PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Chan, King-Pui Florence; Ma, Ting-Fung; Ip, Mary; Ho, Pak-leung

VERSION 1 – REVIEW

REVIEWER	Visaria, Aayush Rutgers The State University of New Jersey
REVIEW RETURNED	13-Aug-2021

GENERAL COMMENTS	Interesting paper on an important topic concerning incidence of pneumococcal disease in the era of COVID-19. The authors found a decrease in pneumococcal pneumonia from pre-COVID-19 to post-COVID-19, which they attributed to social distancing and preventive measures. Although this is a reasonable conclusion, I think it still needs to be shown explicitly that the decrease in pneumococcal pneumonia is due to social distancing/masks. A couple questions/comments: 1. In the abstract, can you provide information on period 2 to orient the reader on why you compare period 1 and 3 but don't refer to 2 at all? 2. In the methods, can you clarify what is included in all-cause pneumonia? Is COVID-19 pneumonia included as part of all-cause pneumonia? Could some people with COVID-19 related pneumonia be classified in the all-cause pneumonia? 3. In terms of statistical analysis, did you consider doing a more formal time-series analysis rather than a pre-post type of analysis? That way you can account for seasonal fluctuations and general trends in pneumonia that may not be due to COVID-19. It may be worthwhile to also calculate incidence rate ratios to a similar time period prior to the pandemic. If you could explain the log-linear model that was used in more detail that would be beneficial as well. 4. Table 2 - should report median (IQR) numbers because it doesn't seem that the LOS values are normally distributed. 5. Figure 1 - please specify what the dotted lines are. 6. In terms of coding issues, could some of the patients in your study have COVID-19 as well as superinfection with pneumonia? What is the incidence of that? Are you able to adjust for comorbidities? It could be that patients prone to get pneumonia are just getting COVID-19 instead and thus pneumococcal pneumonia rates are lower than expected.

REVIEWER	Lin, Chien-Yu Mackay Memorial Hospital Hsinchu, Department of Pediatrics

REVIEW RETURNED	18-Aug-2021

GENERAL COMMENTS	Dear Editor and authors, I'm pleased to review this article to investigate the prevalence of IPD, pneumococcal disease, and all-cause pneumonia. A drastic decrease of these diseases was observed and universal masking and social distancing were believed to be responsible for the observed decrease. The article is well written. I have some questions. 1. The magnitude of decrease is greater than other reports. Do you have some comments? 2. Compared with IPD and pneumococcal disease, the decrease of all-cause pneumonia is less obvious (88.9%, 72.5% vs 17.5%). There is a big gap and aspiration pneumonia is believed to be the cause of the difference. Since the study design is retrospective database research using ICD-9 coding, is it possible to add some data regarding aspiration pneumonia? 3. How did you evaluate the individual effects of universal masking and social distancing? Furthermore, how about the effects of other strategies, such as closure of schools, bars, and pubs, etc.? 4. Although PPSV 23 is less effective than PCV13, most adults receive PPSV23. Did you have vaccination data of PPSV23? Serotype 3 is prevalent in present study and also included in PPSV23. Moreover, the proportion of PPSV23 serotypes may be added. 5. Seasonality is important in these diseases. It's appreciated to compare the incidences of these diseases during the same months in a figure. 6. The incidences of acute kidney injury increased significantly in period 3. Please add some discussion. 7. Why did you choose acute kidney injury, facture hip, and peritonitis as comparable diseases? 8. Please provide the full names of abbreviations for the first time; for example, what are HKSAR or CHP? Thank you very much!

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Mr. Aayush Visaria, Rutgers The State University of New Jersey
Comments to the Author:
Interesting paper on an important topic concerning incidence of pneumococcal disease in the era of COVID-19. The authors found a decrease in pneumococcal pneumonia from pre-COVID-19 to post-COVID-19, which they attributed to social distancing and preventive measures. Although this is a reasonable conclusion, I think it still needs to be shown explicitly that the decrease in pneumococcal pneumonia is due to social distancing/masks.

A couple questions/comments:

1. In the abstract, can you provide information on period 2 to orient the reader on why you compare period 1 and 3 but don't refer to 2 at all?

Statement regarding period 2, January-February 2020 was added in abstract in the design part (line 33-35). January-February 2020 was excluded as it was treated as transitional period between normal time and pandemic, where universal masking was not completely executed. Since our main interest is

the comparison between pre- and post-pandemic (i.e. period 1 and 3), period 2 is not used as the reference, but removed from the analysis.

2. In the methods, can you clarify what is included in all-cause pneumonia? Is COVID-19 pneumonia included as part of all-cause pneumonia? Could some people with COVID-19 related pneumonia be classified in the all-cause pneumonia?

We apologize for not clarifying it in our manuscript. COVID-19 pneumonia was also included as part of all-cause pneumonia (line 39-40, 177-180). A new section was added on the COVID-19 condition in Hong Kong in the study period. For COVID-19 pneumonia, the incidence was 331 among 10,348 patients diagnosed with COVID-19 (line 354-358).

