The impact of childhood pneumococcal conjugate vaccine immunisation on all-cause pneumonia admissions in Hong Kong: a 14-year population-based interrupted time series analysis

ABSTRACT

Background: Nine years after the introduction of pneumococcal conjugate vaccine (PCV) in the US, Hong Kong (HK) introduced the vaccine to its universal childhood immunisation programme in 2009. We aimed to assess the impact of childhood PCV immunisation on all-cause pneumonia (ACP) admissions among the overall population of HK.

Methods: In this population-based interrupted time series analysis, we used territory-wide population-representative electronic health records in HK to evaluate vaccine impacts. We identified hospitalised patients with a diagnosis of pneumonia from any cause between 2004 and 2017. We applied segmented Poisson regression to assess the gradual change in the monthly incidence of ACP admissions between pre- and post-vaccination periods. Negative outcome control, subgroup and sensitivity analyses were used to test the robustness of the main analysis.

Findings: Over the 14-year study period, a total of 587,607 ACP episodes were identified among 357,950 patients. The monthly age-standardised incidence of ACP fluctuated between 33.4 and 87.4 per 100,000-persons. There was a marginal decreasing trend in pneumonia admissions after PCV introduction among overall population (incidence rate ratio: 0·9965, 95% CI: 0·9932-0·9998), and older adults (≥ 65 years, incidence rate ratio: 0·9928, 95% CI: 0·9904-0·9953) but not in younger age groups.

Interpretation: There was a slightly significant trend change in overall ACP admissions in HK up to eight years after PCV introduction, but the significance disappear when fitting sensitivity analyses. The results indicate the complexities of using non-specific endpoints for measuring vaccine effect and the necessity of enhancing serotype surveillance systems for replacement monitoring.

Funding Health and Medical Research Fund, Food and Health Bureau of the Government of Hong Kong (Reference number: 18171272).

Keywords: pneumococcal conjugate vaccines; interrupted time series analysis; herd immunity; population-based electronic health records; all-cause pneumonia; serotype surveillance

INTRODUCTION

Pneumonia remains one of the top three leading causes of death worldwide, associated with considerable morbidity and economic loss.[1,2] Several pneumococcal conjugate vaccines (PCVs) against serotypes of *Streptococcus pneumoniae* have been developed to prevent pneumococcal diseases.[3] PCV7 protects against the seven serotypes that are most commonly associated with invasive pneumococcal disease (IPD) and was first introduced to the routine childhood immunisation programme (CIP) in the US in 2000. It was subsequently replaced in 2010 by PCV13, which protects against six further serotypes, including some which rapidly replaced the original seven following PCV7 introduction in the US. Since 2006, the World Health Organization has recommended incorporating PCV into national CIPs, especially in countries with significant pneumococcal disease burden.[4]

The effectiveness of PCV immunisation in reducing pneumonia-related admissions in children has been consistently reported in countries with PCVs incorporated into the CIP.[5-7] Biologically, PCV immunisation should also offer indirect protection to unvaccinated individuals by reducing bacterial carriage among the vaccinated, and thus, reduce bacterial exposure to the unvaccinated (herd protection). However, the impact of childhood PCV immunisation among the overall population is different due to extensive replacement with non-vaccine serotypes after vaccine introduction, particularly in older adults.[8-10] Current real-world evidence on the indirect effects of PCV has mainly focused on populations in high-income countries, particularly in North America, Europe and Australasia, which were first to introduce PCV. There are several emerging evidence for the delayed PCV introduction effect in African countries that mainly focused on child age group.[7,11] However, the entire benefits of the vaccine across all age groups remain unclear.

