Open Forum Infectious Diseases

MAJOR ARTICLE

Distribution, Trends, and Antimicrobial Susceptibility of *Bacteroides*, *Clostridium*, *Fusobacterium*, and *Prevotella* Species Causing Bacteremia in Japan During 2011–2020: A Retrospective Observational Study Based on National Surveillance Data

Toshiki Kajihara, Koji Yahara, Norikazu Kitamura, Aki Hirabayashi, Yumiko Hosaka, and Motoyuki Sugai

Antimicrobial Resistance Research Center, National Institute of Infectious Diseases, Tokyo, Japan

Background. The increasing prevalence of anaerobic bacteremia is a major concern worldwide and requires longitudinal monitoring.

Methods. We present one of the largest and longest longitudinal studies on the prevalence and antimicrobial resistance of *Bacteroides*, *Clostridium*, *Fusobacterium*, and *Prevotella* spp. isolated from blood culture samples using national comprehensive surveillance data in Japan during 2011–2020 as part of the Japan Nosocomial Infections Surveillance.

Results. Data for 41 949 *Bacteroides* spp., 40 603 *Clostridium* spp., 7013 *Fusobacterium* spp., and 5428 *Prevotella* spp. isolates were obtained. The incidences of bacteremia caused by *Bacteroides fragilis*, *Clostridium perfringens*, and *Fusobacterium nucleatum* significantly increased during the period ($P < .0001$). Among the 20 species analyzed, 18 showed no significant changes in susceptibility over time, including *B. fragilis*, *C perfringens*, and *F. nucleatum*. However, resistance to clindamycin increased in *B. thetaiotaomicron* ($P = .0312$), and resistance to ampicillin increased in *B. ovatus* ($P = .0008$).

Conclusions. Our comprehensive national surveillance data analysis demonstrated a continuous increase in the incidence of anaerobic bacteremia, particularly in *B. fragilis*, *C. perfringens*, and *F. nucleatum*. This may be linked to the increasing number of colorectal cancer cases or advancing methods for species identification and susceptibility testing, requiring cautious interpretation. The discovery of an upsurge in anaerobic bacteremia and potential alterations in susceptibility highlights the necessity for more extensive studies in this field.

Keywords. anaerobe; antimicrobial resistance; bacteremia; bloodstream infections.

Anaerobic bacteria continue to be important causative pathogens of bacteremia, which frequently leads to severe life-threatening conditions [1]. The difficulty in isolating these bacteria leads to delayed diagnosis and treatment. Routine susceptibility testing for anaerobic bacteria should be considered for specific clinical situations and monomicrobial infections [2].

Bacteremia caused by anaerobes is a re-emerging infectious disease. The incidence of anaerobic bacteria among all bacteria from positive blood cultures varies by country: 1.6% in Italy, 4.1% in Singapore, 3% in Iowa and Burlington in the United States in 2000, and 10.4% in Minnesota in the United States in 2004 [3–6]. In the United States, the incidence of bacteremia caused by anaerobes decreased by 45% between 1974 and 1988 [7], but Lassmann et al. reported a 30% increase in 2 hospitals during 1993–2004 [5]. In Italy, a slight upward trend was noted in anaerobic blood infections between 2016 and 2020 [3].

Antibiotic resistance among anaerobic microorganisms has significantly increased in recent decades [8, 9], and the resistance rates vary widely by region. Veloo et al. reported that 9.6% of *Bacteroides* isolates from Kuwait and 4% from Belgium were resistant to meropenem [10]. In the *B. fragilis* group, resistance to penicillin occurred in 80%–90% of isolates, and resistance to amoxicillin-clavulanate rose from 0.8% in 1992% to 6.2% in 2010–2011 [9]. The most significant change in *Bacteroides* spp. in recent years has been an increase in resistance to clindamycin (CLDM) by up to 30%–50% [11, 12]. In vitro susceptibility testing for *Bacteroides* isolates reliably predicts patient response to therapy [13]. Further studies

Received 05 April 2023; editorial decision 22 June 2023; accepted 29 June 2023; published online 3 July 2023

Correspondence: Toshiki Kajihara, MD, Phd, Antimicrobial Resistance Research Center, National Institute of Infectious Diseases, 4-2-1 Aoba-cho Higashimurayama, Tokyo 189-0002, Japan (kajihara@niid.go.jp).

Open Forum Infectious Diseases®

https://doi.org/10.1093/ofid/ofad334

are needed to evaluate trends in incidence and antimicrobial resistance and to inform prescribing and antimicrobial stewardship strategies.

In Japan, comprehensive surveillance data have been collected in a national antimicrobial resistance surveillance program—the Japan Nosocomial Infections Surveillance (JANIS)—in which all routine microbiological test results are being collected for all sample types from both symptomatic and asymptomatic patients from hundreds or thousands of participating hospitals since 2000 [14]. However, comprehensive national surveillance data have not yet been utilized for anaerobic bacteria studies, and only local surveillance in the Kansai region has been conducted for 4 months [15].

In this study, we focused on *Bacteroides*, *Clostridium*, *Fusobacterium*, and *Prevotella* spp. and evaluated their incidence rate, distribution trend, and antimicrobial susceptibility, using comprehensive national data from JANIS for the period 2011–2020.

METHODS

Data Preparation and Tabulation

All inpatient and outpatient data from January 2011 to December 2020 were extracted from the JANIS database, comprising all routine microbiological diagnostic tests (including culture-positive and culture-negative results) and antimicrobial susceptibility testing results [14]. A total of 2167 hospitals across Japan submitted their data to the JANIS database in 2020. These included 46 of 52 (88.5%) hospitals with >900 beds, 287 of 349 (82.2%) hospitals with 500–899 beds, 1031 of 2130 (48.4%) hospitals with 200–499 beds, and 803 of 5769 (13.9%) hospitals with <200 beds. We specifically targeted *Bacteroides* spp., *Clostridium* spp., *Fusobacterium* spp., and *Prevotella* spp. due to their high crude mortality [16]. We used a Java toolkit to extract the data of isolates of *Bacteroides* spp. (*B. fragilis*, *B. thetaiotaomicron*, *B. vulgatus*, *B. uniformis*, *B. ovatus*, *B. caccae*, *Parabacteroides distasonis*, and other *Bacteroides*), *Clostridium* spp. (*C. perfringens*, *C. septicum*, and other *Clostridium*), *Fusobacterium* spp. (*F. nucleatum*, *F. necrophorum*, *F. mortiferum*, *F. varium*, and other *Fusobacterium*), and *Prevotella* spp. (*P. oralis*, *P. meraninogenica*, *P. buccae*, *P. bivia*, *P. intermedia*, *P. denticola*, *P. loescheii*, *P. corporis*, *P. ruminicola*, and other *Prevotella*), which were isolated from blood samples and subjected to antimicrobial susceptibility testing for ampicillin (ABPC), ampicillin-sulbactam (SBT/ABPC), piperacillin-tazobactam (TAZ/PIPC), CLDM, cefmetazole (CMZ), cefotaxime (CTX), imipenem (IPM), and meropenem (MEPM). The antimicrobial susceptibility testing data in JANIS comprises minimum inhibitory concentration (MIC) data. Participating hospitals in JANIS may employ various CLSI methods, but for this study, we used the CLSI 2020 criteria to interpret the MIC data for susceptibility, employing breakpoints. The data were organized using the "one isolate per patient for each species" deduplication algorithm of the World Health Organization's Global Antimicrobial Surveillance System [17, 18]. The collection of data on susceptibility testing methods, such as Walkaway, Vitek II, or Dryplate Eiken, was also implemented for each participating hospital in JANIS and subsequently incorporated into the tabulated results.

Statistical Analysis

The statistical significance of the differences in proportions was tested using the Pearson chi-square or Fisher exact test (when the minimum count in a contingency table was <5). To account for multiple comparisons, we separately applied the Benjamini-Hochberg false discovery rate correction [19] for each species. To maintain a false discovery rate <5% for each species, the significance threshold was established. The Cochran-Armitage trend test was used to test for any trend in the incidence (ie, number of anaerobic bacteremia cases divided by the total number of patients who underwent blood culture testing) across the years. The level of significance was set at $P < .05$. All statistical analyses were performed using R software (version 4.0.5) and JMP Pro (version 13; SAS Institute, Cary, NC, USA).

