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OPEN PEER REVIEW

Serotype Distribution of *Streptococcus pneumoniae* Carriage in Six-Month-Old Infants: A Cross-sectional Study During 2017-18, Tehran, Iran

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

3 comments · 7 Jan 2021 – 20 Mar 2021

Associate Editor

MINOR REVISION 7 Jan 2021

Dear author
1- Please include studies conducted on the 6-month population in other countries in the discussion section.
2- Considering that in this study, the relationship between colonization and other factors has been investigated, this study can be placed in the category of exploratory studies; exploratory studies are studies that mainly lead to the production of hypotheses, and further studies should be performed to investigate these hypotheses; therefore, it is necessary to refer to the studies required to complete the findings of this study in the discussion section. Studies on different vaccines can also be suggested.
Regards

Alireza Nateghian Reviewer

MINOR REVISION 29 Jan 2021

Thank you very much for sending this article to me.
The whole article is OK, interesting, and informative. I would like to ask a question about the utility of the 23-valent polysaccharide vaccine in children over 2 years of age in Iran. Given the good protection and lower cost of the vaccine available in our society, do the authors recommend at least one dose for children over 2 years of age who attend day care? If not, please discuss this in the Discussion.

Associate Editor

MAJOR REVISION 20 Mar 2021

Dear authors
Please follow the reviewer's comments and reply in a point-by-point manner. Please highlight the new changes in the manuscript in a different color.
English copy-editing is warranted before the next submission.

Editor comments:
First of all, use continuous line numbering in the revised manuscript (not separately for each page).
Second, in my opinion, the results of this study are not conclusive due to the very small sample size and the age of the studied cases. If this study is conducted with a similar sample size in the older age group (6-12 mo), the colonization incidence rate may change significantly. In fact, a very low colonization rate is the reason for the few reports in this age group.
Other shortcomings:
Title
The title should be corrected:
Suggested title: "Serotype distribution of Streptococcus pneumoniae carriage among 6-month-old infants: A cross-sectional study during 2017-18, Tehran, Iran"
Abstract
Results: The results in the abstract section are not informative. Add the number (%) for each serotype (also for breastfed and formula-fed infants).
Also, add serotype coverage of PCV-10.

the results section.
Keywords: move "Streptococcus pneumonia" to the beginning of the keyword list.

Introduction:
Line 12-13: As you mentioned an incidence range, more references are needed.
Line 19-20: Regarding this statement: "therefore, the lower the age of colonization, the longer the time of carriage", remove this phrase or add more explanation. As you know, there is a maximum time for pharyngeal colonization. Also, in the first sentence, no data regarding age are presented, so "therefore" is not meaningful.
Page 4, line 3-5: This part is difficult to read, so rewrite it with simpler words and separate sentences. "Breastfeeding protective factors are abundant and include immunoglobulin A (IgA), lactoferrin, and oligosaccharides as analog receptors providing secondary protection against colonization of bacteria in the nasopharynx."
Page 4, line 10-12: "The lack of comprehensive information on circulating serotypes in Iran in different ages is the main reason for designing this study to identify circulating pneumococcal serotypes in infancy in Iran" is not a true statement; there are many reports in this regard.
Methods:
Exclusion criteria should be mentioned, for example, daycare center attendance or receipt of PCV vaccines.
Page 7, line 21: "Overall, the most common isolated serotype was serotype 23F"; what is the total number (%)?
Page 7, line 21: Add some description of PCV-10 coverage.
In my opinion, the data provided regarding PPSV-23 are not informative or relevant in this age group, so replace your comparison with the PCV-10 vaccine.
Page 10, remove line 4-12 (not relevant to the study topic), from "The results also showed that bronchiolitis was significantly" to "such a conclusion could not be judged secondary to the small number of samples".
Add study limitations at the end of the discussion section.
The conclusion should be provided in a distinct section.
Thanks

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Reviewer #1

- **Comment**. I would like to ask a question about utility of 23 valent polysaccharide vaccine in over 2 years kids in Iran. With the good protection and cheaper vaccine, we have in our society, does the authors recommend it at least one dose for kids after 2 years of age who go to day care and if not, please discuss it in discussion.
- **Answer**. Thanks for the precious comment, this study cannot suggest the usefulness or uselessness of early 23-valent polysaccharide vaccination in general infants population, or those with risk factors (i.e. infants or those with siblings, who go to the daycare centers). Considering the implicit and explicit costs, cost-effectiveness studies are needed to evaluate the effectiveness of this early vaccination, and the potential harms of missing it. This fact is added to the end of the discussion part.

