Author's response to reviews

Title: Clinical Features and Risk factors for Severe and Critical Pregnant Women with 2009 Pandemic H1N1 Influenza Infection in China

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Version: 2 Date: 28 November 2011

Author's response to reviews: see over
Dear Roselle Pangilinan,

Thank you for your comments to our manuscript. We are very grateful to have a chance to revise it.

As requested we have dealt with the thoughtful comments of each of the reviewers individually and present these below:

Point-by-point responses to the reviewers’ comments:

Response to Reviewer 1:

1. This paper is a comprehensive survey of clinical features of pregnant women hospitalized in China and deemed to have severe disease during the 2009 pandemic H1N1 epidemic. The study is a retrospective chart review. The study is overall a well-done description of the patients that makes interesting clinical observations and contributes to the literature about 2009 H1N1.

Response: Thanks for your positive comments.

2. The data on steroid usage correlating with worse outcomes is interesting, but data could not be collected on the clinical condition prior to steroid administration, so a potential causative effect could not be supported.

Response: Thanks for your comments. We agree with you that the conclusion of causative effect of steroid on worse outcome could not be made based on our data. Corticosteroids remain controversial in the treatment of viral infection both in China and the whole world. You are right, in our study, we compared the characteristic and prognosis between pregnant women who received steroids and those who did not. Baseline data of the clinical condition were collected prior to steroid administration, so, there were not enough proofs to support the negative effect of steroid. Reviewer 2 also referred this point and suggested deleting this part. Following both reviewers’ comments, we decided to delete the part in this manuscript. Despite the negative effects of steroids on severe or critically ill patients with pH1N1 influenza were recently reported, such as in Kim [1] and Brun-Buisson’s [2] studies, we still believe that there may be a beneficial impact in some selective population. But further detailed analysis should be made by dividing into subgroups.


3. The manuscript could be re-formatted. Much of the discussion section is devoted to reporting statistics that would be better described in the results section. Information that is repeated in the discussion section should be done so only to prepare the reader for the authors’ interpretation of the results. The discussion could be trimmed to be more focused on the main points of the article.

Response: Thanks for your nice suggestions. In the revised version, we had re-written the discussion section as you suggested. Please see the discussion in the new version.

4. It is not clear what is the authors’ position on non-invasive ventilation for pregnant patients with H1N1. This is an important issue. It appears that the method was successful for women without specific risk factors; the authors should expand on their statement, “NIV may be useful in selected women with isolated acute respiratory failure”.

Response: Thanks for your suggestions. Few studies have been reported on the role of non-invasive mechanical ventilation in pregnant women, especially in critically ill patients with H1N1 infection. Our results showed that pregnant women complicated by septic shock were more likely to have treatment failure among those treated with NIV. But we are sure that NIV may be useful in selected pregnant women without specific risk factors such as septic shock.

Response to Reviewer 2:

Major Compulsory Revisions

1. General comments:
   - The purpose of the study should be clearly defined. In its current form, there are discrepancies between objectives presented in the abstract, main text, and results section. Title should be modified in order to convey objectives.

Response: Thanks for your comments. In the revised version, we had modified the title, objectives and texts so that they are same in the whole text. Please see the modified version.

2.- The paper tries to deliver too many messages (characteristics of patients efficacy of NIV and corticosteroid treatment, risk factors for maternal and neonatal death). Some of them are not supported by the methods applied. Choosing 2-3 messages and supporting them with pertinent methodology and interpretation would improve the quality of the paper.

Response: Thank you for your good suggestions. In the revised version, we have focused on 3 main points supported by pertinent methodology: characteristics and prognosis of patients, risk factors for maternal and neonatal death and efficacy of NIV.

3.- Conclusions should concentrate on what this specific study tells us.
Response: Thank you for your suggestions. According to your advices, we had modified the conclusion. As follows:
Severe hypoxemia was associated with adverse outcomes for pregnant women. Preterm delivery was a risk factor for neonates death among pregnant women with pH1N1 influenza infection. NIV may be useful in selected pregnant women without septic shock.

4. Abstract: Should correspond to objectives and messages of the main text

Response: Thanks for your comments. We have revised the abstract responding to the objectives and messages of the main text.

