



Original Article

Nationwide survey of indications for oral antimicrobial prescription for pediatric patients from 2013 to 2016 in Japan[☆]

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ABSTRACT

Background: Antimicrobial resistance is a major public health concern. In 2016, the Japanese government launched a national action plan aimed at achieving a 33% and 50% reduction in the number of total and oral antimicrobial prescriptions (cephalosporins, macrolides, and quinolones) from the 2013 figures by 2020, respectively. The purpose of this study was to investigate the indications for recent antimicrobial prescriptions and to identify the primary targets for intervention to achieve the aims of the government's action plan.

Methods: Using the national health claims database, we retrospectively analyzed oral antibiotic prescriptions for Japanese children aged ≤ 15 years from 2013 to 2016. The trends were analyzed based on days of therapy (DOT) per infectious disease-related visit for each antibiotic. For patients whose chief diagnosis was an infectious disease, the number of antimicrobial prescriptions per diagnosis, their proportion, and the details of the type of antimicrobial were investigated.

Results: In total, 297,197,328 infectious disease-related visits were identified during 2013–2016. Total antimicrobial prescriptions showed a 3.7% reduction from 1.519 DOT/visitor in 2013 to 1.463 DOT/visitor in 2016 ($P_{\text{trend}} < 0.001$). Antimicrobials were prescribed for 31.7% and 36.9% of children with upper and lower respiratory tract infection, accounting for 54.6% and 26.2% of all antimicrobial prescriptions, respectively. Third generation cephalosporins and macrolides comprised the majority of these prescriptions.

Conclusions: Antimicrobials were commonly prescribed for children with respiratory infections. Therefore, promoting appropriate antimicrobial use in this population is required to achieve the 2020 goals set by the action plan.

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1. Introduction

Antimicrobial resistance (AMR) is an important public health issue affecting clinical practice patterns and healthcare expenditures [1–3]. Antimicrobial prescription patterns differ according to the type of health care system, epidemiology of the disease, and prevalence of antimicrobial-resistant organisms [4,5]. The overuse and misuse of antimicrobials have led to the development of AMR [6,7]. Hence, antimicrobial stewardship programs (ASP) are necessary to prevent its progression [8,9].

In Japan, outpatient antimicrobial prescriptions are the main target of ASP due to the fact that 93% of antimicrobials were prescribed for outpatients [10,11]. We previously reported on the nationwide prescription pattern for pediatric patients in Japan, which showed that a large proportion of prescriptions were for pediatric patients 1–5 years old [12]. Moreover, Japanese pediatric patients with an infectious disease have also been prescribed antimicrobials which were inappropriate for their diagnosis. Indeed, previous studies showed that antibiotics were prescribed for 66.4% of preschool children with the diagnosis of upper respiratory tract infection and 29.6% of children with the diagnosis of acute infectious diarrhea while 53.3% of children diagnosed with group A streptococcus infection were prescribed third generation cephalosporins [13–15]. Due to mounting concerns over these figures, the Japanese government launched a nation-wide action plan to achieve a 33% and 50% reduction in the use of total and oral antimicrobials (cephalosporins, macrolides, and quinolones) by 2020, respectively [16].

Previous studies cited inappropriate antimicrobial prescriptions for patients with upper respiratory tract infections and acute diarrhea, which are important targets for intervention. However, the data presented in these studies are unlikely to reflect the actual state of antimicrobial prescription practices, given that the database covered only 5% of the Japanese population [13–15]. In addition, few data are available on prescription patterns for other types of infectious disease. Therefore, our study aimed to capture comprehensive patterns in recent antimicrobial prescription practices to identify the primary targets for intervention for outpatient ASP for the Japanese pediatric population.

2. Materials and methods

2.1. Data source

Japanese national health insurance provides universal coverage for all citizens, whose information is anonymized and stored in a database. The database of all electronic claims data, the so-called national database of health insurance claims and specific health checkups in Japan, currently covers approximately 99% of health-care services paid for by the national health insurance [17]. From this database, we extracted all claims made by pediatric patients \leq 15 years old during the period from 2013 to 2016.

