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Infectious Agents Surveillance Report
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National Institute of Infectious Diseases and Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labour and Welfare

<THE TOPIC OF THIS MONTH>
Carbapenem-resistant Enterobacteriaceae (CRE) Infection, Japan

Carbapenem-resistant Enterobacteriaceae (CRE) infection is a broad term for infections caused by certain types of Enterobacteriaceae such as *Escherichia coli* and *Klebsiella pneumoniae* that are resistant to carbapenem and broad spectrum β-lactam antibiotics. These antibiotics, such as meropenem, are most important for the treatment of Gram-negative bacterial infections. CRE mainly cause infections in patients with compromised immune systems, patients in their postoperative period, and patients who are administered antibiotics over a long period of time. Infection can result in infectious diseases, including respiratory infections, such as pneumonia, urinary tract infections, infections of surgical sites, skin, and soft tissues, medical device-associated infections (e.g. catheter-associated), sepsis, and meningitis, often causing hospital-acquired infections (HAIs). CRE can occasionally infect healthy individuals. In addition, there is often asymptomatic carriage of the bacteria such as in the digestive tract.

National Epidemiological Surveillance of Infectious Diseases (NESID)

Since September 19, 2014, CRE infection has been included in the list of category V infectious diseases (for the notification criteria, see: https://www.niid.go.jp/niid/images/iasr/35/418/de4181.pdf).

Additionally, in this surveillance system, only those who developed clinical manifestations are eligible for notification. While approximately 1,600 CRE infection patients were notified annually between 2015 and 2017, more than 2,000 cases were notified prior to December 25 (week 48) in 2018 (Fig. 1). Over a period of four years, approximately 80% of cases were found in patients aged 65 years or older. By prefecture, Tokyo, Kanagawa, Aichi, Osaka, and Fukuoka were the top five prefectures reporting the largest number of cases, accounting for 43% of all notifications. There were 35 prefectures whose number of annual notifications exceeded 10 in 2015, but this gradually increased to 38 in 2016, and 39 in 2017 and 2018 (through week 48 in 2018) (Fig. 2).

Regarding the distribution of notifications by bacteria species, the top four species with the largest proportions were *Enterobacter cloacae*, *Klebsiella aerogenes* (N.B. the scientific name was changed in 2017), *K. pneumoniae*, and *E. coli* through 2018; the proportion of *K. aerogenes* began to increase from 2017, and it has since become the most notified bacteria species (Fig. 3 in p. 18).

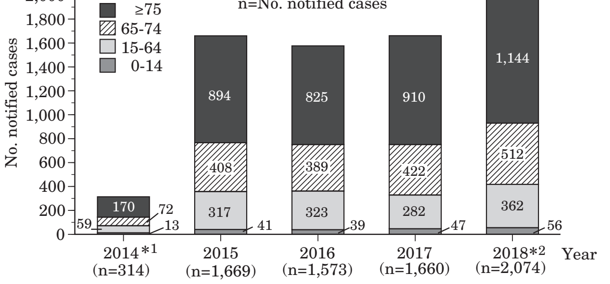
Infectious Agents Surveillance System

Among CRE, carbapenemase-producing Enterobacteriaceae (CPE), which produce enzymes that break down carbapenem, are often resistant to antibiotics other than β-lactam antibiotics, and bacteremia caused by CPE has been reported to have a poorer therapeutic prognosis than that caused by non-carbapenemase-producing CRE (see p. 24 of this issue). In addition, as the carbapenemase gene in CPE is located on mobile genetic elements, such as plasmids, in many cases, the drug-resistant property can be spread across bacterial species. Thus, distinguishing CPE from other CRE is considered to be necessary for both countermeasures against hospital-acquired infections and for therapy, and requires the implementation of carbapenemase gene examinations (see p. 22 of this issue).