5. Introduction: Please keep only the most pertinent references.

Response: According to your suggestion, we had deleted unrelated references.

6. Methods: Study patients: Criteria of patients’ inclusion/exclusion in the study should be clearly presented.

Response: In the methodology, we have added the criteria of patients’ inclusion/exclusion.
As follows: All patients who were admitted to hospitals with confirmed 2009 pH1N1 influenza from September 1 to December 31, 2009 from 27 Chinese provinces were screened if they fulfilled the diagnostic criteria for severe or critical cases. A confirmed case was a person whose influenza A (pH1N1) was verified by real-time reverse-transcriptase polymerase chain reaction (rRT-PCR) with or without the presentation of other clinical symptoms. Patients were excluded if they had been treated as outpatients or in emergency rooms or duration of hospitalization <24 hours, or if they had incomplete records of clinical outcomes. Severe and critical cases were defined according to the H1N1 2009 Clinical guidelines (Third Edition, 2009) released by the MOH.

7. Analysis: How variables for univariate and multivariable analyses were selected? How multivariable models were built?

Response: In the methods, we added how variables were selected and how multivariable models were built. As follows:
We performed univariable logistic analysis to investigate the potential factors on admission that might be associated with the maternal mortality. And then the factors with statistical significance (p < 0.05) in the univariate analyses, then these factors were included the multivariate logistic regression analysis (Enter) to determine the independent factors for maternal outcomes. Meanwhile, we also adjusted maternal baseline clinical factors such as (maternal BMI, gestational age, CNS symptom, AST, APACHE II score and PaO₂/FiO₂ on admission) in multivariable logistic models.

8. Results
Clinical description of the cohort
How BMI was defined? Although it is not indicated, it seems it was collected from hospital charts. When describing pregnant women, previous papers used BMI calculated from
pre-pregnancy period, or from early antenatal period. For example, in the reference 42 cited in your manuscript authors from Australia used the BMI from before 20 weeks of gestation. Since ¾ of your population are in the 3rd trimester of pregnancy, proportion of obesity is most probably overestimated. This is important to verify and correct if necessary because the influence of BMI on outcomes is one of the main study conclusions. Also, why BMI is treated differently depending on the model – as indicator variables for 4 categories in Table 3; as a continuous variable in Tables 4 and 5?

Response: Thank you for your excellent suggestions. In the revised version, we have defined the BMI of pregnant women in Methods Part. Our research retrospectively collected the patient's clinical information recorded in CRFs. We lacked data on mothers' weight before pregnancy. Sorry that we made a mistake in BMI which is treated differently depending on the model in Table3,4,5. We have unified the model, as a continuous variable.

We agree with you that proportion of obesity has been overestimated based on BMI in the 3rd trimester of pregnancy.

In addition, to analyze the efficacy of NIV, we put gestational age, BMI and others into the model to adjust and improve test efficiency.

9. Medication
Additional information is needed regarding the corticosteroid medication (drug, dose, indications). According to supplemental table 2, steroids were given to women with more severe presentation. As such, it is not surprising that you detected a significant difference in disease severity between women who received steroids and those who did not.

Response: Thank you for your suggestions. We have deleted supplemental table 2, as there is no enough proof showing the adverse effects of steroids as more severe pregnant women received corticosteroid.

10. Mechanical ventilation
- What were indications for applying NIV? What is the definition of successful and failed NIV?
- What were indications to change from NIV to invasive ventilation? To conclude about the effectiveness of NIV, the patients with failed NIV should be comparable to those with successful NIV as to basic characteristics, and it is essential controlling for potential confounding factors, especially severity of disease.

Response: Thank you for your advices. In the revised version, we added indications for applying NIV and to change from NIV to invasive ventilation, definition of successful and failed NIV in the methodology.

Indications for applying NIV: Pregnant women who complained shortness of breath or Blood gas analysis confirmed hypoxemia PaO\textsubscript{2} to FiO\textsubscript{2} < 300). One non-pulmonary major organ dysfunction or unconsciousness was contraindications for NIV.

Indications to change from NIV to invasive ventilation: A cautious trial of NIV was attempted and response to NIV was monitored after the first hour or two. If there was a deterioration of oxygenation, invasive ventilation was considered.
Definition of successful NIV: \( \text{PaO}_2 \) to \( \text{FiO}_2 \) improved and respiratory rate decreased down during one or two hour NIV therapy. The patients successfully weaned off NIV and survived.