3. In terms of statistical analysis, did you consider doing a more formal time-series analysis rather than a pre-post type of analysis? That way you can account for seasonal fluctuations and general trends in pneumonia that may not be due to COVID-19. It may be worthwhile to also calculate incidence rate ratios to a similar time period prior to the pandemic. If you could explain the log-linear model that was used in more detail that would be beneficial as well.

We have considered time-series rather than GLM type models in the preparation of the paper, but decided to take the latter approach mainly due to two reasons. First, note that the response is a count variable, time series model for count would usually be more complicated (e.g. involving a latent process, more parameters), especially when the sample size is fairly small. Second, the dependence structure is not clear in nature (more parameters would be required for time series model) and it would make the interpretation of effect of pandemic not straightforward to many readers. To ensure statistical stability, log-linear model approach is adopted for statistical inference. Log-linear model have strengths over the time-series approach for our case. The interpretation of effect due to pandemic is straightforward as it is directly related to some regression coefficients of the log-linear model (line 230-231).

The incidence rate ratios were calculated and included in the text (line 279-280, 307-308, 336-337) and table 1.

4. Table 2 - should report median (IQR) numbers because it doesn't seem that the LOS values are normally distributed.

Thank you for the advice. The median (IQR) length of stay instead of mean length of stay are now used in the main text (line 285-286, 312-315, 340-341) and table 2.

5. Figure 1 - please specify what the dotted lines are.

The two vertical lines delineated the 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). This has been clarified in the Figure legend. The dotted lines in the figures next to the monthly number of IPD, pneumococcal pneumonia, all-cause pneumonia and influenza are the estimated number of episodes based on log-linear model under segmented regression framework. It was included in the figure.

6. In terms of coding issues, could some of the patients in your study have COVID-19 as well as superinfection with pneumonia? What is the incidence of that? Are you able to adjust for comorbidities? It could be that patients prone to get pneumonia are just getting COVID-19 instead and thus pneumococcal pneumonia rates are lower than expected.

In Hong Kong, number of COVID-19 cases was low. The number of adults (aged ≥18 years) with

COVID-19 was 94 in period 2 and 10348 in period 3. Further analysis of COVID-19 patients in period 3 revealed a total of 331 patients with pneumonia (line 354-358).

On reviewing the 331 COVID-19 patients with superinfected pneumonia, median age is 66 years old (IQR 21) while those with pneumococcal pneumonia was 72 years old (IQR 21) in period 1 and 77 years old (IQR 22) in period 3. The patients getting COVID-19 pneumonia were younger than those with pneumococcal pneumonia. Among the 331 patients, two patients had both COVID-19 and pneumococcal pneumonia, both in the age group 50-64 and occurred in 3/2020 and 7/2020.

Reviewer: 2
Dr. Chien-Yu Lin, Mackay Memorial Hospital Hsinchu
Comments to the Author:
Dear Editor and authors,
I'm pleased to review this article to investigate the prevalence of IPD, pneumococcal disease, and all-cause pneumonia. A drastic decrease of these diseases was observed and universal masking and social distancing were believed to be responsible for the observed decrease. The article is well written. I have some questions.

1. The magnitude of decrease is greater than other reports. Do you have some comments?

The decrease in IPD was higher than the overall reduction reported by Brueggemann et al in which the incidence during COVID-19 pandemic and baseline for 2018 and 2019 in 26 countries and area. However, variations in country-specific reductions in IPD incidence was noted.

Brueggemann AB et al, Changes in the incidence of invasive disease due to Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitidis during the COVID-19 pandemic in 26 countries and territories in the Invasive Respiratory Infection Surveillance Initiative: a prospective analysis of surveillance data. Lancet Digit Health 2021; 3(6):e360-e370.

In our study, we compared period 1 and period 3. Universal masking and social distancing were widely practiced in period 3. The decrease in IPD incidence was more drastic as there were less cases in period 3.

Moreover, for pneumococcal pneumonia and all-caused pneumonia, our study included those who were hospitalized under Hospital Authority. Out-patient data from Hospital Authority and those who attended private hospitals were not included. This may account for the greater magnitude of decrease these patients might attended private hospital or preferred out-patient treatment (line 479-484).

2. Compared with IPD and pneumococcal disease, the decrease of all-cause pneumonia is less obvious (88.9%, 72.5% vs 17.5%). There is a big gap and aspiration pneumonia is believed to be the cause of the difference. Since the study design is retrospective database research using ICD-9 coding, is it possible to add some data regarding aspiration pneumonia?

In our study, patients with pneumonia due to inhalation of food or vomitus (ICD-9 507.0) were included and the data was added in the manuscript (line 348-351). As the number of aspiration pneumonia was small at around 200-300 cases, we have further reviewed the data of all-cause pneumonia and elaboration added in the revision. 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 populationof 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. 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 (line 419-429).

3. How did you evaluate the individual effects of universal masking and social distancing? Furthermore, how about the effects of other strategies, such as closure of schools, bars, and pubs, etc.?

