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ORIGINAL ARTICLE

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Monitoring antimicrobial cross-resistance with cross-resistance rate correlation diagrams: Changes in antibiotic susceptibility of *Pseudomonas aeruginosa* due to hospital relocation

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Abstract

What is known and Objective: Though most medical institutions calculate antimicrobial susceptibility and resistance rates of microbes isolated at their own facility as part of their efforts to promote the proper use of antibiotics, very few, if any, regularly monitor cross-resistance rates between antimicrobial agents. The authors have devised a tool in the form of a cross-resistance rate correlation diagram (CRR diagram) that allows easy identification of increases or decreases in, or changes in the pattern of, antimicrobial cross-resistance. The objective was to perform an analysis by CRR diagrams of the effect of relocation to a newly built facility on antimicrobial resistance and cross-resistance rates at a medical facility.

Methods: The Sakai City Medical Center relocated in July 2015 to a newly built facility located in a different primary medical care zone 3.5 km away. Based on the drug susceptibility test data compiled at the Sakai City Medical Center, resistance and cross-resistance rates of *Pseudomonas aeruginosa* before and after the relocation of the hospital facility were calculated, and the rates were assessed using CRR diagrams.

Results and discussion: It was possible to confirm the effect of hospital relocation on antibiotic susceptibility of *P aeruginosa* in terms of changes in resistance and cross-resistance rates. The effect of the facility's relocation on cross-resistance rates was particularly notable with respect to β-lactam antibiotics: cross-resistance rates among β-lactams decreased substantially, represented as a large wedge-shaped change towards the origin on the CRR diagram. Rates of cross-resistance between classes of antibiotics with a different mechanism of antibiotic action changed little.

What is new and conclusion: Including cross-resistance rates in the routine monitoring of resistance and susceptibility rates practiced by a medical institution can provide a comprehensive insight into the dynamics of bacterial flora in the facility. CRR diagrams, which allow visualization of the status and changes in cross-resistance, not only provide a new perspective for clinicians, but they also contribute to the proper use of antibiotics and serve as a tool in the education of healthcare professionals and students about antibiotic resistance.

KEYWORDS
antibiotics, cross-resistance rate, CRR diagram, hospital, *Pseudomonas aeruginosa*

1 | INTRODUCTION

Antibiotic-resistant microbes are a global issue. Most medical institutions monitor antibiotic susceptibility and resistance rates to promote the proper use of antibiotics.[1-3] Meanwhile, rates of antimicrobial cross-resistance are sometimes taken into consideration when prescribing combination antibiotic therapy in the empiric treatment of a severe infectious disease in which a multidrug-resistant pathogen is suspected. However, very few facilities, if any, monitor cross-resistance rates as actively as they check the susceptibility and resistance rates.

With the above in mind, the authors have developed a previously reported cross-resistance rate correlation diagram (CRR diagram) that allows easy determination of the level of antimicrobial resistance rates and the degree of similarity in the pattern of resistance between antimicrobial agents.[4] The Sakai City Medical Center is a regional core hospital with 480 beds for general admission, seven beds for infectious diseases and a tertiary emergency centre. It relocated on 1 July 2015 to a newly built facility at the present location in a different primary medical care zone, approximately 3.5 km away. The present paper reports an analysis of the effect of hospital relocation on antibiotic susceptibility using CRR diagrams plotted with the cross-resistance rates between antimicrobial agents calculated from data obtained from strains of *Pseudomonas aeruginosa* isolated at the Sakai City Medical Center.

2 | METHODS

2.1 | Ethics statement

This research received institutional review board approval from the Sakai City Medical Center (approval No. H30-119). It was also approved by the Bioethics Committee of the Faculty of Pharmaceutical Sciences, Osaka Ohtani University (approval No. BE-0054-20).

2.2 | Survey period

The survey period was 6 years, from January 2013 to December 2018, which included the time of hospital relocation.

2.3 | Antibiotic susceptibility test data

The strains of *P aeruginosa* used were those isolated and tested for antibiotic susceptibility at Sakai City Medical Center during the survey period. The microbial laboratory at the Sakai City Medical Center performed the antibiotic susceptibility tests and determined whether an isolate was susceptible (S), intermediate (I) or resistant (R) in accordance with the Clinical and Laboratory Standards Institute (CLSI) guideline (M100-S26)[5] based on the minimum inhibitory concentration (MIC) obtained in the test.

2.4 | Data tabulation period

There were a few antimicrobial agents for which a data tabulation period of at least 18 months was needed to ensure the isolation of a minimum of 10 strains that were resistant to the agent, the number of which was used as the denominator in cross-resistance rate calculations. Thus, an 18-month period was selected for data tabulation. Furthermore, to avoid straddling the time of hospital relocation (2015-07), the prerelocation period was divided into segments, b1 (2013-1 to 2014-6) and b2 (2014-1 to 2015-6), and the post-relocation period was divided into segments, a1 (2015-7 to 2016-12), a2 (2016-7 to 2017-12) and a3 (2017-7 to 2018-12), as shown in Figure 1.

2.5 | Handling of duplicate bacterial strains

To avoid any impacts from duplicate bacterial strains, in cases where a patient was tested multiple times for antibiotic susceptibility, only the data of the first strain in a data tabulation period were used in calculating resistance and cross-resistance rates[5]; that is, a period of 548 days, which corresponds to the data tabulation period of 18 months, was selected for duplicate strain exclusion.

2.6 | Antimicrobial agents assessed

Of the antimicrobial agents to which *P aeruginosa* isolates were tested for antimicrobial susceptibility, cefozopran, doripenem, tobramycin and colistin were excluded from the assessment, since only a few resistant strains (the number of which was to be used as the denominator in cross-resistance rate calculation) were isolated in most segments. Additionally, fosfomycin, to which *P aeruginosa* showed poor susceptibility, was also excluded from the assessment (Table 1).

2.7 | Resistance and cross-resistance rates

Resistance rates (RR_X [%]) were calculated using the following equation, where N (S_X), N (I_X) and N (R_X), respectively, represent the