Definition of failed NIV: During the one or two NIV trial, a deterioration of oxygenation was observed and invasive ventilation was needed.

As you presented, the basic characteristics is essential to further analysis about the effectiveness of NIV. In Table 5, we have added more basic characteristics.

11. Acute liver damage – It is surprising to see that there is no chronic liver disease as an underlying disease in your population, given high endemicity of hepatitis B infection in China. Were these women tested for HBsAg (in hospital or during prenatal visits)? AST/ALT elevation may be due to exacerbation of chronic liver disease. This should be acknowledged.

Response: Thank you for your good suggestions. Past history of liver cirrhosis was retrospectively collected in our population, but none of them had cirrhosis. HBsAg was not detected during hospitalization. According to a recent report [1] from Jiangsu province of China, the rate of HBsAg among pregnancy was only 6.71% from August 2002 to July 2004, much lower than prevaccination rates. In our study, we believe that the high rate of acute liver damage was mainly due to H1N1 viral infection, not due to viral hepatitis or cirrhosis.


12. Maternal and fetal outcomes:
- Please detail how variables were selected and retained in the multivariable models.

Response: The primary outcome was hospital mortality. We performed univariable logistic analysis to investigate the potential factors on admission that might be associated with the maternal mortality. And then the factors with statistical significance (p < 0.05) in the univariate analyses, then these factors were included the multivariate logistic regression analysis (Enter) to determine the independent factors for maternal outcomes. Meanwhile, we also adjusted maternal baseline clinical factors such as (maternal BMI, gestational age, CNS symptom, AST, APACHE II score and \( \text{PaO}_2/\text{FiO}_2 \) on admission) in multivariable logistic models.

13. How many of patients with lethal outcome had underlying diseases as compared to those who survived?

Response: 25 patients (7.9%) had underlying diseases in pregnant women who survived, and the rate was 7.8% in those who died.

Discussion
14. The discussion resuming study results seems too long. Also, it may be reduced by focusing on 2-3 main messages.
Response: Thank you for your suggestions. We had re-formatted the discussion and focused on 3 main messages, including characteristics of patients, risk factors for maternal and neonatal death, and NIV.

15.- How representative is your population as compared to general population of pregnant women in China?

Response: According to the Ministry of Health (MOH) of the People’s Republic of China, 7.5% were pregnant women. (http://www.chinanews.com/jk/news/2009/12-09/2009439.shtml)
In our cohort, we retrospectively collected 394 pregnant women, which accounted for 11% among those fulfilled the diagnostic criteria for severe or critical cases. So, our population was well representative for pregnant women in China.

16.- How do you explain lower prevalence of underlying diseases in this report as compared to other countries? Is there a possibility that some underlying diseases were missed or underreported (for example, chronic hepatitis B?)

Response: In our study, the prevalence of underlying diseases was much lower than reports from the United States (49.3%) , 56% in Australia, 34% in California, 22.8% in Brazil, and 62% in France. In those studies, the main cause of underlying disease was asthma. A study compared asthma prevalence of Chinese adolescents living in Canada and in China. The authors found that for girls, the range of asthma was 4.3% in Guangzhou to 9.8% in Canadian-born Chinese adolescents. These findings suggest that environmental factors influence asthma prevalence (Wang HY; Wong GWK; Chen YZ, et al. Prevalence of asthma among Chinese adolescents living in Canada and in China. CANADIAN MEDICAL ASSOCIATION JOURNAL, 2008; 179 (11): 1133).
Another reason for the low prevalence of underlying diseases among pregnant is that 73% of our patients came from rural area or those who were unemployed. The poor living conditions made them less likely to have health checkup before pregnancy.