2.2. Type of antimicrobials

Antimicrobials for systemic use were assigned the code, J01, according to the World Health Organization Anatomical Therapeutic Chemical classification system [18]. In total, 41 antimicrobials were included in the analysis and were classified into the following 17 classes and 11 groups: benzylpenicillin and extended spectrum penicillins (J01CE01, J01CA); penicillins with beta-lactamase inhibitors (J01CR); third-generation cephalosporins (J01DD); other cephalosporins (J01DB, J01DC); penems and carbapenems (J01DI03, J01DIXX); fosfomycin (J01XX01); macrolides (J01FA); tetracyclines (J01AA); quinolones (J01M);

sulfamethoxazole and trimethoprim (J01EE01); and others (lincosamides: J01FF, linezolid: J01XX08, chloramphenicol: J01BA01, vancomycin: A07AA09). Metronidazole was categorized as an antiparasitic drug in this database. We excluded parenteral and topical antibiotics, antivirals, antituberculosis medications, antifungals, and antiparasitic agents.

2.3. Types of infectious disease

We included visits for infectious disease-related complaints as classified by the International Classification of Diseases, 10th Revision (ICD-10 code). The diagnoses of the infectious diseases were based on Clinical Classification Software (CCS) codes provided by the Healthcare and Utilization Project to allow meaningful diagnostic categorizations. Categorizations using the CCS codes were considered to be more useful than those using individual ICD-10 codes [19]. We included and classified the following diseases: upper respiratory tract infection (CCS 124: tonsillitis; CCS 126: upper respiratory infections), lower respiratory tract infection (CCS 122: pneumonia; CCS 125: acute bronchitis), gastroenteritis (CCS 135: intestinal infection; CCS 140: gastritis and duodenitis), influenza (CCS123: influenza), skin infection (CCS 197: skin and subcutaneous tissue infections), otitis media (CCS 92: otitis media and related conditions), urinary tract infection (CCS 159: urinary tract infections), lymphadenitis (CCS 247: lymphadenitis), and others (CCS 2: septicemia; CCS 3: bacterial infection unspecified; CCS 7: viral infection; CCS 8: other infections; CCS 142: appendicitis; CCS 201: infective arthritis and osteomyelitis). Group A streptococcus (GAS) infections were identified by the ICD-10 codes (A40.0, A40.9, A49.1, J02.0 and J03.0), and reclassified as GAS infections from their former classification as upper respiratory infections.

2.4. Outcomes of interest and statistical analyses

For this study, we retrospectively analyzed 3.5 billion medical and 2.9 billion prescription receipts from January 2013 to December 2016, which were extracted from the national administrative claims database (NDB). We evaluated the data in the following two steps (Supplementary Fig. 1). First, we obtained information on outpatients with a diagnosis of an infectious disease and days of therapy (DOT), and calculated the DOT per visitors during 2013–2016. The first visit in each month was counted as one visitor for analysis. For trend analyses, we constructed a Poisson regression model containing the number of DOT as a dependent variable, years of visits as an independent categorical variable, and number of visitors as the offset variable with % reduction of DOT per visitor from 2013 to 2016. A two-sided P value < 0.05 was considered to be statistically significant. Second, we focused on 32.4% of visitors who had the main diagnosis provided by physicians, calculated the proportion of total antibiotic use, and stratified the antimicrobial prescribed by the type of infectious disease. All data were analyzed using STATA software version 14.2 (StataCorp LP, TX, USA).

This study was approved by the institutional review board at the National Center for Child Health and Development (IRB-1491).

3. Results

In total, 297,197,328 infectious disease-related visitors (6,191,611 visitors per month) were identified during 2013–2016. Table 1 and Fig. 1 show the trends in DOT per visitor stratified by antimicrobial type to determine the magnitude of change in the proportion of patients prescribed oral antimicrobials (cephalosporins, macrolides, and quinolones). The total antimicrobial prescriptions per visitor showed a 3.7% reduction from 2013 to 2016 ($P_{\text{trend}} < 0.001$). Similarly, a statistically significant decreasing trend was observed

in the prescription of cephalosporins (7.1% reduction), penems and carbapenems (9.2% reduction), fosfomycin (16.2% reduction), and macrolides (6.8% reduction). In contrast, a significantly increasing trend was found in the prescription of benzylpenicillin and extended spectrum penicillins (6.9% increase), penicillins with beta-lactamase inhibitors (5.6% increase), tetracyclines (11.8% increase), quinolones (23.1% increase), and sulfamethoxazole and trimethoprim (17.9% increase).

