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: Cecile Viboud

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The paper by Yang et al is an interesting follow-up study to an article published by the same team in BMC Infect Dis in 2009, describing seasonal variation in the mortality impact of influenza in Hong-Kong. In the present study, the authors study the interaction between influenza-related mortality effects and environmental factors in two subtropical Asian cities, Hong-Kong and Guangdong.

There has been renewed interest in understanding the causes of influenza seasonality recently, especially from the perspective of the Tropics, and this paper is a nice addition to the existing literature.

I have several technical comments that will need to be addressed before the study can be published. I am especially concerned by the short length of the time series analyzed. In addition, more details should be provided on the datasets used, especially for Guangdong, since it is the first time to my knowledge that these data have been published.

Major Compulsory Revisions

1) The authors rely on 3 years of data to fit time series models, 2004-2006, which is really a bare minimum, especially given the variability in influenza seasonal cycles in Tropical locations.

a. We are now in the middle of 2011, aren’t there any data available for more recent years?

b. The Hong-Kong team has published influenza-related mortality estimates for the period 1996-2006 in the past (refs 2-3, 9). It would be particularly useful to repeat the analysis with this longer and more robust dataset, 1996-2006.

2) Can the authors provide more information about the mortality data collection process, especially in Guangdong? The authors model mortality counts, rather than mortality rates: Is the population denominator constant in these mortality surveys? What is the population really covered (just the city or a larger area)? I understand there is a large migrant population in Southern China; is it taken into account here? It may be good to highlight some of these issues for non Chinese readers.

3) Do the results change if separate terms for flu A and flu B are included in the model? We know that that the mortality impact of these two influenza subtypes differs.
4) The use of “arbitrary” cut-off values for meteorological parameters cannot be helped and is well justified in this paper. However, the authors have chosen relatively high cut-off values to define “extreme” meteorological events (p. 6, they use the 25th percentile of the distribution). The 25th percentile does not measure the extremes of a distribution. It would be useful to repeat the analysis with the 2.5th or 5th percentiles, as a sensitivity analysis. Further, have the authors thought about using “anomalies” instead of absolute values, i.e., measuring weekly deviations from the seasonal expectation?

5) It is unfortunate the authors do not present time series graphs in the main paper. I suggest they move Supp Fig 2 to the main paper and add similar plots for cardiorespiratory deaths, and P&I deaths.

6) The study by Shaman et al (Plos Bio 2010) linking influenza-related mortality with environmental factors should be cited and discussed. The first sentence of the abstract should be revised in light of this study (you could add “in the Tropics” at the end).

Minor Essential Revisions

1) Top of p5: Were meteorological data compiled for Hong-Kong and Guangdong cities proper, or for larger areas?

2) Middle of p5, typo in the definition of ns(temp_t,df). You probably mean ns(humd_t,df)

2) Suppl Fig 1 and 2 are missing a legend

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

Quality of written English: Acceptable

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 interests'