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Original Article

Targets for Optimizing Oral Antibiotic Prescriptions for Pediatric Outpatients in Japan

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SUMMARY: In Japan, 92.6% of antibiotics consumed are oral agents; most of these are for outpatients. A significant proportion is known to be dispensed for children; however, the specific pattern of antibiotic prescription in accordance with clinical specialty is still unclear. The aim of our study was to identify the key targets for the optimization of oral antibiotic use in children. We analyzed data on oral antimicrobial prescription patterns for children < 16 years old of age in 3 urban districts by using a national database in Japan. Oral prescriptions were categorized according to their class, spectrum, clinical specialty, and type of clinical setting. The antibiotic spectrum was categorized as narrow, broad, or ultra-broad. In total, 132,869,332 antibiotic prescriptions were collected for analysis. The proportions of narrow-spectrum, broad-spectrum, and ultra-broad-spectrum antibiotics were 10.9%, 73.7%, and 15.4% in primary care clinics and 23.4%, 71.1%, and 5.4% in hospitals, respectively. Prescriptions from pediatricians and otolaryngologists in primary care clinics were predominant in the 3 studied areas. Third-generation cephalosporins, quinolones, penems, and carbapenems were prescribed mostly by pediatricians and otolaryngologists. Ultra-broad spectrum antibiotics used in primary care clinics and antibiotics particular to each specialty were identified as key targets for the optimization of oral antibiotic use for pediatric outpatients.

INTRODUCTION

Antimicrobial resistance (AMR) is recognized as a global problem and a threat to human health and social economics (1–3). Antimicrobial stewardship programs (ASPs), which ensure the proper use of antimicrobials, have been shown to be useful to optimize the treatment of infections, as well as to limit the spread of multi-drug resistant organisms or the adverse events associated with antibiotic use (4–6).

The majority of antimicrobials are prescribed to outpatients; for example, 92.6% of antimicrobials prescribed in Japan are oral agents prescribed predominantly in outpatient settings (7). Thus, the optimization of antimicrobial use in outpatient settings is essential for the optimization of their overall use. However, most ASPs have primarily targeted in-hospital prescriptions, with less regard to those in outpatient settings (8,9). Little evidence is available on the practical interventions to promote ASP in this setting; therefore, an important initial step is the identification of key targets for intervention (10).

Such key targets may differ by population, as each country differs in their health care system, disease epidemiology, and occurrence rates of resistant organisms. One characteristic for Japan that should be incorporated is the system of free medical access in pediatric care that relieves the financial burden on parents or guardians. Universal health insurance and the full reimbursement program for pre-school children by local government enable patients to be treated and obtain prescriptions with little or no charge in a majority of areas in Japan. As most clinics accept walk-in patients without referrals, patients can easily seek care from physicians with many different specialties for the same symptoms. For example, a child with a runny nose or cold may visit an otolaryngologist or an internal medicine physician, as well as a pediatrician. A child with a rash may visit a dermatologist or a pediatrician. As different specialties may follow different practices and guidelines with regard to the prescription of antimicrobials, understanding what type of antimicrobials are being prescribed and where may help to identify areas where the implementation of ASP for children may be most effective.

In 2016, 3 urban cities were selected as pilot areas to test population-based outpatient ASP interventions as part of a government-funded project to formulate

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an effective method of antimicrobial stewardship for pediatric outpatients. The aim of our study was to observe the differences in patterns of oral antimicrobial prescription to children by clinical specialty and to identify key targets for the optimization of oral antibiotic use in children.

MATERIALS AND METHODS

This study was funded by a grant from the Ministry of Health, Labour and Welfare, Japan (MHLW Shinko-02) to promote ASP for children in the community. This study was approved by the institutional review board at the National Center for Child Health and Development (IRB-1491).

Study design: Three designated communities were selected by the Ministry of Health, Labour and Welfare as pilot areas to test ASP interventions for children in the community: area A, Fuchu city (Tokyo); area B, Setagaya-ku (Tokyo); and area C, Kobe city (Hyogo). All 3 areas were urban cities with a tertiary children's hospital in the area. For this study, we retrospectively analyzed data on all antimicrobial dispensing receipts between January 2013 and December 2016 in these 3 communities, identified from the national claims database.

Data source: Japanese social health insurance provides universal coverage for all citizens, with the information available as an electronic claims database. The database of all electronic claims data, known as the national database of health insurance claims, and specific health checkups of Japan, currently cover approximately 99% of healthcare services provided by health insurance (11). In this study, we evaluated the data from the national database of health insurance claims in 2 parts.

First, we used the dispensing receipts database from pharmacists' offices, which include details of the medication dispensed, to identify all oral antibiotics dispensed to children < 16 years of age during the study period (2013–2016). We excluded parenteral antibiotics, topical antibiotics, antivirals, anti-tuberculosis medications, antifungals, and antiparasitic agents. The information obtained from each prescription included age, residence area, type of antibiotic, and days of therapy (DOTs) for each antibiotic.

Second, we used the national medical receipts database, which includes all medical receipts from hospital pharmacies to outpatients, to identify all oral antibiotics dispensed to children < 16 years of age during the study period (2013–2016). This dataset was included as the dispensing receipts database does not cover medications dispensed to patients by in-house pharmacies in clinics, although patients that visit emergency department out-of-hours receive medication from in-hospital pharmacies. Previous studies have shown that such in-house prescriptions may account for 27%–30% of all medications prescribed to outpatients (12).

We also investigated the type of clinical setting (primary care clinic or secondary/tertiary care hospital) and clinical specialties of the prescribing physicians (pediatrician, family physician, internal medicine physician, dermatologist, otolaryngologist, or other specialty) for each prescription in the 3 pilot cities. A "family physician" was defined as a clinic that provides care for both pediatric and internal medicine patients.

