Evaluation of the strategies to reduce third-generation oral cephalosporins in dentistry at a Japanese academic hospital: An interrupted time series analysis.

Running Head: Evaluation of strategies to reduce third-generation oral cephalosporins in dentistry at a Japanese academic hospital.

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PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES: Not applicable.

SUMMARY

What is known and objective: Third-generation oral cephalosporins, especially cefcapene-pivoxil (CFPN-PI), have been used frequently in the Japanese dental field. In December 2014 and April 2016, the newly published clinical guidelines recommended the use of amoxicillin (AMPC). Thus, it is important to evaluate the impact of these guidelines on the prescription profiles of prophylactic antibiotics, clinical outcomes, and cost effectiveness of antibiotics.

Methods: We conducted a retrospective study to analyze an interrupted time-series analysis from April 2013 to March 2020 at the Department of Dentistry of Hokkaido University Hospital. A segmented regression model was used to estimate the changes in the incidence of infectious complications following tooth extraction. Prescribed antibiotic data were evaluated via days of therapy (DOT). Antibiotic costs were calculated in terms of the Japanese yen (JPY).

Results and Discussion: We identified 17,825 eligible patients. The incidence rates of infectious complications (SSI + dry socket) and SSI after tooth extraction were 3.2% and 2.2%, respectively, during the entire period. The extraction of impacted third molars corresponded to 5.0 % and 3.4 %, respectively. However, their incidence rates were not significantly different during this period. The use of prophylactic antibiotics and antibiotic cost showed consistent trends following the implementation of guidelines. The mean DOT of CFPN-PI decreased (ranging from 4893.6 DOTs/1,000 patients [March 2013 to November 2014] to 3856.4 DOTs/1,000 patients [December 2014 to March 2016]; $p < 0.001$, and from 3856.4 DOTs/1,000 patients [December 2014 to March 2016] to 2293.9 DOTs/1,000 patients [April 2016 to March 2020]; $p < 0.001$). In contrast, the mean DOT of AMPC was found to be increased (ranging from 1379.7 DOTs/1,000 patients [March 2013 to November 2014] to 3236.3 DOTs/1,000 patients [December 2014 to March 2016]; $p < 0.001$, and from 3236.3 DOTs/1,000 patients [December 2014 to March 2016] to 4597.8 DOTs/1,000 patients [April 2016 to March 2020]; $p < 0.001$). The mean monthly cost was decreased (ranging from 905.3 JPY [March 2013 to November 2014] to 788.7 JPY [December 2014 to March 2016]; $p = 0.003$, and from 788.7 JPY [December 2014 to March 2016] to 614.0 JPY [April 2016 to March 2020]; $p < 0.001$).

What is new and conclusion: After December 2014, prophylactic antibiotics were switched from CFPN-PI to AMPC, and the incidence rate of infectious complications was not significantly different over time. However, changing antibiotics is useful from a cost-effectiveness perspective.

Keywords: Amoxicillin, Cefcapene-pivoxil, tooth extraction, prophylactic use, interrupted time series analysis

1. WHAT IS KNOWN AND OBJECTIVE

Antimicrobial resistance (AMR) remains a major problem that must be addressed globally in public health. In 2016, the Japanese government declared the “National Action Plan on AMR”.[1] One outcome index was reducing the use of oral cephalosporins, fluoroquinolones, and macrolides per day per 1,000 inhabitants in 2020 by 50% from 2013 levels. In contrast, third-generation oral cephalosporins, especially cefcapene-pivoxil (CFPN-PI), have been used frequently in dentistry in Japan.[2] In December 2014, the Japanese Association for Infectious Disease and Japanese Society of Chemotherapy revised clinical practice guidelines as they reconsidered the use of third-generation oral cephalosporins in the dental field (The JAID/JSC Guide to Clinical Management of Infectious Disease: JAID/JSC 2014 guidelines).[3] This revised guideline provides clinical recommendations for therapeutic antibiotics for odontogenic infections in Japan. Penicillin, with or without β-lactamase inhibitors, is recommended as a first-line drug against odontogenic infections. Although the JAID/JSC 2014 guidelines were revised again in April 2016, these drug recommendations remained consistent. In April 2016, the Japanese Society of Chemotherapy and Japanese Society for Surgical Infection established clinical practice guidelines (Japanese Clinical Practice Guidelines for antimicrobial prophylaxis in surgery: JSC/JSS guidelines). This guideline approved the use of prophylactic antibiotics for surgical site infections (SSI).[4] In the dental field, amoxicillin (AMPC), amoxicillin/clavulanate, and ampicillin, which are types of penicillin, have been used as first-line drugs. These guidelines recommend the use of AMPC for all procedures, except for patients with a β-lactam allergy.

Following the declaration of the "National Action Plan on AMR," several studies have addressed reductions in the use of third-generation oral cephalosporins and increases in the use of AMPC and evaluated clinical outcomes in dentistry at our facilities. A retrospective cohort study reported that the incidence rate of SSI after impacted third molar (ITM) surgery in patients who received third-generation oral cephalosporins (8.8 %) was higher than that of AMPC (0.5 %).[5] another retrospective study reported that oral third-generation cephalosporins decreased from 70.4 to 0.3 %, whereas AMPC increased from 0% to 98 %. However, the incidence rate of SSI did not change over the study period, with an average total incidence of 3.5 %.[6] In our previous retrospective study, we focused on the effectiveness of antibiotics and compared the incidence rates of SSI in patients who were administered AMPC or CFPN-PI orally in ITMs.[7] The incidence rate of SSI with AMPC (2.4 %) was more desirable than that with CFPN-PI (11.6 %). These studies suggest that the use of

AMPC is reasonable in the dental field. However, observational studies are generally considered weak evidence because of the lack of control over confounding variables and the difficulty in establishing causal dependence. Thus, a superior study design is required to evaluate the impact of antibiotic changes.

As a quasi-experimental study, an interrupted time series analysis (ITS) enables the estimation of causal dependence using an observational approach, and is used to assess the impact of an intervention.[8] ITS has been commonly used to evaluate the impact of public health interventions. In addition, analysis along the timeline enabled us to reveal how the "National Action Plan on AMR" improved the prescription of antibiotics and clinical outcomes. These results enable the further control of antibiotic resistance.

We turned our attention to the reality that the infectious guidelines (JAID/JSC 2014 guidelines, JSC/JSS guidelines) affected the prescription rates of antibiotics in the dental field. The aim of this study was to evaluate the relationship between changes in prescribing antibiotics and clinical outcomes, as well as the cost effectiveness of antibiotics over a long period using ITS.

2. **Patients and methods**

2.1 Study design and data sources

We conducted a retrospective study using ITS. All data were obtained from outpatients at the Department of Dentistry of Hokkaido University Hospital. We evaluated the period from April 1, 2013, to March 31, 2020. We defined eligible patients who were prescribed oral antibiotics on the day of tooth extraction. All the patients were assessed during the evaluation period and the following information was collected: (1) patient background (age and sex), (2) type of tooth extraction (whether ordinary tooth or ITMs), and (3) prescription profile (type of antibiotics, dose regimen, duration of administration, and cost of antibiotics). In the AMPC, we identified prophylactic use for infective endocarditis (IE) based on dose regimen and medical records.

2.2 Definition of study endpoints

The primary endpoint was the change in the incidence rate of infectious complications after tooth extraction. We defined infectious complications as SSI and dry socket occurrences based on a systematic review of the prophylactic effect of antibiotics on tooth extraction.[9] We defined two requirements for infectious complications. First, they had to occur within 30 days after tooth extraction based on guidelines for preventing surgical site infection.[10] Second, additional antibiotics had to be prescribed for therapeutic purposes after an event occurrence based on a grade of 2 or higher in the Clavien-Dindo classification.[11,12] The presence of infectious complications was identified from the descriptions in medical records. For the subjects, we evaluated “with infection after tooth extraction” or “with drainage from tooth extraction wound” as SSI, and “with dry socket after tooth extraction” as a dry socket occurrence. We defined tooth extractions as encompassing both ordinary tooth extraction and ITM extractions. The secondary endpoints were the prescription profile of antibiotic use and the change in antibiotic cost in patients who underwent tooth extraction. We focused on CFPN-PI and AMPC to evaluate the switch from third-generation oral cephalosporins that have been frequently used in AMPC, as recommended by the JAID/JSC 2014 and JSC/JSS guidelines. AMPC did not include the AMPC/CVA. We obtained antibiotic consumption data for prescriptions administered orally at monthly intervals. These data were converted to days of therapy (DOT). The denominator was defined as the total number of eligible outpatients in dentistry per month, and the numerator represents the total number of days of antimicrobial use per month for each prophylactic antibiotic.