Table 1. Underlying diseases in our report:

<table>
<thead>
<tr>
<th>Chronic pre-existing disease</th>
<th>11/388 (2.8)</th>
<th>13/393 (3.3)</th>
<th>4/394 (1.0)</th>
<th>3/394 (0.8)</th>
<th>1/390 (0.3)</th>
<th>31/394 (7.9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory diseases* (%)</td>
<td>11/388 (2.8)</td>
<td>13/393 (3.3)</td>
<td>4/394 (1.0)</td>
<td>3/394 (0.8)</td>
<td>1/390 (0.3)</td>
<td>31/394 (7.9)</td>
</tr>
<tr>
<td>Cardiovascular diseases** (%)</td>
<td>13/393 (3.3)</td>
<td>4/394 (1.0)</td>
<td>3/394 (0.8)</td>
<td>1/390 (0.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>4/394 (1.0)</td>
<td>3/394 (0.8)</td>
<td>1/390 (0.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer or hematological diseases (%)</td>
<td>3/394 (0.8)</td>
<td>1/390 (0.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune suppressed (%)</td>
<td>1/390 (0.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any of the above underlying conditions (%)</td>
<td>31/394 (7.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* included asthma, COPD, active tuberculosis and other bronchial disease.
** included coronary heart disease, chronic congestive heart failure, valvular disease.

Study in the United States

### Chronic pre-existing disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma (%)</td>
<td>99 (22.9)</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>56 (13.0)</td>
</tr>
<tr>
<td>Pregestational diabetes (%)</td>
<td>17 (3.9)</td>
</tr>
<tr>
<td>Anemia (%)</td>
<td>15 (3.5)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>13 (3.0)</td>
</tr>
<tr>
<td>Gestational diabetes (%)</td>
<td>12 (2.8)</td>
</tr>
<tr>
<td>Cardiovascular disease (excluding hypertension)</td>
<td>10 (2.3)</td>
</tr>
<tr>
<td>Thyroid disease (%)</td>
<td>8 (1.9)</td>
</tr>
<tr>
<td>Immune suppression (due to underlying disease or meds) (%)</td>
<td>8 (1.9)</td>
</tr>
<tr>
<td>Neurological disease (%)</td>
<td>7 (1.6)</td>
</tr>
<tr>
<td>Chronic lung disease (excluding asthma) (%)</td>
<td>7 (1.6)</td>
</tr>
<tr>
<td>Autoimmune disease (%)</td>
<td>3 (0.7)</td>
</tr>
<tr>
<td>Other (%)</td>
<td>33 (7.6)</td>
</tr>
<tr>
<td>Any of the above underlying conditions (%)</td>
<td>213 (49.3)</td>
</tr>
</tbody>
</table>

### Study in California


### Chronic pre-existing disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic lung disease</td>
<td>16/93 (17)</td>
</tr>
<tr>
<td>Asthma</td>
<td>15/93 (16)</td>
</tr>
<tr>
<td>Other**</td>
<td>2/93 (2)</td>
</tr>
<tr>
<td>Metabolic disease</td>
<td>14/90 (16)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2/90 (2)</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>8/90 (9)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>3/90 (3)</td>
</tr>
<tr>
<td>Other††</td>
<td>1/90 (1)</td>
</tr>
<tr>
<td>Immunosuppressive disorder</td>
<td>4/91 (4)</td>
</tr>
<tr>
<td>Cancer or transplantation-related</td>
<td>3/91 (3)</td>
</tr>
<tr>
<td>HIV or AIDS</td>
<td>1/91 (1)</td>
</tr>
<tr>
<td>Other‡‡</td>
<td>0</td>
</tr>
<tr>
<td>Chronic cardiac disease §§</td>
<td>3/92 (3)</td>
</tr>
<tr>
<td>Neurologic disorder¶¶</td>
<td>1/91 (1)</td>
</tr>
<tr>
<td>Other chronic coexisting illness</td>
<td>6/89 (7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5/94 (5)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disease □□</td>
<td>2/85 (2)</td>
</tr>
<tr>
<td>Any of the above underlying conditions (%)</td>
<td>32/93 (34)</td>
</tr>
</tbody>
</table>

** Other chronic lung diseases included cystic fibrosis (in two patients), bronchiectasis (in two), chronic lung disease of prematurity (in two), pulmonary hypertension (in two), obstructive sleep...
apnea (in one), chronic obstructive pulmonary disease (in one), allergic bronchopulmonary aspergillosis (in one), pulmonary tuberculosis (in one), recurrent pneumonia (in one), pulmonary embolus (in one), restrictive lung disease (in one), and chronic bronchitis (in one).