Patient Consent

Patient identifiers were de-identified by each hospital before data submission to JANIS. The anonymous data stored in the JANIS database were exported and analyzed. The protocol of this study was approved by the Ministry of Health, Labor and Welfare (approval number: 0425–3) according to Article 32 of the Statistics Act and in accordance with the Helsinki Declaration. The requirement for informed consent was waived by the Ministry of Health, Labor and Welfare (approval number: 0425–3).

RESULTS

Trends and Incidence of Bacteremia due to *Bacteroides*, *Clostridium*, *Fusobacterium*, and *Prevotella* Species

The annual number of patients with bacteremia due to *Bacteroides*, *Clostridium*, *Fusobacterium*, and *Prevotella* spp. and the number of patients from whom blood samples were collected from January 2011 to December 2020 are shown in Table 1. A total of 13 118 386 blood samples were collected from patients during this period, with 40 841, 40 214, 6978, and 5367 patients diagnosed with *Bacteroides*, *Clostridium*, *Fusobacterium*, and *Prevotella* bacteremia, respectively.

The incidence of bacteremia due to *Bacteroides* spp., *Clostridium* spp., *Fusobacterium* spp., and *Prevotella* spp. was 354, 350, 64, and 43/100 000 patients, respectively, who underwent blood culture testing in 2020 (Figure 1). The incidence of bacteremia caused by *Bacteroides* spp., *Clostridium* spp., and

Table 1. Distribution and Trend of Bacteremia Caused by *Bacteroides*, *Clostridium*, *Fusobacterium*, and *Prevotella* spp. in Japan Between 2011 and 2020

	Total	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
No. of participating hospitals		593	660	745	883	1435	1653	1795	1947	2075	2167
No. of patients who underwent blood culture testing	13 118 386	565 036	662 045	783 151	915 448	1 403 631	1 577 451	1 672 373	1 811 038	1 930 940	1 797 273
No. of *Bacteroides* isolates	41 949	1794	2041	2533	2844	4328	4852	5205	5874	6109	6369
No. of bacteremia episodes	40 841	1760	2007	2477	2788	4236	4720	5076	5690	5903	6184
Incidence of bacteremia (per 100 000 tested patients)	319.8	317.5	308.3	323.4	310.7	308.3	307.6	311.2	324.3	316.4	354.4
Male sex, %	56.8	59.3	59.9	57.0	58.3	58.3	57.3	56.2	57.0	54.8	54.9
Unknown sex	1176	64	59	74	106	117	151	130	156	149	170
Age, mean ± SD, y	73.4 ± 14.9	70.9 ± 15.3	70.8 ± 15.7	71.8 ± 15.5	71.7 ± 15.7	72.6 ± 14.9	73.2 ± 14.4	74.1 ± 14.9	74.3 ± 14.4	74.4 ± 14.9	75.0 ± 14.6
Unknown age	1465	19	22	24	53	197	164	225	249	263	249
No. of *Clostridium* isolates	40 603	1351	1670	2220	2752	4087	4929	5385	5956	5961	6292
No. of bacteremia episodes	40 214	1336	1655	2192	2725	4048	4887	5344	5899	5898	6230
Incidence of bacteremia (per 100 000 tested patients)	309.5	239.1	252.2	283.5	300.6	291.2	312.5	322.0	328.9	308.7	350.1
Male sex, %	53.9	54.6	57.8	56.0	55.8	55.7	53.0	52.9	52.7	52.8	53.6
Unknown sex	1360	46	43	76	125	167	163	178	197	181	184
Age, mean ± SD, y	79.0 ± 12.5	77.0 ± 14.0	77.3 ± 13.2	77.7 ± 12.8	78.1 ± 11.9	78.6 ± 12.7	79.1 ± 12.2	79.4 ± 12.4	79.5 ± 12.4	79.5 ± 12.3	79.9 ± 12.2
Unknown age	1615	9	20	18	52	179	190	261	291	306	289
No. of *Fusobacterium* isolates	7013	247	275	426	500	704	798	902	948	1055	1158
No. of bacteremia episodes	6978	247	275	422	498	704	791	897	944	1049	1151
Incidence of bacteremia (per 100 000 tested patients)	53.5	43.7	41.5	54.4	54.6	50.2	50.6	53.9	52.3	54.6	64.4
Male sex, %	65.0	69.9	65.0	67.7	63.8	64.8	64.8	66.0	65.0	64.3	62.0
Unknown sex	197	8	9	16	12	19	27	30	23	25	28
Age, mean ± SD, y	68.0 ± 18.4	65.4 ± 18.0	68.6 ± 16.6	66.8 ± 18.4	66.1 ± 18.6	68.0 ± 17.8	67.4 ± 18.0	67.6 ± 19.1	68.1 ± 18.4	69.5 ± 18.0	69.2 ± 19.0
Unknown age	183	1	0	4	3	15	19	30	35	39	37
No. of *Prevotella* isolates	5428	231	257	373	446	596	629	686	689	753	768
No. of bacteremia episodes	5367	229	257	367	439	588	614	677	693	745	758
Incidence of bacteremia (per 100 000 tested patients)	41.4	40.9	38.8	47.6	48.7	42.5	39.9	41.0	38.0	39.0	42.7
Male sex, %	57.7	56.2	54.7	55.0	58.3	60.1	57.7	59.3	55.4	58.3	58.6
Unknown sex	147	10	3	7	15	21	13	23	14	19	22
Age, mean ± SD, y	71.4 ± 15.8	69.8 ± 14.8	70.6 ± 15.5	70.0 ± 17.4	70.5 ± 15.8	71.6 ± 15.5	71.9 ± 15.2	71.8 ± 15.4	71.0 ± 16.7	72.7 ± 15.5	71.4 ± 15.7
Unknown age	104	2	0	0	5	6	8	12	28	28	15

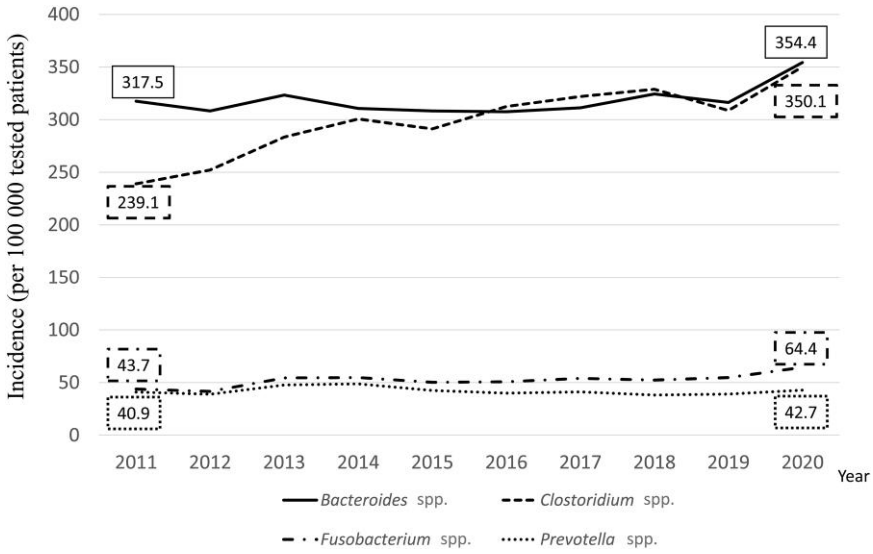

Figure 1. Combined annual incidence of bacteremia caused by *Bacteroides, Clostridium, Fusobacterium,* and *Prevotella* spp. during 2011–2020.

