Author’s response to reviews

Title: The effect of physician's recommendation on seasonal influenza immunization in children with chronic diseases

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Author’s response to reviews: see over
Comments to Reviewers

Reviewer: Bruno Ciancio

Abstract
1. In the methods please mention which type of immunization predictors have been analysed.
The list of predictors of influenza immunization has been incorporated into the Abstract.

2. In the results report the overall number of children recruited.
Accomplished

3. It is not clear what is the reference group for calculating the ORs, e.g. Receiving a recommendation by family pediatricians…was associated with OR=191.93….of being vaccinated compared to what (not receiving a recommendation or receiving a recommendation from someone else?).
We clarified the reference category in the Abstract and we made Table 3 consistent reporting the results of the multivariate analysis that considers the dichotomy variable recommendation/no recommendation.

4. It is not clear whether these are crude or adjusted ORs.
According with the comment of another Reviewer, we reanalyzed data to calculate prevalence ratios (PR). Adjusted prevalence ratios (aPR) were reported in the Abstract, adjusting for number of visits, socio-demographic variables and underlying diseases. We changed the text accordingly and we better described the analysis in the Methods section.

Methods
5. Information should be provided on how many specialty clinics were included overall and in each region. It should also be described whether these clinics were a convenient sample of all the specialty clinics in the three regions or whether any randomization was attempted. The former seems to be the case as described in the discussion, however one should not read until the discussion to get this information.
We chose a convenience sample including the major Reference Center for each pathology in the three Italian Regions in three geographic areas of Italy to account for geographical trends. We added in the Methods section the estimated total number of children with chronic diseases rather than the number of specialty clinics that is much more difficult to describe.

6. Children with neurological disorders should be better described. They seem to represent a different population of children than the others included in the study. They are indeed the least represented category in the study, though depending on who they are they could represent the largest group in the population. They probably have different (less?) access to specialized pediatric services and may follow a different path to influenza immunization. The authors should consider excluding this group from the analysis or providing more information to justify their inclusion.

We included in the analysis 60 patients with chronic neurological diseases corresponding to different conditions, all falling into categories that are targeted for influenza immunization by the Italian Ministry of Health. Specific diagnoses have been added to the text in the Methods section. Regarding the possibility that children with different neurological diseases follow different paths, we do not believe this is the case. Enrolled children in this category have rather severe diseases that require continuous monitoring and who regularly attend specialty clinics. These details have been added into the text.

7. Results should be adjusted for or stratified by number of visits in the previous year/s. Children with a higher number of contacts with the health care system had also more opportunities to receive a vaccine recommendation but also to be vaccinated than children with fewer contacts. Therefore number of visits can be a confounder for many of the determinants described in table 3.

We reanalyzed our data including the number of visits in the previous year as a potential confounder.

Results

8. Table 2: column headings – N and (%) should be removed.
Accomplished
9. Table 3: I would suggest adding one column to describe the actual numbers behind the ORs. I would also suggest reporting the total number of subjects included in the multivariate model to have an idea of the number of records lost due to missing values in one of the included variables. Please specify whether P values from multivariate analysis are from likelihood ratio test of Wald test.

We reanalyzed the data calculating prevalence ratios instead of odds ratios according to the comment of another reviewer. The frequencies behind PRs have been added to Table 2 and Table 3 while the number of observations for each model has been added to Table 4. The statistical test used for statistical significance in multivariate models has been described in the Methods section.

Discussion

10. The study population is that of children with chronic conditions and frequent access to pediatric services, often specialized pediatric services. It is therefore difficult to draw conclusions on the role of recommendations issued by community vaccinators or other health care professionals such as family pediatricians or family doctors. This limitation should be better described in the discussion and results interpreted accordingly.

The observation that the study population is strictly monitored by a specialty clinic does not exclude that children with chronic diseases attend the family pediatrician’s office. We analyzed the frequency of contacts with different providers and we added in the discussion a sentence on the frequency of visits by the family pediatrician to better describe the setting of these patients.

11. Some of the conclusions seem too strong for a cross-sectional study. For example the statement Our path shows that families of patients with chronic diseases refer most frequently to specialty and family pediatricians to receive recommendations on influenza vaccine is difficult to justify. It could well be that a similar or higher number of children with chronic conditions follows a different pattern which could not be described simply because they did not attend a specialized clinic. For instance, this could be the case of children with less severe chronic conditions not requiring frequent specialized assistance but still at high
risk of severe influenza. In general some of the limitations related to the study design should be better described in the discussion.

