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Miscellaneous

The consequence of financial incentives for not prescribing antibiotics: a Japan's nationwide quasi-experiment

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Abstract

Background: For addressing antibiotic overuse, Japan designed a health care policy in which eligible medical facilities could claim a financial reward when antibiotics were not prescribed for early-stage respiratory and gastrointestinal infections. The policy was introduced in a pilot manner in paediatric clinics in April 2018.

Methods: We conducted a quasi-experimental, propensity score-matched, difference-in-differences (DID) design to determine whether the nationwide financial incentives for appropriate non-prescribing of antibiotics as antimicrobial stewardship [800 JPY (≈7.3 US D) per case] were associated with changes in prescription patterns, including antibiotics, and health care use in routine paediatric health care settings at a national level. Data consisted of 9 253 261 cases of infectious diseases in 553 138 patients treated at 10 180 eligible or ineligible facilities.

Results: A total of 2959 eligible facilities claimed 316 770 cases for financial incentives and earned 253 million JPY (≈2.29 million USD). Compared with ineligible facilities, the introduction of financial incentives in the eligible facilities was associated with an excess reduction in antibiotic prescriptions [DID estimate, -228.6 days of therapy (DOTs) per 1000 cases (95% CI, -272.4 to -184.9), which corresponded to a relative reduction of 17.8% (95% CI, 14.8 to 20.7)]. The introduction was also associated with excess reductions in drugs for respiratory symptoms [DID estimates, -256.9 DOTs per 1000 cases (95% CI, -379.3 to -134.5)] and antihistamines [DID estimate, -198.5 DOTs per 1000 cases (95% CI, -282.1 to -114.9)]. There was no excess in out-of-hour visits [DID estimate, -4.43 events per 1000 cases (95% CI, -12.8 to 3.97)] or hospitalizations [DID estimate, -0.08 events per 1000 cases (95% CI, -0.48 to 0.31)].

Conclusions: Our findings suggest that financial incentives to medical facilities for not prescribing antibiotics were associated with reductions in prescriptions for antibiotics without adverse health care consequences. Japan's new health policy provided us with policy options for immediately reducing inappropriate antibiotic prescriptions by relatively small financial incentives.

Key words: National action plan on antimicrobial stewardship, financial incentive, propensity score-matching, difference-in-differences

Key Messages

- We investigated whether the nationwide financial incentives to medical facilities for not prescribing antibiotics as antimicrobial stewardship were associated with changes in prescriptions for antibiotics, drugs for respiratory symptoms and antihistamines, health care use and hospitalization rate in routine paediatric care settings at a national level.
- In this cohort study of 10 180 facilities and 553 138 younger children, 2959 (29%) medical facilities voluntarily applied for the incentive system.
- Financial incentives for not prescribing antibiotics were associated with reductions in prescriptions for antibiotics, drugs for respiratory symptoms and antihistamines and increased health care costs but were not related to the out-of-hour visit and hospitalization rates.
- Our findings support the new health policy for reducing inappropriate antibiotic use by relatively small incentives, which could be a policy option for immediately reducing inappropriate antibiotic prescriptions.

Introduction

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 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 remained high at the national level.[19,20]

The Ministry of Health, Labour and Welfare (MHLW) in Japan designed a novel health care 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) (≈7.3 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 paediatric outpatient clinics in April 2018.[21] However, the changes in practice patterns before and after introducing the health policy have not been examined nationwide.

Therefore, in our study, we aimed to investigate whether the financial incentives for not prescribing antibiotics were associated with changes in prescription behaviours of physicians and health care utilizations following the non-prescribing events, using the full national samples from the National Database of Health Insurance Claims and Specific Health Checkups (NDB).

Methods

Study oversight and data acquisition

The institutional review board at the National Center for Child Health and Development, Japan, and that at the University of California, Los Angeles, USA, approved our study. The MHLW approved our data request and extracted the relevant data from the NDB. Due to Japan's universal health care system,[23] MHLW retained almost all the outpatient claims data (95–99% of claims records for paediatric infectious diseases, ≈1 billion data elements of claims records per year), which were processed and transferred to the NDB for the research purposes.[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 health care 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, in each of which secondary care can be completed).