Fusobacterium spp. significantly increased from 2011 to 2020 by 11.7% ($P < .0001$), 52.2% ($P < .0001$), and 47.4% ($P < .0001$), respectively. In 2016, the incidence rate of bacteremia caused by *Clostridium* spp. was similar to that caused by *Bacteroides* spp. The annual incidence from 2011 to 2020 stratified by species is shown in Figure 2, where only *B. fragilis* showed a 1.12-fold increase in incidence among *Bacteroides* spp. ($P < .0001$, blue in Figure 2*A*); *C. perfringens* and *F. nucleatum* showed a significant increase ($P < .0001$, blue in Figure 2*B* and *C*).

Notable Susceptibility Patterns to Antimicrobial Agents

Only some of the isolates submitted to the JANIS database (32.9% [13 788/41 949] of all *Bacteroides* spp., 33.6% [13 658/40 603] of all *Clostridium* spp., 31.7% [2220/7013 isolates] of all *Fusobacterium* spp., and 36.6% [1985/5428 isolates] of all *Prevotella* spp.) were subjected to antimicrobial susceptibility testing. The susceptibility trends of *Bacteroides* spp., *Clostridium* spp., *Fusobacterium* spp., and *Prevotella* spp. are summarized in Figure 3. All *Bacteroides* isolates remained highly susceptible to CMZ (gray line), IPM (light blue line), MEPM (green line), SBT/ABPC (dark blue line), and TAZ/PIPC (brown line). All *Clostridium* isolates remained highly susceptible to ABPC (blue line), CMZ, CTX (yellow line), IPM, MEPM, SBT/ABPC, and TAZ/PIPC. The resistance rates of *Prevotella* spp. to ABPC, CTX, and CLDM (orange line) were higher (62.7%, 23.3%, and 29.8% in 2020) than those to the others. The resistance rates of *Bacteroides*, *Clostridium*, *Fusobacterium*, and *Prevotella* spp., except for *P. ruminicola* during 2011 and 2020, and the comparison between the early (2011–2015) and late (2016–2020) phases are shown in Table 2. *P. ruminicola* was excluded because the number of isolates subjected to antimicrobial susceptibility testing was <30. Significant increases in resistance rates were observed for *B. thetaiotaomicron* to CLDM and *B. ovatus* to ABPC ($P = .0312$ and $P = .0008$). Conversely, the resistance rates of *P. distasonis* to IPM and *P. loescheii* to ABPC ($P = .0008$ and $P < .0001$) significantly decreased.

DISCUSSION

This study showed a continuous increase in the incidence of anaerobic bacteremia, particularly in *B. fragilis*, *C. perfringens*, and *F. nucleatum*. However, most species (18 of 20) showed no significant changes in susceptibility over the study duration, including *B. fragilis*, *C perfringens*, and *F. nucleatum*. Notably, resistance to CLDM increased in *B. thetaiotaomicron*, and resistance to ABPC increased in *B. ovatus*. Our results provide a comprehensive overview of the epidemiology of the 4 anaerobic species that caused bacteremia in Japan.

Dorsher et al. reported that the incidence rate of anaerobic bacteremia decreased over a 15-year period in Minnesota the United States in 1991 [7]. In contrast, some studies have reported increasing bacteremia caused by anaerobic bacteria [3, 5, 20]. Consistent with these reports, in the present study, we observed an increase in the incidence of anaerobic bacteremia caused by *Bacteroides*, *Clostridium*, and *Fusobacterium* spp. Note that we could not show the incidence of anaerobic bacteremia in terms of the number of hospitalizations because the number of admissions is not mandatory in the voluntary-based JANIS database. Therefore, we used the number of patients who underwent blood culture tests to evaluate the incidence of anaerobic bacteremia.

Table 1 demonstrates that the incidence of anaerobic bacteremia is generally higher in males than in females. Male sex was

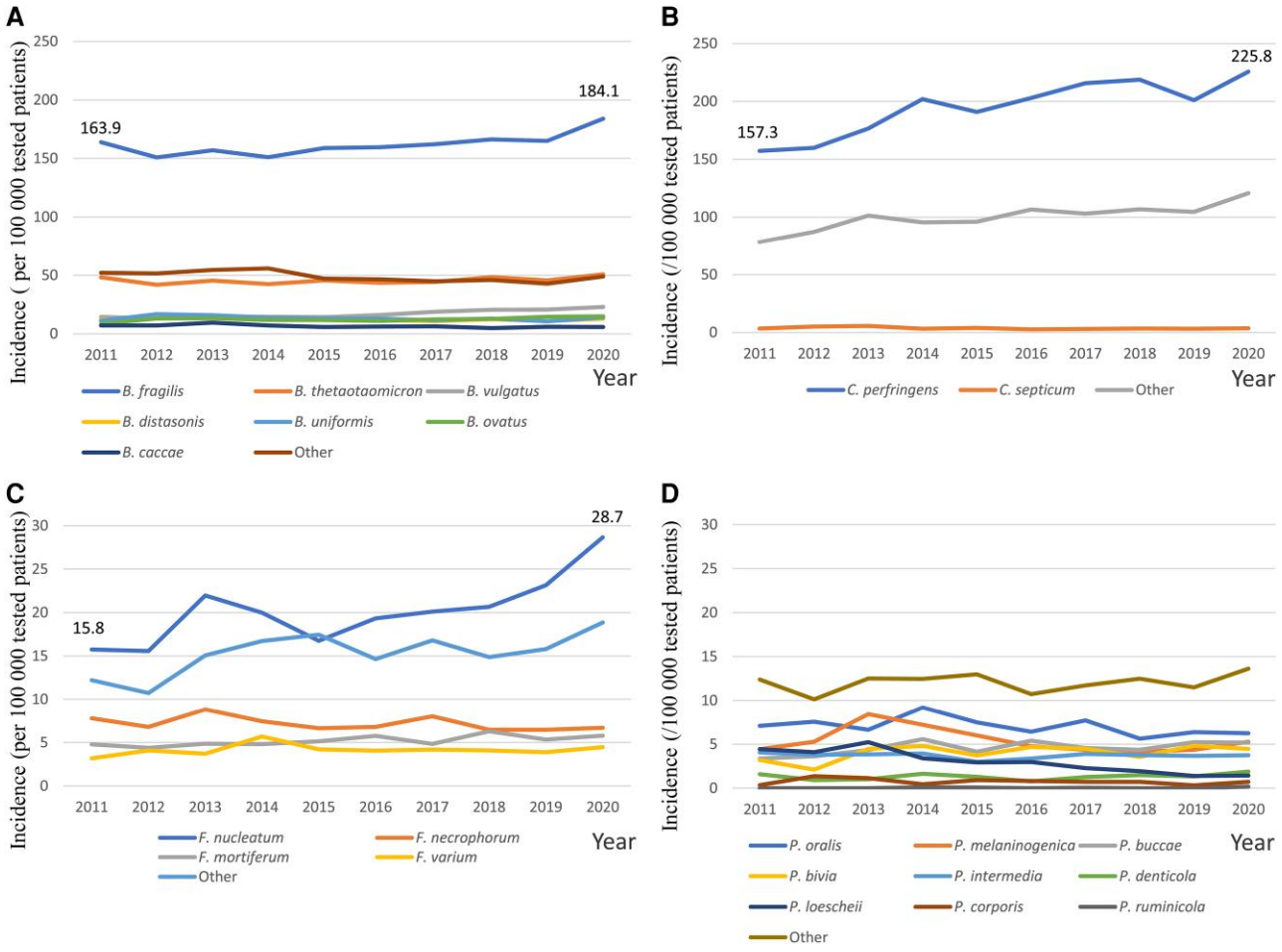

Figure 2. Distribution and individual annual incidences of bacteremia caused by *Bacteroides, Clostridium, Fusobacterium,* and *Prevotella* spp. during 2011–2020. A, *Bacteroides* spp., (B) *Clostridium* spp., (C) *Fusobacterium* spp., and (D) *Prevotella* spp.

identified as a risk factor for the development of anaerobic bacteremia [21]. Notably, the occurrence of *Fusobacterium* spp. is particularly elevated in males, with rates in the range of 64.3%–69.9% (Table 1). Mason et al. have reported that smoking increases the abundance of *Fusobacterium* spp., especially *F. nucleatum*, in both periodontally healthy and diseased individuals [22]. In Japan, the percentage of male smokers has been considerably higher than that of female smokers (35.9% vs 13.6% in 2022) [23]. Hence, smoking habits may be associated with the incidence of bacteremia caused by *Fusobacterium* spp.

