Reviewer's report

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

Version: 2 Date: 14 July 2011

Reviewer: Charlotte Warren-Gash

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Summary: This time series study set in two subtropical Asian cities aimed to explore the effect of interactions between environmental factors (temperature, absolute and relative humidity) and influenza on mortality. A significant interaction was found between high absolute humidity and to a lesser extent relative humidity and influenza for all-cause and cardio-respiratory mortality but not for pneumonia and influenza deaths in both regions. The relationship with temperature was less clear.

Originality/Strengths: While many population level studies have examined the relationship between influenza and mortality, some controlling for confounding effects of environmental factors, few if any have modelled the effect of interactions between influenza and extreme weather conditions on mortality. Strengths of the manuscript include use of data from two separate cities which gave similar results, demonstration that a separate unrelated outcome (accidental deaths) was neither associated with influenza nor affected by interactions between influenza and environmental factors, and similar estimates from sensitivity analyses using different cut offs to categorize environmental variables.

Minor essential revisions

1. On page 5, the sixth line under the heading 'Statistical Methods' seems to describe components of the core model incorrectly
2. The title for table 3 is not complete: this table also looks at low-, middle- and high periods for absolute and relative humidity
3. The legend for figure 1 is confusing as there is no indication of what part A and part B of the figure represent
4. There is no legend for the figure 1 supplementary Powerpoint slide
5. The legend for figure 2 is missing

Discretionary revisions/ clarifications

1. On page 4 under ‘Methods’, it is unclear why influenza surveillance data were obtained for 1998-2006 for Hong Kong but analyses only carried out on data from the period 2004-2006. Use of more years of data would strengthen results, so what was the reason for restricting analyses to three years?
2. On page 6 there is a description of adding interaction terms between virus activity and environmental variables into the core model. However the core model already contained natural cubic spline functions for weekly average temperature and relative humidity to adjust for potential confounding. What is the effect of including the same environmental factors in models as both confounders and interaction terms? Could this be clarified?

3. Under ‘Results’ it would be useful to describe results from the core model (ie without interaction terms) to show the effect of influenza on mortality controlling for temperature and humidity because all other models are then compared to this. Would it be possible to incorporate this result into the abstract and perhaps table 3 (or an additional table)?

4. It has been hypothesized that influenza A and B may be affected differently by environmental conditions. Did you consider looking at their effects separately?

5. Influenza vaccination rates for these populations were not mentioned, but differing levels of vaccine coverage could substantially affect results. Could a sentence be added about this?

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests