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Title: Invasive pneumococcal disease, pneumococcal pneumonia and all-cause pneumonia during COVID-19 in Hong Kong – a retrospective observational study

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Abstract

Objectives: To compare the incidence and severity of invasive pneumococcal diseases (IPD), pneumococcal pneumonia and pneumonia during COVID-19 period with widely practiced of universal masking and social distancing to that of previous 5 years.

Design: Retrospective observational study on incidence of invasive pneumococcal diseases (IPD), pneumococcal pneumonia and all-cause pneumonia between Period 1 (January 2015-December 2019) and period 3 (March 2020-March 2021).

Setting: Episode-based data by retrieval of hospitalization records from the Hospital Authority's territory-wide electronic medical record database.

Participants: Hospitalized patients with invasive pneumococcal diseases (IPD) (n=742), pneumococcal pneumonia (n=2163) and all-cause pneumonia (n=453,999) at age 18 or above. Control diagnoses were included to assess confounding from health-seeking behaviors

Interventions: Period 3 with widely practiced of universal masking

Primary and secondary outcome: Primary outcome is the incidence of diseases between two periods. Secondary outcomes include disease severity surrogated by length of stay and mortality.

Results: Monthly average number of IPD, pneumococcal pneumonia and all-cause pneumonia hospitalization significantly decreased by 88.9%, 72.5% and 17.5% ($p<0.0005$). Change in trend from period 1 to period 3 was -70% ($p=0.0025$), -43% ($p=0.0014$) and -11% ($p<0.0005$). LOS for IPD and pneumococcal pneumonia episodes were insignificantly different in the two periods while that for all-cause pneumonia had a slight decrease from 11.7 days to 10.8 days ($p<0.005$). No reductions in control diagnoses were observed.

Conclusions: Incidence of IPD, pneumococcal pneumonia, and all-cause pneumonia decreased during COVID-19 pandemic. This was observed with universal masking and social distancing. We proposed this is related to reduce transmission of respiratory viruses and bacteria.

Strength and limitations of this study:

- A territory-wide study with near 100% practice of universal masking
- Other factors including temperature and air quality were also included in our analysis
- Disease severity of IPD, pneumococcal pneumonia, and all-cause pneumonia were compared between the two periods
- Data from private sector (<10%) were not included in our study
- The causal relationship cannot be ascertained from this retrospective study

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There are no competing interests.

Authors' contributions:

King-Pui Florence Chan and Ting-Fung Ma were involved in study concept and design; acquisition, analysis and interpretation of data; drafting the work and final approval of the manuscript. **Mary Sau-Man Ip** were involved in critical revision of manuscript for important intellectual content and final approval of the manuscript. **Pak-Leung Ho** was involved in study concept and design; analysis and interpretation of data; drafting of manuscript; critical revision of the manuscript for important intellectual content; study supervision; and approval of the final version of the manuscript.

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Text

Introduction

Coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections was first reported in late 2019 [1]. It became a global pandemic and was declared as a public health emergency of international concern on 30 January 2020 by the World Health Organization [2]. As of 21st June 2021, more than 178 million people were infected, causing more than 3.8 million deaths globally.

Pneumococcal disease is caused by *Streptococcus pneumoniae* infection, with at least 100 known serotypes of pneumococci [3]. Pneumococcal disease can be roughly divided into non-invasive disease and invasive disease. Non-invasive disease includes sinusitis, acute otitis media and pneumonia. Invasive pneumococcal disease (IPD) is defined as isolation of *Streptococcus pneumoniae* from a normally sterile sites, including blood and cerebrospinal fluid [4). IPD is a notifiable disease in Hong Kong since 9th January 2015. Pneumococcal infection is a major cause of morbidity and mortality worldwide [5], with 1.6 million estimated deaths annually in 2005 [6]. Incidence of IPD and mortality of pneumococcal pneumonia are higher in extremes of age [7-8].

The first pneumococcal conjugated vaccine (PCV), Prevnar 7 (PCV7) was introduced to United States in 2000 and incorporated in Hong Kong Childhood Immunisation Programme for children under 2 years old since September 2009. In Hong Kong, PCV7 was replaced by the 10-valent and 13-valent pneumococcal conjugate vaccines (PCV10 and PCV13) in 2010 and 2011 respectively [9-10]. PCV13 was effective in preventing vaccine-type pneumococcal pneumonia, bacteraemia and nonbacteraemic community-acquired pneumonia [11]. Decline in incidences of all-cause pneumonia in children and elderly was reported after implementation of PCV in childhood vaccination program [12-13]. 23-valent polysaccharide vaccine (PPSV23) was effective in preventing pneumococcal pneumonia and reducing mortality from pneumococcal pneumonia in nursing home residents [14]. Pneumonia is a common disease causing hospitalization, accounting for 2.9% of all inpatient discharges and death in Hong Kong [15]. It is the second

leading cause of death with age specific death rates increased markedly after age 65 [16].

Whether patients with COVID-19 are more susceptible to pneumococcal superinfection is still under debate. Superinfection of pneumococcal in COVID-19 patients was reported [17]. Yet, low frequency of bacterial coinfection in patients with early COVID-19 was also observed [18-19]. There is limited evidence on the incidence and severity of IPD, pneumococcal pneumonia, and all-cause pneumonia during COVID-19 pandemic, especially in area where universal masking and social distancing were widely practiced. Since January 2020, universal masking in public area was voluntarily performed by Hong Kong citizens against infection by COVID-19. Cross sectional telephone self-reported surveys by the Hong Kong Public Opinion Research Institute (HKPORI). Percentage of wearing mask was 74.5% on 20th-23rd January 2020 (n=1,008), 97.6% on 5th-20th February (n=10,405) and 98.9% on 4th-19th March (n=15,739) [20]. On 23rd July 2020, masking was mandatory in public area upon the introduction of Prevention and Control of Disease (Wearing of Mask) Regulation (Cap. 599I). Social distancing measurements were voluntarily practiced by public and implemented by government since 25th January 2020. These public health interventions were shown to associated with relatively low rate of COVID-19 and early termination of influenza season in Hong Kong [21]. Our previous studies suggested universal masking and social distancing were associated with significant reduction in acute exacerbation of chronic obstructive pulmonary disease and asthma in Hong Kong [22,23]. In the current study, we hypothesized that the aforementioned COVID-19 related public health interventions and reduction in respiratory virus activities would be associated with reduction in hospitalization due to pneumococcal infections and pneumonia in general.

Materials and Methods

A retrospective study assessing the numbers of IPD, pneumococcal pneumonia, and all-cause pneumonia which required hospital hospitalization during the period of COVID-19 in Hong Kong, comparing with that in the preceding five years as baseline. The study period was 1st January 2015 to 31st March 2021 with exclusion of 1st January 2020 to 28th February 2020 from analysis, when universal masking was not yet completely executed.

Data source

Episode-based data was obtained by retrieval of hospitalization records from the Hospital Authority's territory-wide electronic medical record database, Clinical Data Analysis and Reporting System (CDARS), which provides 90% of in-patient hospital care service in Hong Kong [22,23].

Diagnosis code of pneumococcal pneumonia (ICD-9 code 481) was searched on CDARS. IPD is a notifiable disease since January 2015 with monthly number notified cases and age obtained from the Department of Health, HKSAR. Monthly number of influenza virus detection was collected from a territory-wide laboratory surveillance for both in-patients and out-patients in both public and private medical sectors from the Centre for Health Protection, HKSAR [15].

All-cause pneumonia including the following ICD-9 codes for viral, bacterial, tuberculous, fungal and unspecified pneumonia, pneumonia due to inhalation of food or vomitus and lung abscess were obtained from CDARS (ICD-9 code 003.22, 055.1, 0.1160-1.1166, 112.4, 115, 117.3, 480, 481, 482, 483.1, 483.8, 485, 486, 487, 507.0, 513).

Patient and public involvement

This observational study based on the practice of universal masking by Hong Kong citizens to prevent COVID-19 infections and its relationship with hospital admissions of various diseases, particularly on the infectious disease aided in the development of the research question. Patients who were admitted with the diagnosis of IPD, pneumococcal pneumonia, pneumonia, acute kidney injury fracture hip and

peritonitis due to peritoneal dialysis were included in the study. Demographics data (including sex, age), clinical data (including hospitalization date, length of stay, episode death, date of death) were collected. The results including admission number of various diseases were available in the CHP website and the Hospital Authority Statistics Report [16].

Inclusion/ exclusion criteria

Patients with 1) age 18 or above 2) hospitalization for the listed diseases (pneumococcal pneumonia, IPD and pneumonia) were included in the study.

Children at aged 0 to 17 years old were excluded in this study. Duplicated record of single patient with different diagnoses in same hospital admission were removed.

Other diagnoses

Number of hospitalization for other common medical and surgical conditions including acute kidney injury (ICD-9 code 580, 584), fracture hip (ICD-9 code 820) and peritonitis due to peritoneal dialysis (PD peritonitis) (ICD-9 code 996.68) were collected. These were included to evaluate the possibility of decrease in hospital attendance due to various reasons such as fear of COVID-19 infection in hospital.

Other variables

Monthly mean ambient temperature was obtained from the Hong Kong Observatory [24]. Air quality was measured by air quality health index (AQHI), which is calculated based on the cumulative health risk attributable to a 3-hour moving average concentrations of ozone, nitrogen dioxide, sulphur dioxide and particulate matter [25]. It was reported in scale of 1 to 10 and 10+ and grouped into five health risk categories, namely low [1-3], moderate [4-6], high [7], very high [8-10] and serious [10+] with different precautionary actions were advised. People with respiratory illness were advised to minimize their outdoor stay when AQHI high to serious. The AQHI was reported hourly in 13 stations located in different area of Hong Kong. The total number of hours with AQHI recorded as high to serious grades were expressed as percentage of total number of hours collected in a month.

Statistical method

Total number of hospitalizations due to IPD, pneumococcal pneumonia and all-cause pneumonia were collected and analysed. Each disease was further divided into three different age groups, including 18 to 49 years, 50 to 64 years, and 65 years or above for analysis.

Analysis was done on the number of hospitalizations between January 2015 to December 2019, the period prior COVID-19 (period 1) and March 2020 to March 2021 (period 3), while January to February 2020 (period 2) was treated as transition period and excluded from the analysis. Wilcoxon rank sum test was first used to analyse the statistical significance of number of hospitalizations between period 1 and period 3. Generalized linear models were then applied for statistical inference of various types of responses. Log-linear model was used for studying the effect of pandemic as intervention under segmented regression framework in term of the change in trend (i.e. an increase or decrease in the level of the segment) between period 1 (pre-intervention segment) and period 3 (post-intervention segment) on the monthly hospitalization count [26]. Temporal effect was adjusted by covariates, including AQHI, temperature and effect of masking.

Generalized linear model was used for comparing the mortality rate of individuals between the two time periods [27]. Hospitalization length of stay (LOS) was described in days using mean and standard deviation. Statistical inference of the LOS in hospitalization of individuals was done by Wilcoxon rank sum test with odds ratio and relative risks and confidence intervals calculated [26].

Monthly incidence rate for each disease was calculated using the total population followed by age groups stratification (18 to 49 years, 50 to 64 years and ≥65 years) and expressed as number per 100,000 person-year. Age-specific population data was obtained from the Census and Statistics Department.

Ethics Approval

The study was approved by the Institutional Review Board of the University of Hong Kong/ Hospital Authority Hong Kong West Cluster (Reference Number UW-21-325).

Results

Invasive pneumococcal disease

The total number of notified IPD episodes was 742 in the entire study, with 699 reported in period 1 and 17 reported in period 3. Pneumococcal serotypes for 684 of the 699 episodes in period 1, and 13 of the 17 episodes in period 3m were successfully determined. The proportions attributed to PCV13 serotypes was 66.5% (465/699) and 29.4% (5/17) respectively for period 1 and period 3. Serotype 3 was the commonest serotype in both periods, accounting for 41.3% (289/699) and 17.6% (3/17) of total, respectively. From period 1 to period 3, the monthly number of IPD caused by PCV13 serotypes declined by 95.1% (95%CI 93.4%-96.4%) while those for non-PCV13 serotypes declined by 83.0% (95%CI 78.8%-86.5%).

Monthly number of IPD peaked in January-February each year except in 2016, with the peak in April (Figure 1A). Monthly average number of notified IPD episodes was 11.7±6.2 in period 1, with significant decrease to 1±4.3 in period 3 ($p<0.0005$). By log-linear model segmented regression, relative risk of IPD in period 3 was 0.85 (95%CI 0.75-0.96, $p=0.0089$) (Table S1). Further analysis on the relative risk of different age groups showed significant decline in relative risk of IPD in aged ≥65 years (0.78, 95%CI 0.61-0.99, $p=0.041$). Estimated change in trend in the mean number of cases from period 1 to period 3 was -70% (95%CI -87% to -35%, $p=0.0025$) (Figure 1A, Table S1).

Incidence rate per 100,000 person-years was 2.2 in period 1 and 0.2 in period 3, with an interval reduction of 88.9% (95%CI 79.8%-98.0%, $p<0.0005$) (Table 1). IPD is most prevalent in age ≥65. The magnitude of reduction in incidence rate was similar across different age groups, ranging from 81.3% to 93.5% ($p<0.0005$ for all age groups) (Table 1).

The overall LOS for IPD was 18.8±48.4 days in period 1 and 31.6±79.2 days in period 3 (Table 2), but the difference was statistically insignificant ($p=0.89$). Statistically insignificant variations in LOS of different age groups were observed.

Pneumococcal pneumonia

In the entire study period, there were 2,163 episodes of hospitalization for pneumococcal pneumonia, with 1970 episodes in period 1 and 119 episodes in period 3 (Table 1). Monthly number of pneumococcal pneumonia was peaked in January-February each year except in 2016, with the peak in April (Figure 1B). The average monthly hospitalizations was 32.8±9.9 episodes in period 1, with significant drop to 9.2±3.9 episodes in period 3 ($p<0.0005$). By log-linear model segmented regression, relative risk of pneumococcal pneumonia was 0.90 (95%CI 0.86-0.95, $p<0.005$) in period 3. Trend analysis revealed a change of -43% (95%CI -59% to -19%, $p=0.0014$, Figure 1B, Table S1) from period 1 to period 3. Age groups analysis showed similar change in trend for all age groups, with statistically significance in aged ≥65 years (-41%, 95%CI -61% to -12%, $p=0.010$) from period 1 to period 3 (Table S1, Figure S1).

Overall, the incidence rate of hospitalization for pneumococcal pneumonia decreased significantly by 72.5% (95%CI 65.9%-79.1%, $p<0.0005$), from 6.2 per 100,000 person-years in period 1 to 1.7 per 100,000 person-years in period 3 (Table 1). Incidence rate per 100,000 person year showed statistically significant reduction in all age groups, ranging from 73.0% to 82.5%.

The overall LOS for pneumococcal pneumonia in period 1 and period 3 was 17.7±27.5 days and 19.5±26.3 days in all age group ($p=0.051$) (Table 2). Age group stratification showed insignificant decrease in length of stay in those aged 18-49 years ($p=0.8051$) and aged ≥65 years ($p=0.226$). Increase in length of stay from 18.8±32.6 days to 31.7±48.1 days was observed in age group 50-64 years, and was statistically significant ($p=0.019$). Mortality rate for all ages was 13.1 (95% CI 11.7%-14.8%) in period 1 and 22.7 (95%CI 15.5%-31.3%) in period 3 ($p=0.0187$). Mortality rate was only statistically significant in aged 50-64 years ($p=0.0007$) but not in aged 18-49 years ($p=0.9917$) and aged ≥65 years ($p=0.246$)(Table 2).

All-cause pneumonia

In the entire study period, total hospitalization episodes for all-cause pneumonia was 453,999, of which 372,660 episodes in period 1 and 67,474 episodes in period 3. Monthly number of all-cause pneumonia peaked in January to March each year (Figure 1C). Mean monthly number of hospitalizations for all-cause pneumonia declined by 16.4% (95%CI 15.7%-17.1%, p<0.0005) from 6211±845.0 episodes in period 1 to 5190.3±593.8 episodes in period 3 (p<0.0005) (Figure 1C). Estimated change in trend in the mean number of cases in period 3 was -11% (95%CI -13% to -10%, p<0.0005). By log-linear model segmented regression, relative risk of all-cause pneumonia in period 3 compared with period 1 was 0.98 (95%CI 0.98-0.99, p<0.0005) (Table S1).

Overall, the incidence rate per 100,000 person-years was 1,169.7 in period 1, with 17.5% (95%CI 16.8%-18.2%, p<0.0005) reduction in period 3 to 964.5 per 100,000 person-years in period 3 (Table 1). The incidence rate decrease in period 3 compared to period 1 in all age groups.