Despite an approximate nine-year delay compared to the US, Hong Kong (HK) was one of the first cities in Asia to introduce PCV to the routine CIP. Through HKCIP, the government has provided free and universal PCV7 to children under two years of age since September 2009. Following greater serotype coverage by newly developed PCVs, PCV10 was introduced in October 2010 which was

subsequently replaced by PCV13 in December 2011.[12] The overall immunisation coverage rates of various vaccines under the HKCIP has been maintained at a level of over 95%. For example, the PCV coverage was up to 95% among preschool children born in 2012-2014, reported by Department of Health in 2018.[12] However, the burden of pneumonia in HK remains high even in the post-PCV era.[13] Pneumonia remains the second leading cause of death in HK with pneumonia-related deaths increasing over the past ten years.[14] Given the large disease burden and the need for effective interventions for pneumonia control, it is important to evaluate the cross-age effect of childhood PCV immunisation, particularly in older adults. In this study, we assessed the impact of childhood PCV immunisation on pneumonia admissions among the overall HK population in order to provide information for future PCV immunisation policies.

METHODS

Data source

This study used data from the Clinical Data Analysis and Reporting System (CDARS) - a territory-wide electronic health record (EHR) system developed by the Hospital Authority (HA) of Hong Kong. HA is the statutory body that manages all public hospitals and ambulatory clinics, which are available to all HK residents (over 7.4 million people) and covers 73% of hospital admissions in HK.[15] Patient-specific data include demographics and prescription information, diagnoses, procedures, laboratory tests, consultation dates, admissions and discharge information along with immunisations conducted in public hospitals. A unique anonymous identifier was assigned to each patient to protect patient privacy and facilitate data retrieval. CDARS has demonstrated data quality and accuracy in a variety of population-based clinical and epidemiological studies.[16-20] The study protocol was approved by the institutional review board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (Reference number: UW 19-022).

Study design

We applied a quasi-experimental design with interrupted time series (ITS) analysis to evaluate the impact of childhood PCV immunisation on pneumonia admissions.[21] With the longitudinal data before and after an intervention, ITS analysis has been recognised as a useful tool in evaluating population-level policy effectiveness and is being increasingly used in healthcare policy assessments such as smoking cessation policies, new drug listing policies and vaccine programmes.[22] The study applied the standard ITS method with a segmented Poisson regression model.[23,24]

Outcome measures

Outcomes of interest include hospitalisation due to all-cause pneumonia (ACP, primary outcome) and pneumococcal pneumonia (PP, secondary outcome) between January 2004 and December 2017 recorded in CDARS. Patients with ACP were identified using the principal diagnosis coded at discharge based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes (480-486). Lab tests and bacteria culture results of patients with ACP were retrieved to verify those with PP. Patients with pneumococcal Ag detected in lab tests or *S. pneumoniae* cultured from sputum, blood, urine, or cerebrospinal fluid samples within the same hospitalisation stay was counted as one PP episode.

Admission records from the same patient with an admission interval shorter than 2 days were counted as a single episode, in consideration of the likelihood of hospital transfer. Patients with multiple hospital admissions were considered as independent cases if admission intervals exceeded 2 days.[13] Crude and age-specific incidences of ACP and PP were calculated monthly with the overall incidence standardised using the 2017 HK census population to account for population structure changes.[25]

Main analysis

The comparison period for the ITS analysis was the pre-PCV period (January 2004 to December 2008) and the post-PCV period (January 2012 to December 2017). We excluded data points between January

2009 and December 2011 from the analysis as the transition period of PCV introduction[11] (PCV7 in September 2009, PCV10 in October 2010, and PCV13 in December 2011).[12] Additionally, the year 2009-2011 corresponded to the period of the H1N1 pandemic in HK.[26] Therefore, we defined the post-PCV period as starting from January 2012 to minimise data contamination associated with the influenza outbreak.

We applied segmented Poisson regression to estimate the abrupt (level change) and gradual changes (slope change) of the monthly incidence of ACP and PP. For both pre- and post-PCV periods, logarithm of population was included as offset. We also included logarithm of monthly influenza-related admissions (ICD-9-CM: 487) in the regression model to adjust the potential confounding effect due to the changes of infectious disease surveillance during flu pandemic. To account for the seasonality effect, the model also included a categorical indicator for each calendar month.[27] After fitting the Poisson regression models, we used residual plots, autocorrelation function (ACF) and partial autocorrelation function (PACF) to test the model assumption and the existence of autocorrelation. We further applied Newey-West method to correct for the overdispersion and autocorrelation. Standard errors were adjusted for autocorrelation up to the largest lag detected by the bandwidth selection procedure for all of the primary, secondary and negative control outcomes.[23,28]

