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ORIGINAL RESEARCH

Factors Associated with Geographical Variability of Antimicrobial Use in Japan

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ABSTRACT

Introduction: Evidence regarding the factors affecting the geographical variation of antimicrobial use (AMU) is relatively scarce. This study aimed to evaluate factors potentially associated with geographical variability of AMU per day per 1000 habitants in the 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 1000 inhabitants per day by prefecture. 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 female individuals (adjusted rate ratio [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 to upper respiratory infections (URIs) per 1000 inhabitants per day (aRR 1.21 [1.10–1.34], $p < 0.001$) were significantly correlated with total AMU.

Conclusions: In this ecological study, the variability of total AMU by Japanese prefecture was associated with the proportion of female individuals, 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.

Keywords: Antimicrobials; Antimicrobial stewardship; Upper respiratory infection; Gender; Education

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Key Summary Points

Factors affecting the geographical variation of antimicrobial use (AMU) are not clear.

This observational ecological study used the Japanese national database in 2019.

The number of URI diagnoses per population was strongly associated with AMU.

This suggests the potential need for additional antimicrobial stewardship efforts.

INTRODUCTION

Antimicrobial resistance (AMR) has caused significant global morbidity and mortality [1]. A larger volume of antimicrobial use (AMU) was related to the higher rate of AMR in some ecological studies [2, 3]. Many countries have established their AMR national action plans [4]. Japan's AMR national action plan was established in 2016, aiming to reduce AMU per 1000 inhabitants per day in 2020 to two-thirds of that in 2013 [5, 6]. There has been major progress, 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 future AMR-related measures.

While geographical variabilities of AMU within a country were reported in some studies, evidence regarding the factors affecting the geographical variation of AMU is relatively scarce [8–13]. 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 regarding antimicrobial prescription [13–18]. 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 (East Japan includes Tokyo, Kanto region (The Greater Tokyo Area), and Northern Japan, whereas West Japan includes Kansai region, the second most populated area in Japan, and Southern Japan) [11, 12]. 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 the geographical variability of AMU per day per 1000 habitants in all 47 prefectures of Japan.

METHODS

Ethical Approval

The study was conducted in accordance with the declaration of Helsinki and approved by the 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 and therefore no informed consent was required to conduct the present study.

Study Design

This was an observational ecological study using the Japanese national database (NDB) in 2019. All methods were carried out in accordance with the 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 and inpatient services, diagnostic procedural combinations, dental services, and dispensed medications [19, 20]. Our proposal document for the use of the NDB was reviewed by the Japanese Ministry of Health, Labour and Welfare (MHLW), which granted approval for its use. The outcome of this study was the defined daily doses (DDD) per 1000 inhabitants per day (DID). DDD was calculated according to the World Health Organization (WHO) definition in 2022 [21]. Population referred to that on October 1 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 the Anatomical Therapeutic Chemical (ATC) classification, were included in the study [23]. AMU data 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 to 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. In Japan, physicians are the only practitioners who can prescribe antimicrobials. In hospital settings, antimicrobial stewardship teams often comprise physicians (e.g., infectious disease physicians), pharmacists (e.g., board certified pharmacists in infection control), nurses (e.g., certified nurses in infection control), and clinical laboratory technicians (e.g., infection control microbiological technologists) that support and advise physicians on antimicrobial prescriptions. In community settings, community pharmacists assist and advise physicians on antimicrobial prescribing.

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 this study. In addition, the action plan encourages center hospitals to take initiative 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).

On the basis of the hypotheses described above, the variables evaluated in this study included population sex (the proportion of female individuals), 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 proportion 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 to URI per 1000 inhabitants per day. In this study, all variables were presented at the prefecture level.

Population age and sex, the average income per household, the proportion of upper secondary graduates going to further education, and the average age of physicians were obtained from the Statistic Bureau, Ministry of Internal Affairs and Communications [24]. The physician's age was included in the variables because some studies showed physicians' experience is related to antibiotic prescriptions [13, 17]. The number of clinics, the number of hospitals, the proportion 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) [25, 26]. The requirements for hospitals with additional reimbursement for infection prevention in 2019 are presented in Supplemental Table S1 [27]. The number of certified infectious disease specialist physicians was obtained from the Japanese Association for Infectious Diseases [28]. The annual number of diagnoses related to 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, multivariable negative binomial regression analyses were performed to calculate adjusted rate ratios (aRR) with 95% confidence intervals. The aRRs of proportional variables were presented for 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. After discussion amongst the authors, 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; 5, J01 all other systemic antimicrobials).

Two-sided p values less than 0.05 were considered to show statistical significance. The statistical analyses described above were conducted using 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 the geographical variation of AMU (DID) for all systemic antimicrobials. The trend of higher AMU in Western Japan was observed compared with Eastern Japan.