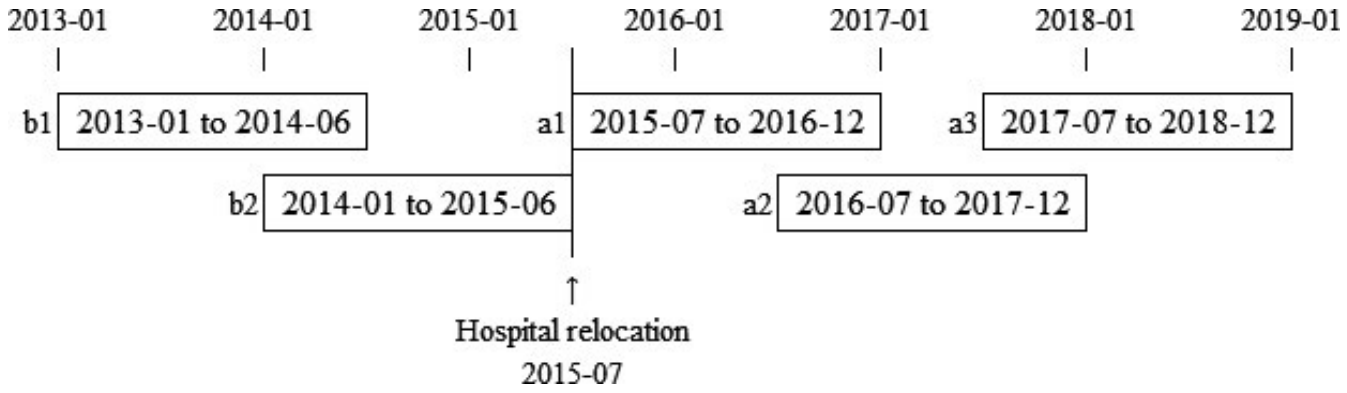

FIGURE 1 Segments of data tabulation period

number of bacterial strains susceptible, intermediate susceptible and resistant to antimicrobial agent X.

$$RR_X = \frac{N(R_X)}{N(S_X)+N(I_X)+N(R_X)} \times 100$$

Cross-resistance rates of antimicrobial X to base antimicrobial B ($CRR_{B\leftarrow X}$ [%]) were calculated by the following equation, where N ($R_B \bigcap Rx$) represents the number of antimicrobial B-resistant strains that were also resistant to antimicrobial X.

$$CRR_{B\leftarrow X} = \frac{N(R_B \cap R_X)}{N(R_B)} \times 100$$

2.8 | CRR diagrams

Correlation diagrams are scatter plots with the x-axis representing the cross-resistance rate of antimicrobial X to base antimicrobial B ($CRR_{B\leftarrow X}$) and the y-axis representing the cross-resistance rate of base antimicrobial B to antimicrobial X ($CRR_{X\leftarrow B}$). In CRR diagrams, the slope of a line between the origin and the plotted data point for antimicrobial X is inversely proportional to the rate of resistance to antimicrobial X. Moreover, if the plotted data point for antimicrobial X is located on the diagonal line, the resistance rate to antimicrobial X is comparable to that to base antimicrobial B. Thus, if the slope of the plotted data points for antimicrobial X is greater than that of the diagonal line that passes through the origin, the resistance rate to antimicrobial X is lower than that to base antimicrobial B; on the other hand, if the slope is smaller, the resistance rate to antimicrobial X is higher than that to base antimicrobial B. Furthermore, the closer the plotted data point for antimicrobial X is to the origin, the lower are the rates of cross-resistance to each other between antimicrobial X and base antimicrobial B, which is an indication that the resistance to antimicrobial X is different in pattern from that to base antimicrobial B. On the other hand, the closer the plotted data point for antimicrobial X is to the upper right corner, the more similar are antimicrobial X and base antimicrobial B in their resistance patterns.

In some segments, there were several antimicrobial agents to which only a few bacterial strains collected showed resistance. In cases where the denominator used in cross-resistance rate calculation was less than 10 strains, the corresponding data point plotted was denoted with an asterisk (*), and its coordinate was shown as a ratio of strain counts in the lower right corner of the CRR diagram.

TABLE 1 Classification of the antimicrobial agents assessed and their abbreviations

Penicillins		**Monobactams**	
Piperacillin	PIPC	Aztreonam	AZT
Piperacillin/Tazobactam	PIPC/TAZ		
Cephalosporins		**Aminoglycosides**	
Ceftazidime	CAZ	Amikacin	AMK
Cefepime	CFPM	Gentamicin	GM
Cefoperazone/Sulbactam	CPZ/SBT		
Carbapenems		**Fluoroquinolones**	
Imipenem	IPM	Ciprofloxacin	CPFX
Meropenem	MEPM	Levofloxacin	LVFX

3 | RESULTS

3.1 | Effects of hospital relocation on disposition of patients

Table 2 shows the biannual numbers of subject patients and numbers and percentages of the subject patients who were tested for antibiotic susceptibility before the relocation. The patients who were tested before the relocation accounted for approximately 13% of the overall patient population in the first half year after the relocation in July 2015 to a newly built hospital, and that percentage dropped precipitously thereafter to between 2% and 6%.

3.2 | Resistance rates

Table 3 shows resistance rates by segment for each antimicrobial agent and compares the resistance rate in each of the segments

TABLE 2 Subject patients and patients tested for antibiotic susceptibility before relocation

Year	Months	Number of patients	Number of patients tested in previous hospital	%
2013	1-6	84	–	–
	7-12	120		
2014	1-6	106		
	7-12	142		
2015	1-6	102		
	7-12	165	21	12.7
2016	1-6	112	10	8.9
	7-12	184	6	3.3
2017	1-6	164	7	4.3
	7-12	178	7	3.9
2018	1-6	133	7	5.3
	7-12	172	4	2.3

from b2 through a3 against that in the previous segment by the chi-squared test. The rates of resistance to the β-lactam class of antibiotics decreased substantially in the first year after the hospital relocation. In particular, the resistance rates to penicillins and cephalosporins in segment a1 differed significantly from the respective rates in segment b2; subsequently, the resistance rates in segment a2 increased to approximately 50% of the respective prerelocation rates in segment b2. The resistance rates to PIPC, PIPC/TAZ and CAZ in segment a2, in particular, differed significantly from the respective rates in segment a1.

The resistance rates to carbapenems, compared with the resistance rates to other antibiotics of the same β-lactam class, decreased only slightly after the hospital relocation, but they showed no subsequent increase as did the rates to the other β-lactams.

To examine the post-relocation increases in resistance rates more closely, resistance rates were calculated in the last 18 months at 1-month intervals after hospital relocation with respect to penicillins and cephalosporins, to which the resistance rate decreased significantly in segment a1 (Figure 2). Across all such antimicrobials, the resistance rate decreased substantially post-relocation and then increased over a period of 3 to 9 months before reaching a steady state.

3.3 | Cross-resistance rates

3.3.1 | Cross-resistance rate charts

Cross-resistance rate charts provide rates of cross-resistance of antimicrobial X to base antimicrobial B ($CRR_{B\leftarrow X}$), with the cross-resistance rates presented in cells arranged in a square matrix of lines and columns, with each line representing the corresponding base antimicrobial B and each column representing the corresponding antimicrobial X. Table 4 show cross-resistance rates by segment.

With the exception of AZT in segment b1, the cross-resistance rates of all β-lactams to AMK, GM, CPFX and LVFX were less than 50% throughout the entire period. In particular, the cross-resistance rates of PIPC, PIPC/TAZ, CAZ and CPZ/SBT to AMK, GM and CPFX were less than 30% at all times. Moreover, the mutual cross-resistance rates between AMK and PIPC, PIPC/TAZ and CPZ/SBT were less than 20% at all times.

