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Original Article

Current Prevalence of Antimicrobial Resistance in Okayama from a National Database between 2018 and 2021

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Antimicrobial resistance is an emerging global threat that must be addressed using a multidisciplinary approach. This study aimed to raise awareness of high-level antimicrobial-resistant (AMR) pathogens in Japan by comparing their recent prevalences among prefectures, particularly Okayama. Data for the isolation proportions of meropenem-resistant *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecium*, cefotaxime-resistant *Escherichia coli* and *Klebsiella pneumoniae*, and levofloxacin-resistant *E. coli* and *K. pneumoniae* were collected from the Japan Nosocomial Infections Surveillance, a national database sponsored by the Japanese Ministry of Health, Labour, and Welfare, between 2018 and 2021. The average isolated proportions of the seven AMR pathogens were higher in Okayama compared to other prefectures: the worst (19.9%) was meropenem-resistant *P. aeruginosa*, the sixth worst (57.2%) was methicillin-resistant *S. aureus*, the eighth worst (3.3%) was vancomycin-resistant *E. faecium*, the second (37.8%) and fifth worst (17.6%) were cefotaxime-resistant *E. coli* and *K. pneumoniae*, respectively, and the fourth (49.9%) and third worst (8.7%) were levofloxacin-resistant *E. coli* and *K. pneumoniae*, respectively. Our study highlights the notably high prevalences of representative AMR pathogens in Okayama, suggesting the need for fundamental infection prevention and control by healthcare professionals, promoting antimicrobial stewardship, and educating undergraduates and postgraduates in Okayama.

Key words: antimicrobial resistance, antimicrobial stewardship, epidemiology, infection prevention and control, Japan Nosocomial Infections Surveillance

Antimicrobial resistance is a developing public health problem that needs to be addressed on a global scale [1,2]. Multidisciplinary and multidimensional strategies are crucial to reducing antimicrobial resistance. These strategies include the appropriate use of antibiotics, universal application of infection prevention and control measures among healthcare professionals, and active surveillance [3-5]. Even so, many patients are at risk of therapeutic failure due to widespread antimicrobial-resistant (AMR) pathogens [6]. To combat this emergency, the Japanese government published the National Action Plan on antimicrobial resistance in April 2016 and promoted various countermeasures in the healthcare and administrative realms [4], following the World Health Organization's endorsement of the antimicrobial resistance Global Action Plan in May 2015 <https://www.who.int/publications/i/item/9789241509763.>.

The achievement of infection prevention and control

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strategies needs to be evaluated at various levels, from healthcare to national levels. Our previous studies showed that the isolation proportions of AMR pathogens differ significantly among prefectures in Japan, with Okayama Prefecture having a relatively high detection rate for various AMR pathogens [7]. However, no regional assessment has been performed in the literature. Therefore, this study aimed to investigate the regional prevalences of AMR pathogens in Japan through quantitative and geographical perspectives, based on a national database, with a particular focus on Okayama. Our main goal is to raise awareness of high-level AMR pathogens in the healthcare environment.

Material and Methods

This retrospective observational study included data from the Japan Nosocomial Infections Surveillance (JANIS) between 2018 and 2021. The JANIS service was launched in 2000 as a sustainable surveillance model for national AMR data with the support of the Japanese Ministry of Health, Labor, and Welfare, which has developed into one of the largest national AMR surveillance systems worldwide [8, 9]. We compared the isolation proportions of AMR pathogens among 47 prefectures in Japan. Data on carbapenem (meropenem; MEPM)-resistant *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin (VCM)-resistant *Enterococcus faecium* (VRE), third-generation cephalosporin (cefotaxime; CTX)-resistant *Escherichia coli* and *Klebsiella pneumoniae*, and fluoroquinolone (levofloxacin; LVFX)-resistant *E. coli* and *K. pneumoniae* were collected from the JANIS database, which is open to the public. <https://janis.mhlw.go.jp/report/kensa_prefectures.html> (accessed 8.31.2022) Although MRSA is generally defined as an *S. aureus* strain showing resistance to either oxacillin or cefoxitin (CFX), we defined MRSA as CFX-resistant *S. aureus* strains because no data on oxacillin susceptibility was available in the JANIS database.

