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Disease pattern and risk factors of antimicrobial resistance in patients with pneumococcal infection in the Hong Kong population

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ABSTRACT

Objectives: Antimicrobial resistance (AMR) presents significant challenges for the effective treatment of pneumococcal disease (PD), disease prevalence, and vaccine effectiveness caused by *S. pneumoniae*. We aimed to describe the pattern of AMR among isolates from patients with PD reported in the Hong Kong population from 2012-2021, and to explore the risk factors associated with AMR among patients hospitalized with PD compared to those with susceptible isolates.
Methods: PD-related hospitalizations were identified and grouped into invasive PD (IPD) or non-IPD patients. Electronic health records were collected to calculate the healthcare resource utilization relevant to each IPD/non-IPD patient. We compared the characteristics of patients with IPD/non-IPD caused by non-susceptible isolates (cases) and those without (controls) using a multivariable logistic regression model, looking for risk factors for AMR.
Results: The PD incidence trend was stable from 2012 to 2019 with a sudden decrease in 2020, coinciding with the beginning of the COVID-19 pandemic. Overall, 80% of patients had *S. pneumoniae* non-susceptible to ≥1 antibiotic. The percentage of non-susceptibility found to tetracyclines, macrolides, penicillin, and fluoroquinolones, were 85%, 79%, 23% and 2%, respectively. Overall, 46% of the patients with serotyping results were serotype 3. Significantly increased odds of AMR infection were found among the non-IPD patients aged 2-17 years when compared to older patients (18-64 years).
Conclusions: Measures to reduce non-susceptible *S. pneumoniae* infections should focus on children and adolescents of school age. Despite the introduction of PCV13 in 2011, serotype 3 and AMR continued to threaten people in the community. Serotype 3-infected patients accounted for nearly half of the patients with PD with serotyping results.

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Background

Pneumococcal disease (PD) is caused by *Streptococcus pneumoniae*, a gram-positive bacterium, which causes a range of infections from non-invasive respiratory tract mucosal infections, such as acute otitis media, sinusitis, and community-acquired pneumonia (CAP), to invasive infections. Invasive PD (IPD) occurs when pneumococcal bacteria enter the bloodstream (bacteremia) or penetrate the blood-brain barrier, causing meningitis. *S. pneumoniae* is the most common bacterial pathogen associated with pneumonia, among all adult CAP with confirmed pathogens in Hong Kong, China (HK) in 2017-18 [1]. Children <2 years and adults >65 years were at an elevated risk of IPD [2]. In Singapore, a retrospective cohort study reported that 27.1% of patients with IPD were aged ≥65 years and 27% were aged <5 years between 1997 and 2013 [3].

Resistant bacterial infections are often hard to treat with limited antimicrobial choices, resulting in a higher healthcare burden and mortality [4–6]. In a retrospective cohort study from the United States (US) of adult inpatients and ambulatory patients in 2018-2019, 39.5% of pneumococcal bacteria exhibited resistance to macrolides, with a resistance rate of 29.6% in blood isolates from patients with IPD compared to 47.3% in respiratory non-IPD isolates [4]. In the US, the active bacterial core surveillance network reported that 21.4% of IPD isolates collected from multistate surveillance during 2017 exhibited penicillin non-susceptibility, characterized by whole-genome sequencing. Of the penicillin non-susceptible strains, 66.9% were macrolide resistant, with 8.8% also demonstrating clindamycin resistance (therefore being multidrug resistant with resistance to three different classes of drugs) 7.

In HK, antibiotic non-susceptibility in *S. pneumoniae* is as high as 75% for penicillin and 80% for erythromycin, with varying degrees of resistance observed in cephalosporins, clindamycin, and fluoroquinolones [8–12]. However, most of these studies were published as early as 2001-2013. Only a limited number of studies examined the trend of PD and antimicrobial resistance (AMR) carriage after 2013 [11]. In addition, these studies did not explore the risk factors associated with AMR infections. Since 2013, the Centre for Health Protection of the Department of Health has transformed the Inter-hospital Multi-disciplinary Programme on Antimicrobial ChemoTherapy (IMPACT) guideline into a mobile app that provides local evidence-based recommendations for clinical antibiotic prescribing, influencing antibiotic prescribing practices in HK [13]. The inpatients received fewer antibiotic classes per hospital stay, reflecting a possible reduction in treatment failure rate [14].

Vaccination is a potential preventative solution to AMR PD infections. The currently available pneumococcal conjugate vaccines (PCVs) only cover certain *S. pneumoniae* serotypes. After the implementation of the 7-valent PCV (PCV7), serotype replacement with non-vaccine serotypes, including serotype 3, was mainly responsible for PD infections globally [15–17]. Similarly, serotype replacement was reported as newer generations of PCV covering additional serotypes were released [18,19]. While other vaccine serotypes were gradually under control, they were replaced by other serotypes. An increase in serotype 3 was observed after implementing PCV13 in Australia despite being covered in the vaccine [20]. A similar increase in cases caused by serotype 3 was also observed in HK after the introduction of PCV13 (since 2011) for all children and adults aged ≥65 years, and those aged ≥18 years and with high-risk conditions (history of IPD, immunocompromised, chronic diseases such as chronic cardiac, pulmonary, liver or renal diseases, and with diabetes mellitus or cerebrospinal fluid leakage) [2].

Despite a recent letter published regarding the increasing case numbers of serotype-specific IPD in HK to pre-pandemic levels in 2023, the epidemiology of antimicrobial-resistant PD (including IPD and non-IPD) and its risk factors have not been explored [21]. There is an urgent need to understand the current epidemiology of antimicrobial-resistant PD to inform public health strategies to describe the serotype distribution, antibiotic sensitivities, patient demographic/clinical characteristics, and analyze potential associations between AMR and PD infections.

Methods

Data source and variables

Data were retrieved from the Clinical Data Analysis and Reporting System (CDARS), a clinical database managed by the HK Hospital Authority (HA), which provides primary, secondary, and tertiary healthcare services to the 7.5 million HK residents through 43 public hospitals and institutions, 49 specialist outpatient clinics, and 74 general outpatient clinics. HA covered 80% of all hospitalization episodes in the population [22–24]. The patient demographic information and clinical data included records of diagnosis, prescriptions, pharmacy dispensing, admission/discharge information, emergency attendance, and laboratory test results from all inpatient, outpatient, and emergency settings for audit and research purposes [25,26]. In CDARS, the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) is followed to record diagnosis and procedure, while the British National Formulary (BNF) is used to categorize medication records, including prescription period, dosage, and dosage form.

