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ORIGINAL ARTICLE

A multicenter surveillance of antimicrobial resistance in *Serratia marcescens* in Taiwan



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Surveillance of Antimicrobial Resistance (TSAR) Hospitals

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Background: *Serratia marcescens* is an important nosocomial pathogen and the characteristic property of resistance conferred by extended-spectrum beta-lactamase or a novel AmpC cephalosporinase was not unusual in Taiwan. This study investigated the trends in antimicrobial resistance in *S. marcescens* from a nationwide surveillance in Taiwan.

Materials and methods: *S. marcescens* isolates were collected biennially between 2002 and 2010 from medical centers and regional hospitals throughout Taiwan, as part of the Taiwan Surveillance of Antimicrobial Resistance program. Minimal inhibitory concentrations were determined by the Clinical and Laboratory Standards Institute reference broth microdilution method.

Results: A total of 403 nonduplicate *S. marcescens* isolates were collected, mostly from respiratory samples (157, 39.0%), followed by the urinary tract samples (90, 22.3%). Overall, 99.3% isolates were susceptible to imipenem, 93.8% to ceftazidime, 89.2% to minocycline, 87.8% to amikacin, 86.8% to cefepime, 82.9% to aztreonam, 73.2% to ceftriaxone, 72.7% to levofloxacin, 63.8% to ciprofloxacin, 60.8% to trimethoprim/sulfamethoxazole (TMP/SMX), and 59.6% to gentamicin. A significantly increased susceptibility rate after 2004 was observed for the following antibiotics: amikacin (73.8% vs. 97.1%), gentamicin (40.0% vs. 72.4%), ciprofloxacin

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(53.8% vs. 70.4%), ceftriaxone (53.8% vs. 86.0%), cefepime (74.4% vs. 95.1%), aztreonam (72.5% vs. 89.7%), and TMP/SMX (41.3% vs. 73.7%).

Conclusion: In this 8-year study, the susceptibility of *S. marcescens* to ceftazidime and imipenem remained consistently high in Taiwan. *S. marcescens* isolates demonstrated relatively higher resistance to ciprofloxacin and levofloxacin, and therefore continued surveillance of antimicrobial resistance, especially for fluoroquinolone, is warranted.

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Introduction

Serratia species are identified as aerobic, motile Gram-negative rods, which occupy various habitats (mainly water, plants, and soil). Human infections by members of the genus *Serratia* were not well recognized until the latter half of the 20th century.¹ *Serratia marcescens* accounts for the majority of isolates and appears to be a pathogen capable of causing a wide spectrum of clinical diseases, including wound infections, urinary tract infections, pneumonia, central nervous system infections such as meningitis, and bloodstream infections.^{1–6} Although *S. marcescens* is a rare cause of community-acquired infections, it has emerged as an important nosocomial pathogen that has been cultured from a variety of sources, including disinfectants,^{7–9} pressure transducers,¹⁰ bronchoscopes,¹¹ and multidose medication vials.¹² Factors such as debilitating clinical condition, lengthy ward stay, exposure to medical interventions, and increased frequency and intensity of direct contact with staff hands predispose patients to *S. marcescens* infection. *S. marcescens* isolates account for 12.6% of nosocomial urinary tract infection and resulted in 4.86% fatality in a single institute in Taiwan.¹³ Although *S. marcescens* has a relatively low virulence, it often causes nosocomial infections in severely immunocompromised or critically ill patients.^{1,2} The mortality rate of *S. marcescens* bacteremia was approximately 40–50% in previous studies.^{14,15}

S. marcescens is usually resistant to ampicillin, amoxicillin, amoxicillin/clavulanate, ampicillin/sulbactam, narrow-spectrum cephalosporins, cefuroxime, cephamycins, nitrofurantoin, and colistin.^{1,16–18} *S. marcescens* also harbors a chromosomal *ampC* gene that can extend resistance to several more β -lactam antibiotics.¹ In a nationwide surveillance of antimicrobial resistance from Taiwan in 2000, over half (52%) of *S. marcescens* were resistant to ciprofloxacin, 48%, 24%, and 23% were resistant to cefotaxime, aztreonam, and cefepime, respectively.¹⁹ However, many studies in recent years suggested that the occurrence of extended-spectrum beta-lactamase (ESBL)-producing isolates of *S. marcescens* was not unusual in Taiwan.^{17,18,20–22} In addition, an institutional prolonged spread of clonally related *S. marcescens* isolates with a novel AmpC cephalosporinase (S4) that confers a phenotype of resistance to cefotaxime was identified.²³ Therefore, continuous and extensive surveillance of the antimicrobial resistance among *S. marcescens* isolates is necessary in Taiwan. The aim of this study was to investigate the trends

in antimicrobial resistance in *S. marcescens* from a nationwide surveillance in Taiwan.