The pediatric population data from each area was obtained from the results of a population survey report that was previously published by the Ministry of Internal Affairs and Communications of Japan between 2013 and 2016 (13).

Type of antibiotic: Antibiotics for systemic use were coded as J01 according to the World Health Organization (WHO) Anatomical Therapeutic Chemical classification system (14). In total, 41 antibiotics were included in the analysis, and were classified into the following 17 classes: benzyl penicillin (J01CE01); penicillins with extended spectrum (J01CA); combinations of penicillins, including beta-lactamase inhibitors (J01CR), first-generation cephalosporins (J01DB), second-generation cephalosporins (J01DC), third-generation cephalosporins (J01DD), faropenem (J01DI03), other cephalosporins, penems, and carbapenems (J01DIXX); vancomycin (A07AA09); fosfomycin (J01XX01); macrolides (J01FA); tetracyclines (J01AA); lincosamides (J01FF); linezolid (J01XX08); chloramphenicol (J01BA01); quinolone antibacterials (J01M); and sulfamethoxazole/trimethoprim (J01EE01). In this database, metronidazole was categorized as an anti-parasitic drug.

We designated the above-mentioned antibiotics into 3 groups; namely, narrow-spectrum, broad-spectrum, and ultra-broad-spectrum antibiotics (15,16). Narrow-spectrum antibiotics included benzyl penicillin (J01CE01), penicillins with extended spectrum (J01CA), first-generation cephalosporins (J01DB), and second-generation cephalosporins (J01DC). Broad-spectrum antibiotics included penicillins with beta-lactamase inhibitors (J01CR), third-generation cephalosporins (J01DD), macrolides (J01FA), sulfamethoxazole/trimethoprim (J01EE01), and lincosamides (J01FF). Ultra-broad-spectrum antibiotics included faropenem (J01DI03), penems, carbapenems (J01DIXX), quinolones (J01M), vancomycin (A07AA09), fosfomycin (J01XX01), tetracyclines (J01AA), linezolid (J01XX08), and chloramphenicol (J01BA01). In Japan, tebipenem pivoxil (carbapenem), faropenem (penem), and tosufloxacin (quinolone) are approved for oral use in children, for which health insurance will provide reimbursement. From the final analysis, we excluded antibiotics that comprised less than 0.01% of the total antimicrobial use.

Statistical analysis: First, we calculated the total and population-adjusted antimicrobial prescriptions for the 3 areas. To provide numbers that were comparable across different populations, we used the unit of DOTs/1,000 pediatric inhabitants/day, calculated as average DOTs over every 1,000 inhabitants of < 16 years of age in each area. Second, to observe how prescription practices differed by setting, we calculated the total DOTs for each antibiotic by medical setting (hospital or clinic), as well as by clinical specialty for each area. For these analyses, antimicrobials for which the percentage of non-adjusted DOTs was less than 0.01% of total antimicrobial use were excluded from the analysis. We also analyzed the proportion of tetracycline prescriptions, which should not be used in children < 8

Table 1. Population, days of therapy, and number of hospitals and clinics in 3 areas

	Area A	Area B	Area C
Population ≤ 15 years old (average between 2013 and 2016)	37,274	108,008	199,116
Days of therapy	1,254,022	3,883,851	7,761,214
Days of therapy (adjusted)	1,513,838	4,554,930	9,363,962
Days of therapy/1,000 pediatric inhabitants/day	23	24.6	26.7
Days of therapy/1,000 pediatric inhabitants/day (adjusted)	27.8	28.9	32.2
Number of clinics and hospitals	176	872	1536
Primary care clinics	-	-	-
Pediatrician	11	68	86
Family physician	38	117	126
Internal medicine physician	53	316	540
Otolaryngologist	11	56	82
Dermatologist	5	65	81
Others*	44	223	506
Hospital-based outpatient clinics	-	-	-
Pediatric secondary and tertiary care hospitals	5	10	30
Non-pediatric secondary and tertiary care hospitals	9	17	85

*Others: general surgeon, plastic surgeon, neurosurgeon, orthopedic surgeon, pain clinic, obstetrics, and gynecology.

Table 2. Detailed ratio of dispensed oral antibiotics and days of therapy (adjusted and non-adjusted) in 3 areas

	Area A (non-adjusted)	Area A (adjusted)	Area B (non-adjusted)	Area B (adjusted)	Area C (non-adjusted)	Area C (adjusted)	Total (non-adjusted)	Total (adjusted)	% (non-adjusted)	% (adjusted)
Population ≤ 15 years old (average between 2013 and 2016)	37,274		108,008		199,116		344,398		—	—
Benzylpenicillin (J01CE01)	3,276	3,276	3,374	3,374	1,003	1,003	7,653	7,653	0.06	0.05
Penicillins with extended spectrum (J02CA)	221,015	257,253	519,710	589,790	563,629	631,572	1,304,354	1,478,615	10.1	9.6
Combinations of penicillins, including beta-lactamase inhibitors (J01CR)	29,350	35,914	109,480	114,177	235,005	256,046	373,835	406,137	2.9	2.6
First-generation cephalosporins (J01DB)	37,604	73,003	10,717	15,557	11,036	22,885	59,357	111,445	0.5	0.7
Second-generation cephalosporins (J01DC)	68,470	88,189	121,487	137,463	51,018	69,862	240,975	295,515	1.9	1.9
Third-generation cephalosporins (J01DD)	313,900	369,005	1,151,191	1,375,364	2,705,684	3,439,091	4,170,775	5,183,459	32.3	33.6
Faropenem (J01DI03)	5,792	5,899	28,083	31,524	145,570	162,195	179,445	199,617	1.4	1.3
Other cephalosporins, penems, and carbapenems (J01DIXX)	7,123	7,590	78,245	81,562	229,616	237,003	314,984	326,155	2.4	2.1
Fosfomycin (J01XX01)	14,489	18,909	48,470	105,750	199,854	313,135	262,813	437,794	2.0	2.8
Macrolides (J01FA)	385,428	446,780	1,252,921	1,473,163	2,823,275	3,348,642	4,461,624	5,268,585	34.6	34.1
Tetracyclines (J01AA)	12,886	13,676	76,909	103,528	195,165	220,457	284,960	337,660	2.2	2.2
Lincosamides (J01FF)	1,642	2,210	935	956	3,105	3,213	5,682	6,379	0.04	0.04
Quinolone antibacterials (J01M)	24,829	31,487	214,973	249,542	544,288	597,742	784,090	878,771	6.1	5.7
Sulfamethoxazole/trimethoprim (J01EE01)	128,175	160,603	267,328	273,154	52,966	61,115	448,469	494,872	3.5	3.2

