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Analysis of potential changes in seriousness of influenza A and B viruses in Hong Kong from 2001 to 2011

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SUMMARY

Continued monitoring of the seriousness of influenza viruses is a public health priority. We applied time-series regression models to data on cardio-respiratory mortality rates in Hong Kong from 2001 to 2011. We used surveillance data on outpatient consultations for influenza-like illness, and laboratory detections of influenza types/subtypes to construct proxy measures of influenza activity. In the model we allowed the regression coefficients for influenza to drift over time, and adjusted for temperature and humidity. The regression coefficient for influenza A(H3N2) increased significantly in 2005. The regression coefficients for influenza A(H1N1) and B were relatively stable over the period. Our model suggested an increase in seriousness of A(H3N2) in 2005, the year after the appearance of the A/Fujian/411/2002(H3N2)-like virus when the drifted A/California/7/2004(H3N2)-like virus appeared. Ongoing monitoring of mortality and influenza activity could permit identification of future changes in seriousness of influenza virus infections.

Key words: Death, human influenza, seriousness.

INTRODUCTION

When a new strain of influenza virus emerges, one of the public health priorities is to assess the risk posed by the new strain which is commonly measured by the impact and seriousness of infection associated with the virus. The impact of infection is often quantified as the cumulative incidence of infection or excess disease burden. It is determined by the transmissibility of the new strain, the seriousness of individual infections, and the degree to which any control measures are effective. The seriousness of infection, i.e. measuring the potential of a virus to cause severe disease is measured in various ways, and one measure of seriousness is the infection fatality risk, which is defined as the probability of death among people infected by the virus [1]. In non-temperate regions, the recommended approach to estimate excess influenza mortality is via regression modelling [2, 3].

In the linear regression model for mortality rates, a proxy measure of incidence of infection is derived from surveillance data and therefore the regression coefficient for this proxy measure of influenza activity (i.e. the increase in the expected mortality rates per unit increase in influenza activity) is, in theory,

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directly proportional to the infection fatality risk [4]. In a previous study, we examined the average associations between influenza subtypes and age-specific excess mortality over a 10-year period [2]. In this study, we investigated drift over time in the regression coefficients for influenza activity to assess potential changes in the association between mortality rates and influenza activity.

METHODS

Sources of data

Cardio-respiratory deaths (ICD-10: I00-J99) and the annual mid-year populations from 2001 to 2011 were obtained from the Hong Kong Government Census and Statistics Department [5]. Surveillance data on influenza-like illness from around 50 sentinel general practitioners were available as the weekly proportion of outpatients reporting a fever $\geqslant 37{\cdot}8$ °C plus a cough or sore throat, along with local laboratory data on the weekly proportion of specimens from sentinel outpatient clinics and local hospitals that tested positive for influenza [6]. Data on temperature and humidity were obtained from the Hong Kong Observatory [7].

Statistical analysis

Time-series regression models were used to model influenza-associated excess deaths based on a proxy measure of local influenza activity [1, 2, 4]. Weekly type-/subtype-specific influenza activity was estimated by the product of the weekly proportion of outpatients reporting influenza-like illness and the weekly proportion of laboratory specimens that tested positive for a particular influenza type/subtype. We applied the regression model to the time series of weekly cardio-respiratory mortality rates from 2001 to 2011, excluding January–September 2003 which was affected by the severe acute respiratory syndrome (SARS) epidemic. In the regression model we included each measure of influenza type/subtype activity as a covariate, lagged by 1 week to allow for a delay between infection and death, and also adjusted for other covariates including respiratory syncytial virus activity, mean temperature and absolute humidity (see Supplementary material). As pandemic A(H1N1) virus replaced seasonal A(H1N1) virus after mid-2009, we combined seasonal A(H1N1) detections and pandemic A(H1N1) detections into a single A(H1N1) variable in the analysis. Trigonometric components were included to allow for cyclic annual seasonality of mortality rates.

