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Disease Pattern, Risk factors of Antimicrobial Resistance in Patients with Pneumococcal Infection in Hong Kong Population

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Highlights

- We examined pneumococcal disease (PD) patient with during PCV13 vaccine era.
- Children and adolescents had an elevated risk of gaining antimicrobial resistance.
- Non-invasive PD from PCV13 vaccine escape strains requiring additional prevention measures.

Title: Disease Pattern, Risk factors of Antimicrobial Resistance in Patients with Pneumococcal Infection in Hong Kong Population

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Abstract

Background: Antimicrobial resistance (AMR) presents significant challenges for the effective treatment of pneumococcal diseases (PD), disease prevalence and vaccine effectiveness caused by *S. pneumoniae*.

Objectives: To describe the pattern of AMR among isolates from PD patients reported in the Hong Kong population from 2012-2021, and to explore the risk factors associated with AMR among patients hospitalised with PD compared to those with susceptible isolates.

Methods: PD-related hospitalizations were identified and grouped into IPD or non-IPD patients. Electronic health records were collected to calculate the healthcare resource utilisation 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 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 COVID-19 pandemic. Overall, 80% of patients had *S. pneumoniae* which were non-susceptible to ≥1 antibiotic. The percentage of non-susceptibility found to tetracyclines, macrolides, penicillins, fluoroquinolones, were 85%, 79%, 23% and 2% respectively. 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 when compared to older patients (18-64 years).

Conclusion: *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 PD patients with serotyping results.

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 pneumococcal disease (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 under 2 years and adults over 65 were at an elevated risk of IPD [2]. In Singapore, a retrospective cohort study reported that 27.1% of IPD patients 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 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 (ABC) 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 (MDR) 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 AMR carriage after 2013 [11]. In addition, these studies did not explore 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 [16].

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 pneumococcal conjugate vaccine (PCV7), serotype replacement with non-vaccine serotypes, including serotype 3, were mainly responsible for PD infections globally [17-19]. Similarly, serotype replacement was reported as newer generations of PCV covering additional serotypes released [20, 21]. 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 [22]. A similar increase in cases caused by serotype 3 was also been 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 level in 2023, the epidemiology of antimicrobial-resistant PD (including IPD and non-IPD) and its risk factors have not been explored [23]. There is an urgent need to understand the current epidemiology of antimicrobial-resistant pneumococcal disease to inform public health strategies to describe the serotype distribution, antibiotic sensitivities, patient demographic/clinical characteristics, and analyse 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 Hong Kong 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 [24-26]. The patient demographic information and clinical data included records of diagnosis, prescriptions, pharmacy dispensing, admission/discharge information, emergency attendance, laboratory test results from all inpatient, outpatient, and emergency settings for audit and research proposes [27, 28]. 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 record, including prescription period, dosage, and dosage form.

Microbiology methods

Culture was requested for patients 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 [29]. AST results were recorded as sensitive (S), intermediate susceptibility (I), and resistant (R) according to the minimum inhibitory concentrations or disc diffusion results following the Clinical & Laboratory Standards Institute (CLSI) standards. Serotyping was conducted by PCR 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 similar kind [29].

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 combination of diagnostic codes in ICD-9-CM indicating a PD-related condition (Supplementary table 1). For the same patient that fulfilled more than one PD-related conditions, the more severe PD-related condition took precedence than that of lower severity to avoid duplication, i.e. starting from the most severe, pneumococcal meningitis, pneumococcal bacteraemia, bacteraemic pneumonia, other IPD, pneumococcal pneumonia, otitis media with effusion (OME), acute otitis media (AOM) [30]. 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 [30-32].

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 patient 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, emergency room visits, were counted towards the HCRU related to the patient.

Statistical analysis

Epidemiology of PD patients, AMR infection status, Healthcare resource utilization (HCRU)

We prepared summary statistics covering patient characteristics and HCRU. Continuous variables, such as age and HCRU, were described using mean and standard deviation. Categorical variables, such as disease type and type of antibiotics, were presented as numbers and proportions. The annual incidence of IPD and non-IPD were 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 [33].