Negative control, subgroup and sensitivity analyses

We conducted negative control analysis using fracture of lower or upper limb (ICD-9-CM: 810-829) as the alternative outcome. With the clinical understanding that fracture should not be affected by PCV immunisation, taking this as the negative control can test the validity of the statistical approach. In subgroup analysis, we stratified the study population into three age groups (0-19, 20-64, ≥ 65years) in order to assess the vaccine's impact. We also conducted a series of sensitivity analyses for the primary outcome to test the robustness of findings from the main analysis, including 1) adding three-months, six-months, and one-year lag on the post-PCV period to assess the time-lag effect of PCV immunisation; 2) changing admission intervals to 30-days and 60-days to define one admission episode. To validate

the cut-off time point in our analysis, we also employed a change-point analysis that can identify the statistically changing timing according to the dataset.[29]

We used R software (version 3.6.1) for data manipulation and analysis. A two-sided P-value of less than 0.05 was considered statistically significant. Data cleaning and analysis was conducted and cross-checked independently by two authors (QYY, MF) for quality control.

RESULTS

Descriptive analysis

Over the 14-year study period, a total of 587,607 ACP episodes among 357,950 patients (54% male) and 12,699 PP episodes among 12,134 patients (71% male) were recorded in CDARS. The annual incidence of ACP fluctuated between 633 and 812 per 100,000-persons, whilst the annual overall incidence of PP fluctuated between 12·2 and 18·5 per 100,000-persons. Major disease burden of ACP and PP was in older adults ≥ 65 years (Table 1). The trend line in Figure 1 details the annual incidence of ACP, PP and limb fracture (negative control) between 2004 and 2017.

The overall dataset has 168 months of routine hospital admissions data with an average of 3,498 ACP [standard deviation (SD): 786] and 76 PP (SD: 24) episodes monthly. Monthly age-standardised incidence ranged between 33·4 and 87·4 per 100,000-persons for ACP and 0·53-2·67 per 100,000-persons for PP. Monthly incidence and its temporal variation were greater in older adults than other age groups (Supplementary Figure 1).

Interrupted time series analysis

In the pre-PCV period, there was no significant changes in monthly incidence of ACP were found. There was an immediate non-significant increase in the incidence of ACP in January 2012 [incidence rate

ratio (IRR) = 1·0117, P = 0·8959]. Throughout the post-PCV period, the monthly incidence of ACP declined gradually by 0·35% with a marginal significance (P=0·0378, Table 2, Figure 2a). For PP as the secondary outcome, there was a significant decrease before PCV introduction. After PCV introduction, slight decreasing slope change without statistical significance was observed (P = 0·1341, Table 2, Figure 2b). In negative control analysis, PCV showed no protective effect on the incidence of fracture (Table 2, Figure 2a). The residuals plot and autocorrelation function for overall ACP are shown in Supplementary Figure 2.

Subgroup and sensitivity analyses

In the subgroup analysis, we focused on the gradual trend changes (slope change effect) in order to analyse the long-term effect of PCV in the post-PCV period. We found a marginal decreasing trend (0.72% reduction) of ACP incidence among older adults aged ≥65 years (Table 3, Figure 3a). No significant findings achieved among children and younger adults. For the incidence of PP, we observed similar trends as that for ACP (Table 3, Figure 3b). For the negative control outcome, there was no reduction trend in the incidence of fracture in all age groups.

We conducted sensitivity analyses for the primary outcome of interest. For the overall population, the decreasing trend of ACP incidence only remained significant up to 3-month lag period of the childhood PCV implementation (no time-lag: 0·35%, P < 0·05; 3-month lag: 0·33%, P < 0·05; 6-month lag: 0·30%, P = 0·0778; 12-month lag: 0·28%, P = 0·0824, Supplementary Table 1). For the time-lag effect on subgroup, the decreasing trend of ACP incidence in older adult group (≥ 65 years) remained significant for all tested time-lag periods (no time-lag: 0·72%, P < 0·05; 3-month lag: 0·70%, P < 0·05; 6-month lag: 0·67%, P < 0·05; 12-month lag: 0·65%, P < 0·05, Supplementary Table 1). In addition, different admission intervals for one hospitalisation episode yielded similar trend as the main analysis but some of the subgroup analysis became non-significant (Supplementary Table 2). The significant point chosen by change-point analysis was in December 2010, which was within the transition period. The examined

decreasing trend of overall ACP incidence is by 0·32% significantly (IRR = 0·9968, P < 0·05), which is similar to the main analysis.