DOT is given by the following equation:

$$DOT = \frac{Total\ number\ of\ days\ on\ antimicrobial\ use}{Total\ number\ of\ eligible\ outpatients\ in\ dentistry} \times 1{,}000$$

All costs were calculated in terms of the Japanese yen (JPY). For monthly total cost, we calculated the sum of the drug prices of all antibiotics prescribed in a month divided by the number of eligible patients in the corresponding month. We adjusted for drug price change by setting the average price per drug (both generic and brand) in each year to their corresponding average price in 2020 based on the method reported earlier.[13]

2.3 Statistical analysis

A segmented regression model was applied to estimate changes in the incidence of each event (infectious complications and SSI) during the study period.[8] The JAID/JSC 2014 and JSC/JSS guidelines were implemented in December 2014 and April 2016, respectively. These guidelines were assigned as interventions for segmented regression analysis. We confirmed that the outcome data had no adjustments for autocorrelation, seasonality, and nonstationarity using the JMP Pro 15.2.0 software (SAS Institute Inc., Cary, NC, USA). We performed Poisson regression using the SAS GENMOD procedure in SAS v9.4 (SAS Institute Inc., Cary, NC) for this analysis. Information on the ITS is summarized in Table 1 and Figure 1. We compared the DOT and monthly cost of the antibiotics in each segment period to evaluate the changes in the antibiotic prescription rates. Continuous variables were compared using the t-test and analyzed using R statistical software (version4.1.1, R Core Team, Vienna, Austria).[14] statistical significance was set at $p < 0.05$.

2.4 Ethics

This study was approved by the Institutional Review Board of Hokkaido University (approval number 019-0148) and was conducted in accordance with the Declaration of Helsinki. Because of the retrospective observational nature of the study, the requirement for informed consent was waived and addressed using the opt-out method of our hospital website.

3. Results

3.1 Patient backgrounds

The patient backgrounds at the segmented period are summarized in Table 2. Before the JAID/JSC 2014 guidelines, the proportion of ITMs to tooth extraction overall was slightly less than the other segmented periods. The other items did not differ mostly in each segmented period. In both the AMPC and CFPN-PI, these conditions remained constant (Table 3).

3.2 DOT of antibiotic consumption

We identified 17,825 patients between April 2013 and March 2020. Prescribed antibiotics were dominated by AMPC and CFPN-PI. The DOT of AMPC showed an increasing trend over time (Fig. 2-1). Additionally, the mean DOT of AMPC increased (from 1379.7 DOTs/1,000 patients [March 2013 to November 2014] to 3236.3 DOTs/1,000 patients [December 2014 to March 2016]; $p < 0.001$) following the implementation of the JAID/JSC 2014 guidelines and further increased (from 3236.3 DOTs/1,000 patients [December 2014 to March 2016] to 4597.8 DOTs/1,000 patients [April 2016 to March 2020]; $p < 0.001$) following the adoption of the JSC/JSS guidelines (Table 3-1). In contrast, the DOT of CFPN-PI showed a decreasing trend over time (Fig. 2-2). The mean DOT of CFPN-PI decreased (from 4893.6 DOTs/1,000 patients [March 2013 to November 2014] to 3856.4 DOTs/1,000 patients [December 2014 to March 2016]; $p < 0.001$) following the implementation of the JAID/JSC 2014 guidelines and decreased further (from 3856.4 DOTs/1,000 patients [December 2014 to March 2016] to 2293.9 DOTs/1,000 patients [April 2016 to March 2020]; $p < 0.001$) following the adoption of the JSC/JSS guidelines (Table 3-2). The DOT of oral fluoroquinolones and macrolides decreased over time, whereas oral lincomycin showed an increasing trend. Lincomycin antibiotics included clindamycin (CLDM) alone. The DOT of beta-lactams (except for AMPC and CFPN-PI) and the other antibiotics remained consistent (Fig. 2-3).

In most cases, the antibiotic dose regimens consisted of three 250 mg doses for AMPC and three 100 mg doses for CFPN-PI (Table 3). In the median duration of administration, the maximum value was an extreme deviation from the median value. In the AMPC group, nine patients had a duration of administration of more than 10 days. Five cases aimed to relieve inflammation caused by past odontogenic infection, and four cases were not included in the medical records. In CFPN-PI, three patients had a duration of administration of more than 10 days. One case included the amount of antibiotics to be used in the next surgery, and two cases were not included in the medical records.

3.3 Cost of antibiotics

The monthly total cost of antibiotics decreased over time (Fig. 3). The mean monthly cost decreased (from 905.3 JPY [March 2013 to November 2014] to 788.7 JPY [December 2014 to March 2016]; $p = 0.003$) following the implementation of the JAID/JSC 2014 guidelines, and decreased further (from 788.7 JPY [December 2014 to March 2016] to 614.0 JPY [April 2016 to March 2020]; $p < 0.001$) following the adoption of the JSC/JSS guidelines.

3.4 Outcome evaluation

Among the 17,825 eligible patients, 6,935 had undergone ITM extraction. Between April 2013 and March 2020, the onset of infectious complications was observed in 579 patients following tooth extraction and in 346 patients following ITM extraction. Among infectious complications, the onset of SSI was observed in 398 patients following tooth extraction and in 238 patients following ITM extraction. The parameter estimates from the segmented regression analysis are presented in Table 4. Regarding the incidence of infectious complications and SSI, the slope of the trend of infectious complications and immediate changes in levels after the implementation of each guideline were not significantly different in each segmented period, both in the tooth extraction overall and in the ITM extraction (Fig. 4 and Table 4).

4. Discussion

This is the first study to evaluate the impact of infectious guidelines on the prescription profile of prophylactic antibiotics and their clinical outcomes in the Japanese dental field using a quasi-experimental study design.

The background of eligible patients was mostly similar in each segmented period. In the antibiotic dose regimen, nine cases of AMPC and three cases of CFPN-PI contained outliers in the duration of antibiotic administration. There were very few of these cases compared to the number of patients who had used less than 10 days, and it is conceivable that they did not affect our results.

In DOT, after the implementation of the JAID/JSC 2014 guidelines, fluoroquinolones, macrolides, and especially CFPN-PI showed a decreasing trend, whereas AMPC and CLDM trends increased (Fig. 2). CLDM is an alternative treatment for patients with β-lactam allergies in both guidelines. Thus, these data showed that prophylactic antibiotics especially switched from CFPN-PI to AMPC and proceeded with the use of recommended antibiotics based on the guidelines. Therefore, although the JAID/JSC 2014 guidelines targeted odontogenic infection, it may also have affected the selection of antibiotics for SSI. These trends continued after the implementation of the JSC/JSS guidelines. A possible explanation for why the antibiotics did not change immediately after the implementation of the guidelines is that in the prophylactic use of antibiotics, clinicians tend to use broad-spectrum antibiotics empirically because it is difficult to identify the pathogen of odontogenic infection due to mixed infection. Consequently, antibiotics that were not recommended as the first choice by the guidelines may have been selected preferentially. In addition, the median duration of administration was three or four days for antibiotics, whereas the recommended administration duration by JSC/JSS guidelines is from once before surgery to 48h after surgery. This is also considered to be due to its empirical use. Finally, the CFPN-PI was switched to AMPC through the dissemination of guidelines. In contrast, the decrease in fluoroquinolones and macrolides may have been affected by the "National Action Plan on AMR"

The monthly total cost of antibiotics decreased significantly over time. The medical cost of CFPN-PI is three to four times higher than that of AMPC, thereby showing that switching from CFPN-PI to AMPC significantly contributes to reducing antibiotic costs.

The incidence rates of infectious complications (SSI + dry socket) and SSI after tooth extraction were 3.2% and 2.2%, respectively, over the entire period. In ITM extraction, it corresponded to 5.0 % and 3.4 %, respectively. The Cochrane database of systematic reviews showed a prophylactic effect of antibiotics against infectious complications following tooth extractions.[9] The incidence of postsurgical infectious complications was 2.6 % with the use of antibiotics and 8.5 % with the placebo. Dry socket incidences were 3.8 % with the use of antibiotics and 6.3 % with placebo. Based on these reports, our results suggest that the incidence of an event controlled by antibiotics is appropriate.

