Carbapenem-resistant *Pseudomonas aeruginosa* and carbapenem use in Japan: an ecological study

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Abstract

**Objective:** This study focused on carbapenem resistance in *Pseudomonas aeruginosa* and examined potential ecological correlations with carbapenem use in Japan.

**Methods:** The proportion of carbapenem-resistant *P. aeruginosa* isolates from 2015 and 2016 by prefecture was obtained from the Japan Nosocomial Infections Surveillance system. Data on carbapenem use was obtained from the National Database of Health Insurance Claims. The correlation between the proportion of carbapenem-resistant isolates and carbapenem consumption was assessed in a cross-sectional manner. The study also collected information on other variables including the numbers of physicians, nurses and medical facilities per 100,000 individuals by prefecture.

**Results:** Both the proportion of carbapenem-resistant *P. aeruginosa* isolates and levels of carbapenem use were higher in western Japan. Using a multivariate model, only carbapenem use remained significantly associated with the proportion of carbapenem-resistant isolates.

**Conclusions:** Carbapenem use and the proportion of carbapenem-resistant *P. aeruginosa* isolates were positively correlated. By longitudinal data collection, this approach offers an avenue to establish causal links as the frequency of carbapenem-resistant *P. aeruginosa* isolates starts to change in the future.

**Keywords**
Antibiotic resistance, *Pseudomonas aeruginosa*, carbapenem, drug prescription, epidemiology, antimicrobial stewardship

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Introduction

Human-induced antimicrobial resistance (AMR), which can develop through the inappropriate use of antimicrobial agents, has been recognized as one of the biggest threats to public health. The World Health Organization (WHO) adopted the Global Action Plan on Antimicrobial Resistance in May 2015, which encouraged each member country to design and issue national action plans within 2 years. Japan released its National Action Plan on Antimicrobial Resistance in April 2016, and one of its aims was to lower the proportion of carbapenem-resistant *Pseudomonas aeruginosa* isolates from 17% in 2014 to less than 10% by 2020, because the bacterium is known to be one of the most common causes of opportunistic infections and death among immunocompromised hosts.

*Pseudomonas aeruginosa* is a gram-negative rod-shaped bacterium that favours moist environments. The bacterium has low virulence and does not usually elicit clinically severe disease in healthy people. However, *P. aeruginosa* is commonly associated with nosocomial infections and is responsible for high mortality among immunocompromised hosts. For severe infections, antipseudomonal drugs (e.g. antipseudomonal carbapenems such as imipenem and meropenem), fluoroquinolones (e.g. ciprofloxacin and levofloxacin) and aminoglycosides (e.g. amikacin) are used for antimicrobial therapy. Resistance to antipseudomonal drugs is increasing and multidrug-resistant *P. aeruginosa* exhibiting resistance to three or more drug classes has emerged and spread across different regions worldwide. This multi-drug resistance poses the serious threat of losing drug options to treat opportunistic infections in hospital settings. Resistance mechanisms of *P. aeruginosa* include selection of bacteria with drug-inactivating enzymes, efflux pumps and target-site or outer membrane modifications. Epidemiological studies have identified several risk factors for carbapenem-resistant *P. aeruginosa* infection including use of medical devices, such as artificial respirators and central intravenous catheters, and admission to an intensive care unit with carbapenem use.

To prevent and monitor the spread of carbapenem-resistant *P. aeruginosa*, the relationship between the prevalence of resistant strains and the use of carbapenems, fluoroquinolones and cephalosporins has been explored in various settings. In some patient-based studies, no correlation between carbapenem use and the prevalence of carbapenem-resistant *P. aeruginosa* strains was reported. However, the published reports have been mostly limited to epidemiological studies conducted at a single healthcare facility or a single geographical location. Thus, a nationwide evaluation of this relationship is called for. Moreover, potential links between imipenem/meropenem use and the prevalence of carbapenem-resistant *P. aeruginosa* strains should be explored while appropriately adjusting for confounders.

In Japan, both nationwide AMR surveillance and a national database of health insurance claims and specific health check-ups publicly share their statistical data. This offers an excellent opportunity to explore the relationship between carbapenem use and the prevalence of resistant *P. aeruginosa* strains. The purpose of this study was to assess ecological associations between carbapenem use and the prevalence of imipenem/meropenem resistance in *P. aeruginosa* using datasets from all 47 prefectures in Japan.

