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Epidemiology and risk factors for carbapenemase-producing Enterobacteriaceae carriage in the hospital: A population-based nested case-control study

Min Fan[a], Shuk-Ching Wong[b], Qiuyan Yu[a], Philip H Li[c], Peng Wu[d,e], Esther Wai Yin Chan[a,e], Ian Chi Kei Wong[a,e,f], Hein M Tun[g,h], Benjamin John Cowling[d,e], Vincent Chi-Chung Cheng[b,i], Celine Sze Ling Chui[e,g,j,*]

[a] *Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China*
[b] *Infection Control Team, Queen Mary Hospital, Hong Kong SAR, China*
[c] *Division of Rheumatology and Clinical Immunology, Department of Medicine, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China*
[d] *World Health Organization Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China*
[e] *Laboratory of Data Discovery for Health (D24H), Hong Kong Science and Technology Park, Hong Kong SAR, China*
[f] *Aston Pharmacy School, Aston University, Birmingham, B4 7ET, United Kingdom*
[g] *School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China*
[h] *The Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong SAR, China*
[i] *Department of Microbiology, Queen Mary Hospital, Hong Kong SAR, China*
[j] *School of Nursing, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China*

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ABSTRACT

Objectives: This study aims to study the epidemiology of carbapenemase-producing Enterobacteriaceae (CPE) in Hong Kong.
Methods: This is a longitudinal population-based study reporting monthly CPE incidence rate and a nested case-control study for identifying risk factors for CPE carriage. The cases were patients with at least one CPE-positive genotypic test, while the controls were randomly selected from the cohort with negative tests. Up to four controls per case were matched by sex, age group, and admission year-month. The independent risk factors were identified from a conditional logistic regression with potential covariates.
Results: From 1 January 2008 to 31 December 2019, 8588 patients received CPE genotyping tests, and 2353 had at least one positive result. Class B carbapenemase was the predominant enzyme in the samples (78.6%). The incidence rate increased from 0.04 in 2015 to 1.62 in 2019 per 10,000 person-year. In the nested case-control study, 1709 cases and 6664 controls were matched. Previous use of any beta-lactam antibiotics (odds ratio:1.37 [1.22–1.53], $P < 0.001$) was found as an independent risk factor for carriage of CPE.
Conclusion: The carriage of CPE was found with an increasing trend in Hong Kong. Previous use of any beta-lactam antibiotics is a risk factor for CPE.

1. Introduction

Antimicrobial resistance (AMR), which significantly hinders the treatment of infections, remains one of the global public health concerns. It is estimated that without effective measurements to tackle AMR, up to 10 million deaths would be attributed to AMR by 2050 [1]. Carbapenemase-producing Enterobacteriaceae (CPE) are

* Corresponding author. Mailing address: 5/F, 3 Sassoon Road, Pokfulam, Hong Kong.
E-mail address: cslchui@hku.hk (C.S.L. Chui).

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some of the most critical AMR pathogens classified by the World Health Organization (WHO). Its associated clinical burden has continuously increased in recent decades [2–4]. Carbapenemase-producing Enterobacteriaceae is a group of Gram-negative bacteria resistant to almost all beta-lactam antibiotics (including penicillins, cephalosporins, monobactams, and carbapenems), the most commonly prescribed antibiotic class in the world [3]. A recent systematic review reported that the CPE-specific mortality rate varies from 26% to 44% worldwide [5]. In Europe, the proportion of disability-adjusted life years (DALYs) increased from 18% in 2007 to 28% in 2015 [6]. Economically, the cost estimation in the United States is unexpectedly higher than many chronic diseases [4]. In Hong Kong, there was an increasing number of CPE specimens identified at the Public Health Laboratory Services Branch from 2009 to 2016 [7]. With the active surveillance implemented, the incidence of CPE identified in a healthcare region, comprised of laboratory records collected directly from a university-affiliated hospital and five extended care hospitals in Hong Kong, has increased by 190 folds from 2011 to 2019 (from 0.01–1.9 CPE per 1000 patient admission) in our recent report [8]. The drastic increase in incidence cases demonstrated the endemicity of CPE in Hong Kong.

