Factors of geographical variability of antimicrobial use in Japan

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Research Article

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Abstract

Background

The evidence regarding the factors affecting the geographical variation of antimicrobial use (AMU) is relatively scarce. The study aimed to evaluate factors potentially associated with geographical variability of AMU per day per 1,000 habitants in 47 prefectures of Japan.

Methods

This is an observational ecological study using the Japanese national database in 2019. The outcome was the defined daily doses per 1,000 inhabitants per day by prefecture. The multivariable negative binomial regression analysis was conducted using patient- and physician-level variables.

Results

The study included 605,391,054 defined daily doses of AMU in 2019 from the 47 prefectures. In the multivariable negative binomial regression analyses for the outcome of total AMU, the proportion of females (RR 1.04 [1.01 – 1.08] per 1% increase, \( p = 0.021 \)), the proportion of upper secondary graduates going to further education (RR 1.01 [1.00 – 1.01] per 1% increase, \( p = 0.005 \)) and the annual number of diagnoses related with upper respiratory infections (URIs) per 1,000 inhabitants per day (RR 1.21 [1.10 – 1.34], \( p < 0.001 \)) were significantly correlated with total AMU.

Conclusions

In the ecological study, the variability of total AMU by Japanese prefecture was associated with the proportion of females, the education level and the number of URI diagnoses per population. The results suggest the potential need for additional stewardship efforts to reduce unnecessary antimicrobial prescriptions for URI.

Introduction

Antimicrobial resistance (AMR) has caused a significant global morbidity and mortality [1]. Some studies showed that the larger volume of antimicrobial use (AMU) was related with the higher rate of antimicrobial resistance in some ecological studies [2, 3]. Many countries have established their AMR national action plans [4]. In Japan, AMR national action plan was established in 2016, aiming the AMU per 1,000 inhabitants per day in 2020 is reduced to two-thirds of that in 2013 [5, 6]. There have been major progresses, including the achievement of the goal to reduce AMU in 2020, although the COVID-19 pandemic may have had a significant impact on the reduction of AMU [7]. However, because there are still
needs to further mitigate the negative impact of AMR, the investigation of potential factors associated with AMU is important to further guide the future AMR-related measures.

While geographical variabilities of AMU within a country were reported in some studies, the evidence regarding the factors affecting the geographical variation of AMU is relatively scarce [8, 9, 10, 11, 12]. In general, physician-level factors (e.g., physician's experiences) and patient-level factors (e.g., patient age, sex and socioeconomic status) have been reported to impact physician's behavior of antimicrobial prescription [13, 14, 15, 16, 17, 18]. The investigation of these factors to evaluate their potential impact on geographical variability using nationwide data may contribute to the identification of potential measures to reduce AMU and the promotion of appropriate AMU in the future. A previous study using AMU data until the year of the introduction of the AMR national action plan in Japan (2013–2016) showed that oral macrolides and quinolones are more frequently used in Western Japan compared to Eastern Japan [11]. However, factors associated with the geographical variation of AMU remain to be investigated. Given the significant reduction in AMU after the implementation of the national action plan since 2016, our study focused on the assessment of factors contributing to high regional AMU using the data after the implementation of the national action plan to elucidate potential interventions in addition to the action plan implementation.

In this ecological study, we aimed to evaluate factors potentially associated with geographical variability of AMU per day per 1,000 habitants in 47 prefectures of Japan.

**Methods**

**Study design**

This is an observational ecological study using the Japanese national database (NDB) in 2019. All methods were carried out in accordance with STROBE statement. The NDB is a database of anonymized electronic health insurance claims covering more than 99% of all national claims with data regarding medical outpatient services, diagnostic procedural combination, dental services and dispensed medications [19, 20]. Our proposal document for the use of the NDB was reviewed by Japanese Ministry of Health, Labour and Welfare (MHLW), obtaining the approval for its use. The outcome of this study was the defined daily doses (DDD) per 1,000 inhabitants per day (DID). DDD was calculated according to the WHO's definition in 2022 [21]. Population was referred on October 1st in the study year [22]. Using dependent variables as described below, a multivariable negative binomial regression analysis was conducted to evaluate the impact of each variable on the outcome.