Materials and methods

Isolate collection and identification

S. marcescens isolates were collected biennially between 2002 and 2010, corresponding to periods III–VII of the Taiwan Surveillance of Antimicrobial Resistance (TSAR) program, from medical centers and regional hospitals throughout Taiwan. In 2002, 2004, 2008, and 2010, isolates were collected between July and September from the same 26 hospitals, except that isolates in 2006 were from 25 hospitals.^{24,25} These hospitals comprised 11 medical centers and 15 regional hospitals, which are located in all four regions of Taiwan, namely seven, eight, eight, and three hospitals in the north, central, south, and east regions, respectively. Details of the collection process of the TSAR program have been described previously.^{19,24,25} Each isolate was subcultured onto the appropriate agar plates (BBL; Becton Dickinson Microbiology Systems, Cockeysville, MD, USA) to check for purity. *S. marcescens* was identified by standard conventional biochemical tests followed by confirmation with the VITEK Gram-negative Identification plus cards (bioMérieux VITEK, Hazelwood, MO, USA), and analytical profile index (API) 20E or API 32GN (bioMérieux, Marcy-l'Etoile, France).

Antimicrobial susceptibility testing

Antimicrobial susceptibility was determined by the reference broth microdilution method using freshly prepared cation-adjusted Mueller–Hinton broth and following the criteria proposed by the Clinical and Laboratory Standards Institute (CLSI).²⁶ Minimum inhibitory concentration (MIC) interpretive criteria were defined by the CLSI guidelines for all drugs except tigecycline, for which the U.S. Food and Drug Administration breakpoints were used.

Statistical analyses

All analyses were performed with SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). Significance of differences in frequencies and proportions were tested by Pearson χ^2 test, and $p \leq 0.05$ was considered to be statically significant.

Table 1 Source breakdown of 403 *Serratia marcescens* isolates by year, hospital type, geographic region, specimen type, and patient location

Source category	Number (% of source category) of isolates from each year					Total
	III (2002)	IV (2004)	V (2006)	VI (2008)	VII (2010)	
TSAR						
Total	95	65	71	88	84	403
Hospital type						
Medical center	33 (34.7)	35 (53.8)	32 (45.1)	39 (44.3)	38 (45.2)	177 (43.9)
Regional hospital	62 (65.3)	30 (46.2)	39 (54.9)	49 (55.7)	46 (54.8)	226 (56.1)
Region of Taiwan						
Northern	34 (35.8)	17 (26.2)	24 (33.8)	41 (46.6)	38 (45.2)	154 (38.2)
Central	28 (29.5)	29 (44.6)	21 (29.6)	31 (35.2)	23 (27.4)	132 (32.8)
Southern	18 (18.9)	16 (24.6)	22 (31.0)	14 (15.9)	20 (23.8)	90 (22.3)
Eastern	15 (15.8)	3 (4.6)	4 (5.6)	2 (2.3)	3 (3.6)	27 (6.7)
Specimen type						
Blood	20 (21.1)	10 (15.4)	8 (11.3)	19 (21.6)	20 (23.8)	77 (19.1)
Respiratory tract	29 (30.5)	19 (29.2)	32 (45.1)	39 (44.3)	38 (45.2)	157 (39.0)
Urine	31 (32.6)	21 (32.3)	19 (26.8)	10 (11.4)	9 (10.7)	90 (22.3)
Pus/abscess/wound	12 (12.6)	15 (23.1)	7 (9.9)	12 (13.6)	12 (14.3)	58 (14.4)
Others ^a	3 (3.2)	0 (0.0)	5 (7.0)	8 (9.1)	5 (6.0)	21 (5.2)
Patient location						
ICU inpatient	18 (18.9)	13 (20.0)	22 (31.0)	19 (21.6)	21 (25.0)	93 (23.1)
Non-ICU inpatient ^b	68 (71.6)	38 (58.5)	34 (47.9)	57 (64.8)	55 (65.5)	252 (62.5)
OPD/ER	9 (9.5)	14 (21.5)	15 (21.1)	12 (13.6)	8 (9.5)	58 (14.4)

^a Others: one from ascites, one from joints, two from bile, four from ears, seven from catheter tips, four from eyes/conjunctiva/corneas, one from urethra, and one from discharge.