Figure 2 illustrates an increase in bacteremia caused by *B. fragilis*, *C. perfringens*, and *F. nucleatum*. This trend may be attributed to the rising incidence of colorectal cancer. Kwong et al. reported significant associations between colorectal cancer and bloodstream infections caused by *Streptococcus gallolyticus*, *B. fragilis*, *F. nucleatum*, *Peptostreptococcus* spp., *C. perfringens*, and other anaerobic bacteria [24]. In Japan, the annual incidence of colorectal cancer continues to increase [25]. The surge in surgical procedures involving the small intestine, colon, rectum, anus, gall bladder, and pancreas may also contribute to this trend [26]. According to a report from the JANIS SSI section, in 2020 *B. fragilis* ranked as the third most frequent pathogen in colon surgeries and the fourth most frequent pathogen in rectal surgeries (source: https://janis.mhlw.go.jp/report/open_report/2021/3/5/SSI_Open_Report_202100.xls). Another potential factor could be advancements in species identification and susceptibility testing methods, such as the Rapid ID 32A API, the system for microorganism identification, susceptibility testing (eg, WalkAway and BD Phoenix), and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, which are commonly utilized in Japanese hospital laboratories. However, the impact of these methods could not be verified because information regarding the species identification practices at each hospital was not recorded in the JANIS system.

The breakdown of 4 anaerobic bacteria causing bacteremia showed little change from 2011 to 2020, except for an increase in *Fusobacterium nucleatum* from 36.0% to 44.5% ($P < .001$)

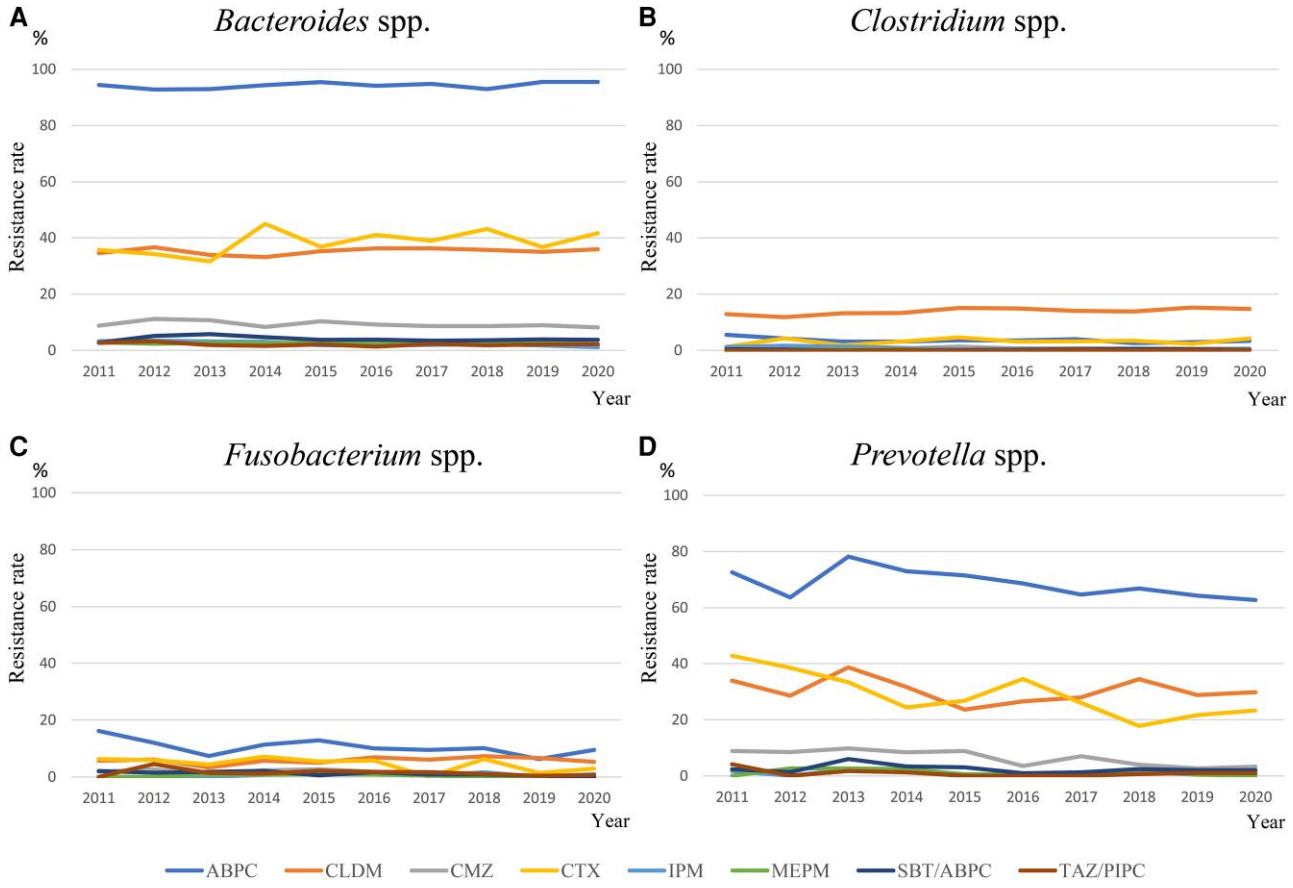

Figure 3. Individual antimicrobial resistance rates of *Bacteroides*, *Clostridium*, *Fusobacterium*, and *Prevotella* spp. during 2011–2020. A, *Bacteroides* spp., (B) *Clostridium* spp., (C) *Fusobacterium* spp., and (D) *Prevotella* spp. The following antibiotics are shown: ABPC is indicated by the blue line, CLDM is indicated by the orange line, CMZ is indicated by the gray line, CTX is indicated by the yellow line, IPM is indicated by the light blue line, MEPM is indicated by the green line, SBT/ABPC is indicated by the dark blue line, and TAZ/PIPC is indicated by the brown line. Abbreviations: ABPC, ampicillin; CLDM, clindamycin; CMZ, cefmetazole; CTX, cefotaxime; IPM, imipenem; MEPM, meropenem; SBT/ABPC, sulbactam/ampicillin; TAZ/PIPC, tazobactam/piperacillin.

(Supplementary Figure 1). This increase may be associated with colorectal cancer and colorectal surgeries [24]. On the other hand, the breakdown (Supplementary Figure 1C) showed a relative decrease in *F. necrophorum*, primarily associated with nongut infections [27, 28], from 17.8% in 2011 to 13.1% in 2020 ($P < .001$), which corresponds to the increase in *F. nucleatum* primarily associated with the gut.

We also analyzed the annual trends in resistance rates for various antimicrobials and compared the data from 2011–2015 with 2016–2020 (Figure 3, Table 2). Metronidazole (MNZ) was not included due to the absence of susceptibility data in the JANIS database, although MNZ injections have been used since 2014. Notably, high resistance rates of *Bacteroides* spp. and *Prevotella* spp. to ABPC were observed (>90% and >60%, respectively, in Figure 3). Eitel et al. have identified the *cepA*, *cfxA*, and *cfiA* genes as β-lactamase genes detected in the *B. fragilis* group. Tran et al. and Hashimoto et al. reported that the *cfxA* gene, specifically associated with resistance to ABPC, has been predominantly found in *Bacteroides* spp. isolates from Japanese patients [29, 30]. In contrast, carbapenems retained high activity against these 4 bacteria, with *Bacteroides* spp., *Clostridium* spp., *Fusobacterium* spp., and *Prevotella* spp. showing resistance rates of <4%, 0.5%, 1%, and 3%, respectively, to meropenem. Among the *Bacteroides* species, the resistance rate of *B. fragilis* to meropenem has been relatively high (up to 3.6%). It was reported that 9.6% of *Bacteroides* isolates in Kuwait and 4% in Belgium were resistant to meropenem, whereas none of the clinical isolates from Germany, Turkey, Hungary, Croatia, and the Netherlands showed resistance to carbapenems [31]. Snydman et al. reported that the resistance rate of carbapenems against *B. fragilis* in United States was low (1.1%–2.5%) [32]. In Canada, the resistance rate of gram-negative anaerobic bacteria to imipenem during 2012–2019 was reported to be <4% [33]. However, in China, 18.2% and 29.5% of *B. fragilis* isolates were found to be resistant to imipenem and meropenem, respectively, during 2009–2015 [34]. SBT/ABPC and TAZ/PIPC also showed low resistance rates against all 4 bacteria. These results are similar to