DISCUSSION

In this interrupted time series analysis, we found a marginal declining trend of ACP but no significant decrease of PP among the overall Hong Kong population up to eight years after childhood PCV immunisation. The series of sensitivity analyses yielded consistent findings that the effect was weak and even became non-significant with a time lag period or admission intervals changes. Our research findings may differ from reports of other countries given the underlying epidemiology of *S. pneumoniae* and the time-lag between PCV introduction in HK and many other high-income settings are different. This indicates that evaluation of the impact of childhood PCV immunisation in the post-PCV era is complex and multifactorial, posing significant challenges for countries with delayed vaccine introduction and incomplete serotype surveillance systems.

The effect of PCV introduction on pneumonia and its magnitude are also restrained by data quality and study design. Most of the relevant literature support the significant effect of PCV on ACP hospitalisation after its introduction, but the effect is regional-specific and age-dependent.[30-36] Lau *et al*[33] reported a gradual decline in ACP incidence (IRR=0.98) among children 0-4 years in the UK after the introduction of PCV7 but no additional benefit from PCV13 was observed. In contrast, Simonsen *et al*[30] reported shortly after its introduction in the US, that PCV13 was associated with significant reduction of ACP hospitalisation for children aged 0-2 years (21%), children aged 2-4 years (17%), and adults aged 18–39 years (12%), but not for other age groups. Pelton *et al*[31] also studied the effect of universal childhood PCV13 immunisation among all age groups in the US 3 years after its introduction and observed a reduction of ACP hospitalisation for children and adults groups, but not for older adults aged ≥75 years. In the current study, we found marginal ACP admission and no reduction in PP admission after PCV introduction. In the older adults' group, despite having captured a significant

declining trend of ACP after the childhood PCV immunisation with the averted ACP cases of 3,234 per year on average (annual incidence reduction of 0·17 per 100,000-persons), we however consider this observation likely to have suffered from type one error given the very marginal effect detected and its divergence from findings in the age group that was actually vaccinated.

Rapid increases of non-PCV serotypes might compromise the benefits of the PCV immunisation for both children and adults.[37,38] Consistent with the global evidence, serotype replacement was reported shortly after the PCV13 introduction in HK.[39-41] This indicates that the vaccine has been used in HK against a backdrop of serotype replacement globally and regionally; a possible explanation as to why we could not detect any declining trend of PP – the specific measurement of PCV effectiveness. Serotyping of *S. Pneumonia* is not available in our study dataset. Due to this limitation, we were unable to test the role of serotype replacement on the occurrence of ACP or PP. However, the publicly-available government report also suggests that invasive pneumococcal disease, one of the statutory notifiable infectious diseases in HK since 2015,[42] has not shown significant decline in trend between 2015 and 2019 (Supplementary Figure 3).

Interpretation of the study findings should be taken cautiously. Of note, the years 2009-2011 were treated as the transition period of PCV introduction covering the sequential implementation of PCV7, PCV10, and PCV13.[12] Coincidentally, there was a H1N1 influenza pandemic in HK during the same period.[26] Hence the study investigated the cumulative effect of PCVs instead of a specific PCV effect and the effect of the influenza pandemic cannot be excluded completely despite the regression adjustment including influenza episodes. Influenza is one of the major components of ACP and a well-known risk factor for secondary bacterial infection including *S. pneumoniae*.[43] The infectious disease surveillance and the propensity of hospital admission and testing for *S. pneumoniae* might also be increased during the pandemic. These factors may all contribute to the increase of both ACP and PP admissions during the pandemic. The seasonal influenza vaccination also played a potential role in the trend of ACP admission. In a recent HK government report, the uptake of influenza vaccine increased

gradually from less than 3% in 2003 in general to over 20% in children and over 40% in older adults in 2017.[44,45] Hence the trend of ACP observed in this study should be considered as an aggregated effect from pneumococcal and influenza vaccines but not PCV alone.