The mutual cross-resistance rates between CPFX and LVFX were 75% or higher at all times. Additionally, $CRR_{MEPM\leftarrow IPM}$ was 70% or higher at all times, and $CRR_{AMK\leftarrow GM}$ was consistently 88% or higher. The rates of cross-resistance of the five antimicrobials belonging to the classes of penicillin and cephalosporin to CPZ/SBT, CFPM, IPM, MEPM and AZT decreased substantially from segments b2 to a1. In particular, the cross-resistance rates to CPZ/SBT and MEPM decreased by 30% or more. Furthermore, the cross-resistance rates to CPFX and LVFX decreased across the board, except for CPZ/SBT and fluoroquinolones. Meanwhile, the cross-resistance rates of fluoroquinolones to PIPC, PIPC/TAZ, CAZ and CPZ/SBT increased across the board.

The rates of cross-resistance of the five antimicrobials belonging to the classes of penicillin and cephalosporin to CPZ/SBT, CFPM, IPM, MEPM and AZT increased substantially from segments a1 to a2. In particular, the cross-resistance rates to CFPM increased by 40% or more, and those to CPZ/SBT increased by 28% or more. On the other hand, the cross-resistance rates of fluoroquinolones to PIPC, PIPC/TAZ, CAZ and CPZ/SBT decreased across the board.

3.3.2 | CRR diagrams

CRR diagrams plotted with CPZ/SBT as the base antimicrobial

Data from Table 4 were used to generate the CRR diagrams presented in Figure 3, which show changes over time in the cross-resistance rates of the base antimicrobial CPZ/SBT to each of the antimicrobial agents.

TABLE 3 Antimicrobial resistance rates by segment of data collection period

	Resistant rate in each segment (%) (resistant strains/total strains)				
Antimicrobial	**b1**	**b2**	**a1**	**a2**	**a3**
PIPC	6.1 (16/261)	9.9 (29/294)	1.8* (7/392)	4.9** (22/451)	4.1 (17/416)
PIPC/TAZ	2.7 (7/261)	6.1 (18/294)	0.5* (2/392)	3.5* (16/451)	3.4 (14/416)
CAZ	5.7 (15/261)	7.1 (21/294)	1.0* (4/392)	4.0** (18/451)	2.9 (12/416)
CPZ/SBT	7.7 (20/261)	8.8 (26/294)	3.6* (14/392)	5.8 (26/451)	4.8 (20/416)
CFPM	7.3 (19/261)	8.5 (25/294)	2.6* (10/392)	3.8 (17/451)	3.8 (16/416)
IPM	8.0 (21/261)	11.6 (34/294)	8.9 (35/392)	8.2 (37/451)	7.2 (30/416)
MEPM	5.7 (15/261)	6.5 (19/294)	5.4 (21/392)	5.5 (25/451)	3.1 (13/416)
AZT	11.9 (31/261)	13.9 (41/294)	6.6 (26/392)	10.0 (45/451)	10.8 (45/416)
AMK	6.9 (18/261)	5.8 (17/294)	2.8 (11/392)	2.0 (9/451)	1.2 (5/416)
GM	15.7 (41/261)	18.7 (55/294)	10.5** (41/392)	8.2 (37/451)	10.8 (45/416)
CPFX	11.1 (29/261)	7.1 (21/294)	4.6 (18/392)	5.3 (24/451)	4.8 (20/416)
LVFX	11.1 (29/261)	7.8 (23/294)	5.4 (21/392)	4.2 (19/451)	5.3 (22/416)

Note: b1 vs b2, b2 vs a1, a1 vs a2, a2 vs a3 tested by χ^2-test.
$P < .01$.*
$P < .05$**

The plotted data points for β-lactams PIPC/TAZ, AZT, CAZ and CFPM, except carbapenems, are closer to the upper right, indicating that these agents and CPZ/SBT are highly cross-resistant to each other, whereas those for carbapenems, aminoglycosides and fluoroquinolones are closer to the origin, indicating that the cross-resistance between these agents and CPZ/SBT is low.

Additionally, the plotted a1-data points for all non-carbapenem β-lactams are far away from other plotted data points, with the lines that connect the plotted data points from b2 through a1 to a2 forming an acute-angled wedge shape. This indicates that the cross-resistance of these agents changed significantly from b2 to a1 and then returned to a closer proximity to the original state at a2. In particular, the wedge shapes of CFPM and PIPC CAZ extend sharply and are elongated towards the origin, clearly showing that the cross-resistance between these agents and CPZ/SBT is decreased significantly at a1.

Regarding resistance rate, the following can be inferred from Figure 3. Over the entire experimental period, PIPC/TAZ, CAZ and CFPM data plots landed above the diagonal line, indicating that the resistance rates of these drugs were consistently lower than that of CPZ/SBT. On the other hand, data plots of AZT always fall below the diagonal line, implying that AZT was always more resistant than CPZ/SBT.

CRR diagrams for cephalosporins (CAZ, CFPM) with CPZ/SBT as the base antimicrobial

To closely examine changes in cross-resistance rates from the immediate post-relocation segment a1 to segment a2, monthly changes from segments a1 to a2 in cross-resistance rates of the base antimicrobial CPZ/SBT to CAZ and CFPM were plotted in the CRR diagrams shown in Figure 4. Changes in cross-resistance rates to both antimicrobial agents were large in the immediate post-relocation segment a1, but they became small after 4 or 5 months. In particular, the increases in cross-resistance rates of the two agents to CPZ/SBT levelled off, and the fluctuations in cross-resistance rates of CPZ/SBT to the two agents became the major changes.