We addressed the limitation relevant to the potential selection bias in the Discussion section. It is clear that this potential bias may overestimate immunization coverage. Nonetheless, since this should be a very well monitored population and coverage figures are poor, we expect that children with less severe chronic conditions may be well below the coverage measured in the present population. We addressed these observations in the discussion. Indeed the access to specialty clinics is free of charge for patients with chronic diseases. On the other hand, other barriers such as remote location and low socio-economic status may influence the access to specialty clinics and poor compliance to follow up visits. We underline, however, that, despite the potential selection bias, the magnitude of the association measures is very high.

12. Recall bias is mentioned but not explained. Are those remembering their vaccination status also more likely to remember whether and who advised them to be immunized?

As the Reviewer noticed, the recall of recommendations may be better in patients who did receive influenza immunization compared with those who did not. The explanation has been added to the Discussion.
1. In Background: The major problem in the background is that there it is not clear what the gap in the literature is that this study is trying to address. This could be addressed with a sentence like this: ‘While it clear that provider recommendation for influenza vaccination is a strong predictor of vaccination, the likelihood of vaccination by type of provider is poorly understood. Therefore, the objectives of this study were to…’ and then continue with the objectives above, or something similar.
We followed the Reviewer’s suggestion to better frame the Background to clarify the study question. We also added some comments on the observation that children with chronic diseases may have different determinants of influenza immunization compared with healthy children, and that therefore require specific investigations

2. The other major issue is to set up the importance of the ‘immunization path.’
While this is an interesting concept, it may be somewhat unique to the healthcare system in Italy. For example, what I can discern from the figure is that very few specialty physicians stock flu vaccine and around half of family pediatricians do.
It would be helpful if the authors could explain why the ‘immunization path’ is important and how these findings are generalizable to a broader population.
Despite the concept of the “immunization path” may be unique to the Italian Health care system, we believe that different actors are often involved in the care of children with chronic diseases. Multiple contacts with different specialists may be required in complex diseases and may result in different paths for immunization decisions. We better clarified this concept in the Discussion.

3. Methods: Was proof of vaccination required to consider the child vaccinated?
Were there any families who said that their child was vaccinated that did not bring in their immunization card? Or were children excluded if they did not bring in an immunization card? Did anyone decline to be part of the study?
Families without child’s immunization card were not considered for the interview. Among suitable families, none declined to participate in the study. These details have been added in the Methods and in the Results sections.
4. Were the differences in specialty related to the practices of a few physicians? If the interviewer visited the health centers on the same day of the week, it is conceivable that they could be interviewing patients of a single physician. The use of three different regions is a strength, but within each region, was there just one center involved in the study? It would be helpful to know not just the study population of the patients interviewed (which is presented), but since the authors are drawing conclusions about the providers, the population of providers as well. In our setting, children with chronic diseases are assigned to the entire specialty clinic group, not to a single physician. Therefore, the likelihood to select health providers was low within the selected clinics. In a separate analysis (not shown in this study) we analyzed the pattern of recommendations provided by different physicians within the same clinics and we observed a very high level of consistency. Finally, since we collected information from families, we did not limit the information on influenza recommendation to specialty clinics only. This information has been incorporated in the Discussion.

5. Another major issue is that asthma is not considered a chronic disease for the purposes of this study, since it is the most common chronic disease for which flu vaccination is recommended. There may be any number of good reasons why the authors chose to exclude these patients (infrequent contact with specialty physicians in Italy?) but this should be made clear in the paragraph on why the conditions that were studied were included. We agree with the Reviewer that asthma is the most common chronic disease for which influenza immunization is recommended. However, while the diseases included in our study show a rather homogeneous pattern of severity, asthma is a disease with a very wide clinical spectrum. We felt that a specific study focusing on asthma only would have been more appropriate to investigate the determinants of influenza immunization. Moreover, several other studies have been already published on this subject. We better clarified in the Methods section which were the criteria for selecting the diseases included in the present study.

6. Results: The numbers in the figure don’t add up. For example, the boxes for ‘recommendation’ add up to 294, not 275. This may be because some of the 275 got recommendations from more than one provider, but that is not clear. Also, the number of unvaccinated patients adds up to 125 in the figure, which would make the percentage vaccinated 54.5, not 57.5. Why the discrepancy?
Figure 1 was completely reformatted. We better framed the resulting “paths” and we added a category of children receiving a recommendation by more than one provider. We also realized that a typing error was present in the previous version (patients receiving recommendation by community vaccinators were 10 and of these 8 has been immunized and 2 unimmunized. We wrote the opposite).