Materials and methods

Study design

This study was designed to explore the ecological relationship between the prevalence
of carbapenem-resistant *P. aeruginosa* isolates and carbapenem use across different regions in Japan. The study aimed to exploit geographical heterogeneities in the observed datasets and was conducted in a cross-sectional manner. The AMR datasets from 2015–2016 were obtained and the spatial datasets over these years were analysed.

This study analysed publicly available data. Microbial testing results were collected as part of the national surveillance activities without individual identifications and the submission of testing results alone did not require informed consent. The datasets used in this study were de-identified and fully anonymized in advance, and the analysis of publicly available data without identifying information did not require ethical approval. All of the datasets were already available in published articles.25,26

**Epidemiological data collection**

Data on *P. aeruginosa* resistance to imipenem/meropenem and epidemiological data were obtained from the clinical laboratory division of the Japan Nosocomial Infections Surveillance (JANIS) system.25 This system includes microbiological testing results of all registered medical facilities. The corresponding data encompass all testing results among both inpatient and outpatient facilities regardless of the characteristics such as infection status, colonization or carrier status. The drug sensitivity testing results were extracted for imipenem or meropenem whenever *P. aeruginosa* was detected from patient laboratory samples. Publicly shared data do not classify results by body samples (i.e. providing summed results of all samples including those obtained from urine, blood and sputum); and from an identical individual, the samples are sometimes taken on multiple occasions during the course of treatment. Based on the sensitivity testing data for each prefecture, prevalence was calculated as the number of resistant isolates detected per 100 000 population. The proportion of resistant *P. aeruginosa* isolates out of the total number of infections was calculated.

Data on carbapenem use were extracted from the National Database of Health Insurance Claims and Specific Health Check-ups of Japan (NDB), representing the total amount of drug used in each prefecture from 2015 to 2016.26 These datasets have been publicly shared over the internet by the AMR Clinical Reference Centre of the National Centre for Global Health and Medicine. Carbapenem use data were standardized in accordance with the Anatomical Therapeutic Chemical classification, using defined daily dose as a measurement unit as recommended by the WHO Collaborating Centre for Drug Statistics and Methodology.27 The population-weighted consumption of oral and parenteral antimicrobial drugs was expressed as the defined daily dose per 1000 inhabitants per day (DID).

As potential confounders of spatial variations in carbapenem resistance, the study also collected the following information in prefectures from 2015 to 2016: (i) the number of physicians per 100 000 individuals;28 (ii) the number of nurses per 100 000 individuals;29 (iii) the number of hospitals and clinics per 100 000 individuals;30 (iv) the number of nursing homes per 100 000 individuals;31 (v) the number of registered medical facilities in JANIS and the number of data-submitting facilities with more than 500 beds;25 (vi) the proportion of elderly individuals in the population;32 and (vii) the mean length of a hospital stay.33

**Statistical analyses**

The statistical analyses were conducted in three steps. First, the study investigated the descriptive characteristics of variables, including their distributions and summary
statistics. Because some variables yielded variance-to-mean ratios greatly exceeding 1, medians and interquartile ranges were consistently used to summarize the distribution of all variables. The data were log-transformed for some variables with skewed distributions so that the data were approximately normally distributed. Secondly, defining the outcome as the proportion of <i>P. aeruginosa</i> isolates resistant to carbapenems, the univariate relationships between this proportion and explanatory variables including use of imipenem and meropenem were explored. Univariate linear regression was used for testing ecological correlations. Thirdly, multiple linear regression analysis was used to adjust for the effects of confounding variables. To appropriately select variables to be included in the final model, multicollinearity between variables was evaluated. Subsequently, variables showing strong multicollinearity were not included in multivariate regression models. All statistical data were analysed using JMP Pro version 14.0 (SAS Institute Inc., Cary, NC, USA). A <i>P</i>-value < 0.05 was considered statistically significant.

**Results**

Table 1 summarizes the descriptive features of the data. The median prevalence of imipenem- and meropenem-resistant <i>P. aeruginosa</i> was 24.4 and 17.4 per 100 000 individuals in 2015, respectively; and 24.1 and 17.8 per 100 000 individuals in 2016, respectively. The median proportion of imipenem- and meropenem-resistant <i>P. aeruginosa</i> isolates was 18.7% and 12.8% in 2015, respectively; and 17.2% and 11.9% in 2016, respectively. The median consumption of carbapenems was 0.11 DID in both 2015 and 2016.