Understanding epidemiology is essential for tackling the increasing burdens of AMR [9]. The risk factors for CPE carriage among hospitalized patients are inconsistent in the literature. The use of antibiotics, proton-pump inhibitors, the presence of indwelling devices, and undergoing mechanical ventilation have been considered potential risk factors in previous studies [10–13]. However, most of these studies were conducted with a small sample size of fewer than 100 participants. A larger sample size is needed to increase study validity for exploring risk factors of CPE carriage among hospitalized patients. Identifying the risk factors for CPE carriage will help clinicians promptly identify high-risk patients and provide measures at an earlier stage to mitigate the risk of developing a CPE infection. With the advancement of technology, most health records are available electronically. We aim to demonstrate the feasibility of using routinely collected electronic health records to study the monthly incidence and risk factors for CPE carriage. We described the epidemiology of CPE carriage in this territory-wide study to better understand the epidemiology of CPE in Hong Kong.

2. Materials and methods

This is a population-based longitudinal study from 1st January 2008 to 31st December 2019. A territory-wide cross-sectional analysis was done to calculate the monthly incidence of CPE in Hong Kong. Furthermore, a case-control study was conducted among hospitalized patients to identify the risk factors for CPE carriage. This study received ethical approval from the Institutional Review Board of The University of Hong Kong/Hospital Authority Hong Kong Western Cluster (UW 19-804). The Institutional Review Board waivered the requirement for informed consent because the study was of retrospective design and utilized a de-identified database.

2.1. Data source and patient identification

We retrieved data from the Clinical Data Analysis and Reporting System (CDARS), an electronic health database managed by the Hospital Authority (HA). The HA is a statutory body that manages all 43 public hospitals in Hong Kong. Our public hospitals provide primary, secondary, and tertiary care to all citizens (7.41 million in 2021). More than 75% of hospital admissions were admitted to the public hospitals under the management of HA [14]. CDARS contains electronic health records which capture data from daily clinical management. The data in the CDARS are de-identified, including patient's demographic, diagnosis, procedure, prescribing history, hospitalization records, date of registered death, and laboratory results. Since its establishment in 1995, CDARS has accumulated medical records of over 11 million patients [15]. CDARS has been used extensively for epidemiological studies published in peer-reviewed journals for various diseases and treatment outcomes [16–19], ensuring its creditability. In Hong Kong, hospitalized patients with CPE colonization or infection require the practice of contact precautions and are preferably isolated in a single room. Further, active surveillance has been progressively implemented in public hospitals since 2010 [7]. Hence, we believe that this data source is appropriate and representative of the whole population in Hong Kong.

Patients who received carbapenemase genotypic screening tests in the study period were identified from the CDARS. Genotypic tests include polymerase chain reaction test for carbapenemase enzymes (*Klebsiella pneumoniae* carbapenemase [KPC], New Delhi metallo-β-lactamases [NDM], Imipenemase [IMP], Oxacillinases [OXA], and Verona integron-encoded metallo-β-lactamase [VIM]), antigen detection for carbapenemases, and Carba-NP test [20]. The inclusion of genotypic tests only ensured the availability of information on specific carbapenemase enzymes.

Because patients can be readmitted to the hospital for the same reason within a short period, any consecutive hospitalizations of the same patient less than 14 days apart were treated as the same hospital episode. Any episode with at least one positive genotypic CPE test was defined as a positive CPE episode. If CPE is detected in specimens from blood or cerebrospinal fluid (CSF), these cases were defined as invasive infections. The index date was defined as the hospital admission date.

2.2. Incidence and microbiological resistant patterns of CPE

The CPE incidence was reported as the monthly number of positive cases per 10,000 population divided by the mid-year population of the corresponding year in Hong Kong. Data on the mid-year population is acquired from the Hong Kong Department of Statistics and Census of the government. [17] The proportions of carbapenemase molecular, according to Ambler Carbapenemase classification (Class A [KPC], Class B [NDM, IMP, or VIM] and Class D [OXA]) and enzyme family, were also reported.

