Author’s response to reviews

Title: Prevalence and clinical impact of Streptococcus pneumoniae nasopharyngeal carriage in solid organ transplant recipients

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Technical Comments:
- Please include a title page at the front of your manuscript file. It contain, at minimum, the names, institutions, countries and email addresses of all authors, and the full postal address of the submitting author.

Following the technical comments, we have added the email addresses of all authors in the title page (Page 1, Lines 13-18).
- Mismatched Title between manuscript and the system
  We have corrected this mistake.
- Provide "Declarations" heading

Following the instructions we have added “Declarations” heading to the manuscript (Page 12, Line 282).
Reviewer 1: Please overwrite this text when adding your comments to the authors.
The study is overall well written and it deals with a so far less studied topic.

I have two comments:
The literature points out that the both invasive and non-invasive diseases caused by S. pneumonia in SOTR are related to fatal outcomes, compared to immunocompetent individuals.

In the conclusion section, the authors state that the mortality due to pneumococcal infections is high. However, this does not fully reflect the results of this study. In fact, only three out of 500 patients developed pneumonia (infection rate 0.6%) and only one died. The small sample size and the heterogeneous carriage status of these three patients, does not allow to establish a firm causal relationship between vaccination/lack of disease development.

I suggest the authors to mention this as main limitation, since this finding supports the main take home message of the study.

The Reviewer is right; our results did not allow to establish a firm causal relationship between vaccination/lack of disease development. In fact, we wanted to support the pneumococcal vaccination in these patients because two out of the three patients with non-bacteraemic pneumococcal pneumonia died. Following the suggestion of the Reviewer we have added a sentence in the paragraph about limitations: “Secondly, the small number of cases of pneumococcal pneumonia did not permit to establish a robust association with the lack of pneumococcal vaccination.” (Page 12, lines 270-271). In the same way, we have reworded the two last sentences of the Conclusions, as follows: “The incidence of non-bacteraemic pneumococcal pneumonia was low, although two out of the three patients died, suggesting the need of pneumococcal vaccination for the SOTR.” (Page 12, lines 276-278).

The table 1 (outcomes part) needs correction: the total number of pneumococcal infection is three (not two).

Following the request of the Reviewer we have corrected this data in the table 1.

2) the description of the antibiotic resistance patterns of S. pneumoniae strains is very detailed and provides interesting and innovative information. Besides outlining the antibiotic resistance pattern in S. pneumonia strains, what is the clinical implication related to this epidemiological description? How can the clinicians move this information into the daily clinical practice?

The detailed information regarding the susceptibility/resistence of pneumococcus is important for the clinical decisions. Azithromycin and clarithromycin are antibiotics frequently used in the empiric treatment of CAP episodes. The fact that approximately 30% of the isolates were resistant in this SORT cohort is important, because it precludes their use in the absence of antimicrobial susceptibility data of the Streptococcus pneumoniae isolates in the clinical samples.

Reviewer 2: In this study, Roca-Oporto et al have conducted a prospective study to assess rate and clinical impact of S. pneumoniae colonization in SOT. Their study is well written and provides useful results for clinicians dealing with these patients. It also highlights the need of increasing the vaccination rate in such population according to current recommendations.
I only have few minor comments to the paper.

- Line 140. The overall colonization rate in the study population was much lower from what expected from the literature. What are possible explanations for this difference according to authors' opinion?

  We believe that it could be due by a herd protection caused by the introduction of PCV13 in Spain. This was also observed in the work published by Câmara J, et al. in PLoS ONE 2017; 12(4): e0175224. https://doi.org/10.1371/journal.pone.0175224, in which they reported a decrease of invasive pneumococcal disease (IPD) in adults after introduction of pneumococcal 13-valent conjugate vaccine in Spain. Additionally, other studies carried out in adults (references 33-36 of the manuscript), no recipients of SOT, have reported a low rate of colonization.

- Line 160. The authors report that during the winter period 36% of isolates were resistant to azithromycin and erythromycin and 34% to clarithromycin. Given that both azithromycin and clarithromycin are first line antibiotics for CAP, it would be good to report in the main text the total percentage of isolates that expressed resistance to macrolides (either azithromycin or clarithromycin).

  The total percentage of isolates that expressed resistance to macrolides (either azithromycin or clarithromycin) was in the main text of the previous manuscript (Page 9, Lines 182 and 183). However, following the suggestion of the Reviewer, we have reworded this paragraph to clarify the data, as follows: “On the basis of CLSI breakpoints, the percentages of resistant isolates were 30.3% for trimethoprim-sulfamethoxazole, azithromycin and erythromycin, 28.79% for clarithromycin, 9.09% and 3.03% for oral penicillin and amoxicillin, respectively. No resistance was observed in the cases of intravenous penicillin, cefotaxime, ceftriaxone, levofloxacin, and vancomycin (Table 4).” (Page 9, lines 191-195).

- Line 234-245: when talking about the resistance pattern of serotype 35B it could be worth mentioning the work of Olarte et al J Clin Microbiol. 2017 who also found a high rate of resistances in serotype 35B.

  Following the suggestion of the Reviewer we have added the resistance pattern of the serotype 35B from the Olarte study, in 2017, in the Discussion Section, as follows: “A higher resistance of the serotype 35B has been reported recently from isolates causing IPD in children, with 91% of the isolates penicillin non-susceptible, 46.2% erythromycin resistant, 21.8% trimethoprim-sulfamethoxazole resistant, and 16.7% were considered multidrug-resistant (42).” (Pages 11-12, lines 255-259).