Original Article

Impact of Geographical Variations on the Prevalence of Multidrug-Resistant Organisms in Japan

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SUMMARY: Emergence and spread of multidrug-resistant organisms (MDRO) is an urgent social and public health problem. Here, we carried out an epidemiological survey to clarify the geographical characteristics and factors influencing the prevalence of MDRO. Data on the prevalence of MDRO in 47 prefectures in Japan were extracted from the Japanese Nosocomial Infection Surveillance, a nationwide database for infection control. Potential factors for MDRO were analyzed using data selected from the pharmacological, medical service, infection control, environmental, social, and food-related categories, based on the characteristics of each organism and the correlations between them and MDRO prevalence. Statistical data for potential factors were obtained from public domains. The use of antibiotics was found to be correlated with the prevalence of penicillin-resistant *Streptococcus pneumoniae*, 3rd-generation cephalosporin- and fluoroquinolone-resistant *Escherichia coli*, and methicillin-resistant *Staphylococcus aureus*. Negative correlation between the consumption of food such as kelp and fermented soybeans that facilitate the growth of lactic acid bacteria and the prevalence of 3rd-generation cephalosporin- and fluoroquinolone-resistant *E. coli* suggested an association between the intestinal microflora and MDRO colonization. In addition to the use of antibiotics, lifestyle, food culture, and social factors such as tobacco smoking, average atmospheric temperature, prevalence of three-generation households, ratio of elderly population, average duration of tourist stay, chicken and fermented soybean consumption, and the competency of healthcare services may also affect MDRO prevalence.

INTRODUCTION

The Japanese government is committed to prevent infections. In 2012, the Japanese Ministry of Health, Labour and Welfare (MHLW) revised the guidelines for additional reimbursements for infection prevention in the Japanese healthcare system. This was done to enable hospitals with a team of dedicated infection control specialists with higher work volume to receive more financial resources (“reimbursement 1”) than those with lesser work volume that does not satisfy the criteria for “reimbursement 1,” categorized as “reimbursement 2.” These financial resources have facilitated infection control activities and antimicrobial stewardship teams.

The Japanese government declared a “National Action Plan on Antimicrobial Resistance (AMR) 2016–2020” on April 5, 2016, which outlined the outcome indices for multidrug-resistant organisms (MDRO) and antimicrobial use reduction (1) that should be achieved by 2020. The dissemination of MDRO is influenced by medical, social, and environmental factors such as the quality of infection control activities, use of antimicrobials (2), population density (3), climate (3), and hygiene and sanitation practices (4). Japan comprises 47 prefectures with a wide variety of social and environmental conditions that could affect MDRO distribution. Understanding the geographical variations in MDRO prevalence would facilitate more efficient approaches to achieve the goals of the National Action Plan. Therefore, we aimed to determine the roles of geographical features and other factors in the prevalence of MDRO.

MATERIALS AND METHODS

Selection of MDRO: Penicillin-resistant *Streptococcus pneumoniae* (PRSP), methicillin-

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resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococcus (VRE), carbapenem-resistant Enterobacteriaceae (CRE), 3rd-generation cephalosporin-resistant *Escherichia coli*, and fluoroquinolone-resistant *E. coli* were selected for analyzing the prevalence of MDRO. Being commonly isolated from outpatient clinics, PRSP is a clinically important cause of respiratory infections among elderly persons and meningitis in children (5). The prevalence of MRSA is decreasing, but it remains as one of the major threats to public health in Japan and globally. The prevalence of VRE and CRE is relatively low in Japan, but outbreaks that have seriously affected healthcare services have been reported almost annually in recent years (6). Third-generation cephalosporin- and fluoroquinolone-resistant *E. coli* have already spread among the general public in Japan with increasing prevalence and clinical importance.

Selection of potential factors related to the spread and prevalence of MDRO: Potential factors responsible for the spread of the selected MDRO based on the characteristics of each organism were categorized as pharmacological, medical service-related, infection control-related, environmental, social, and food-related. The pharmacological category comprises the use of all types of antibiotics and drug-resistance-specific antibiotics (defined daily dose/1,000 inhabitants/day). The medical service-related category included the number of physicians, pulmonologists, and pediatricians ($/10^5$ population). The infection control-related category included the number of infection-control doctors ($/10^5$ population), hospital stay (days), number of beds per certified infection-control nurse, the prevalence of hospitals (%) acquiring additional “reimbursement 1” or “2” as certified by the Japanese MHLW, and the participation of hospitals (%) in the Japan Nosocomial Infections Surveillance (JANIS). The environmental category included the averages for atmospheric temperature and relative humidity. The social category included the ratio (%) of population aged ≥ 65 years, population density, average income, three-generation households, average length of tourist stay (days/1,000 population), and rates of departure by Japanese nationals to other countries (%). The food-related category included the consumption of fermented soybeans (Natto), kelp, chicken, beef, and pork. Tobacco smoking was also included as a potential contributor to the prevalence of PRSP.

