labour and Welfare, Japan (Grant numbers: JPMH20HA2003 and JPMH22AA2003), and ISHIZUE 2022 (https://www.kura.kyoto-u.ac.jp/support/gambare/ishizue/) of Kyoto University to Y.I. The funders played no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Ethical consideration

This study was approved by the Ethics Committee, Graduate School of Medicine, Kyoto University (approval number: R0135).

Appendix A. The model and parameters in a controlled interrupted time series analysis about parenteral antibiotic use

The model used was as follows:

$$\begin{aligned}\log y &= \log n + \beta_0 + \beta_1 \times time + \beta_2 \times intervention1 + \beta_3 \times intervention1 \times timeafterintervention1 + \beta_4 \times intervention2 + \beta_5 \times intervention2 \\ &\quad \times timeafterintervvention2 + G(\beta_6 + \beta_7 \times time + \beta_8 \times intervention1 + \beta_9 \times intervention1 \times timeafterintervention1 + \beta_{10} \\ &\quad \times intervention2 + \beta_{11} \times intervention2 \times timeafterintervention2)(A.\ 1)\end{aligned}$$

where,

y = sum of monthly DOT in each hospital classification,
n = sum of monthly patient-days /100 in each hospital classification,
time = the number of months (0, 1, 2,..., 56, from April 2016),
intervention1 = a dummy variable indicating the start of the CEZ supply disruption,
time after intervention1 = the number of months from the start of the CEZ supply disruption,
intervention2 = a dummy variable indicating the end of the CEZ supply disruption,
time after intervention2 = the number of months from the end of the CEZ supply disruption,
G = a dummy variable indicating the hospital with the shortage.
Estimated coefficients β_0 to β_{11} are defined as shown below:
β_0 is the baseline DOT before the first change point (intercept);.
β_1 is the baseline slope of DOT before the first change point;.
β_2 is the level change immediately after the start of the CEZ shortage in hospitals with shortage;.
β_3 is the slope change between the first and second change point in hospitals with shortage;.
β_4 is the level change immediately after the second change point in hospitals with shortage;.
β_5 is the slope change after the second change point in hospitals with shortage;.
β_6 is the difference in the intercept of hospitals with shortage relative to those without shortage when the number of month = 0;.
β_7 is the slope difference between hospitals with shortage and hospitals without shortage before the first change point;.
β_8 is the difference in level change between hospitals with shortage and hospitals without shortage after the first change point;.
β_9 is the difference in slope change between hospitals with shortage and hospitals without shortage after the first change point;.
β_{10} is the difference in level change between hospitals with shortage and hospitals without shortage after the second change point;.
β_{11} is the difference in slope change between hospitals with shortage and hospitals without shortage after the second change point.

Appendix B. The model and parameters in a controlled interrupted time series analysis about the cost of parenteral antibiotics

The model was the same as in equation A.1 in Appendix A, except for the following:
y = sum of the cost of all parenteral antibiotics per patient day in each hospital classification (Japanese yen).
n = sum of the monthly patient days in each hospital classification.

Appendix C. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2023.01.021.

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