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The Effects of Changes in Health Policies on Antibiotic and non-Antibiotic Prescription Patterns and Healthcare Utilization in Japan

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The Effects of Changes in Health Policies on Antibiotic and non-Antibiotic Prescription Patterns and Healthcare Utilization in Japan

A dissertation submitted in partial satisfaction of the

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in Epidemiology

by

Yusuke Okubo

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ABSTRACT OF THE DISSERTATION

The Effects of Changes in Health Policies on Antibiotic
and non-Antibiotic Prescription Patterns and Healthcare Utilization in Japan

by

Yusuke Okubo

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2021

Professor Karin B. Michels, Chair

Overuse of antibiotics and increases in antibiotic-resistant strains are a global health problem. To address this, the Ministry of Health, Welfare and Labour in Japan introduced several health policies: the National Action Plan on Antimicrobial Resistance in 2016; the financial incentives for not prescribing antibiotics in 2018; and the financial incentives for creating antimicrobial stewardship teams. This dissertation assessed the effects of the newly introduced health policies and current healthcare insurance systems on antibiotic and non-antibiotic prescription patterns and healthcare resource utilization using a nationally representative administrative database from 2012–2019. The quasi-experimental designs allowed to compare the changes in outcomes between the eligible and ineligible medical facilities or areas for the health policies. The studies found that the introduction of the National Action Plan and financial incentives for non-prescribing of antibiotics substantially reduced total and broad-spectrum antibiotics in outpatient settings. In contrast, the introduction of financial

incentives for creating antimicrobial stewardship teams did not affect antibiotic use in inpatient settings. The free medical certificates and free prescription policy did not influence the outpatient antibiotic prescriptions but had effects on increases in non-antibiotic prescriptions and outpatient healthcare expenditures.

The findings suggest that the National Action Plan and financial incentives for not prescribing antibiotics have successfully reduced antibiotic prescriptions, supporting the recent expansion of the age ranges for the financial incentives. Also, the findings infer the need for modifying the current health policies (incentives for creating antimicrobial stewardship teams and free medical certificates for children) to improve inpatient antibiotic prescriptions and outpatient non-antibiotic prescriptions.

The dissertation of Yusuke Okubo is approved.

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2021

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Chapter 1. Introduction

1-1. Overview of the Dissertation

The four-paper dissertation evaluates the variations and trends in antibiotic prescription patterns in Japan and the impacts of health policy changes on antibiotic and non-antibiotic prescription patterns and healthcare utilization. Among a wide variety of exposure and outcomes, the four studies in this dissertation examine the following:

(i) The variations in antibiotic prescription patterns across clinics in Japan (paper #1);

(ii) The effects of financial incentives to medical facilities for not prescribing antibiotics on physicians' prescription patterns and healthcare utilization (paper #2);

(iii) The effects of financial incentives for creating in-hospital antimicrobial stewardship teams on clinical practice patterns (paper #3); and

(iv) The effect of interrupting the free medical care certificates for children on prescription patterns and healthcare utilization (paper #4)

This first chapter introduces the background of the healthcare problems caused by antibiotic-resistant strains worldwide and in Japan, the National Action Plan on Antimicrobial Resistance in Japan, and the epidemiological methods and assumptions used for the analyses in Chapters 2–5. The second, third, fourth, and fifth chapters present papers #1, #2, #3, and #4, respectively. The sixth chapter provides conclusions from these studies.

1-2. **Antibiotic Overuse and the National Action Plan in Japan**

An increase in antimicrobial-resistant strains is a global health problem.[1,2,3] Recently, it is estimated that the number of death owing to antimicrobial-resistant organisms in the world will increase from 700 thousand in 2010 to 10 million per year in 2050.[4] Under these circumstances, ensuring appropriate access to antibiotics while avoiding excess use, especially for unnecessarily broad-spectrum agents, is a major challenge in all settings, including high-income countries. In general, overuse and misuse of antimicrobials are the most important driver in antimicrobial resistance,[5] but the causes of antibiotic resistance are complex, involving human behaviors at many levels of society.[6]

In 2015, global antibiotic sales data were analyzed in 70 middle-income and high-income countries using the IQVIA-Multinational Integrated Data Analysis System database to estimate between-country patterns of antibiotic consumptions and to assess the appropriate use of antibiotics for younger children with respiratory infections using compliance rates with the first-line or second-line medications to treat the underlying infectious disease (e.g., amoxicillin for respiratory tract infections).[7] According to the findings, Japan was the worst of 36 high-income countries and the 3rd worst of 70 countries for the appropriate use of antibiotics.

Correspondingly, recent national surveys in Japan demonstrated the overuse of antibiotics among children.[8] The most commonly prescribed antibiotics were broad-spectrum antibiotics, such as third-generation cephalosporins and macrolides, and this pattern did not change from 2013 to 2016.[8] Furthermore, another national survey in Japan reported that antibiotics were prescribed for approximately 32% of the patients diagnosed with upper respiratory infections.[9] We also observed inappropriate use of broad-spectrum antibiotics for several infectious diseases: the third-

generation cephalosporins for children with Group A streptococcal infections[10]; fluoroquinolones and tetracyclines for children with *Mycoplasma pneumoniae*-related respiratory infections[11]; and fosfomycin for children with acute infectious diarrhea.[12] These findings suggest the need to promote the appropriate use of antibiotics and improve the over-prescription for unnecessary broad-spectrum antibiotics at a national level in Japan.

In 2016, the Japanese government established the National Action Plan on Antimicrobial Resistance to reduce 33% of the total antibiotic use and 50% of broad-spectrum antibiotics at the end of 2020.[8] This multi-faceted strategy consisted of 1) improving public awareness and promoting the education of professionals, 2) strengthening the surveillance and monitoring of the trends in antibiotic use at medical institutions, and 3) promoting antimicrobial stewardship at medical institutions.[13] Additionally, the government introduced new health policies in 2018: financial incentives to medical facilities for not prescribing antibiotics at outpatient settings and financial incentives to hospitals for creating antimicrobial stewardship teams.

1-3. **The Framework of the Study**

Whereas the National Action Plan on Antimicrobial Stewardship and new health policies were implemented in 2016–2018, they have not been assessed at a national level. Therefore, this dissertation investigates the variations in antibiotic prescription patterns and the impacts of changes in health policies on the physicians' prescription behaviors and healthcare utilization as following:

(i) The variations in antibiotic prescription patterns across clinics in Japan (paper #1);

(ii) The effects of financial incentives to medical facilities for not prescribing antibiotics on

physician's prescription patterns and healthcare utilization (paper #2);

(iii) The effects of financial incentives for creating in-hospital antimicrobial stewardship teams that promote appropriate antibiotic use on clinical practice patterns (paper #3); and

(iv) The effect of interrupting free medical certificates for children on prescription patterns and healthcare utilization (paper #4)

(i) The variations in antibiotic prescription patterns across clinics in Japan (paper #1);

First, the prescribed patterns and their variations of antibiotics and other medications across clinics and hospitals are still unclear, although I have previously reported the national trends in antibiotic use among pediatric outpatients.[8] The Key-Access Percentage and Amoxicillin Index were proposed to monitor the trends and variations in oral antibiotics across different medical institutions and geographic locations. However, its validity and applicability at clinic levels are still unknown. The empirical examination results of these measures (paper #1) are presented in Chapter 2.

(ii) The effects of financial incentives to medical facilities for not prescribing antibiotics on physicians' prescription patterns and healthcare utilization (paper #2);

Second, in April 2018, the Ministry of Health, Labour and Welfare in Japan provided a new healthcare policy, which is paying incentives to medical facilities for not prescribing antibiotics to younger children (800 JPY per case).[14] Under the new health policy, pediatric medical facilities received incentives when physicians in the eligible facilities did not prescribe antibiotics to those children who did not have chronic medical conditions and those who had diagnoses of upper respiratory infections or acute infectious diarrhea after explaining the advice of homecare and unnecessity of antibiotics with written documents.[14] Nonetheless, no study has evaluated the effects of incentives on change in antibiotic

prescription patterns and healthcare utilization. The empirical examination results for the association between the introduction of the financial incentives for non-prescribing of antibiotics and the outcomes (paper #2) are presented in Chapter 3.

(iii) The effects of financial incentives for creating in-hospital antimicrobial stewardship teams that promote appropriate antibiotic use on clinical practice patterns (paper #3);

Third, in April 2018, the Ministry of Health, Labour and Welfare in Japan started another new health policy that promoted appropriate antibiotic use for physicians working in hospitals. Hospitals could receive incentives for each inpatient (1,000 JPY≒9.1 USD) if they created appropriate antibiotic use support teams in their hospitals. The main roles of support teams are 1) monitoring broad-spectrum antibiotics, 2) feedback to physicians for their use of antibiotics, 3) appropriate use of diagnostic tests and cultures (blood, urine, sputum, etc.), and 4) promotion and education for appropriate antibiotic use. However, no study investigated the effects of the incentives to medical facilities on changes in clinical practice at a national level. The empirical examination results for the association between the introduction of the financial incentives for creating antimicrobial stewardship teams and the outcomes (paper #3) are presented in Chapter 4.

(iv) The effect of interrupting free medical certificates for children on prescription patterns and healthcare utilization (paper #4);

Fourth, although promoting the appropriate use of antibiotics and parental education is essential, Japan also has a problem with healthcare systems due to no coinsurance rate and a free prescription policy for children (no out-of-pocket for prescribed drugs).[15, 16] Whereas the free prescription policy and antibiotic and non-antibiotic prescriptions appear to be

associated, no studies evaluated these associations at a national level. The empirical examination results for the associations (paper #4) are presented in Chapter 5.

1-4. **Difference-in-Differences method**

For the studies in Chapters 2–5, I will use similar epidemiological methods; (i) Difference-In-Differences (DID) and (ii) Synthetic Control Method (SCM). Here, I introduce these methodologies and the assumptions required to conduct the observational study and to infer the causal estimation from the observational studies.

Comparative effectiveness research has become an important methodology for healthcare decision-making, such as therapeutic options.[17] Although randomized controlled trials are the gold standard of CER, observational studies are increasingly used to infer the causal treatment effects on the outcome of interest. Recently, propensity score matching and g-methods are increasingly used in CER to create groups that hold exchangeability. An important limitation of these methods is the need to control all background information. DID and SCM allow researchers to compare the difference in outcomes, before-and-after intervention and between affected and unaffected groups by controlling for bias from unobserved variables, even when risk-adjustment methods, propensity score, and g-methods are not suitable.[17]

DID has been used to evaluate healthcare policy and/or population-level intervention programs. DID can be used when two periods of data are available for the treatment and control groups. DID allows researchers to compare the difference in the outcomes before and after the intervention (e.g., healthcare policy change) between groups affected and unaffected by the intervention. In other words, the DID estimator measures the treatment effect by looking at the

difference between the average outcome in the treatment and control groups, before and after treatment. DID is appropriate when the intervention involved is as good as random, conditional on time and group fixed effects.[18]

The key assumptions of DID are known as "the parallel trends" assumption.[19] The parallel trends assumption means that in the absence of treatment, the average outcomes of the treated and untreated groups would follow parallel paths over time, which allows DID to account for unobserved time-fixed variables. DID can remove the portion of confounding owing to time-fixed differences between the comparison groups in unobserved covariates that predict the outcome of interest, assuming that the effects of these unobserved confounders do not change over time.[20] The common practice to check the assumption is to examine the outcomes of interest graphically with multiple time points to determine whether the common trend assumption remains in the periods before the treatment is administered.[17] Alternatively, this is evaluated in a regression model by assessing the interaction terms between time and policy exposure in the pre-intervention period.[19] Another key assumption is "common shock assumptions." The common shock assumptions state that any events occurring during or after the time the policy change will equally affect the treatment and comparison groups.[19]

Suppose that the treatment is administered to Group A between periods 0 and 1, and the change in the outcome for this group is $\bar{Y}_{A1} - \bar{Y}_{A0}$.[17] Group B does not receive the treatment at all, and the difference in outcome for this group is $\bar{Y}_{B1} - \bar{Y}_{B0}$. Under the assumption that $\bar{Y}_{B1} - \bar{Y}_{B0}$ provides a good estimate of what would have happened to Group A if they had not received the treatment, the treatment effect (α) can be estimated:

$$\hat{\alpha} = (\bar{Y}_{A1} - \bar{Y}_{A0}) - (\bar{Y}_{B1} - \bar{Y}_{B0})$$

Let $Y_{it} = \beta_0 + \alpha T_{it} + \delta t + \theta_i + \varepsilon_{it}$, where Y_{it} is the outcome for person i at time t, T_{it} indicates whether a person i received the treatment at time t, t is time period (0 or 1) and θ_i is a person fixed effect. Therefore,

$$\hat{\alpha} \approx \big(E(Y_{it}|G_i = A, t = 1) - E(Y_{it}|G_i = A, t = 0)\big) - \big(E(Y_{it}|G_i = B, t = 1) - E(Y_{it}|G_i = B, t = 0)\big)$$

$$= [(\beta_0 + \alpha + \delta + E(\theta_{it}|G_i = A) + \bar{\varepsilon}_{A1}) - (\beta_0 + E(\theta_{it}|G_i = A) + \bar{\varepsilon}_{A0})] - [(\beta_0 + \delta + E(\theta_{it}|G_i = B) + \bar{\varepsilon}_{B1}) - (\beta_0 + E(\theta_{it}|G_i = B) + \bar{\varepsilon}_{B0})]$$

$$= \alpha + (\bar{\varepsilon}_{A1} - \bar{\varepsilon}_{A0}) - (\bar{\varepsilon}_{B1} - \bar{\varepsilon}_{B0})$$

For consistency, we need $E[(\bar{\varepsilon}_{A1} - \bar{\varepsilon}_{A0}) - (\bar{\varepsilon}_{B1} - \bar{\varepsilon}_{B0})] = 0$

This can be further generalized to include more time-periods (T), more groups (G), and additional covariations (X) as one can run the regression:

$$Y_{it} = X_{it}'\beta + \alpha T_{it} + D_t'\delta + G_i'\theta + \varepsilon_{it},$$

where X_{it} represents additional covariates, D_t is a vector of dummy variables indicating the time-period, and G_i is a vector of dummy variables indicating the group to which individual i belongs. Multivariable regression modeling allows the estimates to be adjusted for other factors that may differ between the groups.[19] This notion can also be expanded to non-linear models, such as logit or negative binomial regressions.

The DID approach requires the availability of a control group that reasonably approximates the intervention group before the intervention. Because identifying such a control group is frequently difficult, some studies have used a propensity score matching (PSM) approach. A propensity score (PS) measures the probability that individuals will be exposed to the intervention given their observed covariates. PS can be calculated using a logistic regression model, in which the intervention is regressed against observed covariates of interest. Then, each

unit (e.g., individual, clinic/hospital, area) in the intervention group is matched to a unit in the control group with the closest PS (nearest neighbor). For the matching process, a maximum allowable difference in PS (called "caliper") needs to be set. Matching can be achieved by one-to-one or many-to-many units, depending on the circumstances. Also, we can match on time-fixed confounders and/or pre-intervention outcomes.

The main advantage of DID is to allow researchers to estimate treatment effects while accounting for unobserved variables that are assumed to remain fixed over time. There are several limitations to DID. First, researchers need to find similar study groups; ideally, the only difference between the groups should be the exposure to the intervention. This means that if the trends between the two groups are not parallel, the analysis may be biased. Second, DID accounts for unobservable variables that are fixed over time; it does not account for unobserved variables that are varying over time. Third, Ashenfelter's Dip is known as a problem in DID analysis.[21] The Ashenfelter's Dip refers to the decline in the mean earnings among participants in government training programs just prior to program entry, which may lead to bias before-after estimates in program evaluation, where pre- and post-program earnings are compared. Fourth, spillover effects may occur when some aspect of the policy spills over and influence the outcome of interest in the groups unexposed to the policy change. Spillover can be evaluated by examining whether there is a measurable change in outcomes in the comparison group at the time of the policy implementation.[19] Fifth, DID estimates may be in practice subject to a possibly severe serial correlation problem. One could remove the serial correlation problem by aggregating the data into two periods: pre- and post-intervention or by allowing for an unrestricted covariance structure over time.[18]

Additionally, matching could either reduce or induce bias. In general, matching can be beneficial in DID analysis if the matched variables are correlated with future outcomes. If we have strong theoretical or subject matter evidence that two groups come from the same population, matching can reduce regression to mean bias,[22] also known as "regression fallacy."[23] In contrast, if the two groups come from different populations, matching on the pre-period level may introduce regression to mean bias because the two groups regressed back to the same mean from different places.

1-5. **Synthetic Control Method**

The SCM was pioneered by Abadie et al.,[24] and it can relax the parallel trend assumptions required in the DID analyses.[24] The central idea behind the SCM is to compare the observed outcome with the counterfactual outcome for the exposed unit in the absence of the exposure, using the weighted average of the unexposed units that closely match the exposed unit over the pre-intervention period.[24] Thus, a synthetic control is a weighted average of the available control units. The weights are chosen so that the resulting synthetic control produces the values of a set of predictors of the outcome before the initiation of interventions using a set of potential controls as the "donor pool." A procedure akin to the permutation test is proposed to obtain the statistical significance of the estimated treatment effects by reassigning treatment status for each control unit and re-estimating the treatment effect by applying the SCM and then comparing the estimated treatment effect to the distribution.[24]

The DID model is often applied in empirical studies in the social sciences. DID models allow the presence of unobserved confounders but restrict the effect of those confounders to be constant in time. A major concern for the DID model is whether, in practice, the parallel trend

assumption is plausible.[20] In contrast to the DID method, SCM allows the effects of observed and unobserved predictors of the outcome to change over time while assuming that the pre-intervention covariates have a linear relationship with outcomes in the post-treatment. Therefore, SCM may be useful for health policy evaluations when the validity of the parallel trend assumption is violated.[20]

There are several limitations to SCM. First, SCM is applicable when only one or a few units are subject to intervention. Although SCM has recently been considered for the setting with multiple treatment units, evidence of its validity is still insufficient.[20] Second, the counterfactual outcome in the treated unit, which would have been observed if they had not been treated, is calculated based on a linear function of observed and unobserved potential confounders, but the validity of the linear additive models could be uncertain.[20] However, if the characteristics of treatment and control units are similar, linear models could provide a good approximation even when the true data-generation processes are non-linear.[20] Third, a specific concern for SCM is that the number of pre-treatment periods may be insufficient, and the fit of the pre-treatment outcomes might be owing to change. Fourth, SCM may not work if there is poor overlap in the pre-treatment outcomes between the intervened and control units, especially when the intervention units lie outside the convex hull of the controls.[25] Fifth, there is currently little guidance on the practical implementation of the SCM approach regarding the variable selection in the distance matrix, although previous studies selected variables based on prior knowledge or the mean squared prediction error of the post-intervention outcome as a criterion.

1-6. **Contribution of This Study**

This dissertation aims to show the trends and variations of antibiotic use across different medical facilities, evaluate the effects of the health policy on physicians' prescriptions and healthcare utilization, and provide policy implications for further improving antibiotic overuse and optimizing healthcare resources.

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Chapter 2. Variations for Antibiotic Prescriptions across Different Clinics at a National Level (Paper #1)

2-1. Abstract

Background: In 2016, the Japanese government set the National Action Plan on Antimicrobial Resistance to reduce antibiotic prescriptions. However, the trends and variations of antibiotic prescription patterns in a routine healthcare setting during 2013–2018 across different clinics at a national level have been unclear.

Methods: This cohort study included all clinics with >100 pediatric outpatients with infectious diseases per month during 2013–2018 using a national database in Japan. We investigated the trends in antibiotic prescription rates and their variations across different clinics over the six years following the 2017 World Health Organization Access, Watch, Reserve antibiotic groups and Amoxicillin Index.

Results: A total of 2283 clinics with 88,431,246 visits were eligible for the study. Most clinics showed higher Watch percentages (median 82.8%; IQR, 65.9–93) than Key-Access percentages (median, 13.6%; IQR, 4.1–30.5) and Amoxicillin Index (median, 13.2%; IQR, 3.8– 30.2). The introduction of the National Action Plan on Antimicrobial Resistance in 2016 changed annual absolute reductions in the antibiotic prescription rates from -51.1 DOTs/1000 visitors (95%CI, -51.9–-50.3) to -274.2 per 1000 visitors (95%CI, -275.4–-273.0). However, these impacts were heterogeneous across clinics. From 2013 to 2018, 42.1% reduced the antibiotic prescription rates by >33.3% (median, -1050.7 DOTs/1000 visitors; IQR, -1534.9–-686.1), 18.2% did not change the rates (median, -35.4 DOTs/1000 visitors; IQR, -160.9–74.1), and 7.3% increased the rates by >10% (467.0 DOTs per 1000 visitors; IQR, 231.2–826.1).

Conclusions: We observed the National Action Plan's impacts with extensive prescription variations across different clinics. Our findings indicate the need to monitor heterogeneous antibiotic prescription patterns at clinic levels and suggest the potential intervention to target the clinics below the standard of antibiotic prescription patterns.

2-2. **Background**

Antibiotics are frequently prescribed medications for children. The overuse of antibiotics is an unresolved challenge in global and regional health.[1–10] The annual number of deaths due to antimicrobial-resistant organisms worldwide is estimated to increase from 700 thousand in 2010 to 10 million in 2050, which is higher than the current annual number of deaths due to the most common chronic diseases, such as cancer, and diabetes.[11]

A recent global study has shown that Japan was the worst among the 36 high-income countries in terms of appropriate antibiotic use among pediatric outpatients aged < 5 years.[12] These findings were consistent with those of our previous studies regarding physicians' overuse of broad-spectrum antibiotics, such as third-generation cephalosporins, macrolides, and fluoroquinolones, for the pediatric population in Japan.[13] Specifically, the antibiotic prescription patterns in Japan demonstrated that antibiotics were inappropriately prescribed for children with acute infectious diseases such as acute upper respiratory infection,[7] group A streptococcus infection,[14] *Mycoplasma pneumoniae* infection,[6] and acute infectious diarrhea.[8]

Although the findings mainly reflected outpatient prescription patterns in approximately 90% of the total antibiotic prescriptions at a national level, their patterns and variations at clinic levels remain unclear in order to find the clinics that are operating below the standard of antibiotic prescription patterns. Additionally, in 2016, the Japanese government has set the National Action

Plan on Antimicrobial Resistance (AMR) to reduce total antibiotic use by 33% until 2020 through improving public awareness, promoting education among professionals, strengthening the surveillance and monitoring of the trends in antibiotic use, and promoting antimicrobial stewardship in medical institutions.[13,15,16] However, it is unclear what changes may have occurred in antibiotic prescription patterns after introducing the National Action Plan on AMR.

Therefore, this study examined the trends and variations in antibiotic prescription patterns during 2013–2019 among pediatric outpatients across different clinics at a national level in Japan.

2-3. **Methods**

Study design and data source

We conducted a retrospective cohort study of clinics in Japan from April 2013 to March 2019 using approximately 3 billion administrative data elements from the National Database of Health Insurance Claims and Specific Health Checkups (NDB).[17] In Japan, the national health insurance system provides universal coverage for all individuals,[18] and their claims data are anonymized and stored in the NDB.[17] The NDB covers up to 95%–99% of claims data during 2013–2019 of healthcare services provided by the Ministry of Health, Labor and Welfare in Japan. The NDB includes information on the following: the patient's diagnosis; age, sex, and residential area; dates of procedures and prescriptions; doses and durations of medications; healthcare cost; and unique identification numbers of patients and hospitals. Using the unique identification numbers, we merged the same clinics' claims data over different visitors and timings, allowing us to follow clinics from April 2013 to March 2019.

We extracted data on children aged ≤ 15 years who visited clinics due to infectious diseases and included clinics with at least 100 pediatric outpatients per month over the six years. We included clinics that used out-of-clinic pharmacies and excluded clinics with in-clinic pharmacies because some claims data from in-hospital pharmacies were missing. Approval for the present study was obtained from the Institutional Review Boards at the National Center for Child Health and Development in Japan (IRB number, 1491) and at the University of California, Los Angeles.

Study variables

i) Types of Infectious Diseases

Infectious disease-related visits were identified using the International Classification of Diseases, Tenth Revision code (ICD-10 code) in the database's diagnosis. The diagnoses of infectious diseases were determined based on the Clinical Classification Software (CCS) codes[19] (**Table 2–A**). The CCS codes were provided by the Healthcare and Utilization Project to allow meaningful diagnostic categorizations. Indeed, categorizations using CCS codes were considered to be more useful than categorization using individual ICD-10 codes.[19]

ii) Types of antibiotics and measure of antibiotic use

Information on antibiotic use is coded by the Anatomical Therapeutic Chemical (ATC) system. In Japan, antibiotics are available only with a prescription issued with a physician's prescription and are dispensed by pharmacies.[20] Antimicrobials for systemic use were recorded as J01, according to the WHO Anatomical Therapeutic Chemical (ATC) classification system. Antimicrobials were divided into 15 subgroups (**Tables 2–B and 2–C**), referring to the previous studies.[7,13,21,22] We excluded intravenous and topical antibiotics, antivirals, anti-tuberculosis, antifungals, and antiparasitic agents.

The unit to quantify the total antimicrobial agents used in children was days of therapy (DOTs) calculated from the prescriptions (**Table 2–E**). As the numbers of patients who visited clinics were different across the institutions, we calculated DOTs per 1000 pediatric visitors.

The patterns of antibiotic use were described in accordance with the 2017 World Health Organization (WHO) Essential Medical List for children (EMLc) Access, Watch, Reserve (AWaRe) grouping (**Table 2–D**).[12,23] The Access group had narrow-spectrum antibiotics recommended as the first or second choice for most common infectious diseases. The Watch group consisted of broader spectrum antibiotics and is considered the critically important antibiotics. The Reserve group included the last-resort antibiotics for multidrug-resistant strains. Only the Core-Access antibiotics were considered part of the Access group. We included Access-Watch antibiotics in the Watch group following the previous study.[12]

iii) National Action Plan on Antimicrobial Resistance

In 2016, the Japanese government set goals for the National Action Plan on AMR to reduce 33% of the total antibiotic use until 2020.[13] The aims of the AMR Action Plan consisted of 1) improving public awareness and promoting the education of professionals, 2) strengthening the surveillance and monitoring the trends in antibiotic use at medical institutions, and 3) promoting antimicrobial stewardship at medical institutions, etc.[15]

Statistical analysis

First, we calculated the proportions of visitors who received antibiotic prescriptions given the number of visitors with infectious diseases. Total antibiotic prescription rates were estimated as DOTs/1000 visitors for total antibiotic prescriptions over the six years. Correlation between the proportions and rates (DOTs/1000 visitors) at clinic levels was checked to assess whether

clinics with high proportions of antibiotic prescriptions were more likely to prescribe longer durations of antibiotics for each visitor using Pearson's correlation coefficient.

Second, we investigated prescription rates (DOTs/1000 visitors) for each antibiotic agent (penicillin, first and third-generation cephalosporins, macrolide, quinolone, tetracycline, and oral penem) at hospital levels over the six years.

Third, the Key-Access Percentage and Amoxicillin Index were measured to evaluate the AWaRe distribution by focusing on the Access percentage (**Tables 2–C and 2–D**). The Key-Access Percentage was calculated based on the DOTs of Key-Access antibiotics divided by the total DOTs in the clinics, suggesting the proportions of narrow-spectrum antibiotic use given total antibiotic use. The Amoxicillin Index was calculated as the number of amoxicillin DOTs divided by the total DOTs at each hospital/clinic, which was the most straightforward indicator for the narrow-spectrum antibiotic use. We assessed the correlation between the Key-Access Percentage and Amoxicillin Index, using Pearson's correlation coefficient.

Fourth, we investigated the trends in DOTs/1000 visitors, Key-Access Percentage, and Amoxicillin Index from April 2013 to March 2019. To investigate the changes in trends, the interrupted time-series analyses were utilized with outcomes of interest as dependent variables, continuous time-indicator variables, and categorical time-indicator variables before or after the introduction of the National AMR Action Plan in 2016. We used mixed-effects linear regression with robust variance estimates and an independent covariance matrix to account for the clinics' clustering and reported the coefficients as 1-year absolute changes with 95% confidence intervals (CIs).

Fifth, we analyzed changes in total and specific antibiotic prescriptions at clinic levels between 2013 and 2018 using DOTs/1000 visitors. For the analyses, we classified clinics in 4

groups: 1) > 33.3% reduction, 2) 10–33.3% reduction, 3) 10% reduction to 10% increase, 4) > 10% increase. All data were analyzed using Stata/MP software version 16.1 (StataCorp LP, TX, USA).

2-4. **Results**

We identified a total of 2287 clinics that had at least 100 pediatric outpatients per month over the six years. The clinics had 88,431,246 visitors due to infectious diseases and prescribed 40,088,480 antibiotic prescriptions with 214,036,648 DOTs; 44.3% of visitors with infectious diseases received antibiotic prescriptions; the antibiotic prescription rate was 2420.4 DOTs per 1000 visitors.

Distributions of total antibiotic prescriptions at clinic levels

The proportions of total antibiotic prescriptions and their rates at clinic levels were widely distributed (**Figure 2–A**). The proportions of total antibiotic prescription use at clinic levels ranged from 1.65% to 97.6% (median, 44.5; IQR, 27.0 to 62.7). Similar patterns were found for the total antibiotic prescription rates, ranging from 57.4–11,809.4 DOTs per 1000 visitors (median, 2099.5; IQR, 1274.4 to 3204.2). We observed a very strong correlation between the proportions and rates of total antibiotic prescriptions at clinic levels (correlation coefficient, 0.89; **Figure 2–A**).

Distributions of each antibiotic prescription at a clinic level

Antibiotic prescription rates also differed across antibiotic classes (**Figure 2–B** and **Table 2–F**). Most clinics preferred to prescribe 3rd generation cephalosporins (median, 693.0 DOTs per 1000 visitors; IQR 364.2 to 1239.5), macrolides (median, 536.0 DOTs per 1000 visitors; IQR, 257.0 to 1000.0), and penicillins (median, 227.7 DOTs per 1000 visitors; IQR, 71.2 to 532.4). We

observed low prescription rates for oral penems, quinolones, and 3rd generation cephalosporins, but small proportions of clinics had high prescription rates of these antibiotics.

Distributions of the AwaRe and Amoxicillin Index

The AWaRe distribution and Amoxicillin Index were widely varied across different clinics (**Figure 2–C**; **Table 2–G**). Most clinics showed higher Watch Percentage (median 82.8%; IQR, 65.9% to 93.0%) than Key-Access percentage (median, 13.6%; IQR, 4.1% to 30.5%) and Amoxicillin Index (median, 13.2%; IQR, 3.8% to 30.2%). Only 4.1% of clinics (93/2287) had the Key-Access Percentage > 60%. The correlation between the Key-Access Percentage and Amoxicillin Index was very strong (correlation coefficient, 0.99; **Figure 2–D**). As to the Watch percentage, 3rd generation cephalosporins and macrolides were the most commonly used antibiotics (**Table 2–G**).

Trends in antibiotic prescription rates

Overall, total antibiotic prescription rates showed decreasing trends, but a greater reduction was observed after introducing the National Action Plan on AMR (**Figure 2–E** and **Table 2–H**). The annual absolute reduction in the antibiotic prescription rate before introducing the national action plan was -51.1 DOTs/1000 visitors (95%CI, -51.9 to -50.3), but the annual reduction became steeper after introducing the action plan (-274.2 per 1000 visitors: 95%CI, -275.4 to -273.0). Correspondingly, the trends in Key-Access Percentage and Amoxicillin Index increased after initiating the National Action Plan (**Figure 2–E**). Before the National Action Plan, the absolute annual increases in Key-Access Percentage and Amoxicillin Index were 0.150% (95%CI, 0.146% to 0.153%) and 0.214% (95%CI, 0.213% to 0.215%). After the introduction, the absolute annual increases become greater for Key-Access Percentage (2.219%; 95%CI, 2.213% to 2.225%) and Amoxicillin Index (2.189%; 95%CI, 2.187% to 2.190%).

Comparison of antibiotic use between 2013 and 2018

Compared with antibiotic prescription rates between 2013 and 2018 (**Table 2–I**), 42.1% of total clinics (963/2287) reduced the antibiotic prescription rates by > 33.3%, 32.4% of total clinics (741/2287) reduced the rates by 10%–33.3%, 18.2% (416/2287) did not change the rates, and 7.3% (167/2287) of clinics increased the rates by >10%.

2-5. **Discussion**

This 6-year cohort study, involving 2287 clinics and 88,431,246 visitors, observed extremely wide variations in antibiotic prescription patterns. Although the Key-Access antibiotics are to be used as the first-choice treatment for pediatric outpatients with infectious diseases, the Key-Access Percentage and Amoxicillin Index were low. The National Action Plan on AMR reduced the total antibiotic prescription rates and improved their patterns; however, these effects were heterogeneous across different clinics. Our findings reflect the routine healthcare setting for children with common infectious diseases, support the improvement of antibiotic prescription patterns after the AMR Action Plan, and suggest the need for monitoring antibiotic prescription patterns at clinic levels to account for the heterogeneous changes.

According to the wholesale data in 2015 from 70 middle- and high-income countries,[12] the Key-Access Percentage in Japan (34.4%) was at the lowest rank of those in 36 high-income countries (median, 76.3%), and the Amoxicillin Index in Japan (27.0%) was below the median of the 70 countries (30.7%; IQR, 14.3–47.3). Our findings for the low Key-Access Percentage and Amoxicillin Index in Japan were consistent with those of previous study results, but they were lower than the previous findings; these results could be due merely to the different target populations (0–15 years vs. 0–5 years) and different formulas to calculate these indices (DOTs vs.

child-appropriate formulation (CAF); median vs. mean; prescription at a clinic level vs. overall consumption). Therefore, careful interpretation is needed for external comparison to the global study results, whereas internal comparisons of our results across different clinics or years in Japan could still be valid.

We observed improvements in the antibiotic prescription rates and patterns after introducing the National Action Plan on AMR in 2016. In our 6-year cohort with 2287 clinics, the relative reduction in the antibiotic prescription rate was 25.5% from 2013 to 2018. Over the six years, several new health policies were implemented in pediatric healthcare, such as primary-care physician registration fees in 2016 and antimicrobial stewardship fees in 2018.[21,24] Although these new health policies were mainly targeted to children aged < 3 years, they have impacted the overall physicians' prescription behaviors for all children. However, further improvement is still needed because the indices showed wide variations (e.g., Key-Access percentage in 2018; range, 0%–98.4%), and among most clinics, they were still lower than the average Key-Access Percentage of the top countries (e.g., Netherland's Key-Access percentage in 2015, 92.3%).

Clinical practice variations are unwarranted when the best practice or standard of care is established because they may induce underuse of effective medication, overuse of unnecessary practice, and increase in subsequent adverse events and healthcare expenditure. Our previous studies have found wide variations in clinical practice patterns for pediatric inpatients with common childhood diseases (e.g., infectious diseases, febrile seizure, bronchial asthma, Kawasaki disease).[6,22,25–32] This study added to the novel findings by evaluating the wide antibiotic prescription patterns at the routine outpatient setting and heterogeneities in the impact of the National Action Plan on AMR across different clinics. Monitoring antibiotic prescriptions at clinic

levels and interventions targeting clinics with overuse of broad-spectrum antibiotics could be one option to further improve antibiotic prescription patterns.

Besides its unique strengths, this study had several limitations. First, as we included only clinics with at least 100 pediatric outpatients per month over the study period, this study excluded newly opened, halfway closed clinics and clinics that treat only a small number of children. As a result, although the use of the NDB was the strength of our study in terms of external validity, our findings' generalizability to Japan's entire clinics may still be uncertain. The diagnoses of infectious diseases were based on ICD-10 codes. The detailed clinical presentation, laboratory data, and patient information were unavailable in the NDB; therefore, the diagnoses may have been underestimated or overestimated because of possible underreporting or potential misclassification of ICD-10 codes. The Key-Access Percentage and Amoxicillin Index were calculated based on DOTs, unlike the global comparisons of antibiotic prescription patterns based on CAFs. Thus, careful interpretation is needed when comparing our results with those in global studies. However, we believe that these indices were still valid for the comparison within the same clinics and between the different clinics or different years in Japan.

In summary, we observed improvements in antibiotic prescription patterns during 2013–2018, supporting the National Action Plan's impact. However, extensive variations of antibiotic prescription patterns across different clinics still existed. Our findings indicate a need to monitor heterogeneous antibiotic prescription patterns at clinic levels and suggest the potential intervention to target the clinics below the standard of antibiotic prescription patterns.

2-6. **References**

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2-7. **Tables and Figures**

Table 2-A. Definition of Infectious Diseases

Diagnoses	Lists of CCS code
Infectious disease	2, septicemia; 3, bacterial infection unspecified; 7, viral infection; 8, other infections; 92, otitis media and related conditions;122, pneumonia;123, influenza;124, tonsillitis; 125, acute bronchitis; 126, upper respiratory infections; 135, intestinal infection; 140, gastritis and duodenitis; 142, appendicitis; 159, urinary tract infections; 197, skin and subcutaneous tissue infections; 201, infective arthritis and osteomyelitis; 247, lymphadenitis; 256, fever of unknown origin

Note: Diagnoses and the Clinical Classification Software Codes based on the International Classification of Diseases, Tenth Revision code (ICD-10 code)

Table 2-B. Classifications of Antibiotics based on the ATC codes

The Anatomical Therapeutic Chemical (ATC) codes and corresponding antibiotic classifications.

ATC code	Antibiotic classification
J01AA	tetracyclines
J01BA01	chloramphenicol
J01CE01	benzylpenicillin
J01CA	penicillin with extended-spectrum
J01CR	combinations of penicillin, including beta-lactamase inhibitors
J01DB	first-generation cephalosporins
J01DC	third-generation cephalosporins
J01DI03	faropenem
J01DIXX	other cephalosporins and penems
J01EE01	sulfamethoxazole and trimethoprim
J01FA	macrolides
J01FF	lincosamides
J01M	quinolone antibacterials
J01XX01	fosfomycin
J01XX08	linezolid
A07AA09	vancomycin

Table 2-C. Classification and Lists of Oral Antibiotics

Classification	Details
Penicillin	Benzylpenicillin potassium, benzylpenicillin benzathine hydrate, ampicillin, bacampicillin hydrochloride, amoxicillin hydrate
Penicillin with beta-lactamase inhibitors	Amoxicillin-clavulanate, ampicillin sulbactam
First-generation cephalosporin	Cefalexin, cefroxadine, cefaclor
Second-generation cephalosporin	Cefminox, flomoxef, cefuroxime
Third-generation cephalosporin	Cefdinir, ceftibuten, cefditoren pivoxil, cefixime, cefteram pivoxil, cefpodoxime proxetil, cefcapene pivoxil
Oral penem	Tebipenem pivoxil, faropenem
Macrolide	Erythromycin, clarithromycin, roxithromycin, azithromycin, josamycin
Tetracycline	Tetracycline, doxycycline, minocycline, tigecycline
Quinolone	Norfloxacin, ofloxacin, levofloxacin, ciprofloxacin, lomefloxacin, tosufloxacin, pazufloxacin, prulifloxacin, moxifloxacin, garenoxacin, sitafloxacin
Trimethoprim-sulfamethoxazole	Trimethoprim-sulfamethoxazole
Aminoglycoside	Streptomycin, kanamycin, gentamicin, tobramycin, dibekacin, amikacin, isepamicin, arbekacin
Lincomycin	Lincomycin, clindamycin,
Glycopeptide and lipopeptide	Vancomycin, teicoplanin, daptomycin
Fosfomycin	Fosfomycin (oral)
Other types	Quinoupristin dalfopristin, linezolid, chloramphenicol, colistin, polymyxin B, aztreonam, metronidazole,

Table 2-D. Access, Watch, Reserve Grouping for Antibiotics

Antibiotic classification	Type of antibiotics
Core-Access	amoxicillin, amoxicillin clavulanic acid, ampicillin, benzathine benzylpenicillin, cefalexin or cefazolin, chloram phenicol, clindamycin, cloxacillin, doxycycline, gentamicin or amikacin, metronidazole, nitrofurantoin, phenoxymethylpenicillin, procaine benzyl penicillin, spectinomycin, sulfamethoxazole-trimethoprim
Access-Watch	azithromycin, cefixime, cefotaxime, ceftriaxone, ciprofloxacin, clarithromycin, piperacillin and tazobactum, meropenem, vancomycin
Watch	anti-pseudomonal penicillins with beta-lactamase inhibitor, carbapenems or penems, 3rd generation cephalosporins, glycopeptides, macrolides, quinolones and fluoroquinolones
Reserve	aztreonam, 4th and 5th generation cephalosporins, daptomycin, fosfomycin (intravenous), oxazolidinones, polymixns, fosfomycin (iv), tigecycline,
Unclassified	2nd generation cephalosporin, fosfomycin (oral), minocycline, etc.

Note: Classification of antibiotics defined by Access, Watch, Reserve grouping according to the WHO Essential Medicine List (Sharland M, et al. Lancet Infect Dis.2018;18:18-20).

Table 2-E. The Formula for Measuring Antibiotic Use

Measure	Formula
DOTs/1000 visitors	$\frac{\text{Days of therapy (Total antibiotics)}}{\text{Visitors}}$
Key-Access Percentage	$\frac{\text{Days of therapy (Access antibiotics)}}{\text{Days of therapy (Total antibiotics)}} \times 100\%$
Amoxicillin Index	$\frac{\text{Days of therapy (Amoxicillin)}}{\text{Days of therapy (Total antibiotics)}} \times 100\%$

Note: Formulas for the days of therapy (DOTs) per 1000 visitors per months, Key-Access Percentage, and Amoxicillin Index.

Table 2-F. Antibiotic Prescription Rates across Different Clinics

Measures	Lowest	25%ile	Median	75%ile	Highest
Antibiotic prescription rates, DOTs/1000 visitors					
Total antibiotics	57.4	135.0	2099.5	3204.2	11,809.4
Penicillin	0	71.2	227.7	532.4	4816.7
1st generation cephalosporine	0	0	0	0	1078.0
3rd generation cephalosporine	0	364.2	693.0	1239.5	4404.6
Macrolides	1.9	257.0	536.0	1000.0	10,003.5
Tetracyclines	0	0.2	2.6	11.7	595.9
Quinolone	0	19.4	71.2	196.7	3652.1
Penems	0	1.6	19.5	68.4	2559.5

Abbreviations: DOTs, days of therapy

Table 2-G. Trends in Antibiotic Prescription Rates from 2013 to 2018.

Measures	Lowest	25%ile	Median	75%ile	Highest
Access, Watch, Reserve group					
Key-Access percentage, %	0%	4.1%	13.6%	30.5%	92.9%
Watch percentage, %	6.8%	65.9%	82.8%	93.0%	100%
Reserve percentage, %	0%	0%	0%	0%	0.03%
Unclassified	0%	0.4%	1.8%	4.2%	79.1%
Type of antibiotics /Total antibiotics (DOTs), %					
Amoxicillin Index, %	0%	3.8%	13.2%	30.2%	88.0%
1st generation cephalosporine	0%	0%	0%	0%	36.5%
3rd generation cephalosporine	0%	22.4%	35.8%	52.0%	96.9%
Macrolides	0.2%	17.8%	28.1%	40.8%	92.7%
Tetracyclines	0%	0.007%	0.1%	0.7%	23.1%
Quinolone	0%	1.3%	3.9%	8.4%	91.4%
Penems	0%	0.1%	1.0%	3.1%	47.2%

Abbreviations: DOTs, days of therapy

Table 2-H. Trends in Antibiotic Prescription Rates from 2013 to 2018.

Fiscal year	2013	2014	2015	2016	2017	2018
Total antibiotic prescription rates, DOTs/1000 visitors	2630.4	2614.6	2583.5	2474.9	2200.6	1967.0
Access, Watch, Reserve group						
Key-Access percentage	16.3%	17.0%	16.9%	17.1%	19.0%	21.5%
Watch percentage	81.5%	80.7%	81.0%	80.9%	79.0%	76.5%
Reserve percentage	0%	0%	0%	0%	0%	0%
Unclassified	2.7%	2.6%	2.6%	2.8%	2.4%	2.3%
Amoxicillin Index, %	15.3	16.2	15.9	15.9	18.2	20.7

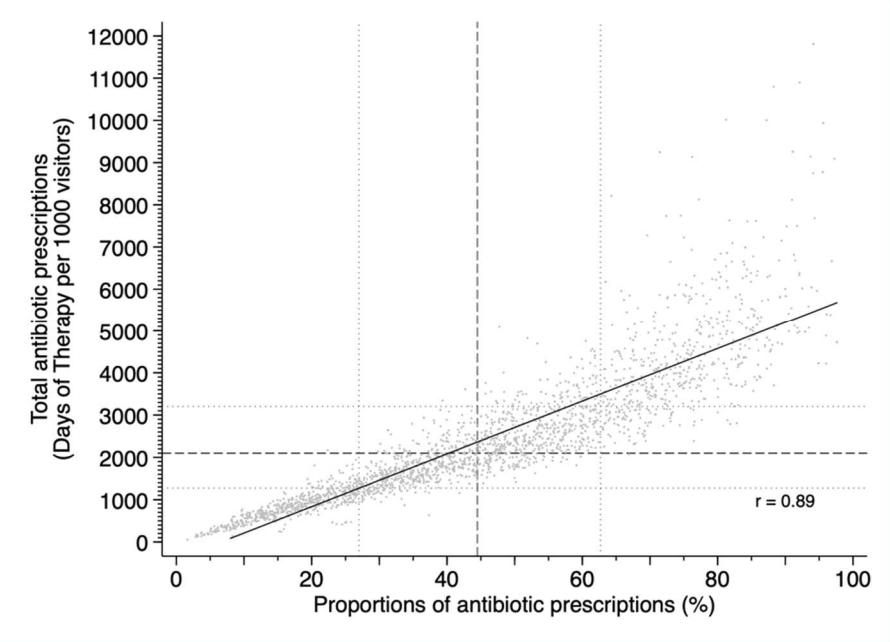
Abbreviations: DOTs, days of therapy

Table 2-I. Antibiotic Prescription Rates between 2013 and 2018.

Types of Clinics	Achieved	Reduced	No change	Increased
Relative change (%)	**< -33.3%**	**-33.3% to -10%**	**-10% to +10%**	**> 10%**
N	963	741	416	167
(%)	(42.1%)	(32.4%)	(18.2%)	(7.3%)
Changes in DOTs per 1000 visitors				
Lowest	-4315.0	-2856.4	-1036.1	33.5
1st quartile	-1534.9	-804.8	-160.9	231.2
Median	-1050.7	-522.9	-35.4	467.0
3rd quartile	-686.1	-339.8	74.1	826.1
Highest	-30.4	-35.6	931.2	4484.6

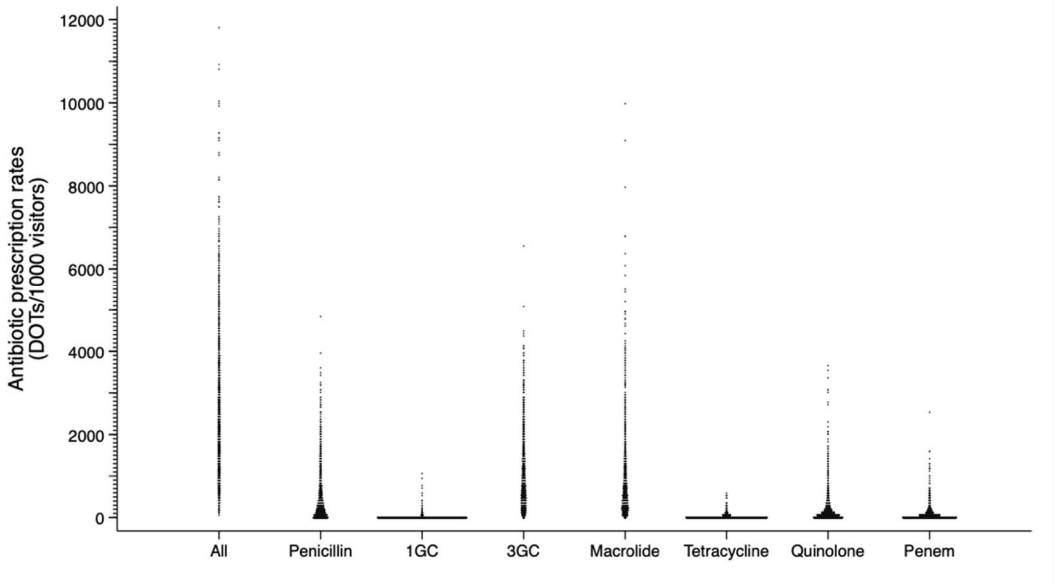
Abbreviations: DOTs, days of therapy

Figure 2-A. Correlation between DOTs and Proportions of Antibiotic Use



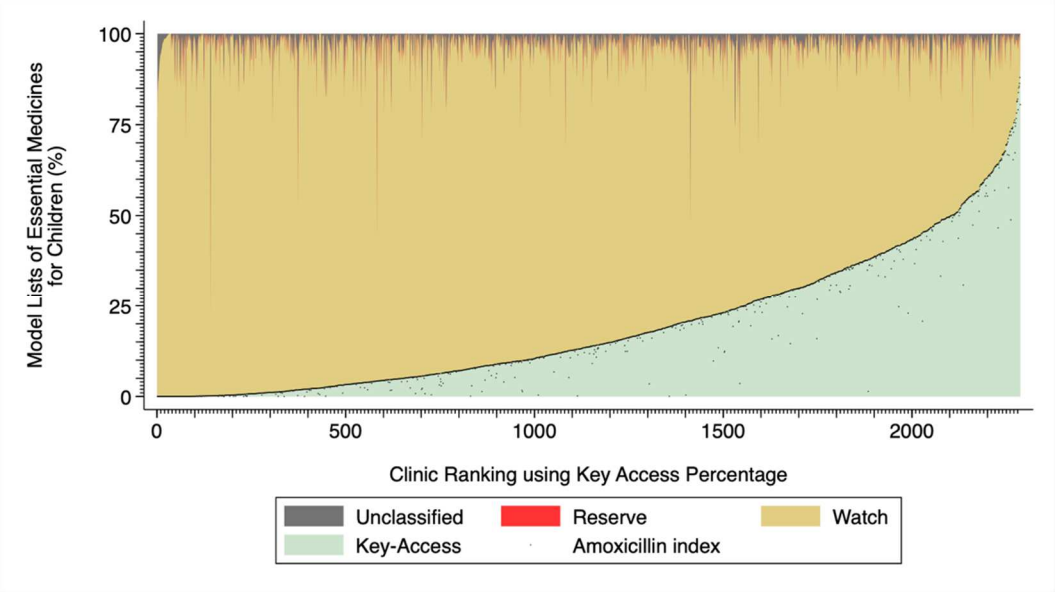
Abbreviations: r, a correlation coefficient
Note: DOTs, days of therapy

Figure 2-B. Total and Types of Antibiotic Use



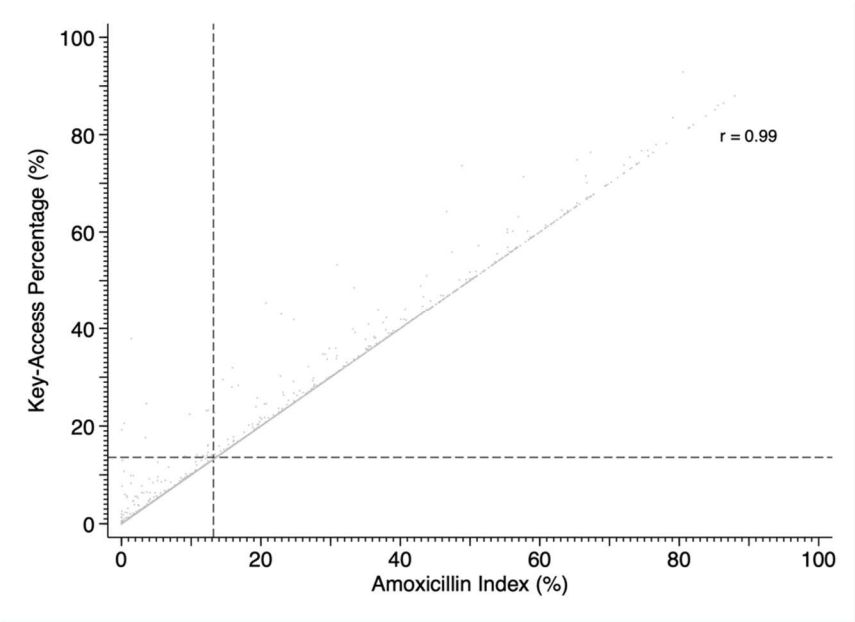
Abbreviations: 1GC, first-generation cephalosporin; 3GC; third-generation cephalosporin

Figure 2-C. Distributions of AwaRe and the Amoxicillin Index



Abbreviations: AwaRe, Access-Watch-Reserve

Figure 2-D. Correlation between AWaRe and the Amoxicillin Index



Abbreviations: AwaRe, Access-Watch-Reserve

Figure 2-E. Trends in Antibiotic Use from 2013 to 2018

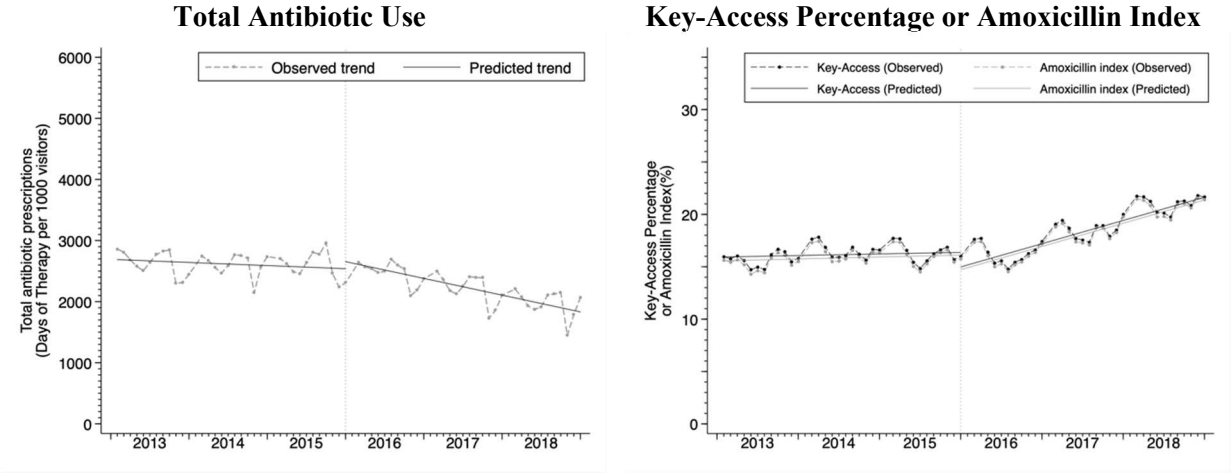
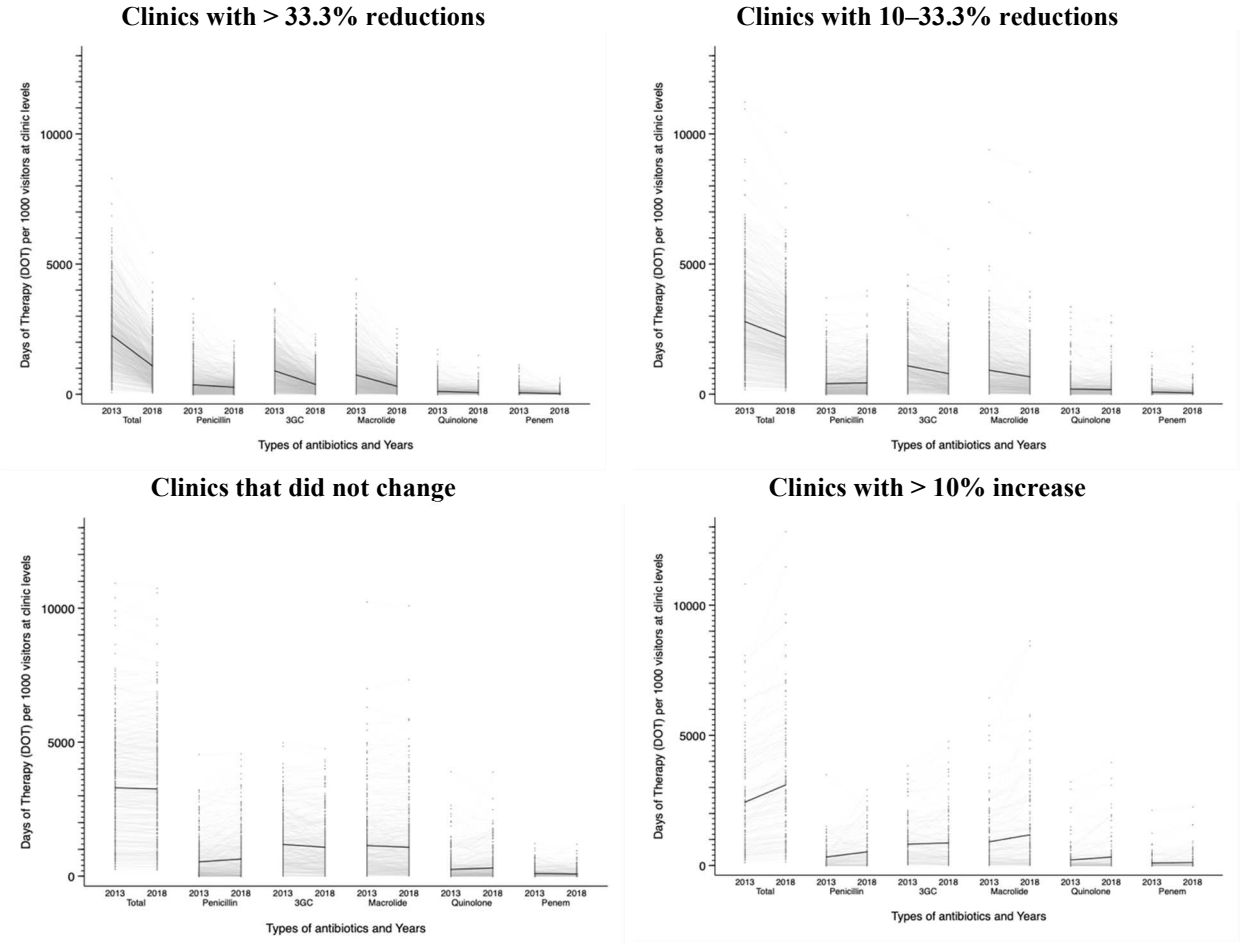


Figure 2-F. Antibiotic Use between 2013 and 2018



Abbreviations: 1GC, first-generation cephalosporin; 3GC, third-generation cephalosporin

Chapter 3. Association between the Introduction of Financial Incentive for Not Prescribing Antibiotics and Physicians' Practice Patterns (Paper #2)

3-1. Abstract

Background: For addressing antibiotic overuse, Japan designed a healthcare policy in which eligible medical facilities could claim a financial reward (800 JPY per case [≈7.2 USD]) when antibiotics were not prescribed for early-stage respiratory and gastrointestinal infections. The policy was introduced in a pilot manner from pediatric clinics in April 2018. However, its effects have not been examined.

Methods: We used the National Database of Health Insurance Claims and Specific Health Checkups, which included approximately 3 billion data elements between April 2016 and March 2019. We constructed the relevant data consisting of 9,253,261 cases of infectious diseases from 553,138 patients treated at 10,180 eligible or ineligible facilities. We applied a quasi-experimental propensity-score matched difference-in-differences (DID) design for estimating the effects.

Results: A total of 2959 eligible facilities claimed 316,770 cases for financial incentives and earned 252 million JPY (≈2.29 million USD). The eligible facilities exhibited an excess reduction in antibiotic prescriptions (DID estimate, -176.4 days of therapy [DOTs] per 1000 cases [95%CI, -193.0 to -159.7], which corresponded to a relative reduction of 14.9% [95%CI, 13.6 to 16.1]). They also exhibited an excess reduction in non-antibiotic prescriptions (e.g., antihistamines' DID estimate, -145.3 DOTs per 1000 cases [95%CI, -180.4 to -110.2]). There was no excess in out-of-hour visits (DID estimate, -0.89 events per 1000 cases [95%CI, -4.23 to 2.45] or after-outpatient-visit hospitalizations (DID estimate, 0.21 events per 1000 cases [95%CI, -0.06 to 0.49]).

Conclusions: Our findings suggest that a relatively small financial incentive can alter physicians' prescription behaviors without adverse healthcare consequences.

3-2. **Background**

The overuse of antimicrobials is an unresolved challenge in global and regional health.[1–10] A 2015 global survey showed that Japan ranked among the lowest for appropriately prescribing antibiotics in the 36 high-income countries.[11] For instance, physicians in Japan had prescribed antibiotics for 31.7%–52.7% of outpatients diagnosed with acute upper respiratory infections,[12,13] for which antibiotics were likely to be ineffective.[14] Although small-scale interventions (e.g., pre-authorization system[15,16] and audit-with-feedback at a single institution[17,18]) partially addressed antibiotic overuse in Japan, the level of the overall antibiotic use stayed high at the national level.[19,20]

The Ministry of Health, Labour and Welfare (MHLW) in Japan designed a novel healthcare policy for incentivizing the non-prescription of antibiotics within the National Action Plan on Antimicrobial Resistance.[21,22] Under the policy, eligible medical facilities could claim a small financial reward (800 Japanese Yen [JPY] ≈ 7.2 US dollar [USD] per case) when they did ***not*** prescribe antibiotics for outpatients with acute upper respiratory infections and acute gastroenteritis.[21] The policy experimentally started at pediatric outpatient clinics in April 2018.[21] However, the effects of the policy have not been examined nationwide.

Therefore, in the present study, we aimed to investigate the effects of the financial incentive for not prescribing antibiotics on antibiotic and non-antibiotic prescription behaviors of physicians and healthcare use following the non-prescribing events using the full national

samples from the National Database of Health Insurance Claims and Specific Health Checkups (NDB).

3-3. **Methods**

Study oversight and data acquisition

Both the institutional review board at the National Center for Child Health and Development, Japan and that at the University of California, Los Angeles approved our study. MHLW approved our data request and extracted the relevant data from NDB. Due to Japan's universal healthcare system,[23] MHLW retains almost all the outpatient claims data (95–99% of claims records for pediatric infectious diseases ≈ 1 billion data elements of claims records per year), which were processed and transferred to the NDB for the research purpose.[24] All data for patients and medical facilities were anonymized. We were permitted to access the necessary variables: cases' age, sex, primary diagnosis, comorbidities, procedures, prescriptions, out-of-hour visits, hospitalizations, and outpatient healthcare expenditure, as well as the identification number of the secondary medical area in which medical facilities were located (the country consists of 341 secondary medical areas in 47 prefectures, each of which secondary care can be completed).

Japan's health policy change (quasi-experiment)

A new health policy was initiated on April 1, 2018, as part of the antimicrobial stewardship program under the National Action Plan on Antimicrobial Resistance.[21,22] The "treatment" of interest in the present study was the eligibility for the policy: claiming a financial reward of 800 JPY (≈ 7.2 USD) for a patient's first visit for a particular disease occurrence (and not prescribing

antibiotics). To be eligible, outpatient departments of pediatrics in clinics and hospitals needed to be registered in advance as medical facilities designated to specialized pediatric care and its specific comprehensive payment system. Once approved, they became eligible for claiming the financial reward.

Physicians in the eligible facilities had two choices when they clinically diagnosed patients aged 0－3 years who had no complex chronic diseases as acute upper respiratory infection and acute gastroenteritis.[21] The first choice is not prescribing antibiotics with explanations to the patients and caregivers (e.g., the rationale for non-prescribing of antibiotics and homecare advice) and claiming the financial reward. The second choice is prescribing antibiotics and not claiming the financial reward. In contrast, physicians in the ineligible facilities (e.g., pediatric clinics on different payment systems, medical facilities with non-pediatric expertise) could not claim the financial reward even if they did not prescribe antibiotics.

Data construction

Using the NDB from April 2016 to March 2019, we constructed a cohort of children treated by eligible or ineligible medical facilities before and after the policy implementation.[24] For pursuing causal inference, the cohort was restricted to all the children who were born between April 2016 and March 2017 (≈ 977,000 infants)[25] and who visited medical facilities at least once due to infectious diseases. The outpatient claims with the clinical diagnoses of acute infectious diseases were identified using the International Classification of Diseases, Tenth Revision (ICD-10) codes. The diagnoses of acute infectious diseases were determined based on the Clinical Classification Software (CCS) codes[26] (**Table 2–A**).

NDB-specific identification numbers of patients and medical facilities allowed us to identify and link the outpatient claims of the same individuals from the same medical facilities

over the three years. We denoted the first year (April 2016 to March 2017) as the look-back period, the second year (April 2017 to March 2018) as the pre-intervention period, and the third year (April 2018 to March 2019) as the post-intervention period.

We excluded the claims of 84,224 individuals with complex chronic diseases defined by the pediatric complex chronic conditions classification system (e.g., congenital diseases, malignancy, and autoimmune diseases).[27] We also excluded the claims of 609 individuals with diagnosis codes of death or cardiac arrest over the study period (**Table 3–A**). The claims records submitted from medical facilities with < 10 pediatric outpatients per month were also excluded (24,923 medical facilities, most of which were those for adults).

Outcome measures

The primary outcome of interest was the amount of total antibiotic prescriptions as days of therapy (DOTs) per 1000 cases. We merged the monthly claims data of a patient over one or more visits to the same facility within the same disease-course and considered them as a case. The secondary outcomes were the amount of broad-spectrum antibiotics, non-antibiotic drugs (drugs for respiratory symptoms and antihistamines; **Table 3–B**), out-of-hours office visits, the amount of the total outpatient healthcare expenditure, and infectious disease-related hospitalizations after the patient's outpatient visits. In Japan, oral antibiotics are available only with physicians' prescriptions and are dispensed by medical facilities or pharmacies.[28] We considered third-generation cephalosporin, oral penem, fosfomycin, tetracycline, and quinolone as broad-spectrum antibiotics in accordance with the previous studies (**Table 2–C**).[7,20,29–31]

Covariates

The baseline characteristics included the patient's sex and comorbidities of asthma/wheezing, rhinitis, sinusitis, atopic dermatitis/eczema, food allergy, and seizure. The

comorbidities were identified using ICD-10 codes (**Table 3–A**) in the 1st year (look-back period). We also obtained the number of prescriptions, out-of-hour visits, healthcare expenditure, and hospitalizations over the first and second years as proxy variables to account for access to healthcare and health conditions. Case-level data over the first and second years were also accumulated at each facility and converted into averages and percentages at the medical facility level. Such composite variables were used for balancing the facility-level characteristics variations in the next section.

Statistical analysis

We applied a quasi-experimental difference-in-differences (DID) design with propensity score (PS) matching.[32] All data were analyzed using Stata/MP software version 16.1 (StataCorp LP, TX, USA). The data analysis has a total of four steps.

First, we summarized baseline characteristics by calculating means and proportions for continuous and categorical variables stratified by the eligibility of the facilities.

Second, we calculated a propensity of each medical facility for being "treated" (eligible for claiming the financial reward) since the characteristics of the eligible facilities might differ from those of the ineligible facilities. Therefore, we aggregated the case-level covariates into the facility level (e.g., the proportion of male cases, that of cases with comorbidities of seizure). We also included the outcomes during the two years falling in the look-back and pre-intervention periods (e.g., DOTs per 1000 cases for antibiotics, drugs for respiratory symptoms, antihistamines) as covariates for predicting PS. Although other facility-level characteristics, such as its specific address and a distance to the nearest train station, were not provided due to the strict rules of the NDB, we could obtain 341 secondary medical areas for locations of the facilities. We constructed a multivariable logistic regression model using the aggregated baseline characteristics and the

indicator variable of the secondary medical area and predicted each medical facility's PS (**Table 3–C**).

Then, we conducted one-to-one matching between the eligible and ineligible facilities using the nearest-neighbor methods within a caliper distance of < 20% of standard deviation in PS.[32] The eligible and ineligible facilities would be omitted from the further data analysis when they were not matched. We checked the balance of the baseline characteristics between the eligible and ineligible facilities based on absolute standardized differences. An absolute standardized difference of > 10% was considered a meaningful imbalance.[32]

Third, we performed a DID analysis using the matched sample with the same number of eligible and ineligible facilities.[33–36] Since the effect of the treatment (the new healthcare policy) could arise only in the eligible facilities after April 2018, it would be captured by the coefficient for an interaction term of a treatment indicator variable (eligible [index] vs. ineligible [control]) and a time indicator variable that represents before and after April 1, 2018 (pre-intervention vs. post-intervention). We did not include the data during the look-back period for the DID models to avoid bias due to left-censoring. Specifically, we fitted the following statistical model:

$$E(Y_{ijk}) = \beta_0 + \beta_1 X_{1i} + \beta_2 X_{2ijk} + \beta_3 X_{1i} X_{2ijk}$$

where E denoted the expected value, Y_{ijk} was the outcome of interest (e.g., the amount of total antibiotic prescriptions as DOTs per case) for the k^{th} case of the j^{th} individual at the i^{th} medical facility. X_{1i} was the treatment indicator variable at the i^{th} medical facility, and X_{2ijk} was the time indicator variable representing that the k^{th} case of the j^{th} individual at the i^{th} medical facility occurred during the pre-intervention or post-intervention period. Other covariates were not included in the DID models in the primary analysis since we assumed no meaningful imbalance in the PS matching above. β_3 is the coefficient of the interest capturing the main treatment effect,

which reports the effect size in an absolute scale. We also obtained the effect sizes in a relative scale (percent reduction); namely, change-in-changes (CiC) estimates.[37] To incorporate the cross-classified hierarchical data structure, we used generalized estimation equations under a normal distribution, identity link function, robust variance estimates, and unstructured correlation.[38]

Sensitivity analyses

Fourth, we conducted a series of sensitivity analyses for evaluating the model assumptions in the above-mentioned primary DID analyses with PS matching. First, we performed propensity-score (PS) matched difference-in-differences (DID) analyses using data from the 1st year (look-back period). Second, we constructed covariate-adjusted models. In the models, we added the covariates listed in the original Method section as a set of potential confounders to the crude models to adjust for time-fixed potential confounders (Table 3–C). Third, we constructed crude DID models and investigated the unadjusted DID estimates. Fourth, we stratified the data by 47 prefectures and estimated 47 prefecture-specific DID estimates and pooled estimates using random-effect models with inverse variance weights for total antibiotics, drugs of respiratory symptoms, and total outpatient healthcare expenditure. Fifth, we calculated the correlation of prefecture-specific DID estimates between total antibiotics and drugs for respiratory symptoms using Pearson's correlation coefficient. Sixth, we analyzed all DID estimates in relative scales using gamma distribution with log link functions as changes-in-changes (CiC) estimates.

3-4. **Results**

We identified 10,180 medical facilities, 553,138 children aged < 12 months in the look-back period, and 9,253,261 relevant cases over the 3-year study period. In the post-intervention

period, we found 316,770 claims of the financial rewards for antibiotic non-prescribing, which resulted in an additional healthcare cost of approximately 253 million JPY (≈ 2.29 million USD). Overall, 2959 (29.1%) facilities were eligible for the financial rewards.

PS matching

Our PS matching procedure (**Figure 3–A**) balanced the distributions of the covariates between the eligible and ineligible facilities, including secondary medical areas of facilities and other composite variables (absolute standardized differences < 10%; **Table 3–D**).[32] **Figures 3–B** showed that we achieved similar trends in the primary and secondary outcomes of interest during the pre-intervention period (until Month -1) as intended.

Antibiotic and non-antibiotic prescriptions

The PS matched DID analyses (**Figure 3–C and Table 3–E**) showed that the introduction of the financial incentive was associated with an excess reduction in the antibiotic prescriptions among the eligible facilities in an absolute scale by -176.4 DOTs per 1000 cases (95%CI, -193.0 to -159.7) and in a relative scale by 0.851 (which means a 14.9% reduction) (95%CI, 0.839 to 0.864).

Similarly, it was associated with an excess reduction in broad-spectrum antibiotic use in an absolute scale (DID estimate, -101.2 DOTs per 1000 cases; 95%CI, -112.1 to -90.2) and in a relative scale (CiC estimate, 0.831; 95%CI, 0.815 to 0.847).

It was also associated with an excess reduction in the non-antibiotic prescriptions, including drugs for respiratory symptoms in an absolute scale (DID estimate, -85.1 DOTs per 1000 cases; 95%CI, -143.7 to -26.5) and in a relative scale (CiC estimate, 0.988; 95%CI, 0.980 to 0.996); antihistamines in an absolute scale (DID estimate, -145.3 DOTs per 1000 cases; -180.4 to -110.2) and in a relative scale (CiC estimate, 0.945; 95%CI, 0.932 to 0.957).

Healthcare use and outpatient healthcare expenditure

The introduction of the financial incentive was not associated with a change in the magnitude of the out-of-hours visits in an absolute scale (DID estimate, -0.89 events per 1000 cases; 95%CI, -4.23 to 2.45) or in a relative scale (CiC estimate, 0.994; 95%CI, 0.974 to 1.015). It was also not associated with a change in the after-outpatient-visit hospitalization in an absolute scale (DID estimate, 0.21 events per 1000 cases; 95%CI, -0.06 to 0.49) or in a relative scale (CiC estimate, 1.043; 95%CI, 0.861 to 1.264). However, we observed an elevation of the total outpatient healthcare expenditure in the eligible facilities compared with the ineligible facilities in an absolute scale (DID estimate, 552.3 JPY per case [≈ 5.0 USD]; 95%CI, 469.2 to 635.3) and in a relative scale (CiC estimate, 1.043; 95%CI, 1.037 to 1.050).

Sensitivity Analyses

First, we conducted PS matching using data on covariates and outcomes of interests during the first year (**Figure 3–D**). After PS matching, the baseline characteristics and outcome of interests in the first and second years were well balanced between the two groups (**Table 3–F**; **Figure 3–E**). The directions of associations between the introduction of financial incentives and outcomes of interest were mostly identical to the primary analyses, but their point estimates were further from the null (**Table 3–G**).

Second, we estimated covariate-adjusted DID estimates. Compared with the PS matched models, the directions of associations between the introduction of financial incentives and changes in primary and secondary outcomes were further from the null, except for total outpatient healthcare expenditures (**Table 3–H**).

Third, we performed crude analyses. Compared with the control group, the index group had lower prescriptions of total and broad-spectrum antibiotics, higher prescriptions of drugs for respiratory symptoms, lower prescriptions of antihistamines, lower out-of-hour visits, lower hospitalizations, and lower outpatient healthcare expenditures during the pre-intervention period (**Figure 3–F**). The crude DID estimates were almost identical to the covariate-adjusted DID estimates (**Table 3–H**).

Fourth, we stratified the data by 47 prefectures and investigated the prefecture-specific DID estimates for total antibiotics, drugs for respiratory symptoms, and total outpatient healthcare expenditure. Overall, we observed the associations between the financial incentives and reductions in prescriptions for total antibiotics (Pooled estimate, -354.3 DOTs per 1000 cases; 95%CI, -391.0 to -317.5; Figure **3–G**) and drugs for respiratory symptoms (Pooled estimate, -491.8 DOTs per 1000 cases; 95%CI, -575.2 to -408.4; Figure **3–H**). The most prefecture-specific DID estimates in areas with large populations (e.g., Tokyo, Kanagawa, Osaka, Aichi) were closer to the pooled results, whereas those in areas with smaller populations (e.g., Tottori, Shimane, Kochi) were heterogeneous. We also observed an increase in total outpatient healthcare expenditures for pooled DID estimate (425 JPY per case; 95%CI, 327 to 523), but the prefecture-specific DID estimates varied, ranging from -557 JPY per case in Fukui Prefecture to 1517 JPY per case in Oita Prefecture (**Figure 3–I**).

Fifth, we investigated the correlation of prefecture-specific DID estimates between total antibiotics and drugs for respiratory tract symptoms. We observed a very weak positive correlation (correlation coefficient, 0.17) between changes in total antibiotics and drugs for respiratory symptoms (**Figure 3–J**).

Sixth, we analyzed DID estimates in relative scales for all statistical models as well as 47 prefecture-specific models (**Figures 3–K, L, M**). The directions of DID estimates in relative scales were identical to those in absolute scales. For example, the introduction of financial incentives was associated with a relative reduction in total antibiotic prescriptions in a relative scale by 14.9% (95%CI, 13.6% to 16.1%; **Table 3–I**).

3-5. **Discussion**

Japan's nationwide quasi-experiment allowed us to quantify the actual effect of the financial incentive policy on reductions in physicians' antibiotic prescription and others. Although the amount of the incentive for not prescribing antibiotics was not very high (800 JPY [≈ 7.2 USD] per case), it led to a reduction in the total antibiotic prescriptions by 14.9% without experiencing excess adverse health consequences, such as elevated hospitalization rates due to severe infectious diseases.

The incentive-induced behavioral changes of physicians occurred immediately at the month of the policy introduction and remained until the end of the 12-month follow-up period. This immediate change sharply contrasts with conventional strategies nationwide to gradually reduce antibiotic prescriptions, which consists of establishing a national target, monitoring the trends in antibiotic prescriptions, implementing surveillance of resistant strains, controlling resistant strains, and commutating closely with physicians.[39–41] For example, such a multi-faceted program in Sweden took 20 years to achieve a 43% reduction in antibiotic prescriptions (≈ 2.2% reduction per year). The Swedish Strategic Programme has been considered a gold standard for reducing antibiotic prescriptions at a national level[39–41]; however, many developing and developed

countries, including Japan, face a time-sensitive situation and thus require a strategy with more prompt impacts. Japan's financial incentive policy may provide these countries with some hints for immediately altering the climate of antibiotic overuse.

From the behavioral economics perspective,[42,43] rewarding no antibiotic use is more constructive than different approaches, such as penalizing inappropriate antibiotics use.[44] With the reward, the government's commitment to reducing inappropriate antibiotics use is more clearly communicated without blaming physicians. However, the cost may be a concern since the use of the financial incentive as a "nudge" (dangling a small financial stake upon the antibiotics prescription decision-making process) could be more expensive than penalties[45] and non-financially-based behavioral interventions (e.g., peer comparison and suggesting alternatives in clinical decision support systems).[46–48] This concern is not the case in the present study because a 14.9% reduction of antibiotics use in acute viral infections among the youngest children, whose gut microbiome is the least developed,[49] was achieved by only 253 million JPY (≈2.3 million USD) nationwide. As a result, the MHLW revised the financial incentive policy at the beginning of the fiscal year 2020 and raised the age limit from 3 to 6 years old. Such a gradual scaling may help Japan achieve the goal set by the comprehensive National Action Plan on Antimicrobial Resistance: a 33.3% reduction in total antibiotic use until the end of the fiscal year 2020. At the end of the fiscal year 2019, antibiotic use in Japan reduced by 4.4% and 21.7% for all age groups and children aged < 15 years, respectively.[50]

The strength of the financial incentive policy stems not only from its immediate impact with relatively a low cost, but also from its ability to offer a fundamental solution to the prisoner's-dilemma-like problem[51] of antibiotics use. Antibiotic use on acute infection may somewhat benefit an index individual with infection by minimizing a small risk from severe bacterial complications

without almost any cost (the cost of potential adverse effects, alteration of the gut microbiome, and cost-sharing for antibiotics may be considered as a minor). Therefore, when a potential benefit from no antibiotic use (protecting a large number of others in the ecosystem in the future from resistant strains[52]) is not incorporated, the small benefit from the "just in case" antibiotic prescription is stressed and largely drives the decision-making process upon the index individual's outpatient visit. This leads to a vicious cycle of the maintenance of antibiotics overuse and the development of resistant strains. Therefore, schemes that invest the current physical and financial resources in healthcare in such ecosystem-level future benefits are warranted for achieving "cooperation with the future."[53] Japan's financial incentive policy is one of them: it has valued and priced no antibiotic use upon acute infections in the current healthcare system even though no antibiotic use does not consume any physical resources (i.e., antibiotic drugs) at the moment. Such a fundamental solution may complement other conventional comprehensive programs[39–41] or non-financially-based programs.[46–48]

Our study has several limitations. First, the biases due to unobserved confounding factors might be inherent in our study while we conducted thorough sensitivity analyses. Since many of the characteristics of the medical facilities were not provided in the NDB for the research purpose, we used the indicator variables representing Japan's 341 secondary medial areas and the composite variables calculated by individual-level characteristics for the PS matching procedure. A cluster randomized controlled trial with a random assignment of the financial incentive eligibility to medical facilities may maximize the quality of causal inference; however, its nationwide implementation is not realistic. Our DID design may be the best alternative, which has partially addressed the potential influence of the unobserved imbalance between the eligible and ineligible

facilities in the matched sample by comparing the pre-intervention state with the post-intervention state under the parallel trend assumption in time-series data.[33–36]

Second, it is difficult to determine the best size of the financial incentive across different contexts. Some may think that an increase in the financial incentive (e.g., 800 to 2000 JPY per case) may further reduce antibiotics prescriptions; however, it may cause inappropriate non-use, which will increase out-of-hour visits and hospitalizations due to severe bacterial complications (e.g., pneumonia, mastoiditis). In Japan, the financial incentive of 800 JPY per case has worked so far; although some physicians might want to claim as many "free" financial rewards as possible, they did not do so and instead might prescribe antibiotics only when necessary (e.g., severe acute otitis media) on average. Such a good balance may vary across different contexts; however, there is no evidence established yet for the adequate pricing of not prescribing antibiotics.

Nevertheless, if a financial incentive policy, including its amount, target, and timing of introduction, is carefully designed for fitting with a given country's sociopolitical contexts and budgets, it may have a strong potential for addressing antibiotic overuse.

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3-7. **Tables and Figures**

Table 3-A. ICD-10 codes for comorbidity

Comorbidities	List of the ICD-10 codes
Asthma/Infantile wheezing	J450-451, J458-459, J46
Food allergy	T781, T782
Atopic dermatitis/eczema	L208, L209,
Allergic rhinitis	J301–304
Sinusitis	J303, J324, J328-329, J111, J019
Seizure and Epilepsy	F445, F453, G401-409, G419 P90, R252, R560, R568,
Death and Cardiac arrest	I461, I469, T751, X61, X67, X69, X70, X71, X74, X75, X76, X80, X81, X83, X84, R960, R98, R99

Abbreviations: ICD-10, the International Classification of Diseases, Tenth Revision

Table 3-B. Lists of non-antibiotic drugs

Classification	Details	
Drugs for respiratory symptoms	Antitussives	Codeine, dextromethorphan hydrobromide hydrate. tipepidine hibernate, others (dimemorphan phosphate, eprazinone hydrochloride, pentoxyverine citrate, cloperastine, clofedanol, noscapine, guaifenesin, Senega®□, cheery bark extract)
	Mucolytics	L-cysteine hydrochloride, bromhexine hydrochloride, dornasealfa, carbocisteine, fudosteine
	Airway lubricant	Ambroxol hydrochloride
	Tranexamic acid	Tranexamic acid
Antihistamines	First-generation	Diphenhydramine, clemastine fumarate, chlorpheniramine maleate, promethazine hydrochloride, alimemazine tartrate, hydroxyzine, homochlorcyclizine hydrochloride, cyproheptadine hydrochloride
	Second-generation sedative	Ketotifen fumarate, azelastine hydrochloride, oxatomide, mequitazine
	Second-generation non-sedative	Fexofenadine hydrochloride, epinastine hydrochloride, ebastine, cetirizine hydrochloride, levocetirizine hydrochloride, bepotastine besilate, emedastine fumarate, olopatadine hydrochloride, loratadine, desloratadine, bilastine rupatadine fumarate
Leukotriene receptor antagonists	Montelukast, pranlukast	
Xanthines	Theophylline, diprophylline, proxyphylline, aminophylline	
Bronchodilators	Short-acting beta-stimulant inhaler	Isoprenaline hydrochloride, salbutamol sulfate, fenoterol hydrobromide, procaterol hydrochloride,
	Oral beta-stimulant	Isoprenaline hydrochloride, salbutamol sulfate, terbutaline sulfate, fenoterol hydrobromide, procaterol hydrochloride, turobuterol
	Tape beta-stimulant	Turobuterol
Antipyretics	Acetaminophen, NSAIDs (ibuprofen, aspirin, etc.)	
Anti-diarrheal drugs	Loperamide, aluminum silicate, scopolia extract, dimethicone, tannate albumin, bismuth, berberine chloride hydrate	

Table 3-C. Statistical models for the difference-in-differences estimates

Model	Equation
Crude	$E(Y_{ijk}) = \beta_0 + \beta_1 X_{1i} + \beta_2 X_{2ijk} + \beta_3 X_{1i} X_{2ijk}$
Adjusted	$E(Y_{ijk}) = \beta'_0 + \beta'_1 X_{1i} + \beta'_2 X_{2ijk} + \beta'_3 X_{1i} X_{2ijk} + \sum_l \beta_l C_{l,k}$
PS calculation	$logit[P(X = 1\|C)] = \delta_0 + \sum_m \delta_m C'_{m,i}$

Note: k = k[th] cases, j = individuals, i = facilities (hospitals and clinics), X_{1i} = intervention at facilities (0 = no incentive [ineligible], 1 = incentive [eligible]), X_{2ijk} = time indicator (0 = pre-intervention, 1 = post-intervention), l = numbers of covariates for adjusted analyses, m = numbers of covariates for logistic regression, C = s set of covariates at patient or hospital levels, β_0 = constant, β_1 = treatment group specific effect, β_2 = time trend common to index and control groupa, β_3 = difference-in-differences estimates, PS = propensity score, δ = coefficient for logistic regression model . For the PS calculation, we utilized hospital-level variables for secondary medical area of facilities, patient characteristics, primary and secondary outcomes, and prescriptions of bronchodilators, xanthines, leukotriene receptor antagonist, antipyretics, probiotics, and antidiarrheals.