In the model, we allowed two types of temporal changes in the regression coefficients for influenza type-/subtype-specific activity. First, the influenza type-/subtype-specific regression coefficients in the model were allowed to change slightly each week (i.e. drift) to reflect possible gradual changes in the association between cardio-respiratory mortality rates and influenza activity. Second, we considered the possibility of substantial and sudden changes in regression coefficients (i.e. jumps), and accordingly we pre-selected potential change points in influenza A that occurred before and after at least three influenza seasons in our study period, namely A(H3N2) in 2005 and 2007, and A(H1N1) in 2008, and used differences in the Akaike Information Criteria (AIC) as a measure of goodness-of-fit between models with different combinations of change points (Supplementary material). We did not include potential change points at the very beginning or very end of our study period due to the limited information at each boundary.

The influenza-associated excess mortality rates were calculated by subtracting the predicted mortality rate estimated from a fitted regression model setting influenza activity as zero from the predicted mortality rate from the same model based on the observed weekly influenza activity [2]. The influenza seasons were defined as time periods of at least two consecutive weeks when the proxy measure of influenza activity (including different types/subtypes) exceeded 0·005 [2]. The predominant strain in a given season was defined as any specific influenza type/subtype that comprised more than 30% of all laboratory detections of influenza in at least four consecutive weeks during an influenza season. Further details of the statistical methods are described in the Supplementary material. All analyses were conducted in R version 3.0.1 (R Foundation for Statistical Computing, Austria).

RESULTS

There were 14 influenza seasons in Hong Kong from 2001 to 2011 (excluding 2003) (Fig. 1*a*). A single influenza season was observed in 6 of the 10 years, while two seasons were observed in the remaining 4 years. The first epidemic wave of the 2009 pandemic influenza A(H1N1) [A(H1N1)pdm09] virus peaked in September–October 2009 and perturbed the usual winter-plus-summer biannual seasonality of influenza

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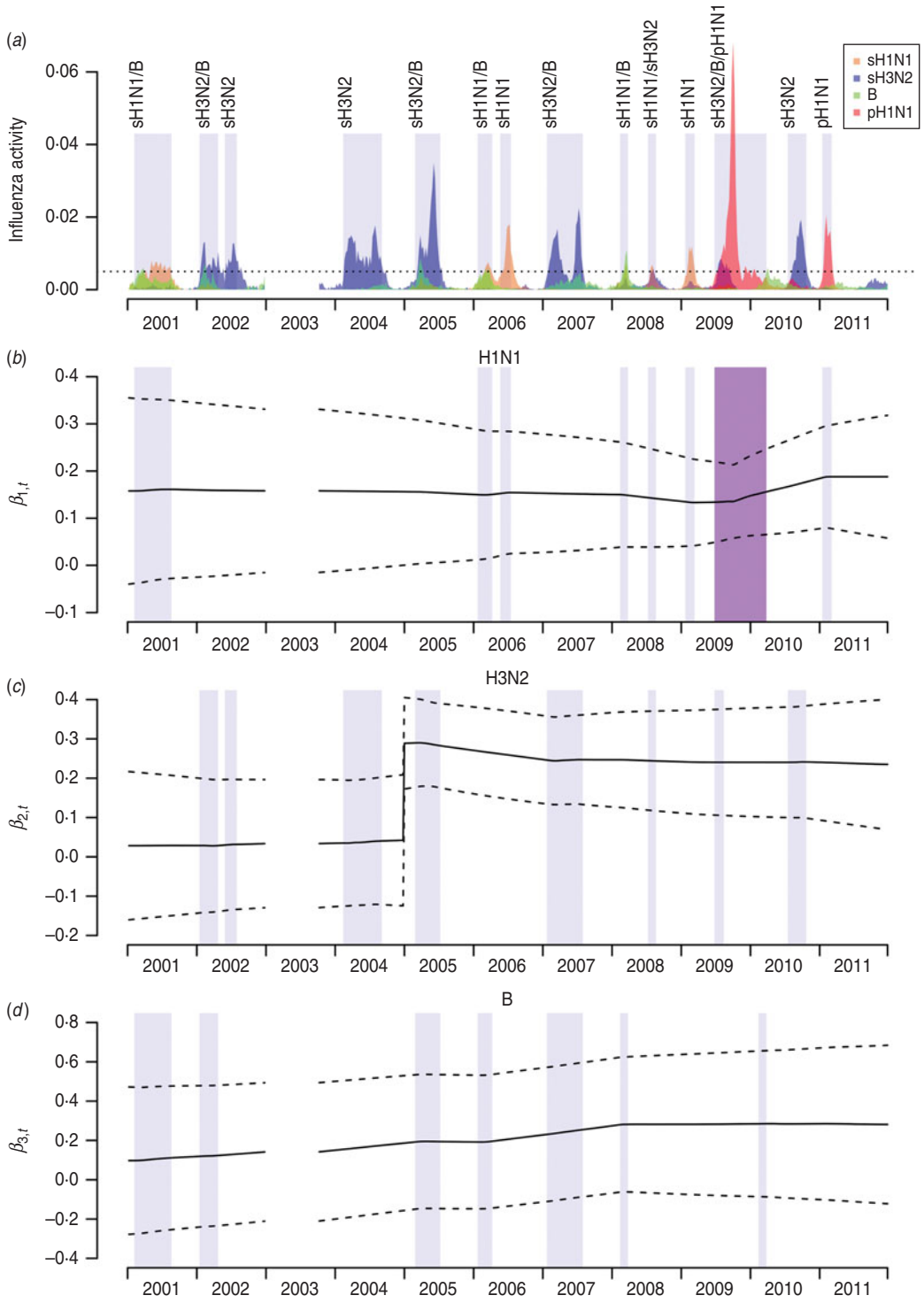

