Author's response to reviews

**Title:** Risk Factors for Serotype 19A Carriage After Introduction of 7-valent Pneumococcal Vaccination

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**Author's response to reviews:** see over
To the Editor,

Thanks you for the comments and helpful suggestions, which we have taken into account in this revised version as described below.

We hope that this amended version of our manuscript will be suitable for publication in *BMC Infectious Diseases Journal*.

Yours faithfully

Robert Cohen
MS: 2036972622502495 - Risk Factors for Serotype 19A Carriage After Introduction of 7-valent Pneumococcal Vaccination

We thank the editor for the comments and suggestions that have helped us to improve the quality of the manuscript.

Additional editorial requirements:

> - Please rewrite your competing interests to make it more clear, for example: "Bernard Fritzell and Eric Bonnet are employed by Pfizer and financial support was given by Pfizer. All other authors declare that they have no competing interests."

As requested we have rewritten our competing interests as follows:
“Bernard Fritzell and Eric Bonnet are employed by Pfizer and financial support was provided by Pfizer. All the other authors declare that they have no competing interests”

> - On the title page please include the full names, institutional addresses, and e-mail addresses for all authors.

We have completed the title page as requested:
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> - We recommend that you copyedit the paper to improve the style of written English.

As requested, a native English medical writer has checked the manuscript.
This is a research type of article and is appropriate for publication at BMC Infectious Diseases. An increase in the incidence of *S. pneumoniae* serotype 19A isolation has been observed in many countries, and 19A is now the serotype most frequently isolated from patients with invasive and mucosal pneumococcal diseases. Serotype 19A is also a frequent nasopharyngeal carriage serotype, and is frequently resistant to antibiotics. The investigation of the factors influencing serotype 19A carriage is important and the question posed by the authors is well defined. The medical records of children managed by 66 French pediatricians and general practitioners distributed throughout France were examined, standard procedures of isolation and identification of *S. pneumoniae* were applied, antimicrobial susceptibility testing was performed using the agar-dilution method, and for the statistical analysis univariate analysis and multivariate logistic regression were applied. All methods selected by authors are appropriate and well described. The data presented in the manuscript are sound and reveal the factors influencing serotype 19A carriage. The paper provides valuable information on the post 7-valent pneumococcal conjugate vaccine effects and contributes to the more effective use of the new pneumococcal conjugate vaccines. The manuscript is prepared according to the relevant standards for reporting and data deposition. Discussion and conclusions are well balanced and adequately supported by the data. The authors do not provide any statement on the limitations of their work.

As requested we have added the following sentences (page 7, lines 6 to 10): “The main limitation of our study is the homogeneity of our population (children aged 6 to 24 months, PCV7-vaccinated, without antibiotics exposure within 7 days before enrolment, and with no severe underlying health disorders) making it more difficult to extrapolate our findings to other populations. Furthermore, our study is based on nasopharyngeal carriage results and cannot be directly extrapolated to invasive pneumococcal disease or middle-ear infections.”

Authors’ contributions and acknowledgements are clearly stated. The title and abstract accurately convey what has been found and the writing is acceptable. After assessment of the validity of the manuscript, I would like to advise to accept this manuscript for publication without revision.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests: Yes, I have received reimbursements and fees for participating in Advisory Board Meetings and serving as a speaker in symposia organized by Pfizer and GlaxoSmithKline Biologicals.
The manuscript of Cohen et al. examined factors potentially related to 19A NP carriage by analyzing data from an ongoing prospective French national surveillance study of pneumococcal NP carriage in young children. However, there are some points that require clarifications.

**Major Revisions**

- A differentiation between children evaluated for check up and those with AOM has to be performed and results have to be presented divided in these two groups.

  **We have added to Table 1 a comparison of the AOM group versus healthy controls and the p values for each characteristic.**

- In the abstract, the results and the discussion, factors associated with 19A carriage but also with carriage of PNSP has to be adequately considered.