2.3. Potential risk factors for CPE carriage

The most reported potential risk factors for CPE carriage in the literature were history of antibiotic use, hospitalization, Accident and Emergency Department (AED) admission, Intensive Care Unit (ICU) admission, chronic health history, and immunosuppressive status and use of indwelling devices. These potential risk factors were obtained in CDARS one year before the index date. A period of one year is chosen because over 30% of CPE carriers remain colonized at 12 months of follow-up in the healthcare setting [21]. The risk factors (Appendix A) were defined as having an International Classification of Diseases, Clinical Modification (ICD-9-CM) codes for diagnostic or procedure records, and a prescription of any medication of interest in the British National Formulary (BNF) classification or drugs names.

2.4. Nested case-control study

To identify the risk factors for CPE carriage, a nested case-control study was conducted among patients who received a carbapenemase screening test during hospitalization. In the primary analysis, the cases were patients who had at least one CPE-positive hospital episode. Only their first positive episode was included to reduce the misclassification bias from recurrent events. The controls were randomly selected from screening patients with a

negative result only during the study period. The cases and controls were matched up to a 1:4 ratio by sex, age group, and admission year-month. One control can be matched to more than one case. Conditional logistic regression was used to estimate the odds ratio (OR) of risk factors. Backward selection by the *P* value cut-off of 0.15 started with a complete model was also applied to identify the significant risk factors. The OR adjusted by risk factors one year before the index date (Appendix A) was also reported. The data cleaning and analysis were performed by R (version 3.6.0). The analysis was cross-checked independently by FM and YQY.

2.5. Subgroup analysis and sensitivity analysis

Since Enterobactericae are usually found in humans' gastrointestinal tract (GI), subgroup analysis for GI specimens was also conducted. Those patients with positive CPE from stool or rectal swab specimens were considered gastrointestinal carriage of CPE (GI CPE) cases. The cases were matched with up to four controls with a CPE screening test of GI specimens, like the primary analysis.

Several sensitivity analyses were also conducted to validate the robustness of the results: 1) We defined the index date as the CPE screening test date (i.e., the date when the test was ordered); 2) Some patients may receive empirical antibiotic treatment if they are admitted with signs of infection or gastrointestinal symptoms. We excluded those patients with any antibiotic exposure seven days before the index date; 3) The risk window for identifying the risk factors was changed from one year to six months.

3. Results and discussion

3.1. Demographic information and incidence

In the study period, there were 23,797 records for CPE genotypic tests in the CDARS. Around 17.9% (n = 4267) of the records were CPE positive. Most of the specimens were collected from the rectal swab (n = 15,713, 66.0%), followed by stool samples (n = 3024, 12.7%). Among positive CPE samples, more than half (n = 3148, 73.8%) were detected with Class B ambler carbapenemase groups in Hong Kong, and NDM (n = 1226, 28.7%) was the predominant enzyme.

A total of 8588 patients were found to be CPE-positive during the study period. On average, 2.78 CPE screening tests were ordered for each patient during the study period. The majority (94.5%, n = 8117) were identified with one hospital episode, and 4.8% were found with two hospital episodes within the study period. When considering each patient's first episode only, 27.4% (n = 2353) were classified as CPE-positive cases. Among the positive patients, the average age at admission was 65.5 years, and 56.4% were males. Forty-seven people had two classes of carbapenemase concurrently, and one person had all three classes. Class B carbapenemase was most found (78.6%), followed by class D (15.2%). Specifically, the NDM is the predominant enzyme family in Hong Kong (31.7%).

The trend of monthly CPE incidence is illustrated in Fig. 1. In our study, the first CPE case with a positive genotypic screening test was identified in mid-2015. The incidence rate increased from 0.04 in 2015 to 1.62 per 10,000 person-year in 2019. There was a steady increasing trend of CPE incidence throughout the study period, with an observed seasonality peaked in summers (July to September). The mortality rates within 28 days after the screening for CPE-positive cases and invasive infection cases were 26.9% and 42.1%, respectively.