Several common factors between the pharmacological and infection control-related categories, and the six MDRO, were selected for evaluation. Additionally, factors categorized as social and environmental were selected based on reported findings that suggest their unique association with the spread of MDRO. Considering the discrepancies in the prevalence of VRE between Japan and other countries (7,8), and the rapidly increasing numbers of tourists visiting Japan (9,10), factors associated with these discrepancies and Japanese tourists returning from other countries were selected for the statistical analysis of the prevalence of VRE. Factors associated with food were selected for the analyses of VRE, CRE, 3rd-generation cephalosporin- and fluoroquinolone-resistant *E. coli*. Chicken, pork, and beef consumption was selected as a potential

route of transmission. Fermented soybeans and kelp were selected for the analyses of 3rd-generation cephalosporin- and fluoroquinolone-resistant *E. coli* because these foods facilitate the growth of lactic acid bacteria (11–13) that could prevent the spread of extended-spectrum β -lactamase (ESBL) (14,15). Food factors were not included in the analyses of the prevalence of MRSA and PRSP. Tobacco smoking and average income were selected for the analysis of the prevalence of PRSP based on the report by García-Rey et al. (16). The prevalence of three-generation households was also selected based on the high prevalence of PRSP among children (5) and the high morbidity of invasive pneumococcal infections among elderly persons (17).

Data collection: Prevalence of drug-resistant bacteria in the 47 prefectures was determined from the data provided by JANIS (18,19), a nationwide database for clinically isolated bacteria established by the Japanese MHLW in 2000. As of January 2019, 2,262 hospitals have been enrolled in JANIS. The clinical laboratory division of JANIS registered 1,947 hospitals (year 2018), which includes 88.7% ($n = 47$) of hospitals with ≥ 900 beds, 81.3% ($n = 291$) of hospitals with 500–899 beds, 45.2% ($n = 996$) of hospitals with 200–499 beds, and 10.6% ($n = 613$) of hospitals with < 200 beds. Using JANIS data in 2017, the prevalence of CRE, PRSP, MRSA, and 3rd-generation cephalosporin- and fluoroquinolone-resistant *E. coli* was calculated as (Number of specific MDRO-positive patients)/(Total number of specimen-submitting patient) $\times 100$. Because VRE-positivity is very rare, prevalence of VRE was calculated as (Number of VRE-positive patients)/(Total number of specimen-submitting patient) $\times 100,000$. Annual sales of antimicrobials were determined based on a nationwide surveillance of antimicrobial sales in 2016 by the AMR Clinical Reference Center (Tokyo, Japan). Data on food consumption in 2017 were obtained from the private database created by Chiiki-no Iremono at <https://region-case.com/>, which is based on a survey of family incomes and expenditures by the Statistics Bureau of Japan, Ministry of Internal Affairs and Communications at <https://www.stat.go.jp/english/index.html>. Statistical data on the total number of foreign visitors (person·days) and the departure rates of Japanese nationals for other countries were obtained from the database of the Japan Tourism Agency, Ministry of Land, Infrastructure, Transport and Tourism (2017) at <https://www.mlit.go.jp/kankocho/siryou/toukei/shukuhakutoukei.html>. Other social and environmental data, such as population density (2018) and meteorological data (2016), were obtained from the database created by the Statistics Bureau of Japan, Ministry of Internal Affairs and Communications at <https://www.stat.go.jp/english/index.html>. The number of infection-control doctors was provided by the Japanese College of Infection Control Doctors (August 2019). The number of nurses certified in infection control (2018) was obtained from the Japanese Nursing Association website at http://nintei.nurse.or.jp/nursing/wp-content/uploads/2018/08/08cn_ic201807.pdf. Data regarding other healthcare personnel were obtained from the MHLW website (2016) at <https://www.mhlw.go.jp/toukei/saikin/hw/ishi/16/index.html>.