Fig. 1. Influenza activity and influenza-associated regression coefficients in Hong Kong, 2001–2011. (*a*) Weekly influenza activity for seasonal influenza A(H1N1) (yellow areas), A(H3N2) (dark blue areas), B (green areas), A(H1N1)pdm09 (red areas) and 14 influenza seasons (light blue areas). (*b*) Weekly regression coefficients (solid line) for influenza A(H1N1) with 95% confidence intervals (dashed lines). Purple area indicates the effect of an increase in laboratory capacity during A(H1N1)pdm09. (*c*) Weekly regression coefficients (solid line) for influenza A(H3N2) with 95% confidence intervals (dashed lines). (*d*) Weekly regression coefficients (solid line) for influenza B with 95% confidence intervals (dashed lines) (see Supplementary material for further details about the notation). sH1N1, Seasonal influenza A(H1N1); sH3N2, seasonal influenza A(H3N2); pH1N1, influenza A(H1N1)pdm09.

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locally, with no substantial winter season in 2010 and no summer season in 2011 (Fig. 1). Seasonal A(H3N2) virus predominated in 8/14 of the seasons. Seasonal A(H1N1) was displaced in Hong Kong as elsewhere by A(H1N1)pdm09 and in Hong Kong this occurred in mid-2009.

We fitted a range of models and examined changes in the regression coefficients for influenza A(H1N1), A(H3N2) and B viruses. We investigated three specific change points based on well-known antigenic changes in the circulating viruses [8] (B. Cowling, unpublished data, 2014), and found the model including a step change in coefficient for A(H3N2) in 2005 had the lowest AIC (Supplementary Table S2). This model was selected as our final model. We did not investigate the presence of step changes in the coefficient for A(H1N1) in 2009 or 2011 because these epidemics were too close to the end of the study period. In the final model, the regression coefficients for A(H1N1) remained fairly stable from 2001 to 2011, while there was a suggestion of an increase in the coefficient at the end of the period during the second epidemic wave of A(H1N1)pdm09 (Fig. 1*b*). The estimated regression coefficients for A(H3N2) remained constant in 2001–2004, there was a substantial step increase at the beginning of 2005 and the coefficient remained fairly stable thereafter (Fig. 1*c*). The A/Fujian/411/2002(H3N2)-like virus caused a major epidemic in Hong Kong in 2004, while the winter 2005 epidemic was dominated by the drifted A/California/7/2004 (H3N2)-like virus. The regression coefficient for influenza virus B was relatively stable over time (Fig. 1*d*).

In sensitivity analyses, we found very similar results when fitting the model to the elderly ($\geqslant$65 years) instead of overall cardio-respiratory death rates, and all-cause mortality rates instead of cardio-respiratory mortality rates (Supplementary material). However, we did not observe a step increase in the regression coefficient for H3N2 in 2005 when fitting the model to the data for adults aged $<$65 years.