^b Included six isolates from respiratory care center/respiratory care ward.

ER = emergency room; ICU = intensive care unit; OPD = outpatient department; TSAR = Taiwan Surveillance of Antimicrobial Resistance program.

Data are presented as *n* (%).

Results

A total of 403 nonduplicate *S. marcescens* isolates were identified and tested for susceptibility during the 8-year study period of 2002–2010. Table 1 summarizes the source breakdown of the 403 isolates from each run of TSAR. Isolates were mostly recovered from respiratory samples (157 isolates, 39.0%), followed by the urinary tract (90, 22.3%), and blood (77, 19.1%). Most isolates (345, 85.6%) were from inpatients, including 93 (23.1%) from the intensive care unit (ICU) and 252 (62.5%) from non-ICU patients. Isolates from northern Taiwan comprised the largest proportion (154, 38.2%). Among the 390 isolates whose patient age was known, the mean age was 65.4 ± 20.5 years and 60.25% were from those aged ≥65 years.

The *in vitro* susceptibilities, MIC₅₀, MIC₉₀ (MIC at which 50% and 90% of isolates were inhibited), and MIC range of the isolates to various antimicrobial agents are shown in Table 2. Overall, 99.3% of isolates were susceptible to imipenem, 93.8% to ceftazidime, 86.0% to piperacillin/tazobactam, 72.7% to levofloxacin, 63.8% to ciprofloxacin, 60.8% to trimethoprim/sulfamethoxazole (TMP/SMX), and 59.6% to gentamicin according to the CLSI criteria. By contrast, susceptibility of ≤10% for each round of TSAR was observed for ampicillin, amoxicillin/clavulanate, cefazolin, ceftiofur, cefuroxime, and tetracycline. The MIC₅₀ and MIC₉₀ of tigecycline were 0.5 µg/mL and 1 µg/mL, respectively. The susceptibility rate of *S. marcescens* from

different patient locations was compared (Table 3). Isolates from the ICU had higher rates of nonsusceptibility than isolates from other locations for amikacin, gentamicin, ciprofloxacin, levofloxacin, ceftazidime, cefepime, and TMP/SMX, but the differences were not significant. The susceptibility rate to ciprofloxacin/levofloxacin was lower in northern Taiwan than other regions (*p* = 0.025 and *p* = 0.002, respectively).

Fig. 1 illustrates the comparison of susceptibility rate for selected antibiotics from different specimen sources. We found that isolates from urine had the lowest susceptibility rate for the various antibiotics. Isolates from urine were significantly less susceptible than those from nonurine sources for amikacin (64.4% vs. 94.6%, *p* < 0.001), gentamicin (38.9% vs. 65.5%, *p* < 0.001), ciprofloxacin (46.7% vs. 68.7%, *p* < 0.001), ceftriaxone (41.1% vs. 82.4%, *p* < 0.001), cefepime (65.6% vs. 93.0%, *p* < 0.001), aztreonam (61.1% vs. 89.1%, *p* < 0.001), and TMP/SMX (37.8% vs. 67.4%, *p* < 0.001). Trends in susceptibility of *S. marcescens* to various antibiotics over 8 years are demonstrated in Fig. 2. *S. marcescens* remained consistently highly susceptible to imipenem and ceftazidime throughout the study period. A significantly increased susceptibility rate after 2004 was observed for the following antibiotics: amikacin (73.8% vs. 97.1%, *p* < 0.001), gentamicin (40.0% vs. 72.4%, *p* < 0.001), ciprofloxacin (53.8% vs. 70.4%, *p* = 0.001), ceftriaxone (53.8% vs. 86.0%, *p* < 0.001), cefepime (74.4% vs. 95.1%, *p* < 0.001), aztreonam (72.5% vs. 89.7%, *p* < 0.001), and TMP/SMX (41.3% vs. 73.7%, *p* < 0.001).

