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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 which are for outpatients. A significant proportion is known to be dispensed for children; however, the specific pattern of antibiotic prescribing according to clinical specialty is still unclear.

The aim of our study was to identify key targets for optimizing oral antibiotic use in children. We analyzed data on oral antimicrobial prescription patterns for children aged < 16 years old in three urban districts 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 predominated in the three studied areas. Third-generation cephalosporins, quinolones, penems, and carbapenems were prescribed mostly by pediatricians and otolaryngologists as well. Ultra-broad-spectrum antibiotics used in primary care clinics and antibiotics particular to each specialty were identified as key targets to optimize oral antibiotic use for pediatric outpatients.
Introduction

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

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

Such key targets may differ by population, as each country has a different health care system, epidemiology of diseases, and occurrence rates of resistant organisms. One characteristic of Japan that we need to incorporate is the system of free medical access in pediatric care without financial burdens for parents or guardians.

Universal health insurance and the full reimbursement program for pre-school children
by local government enables patients to be treated and obtain prescriptions with little or no charge at the majority of areas in Japan. As most clinics accept walk-in patients without referrals, they can easily seek care from physicians with many different specialties for the same symptoms. For instance, a child with a runny nose or cold may visit an otolaryngologist or 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 different guidelines regarding prescription of antimicrobials, understanding what kind of antimicrobials are being prescribed and where may help identify areas where implementing ASP for children may be most effective.

In 2016, three urban cities were selected as pilot areas to try out population-based outpatient ASP interventions, as part of a government-funded project to formulate an effective method of antimicrobial stewardship for pediatric outpatients. The aim of our study was to observe differences in oral antimicrobial prescription patterns to children by clinical specialty and to identify key targets for optimizing 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 try out ASP interventions for children in the community: area A, Fuchu city (Tokyo); area B, Setagaya-ku (Tokyo); and area C, Kobe city (Hyogo). All three areas were urban cities with a tertiary children’s hospital in the area. For this study, we retrospectively analyzed data of all antimicrobial dispensing receipts from January 2013 to December 2016 in these three communities, created from the national claims database.

**Data source**

Japanese social health insurance provides universal coverage for all citizens, whose information is made available as an electronic claims database. The database of all electronic claims data, the so-called 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 two steps.

First, we used the dispensing receipts database from pharmacists’ offices on all oral antibiotics dispensed to children < 16 years old during the study period 2013-2016, which includes details of the medication dispensed. We excluded parenteral antibiotics, topical antibiotics, antivirals, anti-tuberculosis medications, antifungals, and antiparasitic agents. 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 of all oral antibiotics to children < 16 years old during the study period 2013-2016. This database included all medical receipts from hospital pharmacies to outpatients. This dataset was included as the dispensing receipts database does not cover medication dispensed to patients by in-house pharmacies in clinics, although patients that visit emergency department out-of-hours are dispensed medication by in-hospital pharmacies. Previous studies show that such in-house prescriptions may account for 27%-30% of all medications prescribed to out-patients (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, and others) for all prescriptions in the three pilot cities. “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 (ATC) classification system (14). A total of 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). Metronidazole was categorized as an anti-parasitic drug in this database.

We designated the above-mentioned antibiotics into three 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 with reimbursement by health insurance. We excluded antibiotics that were used for less than 0.01% of the total antimicrobial use from the final analysis.
**Statistical analysis**

First, we calculated the total and population-adjusted antimicrobial prescriptions for the three areas. To provide numbers which were comparable across different populations we used the unit DOTs/1000 pediatric inhabitants/day, calculated as average DOTs over every thousand inhabitants < 16 years old in each area. Second, to observe how prescription practices differed by setting, we calculated the total DOTs for each antibiotic by medical setting (hospitals or clinics), as well as by clinical specialty for each area. For these analyses, antimicrobials whose 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 years old because tetracycline is not recommended in this population due to the risk of permanent tooth discoloration (17).

All analyses were performed using the national antimicrobial dispensed receipts database, thus limited to out-patient medication dispensed at pharmacies outside of the hospitals. However, to account for the medication dispensed in the hospitals, we conducted a sensitivity analysis where we calculated an “adjusted DOTs” which was DOTs multiplied by the ratio of the number of total receipts (out-patient dispensed receipts and in-hospital and out-patient medical receipts) over the number of
out-patient 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). 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 $P < 0.05$ (two-sided) was considered significant.