years of age, because tetracycline is not recommended in this population owing to the risk of permanent tooth discoloration (17).

All analyses were performed using the national antimicrobial dispensed receipts database; thus, they were limited to outpatient medication dispensed at pharmacies outside of the hospitals. However, to account for medication dispensed in hospitals, we conducted a sensitivity analysis in which we calculated "adjusted DOTs," which was the DOTs values multiplied by the ratio of the number of total receipts (outpatient-dispensed receipts and in-hospital and outpatient medical receipts) over the number of outpatient-dispensed receipts, with the ratio specific for each medication, type of medical setting, and age.

All data analyses were performed using Stata 13 SE (Stata Corp, College Station, TX, USA). Chi-square tests for categorical variables were used for the analyses and then a Bonferroni correction was applied to the chi-square test results. A value of $P < 0.05$ (2-sided) was considered significant.

RESULTS

A total of 132,869,332 dispensed antibiotics were identified between 2013 and 2016 for the 3 areas. The populations and numbers of clinics/hospitals differed in each of the 3 areas (Table 1). Area A had fewer clinics per pediatric inhabitant than areas B and C. The total number of antimicrobial prescriptions per pediatric inhabitant was lowest in area A and highest in area C. The detailed ratios of the antimicrobial DOTs (adjusted and non-adjusted) in the 3 areas are shown in Table 2. Three antibiotics (vancomycin, linezolid, and chloramphenicol), with a percentage of non-adjusted DOTs of less than 0.01% of total antimicrobial use, were excluded from the analysis.

The total number of antimicrobials prescribed for every 1,000 pediatric inhabitants/day in each area are shown in Fig. 1. The majority of prescriptions were broad-spectrum antibiotics in all 3 areas, with the proportions of narrow-spectrum, broad-spectrum, and ultra-broad-spectrum antibiotics among the dispensed antibiotics of 12.4%, 73.3%, and 14.2%, respectively. Benzyl penicillin and extended-spectrum penicillins, third-generation cephalosporins, and macrolides were the largest antibiotic categories consumed in all 3 areas. Among the ultra-broad-spectrum agents, quinolones, penems, and carbapenems were the most commonly prescribed drugs.

When compared to hospital-based outpatient clinics, the proportion of narrow-spectrum antibiotics in primary care clinics was significantly lower (primary care clinics, 10.9%, hospital-based outpatient clinics, 23.4%; $P < 0.01$) and the proportion of ultra-broad-spectrum antibiotics was higher (primary care clinics, 15.4%; hospital-based outpatient clinics, 5.4%; $P < 0.01$). The proportions of broad-spectrum antibiotics were comparable (primary care clinics, 73.7%; hospital-based outpatient clinics, 71.1%). This discrepancy between prescriptions was observed in all 3 areas (Fig. 2a), and changed only minimally after adjustment for

