Comparing Antimicrobial Resistance Profiles of Patients and Community Residents: Implications for Targeted Interventions

Overview

Antimicrobial resistance (AMR) presents a significant challenge to global health, jeopardising the effectiveness of standard treatments for infectious diseases [1]. Some clinically important bacterial pathogens, such as ESBL-producing or carbapenems-resistant *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae (K. pneumoniae)*, MRSA, vancomycin-intermediate and -resistant *Staphylococcus aureus* (VISA and VRSA), colonised in individuals without causing infections (commensal bacteria) or leading to infections at certain conditions (opportunistic pathogens), exhibiting concerning rates of resistance in healthcare settings [2-5]. However, there is a lack of understanding about the AMR profile and colonisation burden of these bacteria in the community, limiting the development of effective empirical treatments against bacterial infections. By analysing clinical data, including those from inpatients and nursing homes, from Pfizer's ATLAS project alongside community data from a previous study on commensal bacteria in Hong Kong, we have gained valuable insights into these clinically significant bacteria, particularly their AMR profiles in both settings. This comparison enhances our understanding of these pathogens and informs targeted interventions, ultimately improving antimicrobial stewardship and management strategies for resistant infections in clinical and community contexts.

Methods

We analysed the minimal inhibitory concentration (MIC) of 11 antibiotics for clinical isolates of *E. coli*, *K. pneumoniae*, and *S. aureus* collected between 2018 and 2022 from adults over 19 years in mainland China, Taiwan, and Hong Kong, as well as for commensal bacteria isolated from community residents in Hong Kong.

We transformed the MIC values to analyse the AMR profiles of clinically and non-clinically significant bacterial isolates from the studied locations. First, we converted categorical MICs that reached detection limits (denoted as "α") into numerical values by drawing a random variable (X) from a normal distribution ($X \sim N(\mu, \sigma^2)$), with the mean (μ) set to β1 * α and the standard deviation (σ) set to β2 * μ. The constant β1 and β2 were chosen between 0.1 and 0.5 to optimise differentiation while preserving data integrity, resulting in transformed MIC values (MIC') calculated as α ± X.
Next, we standardised phenotypic susceptibility by calculating MIC fold changes against CLSI/EUCAST cutoffs or the lowest detection limits in the community data (e.g., 2 μg/mL for imipenem). Fold changes ≤1 indicated susceptibility (or intermediate susceptibility to imipenem), while values >1 indicated non-susceptibility.
We calculated pairwise Bray-Curtis dissimilarity distances based on the fourth root transformed relative MIC fold changes to assess variability in antimicrobial susceptibility profiles across different settings or regions. We visualised the results using Principal Coordinates Analysis (PCoA) with phyloseq and ggplot2.

To evaluate the statistical significance of inter-group variations in AMR profiles, we performed a PERMANOVA test, which required homogeneity of intra-group beta-dispersion. Pairwise comparisons were conducted using pairwise adonis, and beta-dispersion was assessed with the betadisper function in *vegan*. The contribution of individual antibiotic resistance to group variations was analysed using similarity percentages (SIMPER) based on Bray-Curtis dissimilarities, with significance evaluated via the Kruskal-Wallis rank-sum test. Only antibiotics contributing over 1% of the variance with $p < 0.01$ were reported.

Results

The AMR profiles of the three studied bacterial species differed between clinical and community settings, especially for *E. coli* and *K. pneumoniae* (Figure 1). Resistance rates were notably higher in clinical settings, showing up to 80 folds differences across most antibiotics tested compared with community isolates. Over 98% of the clinical isolates of *E coli* and *K. pneumoniae* are intermediate resistant to colistin, although the resistance rates in the two settings are much closer (2.13% vs.. 0.49%).

The difference in the resistance rate of *S. aureus* against the tested antibiotics is less pronounced between clinical and community settings, compared with the discrepancies in the two Gram-negative bacteria.

Among the studied isolates, carbapenem-resistant *E. coli* and *K. pneumoniae* were more prevalent in clinical environments, especially in China (Figure 2 and Table 1). ESBL-producing *E. coli* and *K. pneumoniae, which are* defined as resistant to third- and fourth-generation cephalosporins, were most common in China, followed by *E. coli* from Taiwan and the Hong Kong community.