Figure 1 shows the geographical distributions of the proportion of imipenem- and meropenem-resistant <i>P. aeruginosa</i> isolates and carbapenem use. There were tendencies toward higher proportions of resistant strains and higher use of carbapenems in the western as compared with the eastern prefectures. In 2015, the highest

| Table 1. Descriptive characteristics of variables potentially related to imipenem/meropenem-resistant <i>Pseudomonas aeruginosa</i> in Japan in 2015 and 2016. |
|Variable| Median (interquartile range) 2015| 2016 |
|Prevalence of imipenem resistance, per 100 000| 24.4 (19.2–30.7)| 24.1 (20.0–33.0) |
|Prevalence of meropenem resistance, per 100 000| 17.4 (14.0–21.0)| 17.8 (14.1–22.5) |
|Proportion of imipenem resistance, %| 18.7 (16.8–21.9)| 17.2 (16.1–19.8) |
|Proportion of meropenem resistance, %| 12.8 (11.4–15.1)| 11.9 (10.3–14.0) |
|Carbapenem consumption, DID × 10⁻¹| 1.1 (0.9–1.3)| 1.1 (0.9–1.3) |
|Number of physicians per 100 000 individuals| 242.4 (217.0–279.8)| 242.4 (217.0–279.8) |
|Number of nurses per 100 000 individuals| 965.5 (817.0–1104.2)| 965.5 (817.0–1104.2) |
|Number of hospitals per 100 000 individuals| 7.1 (5.7–10.0)| 7.2 (5.7–10.0) |
|Number of clinics per 100 000 individuals| 81.1 (72.8–90.2)| 81.3 (90.7–72.7) |
|Number of nursing homes per 100 000 individuals| 7.3 (6.2–8.3)| 6.9 (5.8–8.1) |
|Number of registered medical facilities| 21.0 (15.0–37.0)| 26.0 (17.0–40.0) |
|Number of facilities with over 500 beds| 4 (3–7)| 4 (2–8) |
|Proportion of elderly individuals in the population, %| 28.7 (26.8–30.1)| 28.7 (26.8–30.1) |
|Mean length of hospital stay, days| 32.0 (29.2–34.1)| 31.8 (28.8–33.8) |

DID, defined daily dose per 1000 inhabitants per day.
proportions of imipenem and meropenem resistance were 26.1% and 19.7% in Oita prefecture, located on the westernmost large island, Kyushu. In 2016, the highest proportions of imipenem and meropenem resistance were 27.5% in Miyazaki prefecture and 18.3% in Ehime prefecture, respectively. Again, both prefectures were located in the west of Japan. In 2015 and 2016, the highest use of carbapenem was 0.16 DID in Oita prefecture and Kagawa prefecture.

Table 2 shows the results of univariate analyses of associations between the proportion of imipenem- or meropenem-resistant *P. aeruginosa* isolates and other factors. Carbapenem consumption was
Table 2. Univariate correlations between the proportion of imipenem or meropenem-resistant *Pseudomonas aeruginosa* strains and selected variables in Japan in 2015 and 2016.

| Variable                                | Proportion resistant in 2015 | Proportion resistant in 2016 |
|-----------------------------------------|------------------------------|------------------------------|
|                                         | Imipenem Coefficient | Statistical significance | Meropenem Coefficient | Statistical significance | Imipenem Coefficient | Statistical significance |
| Carbapenem consumption, DID\(^a\)        | 0.53 \(P < 0.01\)     |                            | 0.46 \(P < 0.01\)     |                            | 0.35 \(P = 0.01\)     |                            |
| Number of physicians per 100,000        | 0.18 NS                 |                            | 0.13 NS                 |                            | 0.07 NS                 |                            |
| Number of nurses per 100,000 individuals | 0.30 \(P = 0.04\)      |                            | 0.17 NS                 |                            | 0.16 NS                 |                            |
| Number of hospitals per 100,000          | 0.35 \(P = 0.02\)      |                            | 0.27 NS                 |                            | 0.21 NS                 |                            |
| Number of clinics per 100,000 individuals | 0.22 NS                 |                            | 0.20 NS                 |                            | 0.09 NS                 |                            |
| Number of nursing homes per 100,000      | 0.26 NS                 |                            | 0.15 NS                 |                            | \(<0.01\) NS            |                            |
| Number of medical facilities included in surveillance\(^a\) | \(-0.10\) NS |                            | \(-0.03\) NS |                            | 0.10 NS                 |                            |
| Number of facilities with > 500 beds included in surveillance\(^a\) | \(-0.09\) NS |                            | \(-0.02\) NS |                            | \(-0.05\) NS |                            |
| Mean length of hospital stay, days       | 0.31 \(P = 0.04\)      |                            | 0.23 NS                 |                            | 0.11 NS                 |                            |
| Proportion of elderly individuals in the population, % | 0.25 NS |                            | 0.16 NS |                            | \(<0.01\) NS |                            |

\(^a\)Indicates log-transformed data.