DISCUSSION

We fitted a linear regression model to infer the association between influenza activity and cardio-respiratory mortality rates, and allowed the values of the regression coefficients to drift over calendar time to reflect possible changes in the association between mortality rates and influenza activity indicating potential changes in seriousness. Assuming that the influenza activity proxy is a reasonable correlate of the incidence rates of infection in the community, and assuming that infection fatality risks remain fairly constant through the course of a single epidemic, changes in the regression coefficient could be because of a change in the seriousness of the virus, or because of changes in the prevalence of risk factors for mortality. An example of the latter would be reductions in the prevalence of *Streptococcus pneumoniae* carriage following increases in pneumococcal vaccine coverage [9]. Alternatively, changes in the apparent infection fatality risk at the population level could be artefacts of changes in the age distribution of infections, since the seriousness of influenza virus infections tends to increase with age [10]. In addition, drift in the regression coefficient could occur in the absence of changes in the infection fatality risk, if for example the properties of the influenza activity metric changed due to changes in the surveillance system.

Apparent changes in the seriousness of influenza viruses from this type of analysis must therefore be interpreted with caution. Nevertheless, there are a number of reports of the increased impact of the A/Fujian/411/2002(H3N2)-like viruses that emerged globally in 2003–2004 [11], and its antigenic variant A/California/7/2004(H3N2)-like virus was responsible for a large epidemic in Hong Kong in 2005 (Fig. 1) [12]. Our results are consistent with an increased impact of this virus compared to the preceding A(H3N2) viruses including the A/Fujian/411/2002 virus, perhaps because of increased seriousness of infections, or alternatively because of an age shift in infections leading to an artefactual increase in overall severity. It is less likely that this increase could be explained by pneumococcal vaccine because coverage was around 40% in children in 2005–2009 and only increased to higher levels after the vaccine was included in the Childhood Immunization Programme in 2009. Similarly, the vaccine coverage in the elderly was low before 2009 [13]. A separate study of hospitalizations in children identified similarly high rates associated with A/Fujian/411/2002(H3N2)-like viruses and A/California/7/2004(H3N2)-like viruses in 2004 and 2005, respectively [12]. In contrast, Goldstein *et al.* reported a decline in the regression coefficient for H3N2 after 2003, which could be due to the lower impact of influenza on mortality after the introduction of pneumococcal vaccine in the USA [4, 14].

Regarding artefactual changes in the regression coefficient, the A(H1N1)pdm09 virus was associated with a much higher cumulative incidence of infection in children than seasonal viruses, and consequently

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a lower overall infection fatality risk [1, 15, 16]. The second epidemic wave of A(H1N1)pdm09 in early 2011 had a similar or higher cumulative incidence of infection in adults and therefore an apparent increase in the regression coefficient (Fig. 1*b*) may be an artefact of an age shift in the second epidemic wave rather than a change in seriousness of infection *per se*. It remains unclear whether the pandemic virus had different age-specific infection fatality risk than preceding seasonal A(H1N1) viruses [1].

There are some limitations to our work. First, given that there was insufficient length of time series for patterns to emerge near the boundaries of our study period, the changes in regression coefficient of A(H1N1) in 2006 and 2009, and A(H3N2) in 2004 were excluded in the present analysis. Second, potential changes in seriousness of influenza viruses are not the only factors associated with change in regression coefficients, and as explained above caution must exercised when interpreting the results of ecological analyses. Age-specific surveillance data were not available on patterns in influenza-like illnesses or laboratory detections and therefore we were unable to use an age-specific proxy. We therefore used the all-age proxy to represent the incidence of influenza A(H1N1) virus infection for different age groups during 2009 since we showed that age-specific temporal distributions of incidence were similar in each age group [1]. Using an AIC difference of 2 as a model selection criterion, all three models have included a change point in 2005 (Supplementary material) although we could not exclude the possibility that there was no significant change in the regression coefficient in 2005. Meanwhile, the higher R^2 statistics estimated from models with a change point in 2005 compared to the others (Supplementary material) implied changed seriousness of A(H3N2) in Hong Kong before and after 2005. Given the relatively small differences detected between different models, it may be easier to identify changes in seriousness in larger populations in which greater numbers of deaths occur. Nevertheless, our approach provides a framework for retrospective analysis of potential changes in seriousness of influenza virus infections, and further work could examine the extension of this approach to real-time prospective assessment of seriousness.

SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0950268814001472.

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DECLARATION OF INTEREST

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