3.2. Risk factors for carriage of CPE

The demographic information for case-controls is shown in Table 1. We included 1709 CPE-positive cases and matched them with 6664 controls in the nested case-control study (flowchart in Fig. 2). After matching, the people confirmed as CPE-positive were found with a higher proportion of prior hospital resource utilization (increased hospital admission, increased ICU admission, longer length of stay). No statistical difference was found for ICU admission between the two groups ($P = 0.920$). Cases had more pre-existing comorbidities (39.1% vs. 34.6%, $P = 0.001$) and histories of antibiotic use (55.9% vs. 48.8%, $P < 0.001$) than controls. The multivariable conditional logistic regression is presented in Table 2. The previous use of beta-lactam antibiotics (OR: 1.37 [1.22–1.53], $P < 0.001$) was found as an independent risk factor for the carriage of CPE. Proton-pump inhibitor use was not identified as a risk factor in our study. Similar findings were observed in the GI CPE subgroup analysis (Table 2) and all sensitivity analyses (Appendix B).

To the best of our knowledge, this is one of the first studies to utilize electronic health records to study the epidemiology of CPE in Hong Kong. The CPE trend is increasing globally with a high clinical and economic burden [2–5,22,23]. Our study results show a 40-times increase in CPE incidence within five years (from 0.04–1.62 per 10,000 person-year from 2015 to 2019), which correlates with our recent findings from data from selected hospitals [8]. The publication by the Hong Kong Strategy and Action Plan on Antimicrobial Resistance (Action Plan) in July 2017 also illustrated an increasing trend of CPE from 2011 to 2016 (19–340 patients) [24]. We concur with the Action Plan's hypothesis that the increased number of CPE cases may be due to the improved vigilance in Hong Kong. Despite the seasonal peak in summer, the increasing incidence is particularly worrying, considering the potential burden of CPE outbreaks on the healthcare system.

Our study found that NDM is the predominant subtype in Hong Kong, which is different from most of the western countries. In the United States, the predominant enzyme family is KPC, the most common type in North and South America and Europe [25–27]. NDM was initially identified in New Delhi and is now widely distributed in India [28]. Moreover, because of the large population in India, rapid transmission has become a new global focus [29–31]. The subtype of CPE may lead to different treatment options and patients' prognoses. An in vitro study in China reported that antimicrobial susceptibility is different between KPC and NDM [32]. A six-year prospective survey collected data from 147 patients and found that NDM has a higher probability of clearance during hospitalization compared with KPC [33]. However, the genes in NDM-type CPE were found to be harboring other beta-lactamase genes and some antibiotic resistance determinants [34]. Development of new antibiotic treatments should target the specific target type of enzyme dominant in different regions. In Asia, the distribution of types of enzymes varies across regions [35]. KPC is the most common enzyme in China. One study conducted in Shanghai identified 13 isolates containing KPC from 16 CPE isolates, but the representativeness of the data source is unclear [36]. Another study conducted in a teaching hospital in China found that 71% of 109 isolates contained KPC along with extended-spectrum beta-lactamase (ESBL) enzyme [37], whilst KPC was not commonly found in our study. Cases of VIM were reported in Asia-Pacific regions, such as Taiwan and Japan [31]; however, we did not observe any cases in Hong Kong. IMP was most found in Japan [31] and OXA-48 was the predominant type in Singapore [38], whereas OXA was the second most common in our study. The geographical difference in enzyme distribution may need to be considered for treatment options because indications of new agents against CPE are usually serotype-specific [39].

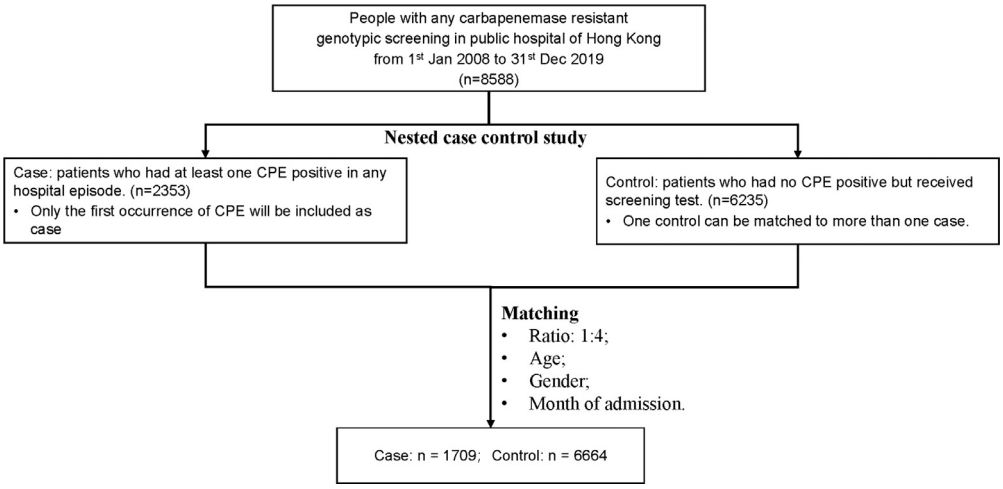

Fig. 1. Number of hospital episodes with positive carbapenemase-producing Enterobacteriaceae test results by month (2015–2019).