Microbiology methods

Culture was requested for patients if deemed necessary by clinicians. Identification of bacterial species and antibiotic susceptibility tests (AST) were performed by microbiology laboratories in the hospitals. In CDARS, the data on laboratory tests ordered within the HA included details on the type of specimen, organisms identified, species, and antibiogram results. The isolates were tested at the laboratory of the same hospital, regional hospitals, university-affiliated hospitals, or the public health laboratory and reported to CDARS to link to the patient's inpatient record [27]. AST results were recorded as sensitive (S), intermediate susceptibility (I), and resistant (R) according to the minimum inhibitory concentrations or disk diffusion results following the Clinical & Laboratory Standards Institute (CLSI) standards. Serotyping was conducted by polymerase chain reaction assays and/or the Quellung reaction of individual isolates in the public health laboratory and retrieved from the study team when available. The laboratory results on CDARS from multiple HA hospitals were reported in previous local epidemiological studies of a similar kind [27].

Study population and patient definition

All hospitalizations were identified between January 1, 2012, to December 31, 2021, based on a diagnosis of PD. A PD diagnosis is defined as having a single or a combination of diagnostic codes in ICD-9-CM indicating a PD-related condition (Supplementary Table 1). For the same patient who fulfilled more than one PD-related condition, the more severe PD-related condition took precedence over that of lower severity to avoid duplication, that is, starting from the most severe, pneumococcal meningitis, pneumococcal bacteremia, bacteremic pneumonia, other IPD, pneumococcal pneumonia, otitis media with effusion (OME), and acute otitis media (AOM) [28]. To avoid confounding, we only considered the first PD episode from each patient.

We defined the date of first PD-related hospital admission as the start of a disease episode, while the date of hospital discharge was the end of a disease episode. If there were other hospitalizations with the same PD-related condition occurring within a specified time period from the date of discharge, these subsequent hospitalizations were assumed to be related to the first episode and were collapsed to form a single episode. A time period of ≥90 days was used for IPD and pneumococcal pneumonia hospitalizations, while ≥14 and ≥28 days were used for AOM and OME hospitalizations, respectively [28–30].

Patients with missing data of date of birth, sex, hospital admission or discharge dates, laboratory confirmation for *S. pneumoniae* or AST, were excluded from the study. Any healthcare resource utilization (HCRU) was considered related to the episode when it occurred within a 90-day follow-up period after the discharge from the last PD-related hospitalization. The PD-related length of stay, the number of all-cause hospitalizations, intensive care usage, outpatient visits, and emergency room visits were counted toward the HCRU related to the episode.

Statistical analysis

Epidemiology of PD patients, AMR infection status, and healthcare resource utilization

We prepared summary statistics covering patient characteristics and HCRU. Continuous variables, such as age and HCRU, were described using mean and standard deviation (SD). Categorical variables, such as disease type and type of antibiotics, were presented as numbers and proportions. The annual incidence of IPD and non-IPD was calculated by dividing the number of patients in each respective category by the mid-year population of HK. For these calculations, the population statistics were requested from the Census and Statistics Department of HK [31].

For the AST results (AMR status), the incidence of non-susceptibility was represented as the percentage of isolates non-susceptible based on the AST results. Antibiotic classes were classified following BNF Chapter 5.1. Any AST results with R or I susceptibility were considered non-susceptible. The annual incidence of non-susceptibility was plotted as a trend. The annual incidence of patients with non-susceptible antibiotics (0, 1, 2, ≥3 antibiotic classes) was also plotted.

HCRU calculations were presented by IPD/non-IPD and AMR status. Length of stay, including the total length of stay, and the intensive care unit (ICU) length of stay, were summarized as mean and SD. The number of inpatient, outpatient, emergency admissions was summarized as mean and SD. ICU use and readmissions (within 30, 60, 90 days) were presented as a percentage of the patient group. Medication use, including total number of medication prescriptions (all medications and antibiotics), days of antibiotic treatment, were summarized as mean and SD.

Risk factor associated with AMR PD infection

Univariable analysis was conducted using univariable logistic regression to examine the association between IPD/non-IPD and infection with non-susceptible *S. pneumoniae* by each risk factor compared to controls.

Risk factors for AMR *S. pneumoniae* infection were identified by comparing the case and control patients using multivariable logistic regression. Cases were defined as patients with *S. pneumoniae* isolates that were non-susceptible to at least one antibiotic. Controls were defined as patients with *S. pneumoniae* isolates susceptible to all antibiotics tested. Potential risk factors included age group, PD type, selected comorbidities status, including cardiovascular, lung, liver, kidney, metabolic, immune system, and neurological diseases as defined by ICD-9-CM codes (Supplementary Table 2). Age group was classified as aged <2 years, 2-17 years, 18-64 years, 65-75 years, and >75 years. The effect of the risk factors in the final model was assessed through the estimated odds ratio (OR) with 95% confidence interval (95% CI). The variables were added in a stepwise manner.

Additional analyses

Sensitivity analysis was conducted to include only patients aged ≥18 years to validate the robustness of correlation results against different comorbidity distributions in age groups.

Post-hoc analysis was conducted to calculate the mortality rate by AMR status and by PD type. Mortality was defined as the death of the patient during a PD episode.

All analyses were conducted using R (version 4.1.2; R Core Team).

Ethics approval

This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (Ref: UW 22-302).

Results

Basic characteristics and clinical features of patients

During the study period, a total of 3784 patients were identified with PD-related hospitalization from CDARS in HK. After excluding two patients with an unknown age, admission date, or discharge date, 3782 patients were identified. A total of 2251 patients with laboratory isolates tested for antimicrobial non-susceptibility were described further below; they were split into 1791 cases with AMR and 460 controls with sensitive strains. The flow chart for the inclusion and exclusion criteria is shown in Supplementary Figure 1. Among all 2251 PD patients, 704 (31%) were female. The age group that contributed to most of the PD patients was >75 years (N = 746, 33%), followed by 18-64 years (N = 613, 27%), 65-75 years (N = 438, 19%), and 2-17 years (N = 415, 18%), respectively. A total of 80% of patients were infected with isolates that were non-susceptible to at least one antibiotic tested. Across all PD types, most of the patients were diagnosed with pneumococcal pneumonia (n = 1780, 79%), followed by bacteremic pneumonia (n = 316, 14%). The clinical and demographic characteristics were described in Table 1. A total of 876 (39%) had prior comorbidities: 455 (20%) had lung diseases, 295 (13%) cardiovascular diseases, while 252 (11%) had metabolic diseases.

The incidence of IPD/non-IPD by age groups was described in Figure 1. People aged >75 years had the highest incidence of IPD/non-IPD compared to other age groups across the study period, while the group of 18-64 years had the lowest incidence. People aged 65-75 years had a higher incidence of non-IPD than IPD. Both IPD and non-IPD incidence for all age groups decreased from 2020, coinciding with the COVID-19 pandemic. Among all detected disease types, pneumococcal pneumonia had the highest incidence. Bacteremic pneumonia has the highest incidence among all invasive disease types (Supplementary Figure 2).