Table 3-D. Baseline characteristics before and after matching

	Before PS matching					After PS matching				
Medical facilities, N	**Control N = 7221**		**Index N = 2959**		**Std. Diff (%)**	**Control N =1491**		**Index N = 1491**		**Std. Diff (%)**
Area of medical facilities, %					23.2					5.4
Hokkaido	312	(4.3)	60	(2.0)		35	(2.3)	34	(2.3)	
Tohoku	542	(7.5)	166	(5.6)		102	(6.8)	99	(6.6)	
Kanto	2413	(33.4)	1165	(39.4)		600	(40.2)	621	(41.6)	
Hokuriku/Koshinetsu	384	(5.3)	186	(6.3)		87	(5.8)	73	(4.9)	
Tokai	791	(11.0)	391	(13.2)		219	(14.7)	208	(14.0)	
Kansai	1236	(17.1)	416	(14.1)		202	(13.5)	207	(13.9)	
Chugoku	450	(6.2)	150	(5.1)		63	(4.2)	70	(4.7)	
Shikoku	222	(3.1)	106	(3.6)		42	(2.8)	46	(3.1)	
Kyushu/Okinawa	871	(12.1)	319	(10.8)		141	(9.5)	133	(8.9)	
Visited patients, N	**350,070**		**203,068**			**81,782**		**100,851**		
Cases, N	6,010,183		3,243,078			1,295,193		1,615,625		
Patient characteristics, N (%)										
Sex					0.7					0.3
Male	182,710	(52.2)	105,406	(51.9)		42,404	(51.6)	52,412	(52.0)	
Female	167,360	(47.8)	97,662	(48.1)		39,428	(48.2)	48,439	(48.0)	
Comorbidity										
Infantile wheezing	84,854	(24.2)	39,150	(19.3)	10.7	16,651	(20.3)	19,596	(19.4)	2.3
Infantile eczema	230,193	(65.8)	135,879	(66.9)	2.0	54,187	(66.2)	66,931	(66.4)	0.4
Food allergy	12,554	(3.6)	5583	(2.8)	4.6	2203	(2.7)	2966	(2.9)	1.5
Rhinitis	87,803	(25.1)	36,313	(17.9)	15.1	16,454	(20.1)	19,918	(19.7)	0.8
Sinusitis	60,480	(17.3)	21,445	(10.6)	13.1	10,044	(12.3)	12,987	(12.9)	1.8
Seizure	2469	(0.7)	1016	(0.5)	1.9	484	(0.6)	539	(0.5)	0.8
1st year (look-back period)										
Medication use, DOTs per 1000 cases (SD)										
Total antibiotics	822.3	(2543.0)	608.5	(1883.7)	9.5	650.7	(1934.6)	648.0	(1968.5)	0.1
Broad. antibiotics	357.8	(1457.4)	253.7	(1150.6)	7.9	272.2	(1189.1)	282.3	(1237.5)	-0.8
Drugs for resp. symp.	4825.6	(7589.4)	5490.7	(7700.5)	-8.7	5220.5	(7683.0)	5200.0	(7533.2)	0.0
Antihistamines	1422.9	(3709.3)	1452.5	(3549.6)	-0.8	1426.5	(508.9)	1515.6	(3630.2)	-2.5
Healthcare costs, JPY per case (SD)	15,680	(42,739)	12,538	(18,004)	9.6	12,781	(20,705)	12,227	(13,947)	2.9
Healthcare utilization, events per 1000 cases (SD)										
Out-of-hour visits	229.8	(745.4)	114.6	(425.0)	19.0	136.3	(498.9)	135.5	(474.5)	0.2
Hospitalizations	9.49	(96.9)	3.28	(57.1)	0.8	4.9	(70.4)	4.3	(65.7)	0.9
2nd year (pre-intervention period)										
Medication use, DOTs per 1000 cases (SD)										
Total antibiotics	1653.2	(3519.1)	1094.8	(2613.0)	18.0	1187.6	(2717.5)	1182.5	(2749.3)	0.2
Broad. antibiotics	823.7	(2248.9)	540.0	(1737.7)	14.1	599.4	(1814.6)	601.7	(1845.7)	-0.1
Drugs for resp. symp.	6650.5	(9546.3)	7047.5	(9443.9)	-4.1	6717.1	(9511.9)	6706.6	(9263.6)	0.1
Antihistamines	2580.5	(5314.5)	2421.8	(4933.9)	3.1	2423.5	(4982.6)	2504.3	(5001.6)	-1.6
Healthcare costs, JPY per case (SD)	13,478	(15119)	13,642	(10434)	-1.2	13,496	(12,864)	13,265	(50,016)	2.0
Healthcare utilization, events per 1000 cases (SD)										
Out-of-hour visits	260.2	(815.6)	144.2	(478.2)	17.4	164.3	(566.6)	160.4	(502.8)	0.7
Hospitalizations	3.83	(61.7)	1.65	(40.5)	4.2	2.29	(47.8)	1.97	(44.3)	0.7

Note: Abbreviations: PS, propensity-score; Broad. antibiotics, broad-spectrum antibiotics; Drugs for resp. symp., drugs for respiratory symptoms; DOTs, days of therapy; SD, standard deviation; JPY, Japanese Yen

Table 3-E. Difference-in-differences estimates in the primary analyses

	Control Facilities (N = 1491)			Index Facilities (N = 1491)			
	Pre	**Post**	**Difference**	**Pre**	**Post**	**Difference**	**DID estimate (CI)**
Medications, DOTs per 1000 cases (SE)							
Total antibiotics	1187.6 (3.4)	1195.1 (4.2)	7.5	1182.5 (3.1)	1013.6 (3.5)	-168.9	-176.4 (-193.0, -159.7)
Broad-spectrum antibiotics	599.4 (2.3)	598.5 (2.3)	-0.9	601.7 (2.1)	499.7 (2.2)	-102.0	-101.2 (-112.1, -90.2)
Drugs for respiratory symptoms	6717.1 (12.1)	7391.9 (15.3)	674.8	6706.6 (10.6)	7296.3 (12.9)	589.7	-85.1 (-143.7, -26.5)
Antihistamines	2423.5 (6.3)	2755.4 (8.5)	331.9	2504.3 (5.7)	2690.9 (7.2)	186.6	-145.3 (-180.4, -110.2)
Healthcare utilization, event per 1000 cases (SE)							
Out-of-hour visits	164.28 (0.71)	164.03 (0.85)	-0.25	160.43 (0.57)	159.30 (0.65)	-1.13	-0.89 (-4.23, 2.45)
Hospitalizations	2.29 (0.06)	1.08 (0.05)	-1.21	1.97 (0.05)	0.97 (0.04)	-1.00	0.21 (-0.06, 0.49)
Outpatient healthcare expenditures, JPY per case (SE)	13,495.8 (16.3)	12,333.1 (17.4)	-1162.7	13,264.9 (11.1)	12,654.4 (10.7)	-610.5	552.3 (469.2, 635.3)

Abbreviations: JPY, Japanese yen; SE, standard error; DID, difference-in-differences; CI, 95% confidence interval

Note: Differences in outcomes between the index (eligible) facilities and control (ineligible) facilities after propensity-score matching using data during the first and second years

Table 3-F. Baseline characteristics after matching in the sensitivity analyses

	Before PS matching			After PS matching		
Facilities, N	**Control N = 7221**	**Index N = 2959**	**StdDiff (%)**	**Control N =1800**	**Index N = 1800**	**StdDiff (%)**
Area of medical facilities, %			23.2			3.4
Hokkaido	312 (4.3)	60 (2.0)		40 (2.2)	39 (2.2)	
Tohoku	542 (7.5)	166 (5.6)		125 (6.9)	118 (6.6)	
Kanto	2413 (33.4)	1165 (39.4)		736 (40.9)	735 (40.8)	
Hokuriku/Koshinetsu	384 (5.3)	186 (6.3)		103 (5.7)	101 (5.6)	
Tokai	791 (11.0)	391 (13.2)		249 (13.8)	257 (14.3)	
Kansai	1236 (17.1)	416 (14.1)		252 (14.0)	257 (14.3)	
Chugoku	450 (6.2)	150 (5.1)		79 (4.4)	86 (4.8)	
Shikoku	222 (3.1)	106 (3.6)		64 (3.6)	58 (3.2)	
Kyushu/Okinawa	871 (12.1)	319 (10.8)		152 (8.4)	149 (8.3)	
Visited patients, N	**350,070**	**203,068**		**93,485**	**121,719**	
Cases, N	6,010,183	3,243,078		1,490,695	1,945,522	
Patient characteristics, N (%)						
Sex						
Male	182,710 (52.2)	105,406 (51.9)	0.7	48,451 (51.8)	63,082 (51.8)	0.0
Female	167,360 (47.8)	97,662 (48.1)		45,034 (48.2)	58,637 (48.2)	
Comorbidity						
Infantile wheezing	84,854 (24.2)	39,150 (19.3)	10.7	18,640 (19.9)	23,406 (19.3)	1.8
Infantile eczema	230,193 (65.8)	135,879 (66.9)	2.0	61,609 (66.1)	80,832 (66.5)	1.1
Food allergy	12,554 (3.6)	5583 (2.8)	4.6	2732 (2.9)	3376 (2.8)	0.9
Rhinitis	87,803 (25.1)	36,313 (17.9)	15.1	18,275 (19.6)	23,941 (19.7)	0.3
Sinusitis	60,480 (17.3)	21,445 (10.6)	13.1	10,665 (11.5)	15,597 (12.8)	4.3
Seizure	2469 (0.7)	1016 (0.5)	1.9	545 (0.6)	647 (0.5)	0.7
1st year (look-back period)						
Medication use, DOTs per 1000 cases (SD)						
Total antibiotics	822.3 (2543.0)	608.5 (1883.7)	9.5	658.2 (2044.9)	636.1 (1950.1)	1.1
Broad-spectrum antibiotics	357.8 (1457.4)	253.7 (1150.6)	7.9	277.8 (1221.7)	277.0 (1215.1)	0
Drugs for resp. symptoms	4825.6 (7589.4)	5490.7 (7700.5)	-8.7	5297.0 (7712.0)	5166.0 (7451.2)	1.7
Antihistamines	1422.9 (3709.3)	1452.5 (3549.6)	-0.8	1422.0 (3548.8)	1480.0 (3588.7)	-1.6
Healthcare costs, JPY per case (SD)	15,680 (42,739)	12,538 (18,004)	9.6	12,790 (26,588)	12,270 (13,249)	2.4
Healthcare utilization, events per 1000 cases (SD)						
Out-of-hour visits	229.8 (745.4)	114.6 (425.0)	19.0	113.0 (446.5)	131.5 (462.8)	-4.1
Hospitalizations	9.49 (96.9)	3.28 (57.1)	0.8	3.64 (60.2)	3.80 (61.5)	-0.3
2nd year (pre-intervention period)						
Medication use, DOTs per 1000 cases (SD)						
Total antibiotics	1653 (3519.1)	1095 (2613.0)	18.0	1296.4 (2917.4)	1121.9 (2661.9)	6.2
Broad-spectrum antibiotics	824 (2248.9)	540 1737.7)	14.1	642.7 (1892.5)	571.7 (1790.8)	3.9
Drugs for resp. symptoms	6650 (9546.3)	7048 (9443.9)	-4.1	6814.3 (9462.0)	6713.8 (9236.0)	1.1
Antihistamines	2580 (5314.5)	2422 (4933.9)	3.1	2420.7 (4937.4)	2410.9 (4922.6)	0.2
Healthcare costs, JPY per case (SD)	13,480 (15119)	13,640 (10434)	-1.2	12,901 (11,403)	13,404 (97,4010)	-4.8
Healthcare utilization, events per 1000 cases (SD)						
Out-of-hour visits	260.2 (815.6)	144.2 (478.2)	17.4	135.8 (496.3)	161.6 (510.3)	-5.1
Hospitalizations	3.83 (61.7)	1.65 (40.5)	4.2	1.76 (41.8)	1.74 (4.17)	0.0

Abbreviations: Drugs for resp. symp., drugs for respiratory symptoms; DOTs, days of therapy; SD, standard deviation; JPY, Japanese Yen

Table 3-G. Difference-in-difference estimates in the sensitivity analyses

	Control Facilities (N = 1800)			Index Facilities (N = 1800)			
	Pre	**Post**	**Difference**	**Pre**	**Post**	**Difference**	**DID estimate (CI)**
Medications, DOTs per 1000 cases (SE)							
Total antibiotics	1296.4 (3.5)	1338.1 (4.3)	41.7	1121.9 (2.8)	933.9 (3.0)	-188.0	-229.7 (-245.7, -213.7)
Broad-spectrum antibiotics	642.7 (2.2)	640.2 (2.7)	-2.5	571.7 (1.9)	460.7 (2.0)	-111.0	-108.5 (-118.8, -98.1)
Drugs for respiratory symptoms	6814.3 (11.2)	7513.7 (14.2)	699.4	6713.8 (9.6)	7275.4 (11.7)	561.6	-137.8 (-191.5, -84.0)
Antihistamines	2420.7 (5.8)	2773.1 (8.0)	352.4	2410.9 (5.1)	2584.7 (6.5)	173.8	-178.6 (-210.7, -146.5)
Healthcare utilization, event per 1000 cases (SE)							
Out-of-hour visits	135.78 (0.58)	141.24 (0.72)	5.46	161.64 (0.53)	163.23 (0.62)	1.59	-3.88 (-6.85, -0.89)
Hospitalizations	1.76 (0.04)	0.83 (0.04)	-0.93	1.74 (0.04)	0.85 (0.04)	-0.89	0.04 (-0.20, 0.28)
Outpatient healthcare expenditure, JPY per case (SE)	12,901.0 (13.1)	11,869.3 (12.9)	-1031.7	13,403.6 (10.1)	12,759.6 (9.9)	-644.0	388.6 (321.7, 455.4)

Abbreviations: DID, difference-in-differences; CI, 95% confidence interval; DOT, days of therapy; SE, standard error; JPY, Japanese yen

Table 3-H. Difference-in-difference estimates in the crude and adjusted analyses

	Control Facilities (N = 7221)			Index Facilities (N = 2959)			Crude DID estimate (CI)	Adjusted DID estimate (CI)
	Pre	Post	Difference	Pre	Post	Difference		
Medications, DOTs per 1000 cases (SE)								
Total antibiotics	1653.2 (2.1)	1805.8 (2.5)	152.6	1094.8 (2.1)	910.9 (2.3)	-183.9	-336.4 (-347.0, -325.9)	-346.4 (-355.2, -337.6)
Broad-spectrum antibiotics	823.7 (1.3)	866.7 (1.6)	43.0	540.0 (1.4)	435.8 (1.5)	-104.2	-147.2 (-154.0, -140.3)	-152.5 (-158.2, -146.8)
Drugs for respiratory symptoms	6650.5 (5.6)	7609.8 (7.2)	959.3	7047.5 (7.6)	7552.7 (9.2)	505.2	-454.2 (-488.2, -420.1)	-453.4 (-482.4, -424.4)
Antihistamines	2580.5 (3.1)	3103.6 (4.3)	523.1	2421.8 (4.0)	2592.3 (5.0)	170.5	-352.6 (-373.3, -331.8)	-358.3 (-374.3, -342.2)
Healthcare utilization, event per 1000 cases (SE)								
Out-of-hour visits	260.22 (0.48)	259.85 (0.56)	-0.37	144.22 (0.38)	146.01 (0.44)	1.79	2.15 (-0.16, 4.47)	1.75 (-0.05, 4.04)
Hospitalizations	3.83 (0.3)	1.64 (0.3)	-2.1	1.65 (0.3)	0.84 (0.3)	-0.8	1.23 (1.03, 1.42)	1.21 (1.02, 1.41)
Outpatient healthcare expenditures, JPY per case (SE)	13,478.4 (8.9)	12,363.1 (8.9)	-1115.3	13,642.2 (8.4)	12,958.9 (7.7)	-683.3	431.1 (381.7, 480.5)	412.2 (363.3, 461.2)

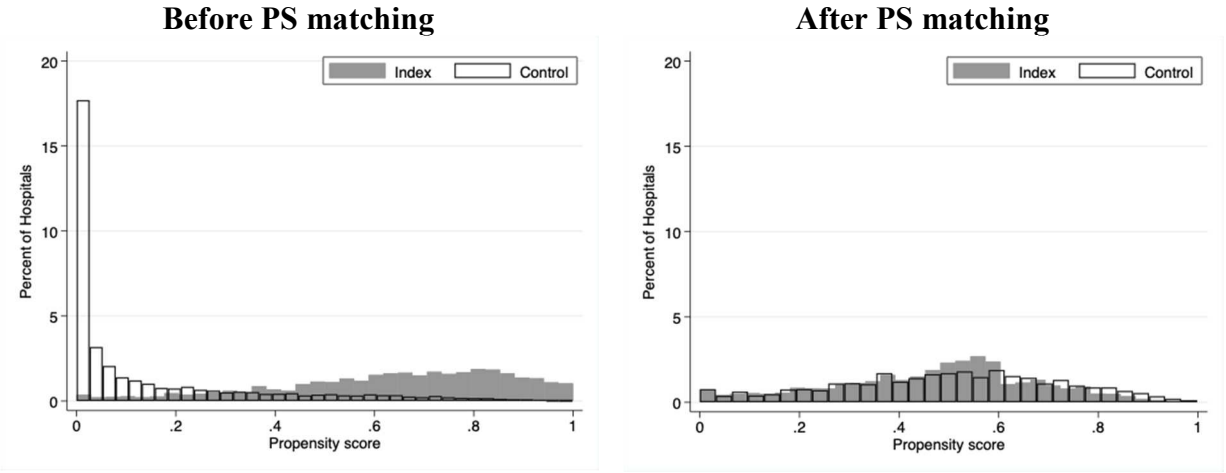
Abbreviations: DID, difference-in-differences; CI, 95% confidence interval; DOT, days of therapy; SE, standard error; JPY, Japanese yen

Table 3-I. Changes-in-Changes estimates for all analyses

	Crude CiC estimate (CI)	Adjusted CiC estimate (CI)	PS match 1 CiC estimate (CI)	PS match 2 CiC estimate (CI)
Medications				
Total antibiotics	0.761 (0.755, 0.768)	0.761 (0.755, 0.768)	0.806 (0.795, 0.817)	0.851 (0.839, 0.864)
Broad-spectrum antibiotics	0.767 (0.758, 0.775)	0.770 (0.761, 0.780)	0.808 (0.794, 0.823)	0.831 (0.815, 0.847)
Drugs for respiratory symptoms	0.936 (0.932, 0.940)	0.936 (0.932, 0.941)	0.982 (0.975, 0.990)	0.988 (0.980, 0.996)
Antihistamines	0.890 (0.883, 0.896)	0.889 (0.882, 0.896)	0.935 (0.924, 0.947)	0.945 (0.932, 0.957)
Healthcare utilization				
Out-of-hour visits	1.013 (1.001, 1.026)	1.004 (0.992, 1.016)	0.970 (0.951, 0.990)	0.994 (0.974, 1.015)
Hospitalizations	1.054 (0.937, 1.186)	0.943 (0.823, 1.080)	1.038 (0.849, 1.269)	1.043 (0.861, 1.264)
Outpatient healthcare expenditures	1.035 (1.031, 1.039)	1.032 (1.028, 1.035)	1.034 (1.029, 1.040)	1.043 (1.037, 1.050)

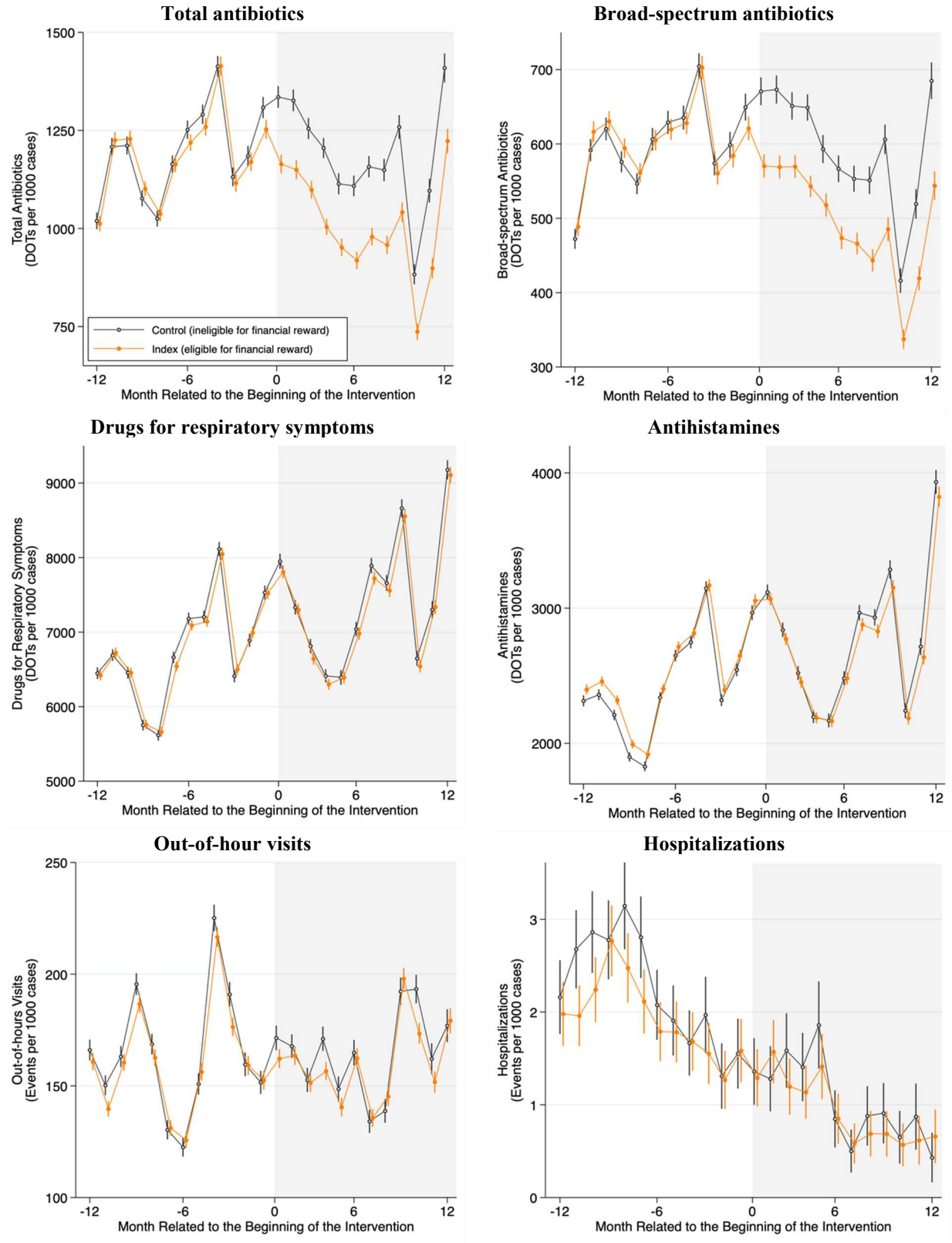
Abbreviations: CI, 95% confidence interval; PS match 1, propensity-score matched analyses using data on the look-back period (the first year); PS match 2, propensity-score matched analyses using data on the look-back and pre-intervention periods (the first and second years)
Note: Differences in outcomes comparing the index (eligible) facilities with the control (ineligible) facilities in ratio scales as Changes-in-Changes (CiC) estimates

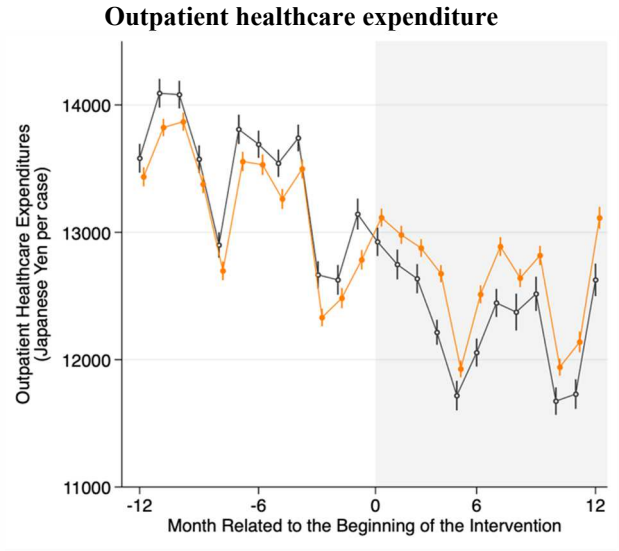
Figure 3-A. Distributions of propensity-score for the primary analyses



Abbreviations: PS, propensity-score
Note: Distributions of propensity scores for the index (eligible) and control (ineligible) groups using variables in the first and second years before matching

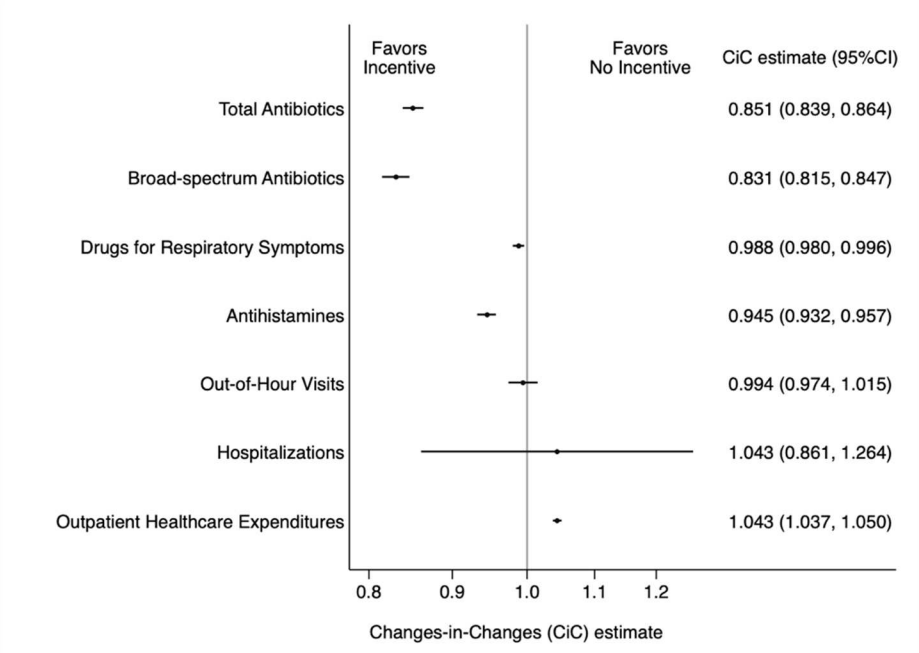
Figure 3-B. Trends in primary and secondary outcomes for the primary analyses





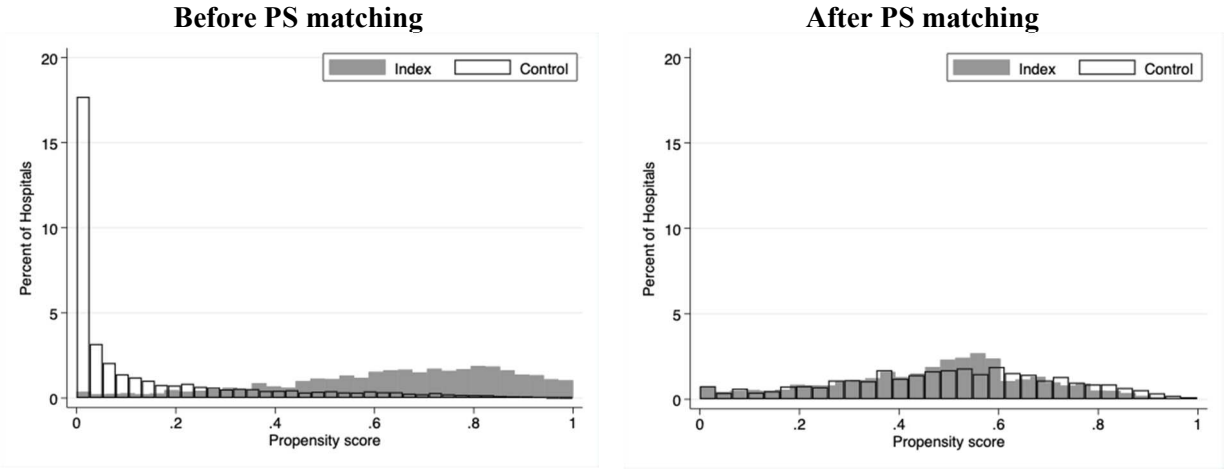
Note: Trends in outcomes of interest with 95% confidence intervals between the eligible (index) and ineligible (control) medical facilities during pre-intervention and post-intervention periods in the propensity-score-matched samples: trends in total antibiotics, broad-spectrum antibiotics, drugs for respiratory symptoms, antihistamines, out-of-hour visits, hospitalizations, and outpatient healthcare expenditures. The introduction of financial incentive policy was introduced at the beginning of Month 0 and has sustained until the end of the study period (gray areas). The decline in antibiotic use during winter seasons (January [Months, -3 and 9] and February [Months, -2 and 10]) was due to increases in seasonal influenza infections reported in Japan.

Figure 3-C. Changes-in-Changes estimates



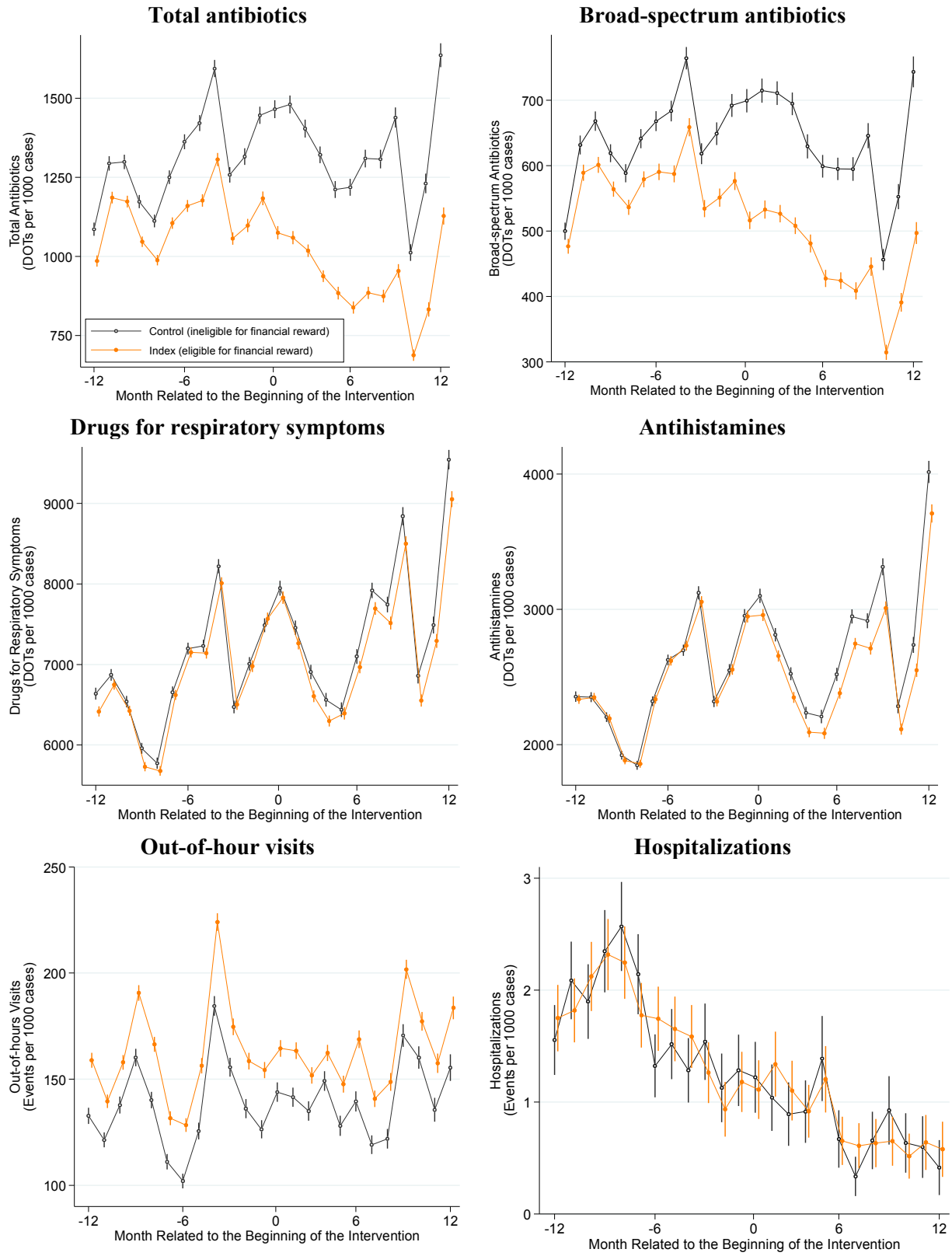
Note: Changes-in-Changes (CiC) estimates with 95% confidence intervals for total and broad-spectrum antibiotics, drugs for respiratory symptoms, antihistamines, out-of-hour visits, hospitalizations, and outpatient healthcare expenditures.

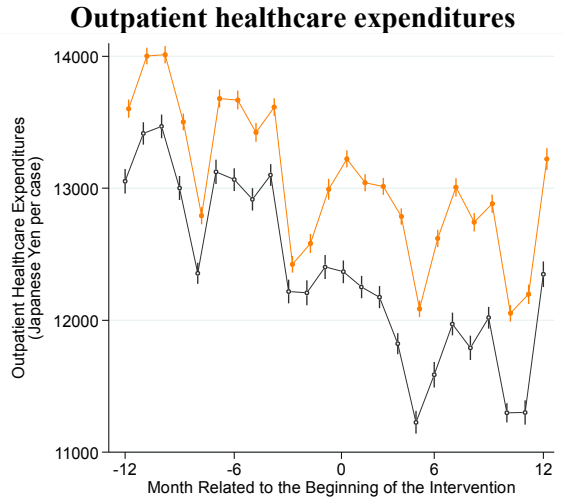
Figure 3-D. Distributions of propensity-score for the sensitivity analyses



Abbreviations: PS, propensity-score
Note: Distributions of propensity scores for the index (eligible) and control (ineligible) groups using variables in the first year.

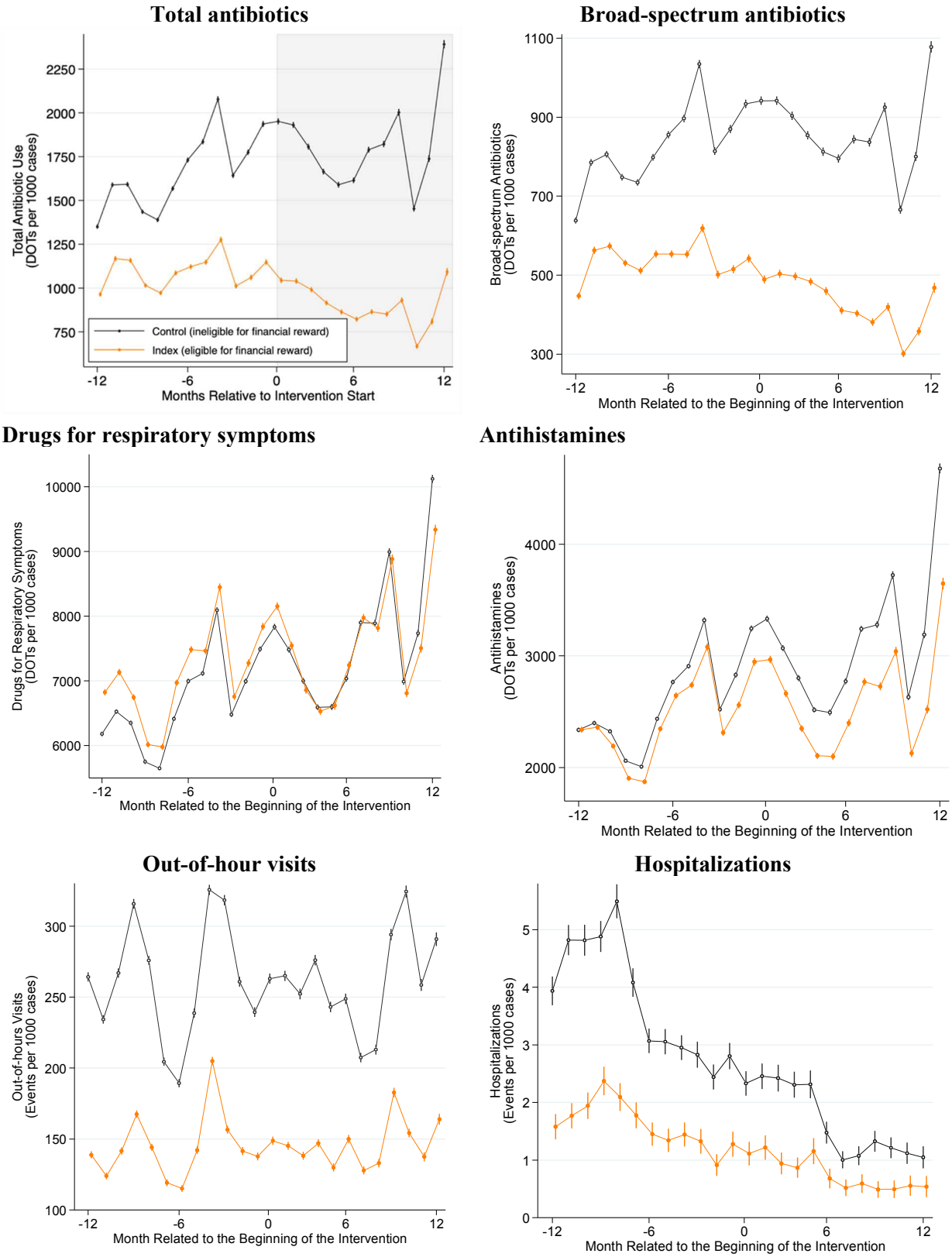
Figure 3-E. Trends in outcomes for the sensitivity analyses

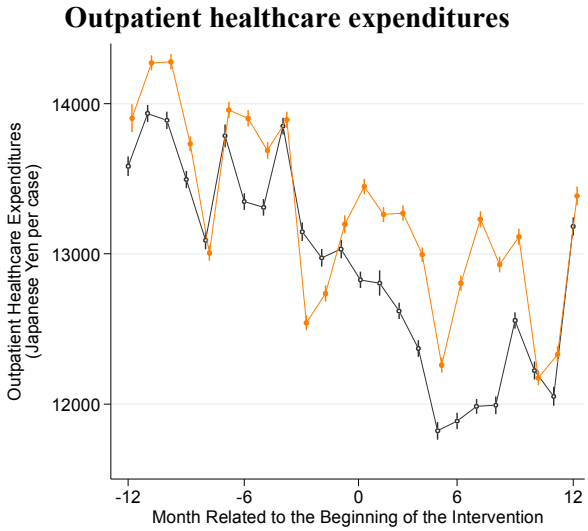




Note: Trends in outcomes of interest between the eligible (index) and ineligible (control) medical facilities during pre-intervention and post-intervention periods. Propensity-score matching was conducted using data during the look-back period (the first year).