†† Other chronic metabolic diseases included thyroid disorders (in two patients), and cystic fibrosis–related diabetes (in one).

‡‡ Other chronic immunosuppressive disorders included systemic lupus erythematosus (in four patients), asplenia (in two), adrenal disorder (in one), and primary T-cell immunodeficiency (in one).

§§ Chronic cardiac diseases included congestive heart failure (in eight patients), congenital heart disease (in six), coronary artery disease (in two), and valvular heart disease (in two).

¶¶ Neurologic disorders included seizure disorder (in 11 patients), developmental delay (in 9), migraines (in 2), spastic quadriplegia (in 2), muscular dystrophy (in 1), hydrocephalus (in 1), cavernous hemangioma (in 1), and microcephaly (in 1).

Other chronic gastrointestinal illnesses included gastroesophageal reflux disease (in nine patients), disorders resulting in gastrostomy-tube dependence (in four), autoimmune hepatitis (in one), liver disease not otherwise specified (in one), irritable bowel syndrome (in one), gastrointestinal cancer not otherwise specified (in one), laparoscopic cholecystectomy (in one), pancreatic insufficiency (in one), and cirrhosis (in one).

Study in Brazil


<table>
<thead>
<tr>
<th>Chronic pre-existing disease</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma (%)</td>
<td>3</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus plus hypertension (%)</td>
<td>2</td>
</tr>
<tr>
<td>Immunosuppressive disorder (HIV infection) (%)</td>
<td>2</td>
</tr>
<tr>
<td>Cardiovascular disease (%)</td>
<td>1</td>
</tr>
<tr>
<td>Other (%)</td>
<td>3</td>
</tr>
<tr>
<td>Any of the above underlying conditions (%)</td>
<td>13</td>
</tr>
</tbody>
</table>

Study in French


<table>
<thead>
<tr>
<th>Chronic pre-existing disease</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity (BMI &gt; 30) (%)</td>
<td>23</td>
</tr>
<tr>
<td>Respiratory disease * (%)</td>
<td>22</td>
</tr>
<tr>
<td>Cardiac or vascular disease (%)</td>
<td>4</td>
</tr>
<tr>
<td>Metabolic disease other than diabetes (%)**</td>
<td>3</td>
</tr>
<tr>
<td>Diabetes except gestational diabetes(%)</td>
<td>2</td>
</tr>
</tbody>
</table>
Neurologic disease (%) 3 (5.4)
Renal disease (%) 0 (0)
Hepatic disease (%) 1 (1.9)
Hematologic disease (%) 3 (5.4)
Immunosuppression (%) 2 (3.7)
Any of the above underlying conditions (%) 55 (36.4)

*includes asthma, restrictive syndrome.
**includes thyroid and adrenal insufficiency.
***includes bronchodilators, insulin, salicylic acid, fractionated heparin, L-thyroxin, antihypertensive agents.

Study in Australia


Chronic pre-existing disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma (%)</td>
<td>21 (33)</td>
</tr>
<tr>
<td>Valvular or congenital heart disease (%)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Depression (receiving treatment) (%)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Essential hypertension (%)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Any of the above underlying conditions (%)</td>
<td>36 (56)</td>
</tr>
</tbody>
</table>

17.- Discussion on corticosteroids and NIV should be focused depending on answers to comments above. In particular, the potential confounding effect of indications should be dealt with a lot of precaution.

Response: Thanks for your nice suggestions. In this revised version, we have followed your comments above.

18.- How obesity was defined? One can presume from table 1 that obesity was defined as a BMI $\geq 30$, however it should be clearly stated.

Response: Thanks for your advices. We added the definition of obesity which was defined as BMI $\geq 30$.

19.- It might be of interest making a link between the vaccination coverage against pandemic influenza in China, and the results observed in pregnant women.

Response: Thanks for your advices. The first 2009 H1N1 vaccine was licensed in September 2009. By Dec 31, 2009, a total of 1400 pregnant women received the vaccine and no adverse events were reported in China. By Mar 30, 2010, a total of 95.70 million patients received the vaccine from 31 provinces in China. 2867 cases were reported had adverse event, the incidence was 11.44
per 100,000 population. The overall severe incidence of vaccine recipients who reported any adverse event was low (0.09 per 100,000 population).