Based on the notice issued on March 28, 2017 by the Director of the Tuberculosis and Infectious Diseases Control Division, Health Service Bureau, Ministry of Health, Labour and Welfare, in the event of a CRE infection notification, prefectural and municipal public health institutes (and other relevant entities) are requested to conduct testing for the carbapenemase gene (resistance gene) in order to ascertain the situation in the area (see p. 19 of this issue). There are several known varieties of carbapenemase; the type frequently found in Japan is the IMP type, and the NDM, KPC, and OXA-48 types are spreading overseas. The types found overseas are often multidrug-resistant, frequently demonstrating resistance not only to carbapenem but also to other antibacterial drugs, and require particular attention in terms of infection control (IASR 35: 283-284, 2014).

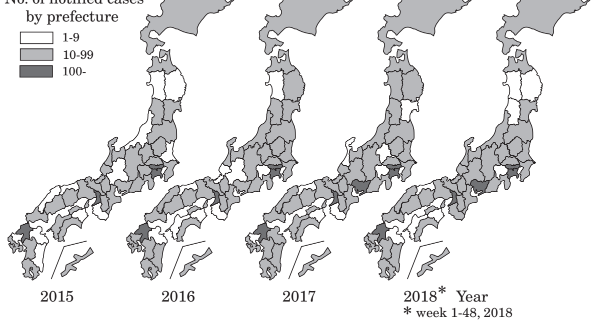
Of the strains registered in the Infectious Agents Surveillance System, at least one of the carbapenemase genes was detected in

Figure 1. Age distribution of notified carbapenem-resistant Enterobacteriaceae infection cases by year, 2014-2018, Japan



(National Epidemiological Surveillance of Infectious Diseases: as of 25 December 2018)

Figure 2. Yearly number of notified carbapenem-resistant Enterobacteriaceae infection cases by prefecture, 2015-2018, Japan

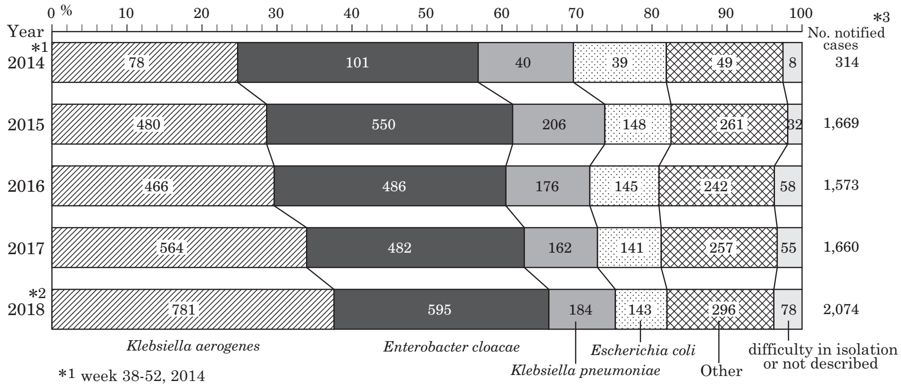


(National Epidemiological Surveillance of Infectious Diseases: as of 25 December 2018)

(Continued on page 18′)

(THE TOPIC OF THIS MONTH-Continued)

Figure 3. Yearly number and proportion of notified carbapenem-resistant Enterobacteriaceae infection cases by bacterial species, 2014-2018, Japan



*1 week 38-52, 2014
*2 week 1-48, 2018
*3 No. notified cases differ from the sum of notifications by bacterial species because multiple strains were isolated from some cases.

(National Epidemiological Surveillance of Infectious Diseases: as of 25 December 2018)

239 and 123 strains in 2017 and in the first half of 2018, respectively; the IMP type was detected in 227 and 111 strains in 2017, and during the first half of 2018, respectively, making it the most common type. In 2017, the proportion of CRE with IMP-type strain detection exhibited large regional differences in bacterial species and genetic types (see IASR 39: 162-163, 2018). On the other hand, six local governments reported cases of overseas-type carbapenemase gene-positive strains, and the majority were identified in patients who had no history of overseas travel.