Japan's health policy change (quasi-experiment)

A new health policy was initiated on 1 April 1 2018, as part of the antimicrobial stewardship programme under the National Action Plan on Antimicrobial Resistance.[21,25] The 'treatment' of interest in our study was the eligibility for the policy: after physicians decided not to prescribe antibiotics, the eligible medical facilities (not physicians) could claim and receive a financial reward of 800 JPY (≈7.2 USD) for a patient's first visit for a particular disease occurrence. To be eligible, outpatient departments of paediatrics in clinics and hospitals needed to be registered in advance as medical facilities designated to specialized paediatric care and its specific comprehensive payment system (details are summarized in Supplementary Material, available as Supplementary data at *IJE* online). Otherwise, medical facilities were ineligible for the policy: for example, medical facilities without paediatric departments (e.g. departments of internal medicine, otolaryngology) and those with fee-for-service systems. Under the universal health care systems in Japan, where no strict primary-care physician system exists, parents of children were free to select any types of facilities (e.g. physicians' specialty, payment system, size of the facility) of their choice.

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 or acute gastroenteritis.[21] The first choice was not prescribing antibiotics, with explanations to the patients and caregivers (e.g. the rationale for non-prescribing antibiotics and home care advice; an acute self-limiting illness, indications for antibiotic use, criteria for a re-visit) and claiming the financial reward. The second choice was prescribing antibiotics and not claiming the financial reward.

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] The cohort was restricted to all the children who were born between April 2016 and March 2017 (≈977 000 infants)[26] and those 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 codes[27] (Supplementary Table S1, available as Supplementary data at *IJE* online). We included all types of infectious diseases, to avoid selection bias and misclassification from changes in diagnostic coding after introducing incentives in the eligible medical facilities.

The NDB had unique identification numbers for patients and medical facilities, which allowed us to follow data at patient- and medical facility-levels over the 3 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 paediatric complex chronic conditions classification system (e.g. congenital diseases, malignancy and autoimmune diseases).[28] We also excluded the claims of 609 individuals with diagnosis codes of death or cardiac arrest over the study period, to exclude individuals who were right-censored (Supplementary Table S1). The claims records submitted from medical facilities with <10 paediatric outpatients per month were also excluded, to focus our analyses on the facilities which routinely treated paediatric outpatients with infectious diseases (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 amounts of broad-spectrum antibiotics, drugs for respiratory symptoms and antihistamines (Supplementary Table S2, available as Supplementary data at *IJE* online), out-of-hours office visits, total outpatient health care expenditure (including financial incentives) and infectious disease-related hospitalizations. In Japan, oral antibiotics were available only with physicians' prescriptions and were filled at medical facilities or pharmacies.[29] We considered third-generation cephalosporin, oral penem, fosfomycin, tetracycline and quinolone as broad-spectrum antibiotics (Supplementary Table S3, available as Supplementary data at *IJE* online).[7,20,30–32]

Covariates

The baseline characteristics included the patient's sex and comorbidities of asthma/wheezing, rhinitis, sinusitis, atopic dermatitis/eczema, food allergy and seizure, as well as facilities' geographical locations (Supplementary Table S4, available as Supplementary data at *IJE* online). The comorbidities were identified using ICD-10 codes (Supplementary Table S1) in the first year (look-back period). We also obtained the number of visits, prescriptions, out-of-hours visits, health care expenditure and hospitalizations over the first and second years as proxy variables to account for access to health care 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 analyses

We applied a quasi-experimental difference-in-differences (DID) design with propensity score (PS)-matching.[33] All data were analysed using Stata/MP software version 16.1 (StataCorp., TX, USA) with four steps.

First, we summarized baseline characteristics by calculating means and proportions 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 2 years falling in the look-back and pre-intervention periods (e.g. DOTs per 1000 cases for antibiotics, antihistamines) as covariates for predicting PS. Although other facility-level characteristics (e.g. specific address) were not provided due to the strict rules of the NDB, we could obtain the average numbers of visitors at facilities and 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 (Supplementary Table S5, available as Supplementary data at *IJE* online). Then, we conducted one-to-one matching between the eligible and ineligible facilities using the nearest-neighbour methods within a calliper distance of <20% of standard deviation in PS.[33] 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 (>10% was considered a meaningful imbalance).[33]