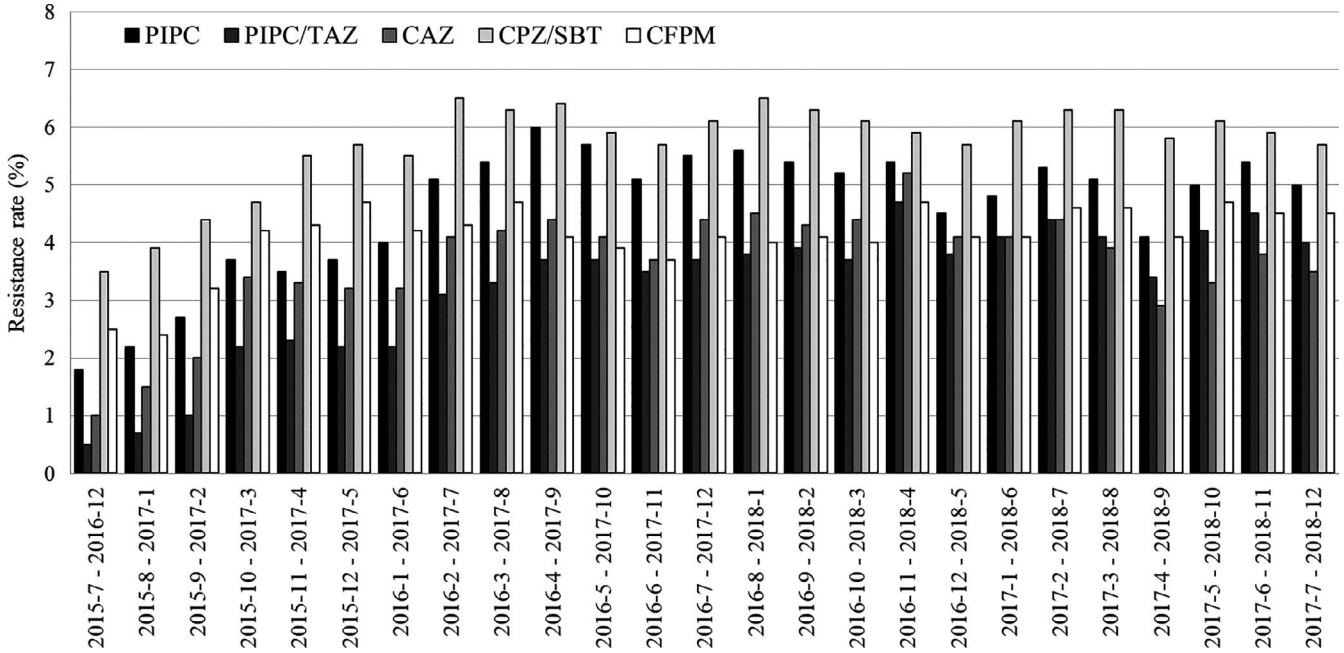

FIGURE 2 Post-relocation monthly changes in resistance rates to PIPC, PIPC/TAZ, CAZ, CPZ/SBT, and CFPM

CRR diagrams with CPFX as the base antimicrobial

Figure 5 shows CRR diagrams with CPFX as the base antimicrobial. Due to the crowded data points, only those in segments b2 and a1 were labelled to make them more easily identifiable.

The plotted data points for non-LVFX antimicrobial agents are close to the origin. The plotted data points for PIPC/TAZ and CAZ in segments b2-a1-a2, respectively, form a large wedge shape.

With respect to IPM and MEPM, the plotted data points for resistance rates in different time segments generally shifted along the diagonal line, and the shifts from b2 to a1 are along the diagonal line towards the origin. The data on AMK and GM showed no common shift. Changes with regard to LVFX showed a shift nearly perpendicular to the diagonal line.

4 | DISCUSSION

4.1 | Resistance rates

After moving to a new building located in a different medical care zone, the Sakai City Medical Center has been serving a patient population that includes few of the patients it used to serve. Thus, the bacterial flora in and around the hospital is believed to have changed drastically immediately after the relocation. Meanwhile, *P aeruginosa* is widely present in moist environments in the hospital. The hands of hospital staff are often the vehicle for its transmission. Furthermore, bacteria are said to be carried around by hospital staff, patients and equipment, among other things.[6-8] The Sakai City Medical Center is no different. The bacterial flora carried from the old facility presumably came in contact and intermingled with those present in the new environment or brought in by the patients, resulting in mutual dilution and interactions.

Part of such a phenomenon can be seen in the changes over time in the antimicrobial resistance rates shown in Table 3 and Figure 2. A comparison of resistance rates between segments b1 and b2 and segment a1 showed that the resistance of *P aeruginosa* to each antibiotic was generally higher around the hospital facility before the relocation than around the new location. With the flora mixed with low-resistance strains of *P aeruginosa* in the new environment right after the relocation, the resistance rates to almost all antimicrobial agents decreased as reflected in the resistance rates in segment a1. Over time, the exposure to the selection pressure from the antibiotics used in the hospital and the acquisition of resistance passed from the resistant strains carried from the old hospital by people or equipment resulted in the changes in resistance rate seen in segments a2 and a3.

In particular, the post-relocation resistance rates to non-carbapenem β-lactams decreased substantially and then increased to approximately 50% of the prerelocation rates over the next 3-6 months.

These data indicated that the spread of the ability to produce β-lactamase played a major role in the increases in resistance rates in association with the hospital relocation.

Additionally, the absence of any substantial effects from the facility's relocation on the resistance rates to aminoglycosides and fluoroquinolones suggested that the spread or acquisition of a mechanism of resistance to these antimicrobial agents is rare.

4.2 | Cross-resistance rate

Generally, cross-resistance is known to occur between drugs similar in chemical structure or mechanism of action.[9] The present research also confirmed low cross-resistance rates of antimicrobials with a different mechanism of action to each other and high cross-resistance