We calculated the 4-year averages of the isolation proportions of each AMR pathogen and ranked them by prefecture. To help understand the regional differences in the prevalences of AMR pathogens, we utilized geography software <https://www.sinfonica.or.jp/kanko/estrela/refer/s35/index.html> (accessed 8.31.2022) and drew the regional distribution of prevalences [10]. Next, we focused on Okayama prefecture and demonstrated the annual rankings of each AMR pathogen in a radar chart and compared Okayama prefecture with the Osaka and Tokyo metropolitan areas. Finally, we referenced data from the AMR Clinical Reference Center for antibiotic consumption in Japan between 2019 and 2020 <https://amrcrc.ncgm.go.jp/surveillance/010/20181128172333.html> (accessed 8.31.2022). We subsequently investigated the association between the worst-order of both the AMR-isolation rank (per 1,000 inhabitants) and of the antibiotic consumption rank of prefectures measured by daily inhabitant dose (DID), which was calculated by the defined daily dose (DDD) divided by 1,000 inhabitants/day. We focused on LVFX-R *E. coli* and the DID of fluoroquinolones, considering the reported relationship between drug exposure and the emergence of drug resistance [11, 12]. Spearman's rank correlation test was used to determine the correlation between two continuous variables. Analyses were performed using EZR version 3.5.2, a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [13]. Statistical significance was set at $p < 0.05$.

The authors assert that all of the procedures contributing to this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and the Helsinki Declaration of 1975, as revised in 2008. The requirement for informed consent was waived because this study was a retrospective analysis of routinely collected data.

Results

We obtained data on the proportions of the seven AMR pathogens from the JANIS database between 2018 and 2021. The geographical distributions of the 4-year average isolation proportions (%) of each pathogen in the 47 prefectures are shown in Fig. 1. MEPM-resistant *P. aeruginosa*, MRSA, VRE, and CTX- and LVFX-resistant *K. pneumoniae* have been sporadically isolated across the country. However, detection of CTX-resistant *E. coli* was prominent in Western Japan. A similar trend was observed for LVFX-resistant *E. coli*. More precisely, Okayama ranked the worst (19.9%) for MEPM-resistant *P. aeruginosa*, the sixth worst (57.2%) for MRSA, the eighth worst (3.3%) for VRE, the second (37.8%) and fourth worst (49.9%) for CTX- and LVFX-resistant *E. coli*, and the fifth (17.6%) and third worst (8.7%) for CTX- and LVFX-resistant *K. pneumo-*

