Journal of Hospital Infection 105 (2020) 188–196

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevier.com/locate/jhin

Antimicrobial resistance in southern China: results of prospective surveillance in Dongguan city, 2017☆

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A R T I C L E I N F O

Article history:
Received 14 January 2020
Accepted 23 March 2020
Available online 31 March 2020

Keywords:
Surveillance
Incidence proportion
Incidence density
Antimicrobial resistance
Multidrug-resistant pathogens
China
Dongguan

S U M M A R Y

Background: Few studies have estimated the burden of infections due to antimicrobial-resistant (AMR) pathogens in China.
Aim: To summarize antimicrobial resistance and assess the frequency of community-associated infections (CAIs) and healthcare-associated infections (HCAIs) due to AMR pathogens in Dongguan city, China.
Methods: Seven acute care hospitals provided antimicrobial susceptibility data for 2017, from which 'bug–drug' combinations were analysed. To calculate incidence proportions of CAI and incidence densities of HCAI, data from three tertiary care hospitals were merged with patient data, obtained from the Dongguan Nosocomial Infection Surveillance System.
Findings: A total of 16,548 pathogens were analysed. Non-susceptibility to third-generation cephalosporins (3GCs) in *Escherichia coli* and *Klebsiella pneumoniae* was 43.9% and 30.2%, respectively. Non-susceptibility to carbapenems in *Pseudomonas aeruginosa* and *Acinetobacter baumannii* was 29.5% and 50.9%, respectively. A quarter of *Staphylococcus aureus* (26.3%) were non-susceptible to oxacillin. The incidence density of HCAI due to *E. coli* non-susceptible to 3GCs and fluoroquinolones combined was 0.09 (95% confidence interval: 0.07–0.11) per 1000 patient-days. Both *E. coli* and *K. pneumoniae* were the predominant pathogens isolated from blood. Compared with the 2017 European Antimicrobial Resistance Surveillance Network report, the incidence proportion of

☆ Partial results were presented at the 5th International Conference on Prevention and Infection Control, Geneva, Switzerland, September 10th–13th, 2019.

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https://doi.org/10.1016/j.jhin.2020.03.029

bloodstream infections due to multidrug-resistant *E. coli* was significantly higher (14.9% and 4.6%, respectively).

Conclusion: The incidence of non-susceptible bug—drug combinations in Dongguan city was lower compared with China as a whole. Non-susceptible bug—drug combinations were significantly more frequent in HCAI compared with CAI. The incidence proportion of bloodstream infections due to multidrug-resistant pathogens in Dongguan City was higher compared with Europe.

Introduction

Healthcare-associated infections (HCAIs) due to antimicrobial-resistant (AMR) pathogens have been recognized as a challenge in modern healthcare [1—3]. The global action plan of the World Health Organization (WHO) on antimicrobial resistance, the World Antibiotic Awareness Week, and WHO's global infection prevention and control (IPC) priorities for 2018—2022 focus on the burden of antimicrobial resistance, especially in Asia [4,5]. Surveillance, especially prospective incidence surveillance, is the cornerstone in understanding and controlling antimicrobial resistance [1,2]. Global surveillance networks such as the Global Antimicrobial Resistance Surveillance System (GLASS) or the European Antimicrobial Resistance Surveillance Network (EARS-Net) report on current status and trends of antimicrobial resistance on a yearly basis [6,7].

A major driver to step up surveillance on infectious diseases in mainland China was the severe acute respiratory syndrome outbreak in 2003 [8,9]. Two national antimicrobial resistance surveillance networks have been established thereafter in 2005: the China Antimicrobial Resistance Surveillance System (CARSS) and the China Antimicrobial Surveillance Network (CHINET) [10,11]. Summary reports of CARSS and CHINET are published annually on the official website of the National Health Commission of the People's Republic of China, and in the *Chinese Journal of Infection and Chemotherapy* [10,11]. From an IPC perspective, there are gaps in reports on infections due to AMR pathogens in Mainland China: (i) most publications in China focus on molecular characteristics rather than on epidemiology [12]; (ii) pooled data on antimicrobial resistance are not de-duplicated [13]; (iii) data on infections due to AMR pathogens are not stratified into HCAI and community-associated infection (CAI) [14]; and (iv) data analysis does not address AMR combinations [7,11,12].