In our previous retrospective study, multivariate analysis showed that the use of

CFPN-PI for prophylactic treatment and hospitalization after tooth extraction contributed to SSI following ITMs surgery in the same facility.[7] In the present study, the rates of hospitalization following tooth extraction did not differ in each segmented period (Table 2). Although prophylactic antibiotics switched from CFPN-PI to AMPC over time, the incidence rates of infectious complications after tooth extraction did not improve (Fig. 4). This result is consistent with a previous retrospective study that evaluated the switch to AMPC from third-generation oral cephalosporins at other facilities.[6] Based on the assumption that AMPC is more effective than CFPN-PI, there are two possible reasons for the lack of improvement in clinical outcomes. First, the effectiveness of AMPC may deteriorate over time due to several factors, including antimicrobial resistance. To our knowledge, there is one report that evaluated the antibiotic resistance of periodontal pathogens over time. This report showed that *Parvimonas micra* resistance to AMPC remained low in 2016 compared with 2006 (2.3 % vs. 1.0 % of patients).[15] Thus, it is difficult to posit that antimicrobial resistance was the cause. Second, the difference in prophylactic antibiotics alone may not be sufficient to control clinical outcomes in the real world. Systematic reviews and meta-analyses reported that AMPC alone was ineffective against SSI following an ITM surgery.[16-18] However, a recent prospective study in Japan showed that three doses of

250 mg for AMPC beginning 1 h before surgery can prevent SSI after an ITM surgery in Japanese patients without SSI risk factors.[19] Similarly, a retrospective study showed that the same dose of AMPC was effective in Japanese patients.[5] These Japanese articles and the aforementioned systematic reviews and meta-analyses differ in target patients; however, these articles targeted Japanese patients, the aforementioned systematic reviews and meta-analyses targeted Caucasians. Thus, this difference in effectiveness may suggest that the antimicrobial effects of AMPC are associated with background factors of the patients. Furthermore, a recent prospective study showed that the administration of 2 g AMPC exceeded the minimum inhibitory concentration (MIC) of some microorganisms that cause odontogenic infection in the third molar socket.[20] This study suggested that a sufficient dose of AMPC is effective against infectious complications after tooth extraction from a pharmacological profile. Thus, to interpret the systematic reviews and meta-analyses, an insufficient dose of AMPC may be ineffective against SSI after tooth extraction, including ITM surgeries. Collectively, no consensus has been reached regarding the reason why the change in antibiotics did not reflect the clinical outcome. In contrast, the antimicrobial effect of AMPC against infectious complications following tooth extraction may involve multiple factors. To ensure the antimicrobial effect of AMPC, further evaluations of

the antibiotic dose, administration time, and period are required. In addition, a risk factor assessment is required to clarify whether antibiotics are necessary in specific patients.

The present study has several limitations. First, segmented regression via ITS cannot control for individual-level covariates. Second, we did not include a placebo group. Third, the data were obtained in the same facility, which may not be generalizable or applicable to other facilities. Fourth, we did not evaluate fever and the results of biochemistry tests because most outpatients did not receive measurements of body temperature and blood sampling. These limitations should be considered when interpreting our results.

5. WHAT IS NEW AND CONCLUSION

Following the switch from CFPN-PI to AMPC as spurred by the implementation of the JAID/JSC 2014 guidelines, the incidence rates of infectious complications following tooth extraction showed no significant difference over time regardless of guideline implementation. However, switching from CFPN-PI to AMPC is effective from a cost-effectiveness perspective.

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Tables:

Table 1.1 Equation of the segmented regression model

Equation	$E(Y/Nt) = \beta_0 + \beta_1{}^{*}time_t + \beta_2{}^{*}intervention1_t + \beta_3{}^{*}time\ after\ intervention1_t + \beta_4{}^{*}intervention2_t + \beta_5{}^{*}time\ after\ intervention2_t$

Table 1.2 Parameter of Equation

Parameter	Meaning
Y	the number of events
N	the number of patients who were administrated antibiotics after tooth extraction
β_0	baseline level of infectious complications at time 0
β_1	slope before implementation of the JAID/JSC 2014 guidelines
Time	trend in the rate of infectious complications prior to implementation of the JAID/JSC 2014 guidelines
β_2	change in level immediately after implementation of the JAID/JSC 2014 guidelines
Intervention1	indicates whether the JAID/JSC 2014 guidelines were implemented at the time
β_3	slope following implementation of the JAID/JSC 2014 guidelines
Time after intervention1	the number of months that passed since the implementation of the JAID/JSC 2014 guidelines
β_4	change in level immediately following the implementation of the JSC/JSS guidelines
Intervention2	indicates whether the JSC/JSS guidelines were implemented at the time
β_5	slope after implementation of the JSC/JSS guidelines
Time after intervention2	the number of months that passed since the implementation of the JSC/JSS guidelines

Table 2 Information of eligible patients

	Before JAID/JSC 2014 guidelines (April 2013 - November 2014)	After JAID/JSC 2014 guidelines (December 2014 - March 2016)	After JSC/JSS guidelines (April 2016 - March 2020)
Number of patients	4,831	4,283	8,711
Age (year)	39 [3, 94]	39 [2, 94]	43 [4, 99]
Gender (Women)	2,856 (59.1 %)	2,538 (59.3%)	5,066 (58.2 %)
Impacted third molars	1,684 (34.9 %)	1,719 (40.1 %)	3,532 (40.5 %)
Hospitalization after tooth extraction	975 (20.2 %)	894 (20.9 %)	1,820 (20.9 %)

JAID/JSC 2014 guidelines: clinical practice guidelines revised in 2014 developed by the Japanese Association for Infectious Disease and Japanese Society of Chemotherapy. JSC/JSS guidelines: clinical practice guidelines developed by the Japanese Society of Chemotherapy and Japanese Surgical Society. DOT: Days of therapy

Table 3.1 Information for Amoxicillin

	Before JAID/JSC 2014 guidelines (April 2013 - November 2014)	After JAID/JSC 2014 guidelines (December 2014 - March 2016)	After JSC/JSS guidelines (April 2016 - March 2020)
Antibiotic profile			
DOT (mean ± SD)	1,379.7 ± 358.4	3,236.3 ± 787.6	4,597.8 ± 809.3
Background of eligible patients			
Number of patients	796	1,463	5,389
Age (year)	40 [4, 94]	41 [3, 94]	43 [5, 99]
Gender (Women)	447 (56.2 %)	841 (57.5 %)	3,110 (57.7 %)
Impacted third molars	276 (34.7 %)	637 (43.5 %)	2,273 (42.2 %)
Prophylactic use for IE	42 (5.3 %)	45 (3.1 %)	137 (2.5 %)
Prescription profile on the day of operation			
Regimen: 250 mg thrice a day	725 (86.8 %)	1,396 (95.4 %)	5,139 (96.1 %)
Duration for antibiotics (Day, median, range)	3 [1.0, 35.0]	3 [1.0, 21.0]	3 [1.0, 47.0]

Table 3.2 Information of Cefcapene-pivoxil

	Before JAID/JSC 2014 guidelines (April 2013 - November 2014)	After JAID/JSC 2014 guidelines (December 2014 - March 2016)	After JSC/JSS guidelines (April 2016 - March 2020)
Antibiotic profile			
DOT (mean ± SD)	4,893.6 ± 475.8	3,856.4 ± 485.8	2,293.9 ± 1,032.3
Background of eligible patients			
Number of patients	3,713	2,575	2,864
Age (year)	38 [6, 92]	38 [6, 92]	41 [6, 94]
Gender (Women)	2,228 (60.0 %)	1,541 (59.9%)	1,697 (59.3 %)
Impacted third molars	1,318 (35.5 %)	1,004 (39.0 %)	1,139 (39.8 %)
Prescription profile on the day of operation			
Regimen: 100 mg thrice a day	3,678 (99.1 %)	2,553 (99.1 %)	2,836 (99.0 %)
Duration for antibiotics (Day, median, range)	4 [1.0, 8.0]	3 [1.0, 36.0]	3 [1.0, 45.0]

JAID/JSC 2014 guidelines: Clinical practice guidelines revised in 2014 developed by the Japanese Association for Infectious Disease and Japanese Society of Chemotherapy. JSC/JSS guidelines: Clinical practice guidelines developed by the Japanese Society of Chemotherapy and the Japanese Surgical Society. DOT: Days of therapy. IE: Infective endocarditis.