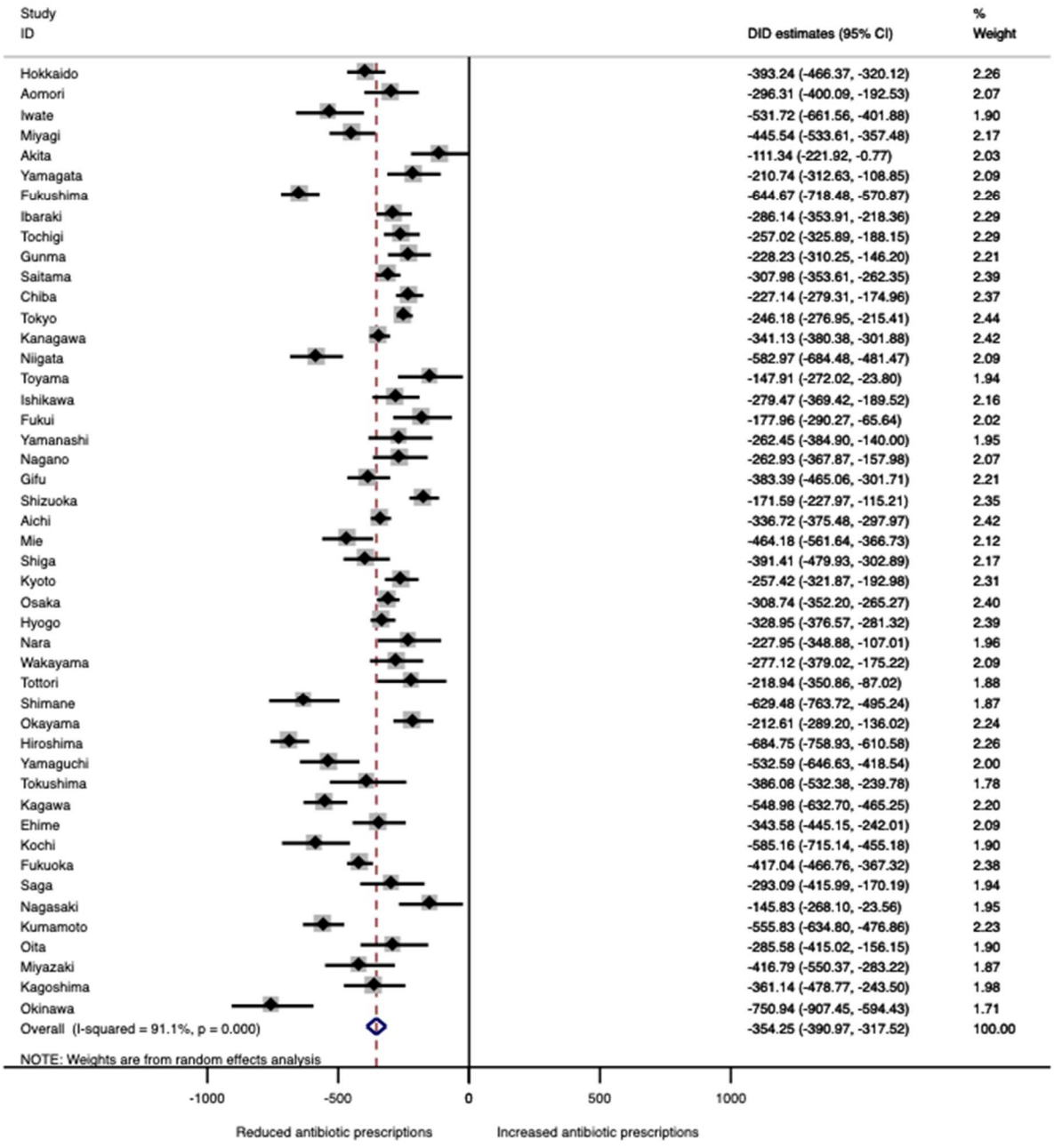
Figure 3-F. Distributions of propensity-score for the crude analyses





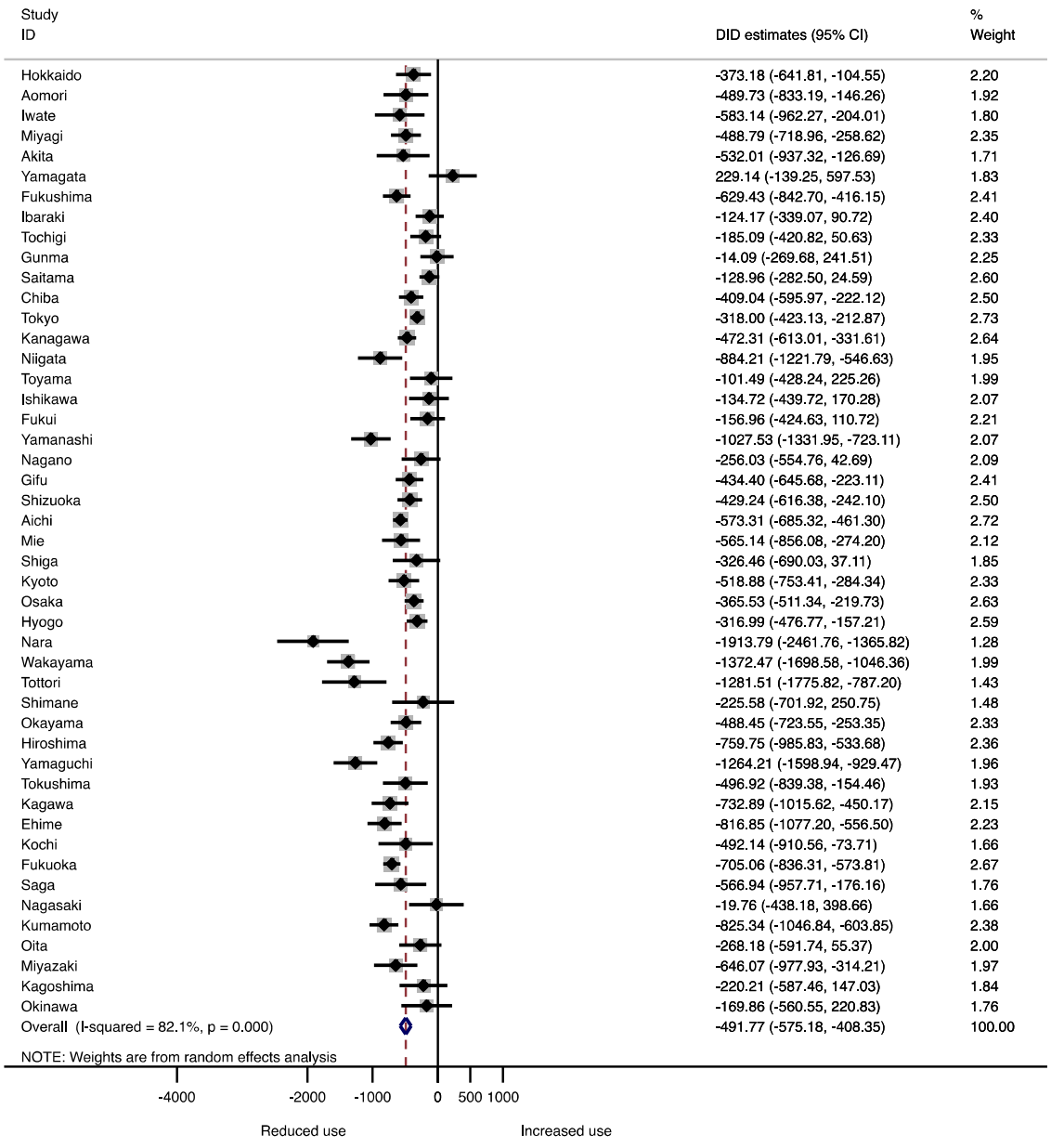
Note: Trends in outcomes of interest between the eligible (index) and ineligible (control) medical facilities during pre-intervention and post-intervention periods for the crude analyses (Propensity-score matching was not conducted for the analyses)

Figure 3-G. Total antibiotics by 47 prefectures



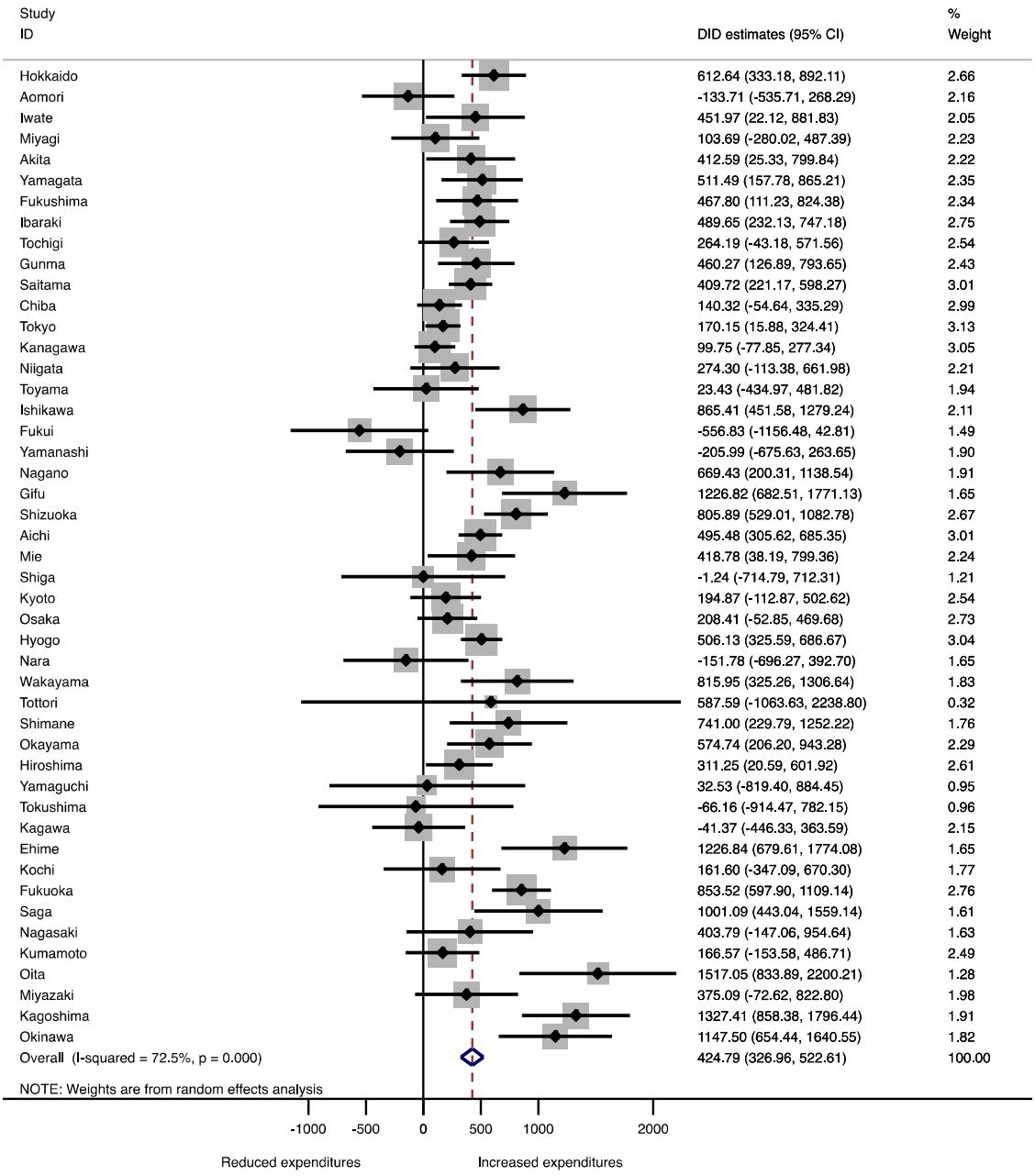
Note: Difference-in-Differences (DID) estimates with 95% confidence intervals (CIs) in 47 prefecture levels and pooled estimates.

Figure 3-H. Drugs for respiratory symptoms by 47 prefectures



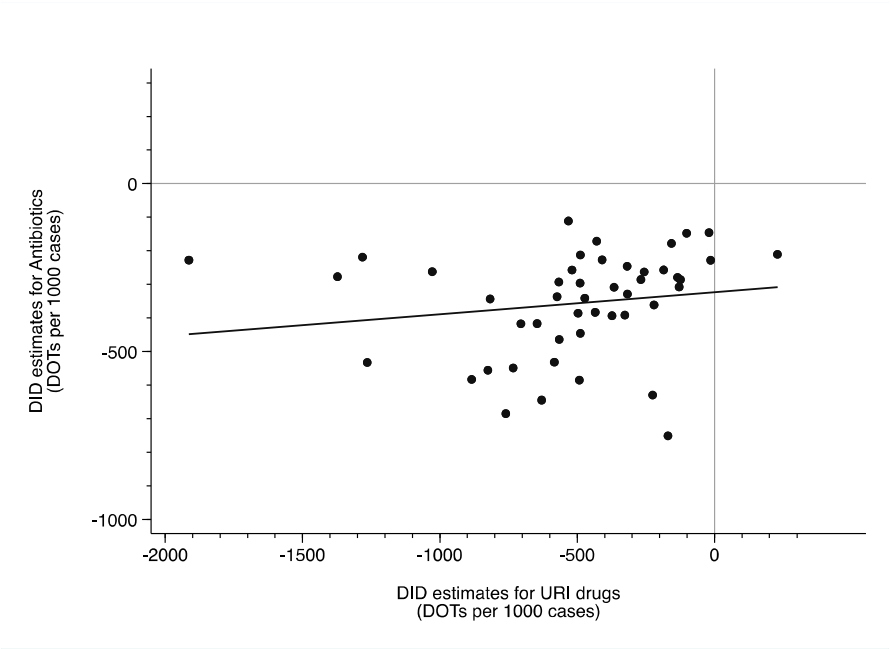
Note: Difference-in-Differences (DID) estimates with 95% confidence intervals (CIs) in 47 prefecture levels and pooled estimates.

Figure 3-I. Outpatient healthcare expenditures by 47 prefectures



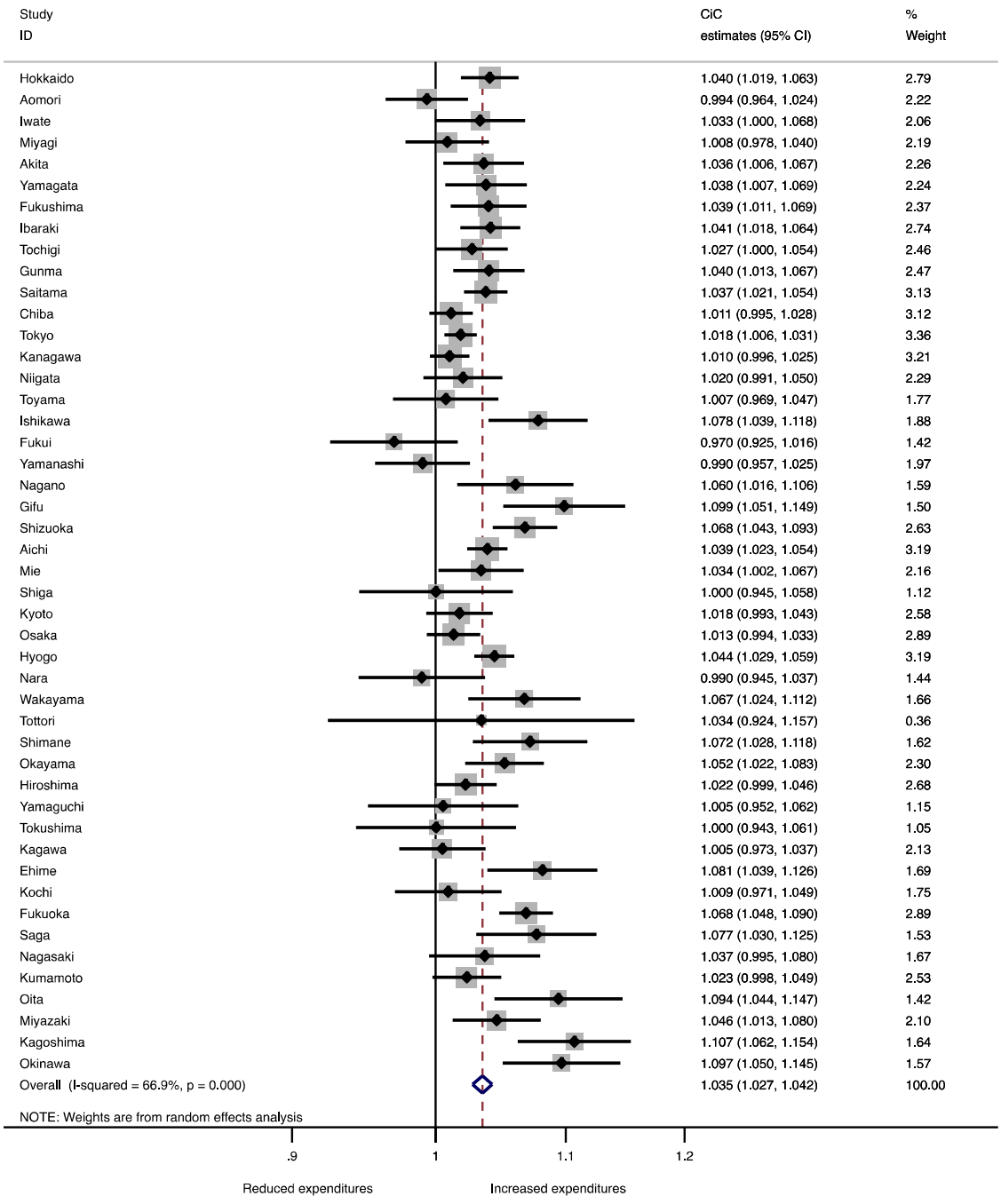
Note: DID estimates with 95% confidence intervals in 47 prefecture levels and pooled estimates

Figure 3-J. Correlation between antibiotics and drugs for respiratory symptoms



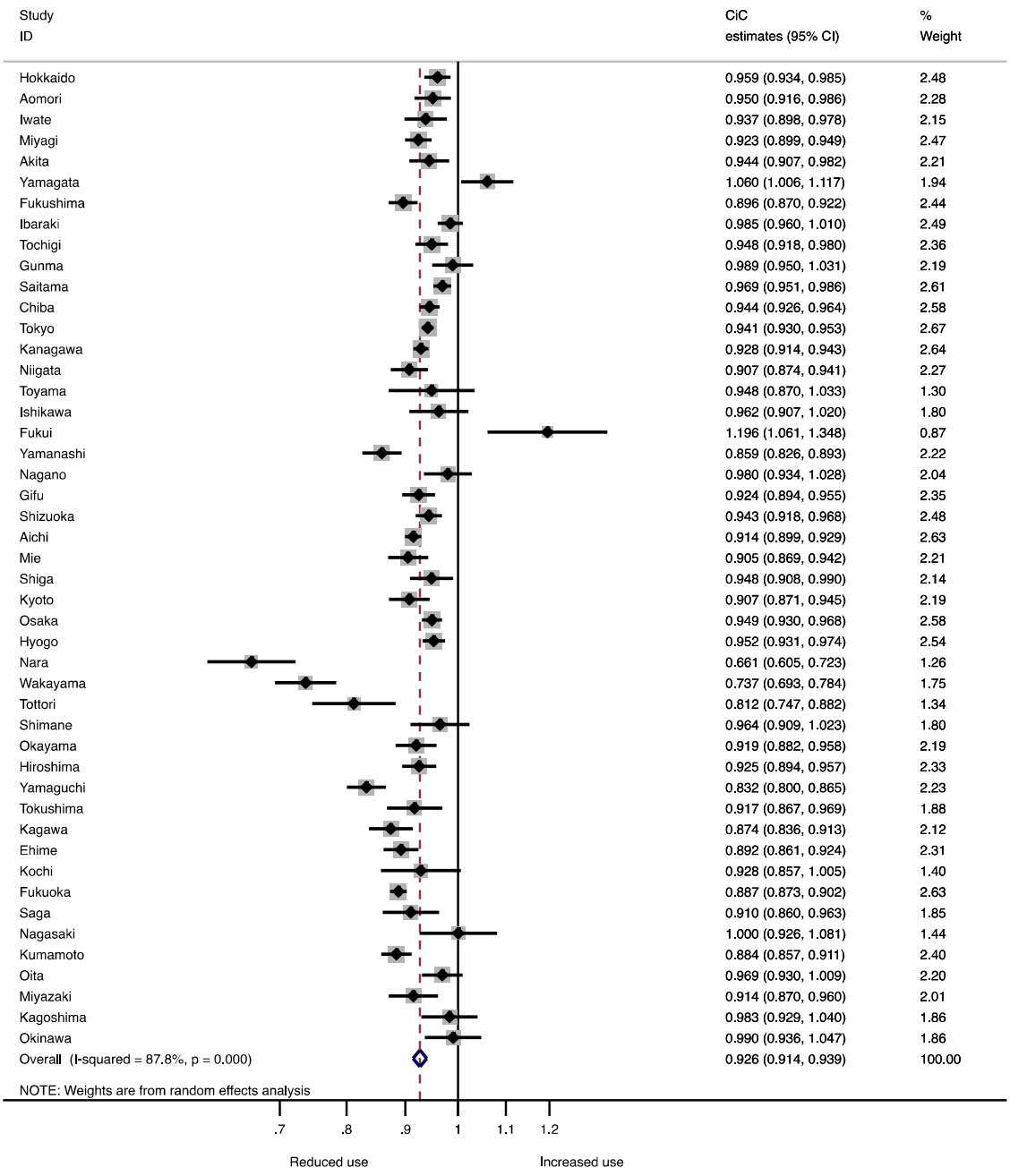
Abbreviations: DOTs, days of therapy; DID, difference-in-differences; URI, upper respiratory infections

Figure 3-K. Total antibiotics in ratio scales by 47 prefectures



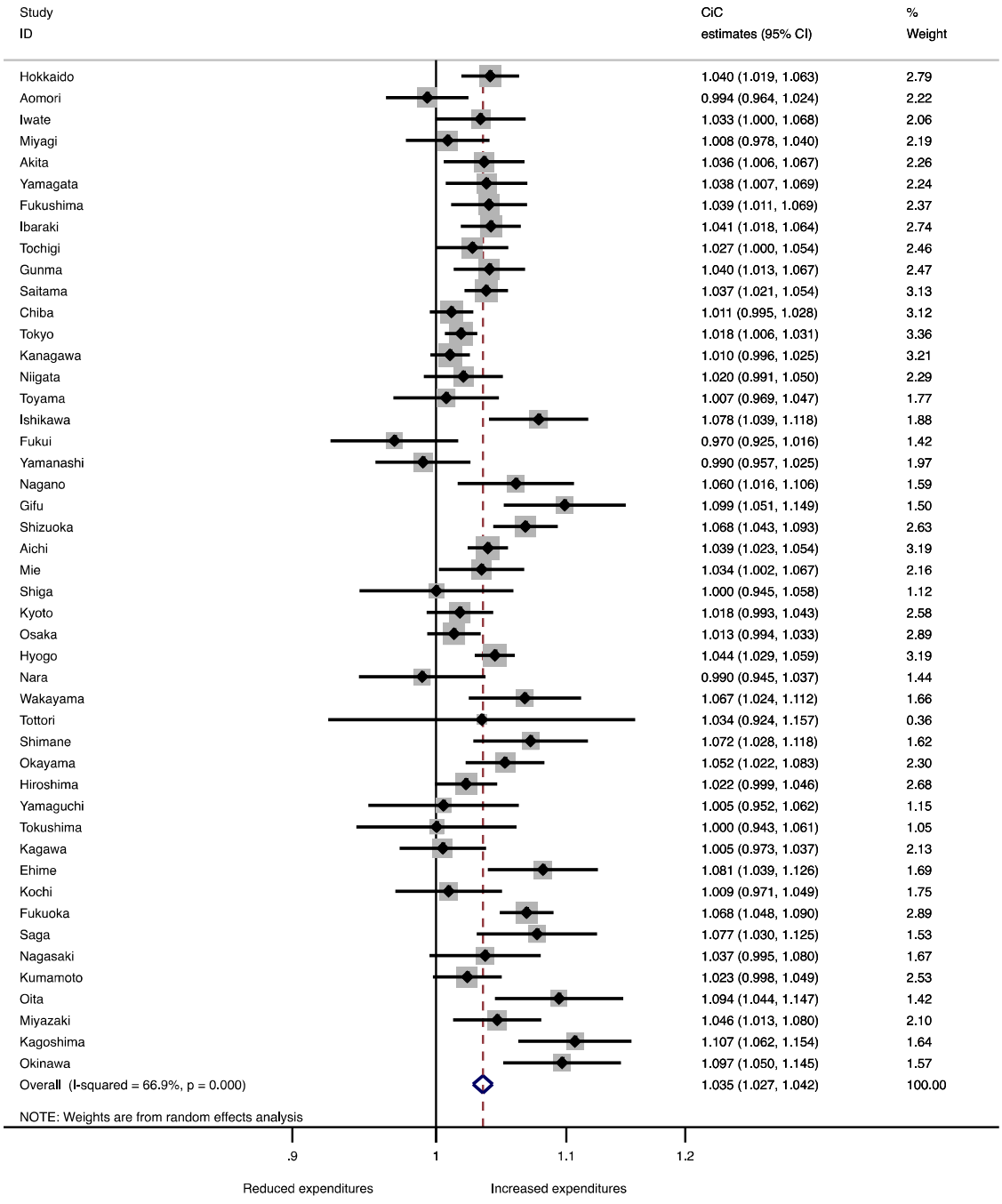
Note: DID estimates with 95% confidence intervals in 47 prefecture levels and pooled estimates

Figure 3-L. Drugs for respiratory symptoms in ratio scales by 47 prefectures



Note: DID estimates with 95% confidence intervals in 47 prefecture levels and pooled estimates

Figure 3-M. Outpatient healthcare expenditure in ratio scales by 47 prefectures



Note: DID estimates with 95% confidence intervals in 47 prefecture levels and pooled estimates

Chapter 4. Associations between the Incentives for Creating Antimicrobial Stewardship Teams and Physicians' Practice Patterns (Paper #3)

4-1. Abstract

Background: In 2018, the Japanese government initiated a new health policy that allowed hospitals to apply an additional reimbursement of 1000 JPY (≈ 7.3 EUR or 9.1 USD per admission) when they created antimicrobial stewardship teams (AST). We examined the effects of this policy on physicians' antibiotic and non-antibiotic prescription patterns, inpatient healthcare spending, and adverse health consequences for children (e.g., need for respiratory support).

Methods: This study included all acute-care hospitals (N = 1016) and children hospitalized with infectious diseases (N = 1,296,428 admissions) between April 2016 and March 2019. We used a quasi-experimental propensity score-matched difference-in-differences (DID) design to estimate the policy's effects.

Results: When the AST fee was initiated, the incentivized hospitals exhibited a greater reduction in total antibiotic prescriptions compared with the unincentivized hospitals (DID estimate, −0.76 days of therapy [DOTs] per 100 patient-days [PDs]; 95%CI, −1.23 to −0.30). The introduction of the AST fee was not associated with non-antibiotic prescriptions (e.g., drugs for respiratory symptoms, antihistamines, etc.), except for an increase in bronchodilators (DID estimate, 4.83 DOTs per 100 PDs; 95%CI, 4.07 to 5.59). The utilization of diagnostic tests, risks of respiratory support, lengths of hospital stay, and healthcare costs were similar between the incentivized and

unincentivized hospitals. Similar results were obtained from covariate-adjusted and crude models.

Conclusion: Our findings suggest that providing financial incentives for creating antimicrobial stewardship teams at hospitals only slightly reduced antibiotic prescriptions among pediatric inpatients. The small effect size indicates a need to modify the current health policies.

4-2. **Background**

The overuse and inappropriate use of antimicrobials is an unresolved challenge in global and regional health.[1–11] A recent global study showed that Japan was ranked the highest of 36 high-income countries in terms of broad-spectrum antibiotic overuse among pediatric outpatients.[12] These findings were consistent with those of our previous studies, suggesting that Japanese physicians preferred to prescribe broad-spectrum antibiotics in the usual healthcare settings.[7–9,13,14] Several strategies (e.g., audit-and-feedback, decision supports, pre-authorization systems) have been implemented to reduce antibiotic overuse and resistant strains at a single hospital level. However, the results have been inconsistent under the various healthcare settings in assessing their effectiveness.[15–25]

In Japan, the professional practice of infection control in the healthcare setting has a short history of less than four decades.[26] From 2010, the Japanese government continuously introduced several health policies for infection control management and antimicrobial stewardship program, including the reimbursement for these practices.[26] In 2018, a new health policy was added to enhance antimicrobial stewardship in the hospital setting as part of the National Action Plan for Antimicrobial Resistance.[27] The team's main roles were to promote adequate diagnostic procedures and appropriate antibiotic prescriptions and educate the medical staff with non-

infectious expertise. According to a national survey in 2019, over 80% of respondents reported that the additional reimbursement for creating an antimicrobial stewardship team helped promote antimicrobial stewardship in hospitals.[28] However, no study has been conducted to investigate whether introducing the additional reimbursement changed physicians' practice patterns and patient outcomes at a national level.

Therefore, this study investigated the effects of additional reimbursement for creating antimicrobial stewardship teams in hospitals on the antibiotic and non-antibiotic prescription patterns, performance of diagnostic procedures, and outcomes of healthcare utilization.

4-3. **Methods**

Data source and study design

We conducted a quasi-experimental propensity-score (PS) matched difference-in-differences (DID) design with a cohort of hospitals and children. Both the institutional review boards at the National Center for Child Health and Development in Japan and the University of California, Los Angeles, approved our study. The Ministry of Health, Labour and Welfare in Japan approved our data request and extracted the relevant claims data from the Diagnosis Procedure Combination (DPC) inpatient database. The DPC database is a part of the National Database of Health Insurance Claims and Specific Health Checkups (NDB),[29] and the details of the database have been described elsewhere.[30] Briefly, the DPC database was collected from > 1,000 hospitals, covering 55% of all inpatient admissions to acute-care hospitals in Japan. It includes information on the following: the patients' age, sex, residential area, diagnosis, pre-existing comorbidities at admission, complications during hospitalization; dates when procedures and treatments were

performed. Using anonymized unique identification numbers in the DPC, we followed the claims data of the same individuals and hospitals over the study period.

Data construction

Using the DPC data, we constructed 3-year cohorts (from April 1, 2016 to March 31, 2019) of hospitals with pediatric inpatients with infectious diseases. All diagnoses of infectious diseases were identified using the International Classification of Diseases, Tenth Revision code (ICD-10 code) (Table 2–A).[31] We excluded 544,029 admissions with complex medical conditions, 132,566 admissions to the neonatal intensive care units, and 646 hospitals with < 10 children hospitalized with infectious diseases per year. Complex medical conditions (including congenital heart, kidney, pulmonary, endocrine, hematologic, gastrointestinal, and neurologic diseases; cancer or leukemia; and autoimmune disease) were defined according to the pediatric complex chronic conditions classification system version 2.[32]

The obtained 3-year cohort data were separated into the three phases: (1) the look-back period (1st year; April 2016 to March 2017), (2) pre-intervention period (2nd year; April 2017 to March 2018), and (3) post-intervention period (3rd year; April 2018 to Match 2019). The 1st year data (look-back period) were used to create baseline characteristics at hospital levels for the following DID analyses.

Exposure of interest: Japan's health policy change as quasi-experiment

The exposure of interest was the additional reimbursement of antimicrobial stewardship for creating antimicrobial stewardship teams in hospitals (an antimicrobial stewardship fee). In April 2018, the antimicrobial stewardship fee was added to promote appropriate antibiotic use in hospital settings as part of a National Action Plan for Antimicrobial Resistance in Japan. Under the new policy, hospitals could receive an additional financial incentive for each admission

(approximately 1,000 JPY [≈ 7.7 EUR or 9.1 USD]) if they created antimicrobial stewardship teams in their hospitals. The team should include at least one physician, nurse, pharmacist, and clinical laboratory technician with infectious disease expertise > 3–5 years and those with more than 0.5 staff full-time equivalent. The main roles of antimicrobial stewardship teams were 1) monitoring the use of broad-spectrum antibiotics; 2) providing audit and feedback to physicians regarding their antibiotic use; 3) suggesting proper use of diagnostic tests and cultures on blood, urine, sputum, etc.; and 4) facilitating promotion and education on appropriate antibiotic use. Those hospitals receiving the antimicrobial stewardship fees during the 3rd year for children hospitalized with infectious diseases were categorized in the index group. The other hospitals were categorized in the control group.

Outcome measures

The primary outcome of interest was total antibiotic use as days of therapy (DOTs) per 100 patient-days. The secondary outcomes consisted of 1) prescriptions of broad-spectrum antibiotics; 2) use of diagnostic procedures (rapid antigen tests, cultures for blood, urine, and pharynx); 3) utilization of an imaging study of ultrasound (US), computed tomography (CT), and/or magnetic resonance imaging (MRI)); 4) need for respiratory support (mechanical ventilation) or admission to the intensive care unit; 5) length of hospital stay in days; and 6) total inpatient healthcare expenditure. Tertiary outcomes were non-antibiotic prescriptions for symptomatic relief (e.g., drugs for respiratory symptoms, antihistamines, and probiotics) (**Table 3–B**). Information on antibiotic prescriptions in the DPC database was converted to the Anatomical Therapeutic Chemical (ATC) system.[33] The ATC system was used to classify the prescriptions. We categorized antipseudomonal beta-lactams, carbapenems, fosfomycin, tetracycline, and quinolone as broad-spectrum antibiotics in accordance with previous studies (**Table 4–A**).[8,13,22,34]

Adjustment Variables

The baseline characteristics included patient age, sex, geographic location (Supplemental Table 4), diagnoses of asthma/wheezing, atopic dermatitis/eczema, food allergy, rhinitis, sinusitis, and seizure. These diagnoses were estimated using ICD-10 codes (**Table 3–A**). Individual-level data during the 1st and 2nd years were converted into average and percentage at the hospital level and used as variables for the PS matching.

Statistical Analysis

Baseline characteristics were summarized for continuous and categorical variables as means and proportions by the exposure of interests at hospital levels. We used PS matched DID analyses to investigate the effects of introducing antimicrobial stewardship fees on physicians' prescription behavior and health resource utilization.

We conducted PS matching because the characteristics of patients and hospitals and the trends in outcomes of interest during pre-intervention periods were expected to differ between the index and control groups. PSs were calculated based on the probability of treatment assignment (the introduction of antimicrobial stewardship fee) conditional on observed baseline covariates and outcomes of interest in the 1st and 2nd years at hospital levels.[35] We calculated PSs using multivariable logistic regression models (**Table 4–B**) and conducted one-to-one matching between hospitals in the index and control groups using the nearest-neighbor methods within a caliper distance of < 20% of standard deviation (SD) for PS.[35] We checked the balance between the index and control groups based on absolute standardized differences. An absolute standardized difference of > 10% was considered a meaningful imbalance.[35]

After we matched the same number of hospitals in the index and control groups, we investigated the PS-matched DID estimates for the outcomes of interest.[36–39] DID analyses

construct time series of the outcome (e.g., total antibiotic use) and statistically test for changes in the outcomes in the periods before and after implementing an intervention (the introduction of antimicrobial stewardship fee).[40] Specifically, we fitted the following statistical model[36–39]:

$$E(Y_{i,t,h}) = \beta_0 + \beta_1 X_h + \beta_2 T_{i,t} + \beta_3 X_h T_{i,t}$$

where E denotes the expected value, $Y_{i,t,h}$ is the outcome of interest for a person (i), the timing of admission (t), and a hospital (h), β s are coefficients, X is a treatment variable for applied vs. non-applied hospitals (index or control), and T is a time indicator variable (pre-intervention vs. post-intervention). The estimates of interest were a coefficient of an interaction term (β_3) of a time indicator variable (T) and a treatment variable (X). To incorporate the hierarchical data structure, we used generalized estimation equations under a normal distribution and identity link function.[36–39,41]

Sensitivity Analysis

We conducted several sensitivity analyses. First, we performed PS matched DID analyses using data from the 1st year (look-back period). Second, we constructed covariate-adjusted models. In these models, we added the covariates listed above as a set of potential confounders to the crude models to adjust for time-fixed potential confounders (**Table 4–B**). Third, crude DID models were constructed to investigate the unadjusted DID estimates. Fourth, we repeated the analyses of the tertiary outcomes. Fifth, all DID estimates were investigated in relative scales using negative binomial distributions with log link functions. All data were analyzed using Stata/MP software version 16.1 (StataCorp LP, TX, USA).

4-4. **Results**

We identified a total of 1016 hospitals and 1,296,428 inpatients aged < 15 years with infectious diseases. Overall, 244 (24.0%) hospitals voluntarily created antimicrobial stewardship teams and claimed the reimbursement fees. The distribution of age, sex, and types of infectious diseases were similar between the index and control groups (**Table 4–C**). In contrast, the index group had slightly higher proportions of patients with seizures and hospitals located in the Kansai, Chugoku, and Kyushu/Okinawa areas.

PS matching between the index and control groups

We conducted PS matching using data on covariates and outcomes during the 1st and 2nd years (**Figure 4–A**). After PS matching, the baseline characteristics and outcomes of interest in the 1st and 2nd years were well balanced between the two groups (**Table 4–C**). The trends in outcomes during the pre-intervention period were almost parallel between the index and control groups (**Figure 4–B**).

Prescription patterns for total and broad-spectrum antibiotics

PS matched DID analyses (**Table 4–D**) found that introducing the antimicrobial stewardship fees was associated with slightly reduced total antibiotic prescriptions by -0.76 DOTs per 100 patient-days (95%CI, -1.23 to -0.30). In contrast, it was not associated with changes in prescriptions of broad-spectrum antibiotics (DID estimate, 0.03 DOTs per 100 patient-days; 95%CI, -0.16 to 0.23).

Healthcare utilization and inpatient healthcare expenditure

The introduction of antimicrobial stewardship fees was not associated with changes in utilization of diagnostic tests for causative pathogens (DID estimate, 2.74 events per 100 admissions; 95%CI, -0.23 to 5.72; **Table 4–D**) and imaging studies (DID estimate, -0.21 events

per 100 admissions; 95%CI, -0.66 to 0.24). There were no differences in healthcare utilization outcomes between the two groups: the risk of respiratory support (DID estimate, -0.04 events per 100 admissions; 95%CI, -0.13 to 0.006), length of hospital stay (DID estimate, -0.03 days; 95%CI, -0.08 to 0.02), and total inpatient healthcare cost (DID estimate, 3.9 JPY; -3486.7 to 3494.5).

Sensitivity Analysis

First, we conducted PS matching using data on covariates and outcomes of interest during the 1st year (**Figure 4–C**). After PS matching, the baseline characteristics and outcome of interests in the 1st years were well balanced between the two groups (**Table 4–E**). **Figure 4–D** shows the trends in the primary and secondary outcomes between the index and control groups. The directions of associations between the introduction of antimicrobial stewardship fees and outcomes of interest were mostly identical, except for the diagnostic test utilization (**Table 4–F**).

Second, we estimated covariate-adjusted DID estimates and observed similar DID estimates to those in the PS matches models, except for slightly reduced diagnostic test utilization and healthcare costs (**Table 4–G**). Third, crude analyses found that DID estimates were mostly identical to the covariate-adjusted DID estimates (**Figure 4–E**; **Table 4–G**).

Fourth, we repeated the same analyses for the tertiary outcomes (**Tables 4–C, F, G**). We observed that the introduction of the antimicrobial stewardship fees was associated with an increase in prescriptions of bronchodilators and not associated with prescriptions of probiotics. The DID estimates for other types of medications were inconsistent with imprecise estimates, depending on the different statistical models.

Fifth, we analyzed DID estimates in relative scales for all statistical models (**Table 4–H**). The directions of DID estimates in relative scales were identical to those in absolute scales. For

example, the introduction of the antimicrobial stewardship fees was associated with a relative reduction in total antibiotic prescriptions by 1.9% (95%CI, 0.7% to 3.2%).

4-5. **Discussion**

In this large study of approximately 1.3 million admissions and 1000 hospitals from the national database, we found that 24% of hospitals voluntarily created antimicrobial stewardship teams and claimed the antimicrobial stewardship reimbursement fees. We observed that the introduction of the antimicrobial stewardship fees was associated with very slight reductions in the total antibiotic prescriptions and was not associated with changes in the risks of requiring intensive care, lengths of hospital stay, and inpatient healthcare costs. These results were mostly consistent across different statistical models used to reduce the potential biases and model misspecifications. Our findings reflect the routine care setting for all children hospitalized with any infectious diseases and indicate limited effectiveness of introducing antimicrobial stewardship fees to improve physicians' antibiotic prescription patterns.

The Ministry of Health, Welfare and Labour in Japan has introduced several health policies for infection control management and antimicrobial stewardship over the past 10 years in recognition that most hospitals did not provide healthcare workers sufficient time for infection control activities until 2010.[26] For instance, the reimbursement of 1,000 JPY per admission for advanced infection control and prevention practice was introduced as part of a revision of the medical reimbursement system in 2010.[26] The reimbursement fee was raised later to 4,000 JPY per admission to further promote antimicrobial stewardship activities further and strengthen the relationship between large-sized and medium- to small-sized hospitals for infection control activities. As a result of this increase, an antimicrobial stewardship program was implemented in

approximately 70% of hospitals according to a nationwide survey in March 2018.[42] This survey also found that hospitals that had antimicrobial stewardship teams with formal approvals were very low at 6.7% in small/medium-sized hospitals and 27.5% of large-sized hospitals. Then, the antimicrobial stewardship fee of 1000 JPY per admission was introduced in April 2018, expecting to provide sufficient healthcare-worker resources for such activities as creating antimicrobial stewardship teams. Consequently, the proportion of hospitals with formally approved antimicrobial stewardship teams increased to 51.8% in November 2019.[28]

Research at single institutions has been conducted to estimate the effects of antimicrobial stewardship implementation on physicians' antibiotic prescription patterns, changes in the number of resistant-strains, patient morbidity and mortality, and inpatient expenditures.[21,43–51] Most studies have shown that implementing an antimicrobial stewardship program decreased antibiotic treatment duration, enhanced patient safety, and reduced inpatient healthcare costs and the number of drug-resistant bacteria. However, our findings showed that the introduction of the antimicrobial stewardship fees contributed to only 2% relative reductions in antibiotic prescription rates in the incentivized hospitals. The reasons for these small reductions were multifactorial, including the unclear goals of the policy (e.g., reduction rates for inpatient antibiotic use, methods of antimicrobial stewardship, etc.), the lack of pediatric infectious disease experts in Japan, and the subsequent difficulty of implementing an antimicrobial stewardship program with pediatric inpatients. For example, children were admitted mainly to the pediatric ward of a hospital complex (e.g., community or university hospital), in which a pediatrician was not always included on the antimicrobial stewardship team. Indeed, a nationwide survey in 2019 found that only 4.9% of hospitals implemented antimicrobial stewardship programs for their departments of pediatrics and neonatology.[28]

In Japan, an imbalance exists between the current number of infectious disease physicians and the needs. For instance, while the number of adult infectious disease physicians in the United States was 2.74 per 100,000 population in 2016, it was only 1.28 per 100,000 in Japan, suggesting a shortage of these physicians.[52] In addition, physicians' and pharmacists' workload for performing antimicrobial stewardship activities in Japan were lower than those in the United States. Whereas the full-time equivalent (FTE) of infectious disease physicians and pharmacists were 0.27–0.46 and 0.61–1.50, respectively, in the US,[53] a survey in Japan reported only 0.025–0.05 FTE for physicians and 0.10–0.13 for pharmacists.[28] These results suggest the need for mitigating this imbalance.

Besides its unique strengths, our study had several limitations. Although we conducted several different statistical analyses to adjust for potential confounders and model misspecifications, these biases might be inherent in the study. For instance, the diagnoses of pre-existing comorbidities may have been underestimated or overestimated because of the possible underreporting or potential misclassification of ICD-10 codes, resulting in biases in either direction. The detailed clinical presentation and laboratory data were unavailable in the NDB, which may have resulted in residual confounding and confounding by indication. However, DID analyses could account for the unobserved covariates if parallel trend assumptions were valid. Most findings from crude, adjusted, and two different PS-matched analyses were similar, suggesting the robustness of our findings. Although the utilization of a national representative database was a strength in our study in terms of generalizability, the transportability of our findings to external populations is uncertain and will likely depend on a variety of factors, including the medical system and prescribing habits.

In summary, the introduction of the antimicrobial stewardship fees for creating antimicrobial stewardship teams was associated with only small reductions in the total antibiotic use and not associated with length of hospital stay and risks of disease severity. Although further studies are crucial to investigate its long-term effects, our results suggest the need to modify the current antimicrobial stewardship policy and include additional or alternative approaches to change antibiotic prescription patterns at hospitals with pediatric departments.

4-6. **References**

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4-7. **Tables and Figures**

Table 4-A. Lists of oral and intravenous antibiotics

Classification	Details
Penicillin	Benzylpenicillin potassium, benzylpenicillin benzathine hydrate, ampicillin, bacampicillin hydrochloride, amoxicillin hydrate
Penicillin with beta-lactamase inhibitors	Amoxicillin-clavulanate, ampicillin-sulbactam, piperacillin sodium, piperacillin-tazobactam
First-generation cephalosporin	Cephazolin, cefalexin, cefroxadine, cefaclor
Second-generation cephalosporin	Cefotiam, cefmetazole, cefminox, flomoxef, cefuroxime
Third-generation cephalosporin	Cefotaxime, cefmnoxime, ceftriaxione, ceftadizime, cefdinir, ceftibuten, cefditren pivoxil, cefixime, cefteram pivoxil, cefpodoxime proxetil, cefcapene pivoxil, ceftizoxime,
Fourth-generation cephalosporin	Cefpirome, cefozopran, cefepime
Carbapenem and oral penem	Imipenem cilastatin, panipenem betamipron, meropenem, biapenem, doripenem, tebipenem pivoxil, faropenem
Macrolide	Erythromycin, clarithromycin, roxithromycin, azithromycin, josamycin
Tetracycline	Tetracycline, doxycycline, minocycline, tigecycline
Quinolone	Norfloxacin, ofloxacin, levofloxacin, ciprofloxacin, lomefloxacin, tosufloxacin, pazufloxacin, prulifloxacin, moxifloxacin, garenoxacin, sitafloxacin
Trimethoprim-sulfamethoxazole	Trimethoprim-sulfamethoxazole
Aminoglycoside	Streptomycin, kanamycin, gentamicin, tobramycin, dibekacin, amikacin, isepamicin, arbekacin
Lincomycin	Lincomycin, clindamycin,
Glycopeptide and lipopeptide	Vancomycin, teicoplanin, daptomycin
Fosfomycin	Fosfomycin

Note: Broad-spectrum antibiotics consisted of antipseudomonal beta-lactams, carbapenems, fosfomycin, tetracycline, and quinolone

Table 4-B. Difference-in-Differences models

Model	Equation
Crude	$Y_{i,h,t} = \beta_0 + \beta_1 X_h + \beta_2 T_{i,t} + \beta_3 X_h T_{i,t}$
Adjusted	$Y_{i,h,t} = \beta'_0 + \beta'_1 X_h + \beta'_2 T_{i,t} + \beta'_3 X_h T_{i,t} + \sum_k \gamma_k C_{i,h,t}$
PS calculation	$logit[P(X = 1\|C)] = \delta_0 + \sum_k \delta_k C_{h,t}$

Abbreviations: PS, propensity score

Notes: i = individual, h = hospital, t = time, X = intervention at facilities (0 = no incentive, 1 = incentive), T = time indicator (0 = pre-intervention, 1 = post-intervention), k = numbers of covariates, C = a set of covariates at patient or hospital levels, β_0 = constant, β_1 = treatment group specific effect, β_2 = time trend common to index and control groups, β_3 = difference-in-differences estimates, PS = propensity score, δ= coefficient for logistic regression model (For PS calculation, we utilized hospital-level variables for secondary medical area of hospitals, patient characteristics, primary, secondary, and tertiary outcomes).