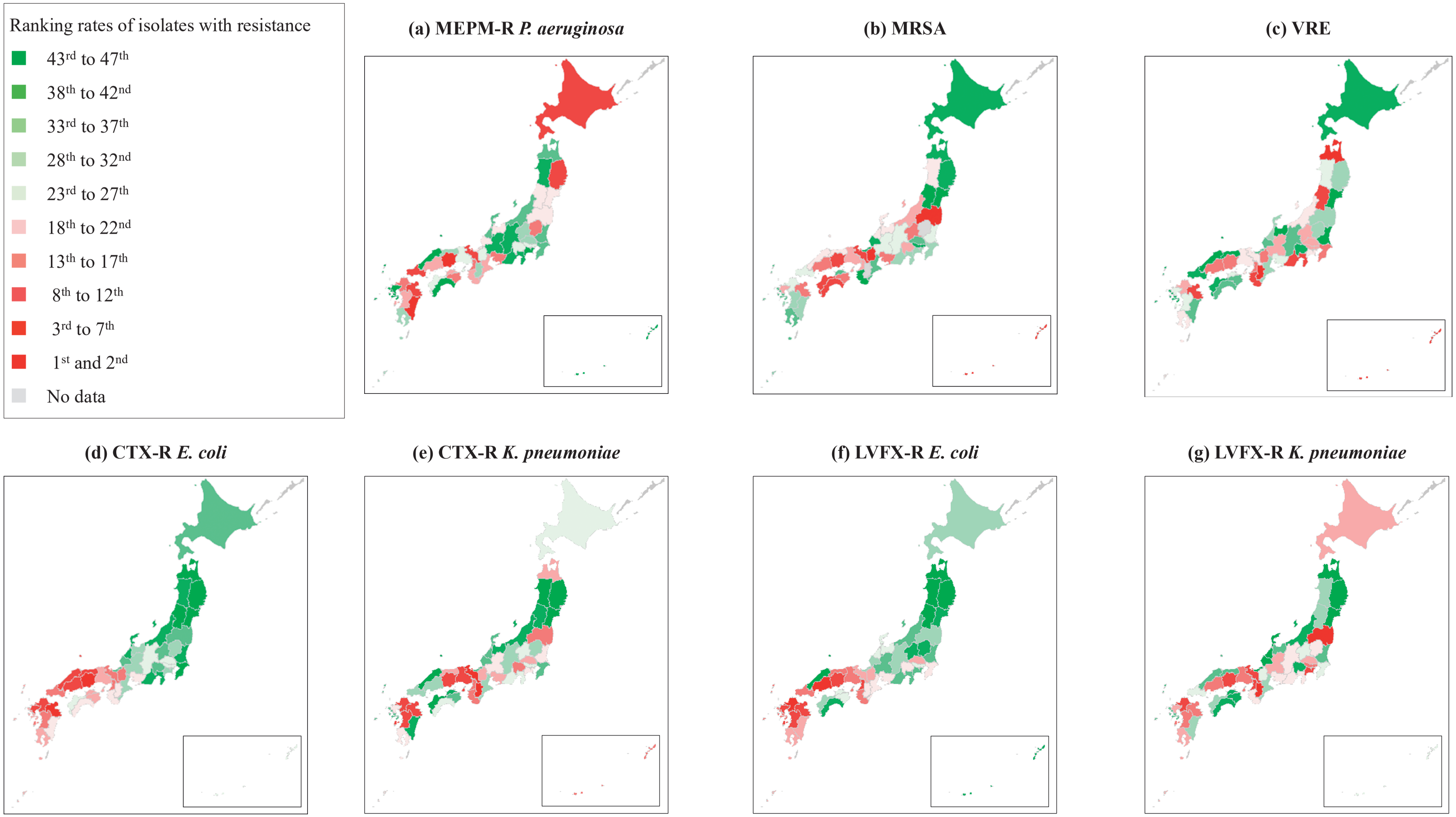

Fig. 1 Regional differences of 4-year (2018-2021) averages of isolation proportions of the seven antimicrobial resistance pathogens in Japan.
MEPM-R *P. aeruginosa*, meropenem-resistant *Pseudomonas aerugionsa*; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus faecium*; CTX-R *E. coli*, cefotaxime-resistant *Escherichia coli*; CTX-R *K. pneumoniae*, cefotaxime-resistant *Klebsiella pneumoniae*; LVFX-R *E. coli*, levofloxacin-resistant *Escherichia coli*; LVFX-R *K. pneumoniae*, levofloxacin-resistant *Klebsiella pneumoniae*.
Average data were ranked among the 47 prefectures and are shown in the gradation map.