Third, using the matched sample with the same number of eligible and ineligible facilities, we performed a DID analysis.[34–37] Since the effect of the treatment could arise only in the eligible facilities after April 2018, it would be captured by the coefficient for an interaction term of the treatment and time-indicator variables (pre- vs post-intervention periods), which reported the effect size in an absolute scale as DID estimates (Supplementary Table S5). We did not include the data during the look-back period for the DID models, to avoid bias due to left-censoring. Other covariates were not included in the DID models in the primary analysis, since we assumed no meaningful imbalance in the PS-matching above. We also obtained the effect sizes in a relative scale (percent reduction) as change-in-changes (CiC) estimates.[38] To incorporate the cross-classified hierarchical data structure, we used generalized estimation equations under robust variance estimates and independence correlation matrix.[39]

Fourth, we conducted a series of sensitivity analyses for evaluating the model assumptions in the above-mentioned primary analyses. In addition, we set antipyretics, antidiarrhoeal agents and bronchodilators as negative outcome controls and undertook negative outcome control analyses because these medications were prescribed as needed (e.g. fever, wheezing), and their use would be constant regardless of the introduction of financial incentives (Supplementary Material).

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 health care cost of approximately 253 million JPY (≈2.29 million USD). Overall, 2959 (29.1%) facilities were eligible for financial rewards.

Propensity score-matching

Our PS-matching procedure (Supplementary Figure S1, available as Supplementary data at *IJE* online) 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 1).[33]

Prescriptions for antibiotics, drugs for respiratory symptoms and antihistamines

The PS-matched DID analyses (Figure 1 and Table 2) showed that the introduction of the financial incentives was associated with an excess reduction in the antibiotic prescriptions among the eligible facilities, compared with the ineligible facilities, on an absolute scale by -228.6 DOTs per 1000 cases (95% CI, -272.4 to -184.9) and on a relative scale by 0.822 (95% CI, 0.793 to 0.852), which meant a 17.8% reduction (Figure 2).

Similarly, it was associated with an excess reduction in broad-spectrum antibiotic use on an absolute scale (DID estimate, -124.7 DOTs per 1000 cases; 95% CI, -156.3 to -93.1) and on a relative scale (CiC estimate, 0.808; 95% CI, 0.768 to 0.851).

It was also associated with excess reductions in drugs for respiratory symptoms on an absolute scale (DID estimate, -256.9 DOTs per 1000 cases; 95% CI, -379.3 to -134.5) and on a relative scale (CiC estimate, 0.965; 95% CI, 0.949 to 0.982); and of antihistamines on an absolute scale (DID estimate, -198.5 DOTs per 1000 cases; -282.1 to -114.9) and on a relative scale (CiC estimate, 0.928; 95% CI, 0.900 to 0.958).

Health care use and outpatient health care expenditure

The introduction of the financial incentives was not associated with a change in the magnitude of the out-of-hours visits on an absolute scale (DID estimate, -4.43 events per 1000 cases; 95% CI, -12.8 to 3.97) or on a relative scale (CiC estimate, 0.972; 95% CI, 0.924 to 1.024). It was also not associated with a change in the hospitalization rates on an absolute scale (DID estimate, -0.08 events per 1000 cases; 95% CI, -0.48 to 0.31) or on a relative scale (CiC estimate, 0.900; 95% CI, 0.680 to 1.191). However, we observed an elevation of the total outpatient health care expenditure (including financial incentives) in the eligible facilities compared with the ineligible facilities on an absolute scale [DID estimate, 512.1 JPY per case (≈4.7 USD); 95% CI, 377.0 to 647.2] and on a relative scale (CiC estimate, 1.042; 95% CI, 1.031 to 1.052).

Sensitivity analyses

Our sensitivity analyses showed findings consistent with our main results regarding the directions in effect estimates and their interpretations (see Supplementary Material).

Discussion

In our nationwide quasi-experiment in Japan, we found that the financial incentives were associated with reductions in the total antibiotic prescriptions by 17.8% and in prescriptions for drugs for respiratory symptoms and antihistamines, without excess adverse health consequences (e.g. hospitalization rates), although the amount of incentives for not prescribing antibiotics was not very high [800 JPY (≈7.2 USD) per case].