Moreover, in 2018, there was an outbreak caused by a KPC-type carbapenemase gene-positive strain (see p. 27 of this issue) and a report concerning contamination of the hospital environment by an NDM-type carbapenemase gene-positive strain (see p. 28 of this issue). Therefore, there is concern regarding the spread of overseas-type carbapenemase gene-positive strains into the community or hospital environments (see p. 25 of this issue).

Since 2018, the Antimicrobial Resistance Research Center and the Infectious Disease Surveillance Center (both part of the National Institute of Infectious Diseases; NIID) have been jointly conducting a weekly teleconference on notified cases of CRE infection, sharing patient information from the NESID system along with the pathogen detection information, conducting risk assessment of notified cases, and contacting local governments as needed (see p. 20 of this issue).

Japan Nosocomial Infections Surveillance (JANIS) system of the Ministry of Health, Labour and Welfare

The Testing Division of JANIS continuously collects and collates all bacterial testing data obtained from over 2,000 participating medical institutions, representing the isolation status of major drug-resistant bacteria in Japan. Unlike the NESID system, no distinction is made between colonization and disease manifestation; data are compiled for bacteria isolated at the participating medical institutions that fulfill the laboratory criteria for notification under the Infectious Diseases Control Law. Although the number of patients with CRE continues to decrease, there were over 7,000 in 2017. As the number of patients with CRE isolation in the JANIS system is markedly higher than the number of patients included in the NESID system (limited to symptomatic cases), it is possible that there are many carriers of CRE. The proportions of CRE bacteria species reported by JANIS are consistent with those reported by NESID, and the increased proportion of *K. aerogenes* was also observed in the 2017 JANIS data (see p. 21 of this issue).

Nippon AMR One Health Report (NAOR)

Measures for responding to the antimicrobial resistance (AMR) problem, including CRE, require the "One Health Approach," i.e., multi-sectoral cooperation and collaboration among the medical care, animal husbandry, and environmental sectors. On the global stage, organizations such as the World Health Organization (WHO), the World Organization for Animal Health (OIE), and the Food and Agriculture Organization (FAO) play a central role in this effort. The AMR National Action Plan (NAP) 2016-2020 stipulates that comprehensive "One Health Surveillance" be implemented for drug-resistant bacteria isolated from humans, animals, food, and the environment. JANIS releases information on resistance rates for human-derived pathogenic bacteria isolated from participating medical institutions, and the Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM) and local public health institutes release information on resistance rates among animal- and food-derived pathogenic bacteria (resistant bacteria as a proportion of all identified bacteria). The AMR One Health Surveillance Committee summarizes these data (Nippon AMR One Health Report 2017: https://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/0000204347.pdf). Environmental AMR surveillance, which deals mainly with rivers and sewage, was initiated by a research group and has been funded by a Health and Labour Sciences Research Grant (HLSRG) since 2018 (see p. 29 of this issue).

National Action Plan and Performance Indicators

The Global Action Plan (GAP) for AMR was adopted at the 2015 World Health Assembly (WHO), and in 2016, Japan drew up its own AMR National Action Plan (NAP) 2016-2020. In response to the NAP, a wide variety of domestic and overseas AMR-related data are collected, and in order to feedback the information to the clinical settings, utilize the information for research, and provide policy guidance to WHO and other stakeholders, the AMR Research Center was established in 2017 in NIID to function as a comprehensive think-tank for AMR. The resistance rates for human-derived pathogenic bacteria, which is used as a performance indicator by NAP, is calculated based on JANIS data managed by the AMR Research Center in NIID. A resistance rate of 0.2% against carbapenem (imipenem and meropenem) for *E. coli* and *K. pneumoniae* is established as the performance indicator by NAP. In 2017, a meropenem resistance rate of 0.4% was found in *K. pneumoniae*, which was higher than the performance indicator, and the number of patients notified under the NESID system also increased in 2018. Therefore, in order to ascertain the epidemiological situation in each region of Japan and strengthen the ability to respond, continued implementation of national surveillance is necessary.

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Environmental Health and Food Safety, the Ministry of Health, Labour and Welfare, and quarantine stations, have provided the above data.

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