BRONCHIAL AND SYSTEMIC RELATIONSHIPS OF HAEMOPHILUS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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POINT BY POINT RESPONSE TO THE REVIEWERS

1.- The authors need to write the whole name of COPD in the title. I found the abbreviation difficult to follow (regarding readers away from the field).

The suggestion of the reviewer has been followed in the revised version of the manuscript. Furthermore, the title has been modified to focus on Haemophilus, and not just on Haemophilus parainfluenzae.

2.- The list of authors is incomplete. It ends with the word “and”.

The list of authors has been reviewed and corrected when needed.

3.- The introduction is very small. The authors need to expand it in more detail.

The introduction has been fully modified, following the suggestions of the reviewers.

4.- Some phrases are difficult to understand. For example, the “in the
first second” in the results. What does this stand for?

The sentence refers to lung function measurements. It has been reviewed in the revised version of the manuscript.

5.- What are the criteria for evaluation of the exacerbations?

Categorization criteria of exacerbations are detailed in the methods section (main text lines 332-335) and its definitions have also been included in the results section of the revised version of the manuscript (main text lines 103-107)

6.- In Table 1, the heading of the table is not clear. What do N and 72 mean in the heading of this table? And the font is not identical!

The heading of the table 1 has been revised and corrected where needed.

7.- What are the criteria for non-admitted patients?

Categorization criteria of admission are detailed in the methods section (main text lines 332-335) and have been also included in the results section in the revised version of the manuscript (main text lines 103-107)

8.- Why are some taxa of *Hemophilus* not identified? And in Table 4, the relative frequency value is unclear. What does it mean?

The difficulties to determine the Haemophilus taxa at species levels is fully addressed in the revised version of the manuscript to clarify the point raised by the reviewer. The variable "relative frequency" in Table 4 has been suppressed from the revised version of the manuscript, as suggested by the reviewer, considering that it is unclear and do not add significant information to the manuscript.

9.- The authors need to indicate the rationale for referring to IL-8 in their findings. I find that just jumping without indicating the reason is not helpful.

The introduction and the discussion sections have been modified to justify the focus on IL8 from the proteomic analyses performed. The theoretical basis to relate the bronchial microbiome and IL8 levels is widely justified in the available literature. Previous publications have focused in IL8 levels of bronchial samples, and the correlations between microbial taxa and IL8 at systemic level have been only marginally assessed, a situation that justifies the focus on this relationship in the current manuscript.

10.- The discussion should be modified to include information about the current therapeutic situation in this kind of disease.

Some sentences and a reference addressing the treatment of the disease and its impact on the bronchial microbiome have been included in the revised version of manuscript. This raised point has been focused on chronic inhaled corticosteroids therapy, that has a measurable impact on the bronchial microbiome and is one of the common treatments of severe disease with frequent exacerbations.

11.- Regarding the ethical approval for this study, the authors need to provide the approval number.

The reference number given by the ethics committee at the approval of the study has been included in the revised version of the manuscript.

12.- How was the bacterial identity determined? And how were the proteins measured? The authors should indicate this in detail.

Details of bacterial and proteins identification are included in the methods section (main text lines 338-349) and in the references 33 and 34.