Table 2 MICs and susceptible percentage of *Serratia marcescens* isolates

Antimicrobial agent	TSAR	MIC (mcg/mL)			% of isolates Susceptible
		MIC ₅₀	MIC ₉₀	Range	
Amikacin	III–VII	≤4	>32	≤2–>32	87.8
Gentamicin	III–VII	1	>8	≤0.5–>8	59.6
Ciprofloxacin	III–VII	0.5	>2	≤0.03–6	63.8
Levofloxacin ^a	VI–VII	≤1	4	≤0.5–>8	72.7
Ceftazidime	III–VII	≤1	4	≤0.5–>16	93.8
Ceftriaxone	III–VII	2	>32	≤0.5–>32	73.2
Cefepime	III–VII	≤1	>16	≤0.5–>16	86.8
Aztreonam	III–VII	≤2	>16	≤1–>16	82.9
Imipenem	III–VII	1	2	≤0.25–>8	99.3
TMP/SMX	III–VII	≤0.5	4	≤0.5–>4	60.8
Piperacillin /Tazobactam ^b	V–VII	8	32	≤4–>64	86.0
Tigecycline ^a	VI–VII	0.5	1	≤0.25–2	98.8

^a Isolates during 2008–2010 = 172.

^b Isolates during 2006–2010 = 243.

MIC = minimum inhibitory concentration; MIC₅₀ and MIC₉₀ = MIC at which 50% and 90% of isolates were inhibited; TMP/SMX = trimethoprim/sulfamethoxazole; TSAR = Taiwan Surveillance of Antimicrobial Resistance program.

Discussion

In the present study, we examined trends in susceptibility to multiple antibiotics for 403 nonduplicate clinical *S. marcescens* isolates in Taiwan between 2002 and 2010. The results show that the activities of ceftazidime and imipenem have remained consistently high over the years. Susceptibilities of ≤10% for each round of TSAR were observed for ampicillin, amoxicillin/clavulanate, ceftazidime, cefoxitin, cefuroxime, and tetracycline. Fluoroquinolones

showed less activity against *S. marcescens* than other β-lactams.

In Taiwan, the occurrence of CTX-M-3 ESBL-producing isolates of *S. marcescens* was not unusual,^{17,18,20–22} and the novel AmpC cephalosporinase (S4) was reported previously.²³ The distinctive property of resistance to cefotaxime but not ceftazidime was due to CTX-M-3 ESBL and SRT-like AmpC such as S4 conferring the same phenotype of resistance to cefotaxime. The antibiogram-based method to simplify the screening of potential ESBL-producing populations among *S. marcescens* isolates has also been reported recently.²² Although the molecular characteristics of isolates were lacking in the current study, the higher susceptibility of ceftazidime than ceftriaxone corresponded to the previous studies,^{17,18,20–23} and further underlined the need to establish practical guidelines for ESBL screening, confirmation, and reporting for chromosomal AmpC producers in Taiwan.²¹

In the Tigecycline Evaluation and Surveillance Trial study, 4857 isolates of *S. marcescens* collected globally between 2004 and 2007 with susceptibilities ≥90% were observed for amikacin, levofloxacin, ceftazidime, cefepime, imipenem, meropenem, piperacillin/tazobactam, and tigecycline.²⁷ A similar study conducted by Hawser et al collected 753 clinical isolates of *S. marcescens* throughout the Asia–Pacific region between 2004 and 2010 and demonstrated constantly high susceptibility to levofloxacin (84–97%).²⁸ A characteristic finding in the present study was the much lower susceptibility to levofloxacin and ceftriaxone compared with the global data. Susceptibility to levofloxacin in the current study was only tested between 2008 and 2010, but susceptibility to ciprofloxacin was tested throughout the study period. The much lower susceptibility to ciprofloxacin suggests that resistance to fluoroquinolones is the major concern surrounding drug-resistant *S. marcescens* in Taiwan. The susceptibility rate to ceftriaxone was 55–85% between 2004 and 2010 in the Asia–Pacific region, which is consistent with our findings.