Antimicrobial susceptibility tests and serotyping

Before the decrease in PD patients in 2020, the incidence of AMR in PD was stable. The incidence of AMR in non-IPD infections was higher than AMR in IPD infections (Supplementary Figure 3a). The proportion of AMR in IPD-infected patients was 68% and that of non-IPD was 82%. Among the 2251 patients in whom *S. pneumoniae* was isolated and AST performed, 896 (40%) patients were infected with *S. pneumoniae* isolates non-susceptible to two classes of antibiotics. Patients with susceptible isolates, resistance to one antibiotic, and multidrug resistant (≥3 antibiotic classes) had a similar breakdown with 20-21% each (464, 477, 452 patients,

Table 1
Basic characteristics and clinical features of included episodes.

Antimicrobial resistance status	N	Overall, N = 2251	Isolates non-susceptible to ≥1 antibiotics, N = 1791	Isolates susceptible to antibiotics, N = 460	Standard mean difference
Sex	2251				0.05
Female		704 (31%)	569 (32%)	135 (29%)	
Male		1547 (69%)	1222 (68%)	325 (71%)	
Age group	2251				0.21
<2		39 (1.7%)	32 (1.8%)	7 (1.5%)	
2-17		415 (18%)	358 (20%)	57 (12%)	
18-64		613 (27%)	472 (26%)	141 (31%)	
65-75		438 (19%)	341 (19%)	97 (21%)	
>75		746 (33%)	588 (33%)	158 (34%)	
Category	2251				0.35
Pneumococcal pneumonia		1780 (79%)	1464 (82%)	316 (69%)	
Pneumococcal bacteremic pneumonia		316 (14%)	219 (12%)	97 (21%)	
Pneumococcal bacteremia		86 (3.8%)	57 (3.2%)	29 (6.3%)	
Pneumococcal meningitis		31 (1.4%)	20 (1.1%)	11 (2.4%)	
Other invasive pneumococcal disease		25 (1.1%)	18 (1.0%)	7 (1.5%)	
Any pneumococcal otitis media		13 (0.6%)	13 (0.7%)	0 (0%)	
Charlson comorbidity score (Median [interquartile range])	2251	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	-0.04
Serotype (listed in vaccine)	352				0.67
PCV13, in addition to PCV7		188 (53%)	150 (54%)	38 (53%)	
PCV7		74 (21%)	68 (24%)	6 (8.3%)	
23 valent PPV, in addition to PCV13		34 (9.7%)	16 (5.7%)	18 (25%)	
Not included in vaccine		56 (16%)	46 (16%)	10 (14%)	
Serotype not tested		1899	1,511	388	
Prior co-morbidities	2251				
Cardiovascular condition	2251	295 (13%)	244 (14%)	51 (11%)	-0.08
Lung condition	2251	455 (20%)	369 (21%)	86 (19%)	-0.05
Liver condition	2251	114 (5.1%)	94 (5.2%)	20 (4.3%)	-0.04
Kidney condition	2251	89 (4.0%)	66 (3.7%)	23 (5.0%)	0.06
Metabolic condition	2251	252 (11%)	198 (11%)	54 (12%)	0.02
Immune condition	2251	47 (2.1%)	40 (2.2%)	7 (1.5%)	-0.05
Neurologic condition	2251	135 (6.0%)	107 (6.0%)	28 (6.1%)	0

PCV, pneumococcal conjugate vaccine.

respectively) (Supplementary Figure 3b). Among the tested isolates, 85% were non-susceptible to tetracyclines, followed by 80% for macrolides and 61% for sulfonamide-trimethoprim combinations (Supplementary Table 3). For penicillin and fluoroquinolones, 23% and 2% of the patients whose isolates tested were resistant, respectively.

A total of 352 patients (16%) had serotyping results available. Almost half of these patients (46%, N = 161) were infected with serotype 3, 21% (N = 75) were serotypes listed in PCV7 (4, 6B, 9V,14, 18C, 19F and 23F), while 16% (N = 57) were serotypes not covered in any PCV vaccines (Table 1 and Supplementary Table 4). For the incidence of serotypes, serotype 3 had the highest incidence between 2012 and 2020. This trend increased from 2012 to the peak in 2017, then decreased rapidly in 2020. The rest of the serotypes remained comparatively low (Figure 2). The matching of patients with both AST results and serotyping results was presented in a heatmap to identify the relationship between the percentage of non-susceptibility among the same class of antibiotics and the top five serotypes of the *S. pneumoniae* isolated (i.e., 3, 14, 19A, 19F, 23A) (Figure 3). Macrolides and lincosamides had similar proportions of AMR isolates across the serotypes. Serotype 3 accounted for 46% of patients with AMR isolates, with a similar proportion in both adult and pediatric subgroups.

Risk factors associated with AMR PD infection

We fitted an univariable logistic regression for each risk factor and found that only age 2-17 years was associated with AMR non-IPD infection when compared to non-IPD patients aged 18-64 years (Table 2, OR: 2.27 [95% CI: 1.54, 3.42, P <0.001]). For prior comorbidities, the ORs were not significant.

For multivariable logistic regression results, non-IPD patients aged 2-17 years had an increased risk of infection with non-susceptible isolates (Model 3, OR: 2.27 [95% CI: 1.53, 3.43, P <0.001]; Model 4, OR: 2.31 [95% CI: 1.55, 3.48, P <0.001]) when compared with age group 18-64 years, while such increased risk was not observed among IPD patients aged 2-17 years. Prior co-morbidities showed no statistical significance in predicting the AMR status in the rest of the models.

Healthcare resources utilization of the included patients

Compared to those without AMR, a shorter length of stay was recorded for both IPD and non-IPD patients. Equally, fewer proportions of them were re-admitted in 60 and 90 days compared to patients without AMR (Supplementary Table 5a). However, these differences did not show statistical significance. Along with other HCRU metrics, it varied between patients with AMR and without AMR, and between patients with IPD and non-IPD. A larger proportion of IPD patients was observed among susceptible isolates compared to those resistant to at least one antibiotic class; while a greater proportion of non-IPD patients was observed with resistance to an increasing number of antibiotic classes. For the post-hoc analysis conducted to explore the mortality rate by AMR status, among patients with any AST performed, the mortality rate was highest in those with an IPD diagnosis regardless of AMR status (Supplementary Table 5b).