In community settings, higher rates of vancomycin-intermediate (VISA) and vancomycin-resistant (VRSA) strains compared to clinical environments, highlighting a significant public health concern. This indicates a worrying trend of increasing prevalence of clinically important pathogens and resistance to critical antibiotics like vancomycin emerging within the community.

The PCoA results revealed significant differences in the AMR profiles, indicated by relative MIC fold changes of 11 antibiotics, between ESBL-producing and non-ESBL-producing nor carbapenem-resistant *E. coli* and *K. pneumoniae* in community and clinical settings across multiple regions (Figure 3 and Table 2). The variation in ESBL-producing isolates was primarily driven by higher nonsusceptibility to third and fourth-generation cephalosporins (ceftazidime and cefepime), aztreonam, ciprofloxacin, and trimethoprim/sulfamethoxazole in clinical isolates. In contrast, non-clinically significant isolates from the community showed significantly higher MIC fold changes for ampicillin, cefepime, gentamicin, and carbapenems. Notably, resistance to ampicillin, cefepime, and gentamicin in these *E. coli* and *K. pneumoniae* isolates highlights the hidden AMR burden among non-ESBL-producing and non-carbapenem-resistant bacteria in the community (Figure 3 and Table 2).

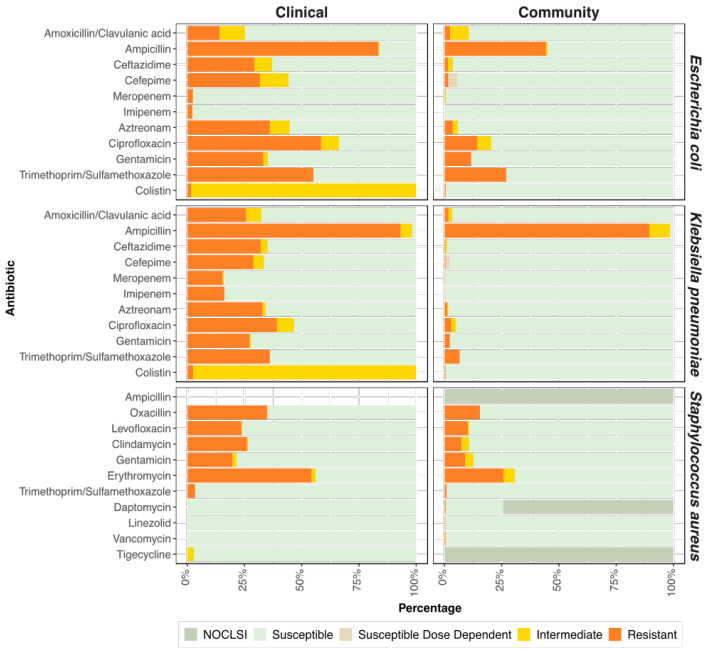

Figure 1. AMR profiles of E. coli, K. pneumoniae and S. aureus from clinical and community settings.

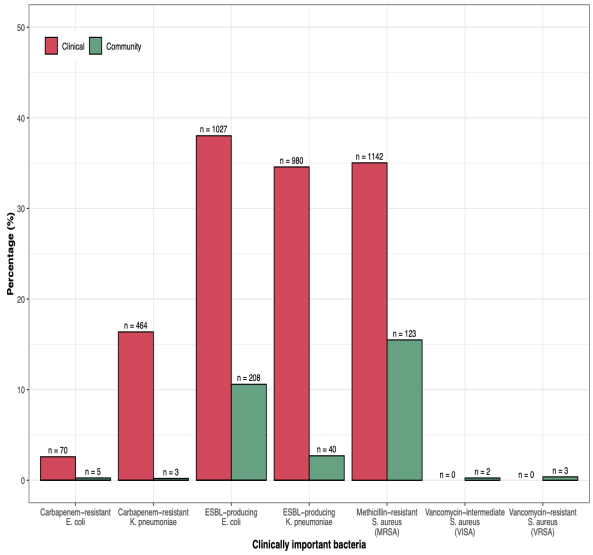

Figure 2. Prevalence of clinically important bacterial isolates from clinical and community settings.