Table 4-C. Baseline characteristics in the primary analyses

	Before PS matching			After PS matching		
Hospitals, N	**Control N = 772**	**Index N = 244**	**StdDiff (%)**	**Control N =198**	**Index N = 198**	**StdDiff (%)**
Area, of medical facilities, N (%)			22.3			8.4
Hokkaido	41 (5.3)	12 (4.9)		11 (5.6)	11 (5.6)	
Tohoku	62 (8.0)	14 (5.7)		11 (5.6)	13 (6.6)	
Kanto	195 (25.3)	59 (24.2)		41 (25.8)	52 (26.3)	
Hokuriku & Koshinetsu	79 (10.2)	18 (7.4)		19 (9.6)	17 (8.6)	
Tokai	78 (10.1)	33 (13.5)		26 (13.1)	24 (12.1)	
Kansai	130 (16.8)	50 (20.5)		39 (19.7)	36 (18.2)	
Chugoku	48 (6.3)	21 (8.6)		14 (7.1)	15 (7.6)	
Shikoku	33 (4.3)	8 (3.3)		6 (3.0)	7 (3.5)	
Kyushu & Okinawa	106 (13.9)	29 (11.9)		21 (10.6)	23 (11.6)	
Patient characteristics in the 1st year						
Age, mean (SE)	3.8 (0.01)	3.7 (0.01)	2.4	3.7 (0.01)	3.7 (0.01)	-0.2
Male, N (%)	157,885 (56.5)	90,245 (56.9)	0.8	62,655 (56.6)	74,444 (56.8)	0.9
Asthma/Infantile wheezing, N (%)	86,358 (30.9)	44,927 (28.3)	5.7	29,466 (26.6)	38,419 (29.3)	2.8
Atopic dermatitis/Eczema, N (%)	5846 (2.1)	2800 (1.8)	2.4	1976 (1.8)	2436 (1.9)	0.4
Food allergy, %	4348 (1.6)	1841 (1.2)	3.4	1079 (1.0)	1631 (1.2)	1.1
Rhinitis, %	18,205 (6.5)	7065 (4.5)	9.1	5525 (5.0)	6185 (4.7)	0.6
Sinusitis, %	6541 (2.3)	3934 (2.5)	0.9	2714 (2.5)	3355 (2.6)	2.5
Seizure, %	18,790 (6.7)	12,795 (8.1)	5.1	8483 (7.7)	9990 (7.6)	0.2
1st year (Look-back period)						
Medication use, DOTs per 100 patient-days (SE)						
Total antibiotic use	97.9 (0.81)	92.3 (0.10)	-5.6	91.0 (0.12)	93.6 (0.11)	2.6
Broad-spectrum antibiotic use	28.9 (0.05)	23.5 (0.05)	-10.2	23.7 (0.06)	24.6 (0.06)	1.7
Drugs for respiratory symptoms	269.7 (0.30)	246.7 (0.39)	-4.8	262.3 (0.46)	256.6 (0.43)	-1.2
Bronchodilators	99.5 (0.13)	90.1 (0.16)	-5.3	93.6 (0.19)	93.7 (0.18)	0.0
Antihistamines	28.5 (0.11)	23.6 (0.14)	-2.1	23.8 (0.15)	25.2 (0.16)	0.6
Leukotriene antagonists	74.9 (0.16)	73.3 (0.24)	-0.5	66.9 (0.25)	75.1 (0.27)	2.5
Probiotics	54.2 (0.10)	50.1 (0.13)	-2.3	49.3 (0.15)	50.3 (0.15)	0.5
Health resource utilization, event per 100 admissions (SE)						
Test for causative pathogen	61.6 (0.09)	64.5 (0.12)	-6.0	65.3 (0.14)	64.3 (0.13)	2.1
Imaging study (US, CT, or MRI)	15.1 (0.07)	19.1 (0.09)	-10.4	16.8 (0.11)	18.4 (0.10)	-4.4
Need for respiratory support	0.2 (0.008)	0.8 (0.02)	-8.8	0.3 (0.01)	0.6 (0.02)	-4.8
Healthcare costs in JPY, mean (SE)	262,536 (423)	320,982 (776)	-21.6	301,475	307,898	-2.3
Length of stay in days, mean (SE)	5.1 (0.07)	5.4 (0.01)	-8.1	5.3 (0.01)	5.3 (0.01)	-0.6
2nd year (Pre-intervention period)						
Medication use, DOTs per 100 patient-days (SE)						
Total antibiotic use	88.6 (0.08)	85.3 (0.10)	2.5	84.6 (0.12)	86.0 (0.11)	1.5
Broad-spectrum antibiotic use	22.5 (0.03)	18.3 (0.04)	10.3	18.4 (0.05)	18.9 (0.05)	1.3
Drugs for respiratory symptoms	271.0 (0.30)	240.0 (0.39)	4.7	263.2 (0.47)	251.1 (0.43)	-2.5
Bronchodilators	99.4 (0.13)	85.3 (0.16)	6.4	91.9 (0.19)	88.6 (0.18)	-1.9
Antihistamines	26.8 (0.11)	22.5 (0.17)	0.5	21.2 (0.16)	24.0 (0.20)	1.0
Leukotriene antagonists	79.7 (0.17)	74.8 (0.26)	-0.9	71.7 (0.27)	77.0 (0.29)	1.4
Probiotics	54.3 (0.10)	51.7 (0.14)	1.0	49.2 (0.16)	52.2 (0.16)	1.6
Health resource utilization, event per 100 admissions (SE)						
Test for causative pathogen	61.5 (0.09)	64.2 (0.12)	-5.6	65.5 (0.14)	64.3 (0.13)	2.5
Imaging study (US, CT, or MRI)	15.3 (0.06)	18.9 (0.09)	-9.5	17.1 (0.11)	18.3 (0.10)	-3.1
Need for respiratory support	0.3 (0.009)	0.5 (0.02)	-9.0	0.5 (0.02)	0.7 (0.02)	-3.1
Healthcare costs in JPY, mean (SE)	262,635 (428)	323,901 (765)	-22.8	301,259	307,423	-2.3
Length of stay in days, mean (SE)	5.0 (0.07)	5.4 (0.01)	-9.2	5.3 (0.01)	5.3 (0.01)	-1.7

Abbreviations: PS, propensity-score; StdDiff, standardized difference (an absolute standardized difference > 10% is a meaningful imbalance between the index and control groups); DOTs, days of therapy; SE, standard error; JPY, Japanese Yen

Table 4-D. Difference-in-difference estimates for the primary analyses

	Control Hospitals (N = 198)			Index Hospitals (N = 198)			
	Before	**After**	**Difference**	**Before**	**After**	**Difference**	**DID estimate (CI)**
Medications, DOTs per 100 patient-days (SE)							
Total antibiotics	84.61 (0.12)	84.51 (0.12)	-0.10	86.08 (0.11)	85.2 (0.11)	-0.88	-0.76 (-1.23, -0.30)
Broad-spectrum antibiotics	18.46 (0.05)	17.71 (0.05)	-0.75	18.99 (0.04)	18.28 (0.04)	-0.71	0.03 (-0.16, 0.23)
Drugs for respiratory tract symptoms	263.26 (0.47)	258.29 (0.50)	-4.97	251.16 (0.43)	248.72 (0.45)	-2.44	2.53 (0.70, 4.37)
Bronchodilators	91.99 (0.19)	88.88 (0.20)	-3.11	88.60 (0.18)	90.33 (0.18)	1.73	4.83 (4.07, 5.59)
Antihistamine	21.22 (0.16)	21.92 (0.21)	0.70	24.00 (0.20)	25.84 (0.24)	1.84	1.13 (0.31, 1.95)
Leukotriene receptor antagonist	71.69 (0.27)	73.10 (0.35)	1.41	77.02 (0.29)	79.84 (0.35)	2.82	1.40 (0.14, 2.67)
Probiotics	49.25 (0.16)	49.32 (0.17)	0.07	52.23 (0.15)	52.35 (0.15)	0.12	0.05 (-0.58, 0.69)
Healthcare utilizations, event per 100 admissions (SE)							
Diagnostic test	65.5 (0.1)	65.5 (0.1)	0.0	64.3 (0.1)	64.5 (0.1)	0.2	0.2 (-0.4, 0.7)
Imaging study (US/CT/MRI)	17.1 (0.1)	17.5 (0.1)	0.4	18.3 (0.1)	18.5 (0.1)	0.2	-0.21 (-0.66, 0.24)
Admission to ICU or need for respiratory support	0.45 (0.009)	0.52 (0.02)	0.07	0.68 (0.009)	0.72 (0.02)	0.04	-0.04 (-0.13, 0.006)
Length of stay in days, mean (SE)	5.27 (0.01)	5.21 (0.01)	-0.06	5.34 (0.01)	5.25 (0.01)	-0.09	-0.03 (-0.08, 0.02)
Healthcare cost, mean JPY (SE)	301,259.2 (795.9)	310,078.1 (830.6)	8818.9	307,423.4 (772.3)	316,246.2 (785.0)	8822.8	3.9 (-3486.7, 3494.5)

Abbreviations: DOTs, days of therapy; JPY, Japanese yen; SE, standard error; DID, difference-in-differences; CI, 95% confidence interval

Note: Differences in outcomes between the index hospitals and control hospitals after propensity-score matching using data during the 1st and 2nd years.

Table 4-E. Baseline characteristics in the sensitivity analyses

	Before PS matching			After PS matching		
Hospitals, N	**Control N = 772**	**Index N = 244**	**StdDiff (%)**	**Control N =142**	**Index N = 142**	**StdDiff (%)**
Area, of medical facilities %			22.3			7.8
Hokkaido	41 (5.3)	12 (4.9)		9 (6.3)	8 (5.6)	
Tohoku	62 (8.0)	14 (5.7)		10 (7.0)	11 (7.7)	
Kanto	195 (25.3)	59 (24.2)		41 (28.9)	38 (26.8)	
Hokuriku & Koshinetsu	79 (10.2)	18 (7.4)		12 (8.5)	12 (8.5)	
Tokai	78 (10.1)	33 (13.5)		19 (13.4)	21 (14.8)	
Kansai	130 (16.8)	50 (20.5)		24 (16.9)	23 (16.2)	
Chugoku	48 (6.3)	21 (8.6)		10 (7.7)	11 (7.7)	
Shikoku	33 (4.3)	8 (3.3)		4 (2.8)	4 (2.8)	
Kyushu & Okinawa	106 (13.9)	29 (11.9)		13 (9.2)	14 (9.9)	
Patient characteristics in the 1st year						
Age, mean (SE)	3.8 (0.01)	3.7 (0.01)	2.4	3.7 (0.01)	3.9 (0.01)	-0.9
Male, N (%)	157,885 (56.5)	90,245 (56.9)	0.8	44,902 (56.6)	54,556 (56.8)	0.4
Comorbidity, N (%)						
Asthma/Infantile wheezing	86,358 (30.9)	44,927 (28.3)	5.7	21,845 (27.5)	27,866 (29.0)	3.3
Atopic dermatitis/Eczema	5846 (2.1)	2800 (1.8)	2.4	1364 (1.7)	1737 (1.8)	0.7
Food allergy	4348 (1.6)	1841 (1.2)	3.4	824 (1.0)	1021 (1.1)	0.2
Rhinitis	18,205 (6.5)	7065 (4.5)	9.1	3336 (4.2)	4732 (4.9)	3.5
Sinusitis	6541 (2.3)	3934 (2.5)	0.9	1993 (2.5)	2455 (2.6)	0.3
Seizure	18,790 (6.7)	12,795 (8.1)	5.1	6235 (7.9)	7466 (7.8)	0.3
1st year						
Medication use, DOTs per 100 patient-days						
Total antibiotic use	97.9 (0.81)	92.3 (0.10)	-5.6	88.4 (0.15)	94.3 (0.13)	5.9
Broad-spectrum antibiotic use	28.9 (0.05)	23.5 (0.05)	-10.2	22.3 (0.07)	24.9 (0.06)	5.3
Drugs for respiratory symptoms	269.7 (0.30)	246.7 (0.39)	-4.8	263.3 (0.56)	263.8 (0.52)	0.1
Bronchodilators	99.5 (0.13)	90.1 (0.16)	-5.3	86.1 (0.22)	94.5 (0.21)	4.9
Antihistamines	28.5 (0.11)	23.6 (0.14)	-2.1	22.0 (0.17)	26.1 (0.16)	2.2
Leukotriene antagonists	74.9 (0.16)	73.3 (0.24)	-0.5	66.2 (0.29)	73.3 (0.29)	2.5
Probiotics	54.2 (0.10)	50.1 (0.13)	-2.3	50.8 (0.18)	55.4 (0.18)	2.6
Health resource utilization, event per 100 admissions (SE)						
Test for causative pathogen	61.6 (0.09)	64.5 (0.12)	-6.0	65.1 (0.16)	65.6 (0.15)	-1.1
Imaging study (US, CT, or MRI)	15.1 (0.07)	19.1 (0.09)	-10.4	17.5 (0.13)	17.8 (0.12)	-0.9
Need for respiratory support	0.2 (0.008)	0.8 (0.02)	-8.8	0.4 (0.02)	0.3 (0.01)	1.8
Healthcare costs in JPY, mean	262,536 (423)	320,982 (776)	-21.6	306,575 (955)	292,085 (829)	5.5
Length of stay in days, mean	5.1 (0.07)	5.4 (0.01)	-8.1	5.4 (0.01)	5.3 (0.01)	3.0
2nd year						
Medication use, DOTs per 100 patient-days (SE)						
Total antibiotic use	88.6 (0.08)	85.3 (0.10)	-3.3	83.0 (0.15)	87.1 (0.13)	4.2
Broad-spectrum antibiotic use	22.5 (0.03)	18.3 (0.04)	-9.4	19.3 (0.06)	19.4 (0.05)	0.2
Drugs for respiratory symptoms	271.0 (0.30)	240.0 (0.39)	-6.4	268.3 (0.58)	262.9 (0.54)	-1.1
Bronchodilators	99.4 (0.13)	85.3 (0.16)	-7.9	90.1 (0.23)	90.3 (0.21)	0.1
Antihistamines	26.8 (0.11)	22.5 (0.17)	-1.6	19.8 (0.17)	23.9 (0.17)	2.3
Leukotriene antagonists	79.7 (0.17)	74.8 (0.26)	-1.3	71.6 (0.32)	76.3 (0.29)	1.5
Probiotics	54.3 (0.10)	51.7 (0.14)	-1.4	50.4 (0.20)	56.2 (0.18)	3.0
Health resource utilization, event per 100 admissions (SE)						
Test for causative pathogen	61.5 (0.09)	64.2 (0.12)	-5.6	64.6 (0.17)	65.5 (0.15)	-1.8
Imaging study (US, CT, or MRI)	15.3 (0.06)	18.9 (0.09)	-9.5	17.6 (0.13)	17.4 (0.12)	0.6
Need for respiratory support	0.3 (0.009)	0.5 (0.02)	-9.0	0.6 (0.02)	0.4 (0.02)	1.9
Healthcare costs in JPY, mean	262,635 (428)	323,901 (765)	-22.8	305,414 (975)	294,263 (837)	4.2
Length of stay in days, mean	5.0 (0.07)	5.4 (0.01)	-9.2	5.3 (0.01)	5.2 (0.01)	2.2

Abbreviations: PS, propensity-score; StdDiff, standardized difference (an absolute standardized difference > 10% is a meaningful imbalance between the index and control groups); DOTs, days of therapy; SE, standard error; JPY, Japanese Yen

Table 4-F. Difference-in-differences estimates for the sensitivity analyses

	Control Hospitals (N = 142)			Index Hospitals (N = 142)			
	Before	**After**	**Difference**	**Before**	**After**	**Difference**	**DID estimate (CI)**
Visitors							
Medications, DOTs per 100 patient-days (SE)							
Total antibiotics	83.01 (0.14)	83.0 (0.15)	-0.01	87.14 (0.13)	86.19 (0.13)	-0.95	-0.96 (-1.52, -0.40)
Broad-spectrum antibiotics	19.32 (0.06)	18.31 (0.06)	-1.01	19.39 (0.05)	18.67 (0.06)	-0.72	0.28 (0.04, 0.53)
Drugs for respiratory tract symptoms	268.35 (0.58)	263.86 (0.61)	-4.49	262.9 (0.54)	258.57 (0.55)	-4.33	0.13 (-2.11, 2.38)
Bronchodilators	90.16 (0.23)	89.51 (0.25)	-0.65	90.32 (0.21)	91.88 (0.22)	-1.56	2.19 (1.28, 3.11)
Antihistamine	19.81 (0.17)	24.16 (0.24)	4.35	23.96 (0.17)	24.16 (0.19)	0.20	-1.14 (-1.93, -0.36)
Leukotriene receptor antagonist	71.65 (0.32)	73.32 (0.40)	1.67	76.36 (0.29)	76.53 (0.33)	0.17	-1.49 (-2.83, -0.15)
Probiotics	50.47 (0.20)	49.73 (0.20)	-0.74	56.25 (0.18)	55.42 (0.19)	-0.83	-0.08 (-0.87, 0.69)
Healthcare utilizations, event per 100 admissions (SE)							
Diagnostic test	64.6 (0.1)	65.3 (0.1)	0.7	65.5 (0.1)	65.4 (0.1)	-0.1	-0.75 (-1.3, -0.1)
Imaging study (US/CT/MRI)	17.5 (0.1)	17.7 (0.1)	0.2	17.3 (0.1)	17.7 (0.1)	0.4	0.21 (-0.42, 0.66)
Admission to ICU or need for respiratory support	0.56 (0.02)	0.57 (0.02)	0.01	0.43 (0.02)	0.46 (0.02)	0.03	0.03 (-0.08, 0.13)
Length of stay in days, mean (SE)	5.31 (0.01)	5.26 (0.01)	-0.05	5.22 (0.01)	5.15 (0.01)	-0.07	-0.02 (-0.08, 0.04)
Healthcare cost, mean JPY (SE)	305,414.1 (975.0)	313,701.5 (1020.1)	8287.4	294263.1 (837.0)	303010.2 (853.1)	8747.1	459.7 (-3636.4, 4555.8)

Abbreviations: JPY, Japanese yen; SE, standard error; DID, difference-in-differences; CI, 95% confidence interval

Table 4-G. Difference-in-differences estimates in the crude and adjusted analyses

	Control Hospitals (N = 722)			Index Hospitals (N = 244)			Crude DID estimate (CI)	Adjusted DID estimate (CI)
	Before	After	Difference	Before	After	Difference		
Medications, DOTs per 100 patient-days (SE)								
Total antibiotics	88.63 (0.08)	87.70 (0.08)	-0.93	85.34 (0.10)	84.06 (0.10)	-1.28	-0.34 (-0.71, 0.01)	-0.47 (-0.82, -0.11)
Broad-spectrum antibiotics	22.54 (0.04)	20.92 (0.03)	-1.62	18.38 (0.04)	17.66 (0.04)	-0.72	0.90 (0.74, 1.06)	0.59 (0.44, 0.75)
Drugs for respiratory tract symptoms	271.09 (0.30)	266.55 (0.31)	-4.54	240.04 (0.39)	237.28 (0.40)	-2.76	1.77 (0.37, 3.18)	3.65 (2.29, 5.00)
Bronchodilators	99.44 (0.13)	100.36 (0.13)	0.92	85.39 (0.16)	85.21 (0.16)	-0.18	-1.09 (-1.69, -0.50)	0.38 (-0.16, 0.93)
Antihistamine	26.87 (0.11)	29.59 (0.15)	2.72	22.55 (0.17)	26.58 (0.24)	4.03	1.31 (0.61, 2.00)	2.12 (1.41, 2.84)
Leukotriene receptor antagonist	79.74 (0.17)	81.6 (0.22)	1.86	74.88 (0.26)	79.28 (0.34)	4.40	2.52 (1.50, 3.53)	4.02 (2.98, 5.05)
Probiotics	54.35 (0.19)	54.40 (0.12)	0.05	51.74 (0.14)	51.96 (0.14)	0.22	0.15 (-0.35, 0.67)	0.33 (-0.16, 0.84)
Healthcare utilizations, event per 100 admission (SE)								
Diagnostic test	61. 5 (0.10)	61.7 (0.09)	0.2	64.2 (0.10)	63.7 (0.11)	-0.5	-0.64 (-1.06, -0.22)	-0.73 (-1.14, -0.33)
Imaging study (US/CT/MRI)	15.3 (0.06)	15.6 (0.07)	0.3	18.9 (0.09)	19.0 (0.09)	0.1	-0.26 (-0.61, 0.07)	-0.19 (-0.53, 0.14)
Admission to ICU or need for respiratory support	0.26 (0.01)	0.27 (0.01)	0.01	0.96 (0.02)	0.99 (0.02)	0.03	0.01 (-0.06, 0.09)	0.0 (-0.07, 0.07)
Length of stay in days, mean	5.05 (0.01)	5.00 (0.01)	-0.05	5.42 (0.01)	5.30 (0.01)	-0.12	-0.08 (-0.11, -0.03)	-0.08 (-0.12, -0.04)
Healthcare cost, mean JPY (SE)	262,634.6 (428.7)	270,891.1 (439.5)	8256.5	323,900.7 (765.5)	330,063.6 (770.9)	6162.9	-2093.5 (-4833.6, 646.5)	-2332.8 (-4915.6, 249.8)

Abbreviations: JPY, Japanese yen; SE, standard error; DID, difference-in-differences; CI, 95% confidence interval

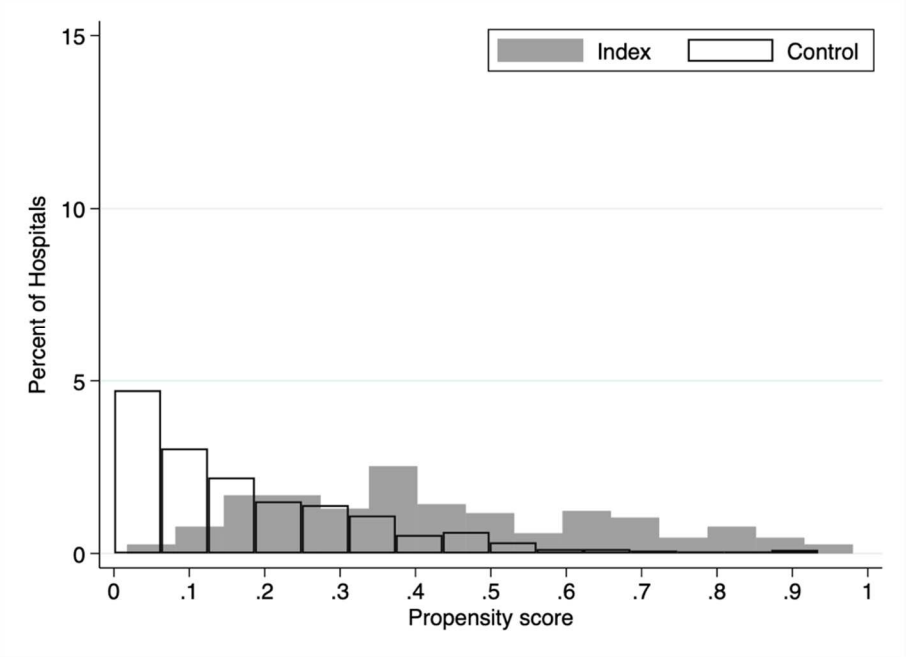
Table 4-H. Difference-in-differences estimates in ratio scales

Methods	Crude DID estimate (CI)	Adjusted DID estimate (CI)	PS match 1 DID estimate (CI)	PS match 2 DID estimate (CI)
Medications				
Total antibiotics	0.986 (0.977, 0.996)	0.983 (0.973, 0.993)	0.971 (0.956, 987)	0.981 (0.968, 0. 993)
Broad-spectrum antibiotics	1.021 (1.000, 1.042)	1.007 (0.985, 1.029)	0.984 (0.954, 1.016)	0.981 (0.955, 1.009)
Drugs for respiratory tract symptoms	1.005 (0.991, 1.020)	1.035 (1.018, 1.052)	1.002 (0.980, 1.023)	1.010 (0.992, 1.030)
Bronchodilators	1.009 (0.903, 1.025)	1.011 (0.995, 1.028)	1.028 (1.004, 1.054)	1.054 (1.032, 1.075)
Antihistamine	1.229 (1.142, 1.322)	1.067 (1.000, 1.138)	0.921 (0.836, 1.013)	1.065 (0. 964, 1.177)
Leukotriene receptor antagonist	1.089 (1.048, 1.133)	1.057 (0.985, 1.040)	0.958 (0.909, 1.009)	1.012 (0.962, 1.064)
Probiotics	0.989 (0.964, 1.015)	1.012 (0.985, 1.040)	0.999 (0.961, 1.037)	0.998 (0.962, 1.030)
Healthcare utilization				
Diagnostic test	0.989 (0.977, 1.002)	0.967 (0.956, 0.977)	0.986 (0.970, 1.001)	1.013 (1.000, 1.026)
Imaging study (US/CT/MRI)	0.982 (0.962, 1.002)	0.988 (0.967, 1.010)	0.969 (0.940, 0.998)	0.999 (0.990, 1.008)
Admission to ICU or need for respiratory support	0.984 (0.860, 1.125)	1.000 (0.820, 1.082)	1.031 (0.829, 1.282)	0.909 (0.772, 1.070)
Length of stay in days	0.986 (0.979, 0.994)	0.984 (0.977, 0.992)	1.006 (1.995, 1.018)	0.994 (0.984, 1.004)
Healthcare costs	0.988 (0.979, 0.996)	0.989 (0.981, 0.996)	1.011 (0.998, 1.024)	0.999 (0.988, 1.010)

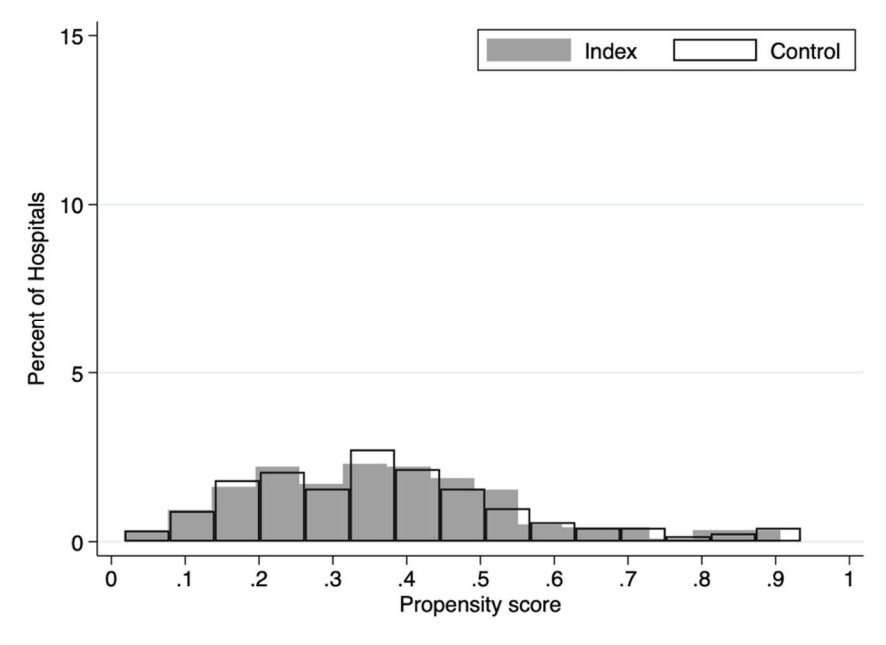
Abbreviations: CI, 95% confidence interval; JPY, Japanese yen; PS match 1, propensity-score matched analyses using data on look-back period (the 1st year); PS match 2, propensity-score matched analyses using data on the look-back and pre-intervention periods (the 1st and 2nd years)

Figure 4-A. Distributions of propensity scores in the primary analyses

Before propensity score matching

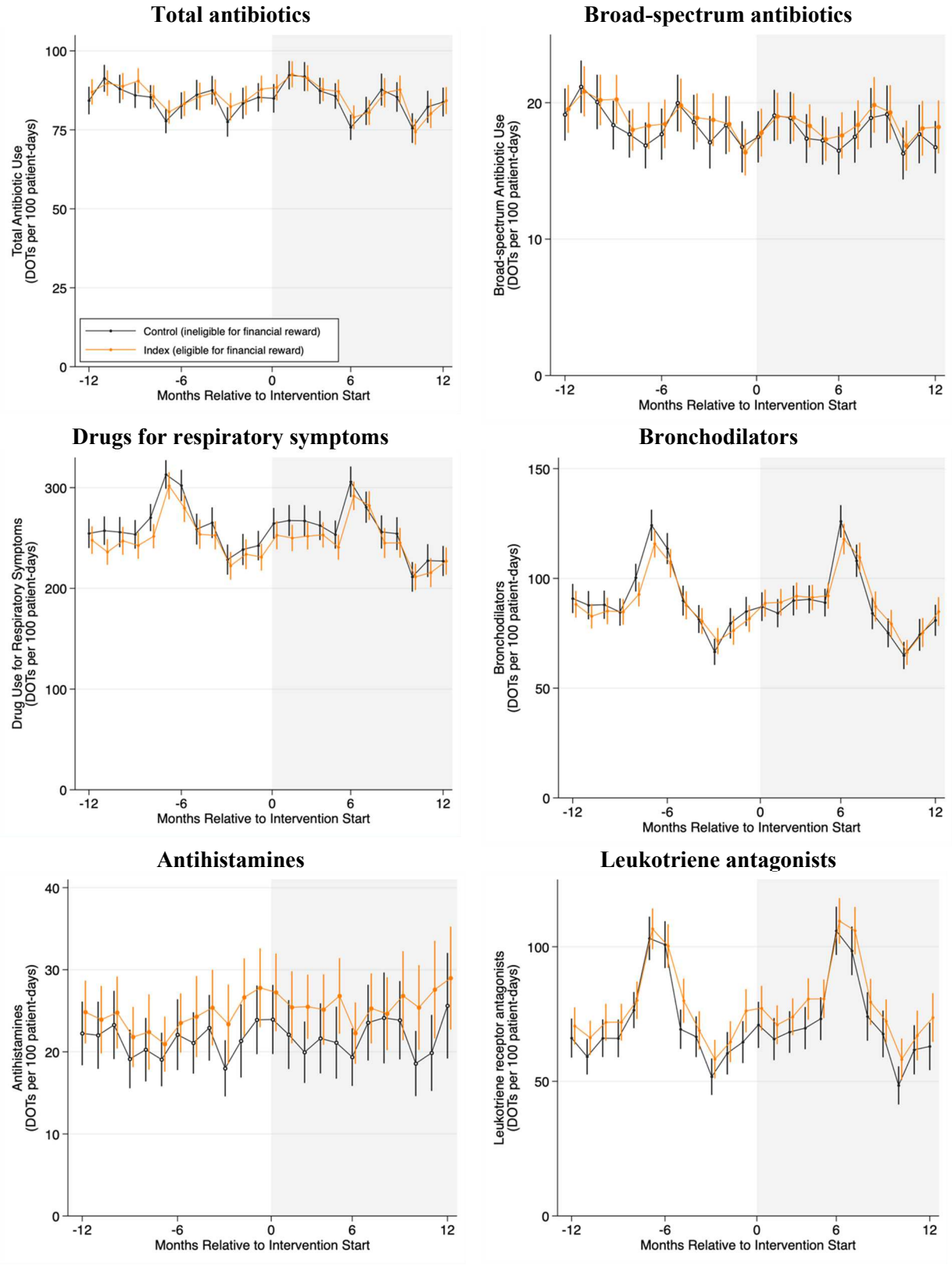


After propensity score matching

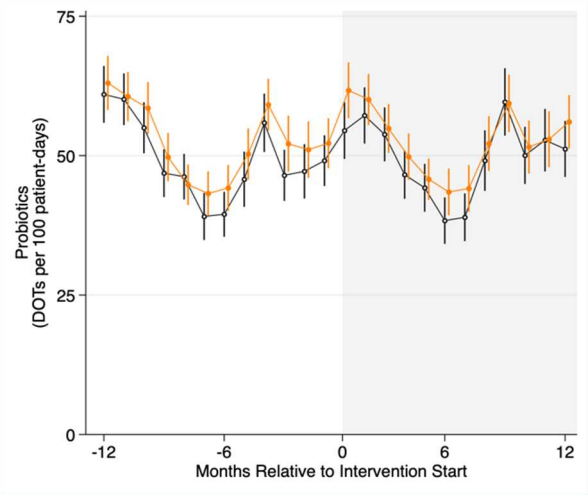


Note: Index, incentivized hospitals; Control, unincentivized hospitals

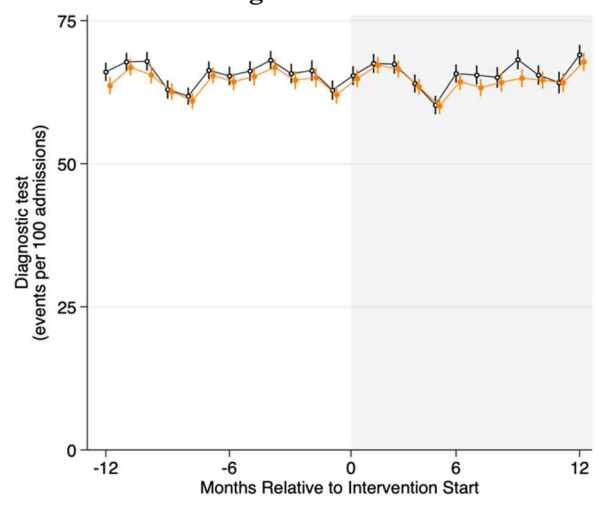
Figure 4-B. Trends in outcomes for the primary analyses



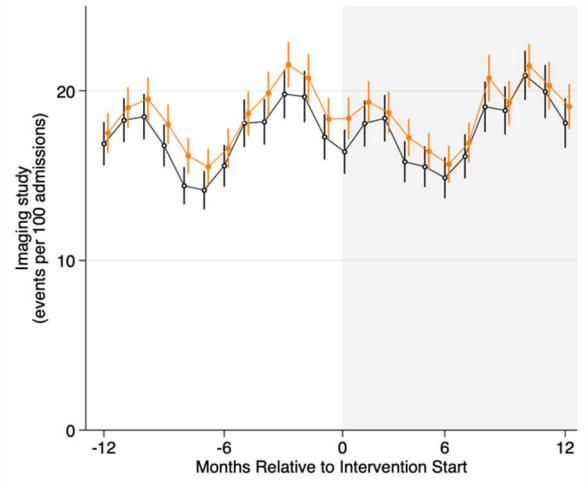
Probiotics



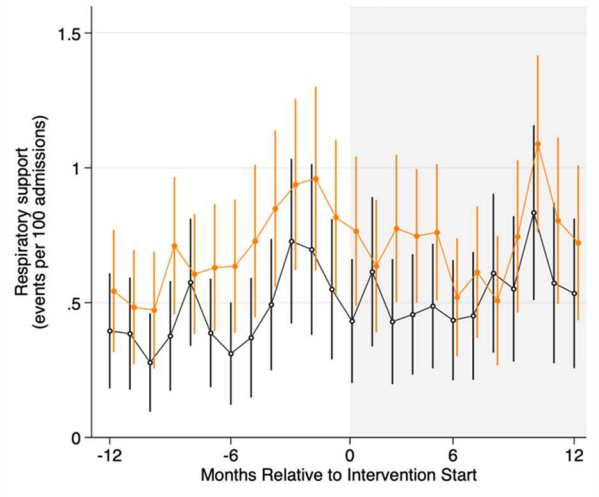
Diagnostic tests



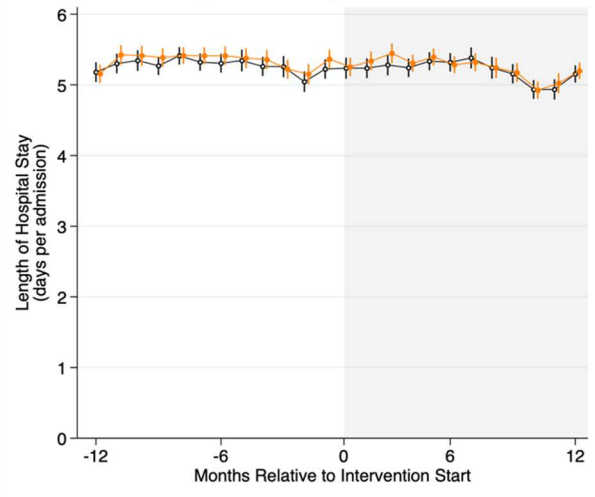
Imaging studies



Respiratory support



Lengths of hospital stay



Inpatient healthcare expenditures

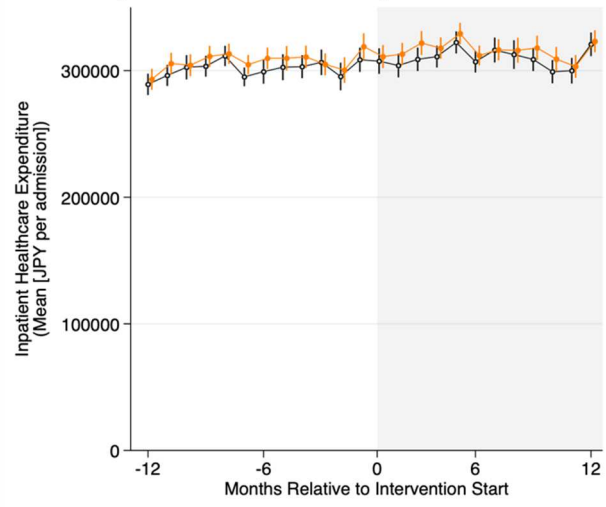
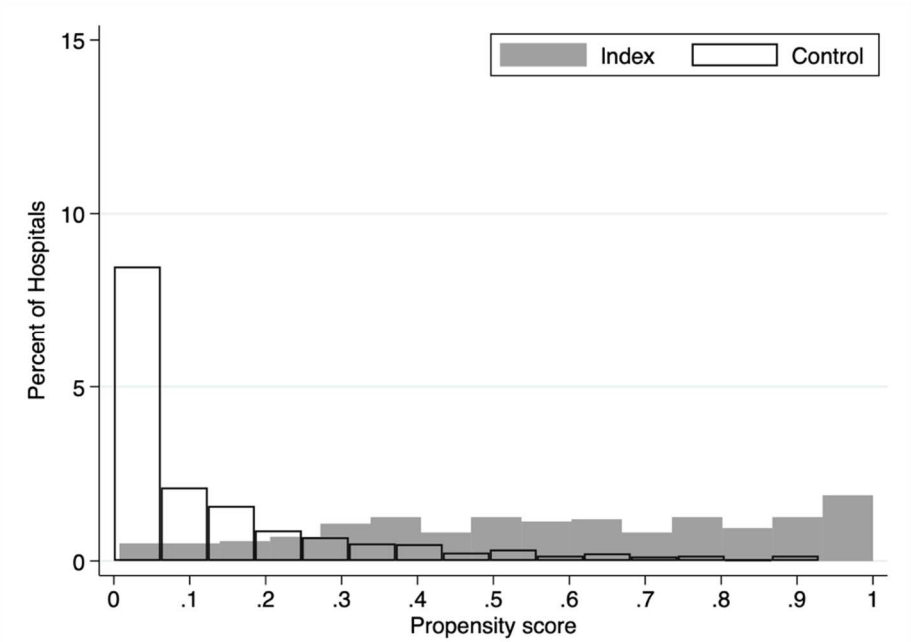
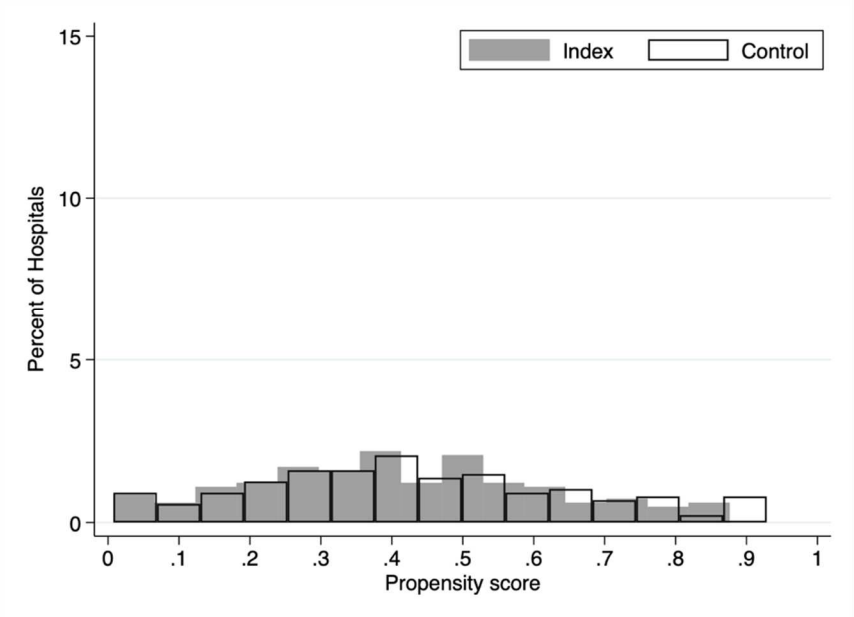