**Outcome**

All systemic antimicrobials, defined as J01 in Anatomical Therapeutic Chemical (ATC) Classification, were included in the study [23]. AMU from January 1 to December 31, 2019 were extracted for all 47 prefectures. The location of prescribing healthcare facilities was used to identify the prefecture of each
prescription. Then, the DID was calculated by prefecture. AMU data extracted from the NDB was categorized using ATC Classification [23].

**Variables**

We hypothesized that antimicrobial stewardship measures are associated with reduced AMU. For example, the national action plan includes the enhancement of education related with AMR as well as the development of infectious disease specialists. Therefore, the average age of physicians (assuming young physicians receive more AMR-related education) and the number of infectious disease physicians are selected as variables. As the action plan also focuses on the reduction of AMU for upper respiratory infections (URIs). The number of URIs was also selected as a variable in the study. In addition, the action plan encourages center hospitals to take initiatives in their local stewardship efforts (additional reimbursement for infection prevention in Supplemental Table S1). The adjustment was conducted with population factors (population age, sex, nationality, income and education level) and other healthcare facility factors (the number of clinics, the number of hospitals and the proportion of large hospitals).

Based on the hypotheses described above, the variables evaluated in this study included population sex (the proportion of females), population age (the proportion of population < 15 years and ≥ 65 years), the average income per household, the population education level (the proportion of upper secondary graduates going to further education), the number of clinics per 10,000 inhabitants, the number of hospitals per 100,000 inhabitants, the rate of hospitals with > = 500 beds, the average age of physicians, the number of certified infectious disease specialist physicians per 100,000 inhabitants, the number of hospitals with additional reimbursement for infection prevention 1 per 100,000 inhabitants, the number of hospitals with additional reimbursement for infection prevention 2 per 100,000 inhabitants and the annual number of diagnoses related with URI per 1,000 inhabitants per day. In this study, all variables were presented by the prefecture level.

Population age and sex, the average income per household, the ratio of upper secondary graduates going to further education and the average age of physicians were obtained from Statistic Bureau, Ministry of Internal Affairs and Communications [22]. The physician’s age was included in the variables because some studies showed physicians’ experience is related with antibiotic prescriptions [13, 17]. The number of clinics, the number of hospitals, the rate of hospitals with > 500 beds and the number of healthcare facilities with additional reimbursement for infection prevention 1 and 2 were obtained from regional bureaus of Health and Welfare (e.g., Kanto-Shinetsu) [24, 25]. In 2019, the requirements for hospitals with additional reimbursement for infection prevention are presented in Supplemental Table S1 [26]. The number of certified infectious disease specialist physicians was from the Japanese Association for Infectious Diseases [27]. The annual number of diagnoses related with URIs was extracted from the NDB. The URI-related diagnoses included in this study are presented in Table S2.

**Statistical analysis**

Characteristics of variables were presented with median and interquartile range (IQR). To investigate the relationship between the outcome of DID and each variable, the multivariable negative binomial
regression analyses were performed to calculate adjusted rate ratios (aRR) with 95% confidence intervals. The aRRs of proportional variables were presented by a 1% increase in each variable. The negative binomial regression model was selected because of the significant overdispersion in the multivariable Poisson regression model and because of DDD being the count data. To avoid multicollinearity, variance inflation factors (VIFs) in all variables were evaluated. With the authors’ discussion, the proportion of >= 65 years, the average income per household and the number of hospitals per 10,000 inhabitants, factors with high VIF, were excluded from the multivariable analysis. The log of the population in the prefecture was used as an offset term in the negative binomial regression analyses. The analyses were implemented for all systemic AMU, and AMU by class (1. J01C penicillins, 2. J01D other beta-lactams, 3. J01M quinolones, 4. J01F macrolides, lincosamides, and streptogramins and 5. J01 all other systemic antimicrobials).

Two-sided p values of < 0.05 were considered to show statistical significance. The statistical analyses described above were conducted by Stata 14.2 (College Station, TX, USA).