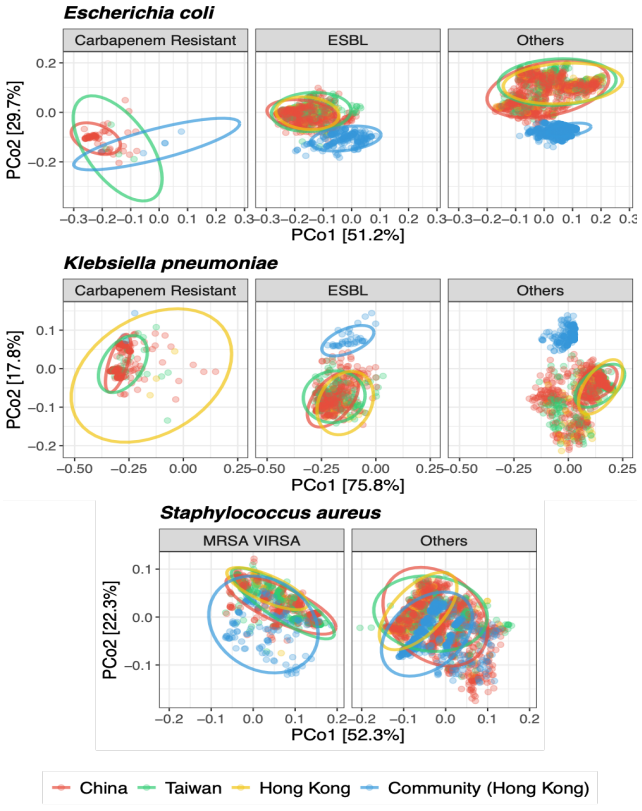

Figure 3. PCoA Analysis of Antimicrobial Resistance Profiles in *E. coli, K. pneumoniae*, and *S. aureus* Across Clinical and Community Settings.

Table 1. Prevalence of clinically important bacterial isolates from clinical and community settings in different regions.

Pathogen*	Location	*E. coli* n	*E. coli* %	*K. pneumoniae* n	*K. pneumoniae* %
Carbapenem Resistant	**China**	66	3.6	418	21.4
	Taiwan	4	0.7	42	6.1
	Hong Kong	0	0.0	4	2.0
	Community (Hong Kong)	5	0.3	3	0.2
ESBL	**China**	779	41.9	742	38.1
	Taiwan	209	34.5	207	30.1
	Hong Kong	39	16.4	31	15.7
	Community (Hong Kong)	208	10.6	40	2.7
Others	**China**	1076	57.9	1198	61.5
	Taiwan	397	21.4	478	69.5
	Hong Kong	199	10.7	164	83.2
	Community (Hong Kong)	1755	94.5	1441	97.3

Pathogen#	Location	*S. aureus* n	*S. aureus* %
MRSA	**China**	663	30.5
	Taiwan	426	47.1
	Hong Kong	53	29.0
	Community (Hong Kong)	123	15.5
VISA	**China**	0	0.0
	Taiwan	0	0.0
	Hong Kong	0	0.0
	Community (Hong Kong)	2	0.3
VRSA	**China**	0	0.0
	Taiwan	0	0.0
	Hong Kong	0	0.0
	Community (Hong Kong)	3	0.4
Others	**China**	1510	69.5
	Taiwan	478	52.9
	Hong Kong	130	71.0
	Community (Hong Kong)	670	84.4

* A carbapenem-resistant and ESBL-producing isolate was defined as a carbapenem resistant isolate.
# A oxacillin-resistant *S. aureus* was defined as MRSA.
# A vancomycin-intermediate *S. aureus* was defined as VISA.
# A vancomycin-resistant *S. aureus* was defined as VRSA.

