PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Study protocol: Pneumonia and Inhaled corticosteroid treatment patterns in Chronic obstructive pulmonary disease – a Cohort study using Sequence analysis (PICCS)
AUTHORS	Klitgaard, Allan; Ibsen, Rikke; Hilberg, Ole; Løkke, Anders

VERSION 1 – REVIEW

REVIEWER	Mohamed, Adel University of Toronto, Pediatrics
REVIEW RETURNED	17-Mar-2023

GENERAL COMMENTS	Congratulation for a well-written protocol I have one comment/question: Do you think adding a fifth group under "Definition of State" named (ICS+Pneumonia) would help capture these cases where the association is potential?

REVIEWER	Mannino, David University of Kentucky
REVIEW RETURNED	18-Mar-2023

GENERAL COMMENTS	In this study sponsored by BI, researchers are examining how treatment of COPD (including ICS treatment) affects outcomes- in particular the outcome of pneumonia. Majopr concerns: The outcome of pneumonia is critical in this study. The definition of "moderate" pneumonia includes the dispensing of antibiotics, including those used to treat things other than pneumonia (ampicillin), and those used to treat AECOPD or even used chronically in COPD (azithromycin). This has the potential to inflate the pneumonia numbers. The authors do not appear to be looking at the non ICS therapies for COPD, which appears to be an oversight ICS therapy in COPD is not picked at random. It tends to be used in patients with asthmatic features and exacerbations. These data should also be collected so the study can be better interpreted.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Adel Mohamed, University of Toronto

Comments to the Author:
Congratulation for a well-written protocol
I have one comment/question: Do you think adding a fifth group under "Definition of State" named (ICS+Pneumonia) would help capture these cases where the association is potential?

- Thank you. This is an interesting question. The sequence analysis is a complex statistical data-driven analysis to both perform and interpret, and because of this we want the model to be as simple as possible. We want to include a minimum of states to address the research question: Can patients with COPD be clustered/phenotyped based on their ICS treatment patterns and pneumonia incidence?
  We believe that this proposed fifth state of ICS+pneumonia will further complicate the model without adding much valuable information. The sequence analysis will provide transition rates between the four states for each identified cluster, and this will convey much of the same information. For example, we will be able to tell for each cluster that X percent transitioned from ICS to pneumonia during the follow-up, while Y percent transitioned from Nothing to pneumonia.

Reviewer: 2
Dr. David Mannino, University of Kentucky

Comments to the Author:
In this study sponsored by BI, researchers are examining how treatment of COPD (including ICS treatment) affects outcomes- in particular the outcome of pneumonia.

- This is correct. To be more precise, we want to address two specific research questions:
  - Can patients with COPD be clustered/phenotyped based on the ICS treatment patterns and pneumonia incidence?
  - If so, is there a difference in patient characteristics between these groups?

Major concerns:
The outcome of pneumonia is critical in this study. The definition of "moderate" pneumonia includes the dispensing of antibiotics, including those used to treat things other than pneumonia (Ampicillin), and those used to treat AECOPD or even used chronically in COPD (Azithromycin). This has the potential to inflate the pneumonia numbers.

- This is correct. Thank you for pointing towards this bias. This comment touches on one of the major limitations of register-based research, and inflated numbers of moderate pneumonia may occur through mainly three types of misclassifications:

1) Misclassification of other infections than pneumonia as pneumonias (Ampicillin).
2) Misclassification of acute exacerbations (AECOPD) as pneumonias (Azithromycin).
3) Misclassification of COPD patients in chronic treatment with azithromycin as pneumonias.

Regarding (1): Ampicillin is used in Denmark for respiratory tract infections, gastroenteritis, and gonorrhea. In gastroenteritis, Ampicillin is neither 1st, 2nd, nor 3rd choice of treatment according to national guidelines, and we do not consider treatment for gastroenteritis as a cause of substantial bias.

Regarding (2): Azithromycin is sometimes used in Denmark for AECOPD suspected of bacterial etiology, but it is neither first nor second choice of antibiotic treatment. The general use of antibiotics in Denmark is low compared to other nations [1], and it is even decreasing [2]. As more than 80% of antibiotics used in Denmark is prescribed by general practitioners [1, 2], this suggests a high degree of adherence to national guidelines of antibiotic treatment. Furthermore, there is a substantial overlap between pneumonia and AECOPD caused by lower respiratory tract infection (LTRI), and this has been included in the discussion section (Lines 267-285). Additionally, most incidents of AECOPD are diagnosed in the primary care setting, where chest x-rays are not routinely available, and the exclusion of pneumonia by chest x-ray is not practically viable. We believe that our method is feasible, because it identifies both pneumonia and AECOPD suspected to be caused by bacterial LRTI, while it likely excludes AECOPD of non-bacterial etiology. Importantly, it does so in a real-world outpatient setting, where the distinction between AECOPD and pneumonia is often not clear.

Regarding (3): In Denmark, Azithromycin is sometimes used chronically in patients who experience frequent pneumonias or frequent AECOPD due to suspected bacterial etiology. This treatment is only managed at hospital-based pulmonary specialist outpatient clinics, and it is not very common. Therefore, we do not believe this to cause substantial bias. Furthermore, patients in chronic azithromycin treatment are going to be classified by prescriptions as patients with frequent pneumonias. As this is the very indication for the treatment, they will be "misclassified correctly", so to speak.

The authors do not appear to be looking at the non-ICS therapies for COPD, which appears to be an oversight.

- This is correct, thank you for allowing us to correct this. In the sequence analysis model, we want to explore ICS, because this treatment is known to be associated with an increased risk of pneumonia. As mentioned previously, this model is complicated, and we want to include a minimum of states to address our research question. While investigating the relationship between non-ICS therapies and pneumonia is outside of the scope of this project, we agree that information on non-ICS therapies is important. Therefore, we have now included non-ICS inhaled therapies as baseline variables (Table 2 and lines 151-153).

ICS therapy in COPD is not picked at random. It tends to be used in patients with asthmatic features and exacerbations. These data should also be collected so the study can be better interpreted.

- Thank you for pointing towards this missing piece of information. ICS therapy in COPD is related to three main patient characteristics: high eosinophil count, asthmatic features, and frequent exacerbations. We do not have access to eosinophil counts. Regarding asthmatic features, we do not have access to bronchodilator reversibility results. We do, however have access to former asthma diagnosis, and this has been included as a baseline variable (Table 2 and lines 150-151). Regarding frequent exacerbations, we have included these as a baseline variable. We have included both pneumonias and non-pneumonic exacerbations prior to baseline (Table 2 and lines 153-164).

We hope that the abovementioned answers, collectively, explain our choices of methodology satisfactorily.

With kind regards on behalf of all authors

Allan Klitgaard, MD

References

[1] NATIONAL ACTION PLAN ON ANTIBIOTICS IN HUMAN HEALTHCARE, Danish Ministry of Health, 2017.
[2] DANMAP 2021 - Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark. ISSN 1600-2032., in: B.B. Høg, U.W. Sönksen (Eds.) Statens Serum Institut and The National Food Institute, Technical University of Denmark, 2021.

VERSION 2 – REVIEW

REVIEWER	Mannino, David University of Kentucky
REVIEW RETURNED	05-May-2023

GENERAL COMMENTS	My concerns have been addressed. Thanks