Carriage prevalence of antimicrobial resistance in Hong Kong: a longitudinal study (abridged secondary publication)

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KEY MESSAGES

1. The decreasing point prevalence of extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBL-E) in the general population from 54.8% (July 2018 to April 2019) to 43.4% (July 2019 to January 2020) suggests that the government's population-wide effort to combat antimicrobial resistance has been effective.
2. The high proportion (29.6%) of individuals who were colonised persistently (for a mean of 42.0 weeks) with ESBL-E is worrying. This suggests potential outbreaks of infections caused by ESBL-E. More understanding on the transient nature of ESBL-E colonisation enables better implementation of prevention strategies.
3. As an additional household member increased the odds of one carrying ESBL-E persistently by 16%; future study of household transmission of ESBL-E is warranted.
4. Owing to the continual presence of methicillin-resistant *Staphylococcus aureus* and carbapenem-producing Enterobacteriaceae in the community, an alert system should be in place to identify carriers discharged from healthcare settings, especially when the prevalence in the community remains low.

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Introduction

Antimicrobial resistance (AMR) is a major threat to public health worldwide. The United States Centers for Disease Control and Prevention identifies extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBL-E), carbapenem-producing Enterobacteriaceae (CPE), and methicillin-resistant *Staphylococcus aureus* (MRSA) as the top drug-resistant threats.[1]

The epidemiology of ESBL-E carriage in Hong Kong community has not been studied. Hong Kong is a densely populated city and hence a potential reservoir for MRSA transmission. This study aims to estimate the colonisation rate of different types of antimicrobial-resistant bacterial strains and their temporal change across time in the community and to identify demographic characteristics and age-structured social mixing behaviours of individuals associated with antibiotic-resistant colonisation of ESBL-E.

Methods

Population-based household cohorts were invited consecutively through telephone until the sample size was reached. Random telephone dialling was used to top up the sample size if necessary. In round 1 conducted from 3 July 2018 to 27 April 2019, 1000 household members were expected to recruit. In round 2 conducted from 3 July 2019 to 3 January 2020, 750 household members were expected to recruit. Interested household members who were Hong Kong residents and resided in the selected households for at least 5 days a week were invited to the Prince of Wales Hospital or a site in Central for an interview about demographics, personal hygiene, and antibiotic use as well as for collection of nasal and handprint samples (by staff) and stool samples (previously collected by participants). Participants were compensated with HK$80 cash.

Nasal swabs were kept into nutrient broth with 7% salt for overnight incubation before subculture onto selective agar (ChromID MRSA, BioMérieux, France). Handprint samples of the non-dominant hand were collected onto the surface of selective agar (ChromID MRSA, BioMérieux, France), which were incubated at 37°C aerobically for 24 to 48 hours. Stool samples were collected within 24 hours of production and plated directly onto selective agar (ChromID ESBL and ChromID Carba SMART, BioMerieux, France) by cotton swab, streaking using 1 µl loop. After overnight culture at 37°C (ambient air), one colony for each morphotype was picked and bacterial identification was performed using MALDI-TOF.

The prevalence of MRSA, CPE, and ESBL-E in round 1 and round 2 was determined. Colonisation status was defined as persistent carriage if a participant tested positive for bacteria in both rounds and as intermittent if tested positive in either round. For MRSA and CPE, the characteristics of their carriers and the corresponding household members were summarised. For ESBL-E, factors associated with their carriage were investigated. To account for within-household correlations, logistic regression analysis in the generalised estimating equation framework with an exchangeable correlation structure was applied to explore the risk factors for ESBL carriage. Explanatory factors included were demographics and personal characteristics (such as age, sex, household income, health conditions, antibiotic use in the past six months, contacts), household characteristics (such as size), and hospitalisations and social activities in the past 6 months. Variables included in the univariate analysis were based on a literature review. Chi-squared test, Fisher's exact test (for small counts), and Student's t-test were used as appropriate to test for associations with the outcome. The initial multivariate model included variables with a P value of <0.1 from the univariate analysis. A stepwise backward elimination technique was used to remove variables based on their P value from the likelihood ratio test. The final multivariate model was determined based on the one with the lowest Akaike information criterion. Adjusted odds ratios with 95% confidence intervals were presented. A statistical significance was set at P<0.05. Missing data were imputed using a multiple imputation technique.