Table 4.1 Parameter estimates, with 95% CIs and P-values from the segmented regression model for infectious complications of tooth extraction overall

	Coefficient	Standard error	95% CI		p-value
Intercept, β0	-3.1308	2.1673	-7.3785	1.117	0.1486
Baseline trend, β1	-0.0235	0.2076	-0.4304	0.3835	0.9099
Level change after intervention 1, β2	0.0791	3.8818	-7.5292	7.6874	0.9837
Trend change after intervention 1, β3	0.0233	0.3748	-0.7113	0.7579	0.9504
Level change after intervention 2, β4	0.0121	3.2038	-6.2672	6.2914	0.997
Trend change after intervention 2, β5	0.0031	0.3173	-0.6187	0.625	0.9921

Table 4.2 Parameter estimates, with 95% CIs and P-values from the segmented regression model for surgical site infections of tooth extraction overall

	Coefficient	Standard error	95% CI		p-value
Intercept, β0	-3.3679	2.444	-8.1581	1.4222	0.1682
Baseline trend, β1	-0.0243	0.2346	-0.4841	0.4356	0.9177
Level change after intervention 1, β2	-0.0911	4.658	-9.2205	9.0383	0.9844
Trend change after intervention 1, β3	0.0214	0.4549	-0.8702	0.913	0.9625
Level change after intervention 2, β4	-0.0671	4.0382	-7.9818	7.8476	0.9867
Trend change after intervention 2, β5	0.0105	0.3962	-0.766	0.787	0.9789

Table 4.3 Parameter estimates, with 95% CIs and P-values from the segmented regression model for infectious complications of impacted third molars extraction

	Coefficient	Standard error	95% CI		p-value
Intercept, β0	-2.9502	1.9127	-6.699	0.7987	0.123
Baseline trend, β1	-0.007	0.1753	-0.3505	0.3365	0.9681
Level change after intervention 1, β2	0.1835	3.0927	-5.8781	6.2451	0.9527
Trend change after intervention 1, β3	-0.0194	0.3126	-0.6321	0.5932	0.9505
Level change after intervention 2, β4	0.4105	2.7105	-4.9019	5.7229	0.8796
Trend change after intervention 2, β5	0.0263	0.2627	-0.4885	0.5411	0.9203

Table 4.4 Parameter estimates, with 95% CIs and P-values from the segmented regression model for surgical site infections of impacted third molars extraction

	Coefficient	Standard error	95% CI		p-value
Intercept, β0	-3.3337	2.2965	-7.8348	1.1674	0.1466
Baseline trend, β1	-0.0029	0.2082	-0.411	0.4052	0.9889
Level change after intervention 1, β2	0.0763	3.7645	-7.302	7.4545	0.9838
Trend change after intervention 1, β3	-0.0294	0.3871	-0.788	0.7292	0.9395
Level change after intervention 2, β4	0.3786	3.4441	-6.3717	7.1289	0.9125
Trend change after intervention 2, β5	0.0385	0.3308	-0.6098	0.6868	0.9074

Figure legends:

Fig. 1 Graphical illustration of interrupted regression analysis

JAID/JSC 2014 guidelines: Clinical practice guidelines revised in 2014 developed by the Japanese Association for Infectious Disease and Japanese Society of Chemotherapy. JSC/JSS guidelines: Clinical practice guidelines developed by the Japanese Society of Chemotherapy and the Japanese Society for Surgery. The JAID/JSC 2014 guidelines were implemented in December 2014, and the JSC/JSS guidelines were published in April 2016. β_0 is the baseline level of infectious complications at time 0. β_1 is the slope prior to the implementation of the JAID/JSC 2014 guidelines. β_2 is the change in level immediately following the implementation of the JAID/JSC guidelines. β_3 is the slope following the implementation of the JAID/JSC 2014 guidelines. β_4 is the change in level immediately following the implementation of the JSC/JSS guidelines. β_5 is the slope following the implementation of the JSC/JSS guidelines.

Fig. 2-1 DOT of Amoxicillin

DOT, days of therapy. AMPC, amoxicillin. R^2, coefficient of determination The DOT of AMPC was recorded for each month in eligible patients (solid line). The red vertical lines indicate December 2014 and April 2016, respectively. An approximate straight line was added as a visual guide.

Fig. 2-2 DOT of Cefcapene-pivoxil

DOT, days of therapy. CFPN-PI, cefcapene-pivoxil. R^2, coefficient of determination. The DOT of CFPN-PI was recorded for each month in eligible patients (solid line). The red vertical lines indicate December 2014 and April 2016, respectively. An approximate straight line was added as a visual guide.

Fig. 2-3 DOT of antibiotics except for Amoxicillin and Cefcapene-pivoxil

DOT, days of therapy. AMPC, amoxicillin. CFPN-PI, cefcapene-pivoxil. R^2, coefficient of determination. The DOT of antibiotics, except for AMPC and CFPN-PI, was recorded for each month in eligible patients (solid line). The red vertical lines indicate December 2014 and April 2016, respectively. An approximate straight line was added as an eye guide. Lincomycin is only a clindamycin.

Fig. 3 Comparison of antibiotic cost per patient segmented by infectious guidelines

JPY, Japanese yen. The monthly total cost was calculated as the sum of the drug price of all antibiotics prescribed in a month divided by the number of eligible patients in the corresponding month. The boxplot indicates the median (bold horizontal line), the 25th and 75th percentiles (box), and the highest and the lowest values (whiskers). *P value by t-test. ***P < 0.001. **P < 0.01.

Fig. 4-1 Incidence of infectious complications after tooth extraction overall

The incidence rates of infectious complications were recorded each month (solid line). The red vertical lines indicate December 2014 and April 2016, respectively.

Fig. 4-2 Incidence rates of surgical site infection following tooth extraction overall

The results were limited to surgical site infections in infectious complications following tooth extraction. The incidence rates of surgical site infections were recorded each month (solid line). The red vertical lines indicate December 2014 and April 2016, respectively.

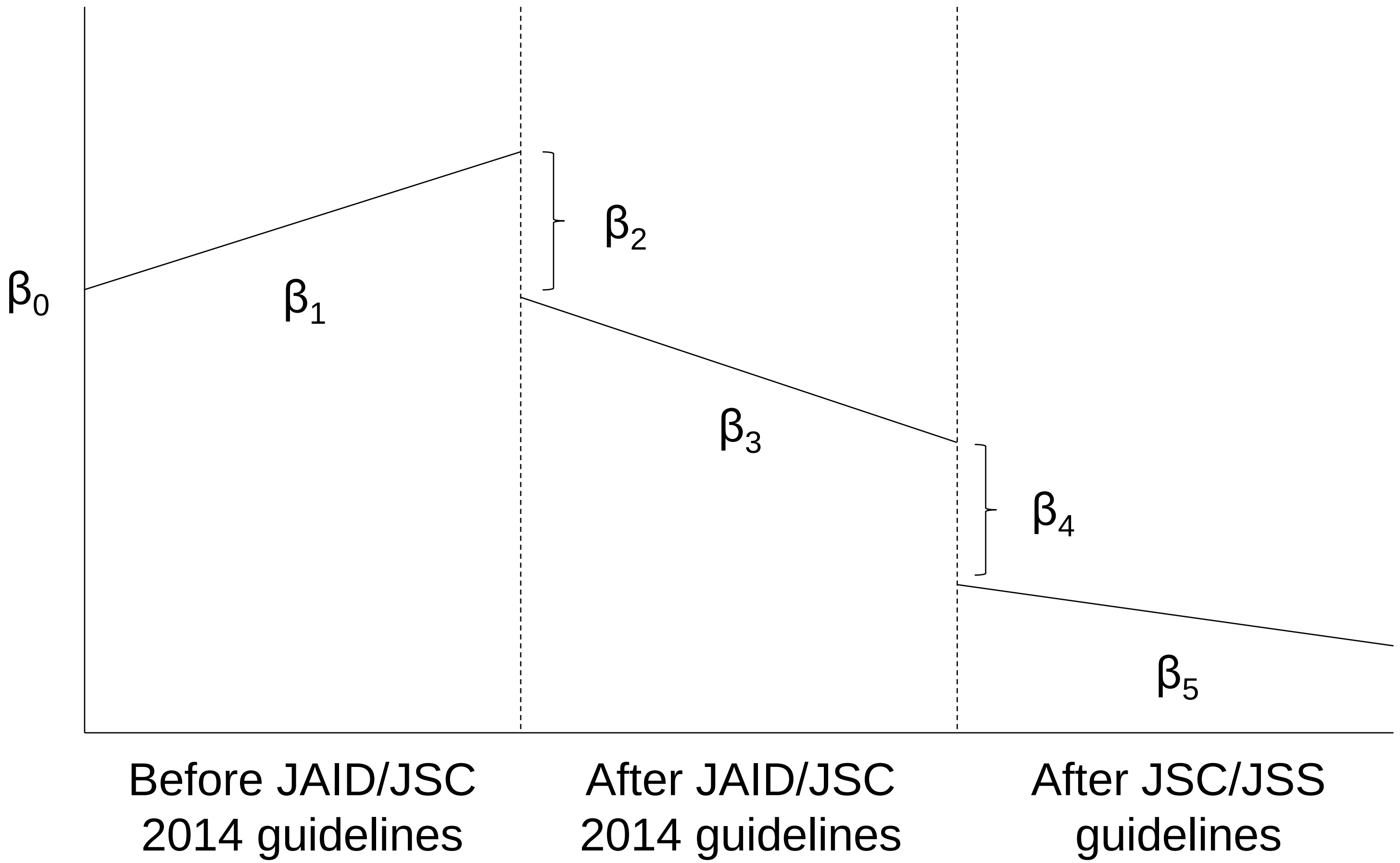
Fig. 4-3 Incidence of infectious complications after impacted tooth extraction

The incidence rates of infectious complications were recorded each month (solid line). The red vertical lines indicate December 2014 and April 2016, respectively.