There are also various limitations to be considered. Firstly, due to data source restrictions, we mainly relied on ICD-9-CM diagnostic codes rather than radiologically confirmed pneumonia to define the primary outcome of interest. The majority (86%) of pneumonia diagnosis was classified as pneumonia with unspecified organism. The definition of "pneumonia" is not well defined in HK (i.e. whether or not chest X-ray was used) - presumably may have changed over time. With regard to this point, using ACP as the primary but less specific outcome will render vaccine effectiveness less significant. Secondly, we were unable to link clinical diagnosis with serotyping from lab tests due to inconsistent practices from different hospitals and the change in *S. pneumonia* serotype surveillance recommendations over the study period.[46,47] Hence, we could not investigate the possibility of serotype replacement after PCV introduction. Future clinical-based studies are warranted to evaluate the long-term effect of PCV immunisation in the dynamic setting of possible serotype replacement. Thirdly, for the secondary outcome as PP, we attempted to extract all the lab testing results among all the patients with ACP diagnosis. However, information about "how" and "who" to test is unknown from the database. It is likely that the test policy has been ad hoc and has changed over time – hence caused the non-significant results. Fourthly, the EHR database we used included hospital admission from all public hospitals in HK so that only data from the public sector were utilised. There is a likelihood of selection bias with neglecting the admission from the private sector. Lastly, we did not include certain potential confounders such as daily temperature or air-condition fluctuations, which may also influence the occurrence of pneumonia.[48]

Findings from this study highlight the challenges in interpreting data on the real-world effectiveness of childhood PCV immunisation among the overall population, and provide important information to inform design of post-introduction surveillance systems. In particular, even in a high-income setting

with good access to hospital care and comprehensive reporting of public hospital admissions, monitoring vaccine effectiveness is difficult without pneumococcal-specific surveillance systems that match clinical diagnoses, laboratory reporting and serotyping. It is particularly relevant to countries and regions with delayed PCV introduction schedules in terms of year and/or with a considerable ageing population. Following the implementation of PCV immunisation, determining specific measurements are important for the evaluation of vaccine effectiveness and cost-effectiveness. Serotype surveillance systems should also be enforced to monitor replacement and examine vaccine benefits dynamically.

In conclusion, eight years after the introduction of childhood PCV immunisation, hospitalised all-cause pneumonia and pneumococcal pneumonia among the overall HK population did not show a highly significant reduction in either children or adults. Future studies should investigate the possible role of *S. pneumoniae* serotype replacement in changing vaccine effectiveness in the long-term.

Acknowledgements

We thank Lisa Y Lam from the Department of Pharmacology and Pharmacy of the University of Hong Kong for proofreading the manuscript.

Funding

This study was supported by Health and Medical Research Fund, Food and Health Bureau of the Government of Hong Kong (Reference number: 18171272).

Conflict of interest

Dr. X Li received research and educational grants from Janssen and Pfizer; internal funding from University of Hong Kong; consultancy fee from Merck Sharp & Dohme, unrelated to this work.

Dr. Chan reports other from Hospital Authority, grants from Research Grants Council (RGC, Hong Kong),

grants from Research Fund Secretariat of the Food and Health Bureau, grants from National Natural Science Fund of China, grants from Wellcome Trust, grants from Bayer, grants from Bristol-Myers Squibb, grants from Pfizer, grants from Janssen, grants from Amgen, grants from Takeda, grants from Narcotics Division of the Security Bureau of HKSAR, outside the submitted work.

Dr. IP has received research grants from Research Grants Council (RGC, Hong Kong) and Health and Medical Research Fund (HMRF), outside the submitted work.

Dr. Cowling reports personal fees from Sanofi Pasteur, personal fees from Roche, outside the submitted work.