  **As requested we have added the following sentences to the abstract (page 2, lines 16 to 21):**

  « Logistic regression analysis showed that the main factors associated with PNSP carriage were AOM (OR=3.09, 95% CI [2.39;3.98]), DCC (OR=1.70, 95% CI [1.42;2.03]), and recent antibiotic use (OR=1.24, 95% CI [1.05;1.47]. The main factors predictive of 19A carriage were recent antibiotic use (OR=1.81, 95% CI [1.42;2.30]), AOM (OR=1.67, 95% CI [1.11;2.49]), DCC (OR=1.56, 95% CI [1.21;2.2] and young age, <12 months (OR=1.51, 95% CI [1.16;1.97]).»

  **We have added the following sentence to the results section this sentence (page 5, lines 24 to 26):**

  « Logistic regression analysis showed that the main factors associated with PNSP carriage were AOM (OR=3.09, 95% CI [2.39;3.98]), DCC (OR=1.70, 95% CI [1.42;2.03]), and recent antibiotic use (OR=1.24, 95% CI [1.05;1.47]. »

  **This point was underlined in the discussion section of the initial version.**

**Level of interest: An article of importance in its field**

**Quality of written English: Needs some language corrections before being published**

**As also requested by the Editor, a native English medical writer has checked the manuscript.**

**Statistical review: No, the manuscript does not need to be seen by a statistician.**

**Declaration of competing interests:'I declare that I have no competing interests’**

**Reviewer's report N°3**

In this study Authors investigated the risk factors potentially related to S.pneumoniae 19A serotype NP carriage in a population of children aged 6 to 24 months after the introduction of PCV7 conjugated vaccine. Multivariate logistic regression was used to analyze factors influencing *S.pneumoniae* carriage, carriage of resistant SPN strains, of 19A serotype strains
and resistant 19A serotypes. Authors demonstrated that 19A carriage could be linked to antibiotic exposure, DCC attendance and to AOM. The subject of the manuscript is of great interest for scientific community in the light of the epidemiological picture. The paper is methodologically and scientifically accurate, data are well presented, table are self explanatory and related to the text.

Minor essential revision:

Methods: Authors should refer to 19A and PNS-19A as 19A serotype strains and PNS-19A serotype strains.

As requested we have changed this sentence as follows (page 4, lines 23 to 24): “19A serotype and penicillin non susceptible 19A serotype (PNS-19A) carriage was also separately analysed among Sp and PNSP carriers, respectively.”

Results: The percentages of penicillin susceptible, intermediate and resistant isolates reported in the text are discordant with the corresponding data reported in Table1. Table 1: Authors should add some explanation about penicillin susceptibility asterisks.

The reviewer is right. We have added explanations regarding the penicillin susceptibility asterisks. Moreover, the percentages of penicillin susceptible, intermediate and resistant isolates reported in the text now correspond to the data reported in Table1.

Discretionary revisions: In background section, there is no mention about the increase in serotype 19A strains in the US due to vaccine escape recombinant strains ST695.

The increase in serotype 19A strains in the US due to vaccine escape ST695 recombinant strains has been added to the Background section of the text, as follows (page 3, lines 10 to 17): “Vaccine escape was first reported in the US by Brueggeman et al. Around 2003, recombination occurred between the recipient ST695 serotype 4 and donor ST199 serotype 19A, simultaneously resulting in the non vaccine capsular type and penicillin intermediate-resistant ST695 19A pneumococci. With the additional selective advantage of penicillin non susceptibility, the ST695 19A variant continued to spread, becoming in 2007 the fourth most common serotype 19A clonal complex in the US. Brueggemann AB, Pai R, Crook DW, Beall B. Vaccine escape recombinants after pneumococcal vaccination in the United States. PLoS Pathog 2007;3(11):e168.”

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I received financial support for scientific research and attendance at international meetings from pneumococcal vaccine manufacturers including Pfizer/Wyeth and Sanofi Pasteur