Fig. 4-4 Incidence rates of surgical site infection following impacted tooth extraction

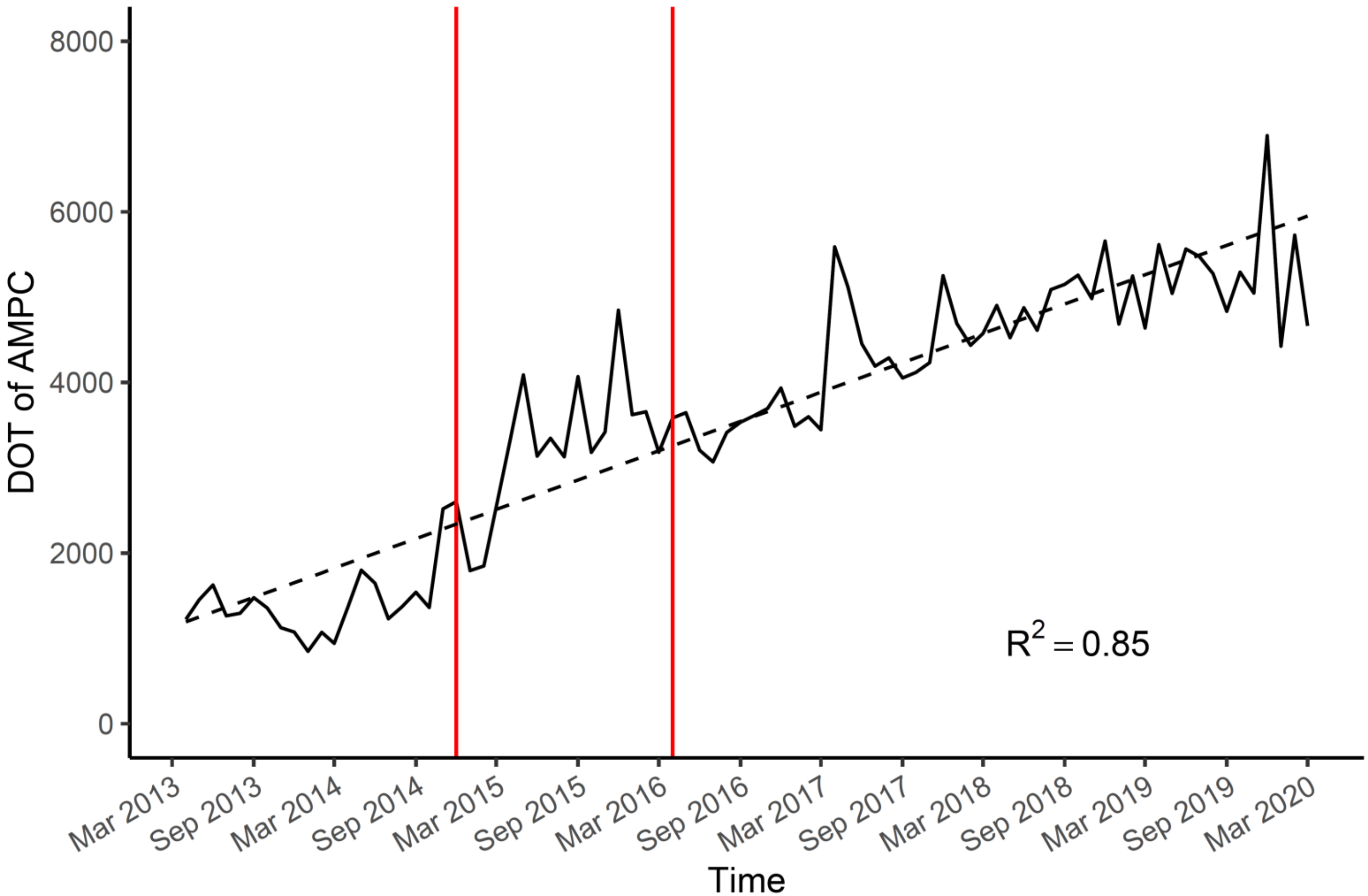
The results were limited to surgical site infections in infectious complications following impacted tooth extraction. The incidence rates of surgical site infections were recorded each month (solid line). The red vertical lines indicate December 2014 and April 2016, respectively.

Fig. 1



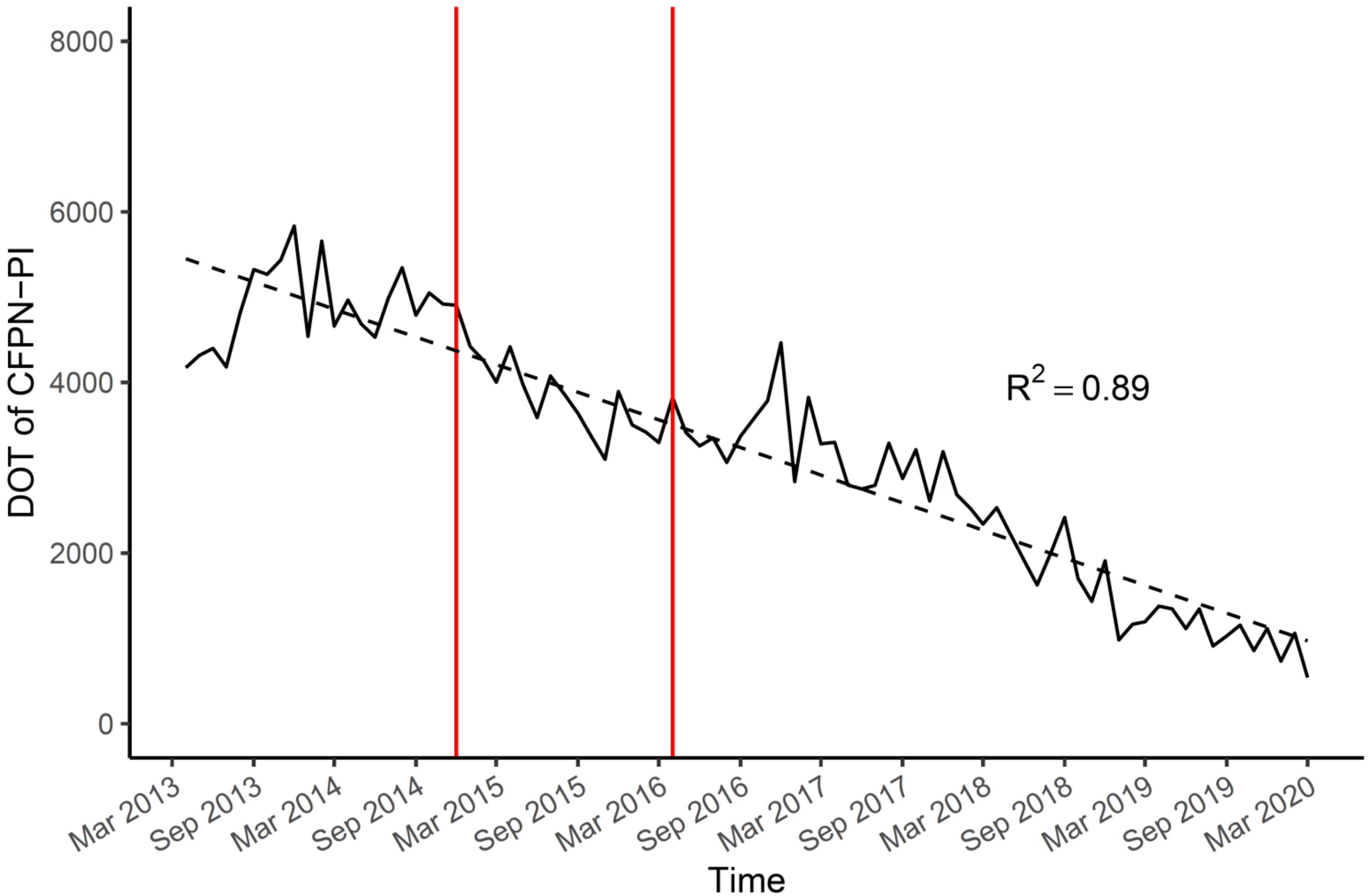
β0
β1
β2
β3
β4
β5
Before JAID/JSC 2014 guidelines
After JAID/JSC 2014 guidelines
After JSC/JSS guidelines