Table 3 Comparison of *Serratia marcescens* susceptibility among isolates from different patient locations and specimen types

Antimicrobial agent	Patient location			p
	Non-ICU (n = 252)	ICU (n = 93)	OPD/ER (n = 58)	
	S	S	S	
Amikacin	88.5	83.9	91.4	0.334
Gentamicin	60.3	54.8	63.8	0.531
Ciprofloxacin	64.3	61.3	65.5	0.849
Levofloxacin	74.1	70.7	72.7	0.841
Ceftazidime	94.0	92.5	94.8	0.803
Ceftriaxone	75.0	73.1	65.5	0.343
Cefepime	87.7	82.8	89.7	0.395
Aztreonam	85.3	75.3	84.5	0.086
Imipenem	98.8	100	100	0.433
TMP/SMX	60.3	59.1	65.5	0.727
Piperacillin /Tazobactam	89.7	82.3	86.0	0.082

Data are presented as %.

ER = emergency room; ICU = intensive care unit; OPD = outpatient department; S = susceptible; TMP/SMX = trimethoprim/sulfamethoxazole.

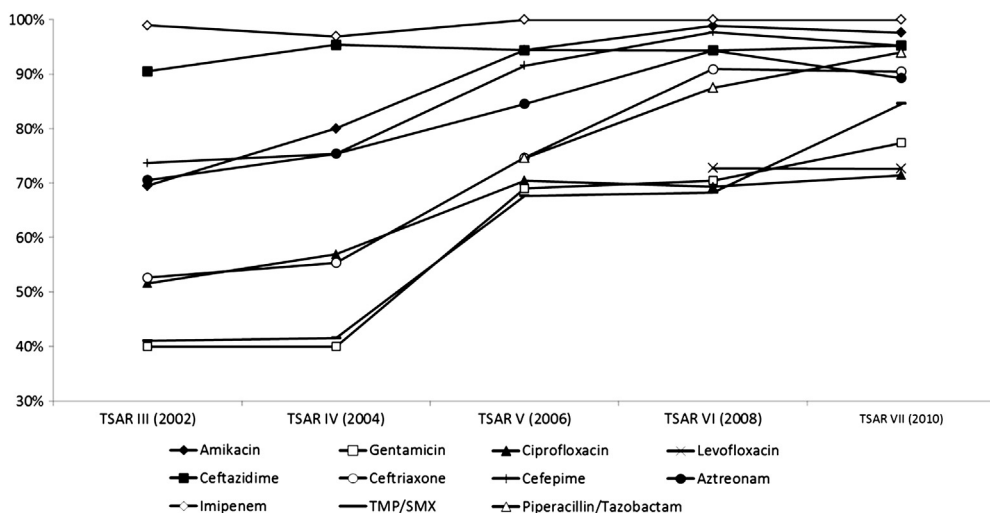


Figure 1. Comparison of susceptibility of *Serratia marcescens* to various antibiotics in different specimens. TSAR = Taiwan Surveillance of Antimicrobial Resistance program.

Hawser et al also demonstrated a decline in susceptibility to minocycline (decreased to 41–60% in 2008–2010) and tigecycline in *S. marcescens*.²⁸ By contrast, susceptibility to minocycline and tigecycline tested in 2010 in the present study showed higher susceptibility rates of 89.2% and 98.8%, respectively.

Shih et al found that 99% of *S. marcescens* blood isolates in 1999–2003 were sensitive to ceftazidime, but only 19% were sensitive to ciprofloxacin, 32% to levofloxacin, and 18% to TMP/SMX in a single institute in Taiwan.¹⁵ The high susceptibility rate of ceftazidime is consistent with the current study. A previous nationwide surveillance of antimicrobial resistance among Enterobacteriaceae at the ICUs of 10 major teaching hospitals in Taiwan in 2005 reported low susceptibility of *S. marcescens* to ciprofloxacin (43%) and levofloxacin (66%).²⁹ Despite ENREF_23 the present study showing increased susceptibilities to ciprofloxacin (64.3%) and levofloxacin (74.1%) compared with previous results in Taiwan, the resistance to fluoroquinolones continues to be a problem in Taiwan.