The overall LOS for all-cause pneumonia episodes was 11.7±31.7 days in period 1 and 10.8±15.0 days in period 3 (p<0.005) (Table 2). Different age groups showed decrease in LOS but were only statistically significant in age 18-49 years and 50-64 years. The mortality rate increased from 20.5% (95% CI 20.4%-20.6%) in period 1 to 24.2% (95%CI 24.9%-25.6%) in period 3 (p<0.005) for all-cause pneumonia. The increase in mortality rate was statistically significant in all age groups (Table 2).

Influenza

The total number of influenza A or B viruses detected from January 2015 to March 2021 in Hong Kong was 123,732. The monthly number of influenza detections decreased drastically by 99.5% (95%CI 99.4%-99.5%, p<0.0005) from 1,966±2179 in period 1 to 10±18 in period 3 (Figure 1D). The monthly average number of respiratory specimens tested was 4313±1172 in period 1 and 3203±1868 in period 3.

By log-linear model segmented regression, relative risk of influenza was 0.92 (95%CI 0.88-0.95, p<0.0005). Estimated change in trend in the mean number of detections in period 3 was -99.0% (95%CI -99.3% to -98.7%, p<0.0005) of that in period 1 (Figure 1D)

Other diagnosis: acute kidney injury, PD peritonitis and fracture hip

The monthly average number of hospitalization episodes for acute kidney injury in period 1 and period 3 was 807.8±87.5 and 911.7±62.6, respectively (p<0.0005) (Figure 2) The monthly average number of hospitalization episodes for PD peritonitis was 246.7±27.7 in period 1 and 255.9±31.9 in period 3 (p=0.23). The monthly average number of hospitalization episodes for fracture hip was 432.9±53.1 in period 1 and 417.3±51.6 in period 3 (p=0.37)

Discussion

Hong Kong is a city with population of 7.5 million where universal masking and social distancing were widely practiced during the COVID-19 pandemic period. This study showed a drastic decrease in numbers of hospitalization for IPD and pneumococcal pneumonia and a lesser but still very significant decrease in all cause pneumonia after anti-COVID-19 measures in March 2020 to March 2021.

During COVID-19 period, decrease in incidence of IPD were observed in Taiwan and Singapore [28-29]. The decrease in IPD in Hong Kong was greater magnitude compare to other countries [30]. Our study added new information on the incidence and severity of IPD, pneumococcal pneumonia and all-cause pneumonia in terms of age-stratification.

Introduction of the current pneumococcal conjugate vaccines has been highly successful in reducing the incidence of pneumococcal diseases worldwide [31, 32]. Vaccine efficacy of PCV13 against vaccine type IPD in children aged ≤5 years was 86%-96% [33]. In adults aged ≥65 years, the vaccine efficacy against vaccine type IPD was reported as 75% and against vaccine type community-acquired pneumonia were reported as 45.6% and 72.8% respectively [11, 34]. In contrast, PPV23 only has vaccine efficacy of 24% against vaccine type community acquired pneumonia in aged ≥65 years [35]. In Hong Kong, a marked reduction in vaccine type IPD was observed in children few years after implementation of PCV in 2009. However, the indirect effect on adult IPD was not evident. Annual number of adult IPD hospitalization remains static in period 1 (Figure 1A). Universal masking in Hong Kong was shown to decrease the incidence of SARS-CoV2 [36-37] and influenza [38] during the COVID-19 pandemic. Our study showed 88.9% reduction in incidence of adult IPD. The drastic decrease in incidence of IPD included both vaccine and non-vaccine types and was comparable and greater than the reported figure after introduction of pneumococcal vaccines [11,32]. IPD can lead to significant mortality and morbidity [39]. Our study showed decrease in incidence and trend of IPD and were statistically significant. The decrease in mortality of IPD during the COVID-19 pandemics was statistically insignificant, which can be contributed by the relative small sample size.

The incidence of all-cause pneumonia showed a much lower magnitude of decrease with the lesser decrease observed in those aged ≥65 years (supplementary file, Figure S1C). This can be explained by subgroup of pneumonia due to inhalation of food or vomitus, i.e. aspiration pneumonia and is more prevalent in age group 65 years old or above. The population of Hong Kong has been seeing an aging trend and the population of 65 years old or above was 1,114,600 in 2015, and increased to 1,371,800 in 2020. In our study, the lesser decrease in incidence of all-cause pneumonia in 2019 – 2020 was observed in those aged 65 years or above, suggesting that the magnitude of decrease in all-cause pneumonia may be limited by any potential increase in aspiration pneumonia in the expanding number of elderly people. Secondly, the risk of aspiration pneumonia would not be affected by measures of universal masking or social distancing, thus reducing their protective effect on all-cause pneumonia.

Pneumococcal pneumonia and IPD are debilitating diseases which have been shown to require long length of hospital stay and high hospital cost [40-41]. The LOS in pneumococcal pneumonia was slightly increased from 17.7 to 19.5 days but was statistically insignificant. Looking into different age groups, only patients with age 50 to 64 years old showed statistically significant increase in LOS, while patients in age group 18 to 49 years old and 65 years old or above showed slight decrease. The severity of pneumococcal pneumonia can be comparable in the two periods.

Health seeking behaviour was also evaluated in our study. Admissions of non-communicable diseases revealed either statistically insignificant decrease in hospital attendance or statistically significant increase in hospital attendance. Our study covered more than one year time for COVID-19 pandemics with a relatively stable number of hospital attendance. Hence, the decrease in incidence of pneumococcal pneumonia, IPD and all-cause pneumonia cannot be explained by health seeking behaviour alone.

Collateral damages were observed during the COVID-19 pandemic [42-43], some of which were contributed by the decrease in general medical services to concentrate healthcare resources for the care of SARS-CoV-2 patients and the prevention of

possible viral spread. However, due to the relatively small number of COVID-19 cases in Hong Kong, provision of acute medical services was minimally disrupted. In our study, the data on admissions for fractures, acute kidney injury and PD peritonitis showed no decrease during the Covid pandemic. Hence the observed decrease in hospital admissions for pneumococcal pneumonia, IPD and all-cause pneumonia should not be artefactual. Masking can be an effective yet low-cost preventive measurement for citizens at high risk of pneumococcal infections.

Limitations

This study is a retrospective observational study and the direct effect of universal masking on pneumococcal pneumonia, IPD and all-cause pneumonia cannot be ascertained. However, our study covered a period of more than one year when universal masking was practiced and a consistent observation of decrease in hospitalization for these diseases were seen. Other factors, namely ambient temperature and AQHI, that might have possible effect on the hospitalization numbers were also included in our analysis.

Our study focused on hospital hospitalization numbers to Hospital Authority. For IPD, the incidence was obtained from Central of Health Protection, HKSAR, which included data from both public and private hospitals data. The LOS and mortality data of IPD were retrieved from the database in Hospital Authority. Admissions to private hospital due to pneumococcal pneumonia and all-cause pneumonia were not included in our study. However, Hospital Authority is the largest healthcare provider in Hong Kong which provides 90% of in-patient services in Hong Kong [44]. Data from Hospital Authority is representable for the general epidemiology of Hong Kong.

Conclusions

The incidence of pneumococcal pneumonia, IPD and all-cause pneumonia decreased during COVID-19 pandemics compare to the data in previous five years. This was observed with widely practice of universal masking and social distancing. We propose the decrease is attributed to universal masking and social distancing which reduced the transmission of bacteria or virus and related bacterial superinfection.

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Table 1. Incidence and number per 100,000 person year of pneumococcal pneumonia, invasive pneumococcal disease (IPD) and pneumonia

	All ages		18-49 years		50-64 years		≥65 years	
Disease [a]	No. of episodes	Incidence rate per 100,000 person-years	No. of episodes	Incidence rate per 100,000 person-years	No. of episodes	Incidence rate per 100,000 person-years	No. of cases	Incidence rate per 100,000 person-years
IPD								
Period 1	699	2.2	125	0.7	195	2.2	379	6.2
Period 2	26	2.4	5	0.9	6	2.0	15	6.6
Period 3	17	0.2	3	0.08	8	0.4	6	0.4
% reduction[b]		88.9% (79.8%- 98.0%)***		88.6% (66.8%-110.4%)***		81.3% (62.1%-100.4%)***		93.5% (82,2%-104.8%)***
Pneumococcal pneumonia								
Period 1	1,970	6.2	217	1.3	435	4.9	1,318	21.7
Period 2	74	6.9	11	2.0	14	4.7	49	32.4
Period 3	119	1.7	8	0.2	24	1.2	87	5.9
% reduction		72.5% (65.9%-79.1%)***		82.5% (64.5%-100.5%)***		74.8% (61.0%-88.6%)***		73.0% (65.2%-80.8%)***
All-cause pneumonia								
Period 1	372,660	1169.7	19,502	115.3	38,360	432.4	314,798	5177.1
Period 2	13,865	1288.2	843	153.6	1,448	484.6	11,574	5062.3
Period 3	67,474	964.5	2,473	69.3	6,181	318.3	58,820	3958.0
% reduction		17.5% (16.8%-18.2%)***		39.9% (37.1%-42.7%)***		26.4% (24.3%-28.5%)***		23.5% (22.8%-24.3%)***

[a]Period 1, January 2015 to December 2019 (before covid-19); period 2, January 2020 to February 2020 (transition period); period 3 March 2020 to March 2021 (post-COVID-19).

[b] Percentage reduction in period 3 relative to period 1 as the baseline

*p <0.05 to 0.01, **p <0.01 to 0.005, ***p<0.005

Table 2. Mean length of stay and mortality rate of pneumococcal pneumonia, invasive pneumococcal disease (IPD) and pneumonia in the periods

	Mean length of stay (days)					Mortality rate (%)			
	All ages	**18-49 years**	**50-64 years**	**≥65 years**		**All ages**	**18-49 years**	**50-64 years**	**≥65 years**
IPD									
Period 1	18.8 ± 48.4	27.9 ± 102.8	17.7 ± 19.1	15.9 ± 18.9		12.1(8.8-16.1)	9.1(3.4-18.7)	8.4(3.7-15.9)	15.3(10.3-21.4)
Period 3	31.6 ± 79.2	6.3 ± 5.2	76.4 ± 140.3	14.1 ± 9.9		6.3(1.6-30.2)	0.0	0.0	14.3(3.6-57.9)
Pneumococcal Pneumonia									
Period 1	17.7 ± 27.5	16.9 ± 28.0	18.8 ± 32.6*	17.5 ± 25.6		13.1(11.7-14.8)*	4.2(1.9-7.7)	7.5(5.3-10.5)**	16.3(13.6-18.7)
Period 3	19.5 ± 26.3	13.6 ± 15.6	31.7 ± 48.1*	16.8 ± 16.6		22.7(15.5-31.3)*	0.0	29.2(12.6-51.1)**	23.0(14.6-33.2)
All-cause pneumonia									
Period 1	11.7 ± 31.7***	10.3 ± 42.5***	13.4 ± 45.1**	11.7 ± 28.9		20.5(20.4-20.6)***	5.3(4.9-5.6)*	13.0(11.4-12.0)***	22.4(22.2-22.4)***
Period 3	10.8 ± 15.0***	9.4 ± 16.5***	11.9 ± 20.1**	10.7 ± 14.3		24.2(24.9-25.6)***	6.8(5.9-7.9)*	16.1(5.2-17.0)***	27.0(26.6-27.3)***

*p <0.05 to 0.01, **p <0.01 to 0.005, ***p<0.005

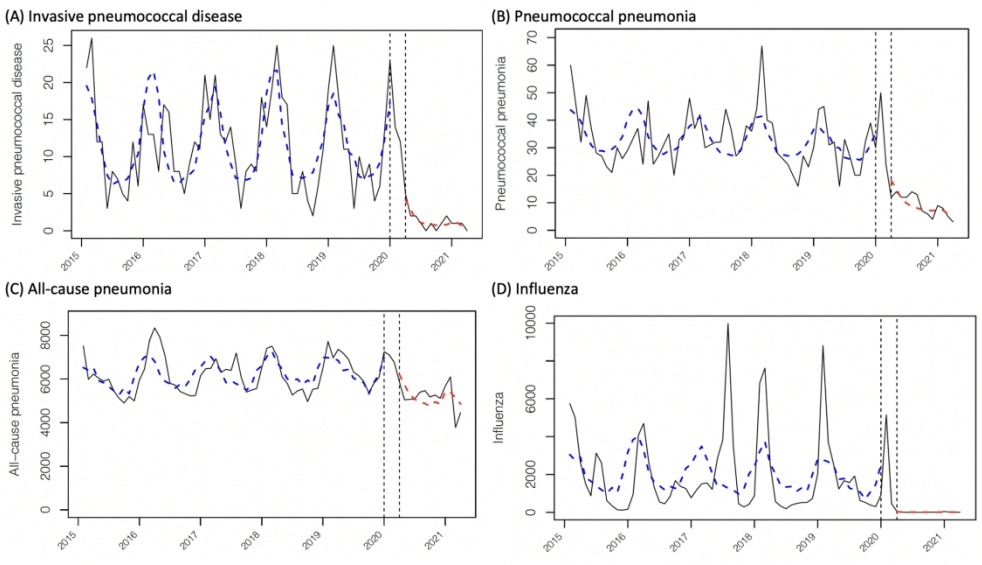

Figure 1. Trend analysis of monthly numbers of invasive pneumococcal disease (IPD), pneumococcal pneumonia, all-cause pneumonia, and influenza in Hong Kong, January 2015 to March 2021. Numbers of IPD were those obtained through mandatory notification. Numbers of pneumococcal pneumonia and all-cause pneumonia were territory-wide hospitalizations by discharge diagnoses. Numbers of influenza viruses were those detected in respiratory specimens in a territory-wide laboratory surveillance.

419x237mm (144 x 144 DPI)

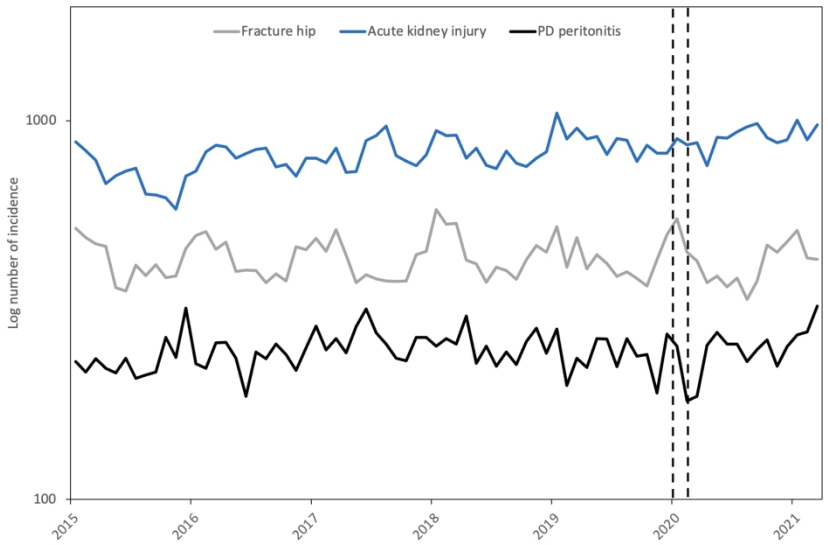

Figure 2. Admission numbers of fracture hip, acute kidney injury and PD peritonitis.

419x237mm (144 x 144 DPI)

Supplementary file.

Figure S1. Trend analysis of monthly number of (A) age-stratified hospitalizations for invasive pneumococcal disease, (B) age-stratified hospitalizations for pneumonococcal pneumonia, (C) age-stratified hospitalizations for and (D) monthly percentage of air quality health index (AQHI) high to serious and (E) monthly average ambient temperature.