Fig. 2-1



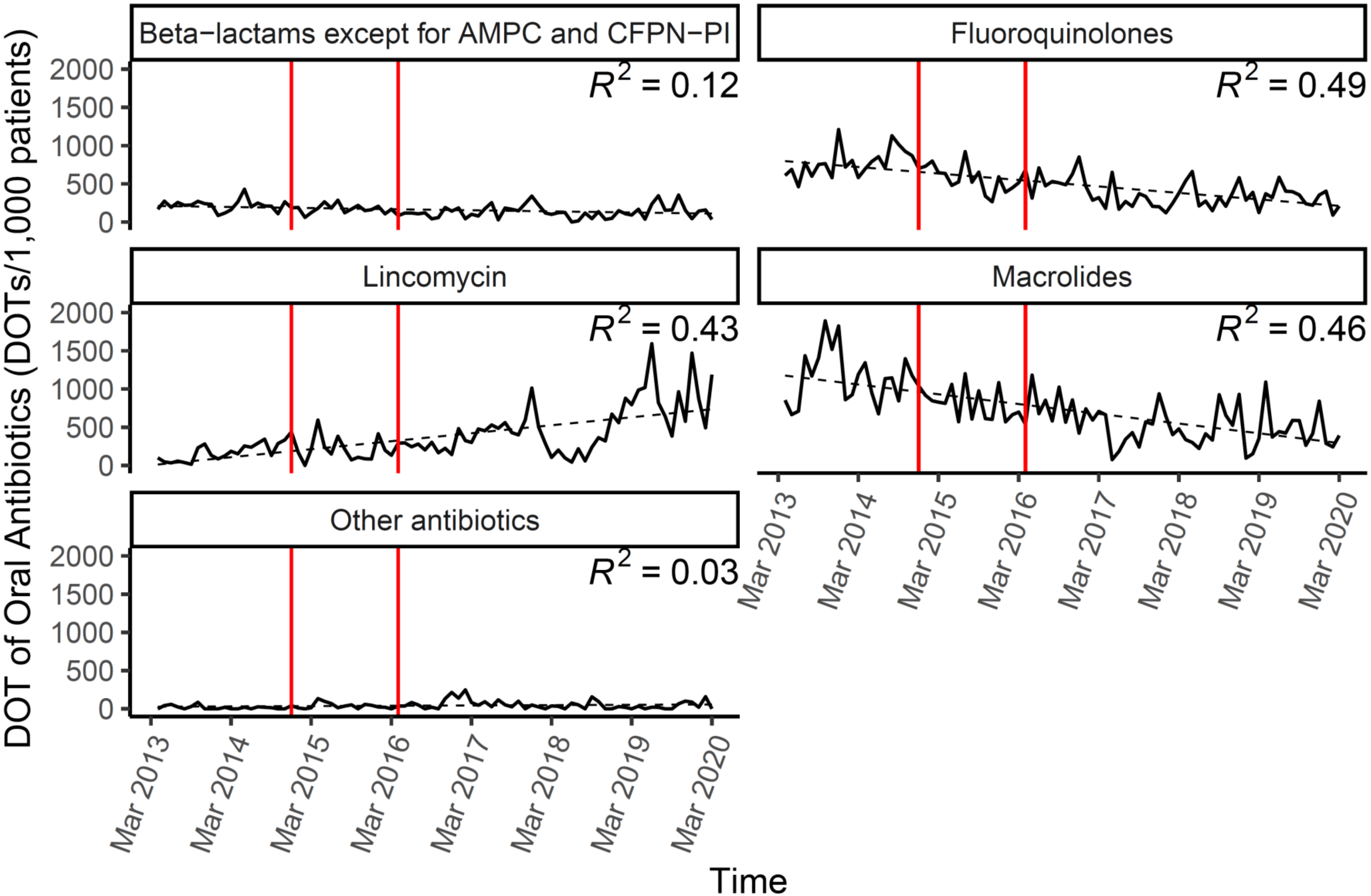
8000
6000
4000
2000
0
DOT of AMPC
Mar 2013
Sep 2013
Mar 2014
Sep 2014
Mar 2015
Sep 2015
Mar 2016
Sep 2016
Mar 2017
Sep 2017
Mar 2018
Sep 2018
Mar 2019
Sep 2019
Mar 2020
Time
$R^2 = 0.85$

Fig. 2-2



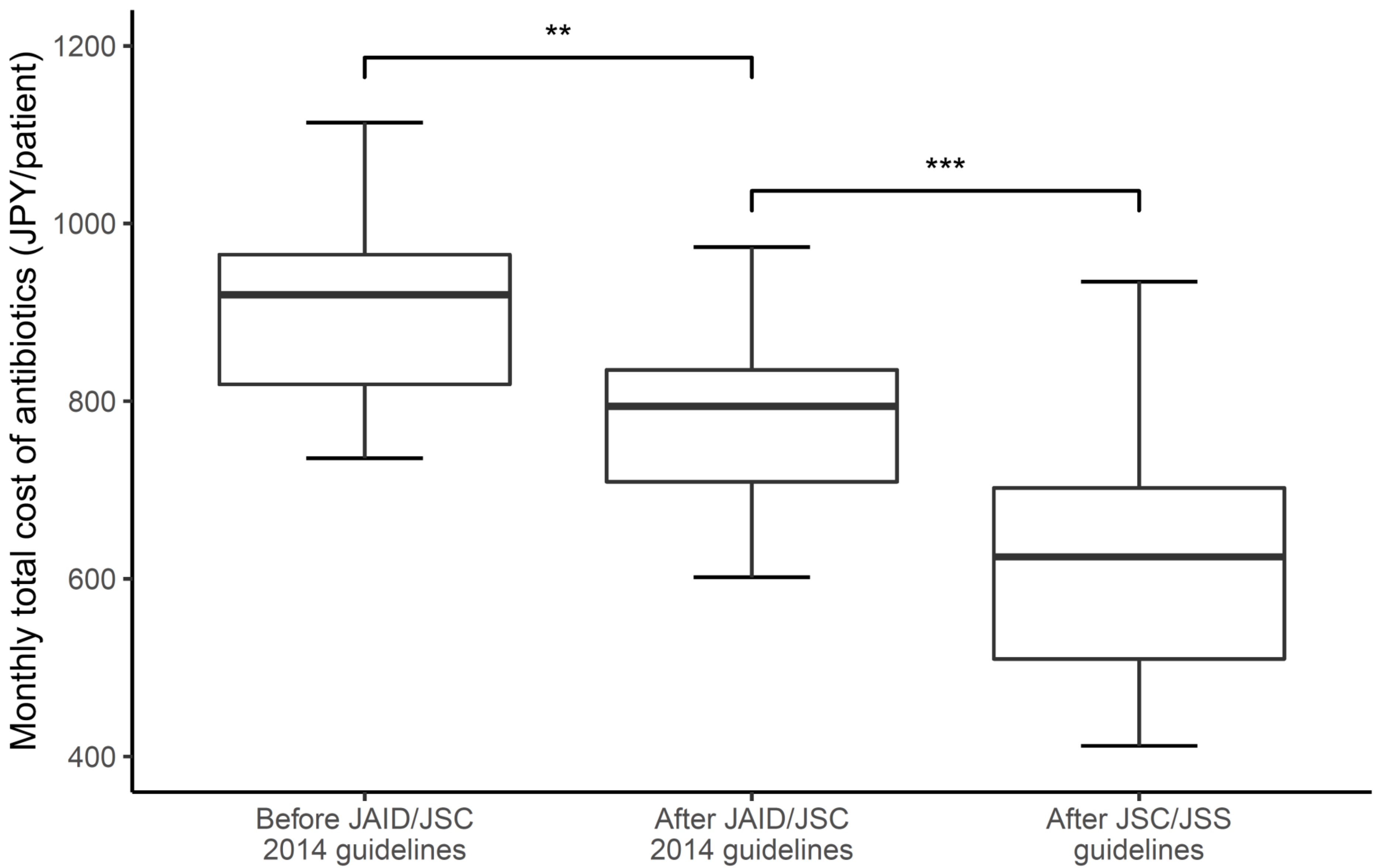
8000
6000
4000
2000
0
DOT of CFPN–PI
$R^2 = 0.89$
Mar 2013
Sep 2013
Mar 2014
Sep 2014
Mar 2015
Sep 2015
Mar 2016
Sep 2016
Mar 2017
Sep 2017
Mar 2018
Sep 2018
Mar 2019
Sep 2019
Mar 2020
Time