Next, we focused on 96,252,259 pediatric outpatients with the main diagnosis of an infectious disease to maximize the diagnostic accuracy and avoid misclassification of the disease (Supplementary Fig. 1). Among these, 25,897,766 (26.9%) pediatric outpatients were prescribed antimicrobials. To determine which antimicrobials and diseases to target in the action plan, we focused on the five most common diseases for which antimicrobials were prescribed, namely, upper respiratory tract infection (URTI), lower respiratory tract infection (LRTI), gastroenteritis, influenza, and skin infections. Fig. 2 shows the proportion of visitors with antimicrobial prescriptions for each of the five infectious diseases. Antimicrobials were prescribed for 31.7% of pediatric patients with URTI, 36.9% of those with LRTI, 10.0% of those with gastroenteritis, 8.0% of those with influenza, and 39.7% of those with a skin infection.

The proportions of each antimicrobial prescribed per diagnosis are shown in Fig. 3. The most common prescriptions were for URTI (54.6%), followed by LRTI (26.2%), otitis media (4.2%), skin infection (4.2%), and gastroenteritis (4.0%). Cephalosporins and macrolides were most commonly prescribed for almost all the diagnoses. It is worth noting that of all cephalosporins prescribed, 96.7% were third generation cephalosporins. Fosfomycin was prescribed for 41.6% of pediatric patients with gastroenteritis, and the proportion of quinolone use (12.7%) was the highest in patients with otitis media. Cephalosporins accounted for 74.1% of antimicrobials for skin infections, with first generation cephalosporins comprising only 5.0% of this figure.

4. Discussion

The present study disclosed two important findings. First, despite a significant decreasing trend in total DOT per visitor, the reduction was merely 3.7% over the 4-year period from 2013 to 2016. Second, antimicrobials prescribed for respiratory tract infection comprised 80.8% (54.6% in URTI and 26.2% in LRTI) of all prescriptions, and the most commonly prescribed antimicrobials were third generation cephalosporins and macrolides. Given that the last year of the study period (2016) is the midpoint between 2013 and 2020, the year targeted for achieving the government's aims, the current pace of improvement is too slow to achieve the goal of a 50% reduction in antimicrobial use. Therefore, more vigorous promotion of appropriate antimicrobial use in the

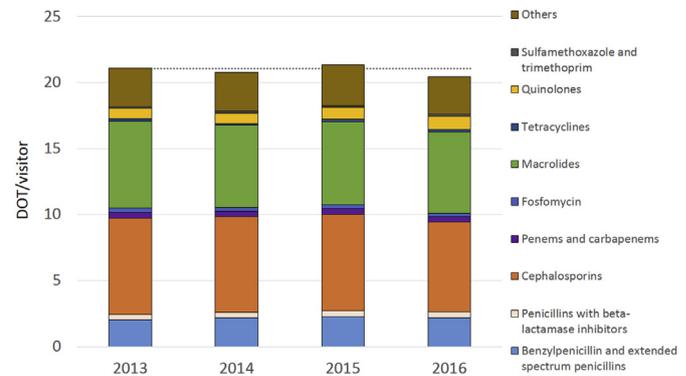


Fig. 1. Annual trend of antimicrobial days of therapy (DOT) per visitor and antimicrobial type during 2013–2016. Majority of antimicrobials prescribed consisted of cephalosporins and macrolides, followed by penicillins and quinolones.

treatment of respiratory tract infections and much greater reductions in their use for the pediatric outpatient population is required.