The aims of this study were: (i) to summarize incidence proportions of pooled antimicrobial resistance data in Dongguan city of Guangdong province in 2017 and to compare the results with the 2017 CHINET report [11]; (ii) to calculate incidence proportions of CAI and incidence densities of HCAI due to AMR pathogens and to compare the results for HCAI with

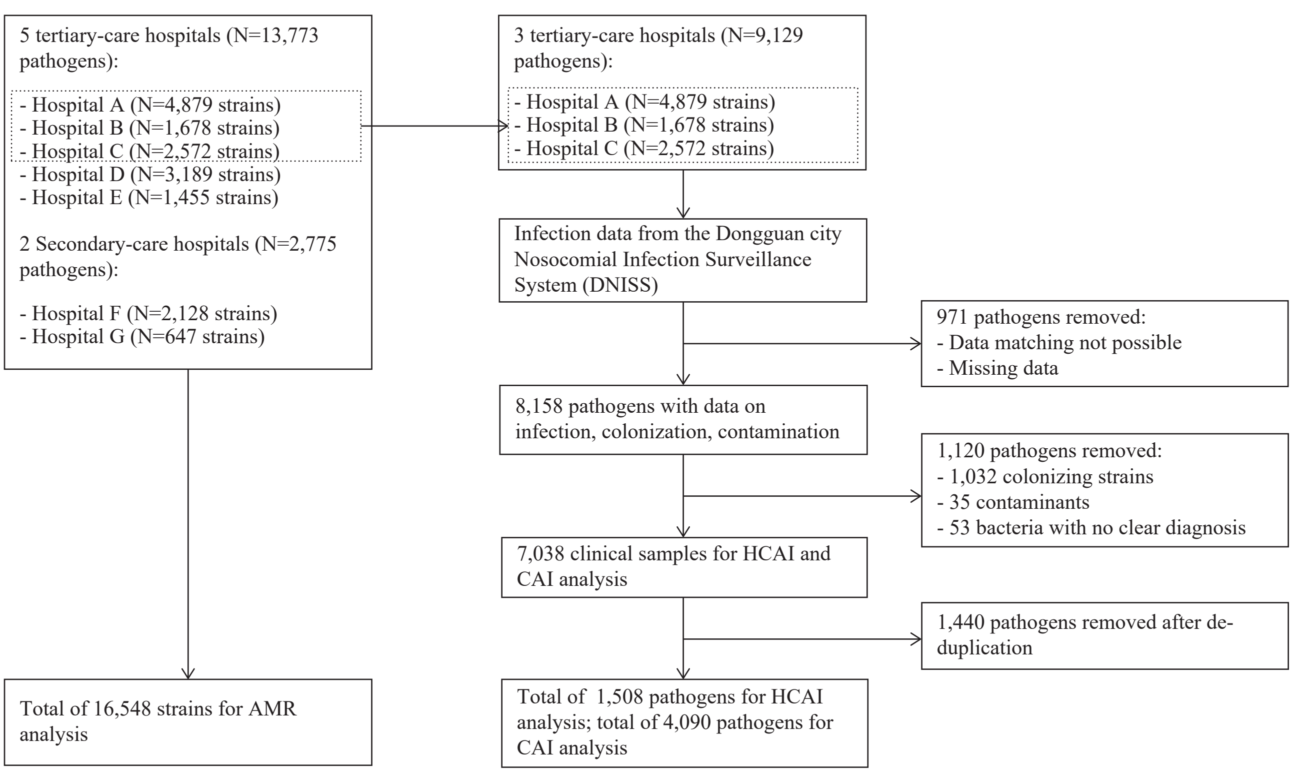

Figure 1. Data extraction flow: antimicrobial resistance surveillance, Dongguan city, 2017. AMR, antimicrobial resistance; CAI, community-associated infection; HCAI, healthcare-associated infection.