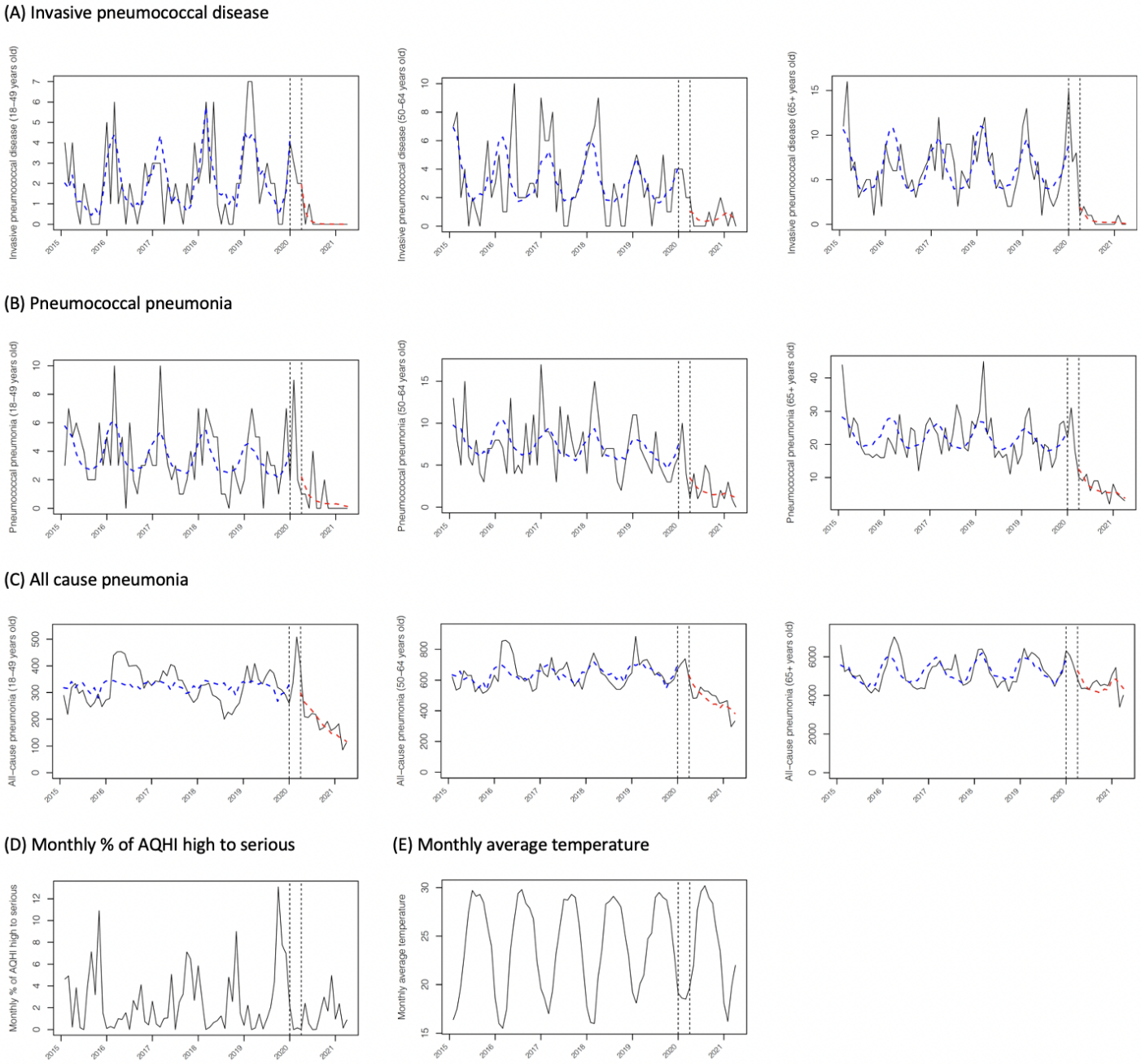

Table S1. Trend analysis of monthly number of hospitalization by age groups in periods before and after the COVID-19 pandemic

	Relative risk (95% CI)		Change in trend#
	Period 1 ^	Period 3^	
IPD			
All ages	1.0020 (0.9977-1.064)	0.8484 (0.7501-0.9597)**	-70.39% (-86.55% to -34.73%)**
18-49 years	1.0129 (1.0022-1.0238)	0.5272 (0.2176-1.2772)	-31.27% (-89.72% to 359.72%)
50-64 years	0.9969 (0.9888-1.0051)	0.9585 (0.8087-1.1362)	-70.43% (-92.80% to 21.42%)
65 years or above	1.0012 (0.9953-1.0071)	0.7777 (0.6111-0.9897)*	-70.83% (-91.59% to 1.12%)
Pneumococcal Pneumonia			
All ages	0.9978(0.9953-1.0004)	0.9042(0.8621-0.9483)***	-42.79% (-59.36% to -19.48%)*
18-49 years	0.9964(0.9887-1.0042)	0.6768(0.2171-2.1093)	-32.32% (-78.29% to 110.93%)
50-64 years	0.9962(0.9907-1.0017)	0.9174(0.8260-1.0189)	-50.21% (-76.93% to 7.48%)
65 years or above	0.9986(0.9954-1.0017)	0.9107(0.8612-0.9640)*	-41.19% (-60.82% to -11.73%)*
All-cause pneumonia			
All ages	1.0014(1.0012-1.0016)***	0.9835(0.9815-0.9855)***	-11.24% (-12.76% to -9.7%)***
18-49 years	1.0000(0.9992-1.0008)	0.9263(0.9164-0.9364)***	-6.05% (-13.41% to 1.94%)
50-64 years	1.0015(1.0009-1.0021)***	0.9620(0.9556-0.9684)***	-9.32% (-14.14% to -4.22%)***
65 years or above	1.0011(1.0009-1.0013)***	0.9879(0.9858-0.9901)***	-13.30% (-12.94% to -9.64%)***

^Trend in period 1 (January 2015 to December 2019) and 3 (March 2020 to March 2021), the (relative risk expressed the month-to-month change in hospitalization numbers

#Estimate the change in trend in the mean monthly number of cases in period 3, compare with the monthly trend in period 1

*p <0.05 to 0.01, **p <0.01 to 0.005, ***p<0.005

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6,7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	6,7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8
		(*b*) Describe any methods used to examine subgroups and interactions	7,8
		(*c*) Explain how missing data were addressed	N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	7,8

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9-12
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-12
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	9-12
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-12
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	13,14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

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

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Keywords:	COVID-19, Respiratory infections < THORACIC MEDICINE, Thoracic medicine < INTERNAL MEDICINE, Epidemiology < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES

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Title: 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

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Abstract

Objectives: To compare the incidence and severity of invasive pneumococcal diseases (IPD), pneumococcal pneumonia and all-cause pneumonia during COVID-19 period with widely practiced of universal masking and social distancing to that of previous 5 years.

Design: Retrospective observational study on incidence of invasive pneumococcal diseases (IPD), pneumococcal pneumonia and all-cause pneumonia between January 2015-December 2019 and March 2020-March 2021. January-February 2020 was excluded from analysis as it was treated as transitional period between normal time and pandemic, where universal masking was not completely executed.

Setting: Episode-based data by retrieval of hospitalization records from the Hospital Authority's territory-wide electronic medical record database in Hong Kong.

Participants: Hospitalized patients with invasive pneumococcal diseases (IPD) (n=742), pneumococcal pneumonia (n=2163) and all-cause pneumonia (including COVID-19 pneumonia, n=453,999) at age 18 or above. Control diagnoses were included to assess confounding from health-seeking behaviors.

Primary and secondary outcome: Primary outcome is the incidence of diseases between two periods. Secondary outcomes include disease severity surrogated by length of stay and mortality.

Results: Monthly average number of IPD, pneumococcal pneumonia and all-cause pneumonia hospitalization significantly decreased by 88.9% (95%CI 79.8%-98.0%, p<0.0005), 72.5% (95%CI 65.9%-79.1%, p<0.0005) and 17.5% (95%CI 16.8%-18.2%, p<0.0005). Change in trend from January 2015-December 2019 to March 2020-March 2021 was -70% (95%CI -87% to -35%, p=0.0025), -43% (95%CI -59% to -19%, p=0.0014) and -11% (95%CI -13% to -10%, p<0.0005). LOS for IPD and pneumococcal pneumonia episodes were insignificantly different in the two periods. No reductions in control diagnoses were observed.

Conclusions: Incidence of IPD, pneumococcal pneumonia, and all-cause pneumonia decreased during COVID-19 pandemic. This was observed with universal masking and social distancing. We proposed this is related to reduce transmission of respiratory viruses and bacteria.

Strength and limitations of this study:

- A territory-wide study with near 100% practice of universal masking
- Other factors including temperature and air quality were also included in our analysis
- Disease severity of IPD, pneumococcal pneumonia, and all-cause pneumonia were compared between the two periods
- Data from private sector (<10%) were not included in our study
- The causal relationship cannot be ascertained from this retrospective study

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests: There are no competing interests.

Data availability statements: No additional data is available.

Authors' contributions:

King-Pui Florence Chan and Ting-Fung Ma were involved in study concept and design; acquisition, analysis and interpretation of data; drafting the work and final approval of the manuscript. **Mary Sau-Man Ip** were involved in critical revision of manuscript for important intellectual content and final approval of the manuscript. **Pak-Leung Ho** was involved in study concept and design; analysis and interpretation of data; drafting of manuscript; critical revision of the manuscript for important intellectual content; study supervision; and approval of the final version of the manuscript.

Word count: 3991

Keywords: pneumococcal, COVID-19, masking, regression analysis

Text

Introduction

Coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections was first reported in late 2019 [1]. It became a global pandemic and was declared as a public health emergency of international concern on 30 January 2020 by the World Health Organization [2]. As of 21st June 2021, more than 178 million people were infected, causing more than 3.8 million deaths globally.

Pneumococcal disease is caused by *Streptococcus pneumoniae* infection, with at least 100 known serotypes of pneumococci [3]. Pneumococcal disease can be roughly divided into non-invasive disease and invasive disease. Non-invasive disease includes sinusitis, acute otitis media and pneumonia. Invasive pneumococcal disease (IPD) is defined as isolation of *Streptococcus pneumoniae* from a normally sterile sites, including blood and cerebrospinal fluid [4). IPD is a notifiable disease in Hong Kong since 9th January 2015. Pneumococcal infection is a major cause of morbidity and mortality worldwide [5], with 1.6 million estimated deaths annually in 2005 [6]. Incidence of IPD and mortality of pneumococcal pneumonia are higher in extremes of age [7-8].

The first pneumococcal conjugated vaccine (PCV), Prevnar 7 (PCV7) was introduced to United States in 2000 and incorporated in Hong Kong Childhood Immunisation Programme for children under 2 years old since September 2009 [9-10]. In Hong Kong, PCV7 was replaced by the 10-valent and 13-valent pneumococcal conjugate vaccines (PCV10 and PCV13) in 2010 and 2011 respectively [11-12]. PCV13 was effective in preventing vaccine-type pneumococcal pneumonia, bacteraemia and nonbacteraemic community-acquired pneumonia [13]. Decline in incidences of all-cause pneumonia in children and elderly was reported after implementation of PCV in childhood vaccination program [14-15]. 23-valent polysaccharide vaccine (PPSV23) was effective in preventing pneumococcal pneumonia and reducing mortality from pneumococcal pneumonia in nursing home residents [16]. In our locality, elderly at age 65 years and above without high risk conditions, namely immunodeficiency or chronic cardiac, pulmonary, liver or renal disease, or diabetes mellitus were recommended to receive either a single dose of

PCV13 or a single dose of PPSV23. Number of PPSV23 vaccine recipients at age 65 years or above increased from 35,000 in year 2015/2016 to 81,700 in 2019/2020, reaching accumulative 45.5% of population in the age group vaccinated in 2019/2020 [17]. Pneumonia is a common disease causing hospitalization, accounting for 2.9% of all inpatient discharges and death in Hong Kong [18]. It is the second leading cause of death with age specific death rates increased markedly after age 65 [17].

Whether patients with COVID-19 are more susceptible to pneumococcal superinfection is still under debate. Superinfection of pneumococcal in COVID-19 patients was reported [19]. Yet, low frequency of bacterial coinfection in patients with early COVID-19 was also observed [20-21]. There is limited evidence on the incidence and severity of IPD, pneumococcal pneumonia, and all-cause pneumonia during COVID-19 pandemic, especially in area where universal masking and social distancing were widely practiced. Since January 2020, universal masking in public area was voluntarily performed by Hong Kong citizens against infection by COVID-19. Cross sectional telephone self-reported surveys by the Hong Kong Public Opinion Research Institute (HKPORI) showed percentage of wearing mask was 74.5% on 20th-23rd January 2020 (n=1,008), 97.6% on 5th-20th February (n=10,405) and 98.9% on 4th-19th March (n=15,739) [22]. On 23rd July 2020, masking was mandatory in public area upon the introduction of Prevention and Control of Disease (Wearing of Mask) Regulation (Cap. 599I). Social distancing measurements were voluntarily practiced by public and implemented by government since 25th January 2020. These public health interventions were shown to associated with relatively low rate of COVID-19 and early termination of influenza season in Hong Kong [23]. Our previous studies suggested universal masking and social distancing were associated with significant reduction in acute exacerbation of chronic obstructive pulmonary disease and asthma in Hong Kong [24,25]. In the current study, we hypothesized that the aforementioned COVID-19 related public health interventions and reduction in respiratory virus activities would be associated with reduction in hospitalization due to pneumococcal infections and pneumonia in general.

Materials and Methods

A retrospective study assessing the numbers of IPD, pneumococcal pneumonia, and all-cause pneumonia which required hospital hospitalization during the period of COVID-19 in Hong Kong, comparing with that in the preceding five years as baseline. The study period was 1st January 2015 to 31st March 2021 with exclusion of 1st January 2020 to 28th February 2020 from analysis, when universal masking was not yet completely executed.

Data source

Episode-based data was obtained by retrieval of hospitalization records from the Hospital Authority's territory-wide electronic medical record database, Clinical Data Analysis and Reporting System (CDARS), which provides 90% of in-patient hospital care service in Hong Kong [24,25].

Diagnosis code of pneumococcal pneumonia (ICD-9 code 481) was searched on CDARS. IPD is a notifiable disease since January 2015 with monthly number notified cases and age obtained from the Department of Health, Hong Kong Special Administrative Region (HKSAR). Monthly number of influenza virus detection was collected from a territory-wide laboratory surveillance for both in-patients and out-patients in both public and private medical sectors from the Centre for Health Protection (CHP), HKSAR [17].

All-cause pneumonia including the following ICD-9 codes for viral, bacterial, tuberculous, fungal and unspecified pneumonia, pneumonia due to inhalation of food or vomitus and lung abscess were obtained from CDARS (ICD-9 code 003.22, 055.1, 0.1160-1.1166, 112.4, 115, 117.3, 480, 481, 482, 483.1, 483.8, 485, 486, 487, 507.0, 513). Patient with COVID-19 associated pneumonia was included in the all-cause pneumonia dataset. The contribution of COVID-19 within all-cause pneumonia was queried using ICD codes for COVID-19 disease (ICD-9 code 079.89, 480.8, 519.8). Demographics data (including sex, age), clinical data (including hospitalization date, length of stay, episode death, date of death) were collected. The results including admission number of various diseases were available in the CHP website and the Hospital Authority Statistics Report [17,26].

Inclusion/ exclusion criteria

Patients with 1) age 18 or above 2) hospitalization for the listed diseases (pneumococcal pneumonia, IPD and pneumonia) were included in the study.

Children at aged 0 to 17 years old were excluded in this study. Duplicated record of single patient with different diagnoses in same hospital admission were removed.

Other diagnoses

Number of hospitalization for other common medical and surgical conditions including acute kidney injury (ICD-9 code 580, 584), fracture hip (ICD-9 code 820) and peritonitis due to peritoneal dialysis (PD peritonitis) (ICD-9 code 996.68) were collected. These were included to evaluate the possibility of decrease in hospital attendance due to various reasons such as fear of COVID-19 infection in hospital. These diseases were selected as are non-communicable diseases and have minimal interactions with environmental factors including mean ambient temperature and air-pollution.

Other variables

Monthly mean ambient temperature was obtained from the Hong Kong Observatory [27]. Air quality was measured by air quality health index (AQHI), which is calculated based on the cumulative health risk attributable to a 3-hour moving average concentrations of ozone, nitrogen dioxide, sulphur dioxide and particulate matter [28]. It was reported in scale of 1 to 10 and 10+ and grouped into five health risk categories, namely low [1-3], moderate [4-6], high [7], very high [8-10] and serious [10+] with different precautionary actions were advised. People with respiratory illness were advised to minimize their outdoor stay when AQHI high to serious. The AQHI was reported hourly in 13 stations located in different area of Hong Kong. The total number of hours with AQHI recorded as high to serious grades were expressed as percentage of total number of hours collected in a month.

Statistical method

Total number of hospitalizations due to IPD, pneumococcal pneumonia and all-cause pneumonia were collected and analysed. Each disease was further divided into three

different age groups, including 18 to 49 years, 50 to 64 years, and 65 years or above for analysis.

Analysis was done on the number of hospitalizations between January 2015 to December 2019, the period prior COVID-19 (period 1) and March 2020 to March 2021 (period 3), while January to February 2020 (period 2) was treated as transition period and excluded from the analysis. Wilcoxon rank sum test was first used to analyse the statistical significance of number of hospitalizations between period 1 and period 3. Generalized linear models were then applied for statistical inference of various types of responses. Log-linear model was used for studying the effect of pandemic as intervention under segmented regression framework in term of the change in trend (i.e. an increase or decrease in the level of the segment) between period 1 (pre-intervention segment) and period 3 (post-intervention segment) on the monthly hospitalization count. Regression coefficients of log-linear model can be interpreted as the effect due to pandemic by log-linear model [29]. Temporal effect was adjusted by covariates, including AQHI, temperature and effect of masking.