For the AST results, 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 resistance (R) or intermediate susceptibility (I) 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 standard deviation. Number of inpatient, outpatient, emergency admissions were summarized as mean and standard deviation. 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 standard deviation.

Risk factor associated with AMR 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 regressions. Cases were defined as patients with *S. pneumoniae* isolates which 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 or above to validate robustness of correlation results against different comorbidity distribution in age groups.

Post-hoc analysis was conducted to calculate 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 3,784 patients were identified with PD-related hospitalization from CDARS in HK. After excluding 2 patients with an unknown age, admission date or discharge date, 3,782 patients were identified. A total of 2,251 patients with laboratory isolate tested for antimicrobial non-susceptibility were described further below, they were split into 1,791 cases with AMR and 460 controls with sensitive strains. The flow chart for the inclusion and exclusion criteria was shown in Supplementary figure 1. Among all 2,251 PD patients, 704 (31%) were female. The age group that contributed to most of the PD patients were >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 proportion 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 = 1,780, 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, whilst 252 (11%) had metabolic diseases.

The incidence of IPD/non-IPD by age groups was described in Figure 1. People aged >75 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 decreases 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 2,251 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 MDR (≥3 antibiotic classes) had a similar breakdown with 20-21% each (464, 477, 452 patients 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 penicillins 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 & 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 5 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 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 odd ratios 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 comorbidities showed no statistical significance in predicting the AMR status in the rest of the models.

Healthcare resources utilisation (HCRU) 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; whilst 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, mortality rate was highest in those with 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 patients. This was not significant when adjusted by sex and age. The ORs of other conditions were not statistically significant.

Discussion

This study utilized territory-wide medical record to identify the antimicrobial resistance 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 were 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 the attention towards the local PCV uptake and the effectiveness of vaccine which is being investigated further.

The trend for PD concurs with other local studies that identified a stable trend of PD before COVID-19 pandemic, followed by a sudden drop in cases, probably due to pandemic control measures [23, 34]. This sudden decline has also been observed in other countries where non-pharmaceutical interventions were in place during the pandemic [22]. In HK, the mask mandate that ended in March 2023 enabled the circulation of common respiratory pathogens such as community-acquired pneumonia, such as PD, and co-infections with those pathogens [34, 35]. 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 [35].

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 [22]. Serotype 3 was also the most prevalent serotype in PD cases in Germany (50.8% prevalence of the 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 [36-38]. 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, 38]. 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, 39]. An Alaskan study displayed a rise in overall non-susceptibility due to increase in PD prevalence and increased non-susceptibility among non-vaccine serotypes, which might bring about a greater effect than serotype redistribution [40]. Moreover, the potential for developing invasive infection varied across serotypes, which complicated the overall estimation of disease burden when serotype distribution changes [42].

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 [39]. 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 with 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). The higher case fatality within an episode of IPD patient 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. With another local study also highlighted the limited efficacy of PCV13 against serotype 3 (16), the role of vaccination in preventing the high prevalence of serotype 3 and its associated HCRU warrants further investigation [17]. Protection against serotype 3 would be deemed essential in future PCV development [43].

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 PD patients 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 [44]. Based on this comparison, we believe that our results are representative of the broader population. Even so, for sake of future surveillance, it would be better for the surveillance cover not only the IPD patients but also non-IPD patients [45].

The vaccination status of elderly patients regarding PCV 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 Hong Kong. Additionally, there were 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 were also inconclusive and not definitive.

Conclusions

As reflected by the higher incidence of younger patients, the elevated risk of AMR PD infection among younger ages in HK suggested that more measures to reduce non-susceptible S. pneumoniae should focus on children and adolescents. Incidence of PD reduced when COVID-19 pandemic hits. However, as the world transition to the COVID-19 post-pandemic era, PD incidence may increase and pose threats to public health. This potential threat urges 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 on novel vaccines for improved protection against serotype 3 PD.