The incentive-induced behavioural changes of physicians occurred immediately in the month of the policy introduction and remained until the end of the 12-month follow-up. The MHLW set the National Action Plan on Antimicrobial Resistance and distributed the guideline for appropriate antibiotic use in 2016 (2 years before introducing the financial incentives). The introduction of financial incentives paid directly to physicians' practice might have encouraged physicians to apply their knowledge to the actual practice. In addition, this immediate change contrasted sharply with conventional strategies nationwide to gradually reduce antibiotic prescriptions, which consisted of establishing a national target, monitoring the trends in antibiotic prescriptions, implementing surveillance of resistant strains, controlling resistant strains and communicating closely with physicians.[40–42] For example, such a multifaceted programme 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;[40–42] however, many developing and developed countries face a time-sensitive situation and thus require a strategy with more prompt impacts. Japan's financial incentive policy may provide these countries with hints for immediately altering the climate of antibiotic overuse.

From the behavioural economics perspective,[43,44] rewarding no antibiotic use is more constructive than different approaches (e.g. penalization).[45] With the reward, the government's commitment to reducing inappropriate antibiotic use was more clearly communicated without blaming physicians. However, several concerns about the financial incentives may arise. One is the increase in prescriptions of cold medicines (e.g. drugs for respiratory symptoms and antihistamines); however, we observed a slight reduction in these medications with potential adverse

Table 1 The geographical location of medical facilities and characteristics of patients during the look-back period and pre-intervention period between the eligible (index) and ineligible (control) facilities, before and after propensity score (PS)-matching. PS matching was performed using variables in the first and second years and secondary medical area of facilities. Standardized differences were used to assess the balances between the eligible and ineligible facilities. An absolute standardised difference: >10% is a meaningful imbalance between the index and control groups

	Before PS matching					After PS matching				
Medical facilities, *N*	Ineligible *N* = 7221		Eligible *N* = 2959		Standardized difference (%)	Ineligible *N* = 1710		Eligible *N* = 1710		Standardized difference (%)
Area of medical facilities, %					23.2					4.2
Hokkaido	312	(4.3)	60	(2.0)		41	(2.4)	41	(2.4)	
Tohoku	542	(7.5)	166	(5.6)		103	(6.0)	108	(6.3)	
Kanto	2413	(33.4)	1165	(39.4)		688	(40.2)	695	(40.6)	
Hokuriku/Koshinetsu	384	(5.3)	186	(6.3)		96	(5.6)	103	(6.0)	
Tokai	791	(11.0)	391	(13.2)		230	(13.5)	232	(13.6)	
Kansai	1236	(17.1)	416	(14.1)		245	(14.3)	241	(14.1)	
Chugoku	450	(6.2)	150	(5.1)		81	(4.7)	73	(4.3)	
Shikoku	222	(3.1)	106	(3.6)		59	(3.5)	53	(3.7)	
Kyushu/Okinawa	871	(12.1)	319	(10.8)		167	(9.8)	154	(9.0)	
Visited patients, *N*	**350 070**		**203 068**			**81 782**		**100 851**		
Cases, *N*	6 010 183		3 243 078			1 602 237		1 550 756		
Patient characteristics, *N* (%)										
Sex					0.7					0.5
Male	182 710	(52.2)	105 406	(51.9)		51 150	(51.6)	51 497	(51.9)	
Female	167 360	(47.8)	97 662	(48.1)		47 947	(48.2)	47 792	(48.1)	
First year (look-back period)										
Cases per clinic (SD)	171.6	(152.5)	219.6	(153.4)	−31.4	193.5	(147)	181.8	(137)	8.2
Comorbidity										
Wheezing	84 854	(24.2)	39 150	(19.3)	10.7	20 553	(20.7)	20 053	(19.4)	2.3
Eczema	230 193	(65.8)	135 879	(66.9)	2.0	65 583	(66.2)	65 712	(66.4)	0.4
Food allergy	12 554	(3.6)	5583	(2.8)	4.6	2843	(2.9)	2833	(2.9)	1.5
Rhinitis	87 803	(25.1)	36 313	(17.9)	15.1	20 132	(20.3)	20 486	(19.7)	0.8
Sinusitis	60 480	(17.3)	21 445	(10.6)	13.1	11 772	(11.9)	13 204	(12.9)	1.8
Seizure	2469	(0.7)	1016	(0.5)	1.9	625	(0.6)	553	(0.5)	0.8
Medication use, DOTs per 1000 cases (SD)										
Total antibiotics	822.3	(2543.0)	608.5	(1883.7)	9.5	662.0	(2016.8)	703.7	(2037.0)	−2.1
Broad-spectrum antibiotics	357.8	(1457.4)	253.7	(1150.6)	7.9	272.1	(1206.6)	309.3	(1284.6)	−2.6
Drugs for resp. symp.	4825.6	(7589.4)	5490.7	(7700.5)	−8.7	5261.0	(7765.2)	5231.6	(7529.1)	0.4
Antihistamines	1422.9	(3709.3)	1452.5	(3549.6)	−0.8	1469.0	(3666.1)	1574.2	(3680.6)	−2.9
Health care costs, JPY per case (SD)	15 680	(42 739)	12 538	(18 004)	9.6	12 864	(18 577)	12 567	(23 143)	1.4
Health care use, events per 1000 cases (SD)										
Out-of-hour visits	229.8	(745.4)	114.6	(425.0)	19.0	141.9	(495.4)	137.0	(488.6)	1.0
Hospitalisations	9.49	(96.9)	3.28	(57.1)	0.8	4.33	(65.6)	4.30	(65.4)	0.0
Second year (pre-intervention period)										
Cases per clinic (SD)	399.3	(311.3)	518.3	(356.6)	−35.5	453.2	(327)	427	(308)	8.3
Comorbidity										
Wheezing	149 186	(52.2)	77 106	(45.9)	12.5	38 466	(47.4)	37 932	(46.6)	1.6
Eczema	211 355	(74.0)	124 495	(74.2)	0.4	59 683	(73.5)	60 104	(73.8)	0.6
Food allergy	24 171	(8.5)	12 139	(7.2)	4.6	6055	(7.5)	6124	(7.5)	0.2
Rhinitis	156 217	(54.7)	76 796	(45.7)	17.9	39 302	(48.4)	39 234	(48.2)	0.5
Sinusitis	107 265	(37.5)	50 489	(30.1)	15.8	24 530	(30.2)	26 117	(32.1)	4.0
Seizure	13 209	(4.6)	6795	(4.0)	2.8	3444	(4.2)	3422	(4.2)	0.2
Medication use, DOTs per 1000 cases (SD)										
Total antibiotics	1653.2	(3519.1)	1094.8	(2613.0)	18.0	1240.5	(2813.8)	1261.5	(2814.6)	−0.7