Results

The study included 605,391,054 defined daily doses of AMU in 2019 from the 47 prefectures. The characteristics of the prefecture-level AMU and variables are presented in Table 1. The AMUs in the 47 prefectures varied with a median of 13.1 DID (IQR 12.0 – 14.3). Figure 1 shows presenting the geographical variation of AMU (DID) for all systemic antimicrobials. The trend of the higher AMU in Western Japan was observed compared with Eastern Japan.
Table 1
Outcome and variable characteristics by prefecture in 2019

| Outcomes                                      | Median (IQR)          | p-value  
|-----------------------------------------------|-----------------------|----------
| All systemic antimicrobials                   | 13.1DID [12.0–14.3]   |          |
| Penicillins                                   | 1.1 DID [1.0–1.2]     |          |
| Other beta-lactams                            | 3.6 DID [3.4–3.9]     |          |
| Quinolones                                    | 2.5 DID [2.2–2.9]     |          |
| Macrolides, lincosamides and streptogramins  | 4.4 DID [4.0–4.8]     |          |
| Others                                        | 1.3 DID [1.2–1.5]     |          |
| Proportion of access in AWaRe                 | 14.6% [13.0–15.9%]    |          |

<table>
<thead>
<tr>
<th>Variables</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Population variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of &lt; 15 years</td>
<td>12.0% [11.6–12.6%]</td>
<td>0.083</td>
</tr>
<tr>
<td>Proportion of &gt;= 65 years</td>
<td>30.8% [29.1–32.5%]</td>
<td>0.929</td>
</tr>
<tr>
<td>Proportion of female</td>
<td>51.8% [50.9–52.6%]</td>
<td>0.009</td>
</tr>
<tr>
<td>Proportion of Japanese nationality</td>
<td>98.7% [98.2–99.2%]</td>
<td>0.928</td>
</tr>
<tr>
<td>Annual Income per household (x 1,000 JPY)</td>
<td>5,421 [5,016–5,846]</td>
<td>0.039</td>
</tr>
<tr>
<td>Rate of upper secondary graduates going to further education</td>
<td>51.2% [46.1–55.2%]</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Abbreviations: AMU; antimicrobial use, AWaRe; Access, Watch, Reserve, DDD; defined daily doses, DID; defined daily doses per 1,000 inhabitants per day, IQR; interquartile range, JPY; Japanese yen.

*p-values were calculated by univariable negative binomial regression models using the outcome of total DDD and each variable with offset of the log of the population.
### Healthcare-related variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (IQR)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>The number of clinics per 10,000 habitants</td>
<td>11.8 [10.8–12.5]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>The number of hospitals per 100,000 habitants</td>
<td>7.7 [6.3–10.2]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Rate of hospitals with &gt; 500 beds</td>
<td>4.3% [3.0–6.4%]</td>
<td>0.296</td>
</tr>
<tr>
<td>The number of healthcare facilities with additional reimbursement for</td>
<td></td>
<td></td>
</tr>
<tr>
<td>infection prevention 1 per 100,000 habitants</td>
<td>1.2 [1.1–1.4]</td>
<td>0.186</td>
</tr>
<tr>
<td>The number of healthcare facilities with additional reimbursement for</td>
<td></td>
<td></td>
</tr>
<tr>
<td>infection prevention 2 per 100,000 habitants</td>
<td>2.3 [1.9–2.9]</td>
<td>0.029</td>
</tr>
<tr>
<td>The annual number of diagnoses related with upper respiratory infections</td>
<td>998.5 [949.8–1,056.5]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>per 1,000 habitants per day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average age of physicians (years)</td>
<td>50.8 [49.7–51.8]</td>
<td>0.412</td>
</tr>
<tr>
<td>The number of certified infectious disease specialist physicians per</td>
<td>1.1 [0.9–1.5]</td>
<td>0.005</td>
</tr>
<tr>
<td>100,000 habitants</td>
<td></td>
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</tbody>
</table>

**Abbreviations:** AMU; antimicrobial use, AWaRe; Access, Watch, Reserve, DDD; defined daily doses, DID; defined daily doses per 1,000 inhabitants per day, IQR; interquartile range, JPY; Japanese yen.

*p*-values were calculated by univariable negative binomial regression models using the outcome of total DDD and each variable with offset of the log of the population.