TABLE 1. Characteristics and medical history of participants (n=1005)

Characteristic	Value*
Sex	
Male	416 (41.39)
Female	589 (58.61)
Age group, y	
3-49	234 (23.28)
50-59	237 (23.58)
60-90	534 (53.13)
Economic activity status	
Employee	389 (38.71)
Retired	386 (38.41)
Home-maker	120 (11.94)
Student, unemployed	50 (5.00)
Self-employed	26 (2.59)
Unknown	28 (2.79)
Educational attainment	
Primary or less	135 (13.43)
Secondary	502 (50.00)
Post-secondary	357 (35.52)
Unknown	11 (1.09)
Monthly household income, HK$	27500 (12500-45000)
Owns pets (cats, dogs, rabbits, hamsters, hedgehogs, fish, shrimp, turtles, parrots, bees, spiders)	187 (18.61)
Medical history	
History of chronic diseases	588 (58.5)
History of antimicrobial-resistant bacteria infection	12 (1.2)
Smoker (current/former)	121 (12.0)
Received antibiotic prescription in the past 6 months	472 (47.0)

* Data are presented as No. (%) of participants or median (interquartile range)

Results

Of 2094 households invited, 814 agreed to be interviewed; the response rate was 38.9%. A total of 589 female and 416 male participants aged 3 to 90 (mean, 57.4) years were recruited (Table 1). 53.1% of participants were aged 60 to 90 years. 58.5% of participants had chronic diseases, with hypertension being the most common (23.7%), followed by hypercholesterolaemia (17.0%), diabetes mellitus (9.2%), and musculoskeletal diseases (9.2%). Twelve participants self-reported a history of an antimicrobial-resistant bacterial infection. 12% of participants were smokers, and 47% of participants had received antibiotics in the previous 6 months.

In round 1, 894 of 1005 participants provided stool samples. In round 2, 634 of 701 participants provided stool samples. The mean time elapsed between two rounds was 42 (range, 14.7-77.0) weeks. For MRSA, the prevalence was 1.69% in round 1 and 1.71% in round 2 and that of persistent carriage was 0.71% (95% confidence interval [CI]=0.23-1.66). For CPE, the prevalence was 2.13% in round 1 and 0.63% in round 2 and that of persistent carriage was 0%. However, for ESBL-E, among 607 participants who provided stool samples in both rounds, the prevalence of carriage was 54.8% (95% CI=51.5%-58.1%) in round 1 and 43.4% (95% CI=39.5%-47.3%) in round 2 and that of persistent carriage was 29.6% (95% CI=26.0%-33.4%) and that of intermittent carriage was 37.7% (95% CI=33.9%-41.8%); 199 subjects had no carriage in either round.

Factors associated with ESBL-E carriage in round 1 included sex (adjusted odds ratio [aOR]=1.34, 95% CI=1.03-1.72), economically active (aOR=1.44, 95% CI=1.09-1.91), receiving at least one course of antibiotics in the previous 6 months (aOR=1.59, 95% CI=1.16-2.18), visiting a clinic in the past 6 months (aOR=1.52, 95% CI=1.08-2.13), and having any close contacts on the day before the interview (aOR=1.48, 95% CI=1.09-2.02) [Table 2].

TABLE 2. Prevalence of extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBL-E), carbapenem-producing Enterobacteriaceae (CPE), and methicillin-resistant *Staphylococcus aureus* (MRSA) in each round*

Bacteria	Round 1 (n=1005)	Round 2 (n=701)	Colonisation transition				
			Persistent carriage	Intermittent carriage			Neither
				Total	-ve to +ve	+ve to -ve	
ESBL-E	54.8 (51.5-58.1)	43.4 (39.5-47.3)	29.6 (26.0-33.4)	37.7 (33.9-41.8)	14.1 (11.5-17.1)	23.6 (20.3-27.2)	32.7 (29.0-36.6)
CPE	2.13 (1.28-3.30)	0.63 (0.17-1.61)	0 (0-0.60)	2.96 (1.76-4.63)	0.66 (0.18-1.67)	2.30 (1.26-3.83)	97.0 (95.4-98.2)
Staphylococcus aureus	23.4 (20.8-26.1)	21.3 (18.3-24.5)	12.7 (10.3-15.4)	19.5 (16.7-22.7)	8.56 (6.59-10.9)	11.0 (8.77-13.5)	67.8 (64.2-71.2)
MRSA	1.69 (0.99-2.69)	1.71 (0.89-2.97)	0.71 (0.23-1.66)	1.85 (0.99-3.15)	1.00 (0.40-2.05)	0.86 (0.31-1.85)	97.4 (96.0-98.5)
(%MRSA among *Staphylococcus aureus* +MRSA)	6.7	7.5	-	-	-	-	-

* Data are presented as % (95% confidence interval)

The odds of ESBL carriage was higher among male (aOR=1.80, 95% CI=1.23-2.64), those who visited a clinic or hospital in the past 6 months (aOR=1.21, 95% CI=1.03-1.43), and those who had a household member hospitalised in the past 6 months (aOR=1.13, 95% CI=1.01-1.28) [Table 3]. Household size was a risk factor for ESBL-E carriage, with the odds increasing by 16% for each additional household member.