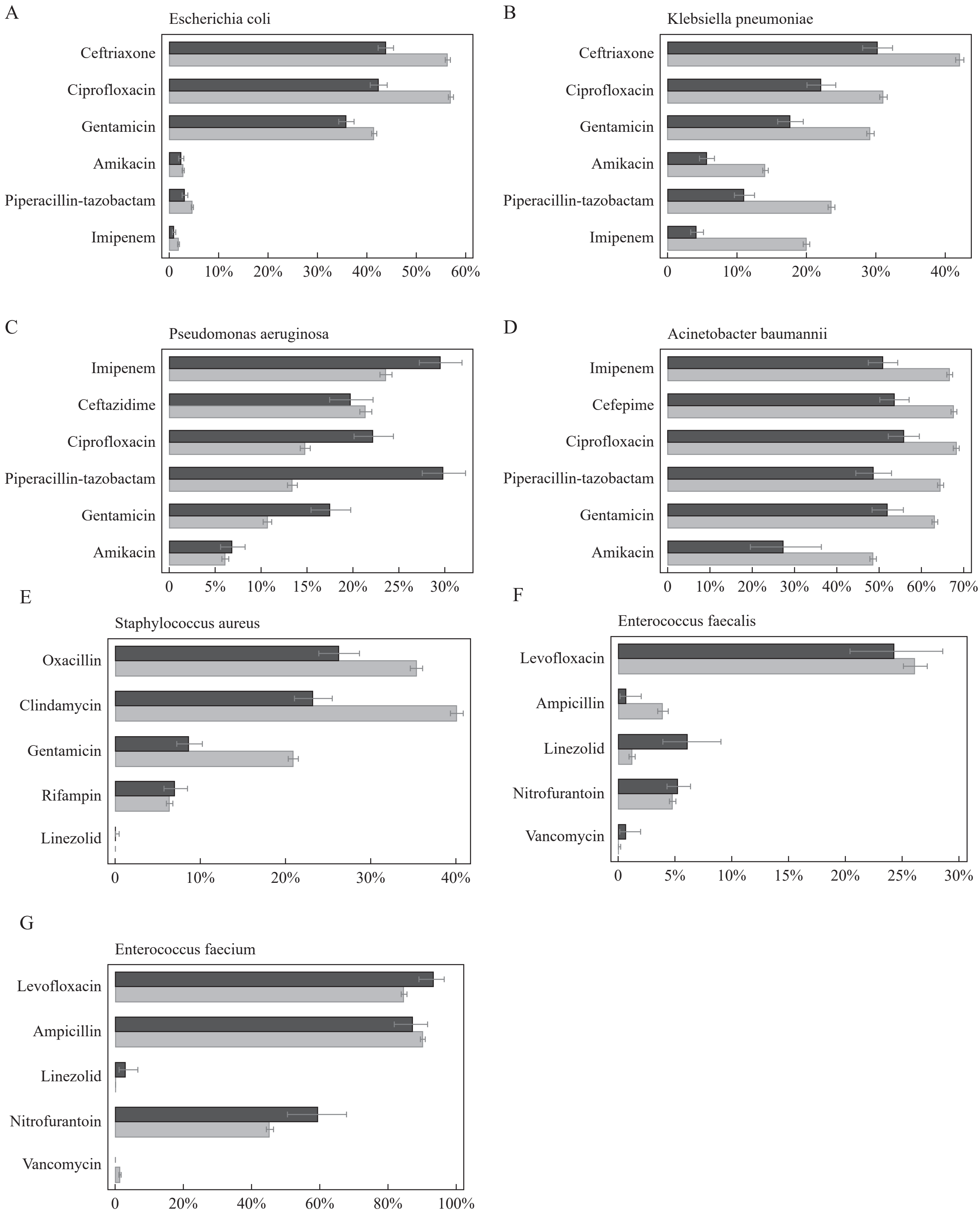

Figure 2. Comparison of non-susceptibility of indicator pathogens to antimicrobial resistance markers between Dongguan city (black bars) and the China Antimicrobial Surveillance Network (grey bars): antimicrobial resistance surveillance, Dongguan city, 2017. T-bars: 95% confidence intervals.

Table I
Distribution of 'bug–drug' combinations, stratified by healthcare-associated infection types and ward specialties: antimicrobial resistance surveillance, Dongguan city, 2017

Infection types and departments	Third-generation cephalosporin-resistant *Escherichia coli*			Third-generation cephalosporin-resistant *Klebsiella pneumoniae*			Carbapenem-resistant *Pseudomonas aeruginosa*			Carbapenem-resistant *Acinetobacter baumannii*			Meticillin-resistant *Staphylococcus aureus*		
	n/N	%	95% CI	n/N	%	95% CI	n/N	%	95% CI	n/N	%	95% CI	n/N	%	95% CI
HCAI types															
LRTI	36/189	19.0	13.7–25.4	40/64	62.5	49.5–74.3	40/54	74.1	60.3–85.0	39/49	79.6	65.7–89.8	4/31	12.9	3.6–29.8
UTI	88/189	46.6	39.3–53.9	11/64	17.2	8.9–28.7	9/54	16.7	7.9–29.3	3/49	6.1	1.3–16.9	2/31	6.5	0.8–21.4
SSI	32/189	16.9	11.9–23.1	4/64	6.3	1.7–15.2	2/54	3.7	0.5–12.7	N/A	N/A	N/A	14/31	45.2	27.3–64.0
BSI	19/189	10.1	6.2–15.3	4/64	6.3	1.7–15.2	N/A	N/A	N/A	3/49	6.1	1.3–16.9	5/31	16.1	5.5–33.7
Other	14/189	7.4	4.1–12.1	5/64	7.8	2.6–17.3	3/54	5.6	1.2–15.4	4/49	8.2	2.3–19.6	6/31	19.4	7.5–37.5
Clinical departments															
ICU	21/189	11.1	7.0–16.5	7/64	10.9	4.5–21.2	16/54	29.6	18.0–43.6	18/49	36.7	23.4–51.7	2/31	6.5	0.8–21.4
MED	49/189	25.9	19.8–32.8	21/64	32.8	21.6–45.7	14/54	25.9	15.0–39.7	9/49	18.4	8.8–32.0	5/31	16.1	5.5–33.7
SUR	88/189	46.6	39.3–53.9	22/64	34.4	22.9–47.3	19/54	35.2	22.7–49.4	16/49	32.7	19.9–47.5	21/31	67.7	48.6–83.3
PED	3/189	1.6	0.3–4.6	3/64	4.7	1.0–13.1	N/A	N/A	N/A	1/49	2.0	0.1–10.9	1/31	3.2	0.1–16.7
Other	28/189	14.8	10.1–20.7	11/64	17.2	8.9–28.7	5/54	9.3	3.1–20.3	5/49	10.2	3.4–22.2	2/31	6.5	0.8–21.4