Dr. Wong reports grants from Amgen, grants from Bristol-Myers Squibb, grants from Pfizer, grants from Janssen, grants from Bayer, grants from Bayer, grants from Novartis, grants from the Hong Kong Research Grants Council, grants from the Hong Kong Health and Medical Research Fund, grants from National Institute for Health Research in England, grants from European Commission, grants from National Health and Medical Research Council in Australia, outside the submitted work; and Also received speaker fee from Janssen and Medice in previous 3 years.

The other authors declared no conflict of interest.

Author contributions

X Li had full access to all data in the study and accepts responsibility for the integrity of the data and the accuracy of the data analysis.

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Reference

1. The World Health Organization. The top 10 causes of death. 2018. https://www.who.int/en/news-room/fact-sheets/detail/the-top-10-causes-of-death (accessed Mar 6, 2020).

2. Naghavi M, Abajobir AA, Abbafati C, et al. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet (London, England)* 2017; **390**: 1151-210.

3. Mirsaeidi M, Schraufnagel D. Pneumococcal Vaccines: Understanding Centers for Disease Control and Prevention Recommendations. *Annals of the American Thoracic Society* 2014; **11**: 980-5.

4. Centers for Disease Control and Prevention. Pneumococcal Home. Global Pneumococcal Disease and Vaccine. 2018. https://www.cdc.gov/pneumococcal/global.html#disease (accessed May 25, 2020).

5. Olarte L, Barson WJ, Barson RM, et al. Pneumococcal pneumonia requiring hospitalization in US children in the 13-valent pneumococcal conjugate vaccine era. *Clinical Infectious Diseases* 2017; **64**: 1699-704.

6. Koshy E, Murray J, Bottle A, Sharland M, Saxena S. Impact of the seven-valent pneumococcal conjugate vaccination (PCV7) programme on childhood hospital admissions for bacterial pneumonia and empyema in England: national time-trends study, 1997–2008. *Thorax* 2010; **65**: 770.

7. Mackenzie GA, Hill PC, Sahito SM, et al. Impact of the introduction of pneumococcal conjugate vaccination on pneumonia in The Gambia: population-based surveillance and case-control studies. *The*

Lancet Infectious Diseases 2017; **17**: 965-73.

8. Nair H, Watts AT, Williams LJ, et al. Pneumonia hospitalisations in Scotland following the introduction of pneumococcal conjugate vaccination in young children. *BMC Infectious Diseases* 2016; **16**: 390.

9. Okasha O, Rinta-Kokko H, Palmu AA, Ruokokoski E, Jokinen J, Nuorti JPJT. Population-level impact of infant 10-valent pneumococcal conjugate vaccination on adult pneumonia hospitalisations in Finland. *Thorax* 2018; **73**: 262-9.

10. Fathima P, Gidding HF, McIntyre PB, et al. Effectiveness of pneumococcal conjugate vaccine against hospital admissions for pneumonia in Australian children: a retrospective, population-based, record-linked cohort study. *The Lancet Child & adolescent health* 2019; **3**: 713.

11. Silaba M, Ooko M, Bottomley C, et al. Effect of 10-valent pneumococcal conjugate vaccine on the incidence of radiologically-confirmed pneumonia and clinically-defined pneumonia in Kenyan children: an interrupted time-series analysis. *The Lancet Global health* 2019; **7**: e337-e46.

12. Centre for Health Protection. Scientific Committee on Vaccine Preventable Diseases. Update d Recommendations on the Use of 13-valent Pneumococcal Conjugate Vaccine in Childhood Immunis ation Programme. 2019. https://www.chp.gov.hk/files/pdf/updated_recommendation_on_the_use_of_pcv3_in_hkcip_march2019_accessibility.pdf (accessed Mar 25, 2020).

13. Li X, Blais J, Wong I, et al. Population-based estimates of the burden of pneumonia hospitalizations in Hong Kong, 2011–2015. *Eur J Clin Microbiol Infect Dis* 2019; **38**: 553-61.

14. Center for Health Protection, Department of Health, and The Government of Hong Kong Special Administrative Region. Number of deaths by leading causes of death, 2001 - 2018. 2018. https://www.chp.gov.hk/en/statistics/data/10/27/380.html (accessed Mar 6, 2020).