In our study, no pregnant women received the H1N1 or seasonal flu vaccination. So it is difficult for us to assess the effectiveness of vaccine.

20.- What new data this study brings? Conclusions in their actual form are not sufficiently supported by the data.

Response: We have modified our conclusion part. This study brings us new data as: 1) Severe hypoxemia was associated with adverse outcomes for pregnant women. 2) Preterm delivery was a risk factor for neonatal death among pregnant women with pH1N1 influenza Infection. 3) NIV may be useful in selected pregnant women without septic shock.

21. References: number of references could be reduced

Response: According to your suggestion, in our revised version, we had deleted some references.

22. Figure 1
Why patients are divided into 2 groups (received mechanical ventilation and women who delivered)? Does this mean that women who delivered did not receive mechanical ventilation? If groups are mutually exclusive, numbers do not sum up to the total of 394 (186+211= 397)

Response: We are so sorry to make misunderstanding. In the revised version, we have modified the figure 1 to clarify the distribution of the patients.

23. Table 1
- BMI – see comments above
- Gestational age: should define trimesters

Response: Thank you for your remind. We had defined BMI and trimesters as shown in table 1.

24. Table 3 and Table 4
What variables were adjusted for in the multivariable analysis?

Response: In table 3 and Table 4, firstly, we performed univariable logistic analysis to investigate the potential factors on admission. And then the factors with statistical significance (p < 0.05) in the univariable analyses, then these factors were included the multivariate logistic regression analysis.

In Table 3 (Table 5 in the new version), Variables included in multivariate model: BMI, Gestational age, CNS symptom, APACHE II score, septic shock, acute liver damage

In Table 4 (Table 3 in the new version), Variables included in multivariate model: BMI, Gestational age, PaO2/FiO2 on admission, APACHE II score, dyspnoea, hemoptysis, CNS symptom, AST.
**Minor Essential Revisions**

25. **Table 1**

   Line "H1N1 or seasonal flu vaccination" may be deleted since this is presented in the text. In the Notes to all tables, correct "no.(%) /total no. (%)" to "no./total no. with data available(%)"

   **Response**: Thanks for your comments. In the new version, we have deleted the line "H1N1 or seasonal flu vaccination" and also have corrected the "no.(%) /total no. (%)" in the notes.

26. **Table 2**

   Add heading to the table. Minor issues not for publication. Spelling and grammatical errors should be verified

   **Response**: Thank you for your good reminder. We have revised the heading to the table 2 and verified the spelling and grammatical errors.

**Discretionary Revisions**

27. **Supplemental table 2 may be deleted**

   **Response**: We agreed with your suggestion. In the new version, we have deleted Supplemental table 2.

28. **Brief description of pandemic wave in China would be useful**

   **Response**: We accepted your advices. In the introduction and discussion, we all referred the pandemic wave in China, especially in pregnant women.

   The first case of 2009 pandemic influenza A (H1N1) virus infection in China was documented on May 10, the virus has rapidly spread throughout the mainland. A total of 126,000 confirmed cases were reported by Mar 31, 2010, including 7414 patients severe and 800 patients died. Among all these severe cases, about 13.7% of patients were pregnant women. Data from Chinese Center for Disease Control and Prevention showed that the overall hospitalization and mortality rates during Sep 2009–Feb 2010 were 2.4 hospitalizations per 100,000 population and 0.6 deaths per 1,000,000 population. Hospitalization rates ranged from 6.1 hospitalizations per 100,000 population among children 5–14 years of age to 0.6 hospitalizations per 100,000 population among persons >65 years of age. Mortality rates ranged from 1.2 deaths per 1,000,000 population in children, 5 years of age to 0.3 deaths per 1,000,000 population in children 5–14 years of age. Death-hospitalization ratios were highest among those >65 years of age and lowest among children 5–14 years of age.

29. **How many hospitals participated in the study? Where are located the 27 provinces participating in the study (north/south)? Are there any differences in the population from these provinces/hospitals?**

   **Response**: There were 424 hospitals participated in the study and the 27 Provinces, distributed both south and north of China. All the hospitals followed the guideline for prevention and control
of H1N1 2009 released by the MOH. There were no any significant differences in the population from these provinces/hospitals.