Examination of trends in antimicrobial susceptibility has revealed higher resistant rates for amikacin, gentamicin,

ciprofloxacin, ceftriaxone, cefepime, aztreonam, and TMP/SMX prior to 2004 than those after that date. The higher proportion of isolates recovered from urine between 2002 and 2004 may have influenced the results. The significantly higher proportion of isolates recovered from urine between 2002 and 2004 (32.5%) than that after 2004 (15.6%, $p < 0.001$) may have influenced the results. The reasons why isolates from urine had the lowest susceptibility rate for the various antibiotics cannot be clearly defined. It might imply that we should put more focus on the resistance pattern in the urinary isolates. In addition, after the emergence of severe acute respiratory syndrome in 2003, the reinforcement of prevention of health care-associated infection in hospitals resulted in a more cautious approach to intervention with antimicrobials as a part of the infection control policy.³⁰ The trends in total consumption of aminoglycosides, extended-spectrum cephalosporins, and fluoroquinolones significantly increased prior to 2004 and remained stable after 2004 in the hospital-wide investigation.^{30,31} The reduced consumption of antibiotics in Taiwan may explain the observation of greater susceptibility after 2004 in the present study.

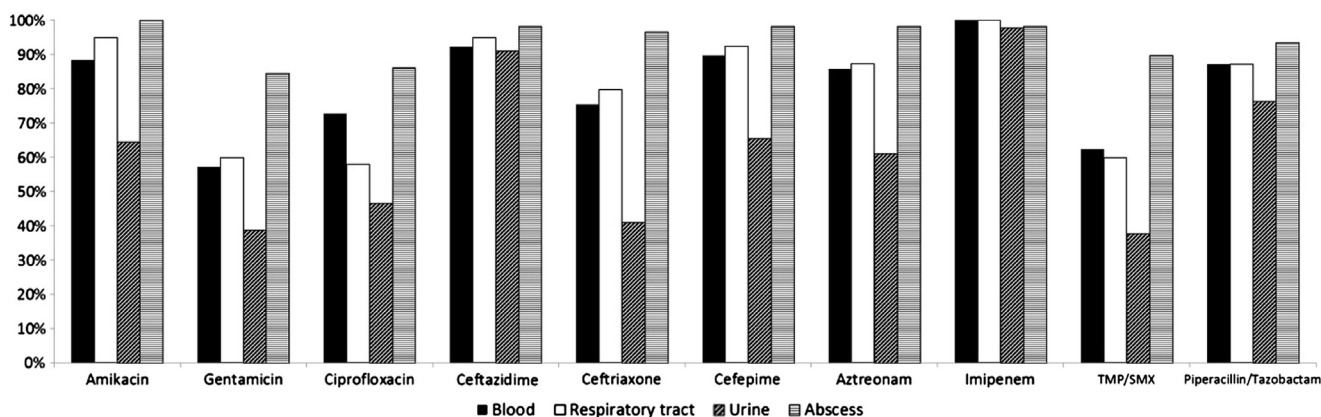


Figure 2. Trends in susceptibility of *Serratia marcescens* to various antibiotics over 10 years.

We recognize a number of potential biases in the present study. The first limitation concerns the specimen types. Isolates from the urinary tract showed higher resistance rates to many antibiotics than those from other sites; therefore, the higher percentage of urine specimen prior to 2004 may result in lower overall susceptibility in this period. Second, <10% of isolates were collected from eastern Taiwan and the data are likely to have underestimated the events occurring in this region. Third, we did not analyze the resistant mechanism due to the lack of molecular method such as multiplex polymerase chain reaction screening of *ampC* genes in these *S. marcescens* isolates. Finally, given the limited clinical information from this surveillance, we cannot exactly determine the clinical significance of these isolates.

In conclusion, the results of this study suggest that the susceptibility of *S. marcescens* to ceftazidime and imipenem in Taiwan remained consistently high over the study period. *S. marcescens* isolates from Taiwan demonstrated relatively higher resistance to ciprofloxacin and levofloxacin than other β -lactams, and continued surveillance of antimicrobial resistance in *S. marcescens*, especially for fluoroquinolones, is warranted. TSAR is ongoing in Taiwan involving clinically important bacteria. The longitudinal surveillance study will continue to provide key information related to antimicrobial resistance over time.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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