Sensitivity analysis of adult PD patients

Among the included adult IPD/non-IPD patients, the odds of having an infection with bacteria that were resistant did not increase with sex and age (Supplementary Table 6). However, having prior cardiovascular disease could increase the risk of having AMR with an OR of 1.47 (95% CI: 1.01, 2.21, P = 0.053) among non-IPD

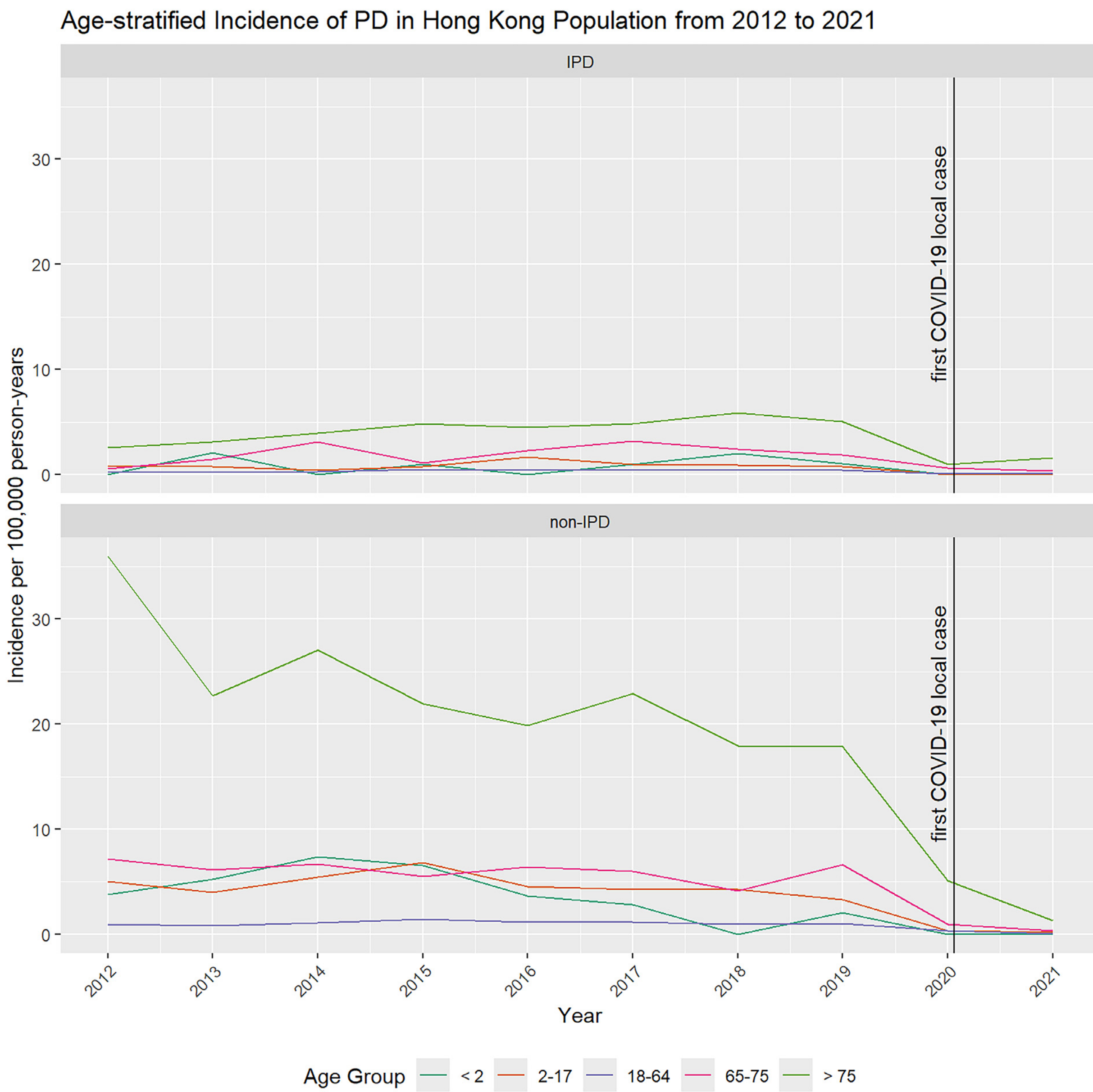

Figure 1. Age-stratified incidence of PD in the Hong Kong population from 2012 to 2021. Upper pane: IPD; Lower pane: PD, non-IPD. IPD, invasive pneumococcal disease.

patients. This was not significant when adjusted for sex and age. The ORs of other conditions were not statistically significant.

Discussion

This study used territory-wide medical records to identify the AMR to ensure sufficient coverage of patients admitted into HK's public healthcare service. Pneumococcal pneumonia was the prominent type of infection for all PD, while bacteremic pneumonia was the prominent type for IPD. The proportion of AMR in non-IPD-infected patients was higher than that of IPD. The proportion of resistance among identified *S. pneumoniae* with AST results was highest for tetracyclines, lincosamides, and macrolides. The patients who were infected with non-susceptible strains were likely to have a shorter length of stay. The increasing prevalence of serotype 3 has drawn attention toward the local PCV uptake and the effectiveness of the vaccine, which is being investigated further.

The trend for PD concurs with other local studies that identified a stable trend of PD before the COVID-19 pandemic, followed by a sudden drop in cases, probably due to pandemic control measures [21,32]. This sudden decline has also been observed in other countries where non-pharmaceutical interventions were in place during the pandemic [20]. In HK, the mask mandate that ended in March 2023 enabled the circulation of common respiratory pathogens, such as CAP, PD, and co-infections with those pathogens [32,33]. Surveillance and monitoring of disease trends were recommended following the removal of stringent non-pharmaceutical interventions in the region for the possible increasing incidence of AMR PD infection [33].

In our study, despite the stable incidence of PD before the COVID-19 pandemic, the proportion of serotype 3 cases increased after the introduction of PCV13 since 2011. In Australia, serotype 3 has also become the most prevalent serotype causing PD infections, similar to HK [20]. Serotype 3 was also the most prevalent serotype in PD cases in Germany (50.8% prevalence of the