Fig. 1. Prevalence of MDRO in Japan. Prefectures are graded according to quartiles from 0–25% (white), 25–50% (light gray), 50–75% (dark gray) and 75–100% (black). Darker color indicates higher prevalence of each type of MDRO. Prevalence except for that of VRE were calculated as number of MDRO-positive patients/total number of patients) $\times$ 100. Prevalence of VRE were calculated as number of VRE-positive patients/total number of patients) $\times$ 100,000 because VRE-positivity was rare. Minimal, 25th percentile, median, 75th percentile and maximal values were respectively 0.16, 0.37, 0.51, 0.64 and 1.25 for PRSP; 4.07, 5.94, 6.49, 7.25 and 11.6 for MRSA; 0.08, 0.175, 0.25, 0.325 and 0.53 for CRE; 1.41, 1.92, 2.14, 2.71 and 3.78 for 3rd-generation cephalosporin-resistant *E. coli* and 2.78, 3.86, 4.26, 4.78 and 5.98 for fluoroquinolone-resistant *E. coli*. These values for VRE ($\times$ 1,000) were 0, 0, 5.06, 12.9 and 161, respectively.

Statistical analysis: Univariate analyses were performed using Statcel 3rd Add-in forms on Excel (OMS Publications, Saitama, Japan). Values with $p < 0.05$ were considered statistically significant. Due to the small case numbers, multivariable analysis was not performed.

Prevalence was calculated as the number of MDRO-positive patients/total number of patients $\times$ 100. Since VRE-positivity is very rare, we calculated VRE prevalence as the number of VRE-positive patients/total number of patients $\times$ 100,000.

Ethical statement: Ethics approval was not required for this retrospective study as it was conducted based on freely accessible data in the public domain.

RESULTS

Prevalence of MDRO in Japanese prefectures:

We divided the 47 prefectures into groups according to the 25th, 50th, and 75th percentile prevalence of each MDRO (Fig. 1). The median prevalence of CRE, PRSP, MRSA, 3rd-generation cephalosporin- and fluoroquinolone-resistant *E. coli*, were 0.25, 0.51, 6.49, 2.14, and 4.26, respectively. The median value for VRE ($\times$ 1,000) was 5.06. The distribution of MRSA, 3rd-generation cephalosporin- and fluoroquinolone-resistant *E. coli* in prefectures with values above the medians were mainly distributed in the southwest region, and those for PRSP were predominantly in the northeast region. Prefectures with a relatively high prevalence of VRE tended to be located in the Taiheiyo belt, also known as the Tokaido corridor, namely, the urbanized areas of Japan extending from Tokyo to Fukuoka in Kyushu. No distinctive distribution was found for the

prevalence of CRE.

Univariate analysis of geographical characteristics and possible factors influencing the prevalence of MDRO:

PRSP

Two factors namely, tobacco smoking and three-generation households positively correlated with the prevalence of PRSP (coefficients 0.44 and 0.3, respectively). While, factors such as total use of antibiotics, oral antibiotics, oral penicillins (including penicillin- β -lactamase-inhibitor combinations), and average atmospheric temperature, negatively correlated with the prevalence of PRSP (coefficients: -0.37 , -0.39 , -0.32 , -0.35 , respectively). (Table 1).

MRSA

Total use of antibiotics and average atmospheric temperature significantly correlated with the prevalence of MRSA (coefficients: 0.46 and 0.3, respectively) (Table 1).

VRE

Average atmospheric temperature and average duration of tourist stay (days/1,000 population) significantly correlated with the prevalence of VRE (coefficients: 0.35 and 0.36, respectively). Whereas, the ratio of population aged ≥ 65 years negatively correlated with the prevalence of VRE (coefficients: -0.43) (Table 1).

CRE

We did not find any factors that significantly correlated with the prevalence of CRE (Table 2).