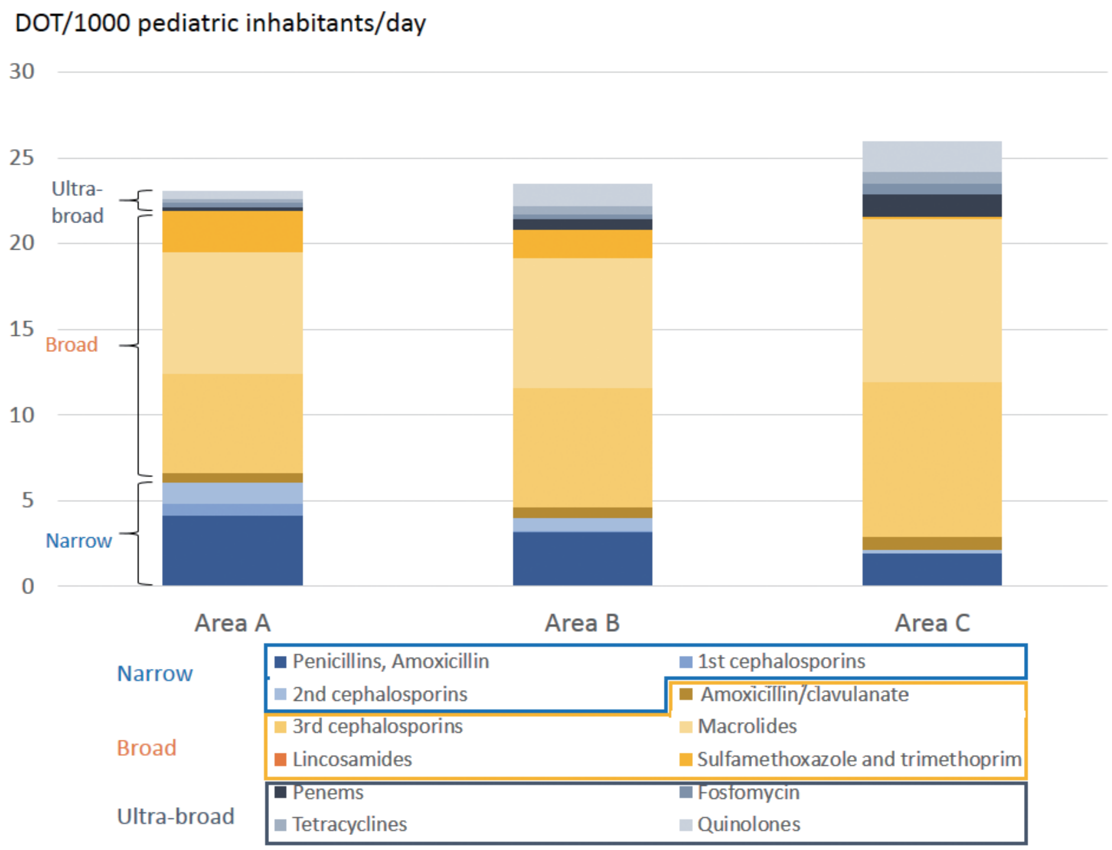
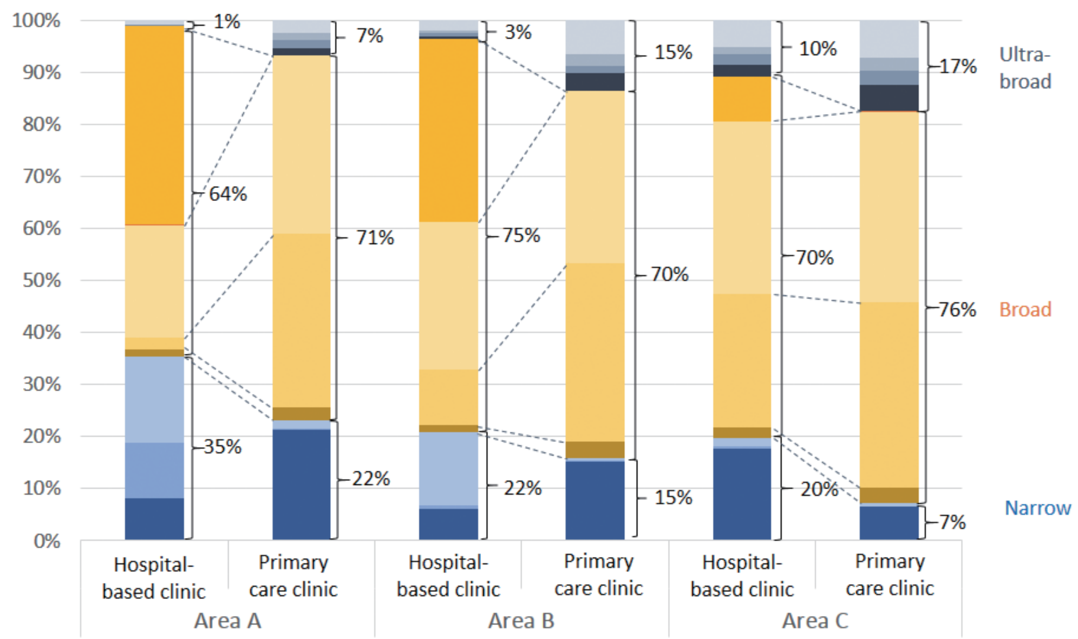


Fig. 1. (Color online) The majority of prescriptions were broad-spectrum antibiotics, including third-generation cephalosporins and macrolides. Days of therapy/1,000 pediatric inhabitants/day in 3 areas: Fuchu city (A), Setagaya-ku (B), and Kobe city (C).

a)



b)