Fig. 2-3



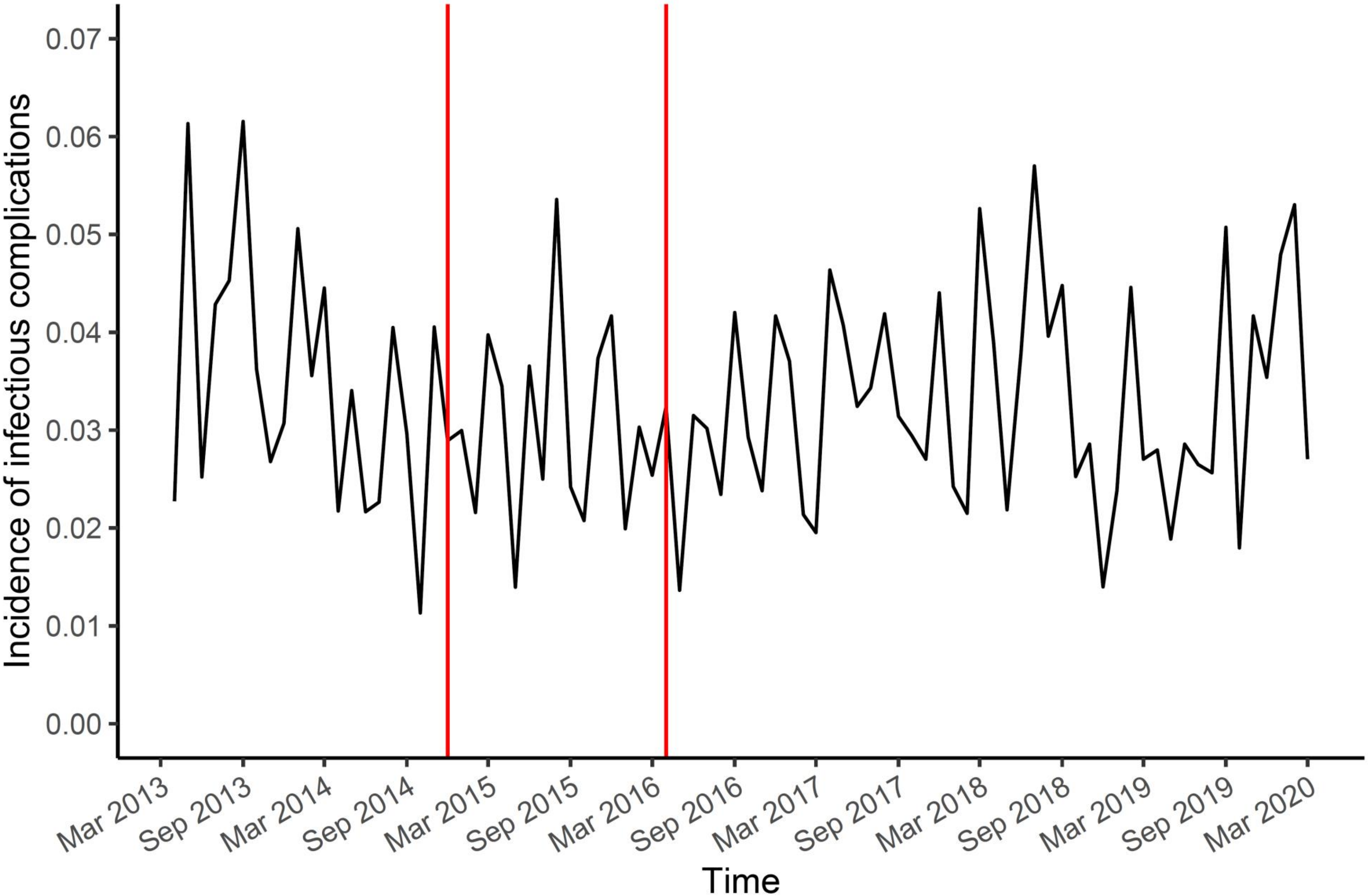
Beta−lactams except for AMPC and CFPN−PI
R^2 = 0.12
Fluoroquinolones
R^2 = 0.49
Lincomycin
R^2 = 0.43
Macrolides
R^2 = 0.46
Other antibiotics
R^2 = 0.03
DOT of Oral Antibiotics (DOTs/1,000 patients)
2000
1500
1000
500
0
Mar 2013
Mar 2014
Mar 2015
Mar 2016
Mar 2017
Mar 2018
Mar 2019
Mar 2020
Time

Fig. 3



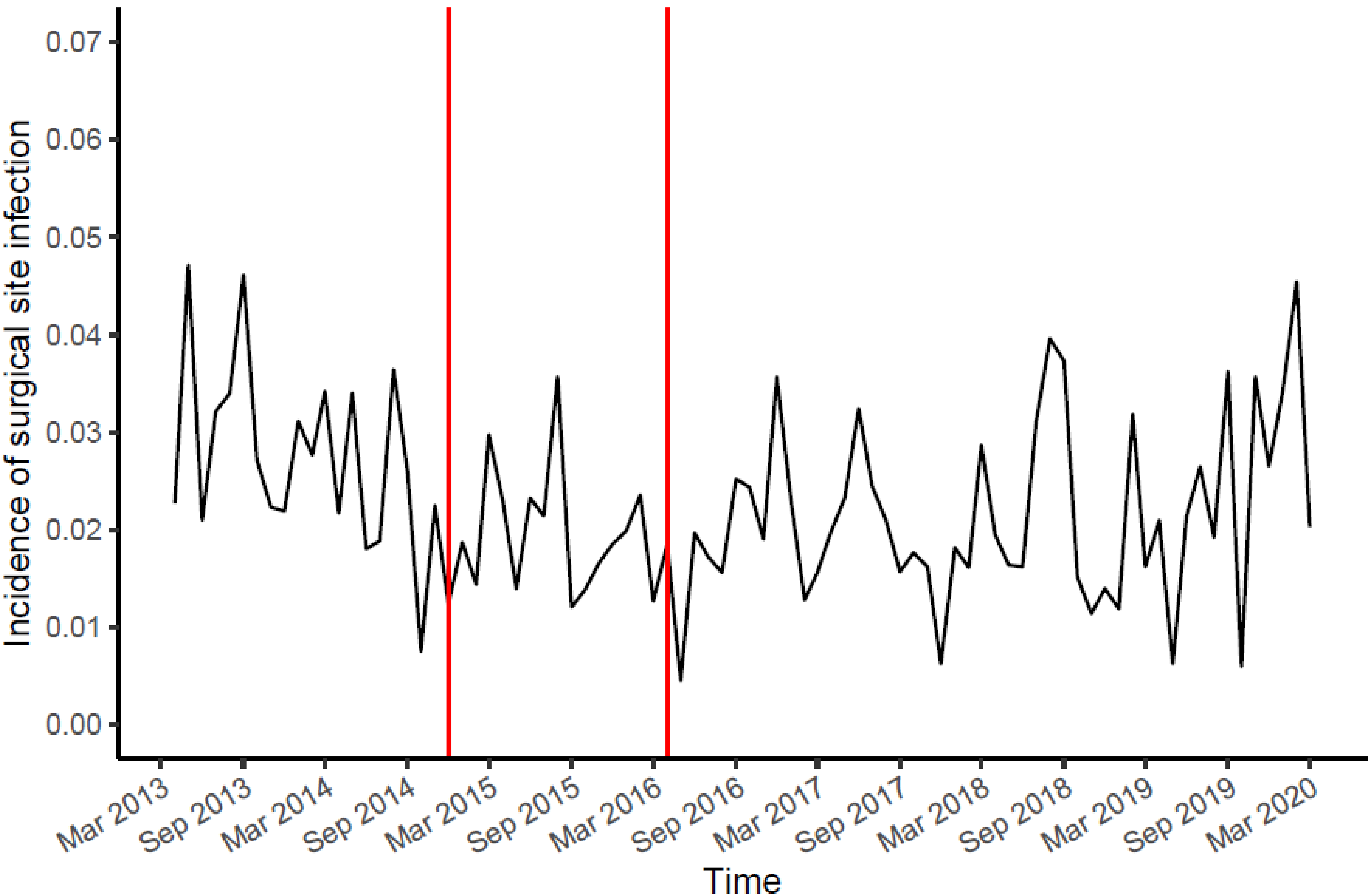
Monthly total cost of antibiotics (JPY/patient)
1200
1000
800
600
400
**
***
Before JAID/JSC
2014 guidelines
After JAID/JSC
2014 guidelines
After JSC/JSS
guidelines