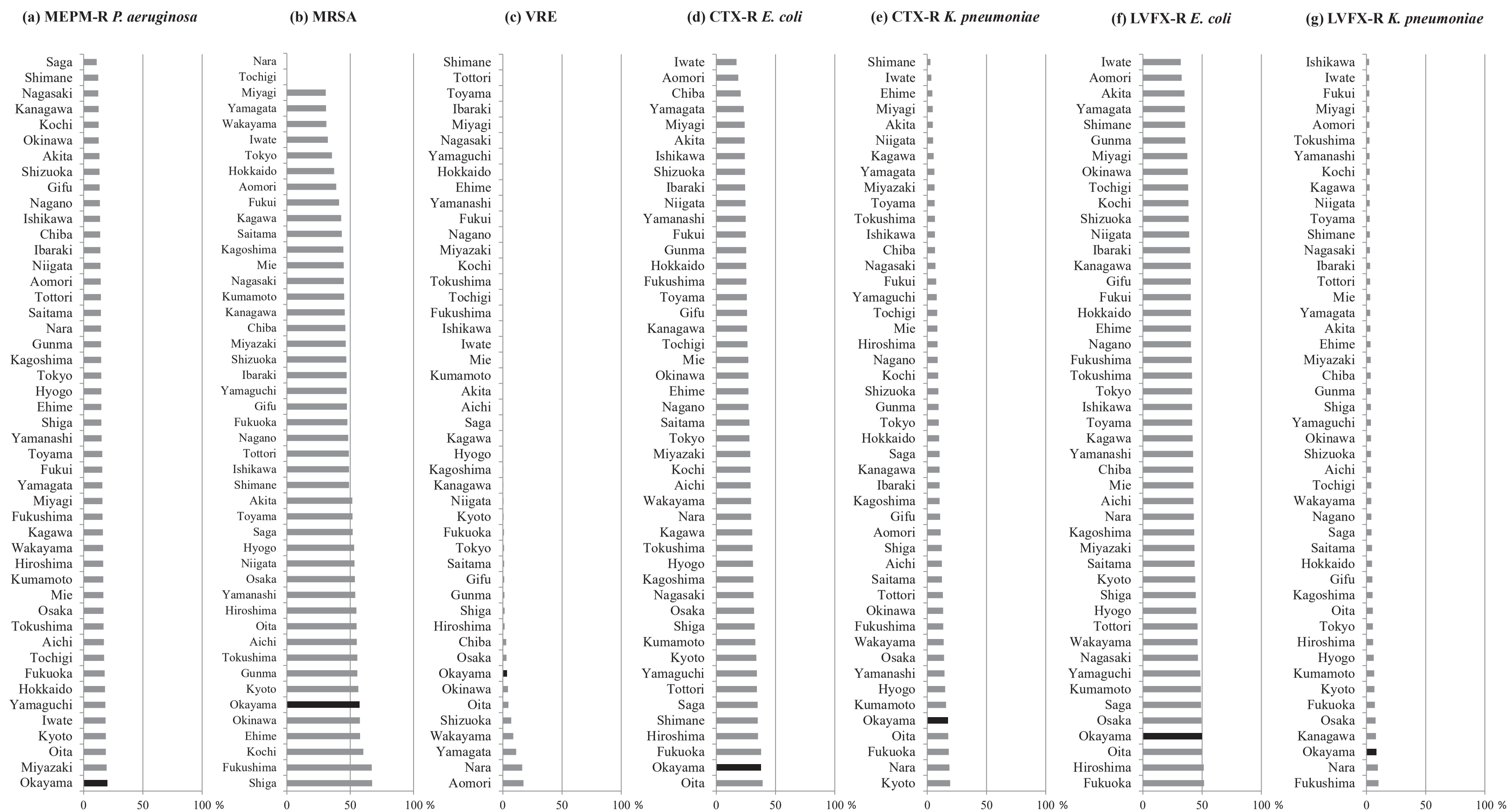

Fig. 2 4-year (2018-2021) averages of isolation proportions of the seven antimicrobial resistance pathogens in Japan, by 47 prefectures.
MEPM-R *P. aeruginosa*, meropenem-resistant *Pseudomonas aerugionsa*; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus faecium*; CTX-R *E. coli*, cefotaxime-resistant *Escherichia coli*; CTX-R *K. pneumoniae*, cefotaxime-resistant *Klebsiella pneumoniae*; LVFX-R *E. coli*, levofloxacin-resistant *Escherichia coli*; LVFX-R *K. pneumoniae*, levofloxacin-resistant *Klebsiella pneumoniae*.
MRSA data for Nara and Tochigi prefectures were unavailable.