Associate Editor #1

- **Comment**. Please include studies conducted on the 6-month population in other countries in the discussion section.
- **Answer**. Unfortunately, there are no similar studies with exact age group match. Studies with similar age groups are added.

- **Comment**. Considering that in this study, the relationship between colonization and other factors has been investigated, this study can be placed in the category of exploratory studies; Exploratory studies are studies that mainly lead to the production of hypotheses, and further studies should be performed to investigate these hypotheses; Therefore, it is necessary to refer to the studies required to complete the findings of this study in the discussion section. Studies on different vaccines can also be suggested.
- **Answer**. The need for future researchers are now noted in the end of the discussion part.

Editor Comments

- **Comment**. use continuous line numbering in the revised manuscript (not separately for each page).
- **Answer**. Thanks for your comment. The line numbering is corrected now.

- **Comment**. the results of this study are not conclusive due to the very small sample size, and also the age of studied cases. If this study is conducted in a similar sample size in the older age group (6-12 mo), the colonization incidence rate may be changed significantly. In fact, a very low colonization rate is the reason for the little reports in this age group
- **Answer**. Thanks for your precise comment. This is a limitation for this study and has added to the end of the discussion part. It is suggested to run future studies in higher sample sizes, or wider age groups.

- **Comment**. The title should be correct.
- **Answer**. The title is edited as your precious suggestion.

- **Comment**. the results of the abstract section is not informative. Add a number (%) of each serotype (also for breastfed and formula-fed infants). Also, add serotype coverage of PCV-10. The author concludes that "At this age, the type of feeding could not significantly influence the frequency rate of S. pneumoniae colonization", so you mandate to add the incidence rate of breastfed and formula-fed infants in the result section.
- **Answer**. The abstract is enriched with numbers and percentages.

- **Comment**. move "Streptococcus pneumonia" at the first of the keywords.
- **Answer**. Thanks for your precise comment. The keyword is moved now.

- **Comment**. as you mentioned incidence range more references are needed

- **Answer**. Thanks for your precise comment. The written rate is deducted from a variety of papers, all referenced now.

- **Comment**. about this statement: "therefore, the lower the age of colonization, the longer the time of carriage", remove this phrase or add more description. As you know, there is a maximum time for pharyngeal colonization. Also, in the first sentence, no data regarding age is presented, so "therefore" is not meaningful.
- **Answer**. The phrase is removed.

- **Comment**. This part is difficult to read, so rewrite it with simpler words and separate sentences. "Breastfeeding protective factors are abundant and include immunoglobulin A (IgA), lactoferrin, and oligosaccharides as analog receptors providing secondary protection against colonization of bacteria in the nasopharynx."
- **Answer**. Thanks for your valuable comment. The sentences are paraphrased now.

- **Comment**. "The lack of comprehensive information on circulating serotypes in Iran in different ages is the main reason for designing this study to identify circulating pneumococcal serotypes in infancy in Iran", this is not true statement, there are lots of report in this regard.
- **Answer**. Thanks for your precise comment. The sentence is clarified in this way: “This study is designed to increase the information on circulating serotypes in Iran in different ages.”

- **Comment**. Exclusion criteria should be mentioned. For example, daycare center attendance or recipient of PCV vaccines.
- **Answer**. The exclusion criteria are highlighted in the end of the “Sample size and study design” subheading.
- **Comment**. Overall, the most common isolated serotype was serotype 23F", what is the total number (%)?

- **Answer**. The n and the percentage is added now.

- **Comment**. add some description for PCV-10 coverage. In my opinion, the data provided regarding PPSV-23 is not informative and relevant in this age group. so replace your comparison with the PCV-10 vaccine.
- **Answer**. The data PCV10 vaccine is added now.

- **Comment**. remove line 4-12 (not relevant to the study topic). From "The results also showed that bronchiolitis was significantly" to "such a conclusion could not be judged secondary to the small number of samples".
- **Answer**. The term is removed, due to your valuable comment.

- **Comment**. Add study limitations at the end of the discussion part.
- **Answer**. The limitations are now added in the end of the discussion part.

- **Comment**. The conclusion should be provided in a distinct section.
- **Answer**. Thanks for your comment. The conclusion part is separated now.

