Reviewer’s report

Title: Effect Modification of Environmental Factors on Influenza-Associated Mortality: A Time-Series Study in Two Asian Cities

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Reviewer: Jeffrey Shaman

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This paper looks for interactive effects of environmental conditions on influenza associated mortality in Hong Kong and Guangzhou during 2004-2006. A model is built in which seasonal and trend effects of environmental conditions are controlled for and then interactions between environmental conditions and influenza incidence are accounted for with dummy variables. The authors find stronger interactive effects w.r.t all-cause and cardiorespiratory mortality than P&I mortality (though this may in part be a function there being fewer P&I mortalities).

The approach is fine, though my preference would be to see the authors also examine, present, and work from the residuals of the core model (middle of page 5). I would like to see time series of these residuals. A similar model built for weekly proportions positive for influenza (again in which seasonality and trends associated with weather are removed) should also be tested and the residuals of this presented/plotted and directly compared to/statistically analyzed with the mortality residuals. This way we see how anomalous influenza is associated with anomalous mortality.

MAJOR COMPULSORY REVISIONS

Rather than just showing the interactive effects in Table 3, it would be nice first to see how well the model at the bottom of page 5 does. Does assayed weekly positive flu explain any of the mortality indicators used (including accidental deaths)? We need the base model to know if there is good correspondence between assayed positive flu and P&I mortality before looking for interactive effects. Metrics of overall model improvement with the interactive effects should be presented.
The statistical significance of individual effects and overall model
goodness-of-fit needs to be better represented in the paper. This would
help better discriminate some of the findings. For instance, the
effects of humidity (both relative and absolute) are opposite for the
low tercile between Guangzhou and Hong Kong. This might indicate that
the effect is not meaningful; however, these effects appear large and
statistically significant for some of the city-mortality combinations.
More detailed metrics of fit would help clarify the findings.

Figure 1 and Supplement 1 are not labelled well. We don't know which
mortality is shown in each subplot. Nor is statistical significance
well represented. Different symbols should be used to denote
statistical significant effects--i.e. circle for no significance,
triangle if the percentage change in mortality is significant, and a
square if the trend from low to middle to high is significant.

Both supplements require more information than just plots. Full
explanations and figure captions are needed.

The time series shown in Supp 2 are very informative and should be in
the main paper. All-cause mortality peaks strongly in winter, but
influenza virus is not phased the same way, particularly in Hong Kong.
We should see this. In fact time series for all variables, including
all mortality groupings, should be presented.

The control mortality is not mentioned until the end of the discussion,
nor are the results for this shown, and they should be.

Per the reference to temperate absolute humidity findings. The results
of Shaman and Kohn show a nonlinear relationship between humidity and
influenza survival. If you match the humidity ranges of Hong Kong and
Guangzhou with the range of humidities tested in those lab experiments,
it appears that both cities are generally in the more humid range where
humidity has little effect on influenza survival (both are generally
above 10-14 hPa 75% of the time, see Figure 3E of Shaman and Kohn). As
a consequence, for only for a small portion of the year, during deep
winter, are conditions dry enough such that day-to-day changes in
humidity would be expected to modulate influenza survival markedly and
produce a strong a negative relationship/change in survival. This may explain the weak effect for the lower tercile of absolute humidities (not low enough humidities in these cities to produce a pronounced effect, nor is the record long enough), as well as the appearance of the opposite effect at the typical high humidities for these cities where absolute humidity has little effect on influenza (in the lab) and therefore other factors (such as heat-mediated changes to blood viscosity and intravascular coagulation) may exert more influence on influenza transmission and severity.

MINOR ESSENTIAL REVISIONS

Presentation of the numbers of cases in the 65+ and <65 groups would be helpful, as these numbers influence the statistical power of these analyses and may explain why there is an effect for 65+ (high numbers/mortality in this group), but not <65 (fewer mortalities in this group, less likely to capture an effect with just 3 years of data).

There is mention that 65% of deaths occurred in the 65+ age group, but all the data should be shown in Table 1.

The authors have 1998-2006 DH data from Hong Kong, but only 2004-2006 is used. Why? Please clarify and be more explicit in the text about the time period used in the study.

'Quartiles' should be replaced with 'terciles' throughout the text as only 3 groupings are used.

Page 13. Does a linear trend in the percentage change in mortality per 1% increase in flu across humidity terciles, suggest a linear relationship, or an exponential one (i.e. really a linear relationship with log(mortality))? 

DISCRETIONARY REVISIONS

Page 8, the statement 'whereas for Hong Kong the highest risks' should be changed to 'whereas for Hong Kong the largest changes in risk'.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published
Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interest