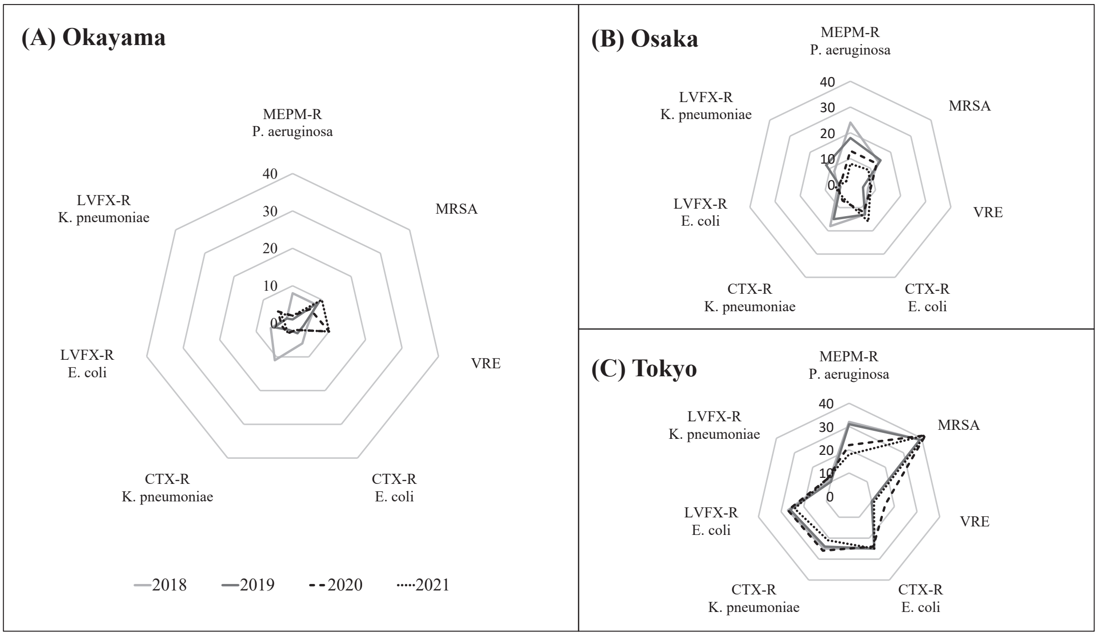

Fig. 3 Radar chart graphics showing the prevalence ranking of the seven antimicrobial resistance pathogens in Okayama, Osaka, and Tokyo, between 2018 and 2021. MEPM-R *P. aeruginosa*, meropenem-resistant *Pseudomonas aerugionsa*; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus faecium*; CTX-R *E. coli*, cefotaxime-resistant *Escherichia coli*; CTX-R *K. pneumoniae*, cefotaxime-resistant *Klebsiella pneumoniae*; LVFX-R *E. coli*, levofloxacin-resistant *Escherichia coli*; LVFX-R *K. pneumoniae*, levofloxacin-resistant *Klebsiella pneumoniae*.
In this graphic, a smaller chart indicates more frequent isolation of antimicrobial-resistant pathogens. Okayama has been reporting high isolation proportions of these organisms for over 4 years (**A**). For comparison, data for Osaka (**B**) and Tokyo (**C**) are shown as well.

niae, respectively (Fig. 2). The inter-prefectural rankings for the isolation of AMR pathogens during the past 4 years are shown in Fig. 3. Okayama has continued to be ranked worse than the Osaka and Tokyo metropolitan areas in terms of frequency of detection of AMR pathogens.