(Continued)

Table 1 Continued

Medical facilities, *N*	Before PS matching					After PS matching				
	Ineligible *N* = 7221		Eligible *N* = 2959		Standardized difference (%)	Ineligible *N* = 1710		Eligible *N* = 1710		Standardized difference (%)
Broad-spectrum antibiotics	823.7	(2248.9)	540.0	(1737.7)	14.1	623.3	(1862.9)	649.3	(1903.1)	−1.3
Drugs for resp. symp.	6650.5	(9546.3)	7047.5	(9443.9)	−4.1	6727.9	(9512.2)	6734.9	(9234.0)	0.0
Antihistamines	2580.5	(5314.5)	2421.8	(4933.9)	3.1	2479.8	(5098.4)	2533.9	(5034.7)	−1.1
Health care costs, JPY per case (SD)	13 478	(15 119)	13 642	(10 434)	−1.2	13 352	(12 710)	13 376	(11 369)	−0.2
Health care use, events per 1000 cases (SD)										
Out-of-hour visits	260.2	(815.6)	144.2	(478.2)	17.4	164.5	(561.1)	163.3	(512.7)	0.2
Hospitalizations	3.83	(61.7)	1.65	(40.5)	4.2	2.02	(44.9)	1.98	(44.4)	0.0

PS, propensity score; resp. symp., respiratory symptoms; DOTs, days of therapy; SD, standard deviation; JPY, Japanese Yen.

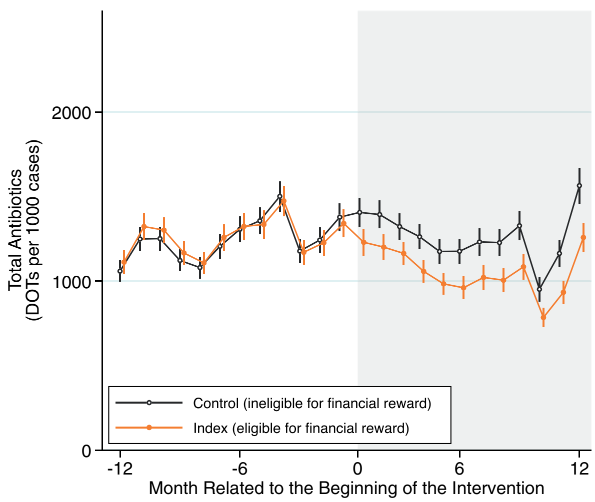

Figure 1 Trends in total antibiotic use as days of therapies [DOTs] per case with 95% confidence intervals between the eligible (index) and ineligible (control) medical facilities during pre-intervention and post-intervention periods in the propensity score-matched samples.