In the multivariable negative binomial regression analyses for the outcome of total AMU, the proportion of females (aRR 1.04 [1.01–1.08] per 1% increase, *p* = 0.021), the proportion of upper secondary graduates going to further education (aRR 1.01 [1.00–1.01] per 1% increase, *p* = 0.005) and the annual number of diagnoses related with URIs per 1,000 inhabitants per day (aRR 1.21 [1.10–1.34], *p* < 0.001) were significantly associated with total AMU (Fig. 2). Other variables were not significantly associated with total AMU.

The results of multivariable negative binomial regression analyses by antimicrobial class are presented in Supplemental Figures S1 – S5. For the outcome of AMU in penicillins, the proportion of < 15 years (aRR 1.10 [1.05–1.14] per 1% increase, *p* < 0.001) had a positive correlation, while the average age of physicians (aRR 0.93 [0.90–0.97], *p* = 0.001) had a significant negative correlation (Figure S1). In the AMU of other beta-lactam antimicrobials, the proportion of females (aRR 1.04 [1.00–1.08], *p* = 0.027), the proportion of upper secondary antimicrobials going to further education (aRR 1.01 [1.00–1.02], *p* < 0.001) and the annual number of diagnoses related with URIs per 1,000 inhabitants per day (aRR 1.19 [1.07–
1.31, \( p = 0.001 \) were significantly correlated (Figure S2). These three variables were also statistically significant in quinolones (Figure S3), with aRR 1.07 [1.01 – 1.013] and \( p = 0.030 \) in the female proportion, aRR 1.01 [1.00 – 1.02] and \( p = 0.012 \) in the proportion of further education and aRR 1.48 [1.26 – 1.74] and \( p < 0.001 \) in the annual number of diagnoses related with URIs per 1,000 inhabitants per day. The number of hospitals with additional reimbursement for infection prevention 1 per 100,000 inhabitants was positively correlated with the AMU of macrolides, lincosamides, and streptogramins (aRR 4.32 [1.87 – 10.01], \( p = 0.001 \) in Figure S4) and all other systemic antimicrobials (aRR 4.56 [1.16 – 17.85], \( p = 0.029 \) in Figure S5).

**Discussion**

The study evaluated the relationship between AMU and patient-and physician-level variables in 47 Japanese prefectures. The proportion of females, the education level, and the number of URI diagnoses were positively correlated with the total AMU as well as the AMU beta-lactams other than penicillins and quinolones in the analysis by antimicrobial class. On the other hand, the use of penicillins was positively correlated with the proportion of the pediatric population and negatively correlated with physicians’ age.

Our study resulted in a higher AMU in Western Japan than that in Eastern Japan, which was described in the previous study using data before the action plan implementation. For the AMU in general, previous studies, including a systematic review, revealed that females were more likely to receive antimicrobials compared with males [28, 29, 30, 31], although other studies showed that males had more antibiotic prescriptions than females [32, 33]. While the impact of gender on the AMU varies by situation, further investigations regarding the factors related with gender difference in the population are warranted. Our study suggests that higher education level may be correlated with more AMU. Previous studies outside of Japan showed that lower education was correlated with more AMU or misuse of antimicrobials [34, 35]. However, patient pressure to prescribe antibiotic is a recognized issue on inappropriate antimicrobial prescriptions [36, 37]. A potential hypothesis explaining our result is higher patient education is correlated with high demand for antimicrobial prescriptions in Japan. Additional studies with a different study design from ours are important to evaluate the impact of overall education level on the Japanese population.

While the vast majority of URIs are caused by viruses, inappropriate antimicrobial prescriptions are frequently reported by many studies [38, 39, 40]. A previous Japanese study revealed that antimicrobials were prescribed in 60% of cases with claim diagnoses of non-bacterial upper respiratory infections [40]. To reduce unnecessary AMU for URIs in Japan, the national guideline was developed in 2017. However, the recent study after the dissemination of the guideline showed that AMU for URIs was still common [41]. Our study also showed the positive correlation with the number of visits with URI diagnoses and AMU, suggesting the need for further efforts, including the enhancement of education regarding appropriate AMU targeting the general population, to reduce antibiotic prescriptions for URI [42].
Regarding AMU by antibiotic class, beta-lactams other than penicillins and quinolones comprise approximately a half of total AMU. Given that the three factors associated with the AMU of these two antibiotic classes are the same as those of total AMU, the same rationales of the associations with the total AMU may be applied to these two antibiotic classes. Stewardship measures to reduce unnecessary prescriptions of these two antibiotic classes are vital to further reduce total AMU in the future. On the other hand, AMU in penicillins was correlated with a larger proportion of the pediatric population and the younger physician age. As recommended by a Japanese guideline, pediatric patients may often receive penicillins for certain types of respiratory infections [43]. In general, the spectrums of penicillins in the ATC classification are narrower than those of other beta-lactams with amoxicillin index used as an indicator of quality measure regarding AMU. Some studies revealed that long career physicians were more likely to prescribe antimicrobials than younger physicians [17, 40].