The DID data for 2020 are summarized in Fig. 4. Overall antibiotic consumption is higher in Western Japan, and Okayama Prefecture ranked ninth of the 47 prefetures in per-1000-inhabitants antibiotic consumption. In terms of fluoroquinolones, Okayama Prefecture ranked third in antibiotic consumption in 2020. In addition, there was a significant correlation between the isolation of LVFX-resistant *E. coli* and the DID of fluoroquinolones across the prefectures in 2019 and 2020 (Fig. 5), seeming to provide direct support for the hypothesis that the greater the antibiotic administration, the greater the emergence of resistant organisms.

Discussion

This study revealed the 4-year (2018-2021) prevalences of seven representative AMR pathogens among the 47 prefectures across Japan, based on a national surveillance system known as JANIS. JANIS collects microbiological data from domestic hospitals to monitor the isolation of AMR pathogens <https://janis.mhlw.go.jp/report/kensa_prefectures.html> (accessed 8.31.2022), and the number of participating hospitals has increased since 2008 [4]. The usefulness of this well-established system, which helps to promote an understanding of AMR prevalence in Japan and sets the goal of controlling each AMR pathogen at the hospital and national levels [9, 13], has received positive evaluations [8, 9, 14]. Overall, the present data indicate that Okayama Prefecture had the highest proportions of isolated AMR pathogens among prefectures in Japan in recent years.

Among the various types of genotypic and phenotypic AMR pathogens, highly resistant gram-negative