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List of tables & figures

List of abbreviations

23vPPV	23-valent Pneumococcal polysaccharide vaccine
ABC	Active Bacterial Core
AIC	Akaike information criterion
ALaRMS	Acute Laboratory Risk of Mortality Score
AMR	Antimicrobial resistance
AOM	Acute otitis media
AST	antimicrobial susceptibility
BNF	British National Formulary
CAP	Community acquired pneumonia
CDARS	Clinical Data Analysis and Reporting System, Hong Kong
CSF	Cerebrospinal fluid
ENT	Ear, nose, throat
GLM	Generalized linear models
GLMM	Generalized linear mixed models
HCRU	Healthcare resources utilisation
HK	Hong Kong
I	Intermediate susceptibility
I/R	Intermediate or Resistant
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICU	Intensive care unit
IPD	Invasive pneumococcal disease
IV	Intravenous
LOS	Length of hospital stay
OME	Otitis media with effusion
PCV	Pneumococcal conjugate vaccines
PCV13	13-valent Pneumococcal Conjugate Vaccine
PCV7	7-valent Pneumococcal Conjugate Vaccine
PD	Pneumococcal disease
PO	Per oral route
R	Resistant susceptibility
SP	Streptococcus pneumoniae
WGS	Whole genome sequence

Conflict of interest declaration

ICKW has received research grants from Amgen, Janssen, GSK, Novartis, Pfizer, Bayer and Bristol-Myers Squibb and Takeda, Institute for Health Research in England, European Commission, National Health and Medical Research Council in Australia, The European Union's Seventh Framework Programme for research, technological development, Research Grants Council Hong Kong and Health and Medical Research Fund Hong Kong; consulting fee from IQVIA and WHO; payment for expert testimony for Appeal Court in Hong Kong; serves on advisory committees for Member of Pharmacy and Poisons Board; Member of the Expert Committee on Clinical Events Assessment Following COVID-19 Immunization; Member of the Advisory Panel on COVID-19 Vaccines of the Hong Kong Government; is the non-executive director of Jacobson Medical in Hong Kong; is the Founder and Director of Therakind Limited (UK), ADAMS Limited (HK), Asia Medicine Regulatory Affairs (AMERA) Services Limited and OCUS Innovation Limited (HK, Ireland and UK).

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All other authors have nothing to declare.

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Author contribution

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

Keywords

Pneumococcal disease, pneumococcal conjugate vaccine, antimicrobial resistance, electronic health record