Third-generation cephalosporin-resistant *E. coli*:

Total use of antibiotics, number of physicians (/10⁵ population), number of infection control doctors (/10⁵ population), average atmospheric temperature, and

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Table 1. Univariate analysis of prevalence of PRSP, MRSA and VRE

Category	Variables	Univariate correlation with PRSP prevalence (%)	
		Coefficient	<i>p</i>
Pharmacological	Total administration of antibiotics ¹⁾	-0.37	0.01
	Total oral administration of antibiotics ¹⁾	-0.39	7.0 × 10⁻³
	Oral administration of penicillins (including penicillin-β-lactamase combinations) ¹⁾	-0.32	0.03
Medical service	Number of pediatricians (/10 ⁵ population)	-0.25	0.09
	Number of pulmonologists (/10 ⁵ population)	-0.15	0.30
	Number of physicians (/10 ⁵ population)	-0.21	0.15
Infection control	Number of infection control doctors (/10 ⁵ population)	-0.13	0.40
	Hospital stay (days)	-0.01	0.93
	Number of beds per certified infection-control nurse	0.07	0.66
Environmental	Average temperature (°C)	-0.35	0.02
	Average relative humidity (%)	-0.18	0.24
	Ratio (%) of population aged ≥ 65 yr	0.05	0.72
Social	Population density	-0.17	0.25
	Average income	-0.06	0.66
	Prevalence of three-generation households	0.30	0.04
Other	Prevalence of tobacco smoking	0.44	2.0 × 10⁻³

Category	Variables	Univariate correlation with MRSA (%)	
		Coefficient	<i>p</i>
Pharmacological	Total administration of antibiotics ¹⁾	0.46	1.3 × 10⁻³
	Administration of carbapenems ¹⁾	0.22	0.14
Medical service	Number of physicians (/10 ⁵ population)	0.11	0.48
	Number of infection-control doctors (/10 ⁵ population)	0.11	0.45
Infection control	Hospital stay (days)	0.28	0.06
	Number of beds per certified infection-control nurse	-0.03	0.84
	Prevalence of hospitals participating in JANIS (%)	-0.1	0.52
Environmental	Average temperature (°C)	0.3	0.04
	Average relative humidity (%)	0.14	0.36
Social	Ratio (%) of population aged ≥ 65 yr	0.09	0.53
	Population density	-0.17	0.24

Category	Variables	Univariate correlation with VRE prevalence (/100,000 culture samples)	
		Coefficient	<i>p</i>
Pharmacological	Total consumption of antibiotics ¹⁾	-0.02	0.87
	Total intravenous and oral glycopeptide administration ¹⁾	-0.04	0.8
Medical service	Number of physicians (/10 ⁵ population)	-0.10	0.52
	Number of infection-control doctors (/10 ⁵ population)	0.04	0.81
Infection control	Hospital stay (days)	-0.20	0.19
	Number of beds per certified infection-control nurse	0.03	0.85
Environmental	Average temperature (°C)	0.35	0.02
	Average relative humidity (%)	0.005	0.97
	Ratio (%) of population aged ≥ 65 yr	-0.43	2.6 × 10⁻³
Social	Population density	0.164	0.27
	Average length of tourist stay (days/1000 population)	0.36	0.01
	Departure rate to foreign countries (%)	0.20	0.19
Annual food consumption	Fermented soybeans, "Natto" (packs/person)	-0.26	0.081
	Kelp (g/person/year)	-0.04	0.79
	Chicken (kg/person)	-0.2	0.17
	Beef (kg/person)	-0.06	0.71
	Pork (kg/person)	0.04	0.77

¹⁾: Defined daily dose/1,000 inhabitants/day.

Table 2. Univariate analysis of prevalence of CRE, 3rd-generation cephalosporin-resistant *E. coli* and fluoroquinolone-resistant *E. coli*

Category	Variables	Univariate correlation with CRE prevalence (%)	
		Coefficient	<i>p</i>
Pharmacological	Total consumption of antibiotics ¹⁾	-0.01	0.94
	Total consumption of intravenous and oral carbapenems ¹⁾	-0.01	0.93
Medical service	Number of physicians (/10 ⁵ population)	0.05	0.74
	Number of infection control doctors (/10 ⁵ population)	-0.03	0.84
Infection control	Length of hospital stay (days)	-0.15	0.32
	Number of beds per certified infection-control nurse	0.26	0.08
Environmental	Average temperature (°C)	0.16	0.28
	Average relative humidity (%)	-5.0 × 10 ⁻⁴	1.00
Social	Percentage of the population aged 65 or older	-0.13	0.37
	Population density	0.10	0.50
Annual food consumption	Average length of tourist visits (days/1,000 population)	-0.06	0.68
	Departure rate to Japanese nationals other countries	0.08	0.57
	Fermented soybeans, "Natto" (packs/person)	-0.06	0.69
	Kelp (g/person)	0.87	0.56
	Chicken (kg/person)	-0.09	0.54