We observed a 3.7% reduction in total DOT per visitors. The significant decrease we observed in this study is at first glance inconsistent with the findings of our previous report based on the same data and population, which did not show any significant changes in the same period¹². This discrepancy was due to differences in the numerator and denominator presented as the DOT per visitors in patients with the primary diagnosis of infectious disease versus DOT per 1000 pediatric inhabitants per day in the all antimicrobials dispensed to outpatients. However, both studies suggest that changes in the antimicrobial prescribing pattern was too marginal to meet the action plan goal for 2020.

We observed that 54.6% of all antimicrobials prescribed for pediatric outpatients were for URTI and that 31.7% of pediatric outpatients with URTI were prescribed antimicrobials. Reducing prescriptions for URTI may be the key intervention for reducing antimicrobial use in general. A previous report in Japan using a smaller database also found that 66.4% of preschool children were prescribed antimicrobials. In view of the fact that systematic reviews and meta-analyses have shown antimicrobials to be ineffective in curing or resolving the symptoms of URTI [20], it is unlikely that over 30% of URTI cases would require antimicrobials for treatment; thus, overprescribing antimicrobials for URTI in pediatric patients constitutes a major problem in Japanese healthcare. This problem is not unique to Japan; reports show that primary care physicians in Switzerland prescribed antimicrobials for 27.4% of pediatric patients with acute rhinosinusitis and 24.4% of those with acute pharyngitis [21]. In the United States as well, URTI accounts for a large percentage of antimicrobial prescriptions, with reports

Table 1
Trends in days of therapy (DOT) per visitor for each antimicrobial from 2013 to 2016.

	2013	2014	2015	2016	% change	% reduction	P _{trend}
Total DOT per visitor	1.519	1.486	1.524	1.463	96.35	3.65	<0.001
Benzylpenicillin and extended spectrum penicillins	0.171	0.182	0.189	0.182	106.91	−6.91	<0.001
Penicillins with beta-lactamase inhibitors	0.034	0.034	0.036	0.036	105.62	−5.62	<0.001
Cephalosporins	0.606	0.600	0.609	0.563	92.95	7.05	<0.001
Third-generation cephalosporins	0.587	0.581	0.591	0.545	92.97	7.03	<0.001
Penems and carbapenems	0.036	0.036	0.036	0.032	90.79	9.21	<0.001
Fosfomycin	0.025	0.024	0.023	0.021	83.84	16.16	<0.001
Macrolides	0.555	0.522	0.529	0.517	93.17	6.83	<0.001
Tetracyclines	0.015	0.013	0.015	0.017	111.82	−11.82	<0.001
Quinolones	0.066	0.064	0.075	0.081	123.11	−23.11	<0.001
Sulfamethoxazole and trimethoprim	0.011	0.011	0.012	0.013	117.92	−17.92	<0.001
Others	0.245	0.247	0.257	0.237	96.72	3.28	<0.001

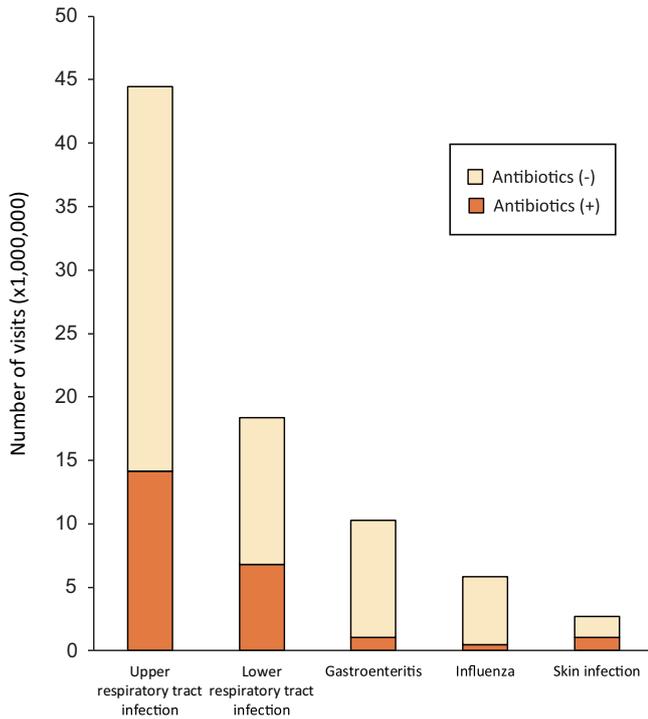


Fig. 2. Top 5 infectious diseases and proportion of antimicrobial prescriptions. Antimicrobials were prescribed for 31.7% of pediatric patients with URTI, 36.9% of those with LRTI, 10.0% of those with gastroenteritis, 8.0% of those with influenza, and 39.7% of those with a skin infection.