Table 2. Resistance Rates of Anaerobic Bacteria to Eight Antibiotics During 2011–2020 and Comparison With the Findings Obtained During 2011–2015 and 2016–2020

Species	Total, % (No.) 2011–2020	Early Period, % (No.) 2011–2015	Late Period, % (No.) 2016–2020	Difference, %	Adjusted *P* Value*
Bacteroides fragilis					
ABPC	96.8 (7167/7401)	96.6 (2190/2268)	97.0 (4977/5133)	+0.4	n.s.
CLDM	32.7 (2557/7824)	32.1 (733/2284)	32.9 (1824/5540)	+0.8	n.s.
CMZ	5.6 (401/7127)	6.6 (132/2009)	5.3 (269/5118)	−1.3	n.s.
CTX	38.1 (758/1991)	35.9 (208/579)	39.0 (550/1412)	+3.1	n.s.
IPM	2.0 (152/7625)	2.6 (58/2259)	1.8 (94/5366)	−0.8	n.s.
MEPM	3.6 (253/7126)	3.5 (71/2056)	3.6 (182/5070)	+0.1	n.s.
SBT/ABPC	3.3 (242/7224)	3.6 (73/2052)	3.3 (169/5172)	−0.3	n.s.
TAZ/PIPC	1.5 (82/5344)	1.5 (21/1368)	1.5 (61/3976)	0	n.s.
Bacteroides thetaiotaomicron					
ABPC	97.6 (2008/2058)	97.3 (619/636)	97.7 (1389/1422)	+0.4	n.s.
CLDM	51.5 (1128/2190)	46.7 (307/657)	53.6 (821/1533)	+7.1	0.0312
CMZ	32.3 (652/2016)	33.9 (205/605)	31.7 (447/1411)	−2.2	n.s.
CTX	64.0 (311/486)	57.0 (86/151)	67.2 (225/335)	+10.2	n.s.
IPM	1.5 (32/2142)	1.2 (8/663)	1.6 (24/1479)	+0.4	n.s.
MEPM	1.8 (35/1944)	1.5 (8/551)	1.9 (27/1393)	+0.4	n.s.
SBT/ABPC	4.0 (80/2015)	3.3 (19/572)	4.2 (61/1443)	+0.9	n.s.
TAZ/PIPC	2.8 (40/1432)	2.6 (9/350)	2.9 (31/1082)	+0.3	n.s.
Bacteroides caccae					
ABPC	95.5 (299/313)	95.2 (100/105)	95.7 (199/208)	+0.5	n.s.
CLDM	35.5 (119/335)	32.7 (37/113)	36.9 (82/222)	+3.2	n.s.
CMZ	7.7 (21/272)	8.5 (8/94)	7.3 (13/178)	−1.2	n.s.
CTX	35.5 (27/76)	N/A	39.3 (22/56)	N/A	N/A
IPM	2.4 (8/328)	2.8 (3/109)	2.3 (5/219)	−0.5	n.s.
MEPM	3.4 (10/296)	4.7 (4/85)	2.8 (6/211)	−1.9	n.s.
SBT/ABPC	3.8 (11/289)	4.4 (4/90)	3.5 (7/199)	−0.9	n.s.
TAZ/PIPC	3.1 (7/223)	3.3 (2/60)	3.1 (5/163)	−0.2	n.s.
Bacteroides vulgatus					
ABPC	95.5 (779/816)	93.1 (176/189)	96.2 (603/627)	+3.2	n.s.
CLDM	42.4 (342/806)	44.6 (82/184)	41.8 (260/622)	−2.8	n.s.
CMZ	5.3 (42/797)	7.1 (13/184)	4.7 (29/613)	−2.4	n.s.
CTX	35.2 (62/176)	36.2 (17/47)	34.9 (45/129)	−1.3	n.s.
IPM	1.3 (11/816)	1.6 (3/185)	1.3 (8/628)	−0.3	n.s.
MEPM	0.8 (6/757)	0.6 (1/169)	0.9 (5/588)	+0.3	n.s.
SBT/ABPC	3.1 (24/778)	1.8 (3/166)	3.4 (21/612)	+1.6	n.s.
TAZ/PIPC	2.0 (12/593)	2.7 (3/112)	1.9 (9/481)	−0.8	n.s.
Parabacteroides distasonis					
ABPC	94.2 (537/570)	93.3 (194/208)	94.8 (343/362)	+1.5	n.s.
CLDM	39.1 (218/557)	41.3 (76/184)	38.1 (142/373)	−3.2	n.s.
CMZ	25.2 (130/515)	26.5 (43/162)	24.6 (87/353)	−1.9	n.s.
CTX	47.5 (58/122)	45.5 (20/44)	48.7 (38/78)	+3.2	n.s.
IPM	6.0 (36/605)	11.3 (24/213)	3.1 (12/392)	−8.2	0.0008
MEPM	1.5 (8/509)	1.2 (2/166)	1.7 (4/341)	+0.5	n.s.
SBT/ABPC	16.1 (87/542)	21.1 (38/180)	13.5 (49/362)	−7.6	n.s.
TAZ/PIPC	5.8 (23/398)	6.9 (7/102)	5.4 (16/298)	−1.5	n.s.
Bacteroides uniformis					
ABPC	94.3 (549/582)	92.1 (152/165)	95.2 (397/417)	+3.1	n.s.
CLDM	49.7 (286/576)	43.8 (64/146)	51.6 (222/430)	+7.8	n.s.
CMZ	9.7 (53/549)	9.7 (14/145)	9.7 (39/404)	0	n.s.
CTX	51.1 (69/135)	48.9 (22/45)	52.2 (47/90)	+3.3	n.s.
IPM	1.0 (6/586)	1.3 (2/156)	0.9 (4/430)	−0.4	n.s.
MEPM	0.9 (5/567)	1.3 (2/154)	0.7 (3/413)	−0.6	n.s.
SBT/ABPC	2.9 (16/556)	4.8 (7/145)	2.2 (9/411)	−2.6	n.s.
TAZ/PIPC	0.9 (4/428)	1.1 (1/91)	0.9 (3/337)	−0.2	n.s.

