Reviewer's report

Title: Impact of antiviral treatment and hospital admission delay on severity of 2009 A/H1N1 pandemic influenza in Mexico, April-December 2009

Version: 2  Date: 13 February 2012

Reviewer: Mark I-Cheng Chen

Reviewer's report:

General comments

This manuscript addresses an important issue. Though an observational study with its inherent biases, it presents reasonable findings that may have relevance to public health and case management of influenza.

The are specific issues where clarification and revisions are requested.

Major Compulsory Revisions

1. One key issue not raised in the methods was how the authors dealt with missing data. Certainly in such a large dataset based on routine medical notes, there would be missing data on details like onset dates and antiviral use. Were these cases excluded? Or, in the case of antiviral use, was it just assumed not to be prescribed if it was not in the system (or there was no medical record of it)? And in the case of onset dates, it would be helpful to know what proportion were missing the onset dates if excluded, or if some data imputation method was used. Onset dates can be particularly tricky for individuals who end up in ICU and are unable to give good clinical history.

Minor Essential Revisions

2. Line 80: "prospective epidemiological surveillance system put in place especially for the 2009 influenza pandemic by the Mexican Institute for Social Security (IMSS)"

I think the word "especially" should be changed to "specifically".

3. Line 92: "ILI was defined as a combination of cough, headache, and fever (except for persons over 65 years)…"

Then what about those over 65 years? Was a different case definition used? This needs to be clarified by a follow-up statement. Alternatively, drop this idea of ILI altogether (see below).

4. Line 121: "we stratified admission delay into two groups <=2 and >2"

I think there should be a colon after the word groups.

5. Line 130-131: "The case fatality rate (CFR) measures the proportion of deaths
from all symptomatic infections,"
CFR is actually a ratio / proportion, not a rate. Suggest the authors consistently use the term “case fatality ratio” instead.

6. Line 133: "Here we estimated the case fatality rate among ILI cases (CFRili)” - denominator is all ILI?
The reviewer is uncertain if using ILI without confirmation adds much value. The denominator here includes non-influenza ILI, but it seems to me the the numerator (for CFRili) here is not ILI but deaths in confirmed cases who also had ILI. Or did the reviewer read this wrongly? If the intention is to capture some idea of the extent of ILI from pdmH1N1 influenza that was not tested, it must be noted that:

a) there’s a lot of influenza that is asymptomatic or does not fulfil the rather stringent criteria for ILI.
b) the numerator also misses deaths from influenza that were not tested (if they are referring to cases which were confirmed) or did not fulfil ILI criteria.

As a result, it is difficult to meaningfully compare CFRili with other quantities in the literature such as symptomatic CFR (which is somewhat similar to your CFRflu) or CFR estimates based on serology. Perhaps the authors could elaborate in the discussion on why they think CFRili was important, if they wish to retain it. One possibility is to use this for within Mexico comparisons (across states and waves), in which case the authors must provide satisfactory evidence that ILI data collection is consistent over time and geography, and emphasize that this is the key use of bringing up CFRili.

7. Table 1: how are confirmed cases that say presented to outpatient and then subsequently hospitalised counted? Can the authors confirm that there is no double counting (e.g. that someone is counted in the hospitalized group even if already seen as outpatient?) The same applies to hospitalised cases that eventually die.

8. Line 194-197: “Southeastern states had 2.6-3.3 fold higher rates of neuraminidase inhibitor administration compared to other regions (Table 3). This is consistent with most of the A/H1N1 burden in this geographic region occurring in summer 2009, when antiviral administration rates were highest (Figure 2B).”
I’m not sure what the authors are referring to above. Since antiviral administration is measured as a proportion of confirmed cases diagnosed, why would the burden of disease (incidence) affect the proportion treated with antivirals? Unless the authors are actually referring to true antiviral treatment rate which is doses per population? The authors should clarify firstly what they mean here by “antiviral administration rates”, and if they are actually referring to proportions treated, then they should remove the line which correlates burden in the geographic region with the higher proportion treated.

9. Line 246-7: “whereas for the group of A/H1N1 inpatients with admission delays >2days, antiviral treatment was not significantly associated with risk of death”
The above is an important point. Suggest to rephrase to increase the emphasis, “whereas for the group of A/H1N1 inpatients with admission delays >2days, antiviral treatment did not significantly reduce the risk of death…”

Discretionary Revisions

10. Lines299-304, on the “southeastern region”

Their discussion on the above is a little disappointing. Was the southeastern region different in terms of socioeconomics? Or ethnic differences? Or urbanisation? A brief mention of such factors could strengthen the discussion.

Level of interest: An article of importance in its field

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.