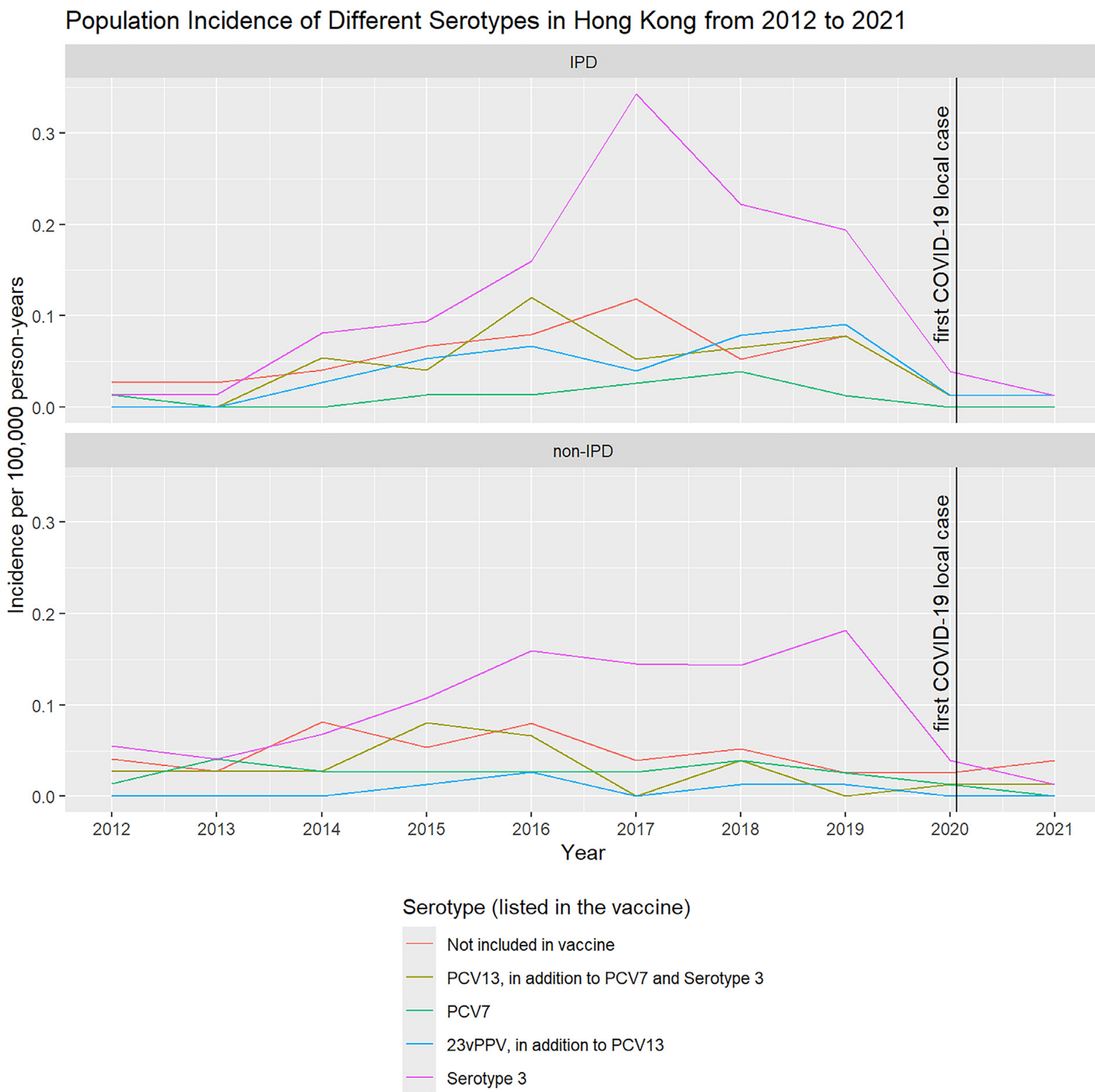

Figure 2. Population incidence of serotypes.
Upper pane: IPD; Lower pane: PD, non-IPD. IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine.

PCV13-covered serotypes), Canada (where prevalence increased from 15.5% to 31.1% in 2011-2015), and the United Kingdom (56.9% of PCV13-non7 serotypes) after the introduction of PCV13 in 2010-11 [34–36]. These findings reveal a high incidence of serotype 3 after PCV13 implementation, suggesting this high incidence remains a prolonged problem locally and a common issue occurring globally [11,36]. Regarding the association between serotype and AMR, other studies have identified a link between non-susceptibility to penicillin and third-generation cephalosporins in serotype 3 strains [11,37]. An Alaskan study displayed a rise in overall non-susceptibility due to an increase in PD prevalence and increased non-susceptibility among non-vaccine serotypes, which might bring about a greater effect than serotype redistribution [38]. Moreover, the potential for developing invasive infection varied across serotypes, which complicated the overall estimation of disease burden when serotype distribution changes [39].

For identifying risk factors associated with infections with resistant *S. pneumoniae*, even though the age groups with the highest incidence of PD were >75-year-old and <2-year-old age groups, our logistic regression model did not identify any association between very young (<2-year-old) or older age (>65-year-old) and AMR PD/non-IPD infection. This finding is similar to a previous Korean multicenter study on 160 adult IPD cases in 2019-2021 [37]. Interestingly, the school-age children (2-17 years) with non-IPD had an increased risk for AMR, which might suggest more effort to prevent non-IPD infection.

In our study, the HCRU does not seem to relate to AMR status in either IPD or non-IPD groups; however, it seems to be more correlated with the severity of the PD (invasive vs non-invasive). Due to the higher case fatality within an episode of IPD, patients may account for the shorter average length of stay and less relevant HCRU observed in patients with *S. pneumoniae* isolates susceptible to all antibiotics tested. Another local study also highlighted the limited

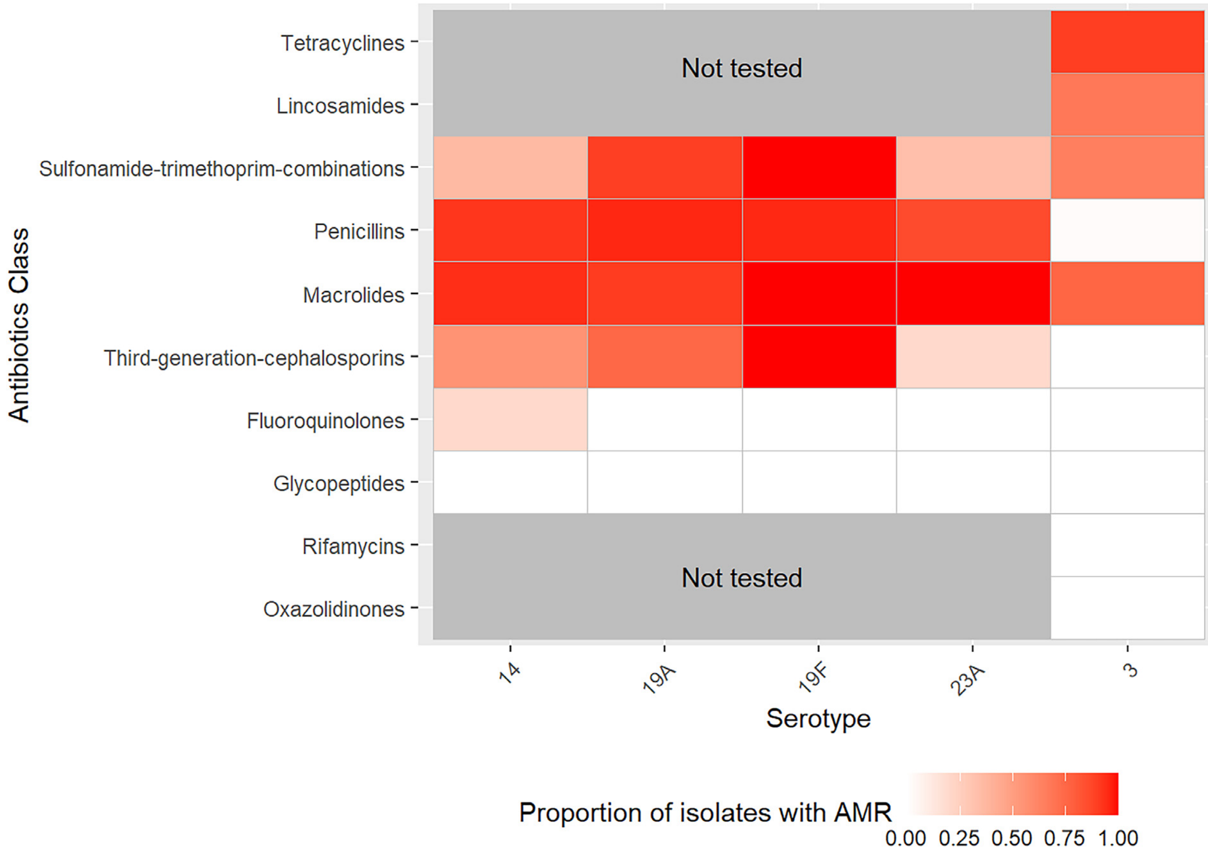

Figure 3. Relationship between high-incidence serotypes and non-susceptibility to selected antibiotic classes.
AMR, antimicrobial resistance. This heatmap identified the relationship between the percentage of non-susceptibility among the same class of antibiotics and the top five serotypes of the *S. pneumoniae* isolated (i.e., 3, 14, 19A, 19F, 23A).