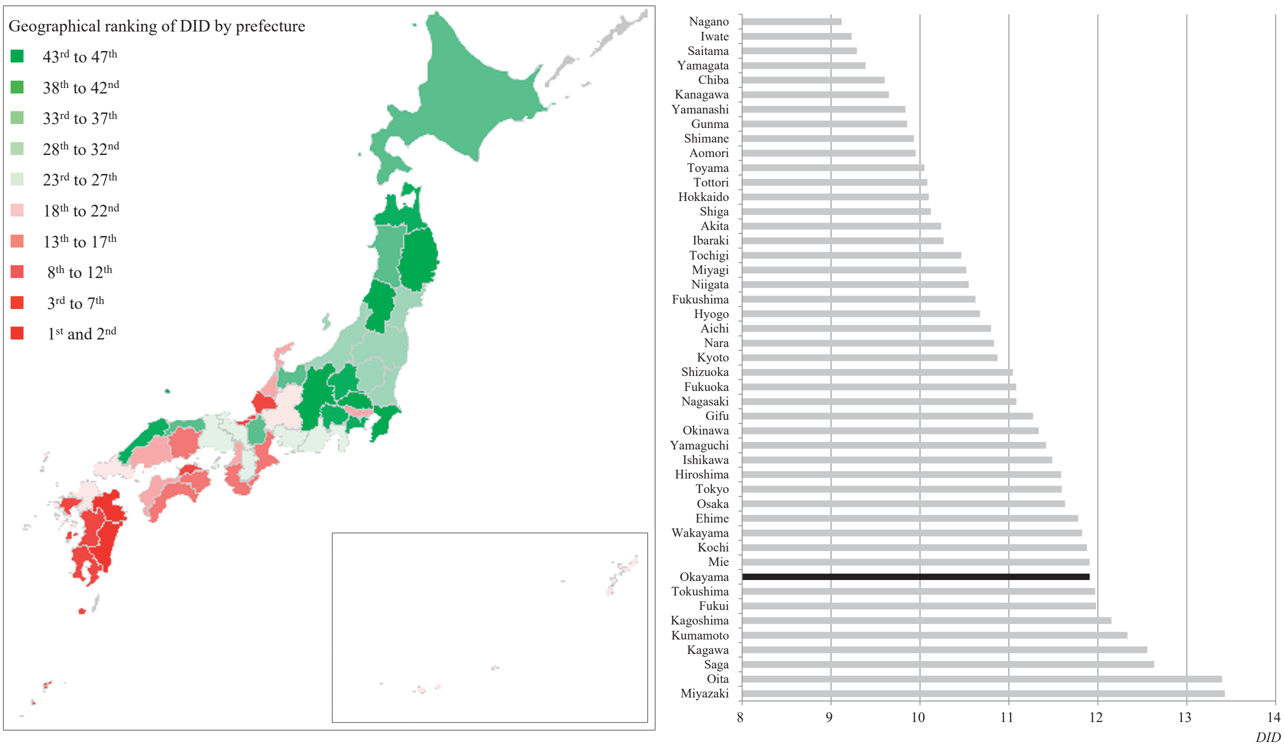

Fig. 4 Overall antibiotics consumption in 2020 in Japan.
DID; defined daily dose (DDD) /1,000 inhabitants/day. DDD is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults. The data source was the website of the AMR Clinical Reference Center. In this chart, the highest ranking indicates the most antibiotics prescribed.

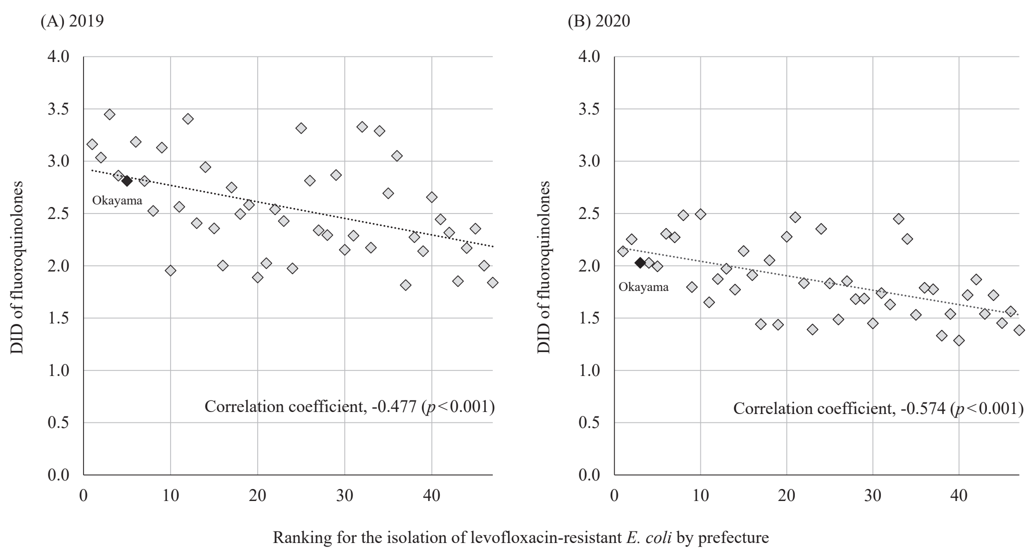

Fig. 5 Correlation diagram between the isolation ranking of levofloxacin-resistant *Escherichia coli* and DID of fluoroquinolone in 2019 (**A**) and 2020 (**B**) in Japan.
DID; defined daily dose (DDD) /1,000 inhabitants/day. DDD is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults. Spearman's rank correlation coefficient test was performed.

organisms are listed as critical pathogens that require high priority for prevention and control by the World Health Organization. These include carbapenem-resistant *Acinetobacter baumannii* and *P. aeruginosa* and extended-spectrum beta-lactamase-producing *Enterobacterales* [15]. Of the seven targeted AMR pathogens in the present study, MEPM-resistant *P. aeruginosa* and CTX-resistant *E. coli* and *K. pneumoniae* met these criteria. However, epidemiological features, as well as emerging and spreading factors, differ among AMR pathogens; thus, understanding the characteristics of each AMR pathogen is essential for establishing an infection prevention and control strategy.