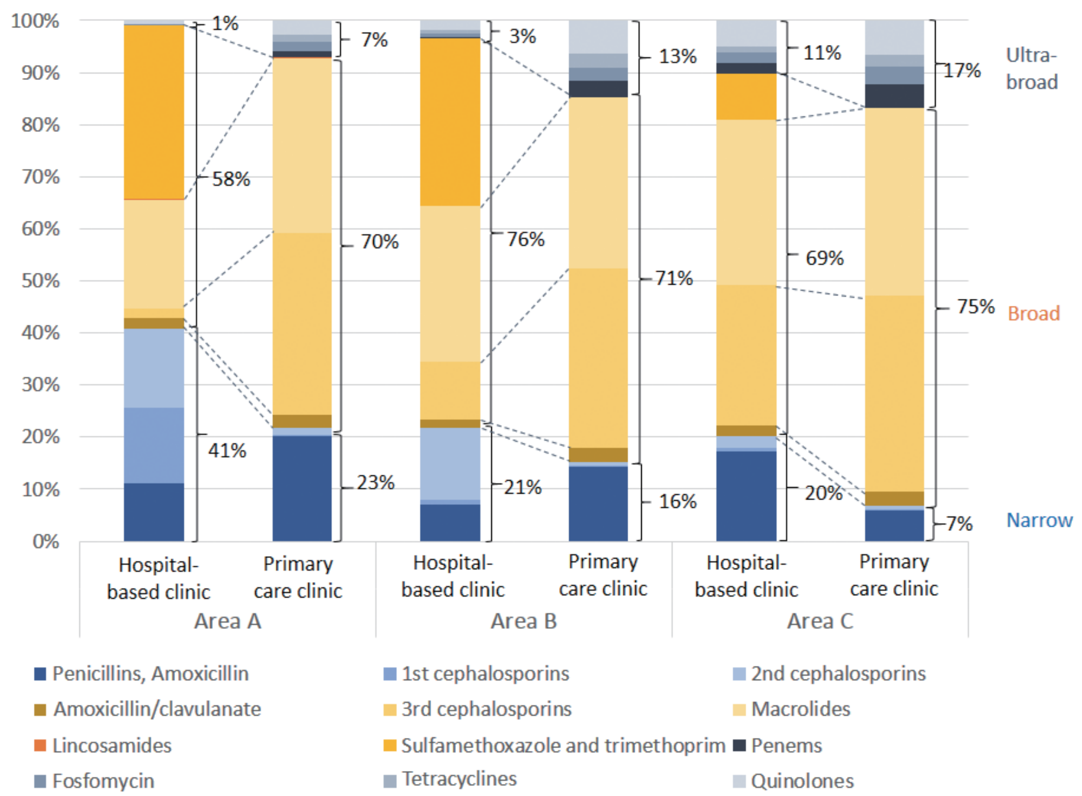


Fig.2. (Color online) Proportions of ultra-broad-spectrum antibiotics were higher and the proportions of narrow-spectrum antibiotics lower in clinics than in hospitals. (a) Detailed proportions of antibiotics, days of therapy in 3 areas, and type of medical setting. (b) Detailed proportions of antibiotics, adjusted days of therapy in 3 areas, and type of medical setting.

the proportion of in-hospital prescriptions (Fig. 2b).

The numbers of antibiotics dispensed by clinical specialty and type of medical setting in each area are shown in Fig. 3a. The prescriptions from pediatricians and otolaryngologists in primary care clinics accounted for the majority of prescriptions in each area. In area A, the numbers of prescriptions from pediatric secondary and tertiary care hospitals and family physician clinics were also notably high, whereas in area B they were moderate, and in area C they were low. The values adjusted for proportion of in-hospital prescriptions were very similar (Fig. 3b).

The derivations of each antibiotic according to clinical specialty and type of medical setting are shown in Fig. 4. Penicillins with beta-lactamase inhibitors were used largely by clinic-based otolaryngologists, first-generation cephalosporins were used by hospital-based pediatricians, third-generation cephalosporins, penems, carbapenems, and quinolones were used by clinic-based pediatricians and otolaryngologists, fosfomycin was used by clinic-based pediatricians, tetracyclines were used by clinic-based dermatologists, and sulfamethoxazole/trimethoprim was mainly used by hospital-based pediatric clinics.

The proportion of tetracycline prescriptions in children $<$ 8 years of age was 21.4% of the prescription of all tetracyclines , which were mainly prescribed by dermatologists (30.8%), otolaryngologists (29.7%), and clinic-based pediatricians (15.5%).

DISCUSSION

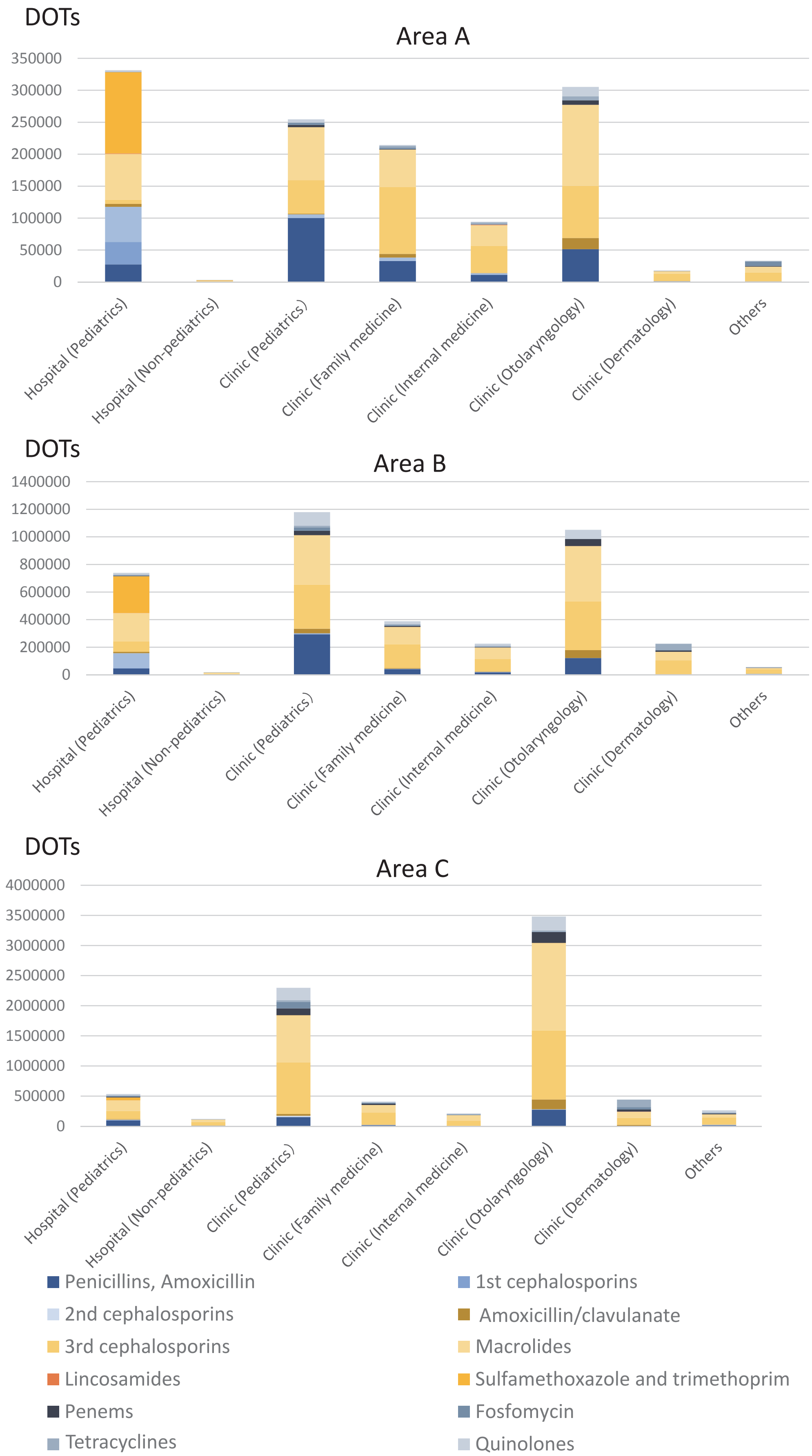
In our study, we made 2 relevant observations that should be taken into account when considering targets for intervention in the promotion of ASP for pediatric outpatients. First, a higher proportion of ultra-broad-spectrum antibiotics tended to be prescribed in primary care clinics than in hospital-based clinics. Second, various specialties were involved in prescribing antibiotics for children, and each had a unique pattern of antibiotic prescription.