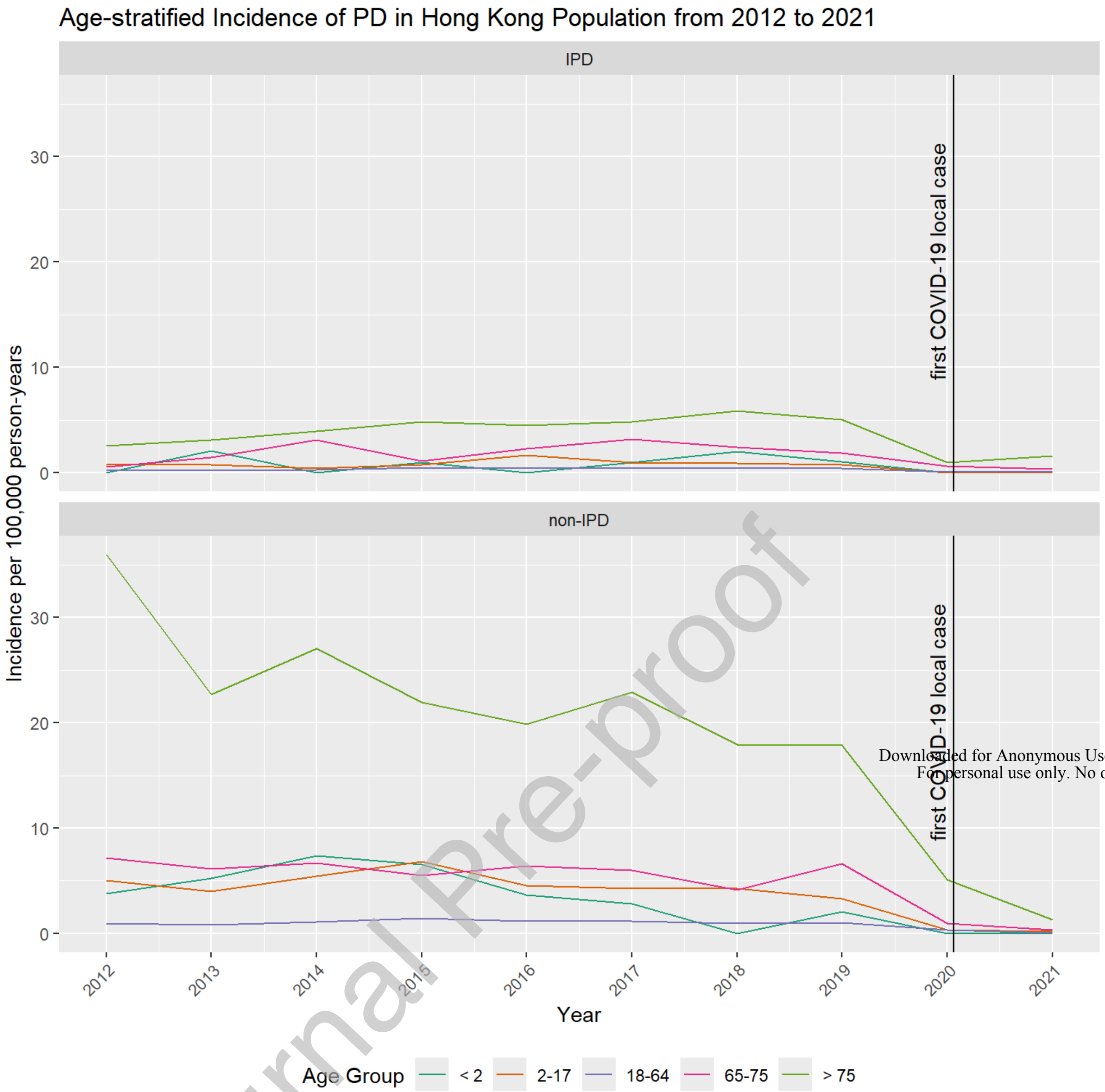

Figure 1 -- Age-Stratified Incidence of Pneumococcal Disease in Hong Kong Population from 2012 to 2021
Upper pane: invasive pneumococcal disease, IPD; Lower pane: pneumococcal disease, non-IPD

