Reviewer’s report

Title: Seasonal Effects of Influenza on Mortality in a Subtropical City

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Reviewer: Cecile Viboud

Reviewer’s report:

This interesting paper explores seasonal variation in the severity of influenza viruses in Hong-Kong, using a variety of mortality outcomes. In other words, the authors test the hypothesis that a given level of virus activity will have a different mortality impact depending on the season. Hong-Kong is the perfect location to test this kind of hypothesis due to the pattern of near year-round influenza activity there. The authors conclude that for most (but not all) disease categories, the influenza impact is most pronounced in winter and late spring/early summer.

I have a few comments that may help improve the interpretation of results, including differences in seasonal effect by disease category, and refine the proposed mechanism responsible for such effects.

Major Compulsory Revisions

- As the authors mention in the discussion, a confounding factor in their study is virus subtype, since different influenza subtypes are known to be associated with different mortality impact. If I understand correctly, influenza A/H3N2 is more predominant in summer in Hong-Kong (p.15), which could explain summer peaks in “excess risk” in some disease categories. Since the authors appear to have some data on the weekly proportion of H3N2, could they include this information in their model and test whether seasonal effects remain for H3N2 viruses?

- It is somewhat surprising seasonal effects vary by mortality outcome, not only in amplitude, but also in seasonal patterns. For instance, there is no evidence of seasonal effect for P&I, which is supposed to be the most specific indicator of influenza-related mortality. Also, there is a very high winter maximum of excess risk for COPD; while peaks in other disease categories are most pronounced in spring/summer (Fig 2). Is there a biological mechanism related to how influenza virus infection triggers death, directly or indirectly, which could explain these differences by disease category? Also, the fact that there is no seasonal effect on P&I is worrying – I understand that P&I provides an underestimate of influenza burden, however it is very specific and should reflect the same seasonal variations as the other death categories (unless we assume a seasonal bias in coding of deaths).

- I think generally the mechanistic explanations proposed in the discussion lack precision.

  o For instance, it is assumed that since influenza excess risk peaks in winter and spring/summer in cardio-respiratory diseases, there may be a synergistic
interaction between influenza virus infection and very hot or very cold temperatures (end of p13). However what are the average temperatures in winter, late spring and early summer in Hong-Kong, and how different are these temperatures from temperatures in autumn, a season in which a clear dip in excess risk is found (Table 2)?

- The authors propose that virulence could vary over the course of one season, as viruses drift antigenically. They cite phylogenetic evidence from New York state data (ref 26), however all New York state analyses so far have revealed that there is indeed *no* evidence of local evolution within a season – in fact that is one of the major reasons for suspecting that the Tropics could be a source of new influenza viruses. Obviously the situation in Hong-Kong could be different from that of NY, but the NY data are probably not the right data to cite here in support of local evolution within a season.

- I think the authors should distinguish between probability of infection (which may be related to antigenic drift and population immunity, and which is not what their excess risk measures) and probability of death given infection (which is related to virus pathogenicity, and is perhaps more related to what this excess risk analysis gets at, and could be mediated by internal genes and/or interaction between influenza virus and other pathogens responsible for lethal superinfections).

- Isn’t the analysis of morbidity the natural next step to attempt to distinguish between severity of disease and clinical infection?

- Separate analyses are presented for all ages and 65 yrs and over, but it appears as the results for all ages are driven by the 65+. Could the authors perform the same analyses for children (eg, under 5 ?) It would be interesting to see whether seasonal mortality effects varied by age.

- One of the sensitivity analyses considers similar seasonal effects for RSV, as I understand (p 10). Was there evidence of seasonality in excess risk for RSV as well?

Discretionary Revisions
- Did the authors consider lags for RSV and the other viruses?
- What do negative excess risk estimate mean (fig 2)? Is influenza virus infection protective against mortality in fall (Table 2)?

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

'I declare that I have no competing interests'