Table 2. Continued

Species	Total, % (No.) 2011–2020	Early Period, % (No.) 2011–2015	Late Period, % (No.) 2016–2020	Difference, %	Adjusted *P* Value*
Bacteroides ovatus					
ABPC	93.3 (567/608)	87.3 (172/197)	96.1 (395/411)	+8.8	.0008
CLDM	39.8 (229/576)	35.2 (64/182)	41.9 (165/394)	+6.7	n.s.
CMZ	23.0 (139/605)	20.2 (39/193)	24.3 (100/412)	+4.1	n.s.
CTX	46.7 (64/137)	46.5 (20/43)	46.8 (44/94)	+0.3	n.s.
IPM	1.8 (11/607)	1.0 (2/203)	2.2 (9/403)	+1.2	n.s.
MEPM	1.2 (7/568)	1.2 (2/166)	1.2 (5/402)	0	n.s.
SBT/ABPC	3.3 (19/575)	3.3 (6/183)	3.3 (13/392)	0	n.s.
TAZ/PIPC	2.6 (11/417)	0.9 (1/115)	3.3 (10/302)	+2.4	n.s.
Clostridium perfringens					
ABPC	1.8 (138/7696)	1.8 (40/2180)	1.8 (98/5516)	0	n.s.
CLDM	9.8 (794/8064)	9.5 (203/2137)	10.0 (591/5927)	+0.5	n.s.
CMZ	0.3 (19/7344)	0.3 (6/1922)	0.2 (13/5422)	−0.1	n.s.
CTX	0.4 (7/1843)	0.6 (3/507)	0.3 (4/1336)	−0.3	n.s.
IPM	0.3 (21/7802)	0.3 (6/2096)	0.3 (15/5706)	0	n.s.
MEPM	0.1 (7/7204)	0.2 (3/1901)	0.1 (4/5303)	−0.1	n.s.
SBT/ABPC	0.3 (24/7410)	0.2 (3/1900)	0.4 (21/5470)	+0.2	n.s.
TAZ/PIPC	0.1 (6/5367)	0 (0/1202)	0.1 (6/4165)	+0.1	n.s.
Clostridium septicum					
ABPC	2.5 (4/157)	1.7 (1/59)	3.1 (3/98)	+1.4	n.s.
CLDM	17.6 (26/148)	18.9 (10/53)	16.8 (16/95)	−2.1	n.s.
CMZ	0 (0/138)	0 (0/49)	0 (0/89)	0	n.s.
CTX	0 (0/40)	N/A	N/A	N/A	N/A
IPM	0 (0/142)	0 (0/50)	0 (0/92)	0	n.s.
MEPM	0 (0/141)	0 (0/50)	0 (0/91)	0	n.s.
SBT/ABPC	0 (0/144)	0 (0/49)	0 (0/95)	0	n.s.
TAZ/PIPC	0 (0/97)	N/A	0 (0/71)	N/A	N/A
Fusobacterium nucleatum					
ABPC	3.6 (27/759)	6.2 (14/225)	2.4 (13/534)	−3.8	n.s.
CLDM	1.6 (12/757)	1.4 (3/221)	1.7 (9/536)	+0.3	n.s.
CMZ	0.4 (3/730)	1.4 (3/212)	0 (0/518)	−1.4	n.s.
CTX	1.0 (2/198)	1.8 (1/55)	0.7 (1/143)	−1.1	n.s.
IPM	0 (0/732)	0 (0/222)	0 (0/510)	0	n.s.
MEPM	0.1 (1/724)	0.5 (1/219)	0 (0/505)	−0.5	n.s.
SBT/ABPC	0.5 (4/740)	1.4 (3/209)	0.2 (1/531)	−1.2	n.s.
TAZ/PIPC	0.7 (4/566)	2.2 (3/137)	0.2 (1/429)	−2.0	n.s.
Fuobacterium necrophorum					
ABPC	4.7 (11/235)	7.1 (6/84)	3.3 (5/151)	−3.8	n.s.
CLDM	2.8 (7/246)	3.3 (3/91)	2.6 (4/155)	−0.7	n.s.
CMZ	1.8 (4/221)	3.9 (3/76)	0.7 (1/145)	−3.2	n.s.
CTX	5.5 (3/55)	N/A	0 (0/34)	N/A	N/A
IPM	0.8 (2/242)	1.2 (1/81)	0.6 (1/161)	−0.6	n.s.
MEPM	0.4 (1/234)	1.1 (1/89)	0 (0/145)	−1.1	n.s.
SBT/ABPC	0.4 (1/251)	1.1 (1/91)	0 (0/160)	−1.1	n.s.
TAZ/PIPC	0.6 (1/157)	0 (0/49)	0.9 (1/109)	+0.9	n.s.
Fusobacterium mortiferum					
ABPC	20.4 (44/216)	23.3 (14/60)	19.2 (30/156)	−4.1	n.s.
CLDM	1.8 (4/221)	3.2 (2/63)	1.3 (2/158)	−1.9	n.s.
CMZ	1.5 (3/205)	1.7 (1/58)	1.4 (2/147)	−0.3	n.s.
CTX	14.9 (7/47)	N/A	11.4 (4/35)	N/A	N/A
IPM	1.4 (3/218)	1.6 (1/62)	1.3 (2/156)	−0.3	n.s.
MEPM	1.4 (3/216)	0 (0/65)	2.0 (3/151)	+2.0	n.s.
SBT/ABPC	2.9 (6/210)	3.4 (2/58)	2.6 (4/152)	−0.8	n.s.
TAZ/PIPC	4.0 (6/151)	5.6 (2/36)	3.5 (4/115)	−2.1	n.s.

Table 2. Continued

Species		Total, % (No.) 2011–2020	Early Period, % (No.) 2011–2015	Late Period, % (No.) 2016–2020	Difference, %	Adjusted *P* Value*
Fusobacterium varium						
	ABPC	42.2 (70/166)	40 (18/45)	43.0 (52/121)	+3.0	n.s.
	CLDM	37.8 (62/164)	28.9 (13/45)	41.2 (49/119)	+12.3	n.s.
	CMZ	3.3 (5/153)	5.1 (2/39)	2.6 (3/114)	−2.5	n.s.
	CTX	2.4 (1/42)	N/A	3.2 (1/31)	N/A	N/A
	IPM	4.2 (7/165)	2.4 (1/42)	4.9 (6/123)	+2.5	n.s.
	MEPM	1.3 (2/152)	2.3 (1/44)	0.9 (1/108)	−1.4	n.s.
	SBT/ABPC	2.5 (4/161)	5.0 (2/40)	1.7 (2/121)	−3.3	n.s.
	TAZ/PIPC	3.2 (4/126)	N/A	3.1 (3/97)	N/A	N/A
Prevotella oralis						
	ABPC	73.9 (224/276)	78.4 (87/111)	70.9 (117/165)	−7.5	n.s.
	CLDM	32.6 (95/291)	33.0 (37/112)	32.4 (58/179)	−0.6	n.s.
	CMZ	10.4 (25/240)	11.4 (10/88)	9.7 (15/152)	−1.7	n.s.
	CTX	38.9 (35/90)	41.9 (13/31)	37.3 (22/59)	−4.6	n.s.
	IPM	1.1 (3/276)	1.0 (1/102)	1.1 (2/174)	+0.1	n.s.
	MEPM	0.4 (1/260)	1.0 (1/105)	0 (0/155)	−1.0	n.s.
	SBT/ABPC	3.4 (9/268)	3.0 (3/99)	3.6 (6/169)	+0.6	n.s.
	TAZ/PIPC	2.2 (4/181)	3.4 (2/58)	1.6 (2/123)	−1.8	n.s.
Prevotella melaninogenica						
	ABPC	70.3 (142/202)	74.7 (68/91)	66.7 (74/111)	−8.0	n.s.
	CLDM	29.0 (61/210)	31.9 (30/94)	26.7 (31/116)	−5.2	n.s.
	CMZ	11.5 (21/183)	16.7 (14/84)	7.1 (7/99)	−9.6	n.s.
	CTX	36.5 (19/52)	N/A	N/A	N/A	N/A
	IPM	1.4 (3/215)	2.0 (2/98)	0.9 (1/117)	−1.1	n.s.
	MEPM	2.1 (4/191)	2.5 (2/80)	1.8 (2/111)	−0.7	n.s.
	SBT/ABPC	3.7 (7/189)	6.5 (5/77)	1.8 (2/112)	−4.7	n.s.
	TAZ/PIPC	1.4 (2/139)	2.0 (1/51)	1.1 (1/88)	−0.9	n.s.
Prevotella buccae						
	ABPC	54.3 (120/221)	59.6 (34/57)	52.4 (86/164)	−7.2	n.s.
	CLDM	25.6 (57/223)	29.1 (16/55)	24.4 (41/168)	−4.7	n.s.
	CMZ	2.3 (5/215)	5.4 (3/56)	1.3 (2/159)	−4.1	n.s.
	CTX	19.6 (9/46)	N/A	19.4 (6/31)	N/A	N/A
	IPM	0.4 (1/231)	0 (0/58)	0.6 (1/173)	+0.6	n.s.
	MEPM	1.9 (4/210)	4.3 (2/47)	1.2 (2/163)	−3.1	n.s.
	SBT/ABPC	0.5 (1/203)	0 (0/46)	0.6 (1/157)	+0.6	n.s.
	TAZ/PIPC	0 (0/153)	N/A	0 (0/129)	N/A	N/A
Prevotella bivia						
	ABPC	73.4 (127/173)	63.8 (30/47)	77.0 (97/126)	+13.2	n.s.
	CLDM	35.1 (65/185)	21.6 (11/51)	40.3 (54/134)	+18.7	n.s.
	CMZ	2.9 (5/175)	7.0 (3/43)	1.5 (2/132)	−5.5	n.s.
	CTX	11.9 (7/59)	N/A	10.5 (4/38)	N/A	N/A
	IPM	1.2 (2/173)	4.5 (2/44)	0 (0/124)	−4.5	n.s.
	MEPM	0 (0/156)	0 (0/33)	0 (0/124)	0	n.s.
	SBT/ABPC	0.6 (1/171)	2.8 (1/36)	0 (0/135)	−2.8	n.s.
	TAZ/PIPC	0 (0/126)	N/A	0 (0/103)	N/A	N/A
Prevotella intermedia						
	ABPC	41.0 (64/156)	40.0 (20/50)	41.5 (44/106)	+1.5	n.s.
	CLDM	13.9 (23/166)	13.5 (7/52)	14.0 (16/114)	+0.5	n.s.
	CMZ	0 (0/143)	0 (0/43)	0 (0/100)	0	n.s.
	CTX	2.7 (1/37)	N/A	N/A	N/A	N/A
	IPM	0 (0/164)	0 (0/52)	0 (0/112)	0	n.s.
	MEPM	0 (0/146)	0 (0/40)	0 (0/106)	0	n.s.
	SBT/ABPC	0 (0/151)	0 (0/42)	0 (0/109)	0	n.s.
	TAZ/PIPC	0 (0/110)	N/A	0 (0/84)	N/A	N/A