Fig. 4-1



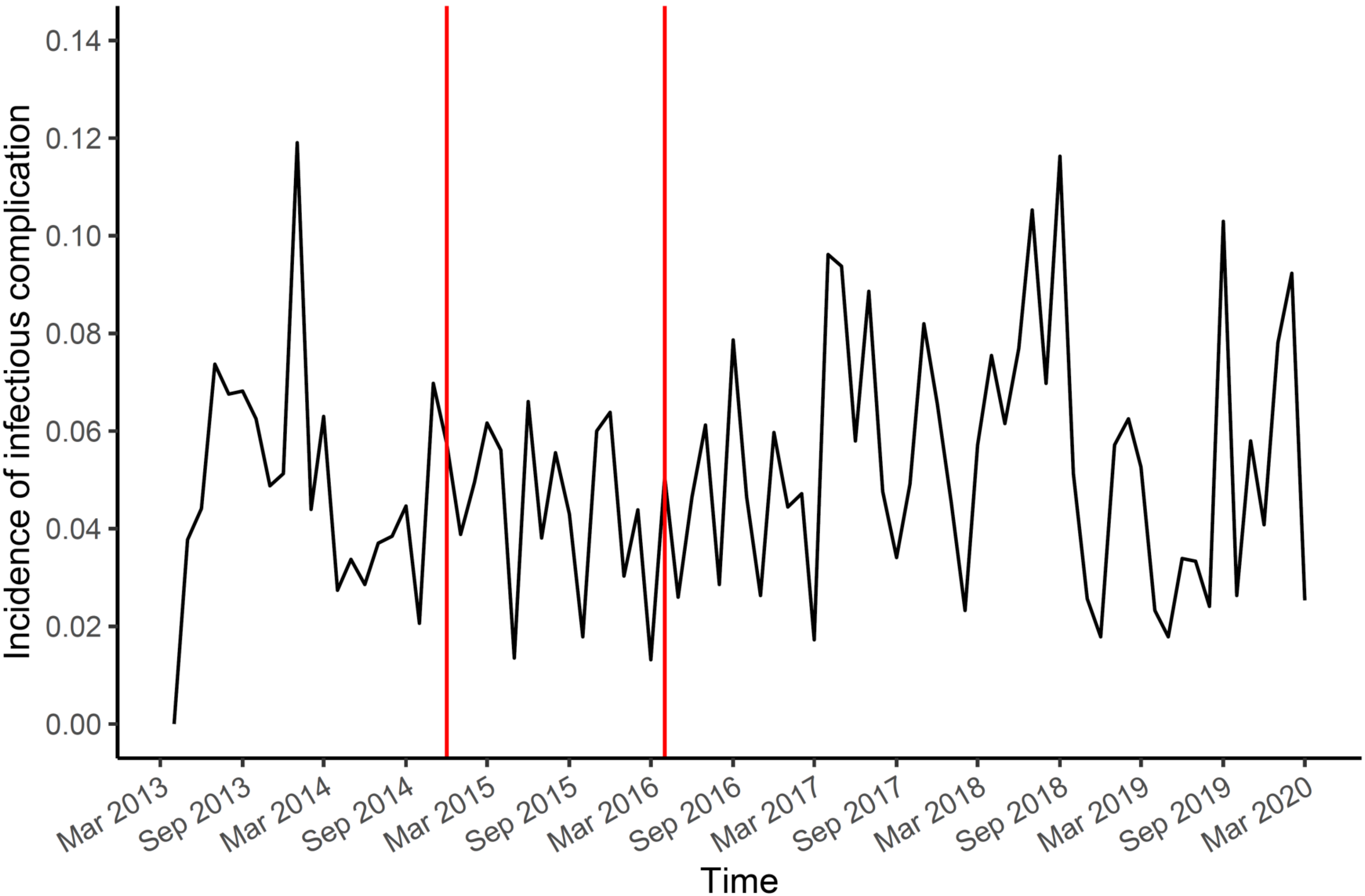
Incidence of infectious complications
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00
Mar 2013
Sep 2013
Mar 2014
Sep 2014
Mar 2015
Sep 2015
Mar 2016
Sep 2016
Mar 2017
Sep 2017
Mar 2018
Sep 2018
Mar 2019
Sep 2019
Mar 2020
Time

Fig. 4-2



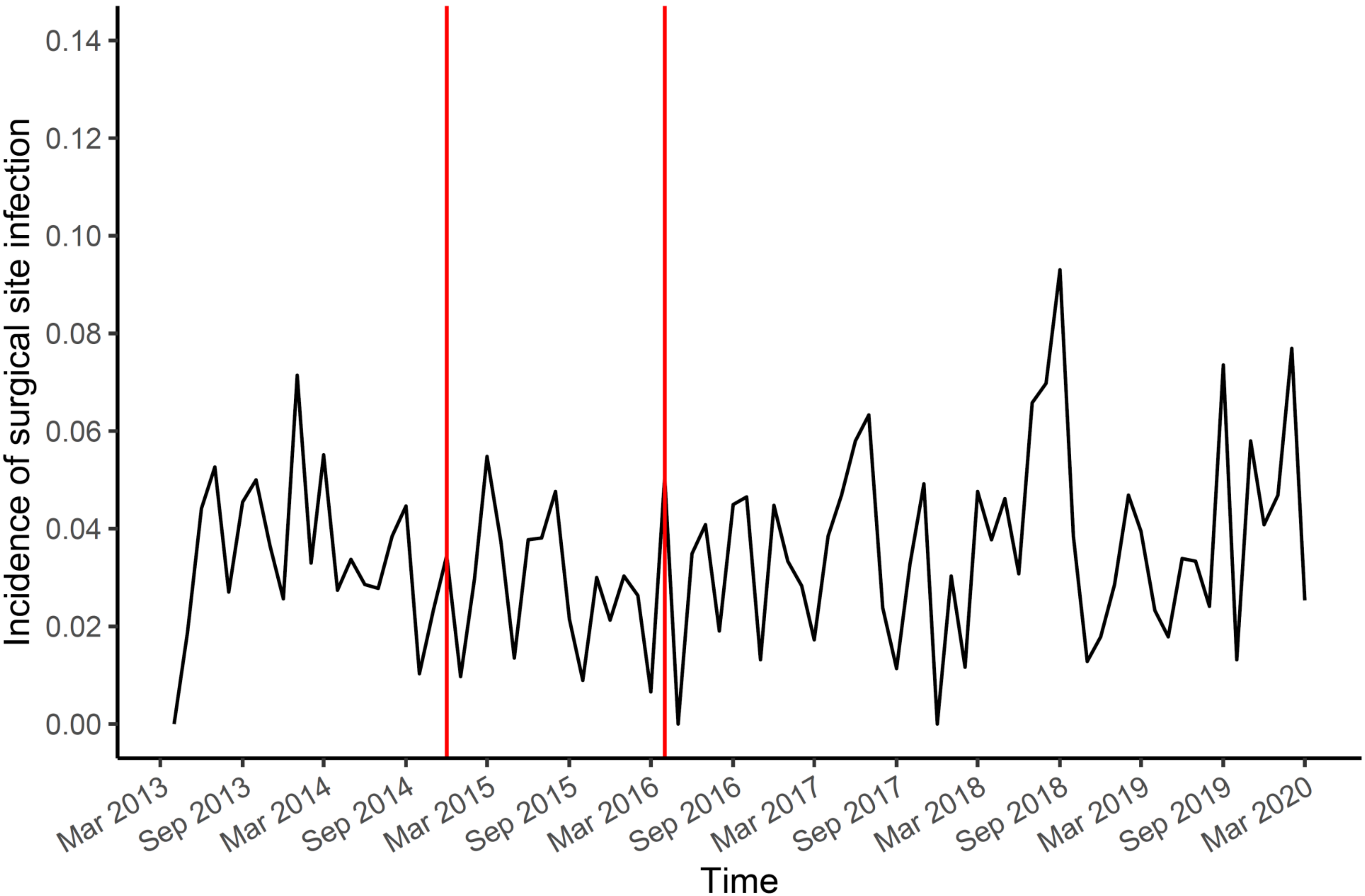
Incidence of surgical site infection
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00
Mar 2013
Sep 2013
Mar 2014
Sep 2014
Mar 2015
Sep 2015
Mar 2016
Sep 2016
Mar 2017
Sep 2017
Mar 2018
Sep 2018
Mar 2019
Sep 2019
Mar 2020
Time

Fig. 4-3



Incidence of infectious complication
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
Mar 2013
Sep 2013
Mar 2014
Sep 2014
Mar 2015
Sep 2015
Mar 2016
Sep 2016
Mar 2017
Sep 2017
Mar 2018
Sep 2018
Mar 2019
Sep 2019
Mar 2020
Time

Fig. 4-4



Incidence of surgical site infection
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
Mar 2013
Sep 2013
Mar 2014
Sep 2014
Mar 2015
Sep 2015
Mar 2016
Sep 2016
Mar 2017
Sep 2017
Mar 2018
Sep 2018
Mar 2019
Sep 2019
Mar 2020
Time