CI, confidence interval; LRTI, lower respiratory tract infection; UTI, urinary tract infection; SSI, surgical site infection; BSI, bloodstream infection; HCAI, healthcare-associated infection; ICU, intensive care unit; MED, internal medicine; SUR, surgery; PED, paediatrics and neonatology; N/A, not applicable.

data from Germany [14]; and (iii) to calculate incidence proportions of bloodstream infection (BSI) due to AMR pathogens in tertiary care hospitals and to compare the results with the 2017 EARS-Net report [7].

Methods

Settings

Dongguan city is located in Guangdong province in southern China and has a population of about eight million [15,16]. In 2014, the city established the Dongguan city Nosocomial Infection Surveillance System (DNISS) to organize yearly point prevalence surveys, prospective surgical site infection surveillance, and prospective antimicrobial resistance surveillance [15]. Data on antimicrobial resistance incidence of 2017 was provided by seven public/not-for-profit hospitals, two secondary- and five tertiary-care hospitals of the city. All institutions are general hospitals with a mixed patient population. Data collection on antimicrobial resistance follows the national surveillance protocol [11,12].

Databases

Antimicrobial susceptibility data were obtained from the microbiology laboratories of the seven hospitals. Clinical data were obtained from DNISS [17]: (i) anonymous patient identifier, age, gender, date of hospital admission, department of admission, date of hospital discharge, length of stay, and in-hospital mortality; (ii) presence of healthcare/community-associated infection or colonization, infection type, date of infection/colonization; (iii) type and date of microbiological sampling (i.e. sputum, urine, blood, pus, and other clinical specimens), pathogen, date of microbiological reporting, and microbiological identifier. The definitions of HCAI included temporal (>48 h after admission), clinical, and microbiological criteria; otherwise, infections diagnosed within 48 h of admission without any previous encounter with healthcare were defined as CAI [15,18]. HCAIs and CAIs due to AMR pathogens were obtained by merging the microbiology databases with the DNISS database, using the anonymous patient identifier (the same for both databases), date of microbiological sampling, date of microbiological reporting, pathogen, and microbiological identifier. Figure 1 summarizes the data extraction flow for the analysis of AMR and HCAI/CAI due to AMR pathogens.

Antimicrobial resistance

The following HCAI-relevant indicator pathogens were addressed: *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Staphylococcus aureus*, *Enterococcus faecalis*, and *Enterococcus faecium* [7,11,13,19]. Identification and susceptibility testing was performed using Vitek® 2 (bioMérieux, Marcy l'Etoile, France) in all hospitals. Breakpoints for minimum inhibitory concentrations were based on the US National Clinical and Laboratory Standards Institute (NCLSI) guidelines (modified version based on M100, 28th edition in 2017) (Supplementary Table S1) [20]. Primary outcome was non-susceptibility to antimicrobial agents of epidemiologically significant antimicrobial