showing prescriptions for sinusitis, pharyngitis, and viral upper respiratory infection accounting for 11%, 9%, and 5% of total antimicrobial use in ambulatory care, respectively [22].

Our study also revealed that LRTI (bronchitis, bronchiolitis, and pneumonia) was the second most common reason for antibiotic prescriptions (26.2% of all antibiotic prescriptions). In addition, 36.9% of pediatric outpatients with LRTI were prescribed antibiotics, indicating an over-prescription of these antibiotics based on comparisons with figures from other countries, the assumed causative pathogens, and the actual effectiveness of antibiotics

against LRTI. First, previous studies in Switzerland and the Netherlands reported much lower prescription rates for antimicrobials of 11.5% and 26%, respectively, of patients with acute bronchitis than the rate of 36.9% found in the present study, suggesting that antibiotics are being overprescribed for LRTI in Japan [21,23]. Second, almost all of the causative pathogens for acute bronchiolitis were reportedly viruses, such as respiratory syncytial virus, human rhinovirus, human metapneumovirus, etc [24]. Furthermore, bacterial pathogens were detected in only 15% of pediatric inpatients with pneumonia in the post-pneumococcal conjugate vaccine and *Haemophilus influenzae* type B vaccine era [25]. Third, recent systematic reviews and meta-analyses failed to show sufficient evidence supporting the routine use of antibiotics for pediatric patients with acute bronchitis or bronchiolitis [26,27]. These previous findings suggest that antibiotics were overprescribed for pediatric patients with LRTIs in Japan and that promoting appropriate prescription practices for LRTI is needed.

This study found that cephalosporins and macrolides were the most commonly prescribed antimicrobials for URTI (cephalosporins: 50.1%, macrolides: 30.8%) and LRTI (cephalosporins: 36.8%, macrolides: 47.4%). According to our data, third generation cephalosporins comprised 96.7% of the cephalosporins prescribed. The overuse of third generation cephalosporins is undesirable due to their poor bioavailability and potential adverse events, including diarrhea, allergic reactions, increased AMR, and hypoglycemia via secondary carnitine deficiency due to pivalate-conjugated antibiotics [28,29]. Although macrolides may be prescribed for the treatment of *Mycoplasma pneumoniae* and *Bordetella pertussis*, laboratory tests to detect these pathogens have recently become available in Japan and they may help physicians avoid prescribing antimicrobials unnecessarily. Furthermore, amoxicillin is recommended as first line therapy of respiratory tract infections in younger children [30,31]. In addition to reducing the prescription of third generation cephalosporins and macrolides for URTI, promoting amoxicillin as a first line treatment for LRTI may be a feasible method of achieving the goals of the AMR action plan in Japan.

Interestingly, we found several inappropriate practice patterns in antimicrobial use for otitis media, GAS infections, and gastroenteritis. The overuse of extremely broad-spectrum antimicrobials (quinolones, penems, and carbapenems) may reflect the influence