In the multivariable negative binomial regression analyses for the outcome of total AMU, the proportion of female individuals (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 to URIs per 1000 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 Figs. 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 (Fig. S1). In the AMU of other beta-lactam antimicrobials, the proportion of female individuals (aRR 1.04 [1.00–1.08], $p = 0.027$), the proportion of upper secondary graduates going to further education (aRR 1.01 [1.00–1.02], $p < 0.001$), and the annual number of diagnoses related to URIs per 1000 inhabitants per day (aRR 1.19 [1.07–1.31], $p = 0.001$) were significantly correlated (Fig. S2). These three variables were also statistically significant in quinolones (Fig. S3), with aRR 1.07 [1.01–1.013] and $p = 0.030$ for the female proportion, aRR 1.01 [1.00–1.02] and $p = 0.012$ for the proportion of upper secondary graduates

Table 1 Outcome and variable characteristics by prefecture in 2019

	Median (IQR)	*p* value[a]
Outcomes		
All systemic antimicrobials	13.1 DID [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%]	
Variables		
Population variables		
Proportion of < 15 years	12.0% [11.6–12.6%]	0.083
Proportion of ≥ 65 years	30.8% [29.1–32.5%]	0.929
Proportion of female individuals	51.8% [50.9–52.6%]	0.009
Proportion of Japanese nationality	98.7% [98.2–99.2%]	0.928
Annual income per household (× 1000 JPY)	5421 [5016–5846]	0.039
Proportion of upper secondary graduates going to further education	51.2% [46.1–55.2%]	0.31
Healthcare-related variables		
Number of clinics per 10,000 habitants	11.8 [10.8–12.5]	< 0.001
Number of hospitals per 100,000 habitants	7.7 [6.3–10.2]	< 0.001
Proportion of hospitals with > 500 beds	4.3% [3.0–6.4%]	0.296
Number of healthcare facilities with additional reimbursement for infection prevention 1 per 100,000 habitants	1.2 [1.1–1.4]	0.186
Number of healthcare facilities with additional reimbursement for infection prevention 2 per 100,000 habitants	2.3 [1.9–2.9]	0.029
Annual number of diagnoses related to upper respiratory infections per 1000 habitants per day	998.5 [949.8–1056.5]	< 0.001
Average age of physicians (years)	50.8 [49.7–51.8]	0.412
Number of certified infectious disease specialist physicians per 100,000 habitants	1.1 [0.9–1.5]	0.005

AMU antimicrobial use, *AWaRe* access, watch, reserve, *DDD* defined daily doses, *DID* defined daily doses per 1000 inhabitants per day, *IQR* interquartile range, *JPY* Japanese yen

[a]*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

going to further education, and aRR 1.48 [1.26–1.74] and $p < 0.001$ for the annual number of diagnoses related to URIs per 1000 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 Fig. S4) and all other

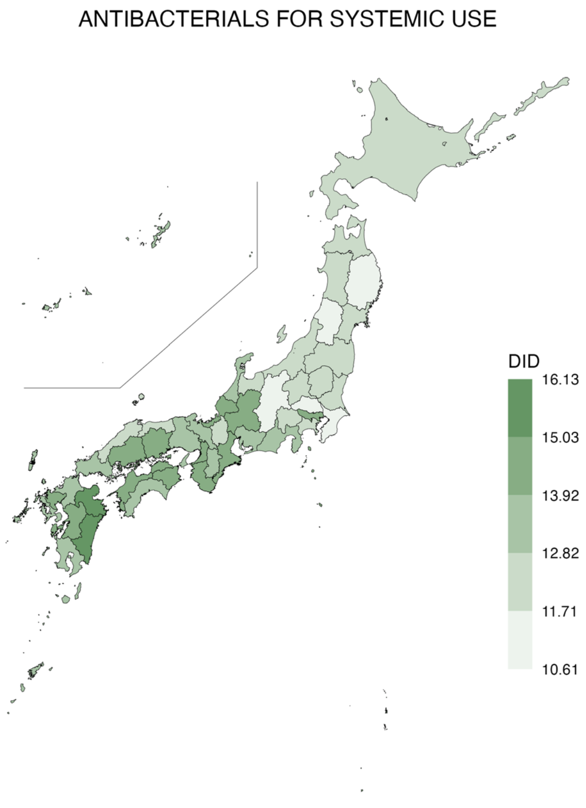

Fig. 1 Total antimicrobial use (DID) by prefecture in 2019. Antimicrobial use was calculated using the defined daily doses per 1000 inhabitants per day (DID)

