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Influenza as a trigger for cardiovascular disease: An investigation of serotype, subtype and geographic location

D.C. Pearce[a,b,*], J.M. McCaw[a,c,d], J. McVernon[a,c], J.D. Mathews[a]

[a] Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, Level 3, 207 Bouverie Street, The University of Melbourne, Victoria 3010, Australia

[b] Faculty of Science & Technology, Federation University Australia, University Drive, Mt Helen, Victoria 3350, Australia

[c] Modelling and Simulation, Infection and Immunity Theme, Murdoch Childrens Research Institute, 9th floor, The Royal Children's Hospital, 50 Flemington Road, Parkville, Victoria 3052, Australia

[d] School of Mathematics and Statistics, Level 3, Old Geology South, The University of Melbourne, Victoria 3010, Australia

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ABSTRACT

Background: Seasonal peaks of influenza and cardiovascular disease tend to coincide. Many excess deaths may be triggered by influenza, and the severity of this effect may vary with the virulence of the circulating influenza strain and host susceptibility. We aimed to explore the association between hospital admissions for influenza and/or pneumonia (IP) and acute myocardial infarction (AMI) or ischaemic heart disease (IHD) in Queensland, Australia, taking into account temporal and spatial variation of influenza virus type and subtype in 2007, 2008 and 2009.

Methods: This ecological study at Statistical Subdivision level (SSD, $n=38$) used linked patient-level data. For each study year, Standardized Morbidity Ratios (SMRs) were calculated for hospital admissions with diagnoses of IP, AMI and IHD. We investigated the associations between IP and AMI or IHD using spatial autoregressive modelling, adjusting for socio-demographic factors.

Results: Spatial autocorrelation was detected in SMRs, possibly reflecting underlying social and behavioural risk factors, but consistent with infectious disease spread. SMRs for IP were consistently predictive of SMRs for AMI and IHD when adjusted for socioeconomic status, population density and per cent Indigenous population (coefficient: 0.707, 95% confidence interval (CI): 0.318 – 1.096; 0.553, 0.222 – 0.884; 0.598, 0.307 – 0.888 and 1.017, 0.711 – 1.323; 0.650, 0.342 – 0.958; 1.031, 0.827 – 1.236) in 2007, 2008 and 2009, respectively.

Conclusions: This ecological study provides further evidence that severe respiratory infections may trigger the onset of cardiovascular events, implicating the influenza virus as a contributing factor.

1. Introduction

Seasonal peaks of all-cause and cardiovascular mortality coincide with seasonal peaks in influenza and pneumonia (Collins, 1932; Manfredini et al., 2009; Reichert et al., 2004). Deferred mortality from cardiovascular disease may also be attributable to influenza infections due to the longer-term consequences of autoimmune inflammatory mechanisms associated with "cytokine storms" triggered in response to an initial exposure to influenza, and boosted by re-exposure (Ahmed et al., 2007; Azambuja et al., 2002; Gurevich, 2005; Mathews et al., 1974). Many excess seasonal deaths, including those not attributed to influenza or pneumonia, may be triggered by influenza, and the severity of this effect has previously been suggested to vary with the circulating influenza strain (Reichert et al., 2004).

The virulence of influenza A viruses may vary due to antigenic drift or re-assortment between human and animal influenza A viruses, enabling the virus to escape host immunity (Schrauwen et al., 2014). Conversely, pre-existing immunity may reflect prior influenza infection (Mathews et al., 2010). Chaves et al. (2013) detected differences in disease severity between co-circulating influenza A(H1N1) pdm09,

Abbreviations: ABS, Australian Bureau of Statistics; ASGC, Australian Standard Geographical Classification; GDA94, Geocentric Datum of Australia with geodetic coordinates computed in 1994; NOCS, Notifiable Conditions System; QHAPDC, Queensland Hospital Admitted Patient Data Collection; SARAR, spatial-autoregressive models with spatial-autoregressive errors; SEIFA, Socio-Economic Indexes for Areas; SSD, Statistical Subdivision; SLA, Statistical Local Area

* Corresponding author at: Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, Level 3, 207 Bouverie Street, The University of Melbourne, Victoria 3010, Australia.

E-mail addresses: dpearce@unimelb.edu.au (D.C. Pearce), jamesm@unimelb.edu.au (J.M. McCaw), j.mcvernon@unimelb.edu.au (J. McVernon), mathewsj@unimelb.edu.au (J.D. Mathews).

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A(H3N2) and B viruses during the 2010–2011 season; however, patients with underlying medical conditions had more severe outcomes irrespective of the infecting strain.

Several observational studies have suggested a causal association between influenza activity and ischaemic heart disease. Gwini et al. (2011) found a reduction in the relative incidence of acute myocardial infarction (AMI) following influenza vaccination, while Clayton et al. (2008) showed that myocardial infarction and stroke risks were increased within 7 days of respiratory infection. Autopsy-confirmed coronary heart disease was increased in the 10 weeks following seasonal influenza activity (Madjid et al., 2007). Further, a peak in incidence of AMI was detected during the second wave of the 2009 influenza pandemic in a non-winter month (Foster et al., 2013).

Seasonal changes in absolute humidity have been shown to influence the onset and transmission of epidemic and pandemic influenza outbreaks (Shaman et al., 2011). Queensland, Australia, is a large state, covering multiple climate zones: tropical, subtropical, hot arid and warm temperate (Queensland Government, Department of Housing and Public Works, 2012). Cardiovascular disease, particularly ischaemic heart disease (IHD), contributes substantially to the health gap between Indigenous and non-Indigenous Australians (Vos et al., 2009). Indigenous Australians, comprising 3.6% of the Queensland population in 2006, tend to live in remote and northern areas (Australian Bureau of Statistics (ABS), 2007), and in 2009 were disproportionately affected by the A(H1N1) influenza pandemic (Harris et al., 2010). Queensland is therefore an ideal location to investigate the spread of influenza and its implications for cardiovascular disease.