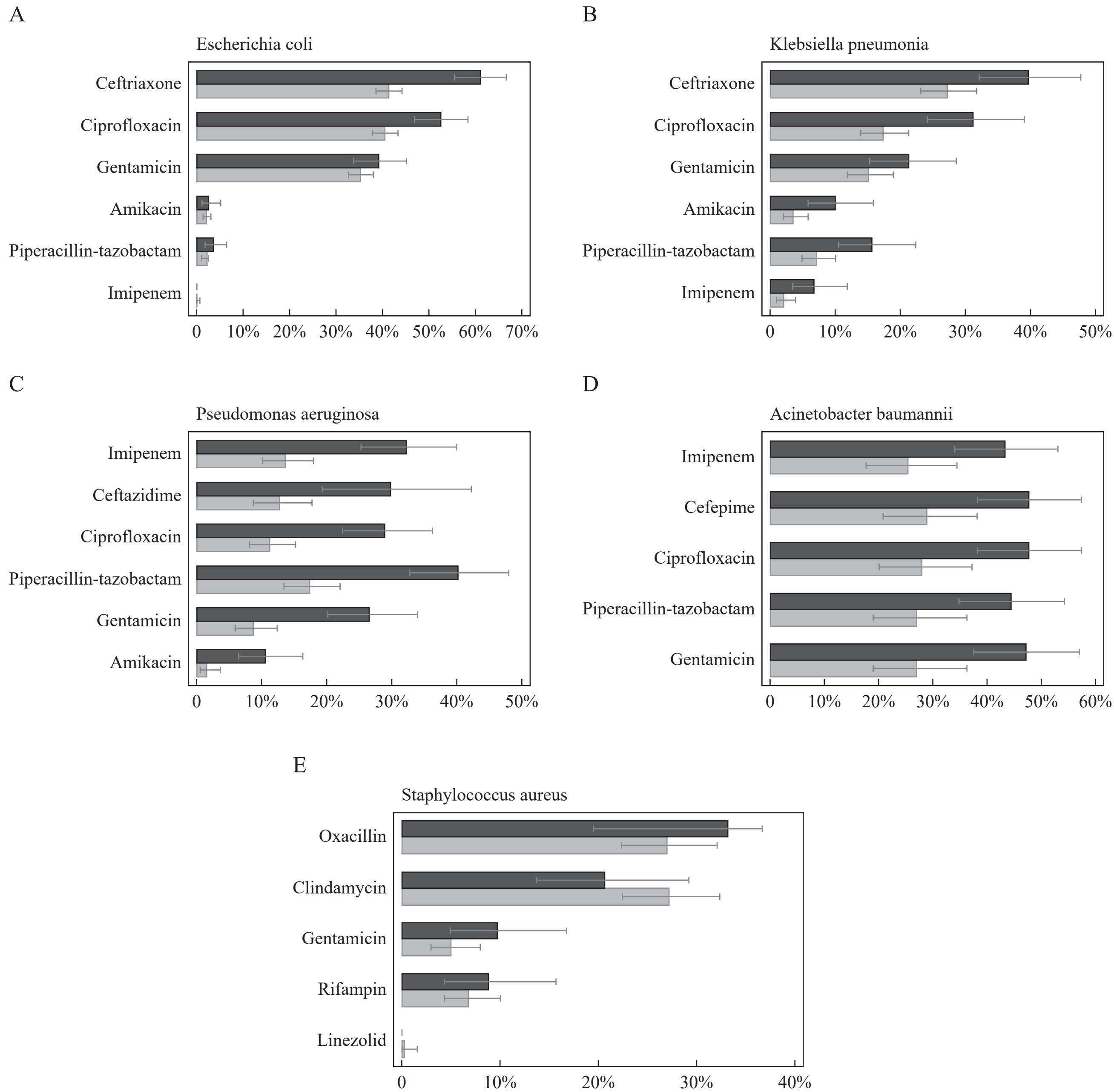

Figure 3. Comparison of non-susceptibility of indicator pathogens to antimicrobial resistance markers between healthcare-associated infections (HCAIs; black bars) and community-acquired infections (CAIs; grey bars): antimicrobial resistance surveillance, Dongguan city, 2017. T-bars: 95% confidence intervals.

categories, termed antimicrobial resistance markers [7,13]. Multidrug-resistant (MDR) pathogens were defined as pathogens with non-susceptibility to at least one agent of three or more relevant antimicrobial categories [21].

Data analysis

Incidence proportions of pooled bacterium—antimicrobial ('bug—drug') combinations as used by the European Centre for Disease Prevention and Control were calculated, with the corresponding 95% confidence intervals (CIs) [7,13]. Results were compared with the 2017 national CHINET report [11]. Data were de-duplicated using the criteria of the EARS-Net surveillance protocol and taking into account all pathogens in context with the first infection during hospitalization. Incidence proportions of CAI (number per 100 admissions) as well as incidence densities of HCAI (number per 1000 patient-days) due to AMR pathogens were calculated [13]. HCAIs due to *E. coli* and *K. pneumoniae* non-susceptible to third-generation cephalosporins (3GC), fluoroquinolones, carbapenems, or any combination of these agents were compared with a multicentre surveillance report, performed in Germany in 2014/2015 [14]. Bloodstream infections due to AMR pathogens were calculated following the EARS-Net protocol for pathogen—resistance