**Results**

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

The total amounts of antimicrobials prescribed for every 1000 pediatric inhabitants/day in each area are shown in Figure 1. The majority of prescriptions were
broad-spectrum antibiotics in all three areas, with proportions of narrow-spectrum, broad-spectrum, and ultra-broad-spectrum antibiotics among dispensed antibiotics being 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 three areas. Among ultra-broad-spectrum agents, quinolones, penems, and carbapenems were the most commonly prescribed drugs.

When compared to hospital-based outpatient clinics, in primary care clinics the proportion of narrow-spectrum antibiotics 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 three areas (Figure 2-a), and changed minimally after adjusting for proportion of in-hospital prescriptions (Figure 2-b).

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

The derivations of each antibiotic according to clinical specialty and type of medical setting are shown in Figure 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 old was 21.4% 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 two relevant observations that should be taken into account when considering targets for intervention in promoting ASP for pediatric outpatients. First, ultra-broad-spectrum antibiotics tended to be prescribed at a greater proportion at primary care clinics compared to hospital-based clinics. Second, various specialties were involved in prescribing antibiotics for children, each with a unique pattern of antibiotic prescription.

There was a significant tendency for primary care physicians to prescribe more frequently ultra-broad-spectrum antibiotics and less frequently narrow-spectrum antibiotics compared to 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 be explained by the following reason. 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 be evaluated in further studies.

We observed that antibiotics were prescribed to children by multiple specialists that include 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 amount prescribed in pediatric clinics and hospitals.

The numbers of private pediatric and otolaryngology clinics were almost the same in the three areas (Table 1). Diseases of patients visiting an otolaryngology clinic may include more severe otitis media or sinusitis, which may require antibiotics. On the other hand, in a previous Japanese report, the children with acute otitis media older than 2 years tended to more frequently visit an otolaryngology clinic at the early phase of the disease.
onset, suggesting mild illness (21). Although the interpretation of antibiotic appropriateness was difficult, large numbers of prescriptions were found. Therefore, otolaryngologists are an important target to promote out-patient ASP. DOTs of hospitals and clinics in each area differed for various reasons. Greater patient volume or greater proportion of antibiotic prescriptions could 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 to be used as the denominator. Only the DOTs of antimicrobial prescriptions for the target population in each area was 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. 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 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 prominently prescribed by otolaryngologists. Although reduction in macrolide use was set as a goal of the national AMR action plan, macrolides were commonly prescribed by otolaryngologists despite frequent resistance to them by *Streptococcus pneumoniae* in Japan. There might be a need for intervention for the appropriate use of macrolides. The clinical practice guidelines for diagnosis and management of acute otitis media in children in Japan recommend observation for mild cases and first-line use of amoxicillin and second-line use of third-generation cephalosporins and new quinolones for children with acute otitis media, considering the beta-lactam–resistant strains of *H. influenza* (23). The high prescription rate of broad-spectrum or ultra-broad-spectrum antibiotics in this specialty may be reflecting prescriptions to children who visit otolaryngologists with acute otitis media or acute sinusitis.

The prescription rate of tetracyclines was 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 due to prescriptions to treat acne or skin infections.

Alarmingly, 21% of children who were prescribed tetracyclines were less than 8 years old. They are mainly prescribed by dermatologists and otolaryngologists, even though tetracycline is not recommended in this population due to the risk of permanent tooth discoloration. Efforts to educate dermatologists, otolaryngologists, and pharmacists on this matter may be needed.

The prescription rate of fosfomycin was high by clinic-based pediatricians. 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 developing hemolytic uremic syndrome and its use is contraindicated in many countries (25). However, a few studies from Japan provide modest evidence to support use of fosfomycin for patients with STEC in the early stage, particularly before cultures become available (26, 27). 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 caused by viruses in the vast majority of cases. The Japanese guidelines on hemolytic uremic syndrome remain
obscure on use of fosfomycin in patients with enterocolitis due to STEC (28). Definitive evidence resolving this controversy and filling 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 be a key for interventions in 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 would be necessary to bridge this gap.