15. Census and Statistics Department. Thematic Household Survey Report No. 71. Hong Kong. https://www.statistics.gov.hk/pub/B11302712020XXXXB0100.pdf.

16. Wong AY, Wong IC, Chui CS, et al. Association Between Acute Neuropsychiatric Events and Helicobacter pylori Therapy Containing Clarithromycin. *JAMA internal medicine* 2016; **176**: 828-34.

17. Cheung KS, Chan EW, Wong AYS, Chen L, Wong ICK, Leung WK. Long-term proton pump inhibitors and risk of gastric cancer development after treatment for Helicobacter pylori: a population-based study. *Gut* 2018; **67**: 28-35.

18. Chui CSL, Cowling BJ, Lim WW, et al. Patterns of Inpatient Antibiotic Use Among Public Hospitals in Hong Kong from 2000 to 2015. *Drug Saf* 2020; **43**: 595-606.

19. Lau WCY, Chan EW, Cheung C-L, et al. Association Between Dabigatran vs Warfarin and Risk of Osteoporotic Fractures Among Patients With Nonvalvular Atrial Fibrillation. *JAMA* 2017; **317**: 1151-8.

20. Man KKC, Chan EW, Ip P, et al. Prenatal antidepressant use and risk of attention-deficit/hyperactivity disorder in offspring: population based cohort study. *BMJ* 2017; **357**: j2350.

21. Jandoc R, Burden AM, Mamdani M, Lévesque LE, Cadarette SM. Interrupted time series analysis in drug utilization research is increasing: systematic review and recommendations. *Journal of Clinical Epidemiology* 2015; **68**: 950-6.

22. Lagarde M. How to do (or not to do) … Assessing the impact of a policy change with routine longitudinal data. *Health Policy and Planning* 2012; **27**: 76-83.

23. Bottomley C, Scott JAG, Isham V. Analysing Interrupted Time Series with a Control. *Epidemiologic Methods*. 2019; **8**: 20180010.

24. Xiao H, Augusto O, Wagenaar BH. Reflection on modern methods: a common error in the segmented regression parameterization of interrupted time-series analyses. *International Journal of Epidemiology* 2020.

25. Census and Statistics Department. The Government of the Hong Kong Special Administrative Region. 2020. https://www.censtatd.gov.hk/hkstat/sub/sp150.jsp?subjectID=150&tableID=002&ID=0&productType=8 (accessed June 2, 2020).

26. Wu P, Goldstein E, Ho L-M, et al. Excess mortality impact of two epidemics of pandemic influenza A(H1N1pdm09) virus in Hong Kong. *Influenza Other Respir Viruses* 2014; **8**: 1-7.

27. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of

interrupted time series studies in medication use research. *Journal of Clinical Pharmacy and Therapeutics* 2002; **27**: 299-309.

28. Newey WK, West KD. Automatic Lag Selection in Covariance Matrix Estimation. *The Review of Economic Studies* 1994; **61**: 631-53.

29. Cruz M, Gillen DL, Bender M, Ombao H. Assessing health care interventions via an interrupted time series model: Study power and design considerations. *Statistics in medicine* 2019; **38**: 1734-52.

30. Simonsen L, Taylor RJ, Schuck-Paim C, Lustig R, Haber M, Klugman KP. Effect of 13-valent pneumococcal conjugate vaccine on admissions to hospital 2 years after its introduction in the USA: a time series analysis. *The Lancet Respiratory Medicine* 2014; **2**: 387-94.

31. Pelton SI, Bornheimer R, Doroff R, Shea KM, Sato R, Weycker D. Decline in Pneumococcal Disease Attenuated in Older Adults and Those With Comorbidities Following Universal Childhood PCV13 Immunization. *Clinical Infectious Diseases* 2019; **68**: 1831-8.

32. Faye PM, Sonko MA, Diop A, et al. Impact of 13-Valent Pneumococcal Conjugate Vaccine on Meningitis and Pneumonia Hospitalizations in Children aged< 5 Years in Senegal, 2010–2016. *Clinical Infectious Diseases* 2019; **69**: S66-S71.