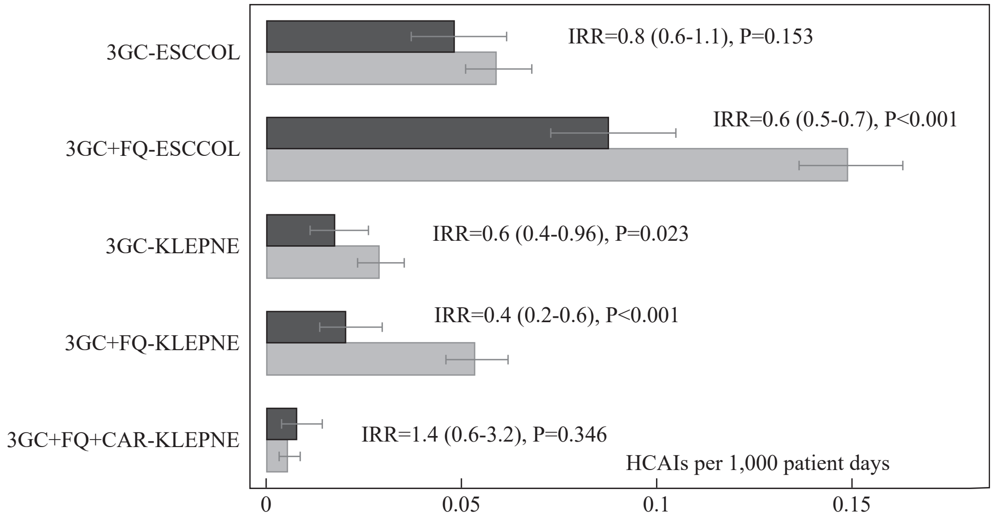

Figure 4. Incidence densities of healthcare-associated infections due to resistant *Escherichia coli* and *Klebsiella pneumoniae* — Differences between Dongguan city, 2017 (black bars) and Germany, 2014 and 2015 (grey bars). T-bars: 95% confidence intervals. No healthcare-associated infection due to *E. coli* resistant to 3GCs, fluoroquinolones and carbapenem combined were reported. 3GC, third-generation cephalosporin; ESCCOL, *Escherichia coli*; FQ, fluoroquinolone; KLEPNE, *Klebsiella pneumoniae*; CAR, carbapenem; IRR, incidence rate ratio.

combinations [13]. Incidence proportions of BSI due to MDR pathogens were compared with the 2017 EARS-Net report [7].

Statistical analysis

Healthcare-associated infections due to AMR *E. coli* and AMR *K. pneumoniae* were compared with German surveillance data using Pearson's χ^2-test [14]. Bloodstream infections due to MDR pathogens were compared with the EARS-Net data using Fisher's exact test [7]. Two-sided $P < 0.05$ was considered statistically significant. All statistical analyses and graphs were performed using Stata 15.1 version (Stata Corp., College Station, TX, USA).

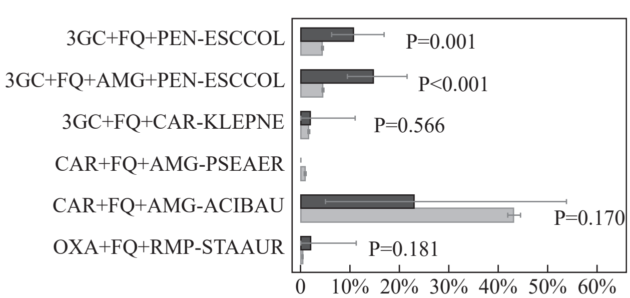

Figure 5. Incidence proportions of bloodstream infections due to multidrug-resistance indicator pathogens between Dongguan city, 2017 (black bars) and the 2017 European Antimicrobial Resistance Surveillance Network report (grey bars). No bloodstream infection due to multidrug-resistant *Pseudomonas aeruginosa* was reported in Dongguan city. T-bars, 95% confidence intervals. 3GC, third-generation cephalosporin; FQ, fluoroquinolone; PEN, penicillin; ESCCOL, *Escherichia coli*; AMG, aminoglycoside; CAR, carbapenem; KLEPNE, *Klebsiella pneumoniae*; PSEAER, *Pseudomonas aeruginosa*; ACIBAU, *Acinetobacter baumannii*; OXA, oxacillin; RMP, rifampicin; STAAUR, *Staphylococcus aureus*.

Ethics

The Chinese Ethics Committee of Registering Clinical Trials waived patient informed consent and approved data analysis for this study (ChiECRCT20190134).

Results

The seven hospitals provided 16,548 microbiology results on bacteria. Together, they represented a total of 246,266 admissions accumulating 2,218,861 patient-days in 2017. The average length of stay was 9.0 days. The ratio of IPC professionals per 250 hospital beds was 0.83 (95% CI: 0.52—1.24) (Supplementary Table S2e).

Figure 2 summarizes susceptibility of indicator pathogens and compares antimicrobial resistance data with CHINET [11]. Numbers can be found in Supplementary Table S3e. Among Gram-negative bacteria, non-susceptibility to 3GCs in *E. coli* and *K. pneumoniae* were 43.9% and 30.2%, respectively. Non-susceptibility to carbapenems in *E. coli* and *K. pneumoniae* were 0.9% and 4.2%, respectively. Among Gram-positive bacteria, 26.3% of *S. aureus* were non-susceptible to oxacillin.