TABLE 4 Cross-resistance rates by segment

b1 (2013-01-01 ~ 2014-06-30)												
	Cross-resistant rate (%) to base antimicrobial (resistant strains/total strains)											
Base antimicrobial	PIPC	PIPC/TAZ	CAZ	CPZ/SBT	CFPM	IPM	MEPM	AZT	AMK	GM	CPFX	LVFX
PIPC	–	37.5 (6/16)	62.5 (10/16)	68.8 (11/16)	50 (8/16)	43.8 (7/16)	43.8 (7/16)	81.3 (13/16)	18.8 (3/16)	50 (8/16)	31.3 (5/16)	50 (8/16)
PIPC/TAZ	85.7 (6/7)	–	100 (7/7)	71.4 (5/7)	71.4 (5/7)	42.9 (3/7)	42.9 (3/7)	85.7 (6/7)	0 (0/7)	42.9 (3/7)	28.6 (2/7)	57.1 (4/7)
CAZ	66.7 (10/15)	46.7 (7/15)	–	73.3 (11/15)	53.3 (8/15)	40 (6/15)	40 (6/15)	73.3 (11/15)	20 (3/15)	46.7 (7/15)	40 (6/15)	60 (9/15)
CPZ/SBT	55 (11/20)	25 (5/20)	55 (11/20)	–	45 (9/20)	30 (6/20)	35 (7/20)	85 (17/20)	15 (3/20)	40 (8/20)	40 (8/20)	60 (12/20)
CFPM	42.1 (8/19)	26.3 (5/19)	42.1 (8/19)	47.4 (9/19)	–	21.1 (4/19)	26.3 (5/19)	52.6 (10/19)	42.1 (8/19)	68.4 (13/19)	63.2 (12/19)	73.7 (14/19)
IPM	33.3 (7/21)	14.3 (3/21)	28.6 (6/21)	28.6 (6/21)	19 (4/21)	–	52.4 (11/21)	33.3 (7/21)	19 (4/21)	33.3 (7/21)	28.6 (6/21)	33.3 (7/21)
MEPM	46.7 (7/15)	20 (3/15)	40 (6/15)	46.7 (7/15)	33.3 (5/15)	73.3 (11/15)	–	40 (6/15)	26.7 (4/15)	46.7 (7/15)	46.7 (7/15)	46.7 (7/15)
AZT	41.9 (13/31)	19.4 (6/31)	35.5 (11/31)	54.8 (17/31)	32.3 (10/31)	22.6 (7/31)	19.4 (6/31)	–	16.1 (5/31)	32.3 (10/31)	35.5 (11/31)	48.4 (15/31)
AMK	16.7 (3/18)	0 (0/18)	16.7 (3/18)	16.7 (3/18)	44.4 (8/18)	22.2 (4/18)	22.2 (4/18)	27.8 (5/18)	–	94.4 (17/18)	50 (9/18)	44.4 (8/18)
GM	19.5 (8/41)	7.3 (3/41)	17.1 (7/41)	19.5 (8/41)	31.7 (13/41)	17.1 (7/41)	17.1 (7/41)	24.4 (10/41)	41.5 (17/41)	–	24.4 (10/41)	26.8 (11/41)
CPFX	17.2 (5/29)	6.9 (2/29)	20.7 (6/29)	27.6 (8/29)	41.4 (12/29)	20.7 (6/29)	24.1 (7/29)	37.9 (11/29)	31 (9/29)	34.5 (10/29)	–	86.2 (25/29)
LVFX	27.6 (8/29)	13.8 (4/29)	31 (9/29)	41.4 (12/29)	48.3 (14/29)	24.1 (7/29)	24.1 (7/29)	51.7 (15/29)	27.6 (8/29)	37.9 (11/29)	86.2 (25/29)	–
b2 (2014-01-01 ~ 2015-06-30)												
	Cross-resistant rate (%) to base antimicrobial (resistant strains/ total strains)											
Base antimicrobial	PIPC	PIPC/TAZ	CAZ	CPZ/SBT	CFPM	IPM	MEPM	AZT	AMK	GM	CPFX	LVFX
PIPC	–	58.6 (17/29)	58.6 (17/29)	72.4 (21/29)	55.2 (16/29)	34.5 (10/29)	34.5 (10/29)	75.9 (22/29)	6.9 (2/29)	34.5 (10/29)	20.7 (6/29)	27.6 (8/29)
PIPC/TAZ	94.4 (17/18)	–	88.9 (16/18)	88.9 (16/18)	66.7 (12/18)	38.9 (7/18)	38.9 (7/18)	88.9 (16/18)	0 (0/18)	27.8 (5/18)	11.1 (2/18)	16.7 (3/18)
CAZ	81 (17/21)	76.2 (16/21)	–	76.2 (16/21)	61.9 (13/21)	33.3 (7/21)	33.3 (7/21)	81 (17/21)	9.5 (2/21)	28.6 (6/21)	19 (4/21)	23.8 (5/21)
CPZ/SBT	80.8 (21/26)	61.5 (16/26)	61.5 (16/26)	–	57.7 (15/26)	34.6 (9/26)	38.5 (10/26)	92.3 (24/26)	7.7 (2/26)	38.5 (10/26)	15.4 (4/26)	19.2 (5/26)
CFPM	64 (16/25)	48 (12/25)	52 (13/25)	60 (15/25)	–	36 (9/25)	28 (7/25)	68 (17/25)	28 (7/25)	64 (16/25)	40 (10/25)	44 (11/25)

(Continues)

TABLE 4 (Continued)

b2 (2014-01-01 ~ 2015-06-30)

Base antimicrobial	Cross-resistant rate (%) to base antimicrobial (resistant strains/ total strains)											
	PIPC	PIPC/ TAZ	CAZ	CPZ/ SBT	CFPM	IPM	MEPM	AZT	AMK	GM	CPFX	LVFX
IPM	29.4 (10/34)	20.6 (7/34)	20.6 (7/34)	26.5 (9/34)	26.5 (9/34)	–	44.1 (15/34)	38.2 (13/34)	14.7 (5/34)	41.2 (14/34)	8.8 (3/34)	11.8 (4/34)
MEPM	52.6 (10/19)	36.8 (7/19)	36.8 (7/19)	52.6 (10/19)	36.8 (7/19)	78.9 (15/19)	–	47.4 (9/19)	15.8 (3/19)	52.6 (10/19)	15.8 (3/19)	15.8 (3/19)
AZT	53.7 (22/41)	39 (16/41)	41.5 (17/41)	58.5 (24/41)	41.5 (17/41)	31.7 (13/41)	22 (9/41)	–	12.2 (5/41)	39 (16/41)	17.1 (7/41)	22 (9/41)
AMK	11.8 (2/17)	0 (0/17)	11.8 (2/17)	11.8 (2/17)	41.2 (7/17)	29.4 (5/17)	17.6 (3/17)	29.4 (5/17)	–	88.2 (15/17)	47.1 (8/17)	47.1 (8/17)
GM	18.2 (10/55)	9.1 (5/55)	10.9 (6/55)	18.2 (10/55)	29.1 (16/55)	25.5 (14/55)	18.2 (10/55)	29.1 (16/55)	27.3 (15/55)	–	18.2 (10/55)	21.8 (12/55)
CPFX	28.6 (6/21)	9.5 (2/21)	19 (4/21)	19 (4/21)	47.6 (10/21)	14.3 (3/21)	14.3 (3/21)	33.3 (7/21)	38.1 (8/21)	47.6 (10/21)	–	90.5 (19/21)
LVFX	34.8 (8/23)	13 (3/23)	21.7 (5/23)	21.7 (5/23)	47.8 (11/23)	17.4 (4/23)	13 (3/23)	39.1 (9/23)	34.8 (8/23)	52.2 (12/23)	82.6 (19/23)	–

a1 (2015-07-01 ~ 2016-12-31)