effects (e.g. antihistamines). The introduction of new health policies may have had the added benefit of prompting physicians to review their prescribing patterns. Another is the cost, considering the additional outpatient health care expenditure [512.1 JPY per case (≈4.7 USD)] from the financial incentive scheme [800 JPY per case (≈7.1 USD)]. Although the reductions in prescriptions for antibiotics, drugs for respiratory symptoms and antihistamines partially offset the increase in health care costs, the use of the financial incentives as a 'nudge' (dangling a small financial stake upon the antibiotics prescription decision-making process) could be more expensive than penalties[46] and non-financially-based behavioural interventions [e.g. changes in antibiotic prescription among adult outpatients: peer comparison (absolute reduction by 5.2%) and accountable justification (absolute reduction by 7.0%)].[47–49] This concern was not the case in our study because a 17.8% relative reduction of antibiotic use in acute viral infections among the youngest children, whose gut microbiome was the least developed,[50] 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.[51]

The strength of the financial incentive policy stems not only from its immediate impact with relatively low cost but also from its ability to offer a fundamental solution to the prisoner's dilemma-like problem[52] of antibiotic 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 (potential adverse effects, alteration of the gut microbiome and cost-sharing for antibiotics may be considered 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[53]) 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; for physicians, this is a bias towards action in the face of uncertainty. This practice leads to a vicious cycle of the maintenance of antibiotic overuse and the development of resistant strains. Therefore, schemes that invest the current physical and financial resources in health care in such ecosystem-level future benefits are warranted for achieving 'cooperation with the future'.[54] Japan's financial incentive policy was one of them: it valued and priced no antibiotic use upon acute infections in the current health care system, even though no antibiotic use did not consume

Table 2 Differences in outcomes between the eligible (index) facilities and ineligible (control) facilities after propensity score-matching using data during the first and second years

	Ineligible facilities ($N = 1710$)			Eligible facilities ($N = 1710$)			
	Pre	Post	Difference	Pre	Post	Difference	DID estimate (CI)
Medications, DOTs per 1000 cases (SE)							
Total antibiotics	1240.5	1268.9	28.4	1261.5	1061.3	−200.2	−228.6
	(3.2)	(4.0)		(3.3)	(3.6)		(−272.4, −184.9)
Broad-spectrum antibiotics	623.3	627.2	−0.9	649.3	528.5	−102.0	−124.7
	(2.1)	(2.6)		(2.2)	(2.4)		(−156.3, −93.1)
Drugs for respiratory symptoms	6727.9	7471.7	3.9	6734.9	7221.7	−120.8	−256.9
	(10.8)	(13.8)		(10.8)	(13.0)		(−379.3 −134.5)
Antihistamines	2479.8	2841.8	331.9	2533.8	2697.4	186.6	−198.5
	(5.7)	(7.9)		(5.8)	(7.4)		(−282.1, −114.9)
Health care use, event per 1000 cases (SE)							
Out-of-hour visits	164.54	164.69	0.15	163.29	159.00	−4.29	−4.43
	(0.63)	(0.78)		(0.60)	(0.66)		(−12.8, 3.97)
Hospitalizations	2.02	1.08	−1.21	1.97	0.95	−1.00	−0.08
	(0.05)	(0.05)		(0.05)	(0.04)		(−0.48, 0.31)
Outpatient health care expenditures, JPY per case	13 352.7	12 179.9	−0.94	13 376.4	12 715.6	−1.02	512.1
(SE)	(14.4)	(15.9)		(13.3)	(11.0)		(377.0, 647.2)