There was a significant tendency for primary care physicians to dispense more frequent prescriptions of ultra-broad-spectrum antibiotics and less frequent prescriptions of narrow-spectrum antibiotics compared with hospital-based clinics. Specifically, the use of third-generation cephalosporins, penems, carbapenems, and fluoroquinolones was greater. In general, patients who visit primary care clinics are expected to be less severely ill and require fewer broad-spectrum antibiotics. However, our study showed the opposite tendency. This may have the following explanation. The promotion of education and implementation of ASP in teaching hospitals may have led to fewer prescriptions in hospitals (18,19). The pediatric hospitals in area A implemented restrictions on the use of third-generation cephalosporins and quinolones in 2015 (20). The variation in the amount and proportion of antibiotics used in each area may reflect the differences in the community efforts to promote ASP, although the conclusions cannot be derived from our study design. In Japan, economic incentives for appropriate prescriptions in children were implemented in April 2018, which was outside of our study period. If physicians provided an appropriate explanation for home care without prescribing antibiotics for the common cold or mild gastroenterocolitis, health insurance reimbursed JPY800 per patient to the clinics. This unique intervention may motivate optimal antibiotic prescriptions by physicians. The impact on pediatric practice should therefore be evaluated in further studies.

We observed that antibiotics were prescribed to children by multiple specialists, including otolaryngologists, family physicians, dermatologists, and internists. This wide distribution of specialties likely reflects the Japanese insurance system that permits visitations to any clinical specialty without referral. Most noticeably, the number of antibiotic prescriptions that otolaryngologists prescribed to children were similar to, or in some areas even surpassed, the number prescribed in pediatric clinics and hospitals. The numbers of prescriptions of private pediatric and otolaryngology clinics were almost the same in each of the 3 areas (Table 1). Diseases of patients visiting an otolaryngology clinic may include more severe otitis media or sinusitis, which may require antibiotics. In contrast, in a previous Japanese report, children of more than 2 years of age with acute otitis media tended to visit an otolaryngology clinic more frequently at the early phase of the disease onset, which was suggestive of a mild illness (21). Although the interpretation of antibiotic appropriateness was difficult, large numbers of prescriptions were recorded. Therefore, otolaryngologists are an important target to promote outpatient ASP. The DOTs of hospitals and clinics in each area differed for various reasons. Greater patient volume or greater proportion of antibiotic prescriptions may result in higher DOTs. Patients in areas B and C tended to visit or receive more antibiotics at clinics rather than hospital-based clinics. A detailed direct comparison between DOTs at clinics and hospitals could not be made because the number of visiting patients was unavailable for use as the denominator. Only the DOTs of antimicrobial prescriptions for the target population in each area were available to evaluate the targets for implementing ASP, which was the main focus of this study.

There were variations in prescription patterns among clinical specialties, including those regarding broad-spectrum and ultra-broad-spectrum antibiotics. The first-line use of a particular broad-spectrum antibiotic for any indication may lower the threshold for its use for other indications, and may be associated with a subsequent increase in antimicrobial resistance. The action plan set forth by the Japanese government aims to reduce the use of third-generation cephalosporins, macrolides, and quinolones by half from 2013 by 2020 (22). Thus, the consumption of these antibiotics serves as an important process measure of ASP. Specific guidelines targeting practitioners in each specialty or economic incentives for appropriate antimicrobial prescriptions may lead to effective ASP.

Third-generation cephalosporins, macrolides, fluoroquinolones, penems, and carbapenems were more often prescribed by otolaryngologists. Although a reduction in macrolide use was set as a goal of National Action Plan on AMR, macrolides were often prescribed by otolaryngologists, despite frequent resistance to them a)


DOTs
Area A
350000
300000
250000
200000
150000
100000
50000
0
Hospital (Pediatrics)
Hsopital (Non-pediatrics)
Clinic (Pediatrics)
Clinic (Family medicine)
Clinic (Internal medicine)
Clinic (Otolaryngology)
Clinic (Dermatology)
Others
DOTs
Area B
1400000
1200000
1000000
800000
600000
400000
200000
0
Hospital (Pediatrics)
Hsopital (Non-pediatrics)
Clinic (Pediatrics)
Clinic (Family medicine)
Clinic (Internal medicine)
Clinic (Otolaryngology)
Clinic (Dermatology)
Others
DOTs
Area C
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
Hospital (Pediatrics)
Hsopital (Non-pediatrics)
Clinic (Pediatrics)
Clinic (Family medicine)
Clinic (Internal medicine)
Clinic (Otolaryngology)
Clinic (Dermatology)
Others
Penicillins, Amoxicillin
1st cephalosporins
2nd cephalosporins
Amoxicillin/clavulanate
3rd cephalosporins
Macrolides
Lincosamides
Sulfamethoxazole and trimethoprim
Penems
Fosfomycin
Tetracyclines
Quinolones

