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Estimating the contribution of influenza to hospitalisations in New Zealand from 1994 to 2008

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ABSTRACT

Background: Influenza has a substantially but poorly measured impact on population health. Estimating its true contribution to hospitalisations remains a challenge.
Methods: We used simple and comprehensive negative binomial regression models with weekly counts of hospitalisations and isolates of influenza A, B and respiratory syncytial virus for the period 1994– 2008.
Results: The estimated annual national average number of hospitalisations attributable to influenza was 822.1(95% CI: 815.3, 828.9) for pneumonia and influenza, 1861.3 (95% CI: 1842.9, 1879.7) for respiratory illness, 12.1 (95% CI: 2.6, 21.6) for circulatory illness, 2260.0 (95% CI: 2212.2, 2307.8) for all medical illness and 2419.9 (95% CI: 2356.4, 2483.4) for all causes. The contribution of influenza to total hospitalisations was about nine times larger than indicated by routine discharge data. New Zealanders 80 years of age and older had the highest annual excess rates of influenza-related hospitalisations (327.8 per 100,000); followed by infants under 1 year (244.5 per 100,000). Estimated influenza hospitalisation rates were also markedly higher in Pacific (83.3 per 100,000) and Māori (80.0 per 100,000) compared with European/Others (58.1 per 100,000).

Respiratory illness was the major contributor to all cause hospitalisations attributed to influenza accounting for 77%. Influenza hospitalisations included only a negligible contribution from circulatory illness.
Conclusion: These findings support efforts to reduce the impact of influenza, particularly for the most vulnerable population groups highlighted here. Analysis of the cost-effectiveness of such interventions needs to consider these higher modelled estimates of disease impact.

1. Background

Influenza virus is responsible for an important proportion of the global burden of diseases [1,2]. In New Zealand, respiratory infections (including influenza) are the largest component of infectious disease hospitalisations, accounting for 38.5% of acute infectious disease hospitalisations and 9.5% of all acute admissions over the 1989–2008 period [3]. Although influenza is a common respiratory infection, it is not systemically tested for when patients are hospitalised, even for respiratory illnesses. The lack of laboratory results, indicative signs or supporting symptoms or ambiguous aetiology [4–7] mean many cases are not identified.

Much of the disease burden is thought to come from triggering respiratory or circulatory events (notably myocardial infarctions and strokes) [8] or other medical events [9] where an influenza diagnosis is not suspected or investigated. Consequently, the recorded contribution of influenza to hospitalisations is likely to greatly underestimate the true burden of this largely preventable disease [10,11].

In a number of international studies, statistical methods such as Poisson or negative binomial regression modelling have been applied to fill in the anticipated gaps and estimate hospitalisations attributable to influenza [7,12,13]. The reported rates vary by population, place and year of study. For example, in Australia, from 1998 to 2005 the average annual rate of admission for influenza-associated respiratory illness was highest with 444.1 per 100,000 in those 85 years of age and older and lowest in children 5–14 years old at −1.2 per 100,000 [14]. This present study thus seeks to estimate the total impact of influenza on hospitalisations for all age

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and ethnic groups in New Zealand over the pre-pandemic period of 1994 to 2008.

2. Method

2.1. Data sources

Weekly counts of hospitalisations were obtained from the national hospitalisation dataset for the 15 year period from 1994 to 2008. Influenza hospitalisations were broadly categorised based on the International Classification of Diseases (ICD) 9th Revision (ICD-9) (to July 1999) and 10th Revision (ICD-10) as influenza and pneumonia (J09-J18, 480-488), respiratory (J00-J99, 460-519), circulatory (I00-I99, 380-459), medical illness (A00-N99, R00-R99, 001-629, 680-739, 780-799) and all causes (including childbirth, perinatal, congenital, injury) (A00–Y99, 001–999). Thus, "pneumonia and influenza" hospitalisation is a subset of respiratory illness and both respiratory and circulatory illness are a subset of medical illness. The analysis was limited to principal causes of hospitalisation, which were defined as the diagnosis code assigned after discharge as chiefly responsible for occasioning an episode of admitted patient care, an episode of residential care or attendance at the healthcare establishment. Hospitalisation age was disaggregated into nine groups (all ages; under 1; 1–4; 5–19; 20–34; 35–49; 50–64; 65–79; 80+). Ethnicity was classified into three groups (Māori, Pacific and European/Others) using prioritised ethnicity. Statistics New Zealand defines that "Prioritisation is a classification which assigns the ethnicity of a person who has given multiple responses to just one ethnicity" [15].

We interpolated and extrapolated population counts for every week in the study period from New Zealand Census of Population and Dwellings (Statistics New Zealand) population data for 1996, 2001, 2006 and 2013.