Category	Variables	Univariate correlation with 3rd-generation cephalosporin-resistant <i>E. coli</i> prevalence (%)	
		Coefficient	<i>p</i>
Pharmacological	Total consumption of antibiotics ¹⁾	0.31	0.04
	Consumption of 3rd-generation cephalosporins (oral administration) ¹⁾	0.08	0.60
Medical service	Number of physicians (/10 ⁵ population)	0.39	6.3 × 10⁻³
	Number of infection control doctors (/10 ⁵ population)	0.38	7.9 × 10⁻³
Infection control	Hospital stay (days)	0.04	0.77
	Number of beds per nurse certified in infection control	-0.09	0.54
Environmental	Average temperature (°C)	0.43	2.6 × 10⁻³
	Average relative humidity (%)	0.08	0.61
Social	Ratio (%) of population aged ≥ 65 yr	-0.04	0.77
	Population density	-0.01	0.95
Annual food consumption	Fermented soybeans, "Natto" (packs/person)	-0.42	3.2 × 10⁻³
	Kelp (g/person)	-0.44	2.2 × 10⁻³
	Chicken (kg/person)	0.35	0.02

Category	Variables	Univariate correlation with fluoroquinolone-resistant <i>E. coli</i> prevalence (%)	
		Coefficient	<i>p</i>
Pharmacological	Total consumption of antibiotics ¹⁾	0.57	2.6 × 10⁻⁵
	Consumption of oral fluoroquinolone ¹⁾	0.66	3.9 × 10⁻⁷
Medical service	Number of physicians (/10 ⁵ population)	0.41	4.1 × 10⁻³
	Number of infection control doctors (/10 ⁵ population)	0.45	1.4 × 10⁻³
Infection control	Hospital stay (days)	0.24	0.10
	Number of beds per nurse certified for infection control	-0.11	0.46
Environmental	Average temperature (°C)	0.34	0.02
	Average relative humidity (%)	0.13	0.4
Social	Ratio (%) of population aged ≥ 65 yr	0.11	0.47
	Population density	-0.05	0.76
Annual food consumption	Fermented soybeans, "Natto" (packs/person)	-0.43	2.4 × 10⁻³
	Kelp (g/person)	-0.37	0.01
	Chicken (kg/person)	0.35	0.02

¹⁾: Defined daily dose/1,000 inhabitants/day.

annual consumption of chicken (kg/person) significantly correlated with the prevalence of 3rd-generation cephalosporin-resistant *E. coli* (coefficients: 0.31, 0.39, 0.38, 0.43, and 0.35, respectively). In contrast, annual consumption of fermented soybeans (Natto packs/person) and kelp (g/person) negatively correlated with the prevalence of 3rd-generation cephalosporin-resistant *E. coli* (coefficients: -0.42 and -0.44, respectively) (Table 2).

Fluoroquinolone-resistant *E. coli*: Total use of antibiotics, including oral fluoroquinolone, the numbers of physicians (/10⁵ population), and infection control doctors (/10⁵ population), average temperature, and annual consumption of chicken (kg/person), significantly correlated with the prevalence of fluoroquinolone-resistant *E. coli* (coefficients: 0.57, 0.66, 0.41, 0.45, 0.34, and 0.35, respectively). While, annual consumption of fermented soybeans (Natto packs/person) and kelp (g/person), negatively correlated with the prevalence of fluoroquinolone-resistant *E. coli* (coefficients: -0.43 and -0.37, respectively) (Table 2).

DISCUSSION

The prevalence of MDRO varies across Japan. The prevalence of PRSP was higher in north-east, than in south-west prefectures, whereas the prevalence of MRSA, 3rd-generation cephalosporin- and fluoroquinolone-resistant *E. coli*, and VRE were higher in the south-west, even though the prevalence of VRE was lower in Japan than elsewhere (20). Differences in microbial characteristics such as optimal growth conditions and colonization sites in humans might have influenced the geographical distributions of these MDRO.