Escherichia coli, *K. pneumoniae*, and *A. baumannii* were consistently and significantly more susceptible in Dongguan city compared with the national data. However, *P. aeruginosa* were significantly less susceptible to piperacillin—tazobactam (29.9% vs 13.4%), imipenem (29.5% vs 23.6%), gentamicin (17.5% vs 10.7%), and ciprofloxacin (22.2% vs 14.8%) in Dongguan city. Supplementary Figure S1 compares antimicrobial resistance data of indicator pathogens between secondary care and tertiary care hospitals in Dongguan city. With the exception of *S. aureus*, non-susceptibility was consistently higher in tertiary care hospitals.

A total of 1508 and 4090 pathogens were allocated to HCAI and CAI, respectively (Figure 1). Non-susceptibility was consistently higher in HCAI compared with CAI. However, statistically significant differences were identified only for

P. aeruginosa to all antimicrobials, and for *E. coli* and *K. pneumoniae* to both ceftriaxone and ciprofloxacin (Figure 3). Table I summarizes 'bug–drug' combinations by HCAI types and clinical departments. Supplementary Tables S4 and S5 summarize distributions and incidence densities of HCAI and CAI due to indicator pathogens non-susceptible to one or more antimicrobial combinations. No HCAI due to carbapenem non-susceptible *E. coli* was reported. The incidence density of HCAI due to *E. coli* non-susceptible to 3GCs and fluoroquinolones combined was 0.09 (95% CI: 0.07–0.11) per 1000 patient-days. The incidence proportion of CAI due to *E. coli* non-susceptible to 3GCs and fluoroquinolones combined was 0.24 (95% CI: 0.22–0.27) per 100 admissions. The incidence density of HCAI due to *K. pneumoniae* non-susceptible to 3GCs, fluoroquinolones and carbapenem combined was 0.008 (0.004–0.014) per 1000 patient-days. Incidence densities of HCAI due to *E. coli* and *K. pneumonia* non-susceptible to 3GCs and fluoroquinolones combined were significantly lower compared with the 2014/2015 multicentre surveillance report in Germany (Figure 4) [14]. No significant differences in incidence densities of HCAI due to MDR *K. pneumoniae* were identified between Dongguan city and Germany.

Ten percent (562/5598) of the pathogens in the combined dataset were isolated from blood. Among these, 41.4% (65/157) of *E. coli* were non-susceptible to 3GCs, but all were susceptible to carbapenems; 19.6% (10/51) and 2.0% (1/51) of *K. pneumoniae* were non-susceptible to 3GCs and carbapenems, respectively; all of the 15 isolated *P. aeruginosa* were susceptible to carbapenems; 28.6% (4/14) of *A. baumannii* were non-susceptible to carbapenems; 21.3% (10/47) of *S. aureus* were non-susceptible to oxacillin; all 14 isolated *E. faecalis* and all four isolated *E. faecium* were susceptible to vancomycin. Figure 5 compares the incidence proportion of BSI due to MDR indicator pathogens with the 2017 EARS-Net report [7]. Incidence proportions of BSI due to MDR *E. coli* were significantly higher compared with the 2017 EARS-Net report (14.9% vs 4.6%; $P < 0.001$). There were no significant differences for MDR *K. pneumoniae* (2.1% vs 1.7%; $P = 0.566$), MDR *A. baumannii* (23.1% vs 43.2%, $P = 0.170$), or MDR *S. aureus* (2.1% vs 0.4%; $P = 0.181$), respectively.

Discussion

This study summarizes susceptibility of indicator pathogens in southern China, and highlights incidence proportions of CAI and incidence densities of HCAI due to non-susceptible pathogens. It not only fills a research gap on prospective AMR incidence surveillance in general, but also provides clinical perspectives about infections due to MDR pathogens in one of the most rapidly developing regions in the world [15,16]. Interestingly, non-susceptibility was lower than average incidence proportions in mainland China, and lower than anticipated.

Third-generation cephalosporin resistance in *E. coli* and *K. pneumoniae* remains a major challenge in Dongguan city. It is lower compared with the 2017 CHINET report and other Chinese studies (2017/2018 AMR data: 3GC-resistant *E. coli*: 56%; 3GC-resistant *K. pneumoniae*: 30%), but similar compared with Thailand (3GC-resistant *E. coli* in blood: 40%; 3GC-resistant *E. coli* in urine: 45%) [6,11,22]. The proportion of resistance to carbapenem in *K. pneumoniae* has emerged from 3.0% in 2005 to 20.9% in 2017 in China [23]. With 4.2%, this proportion was much lower in Dongguan city, but similar to the average of invasive pathogens in Europe (7.2%) [7]. Also similar to the average of invasive MDR pathogens in Europe (3.9%), 5% of *P. aeruginosa* were MDR in Dongguan city [7]. The proportion of vancomycin-resistant *E. faecalis* (0.7%) in our study was lower compared with the USA (8.5%), but similar to Canada (0.1%) and the Asia–Pacific region (0.01%) [24,25].