There are several of limitations to this study. First, there was a lack of clinical information on the indications for the antibiotic prescriptions because of the characteristics of the database, and we were unable to assess the appropriateness of the use of each medication. However, previous studies examining the rate of antibiotic use according to diagnoses indicate the overuse of antibiotics for upper respiratory infections and broad-spectrum antibiotics for pharyngitis in Japan (29,30). Thus, inappropriate prescriptions would be included in this study population and they would be important targets of ASP. Second, we evaluated the antibiotic prescriptions using adjusted and non-adjusted DOTs. Non-adjusted DOTs might be 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 in-house prescriptions were usually shorter than out-of-hospital prescriptions, which implies that most in-house prescriptions were from the nighttime emergency room. The adjustment was performed using 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 number of visits to each facility. Our database was unable to account for number of visits in each hospital and clinic. The patients’ visiting pattern variation in each area might affect the analysis. However, data from the three areas showed that results were similar. We believe that it is acceptable to discuss the target of ASP and tendency of prescriptions.

In conclusion, we found that ultra-broad-spectrum antibiotics are more often used and narrow-spectrum antibiotics were less commonly used in primary care clinics. 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:

The authors have no conflicts of interest to declare.

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Result of the population estimates. Available at


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Figure 1: Days of therapy/1000 pediatric inhabitants/day in three areas: Fuchu city (A), Setagaya-ku (B), and Kobe city (C)

Figure legend: The majority of prescriptions were broad-spectrum antibiotics, including third-generation cephalosporins and macrolides.

Figure 2-a: Detailed proportions of antibiotics, days of therapy in three areas, and type of medical setting

Figure 2-b: Detailed proportions of antibiotics, adjusted days of therapy in three areas, and type of medical setting

Figure legend: Proportions of ultra-broad-spectrum antibiotics were higher and the proportions of narrow-spectrum antibiotics lower in clinics than in hospitals.

Figure 3-a: Days of therapy of all hospitals and clinics in areas A, B, and C

Figure 3-b: Adjusted days of therapy for all hospitals and clinics in areas A, B, and C

Figure legend: Days of therapy (DOTs) values were observed to be high in clinics (pediatricians and otolaryngologists) in every area.

Figure 4: Derivations of prescribing antibiotics and type of medical setting
Figure legend: The patterns of antibiotic prescriptions varied in each specialty.
Table 1: Population, days of therapy, and number of hospitals and clinics in three areas

<table>
<thead>
<tr>
<th></th>
<th>Area A</th>
<th>Area B</th>
<th>Area C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population ≤ 15 years old (average between 2013 and 2016)</td>
<td>37,274</td>
<td>108,008</td>
<td>199,116</td>
</tr>
<tr>
<td>Days of therapy</td>
<td>1,254,022</td>
<td>3,883,851</td>
<td>7,761,214</td>
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<tr>
<td>Days of therapy (adjusted)</td>
<td>1,513,838</td>
<td>4,554,930</td>
<td>9,363,962</td>
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<tr>
<td>Days of therapy/1000 pediatric inhabitants/day</td>
<td>23</td>
<td>24.6</td>
<td>26.7</td>
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<tr>
<td>Days of therapy/1000 pediatric inhabitants/day (adjusted)</td>
<td>27.8</td>
<td>28.9</td>
<td>32.2</td>
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<td>Number of clinics and hospitals</td>
<td>176</td>
<td>872</td>
<td>1536</td>
</tr>
<tr>
<td>Primary care clinics</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pediatric</td>
<td>11</td>
<td>68</td>
<td>86</td>
</tr>
<tr>
<td>Family physician</td>
<td>38</td>
<td>117</td>
<td>126</td>
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<tr>
<td>Internal medicine physician</td>
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<td>316</td>
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<td>Otolaryngologist</td>
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<td>Dermatologist</td>
<td>5</td>
<td>65</td>
<td>81</td>
</tr>
<tr>
<td>Others*</td>
<td>44</td>
<td>223</td>
<td>506</td>
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<tr>
<td>Hospital-based outpatient clinics</td>
<td>-</td>
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<tr>
<td>Pediatric secondary and tertiary care hospitals</td>
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<td>30</td>
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<tr>
<td>Non-pediatric secondary and tertiary care hospitals</td>
<td>9</td>
<td>17</td>
<td>85</td>
</tr>
</tbody>
</table>

*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 three areas

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

DOTs

Area A

Area B

Area C

Legend:
- Penicillins, Amoxicillin
- 1st cephalosporins
- Amoxicillin/clavulanate
- 2nd cephalosporins
- Macrolides
- 3rd cephalosporins
- Sulfamethoxazole and trimethoprim
- Lincosamides
- Fosfomycin
- Penems
- Tetracyclines
- Quinolones
Figure 4