Answers to reviewer 00504271 comments

We thank reviewer 00504271 for the critical review that raised some ambiguous points. We provide below answers to your judicious comments with consecutive revision of the manuscript:

1. In table 2, the rate of ARDS, seizures and nosocomial infections (nosocomial infection and ventilator-associated pneumonia) were higher in France than in Canada with greater P value compared to that of invasive ventilation. Are there any relationship between vaccination coverage and the rate of ARDS, seizures and nosocomial infections?

Thank you for this comment. ARDS, seizures and nosocomial infection are markers of severity of the H1N1 infection and could have been reduced by vaccination coverage. However this is an association and we cannot conclude that a causal link exists. We modified the method, result and discussion sections to better report this finding.

2. In outcomes section, there is an association of vaccination and asthma with the risk of invasive ventilation (p. 12, table 3). This is controversial with the relationship between decrease risk of invasive and vaccination coverage.

Thank you for this comment. Among diseases that require invasive ventilation, asthma is well known to be associated with a low incidence of invasive ventilation. It is why we are not surprised to observe this result. In the multivariate analysis, vaccination coverage was significant as well as asthma. This suggests that both are independent factors associated with invasive ventilation decrease. We included this comment in the discussion section.

Answers to reviewer 01213276 comments:

We thank reviewer 00213276 for the critical review and especially for his very encouraging comments on of our manuscript : "A very interesting, well written paper. Congratulation, the manuscript is very good!"

Answers to reviewer 00214274 comments:

We thank reviewer 00214274 for the critical review that raised some ambiguous points. We provide below answers to your judicious comments with consecutive revision of the manuscript:

1. The authors pointed out that there are significant benefits related to the vaccination, however: - The incidence of PICU hospitalization in Canada is twice as much as the incidence in France despite vaccination coverage ten times lower in France than in Canada. If this fact is explained by a difference in virulence of H1N1 pdmO9 strains between the two countries (a fact not studied) this means that we are comparing apples with oranges.

Thank you for your comment. We agree that the virulence of the virus seemed higher in Canada. This may have created a bias in the comparison. However, the analysis of critically ill children in Canada provided an association between vaccine delivery and reduction in the risk of invasive ventilation (Table 3). We added a sentence in the discussion to clarify this point.

- There is no difference in mortality - There is no difference in mechanical ventilation duration The difference in PICU length of stay is present only on the mean and not on the median. I am not convinced that these data will persuade on the significant benefits of vaccination.

Thank you for your comment. We agree that there are only slight arguments on the benefit of vaccination. We only reported the data collected and we modified the conclusion according to reviewer suggestion.

2. Abstract:

- In your first sentence the name of the two countries is missing.

Thank you. Done

- Data collection and outcomes: There was 160 children hospitalized in 17 PICUs in Canada corresponding to a population of 5600000 children. You should explain how do you calculate the incidence? (same remark for incidence in France).

Thank you for this comment. The population characteristics obtained by the public agencies are at ages of 15 and 20 years old. The threshold age for PICU admissions in France is 16 years old and 18 years old in Canada. In the method section, we initially provided the true population given by French and Canadian agencies (at 15 years old), we then estimated the incidence using the true respective age PICU threshold for each country (16 yo and 18 yo respectively). We modified the method section to be consistent in the method and result sections.

- Clinical presentation and hospital course. You should explain the difference between critical illness due to influenza and ARDS.

Thank you for your comment. We added a sentence in the method section to explain this.

- Is there any difference in sedation between the two countries that could explain the difference in higher rate of seizures in France?

Thank you for your comment. It is true that sedation used in mechanically ventilated children, benzodiazepine for example, could treat seizures and then decrease seizure incidence. We did not collect data on sedation characteristics between the two countries. However, seizures are usually a reason for admission in PICU and sedation usually occurs during and after the management of seizures, not prior.

- Outcomes. I do agree on the fact that duration of invasive mechanical ventilation was shorter in Canada but total mechanical ventilation was not significantly different.

Thank you for your comment. Reviewer is right, total mechanical ventilation includes invasive and non invasive ventilation durations. This explains why we can have a reduction in invasive ventilation without impact on the total duration. Invasive ventilation is performed in more severe diseases than non invasive ventilation and this can be considered as an indirect sign of decrease in viral infection severity. We added a sentence on this point in the key findings section.

3. Discussion

- Key findings Indeed there is a difference in duration of invasive mechanical ventilation but for the PICU length of stay this difference is less evident. As stated before, if there is a difference in virulence, you cannot compare fairly the two groups. We need more data on the short-term effects of vaccination on the pandemic second wave.

Thank you for your comment. We agree with reviewer suggestion and modified key findings section and conclusion accordingly.

- As far as I understand correctly your fig 1, the decrease in incidence begins, before the expected effect of vaccination (2 weeks).

Thank you for your comment. In Canada, the H1N1 incidence decreased 2 weeks after vaccination campaign start. We are not able to conclude if the vaccination had a causal relationship with this decrease. We included a sentence on this decrease in incidence in the figure 1 legend.

- Conclusions: Despite the fact that critically ill children with H1N1pdm09 were much less likely to have received vaccination against influenza A prior to hospitalization when compared with children in the general population, the country where the vaccination coverage was the higher (21% versus 2%) was the country with the higher incidence of hospitalization was observed and this is a major issue. The study fails to demonstrate the expected primary objective.

Thank you for this comment. Reviewer is right and we added the higher incidence in the first sentence of the conclusion to report this observation.

- Furthermore, few of the secondary objectives were in favor of vaccination.

Thank you. We modified the key findings and conclusions according to this comment.

- In summary: We need more convincing data to demonstrate the benefit of vaccination. May I suggest rewriting this manuscript focusing on the difficulties on comparison between impacts of pandemic viral infection in different countries.

Thank you for this suggestion. This research question is another question and we will consider writing a manuscript on this topic.

Answers to reviewer 02446483 comments:

We thank reviewer 02446483 for the critical review and especially for his/her positive cotation of our manuscript.

The modifications of the manuscript include all the comments suggested:

Postal code provided

Co-authors were place in the acknowledge section

There is two financial supports and they are provided

Audio care tip done

Comments done

References: Done. However, there is references with no PMID and/or DOI. So I cannot provide them