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

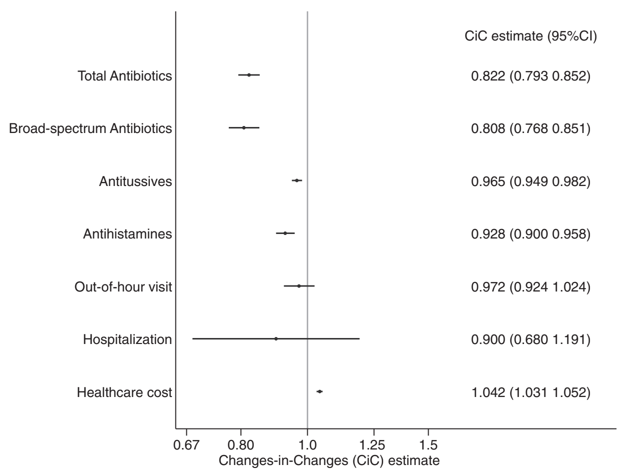

Figure 2 Changes-in-changes (CiC) estimates with 95% confidence intervals for total and broad-spectrum antibiotics, drugs for respiratory symptoms, antihistamines, out-of-hour visits, hospitalizations and outpatient health care expenditures.

any physical resources (i.e. antibiotic drugs) at the moment. Such a fundamental solution may complement other conventional comprehensive programmes[40–42] or non-financially-based programmes.[48,55,56]

Our study has several limitations. Biases due to unobserved confounding factors and model mis-specification might be inherent although 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 medical areas and the composite variables calculated by individual-level characteristics for the PS-matching, assuming that the eligible and ineligible facilities were conditionally exchangeable on the observed covariates. A cluster randomized controlled trial with a random assignment of the financial incentives 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 under the parallel trend assumption in time-series data.[34–37] However, if the assumption is violated, DID estimates could be biased because of the time-varying confounders (e.g. changes in outpatient characteristics). In addition, in the presence of spillover effects, our DID estimates could be biased toward the null. Furthermore, PS-matching could either reduce or induce bias in the DID analysis, depending on the sampled population (e.g. regression to the mean bias).[35,37] To address these issues, we conducted several sensitivity analyses. First, we observed similar directions of associations, although effect sizes were different across different statistical models (Supplementary Tables S6–S12, available as Supplementary data at *IJE* online). Second, we used antipyretics, antidiarrhoeal agents and bronchodilators as negative outcome controls and conducted DID analyses, which observed almost null or slightly reduced prescriptions (Supplementary Table S16, available as Supplementary data at *IJE* online).

Furthermore, the best size of the financial incentives across different contexts is difficult to determine. For example, an increase in the financial incentives (e.g. 800 to 2000 JPY per case) may further reduce antibiotic prescriptions. However, it may cause inappropriate non-use, which will increase out-of-hour visits and hospitalizations because of under-treatment and subsequent severe bacterial complications. In Japan, the financial incentive of 800 JPY per case has worked so far with relatively small incremental cost (1.8% of total health care expenditure, see Supplementary Material). Although some physicians might want to claim as many 'free' financial rewards as possible, we found that, in general, they did not do so and instead might prescribe antibiotics only when necessary. Such a good balance may vary across different contexts; however, no evidence has been established yet for the adequate pricing of not prescribing antibiotics.

Conclusion

Our results should also be interpreted as early evidence of financial incentives for appropriate non-prescribing of antibiotics: it could be transient, and the external validity of other populations (e.g. older children, adults) is uncertain. Nevertheless, if a financial incentive policy, including its amount, target and timing of introduction, is carefully designed to fit a given country's sociopolitical contexts and budgets, it may have a strong potential for addressing antibiotic overuse.

Ethics approval

The institutional review board at the National Center for Child Health and Development, Japan (IRB number: 1491) and that at the University of California Los Angeles, USA (IRB number: 20–002199), approved our study. The boards waived informed consent because of the anonymous nature of the database.

Data availability

Due to the data protection policy of the Ministry of Health, Welfare and Labour in Japan, supporting data cannot be made openly available.

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

Y.O, K.U, N.K.,I.M. obtained the national data from the Ministry of Health, Welfare and Labour in Japan. Y.O. coordinated the data management, drafted the initial manuscript and performed the initial analyses. A.N., H.N., K.U., N.K., O.A.A., R.J.K-F., K.B.M.,I.M., supervised the study design and analyses, revised the manuscript and approved the final manuscript as submitted. Each author has seen and approved the submission of the manuscript and takes full responsibility for its contents.

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Conflict of interest

There is no conflict of interest for this study.

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