7. I am not able to check the odds ratios from the information given. This could be fixed by adjusting the figure to have 5 options for recommendations: 1) family pediatricians, 2) specialty pediatricians, 3) community vaccinator, 4) recommendation from more than one type of provider (with a footnote describing this population), and 5) those receiving no recommendation. Not only would this clarify the figure, but it would also be interesting to see the odds ratio for those patients receiving more than one recommendation. Theoretically, all of these children should receive a recommendation for a flu vaccination at every visit with a medical provider, at least in influenza season.
We agree that adding this information better clarifies the results. We changed Figure 1, Table 2 and Table 3 accordingly.

8. Why are the odds ratios by specialty not shown in Table 3? Table 3 shows odds ratios by disease, but the text of the abstract and results gives results by specialty. In these calculations, did the authors adjust for random effects? When doing a logistic regression like this, I think this would be important.
Table 4 (previously Table 3) and the abstract have been modified to reflect the same information. We did adjust the multivariable model for random effects and no changes were highlighted.

9. Discussion: Fourth paragraph about the ‘immunization path’ is simply a restatement of the results. Again, somehow the authors need to convey why this is important.
We better addressed the concept of “immunization path” (see also comment 2) and explained why it may be relevant to the immunization decision process in children with chronic diseases.
10. **Abstract:**

Background: Make into one paragraph. ‘Authorities’ is misspelled. Change ‘medical profiles’ to ‘medical providers.’ A stylistic issue: rather than stating ‘we measured…’, clearly written objectives would help the reader. For example: “In this study of a nationally representative sample of children with chronic medical conditions, we sought to assess: 1) percent of children with documented receipt of influenza vaccine in the prior season by type of medical provider; 2) factors associated with receipt of influenza vaccine; and 3) the mechanisms by which these children received their immunizations.”

Accomplished

11. **Methods:** Information on recommendations by physicians (should this be ‘providers’ since presumably community vaccinators are not physicians?) was collected by face-to-face interview, but it appears that information on influenza recommendation was collected only by proof of vaccination.

We clarified that community vaccinators are physicians often specialized in public health. We selected children with written proof of immunization only as described in the Methods (see comment 3).

12. **Results:** Way too many digits in the Odds Ratios, particularly for the CIs. One or two is fine.

Accomplished

13. **Main text**

Background: The first sentence shouldn’t be a paragraph by itself. The mechanisms paragraph is helpful although it could be tightened up a bit. Also, actual mechanisms are stated for CF, neurologic conditions, and diabetes, but for HIV and Down Syndrome, no mechanisms are listed – just a re-statement that they are high risk.

We performed a review of the literature on the mechanisms that may increase the risk of influenza (increased susceptibility or severity) in children with Down syndrome of HIV infection, but none of the retrieved publications stated a specific mechanism for these diseases. One can speculate that immunodeficiency may explain why these disease are at
high risk, but since no clear demonstration of such an explanation was available we preferred to quote just the publications that indicated these diseases as at high risk.

14. **Next paragraph – ‘contrarily’ is awkward.**
We changed the text to make it more fluent.

15. **Methods:**
Regarding the actual interviews, was there a standardized form that the interviewer used to collect the information, or were these more open-ended qualitative interviews? Based on the results, it seemed that only information collected was “Did you receive a recommendation from a provider for flu vaccine last season? If yes, from who?” And then an examination of the vaccine card. Was there more to this interview?
Indeed, we used a standardized questionnaire to collect information on vaccination history, recommendation received by type of provider but also on barriers encountered by parents to completing immunizations in a timely manner. Information on hospitalizations or any other contact with health care centers was also recorded. We reported more details in the Methods section.

16. **Results**
The first two paragraphs of the text of the results are generally clear. However, the sentence that begins ‘Community vaccinators..’ should be re-stated since there is no denominator information. While technically correct, it is somewhat misleading. Would suggest re-stating to say something like ‘Fewer families reported receiving an influenza recommendation from community vaccinators, although it is unclear how many families had contact with one.’ For all the sub-specialties, the reader has some idea that they have been seen by that provider, since they are actually in their clinic. Presumably, most also have a pediatrician too, although conditions with more frequent visits may be less likely to see their general pediatricians than their specialist (like CF and HIV).