Uncontrolled confounding, even in individual-level prospective case control studies, may bias associations detected between influenza infection, influenza vaccination and ischaemic heart disease (Rogawski et al., 2014). However, if an hypothesised causal pathway is strong and biologically-plausible, an ecological study design can allow for social and environmental determinants of health behaviours and outcomes that vary between geographic locations when randomised control trials are inappropriate or impracticable (Elliott and Wartenberg, 2004; Tu and Ko, 2008). Socioeconomic status is likely to confound ecological studies (Elliott and Wartenberg, 2004), and lower socioeconomic status has been found to increase the risk of hospitalisation with influenza-related illness (Tam et al., 2014) and onset of cardiovascular disease (Clark et al., 2009).

We conducted an ecological study to determine if Standardized Morbidity Ratios (SMRs) for hospital admissions for influenza and/or pneumonia (IP) were predictive of SMRs for AMI and IHD, using individual-level hospital admission record-linkage data aggregated to geographic area of residence for the years 2007, 2008 and 2009, when the dominant circulating influenza virus was influenza A(H3N2), influenza B, and pandemic influenza A(H1N1), respectively (Harris et al., 2010; Kaczmarek et al., 2010; Owen et al., 2008), while adjusting for geographic location, social and demographic factors.

2. Materials and methods

2.1. Data sources

2.1.1. Hospital admission data

We used de-identified data from the Queensland Hospital Admitted Patient Data Collection (QHAPDC) provided by the Integration and Linkage Unit, Health Statistics Centre, Queensland Health. Records were selected if patients had any diagnosis codes (International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification (ICD-10-AM)) for influenza or pneumonia (J09-J18), IHD (I20-I25) or cerebrovascular disease (I60-I69) when admitted to a public hospital aged 40 years or more, and further linked to all previous and subsequent admission records. Admissions for influenza (J09-J11) or AMI (I21) were also identified. Each record was dated by week of admission and linked to Statistical Local Area (SLA) of residence at time of admission.

2.1.2. Study time frame

Linked records were available from 1 July 2003 through 30 June 2010. However, because of our interest in influenza, for this study we used patient data from calendar years 2007, 2008 and 2009, when laboratory tests for the diagnosis of influenza had been more frequently made. In 2007 influenza A(H1N1) virus co-circulated with A(H3N2); in 2008 influenza B predominated; 2009 was the A(H1N1) pandemic year (Harris et al., 2010; Kaczmarek et al., 2010; Owen et al., 2008).

2.1.3. Laboratory confirmed influenza diagnoses

Summary data for Queensland were also provided on influenza serotyping, irrespective of hospital admission, from the Notifiable Conditions System (NOCS) database. Counts of laboratory confirmed influenza cases were aggregated by SLA of residence and week of notification for 2009. Laboratory-based diagnoses were also linked to QHAPDC data but not all cases assigned diagnostic codes of J09-J11 underwent serotyping.

2.1.4. Demographic data

Population numbers were available from the 2006 census by SLA, gender, age in 5 year groups, and Indigenous status (ABS, 2006). The percentage of the population self-reported as Indigenous, or Aboriginal and Torres Strait Islander (ATSI), aged 40 years or older was calculated (ABS, 2006, 2007). Data were subsequently aggregated to Statistical Subdivision (SSD) level, next in the geographical hierarchy (ABS, 2008b). Population density was calculated as the ratio of total persons to SSD area in square kilometres.

Socio-Economic Indexes for Areas (SEIFA) were obtained for 2006 (ABS, 2008a) at SLA level, the largest spatial unit for which SEIFA scores were produced (ABS, 2008b). Australian deciles of the Index of Relative Socio-Economic Advantage and Disadvantage were aggregated from SLA to SSD level using the median score as an approximate indicator of socioeconomic status.

2.1.5. Climate data

Meteorological factors in Queensland are highly correlated (Hu et al., 2012). Since humidity influences influenza virus survival and transmission (Shaman et al., 2011), we used humidity (vapour pressure) in hectopascals (hPa) from the Bureau of Meteorology (Bureau of Meteorology, 2014) and estimated summary values at SSD level. See Supplementary Methods for details.

2.2. Geographic framework

Patient residence at time of admission was georeferenced to SLA according to the current Australian Standard Geographical Classification (ASGC) definition. The Australian census is quinquennial, with SLA coding corresponding to 2001, 2006 and 2011 censuses. We used 2006 SLA digital boundaries (ABS, 2011a) for this study (N = 477) for consistency. For details of mapping 2001 (ABS, 2012) and 2011 (ABS, 2011b) SLA boundaries to 2006, see the Supplementary Methods. ArcGIS 10.2.1 geographic information system software (Environmental Systems Research Institute, (ESRI), Redlands, California, 2013) was used to manipulate digital boundaries and geospatial data.

2.3. Standardised morbidity ratios

SMRs for years 2007, 2008 and 2009 were calculated using total admissions for each diagnosis. Influenza admission data was sparse at SLA level, with zero cases recorded for numerous SLAs, and also when aggregated to Statistical Subdivision (SSD) level; only in 2009 were influenza cases reported for all Queensland SSDs and used to calculate SMRs. Observed numbers of admissions for IP, AMI and IHD were calculated by SSD for each study year. Rates of admissions for each