Figure 4-C. Distributions of propensity scores in the sensitivity analyses

Before propensity score matching

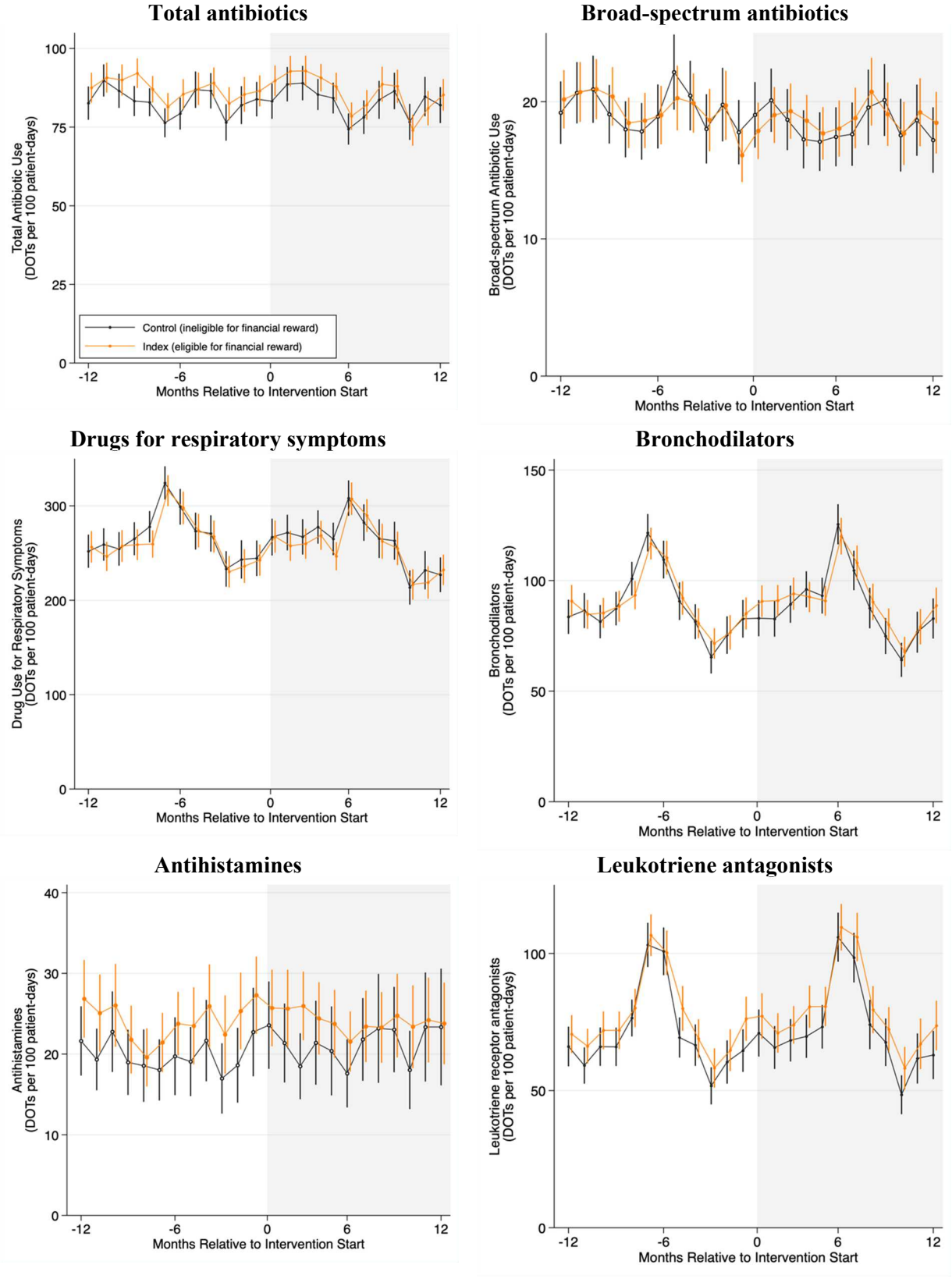


After propensity score matching



Note: Index, incentivized hospitals; Control, unincentivized hospitals

Figure 4-D. Trends in outcomes for the sensitivity analyses



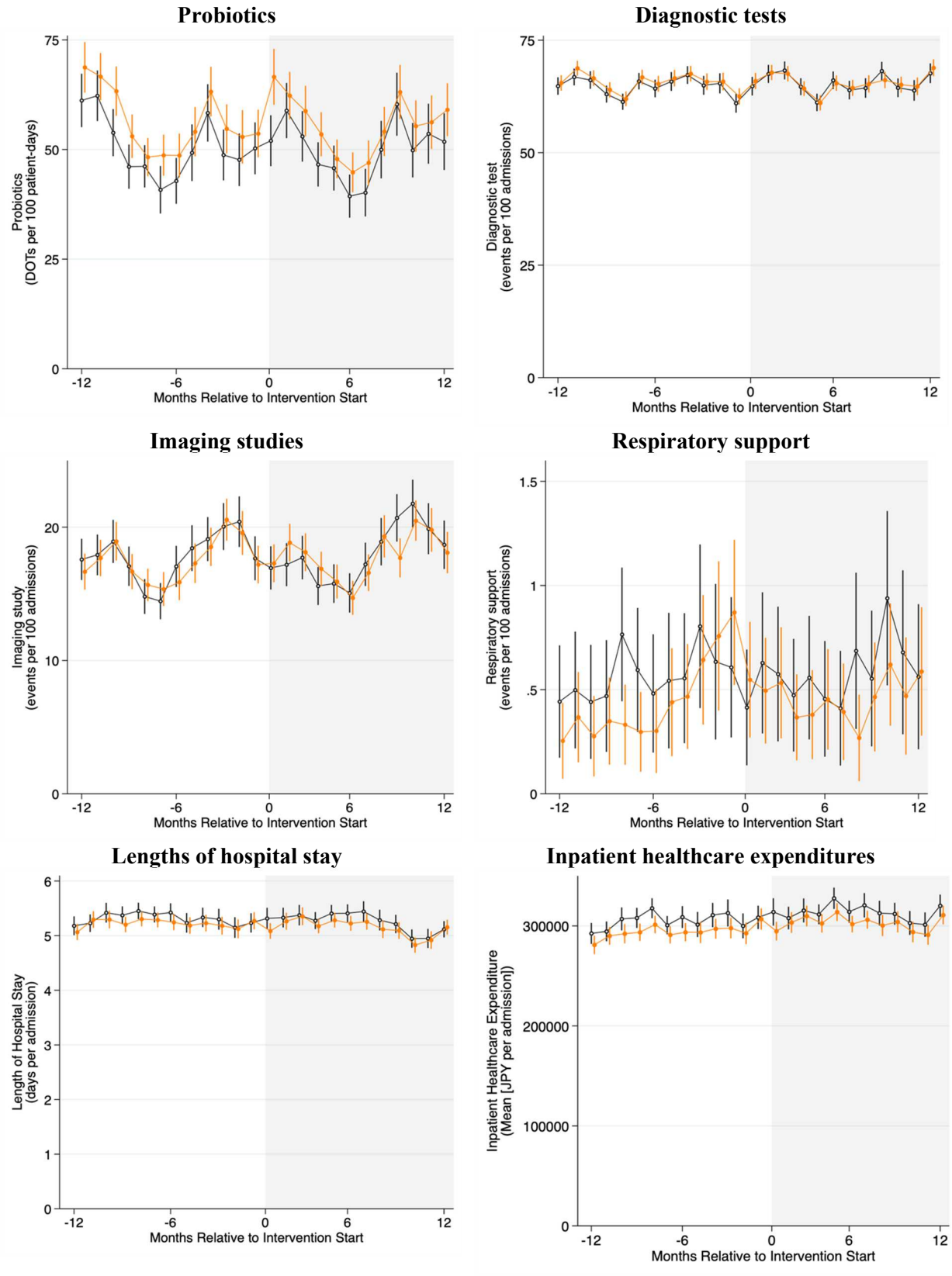
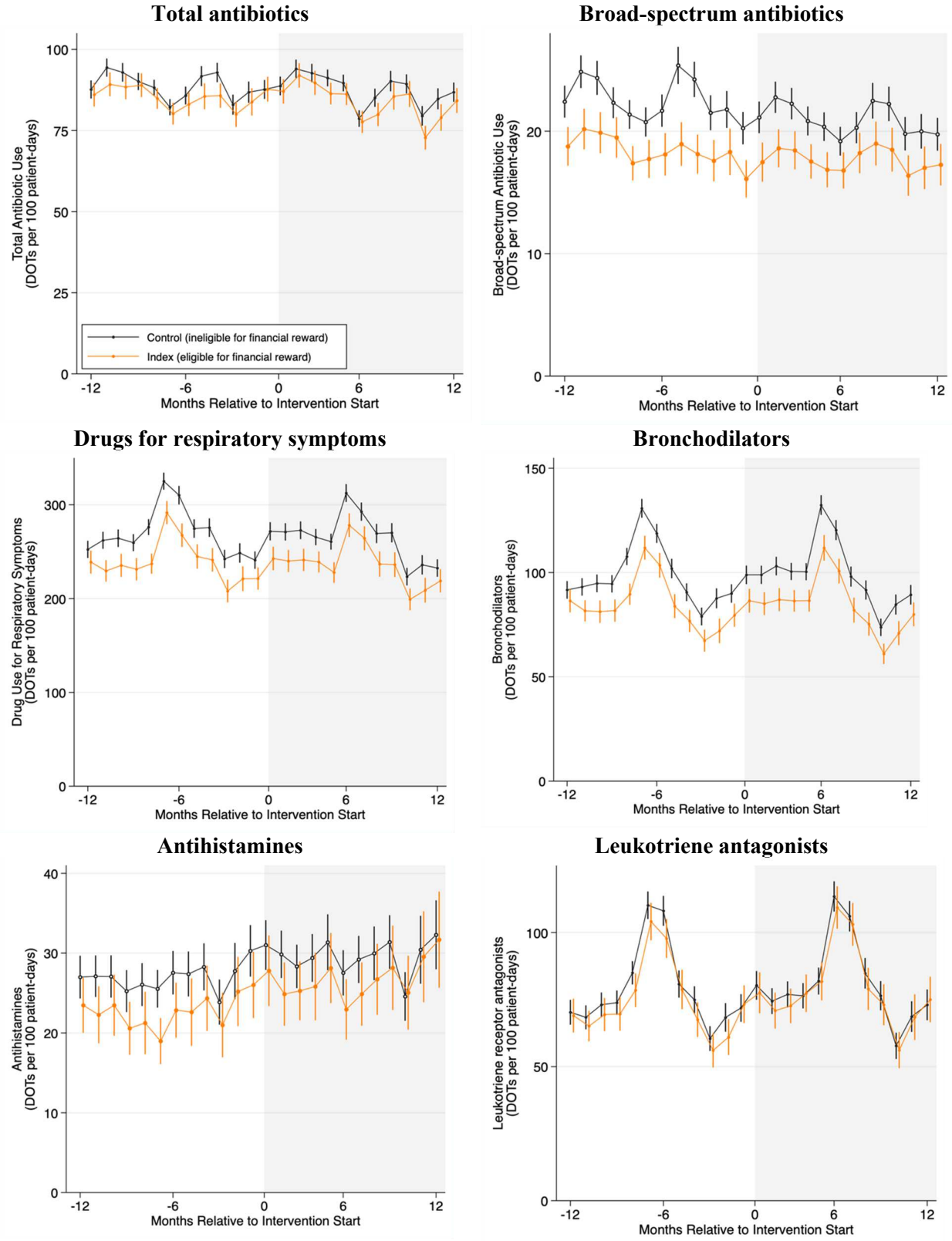
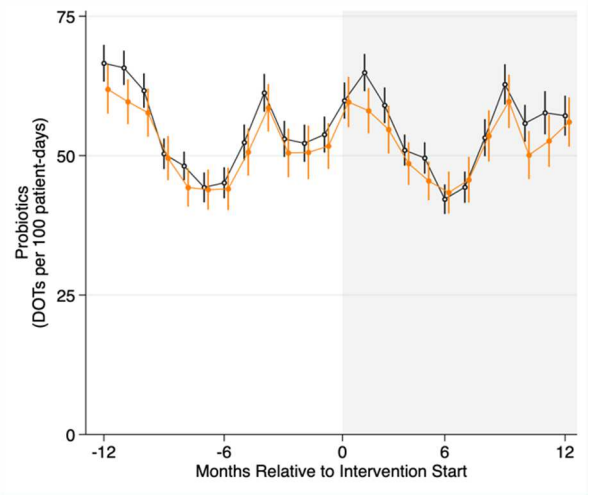

Probiotics
Probiotics (DOTs per 100 patient-days)
Months Relative to Intervention Start
Diagnostic tests
Diagnostic test (events per 100 admissions)
Months Relative to Intervention Start
Imaging studies
Imaging study (events per 100 admissions)
Months Relative to Intervention Start
Respiratory support
Respiratory support (events per 100 admissions)
Months Relative to Intervention Start
Lengths of hospital stay
Length of Hospital Stay (days per admission)
Months Relative to Intervention Start
Inpatient healthcare expenditures
Inpatient Healthcare Expenditure (Mean [JPY per admission])
Months Relative to Intervention Start

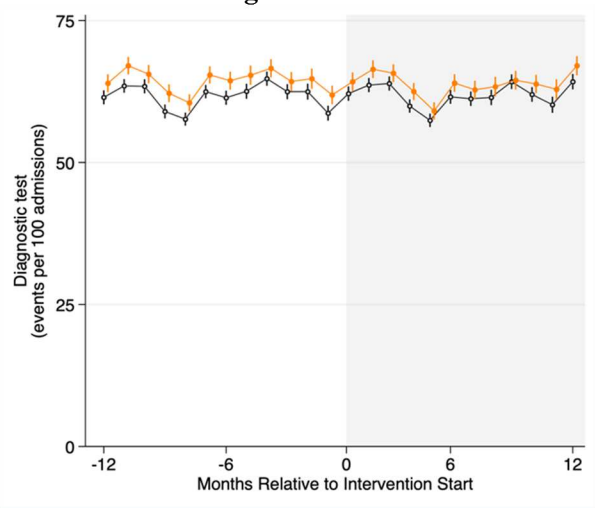
Figure 4-E. Trends in outcomes for crude analyses



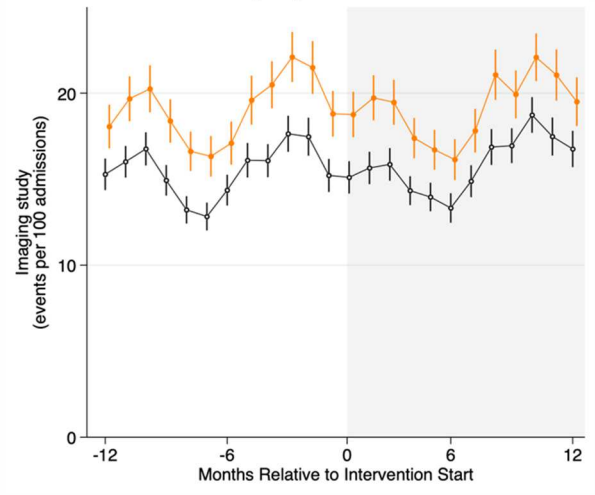
Probiotics



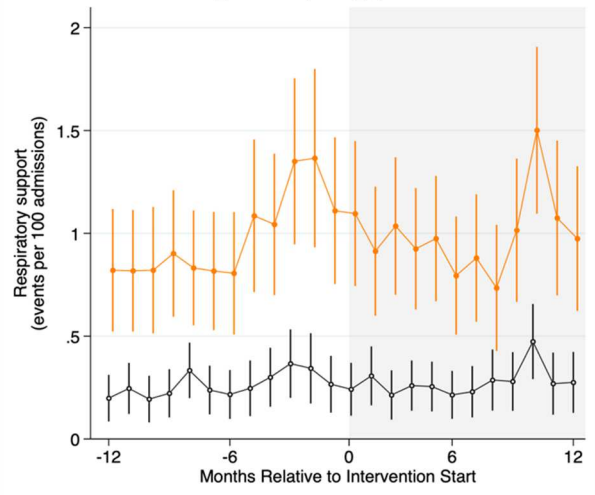
Diagnostic tests



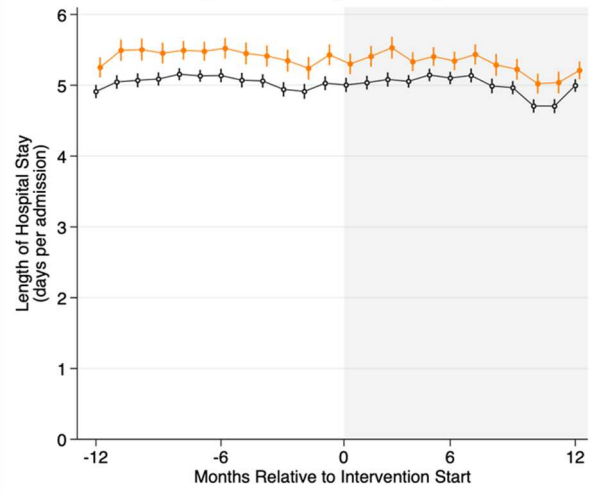
Imaging studies



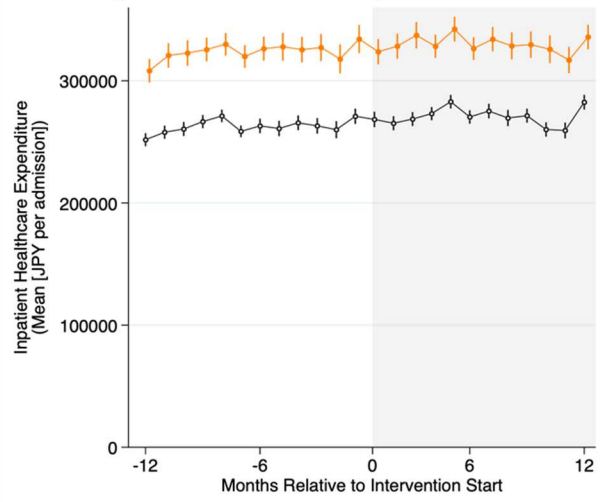
Respiratory support



Lengths of hospital stay



Inpatient healthcare expenditures



Chapter 5. Association between the Interruption of Free Medical Certificates for Children and Physicians' Practice Patterns (Paper #4)

5-1. Abstract

Background: Finding an economically optimal point in cost-sharing for healthcare is complicated because it involves a tradeoff between the reduction of financial uncertainty and the overutilization of healthcare resources. Although adequate coinsurance rates can optimize healthcare utilization without affecting adverse health consequences among those with non-poverty, most municipalities in Japan introduced the free medical care certificates (FMC) for children.

Methods: We conducted a quasi-experimental difference-in-differences (DID) design using national data of 1,642,113 children who visited medical facilities because of any infectious diseases in 2012 or 2013. We estimated the impacts of the interruption of FMC on antibiotic and non-antibiotic prescription patterns and health resource utilization.

Results: When the FMC was interrupted at ages of 7 or 13, we observed no changes in antibiotic prescriptions and modest reductions in non-antibiotic prescriptions, such as drugs for respiratory symptoms (DID estimate, −76.8 DOTs per 1000 cases; 95%CI, −139.6 to −14.0) and antihistamines (DID estimate, −195.0 DOTs per 1000 cases; 95%CI, −266.1 to −123.8). The interruption of the FMC was also associated with slight reductions in hospitalization rates (DID estimate, −0.39 events per 1000 cases; 95%CI, −0.67 to −0.01) and total outpatient healthcare costs (DID estimate, −165.9 JPY per case; 95%CI, −314.2 to −17.5). Similar results were

obtained from covariate-adjusted and crude models, stratified analyses by patient ages and years of the cohort, and the findings of synthetic control methods.

Conclusions: Our findings suggest that interruption of FMC substantially reduced non-antibiotic prescriptions and healthcare costs without elevating hospitalization rates.

5-2. **Background**

Payment systems in healthcare insurance, such as deductibles, coinsurances, and copayments, can change demand for health resource utilization, physicians' practice patterns, and total healthcare expenditure. Whereas low health insurance coverage induces poor access to healthcare, under-treatment, and subsequently elevated risks of morbidity and mortality, high health insurance coverage leads to over access to healthcare, increased demands for medical care, and elevated healthcare expenditure.[1–4] Finding an economically optimal point in health insurance coverage is complicated because it involves a tradeoff between the risk reduction of financial uncertainty and the overutilization of healthcare through moral hazards under different settings of usual healthcare.[1]

Previous studies have been conducted to examine the associations between health insurance coverage and health services provided.[2–8] The most famous experiment was the RAND experiment in the 1970s, which showed that modest cost-sharing decreased healthcare utilization with little effect on the average persons' health, but it had adverse health consequences for the poor and sick.[2–4] Similar findings were reported in pediatric healthcare, showing that public health insurance coverage, especially for previously uninsured children in low-income families, improved healthcare access and increased essential pediatric primary and preventive care.[5–8] Based on this accumulated evidence, public health insurance coverage for individuals with low-income

levels could provide necessary healthcare, while an adequate coinsurance rate could decrease unnecessary healthcare utilization without affecting health consequences among those with non-poverty.

Nonetheless, in Japan, the Free Medical Care Certificate for Children (FMC) was widely introduced in the 2000s. The FMC was expected to improve child health, offer financial support for the child-rearing generation, and counteract declining birth rates.[9,10] Under the FMC, parents of children aged 0–15 years pay 0% of the total healthcare costs for prescriptions and healthcare services, whereas the age and income limits of FMC were different across 1718 municipalities of 47 prefectures.[10,11] However, evidence regarding the effectiveness of FMC in pediatric healthcare has been scarce. A previous study in 2013 suggested that reduced cost-sharing through the FMC did not improve health statuses, such as subjective health and hospitalization rates.[12] Other studies, using data from the Tokyo metropolitan area, revealed that the increase in cost-sharing reduced outpatient service utilization, and a free prescription policy (covering 100% of out-of-pocket payments at pharmacies) increased prescription drug expenditure in low-volume users.[13,14] These findings suggest the need for extending the existing knowledge to more detailed practice patterns and healthcare utilization at a national level.

Therefore, this study investigated the impact of FMC on physicians' prescription behaviors and healthcare utilization outcomes among children aged < 15 years with infectious diseases. Furthermore, we simulated the interruption of FMC by targeting children living in Tokyo using Synthetic Controlled Methods. We hypothesized that the interruption of FMC could reduce antibiotic and non-antibiotic prescription patterns, health resource utilization (e.g., out-of-hour visits), and outpatient healthcare expenditures.

5-3. **Methods**

Study design, data source, data acquisition

We conducted a quasi-experimental propensity-score (PS) matched difference-in-differences (DID) design with a cohort of pediatric medical facilities (clinics/hospitals) using the National Database of Health Insurance Claims and Specific Health Checkups (NDB). In Japan, the national health insurance system provides universal coverage for all,[15] and their claims data are anonymized and stored in the NDB.[16] The NDB currently covers up to 95%–99% of claims data of healthcare services provided by the Ministry of Health, Labour and Welfare.

The present study's approval was obtained from the Institutional Review Boards at the National Center for Child Health and Development in Japan and at the University of California, Los Angeles. The Ministry of Health, Labour and Welfare approved our request and extracted the administrative claims records of pediatric infectious diseases from the NDB. We received approximately 1 billion administrative data elements of the records per year.[16] We were permitted to access the necessary variables: patients' age, sex, primary diagnosis, comorbidity, procedures, prescriptions, out-of-hour visits, hospitalization, and outpatient healthcare expenditure, as well as the secondary medical area of medical facilities.

Data construction

Using the NDB from April 2012 to March 2016, we constructed 3-year cohorts of children and medical facilities. The 3-year cohorts were separated into three phases (**Table 5–A**): (1) look-back period (1st year), (2) pre-intervention period (2nd year), and (3) post-intervention period (3rd year). We included all children aged 5 or 11 years who visited medical facilities during the 1st year (look-back period). The outpatient claims with the clinical diagnoses of infectious diseases were identified using the International Classification of Diseases, Tenth Revision code (ICD-10 code)

as noted in the database's diagnosis field. The diagnoses of infectious diseases were determined based on the Clinical Classification Software codes[17] (**Tables 2–C, 3–B**). Unique identification numbers for the NDB allowed us to identify and link the outpatient claims of the same individuals from the same medical facilities over the three years.

We excluded patients with complex medical conditions and medical facilities with < 10 pediatric outpatients per month. Complex medical conditions (e.g., congenital diseases, cancer or leukemia, and autoimmune disease) were defined according to the pediatric complex chronic conditions classification system version 2.[18] We also excluded children who died over the study period. The claims records submitted from medical facilities with < 10 pediatric outpatients per month were also excluded.

Exposure of interest (a quasi-experiment)

The exposure of interest was the interruption of FMC and subsequent changes in coinsurance rates from 0% to 30% in the post-intervention period (3rd year). In Japan, the coinsurance rates under the national insurance range from 20%–30% of the total healthcare costs, which are different across municipalities, patient age, the presence of chronic disease, and socioeconomic status. The coinsurance rates of some children ≤ 15 years of age are 0% under the FMC (no out-of-pocket payments for office visits, procedures, and prescriptions) provided by municipalities. The age limits for the FMC are different across 1718 municipalities in 47 prefectures with considerations for parental income levels. When children reached the age limit (in our study, 7 or 13 years old depending on the living area), children's coinsurance rates changed from 0% to 30%.[10,19]

To categorize the areas as the index and control groups, we utilized 344 secondary medical areas, which were established as an area unit appropriate for providing medical care for

general hospitalization considering the social aspects (e.g., geographic conditions, fulfillment of demand in daily life, and traffic situation). Secondary medical areas with > 80% of children whose FMCs were interrupted at the beginning of the post-intervention period (3rd year) were considered the index group. The secondary medical areas with almost 100% of children who received FMC over the 3 years were considered the control group. The remaining areas were excluded from the analyses (**Figure 5–A**).

Outcome measures

The primary outcomes of interest were antibiotic and non-antibiotic prescriptions as the days of therapy (DOTs) per 1000 cases. We considered third-generation cephalosporin, oral penem, fosfomycin, tetracycline, and quinolone as broad-spectrum antibiotics in accordance with previous studies (**Table 2–C and 3–B**).[19–22] Non-antibiotic prescriptions included drugs for respiratory symptoms (e.g., antitussives, etc.), antihistamines, bronchodilators, leukotriene receptor antagonists, and probiotics. In Japan, antibiotics are available only with physicians' prescriptions and are dispensed by pharmacies.[23]

The secondary outcomes consisted of 1) out-of-hours visits to physicians' offices due to infectious diseases, and 2) rapid diagnostic tests for infectious diseases (e.g., group A streptococcus, adenovirus, norovirus, influenza virus), 3) infectious disease-related hospitalizations, and 4) total healthcare expenditure for outpatient visits as events per 1000 cases.

Adjustment covariates

The baseline characteristics included patient age, sex, diagnoses of asthma/wheezing, rhinitis, skin diseases (e.g., atopic dermatitis/eczema), and seizure. These diagnoses were estimated using ICD-10 codes (**Table 3–A**) in the 1st year (look-back period). We also obtained the number of out-of-hour visits, prescriptions, and hospitalizations over the 1st and 2nd year to

account for access to healthcare and health conditions and used them as covariates for the exposure and outcomes for the DID analyses. Individual data were also accumulated at each clinic and converted into average and percentage at the medical facility level and were used for the PS matching.

Statistical Analysis

Baseline characteristics were summarized for continuous and categorical variables as means and proportions by the exposure of interests. To investigate the effects of FMC on physicians' prescription behavior and health resource utilization, we used propensity-score (PS) matched difference-in-differences (DID) analyses.

We conducted PS matching because the characteristics of medical facilities and the trends in outcomes of interest during pre-intervention periods were expected to differ between the index and control groups. PSs were calculated based on the probability of treatment assignment (interruption of FMC in secondary medical areas) conditional on observed baseline covariates and outcomes of interest in the 1st and 2nd years at facility levels.[24] We calculated PSs using multivariable logistic regression models (**Table 5–B**) and conducted one-to-one matching between medical facilities in the index and control groups using the nearest-neighbor methods within a caliper distance of < 20% of standard deviation (SD) for PS.[24] We checked the balance between the index and control groups based on absolute standardized differences. An absolute standardized difference of > 10% was considered a meaningful imbalance.[24]

After we matched the same number of facilities in the index and control groups, we investigated the PS-matched DID estimates for the outcomes of interest.[25–28] DID analyses construct time series of the outcome (e.g., total antibiotic prescriptions) and statistically test for changes in the outcomes in the periods before and after implementing an intervention (e.g.,

interruption of FMC).[29] We divided medical facilities in our cohort into two groups based on the secondary medical area for interruption vs. continuation of FMC (Table 5–B). Specifically, we fitted the following statistical model[25–28]:

$$E(Y_{i,s,t}) = \beta_0 + \beta_1 X_s + \beta_2 T_t + \beta_3 X_s T_t$$

where E denotes the expected value, $Y_{i,s,t}$ is the outcome of interest for a person (i), the timing of visits (t), and a secondary medical area of a facility (s), βs are coefficients, X is a treatment variable for interruption vs. continuation of FMC (index or control), and T is a time indicator variable (pre-intervention vs. post-intervention). The estimates of interest were a coefficient of an interaction term (β_3) of a time indicator variable (T) and a treatment variable (X). To incorporate the hierarchical data structure, we used generalized estimation equations under a normal distribution and identity link function[25–28] and their 95% confidence intervals (95%CIs).[30]

Sensitivity Analysis

We conducted a series of sensitivity analyses. First, we performed PS matched DID analyses using data from the 1st year (look-back period). Second, we constructed covariate-adjusted models. In the models, we added the covariates listed above to the crude DID models to adjust for time-fixed potential confounders (**Table 5–B**). Third, we constructed crude DID models and investigated the unadjusted DID estimates. Fourth, we performed all of the analyses listed above using gamma distribution with log link function to investigate the DID estimates in relative scales (Changes-in-Changes estimates).[31] Fifth, we stratified the data by four cohorts (**Table 5–A**) and estimated cohort-specific DID estimates for total antibiotics, drugs for respiratory symptoms, antihistamines, and total outpatient healthcare expenditure to check the heterogeneity of our results.

Finally, we used the synthetic control method (SCM) to simulate the impact of interrupting FMC on the outcome of interests among children living in Tokyo. SCM was pioneered by Abadie et al., and it could relax the parallel trends assumptions required in the DID analyses.[32] The central idea behind the SCM is to compare the observed outcome (in Tokyo) with the counterfactual outcome for the exposed unit in the absence of the exposure, using the weighted average of the unexposed units (no FMC area) that closely matches the exposed unit (Tokyo) over the pre-intervention period.[32] We targeted children in Tokyo as a population of interest because Tokyo had approximately 10% of the total children in the cohort, and it provides FMC for all children aged < 15 years. We utilized data in the secondary medical area in the index group to estimate the counterfactual outcome if Tokyo had interrupted FMC as "synthetic-Tokyo." To account for the baseline difference between Tokyo and the unexposed units, we used data on the outcome and covariates listed above and statistics of secondary medical area (the number of pediatricians per 1000 children, mortality rate of children, proportions of people aged > 65 years, higher educational levels (university graduates or above), proportions of workers in the tertiary industry, and unemployment rates).[33,34] All data were analyzed using Stata/MP software version 16.1 (StataCorp LP, College Station, TX, USA).

5-4. **Results**

We identified a total of 1,630,609 children and 172,093 medical facilities for our study. Overall, less than 10% of secondary medical areas interrupted FMC in the post-intervention period (**Table 5–C**). PS matching successfully balanced the covariates, such as areas of facilities, age group, and comorbidity of sinusitis (absolute standardized differences < 10%; **Figure 5–B** and

Table 5–D). Also, **Figures 5–C** showed similar trends in the primary and secondary outcomes during the pre-intervention periods.

Prescription patterns for total antibiotics, drugs for respiratory symptoms, and antihistamines

PS matched DID analyses (**Table 5–E**) found that the interruption of FMC in the 3rd year was not associated with changes in total antibiotic prescriptions (-10.3 DOTs per 1000 cases; 95%CI, -40.3 to 19.5), broad-spectrum antibiotics (7.4 DOTs per 1000 cases; 95%CI, -11.5 to 26.4), and probiotics (18.9 DOTs per 1000 cases; 95%CI, -1.9 to 39.8). In contrast, the interruption of FMC was associated with the decreases in prescriptions of drugs for respiratory symptoms (-76.8 DOTs per 1000 cases; 95%CI, -139.6 to -14.0) and antihistamines (-195.0 DOTs per 1000 cases; 95%CI, -266.1 to -123.8).

Healthcare utilization and outpatient healthcare expenditure

The interruption of FMC was not associated with changes in diagnostic tests for infectious diseases (3.7 events per 1000 cases; 95%CI, -0.2 to 7.5) and out-of-hours visits (-4.5 events per 1000 cases; 95%CI, -9.8 to 0.7). The interruption of FMC was associated with a very slight reduction in hospitalization rate (-0.39 events per 1000 cases; 95%CI, -0.67 to -0.01) and a modest reduction in outpatient healthcare expenditure (-165.9 JPY per case; 95%CI, -314.2 to -17.5).

Sensitivity Analysis

First, we conducted PS matching using data on covariates and outcomes of interests during the 1st year (**Figure 5–D**). After PS matching, the baseline characteristics and outcome of interests in the 1st years were well balanced between the two groups (**Table 5–F**). The trends in outcomes of interest during the 1st year were similar between the index and control groups (**Figure 5–E**). The directions and magnitudes of associations between the interruption of FMC and outcomes of

interest were mostly identical to the results in the PS matching during the 1st and 2nd years (**Table 5–G**).

Second, we estimated covariate-adjusted DID estimates (**Table 5–H**). Compared with the PS matched models, the directions of associations between the interruption of FMC and changes in prescription patterns were further from the null, except for broad-spectrum antibiotics. Third, we performed crude analyses (**Figure 5–F**). The crude DID estimates were mostly identical to the covariate-adjusted DID estimates (**Table 5–H**).

Fourth, we performed the same analyses to investigate the DID estimates in relative scales (**Table 5–I**). The largest relative reductions because of the interruption of FMC were prescriptions in antihistamines and leukotriene receptor antagonists. The relative reduction in total and broad-spectrum antibiotic prescriptions was null or very slight, depending on the statistical models.

Fifth, we stratified the data by years and ages of four cohorts and investigated the cohort-specific DID estimates for total antibiotics, drugs for respiratory symptoms, antihistamines, and total outpatient healthcare expenditure (**Table 5–J**).

Finally, we conducted the SCM to simulate the impacts of FMC on the outcome of interests among children living in Tokyo. A total of 20 secondary medical areas were selected as control units among cohorts with children aged 5–7 years, while 36 areas were chosen as control units among those aged 11–13 years (**Figure 5–G**; **Tables 5–K, L**). The outcomes, patient-level covariates, and secondary medical areas' characteristics were well-balanced between Tokyo and Synthetic Tokyo (**Tables 5–M, N**). Compared with the observed outcomes in Tokyo, the data on Synthetic Tokyo showed a slight reduction in antibiotic use among children aged 5–7 years, a decrease in drugs for respiratory symptoms among children aged 11–13 years, decreased

antihistamine prescriptions among both age groups, no changes in out-of-hour visits and admission rates, and decreased outpatient healthcare expenditure for both age groups (**Figure 5–H**).

5-5. **Discussion**

In this nationwide study with approximately 1.6 million children, we found that the interruption of FMC was associated with substantial decreases in prescriptions for respiratory symptoms and antihistamines, and reduced outpatient healthcare costs without adversely affecting hospitalization rates. These results were mostly consistent across different statistical models used to reduce potential biases and model misspecifications. Our findings reflect the routine care setting for children with common infectious diseases and support the impacts of FMC on over-prescriptions of several medications for infectious diseases and subsequently increased healthcare costs.

The overuse of antibiotics is an unresolved challenge in global and regional health. A recent global study showed that Japan was the worst among 36 high-income countries regarding appropriate antibiotic use among pediatric outpatients.[35] These findings were consistent with our previous studies at national levels, showing overuse of antibiotics for common pediatric infectious diseases.[19–22,36–41] Although we assumed that the interruption of FMC and free prescription policy could have reduced antibiotic prescriptions, almost no reductions of antibiotic prescriptions were observed after the interruption of FMC. The findings could reflect physicians' decisions of prescribing antibiotics based on clinical information rather than the patients' financial burden as out-of-pocket for drug costs.

Based on findings from systematic review and meta-analyses, the evidence regarding the effectiveness of cold medicine (e.g., antitussives, expectorants, antihistamines) for children is

extremely limited.[42–45] Additionally, adverse effects had been widely reported for cold medicine, such as antitussives and antihistamines.[46,47] We observed the association between the interruption of FMC and decreased prescription rates for drugs for respiratory symptoms and antihistamines. The free prescription policy of FMC may have induced the parental demands for cold medicine and changed physicians' prescription behavior.

The overutilization of healthcare has been a public health problem in Japan. Indeed, the utilization of healthcare (e.g., physician visits) was approximately two times higher than that of the averages of the countries in the Organization for Economic Cooperation and Development.[48,49] Moreover, children in Japan had 2.5 times higher clinic visits and 11 times higher hospital visits than children in the US.[50] The main drivers for overutilization in pediatric healthcare are elevated parental anxiety over raising children, the low unit price of healthcare through governmental control, and improved access to healthcare by FMC.[51] A previous study conducted in Tokyo found that imposing a small copayment could prevent unnecessary visits to medical facilities for mild upper respiratory symptoms without affecting visits for severe symptoms.[51] Similarly, our findings indicate that the interruption of FMC could contribute to slightly decreased out-of-hour visits to pediatricians without adversely affecting hospitalization rates. These findings suggest the further need for seeking an optimal point of copayment rate to mitigate over-access to healthcare without worsening health status in children.

Besides its unique strengths, this study had several limitations. Although we conducted a series of sensitivity analyses to adjust for potential confounders and model misspecification, these biases could be inherent in our study. For example, the diagnoses of preexisting comorbidities may have been underestimated or overestimated because of possible underreporting or potential misclassification of ICD-10 codes, resulting in biases in either direction. A detailed clinical

presentation, laboratory data, and patient information (e.g., socioeconomic status) were unavailable in the NDB, which may have resulted in residual confounding and confounding by the indication. However, the DID analyses could account for time-fixed confounders when the parallel trend assumptions were valid. Moreover, most findings from crude, adjusted, and two different PS matched analyses reached the same results, suggesting the robustness of our results. Although the utilization of a national representative database was the strength of our study in terms of generalizability, the transportability of our findings to external populations may still be uncertain. Further studies are desirable to determine the optimal levels of cost-sharing for healthcare.

In summary, the interruption of FMC was associated with reductions in non-antibiotic prescriptions and outpatient healthcare expenditures without adversely affecting hospitalization rates. Our results suggest the need to seek an optimal point of cost-sharing for the health insurance system for children.

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5-7. **Tables and Figures**

Table 5-A. Overview of the 3-year cohort

Period	1st year Look-back	2nd year Pre-intervention	3rd year Post-intervention
Cohort 1, fiscal year	2012	2013	2014
(Age of children)	(5 or 11 years)	(6 or 12 years)	(7 or 13 years)
Cohort 2, fiscal year	2013	2014	2015
(Age of children)	(5 or 11 years)	(6 or 12 years)	(7 or 13 years)

Table 5-B. Statistical model for difference-in-difference analyses

Model	Equation
Crude	$E(Y_{i,s,t}) = \beta_0 + \beta_1 X_s + \beta_2 T_t + \beta_3 X_s T_t$
Adjusted	$E(Y_{i,s,t}) = \beta'_0 + \beta'_1 X_s + \beta'_2 T_t + \beta'_3 X_s T_t + \sum_k \gamma_k C_{i,s,t}$
PS calculation	$logit[P(X = 1\|C)] = \delta + \sum_k \delta_k C_{i,s,t}$

Abbreviations: PS, propensity-score

Notes: i = individual, s = secondary medical area of facility, t = timing of visit, X = Intervention (0 = continuation of free medical care certificate (FMC), 1 = interruption of FMC), T = timing (0 = pre-intervention period, 1 = post-intervention period), k = numbers of covariates, C = a set of covariates, PS = Propensity score. For PS calculation, we utilized hospital-level variables for secondary medical area of hospitals, patient characteristics, primary and secondary outcomes, and prescriptions of bronchodilators, xanthine, leukotriene receptor antagonist, antipyretics, probiotics, and antidiarrheals.