We changed the text according to the Reviewer’s suggestions. Moreover we added information on the number of contacts with family pediatricians in the previous year and the proportion of children immunized in public practices led by community vaccinators to give an idea of the pattern of contacts with other health providers.
17. It might be useful to include p values in Table 1 so that the reader can more easily see the differences in the 5 patient populations.
A column with p values has been added to Table 1.

18. Why isn’t neurologic disease in Table 3? It looks like maybe it’s the reference, but that’s not clear from the table.
We better explained in the Methods section that neurological diseases have been used as the reference category. We added a line in Table 4 with information on reference categories

19. The n's are left off of the row on immunization coverage in Table 2.
Table 2 now shows the number of children who received a recommendation by each provider.

20. Discussion
First two paragraphs are generally fine. Third paragraph should be part of the second paragraph.
The fifth paragraph fairly wordy, and it’s not clear why it starts with the discussion of what is effective in improving immunization coverage. The first four sentences are extraneous. It appears that the authors are stating current evidence, but are not really relating it back to the current study.
We thoroughly reviewed the Discussion to better incorporate the observations already published about interventions with proved efficacy in increasing immunization coverage. We also highlighted how information available for the general population may not entirely apply to children with chronic diseases.

21. Also, the sentence “In our study we found that even a specific recommendation by a physician alone is effective...” is not entirely accurate. It would be more correct to say, “In our study, we found that a specific recommendation from a physician was highly associated with receipt of influenza vaccine” since there were many factors that were unmeasured. The next paragraph that begins ‘our path’ could actually conclude the preceding paragraph and would suggest saying ‘our study’ instead of ‘our path.’
We agree with the Reviewer’s comment and we changed the text in the Discussion. However we added the observation that in a setting like the one in which our study was conducted other relevant interventions usually included in multilevel interventions are simply not in place (see Briss AM J Prev Med 2000). For this reason we reframed our statement clarifying that in our setting, in absence of recall systems or other educational initiatives, the recommendation provided by a physician was strongly associated with immunization.

22. In the next paragraph, what is a ‘clinical reference centre?’ Is it a large referral center? That paragraph and the one following appear to be the ‘Strengths and Limitations’ section. This should be made clear (“This study had several strengths and limitations. First…”). Also, the writing is a little awkward through these two paragraphs and could be tightened up.

We better introduced a section on strengths and limitations and we better explained what a clinical reference centre is intended in our setting. We also shortened the sentences to make them more fluent.

23. There are two more paragraphs that are single sentences and should be included all as one paragraph. A further limitation of this study (as alluded to above) is that there is not denominator data on patient encounters with specific types of providers. For example, in the figure, only 10 patients received a recommendation from a community provider, but we don’t know how many actually came in contact with a community provider, other than to get an immunization. Community providers may actually be doing an excellent job of making recommendations to patients, but we don’t know that (for them or any of the others).

We added information on the contacts with other providers and we adjusted results in the multivariate analyses for the number of visits in the previous year by specific provider. In our setting, however, the number of contacts with other providers did not show any effect on the association with immunization. This result suggests that the impact of recommendation is independent from the number of contacts with the health provider. We added a comment on this observation in the results.

24. In the concluding paragraph, would suggest using a different word than ‘attitude.’

Accomplished
25. In the bibliography, some of the titles are in italics and some aren’t. We reformatted the reference section.
Reviewer: Fredi Alexander Diaz

1. Regarding the measures of association, I think it would be better to use prevalence ratios instead of odds ratio. This is because immunizations are common and in these cases, OR overestimate the strength of associations.
We agree with the Reviewer and we reanalyzed the data calculating prevalence ratios instead. For this reason the multivariable analysis was conducted through a generalized linear model with Poisson family, log link and robust error variance. The interpretation of results is obviously the same.

2. In the particular case of the association between immunization and recommendation, I would prefer expressing the frequency of immunization in both groups: with and without recommendation.
We did add to Table 3 the immunization coverage observed in different groups together with numerators and denominators

3. Also in the abstract, please include coverage (%) by level of recommendation, instead of odds ratios.
Accomplished

4. In the discussion, I recommend an extension of the comment about recall bias.
It is clear that those who received immunization could remember better the recommendation, which would overestimate the association.
We extended our previous comment on recall bias to discuss how this could have affected the results.

5. In Table 1, the first row has percentages relative to the total horizontal and the other rows are percentages relative to the total vertical. That may be confusing, I think in the subtitle of each comorbidity could put the number of participants in parentheses, for example: "Cystic fibrosis (n = 57)."
Accomplished.