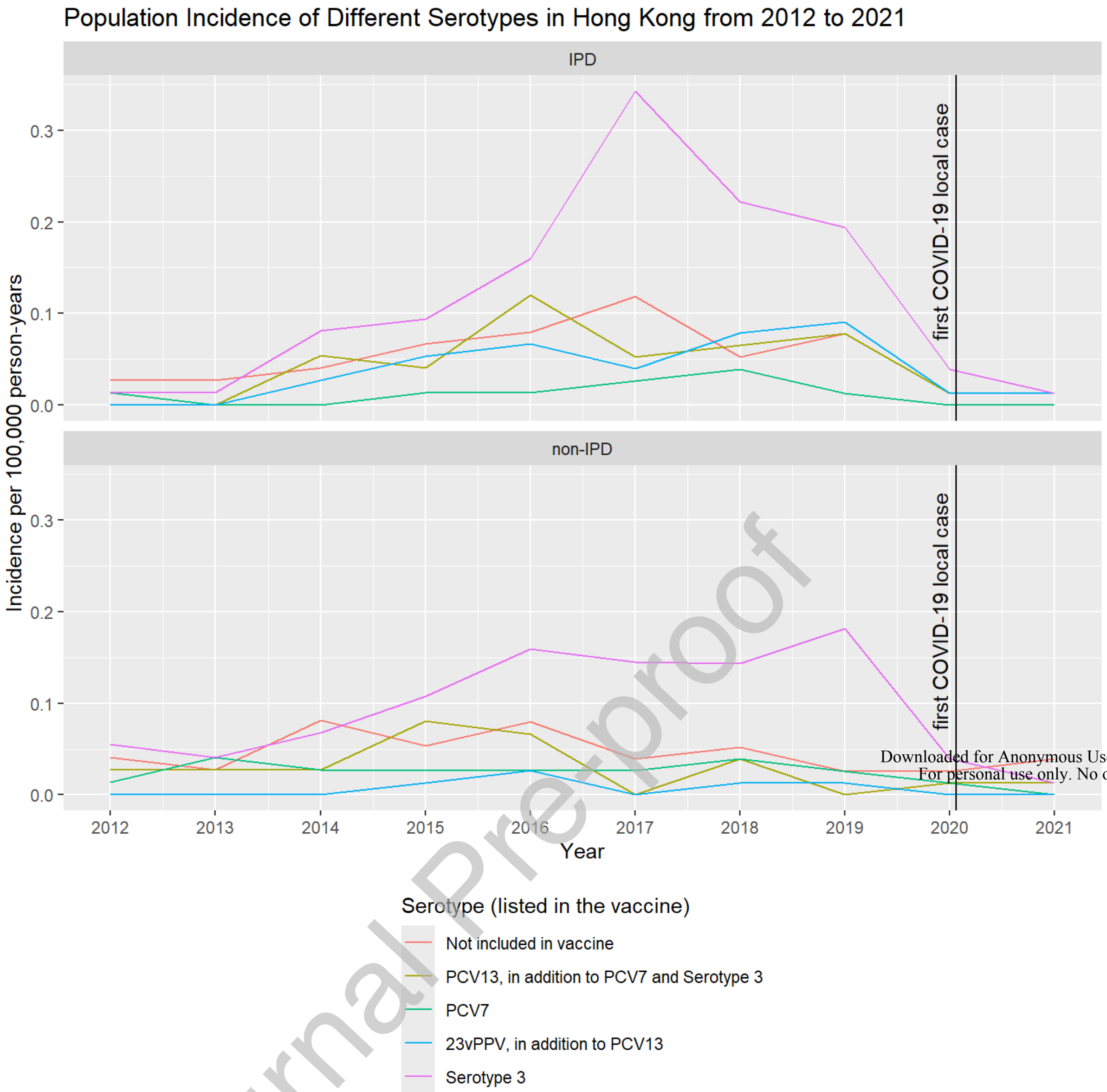

Figure 2 -- Population incidence of Serotypes
Upper pane: invasive pneumococcal disease, IPD; Lower pane: pneumococcal disease, non-IPD