33. Lau WCY, Bielicki J, Tersigni C, et al. All-cause pneumonia in children after the introduction of pneumococcal vaccines in the United Kingdom: A population-based study. *Pharmacoepidemiology and Drug Safety* 2019; **28**: 821-9.

34. Berglund A, Ekelund M, Fletcher MA, Nyman LJPO. All-cause pneumonia hospitalizations in children< 2 years old in Sweden, 1998 to 2012: impact of pneumococcal conjugate vaccine introduction. *PLoS One* 2014; **9**.

35. Griffin MR, Mitchel E, Moore MR, Whitney CG, Grijalva CG. Declines in Pneumonia Hospitalizations of Children Aged <2 Years Associated with the Use of Pneumococcal Conjugate Vaccines — Tennessee, 1998–2012. *MMWR Morbidity and Mortality Weekly Report* 2014; **63**: 995-8.

36. Andrade AL, Afonso ET, Minamisava R, et al. Direct and indirect impact of 10-valent pneumococcal conjugate vaccine introduction on pneumonia hospitalizations and economic burden

in all age-groups in Brazil: A time-series analysis. *PLoS One* 2017; **12**.

37. Ladhani SN, Collins S, Djennad A, et al. Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000–17: a prospective national observational cohort study. *The Lancet Infectious Diseases* 2018; **18**: 441-51.

38. Lo SW, Gladstone RA, van Tonder AJ, et al. Pneumococcal lineages associated with serotype replacement and antibiotic resistance in childhood invasive pneumococcal disease in the post-PCV13 era: an international whole-genome sequencing study. *The Lancet Infectious Diseases* 2019; **19**: 759-69.

39. Tai SS. Streptococcus pneumoniae Serotype Distribution and Pneumococcal Conjugate Vaccine Serotype Coverage among Pediatric Patients in East and Southeast Asia, 2000-2014: a Pooled Data Analysis. *Vaccines* 2016; **4**.

40. Chan KCC, Subramanian R, Chong P, et al. Pneumococcal carriage in young children after introduction of PCV13 in Hong Kong. *Vaccine* 2016; **34**: 3867-74.

41. Liyanapathirana V, Nelson EA, Ang I, Subramanian R, Ma H, Ip M. Emergence of serogroup 15 Streptococcus pneumoniae of diverse genetic backgrounds following the introduction of pneumococcal conjugate vaccines in Hong Kong. *Diagnostic microbiology and infectious disease* 2015; **81**: 66-70.

42. Centre for Health Protection. Department of Health. Notifiable Infectious Diseases. https://www.chp.gov.hk/en/statistics/data/10/26/43/3829.html (accessed June 26, 2019).

43. Joseph C, Togawa Y, Shindo N. Bacterial and viral infections associated with influenza. *Influenza Other Respir Viruses* 2013; **7 Suppl 2**: 105-13.

44. Yang L, Chan KP, Wong CM, et al. Comparison of influenza disease burden in older populations of Hong Kong and Brisbane: the impact of influenza and pneumococcal vaccination. *BMC Infectious Diseases* 2019; **19**: 162.

45. Centre for Health Protection. Department of Health. Statistics on Vaccination Programmes in the Past 3 years. https://www.chp.gov.hk/en/features/102226.html (accessed Sept 14, 2020).

46. World Health Organization. Vaccine-Preventable Diseases Surveillance Standards. Pneumococcus. https://www.who.int/immunization/monitoring_surveillance/burden/vpd/WHO_SurveillanceVaccinePreventable_17_Pneumococcus_R2.pdf?ua=1, (accessed Sept 14, 2020).

47. Centre for Health Protection. Department of Health. Communicable Diseases Watch. Review of Pneumococcal Vaccination and Invasive Pneumococcal Disease in Hong Kong. https://www.chp.gov.hk/files/pdf/cdw_v15_1.pdf (accessed Sept 14, 2020).

48. Qiu H, Sun S, Tang R, Chan K-P, Tian L. Pneumonia Hospitalization Risk in the Elderly Attributable to Cold and Hot Temperatures in Hong Kong, China. *American Journal of Epidemiology* 2016; **184**: 570-8.