Generalized linear model was used for comparing the mortality rate of individuals between the two time periods [30]. Hospitalization length of stay (LOS) was described in days using median and standard deviation. Statistical inference of the LOS in hospitalization of individuals was done by Wilcoxon rank sum test with odds ratio and relative risks and confidence intervals calculated [29].

Monthly incidence rate for each disease was calculated using the total population followed by age groups stratification (18 to 49 years, 50 to 64 years and ≥65 years) and expressed as number per 100,000 person-year. Age-specific population data was obtained from the Census and Statistics Department.

Ethics Approval

The study was approved by the Institutional Review Board of the University of Hong Kong/ Hospital Authority Hong Kong West Cluster (Reference Number UW-21-325).

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Invasive pneumococcal disease

The total number of notified IPD episodes was 742 in the entire study, with 699 reported in period 1 and 17 reported in period 3. Pneumococcal serotypes for 684 of the 699 episodes in period 1, and 13 of the 17 episodes in period 3 were successfully determined. The proportions attributed to PCV13 serotypes was 66.5% (465/699) and 29.4% (5/17) respectively for period 1 and period 3. Serotype 3 was the commonest serotype in both periods, accounting for 41.3% (289/699) and 17.6% (3/17) of total, respectively. From period 1 to period 3, the monthly number of IPD caused by PCV13 serotypes declined by 95.1% (95%CI 93.4%-96.4%) while those for non-PCV13 serotypes declined by 83.0% (95%CI 78.8%-86.5%), and those for PPSV23 serotypes declined by 94.1% (95% CI 92.3%-95.5%). The small difference between declines in PCV13 and PPSV23 serotypes was mainly attributed to serotype 6A which was included in PCV13 but not in PPVS23.

Monthly number of IPD peaked in January-February each year except in 2016, with the peak in April (Figure 1A and Figure S2). Monthly average number of notified IPD episodes was 11.7±6.2 in period 1, with significant decrease to 1±4.3 in period 3 ($p<0.0005$). By log-linear model segmented regression, relative risk of IPD in period 3 was 0.85 (95%CI 0.75-0.96, p=0.0089) (Table S1). Further analysis on the relative risk of different age groups showed significant decline in relative risk of IPD in aged ≥65 years (0.78, 95%CI 0.61-0.99, p=0.041). Estimated change in trend in the mean number of cases from period 1 to period 3 was -70% (95%CI -87% to -35%, p=0.0025) (Figure 1A, Table S1).

Incidence rate per 100,000 person-years was 2.2 in period 1 and 0.2 in period 3, with an interval reduction of 88.9% (95%CI 79.8%-98.0%, $p<0.0005$). Incidence rate ratio between period 1 and period 3 was 0.11 (95%CI 0.07-0.18, $p<0.0005$) (Table 1). IPD is most prevalent in age ≥65. The magnitude of reduction in incidence rate was similar across different age groups, ranging from 81.3% to 93.5% ($p<0.0005$ for all age groups) (Table 1).

The overall median LOS for IPD was 12 (Interquartile range, IQR 16) days in period 1 and 12 (IQR 11) days in period 3 (Table 2), with statistically insignificant difference (p=0.89). Statistically insignificant variations in LOS of different age groups were observed.

Pneumococcal pneumonia

In the entire study period, there were 2,163 episodes of hospitalization for pneumococcal pneumonia, with 1970 episodes in period 1 and 119 episodes in period 3 (Table 1). Monthly number of pneumococcal pneumonia was peaked in January-February each year except in 2016, with the peak in April (Figure 1B and Figure S2). The average monthly hospitalizations was 32.8±9.9 episodes in period 1, with significant drop to 9.2±3.9 episodes in period 3 (p<0.0005). By log-linear model segmented regression, relative risk of pneumococcal pneumonia was 0.90 (95%CI 0.86-0.95, p<0.005) in period 3. Trend analysis revealed a change of -43% (95%CI -59% to -19%, p=0.0014, Figure 1B, Table S1) from period 1 to period 3. Age groups analysis showed similar change in trend for all age groups, with statistically significance in aged ≥65 years (-41%, 95%CI -61% to -12%, p=0.010) from period 1 to period 3 (Table S1, Figure S1).

Overall, the incidence rate of hospitalization for pneumococcal pneumonia decreased significantly by 72.5% (95%CI 65.9%-79.1%, p<0.0005), from 6.2 per 100,000 person-years in period 1 to 1.7 per 100,000 person-years in period 3. Incidence rate ratio between period 1 and period 3 was 0.28 (95%CI 0.23-0.33, p<0.0005) (Table 1). Incidence rate per 100,000 person year showed statistically significant reduction in all age groups, ranging from 73.0% to 82.5%.

The overall median LOS for pneumococcal pneumonia in period 1 and period 3 was 9 (IQR 14) days and 12 (IQR 17) days in all age group (p=0.051) (Table 2). Age group stratification showed insignificant changes in length of stay in those aged 18-49 years (p=0.8051) and aged ≥65 years (p=0.226). Increase in length of stay from 9 (IQR 15) days to 13 (IQR 20) days was observed in age group 50-64 years, and was statistically significant (p=0.019). Mortality rate for all ages was 13.1% (95% CI 11.7%-14.8%) in period 1 and 22.7% (95%CI 15.5%-31.3%) in period 3 (p=0.0187).

Mortality rate was only statistically significant in aged 50-64 years (p=0.0007) but not in aged 18-49 years (p=0.9917) and aged ≥65 years (p=0.246) (Table 2).

All-cause pneumonia

In the entire study period, total hospitalization episodes for all-cause pneumonia was 453,999, of which 372,660 episodes in period 1 and 67,474 episodes in period 3. Monthly number of all-cause pneumonia peaked in January to March each year (Figure 1C and Figure S2). Mean monthly number of hospitalizations for all-cause pneumonia declined by 16.4% (95%CI 15.7%-17.1%, p<0.0005) from 6211±845.0 episodes in period 1 to 5190.3±593.8 episodes in period 3 (p<0.0005) (Figure 1C). Estimated change in trend in the mean number of cases in period 3 was -11% (95%CI -13% to -10%, p<0.0005). By log-linear model segmented regression, relative risk of all-cause pneumonia in period 3 compared with period 1 was 0.98 (95%CI 0.98-0.99, p<0.0005) (Table S1).

Overall, the incidence rate per 100,000 person-years was 1,169.7 in period 1, with 17.5% (95%CI 16.8%-18.2%, p<0.0005) reduction in period 3 to 964.5 per 100,000 person-years in period 3. Incidence rate ratio between period 1 and period 3 was 0.83 (95%CI 0.82-0.83, p<0.0005) (Table 1). The incidence rate decrease in period 3 compared to period 1 in all age groups.

The overall median LOS for all-cause pneumonia episodes was 6 (IQR 9) days in period 1 and 6 (IQR 10) days in period 3 (p<0.005) (Table 2). Different age groups showed decrease in LOS but were only statistically significant in age 18-49 years and 50-64 years. The mortality rate increased from 20.5% (95% CI 20.4%-20.6%) in period 1 to 24.2% (95%CI 24.9%-25.6%) in period 3 (p<0.005) for all-cause pneumonia. The increase in mortality rate was statistically significant in all age groups (Table 2).

For subgroup of aspiration pneumonia, total number of hospitalization in the entire study period was 21,183, with 17990 episodes in period 1 and 2684 episodes in

period 3. Mean monthly number of aspiration pneumonia was 299.8±31.3 in period 1 and 206.5±30.5 in period 3 (p<0.0005).

COVID-19

In period 3, the total reported cases of COVID-19 infection at age 18 or above was 10,348 [15]. Among these patients, 331 were diagnosed with pneumonia. Majority of them were in the age group 65 years old or above (n=175). 58 of them were in age group 18-49 while 98 patients in age group 50-64.

Influenza

The total number of influenza A or B viruses detected from January 2015 to March 2021 in Hong Kong was 123,732. The monthly number of influenza detections decreased drastically by 99.5% (95%CI 99.4%-99.5%, p<0.0005) from 1,966±2179 in period 1 to 10±18 in period 3 (Figure 1D and Figure S2). The monthly average number of respiratory specimens tested was 4313±1172 in period 1 and 3203±1868 in period 3.

By log-linear model segmented regression, relative risk of influenza was 0.92 (95%CI 0.88-0.95, p<0.0005). Estimated change in trend in the mean number of detections in period 3 was -99.0% (95%CI -99.3% to -98.7%, p<0.0005) of that in period 1 (Figure 1D)

Other diagnosis: acute kidney injury, PD peritonitis and fracture hip

The monthly average number of hospitalization episodes for acute kidney injury in period 1 and period 3 was 807.8±87.5 and 911.7±62.6, respectively (p<0.0005) (Figure 2) The monthly average number of hospitalization episodes for PD peritonitis was 246.7±27.7 in period 1 and 255.9±31.9 in period 3 (p=0.23). The monthly average number of hospitalization episodes for fracture hip was 432.9±53.1 in period 1 and 417.3±51.6 in period 3 (p=0.37)

Discussion

Hong Kong is a city with population of 7.5 million where universal masking and social distancing were widely practiced during the COVID-19 pandemic period. This study showed a drastic decrease in numbers of hospitalization for IPD and pneumococcal pneumonia and a lesser but still very significant decrease in all cause pneumonia after anti-COVID-19 measures in March 2020 to March 2021.

During COVID-19 period, decrease in incidence of IPD were observed in Taiwan and Singapore [31-32]. The decrease in IPD in Hong Kong was greater magnitude compare to other countries [33]. Our study added new information on the incidence and severity of IPD, pneumococcal pneumonia and all-cause pneumonia in terms of age-stratification.

Introduction of the current pneumococcal conjugate vaccines has been highly successful in reducing the incidence of pneumococcal diseases worldwide [34,35]. Vaccine efficacy of PCV13 against vaccine type IPD in children aged ≤5 years was 86%-96% [36]. In adults aged ≥65 years, the vaccine efficacy against vaccine type IPD was reported as 75% and against vaccine type community-acquired pneumonia were reported as 45.6% and 72.8% respectively [13,37]. In contrast, PPV23 only has vaccine efficacy of 24% against vaccine type community acquired pneumonia in aged ≥65 years [38]. In Hong Kong, a marked reduction in vaccine type IPD was observed in children few years after implementation of PCV in 2009 [10,12]. However, the indirect effect on adult IPD was not evident. Annual number of adult IPD hospitalization remains static in period 1 (Figure 1A). Universal masking in Hong Kong was shown to decrease the incidence of SARS-CoV2 [39,40] and influenza [41] during the COVID-19 pandemic. Our study showed 88.9% reduction in incidence of adult IPD. The drastic decrease in incidence of IPD included both vaccine and non-vaccine types and was comparable and greater than the reported figure after introduction of pneumococcal vaccines [13,35]. IPD can lead to significant mortality and morbidity [42]. Our study showed decrease in incidence and trend of IPD and were statistically significant. The decrease in mortality of IPD during the COVID-19 pandemics was statistically insignificant, which can be contributed by the relative small sample size.

Incidence of all-cause pneumonia showed a much lower magnitude of decrease with the lesser decrease observed in those aged ≥65 years (supplementary file, Figure S1C). In our study, patients with diagnosis of pneumonia during the hospital stay were included. On review of data, majority of pneumonia patients in age group 65 years or above had other comorbidities including dementia, diabetes mellitus and malignancy included in the same admission. The prevalence of chronic disease is higher in elderly. The population of Hong Kong has been seeing an aging trend and the population of 65 years old or above was 1,114,600 in 2015, and increased to 1,371,800 in 2020. The incidence of chronic disease, for example, malignancy increased for 38.1% from 2008 to 2018 [17]. Patients with chronic diseases are at higher risk of acquiring infection including pneumonia. Moreover, chronic disease can be the cause leading to hospital admission with subsequent development of hospital acquired pneumonia.

Pneumococcal pneumonia and IPD are debilitating diseases which have been shown to require long length of hospital stay and high hospital cost [43-44]. The LOS in pneumococcal pneumonia was slightly increased from 17.7 to 19.5 days but was statistically insignificant. Looking into different age groups, only patients with age 50 to 64 years old showed statistically significant increase in LOS, while patients in age group 18 to 49 years old and 65 years old or above showed slight decrease. The severity of pneumococcal pneumonia can be comparable in the two periods.

Health seeking behaviour was also evaluated in our study. Admissions of non-communicable diseases revealed either statistically insignificant decrease in hospital attendance or statistically significant increase in hospital attendance. The incidence of AKI increased in our study from 807.8±87.5 in period 1 to 911.7±62.6 in period 3. Drug induced AKI is an important cause in Asia [45]. Possible explanation can be due to the health seeking behaviour of patients with intake of over-the counter medication for mild diseases prior seeking help from the hospital. Yet the exact cause of increase in incidence of AKI should be investigated. Our study covered more than one year time for COVID-19 pandemics with a relatively stable number of hospital attendance. Hence, the decrease in incidence of pneumococcal pneumonia,

IPD and all-cause pneumonia cannot be explained by health seeking behaviour alone.

Collateral damages were observed during the COVID-19 pandemic [46-47], some of which were contributed by the decrease in general medical services to concentrate healthcare resources for the care of SARS-CoV-2 patients and the prevention of possible viral spread. However, due to the relatively small number of COVID-19 cases in Hong Kong, provision of acute medical services was minimally disrupted. In our study, the data on admissions for fractures, acute kidney injury and PD peritonitis showed no decrease during the Covid pandemic. Hence the observed decrease in hospital admissions for pneumococcal pneumonia, IPD and all-cause pneumonia should not be artefactual. Masking can be an effective yet low-cost preventive measurement for citizens at high risk of pneumococcal infections.

Limitations

This study is a retrospective observational study and the direct effect of universal masking on pneumococcal pneumonia, IPD and all-cause pneumonia cannot be ascertained. However, our study covered a period of more than one year when universal masking was practiced and a consistent observation of decrease in hospitalization for these diseases were seen. Other factors, namely ambient temperature and AQHI, that might have possible effect on the hospitalization numbers were also included in our analysis. However, the individual effects of universal masking, social distancing (e.g. closure of schools, bars and pubs) and other strategies cannot be evaluated separately. It is modelled by the effect of pandemic as a whole in our study.

Our study focused on hospital hospitalization numbers to Hospital Authority. For IPD, the incidence was obtained from Central of Health Protection, HKSAR, which included data from both public and private hospitals data. The LOS and mortality data of IPD were retrieved from the database in Hospital Authority. Admissions to private hospital or those received out-patient treatment for pneumococcal pneumonia and all-cause pneumonia were not included in our study. However, Hospital Authority is the largest healthcare provider in Hong Kong which provides 90% of in-

patient services in Hong Kong [26]. Data from Hospital Authority is representable for the general epidemiology of Hong Kong.

Conclusions

The incidence of pneumococcal pneumonia, IPD and all-cause pneumonia decreased during COVID-19 pandemics compare to the data in previous five years. This was observed with widely practice of universal masking and social distancing. We propose the decrease is attributed to universal masking and social distancing which reduced the transmission of bacteria or virus and related bacterial superinfection.

Figure caption

Figure 1. Trend analysis of monthly numbers of invasive pneumococcal disease (IPD), pneumococcal pneumonia, all-cause pneumonia, and influenza in Hong Kong, January 2015 to March 2021. Numbers of IPD were those obtained through mandatory notification. Numbers of pneumococcal pneumonia and all-cause pneumonia were territory-wide hospitalizations by discharge diagnoses. Numbers of influenza viruses were those detected in respiratory specimens in a territory-wide laboratory surveillance. The two vertical lines delineated the time intervals from January 2015 to December 2019 (period 1, prior to COVID-19), January to February 2020 (period 2, excluded form analysis) and March 2020 to March 2021 (period 3, COVID-19 pandemic).

Figure 2. Admission numbers of fracture hip, acute kidney injury and PD peritonitis.