Table 2
Demographic characteristics and risk factors associated with antimicrobial resistance status in all patients identified with PD episodes.

		IPD			Non-IPD		
		Univariable OR (95% CI)	Multivariable OR (95% CI)		Univariable OR (95% CI)	Multivariable OR (95% CI)	
Covariate	Subgroup		Model 1: sex, age	Model 2: sex, age, prior co-morbidities		Model 3: sex, age	Model 4: sex, age, prior co-morbidities
Sex							
	Female	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Male	0.81 (0.52, 1.23)	0.82 (0.53, 1.26)	0.77 (0.49, 1.20)	0.92 (0.70, 1.19)	1 (0.76, 1.31)	0.97 (0.73, 1.27)
Age group							
	18-64	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	<2	0.27 (0.05, 1.26)	0.26 (0.05, 1.21)	0.27 (0.05, 1.27)	2.74 (0.95, 11.6)	2.74 (0.95, 11.6)	2.77 (0.96, 11.8)
	2-17	0.91 (0.48, 1.78)	0.91 (0.48, 1.77)	0.96 (0.50, 1.89)	**2.27 (1.54, 3.42)**[a]	**2.27 (1.53, 3.43)**[a]	**2.31 (1.55, 3.48)**[a]
	65-75	0.66 (0.39, 1.12)	0.67 (0.40, 1.14)	0.76 (0.44, 1.32)	1.3 (0.91, 1.88)	1.3 (0.91, 1.88)	1.25 (0.87, 1.81)
	>75	0.67 (0.40, 1.13)	0.68 (0.40, 1.15)	0.79 (0.45, 1.38)	1.25 (0.92, 1.68)	1.25 (0.92, 1.68)	1.15 (0.84, 1.57)
Prior co-morbidities							
Cardiovascular disease	No	1.00 (ref)		1.00 (ref)	1.00 (ref)		1.00 (ref)
	Yes	1.1 (0.57, 2.25)		1.49 (0.73, 3.21)	1.24 (0.87, 1.82)		1.26 (0.86, 1.90)
Lung disease	No	1.00 (ref)		1.00 (ref)	1.00 (ref)		1.00 (ref)
	Yes	0.67 (0.38, 1.18)		0.64 (0.35, 1.19)	1.2 (0.89, 1.63)		1.25 (0.91, 1.73)
Liver disease	No	1.00 (ref)		1.00 (ref)	1.00 (ref)		1.00 (ref)
	Yes	2.2 (0.88, 6.65)		2.23 (0.85, 7.07)	1.02 (0.59, 1.87)		1.12 (0.64, 2.07)
Kidney disease	No	1.00 (ref)		1.00 (ref)	1.00 (ref)		1.00 (ref)
	Yes	0.56 (0.22, 1.49)		0.54 (0.19, 1.59)	0.79 (0.46, 1.47)		0.74 (0.41, 1.41)
Metabolic disease	No	1.00 (ref)		1.00 (ref)	1.00 (ref)		1.00 (ref)
	Yes	0.62 (0.33, 1.17)		0.67 (0.34, 1.35)	1.06 (0.73, 1.58)		1.15 (0.77, 1.76)
Immune disease	No	1.00 (ref)		1.00 (ref)	1.00 (ref)		1.00 (ref)
	Yes	2.82 (0.76, 18.3)		2.95 (0.73, 20.0)	1.21 (0.50, 3.58)		1.1 (0.45, 3.32)
Neurological disease	No	1.00 (ref)		1.00 (ref)	1.00 (ref)		1.00 (ref)
	Yes	1.05 (0.44, 2.79)		1.12 (0.44, 3.16)	0.93 (0.58, 1.55)		0.86 (0.53, 1.45)

CI, confidence interval; IPD, invasive pneumococcal disease; OR, odds ratio; ref, reference.
[a] Statistically significant result ($P < 0.05$).

efficacy of PCV13 against serotype 3 [15]. The role of vaccination in preventing the high prevalence of serotype 3 and its associated HCRU warrants further investigation [15]. Protection against serotype 3 would be deemed essential in future PCV development [40].

Limitations

The determination of patient diagnoses, particularly for IPD, was based on matching ICD-9-CM codes following the isolation of *S. pneumoniae* from sterile sites. However, the corresponding microbiological records may not have been captured in our data. Additionally, whether a sample was collected and the extent of AST depended on the clinician's judgment of the patient's clinical prognosis, which was influenced by surveillance practices that varied between hospitals and by differing antimicrobial usage guidelines. As such, the findings were likely representing more severely ill patients hospitalized due to PD for whom samples were taken and AST performed as part of further clinical evaluation.

A substantial proportion of serotyping results were missing, which likely did not impact treatment decisions. Nevertheless, understanding the serotype distribution among all patients with PD would have been valuable. Since IPD became a notifiable condition in 2015, public health laboratories began conducting serotyping on confirmed IPD cases. According to publicly available data from the Department of Health, the distribution of IPD serotypes closely matched our findings [41]. Based on this comparison, we believe that our results are representative of the broader population. Even so, for the sake of future surveillance, it would be better for the laboratory surveillance to cover not only the IPD patients but also non-IPD patients [42].

The PCV vaccination status of elderly patients was unknown because this information was not captured in the data. As the PCV uptake among children is over 95%, we believe the disease incidence and AMR status among children were representative of the general population in HK. Additionally, there was a possible delay in vaccination due to suspension of non-emergency services during the COVID-19 pandemic, which changes in treatment guidelines over the study period and may have influenced the observed AMR trends. Other clinical interventions indicative of disease severity, such as mechanical ventilation, were not recorded, and outcomes reflecting severity or worse prognosis were unavailable for analysis. Consequently, disease severity could only be inferred from the type of PD and HCRU, which might be inconclusive and not definitive.

Conclusion

As reflected by the higher incidence of younger patients, the elevated risk of AMR PD infection among younger ages in HK suggests that measures to reduce non-susceptible *S. pneumoniae* should focus on children and adolescents. Incidence of PD reduced when the COVID-19 pandemic hit. However, as the world transitions to the COVID-19 post-pandemic era, PD incidence may increase and pose threats to public health. This potential threat calls for broader coverage for surveillance in non-IPD patients. Since the introduction of PCV13 in HK in 2011, serotype 3 has remained high among all PD patients. It also warrants further studies of PCV effectiveness and development of novel vaccines for improved protection against serotype 3 PD.