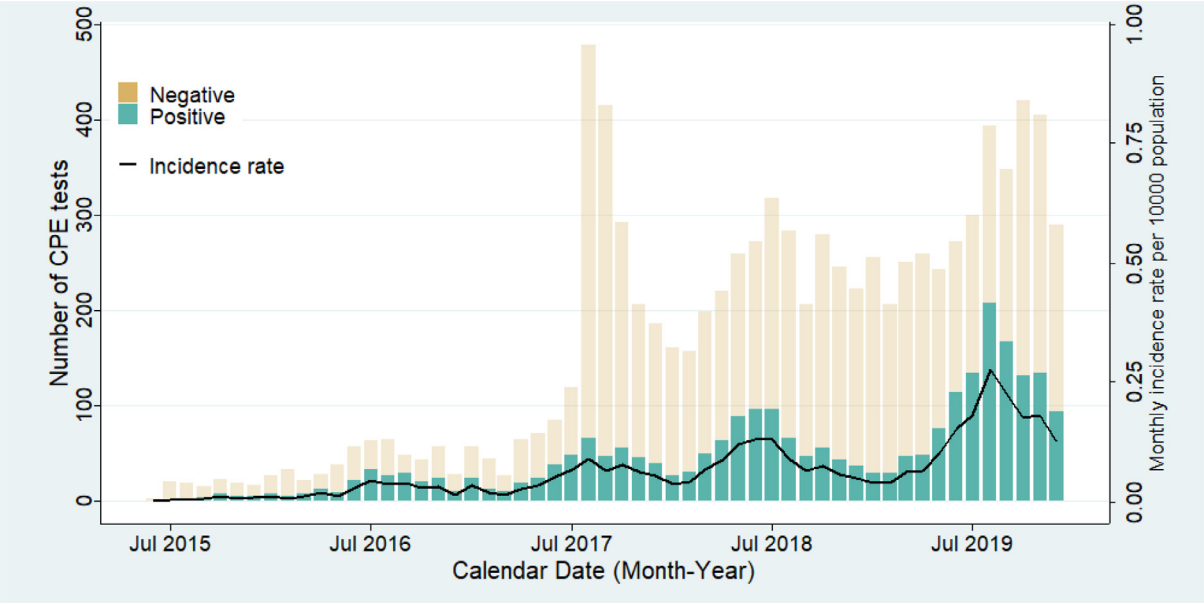

Fig. 2. Flowchart of nested case-control study.

Most previous literature focused on the history of antibiotic or carbapenem use as the risk factor for CPE [40–42]. One study detected beta-lactam use in the ICU as a risk factor (OR 11.71, 95% CI 4.51–30.43), including small sample sizes (n = 41 positive cases) [43]. Another study in the US had a similar finding, but they were predominantly of KPC [11]. Our study found that previous beta-lactam antibiotic use is a statistically significant predictor for CPE carriage in the multivariable analysis, not specifically carbapenem or any previous antibiotic use. A possible explanation is that exposure to beta-lactam antibiotics encourages a selective pressure that allows beta-lactam resistance Enterobacteriaceae to thrive. From the earlier studies, this selective pressure is an important issue contributing to the development of AMR [44,45]. In Hong Kong, the most predominant enzyme family is NDM, whose activity is inhibited by metal-chelating agents and always carries other resistant enzymes, including ESBL [46]. In an in vitro experiment, a gut model was inoculated with KPC and NDM with carbapenem class antibiotics. The results showed an increase in clonal expansion with new resistant populations emerging [47].