MEPM-resistant *P. aeruginosa* emerges due to the frequent administration of broad-spectrum antibiotics, and it spreads across the hospital environment as a nosocomial infection [16,17]. Methicillin-resistant *Staphylococcus aureus* (MRSA) is a classic AMR pathogen in hospitals that mainly spreads by contact [18]. Although previously known as strictly nosocomial, the emergence of community-acquired MRSA strains has changed the epidemiological perspective of this organism. Briefly, MRSA strains should be recognized as being able to proliferate in community settings; thus, enhancement of nosocomial infection prevention strategies is not enough to lessen the disease burden [19]. VRE can be isolated from both nosocomial and community samples. The literature has described various VRE outbreaks at healthcare and regional levels in Japan [20]. In contrast to the above microorganisms, CTX- or LVFX-resistant *E. coli* and *K. pneumoniae* have emerged, persisted, and proliferated primarily in community settings [21,22]. The main cause of this is considered to be the overuse of antibiotics in the outpatient setting [21-24]. As shown in Fig. 4, overall antibiotic consumption is much higher in Western Japan than in Eastern and Northern Japan, although the exact reason for the regional difference across the country is unknown. This difference in antibiotic consumption suggests that the increased number of antibiotics prescribed possibly contributes to the high prevalence of CTX- or LVFX-resistant *E. coli* and *K. pneumoniae* in Western Japan. Notably, among the 47 prefectures, there was a clear correlation between the isolation of LVFX-R *E. coli* and the DID of fluoroquinolones. Previous reviews have proposed that the clinical use of fluoroquinolones may cause the emergence of fluoroquinolone-resistant organisms by mechanisms such as point mutation of the *gyrA* gene, activation of intrinsic efflux pumps, acquisition of *qnr* genes, and modification of the enzyme gene *aac(6')-Ib-cr* [11,12]. However, the associations of these mechanisms with antibiotic overuse do not necessarily demonstrate causal relationships, but rather aspects of the influence of antibiotic overuse on the emergence of AMR pathogens.

The comprehensive rise in AMR detection rates in Okayama suggests the need to highlight and strengthen infection prevention and control strategies at the healthcare, primary care, and community levels in the region. Countermeasures against AMR require continuous efforts from multidisciplinary teams, and healthcare professionals specializing in infectious diseases (ID) need to play a central role on behalf of the medical and non-medical persons concerned. Our previous study revealed that although the proportion of ID doctors in Okayama prefecture was the eleventh highest among the 47 prefectures, their deployed affiliations were regionally uneven [7]. In addition, the proportion of nurses certified as infectious disease experts per 100,000 individuals in Okayama was lower than the domestic average. As an example case, our precture was the first ever to detect bla_{NDM}-harboring carbapenemase-producing *Enterobacterales* in an older woman without a history of international travel [25]. This implies the presence of an inflow route of AMR pathogens to Japan from abroad and the possibility of encountering such hard-to-treat AMR pathogens elsewhere. In such a situation, as we have highlighted previously, the following issues should be further addressed [7]: (i) establishment of educational platforms to develop ID specialists, as well as experts among nurses, pharmacists, and clinical laboratory technicians; (ii) full-time employment of ID doctors and certified nurses in infection control, at least at core hospitals in each area; (iii) balanced deployment of such ID experts as appropriate; (iv) mandatory ID training during postgraduate training; and (v) enforcement of the educational curriculum focusing on ID in medical schools.

This study has a few limitations. First, participation in JANIS was voluntary, and not all data from Japanese hospitals were included. In addition, fewer clinical specimens were estimated to be tested for AMR pathogens, especially in chronic care hospitals and facilities where a microbiology laboratory was outsourced. Therefore, underreporting of AMR pathogens could be possible. Second, we presented antibiotic consumption as a potentially related factor for AMR prevalence; however, the causal relationship is uncertain. Finally, the JANIS data lacked clinical data including patient outcomes; thus, the impact of differences in the isolation rates of AMR pathogens was undetermined.

In summary, we revealed the prevalences and regional differences in AMR pathogens in Japan over the past four years. Okayama has been facing particularly high detection rates of representative AMR pathogens, for which a further multifaceted education program for undergraduates and postgraduates is required to prevent the emergence and spread of AMR pathogens.

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