TABLE 3. Logistic generalised estimating equation analysis of persistent carriage of extended-spectrum beta-lactamase-producing Enterobacteriaceae (n=607)

Variable	Univariate analysis, OR (95% CI)	Multivariate analysis, adjusted OR (95% CI)
Sex		
Female (reference)	-	-
Male	1.81 (1.23-2.66)	1.80 (1.23-2.64)
Visited a clinic/hospital in the past 6 months		
No (reference)	-	-
Yes	1.17 (0.99-1.38)	1.21 (1.03-1.43)
No. of household members	1.21 (1.05-1.39)	1.16 (1.01-1.34)
Any household member hospitalised		
No (reference)	-	-
Yes	1.14 (1.01-1.28)	1.13 (1.01-1.28)

Discussion

This population-based study assessed the background asymptomatic carriage of MRSA, CPE, and ESBL-E in the community. The prevalence of ESBL-E in the community was high, with *Escherichia coli* being the most common organism, and the prevalence of persistent carriage of ESBL-E was 29.6%. Colonisation of ESBL-E was a dynamic process from round 1 to round 2, with 14.1% (95% CI=11.5-17.1) acquired colonisation, compared with 23.6% (95% CI=20.3-27.2) lost colonisation. In contrast, the prevalence of CPE and MRSA in the community were low.

The significant decrease in the prevalence of ESBL-E carriage from 54.8% to 43.4% in the community suggests that the government effort in reducing AMR was effective. In 2017, Hong Kong Strategy and Action Plan on Antimicrobial Resistance was launched to improve awareness and understanding of antimicrobial resistance through effective communication, education, and training.

Future study of household transmission of ESBL-E is warranted, because an additional household member increased the odds of one carrying ESBL-E persistently by 16% (even after adjusting for having household members hospitalised), which is lower than the 23% to 25% reported in a study.[2] This may be due to the abundance of ESBL-E in the community.

The prevalence of persistent carriage of ESBL-E of 29.6% is worrying, which is lower than the 40% reported in a study.[3] With the average time elapsed between two rounds being 42.0 weeks, the rate of acquiring colonisation was 14.1% and that of clearance was 23.6%. The median time to clear ESBL-E colonisation was reported to be 6.6 months,[3] and the period to gradual clearance of ESBL-E was reported to be 12 to 54 weeks.[4] The different colonisation rate in our study may be masked by several cycles of colonisation and clearance. Further study on the transient nature of colonisation with more frequent rounds of recruitment is warranted.

Owing to the persistent presence of MRSA and CPE in the community, an alert system should be in place to identify carriers after discharged from healthcare settings, especially when the prevalence in the community remains low. MRSA and CPE used to be found only in hospitals. For CPE, plasmid-mediated genes in hospitals are effective in spreading in the community. Such spread was exacerbated by patients' persistent carriage of CPE after discharge (mean time to clearance is 387 days). With an increasing rate of hospital-acquired CPE in Hong Kong,[5] strategic control measures are needed. Similar situation applies to MRSA.

There are limitations to the present study. Only two rounds of recruitment across a mean of 42 weeks were conducted. The observed transient rate of colonisation or clearance may be masked by multiple cycles. More rounds of recruitment should have been performed. Not all members of a household were enrolled and thus the effect of household transmission may not have been assessed. Not all sources of AMR transmission such as dietary intake (the prevalence of ESBL-E and CPE in pig and fish samples from wet markets was high[5]) were studied given limited resources. Caution should be exercised when extrapolating the findings from this study to the current situation of AMR because of the knock-on effect of COVID-19 pandemic on AMR.

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Disclosure

The results of this research have been previously published in:

1. Kwok KO, Chan E, Chung PH, et al. Prevalence and associated factors for carriage of Enterobacteriaceae producing ESBLs or carbapenemase and methicillin-resistant Staphylococcus aureus in Hong Kong community. J Infect 2020;81:242-7.

References

1. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2019. Available from: https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf
2. Hilty M, Betsch BY, Bogli-Stuber K, et al: Transmission dynamics of extended-spectrum β-lactamase-producing Enterobacteriaceae in the tertiary care hospital and the household setting. Clin Infect Dis 2012;55:967-75.
3. Birgand G, Armand-Lefevre L, Lolom I, Ruppe E, Andremont A, Lucet JC. Duration of colonization by extended-spectrum β-lactamase-producing Enterobacteriaceae after hospital discharge. Am J Infect Control 2013;41:443-7.
4. ÖstholmBalkhed Å, Tärnberg M, Nilsson M, et al. Duration of travel-associated faecal colonisation with ESBL-producing Enterobacteriaceae: a one year follow-up study. PLoS One 2018;13:e0205504.
5. Wong SC, Chan VWM, Lam GK, et al. The use of multi-pronged screening strategy to understand the epidemiology of carbapenemase-producing Enterobacteriaceae in Hong Kong: transition from epidemic to endemic setting. Eur J Clin Microbiol Infect Dis 2021;40:2017-22.