Table 2. Continued

Species	Total, % (No.) 2011–2020	Early Period, % (No.) 2011–2015	Late Period, % (No.) 2016–2020	Difference, %	Adjusted *P* Value*
Prevotella denticola					
ABPC	71.9 (46/64)	N/A	65.1 (28/43)	N/A	N/A
CLDM	28.3 (17/60)	N/A	27.3 (12/44)	N/A	N/A
CMZ	1.8 (1/55)	N/A	2.6 (1/39)	N/A	N/A
CTX	N/A	N/A	N/A	N/A	N/A
IPM	0 (0/58)	N/A	0 (0/39)	N/A	N/A
MEPM	1.6 (1/61)	N/A	2.3 (1/43)	N/A	N/A
SBT/ABPC	1.6 (1/62)	N/A	2.3 (1/43)	N/A	N/A
TAZ/PIPC	0 (0/45)	N/A	0 (0/34)	N/A	N/A
Prevotella loescheii					
ABPC	78.0 (96/123)	94.4 (67/71)	55.8 (29/52)	−38.6	<0.0001
CLDM	40.7 (57/140)	49.3 (36/73)	31.3 (21/67)	−18.0	n.s.
CMZ	11.0 (10/91)	9.8 (5/51)	12.5 (5/40)	+2.7	n.s.
CTX	46.2 (24/52)	N/A	N/A	N/A	N/A
IPM	1.5 (2/135)	2.9 (2/68)	0 (0/67)	−2.9	n.s.
MEPM	1.6 (2/122)	3.0 (2/66)	0 (0/66)	−3.0	n.s.
SBT/ABPC	5.6 (7/126)	9.7 (6/62)	1.5 (1/64)	−8.2	n.s.
TAZ/PIPC	0 (0/51)	N/A	N/A	N/A	N/A

Abbreviations: ABPC, ampicillin; CLDM, clindamycin; CMZ, cefmetazole; CTX, cefotaxime; IPM, imipenem; MEPM, meropenem; N/A, not analyzed because the total number of tests was <30 for the period; n.s., not significant; SBT/ABPC, sulbactam/ampicillin; TAZ/PIPC, tazobactam/piperacillin.

those obtained in Canada, Argentina, and European countries [3, 35–38].

The resistance rate of *B. thetaiotaomicron* to CLDM, CTX, and CMZ was higher than that of *B. fragilis* (Table 2), consistent with previous reports of higher resistance to cephalosporins and CLDM in Korea, Canada, Argentina, and European countries [9, 35, 39, 40]. Kierzkowska et al. reported a higher resistance rate to CLDM in non-*fragilis Bacteroides* during 2013–2017 than during 2007–2012 [41]. The observed resistance to CLDM in *Bacteroides*, *Fusobacterium*, *and Prevotella* spp. was found to be related to the presence of *ermF* genes [42, 43]. This study revealed a significant increase in the resistance rate to CLDM by *B. thetaiotaomicron*. The resistance rate of *C. perfringens* to CLDM was higher (7.3%–11.6%) than to other antimicrobials. The resistance rates of *Prevotella* spp. to ABPC (62.8%), CLDM (29.8%), IPM, and SBT/ABPC were similar to those observed in Italy [3].

This study had several limitations. First, the JANIS surveillance system relies on voluntary participation. Thus, the number of participating hospitals can vary each year. Second, JANIS did not collect information on how species identification is conducted in each hospital. Third, JANIS has not collected strains but has rather collected data on species, specimens, and antimicrobial susceptibility reported by the participating hospitals. Fourth, drug susceptibility tests were conducted only for 30%–40% of the strains isolated in these hospitals, and there were no data on MNZ susceptibility tests. Additionally, each participating hospital used their own microbiological diagnostic and antimicrobial susceptibility testing instruments, which could introduce variability in the results.

Despite the limitations of this study, it provides the largest longitudinal overviews using national surveillance data of culturing and antimicrobial susceptibilities of 41 949 *Bacteroides*, 40 603 *Clostridium*, 7013 *Fusobacterium*, and 5428 *Prevotella* isolates from >2000 hospitals collected for 10 years. The incidence of anaerobic bacteremia, particularly *B. fragilis*, *C. perfringens*, and *F. nucleatum*, has been continuously increasing, which may be attributed to the rising number of patients with colorectal cancer or the advancing methods for species identification and susceptibility testing, requiring cautious interpretation. The resistance rate of *B. thetaiotaomicron* to CLDM and CTX was significantly increased. These results could help guide empirical therapies for anaerobic bacteremia, and the findings of increased anaerobic bacteremia and possible changes in susceptibility highlight the need for further extensive and diverse studies in this field.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

We are grateful to all the hospitals that participated and contributed data to JANIS as well as Editage (www.editage.jp) for English language editing.

Financial support. This study was supported by the Research Program on Emerging and Re-emerging Infectious Diseases from the Japan Agency for Medical Research and Development under grant number 21fk0108604j0001 to M.S.

Potential conflicts of interest. All authors: no reported conflicts.