DID, defined daily dose per 1000 inhabitants per day; NS, no significant association \((P \geq 0.05)\).
positively correlated with the proportion of imipenem- and meropenem-resistant *P. aeruginosa* isolates in both years examined (*P* < 0.05 for all comparisons). The following variables were positively correlated with the proportion of imipenem-resistant isolates in 2015: number of nurses (*P* = 0.04), number of hospitals (*P* = 0.02) and mean length of hospital stay (*P* = 0.04). The number of physicians was not correlated with the proportion of imipenem- and meropenem resistant isolates both in 2015 and 2016.

Figure 2 shows the univariate correlation between carbapenem use and the prevalence of carbapenem-resistant *P. aeruginosa* strains in 2015 and 2016. The proportion of resistant strains was strongly correlated with carbapenem consumption and the correlation coefficient did not greatly differ between the 2 years examined.

Table 3 shows the results of multivariate analyses of the proportion of imipenem- and meropenem-resistant *P. aeruginosa* strains. Due to strong collinearity between the numbers of nurses and hospitals, the latter variable was removed from the model. Thus, three variables (carbapenem consumption, number of nurses and mean length of hospital stay) were explored. In the final multivariate model, only carbapenem consumption remained significantly
Table 3. Multiple regression analysis of the proportion of imipenem or meropenem-resistant *Pseudomonas aeruginosa* strains in Japan in 2015 and 2016.

| Variable                                      | Proportion resistant in 2015 |       |       | Proportion resistant in 2016 |       |       |
|-----------------------------------------------|------------------------------|-------|-------|-------------------------------|-------|-------|
|                                               | Imipenem                     | Meropenem | Imipenem | Meropenem | Imipenem | Meropenem |
|                                               | PRC  | SE  | t  | Statistical significance | PRC  | SE  | t  | Statistical significance | PRC  | SE  | t  | Statistical significance |
| Intercept constant                             | 41.9 | 8.4 | 5.00 | *P* < 0.01 | 32.6 | 6.6 | 4.95 | *P* < 0.01 | 35.8 | 9.3 | 3.86 | *P* < 0.01 |
| Carbapenem consumption, DID<sup>a</sup>        | 9.4  | 2.7 | 3.49 | *P* < 0.01 | 7.1  | 2.1 | 3.37 | *P* < 0.01 | 6.9  | 3.0 | 2.31 | *P* = 0.03 |
| Number of nurses per 100 000 individuals       | >−0.1<sup>a</sup> < 0.1 | −0.20 | NS   | >−0.1<sup>a</sup> < 0.1 | −0.28 NS | >−0.1<sup>a</sup> < 0.1 | −0.36 NS | >−0.1<sup>a</sup> < 0.1 | −0.21 NS |
| Mean length of hospital stay, days             | >−0.1<sup>a</sup> 0.1 | −0.23 | NS   | −0.1 0.1 | 0.89 NS | >−0.1<sup>a</sup> 0.1 | −0.2 NS | −0.1 0.1 | −0.83 NS |

<sup>a</sup>Indicates log-transformed data.

Summary statistics for assessing the fit of multivariate models: 2015, imipenem: $R^2 = 0.29, F = 5.88, P < 0.01$; 2015, meropenem: $R^2 = 0.25, F = 4.67, P = 0.01$; 2016, imipenem: $R^2 = 0.14, F = 2.26, P = 0.10$; 2016, meropenem: $R^2 = 0.13, F = 2.06, P = 0.12$.

PRC, partial regression coefficient; SE, standard error; DID, defined daily dose per 1000 inhabitants per day; NS, no significant association ($P \geq 0.05$).
associated with the proportion of resistant strains ($P < 0.05$ for both 2015 and 2016).