Compared with Germany, incidence densities of HCAI due to *E. coli* and *K. pneumoniae* with resistance to 3GC and fluoroquinolones combined were significantly lower [14]. On the other hand, the incidence densities of CAI due to *E. coli* and *K. pneumoniae* with resistance to 3GC, or to 3GC and fluoroquinolones combined, were significantly higher. One reason for this may be that 50% of outpatients in China receive antibiotics, particularly cephalosporins and fluoroquinolones [26,27]. In addition, there is little antimicrobial stewardship in primary care hospitals [28]. Because CAIs are treated without performing microbiological testing, far too many broad-spectrum antimicrobials are prescribed [29]. Urinary tract infection was the most common HCAI type due to 3GC-resistant *E. coli*, which is consistent with the German National study of 2014/2015 [14].

The incidence density of infections due to carbapenem-resistant *E. coli* and *K. pneumoniae* together in our study was 0.017 (95% CI: 0.011–0.025) per 1000 patient-days. This is lower compared with the 2015 China Carbapenems Resistant Enterobacteriaceae Surveillance Project (0.041; 95% CI: 0.038–0.044 per 1000 patient-days), but was four-fold higher compared with the French National Carbapenem Resistant Enterobacteriaceae Surveillance Project (0.0041 per 1000 patient-days) from 2011 and 2012 [30,31]. More than two-thirds of infections due to carbapenem-resistant *A. baumannii* (CRAB) were in the lower respiratory tract, of which almost half occurred in the ICU. This may be associated with high incidence densities of ventilator-associated pneumonia in China, which ranges from 19.5 to 30.8 infections per 1000 ventilator-days [32,33]. Therefore, active CRAB screening in patients in the ICU should be envisaged [34].

Both *E. coli* and *K. pneumoniae* were the predominant pathogens isolated from blood. The incidence proportion of BSI due to MDR *E. coli* was significantly higher compared with the 2017 EARS-Net report, whereas the incidence proportion of BSI due to MDR *K. pneumoniae* was similar [7]. The incidence proportion of BSIs due to MDR *S. aureus* in our study was higher compared with the 2017 EARS-Net report, although the difference was not statistically significant. Interestingly, the incidence density of hospital-onset BSI due to meticillin-resistant *S. aureus* in our study was very low (0.004; 95% CI: 0.001–0.009 per 1000 patient-days), even lower compared with Europe (0.026; 0.021–0.031) [35]. Two factors may explain this finding: (i) the average length-of-stay in our hospitals was longer (6.2–10.6 days) compared with the USA (4.5 days) or Europe (5.1 days), which inflates the denominator; (ii) blood culture sampling was low, with a rate of 10.4 (95% CI: 10.1–10.8) performed blood culture sets per 1000 patient-days [18,19,36]. This is significantly lower than in Denmark, Finland, Sweden, France, or the UK (>50 blood culture sets per 1000 patient-days), for example [7].

This study has limitations. First, microbiology and clinical data could be merged for the subset of three tertiary care hospitals only. Although the results can be considered representative for tertiary care hospitals in Dongguan city, they may not be for the entire province or other hospital types. Prospective AMR surveillance in the future should aim to link clinical and AMR data. Second, Chinese microbiology laboratories follow the US breakpoints for susceptibility testing, which allowed comparison to CHINET (and other Asian databases) but was limited to compare results with European data, where the European Committee on Antimicrobial Susceptibility Testing (EuCAST) breakpoints are used [20,37]. To variable degrees, this may have resulted in underestimating the burden of AMR/MDR pathogens in Dongguan city compared with Europe. Third, no colistin-resistant *E. coli* or *K. pneumoniae* were reported in our study, which was unexpected given that colistin-resistant Enterobacterales have been isolated from food animals in China [38,39]. Colistin susceptibility was reported only for *P. aeruginosa* and *A. baumannii* non-susceptible to imipenem in our study; and only rarely for *E. coli* and *K. pneumoniae*. This may have underestimated the burden of colistin resistance.

In conclusion, this is the first study summarizing susceptibility of indicator pathogens in southern China, highlighting incidence proportions of CAI and incidence densities of HCAI due to non-susceptible pathogens. This study applied a standardized protocol to conduct prospective antimicrobial resistance surveillance and data analysis. The outcomes serve as a reference of antimicrobial resistance not only in China, but also in other South Asian countries.

Acknowledgements

The authors thank the Dongguan city Nosocomial Infection Control and Quality Improvement Centre for providing the microbiology dataset and clinical dataset.

Declaration of Competing Interest
None declared.

Funding source
J.W. was supported and funded by Chinese Professional Talent Training Programme Scholarship, Dongguan city, Guangdong Province, China.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2020.03.029.

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