Streptococcus pneumoniae is commonly isolated from the nasopharynx of children. According to a report by Regev-Yochay et al. (21), the prevalence of *S. pneumoniae* in children aged < 6 years and adults are 53% and 4%, respectively. The reason why children have a higher prevalence of *S. pneumoniae* is not fully understood. The negative correlations between administration of antibiotics and prevalence of PRSP shown in this study seemed to differ from the general understanding that the overuse of antibiotics is an important factor for the emergence of drug-resistant bacteria (22). Syrjänen et al. (23) found no association between the prevalence of *S. pneumoniae* and oral antimicrobial treatment course of 28 days. We could not find clear explanations for the negative correlation between administration of antibiotics and prevalence of PRSP in this study. Furthermore, univariate analyses revealed the positive correlation between three-generation households and the prevalence of PRSP. Regev-Yochay et al. (21) did not identify intra-familial *S. pneumoniae* transmission in an analysis involving 151 pairs of children and their parents, and 32 pairs of siblings. The routes through which *S. pneumoniae* (including PRSP) were transmitted are not obvious in the present study. Socioeconomic factors that significantly influence lifestyles were reported to correlate with the prevalence of PRSP (16). The northeast of Japan is less urbanized than the metropolitan areas. Therefore, the lifestyles of residents

in these areas might be more conservative compared to those in the metropolitan areas where the prevalence of three-generation households and smokers are lower, with higher average income and warmer climate, all of which are inter-related. Other factors that strongly influence the prevalence of PRSP might exist. *S. pneumoniae* vaccine coverage is a possible factor, but exact data are not available.

The number of infection control doctors per population and the number of beds per certified infection control nurse did not significantly correlate with the prevalence of MRSA in the present study. This might be a discouraging finding for personnel who are dedicated to infection control in healthcare settings. However, infection control activities should continue to play their vital roles in reducing the prevalence of MDRO (24). Further information about infection control activities such as the use of alcohol-based hand sanitizers, personal protective equipment, and direct stratification of facilities based on the established factors might reveal other factors that are related to the effectiveness of infection control efforts.

We could not identify any factors that are significantly correlated with CRE prevalence. Continuous monitoring and data accumulation may yield better understanding.

Univariate analysis revealed the correlations between the prevalence of VRE with average atmospheric temperature, the ratio of populations aged ≥ 65 years, and the average duration of tourist visit. The popular sites stayed by tourists are mainly located in the metropolitan areas of Japan with a relatively low ratio of population aged ≥ 65 years. There could be interaction between the two factors. Furthermore, about 70% of tourists who visit Japan come from countries with a high prevalence of VRE (9). VRE can spread through human to human transmission, and often via contaminated hands or surfaces in the environment. It would also be possible for tourists from countries with a high prevalence of VRE to bring VRE into the visited sites during their stay. The dissemination of MDRO via international travel and health tourism has been reported (25,26). Therefore, correlations between the average duration of tourist stay and the prevalence of VRE as revealed through the univariate analysis suggest that visiting tourists are associated with the prevalence of VRE in Japan.

Common factors that positively correlated with the prevalence of 3rd-generation cephalosporin- and fluoroquinolone-resistant *E. coli*, are the number of physicians and infection-control doctors, average atmospheric temperature, and chicken consumption. The present findings are consistent with the report of Terahara et al. (2019) on the correlations between antibiotic use and the prevalence of fluoroquinolone-resistant *E. coli* among the 47 prefectures in Japan (27). Notably, the consumption of kelp and fermented soybeans negatively correlated with the prevalence of 3rd-generation cephalosporin- and fluoroquinolone-resistant *E. coli*. Therefore, food intake influences the intestinal microbiota and plays an important role in intestinal colonization of MDRO in humans (11–15).

The use of antibiotics positively correlated with the prevalence of 3rd-generation cephalosporin- and fluoroquinolone-resistant *E. coli* and MRSA. These

correlations suggest the importance of appropriate antibiotic use and antimicrobial stewardship to reduce the prevalence of MDRO. Taken together, these results suggest the intended goals for appropriate use of antibiotics by physicians and sufficient antimicrobial stewardship interventions by infection control doctors, are yet to be achieved. Therefore, evaluations on the antimicrobial stewardship programs and interventions are necessary to determine the effectiveness of such efforts.

Study limitations: The present study was conducted based on data that are freely accessible in the public domains. Factors that have a stronger influence on the prevalence of MDRO may be discovered through other avenues of investigation. Multivariate analysis could not be performed due to the small fixed sample size (namely, the 47 Japanese prefectures). The quality of our statistical analyses could have been significantly improved with more dependent variables.

We uncovered geographical characteristics for the prevalence of MDRO in Japan. The use of antibiotics is a major factor, but lifestyle, food culture, and social factors might modify the prevalence of MDRO. Although infection control activities did not correlate with the prevalence MDRO, a decrease in the prevalence of MDRO would be an important indicator of the effectiveness of overall infection control activities.

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Conflict of interest None to declare.

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