For *S. aureus*, the AMR profiles of MRSA/VIRSA were distinct and partially overlapping between settings, whereas non-MRSA/VIRSA profiles were more similar. Unlike *E. coli* and *K. pneumoniae*, *S. aureus* showed higher ampicillin resistance in clinical settings, while community isolates exhibited more resistance to clindamycin,

gentamicin, and erythromycin (Figure 3 and Table 2). This underscores that assessing AMR burden solely by resistance status (susceptible, intermediate, or resistant) is insufficient. Our analysis offers a refined approach to examining AMR burden through relative MIC fold changes across multiple antibiotics for each isolate. However, varying MIC detection capabilities may limit this method's effectiveness. Therefore, establishing internationally standardised MIC detection ranges and techniques is essential for enhancing the comparability of AMR results across different countries and regions.

Table 2. Percentage Contribution of Specific Antibiotics to Variance in MIC Fold Changes in Susceptibility Tests for Bacterial Isolates from Clinical and Community Settings.

Escherichia coli

	Betadispersion		PERMANOVA		#Antibiotic relative MIC fold change-based SIMPER (% Contribution)							Sum
Carbapenem Ressistant	*p*-value	Sig	*p*-value	Sig	Penicillins (aminopenicillins) Ampicillin	3rd/4th Gen Cephalosporins Ceftazidime	Cefepime	Carbapenems Meropenem	Monobactams Aztreonam	Fluoroquinolones Ciprofloxacin	Aminoglycosides Gentamicin	Folate pathway inhibitors Trimethoprim/ Sulfamethoxazole	
China vs Community (Hong Kong)	0.000323	*	0.003	*		*21.4		*11.7	*16.8	*13.3		*13.5	76.7
Taiwan vs Community (Hong Kong)	0.0148	.	0.153			*21.4							21.4
China vs Taiwan	0.9985		0.117							*16			16
ESBL													
Hong Kong vs Community (Hong Kong)	0.8409		0.006	*	23.5	*7.9	*17.6		*10.5	*14.3		*15.4	89.2
China vs Community (Hong Kong)	0.98		0.006	*	21.8	*9.6	*17		*13.7	*13		*15	90.1
Taiwan vs Community (Hong Kong)	2.07E-06	*	0.006	*	24.2	*11.7	*12.9		*9.9			*16.1	74.8
Taiwan vs Hong Kong	0.0011	*	0.012	.			20.1						20.1
Others													
Hong Kong vs Community (Hong Kong)	9.74E-10	*	0.006	*			5.2	4.8		*20.4	7.6	*23.7	61.7
China vs Community (Hong Kong)	9.74E-10	*	0.006	*	21.4		4.4	3.8		*27.8	6.6	*24.2	88.2
Taiwan vs Community (Hong Kong)	9.74E-10	*	0.006	*	22.7		4.7	4.2			6.2	*30.1	67.9
China vs Hong Kong	0.0218	.	0.006	*						*37.7	*7.6	*35.7	81
Taiwan vs Hong Kong	0.5781		0.048	.								*41.9	41.9

Klebsiella pneumoniae

	Betadispersion		PERMANOVA		#Antibiotic relative MIC fold change-based SIMPER (% Contribution)										Sum
Carbapenem Ressistant	*p*-value	Sig	*p*-value	Sig	Penicillins (aminopenicillin/beta-lactamase inhibitors) Amoxicillin/Clavulanic acid	Penicillins (aminopenicillins) Ampicillin	3rd/4th Gen Cephalosporins Ceftazidime	Cefepime	Carbapenems Meropenem	Imipenem	Monobactams Aztreonam	Fluoroquinolones Ciprofloxacin	Aminoglycosides Gentamicin	Folate pathway inhibitors Trimethoprim/ Sulfamethoxazole	Polymyxins Colistin	
China vs Community (Hong Kong)	0.9999		0.006	*		15.5					*15.5	*12				43
Taiwan vs Community (Hong Kong)	0.8236		0.03	.		17.2										17.2
China vs Hong Kong	0.01	.	0.012	.					*14.4							14.4
China vs Taiwan	0.017	.	0.006	*			*19.8		*12.9		*24.6					57.3
ESBL																
Hong Kong vs Community (Hong Kong)	0.059		0.006	*		25.2	*14.6				*9.7			*18		67.5
China vs Community (Hong Kong)	0.6566		0.006	*		21.8	*12.3	*13.7			*15.6	*11.4		*15.2		90
Taiwan vs Community (Hong Kong)	0.0951		0.006	*		21.7	*18.1				*14.7			*15.5		70
China vs Hong Kong	0.1281		0.006	*				*19.8			*21.6					41.4
Taiwan vs Hong Kong	0.7461		0.054				*21.4				*21.3					42.7
Others																
Hong Kong vs Community (Hong Kong)	0.0000	*	0.006	*		27.8		8.7	8.7	7.3	4.6	*11.8	5.1	*15.3		89.3
China vs Community (Hong Kong)	0.0000	*	0.006	*		28.6		9.4	9.3	7.4	5.3	*11.3	5.3	*13.1		89.7
Taiwan vs Community (Hong Kong)	0.0000	*	0.006	*		28.5		8.8	8.7	7.2	4.8	*8.1	5.8	*17.6		89.5
China vs Hong Kong	0.466		0.204		7	*5.4							*4.1		*4.9	21.4