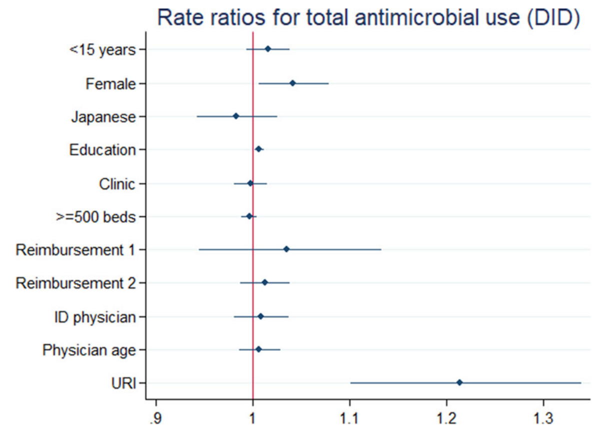

Fig. 2 Adjusted rate ratios of prefecture-level total antimicrobial use (DID) in 2019 by investigated variables. The dots and lines represent the point estimates and 95% confidence intervals, respectively. The adjusted rate ratios of proportional variables are presented for a 1% increase in each variable. The variable labels are defined as follows. Female, the proportion of female individuals in the population; $<$ 15 years, the proportion of people aged $<$ 15 years in the population; Education, the proportion of upper secondary graduates going to further education; Clinic, the number of clinics per 1000 inhabitants; $\geq$ 500 beds, the proportion 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 1000 inhabitants; Physician age, the average age of physicians; URI, the annual number of diagnoses related to upper respiratory infections per inhabitant

systemic antimicrobials (aRR 4.56 [1.16–17.85], $p = 0.029$ in Fig. S5).

DISCUSSION

The study evaluated the relationship between AMU and patient- and physician-level variables in 47 Japanese prefectures. The proportion of female individuals, 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. Compared with other countries, the median 13.1 DID in our study was in lower than those of most European countries, but was still higher than the lowest countries [29].

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 female individuals were more likely to receive antimicrobials compared with male individuals [30–33], although other studies showed that male individuals had more antibiotic prescriptions than female individuals [34, 35]. The study could not evaluate the impact of urinary tract infection, which was more frequently reported in female individuals compared to male individuals [36]. While the impact of gender on the AMU varies by situation, further investigations, including the impact of urinary tract infection [37], regarding the factors related to gender differences in the population are warranted. Our study suggests that higher education levels may be correlated with more AMU. Previous studies outside of Japan showed that lower education was correlated with more AMU or misuse of antimicrobials [38, 39]. However, patient pressure to prescribe antibiotics is a recognized issue in inappropriate antimicrobial prescriptions [40, 41]. A potential hypothesis explaining our result is that 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 [42–45]. A previous Japanese study revealed that antimicrobials were prescribed in 60% of cases with claim diagnoses of non-bacterial URIs [42]. To reduce unnecessary AMU for URIs in Japan, the national guideline was developed in 2017. However, a recent study after the dissemination of the guideline showed that AMU for URIs was still common [46]. Our study also showed a positive correlation between 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 [47]. In addition, it is important to note that most URIs are diagnosed and managed in outpatient settings. Stewardship measures specifically focusing on these outpatient settings are required to reduce antibiotic prescriptions for URI.

Regarding AMU by antibiotic class, beta-lactams other than penicillins and quinolones comprise approximately 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 younger physician age. As recommended by a Japanese guideline, pediatric patients may often receive penicillins for certain types of respiratory infections [48]. Because our study used DID as the outcome, AMU for children may have been underestimated given some studies from other countries reported more frequent antimicrobial prescriptions for children than those for adults [49]. Therefore, the lack of significant correlation between the pediatric population and DID in overall AMU and AMU in other classes may have not been applied if the number of antimicrobial prescriptions had been selected as our outcome. 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 [50]. Some studies revealed that physicians with a long career duration were more likely to prescribe antimicrobials than younger physicians [17, 44].

The number of hospitals with additional reimbursement for infection prevention 1 per population was positively correlated with the larger AMUs in macrolides, lincosamides, 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 findings from Japan may not be generalized to other countries. However, our result that the number of URI diagnoses was significantly correlated with higher AMU after adjusting population and healthcare-related factors may provide a global insight into 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 the geographical variability of AMU in Japan.

CONCLUSIONS

In this ecological study, the variability of total AMU by Japanese prefecture was associated with the proportion of female individuals, 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 the younger age of physicians was correlated with the AMU of penicillins, suggesting that the impact of stewardship education for young physicians.

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Data Availability. 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.

Declarations

Conflict of Interest. Taito Kitano, Shinya Tsuzuki, Ryuji Koizumi, Kensuke Aoyagi, Yusuke Asai, Yoshiki Kusama, and Norio Ohmagari have nothing to disclose.

Ethical Approval. The study was conducted in accordance with the declaration of Helsinki and approved by the 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 and therefore no informed consent was required to conduct the present study.

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