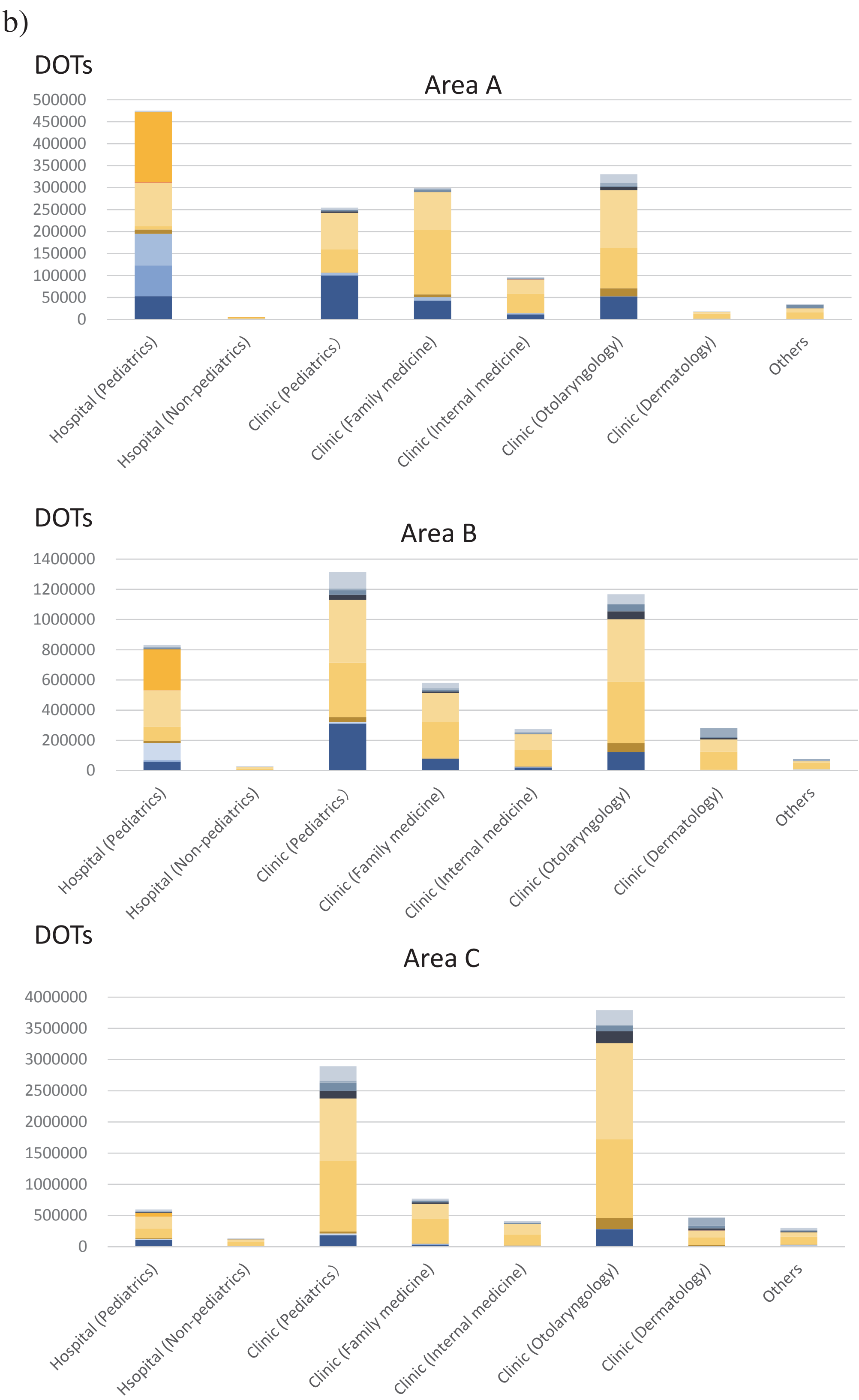


Fig. 3. (Color online) Days of therapy (DOTs) values were observed to be high in clinics (pediatricians and otolaryngologists) in every area. (a) Days of therapy of all hospitals and clinics in areas A, B, and C. (b) Adjusted days of therapy for all hospitals and clinics in areas A, B, and C.