Staphylococcus aureus

	Betadispersion		PERMANOVA		#Antibiotic relative MIC fold change-based SIMPER (% Contribution)					Sum
	Betadispersion		PERMANOVA		Penicillins (aminopenicillins)	Fluoroquinolones	Lincosamides	Aminoglycosides	Macrolides	
MRSA or VIRS	*p*-value	Sig	*p*-value	Sig	Ampicillin	Levofloxacin	Clindamycin	Gentamicin	Erythromycin	
Hong Kong vs Community (Hong Kong)	0.000	*	0.006	*	*29.4	*16.1	8.1	7.4		61
China vs Community (Hong Kong)	0.000	*	0.006	*	*26.7	*10.6		*8	*27	72.3
Taiwan vs Community (Hong Kong)	0.000	*	0.006	*	*26.6	*12.3	*11	*10	*26	85.9
China vs Hong Kong	0.9412		0.006	*		19.3	*16.4		*37.4	73.1
Taiwan vs Hong Kong	0.9019		0.006	*		18.3	*14.1	*15.2	*38.5	86.1
Others										
Hong Kong vs Community (Hong Kong)	0.9997		0.006	*	*43	*6.6	9.5	5.6	24.8	89.5
China vs Community (Hong Kong)	0.00e+00	*	0.006	*	*34.9	*6.3	*9.8		*34.1	85.1
Taiwan vs Community (Hong Kong)	7.08e-05	*	0.006	*	*38.6		9.1	*9.7	*28.6	86
China vs Hong Kong	0.0087	*	0.006	*			*6.8		*35	41.8
Taiwan vs Hong Kong	0.0505		0.006	*				*8.9		8.9

Sig: Significance. A p-value < 0.001 is denoted by ".", while a p-value < 0.05 is indicated by "*".
#For pairs where the left group has higher mean relative MIC fold changes, the SIMPER contributions are indicated by "*".

Impact of Work

The study on antimicrobial resistance provides vital insights into the prevalence of resistance in both clinical and community settings within the Greater China region. Our analysis shows that *E. coli* and *K. pneumoniae* have significantly higher resistance rates in clinical environments, especially regarding colistin, a last-resort antibiotic for severe gram-negative infections. Alarmingly, the presence of carbapenem-resistant strains in clinical settings highlights the growing challenges faced by healthcare systems.

In community settings, an emerging threat is evident with increased rates of vancomycin-intermediate and vancomycin-resistant strains, indicating a concerning trend of resistance affecting the general population. Furthermore, similar AMR profiles for MRSA were observed in both community and clinical environments, potentially linked to the recent rise in community-associated MRSA infections. This suggests substantial transmission of *S. aureus* between these settings.

This dual burden of AMR underscores the urgent need for robust surveillance and targeted interventions, as the differences between clinical and community resistance profiles are diminishing, particularly for *S. aureus*. The findings highlight the importance of addressing AMR as a public health priority, necessitating international collaboration to standardise detection efforts.

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