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Table 1. Incidence and number per 100,000 person year of pneumococcal pneumonia, invasive pneumococcal disease (IPD) and pneumonia

	All ages		18-49 years		50-64 years		≥65 years	
Disease [a]	No. of episodes	Incidence rate per 100,000 person-years	No. of episodes	Incidence rate per 100,000 person-years	No. of episodes	Incidence rate per 100,000 person-years	No. of cases	Incidence rate per 100,000 person-years
IPD								
Period 1	699	2.2	125	0.7	195	2.2	379	6.2
Period 2	26	2.4	5	0.9	6	2.0	15	6.6
Period 3	17	0.2	3	0.08	8	0.4	6	0.4
% reduction[b]		88.9% (79.8%-98.0%)***		88.6% (66.8%-110.4%)***		81.3% (62.1%-100.4%)***		93.5% (82,2%-104.8%)***
IRR[c]		0.11(0.07-0.18)***		0.11(0.04-0.36)***		0.19(0.09-0.38)***		0.07(0.03-0.15)***
Pneumococcal pneumonia								
Period 1	1,970	6.2	217	1.3	435	4.9	1,318	21.7
Period 2	74	6.9	11	2.0	14	4.7	49	32.4
Period 3	119	1.7	8	0.2	24	1.2	87	5.9
% reduction		72.5% (65.9%-79.1%)***		82.5% (64.5%-100.5%)***		74.8% (61.0%-88.6%)***		73.0% (65.2%-80.8%)***
IRR[c]		0.28(0.23-0.33)***		0.18(0.09-0.35)***		0.25(0.17-0.38)***		0.27(0.22-0.34)***
All-cause pneumonia								
Period 1	372,660	1169.7	19,502	115.3	38,360	432.4	314,798	5177.1
Period 2	13,865	1288.2	843	153.6	1,448	484.6	11,574	5062.3
Period 3	67,474	964.5	2,473	69.3	6,181	318.3	58,820	3958.0
% reduction		17.5% (16.8%-18.2%)***		39.9% (37.1%-42.7%)***		26.4% (24.3%-28.5%)***		23.5% (22.8%-24.3%)***
IRR[c]		0.83(0.82-0.83)***		0.60(0.58-0.63)***		0.74(0.72-0.76)***		0.77(0.76-0.77)***

[a] Period 1, January 2015 to December 2019 (before covid-19); period 2, January 2020 to February 2020 (transition period); period 3 March 2020 to March 2021 (post-COVID-19).

[b] Percentage reduction in period 3 relative to period 1 as the baseline

[c] Incidence ratio between period 1 and period 3

*p <0.05 to 0.01, **p <0.01 to 0.005, ***p<0.005

Table 2. Median length of stay and mortality rate of pneumococcal pneumonia, invasive pneumococcal disease (IPD) and pneumonia in the periods

	Median length of stay; days (IQR)#				Mortality rate; % (95%CI)			
	All ages	**18-49 years**	**50-64 years**	**≥65 years**	**All ages**	**18-49 years**	**50-64 years**	**≥65 years**
IPD								
Period 1	12 (16)	13 (19)	13 (17)	12 (13)	12.1 (8.8-16.1)	9.1 (3.4-18.7)	8.4 (3.7-15.9)	15.3 (10.3-21.4)
Period 3	12 (11)	4 (3)	16 (19)	12 (6)	6.3 (1.6-30.2)	0.0	0.0	14.3 (3.6-57.9)
Pneumococcal Pneumonia								
Period 1	9 (14)	7 (14)	9 (15)*	10 (14)	13.1 (11.7-14.8)*	4.2 (1.9-7.7)	7.5 (5.3-10.5)**	16.3 (13.6-18.7)
Period 3	12 (17)	7 (13)	13 (20)*	12 (16)	22.7 (15.5-31.3)*	0.0	29.2 (12.6-51.1)**	23.0 (14.6-33.2)
All-cause pneumonia								
Period 1	6 (9)***	4 (6)***	6 (9)**	6 (10)	20.5 (20.4-20.6)***	5.3 (4.9-5.6)*	13.0 (11.4-12.0)***	22.4 (22.2-22.4)***
Period 3	6 (10)***	4 (8)***	6 (10)**	6 (10)	24.2 (24.9-25.6)***	6.8 (5.9-7.9)*	16.1 (5.2-17.0)***	27.0 (26.6-27.3)***

*p <0.05 to 0.01, **p <0.01 to 0.005, ***p<0.005

IQR= interquartile range

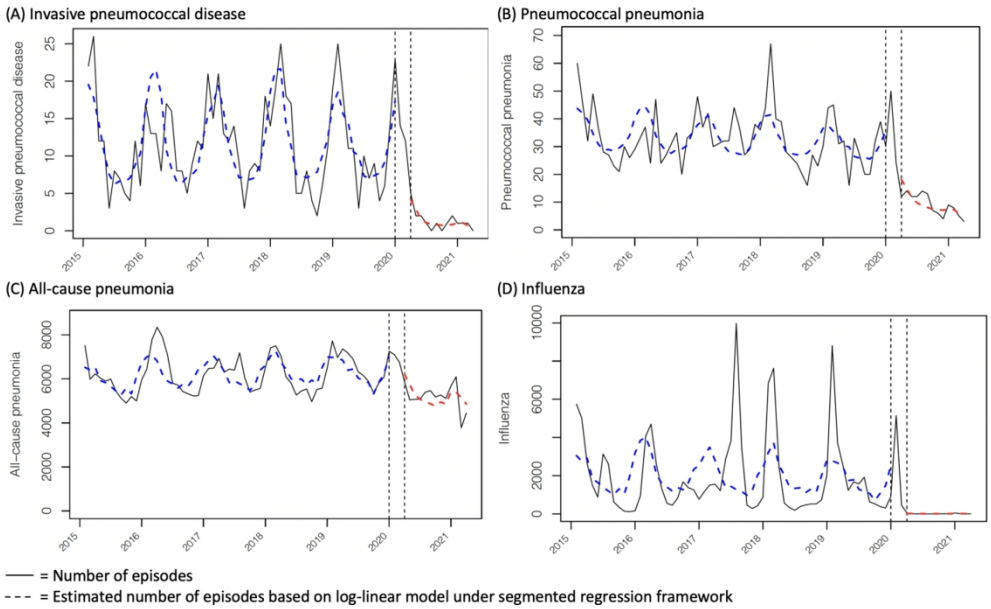

Figure 1. Trend analysis of monthly numbers of invasive pneumococcal disease (IPD), pneumococcal pneumonia, all-cause pneumonia, and influenza in Hong Kong, January 2015 to March 2021. Numbers of IPD were those obtained through mandatory notification. Numbers of pneumococcal pneumonia and all-cause pneumonia were territory-wide hospitalizations by discharge diagnoses. Numbers of influenza viruses were those detected in respiratory specimens in a territory-wide laboratory surveillance. The two vertical lines delineated the time intervals from January 2015 to December 2019 (period 1, prior to COVID-19), January to February 2020 (period 2, excluded form analysis) and March 2020 to March 2021 (period 3, COVID-19 pandemic).

352x218mm (144 x 144 DPI)

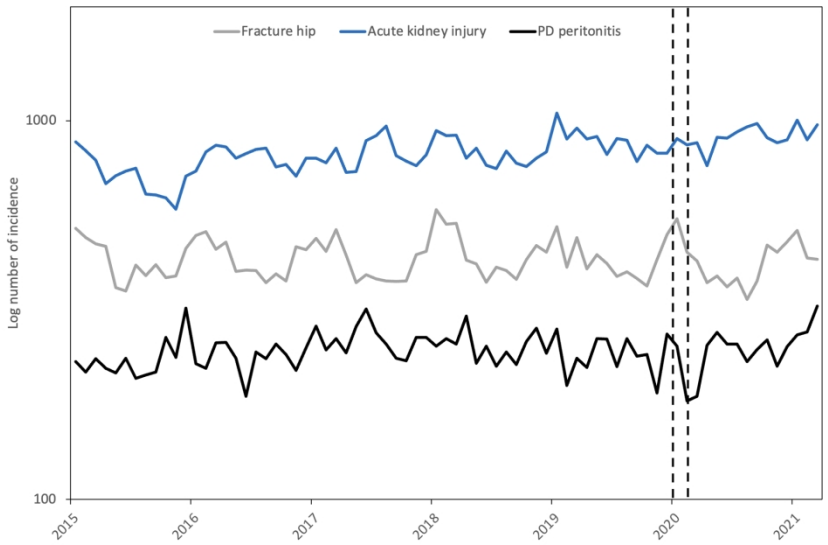

Figure 2. Admission numbers of fracture hip, acute kidney injury and PD peritonitis.

419x237mm (144 x 144 DPI)

Supplementary file.

Figure S1. Trend analysis of monthly number of (A) age-stratified hospitalizations for invasive pneumococcal disease, (B) age-stratified hospitalizations for pneumonococcal pneumonia, (C) age-stratified hospitalizations for and (D) monthly percentage of air quality health index (AQHI) high to serious and (E) monthly average ambient temperature.

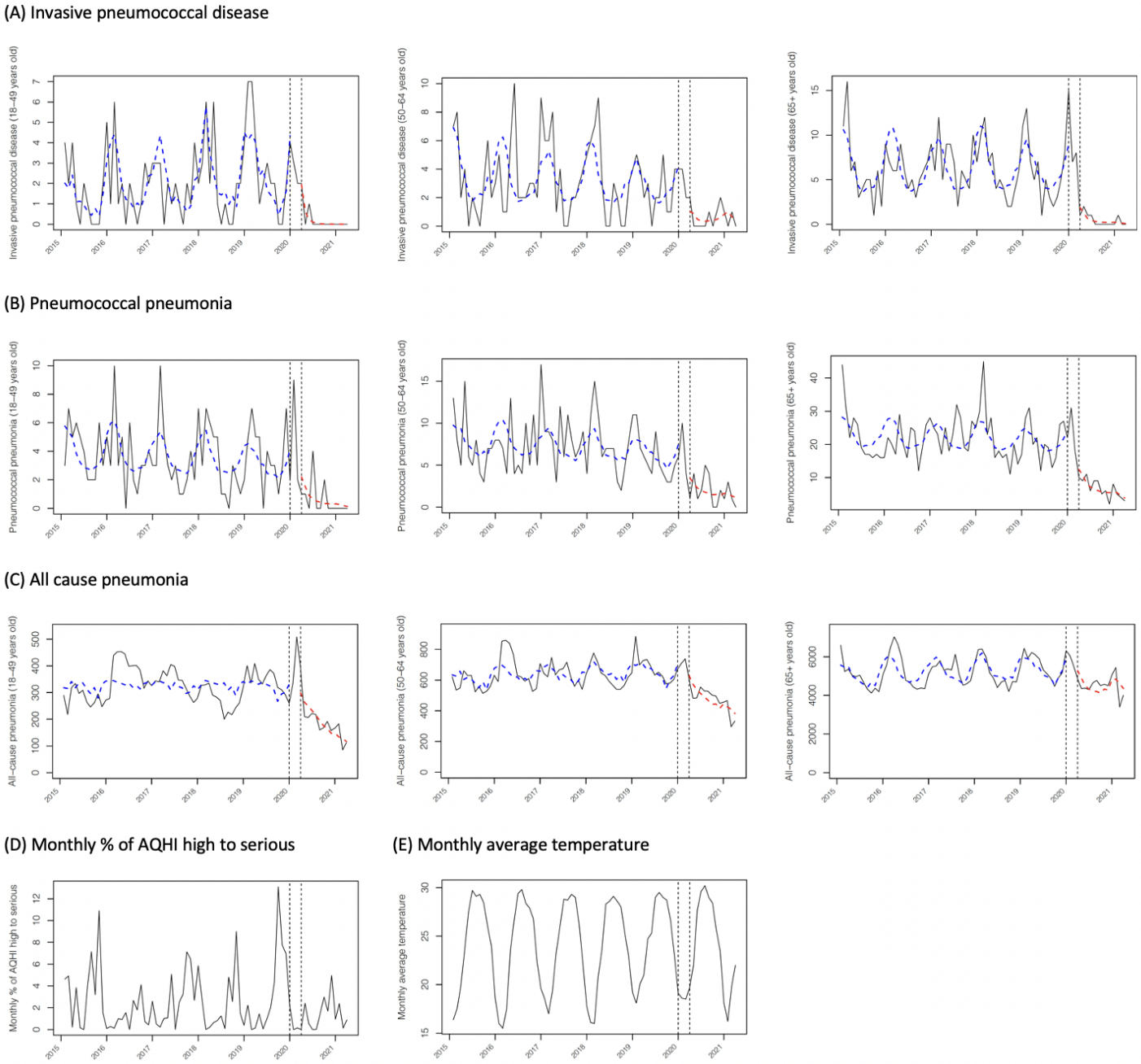

Figure S2. Monthly incidence of (A) Invasive pneumococcal disease (IPD), (B) Pneumococcal pneumonia, (C) All-cause pneumonia and (D) Influenza in January 2015 to March 2021.

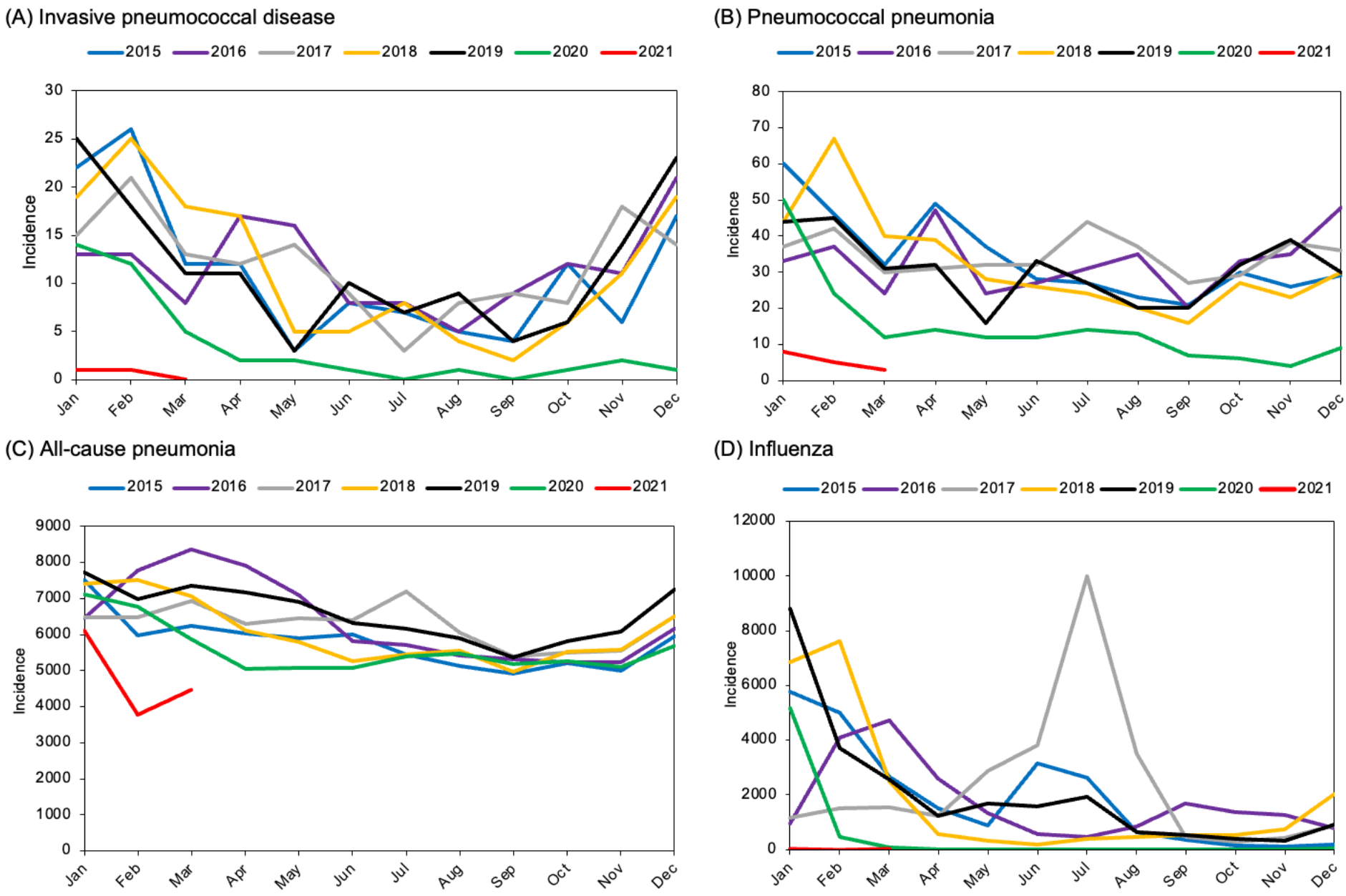

Table S1. Trend analysis of monthly number of hospitalization by age groups in periods before and after the COVID-19 pandemic