We used weekly counts of isolates of influenza A (H1N1, H3N2 and A not-subtyped) and influenza B and respiratory syncytial virus (RSV) from the virology weekly report of the Institute of Environmental Science & Research (ESR) for the period 1994 to 2008. The four regional laboratories (Auckland, Waikato, Wellington and Christchurch) and the WHO National Influenza Centre at ESR virology laboratory conduct influenza and other virus surveillance in New Zealand. These laboratories report nationwide inpatient and outpatient virus diagnoses (including influenza A and B, and RSV) to ESR. Like influenza, RSV infections are hard to detect due to a lack of specific symptoms and insufficient information in the medical record [11,16]. The Southern Hemisphere Influenza and Vaccine Effectiveness Research and Surveillance (SHIVERS) has found that RSV contributes up to about one third of influenza like illnesses in New Zealand [17]. RSV was added as a model input to prevent confounding with influenza hospitalisations [14].

2.2. Statistical methods

For each cause of hospitalisation category (influenza and pneumonia; respiratory; circulatory; all medical; and all causes), age grouping (all ages; under 1; 1–4; 5–19; 20–34; 35–49; 50–64; 65–79; 80+) and ethnic grouping (Māori, Pacific, European/Others), negative regression models were applied to estimate influenza-related hospitalisations. All statistical analysis was carried out with R software version 3.1.0.

The hospital dataset has annual outlying low points during Christmas and New Year which coincide with New Zealand summer holidays. Hence, the two weeks around Christmas and New Year were excluded and the models were run on a 50 week year.

A simple initial model was run based on that used in the USA and Australia [13,14] with the predicted number of hospitalisations per week estimated as:

The simple model:

$$Y_i = \text{offset (population)} + \beta_1(t_i) + \beta_2(t_i^2) + \beta_3(t_i^3) + \beta_4[\sin(2t_i\pi/50)] + \beta_5[\cos(2t_i\pi/50)] + \beta_6[A] + \beta_7[B] + \beta_8[RSV]$$

As our data contain only positive tests for influenza and RSV we developed a comprehensive model, which allowed for the possibility of increased testing by adding an interaction term for year separately with each virus type.

The comprehensive model:

$$Y_i = \text{offset (population)} + \beta_1(t_i) + \beta_2(t_i^2) + \beta_3(t_i^3) + \beta_4[\sin(2t_i\pi/50)] + \beta_5[\cos(2t_i\pi/50)] + \beta_6[A] + \beta_7[B] + \beta_8[RSV] + \beta_9[A]^{*}\text{year} + \beta_{10}[B]^{*}year + \beta_{11}[RSV]^{*}year$$

In these models subscript i is the week number; Y_i is the output of the modelling process for that week (predicted hospitalisation count); and t_i represents number of weeks since the start of the modelling period. For the estimated regression parameters, $\beta_1(t_i)$ models linear trend and $\beta_2(t_i^2) + \beta_3(t_i^3)$ represent nonlinear time trends. $\beta_4[\sin(2t_i\pi/50)]$ and $\beta_5[\cos(2t_i\pi/50)]$ are proxy parameters of weekly fluctuations of virus. $\beta_6[A]$ and $\beta_7[B]$ are the weekly influenza *A* and *B* counts, respectively; and $\beta_8[RSV]$ is the weekly RSV counts. In the comprehensive model $\beta_9[A]^{*}year$, $\beta_{10}[B]^{*}year$ and $\beta_{11}[RSV]^{*}year$ allow for changes in the number of virus tests by year.

The estimated number of influenza related hospital admission was calculated as the discrepancy between the number estimated by the model and the number estimated by the model if virus counts were set to zero. The results were expressed as hospitalisation numbers or hospitalisation rates per 100,000 populations. The annual mean number of influenza related hospitalisations and rates per 100,000 were also calculated.

3. Results

The estimated annual average number of hospitalisations attributable to influenza for pneumonia and influenza (P&I) and respiratory illness were 743.8 (95% CI: 737.8, 749.8) and 1679.2 (95% CI: 1663.1, 1695.3), and 822.1 (95% CI: 815.3, 828.9) and 1861.3 (95% CI: 1842.9, 1879.7) for the simple and the comprehensive models, respectively. The estimated average rates per 100,000 people for P&I and respiratory illness respectively were 19.2 and 43.3 for the simple model and 21.2 and 48.0 for the comprehensive model. The numbers and rates estimated with the comprehensive model were consistently higher than for the simple one (Table 1).

Hospitalisations varied by study year. Year 1996 had the highest estimated number of influenza-associated hospitalisations, followed by 1997 and 2003. Our estimates of P&I and respiratory influenza-associated hospital admissions in the period 1994 to 2008 were 2.8 and 6.6 (for comprehensive model) times higher than the observed influenza hospitalisations from the National Hospitalisations Dataset (Table 1).

Fig. 1 illustrates the yearly influenza virus isolates (influenza A and influenza B) from virology weekly reports by the Institute of Environmental Science & Research Limited (ESR), weekly number of respiratory admissions and estimates of influenza-associated respiratory illness hospitalisation (by simple and comprehensive models) for the period 1994–2008 in New Zealand.

Influenza A virus was dominant in 12 seasons 1994, 1996, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2006 and 2007. In contrast, influenza B was a minor component in the period 1994–2008, except in 1995, 2005 and 2008.

Hospitalisations (both observed and estimated numbers) and virus isolates differed by week and reached a peak in winter each year (for the 15 years modelled, peaks were in July in 9 years, in