2 Revision 1

1 comment · 14 Jul 2021

Associate Editor

MINOR REVISION 14 Jul 2021

Editorial comments
Dear authors
The manuscript's overall presentation improved after amendments. Although your replies to the concerns of the reviewers are satisfactory, you need to address the following shortcomings:
Line 17: add serotype coverage of PCV-10 in your studied infants.
Line 22: remove "Pharynx, Breast milk, and, Formula milk" from the keywords and reorder the keywords as follows: "Streptococcus pneumoniae, Colonization, infants, serotypes, vaccine".
Line 42: replace "a study from Finland had further" with "previous studies".
Lines 48-50 need a reference.
Lines 135-137: Rewrite this part: "Totally, the isolated stereotypes were 73%, 50%, and 84% common with the stereotypes included in the PCV13, PCV10, and PPSV23; respectively." as "Accordingly, PCV13, PCV10, and PPSV23 pneumococcal vaccines, have 73%, 50%, and 84% stereotype-specific coverage in our study".
Line 136-140: rewrite this part: "In the breastfed group, 30%, 18%, and 100% of the isolated serotypes were respectively common with PCV13, PCV10, and PPSV23; whereas, in the formula-fed infants, 62%, 100%, and 66% of the isolated serotypes were common with PCV13, PCV10, and PPSV23; respectively." as "In subgroup analysis, stereotype-specific pneumococcal vaccine coverage were 30%, 18%, 100%, and 62%, 100%, 66% in breastfed and formula-fed infants for PCV13, PCV10, and PPSV23; respectively".
Table3: title should be corrected: "Clinical characteristics of breastfed and formula-fed infants".
Table3: replace "Etiology of Hospitalization" with "admission cause".
Table4: title should be corrected: "Clinical characteristics of colonized infants (pharyngeal culture-positive) versus non-colonized infants."
Table5: The sum of the recorded "Breastfed" colonized infants is 10. Recalculate and correct missing data (it seems that "11A" is missing).

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Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Associate Editor #1

- **Comment**. Line 17: add serotype coverage of PCV-10 in your studied infants.
- **Answer**. The coverage rate is added to the abstract, regarding your valuable comment.

- **Comment**. Line 22: remove "Pharynx, Breast milk, and, Formula milk" from keywords and reorder keywords as follow: "Streptococcus pneumoniae, Colonization, infants, serotypes, vaccine"
- **Answer**. The keywords are rewritten now.

- **Comment**. Line 42: replace "a study from Finland had further" with "previous studies"
- **Answer**. The phrase is rewritten.

- **Comment**. Lines 48-50 need reference.
- **Answer**. The paragraph reference is clarified, regarding your precise comment.

- **Comment**. Lines 135-137: Rewrite this part: "Totally, the isolated stereotypes were 73%, 50%, and 84% common with the stereotypes included in the PCV13, PCV10, and PPSV23; respectively."; as "Accordingly, PCV13, PCV10, and PPSV23 pneumococcal vaccines, have 73%, 50%, and 84% stereotype-specific coverage in our study"
- **Answer**. The phrase is rewritten

- **Comment**. Line 136-140: rewrite this part: "In the breastfed group, 30%, 18%, and 100% of the isolated serotypes were respectively common with PCV13, PCV10, and PPSV23; whereas, in the formula-fed infants, 62%, 100%, and 66% of the isolated serotypes were common with PCV13, PCV10, and PPSV23; respectively.", as "In subgroup analysis, stereotype-specific pneumococcal vaccine coverage were 30%, 18%, 100%, and 62%, 100%, 66% in breastfed and formula-fed infants for PCV13, PCV10, and PPSV23; respectively".

- **Answer**. Thanks to your precise comment, the sentence is rewritten.

- **Comment**. Table3: title should be corrected. "Clinical characteristics of breastfed and formula-fed infants"
- **Answer**. The table caption is revised, according to your precise comment.

- **Comment**. Table3: replace "Etiology of Hospitalization" with "admission cause"
- **Answer**. The phrase is replaced.

- **Comment**. Table4: title should be corrected. "Clinical characteristics of colonized infants (pharyngeal culture-positive) versus non-colonized infants.
- **Answer**. The title is corrected.

- **Comment**. Table5: The sum of the recorded "Breastfed" colonized infants is 10. Recalculate and correct missing data (it seems that "11A" is missed).
- **Answer**. The 11A prevalence for breastfed group is corrected, thanks to your valuable comment.

3 Revision 2

1 comment · 4 Aug 2021

Associate Editor

ACCEPT 4 Aug 2021

I read the revised manuscript.
I have no further comments to add. I thank the authors for their very detailed replies to my comments.