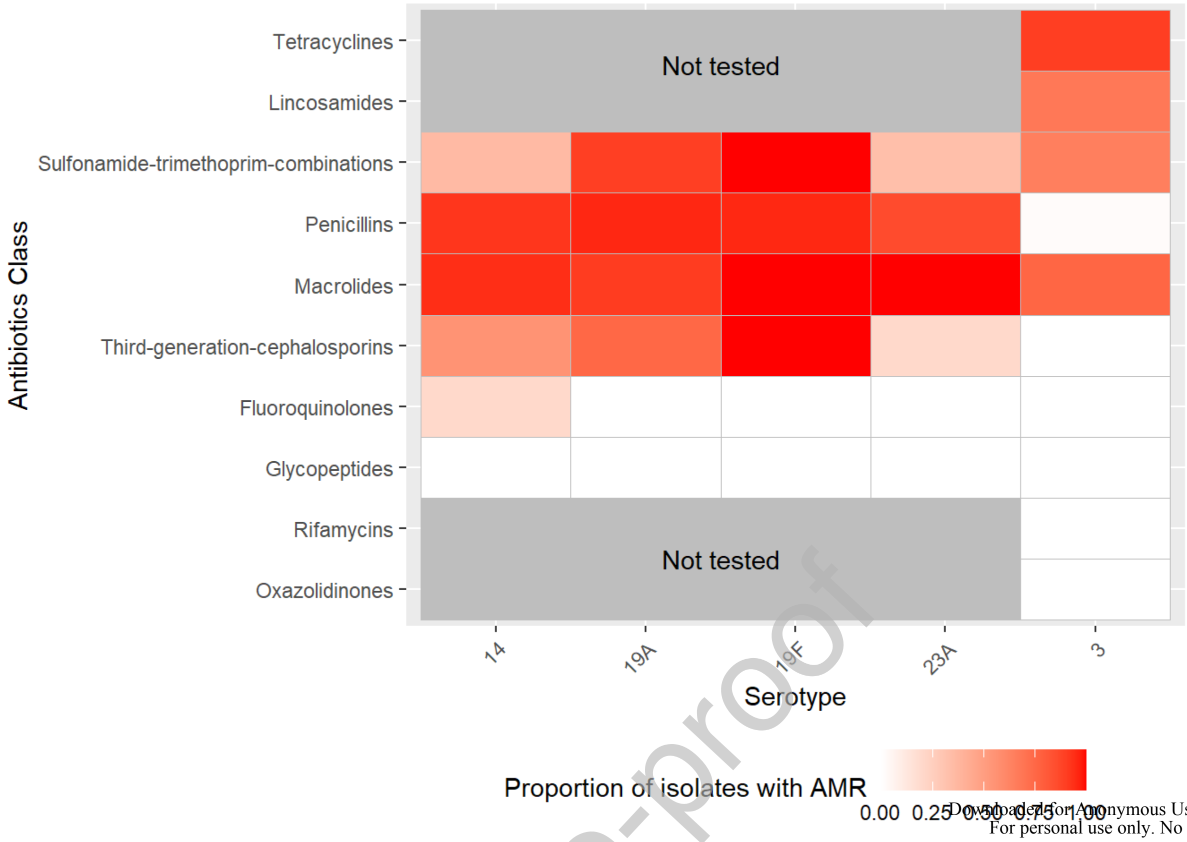

Figure 3 -- Relationship between high incidence serotypes and non-susceptibility with selected antibiotic classes

This heatmap identified the relationship between the percentage of non-susceptibility among the same class of antibiotics and the top 5 serotypes of the *S. pneumoniae* isolated (i.e. 3, 14, 19A, 19F, 23A)

Table 1 -- Basic characteristics and clinical features of included episodes

AMR Status	**N**	Overall, N = 2,251	Isolates non-susceptible to ≥1 antibiotics, N = 1,791	Isolates susceptible to antibiotics, N = 460	Standard mean difference
Sex	2,251				0.05
F		704 (31%)	569 (32%)	135 (29%)	
M		1,547 (69%)	1,222 (68%)	325 (71%)	
Age Group	2,251				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	2,251				0.35
Pneumococcal pneumonia		1,780 (79%)	1,464 (82%)	316 (69%)	
Pneumococcal bacteremic pneumonia		316 (14%)	219 (12%)	97 (21%)	
Pneumococcal bacteraemia		86 (3.8%)	57 (3.2%)	29 (6.3%)	
Pneumococcal meningitis		31 (1.4%)	20 (1.1%)	11 (2.4%)	
Other IPD		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 (IQR)]	2,251	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%)	
23vPPV, 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		1,899	1,511	388	
Prior co-morbidities	2,251				
cardiovascular condition	2,251	295 (13%)	244 (14%)	51 (11%)	-0.08
lung condition	2,251	455 (20%)	369 (21%)	86 (19%)	-0.05
liver condition	2,251	114 (5.1%)	94 (5.2%)	20 (4.3%)	-0.04
kidney condition	2,251	89 (4.0%)	66 (3.7%)	23 (5.0%)	0.06
metabolic condition	2,251	252 (11%)	198 (11%)	54 (12%)	0.02
immune condition	2,251	47 (2.1%)	40 (2.2%)	7 (1.5%)	-0.05
neurologic condition	2,251	135 (6.0%)	107 (6.0%)	28 (6.1%)	0

Table 2 -- Demographic characteristics and risk factors associated with AMR status in all patients identified with PD episodes

		IPD			**Non-IPD**		
		Univariable Odds ratio (95% CI)	Multivariable Odds ratio (95% CI)		Univariable Odds ratio (95% CI)	Multivariable Odds ratio (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) ****	**2.27 (1.53, 3.43) ****	**2.31 (1.55, 3.48) ****
	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)

**** statistically significant result ($p < 0.05$)**

Declaration of Interest Statement

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The author is an Editorial Board Member/Editor-in-Chief/Associate Editor/Guest Editor for this journal and was not involved in the editorial review or the decision to publish this article.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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All other authors have nothing to declare