Author's response to reviews

Title: Hospitalizations for varicella in children and adolescents in a referral hospital in Hong Kong, 2004 to 2008: A time series study.

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Author's response to reviews: see over
Reply to Dr. Luan-Yin Y Chang

Overall comments

This article reported the epidemiology of varicella in paediatric patients hospitalized at a tertiary referral hospital in Hong Kong from 2004 to 2008, and to explore the possible association between the occurrence of varicella infection and various climatic factors. The author found that lower relative humidity is associated with higher number of paediatric varicella hospital admissions.

Major Compulsory Revisions

1. Result on Page 8 (lines 3-4) described that “However, monthly mean air temperatures and monthly rainfall, at lags of zero to two months, were not associated with the monthly number of varicella cases” but Table 1 shows that rainfall at lags of zero was significantly associated with the monthly number of varicella cases (r= -0.294, p<0.05). Which is correct?

Thanks for spotting the mistake. Table 1 is correct. We have revised the related text.

2. If Table 1 is correct, that is, both humidity and rainfall were inversely correlated with varicella cases at lag of zero, why not reported the best fitting model with GEE analysis, ARIMA Model between rainfall and varicella cases?

In the regression models that included rainfall (see below for two sets of results), rainfall was not found to be a statistically significant predictor and the QICu values of the models were larger than the model presented in Table 2.

| Parameter | Standard Error | 95% Confidence Limits | Z Pr > |2| |
|-----------|----------------|-----------------------|--------|
| Intercept | 1.9567         | 0.1582                | 1.6467 2.2667 | 12.37 < .0001 |
| ylag      | 0.0887         | 0.0108                | 0.175 0.3099 | 5.58 < .0003 |
| rain      | -0.0993        | 0.0002                | -0.0908 0.0992 | -1.28 0.2088 |

Responding also to similar comments by other reviewers, we have added the following text to Results: “Forcing average temperature and total rainfall into the model did not change the coefficient estimates for relative humidity significantly.”

3. Was there any confounding, interaction or correlation between rainfall and humidity? If there was, it should be taken into consideration and be adjusted during analysis.

Rainfall and humidity are highly correlated with each other, as seen below. Rainfall itself, however, was not a predictor of the monthly varicella cases. Therefore, rainfall cannot be a confounding factor in this situation.

<table>
<thead>
<tr>
<th></th>
<th>Humid0</th>
<th>Humid1</th>
<th>Humid2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rain0</td>
<td>0.67268</td>
<td>0.70363</td>
<td>0.56687</td>
</tr>
<tr>
<td></td>
<td>&lt; .0001</td>
<td>&lt; .0001</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>
Reply to Dr. Samer El-Kamary

Overall comments

This is a very well written manuscript that provides interesting and biologically plausible association between decreased humidity and increased incidence of Varicella infections.

Major compulsory revisions

1. The authors used GEE to model the monthly varicella incidence. However, this method is used to account for clustering, whether in cases where there are multiple repetitive admissions of the same subject, or if there were multiple admissions at different units e.g. at each hospital. In this study, there is only one hospital and the admissions across time or of different individuals. Hence, this method is not appropriate for this study, and should be eliminated from the analysis.

We are afraid that we do not agree. In the present study we recorded the number of varicella cases over time. We believe the GEE method is appropriate for this study. The generalized estimating equations (GEE), introduced by Liang and Zeger [Zeger and Liang, 1986, Liang and Zeger, 1986], is a method of analyzing correlated data that otherwise could be modeled as a generalized linear model. The correlated data can arise from longitudinal studies, in which subjects are measured at different points in time, or from clustering, in which measurements are taken on subjects who share a common characteristic.

The Poisson regression model using generalized estimating equations (GEE) of Liang and Zeger [Zeger and Liang, 1986, Liang and Zeger, 1986] has been used to to assess the association between air pollution, meteorological factors and hospital admissions for various diseases plus daily mortality [Schwartz et al., 1993, Schwartz and Dockery, 1992b, Schwartz and Dockery, 1992a, Koken et al., 2003, Hajat et al., 2006].


2. The authors used ARIMA (auto-regressive, intergrated, moving average) model as an alternative modeling methodology for comparison. However, ARIMA is used for continuous data not for counts which is the data used in this study. One option is to use other time-series methods such as GARMA (generalized autoregressive moving average), or methods such as those described in Dominici F et al, JAMA. 2006 Mar 8;295(10):1127-34; and Peng RD et al, JAMA. 2008 May 14;299(18):2172-9.

As also suggested by another reviewer Dr. Roger D Peng, we have removed the ARIMA modeling part from the manuscript.

3. In their results section, the authors show an inverse correlation between humidity and varicalla cases without adjusting for temperature and rainfall. They should include rainfall and temperature in their model. It is possible that the authors found no correlation after the adjustment. However, this does not invalidate their findings and they should display the results with and without adjusting.