Table 5-C. Individuals and secondary medical areas for each cohort

		Index group		Control group	
1st year	Age group	Area, N	Individuals, N	Area, N	Individuals, N
2012	5 years old	21	20,161	293	499,374
2013	5 years old	17	19,735	308	590,319
2012	11 years old	33	18,757	225	200,917
2013	11 years old	24	19,508	254	261,838

Table 5-D. Baseline characteristics for the primary analyses

	Before PS matching			After PS matching		
Medical facilities in cohorts, N	**Control N = 161,414**	**Index N =10,679**	**StdDiff (%)**	**Control N = 7103**	**Index N = 7103**	**StdDiff (%)**
Area of facilities, N (%)			15.8			1.6
Hokkaido	3260 (2.2)	875 (8.2)		452 (6.4)	732 (10.3)	
Tohoku	10624 (6.6)	761 (7.1)		810 (11.4)	710 (10.0)	
Kanto	61,862 (38.3)	571 (5.3)		543 (7.6)	551 (7.8)	
Hokuriku/Koshinetsu	10,360 (6.4)	603 (5.6)		448 (6.3)	522 (7.3)	
Tokai	23,677 (14.7)	11 (0.1)		8 (0.1)	9 (0.1)	
Kansai	27,519 (17.0)	1522 (14.3)		748 (10.5)	771 (10.9)	
Chugoku	5686 (3.5)	3116 (29.2)		1800 (25.3)	1698 (23.9)	
Shikoku	5072 (3.1)	74 (0.7)		49 (0.7)	71 (1.0)	
Kyushu/Okinawa	12,994 (8.1)	3146 (29.5)		2245 (31.6)	2039 (28.7)	
Outpatients, N	1,552,448	78,161		53,364	58,057	
Patient characteristics, N (%)						
Age and Cohort			14.6			1.7
5 years old in 2012–2014	499,374 (32.2)	20,161 (25.8)		10,248 (19.2)	13,490 (23.2)	
5 years old in 2013–2015	590,319 (38.0)	19,735 (25.3)		11,249 (21.1)	14,835 (25.6)	
11 years old in 2012–2014	200,917 (12.9)	18,757 (24.0)		14,495 (27.2)	13,778 (23.7)	
11 years old in 2013–2015	261,838 (16.9)	19,508 (25.0)		17,372 (32.6)	15,954 (27.5)	
Male	825,122 (53.2)	42,107 (53.8)	1.4	28,747 (53.9)	31,105 (53.6)	0.6
Asthma/Wheezing	607,505 (39.1)	31,232 (40.0)	1.5	20,531 (38.5)	22,750 (39.2)	1.5
Atopic dermatitis/Eczema	714,038 (46.0)	34,368 (44.0)	4.2	21,591 (40.5)	25,295 (43.6)	6.3
Food allergy	24,218 (1.6)	1,033 (1.3)	2.1	796 (1.5)	708 (1.2)	2.3
Rhinitis	893,069 (57.5)	43,079 (55.1)	4.8	30,896 (57.9)	32,503 (56.0)	3.8
Sinusitis	770,530 (49.6)	34,744 (44.5)	10.4	24,432 (45.8)	25,870 (44.6)	2.4
Seizure	30,753 (2.0)	1,322 (1.7)	2.3	831 (1.6)	975 (1.7)	0.9
1st year (look-back period)						
Medication use, DOTs per 1000 cases (SE)						
Total antibiotic use	2252.8 (1.0)	2534.4 (5.4)	-7.3	2517.4 (6.6)	2446.6 (6.2)	1.8
Broad-spectrum antibiotic use	1060.3 (0.6)	1210.0 (3.3)	-6.4	1215.7 (4.0)	1150.1 (3.7)	2.7
Drugs for respiratory symptoms	5982.8 (2.5)	5414.6 (11.8)	6.5	5488.2 (14.4)	5499.5 (13.6)	-0.1
Bronchodilators	910.0 (0.8)	799.9 (3.7)	3.9	783.7 (4.4)	765.8 (4.0)	0.7
Antihistamines	3856.1 (2.2)	3843.3 (11.3)	0.2	3992.1 (14.4)	3862.9 (13.1)	1.3
Leukotriene receptor antagonists	2211.1 (2.0)	2355.2 (10.1)	-1.9	2495.1 (13.4)	2305.7 (11.7)	2.5
Probiotics	1203.0 (0.8)	1143.1 (3.7)	2.2	1124.4 (4.5)	1123.0 (4.1)	0.5
Healthcare costs, mean JPY (SE)	11,274 (4.2)	10,984 (22.2)	1.8	11,221 (26.5)	10,966 (27.2)	1.5
Healthcare utilization, events per 1000 cases (SE)						
Out-of-hour visits	233.7 (0.2)	214.1 (0.9)	2.9	228.1 (1.2)	221.3 (1.0)	0.9
Rapid diagnostic tests	144.5 (0.1)	154.3 (0.6)	-2.3	155.3 (0.7)	160.7 (0.7)	-1.2
Hospitalization	2.03 (0.013)	1.35 (0.051)	1.7	1.83 (0.07)	1.31 (0.05)	1.3
2nd year (pre-intervention period)						
Medication use, DOTs per 1000 cases (SE)						
Total antibiotic use	2197.3 (1.1)	2497.5 (5.9)	-7.9	2495.0 (7.1)	2425.7 (6.7)	0.09
Broad-spectrum antibiotic use	1046.4 (0.7)	1203.4 (3.6)	-6.7	1204.7 (4.3)	1153.1 (4.0)	-2.5
Drugs for respiratory symptoms	5626.6 (2.6)	5209.2 (12.5)	4.9	5295.7 (15.0)	5298.8 (14.5)	-0.4
Bronchodilators	756.9 (0.8)	677.2 (3.7)	3.1	668.6 (4.5)	646.2 (4.1)	-3.4
Antihistamines	4007.8 (2.6)	3962.1 (13.0)	0.5	4191.5 (16.5)	3975.1 (15.1)	1.6
Leukotriene receptor antagonists	2292.8 (2.3)	2406.0 (11.4)	-1.5	2519.4 (14.7)	2366.2 (13.2)	-0.7
Probiotics	1126.9 (0.8)	1090.4 (4.0)	1.3	1062.1 (5.0)	1078.0 (4.5)	-2.0
Healthcare costs, mean JPY (SE)	10,647 (4.4)	10,530 (21.5)	0.8	10,798 (37.4)	10,551 (40.0)	0.9
Healthcare utilization, events per 1000 cases (SE)						
Out-of-hour visits	219.3 (0.2)	214.9 (1.0)	0.6	225.7 (1.3)	222.5 (1.1)	-2.9
Rapid diagnostic tests	165.1 (0.1)	176.0 (0.7)	-2.4	178.4 (0.8)	184.4 (0.8)	-5.4
Hospitalization	1.49 (0.012)	1.58 (0.060)	-0.2	1.40 (0.06)	1.58 (0.07)	0.4

Abbreviations: PS, propensity-score; Std. Diff., a standardized difference (an absolute standardized difference > 10% is a meaningful imbalance between the index and control groups); DOTs, days of therapy; SD, standard deviation; JPY, Japanese Yen

Table 5-E. Difference-in-difference estimates in the primary analyses

	Control facilities (N = 7103)			Index facilities (N = 7103)			
	Pre	Post	Difference	Pre	Post	Difference	DID estimate (CI)
Medications, DOTs per 1000 visitors (SE)							
Total antibiotics	2495.0 (7.1)	2604.2 (8.0)	109.2	2425.7 (6.7)	2524.5 (7.7)	98.8	-10.3 (-40.3, 19.5)
Broad-spectrum antibiotics	1204.7 (4.3)	1277.9 (5.1)	73.2	1153.1 (4.0)	1233.8 (4.8)	80.7	7.4 (-11.5, 26.4)
Drugs for respiratory tract symptoms	5295.7 (15.0)	5109.3 (16.3)	-186.4	5298.8 (14.5)	5035.7 (15.8)	-263.1	-76.8 (-139.6, -14.0)
Bronchodilators	668.6 (4.5)	546.0 (4.5)	-122.6	646.2 (4.1)	513.0 (4.2)	-133.2	-10.5 (-28.7, 7.5)
Antihistamine	4191.5 (16.5)	4337.2 (19.6)	145.7	3975.1 (15.1)	3925.8 (17.5)	-49.3	-195.0 (-266.1, -123.8)
Leukotriene receptor antagonist	2519.4 (14.7)	2373.3 (16.0)	-146.1	2366.2 (13.2)	2168.3 (14.6)	-197.9	-51.8 (-113.1, 9.5)
Probiotics	1062.1 (5.0)	1005.4 (5.5)	-56.7	1078.0 (4.5)	1040.4 (5.1)	-37.6	18.9 (-1.9, 39.8)
Healthcare utilizations, event per 1000 visitors (SE)							
Diagnostic tests for infectious disease	178.4 (0.8)	209.5 (1.0)	31.1	184.4 (0.8)	219.2 (1.0)	34.8	3.7 (-0.2, 7.5)
Out-of-hour visit	225.7 (1.3)	226.2 (1.4)	0.5	222.5 (1.1)	218.4 (1.2)	-4.1	-4.5 (-9.8, 0.7)
Hospitalization	1.40 (0.06)	1.50 (0.01)	0.10	1.58 (0.07)	1.29 (0.07)	-0.29	-0.39 (-0.67, -0.01)
Healthcare cost, mean JPY	10,798.3 (37.4)	10,551.4 (40.0)	-246.9	10,516.3 (25.9)	10103.4 (45.2)	-412.9	-165.9 (-314.2, -17.5)

Abbreviations: DOTs, days-of-therapy; SE, standard error; JPY, Japanese yen; CI, 95% confidence interval

Table 5-F. Baseline characteristics for the sensitivity analyses

	Before PS matching			After PS matching		
Medical facilities in cohorts, N	**Control N = 161,414**	**Index N =10,679**	StdDiff (%)	**Control N = 6188**	**Index N = 6188**	StdDiff (%)
Area of facilities, N (%)			15.8			1.5
Hokkaido	3260 (2.2)	875 (8.2)		413 (6.7)	643 (10.4)	
Tohoku	10624 (6.6)	761 (7.1)		740 (12.0)	631 (10.2)	
Kanto	61,862 (38.3)	571 (5.3)		459 (7.4)	492 (8.0)	
Hokuriku/Koshinetsu	10,360 (6.4)	603 (5.6)		417(6.7)	474 (7.7)	
Tokai	23,677 (14.7)	11 (0.1)		13 (0.2)	10 (0.2)	
Kansai	27,519 (17.0)	1522 (14.3)		645 (10.4)	639 (10.3)	
Chugoku	5686 (3.5)	3116 (29.2)		1604 (25.9)	1492 (24.1)	
Shikoku	5072 (3.1)	74 (0.7)		42 (0.7)	56 (0.9)	
Kyushu/Okinawa	12,994 (8.1)	3146 (29.5)		1855 (30.0)	1751 (28.3)	
Individuals, N	1,552,448	78,161		53,323	57,533	
Patient characteristics, N (%)						
Age and Cohort			14.6			4.3
5 years old in 2012–2014	499,374 (32.2)	20,161 (25.8)		10,805 (20.3)	13,916 (24.2)	
5 years old in 2013–2015	590,319 (38.0)	19,735 (25.3)		11,640 (21.8)	14,374 (25.0)	
11 years old in 2012–2014	200,917 (12.9)	18,757 (24.0)		14,196 (26.6)	13,680 (23.8)	
11 years old in 2013–2015	261,838 (16.9)	19,508 (25.0)		16,682 (31.3)	15,563 (27.1)	
Male	825,122 (53.2)	42,107 (53.8)	1.4	28,620 (53.7)	30,912 (53.7)	0.1
Asthma/Wheezing	607,505 (39.1)	31,232 (40.0)	1.5	20,719 (38.9)	22,720 (39.5)	6.8
Atopic dermatitis/Eczema	714,038 (46.0)	34,368 (44.0)	4.2	21,530 (40.4)	25,276 (43.9)	3.2
Food allergy	24,218 (1.6)	1,033 (1.3)	2.1	791 (1.5)	725 (1.3)	0.9
Rhinitis	893,069 (57.5)	43,079 (55.1)	4.8	30,689 (57.6)	32,453 (56.4)	7.4
Sinusitis	770,530 (49.6)	34,744 (44.5)	10.4	24,317 (45.6)	26,000 (45.2)	7.2
Seizure	30,753 (2.0)	1,322 (1.7)	2.3	905 (1.7)	951 (1.7)	1.5
1st year						
Medication use, DOTs per 1000 cases (SE)						
Total antibiotic use	2252.8 (1.0)	2534.4 (5.4)	-7.3	2543.5 (6.6)	2476.5 (6.3)	1.7
Broad-spectrum antibiotic use	1060.3 (0.6)	1210.0 (3.3)	-6.4	1211.9 (4.0)	1140.5 (3.7)	3.0
Drugs for respiratory symptoms	5982.8 (2.5)	5414.6 (11.8)	6.5	5682.7 (14.8)	5501.6 (13.7)	2.1
Bronchodilators	910.0 (0.8)	799.9 (3.7)	3.9	831.2 (4.5)	774.6 (4.1)	2.1
Antihistamines	3856.1 (2.2)	3843.3 (11.3)	0.2	4027.4 (14.2)	3896.4 (13.2)	1.5
Leukotriene receptor antagonists	2211.1 (2.0)	2355.2 (10.1)	-1.9	2487.0 (13.3)	2333.3 (11.7)	2.0
Probiotics	1203.0 (0.8)	1143.1 (3.7)	2.2	1152.2 (4.6)	1153.3 (4.2)	0.0
Healthcare costs, mean JPY (SE)	11,274 (4.2)	10,984 (22.2)	1.8	11,249.7 (27.8)	10,952.6 (27.2)	1.8
Healthcare utilization, events per 1000 cases (SE)						
Out-of-hour visits	233.7 (0.2)	214.1 (0.9)	2.9	229.1 (1.1)	217.1 (1.0)	1.7
Rapid diagnostic tests	144.5 (0.1)	154.3 (0.6)	-2.3	157.4 (0.7)	154.7 (0.7)	0.6
Hospitalization	2.03 (0.013)	1.35 (0.051)	1.7	1.96 (0.074)	1.37 (0.060)	1.4
2nd year						
Medication use, DOTs per 1000 cases (SE)						
Total antibiotic use	2197.3 (1.1)	2497.5 (5.9)	-7.9	2504.0 (7.0)	2456.6 (6.9)	1.2
Broad-spectrum antibiotic use	1046.4 (0.7)	1203.4 (3.6)	-6.7	1207.7 (4.3)	1141.0 (4.0)	2.8
Drugs for respiratory symptoms	5626.6 (2.6)	5209.2 (12.5)	4.9	5504.8 (15.6)	5333.4 (14.7)	2.0
Bronchodilators	756.9 (0.8)	677.2 (3.7)	3.1	726.2 (4.6)	651.8 (4.2)	3.0
Antihistamines	4007.8 (2.6)	3962.1 (13.0)	0.5	4218.9 (16.5)	4042.7 (15.4)	2.0
Leukotriene receptor antagonists	2292.8 (2.3)	2406.0 (11.4)	-1.5	2526.5 (14.8)	2412.2 (13.4)	1.5
Probiotics	1126.9 (0.8)	1090.4 (4.0)	1.3	1069.2 (4.9)	1109.5 (4.6)	-1.5
Healthcare costs, mean JPY (SE)	10,647 (4.4)	10,530 (21.5)	0.8	10,788 (30.5)	10,508 (26.1)	1.8
Healthcare utilization, events per 1000 cases (SE)						
Out-of-hour visits	219.3 (0.2)	214.9 (1.0)	0.6	222.2 (1.2)	217.9 (1.1)	0.6
Rapid diagnostic tests	165.1 (0.1)	176.0 (0.7)	-2.4	177.3 (0.8)	178.0 (0.8)	-0.4
Hospitalization	1.49 (0.012)	1.58 (0.060)	-0.2	1.35 (0.67)	1.59 (0.070)	0.6

Abbreviations: PS, propensity-score; Std. Diff., standardized difference (an absolute standardized difference > 10% is a meaningful imbalance between the index and control groups); DOTs, days of therapy; SD, standard deviation; JPY, Japanese Yen

Table 5-G. Difference-in-differences estimates for the sensitivity analyses

	Control Facilities (N = 6188)			Index Facilities (N = 6188)			
	Before	After	Difference	Before	After	Difference	DID estimate (CI)
Visitors							
Medications, DOTs per 1000 cases (SE)							
Total antibiotics	2504.0 (7.0)	2599.1 (7.9)	95.1	2456.6 (6.9)	2546.0 (7.8)	89.4	-5.5 (-35.7, 24.6)
Broad-spectrum antibiotics	1207.7 (4.3)	1257.8 (5.0)	50.1	1141.0 (4.0)	1219.6 (4.9)	78.6	28.5 (9.7, 47.3)
Drugs for respiratory tract symptoms	5504.8 (15.6)	5293.2 (16.7)	-211.6	5333.4 (14.7)	5083.2 (16.0)	-250.2	-38.5 (-103.7, 26.7)
Bronchodilators	726.2 (4.6)	597.4 (4.7)	-128.8	651.8 (4.2)	516.2 (4.2)	-135.6	-6.7 (-25.5, 12.0)
Antihistamine	4218.9 (16.5)	4369.2 (19.6)	150.3	4042.7 (15.4)	3994.5 (17.8)	-48.2	-198.5 (-269.1, -127.8)
Leukotriene receptor antagonist	2526.5 (14.8)	2428.7 (16.3)	-97.8	2412.2 (13.4)	2222.2 (14.9)	-190.0	-92.1 (-153.2, -30.9)
Probiotics	1069.2 (4.9)	1018.1 (5.6)	-51.1	1109.5 (4.7)	1067.0 (5.2)	-42.5	8.4 (-12.8, 29.8)
Healthcare utilizations, event per 1000 cases (SE)							
Diagnostic tests for infectious disease	177.3 (0.8)	204.2 (0.9)	26.9	178.0 (0.8)	213.4 (0.9)	35.4	8.5 (4.8, 12.2)
Out-of-hour visit	222.2 (1.2)	232.2 (1.4)	10.0	217.9 (1.1)	218.8 (1.2)	0.90	-9.1 (-14.7, -3.5)
Hospitalization	1.35 (0.06)	1.45 (0.08)	0.10	1.59 (0.07)	1.35 (0.08)	-0.24	-0.35 (-0.64, -0.06)
Healthcare cost, mean JPY per case (SE)	10,788.4 (30.5)	10,623.8 (45.2)	-164.6	10,508.6 (26.1)	10,127.4 (46.9)	-381.2	-216.6 (-368.0, -65.1)

Abbreviations: DOTs, days-of-therapy; SE, standard error; JPY, Japanese yen; CI, 95% confidence interval

Table 5-H. Difference-in-differences estimates for the crude and adjusted analyses

	Control Facilities (N = 163,815)			Index Facilities (N = 10,693)			Crude DID estimate (CI)	Adjusted DID estimate (CI)
	Before	After	Difference	Before	After	Difference		
Medications, DOTs per 1000 cases (SE)								
Total antibiotics	2197.3 (1.1)	2317.5 (1.3)	120.2	2497.5 (5.8)	2576.3 (6.6)	78.8	-41.4 (-59.4, -23.4)	-42.3 (-59.7, -25.0)
Broad-spectrum antibiotics	1046.4 (0.7)	1105.1 (0.8)	58.7	1203.3 (3.5)	1274.0 (4.2)	70.7	12.0 (0.9, 23.2)	12.1 (1.1, 23.0)
Drugs for respiratory tract symptoms	5626.6 (2.6)	5510.5 (2.8)	-116.1	5209.1 (12.5)	4916.0 (13.4)	-293.1	-177.0 (-215.9, -138.1)	-200.7 (-238.2, -163.3)
Bronchodilators	756.9 (0.8)	654.9 (0.8)	-102.0	677.2 (3.7)	538.7 (3.7)	-138.5	-36.4 (-47.8, -24.9)	-38.8 (-49.7, -27.7)
Antihistamine	4007.8 (2.5)	4311.9 (3.1)	304.1	3962.0 (13.0)	3879.3 (14.9)	-82.7	-386.8 (-427.8, -345.8)	-364.3 (-403.5, -325.0)
Leukotriene receptor antagonist	2292.8 (2.3)	2382.1 (2.6)	89.3	2405.8 (11.4)	2178.8 (12.4)	-227.0	-316.4 (-353.5, -279.2)	-291.8 (-327.0, -256.6)
Probiotics	1126.9 (0.8)	1092.2 (0.9)	-34.7	1090.4 (4.0)	1025.8 (4.3)	-64.6	-30.4 (-42.7, -17.4)	-26.7 (-38.9, -14.5)
Healthcare utilizations, event per 1000 cases (SE)								
Diagnostic tests for infectious disease	165.1 (0.2)	196.0 (0.2)	30.9	176.0 (0.7)	211.7 (0.9)	35.7	4.8 (2.7, 6.9)	3.1 (1.1, 5.1)
Out-of-hour visit	196.4 (0.9)	208.9 (1.0)	12.5	214.9 (1.0)	218.1 (1.1)	4.2	-5.8 (-8.9, -2.8)	-4.6 (-7.5, -1.6)
Hospitalization	1.49 (0.01)	1.14 (0.01)	-0.35	1.58 (0.06)	1.41 (0.07)	-0.17	0.17 (-0.13, 0.47)	0.12 (-0.18, 0.42)
Healthcare costs, mean JPY (SE)	10,646.6 (4.4)	10,496.5 (4.9)	-150.1	10,530.1 (21.6)	10112.1 (35.7)	-418.0	-268.0 (-393.4, -142.4)	-272.0 (-391.1, -152.9)

Abbreviations: DOTs, days-of-therapy; SE, standard error; JPY, Japanese yen; CI, 95% confidence interval

Table 5-I. Difference-in-differences estimates in ratio scales

	Crude	Adjusted	PS match 1	PS match 2
	DID estimate (CI)	DID estimate (CI)	DID estimate (CI)	DID estimate (CI)
Medications				
Total antibiotics	0.978 (0.971, 0.985)	0.978 (0.971, 0.985)	0.998 (0.986, 1.010)	0.997 (0.985, 1.009)
Broad-spectrum antibiotics	1.002 (0.993, 1.011)	0.999 (0.989, 1.009)	1.026 (1.010, 1.042)	1.008 (0.993, 1.024)
Drugs for respiratory tract symptoms	0.964 (0.956, 0.971)	0.956 (0.949, 0.964)	0.991 (0.979, 1.003)	0.984 (0.973, 0.996)
Bronchodilators	0.920 (0.902, 0.937)	0.905 (0.886, 0.925)	0.962 (0.934, 0.992)	0.972 (0.943, 1.002)
Antihistamine	0.910 (0.901, 0.920)	0.904 (0.894, 0.913)	0.954 (0.938, 0.970)	0.954 (0.938, 0.971)
Leukotriene receptor antagonist	0.872 (0.858, 0.887)	0.841 (0.825, 0.858)	0.958 (0.934, 0.983)	0.972 (0.947, 0.998)
Probiotics	0.970 (0.959, 0.982)	0.971 (0.960, 0.983)	1.009 (0.989, 1.030)	1.019 (0.999, 1.040)
Healthcare utilization				
Out-of-hour visit	0.974 (0.961, 0.988)	0.971 (0.956, 0.986)	0.960 (0.937, 0.984)	0.979 (0.956, 1.002)
Diagnostic test	1.013 (1.002, 1.024)	1.008 (0.997, 1.019)	1.041 (1.021, 1.061)	1.012 (0.993, 1.032)
Hospitalization	1.160 (0.949, 1.417)	1.083 (0.866, 1.355)	0.786 (0.642, 0.961)	0.761 (0.624, 0.928)
Healthcare cost, mean JPY	0.974 (0.962, 0.986)	0.969 (0.963, 0.975)	0.978 (0.964, 0.992)	0.983 (0.969, 0.997)

Abbreviations: PS, propensity score; DID, difference-in-differences; DOTs, days-of-therapy; SE, standard error; JPY, Japanese yen; CI, 95% confidence intervals

Note: "PS match 1" is PS matched DID models using data in the first year. "PS match 2" is PS matcched DID models using data in the first and second years.

Table 5-J. Difference-in-differences estimates for each cohort

	Control Facilities			Index Facilities			Crude DID estimate (CI)	Adjusted DID estimate (CI)
	Before	After	Difference	Before	After	Difference		
Total antibiotics, DOTs per 1000 cases (SE)								
2012–2015, Age 5–7 years	2177.3 (1.8)	2299.8 (2.1)	122.5	2479.7 (10.2)	2579.1 (11.6)	99.4	-23.1 (-56.1, 9.8)	-20.6 (-53.0, 11.7)
2013–2016, Age 5–7 years	2174.2 (1.7)	2266.8 (1.9)	92.6	2497.7 (10.1)	2533.9 (11.4)	36.3	-56.4 (-88.0, -24.8)	-64.2 (-95.2, -33.3)
2012–2015, Age 11–13 years	2303.8 (3.8)	2449.0 (4.2)	145.2	2516.2 (14.8)	2583.3 (16.3)	67.1	-78.0 (-125.7, -30.4)	-85.6 (-130.7, -40.5)
2013–2016, Age 11–13 years	2291.0 (3.3)	2486.2 (3.8)	195.2	2511.3 (14.3)	2636.3 (15.7)	125.0	-68.2 (-114.8, -21.7)	-64.0 (-108.4, -19.6)
Drugs for respiratory symptoms, DOTs per 1000 cases (SE)								
2012–2015, Age 5–7 years	5876.4 (4.3)	5713.0 (4.7)	-163.4	5484.0 (22.5)	5142.9 (24.4)	-341.1	-177.8 (-251.7, -103.9)	-231.7 (-302.6, -160.8)
2013–2016, Age 5–7 years	5910.2 (4.0)	5746.2 (4.4)	-164.0	5544.3 (22.5)	5047.8 (24.1)	-496.5	-332.6 (-404.4, -260.7)	-344.5 (-414.9, -274.2)
2012–2015, Age 11–13 years	4322.9 (7.6)	4485.2 (8.5)	162.3	4663.5 (28.9)	4557.8 (30.8)	-105.7	-268.6 (-362.6, -174.6)	-237.1 (-325.5, -148.6)
2013–2016, Age 11–13 years	4457.6 (6.7)	4627.2 (7.5)	169.6	4619.1 (27.8)	4664.1 (30.3)	45.0	-124.6 (-214.2, -35.0)	-102.3 (-188.0, -16.5)
Antihistamines, DOTs per 1000 cases (SE)								
2012–2015, Age 5–7 years	3756.8 (3.8)	4186.0 (4.8)	429.2	3604.7 (20.5)	3574.3 (23.7)	-30.4	-459.7 (-530.0, -389.2)	-488.4 (-590.1, -377.4)
2013–2016, Age 5–7 years	3853.5 (3.6)	4048.0 (4.3)	194.5	3733.0 (20.2)	3574.8 (23.3)	-158.2	-352.8 (-421.7, -283.8)	-345.6 (-412.3, -278.8)
2012–2015, Age 11–13 years	4821.5 (10.9)	5244.3 (12.7)	422.8	4528.1 (37.6)	4479.1 (41.7)	-49.0	-471.8 (-590.5, -353.3)	-413.1 (-525.7, -300.5)
2013–2016, Age 11–13 years	4992.6 (9.8)	5117.1 (11.2)	124.6	4486.1 (36.4)	4320.8 (39.2)	-165.3	-289.8 (-402.4, -177.3)	-309.3 (-417.2, -204.5)
Healthcare utilizations, JPY per case (SE)								
2012–2015, Age 5–7 years	10,716.5 (6.3)	10,297.8 (6.3)	-418.7	10,573.3 (27.1)	9696.2 (32.5)	-877.1	-458.4 (-563.3, -353.7)	-478.6 (-581.0, -376.2)
2013–2016, Age 5–7 years	10,654.3 (6.3)	10,473.7 (6.3)	-180.6	10,712.4 (33.7)	9855.6 (40.4)	-856.8	-676.2 (-804.4, -547.9)	-674.2 (-800.6, -547.7)
2012–2015, Age 11–13 years	10,335.3 1(17.2)	10,851.0 (25.2)	515.7	10,260.7 (59.1)	10,642.6 (91.6)	381.9	-133.9 (-418.3, 150.4)	-79.6 (-359.1, 199.9)
2013–2016, Age 11–13 years	10,589.7 (19.3)	11,004.7 (23.8)	415.0	10,373.2 (71.3)	10716.3 (141.7)	343.1	-71.8 (-677.9, 534.3)	-84.6 (-630.5, 461.3)

Abbreviations: PS, propensity score; DID, difference-in-differences; DOTs, days-of-therapy; SE, standard error; JPY, Japanese yen; CI, 95% confidence intervals

Table 5-K. Synthetic weights for areas in children aged 5–7 years

Prefecture	Area name	Antibiotics	Respiratory drugs	Anti-histamine	Out-of-hour visit	Admission	Healthcare expenditure
Shimane	Izumo		.49		.257		.227
Shimane	Masuda					.068	
Shimane	Oki						
Hiroshima	Hiroshima	.357	.025	.836	.009	.283	.56
Hiroshima	Hiroshima Nishi	.168			.168	.154	
Yamaguchi	Yanai						
Yamaguchi	Yamaguchi/ Houfu	.033				.06	.117
Yamaguchi	Shimonoseki	.033				.111	
Yamaguchi	Nagato	.287	.105	.098		.01	
Yamaguchi	Hagi						
Nagasaki	Nagasaki		.061		.227	.119	
Nagasaki	Sasebo					.03	
Nagasaki	Kenou			.016		.004	
Nagasaki	Shin-kami-gotou-chou		.013				
Nagasaki	Ikinoshima		.013				
Nagasaki	Tsushima	.123	.116		.131		.019
Miyazaki	Higashi-shoken				.209	.141	.077
Miyazaki	Tojyo-kita-shoken			.047		.02	
Miyazaki	Hokubu			.004			
Kagoshima	Amami		.177				
RMSPE		.093	.254	.140	.014	.001	15.931

Abbreviations: RMSPE, root mean square prediction error

Table 5-L. Synthetic weights for areas in children aged 11–13 years

Prefecture	Area name	Antibiotics	Respiratory drugs	Anti-histamine	Out-of-hour visit	Admission	Healthcare expenditure
Hokkaido	Minami-sorachi			.028			
Hokkaido	Nishi-Iburi						
Hokkaido	Higashi-iburi						
Hokkaido	Hidaka						
Hokkaido	Kamikawa-chubu		.088	.069	.12		.217
Hokkaido	Souya				.007		
Hokkaido	Hokumou		.074	.007			
Hokkaido	Kushiro	.237					
Hokkaido	Nemuro	.077				.053	
Aomori	Aomori						
Iwate	Tankou					.013	
Iwate	Ryouban						
Akita	Kazuno/ Odate						
Akita	Noshiro/ Yamamoto						
Akita	Akita				.054	.125	
Akita	Yokote				.123		
Akita	Yuzawa/ Ogatsu						
Tochigi	Kentouou	.526	.443	.485	.337	.285	.226
Niigata	Chuetsu	.009					
Yamanashi	Chu-hoku			.078			
Kyoto	Kyoto/ Otokuni	.131	.153	.012	.218	.117	.024
Kyoto	Yamashiro-minami		.054			.104	
Wakayama	Wakayama						
Wakayama	Hashimoto	.013	.039	.083		.075	.026
Shimane	Matsue						
Hiroshima	Kure					.063	.234
Hiroshima	Hiroshima-Chuou						
Hiroshima	Bisan						.065
Hiroshima	Fukuyama/ Fuchu						
Yamaguchi	Iwakuni						
Fukuoka	Fukuoka/ Itoshima	.008	.148	.238	.142	.164	.078
Saga	Hokubu						
Kumamoto	Uki						.125
Kumamoto	Kamoto						
Miyazaki	Nishimoro						.004
Kagoshima	Kagoshima						
RMSPE		.098	.263	.325	.013	.001	28.862

Abbreviations: RMSPE, root mean square prediction error

Table 5-M. Pre-intervention variables among children aged 5–7 years

Outcome of interest for analyses	Tokyo	Synthetic Control (Synthetic Tokyo)					
	–	Antibiotics	Respiratory Drugs	Anti-histamine	Out-of-hour visit	Admission Rate	Cost
Outcome of interest, DOTs or event per 1000 visitors							
Total antibiotics	1951	–	2288.1	2400.8	2427.1	2497.1	2452.1
Broad-spectrum antibiotics	926.9	1079.3	973.8	1313.8	1101.7	1244.4	1179.5
Healthcare expenditure, JPY	11082.6	10945.5	10259.5	11259.3	10538.2	10920.1	–
Out-of-hour visits	244.3	246.6	237.8	229	–	231.2	233.5
Diagnostic tests	145.3	162.3	163.1	161.7	145.4	149	164.9
Hospitalization rates	1.4	2.9	2.2	1.1	1.6	–	0.6
Respiratory drugs	6097.2	5771.1	–	5792.7	5420.4	5661.9	5832.7
Bronchodilators	787.6	1020.4	1208.6	809.4	1095.5	812.6	921.1
Antihistamines	3850.8	3860.8	3680.6	–	3848.8	3720.4	3750.2
Leukotriene receotir antagonists	2415.8	2890.5	2746.8	2435.1	2532.4	2408.4	2326.9
Probiotics	1280.9	1344.8	874.6	1654.5	991.8	1348.8	1393.1
Patient background, %							
Asthma/Wheeze	16.8	15.4	12.9	16.1	17.4	17.9	16.1
Atopic dermatitis/eczema	16.3	16.3	13.8	18.7	15.8	16.5	18.1
Food allergy	0.5	0.4	0.3	0.3	0.4	0.3	0.2
Allergic rhinitis	29.1	25	17	26.9	19.9	23	23.2
Sinusitis	33.3	27	18.1	31.5	22.1	28.3	28.2
Seizure	0.7	0.7	0.7	0.7	0.9	0.8	0.7
Female	46.2	44.6	46.0	45.3	46.2	45.5	45.7
Characteristics of the area							
Pediatricisn/1000 children	1.5	1	1.4	0.9	1.4	1.1	1.2
Pediatric mortality/1000	0.2	0.4	0.4	0.4	0.2	0.2	0.3
Proportion of elderly, %	20.1	26.8	27.9	22.3	25	24.2	22.6
Higher education, %	24.7	15.5	10.8	19.5	13.6	16.5	17.9
Tertiary employment, %	70.6	67.8	65.6	70.7	69	70.6	69.9
Unemployment rate, %	5.9	5.9	5.7	5.7	5.9	5.9	5.4
Outcome of interest during 1st and 2nd years							
Total antibiotics at 24 months	1965.5	2104.3	–	–	–	–	–
Total antibiotics at 12 months	2016.8	2020.0	–	–	–	–	–
Total antibiotics at 1 month	2000.3	1999.4	–	–	–	–	–
Respiratory drugs at 24 months	6220.0	–	6672.6	–	–	–	–
Respiratory drugs at 12 months	6163.2	–	6107.4	–	–	–	–
Respiratory drugs at 1 months	6340.1	–	6168.1	–	–	–	–
Antihistamines at 24 months	5889.1	–	–	6011.9	–	–	–
Antihistamines at 12 months	4446.8	–	–	4229.7	–	–	–
Antihistamines at 1 month	4082.3	–	–	4114.3	–	–	–
Out-of-hour visits at 24 months	260.3	–	–	–	279.7	–	–
Out-of-hour visits at 12 months	228.4	–	–	–	243.0	–	–
Out-of-hour visits at 1 month	243.4	–	–	–	237.7	–	–
Admission rates at 24 months	0.7	–	–	–	–	0.8	–
Admission rates at 12 months	1.2	–	–	–	–	1.4	–
Admission rates at 1 month	1.9	–	–	–	–	1.5	–
Healthcare costs at 24 months	11700.9	–	–	–	–	–	11991.0
Healthcare costs at 12 months	11069.4	–	–	–	–	–	11140.5
Healthcare costs at 1 month	11623.6	–	–	–	–	–	11378.4

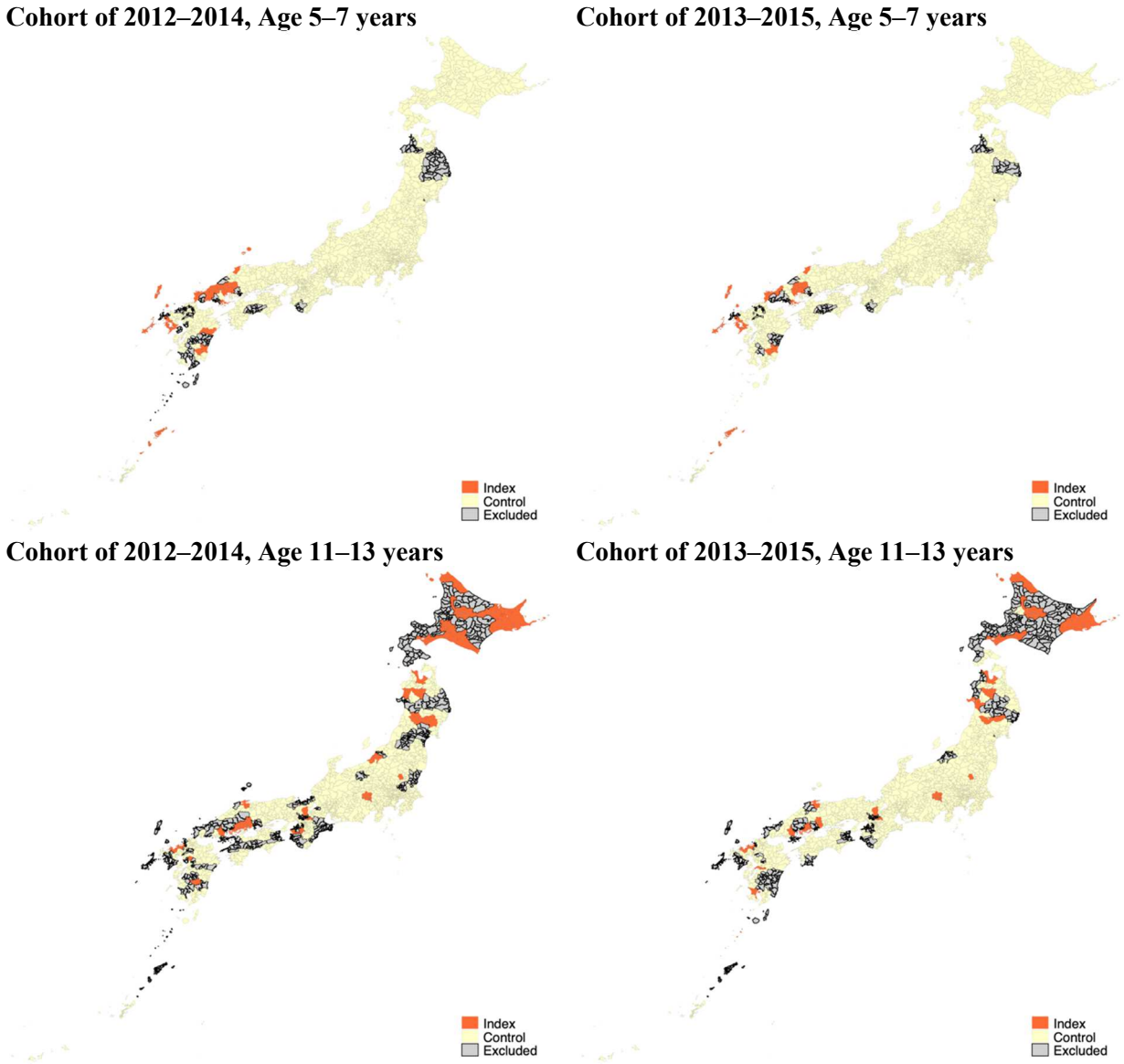
Abbeviations: DOTs, days of therapy; JPY, Japanese yen

Table 5-N. Pre-intervention variables among children aged 11–13 years

Outcome of interest for analyses	Tokyo	Synthetic Control (Synthetic Tokyo)					
	–	Total antibiotics	Respiratory Drugs	Anti-histamine	Out-of-hour visit	Admission Rate	Cost
Outcome of interest, DOTs or event per 1000 visitors							
Total antibiotics	2112	–	2429.6	2401.5	2472.7	2474.2	2632.3
Broad-spectrum antibiotics	1030.9	1011.9	1117.1	1080.7	1091.9	1183	1163.2
Healthcare expenditure, mean	10779.4	10401.1	10196.7	10087.3	10429.3	10358.5	–
Out-of-hour visits	216	228.5	225.5	211.7	–	215	244.3
Diagnostic tests	144.2	144.1	141.4	139.6	146.7	143.7	168.9
Hospitalization rates	1.7	1.6	1.5	1.6	1.7	–	1.7
Respiratory drugs	4367	4872.6	–	4401.4	4580.2	4291.2	4721.5
Bronchodilators	341.4	395.4	294.4	318.6	316.8	355.3	338.7
Antihistamines	5219.7	5217.5	4923.7	–	4934.8	4936.7	5310.1
Leukotriene receotir antagonists	2592.9	2882.2	2440.1	2640	2560.7	2464.9	2846.7
Probiotics	885.8	792.7	837.1	814.2	832.2	942.4	785
Patient background, %							
Asthma/Wheeze	12.1	12.9	11.9	12.5	11.8	12	13.3
Atopic dermatitis/eczema	12.4	13.2	12.4	12.5	12	10.9	11.3
Food allergy	0.4	0.3	0.3	0.3	0.3	0.3	0.3
Allergic rhinitis	33	27.6	30.6	30.7	28.3	29.2	32.4
Sinusitis	31.6	28.2	31.8	31.7	29.3	30.5	31.6
Seizure	0.1	0.2	0.1	0.1	0.1	0.1	0.1
Female	45.1	46.4	44.9	45.1	45	44	45.4
Characteristics of the area							
Pediatrician/1000 children	1.5	0.9	1.1	1	1.2	1.1	1.2
Pediatric mortality/1000	0.2	0.2	0.3	0.3	0.2	0.3	0.2
Proportion of elderly, %	20.1	21.6	21	20.8	22.6	21.7	25.4
Higher education, %	24.7	15.2	18.1	17.7	16.7	18.2	14.4
Tertiary employment, %	70.6	66.6	69.1	69.3	68.8	69.1	67.4
Unemployment rate, %	5.9	6.1	6.2	6.3	6.5	6.2	6.2
Outcome of interest during 1st and 2nd years							
Total antibiotics at 24 months	2014.4	2157.4	–	–	–	–	–
Total antibiotics at 12 months	2187.1	2230.9	–	–	–	–	–
Total antibiotics at 1 month	2217.9	2269.4	–	–	–	–	–
Respiratory drugs at 24 months	4700	–	5244.8	–	–	–	–
Respiratory drugs at 12 months	4283.4	–	4463.8	–	–	–	–
Respiratory drugs at 1 month	4378.9	–	4575.8	–	–	–	–
Antihistamines at 24 months	9207.2	–	–	9658.6	–	–	–
Antihistamines at 12 months	6218.7	–	–	6397.5	–	–	–
Antihistamines at 1 month	5685.1	–	–	5741.7	–	–	–
Out-of-hour visits at 24 months	245.7	–	–	–	260	–	–
Out-of-hour visits at 12 months	215.2	–	–	–	222.1	–	–
Out-of-hour visits at 1 months	211.6	–	–	–	232.5	–	–
Admission rates at 24 months	0.4	–	–	–	–	0.9	–
Admission rates at 12 months	1.4	–	–	–	–	2	–
Admission rates at 1 month	2.4	–	–	–	–	2	–
Healthcare costs at 24 months	12513.4	–	–	–	–	–	12501.5
Healthcare costs at 12 months	11016.6	–	–	–	–	–	11060.5
Healthcare costs at 1 month	10644.6	–	–	–	–	–	10885.1

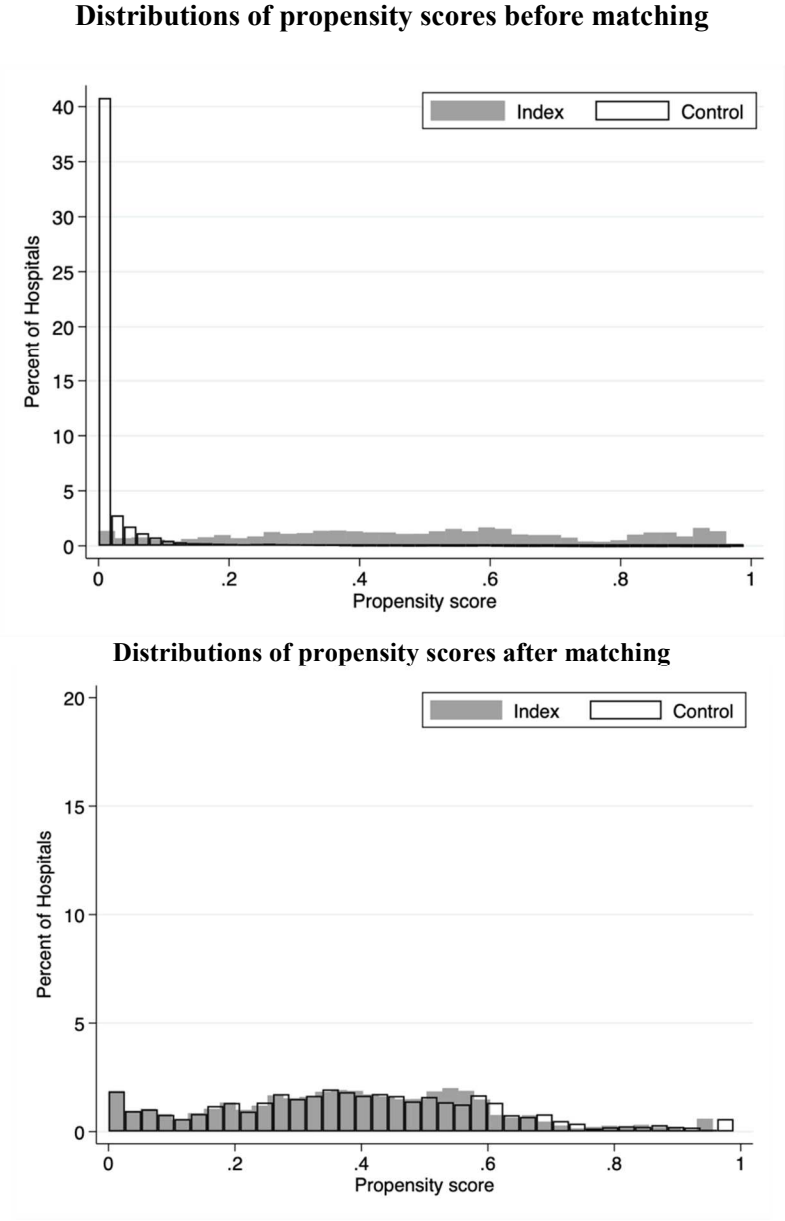
Abbeviations: DOTs, days of therapy; JPY, Japanese yen