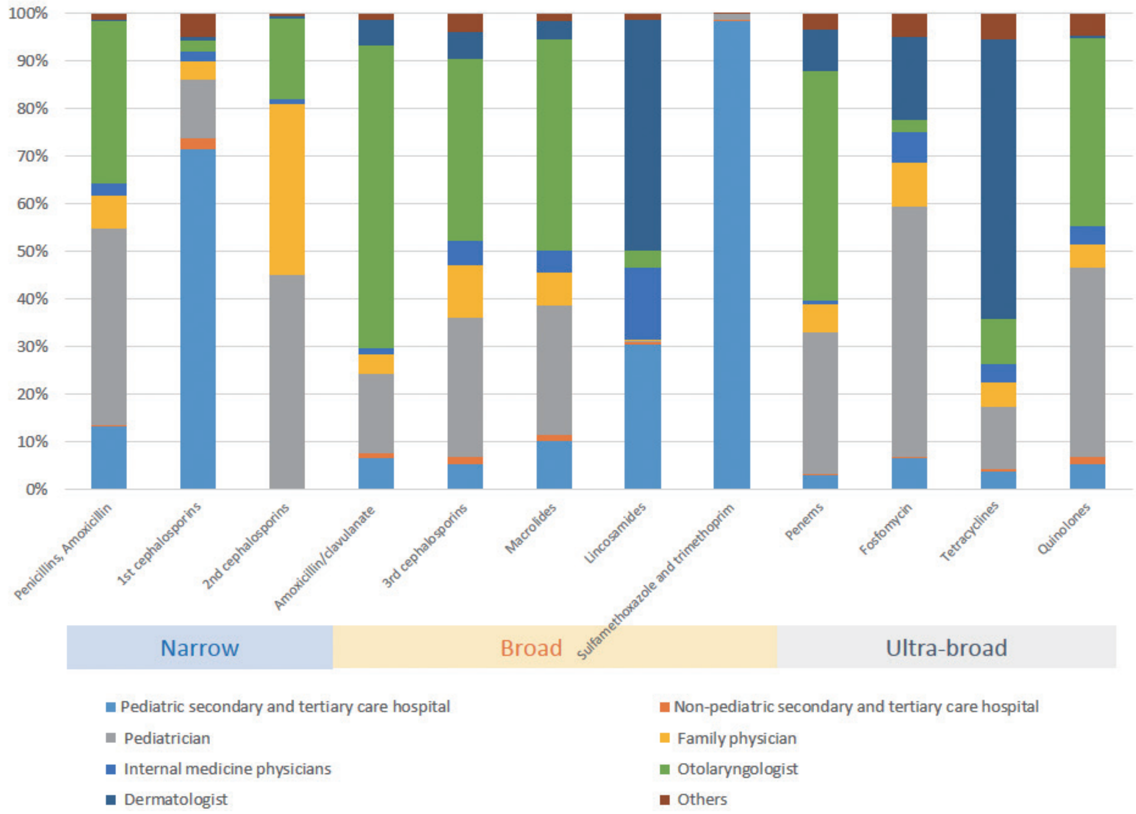


Fig.4. (Color online) The patterns of antibiotic prescriptions varied in each specialty. Derivations of prescribing antibiotics and type of medical setting.

by *Streptococcus pneumoniae* in Japan. There may be a need for an intervention to determine the appropriate use of macrolides. The clinical practice guidelines for the diagnosis and management of acute otitis media in children in Japan recommend observation for mild cases and the first-line use of amoxicillin and the second-line use of third-generation cephalosporins and new quinolones for children with acute otitis media, owing to the beta-lactam-resistant strains of *Haemophilus influenzae* (23). The high prescription rate of broad-spectrum or ultra-broad-spectrum antibiotics in this specialty may be a reflection of the prescriptions to children who visit otolaryngologists with acute otitis media or acute sinusitis.

The prescription rate of tetracyclines is remarkably high in dermatologists. The Japanese Dermatological Association Guidelines on acne vulgaris (2017) recommend using minocycline or doxycycline for first-line therapy (24). Therefore, the significant use of tetracyclines may be owing to prescriptions to treat acne or skin infections. Alarmingly, 21% of children who were prescribed tetracyclines were less than 8 years of age. They are mainly prescribed by dermatologists and otolaryngologists, even though tetracycline is not recommended in this population owing to the risk of permanent tooth discoloration. Therefore, efforts to educate dermatologists, otolaryngologists, and pharmacists on this matter may be needed.

The prescription rate of fosfomycin by clinic-based pediatricians was high. Fosfomycin is approved for use against bacterial enterocolitis in Japan. Beta-lactam antibiotics used against shiga toxin-producing *Escherichia coli* (STEC) have been shown to be associated with the development of hemolytic uremic syndrome and its use is contraindicated in many countries (25). However, several studies from Japan have provided modest evidence to support the use of fosfomycin for patients with early-stage STEC, particularly before cultures become available (26,27). The early administration of fosfomycin was encouraged for STEC infection in the 1990s to prevent hemolytic uremic syndrome in Japan. This resulted in the excessive use of antibiotics for any gastroenterocolitis-associated symptoms, which were, in the vast majority of cases, caused by viruses. The Japanese guidelines on hemolytic uremic syndrome remain obscure on the use of fosfomycin in patients with enterocolitis owing to STEC (28). Definitive evidence to resolve this controversy and fill in diagnostic gaps are required to prevent overprescription.

The use of broad and ultra-broad-spectrum antibiotics, which target acute otitis media, acne, skin infections, and bacterial enterocolitis, can act as a key intervention for children. Despite newly published or revised practice guidelines available during the study period, we found a gap between these guidelines and actual clinical practice. Although we did not evaluate adherence to guidelines by clinicians in this study, we recognize that implementation research is necessary to bridge this gap.

There are several limitations to this study. First, there was a lack of clinical information on the indications for the antibiotic prescriptions, which was a characteristic of the database; and second, we were unable to assess the appropriateness of the use of each medication. However, previous studies that have examined the rate of antibiotic use based on diagnosis have indicated the overuse of antibiotics for upper respiratory infections and broad-spectrum antibiotics for pharyngitis in Japan (29,30). Thus, inappropriate prescriptions may be included in this study population and these would be important targets of ASP. Second, we evaluated the antibiotic prescriptions using adjusted and non-adjusted DOTs. Non-adjusted DOTs may have been underestimated because the coverage rate of dispensary data is estimated to be 70.2%–72.7% and specific populations that receive medications from in-house pharmacies cannot be accounted for. Adjusted DOTs might be overestimated for DOTs, because the duration of in-house prescriptions was usually shorter than that of out-of-hospital prescriptions, which implied that most in-house prescriptions were from the nighttime emergency room. The adjustment was performed by using a number of dispensed prescriptions and medical receipts. We wanted to be able to access the new targets for intervention. Third, we compared DOTs in all hospitals and clinics without adjustments for the number of visits to each facility. Our database was unable to account for the number of visits in each hospital and clinic. The patients' visiting pattern variation in each area might affect the analysis. However, data from the 3 areas showed that the results were similar. We believe that it is acceptable to discuss the targets of ASP and the trends in prescriptions.

In conclusion, we found that ultra-broad-spectrum antibiotics were more often used and narrow-spectrum antibiotics were less commonly used in primary care clinics. The antibiotics particular to each specialty were identified as key targets to optimize oral antibiotic use for pediatric outpatients.

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Conflict of interest None to declare.

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