Base antimicrobial	Cross-resistant rate (%) to base antimicrobial (resistant strains/ total strains)											
	PIPC	PIPC/ TAZ	CAZ	CPZ/ SBT	CFPM	IPM	MEPM	AZT	AMK	GM	CPFX	LVFX
PIPC	–	28.6 (2/7)	42.9 (3/7)	42.9 (3/7)	42.9 (3/7)	42.9 (3/7)	28.6 (2/7)	57.1 (4/7)	14.3 (1/7)	28.6 (2/7)	28.6 (2/7)	42.9 (3/7)
PIPC/TAZ	100 (2/2)	–	100 (2/2)	100 (2/2)	100 (2/2)	0 (0/2)	0 (0/2)	100 (2/2)	0 (0/2)	50 (1/2)	50 (1/2)	100 (2/2)
CAZ	75 (3/4)	50 (2/4)	–	50 (2/4)	75 (3/4)	25 (1/4)	25 (1/4)	75 (3/4)	50 (2/4)	50 (2/4)	50 (2/4)	75 (3/4)
CPZ/SBT	21.4 (3/14)	14.3 (2/14)	14.3 (2/14)	–	21.4 (3/14)	35.7 (5/14)	28.6 (4/14)	71.4 (10/14)	7.1 (1/14)	21.4 (3/14)	28.6 (4/14)	42.9 (6/14)
CFPM	30 (3/10)	20 (2/10)	30 (3/10)	30 (3/10)	–	10 (1/10)	10 (1/10)	40 (4/10)	30 (3/10)	80 (8/10)	30 (3/10)	40 (4/10)
IPM	8.6 (3/35)	0 (0/35)	2.9 (1/35)	14.3 (5/35)	2.9 (1/35)	–	60 (21/35)	17.1 (6/35)	8.6 (3/35)	17.1 (6/35)	5.7 (2/35)	8.6 (3/35)
MEPM	9.5 (2/21)	0 (0/21)	4.8 (1/21)	19 (4/21)	4.8 (1/21)	100 (21/21)	–	28.6 (6/21)	9.5 (2/21)	9.5 (2/21)	4.8 (1/21)	9.5 (2/21)
AZT	15.4 (4/26)	7.7 (2/26)	11.5 (3/26)	38.5 (10/26)	15.4 (4/26)	23.1 (6/26)	23.1 (6/26)	–	7.7 (2/26)	23.1 (6/26)	19.2 (5/26)	26.9 (7/26)
AMK	9.1 (1/11)	0 (0/11)	18.2 (2/11)	9.1 (1/11)	27.3 (3/11)	27.3 (3/11)	18.2 (2/11)	18.2 (2/11)	–	90.9 (10/11)	54.5 (6/11)	54.5 (6/11)
GM	4.9 (2/41)	2.4 (1/41)	4.9 (2/41)	7.3 (3/41)	19.5 (8/41)	14.6 (6/41)	4.9 (2/41)	14.6 (6/41)	24.4 (10/41)	–	19.5 (8/41)	19.5 (8/41)

(Continues)

TABLE 4 (Continued)

a1 (2015-07-01 ~ 2016-12-31)

Base antimicrobial	Cross-resistant rate (%) to base antimicrobial (resistant strains/ total strains)											
	PIPC	PIPC/TAZ	CAZ	CPZ/SBT	CFPM	IPM	MEPM	AZT	AMK	GM	CPFX	LVFX
CPFX	11.1 (2/18)	5.6 (1/18)	11.1 (2/18)	22.2 (4/18)	16.7 (3/18)	11.1 (2/18)	5.6 (1/18)	27.8 (5/18)	33.3 (6/18)	44.4 (8/18)	–	88.9 (16/18)
LVFX	14.3 (3/21)	9.5 (2/21)	14.3 (3/21)	28.6 (6/21)	19 (4/21)	14.3 (3/21)	9.5 (2/21)	33.3 (7/21)	28.6 (6/21)	38.1 (8/21)	76.2 (16/21)	–

a2 (2016-07-01 ~ 2017-12-31)

Base antimicrobial	Cross-resistant rate (%) to base antimicrobial (resistant strains/ total strains)											
	PIPC	PIPC/TAZ	CAZ	CPZ/SBT	CFPM	IPM	MEPM	AZT	AMK	GM	CPFX	LVFX
PIPC	–	68.2 (15/22)	68.2 (15/22)	63.6 (14/22)	59.1 (13/22)	36.4 (8/22)	36.4 (8/22)	72.7 (16/22)	4.5 (1/22)	22.7 (5/22)	22.7 (5/22)	27.3 (6/22)
PIPC/TAZ	93.8 (15/16)	–	87.5 (14/16)	81.3 (13/16)	75 (12/16)	43.8 (7/16)	37.5 (6/16)	75 (12/16)	0 (0/16)	25 (4/16)	18.8 (3/16)	18.8 (3/16)
CAZ	83.3 (15/18)	77.8 (14/18)	–	66.7 (12/18)	66.7 (12/18)	38.9 (7/18)	33.3 (6/18)	72.2 (13/18)	11.1 (2/18)	27.8 (5/18)	16.7 (3/18)	16.7 (3/18)
CPZ/SBT	53.8 (14/26)	50 (13/26)	46.2 (12/26)	–	50 (13/26)	46.2 (12/26)	34.6 (9/26)	76.9 (20/26)	3.8 (1/26)	23.1 (6/26)	15.4 (4/26)	19.2 (5/26)
CFPM	76.5 (13/17)	70.6 (12/17)	70.6 (12/17)	76.5 (13/17)	–	52.9 (9/17)	47.1 (8/17)	82.4 (14/17)	17.6 (3/17)	35.3 (6/17)	35.3 (6/17)	35.3 (6/17)
IPM	21.6 (8/37)	18.9 (7/37)	18.9 (7/37)	32.4 (12/37)	24.3 (9/37)	–	64.9 (24/37)	29.7 (11/37)	8.1 (3/37)	32.4 (12/37)	18.9 (7/37)	16.2 (6/37)
MEPM	32 (8/25)	24 (6/25)	24 (6/25)	36 (9/25)	32 (8/25)	96 (24/25)	–	36 (9/25)	12 (3/25)	28 (7/25)	16 (4/25)	16 (4/25)
AZT	35.6 (16/45)	26.7 (12/45)	28.9 (13/45)	44.4 (20/45)	31.1 (14/45)	24.4 (11/45)	20 (9/45)	–	4.4 (2/45)	13.3 (6/45)	11.1 (5/45)	13.3 (6/45)
AMK	11.1 (1/9)	0 (0/9)	22.2 (2/9)	11.1 (1/9)	33.3 (3/9)	33.3 (3/9)	33.3 (3/9)	22.2 (2/9)	–	88.9 (8/9)	44.4 (4/9)	44.4 (4/9)
GM	13.5 (5/37)	10.8 (4/37)	13.5 (5/37)	16.2 (6/37)	16.2 (6/37)	32.4 (12/37)	18.9 (7/37)	16.2 (6/37)	21.6 (8/37)	–	16.2 (6/37)	16.2 (6/37)
CPFX	20.8 (5/24)	12.5 (3/24)	12.5 (3/24)	16.7 (4/24)	25 (6/24)	29.2 (7/24)	16.7 (4/24)	20.8 (5/24)	16.7 (4/24)	25 (6/24)	–	75 (18/24)
LVFX	31.6 (6/19)	15.8 (3/19)	15.8 (3/19)	26.3 (5/19)	31.6 (6/19)	31.6 (6/19)	21.1 (4/19)	31.6 (6/19)	21.1 (4/19)	31.6 (6/19)	94.7 (18/19)	–

(Continues)