The individual effect of universal masking, social distancing and other strategies cannot be evaluated separately. This is included in the limitation part of the discussion (line 471-474). The effect was assumed as a whole and modelled by the effect of pandemic.

4. Although PPSV 23 is less effective than PCV13, most adults receive PPSV23. Did you have vaccination data of PPSV23? Serotype 3 is prevalent in present study and also included in PPSV23. Moreover, the proportion of PPSV23 serotypes may be added.

Data of PSSV23 vaccination in Hong Kong was only available for those age at 65 years old and above and was included in the background (line 115-121). PPSV23 serotypes data was included in the revision (line 263-266).

5. Seasonality is important in these diseases. It's appreciated to compare the incidences of these diseases during the same months in a figure.

The new figure comparing incidence of disease during same month over year 2015-2021 was included in Figure S2 and cited in the result (line 269, 295, 326).

6. The incidences of acute kidney injury increased significantly in period 3. Please add some discussion.

Discussion was added on increase in incidence of acute kidney injury (line 443-446). Drug induced AKI is an important cause in Asia. 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.

7. Why did you choose acute kidney injury, facture hip, and peritonitis as comparable diseases?

We chose these as comparable diseases as these are non-communicable disease and the incidence of these diseases would not be affected by environmental factors including mean ambient temperature (line 197-199).

8. Please provide the full names of abbreviations for the first time; for example, what are HKSAR or CHP?

Apologize for not providing the full names of abbreviations. The full names were added of the abbreviations for the first time Hong Kong Special Administrative Region (HKSAR) (line 168) and Centre for Health Protection (CHP) (line 171).
Thank you very much!

VERSION 2 – REVIEW

REVIEWER	Visaria, Aayush

	Rutgers The State University of New Jersey
REVIEW RETURNED	20-Sep-2021

GENERAL COMMENTS	The edits made to the prior reviews are all very informative and improve the paper greatly. In Table S1, I would just specify more clearly what the reference group is. I have no further edits.

REVIEWER	Lin, Chien-Yu Mackay Memorial Hospital Hsinchu, Department of Pediatrics
REVIEW RETURNED	07-Sep-2021

GENERAL COMMENTS	Dear Editor and authors, Thank you for your revision and it's clearer. I'll recommend its publication. I have some further comments. 1. The authors thought people may have health seeking behaviors for intake of over-the-counter medication. Mild pneumocaccal pneumonia may be treated as outpatients. It's appreciated to summarize the change of hospital visits in different periods. 2. Were 331 patients with COVID-19 pneumonia included in all-cause pneumonia? The role of coinfection/superinfection of COVID-19 may be discussed. 3. In tables, IRR should be incidence rate ratio. Please modify. 4. The abbreviation of "LOS" in the abstract should be spelled out. 5. Please modify references in concordance to journal style. Please add assess dates for websites. Thank you.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Dr. Chien-Yu Lin, Mackay Memorial Hospital Hsinchu

Comments to the Author:

Dear Editor and authors,

Thank you for your revision and it's clearer. I'll recommend its publication. I have some further comments.

RESPONSE: Thank you for the comments in improving our manuscript.

1. The authors thought people may have health seeking behaviors for intake of over-the-counter medication. Mild pneumocaccal pneumonia may be treated as outpatients. It's appreciated to summarize the change of hospital visits in different periods.

RESPONSE: The following has been added to summarize the changes. "Majority of the patients with pneumococcal pneumonia were treated with in-patient care. The total number of patients treated outpatients and discharged from emergency department was 30 in period 1 and 0 in period 2" (line 317-319).

2. Were 331 patients with COVID-19 pneumonia included in all-cause pneumonia? The role of coinfection/superinfection of COVID-19 may be discussed.

RESPONSE: The 331 patients with COVID-19 pneumonia were included in all-cause pneumonia (line 334-335). Among those patients, none were diagnosed with coinfection of COVID-19 and pneumococcal pneumonia (line 368-369).

Discussion on coinfection/ superinfection of COVID-19 with pneumococcal was added . “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]” (line 407-414).

3. In tables, IRR should be incidence rate ratio. Please modify.

RESPONSE: IRR was amended to incidence rate ratio.

4. The abbreviation of “LOS” in the abstract should be spelled out.

RESPONSE: We apologise for that. “LOS” was changed to length of stay (line 51).

5. Please modify references in concordance to journal style. Please add access dates for websites.

RESPONSE: Thank you for the comment. The references are modified to the journal style. Access dates for websites were added.

Reviewer: 1

Mr. Aayush Visaria, Rutgers The State University of New Jersey

Comments to the Author:

The edits made to the prior reviews are all very informative and improve the paper greatly. In Table S1, I would just specify more clearly what the reference group is.

RESPONSE: Thank you for the reviewer’s comment. We have clarified the reference group of relative risk, with addition of “the relative risk expressed the month-to-month change in hospitalization numbers of period 3 compared to period 1”.