We added the following description to the Results section: “Forcing average temperature and total rainfall into the model did not change the coefficient estimates for relative humidity significantly.”

| Parameter | Estimate | Standard Error | 95% Confidence Limits | Z Pr > |t| |
|-----------|----------|----------------|------------------------|--------|---|
| Intercept | 4.1076   | 0.0411         | 2.6539 5.5610          | 4.87   | <.0001 |
| ylag      | 0.0997   | 0.0113         | 0.0775 0.1220          | 3.51   | <.0004 |
| Humidity  | -3.0252  | 1.0178         | -5.0201 -1.0303         | -2.97  | <.0030 |
| Rain      | 0.0001   | 0.0003         | -0.0005 0.0007         | 0.33   | 0.7384 |
| ave0      | 0.0047   | 0.0201         | -0.0347 0.0440         | 0.23   | 0.8106 |
Reply to Dr. Roger D Peng

Overall comments

This paper examines pediatric hospital admissions for varicella in Hong Kong for the period 2004 to 2008. The authors examine monthly counts of hospital admissions and compare them to monthly mean levels of temperature, relative humidity, and rainfall. They find that monthly changes in relative humidity are inversely associated with monthly counts of varicella admissions at a lag of 0 and 1 months (but not 2 months) using a GEE model. They also use an ARIMA model which leads to similar findings.

Overall, the paper is well-written and easy to follow. I have a few major comments.

Major comments

1. Given the use of monthly data here, I am a little concerned that there may be seasonal non-meteorological factors not captured by the model that could explain the relationship observed (e.g. changes in population behavior across seasons, air pollution, etc.). Often in time series models of this nature, a term is included to adjust for the natural seasonality of the outcome. It is difficult here because relative humidity is also seasonal so adjusting for seasonality may washout the effect. However, if that is true, then it would greatly weaken the conclusion of the paper. Ultimately, with monthly data, it is difficult to separate out the effect of season from meteorological factors. I would suggest as a sensitivity analysis that the authors either conduct a stratified analysis by different seasons or include a seasonally varying term in their model to see how the association parameters change.

Thanks for the good suggestion. We have done stratified analysis by cool or hot seasons. The months from October to March were defined as cool season, and the other months hot season. Humidity remained a significant predictor of varicella in the cool season model (Beta = -3.02, 95% confidence interval -5.47, -0.58, p = 0.0152), while it was not significant in the hot season model.

We have added the following text into the Results.

We also conducted a stratified analysis by two seasons (October-March defined as cool seasons and the other months hot season) to see how the effect of humidity varies. Humidity remained a significant predictor of varicella in the cool season model (Beta = -3.02, 95% confidence interval -5.47, -0.58, p = 0.0152), while it was not significant in the hot season model.
2. It is not clear from the text if all three predictors (relative humidity, temperature, and rainfall) were considered simultaneously in one model (i.e. multivariate) or if they were examined separately in different models. This should be clarified.

We added this to Methods: “The weather variables found to be correlated with varicella incidence were included in univariate and multivariate regression models.”

Responding also to similar comments by other reviewers, we have added the following text to Results: “Forcing average temperature and total rainfall into the model did not change the coefficient estimates for relative humidity significantly.”

Minor comments

1. Were all hospital admissions satisfying a given ICD-9 code used or were they emergency only? This should be clarified.

We have added the following to the Method section: “All hospital admissions, not limited to emergency admissions, were included for time series analysis.

2. It is not clear what additional terms besides the meteorological factors were included in the GEE model. This should be clarified.

We have added the following to the Method section: “Besides the meteorological factors, the autoregression term ylag (number of varicella cases at one month lag) was also included in the model.”

3. The analysis using the ARIMA model did not seem to add much to the findings. It’s not clear to me why this was included.

We have removed the ARIMA analysis from the manuscript completely.

4. What was the estimated amount of overdispersion in the GEE Poisson model? This should be reported.

We are not sure about this. Without the REPEATED statement, the model gave an overdispersion estimate of 2.60. With the REPEATED statement, the GEE modeling did not give deviance or overdispersion estimates. From the SAS manual it has “For GEE models, which are available in PROC GENMOD via the REPEATED statement, there is no overall fit statistic currently available within PROC GENMOD. Note that the Pearson and deviance statistics apply only to the initial model that begins the GEE estimation, not to the final GEE model.”

5. Some results are repeated in the Discussion—this is not necessary.

As suggested, we have removed some redundant description in the Discussion section, especially in the first two paragraphs of the Discussion.

6. On p. 9, the first model displayed should be log(E[Y]) = It is the log of the expected value of Y that is modeled.

Thanks. We have corrected this.