Author’s response to reviews

Title: Influenza Vaccination among children with Idiopathic Nephrotic Syndrome: an investigation of practices

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Author’s response to reviews:

Dear Editor,

We would like to thank you for giving us the opportunity to resubmit a revised version of our manuscript entitled “Influenza vaccination among children with idiopathic nephrotic syndrome: an investigation of practices” (Ref). The comments made by the reviewers have been taken into account, and the manuscript has been modified accordingly, as detailed in the point-by-point answer below. The revised version has been seen and approved by all co-authors. We hope you will find this revised version suitable for publication in the BMC Nephrology, and we would be pleased to provide you with any additional information you may require.
We look forward to hearing from you,

Sincerely,

Reviewer reports:

Reviewer 1 (Paloma Parvex):

Method

1. My understanding is that the diagnosis of Flu was done by phone according to presented symptoms and not by PCR? What is the probability that this children present another viral infection rather than flu?

Our study was a retrospective survey and the 3 influenza-like illnesses were diagnosed by the primary care physician based upon clinical symptoms, as recommended for outpatients in France and USA (https://www.cdc.gov/flu/professionals/diagnosis/molecular-assays.htm). This is why we defined these episodes as influenza-like illnesses as opposed to flu illnesses throughout the text.

We agree with the reviewer that some of these influenza-like illnesses may be caused by another virus. The CDC reported only 54.6% PCR positivity among US patients diagnosed with influenza-like illness during the 2017-2018’s winter.9

The discussion was modified as suggested:

“In this retrospective survey, the diagnosis of influenza-like illness was based on symptoms, as recommended for outpatients. Therefore some of these influenza-like illnesses may be caused by another virus. The CDC reported only 54.6% PCR positivity among US patients diagnosed with influenza-like illnesses during the 2017-2018’s winter.9”

The flow chart was also modified for more clarity.

2. The relapse was defined by 3+++ for 3 days. In clinical practice, we sometimes wait a few days after a viral infection to treat the relapse. Did all this children with these criteria were treated for relapse?
We thank the reviewer for this very relevant remark.

We have therefore taken into account only the relapses that required intensification of steroid-therapy. Indeed, only 1 of the vaccinated patients required an increase of steroid doses. The other child only presented transient proteinuria 5 months following the shot.

We modified the method section as follows:

“The relapse was defined by (i) a proteinuria $\geq 3+$, for three consecutive days and (ii) the need for intensified steroid therapy. Transient proteinuria was not considered as a relapse.”

And the results as follows:

“Conversely, none of the 14 immunized children presented any influenza-like illness and only one (7%) relapsed 15 days following vaccination. Another child presented transient proteinuria 5 months following vaccination. The relapse rate did not significantly differ between vaccinated and unvaccinated children ($p=0.15$).”

Results

1. Among the 43 non vaccinated children, 7% presented an influenza-like syndrome. No PCR was done at that time?

Again, our study was retrospective in nature and the 3 influenza-like illnesses were diagnosed by the primary care physician based upon clinical symptoms. It is not recommended in France or USA to prescribe PCR testing to non-hospitalized patients with flu symptoms, except in selected cases for epidemiology purposes.

2. The authors considered "the relapse events" during the 6-month of the flu season period. The rate of relapse in children who did not present a flu (even if it was not significant) was increased in pts who did not receive the vaccine (11/40). Did authors think that the vaccination may be protective? and non-vaccinated children are more at risk of relapse during this flu-season even if they do not have flu? May authors comment this point?

We thank the reviewer for pointing out this.
First, we must acknowledge that the difference was not significant (p = 0.15).

Second, we do not believe that vaccination in itself may have a flu-independent protective effect on the relapse-risk. Even if not significant, these differences may due to a selection bias. Indeed the parental mistrust in vaccination may be associated to a poorer adhesion to other NS treatments in the group of unvaccinated children.

We have incorporated this to the discussion section

The relapse rate in children who did not present an influenza-like illness seems increased in patients who did not receive the vaccine 11/40 (28%) compared to vaccinated children 1/14 (7%), but the difference is not significant (p=0.15). We do not believe that vaccination has a flu-independent protective effect on the relapse-risk. This trend may due to a selection bias. Moreover, the parental mistrust in vaccination may be associated to a poorer adhesion to other NS treatments in the group of unvaccinated children.

3. Figure 1: The chart with the description of inclusion (arrows): I do not understand the difference between 0 Flu and 14 no Flu in the 14 vaccinated children

We have modified the graph for more clarity.

Antonio Gatto (Reviewer 2): Major comments:

1/ The manuscript is well structured but limited only to adherence to vaccination.

We agree, the aim of this survey was to evaluate vaccination practices and family adherence at our center.

2/ It may also be very useful to evaluate the safety and tolerability of influenza vaccination in patients with nephrotic syndrome with available data.

We agree with the reviewer.

The aim of this survey was to evaluate vaccination practices and family adherence at our center. It was not designed to evaluate the safety of the vaccination as previously mentioned herein and
in the manuscript. Concerning relapses, we can only acknowledge that: “we did not observe an increased risk of vaccine-induced relapse of INS (1/14 relapses after vaccination versus 5/14 before vaccination p=0.38), even though our study was not designed to evaluate the safety of vaccination and the risk of vaccine-induced relapse.” Concerning other complications, no vaccinated child presented any vaccine-induced influenza-like illness and parents reported no significant side effect.

This was added to the discussion.

“In the present study, patients’ parents/legal guardians reported no flu-like illness in the vaccinated group. However, these results are to be taken with caution since this study was not designed to evaluate the efficacy of influenza vaccination or vaccine-induced disease.”

“In the present survey, no vaccinated child presented any vaccine-induced influenza-like illness and parents reported no significant side effect.”

3/In the 2/14 patients vaccinated with relapse, how long from the vaccination has the relapse occurred?

Following Reviewer 1 suggestion, we only took into account the relapses that required intensified steroid therapy and not transient proteinuria. Therefore only 1 patient had a relapse 15 days after vaccination.

4/ It should be emphasized even if on a very small number of patients the reduction in the rate of relapse in patients vaccinated in the 6 months before (36%) and in the 6 months after vaccination (7%).

We thank the reviewer for pointing out this. We have added the following sentence to the abstract and conclusion:
“Relapse rates were not increased in vaccinated children compared to unvaccinated children (p=0.15), nor in the 6 months following vaccination compared to the 6 months prior (5/14 vs 1/14, p=0.20).”

And in the discussion

“Indeed, we did not observe an increased risk of vaccine-induced relapse of INS (1/14 (7%) relapses in the 6 months after vaccination versus 5/14 (36%) in the 6 months before vaccination p=0.20), even though our study was not designed to evaluate the safety of vaccination and the risk of vaccine-induced relapse.”

Minor comments

5/ English must be reviewed in particular in the abstract and in the discussion section.

The first submitted manuscript had been corrected and approved by an English academic teacher before submission. As suggested, we had the second version reviewed by another native-English speaker.

References