	Relative risk (95% CI)		Change in trend#
	Period 1 ^	Period 3^	
IPD			
All ages	1.0020 (0.9977-1.064)	0.8484 (0.7501-0.9597)**	-70.39% (-86.55% to -34.73%)**
18-49 years	1.0129 (1.0022-1.0238)	0.5272 (0.2176-1.2772)	-31.27% (-89.72% to 359.72%)
50-64 years	0.9969 (0.9888-1.0051)	0.9585 (0.8087-1.1362)	-70.43% (-92.80% to 21.42%)
65 years or above	1.0012 (0.9953-1.0071)	0.7777 (0.6111-0.9897)*	-70.83% (-91.59% to 1.12%)
Pneumococcal Pneumonia			
All ages	0.9978(0.9953-1.0004)	0.9042(0.8621-0.9483)***	-42.79% (-59.36% to -19.48%)*
18-49 years	0.9964(0.9887-1.0042)	0.6768(0.2171-2.1093)	-32.32% (-78.29% to 110.93%)
50-64 years	0.9962(0.9907-1.0017)	0.9174(0.8260-1.0189)	-50.21% (-76.93% to 7.48%)
65 years or above	0.9986(0.9954-1.0017)	0.9107(0.8612-0.9640)*	-41.19% (-60.82% to -11.73%)*
All-cause pneumonia			
All ages	1.0014(1.0012-1.0016)***	0.9835(0.9815-0.9855)***	-11.24% (-12.76% to -9.7%)***
18-49 years	1.0000(0.9992-1.0008)	0.9263(0.9164-0.9364)***	-6.05% (-13.41% to 1.94%)
50-64 years	1.0015(1.0009-1.0021)***	0.9620(0.9556-0.9684)***	-9.32% (-14.14% to -4.22%)***
65 years or above	1.0011(1.0009-1.0013)***	0.9879(0.9858-0.9901)***	-13.30% (-12.94% to -9.64%)***

^Trend in period 1 (January 2015 to December 2019) and 3 (March 2020 to March 2021), the (relative risk expressed the month-to-month change in hospitalization numbers

#Estimate the change in trend in the mean monthly number of cases in period 3, compare with the monthly trend in period 1

*p <0.05 to 0.01, **p <0.01 to 0.005, ***p<0.005

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6,7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	6,7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	6,7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8
		(*b*) Describe any methods used to examine subgroups and interactions	7,8
		(*c*) Explain how missing data were addressed	N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	7,8

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10-13
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-13
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10-13
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-13
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

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

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Keywords:	COVID-19, Respiratory infections < THORACIC MEDICINE, Thoracic medicine < INTERNAL MEDICINE, Epidemiology < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES

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Title: 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

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Abstract

Objectives: To compare the incidence and severity of invasive pneumococcal diseases (IPD), pneumococcal pneumonia and all-cause pneumonia during COVID-19 pandemic period with universal masking and social distancing to that of previous 5 years.

Design: Retrospective observational study on incidence of invasive pneumococcal diseases (IPD), pneumococcal pneumonia and all-cause pneumonia between January 2015-December 2019 and March 2020-March 2021. January-February 2020 was excluded from analysis as it was treated as transitional period between normal time and pandemic.

Setting: Episode-based data by retrieval of hospitalization records from the Hospital Authority's territory-wide electronic medical record database in Hong Kong.

Participants: Hospitalized patients with invasive pneumococcal diseases (IPD) (n=742), pneumococcal pneumonia (n=2163) and all-cause pneumonia (including COVID-19 pneumonia, n=453,999) at age 18 or above. Control diagnoses were included to assess confounding from health-seeking behaviors.

Primary and secondary outcome: Primary outcome is the incidence of diseases between two periods. Secondary outcomes include disease severity surrogated by length of stay and mortality.

Results: Monthly average number of IPD, pneumococcal pneumonia and all-cause pneumonia hospitalization significantly decreased by 88.9% (95%CI 79.8%-98.0%, p<0.0005), 72.5% (95%CI 65.9%-79.1%, p<0.0005) and 17.5% (95%CI 16.8%-18.2%, p<0.0005), respectively. Change in trend from January 2015-December 2019 to March 2020-March 2021 was -70% (95%CI -87% to -35%, p=0.0025), -43% (95%CI -59% to -19%, p=0.0014) and -11% (95%CI -13% to -10%, p<0.0005), respectively. Length of stay for IPD and pneumococcal pneumonia episodes were insignificantly different in the two periods. No reductions in hospitalizations for control diagnoses were observed.

Conclusions: Incidence of IPD, pneumococcal pneumonia, and all-cause pneumonia decreased during COVID-19 pandemic. This was observed with

universal masking and social distancing. We postulated this is related to reduced transmission of respiratory viruses and bacteria.

Strength and limitations of this study:

- A territory-wide study with near 100% practice of universal masking and wide practice of social distancing
- Other factors including temperature and air quality were also included in our analysis
- Disease severity of IPD, pneumococcal pneumonia, and all-cause pneumonia were compared between the two periods
- Data from private sector (<10%) were not included in our study
- The causal relationship cannot be ascertained from this retrospective study

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Competing interests: There are no competing interests.

Data availability statements: No additional data is available.

Authors' contributions:

King-Pui Florence Chan and Ting-Fung Ma were involved in study concept and design; acquisition, analysis and interpretation of data; drafting the work and final approval of the manuscript. **Mary Sau-Man Ip** were involved in critical revision of manuscript for important intellectual content and final approval of the manuscript. **Pak-Leung Ho** was involved in study concept and design; analysis and interpretation of data; drafting of manuscript; critical revision of the manuscript for important intellectual content; study supervision; and approval of the final version of the manuscript.

Word count: 4174

Keywords: pneumococcal, COVID-19, masking, regression analysis

Text

Introduction

Coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections was first reported in late 2019 [1]. It became a global pandemic and was declared as a public health emergency of international concern on 30 January 2020 by the World Health Organization [2]. As of 22 September2021, more than 229 million people were infected, causing more than 4.7 million deaths globally.

Pneumococcal disease is caused by *Streptococcus pneumoniae* infection, with at least 100 known serotypes of pneumococci [3]. Pneumococcal disease can be roughly divided into non-invasive disease and invasive disease. Non-invasive disease includes sinusitis, acute otitis media and pneumonia. Invasive pneumococcal disease (IPD) is defined as isolation of *Streptococcus pneumoniae* from a normally sterile sites, including blood and cerebrospinal fluid [4]. IPD is a notifiable disease in Hong Kong since 9th January 2015. Pneumococcal infection is a major cause of morbidity and mortality worldwide [5], with 1.6 million estimated deaths annually in 2005 [6]. Incidence of IPD and mortality of pneumococcal pneumonia are higher at extremes of age [7-8].

The first pneumococcal conjugated vaccine (PCV), Prevnar 7 (PCV7) was introduced to United States in 2000 and incorporated in Hong Kong Childhood Immunisation Programme for children under 2 years old since September 2009 [9-10]. In Hong Kong, PCV7 was replaced by the 10-valent and 13-valent pneumococcal conjugate vaccines (PCV10 and PCV13) in 2010 and 2011 respectively [11-12]. PCV13 was effective in preventing vaccine-type pneumococcal pneumonia, bacteraemia and nonbacteraemic community-acquired pneumonia [13]. Decline in incidences of all-cause pneumonia in children and elderly was reported after implementation of PCV in childhood vaccination program [14-15]. 23-valent polysaccharide vaccine (PPSV23) was effective in preventing pneumococcal pneumonia and reducing mortality from pneumococcal pneumonia in nursing home residents [16]. In our locality, elderly at age 65 years and above without high risk conditions, namely immunodeficiency or chronic cardiac, pulmonary, liver or renal disease, or diabetes mellitus were recommended to receive either a single dose of

PCV13 or a single dose of PPSV23. Number of PPSV23 vaccine recipients at age 65 years or above increased from 35,000 in year 2015/2016 to 81,700 in 2019/2020, with approximately 46% of population in the age group cumulatively vaccinated in 2020 [17]. Pneumonia is a common disease causing hospitalization, accounting for 2.9% of all inpatient discharges and death in Hong Kong [18]. It is the second leading cause of death with age specific death rates increased markedly after age 65 [17].

Whether patients with COVID-19 are more susceptible to pneumococcal superinfection is still under debate. Superinfection of pneumococcal in COVID-19 patients was reported [19]. Yet, low frequency of bacterial coinfection in patients with early COVID-19 was also observed [20-21]. There is limited evidence on the incidence and severity of IPD, pneumococcal pneumonia, and all-cause pneumonia during COVID-19 pandemic, especially in area where universal masking and social distancing were widely practiced. Since January 2020, universal masking in public area was voluntarily performed by Hong Kong citizens against COVID-19. Cross sectional telephone self-reported surveys by the Hong Kong Public Opinion Research Institute (HKPORI) showed percentage of wearing mask was 74.5% on 20th-23rd January 2020 (n=1,008), 97.6% on 5th-20th February (n=10,405) and 98.9% on 4th-19th March (n=15,739) [22]. On 23rd July 2020, masking was mandatory in public area upon the introduction of Prevention and Control of Disease (Wearing of Mask) Regulation (Cap. 599I). Social distancing measurements were voluntarily practiced by public and implemented by government since 25th January 2020. These public health interventions were shown to associate with relatively low rate of COVID-19 and early termination of influenza season in Hong Kong [23]. Our previous studies suggested universal masking and social distancing were associated with significant reduction in acute exacerbation of chronic obstructive pulmonary disease and asthma in Hong Kong [24,25]. In the current study, we hypothesized that the aforementioned COVID-19 related public health interventions and reduction in respiratory virus activities would be associated with reduction in hospitalization due to pneumococcal infections and pneumonia in general.

Materials and Methods

A retrospective study assessing the numbers of IPD, pneumococcal pneumonia, and all-cause pneumonia which required hospital hospitalization during the period of COVID-19 in Hong Kong, comparing with that in the preceding five years as baseline was conducted. The study period was 1st January 2015 to 31st March 2021 with exclusion of 1st January 2020 to 28th February 2020 from analysis, when public health practices such as mask wearing were not yet fully adopted.

Data source

Episode-based data was obtained by retrieval of hospitalization records from the Hospital Authority's territory-wide electronic medical record database, Clinical Data Analysis and Reporting System (CDARS), which provides 90% of in-patient hospital care service in Hong Kong [24,25].

Diagnosis code of pneumococcal pneumonia (ICD-9 code 481) was searched on CDARS. IPD is a notifiable disease since January 2015 with monthly number notified cases and age obtained from the Department of Health, Hong Kong Special Administrative Region (HKSAR). Monthly number of influenza virus detection was collected from a territory-wide laboratory surveillance for both in-patients and out-patients in both public and private medical sectors from the Centre for Health Protection (CHP), HKSAR [17].

All-cause pneumonia including the following ICD-9 codes for viral, bacterial, tuberculous, fungal and unspecified pneumonia, pneumonia due to inhalation of food or vomitus and lung abscess were obtained from CDARS (ICD-9 code 003.22, 055.1, 0.1160-1.1166, 112.4, 115, 117.3, 480, 481, 482, 483.1, 483.8, 485, 486, 487, 507.0, 513). Patient with COVID-19 associated pneumonia was included in the all-cause pneumonia dataset. The contribution of COVID-19 within all-cause pneumonia was queried using ICD codes for COVID-19 disease (ICD-9 code 079.89, 480.8, 519.8). Demographics data (including sex, age), clinical data (including hospitalization date, length of stay, episode death, date of death) were collected. The results including admission number of various diseases were available in the CHP website and the Hospital Authority Statistics Report [17,26].

Inclusion/ exclusion criteria

Patients with 1) age 18 or above 2) hospitalization for the listed diseases (pneumococcal pneumonia, IPD and pneumonia) were included in the study.

Children at aged 0 to 17 years old were excluded in this study. Duplicated record of single patient with different diagnoses in same hospital admission were removed.

Other diagnoses

Number of hospitalization for other common medical and surgical conditions including acute kidney injury (ICD-9 code 580, 584), fracture hip (ICD-9 code 820) and peritonitis due to peritoneal dialysis (PD peritonitis) (ICD-9 code 996.68) were collected. These were included to evaluate the possibility of decrease in hospital attendance due to various reasons such as fear of COVID-19 infection in hospital. These diseases were selected as are non-communicable diseases and have minimal interactions with environmental factors including mean ambient temperature and air-pollution.

Other variables

Monthly mean ambient temperature was obtained from the Hong Kong Observatory [27]. Air quality was measured by air quality health index (AQHI), which is calculated based on the cumulative health risk attributable to a 3-hour moving average concentrations of ozone, nitrogen dioxide, sulphur dioxide and particulate matter [28]. It was reported in scale of 1 to 10 and 10+ and grouped into five health risk categories, namely low [1-3], moderate [4-6], high [7], very high [8-10] and serious [10+] with different precautionary actions were advised. People with respiratory illness were advised to minimize their outdoor stay when AQHI high to serious. The AQHI was reported hourly in 13 stations located in different area of Hong Kong. The total number of hours with AQHI recorded as high to serious grades were expressed as percentage of total number of hours collected in a month.

Statistical method

Total number of hospitalizations due to IPD, pneumococcal pneumonia and all-cause pneumonia were collected and analysed. Each disease was further divided into three

different age groups, including 18 to 49 years, 50 to 64 years, and 65 years or above for analysis.

Analysis was done on the number of hospitalizations between January 2015 to December 2019, the period prior COVID-19 (period 1) and March 2020 to March 2021 (period 3), while January to February 2020 (period 2) was treated as transition period and excluded from the analysis. Wilcoxon rank sum test was first used to analyse the statistical significance of number of hospitalizations between period 1 and period 3. Generalized linear models were then applied for statistical inference of various types of responses. Log-linear model was used for studying the effect of pandemic as intervention under segmented regression framework in term of the change in trend (i.e. an increase or decrease in the level of the segment) between period 1 (pre-intervention segment) and period 3 (post-intervention segment) on the monthly hospitalization count. Regression coefficients of log-linear model can be interpreted as the effect due to pandemic by log-linear model [29]. We assumed temporal dependence can be adjusted by the effect of pandemic, including masking, social distancing and other behavioural changes, and climate related variables including temperature and AQHI.

Generalized linear model was used for comparing the mortality rate of individuals between the two time periods [30]. Hospitalization length of stay (LOS) was described in days using median and standard deviation. Statistical inference of the LOS in hospitalization of individuals was done by Wilcoxon rank sum test with odds ratio and relative risks and confidence intervals calculated [29].

Monthly incidence rate for each disease was calculated using the total population followed by age groups stratification (18 to 49 years, 50 to 64 years and ≥65 years) and expressed as number per 100,000 person-year. Age-specific population data was obtained from the Census and Statistics Department.

Ethics Approval

The study was approved by the Institutional Review Board of the University of Hong Kong/ Hospital Authority Hong Kong West Cluster (Reference Number UW-21-325).

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Invasive pneumococcal disease

The total number of notified IPD episodes was 742 in the entire study, with 699 reported in period 1 and 17 reported in period 3. Pneumococcal serotypes for 684 of the 699 episodes in period 1, and 13 of the 17 episodes in period 3 were successfully determined. The proportions attributed to PCV13 serotypes was 66.5% (465/699) and 29.4% (5/17) respectively for period 1 and period 3. Serotype 3 was the commonest serotype in both periods, accounting for 41.3% (289/699) and 17.6% (3/17) of total, respectively. From period 1 to period 3, the monthly number of IPD caused by PCV13 serotypes declined by 95.1% (95%CI 93.4%-96.4%) while those for non-PCV13 serotypes declined by 83.0% (95%CI 78.8%-86.5%), and those for PPSV23 serotypes declined by 94.1% (95% CI 92.3%-95.5%). The small difference between declines in PCV13 and PPSV23 serotypes was mainly attributed to serotype 6A which was included in PCV13 but not in PPVS23.

Monthly number of IPD peaked in January-February each year except in 2016, with the peak in April (Figure 1A and Figure S1). Monthly average number of notified IPD episodes was 11.7±6.2 in period 1, with significant decrease to 1±4.3 in period 3 ($p<0.0005$). By log-linear model segmented regression, relative risk of IPD in period 3 was 0.85 (95%CI 0.75-0.96, $p=0.0089$) (Table S1). Further analysis on the relative risk of different age groups showed significant decline in relative risk of IPD in aged ≥65 years (0.78, 95%CI 0.61-0.99, $p=0.041$). Estimated change in trend in the mean number of cases from period 1 to period 3 was -70% (95%CI -87% to -35%, $p=0.0025$) (Figure 1A, Table S1).

Incidence rate per 100,000 person-years was 2.2 in period 1 and 0.2 in period 3, with an interval reduction of 88.9% (95%CI 79.8%-98.0%, $p<0.0005$). Incidence rate ratio between period 1 and period 3 was 0.11 (95%CI 0.07-0.18, $p<0.0005$) (Table 1). IPD is most prevalent in age ≥65. The magnitude of reduction in incidence rate was similar across different age groups, ranging from 81.3% to 93.5% ($p<0.0005$ for all age groups) (Table 1).