Declaration of competing interest

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Author contributions

KSL, CSLC, ICKW, TKK, and IS conceptualized the study; PW, CEM designed the study; JCHL, KWKC, and QY conducted the analysis and drafted the manuscript; all other authors had reviewed the manuscript and provided critical comments and consented for publication.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2025.108174.

References

[1] Lui G, To HKW, Lee N, Chan RWY, Li T, Wong RYK, et al. Adherence to treatment guideline improves patient outcomes in a prospective cohort of adults hospitalized for community-acquired pneumonia. *Open Forum Infect Dis* 2020;**7**:ofaa146. doi:10.1093/ofid/ofaa146.

[2] Centre for Health Protection. Updated recommendations on the use of pneumococcal vaccines for high-risk individuals. Hong Kong: The Government of the Hong Kong Special Administrative Region. *PRC* 2016.

[3] Martinez-Vega R, Jauneikaite E, Thoon KC, Chua HY, Huishi Chua A, Khong WX, et al. Risk factor profiles and clinical outcomes for children and adults with pneumococcal infections in Singapore: a need to expand vaccination policy? *PLoS One* 2019;**14**:e0220951. doi:10.1371/journal.pone.0220951.

[4] Gupta V, Yu KC, Schranz J, Gelone SP. A multicenter evaluation of the US prevalence and regional variation in macrolide-resistant S. pneumoniae in ambulatory and hospitalized adult patients in the United States. *Open Forum Infect Dis* 2021;**8**:ofab063. doi:10.1093/ofid/ofab063.

[5] Kim L, McGee L, Tomczyk S, Beall B. Biological and epidemiological features of antibiotic-resistant Streptococcus pneumoniae in pre- and post-conjugate vaccine eras: a United States perspective. *Clin Microbiol Rev* 2016;**29**:525–52. doi:10.1128/CMR.00058-15.

[6] Quach C, Weiss K, Moore D, Rubin E, McGeer A, Low DE. Clinical aspects and cost of invasive Streptococcus pneumoniae infections in children: resistant vs. susceptible strains. *Int J Antimicrob Agents* 2002;**20**:113–18. doi:10.1016/s0924-8579(02)00127-9.

[7] Varghese J, Chochua S, Tran T, Walker H, Li Z, Snippes Vagnone, Lynfield R, McGee L, Li Y, Metcalf B J, Pilishvili T, Beall B. Multistate population and whole genome sequence-based strain surveillance of invasive pneumococci recovered in the USA during 2017. *Clinical microbio. infection : official publicat. European Soc. Clin. Microbio. Infect. Dise.* 2020;**26**(4):512.e1–512.e10. doi:10.1016/j.cmi.2019.09.008.

[8] Chan IM-C, Ng DK-K, Miu T-Y, Lam P, Tse CW-S, Chan C-H, et al. Invasive pneumococcal disease in Hong Kong children. *J Paediatr Respirol Crit Care* 2013;**9**:4–8.

[9] Ho PL, Yam WC, Cheung TK, Ng WW, Que TL, Tsang DN, et al. Fluoroquinolone resistance among Streptococcus pneumoniae in Hong Kong linked to the Spanish 23F clone. *Emerg Infect Dis* 2001;**7**:906–8. doi:10.3201/eid0705.010526.

[10] Song JH, Jung SI, Ko KS, Kim NY, Son JS, Chang HH, et al. High prevalence of antimicrobial resistance among clinical Streptococcus pneumoniae isolates in Asia (an ANSORP study). *Antimicrob Agents Chemother* 2004;**48**:2101–7. doi:10.1128/AAC.48.6.2101-2107.2004.

[11] Subramanian R, Liyanapathirana V, Barua N, Sun R, Wang MH, Ng R, et al. Persistence of pneumococcal Serotype 3 in adult pneumococcal disease in Hong Kong. *Vaccines (Basel)* 2021;**9**:756. doi:10.3390/vaccines9070756.

[12] Chiu SS, Ho PL, Chow FK, Yuen KY, Lau YL. Nasopharyngeal carriage of antimicrobial-resistant Streptococcus pneumoniae among young children attending 79 kindergartens and day care centers in Hong Kong. *Antimicrob Agents Chemother* 2001;**45**:2765–70. doi:10.1128/AAC.45.10.2765-2770.2001.

[13] Ma ESK, Tsui ELK, Wu TC, Ho PL. New Impact Guideline to help doctors on rational prescription of antimicrobials. *Hong Kong Med J* 2025;**31**:262–4. doi:10.12809/hkmj255183.

[14] Chui CSL, Cowling BJ, Lim WW, Hui CKM, Chan EW, Wong ICK, et al. Patterns of inpatient antibiotic use among public hospitals in Hong Kong from 2000 to 2015. *Drug Saf* 2020;**43**:595–606. doi:10.1007/s40264-020-00920-9.

[15] Ho PL, Law PYT, Chiu SS. Increase in incidence of invasive pneumococcal disease caused by serotype 3 in children eight years after the introduction of the Pneumococcal Conjugate Vaccine in Hong Kong. *Hum Vaccin Immunother* 2019;**15**:455–8. doi:10.1080/21645515.2018.1526555.

[16] Katoh S, Suzuki M, Ariyoshi K, Morimoto K. Serotype replacement in adult pneumococcal pneumonia after the introduction of seven-valent pneumococcal conjugate vaccines for children in Japan: a systematic literature review and pooled data analysis. *Jpn J Infect Dis* 2017;**70**:495–501. doi:10.7883/yoken.JJID.2016.311.

[17] Hyams C, Challen R, Hettle D, Amin-Chowdhury Z, Grimes C, Ruffino G, et al. Serotype distribution and disease severity in adults hospitalized with Streptococcus pneumoniae infection, bristol and Bath, UK, 2006–2022. *Emerg Infect Dis* 2023;**29**:1953–64. doi:10.3201/eid2910.230519.

[18] Huang H, Lin CY, Chiu NC, Huang DTN, Huang CY, Chi H. Antimicrobial susceptibility and serotype replacement of Streptococcus pneumoniae in children before and after PCV13 introduction in Taiwan. *J Microbiol Immunol Infect* 2023;**56**:299–310. doi:10.1016/j.jmii.2022.08.018.

[19] Hanquet G, Krizova P, Dalby T, Ladhani SN, Nuorti JP, Danis K, et al. Serotype replacement after introduction of 10-valent and 13-valent Pneumococcal Conjugate Vaccines in 10 countries. *Europe. Emerg Infect Dis* 2022;**28**:137–8. doi:10.3201/eid2801.210734.

[20] Higgs C, Kumar LS, Stevens K, Strachan J, Sherry NL, Horan K, et al. Population structure, serotype distribution and antibiotic resistance of Streptococcus pneumoniae causing invasive disease in Victoria. *Australia. Microb Genom* 2023;**9**:mgen001070. doi:10.1099/mgen.0.001070.