TABLE 4 (Continued)

a3 (2017-07-01 ~ 2018-12-31)												
	Cross-resistant rate (%) to base antimicrobial (resistant strains/ total strains)											
Base antimicrobial	PIPC	PIPC/TAZ	CAZ	CPZ/SBT	CFPM	IPM	MEPM	AZT	AMK	GM	CPFX	LVFX
PIPC	–	64.7 (11/17)	64.7 (11/17)	64.7 (11/17)	70.6 (12/17)	35.3 (6/17)	29.4 (5/17)	70.6 (12/17)	5.9 (1/17)	29.4 (5/17)	23.5 (4/17)	23.5 (4/17)
PIPC/TAZ	78.6 (11/14)	–	71.4 (10/14)	71.4 (10/14)	64.3 (9/14)	35.7 (5/14)	28.6 (4/14)	71.4 (10/14)	0 (0/14)	21.4 (3/14)	14.3 (2/14)	14.3 (2/14)
CAZ	91.7 (11/12)	83.3 (10/12)	–	83.3 (10/12)	75 (9/12)	33.3 (4/12)	25 (3/12)	75 (9/12)	0 (0/12)	16.7 (2/12)	8.3 (1/12)	8.3 (1/12)
CPZ/SBT	55 (11/20)	50 (10/20)	50 (10/20)	–	50 (10/20)	40 (8/20)	30 (6/20)	95 (19/20)	0 (0/20)	25 (5/20)	15 (3/20)	15 (3/20)
CFPM	75 (12/16)	56.3 (9/16)	56.3 (9/16)	62.5 (10/16)	–	37.5 (6/16)	31.3 (5/16)	75 (12/16)	12.5 (2/16)	56.3 (9/16)	31.3 (5/16)	31.3 (5/16)
IPM	20 (6/30)	16.7 (5/30)	13.3 (4/30)	26.7 (8/30)	20 (6/30)	–	43.3 (13/30)	33.3 (10/30)	3.3 (1/30)	23.3 (7/30)	20 (6/30)	23.3 (7/30)
MEPM	38.5 (5/13)	30.8 (4/13)	23.1 (3/13)	46.2 (6/13)	38.5 (5/13)	100 (13/13)	–	53.8 (7/13)	0 (0/13)	38.5 (5/13)	30.8 (4/13)	30.8 (4/13)
AZT	26.7 (12/45)	22.2 (10/45)	20 (9/45)	42.2 (19/45)	26.7 (12/45)	22.2 (10/45)	15.6 (7/45)	–	0 (0/45)	20 (9/45)	13.3 (6/45)	17.8 (8/45)
AMK	20 (1/5)	0 (0/5)	0 (0/5)	0 (0/5)	40 (2/5)	20 (1/5)	0 (0/5)	0 (0/5)	–	100 (5/5)	40 (2/5)	40 (2/5)
GM	11.1 (5/45)	6.7 (3/45)	4.4 (2/45)	11.1 (5/45)	20 (9/45)	15.6 (7/45)	11.1 (5/45)	20 (9/45)	11.1 (5/45)	–	13.3 (6/45)	13.3 (6/45)
CPFX	20 (4/20)	10 (2/20)	5 (1/20)	15 (3/20)	25 (5/20)	30 (6/20)	20 (4/20)	30 (6/20)	10 (2/20)	30 (6/20)	–	95 (19/20)
LVFX	18.2 (4/22)	9.1 (2/22)	4.5 (1/22)	13.6 (3/22)	22.7 (5/22)	31.8 (7/22)	18.2 (4/22)	36.4 (8/22)	9.1 (2/22)	27.3 (6/22)	86.4 (19/22)	–

rates of antimicrobials with the same or similar mechanism of action to each other. This was also confirmed by the CRR diagrams showing that plotted data points for antimicrobials with a different mechanism of action are closer to the origin, and those for antimicrobials with a similar mechanism of action are closer to the upper right corner.

The effect of hospital relocation on *P aeruginosa* flora was also confirmed by changes in cross-resistance rates, just as with resistance rates, and the effect was particularly strong on the cross-resistance rates of β-lactams, with cross-resistance rates of β-lactams to each other decreased substantially, but temporarily. However, the cross-resistance rates between classes of antimicrobials with a different mechanism of action showed no substantial changes.

The temporary decreases in cross-resistance rates of β-lactams to each other appeared as large wedge-shaped plots of segments b2, a1 and a2 on CRR diagrams. In particular, the large wedge shapes formed by data points from segments b2, a1 and a2 for CAZ, CFPM and PIPC/TAZ on the CRR diagram with CPZ/SBT as the base antimicrobial pointed to the origin and allowed easy visualization of the decreases in cross-resistance rates of CPZ/SBT to these antimicrobials.

5 | CONCLUSIONS

Including cross-resistance rates in the routine monitoring of resistance rates (susceptibility rates) practiced now by medical institutions can provide a comprehensive insight into changes in the bacterial flora in a facility.

When monitoring cross-resistance rates, the only way to get a full picture is to present data in a two-dimensional matrix such as those shown in Table 2, since cross-resistance rates involve multiple antimicrobial agents. However, it is difficult to discern any trend from row upon row of numbers provided in two-dimensional matrices. Neither are such matrices suitable for tracing temporal changes.