The overall median LOS for IPD was 12 (Interquartile range, IQR 16) days in period 1 and 12 (IQR 11) days in period 3 (Table 2), with statistically insignificant difference (p=0.89). Statistically insignificant variations in LOS of different age groups were observed.

Pneumococcal pneumonia

In the entire study period, there were 2,163 episodes of hospitalization for pneumococcal pneumonia, with 1970 episodes in period 1 and 119 episodes in period 3 (Table 1). Monthly number of pneumococcal pneumonia was peaked in January-February each year except in 2016, with the peak in April (Figure 1B and Figure S1). The average monthly hospitalizations was 32.8±9.9 episodes in period 1, with significant drop to 9.2±3.9 episodes in period 3 (p<0.0005). By log-linear model segmented regression, relative risk of pneumococcal pneumonia was 0.90 (95%CI 0.86-0.95, p<0.005) in period 3. Trend analysis revealed a change of -43% (95%CI -59% to -19%, p=0.0014, Figure 1B, Table S1) from period 1 to period 3. Age groups analysis showed similar change in trend for all age groups, with statistically significance in aged ≥65 years (-41%, 95%CI -61% to -12%, p=0.010) from period 1 to period 3 (Table S1, Figure S2).

Overall, the incidence rate of hospitalization for pneumococcal pneumonia decreased significantly by 72.5% (95%CI 65.9%-79.1%, p<0.0005), from 6.2 per 100,000 person-years in period 1 to 1.7 per 100,000 person-years in period 3. Incidence rate ratio between period 1 and period 3 was 0.28 (95%CI 0.23-0.33, p<0.0005) (Table 1). Incidence rate per 100,000 person year showed statistically significant reduction in all age groups, ranging from 73.0% to 82.5%.

Majority of the patients with pneumococcal pneumonia were treated with in-patient care. The total number of patients treated as outpatients and discharged from emergency department was 30 in period 1 and 0 in period 3.

The overall median LOS for pneumococcal pneumonia in period 1 and period 3 was 9 (IQR 14) days and 12 (IQR 17) days in all age group (p=0.051) (Table 2). Age group stratification showed insignificant changes in length of stay in those aged 18-

49 years (p=0.8051) and aged ≥65 years (p=0.226). Increase in length of stay from 9 (IQR 15) days to 13 (IQR 20) days was observed in age group 50-64 years, and was statistically significant (p=0.019). Mortality rate for all ages was 13.1% (95% CI 11.7%-14.8%) in period 1 and 22.7% (95%CI 15.5%-31.3%) in period 3 (p=0.0187). Mortality rate was only statistically significant in aged 50-64 years (p=0.0007) but not in aged 18-49 years (p=0.9917) and aged ≥65 years (p=0.246) (Table 2).

All-cause pneumonia

In the entire study period, total hospitalization episodes for all-cause pneumonia was 453,999, of which 372,660 episodes in period 1 and 67,474 episodes in period 3. Among the 67,474 patients in period 3, 331 were diagnosed with COVID-19 and pneumonia. Monthly number of all-cause pneumonia peaked in January to March each year (Figure 1C and Figure S1). Mean monthly number of hospitalizations for all-cause pneumonia declined by 16.4% (95%CI 15.7%-17.1%, p<0.0005) from 6211±845.0 episodes in period 1 to 5190.3±593.8 episodes in period 3 (p<0.0005) (Figure 1C). Estimated change in trend in the mean number of cases in period 3 was -11% (95%CI -13% to -10%, p<0.0005). By log-linear model segmented regression, relative risk of all-cause pneumonia in period 3 compared with period 1 was 0.98 (95%CI 0.98-0.99, p<0.0005) (Table S1).

Overall, the incidence rate per 100,000 person-years was 1,169.7 in period 1, with 17.5% (95%CI 16.8%-18.2%, p<0.0005) reduction in period 3 to 964.5 per 100,000 person-years in period 3. Incidence rate ratio between period 1 and period 3 was 0.83 (95%CI 0.82-0.83, p<0.0005) (Table 1). The incidence rate decrease in period 3 compared to period 1 in all age groups.

The overall median LOS for all-cause pneumonia episodes was 6 (IQR 9) days in period 1 and 6 (IQR 10) days in period 3 (p<0.005) (Table 2). Different age groups showed decrease in LOS but were only statistically significant in age 18-49 years and 50-64 years. The mortality rate increased from 20.5% (95% CI 20.4%-20.6%) in period 1 to 24.2% (95%CI 24.9%-25.6%) in period 3 (p<0.005) for all-cause pneumonia. The increase in mortality rate was statistically significant in all age groups (Table 2).

For subgroup of aspiration pneumonia, total number of hospitalization in the entire study period was 21,183, with 17990 episodes in period 1 and 2684 episodes in period 3. Mean monthly number of aspiration pneumonia was 299.8±31.3 in period 1 and 206.5±30.5 in period 3 (p<0.0005).

COVID-19

In period 3, the total reported cases of COVID-19 infection at age 18 or above was 10,348 [15]. Among these patients, 331 were diagnosed with pneumonia. Majority of them were in the age group 65 years old or above (n=175). 58 of them were in age group 18-49 while 98 patients in age group 50-64. None of the patients were diagnosed with coinfection of COVID-19 and pneumococcal pneumonia.

Influenza

The total number of influenza A or B viruses detected from January 2015 to March 2021 in Hong Kong was 123,732. The monthly number of influenza detections decreased drastically by 99.5% (95%CI 99.4%-99.5%, p<0.0005) from 1,966±2179 in period 1 to 10±18 in period 3 (Figure 1D and Figure S1). The monthly average number of respiratory specimens tested was 4313±1172 in period 1 and 3203±1868 in period 3.

By log-linear model segmented regression, relative risk of influenza was 0.92 (95%CI 0.88-0.95, p<0.0005). Estimated change in trend in the mean number of detections in period 3 was -99.0% (95%CI -99.3% to -98.7%, p<0.0005) of that in period 1 (Figure 1D)

Other diagnosis: acute kidney injury, PD peritonitis and fracture hip

The monthly average number of hospitalization episodes for acute kidney injury in period 1 and period 3 was 807.8±87.5 and 911.7±62.6, respectively (p<0.0005) (Figure 2) The monthly average number of hospitalization episodes for PD peritonitis

was 246.7±27.7 in period 1 and 255.9±31.9 in period 3 (p=0.23). The monthly average number of hospitalization episodes for fracture hip was 432.9±53.1 in period 1 and 417.3±51.6 in period 3 (p=0.37)

Discussion

Hong Kong is a city with population of 7.5 million where universal masking and social distancing were widely practiced during COVID-19 pandemic period. This study showed a drastic decrease in numbers of hospitalization for IPD and pneumococcal pneumonia and a lesser but still very significant decrease in all cause pneumonia after anti-COVID-19 measures in March 2020 to March 2021.

During COVID-19 period, decrease in incidence of IPD were observed in Taiwan and Singapore [31,32]. The decrease in IPD in Hong Kong was greater magnitude compare to other countries [33]. Our study added new information on the incidence and severity of IPD, pneumococcal pneumonia and all-cause pneumonia in terms of age-stratification.

In our COVID-19 patients, there was no pneumococcal co-infection. This may partly be contributed by the infrequent investigation of pneumonia with pneumococcal urinary tests and PCR assays. In an Italian study of 469 COVID-19 patients, 9% was found to be positive for urinary pneumococcal antigen. However, the positive result had no impact on clinical outcome [34]. In another study that investigated the respiratory specimens of COVID-19 patients using PCR assays, 60% were found to be positive for *Streptococcus pneumoniae* but it was unable to distinguish between colonization and infection [35]

Introduction of the current pneumococcal conjugate vaccines has been highly successful in reducing the incidence of pneumococcal diseases worldwide [36,37]. Vaccine efficacy of PCV13 against vaccine type IPD in children aged ≤5 years was 86%-96% [38]. In adults aged ≥65 years, the vaccine efficacy against vaccine type IPD was reported as 75% and against vaccine type community-acquired pneumonia were reported as 45.6% and 72.8% respectively [13,39]. In contrast, PPV23 only has vaccine efficacy of 24% against vaccine type community acquired pneumonia in aged ≥65 years [40]. In Hong Kong, a marked reduction in vaccine type IPD was observed in children few years after implementation of PCV in 2009 [10,12]. However, the indirect effect on adult IPD was not evident. Annual number of adult IPD hospitalization remains static in period 1 (Figure 1A). Universal masking and

social distancing measures in Hong Kong was shown to have an association with decrease in the incidence of SARS-CoV2 [41,42] and influenza [43] during the COVID-19 pandemic. Our study showed 88.9% reduction in incidence of adult IPD. The drastic decrease in incidence of IPD included both vaccine and non-vaccine types and was comparable and greater than the reported figure after introduction of pneumococcal vaccines [13,37]. IPD can lead to significant mortality and morbidity [44]. Our study showed decrease in incidence and trend of IPD and were statistically significant. The decrease in mortality of IPD during the COVID-19 pandemics was statistically insignificant, which can be contributed by the relative small sample size.

Incidence of all-cause pneumonia showed a much lower magnitude of decrease with the lesser decrease observed in those aged ≥65 years (supplementary file, Figure S2C). In our study, patients with diagnosis of pneumonia during the hospital stay were included. On review of data, majority of pneumonia patients in age group 65 years or above had other comorbidities including dementia, diabetes mellitus and malignancy included in the same admission. The prevalence of chronic disease is higher in elderly. The population of Hong Kong has been seeing an aging trend and the population of 65 years old or above was 1,114,600 in 2015, and increased to 1,371,800 in 2020. The incidence of chronic disease, for example, malignancy increased by 38.1% from 2008 to 2018 [17]. Patients with chronic diseases are at higher risk of acquiring infection including pneumonia. Moreover, chronic disease can be the cause leading to hospital admission with subsequent development of hospital acquired pneumonia.

Pneumococcal pneumonia and IPD are debilitating diseases which have been shown to require long length of hospital stay and high hospital cost [45,46]. The LOS in pneumococcal pneumonia was slightly increased from 17.7 to 19.5 days but was statistically insignificant. Looking into different age groups, only patients with age 50 to 64 years old showed statistically significant increase in LOS, while patients in age group 18 to 49 years old and 65 years old or above showed slight decrease. The severity of pneumococcal pneumonia were comparable in the two periods.

Health seeking behaviour was also evaluated in our study. Admissions of non-communicable diseases revealed either statistically insignificant decrease in hospital

attendance or statistically significant increase in hospital attendance. The incidence of AKI increased in our study from 807.8±87.5 in period 1 to 911.7±62.6 in period 3. Drug induced AKI is an important cause in Asia [47]. Possible explanation can be due to the health seeking behaviour of patients with intake of over-the counter medication for mild diseases prior seeking help from the hospital. Yet the exact cause of increase in incidence of AKI should be investigated. Our study covered more than one year time for COVID-19 pandemics with a relatively stable number of hospital attendance. Hence, the decrease in incidence of pneumococcal pneumonia, IPD and all-cause pneumonia cannot be explained by health seeking behaviour alone.

Collateral damages were observed during the COVID-19 pandemic [48-49], some of which were contributed by the decrease in general medical services to concentrate healthcare resources for the care of SARS-CoV-2 patients and the prevention of possible viral spread. However, due to the relatively small number of COVID-19 cases in Hong Kong, provision of acute medical services was minimally disrupted. In our study, the data on admissions for fractures, acute kidney injury and PD peritonitis showed no decrease during the COVID-19 pandemic. Hence the observed decrease in hospital admissions for pneumococcal pneumonia, IPD and all-cause pneumonia should not be artefactual.

Limitations

This is a retrospective observational study and the direct effect of universal masking, social distancing (e.g. closure of schools, bars and pubs) and other strategies on pneumococcal pneumonia, IPD and all-cause pneumonia cannot be ascertained. However, our study covered a period of more than one year when infection control related behavioral changes were made throughout, with a consistent observation of decrease in hospitalization for these diseases seen. Other factors, namely ambient temperature and AQHI, that might have possible effect on the hospitalization numbers were also included in our analysis. However, the individual effects of universal masking, social distancing and other strategies cannot be evaluated separately. It is modelled by the effect of pandemic as a whole in our study.

Our study focused on hospital hospitalization numbers in the Hospital Authority. For IPD, the incidence was obtained from Central of Health Protection, HKSAR, which included data from both public and private hospitals data. The LOS and mortality data of IPD were retrieved from the database in Hospital Authority. Admissions to private hospital or those received out-patient treatment for pneumococcal pneumonia and all-cause pneumonia were not included in our study. However, Hospital Authority is the largest healthcare provider in Hong Kong which provides 90% of in-patient services in Hong Kong [26]. Data from Hospital Authority is representable for the general epidemiology of Hong Kong.

Conclusions

The incidence of pneumococcal pneumonia, IPD and all-cause pneumonia decreased during COVID-19 pandemics compare to the data in previous five years. This was observed with widespread practice of universal masking and social distancing. While causality cannot be shown from our data, it is likely that the decrease could be attributed to universal masking and social distancing, which would have reduced the transmission of bacteria and viruses and related bacterial superinfection.

Figure caption

Figure 1. Trend analysis of monthly numbers of invasive pneumococcal disease (IPD), pneumococcal pneumonia, all-cause pneumonia, and influenza in Hong Kong, January 2015 to March 2021. Numbers of IPD were those obtained through mandatory notification. Numbers of pneumococcal pneumonia and all-cause pneumonia were territory-wide hospitalizations by discharge diagnoses. Numbers of influenza viruses were those detected in respiratory specimens in a territory-wide laboratory surveillance. The two vertical lines delineated the time intervals from January 2015 to December 2019 (period 1, prior to COVID-19), January to February 2020 (period 2, excluded form analysis) and March 2020 to March 2021 (period 3, COVID-19 pandemic).

Figure 2. Admission numbers of fracture hip, acute kidney injury and PD peritonitis.

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Table 1. Incidence and number per 100,000 person year of pneumococcal pneumonia, invasive pneumococcal disease (IPD) and pneumonia

	All ages		18-49 years		50-64 years		≥65 years	
Disease [a]	No. of episodes	Incidence rate per 100,000 person-years	No. of episodes	Incidence rate per 100,000 person-years	No. of episodes	Incidence rate per 100,000 person-years	No. of cases	Incidence rate per 100,000 person-years
IPD								
Period 1	699	2.2	125	0.7	195	2.2	379	6.2
Period 2	26	2.4	5	0.9	6	2.0	15	6.6
Period 3	17	0.2	3	0.08	8	0.4	6	0.4
% reduction[b]		88.9% (79.8%-98.0%)***		88.6% (66.8%-110.4%)***		81.3% (62.1%-100.4%)***		93.5% (82,2%-104.8%)***
IRR[c]		0.11(0.07-0.18)***		0.11(0.04-0.36)***		0.19(0.09-0.38)***		0.07(0.03-0.15)***
Pneumococcal pneumonia								
Period 1	1,970	6.2	217	1.3	435	4.9	1,318	21.7
Period 2	74	6.9	11	2.0	14	4.7	49	32.4
Period 3	119	1.7	8	0.2	24	1.2	87	5.9
% reduction		72.5% (65.9%-79.1%)***		82.5% (64.5%-100.5%)***		74.8% (61.0%-88.6%)***		73.0% (65.2%-80.8%)***
IRR[c]		0.28(0.23-0.33)***		0.18(0.09-0.35)***		0.25(0.17-0.38)***		0.27(0.22-0.34)***
All-cause pneumonia								
Period 1	372,660	1169.7	19,502	115.3	38,360	432.4	314,798	5177.1
Period 2	13,865	1288.2	843	153.6	1,448	484.6	11,574	5062.3
Period 3	67,474	964.5	2,473	69.3	6,181	318.3	58,820	3958.0
% reduction		17.5% (16.8%-18.2%)***		39.9% (37.1%-42.7%)***		26.4% (24.3%-28.5%)***		23.5% (22.8%-24.3%)***
IRR[c]		0.83(0.82-0.83)***		0.60(0.58-0.63)***		0.74(0.72-0.76)***		0.77(0.76-0.77)***

[a] Period 1, January 2015 to December 2019 (before covid-19); period 2, January 2020 to February 2020 (transition period); period 3 March 2020 to March 2021 (post-COVID-19).