In recent literature, PPIs, a subtype of gastric acid suppressants, were considered related to gastrointestinal infections [41,48–50]. A meta-analysis with twenty-four observational studies showed increased OR (3.33 [95% CI 1.84–6.02]) for the relationship between PPIs and infections, but the condition of interest was associated with *Clostridium difficile* rather than Enterobactericeae [49]. Another meta-analysis included twenty-six observational studies and showed increased odds of intestinal carriage of AMR after the prescription of acid suppressants. However, high heterogeneity was reported for the different study settings and types of drugs [50]. A few studies explored the relationship between PPIs and CPE. The earliest exploration was a single-center study conducted in the United Kingdom which did not find any statistical association between PPIs and CPE [13]. On the other hand, our previous study reported PPIs as independent risk factors for gastrointestinal colonization of CPE [41], whilst our present study did not identify any association between PPI use and CPE carriage. There are several possible reasons for such discrepancies. First, our current study was limited to data from genotypic screening tests as opposed to the previous study, which was based on prospective screening results from both phenotypic and genotypic tests. However, case identification by genotypic testing ensures the validity of result. Second, our study is territory-wide, providing a larger sample of

Table 1
Baseline characteristics of patients in the nested case control study for the risk factors of carbapenemase-producing Enterobacteriaceae carriage

Characteristics	Patients with CPE negative (n=6664)	Patients with CPE positive (n=1709)	*P* value
Age [mean ± SD]	67 (20.8)	67 (21.0)	0.382
Sex, Male	3465 (52.0)	888 (52.0)	1
Age group – n (%)			0.932
<5	126 (1.9)	35 (2.0)	
<20	88 (1.3)	28 (1.6)	
<45	713 (10.7)	186 (10.9)	
<65	1703 (25.6)	436 (25.5)	
<85	2644 (39.7)	668 (39.1)	
>=85	1390 (20.9)	356 (20.8)	
Season when admitted – n (%)			0.999
Spring (Mar-May)	1429 (21.4)	369 (21.6)	
Summer (Jun-Aug)	1933 (29.0)	497 (29.1)	
Autumn (Sep-Nov)	2037 (30.6)	520 (30.4)	
Winter (Dec-Feb)	1265 (19.0)	323 (18.9)	
Specimen – n (%)[a]			
Rectal swab	4964 (74.5)	1404 (82.2)	<0.001
Stool	589 (8.8)	263 (15.4)	<0.001
Blood	163 (2.4)	17 (1.0)	<0.001
Cerebrospinal fluid	4 (0.1)	0 (0.0)	0.695
Urine	427 (6.4)	141 (8.3)	0.008
Ambler Carbapenemase group – n (%)			
Class B	NA	1161 (67.9)	
Class D	NA	221 (12.9)	
Class A	NA	116 (6.8)	
Enzyme family – n (%)			
NDM	NA	511 (29.9)	
IMP	NA	18 (1.1)	
KPC	NA	14 (0.8)	
OXA	NA	211 (12.9)	
VIM	NA	0 (0.0)	
Unspecific	NA	558 (32.7)	
Hospital resource utilization – no. (%)[b]			
Hospital Admission	3846 (57.7)	1025 (60.0)	0.096
Intensive care unit	23 (0.3)	5 (0.3)	0.920
Accident and emergency department	3207 (48.1)	870 (50.9)	0.043
Indwelling medical devices	162 (2.4)	43 (2.5)	0.908
Length of stay, days [mean (SD)]	58.17 (183.65)	74.17 (230.85)	0.002
Pre-existing comorbidities – no. (%)[b]			
Any comorbidities below (%)	1935 (29.0)	572 (33.5)	0.002
Diabetes mellitus	784 (11.8)	219 (12.8)	0.25
Hypertension	1161 (17.4)	318 (18.6)	0.267
COPD	313 (4.7)	97 (5.7)	0.107
Renal disease	709 (10.6)	234 (13.7)	<0.001
Congestive heart failure	419 (6.3)	119 (7.0)	0.337
Immunosuppressive status	263 (3.9)	75 (4.4)	0.448
Chronic liver disease	184 (2.8)	62 (3.6)	0.07
Medication use – no. (%)[b]			
Antibacterial	3254 (48.8)	956 (55.9)	<0.001
Beta-lactam antibacterial	3209 (48.2)	943 (55.2)	<0.001
Carbapenem	411 (6.2)	136 (8.0)	<0.001
Non-beta-lactam antibacterial	3455 (51.8)	766 (44.8)	0.009
Proton-pump inhibitor	2416 (36.3)	673 (39.4)	<0.001
H2 antagonists	2133 (32.0)	558 (32.7)	0.018