[21] Pang CWK, Vale R, Lao KS, Khan ATK, Wu JT, Leung K. Increased incidence of invasive pneumococcal disease in Hong Kong in 2023. *J Infect* 2024;**89**:106178. doi:10.1016/j.jinf.2024.106178.

[22] Leung GM, Wong IOL, Chan WS, Choi S, Lo SV. Health Care Financing Study Group. The ecology of health care in Hong Kong. *Soc Sci Med* 2005;**61**:577–90. doi:10.1016/j.socscimed.2004.12.029.

[23] Lai ECC, Man KKC, Chaiyakunapruk N, Cheng CL, Chien HC, Chui CSL, et al. Brief report: databases in the Asia-pacific region: the potential for a distributed network approach. *Epidemiology* 2015;**26**:815–20. doi:10.1097/EDE.0000000000000325.

[24] Hospital Authority. Clusters, hospitals & institutions: Hospital Authority, https://www.ha.org.hk/visitor/ha_visitor_index.asp?Content_ID=10036&Lang=ENG&Ver=HTML; 2023 [accessed 01 Sept 2023].

[25] Fombonne E. The prevalence of autism. *JAMA* 2003;**289**:87–9. doi:10.1001/jama.289.1.87.

[26] Lao KSJ, Chui CSL, Man KKC, Lau WCY, Chan EW, Wong ICK. Medication safety research by observational study design. *Int J Clin Pharm* 2016;**38**:676–84. doi:10.1007/s11096-016-0285-6.

[27] Ho PL, Chiu SS, Ang I, Lau YL. Serotypes and antimicrobial susceptibilities of invasive Streptococcus pneumoniae before and after introduction of 7-valent Pneumococcal Conjugate Vaccine, Hong Kong, 1995–2009. *Vaccine* 2011;**29**:3270–5. doi:10.1016/j.vaccine.2011.02.025.

[28] Hu T, Song Y, Done N, Liu Q, Sarpong EM, Lemus-Wirtz E, et al. Incidence of invasive pneumococcal disease in children with commercial insurance or Medicaid coverage in the United States before and after the introduction of 7- and 13-valent pneumococcal conjugate vaccines during 1998–2018. *BMC Public Health* 2022;**22**:1677. doi:10.1186/s12889-022-14051-6.

[29] Hu T, Sarpong EM, Song Y, Done N, Liu Q, Lemus-Wirtz E, et al. Incidence of non-invasive all-cause pneumonia in children in the United States before and after the introduction of pneumococcal conjugate vaccines: a retrospective claims database analysis. *Pneumonia (Nathan)* 2023;**15**:8. doi:10.1186/s41479-023-00109-5.

[30] Hu T, Done N, Petigara T, Mohanty S, Song Y, Liu Q, et al. Incidence of acute otitis media in children in the United States before and after the introduction of 7- and 13-valent Pneumococcal Conjugate Vaccines during 1998–2018. *BMC Infect Dis* 2022;**22**:294. doi:10.1186/s12879-022-07275-9.

[31] Census and Statistics Department *Table 110-01001A : Mid-year population (excluding foreign domestic helpers) by Sex and Age group. Demographic statistics section CaSD*. Hong Kong: Census and Statistics Department; 2023.

[32] Chan KF, Ma TF, Ip MSM, Ho PL. Invasive pneumococcal disease, pneumococcal pneumonia and all-cause pneumonia in Hong Kong during the COVID-19 pandemic compared with the preceding 5 years: a retrospective observational study. *BMJ Open* 2021;**11**:e055575. doi:10.1136/bmjopen-2021-055575.

[33] Dyda A, Karki S, Hayen A, MacIntyre CR, Menzies R, Banks E, et al. Influenza and pneumococcal vaccination in Australian adults: a systematic review of coverage and factors associated with uptake. *BMC Infect Dis* 2016;**16**:515. doi:10.1186/s12879-016-1820-8.

[34] Forstner C, Kolditz M, Kesselmeier M, Ewig S, Rohde G, Barten-Neiner G, et al. Pneumococcal conjugate serotype distribution and predominating role of serotype 3 in German adults with community-acquired pneumonia. *Vaccine* 2020;**38**:1129–36. doi:10.1016/j.vaccine.2019.11.026.

[35] LeBlanc JJ, ElSherif M, Ye L, MacKinnon-Cameron D, Ambrose A, Hatchette TF, et al. Streptococcus pneumoniae serotype 3 is masking PCV13-mediated herd immunity in Canadian adults hospitalized with community acquired pneumonia: a study from the Serious Outcomes Surveillance (SOS) Network of the Canadian immunization research Network (CIRN). *Vaccine* 2019;**37**:5466–73. doi:10.1016/j.vaccine.2019.05.003.

[36] Pick H, Daniel P, Rodrigo C, Bewick T, Ashton D, Lawrence H, et al. Pneumococcal serotype trends, surveillance and risk factors in UK adult pneumonia, 2013–18. *Thorax* 2020;**75**:38–49. doi:10.1136/thoraxjnl-2019-213725.

[37] Yoon JG, Jang AY, Kim MJ, Seo YB, Lee J, Choi YH, et al. Persistent serotype 3 and 19A invasive pneumococcal diseases in adults in vaccine era: serotype-dependent difference in ceftriaxone susceptibility. *Vaccine* 2022;**40**:2258–65. doi:10.1016/j.vaccine.2022.03.004.

[38] Plumb ID, Gounder PP, Bruden DJT, Bulkow LR, Rudolph KM, Singleton RJ, et al. Increasing non-susceptibility to antibiotics within carried pneumococcal serotypes – Alaska, 2008–2015. *Vaccine* 2020;**38**:4273–80. doi:10.1016/j.vaccine.2020.04.048.

[39] Sá-Leão R, Pinto F, Aguiar S, Nunes S, Carriço JA, Frazão N, et al. Analysis of invasiveness of pneumococcal serotypes and clones circulating in Portugal before widespread use of conjugate vaccines reveals heterogeneous behavior of clones expressing the same serotype. *J Clin Microbiol* 2011;**49**:1369–75. doi:10.1128/JCM.01763-10.

[40] Goettler D, Streng A, Kemmling D, Schoen C, von Kries R, Rose MA, et al. Increase in Streptococcus pneumoniae serotype 3 associated parapneumonic pleural effusion/empyema after the introduction of PCV13 in Germany. *Vaccine* 2020;**38**:570–7. doi:10.1016/j.vaccine.2019.10.056.

[41] Report on invasive pneumococcal disease *Communicable Disease Branch of the Centre for Health Protection*, Hong Kong: Department of Health, HKSAR Government; 2024. editor.

[42] Aboulatta L, Peymani P, Vaccaro C, Leong C, Kowalec K, Delaney J, et al. Drug utilization patterns before and during COVID-19 pandemic in Manitoba, Canada: a population-based study. *PLoS One* 2022;**17**:e0278072. doi:10.1371/journal.pone.0278072.