The number of hospitals with additional reimbursement for infection prevention 1 per population was positively correlated with the larger AMUs in macrolides, lincosamides, and streptogramins and other systemic antimicrobials. While these hospitals may be more likely to see complex patients requiring the antimicrobial treatments of these classes, the reason for the result is currently being investigated.

There are some limitations in the study. First, because this is an ecological study, the possibility of an ecological fallacy cannot be eliminated. Other factors which were not investigated in this study may have affected the AMU. Second, the study used the data before the COVID-19 pandemic. The exploration of the impact of the COVID-19 pandemic on the factors of antibiotic prescription is an interesting future research topic. Third, the study finding from Japan may not generalized to other countries. However, our result that the number of URI diagnoses had a significant correlated with higher AMU after adjusting population and healthcare-related factors may provide a global insight on the need to emphasize antimicrobial stewardship for URIs. While the results need to be interpreted with caution given these limitations, our results generated hypotheses to address geographical variability of AMU in Japan.

**Conclusions**

In the ecological study, the variability of total AMU by Japanese prefecture was associated with the proportion of females, the education level and the number of URI diagnoses per population. The results suggest the potential need for additional stewardship efforts to reduce unnecessary antimicrobial prescriptions for URI. The analysis by antimicrobial class showed that younger age of physicians was correlated with the AMU of penicillins, suggesting that the impact of stewardship education for young physicians.

**Declarations**

Ethics approval: The study was approved by Institutional Review Board at National Center for Global Health and Medicine (Approval No. NCGM-G-003098-01). Patient identifiers were not included in our data used in this study then therefore no informed consent was required to conduct the present study.
Consent for publication: Not applicable due to the reason mentioned above.

Availability of data and materials: Data from this study cannot be shared. Data are available from the Ministry of Health, Labour, and Welfare of Japan for researchers who meet the criteria for access to confidential data. Please contact the corresponding author for further information.

Competing interests: None declared.

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Authors’ contributions: Taito Kitano: Study design, Data analysis, Writing the first draft; Shinya Tsuzuki: Study design, Data analysis, Editing, supervision; Ryuji koizumi: Data collection, Data curation, Editing; Kensuke Aoyagi: Data collection, Data curation; Yusuke Asai: Data analysis, Editing; Yoshiki Kusama: Study design, Editing; Norio Ohmagari: Editing, Supervision

Acknowledgements: Not applicable.

References


Figures
Figure 1

Total antimicrobial use (DID) by prefecture in 2019.

Antimicrobial use was calculated using the defined daily doses per 1,000 inhabitants per day (DID).
Figure 2

Adjusted rate ratios of prefecture-level total antimicrobial use (DID) in 2019 by investigated variables.

The dots and lines in the figure represent the point estimates and 95% of confidence intervals.

The adjusted rate ratios of proportional variables are presented by a 1% increase in each variable.

The variable labels were defined as follows. Female; the proportion of females in the population, <15 years; the proportion of <15 years in the population, Education; the proportion of upper secondary graduates going to further education, Clinic; the number of clinics per 1,000 inhabitants, >=500 beds, the rate of hospitals with >500 beds, Reimbursement 1; the number of hospitals with additional reimbursement for infection prevention 1 per 100,000 inhabitants, Reimbursement 2; the number of hospitals with additional reimbursement for infection prevention 2 per 100,000 inhabitants, ID physician; the number of certified infectious disease specialist physicians per 1,000 inhabitants, Physician age; the average age of physicians, and URI; the annual number of diagnoses related with upper respiratory infections per inhabitant.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.