References

1. Goldstein EJ. Anaerobic bacteremia. Clin Infect Dis **1996;** 23(Suppl 1):S97–101.
2. Brook I. Spectrum and treatment of anaerobic infections. J Infect Chemother **2016;** 22:1–13.
3. Di Bella S, Antonello RM, Sanson G, et al. Anaerobic bloodstream infections in Italy (ITANAEROBY): a 5-year retrospective nationwide survey. Anaerobe **2022;** 75:102583.
4. Diekema DJ, Beekmann SE, Chapin KC, Morel KA, Munson E, Doern GV. Epidemiology and outcome of nosocomial and community-onset bloodstream infection. J Clin Microbiol **2003;** 41:3655–60.
5. Lassmann B, Gustafson DR, Wood CM, Rosenblatt JE. Reemergence of anaerobic bacteremia. Clin Infect Dis **2007;** 44:895–900.
6. Ng LSY, Kwang LL, Rao S, Tan TY. Anaerobic bacteraemia revisited: species and susceptibilities. Ann Acad Med Singap **2015;** 44:13–8.
7. Dorsher CW, Rosenblatt JE, Wilson WR, Ilstrup DM. Anaerobic bacteremia: decreasing rate over a 15-year period. Rev Infect Dis **1991;** 13:633–6.
8. Hecht DW. Prevalence of antibiotic resistance in anaerobic bacteria: worrisome developments. Clin Infect Dis **2004;** 39:92–7.
9. Karlowsky JA, Walkty AJ, Adam HJ, Baxter MR, Hoban DJ, Zhanel GG. Prevalence of antimicrobial resistance among clinical isolates of *Bacteroides fragilis* group in Canada in 2010-2011: CANWARD surveillance study. Antimicrob Agents Chemother **2012;** 56:1247–52.
10. Veloo ACM, Baas WH, Haan FJ, Coco J, Rossen JW. Prevalence of antimicrobial resistance genes in *Bacteroides* spp. and *Prevotella* spp. Dutch clinical isolates. Clin Microbiol Infect **2019;** 25:1156.e9–13.
11. Boyanova L, Kolarov R, Mitov I. Recent evolution of antibiotic resistance in the anaerobes as compared to previous decades. Anaerobe **2015;** 31:4–10.
12. Cobo F, Rodriguez-Granger J, Perez-Zapata I, Sampedro A, Aliaga L, Navarro-Mari JM. Antimicrobial susceptibility and clinical findings of significant anaerobic bacteria in southern Spain. Anaerobe **2019;** 59:49–53.
13. Nguyen MH, Yu VL, Morris AJ, et al. Antimicrobial resistance and clinical outcome of *Bacteroides* bacteremia: findings of a multicenter prospective observational trial. Clin Infect Dis **2000;** 30:870–6.
14. Kajihara T, Yahara K, Hirabayashi A, et al. Japan nosocomial infections surveillance (JANIS): current status, international collaboration, and future directions for a comprehensive antimicrobial resistance surveillance system. Jpn J Infect Dis **2021;** 74:87–96.
15. Shimura S, Watari H, Komatsu M, et al. Antimicrobial susceptibility surveillance of obligate anaerobic bacteria in the Kinki area. J Infect Chemother **2019;** 25: 837–44.
16. Wilson JR, Limaye AP. Risk factors for mortality in patients with anaerobic bacteremia. Eur J Clin Microbiol Infect Dis **2004;** 23:310–6.
17. Kajihara T, Yahara K, Stelling J, et al. Comparison of de-duplication methods used by WHO Global Antimicrobial resistance Surveillance System (GLASS) and Japan Nosocomial Infections Surveillance (JANIS) in the surveillance of antimicrobial resistance. PLoS One **2020;** 15:e0228234.
18. World Health Organization. *Global Antimicrobial Resistance Surveillance System (GLASS) Guide to Preparing Aggregated Antimicrobial Resistance Data Files*. World Health Organization; **2016**.
19. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc B **1995;** 57:289–300.
20. Sarvari KP, Racz NB, Burian K. Epidemiology and antibiotic susceptibility in anaerobic bacteraemia: a 15-year retrospective study in south-eastern Hungary. Infect Dis **2022;** 54:16–25.
21. Ngo JT, Parkins MD, Gregson DB, et al. Population-based assessment of the incidence, risk factors, and outcomes of anaerobic bloodstream infections. Infection **2013;** 41:41–8.
22. Mason MR, Preshaw PM, Nagaraja HN, et al. The subgingival microbiome of clinically healthy current and never smokers. ISME J **2015;** 9:268–72.
23. Odani S, Tabuchi T. Prevalence and denial of current tobacco product use: combustible and heated tobacco products, Japan, 2022. Prev Med Rep **2022;** 30: 102031.
24. Kwong TNY, Wang X, Nakatsu G, et al. Association between bacteremia from specific microbes and subsequent diagnosis of colorectal cancer. Gastroenterology **2018;** 155:383–8.
25. Foundation for Promotion of Cancer Research. Cancer statistics in Japan. **2022**. Available at: https://ganjoho.jp/public/qa_links/report/statistics/pdf/cancer_statistics_2022.pdf. Accessed March 8, 2023.
26. Marubashi S, Takahashi A, Kakeji Y, et al. Surgical outcomes in gastroenterological surgery in Japan: report of the National Clinical Database 2011-2019. Ann Gastroenterol Surg **2021;** 5:639–58.
27. Kristensen LH, Prag J. Lemierre's syndrome and other disseminated *Fusobacterium necrophorum* infections in Denmark: a prospective epidemiological and clinical survey. Eur J Clin Microbiol Infect Dis **2008;** 27:779–89.
28. Riordan T. Human infection with *Fusobacterium necrophorum* (necrobacillosis), with a focus on Lemierre's syndrome. Clin Microbiol Rev **2007;** 20:622–59.
29. Hashimoto T, Hashinaga K, Komiya K, Hiramatsu K. Prevalence of antimicrobial resistant genes in *Bacteroides* spp. isolated in Oita Prefecture, Japan. J Infect Chemother **2023;** 29:284–8.
30. Tran CM, Tanaka K, Watanabe K. PCR-based detection of resistance genes in anaerobic bacteria isolated from intra-abdominal infections. J Infect Chemother **2013;** 19:279–90.
31. Veloo ACM, Tokman HB, Jean-Pierre H, et al. Antimicrobial susceptibility profiles of anaerobic bacteria, isolated from human clinical specimens, within different European and surrounding countries. A joint ESGAI study. Anaerobe **2020;** 61:102111.
32. Snydman DR, Jacobus NV, McDermott LA, et al. Trends in antimicrobial resistance among *Bacteroides* species and *Parabacteroides* species in the United States from 2010-2012 with comparison to 2008-2009. Anaerobe **2017;** 43:21–6.
33. Forbes JD, Kus JV, Patel SN. Antimicrobial susceptibility profiles of invasive isolates of anaerobic bacteria from a large Canadian reference laboratory: 2012-2019. Anaerobe **2021;** 70:102386.
34. Gao Q, Wu S, Xu T, Zhao X, Huang H, Hu F. Emergence of carbapenem resistance in *Bacteroides fragilis* in China. Int J Antimicrob Agents **2019;** 53:859–63.
35. Fernandez-Canigia L, Litterio M, Legaria MC, et al. First national survey of antibiotic susceptibility of the *Bacteroides fragilis* group: emerging resistance to carbapenems in Argentina. Antimicrob Agents Chemother **2012;** 56:1309–14.
36. Seifert H, Dalhoff A; PRISMA Study Group. German multicentre survey of the antibiotic susceptibility of *Bacteroides fragilis* group and *Prevotella* species isolated from intra-abdominal infections: results from the PRISMA study. J Antimicrob Chemother **2010;** 65:2405–10.
37. Soki J, Wybo I, Hajdu E, et al. A Europe-wide assessment of antibiotic resistance rates in *Bacteroides* and *Parabacteroides* isolates from intestinal microbiota of healthy subjects. Anaerobe **2020;** 62:102182.
38. Wybo I, Van den Bossche D, Soetens O, et al. Fourth Belgian multicentre survey of antibiotic susceptibility of anaerobic bacteria. J Antimicrob Chemother **2014;** 69: 155–61.
39. Nagy E, Urban E, Nord CE, et al. Antimicrobial susceptibility of *Bacteroides fragilis* group isolates in Europe: 20 years of experience. Clin Microbiol Infect **2011;** 17:371–9.
40. Yim J, Lee Y, Kim M, et al. Antimicrobial susceptibility of clinical isolates of *Bacteroides fragilis* group organisms recovered from 2009 to 2012 in a Korean hospital. Ann Lab Med **2015;** 35:94–8.
41. Kierzkowska M, Majewska A, Mlynarczyk G. Trends and impact in antimicrobial resistance among *Bacteroides* and *Parabacteroides* species in 2007-2012 compared to 2013-2017. Microb Drug Resist **2020;** 26:1452–7.
42. Kierzkowska M, Majewska A, Szymanek-Majchrzak K, et al. In vitro effect of clindamycin against *Bacteroides* and *Parabacteroides* isolates in Poland. J Glob Antimicrob Resist **2018;** 13:49–52.
43. Sood A, Ray P, Angrup A. Anaerobic gram-negative bacteria: role as a reservoir of antibiotic resistance. Antibiotics (Basel) **2023;** 12:942.