[a] Each patient may have more than one type of specimen collected.
[b] All the risk windows of history were checked within the past one year prior to the index date.

positive CPE cases. We also controlled for confounding factors by adjustment in a regression model [51,52]. It is also worth noting that our study had a longer study period with more recent data that covered the implementation of the CPE surveillance program in Hong Kong public hospitals. We believe that the previous and current local studies' findings are complementary to different objectives.

This study includes several limitations. First, we could only capture carriers that sought healthcare attention within the Hong Kong public healthcare system. We limited our sample to genotypic tests, which were mostly confirmatory tests of those with certain risk factors for CPE carriage; therefore, the proportion of positive samples could be overestimated. The extent of the implementation of CPE screening may have varied across study hospitals; however, the asymptomatic carriage in the community is not captured in this study. Given that incidence increases throughout the study period, the absolute number of CPE cases presented in this study is likely an underestimation of the reality. Nevertheless, such underestimation does not affect the validity of our nested case-control study. Second, the controls in our nested case-control study were not representative of the general population. We used hospitalized patients who had CPE screening tests with negative results as controls. To minimize selection bias, a matching process with age, sex, and admission year-month was conducted to

Table 2
Multivariable analysis for adjusted odds ratios for CPE and gastrointestinal CPE carriage after adjusting for confounding factors

Characteristics	Adjusted Odds Ratio (95% CI)[a]	*P* value[b]
Primary analysis[c]		
Beta-lactam antibiotics	1.37 (1.22–1.53)	<.001***
Subgroup analysis – GI cases[c]		
Carbapenem	1.32 (1.04–1.67)	0.02*
Beta-lactam antibiotics	1.45 (1.28–1.64)	<.001***

[a] Final model was fitted by backward selection based on *P* value with all potential risk factors, including carbapenem use, beta-lactam use, Accident and Emergency Department (A&E) admission, Intensive Care Unit (ICU) admission, immunosuppressive status, chronic disease history, indwelling devices history, H2-receptor antagonists (H2RA) use, and Proton pump inhibitors (PPI) use.
[b] Symbols for *P* values: NS >.05; *<.05; ** <.01; *** <.001.
[c] The interaction terms between beta-lactam and acid suppressants (PPI and H2RA) were included in the multivariable analysis but excluded by stepwise selection procedure.

balance baseline characteristics between case and control groups. We also cannot differentiate between nosocomial or community carriage because surveillance for CPE is only performed for hospitalized patients. Further studies are warranted to investigate the differences between nosocomial and community carriage. Lastly, the proportions of people with indwelling medical devices or a history of ICU admission are low in Hong Kong. It may be difficult to draw a meaningful conclusion on these potential risk factors. Further investigations should be conducted when more data are available.

This study demonstrated the feasibility of using electronic health records to help evaluate and understand the risk profiles of potential CPE carriers. Our absolute number of positive CPE cases is like that previously reported, which supports the reliable sensitivity of using electronic health records across all public health services provided by the HA. It is worth noting that the CDARS is one of the very few data sources with laboratory data of AMR linked to medical records. Since the rollout of superbugs surveillance in Hong Kong [24], the amount of data accumulated from daily clinical management is extremely useful for studying the epidemiology of superbugs, especially CPE. And it can provide evidence to improve infection control. With the advancement of technology and the rich source of electronic health records, further research should explore the use of big data in AMR surveillance. Such evidence will help supplement traditional clinical studies with robust clinical workup and detailed laboratory results to help combat AMR.

The incidence of CPE in Hong Kong dramatically increased from 2015 and peaked at 1.64 per 10,000 person-year in 2019, with NDM being the predominant enzyme family. The use of beta-lactam antibiotics may encourage the carriage of CPE. This study also demonstrated the feasibility of using big data in AMR research. The use of big data for AMR surveillance and to supplement clinical research should be encouraged.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jgar.2023.03.013.

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