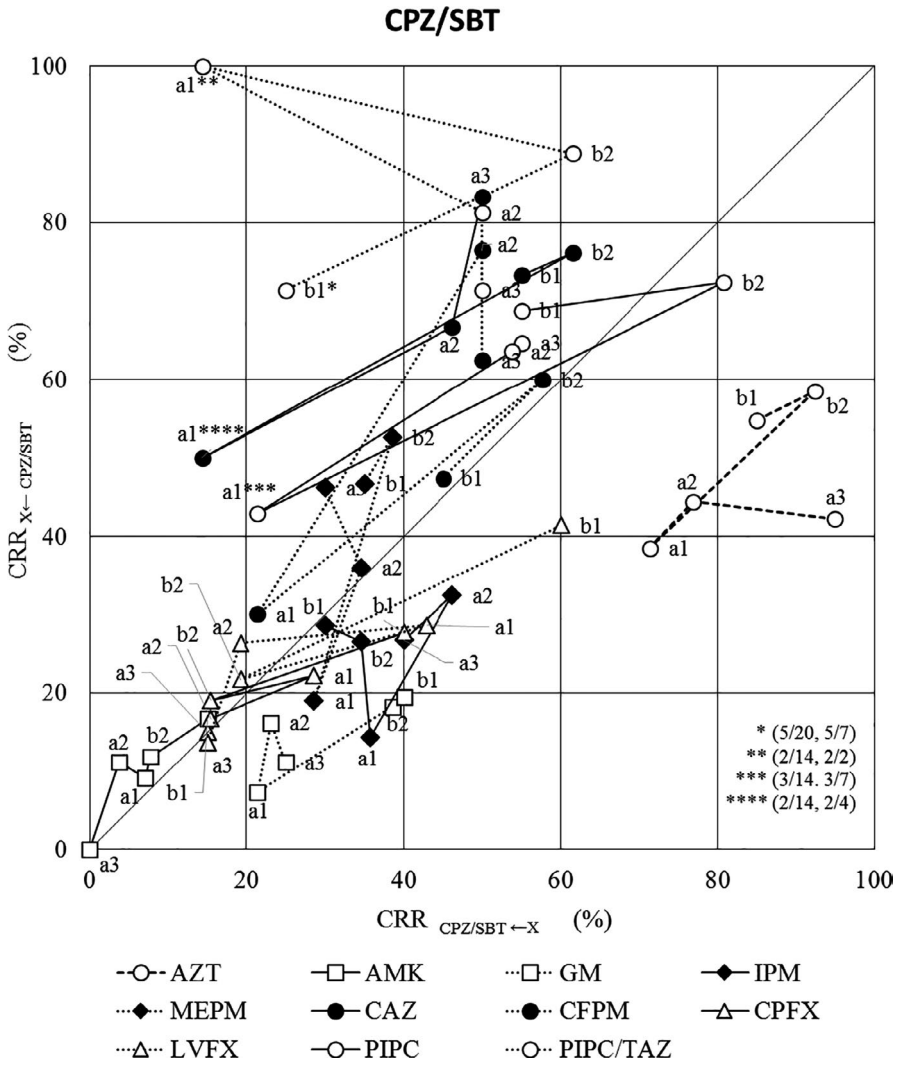

FIGURE 3 CRR diagrams by segment, with CPZ/SBT as the base antimicrobial

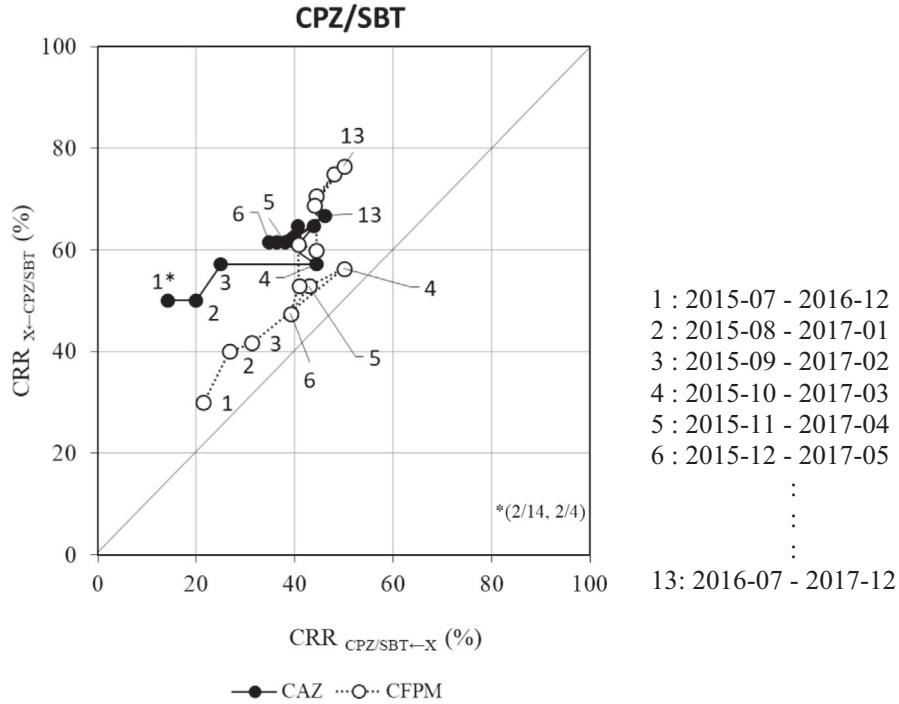

FIGURE 4 CRR diagrams for CAZ and CFPM from segments a1 to a2 by month, with CPZ/SBT as the base antimicrobial

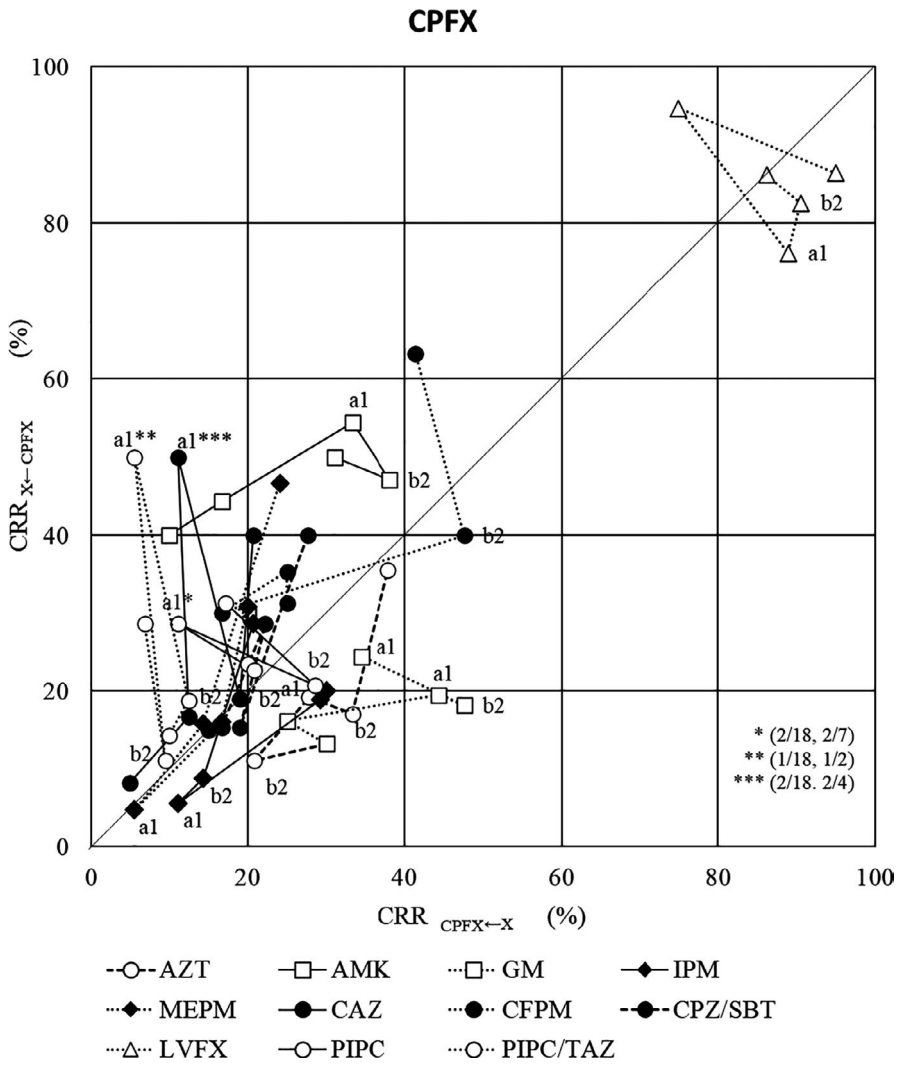

FIGURE 5 CRR diagrams by segment, with CPFX as the base antimicrobial

The CRR diagrams that were proposed allow presentation of the statuses of and temporal changes in cross-resistance between the base antimicrobial and multiple antimicrobial agents.

Correlation diagrams allow visualization of the status of and changes in cross-resistance. They can provide a new perspective for clinicians, contribute to the proper use of antibiotics and serve as a tool in the education of healthcare professionals and students about antibiotic resistance.

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CONFLICT OF INTEREST

None declared.

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