[b] Percentage reduction in period 3 relative to period 1 as the baseline

[c] Incidence rate ratio between period 1 and period 3

*p <0.05 to 0.01, **p <0.01 to 0.005, ***p<0.005

Table 2. Median length of stay and mortality rate of pneumococcal pneumonia, invasive pneumococcal disease (IPD) and pneumonia in the periods

	Median length of stay; days (IQR)#				Mortality rate; % (95%CI)			
	All ages	**18-49 years**	**50-64 years**	**≥65 years**	**All ages**	**18-49 years**	**50-64 years**	**≥65 years**
IPD								
Period 1	12 (16)	13 (19)	13 (17)	12 (13)	12.1 (8.8-16.1)	9.1 (3.4-18.7)	8.4 (3.7-15.9)	15.3 (10.3-21.4)
Period 3	12 (11)	4 (3)	16 (19)	12 (6)	6.3 (1.6-30.2)	0.0	0.0	14.3 (3.6-57.9)
Pneumococcal Pneumonia								
Period 1	9 (14)	7 (14)	9 (15)*	10 (14)	13.1 (11.7-14.8)*	4.2 (1.9-7.7)	7.5 (5.3-10.5)**	16.3 (13.6-18.7)
Period 3	12 (17)	7 (13)	13 (20)*	12 (16)	22.7 (15.5-31.3)*	0.0	29.2 (12.6-51.1)**	23.0 (14.6-33.2)
All-cause pneumonia								
Period 1	6 (9)***	4 (6)***	6 (9)**	6 (10)	20.5 (20.4-20.6)***	5.3 (4.9-5.6)*	13.0 (11.4-12.0)***	22.4 (22.2-22.4)***
Period 3	6 (10)***	4 (8)***	6 (10)**	6 (10)	24.2 (24.9-25.6)***	6.8 (5.9-7.9)*	16.1 (5.2-17.0)***	27.0 (26.6-27.3)***

*p <0.05 to 0.01, **p <0.01 to 0.005, ***p<0.005

IQR= interquartile range

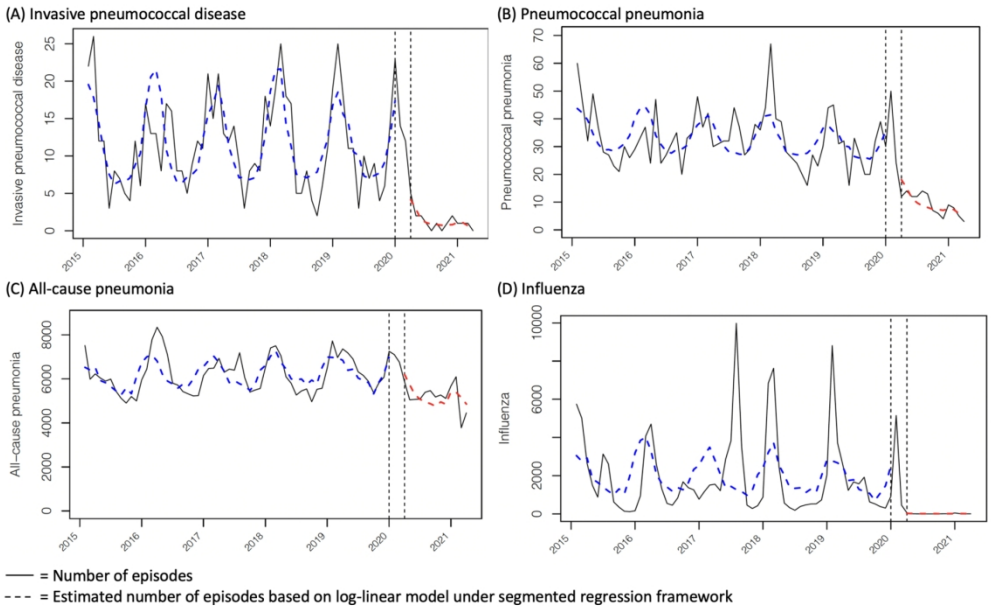

Figure 1. Trend analysis of monthly numbers of invasive pneumococcal disease (IPD), pneumococcal pneumonia, all-cause pneumonia, and influenza in Hong Kong, January 2015 to March 2021. Numbers of IPD were those obtained through mandatory notification. Numbers of pneumococcal pneumonia and all-cause pneumonia were territory-wide hospitalizations by discharge diagnoses. Numbers of influenza viruses were those detected in respiratory specimens in a territory-wide laboratory surveillance. The two vertical lines delineated the time intervals from January 2015 to December 2019 (period 1, prior to COVID-19), January to February 2020 (period 2, excluded form analysis) and March 2020 to March 2021 (period 3, COVID-19 pandemic).

352x218mm (144 x 144 DPI)

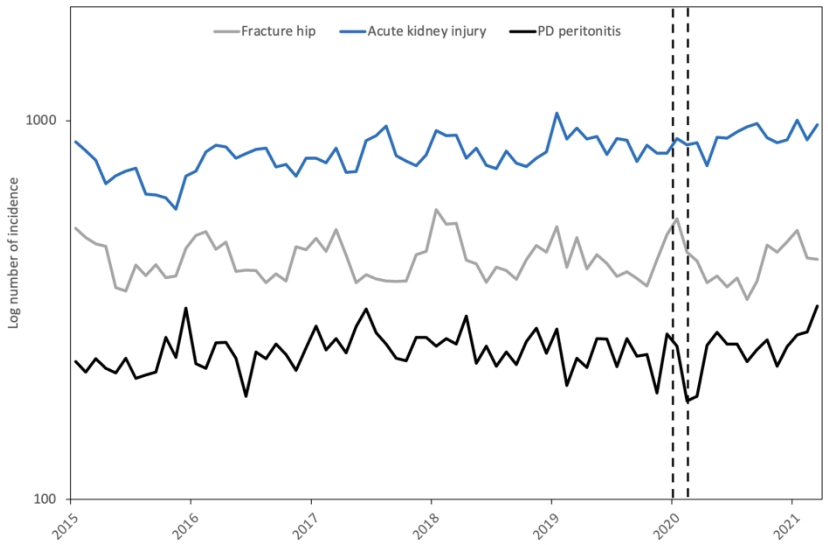

Figure 2. Admission numbers of fracture hip, acute kidney injury and PD peritonitis.

419x237mm (144 x 144 DPI)

Supplementary file.

Figure S1. Monthly incidence of (A) Invasive pneumococcal disease (IPD), (B) Pneumococcal pneumonia, (C) All-cause pneumonia and (D) Influenza in January 2015 to March 2021.

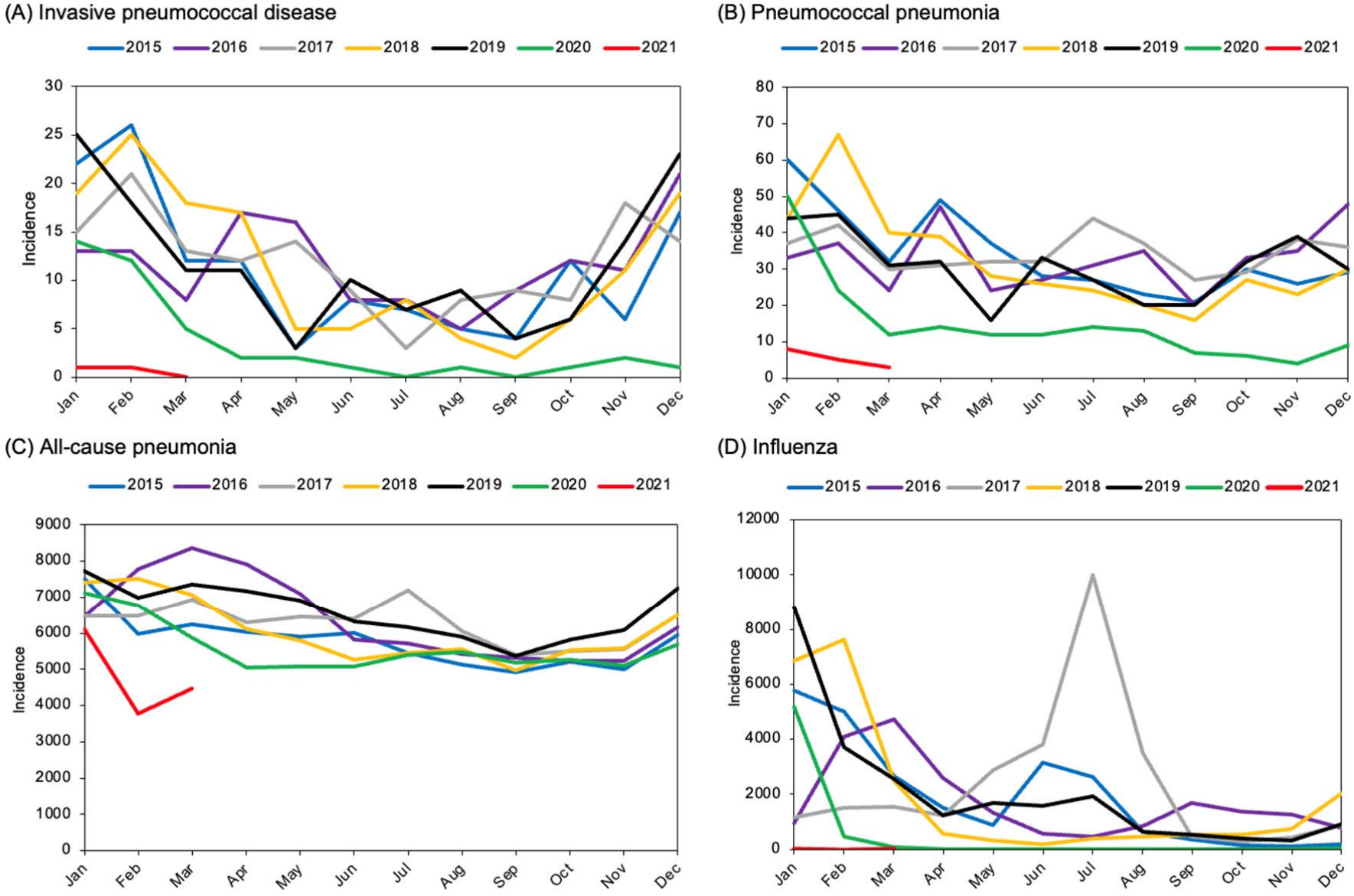

Figure S2. Trend analysis of monthly number of (A) age-stratified hospitalizations for invasive pneumococcal disease, (B) age-stratified hospitalizations for pneumonococcal pneumonia, (C) age-stratified hospitalizations for and (D) monthly percentage of air quality health index (AQHI) high to serious and (E) monthly average ambient temperature.

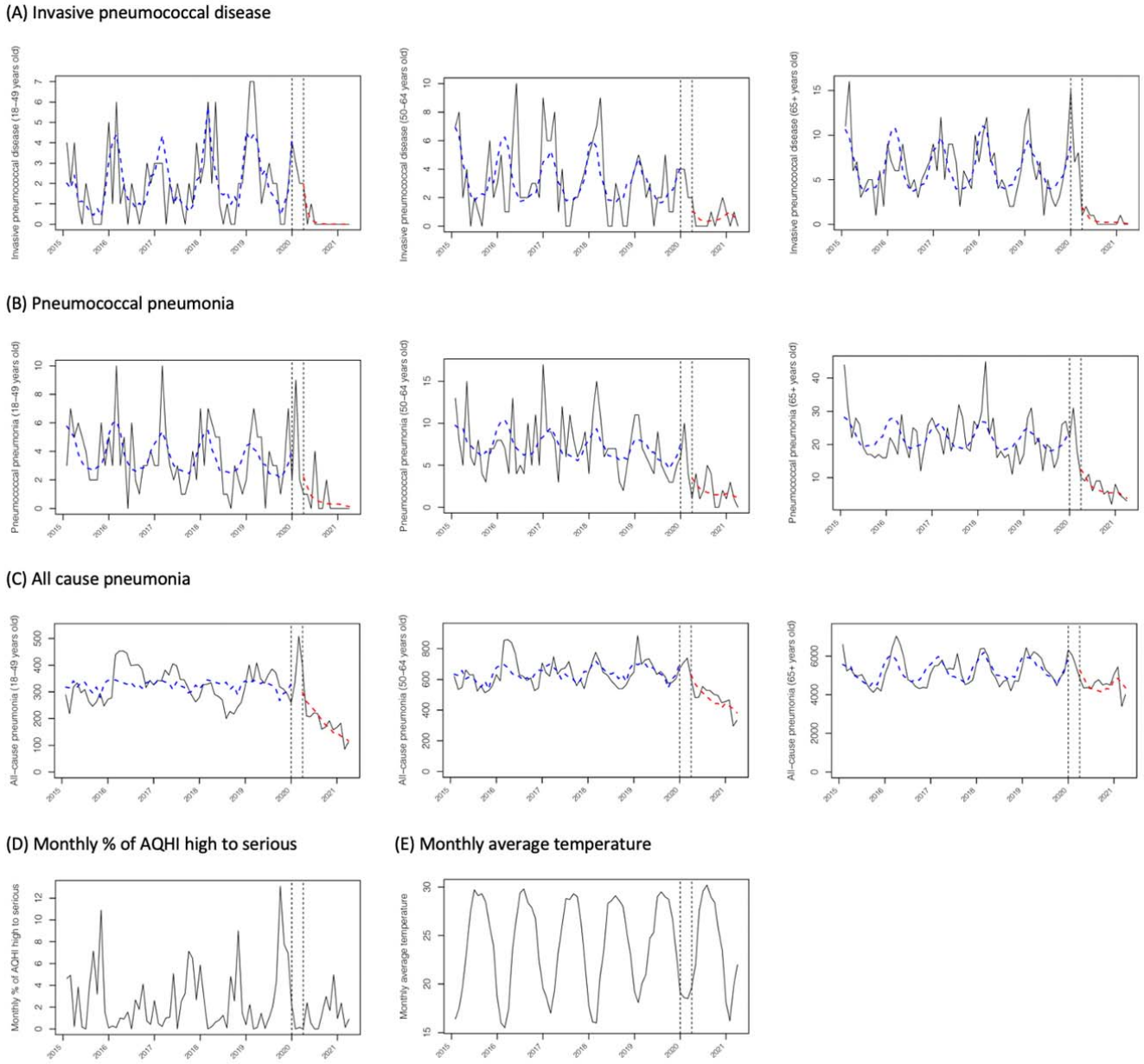

Table S1. Trend analysis of monthly number of hospitalization by age groups in periods before and after the COVID-19 pandemic

	Relative risk (95% CI)		Change in trend#
	Period 1 ^	Period 3^	
IPD			
All ages	1.0020 (0.9977-1.064)	0.8484 (0.7501-0.9597)**	-70.39% (-86.55% to -34.73%)**
18-49 years	1.0129 (1.0022-1.0238)	0.5272 (0.2176-1.2772)	-31.27% (-89.72% to 359.72%)
50-64 years	0.9969 (0.9888-1.0051)	0.9585 (0.8087-1.1362)	-70.43% (-92.80% to 21.42%)
65 years or above	1.0012 (0.9953-1.0071)	0.7777 (0.6111-0.9897)*	-70.83% (-91.59% to 1.12%)
Pneumococcal Pneumonia			
All ages	0.9978(0.9953-1.0004)	0.9042(0.8621-0.9483)***	-42.79% (-59.36% to -19.48%)*
18-49 years	0.9964(0.9887-1.0042)	0.6768(0.2171-2.1093)	-32.32% (-78.29% to 110.93%)
50-64 years	0.9962(0.9907-1.0017)	0.9174(0.8260-1.0189)	-50.21% (-76.93% to 7.48%)
65 years or above	0.9986(0.9954-1.0017)	0.9107(0.8612-0.9640)*	-41.19% (-60.82% to -11.73%)*
All-cause pneumonia			
All ages	1.0014(1.0012-1.0016)***	0.9835(0.9815-0.9855)***	-11.24% (-12.76% to -9.7%)***
18-49 years	1.0000(0.9992-1.0008)	0.9263(0.9164-0.9364)***	-6.05% (-13.41% to 1.94%)
50-64 years	1.0015(1.0009-1.0021)***	0.9620(0.9556-0.9684)***	-9.32% (-14.14% to -4.22%)***
65 years or above	1.0011(1.0009-1.0013)***	0.9879(0.9858-0.9901)***	-13.30% (-12.94% to -9.64%)***

^Trend in period 1 (January 2015 to December 2019) and 3 (March 2020 to March 2021), the relative risk expressed the month-to-month change in hospitalization numbers of period 3 compared to period 1

#Estimate the change in trend in the mean monthly number of cases in period 3, compare with the monthly trend in period 1

*p <0.05 to 0.01, **p <0.01 to 0.005, ***p<0.005

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	7-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	8-9

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11-15
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11-15
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11-15
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-15
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-15
Discussion			
Key results	18	Summarise key results with reference to study objectives	16-17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18-19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.