**Discussion**

This study examined the ecological correlation between the proportion of carbapenem-resistant *P. aeruginosa* isolates and carbapenem consumption by examining the spatial distribution of these factors in 47 prefectures in Japan in 2015 and 2016. Univariate analysis showed that carbapenem consumption, numbers of nurses, numbers of hospitals and mean length of hospital stay were positively correlated with the proportion of carbapenem-resistant *P. aeruginosa* isolates. In a multivariate analysis, only carbapenem consumption remained significantly associated with the proportion of carbapenem-resistant *P. aeruginosa* isolates. Mapping the geographical distribution of resistant strains, western Japan was found to have higher proportions of resistant strains in 2015 and 2016 than the rest of Japan. Importantly, this geographical variation over different prefectures was consistent with that of carbapenem consumption.

Although a cross-sectional survey of over 200 hospitals reporting potential links between antimicrobial consumption and the prevalence of resistant *P. aeruginosa* isolates has already been published, this current study used national datasets both for carbapenem consumption (NDB) and for surveillance data (JANIS) that encompassed about 20% of all healthcare facilities. More than 50% of larger hospitals with more than 200 beds and more than 80% of those with more than 500 beds contribute data to JANIS. Using a larger sample size that better represented the population of Japan, this current study demonstrated a relationship between the prevalence of carbapenem-resistant *P. aeruginosa* isolates and carbapenem use based on national databases. This current study also endeavoured to identify and account for other possible explanatory factors for this association.

The link between the prevalence of carbapenem-resistant *P. aeruginosa* isolates and carbapenem use is not novel. However, this current study shows that publicly accessible datasets can jointly be analysed and that such associations can be monitored in a longitudinal manner. For instance, the Japanese government has started to financially subsidize healthcare facilities in which antimicrobial stewardship teams (ASTs) are organized and actively engaged in regulating the use of antimicrobial agents. ASTs restrict the use of carbapenems. If the proportion of resistant strains decreases and carbapenem sensitivity recovers, that would strongly indicate a causal relationship between carbapenem use and the development of resistance. Thus, this current study should be used as the methodological basis for establishing such a causal link.

The potential causal link between the prevalence of carbapenem-resistant *P. aeruginosa* isolates and carbapenem use suggests that strong selection pressure at the population level, leading to *de novo* emergence of resistance, is the dominant mechanism of resistance as opposed to the spread via transmission. *P. aeruginosa* is an environmentally abundant bacterium and a common nosocomial infection. Although transmission of resistant strains and also the spread of resistance via plasmids are not refuted by this current study, these data were based on prefectural units and the mode of spread was not separately captured from the dataset. Similarly, the use of medical devices including intravenous catheters was not captured in this current study’s dataset, and if such datasets were collected at greater resolution (e.g. by hospital or by hospital ward), associations between these risk factors and *P. aeruginosa* resistance in Japan could be analysed.
Medical expenditure in Japan is geographically heterogeneous, with higher costs in the west compared with the east. Both increased carbapenem consumption and a higher proportion of resistant *P. aeruginosa* strains in the west may have reflected the less restricted use of antibiotics in the west compared with the east. While medical services are provided under identical rules and regulations, geographical heterogeneity apparently still arises although the underlying mechanisms have yet to be explored in detail.

This current study had several limitations. First, the study had an ecological design, which is prone to confounding. In addition, the results at the population level cannot be extended to a direct causal link at the individual level. Secondly, as acknowledged in the Methods section, the JANIS data did not include information on type of clinical specimens (i.e. including those obtained from urine, blood and sputum) or sensitivity to other antimicrobial agents. Additional insights into carbapenem resistance could be gained by exploring additional sampling details and microbiological testing results. Similarly, the study was not able to classify functional types of hospitals (e.g. acute or chronic care hospitals) among those registered with the surveillance system. Thirdly, antimicrobial consumption was measured by defined daily dose, but this method overlooks individual heterogeneity in the prescribed dose (e.g. lower doses in children). Fourthly, the study was unable to evaluate factors potentially associated with nosocomial transmission due to the analysis at the prefectural resolution. Fifthly, as test samples were possibly taken from an individual patient on multiple occasions during their course of treatment, the post-treatment samples were more likely to be resistant. Improvements in design and sampling schemes are called for.

In conclusion, despite these limitations, this current study has shown an ecological correlation between carbapenem consumption and the prevalence of carbapenem-resistant *P. aeruginosa* isolates in Japan by analysing prefectural datasets. The geospatial patterns of carbapenem use correlated with the prevalence of resistance in *P. aeruginosa* at the national scale. The use of two large-scale databases showed their potential usefulness to monitor and evaluate causal links and future declines of carbapenem-resistant *P. aeruginosa* in a longitudinal manner.

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The authors declare that there are no conflicts of interest.

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