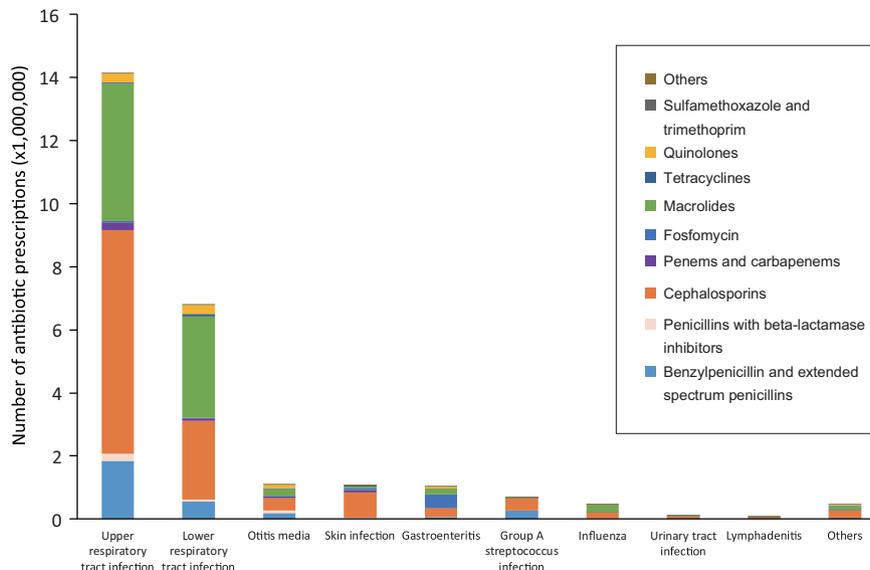


Fig. 3. Amount of antimicrobial prescriptions in each infectious diseases. The infectious disease for which antimicrobials were most commonly prescribed was URTI (54.6%), followed by LRTI (26.2%), otitis media (4.2%), skin infections (4.2%), and gastroenteritis (4.0%).

of the Japanese guidelines for otitis media treatment, which recommend quinolones, penems, and carbapenems in second or third line therapy as a countermeasure against the recent increase in resistant pathogens [32]. Our previous studies found that third-generation cephalosporins were over-used in the treatment of GAS infections, probably as a result of a meta-analysis reporting the slight superiority of cephalosporin over other antimicrobials in GAS pharyngitis treatment in pediatric patients as well as physicians' concerns about treatment failure [33]. Furthermore, fosfomycin was used for gastroenteritis, a fact which may be explained by the findings of previous studies. Indeed, retrospective studies in Japan showed the potential benefits of fosfomycin use in the early stages of shiga toxin-producing *Escherichia coli* (STEC) colitis for preventing hemolytic uremic syndrome (HUS) [34,35]. However, the findings of these studies were limited and are cannot be generalized due to the statistical methodology employed and the retrospective nature of the study design. Additionally, other studies reported a potential association between antibiotic use against STEC and HUS development [36]. We believe that current evidence is insufficient to justify any increase in the use of fosfomycin for the treatment of gastroenteritis in Japan.

There are several limitations to our study. First, we may have wrongly estimated the types of infectious disease-related outpatient visits due to a potential misclassification of the diagnoses based on the ICD-10 codes. Indeed, the CCS classification of otitis media includes both the acute and exudative forms, which may have led to an overestimate of the number of outpatient visits. Second, we were unable to capture the baseline patient characteristics in detail, such as their socioeconomic status and laboratory data, due to limitations in the database. Third, restricting our analysis to 32.4% of outpatients with the primary diagnosis of an infectious disease may have led to selection bias, which may have distorted the proportion of antibiotic use in the infectious disease categories. The strength of our study is the use of a national database covering up to 99% of the total population in Japan. We were able to produce robust national estimates for antibiotic prescription patterns on which to base future strategies for achieving the AMR action plan's goal. However, we would like to note that the target process measures of the AMR action plan are somewhat arbitrary and the true goal is to achieve appropriate antimicrobial use among all physicians. The appropriate use of antimicrobials consists of not only the reduction of unnecessary use, but the timely use of antimicrobials at the recommended dose and duration for bacterial infection.

In conclusion, we observed only a 3.4% reduction in total antimicrobial use during 2013–2016, which is an insufficient rate for achieving a 50% reduction by 2020. However, our findings revealed that antibiotics were commonly prescribed for pediatric outpatients with a respiratory infection; therefore, promoting appropriate antimicrobial use for the treatment of respiratory infections may provide us with a feasible strategy for achieving an immediate reduction in their use. Our study provides important information in terms of physicians' education and health policy considerations relevant to appropriate practice in the treatment of pediatric patients with an infectious disease in Japan.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jiac.2019.03.004>.

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Conflicts of interest

The authors have no conflict of interest relevant to this article to disclose.

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