Figure 5-A. Free medical certificate by years and areas



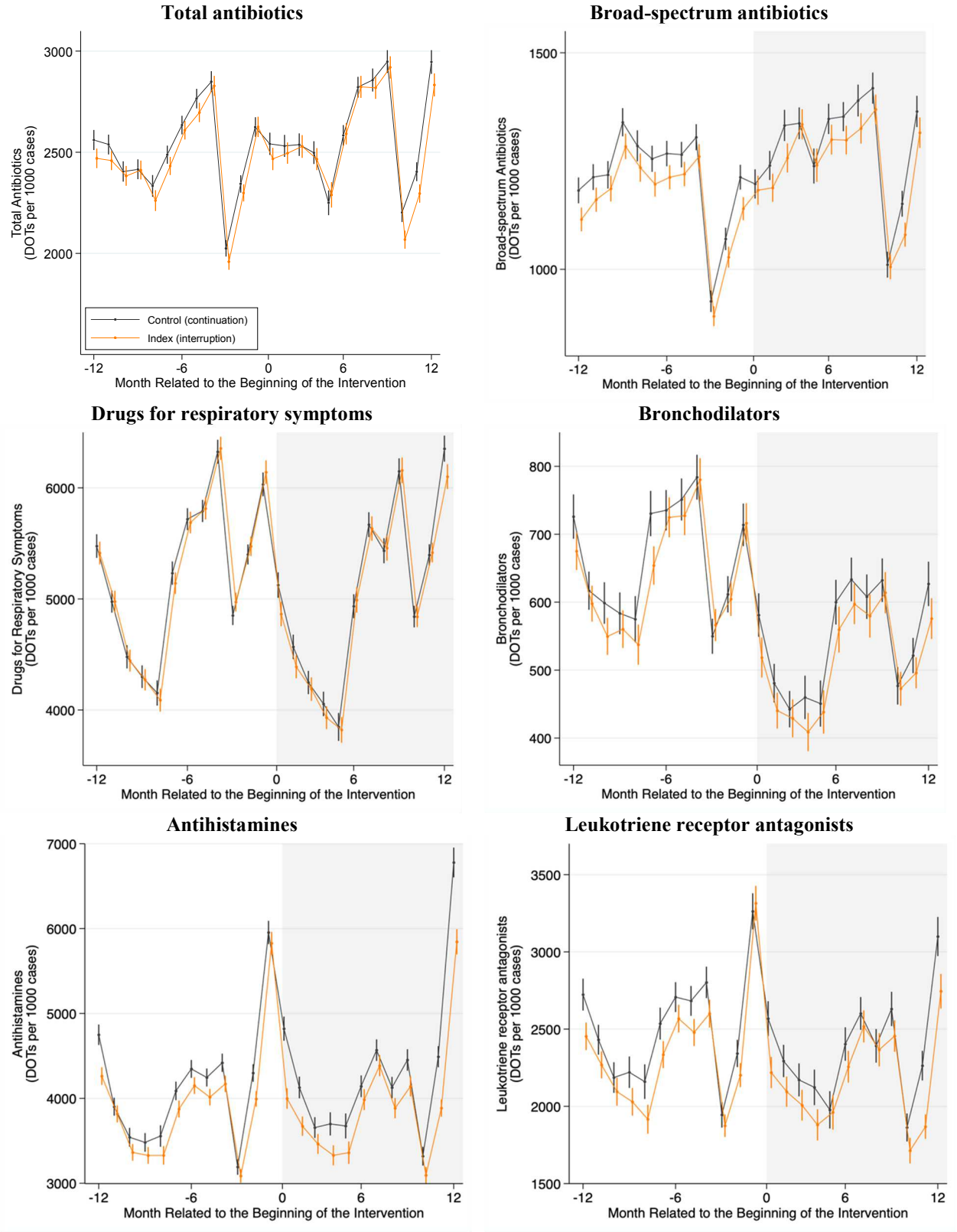
Note: Index, secondary medical areas with > 80% of children whose FMCs were interrupted at the beginning of the post-intervention period (3rd year); Control, secondary medical areas with almost 100% of children who received FMC over the 3 years; Excluded, the remaining areas

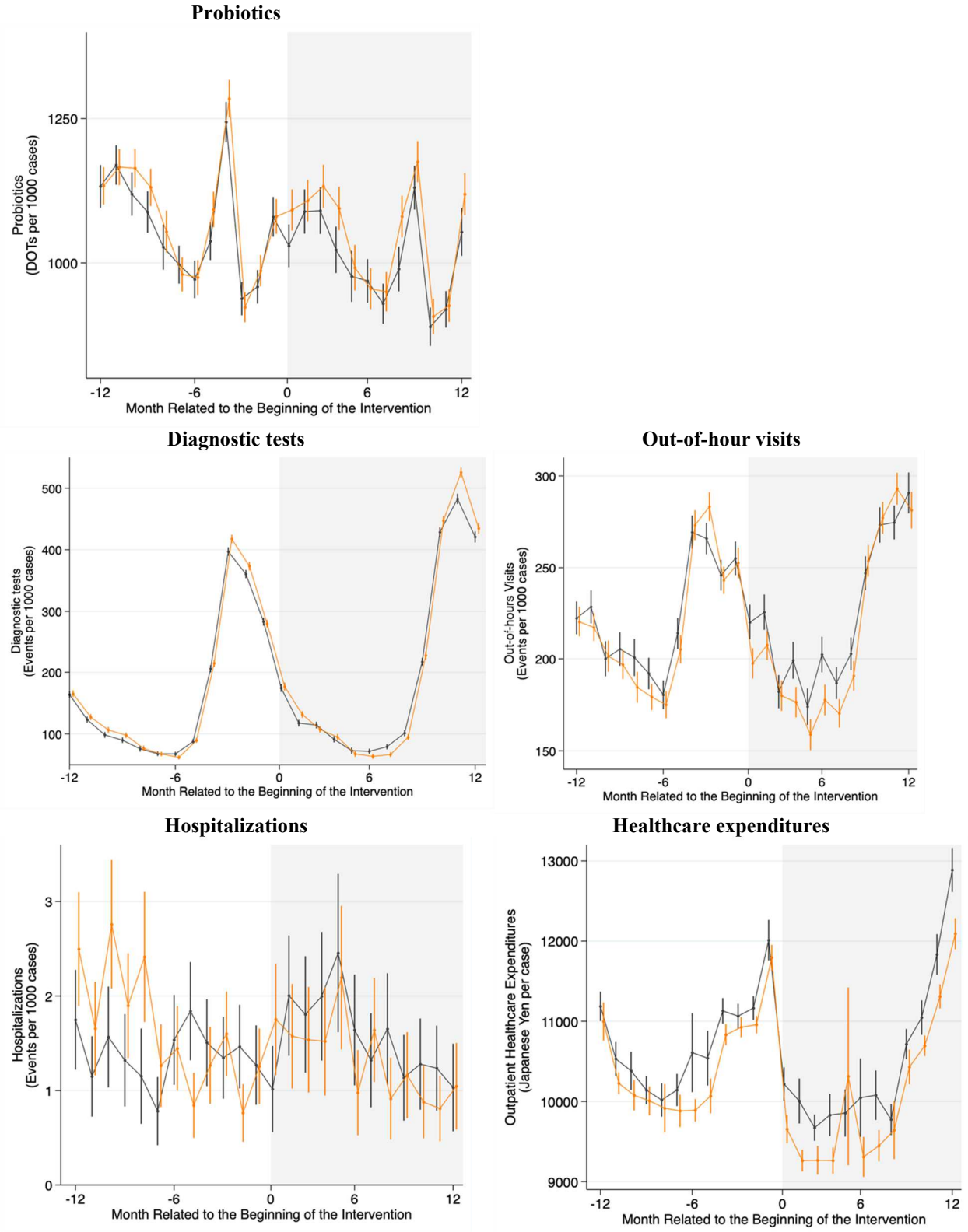
Figure 5-B. Distributions of propensity scores for the primary analyses



Notes: Distribution of propensity score for the index and control groups using variables in the 1st and 2nd years, before and after matching.

Figure 5-C. Trends in outcomes for the primary analyses

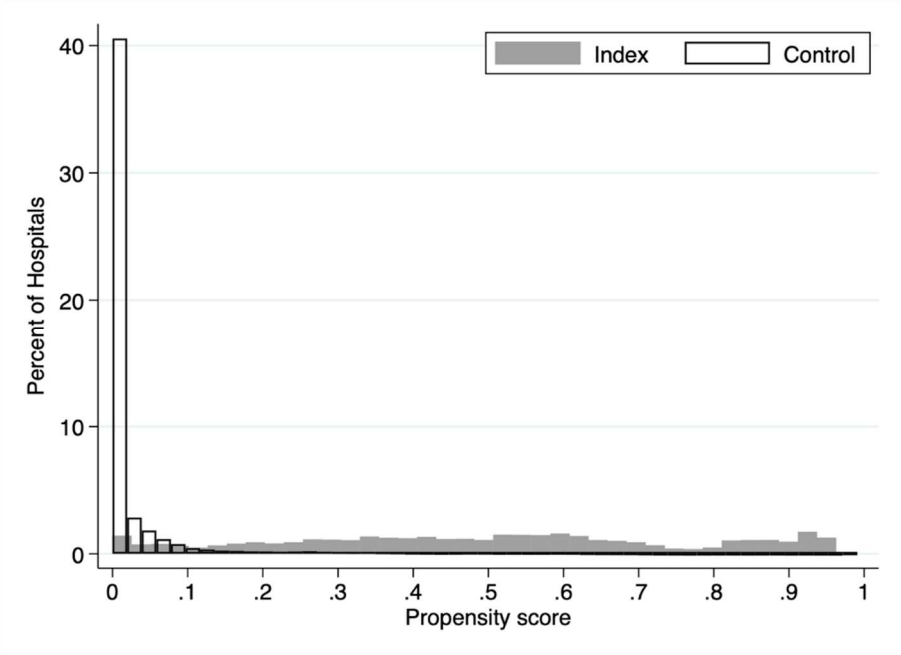




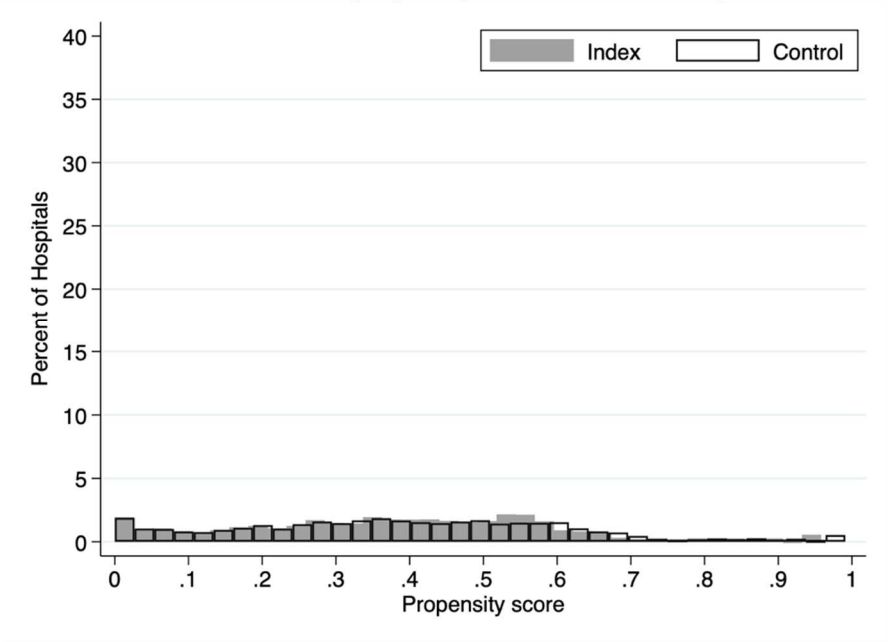
Notes: Trends in total antibiotics, drugs for respiratory symptoms, antihistamines, out-of-hour visits, hospitalization rates, and out-patient healthcare expenditure for propensity-score matching using data during 1st and 2nd years.

Figure 5-D. Distributions of propensity scores for the sensitivity analyses

Distributions of propensity scores before matching

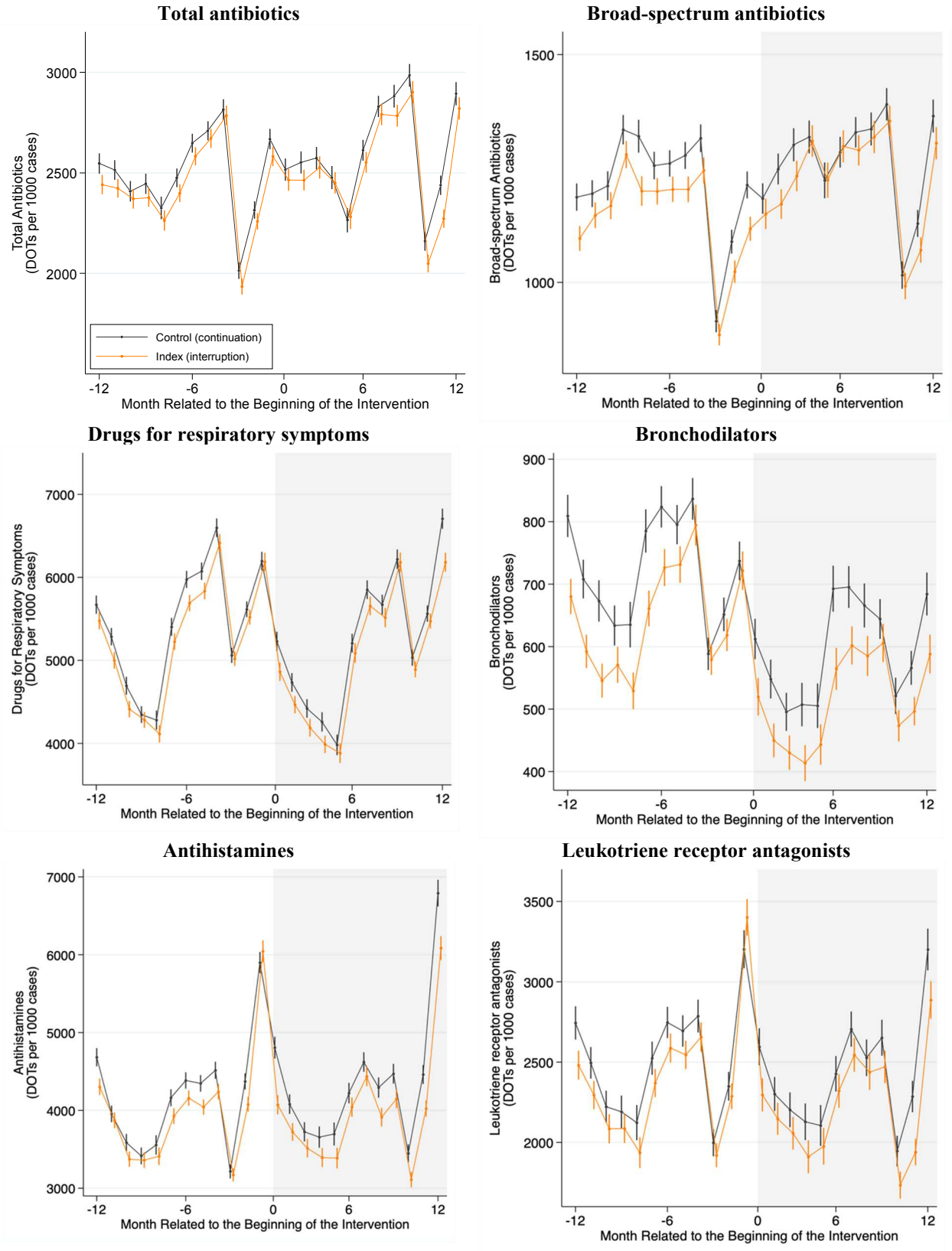


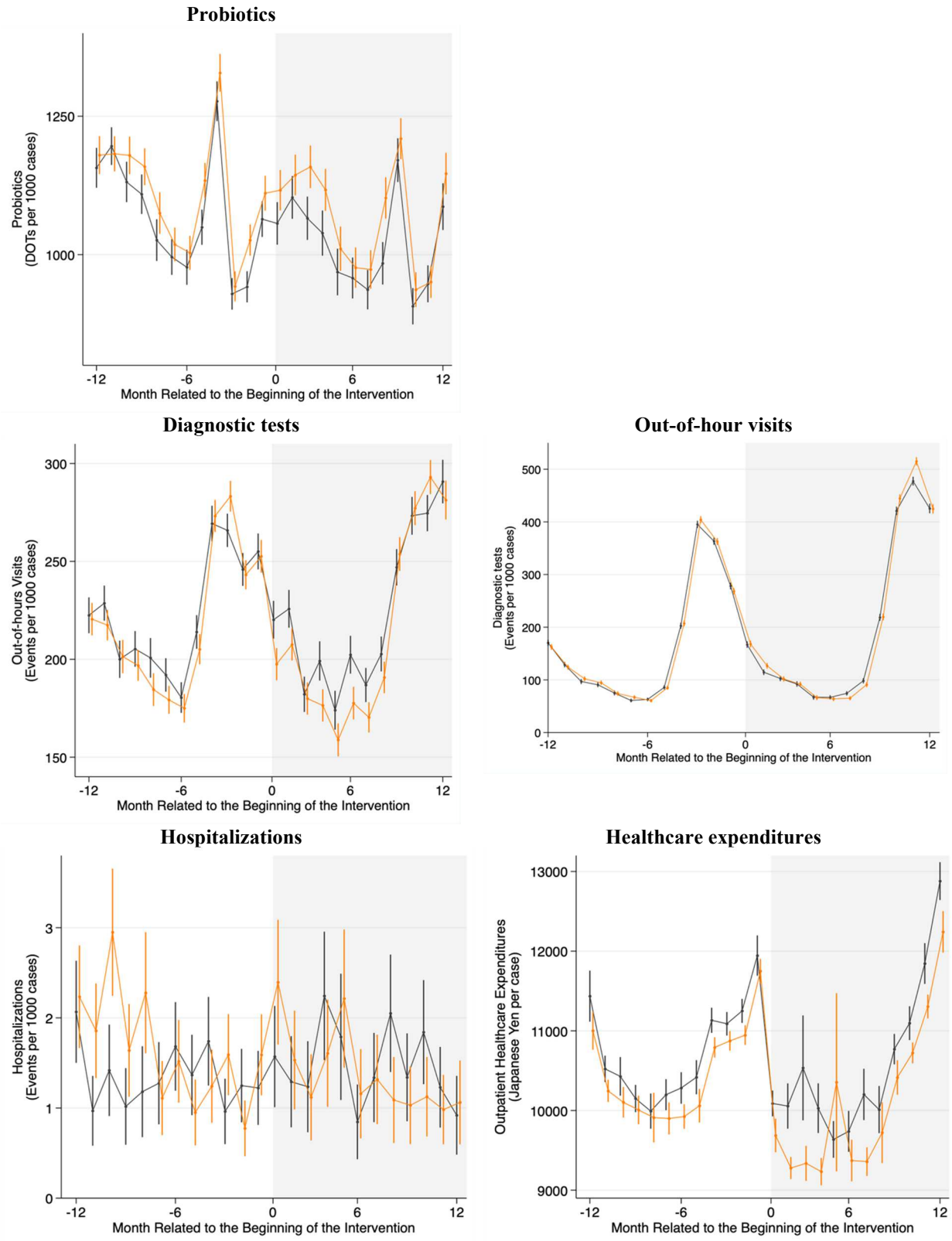
Distributions of propensity scores after matching



Notes: Distribution of propensity score for the index and control groups using variables in the 1st year, before and after matching.

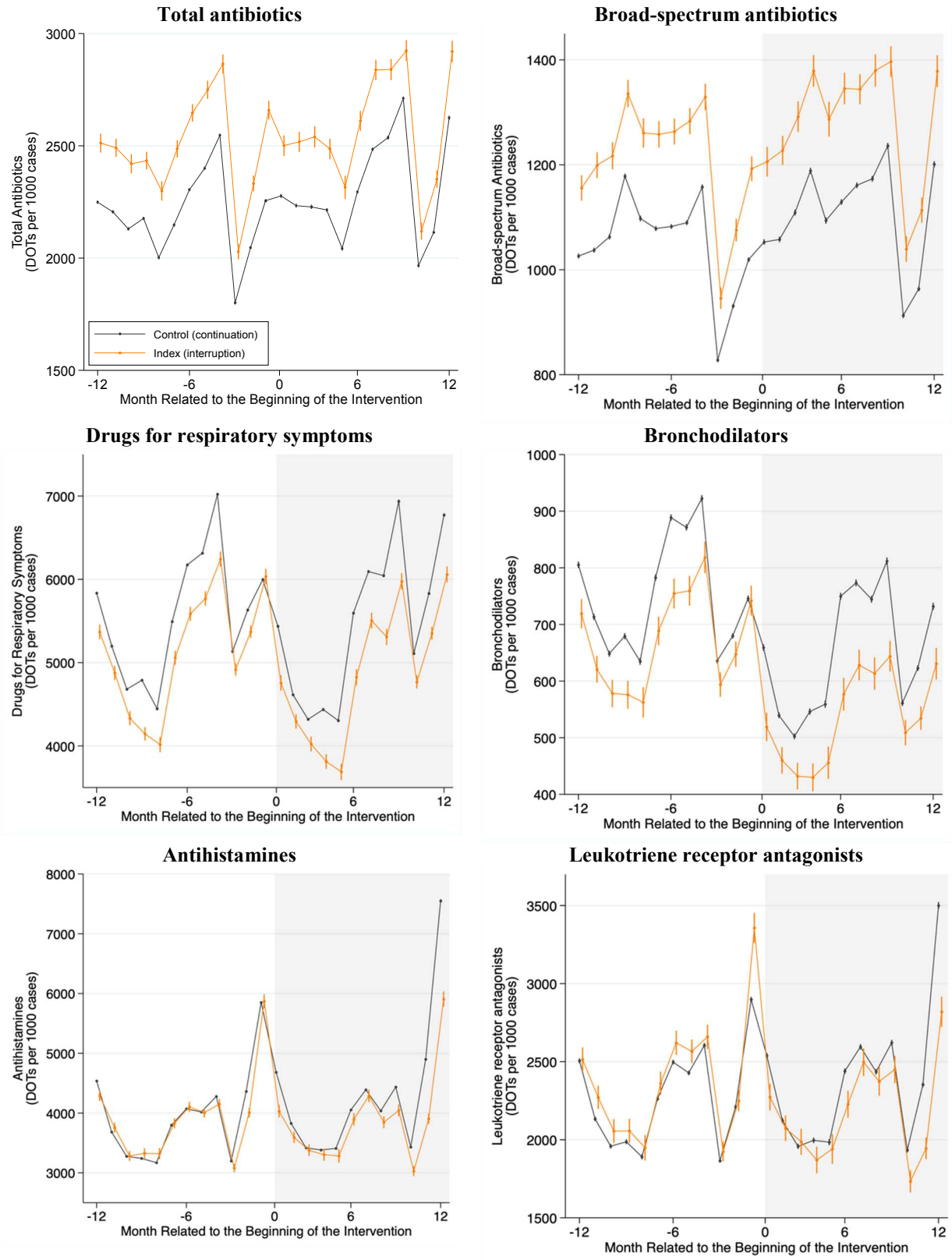
Figure 5-E. Trends in outcomes for the sensitivity analyses

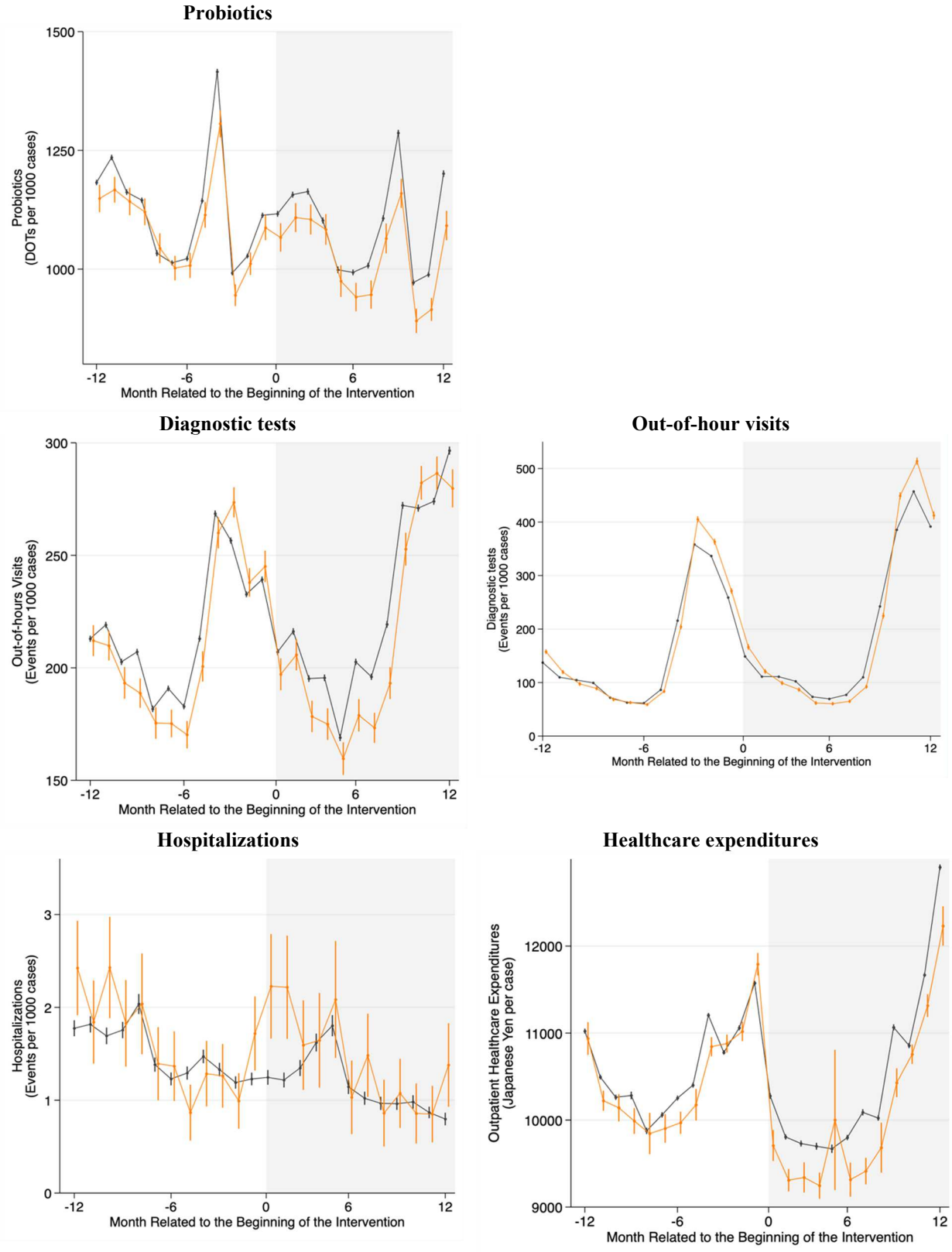




Notes: Trends in total antibiotics, drugs for respiratory symptoms, antihistamines, out-of-hour visits, hospitalization rates, and out-patient healthcare expenditure for propensity-score matching using data during 1st year.

Figure 5-F. Trends in outcomes for the crude analyses

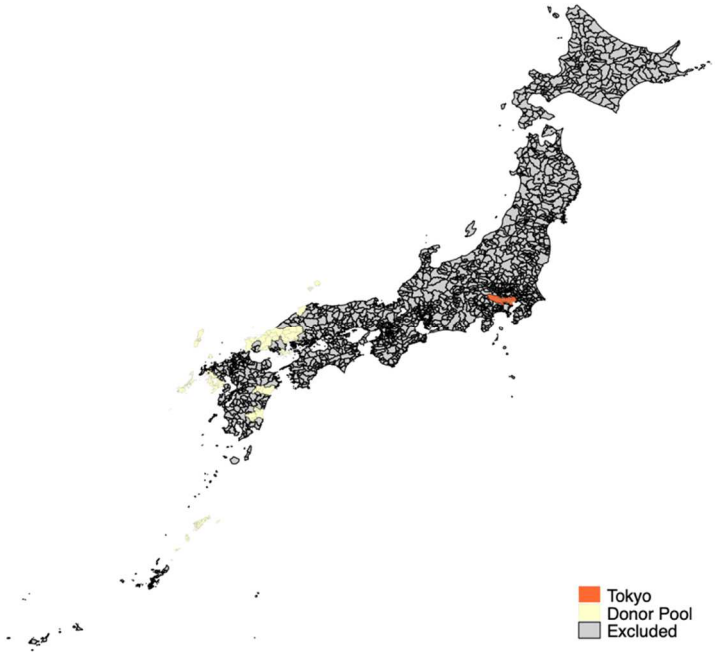




Notes: Trends in total antibiotics, drugs for respiratory symptoms, antihistamines, out-of-hour visits, hospitalization rates, and out-patient healthcare expenditure for crude analyses.

Figure 5-G. Tokyo and donor pool for synthetic controls

Cohort of children aged 5–7 years



Cohort of children aged 11–13 years

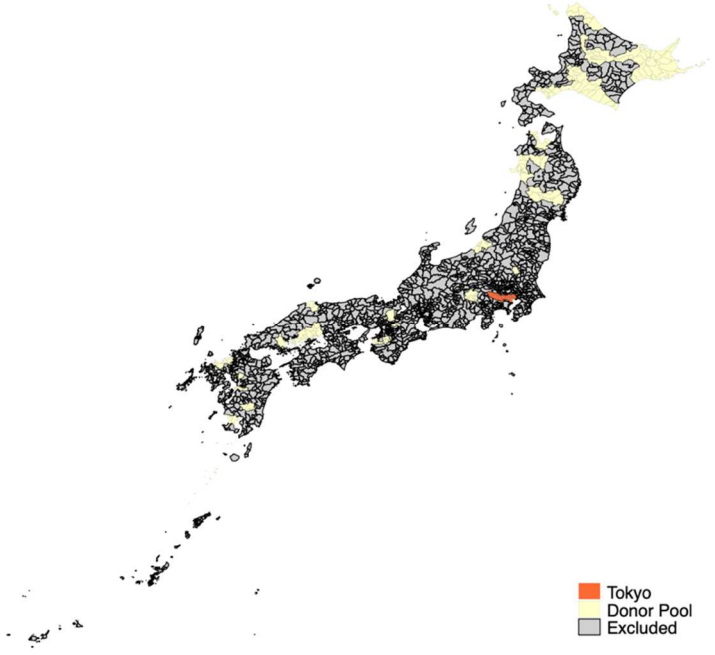
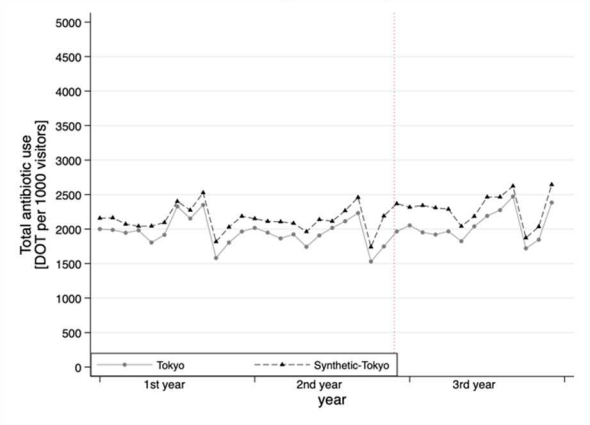


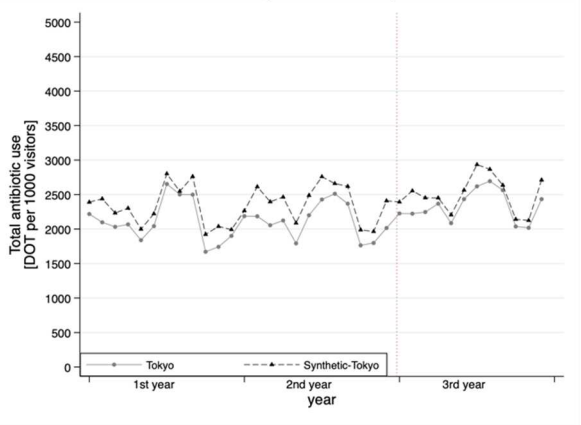
Figure 5-H. Results from the Synthetic Control Methods

Total antibiotics

Children aged 5–7 years

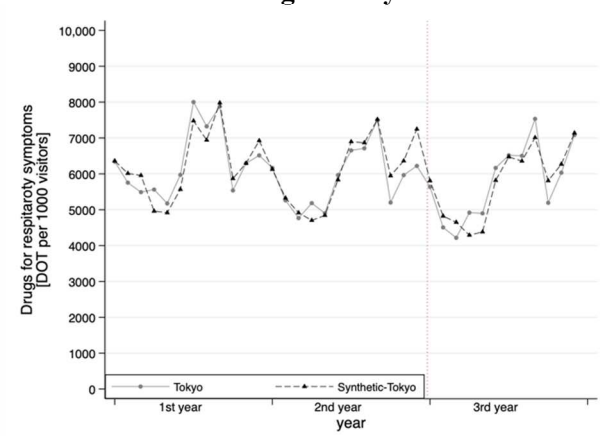


Children aged 11–13 years

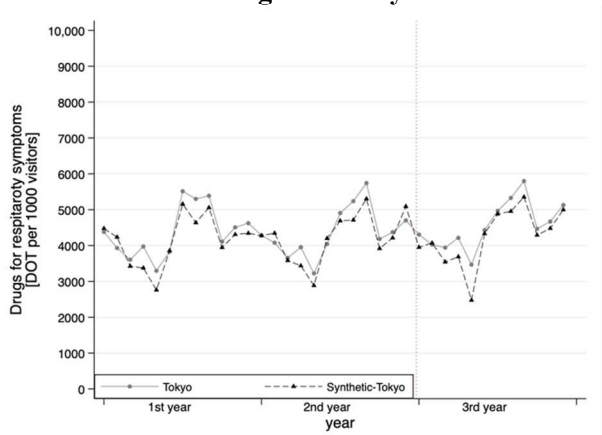


Drugs for respiratory symptoms

Children aged 5–7 years

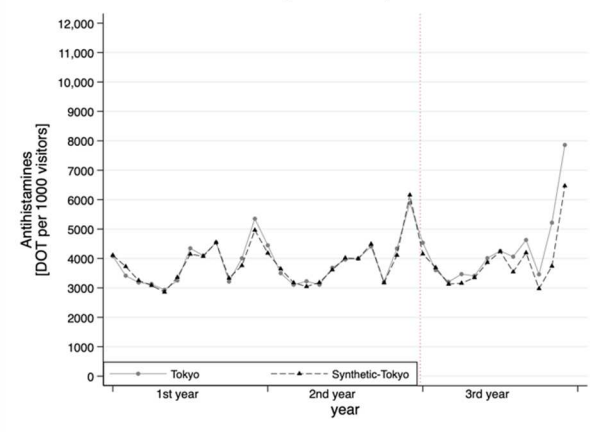


Children aged 11–13 years

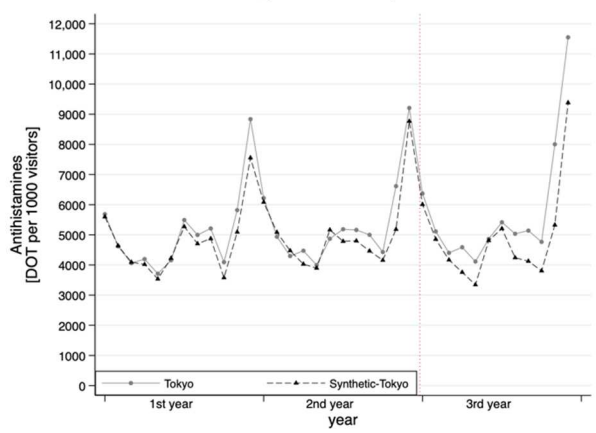


Antihistamines

Children aged 5–7 years

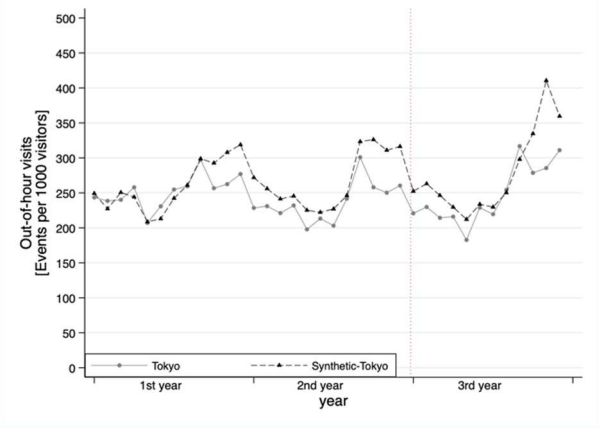


Children aged 11–13 years

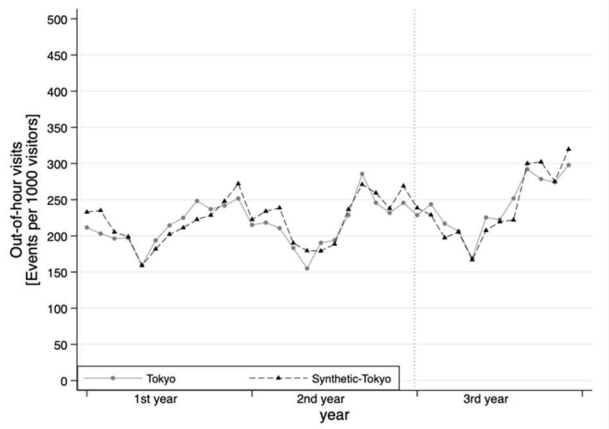


Out-of-hour visits

Children aged 5–7 years

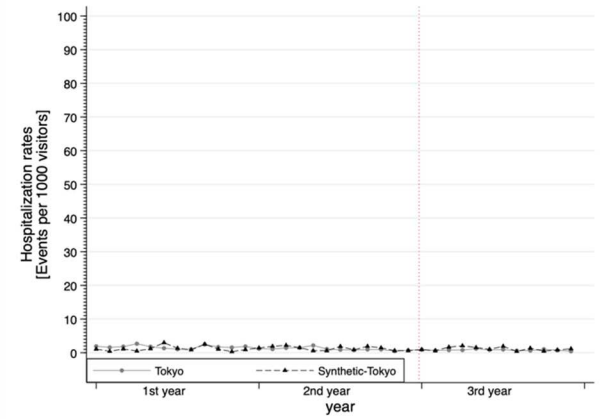


Children aged 11–13 years

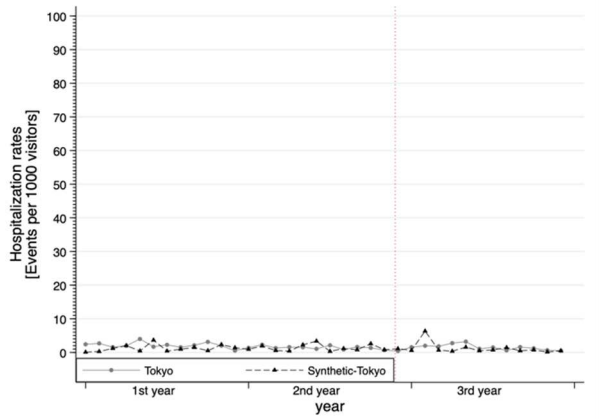


Hospitalization rates

Children aged 5–7 years

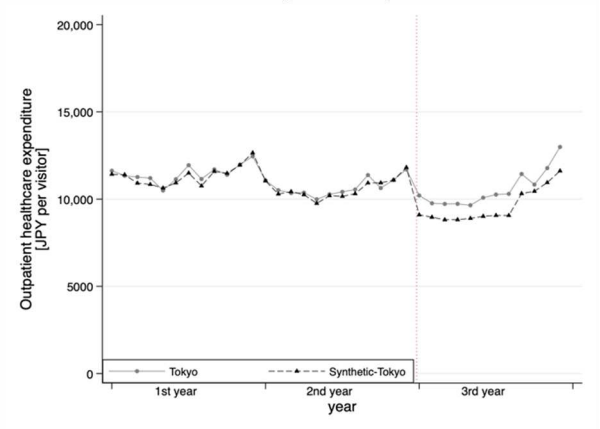


Children aged 11–13 years

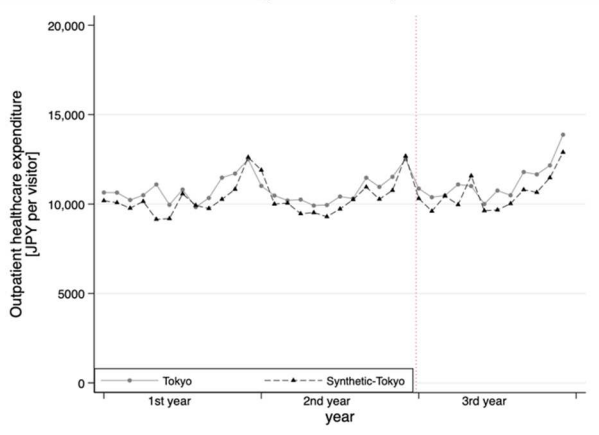


Healthcare expenditures

Children aged 5–7 years



Children aged 11–13 years



Abbreviations: DOTs, days of therapy

Conclusions

5-1. Summary of Key Findings

This dissertation evaluated the impacts of health policy changes on antibiotic and non-antibiotic prescription patterns and healthcare resource utilization using a nationally representative administrative database in Japan with quasi-experimental study designs of difference-in-differences and synthetic control methods.

Paper #1 (Chapter 2) examined the trends and variations of antibiotic use across different clinics. The National Action Plan on Antimicrobial Resistance in 2016 reduced the total antibiotic prescription rates and improved their patterns. However, these effects were heterogeneous across different clinics, suggesting the need for monitoring antibiotic prescription patterns at clinic levels that were below the standard levels.

Paper #2 (Chapter 3) evaluated the impacts of introducing financial incentives for not prescribing antibiotics on antibiotic prescription and healthcare utilization. It showed that the introduction of incentives was associated with reductions in antibiotic and non-antibiotic prescriptions and a slight increase in outpatient healthcare expenditures.

Paper #3 (Chapter 4) investigated the effects of introducing financial incentives for creating antimicrobial stewardship teams on antibiotic and non-antibiotic prescriptions and healthcare utilization in hospitals. The introduction of incentives was associated with very slight reductions in antibiotic prescriptions and increases in non-antibiotic prescriptions.

Paper #4 (Chapter 5) assessed the effects of interrupting free medical care certificates for children on the antibiotic and non-antibiotic prescriptions and healthcare utilization. The

interruption of free medical certificates was not associated with antibiotic prescriptions but was associated with reductions in non-antibiotic prescriptions and outpatient healthcare expenditures.

5-2. Implications and future research directions

The dissertation's findings suggest that small financial incentives for not prescribing antibiotics have successfully reduced outpatient antibiotic use. However, the incentives for creating antimicrobial stewardship teams and interruption of free medical certificates did not contribute to sufficient antibiotic use reductions. These findings have important implications for modifying current health policies.

First, we observed substantial reductions in antibiotic use after introducing financial incentives for appropriate non-prescribing of antibiotics in April 2018. The policy experimentally started at pediatric outpatient clinics targeting children aged < 3 years. In April 2020, this health policy was revised; the age range was extended from 0–3 years to 0–6 years. The changes in health policy and their long-term effects would be of specific interest to policymakers.

Second, the incentives for creating antimicrobial stewardship teams did not sufficiently reduce antibiotic prescriptions for pediatric inpatients. This health policy was originally introduced for optimizing broad-spectrum antibiotics among adult inpatients. As the policy effects on adult inpatients with infectious diseases have not been assessed, future studies targeting adult inpatients would have significant implications.

Third, the free medical certificates and free prescription policy was contributed to the overprescription of non-antibiotic drugs and elevated healthcare expenditure. It would be meaningful to seek an optimal cost-sharing point for the health insurance system for children.