Author's response to reviews

Title: Healthcare Utilization and Costs Associated with S. aureus and P. aeruginosa Pneumonia in the Intensive Care Unit: A Retrospective Observational Cohort Study in a US Claims Database

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Version: 3
Date: 13 May 2015

Author's response to reviews: see over
May 13, 2015

Armee Valencia
Journal Editorial Office

Dear *BMC Health Services Research* Editorial Office,

In regards to manuscript MS 8021045615119086 entitled ‘Healthcare Utilization and Costs Associated with S. aureus and P. aeruginosa Pneumonia in the Intensive Care Unit: A Retrospective Observational Cohort Study in a US Claims Database’, we appreciate the comments from the two reviewers. We detail our responses to these comments below.

Editor’s comments:

1. In addition to the comments from the reviewers, please add sentence in Method to describe the population in the claim database and how different/similar the patients were compared to the general US population.

   A sentence was added to the methods to describe how the database compares to the general population, lines 71-74. We also added language to the discussion on the limitations of representativeness of our commercially insured sample population, line 305.

2. Table 3, please only include most important comparisons and remove the others to the supplement file.

   To make Table 3 easier to interpret, we have split it into 3 tables, with Pre-index utilization data becoming a supplemental e table (eTable 7), and index hospitalization and post hospitalization data provided separately. In addition, the lines that provided “mean (SD) events per patient” has been eliminated, and more clear terms substituted for the term “per treated patient”.

3. Also please correct multiple citation errors in the manuscript (e.g. Page 4, 8 ).

   It was unclear which specific citations the Editor was referencing in this comment. The authors have gone back and reviewed all citations to make sure there are no errors.

Reviewer Li:

1. Lines 288-289: Please add “solely” before “covered” in the sentence “patients covered by Medicare or Medicaid were excluded”:

   Edit made and now corresponds to line 306

2. On page 33 of the PDF file “8021045615119086_article”, “Figure 2” should be changed to “Figure 1”. Please add “ICU” to the figure:

   Done. “ICU” added to Figure 1. We also have corrected the file so that the figure is appropriately labelled Figure 1.

3. Please correct table numbers in the document for “additional files”. The last three tables should be renamed to eTable4, eTable5, and eTable6.
When we checked the link to the file, we see the correct table numbers (i.e. last three tables are named eTable4, eTable5, and eTable6). Please note that in response to a comment from Reviewer 2 we have added an additional table to the appendix so there is now an eTable7.

4. Please clarify if the three cohorts were defined based on primary diagnosis only, or either primary or secondary diagnoses.
   The following sentence was added (lines 97-98): Both primary and secondary diagnosis codes for the index hospitalization were used to assign subjects into groups.

5. Please clarify that HealthCore data were linked to Social Security Death Index and mortality assessment after index hospitalization were based on Social Security Death Index.
   HealthCore data were linked to the Social Security Death Index to capture deaths after the hospitalization. Text was added to the Methods (Lines 111-113) to clarify.

6. Please clarify if other non-pneumonia diagnosis codes associated with the index hospitalization were also used to measure comorbidities. If not, authors may want to experiment with the alternative definition of comorbidities to see if the results regarding association between comorbidities and costs would be different.
   Comorbidities were defined based on having at least one medical claim with an ICD-9 diagnosis code for the condition of interest in the 12-month period prior to the index hospitalization. The following sentence was added to the Methods section to clarify this point (Lines 106-108): A comorbid condition was defined as the presence of ≥1 medical claim with a diagnosis code for the condition of interest for an individual during the 12 months prior to the index hospitalization.
   The following sentence was added (Lines 297-299): Diagnoses made during the index hospitalization were not included, because the goal was to assess the information available to clinicians upon admission; this may have contributed to underdiagnosis of co-morbid conditions.
   As our analysis did not include alternative definitions of comorbidities, we have added the following sentence (Lines 299-301): Future studies may want to examine the association between costs and both pre-existing and new comorbidities to explore the impact of how comorbidities are defined.

Reviewer Kollef:

1. Kyaw provide an analysis of costs and outcomes for ICU patients with S.aureus (SA) pneumonia and P. aeruginosa (PA) pneumonia compared to patients without pneumonia. Not surprisingly those with SA and PA pneumonia had greater costs and LOS. I am not sure how much these data add to the existing literature on this topic. It is well know that SA and PA pneumonia are a/w with worse outcomes including mortality, LOS, and hospital costs compared to ICU patients without pneumonia. The authors need to make a better case justifying the need for this study/analysis.
   The study purpose was clarified to say that it was in support of the development of drugs for the prevention of S. aureus and P. aeruginosa pneumonias. While there are existing data
that document greater costs and longer lengths of stay occurring in patients with these diagnoses (referenced on lines 55-58), the data were not sufficient to permit the detailed understanding of potential impacts on morbidity and costs that are necessary when considering the optimal characteristics of such drugs. We have added language to clarify these points and explain why we felt analysis was needed.

2. It might have been more interesting to have compared SA and PA pneumonia to other causes of less virulent and antibiotic resistant pneumonia, such as E. coli and MSSA pneumonia (differentiating MSSA from MRSA). This would have been a more novel analysis.

While we agree it would be interesting to compare the burden of pneumonia across causative pathogens, the purpose of this study was to describe pneumonia due to staphylococcus and pseudomonas in the ICU, representing the two most common ICU pneumonias. The claims database method is not optimally suited to compare MSSA and MRSA pneumonia, because while there are ICD-9-CM diagnosis codes that specify susceptibility and resistance to methicillin (482.41 for MSSA and 482.42 for MRSA), we know that they are not always well used and reliance on the codes may under-represent true rate of resistance. Additionally, since this analysis was conducted using claims data, we did not have access to microbiological testing information limiting our ability to look at other antibiotic resistant pneumonias.

3. Table 3 is long and difficult to interpret. I would suggest condensing it or eliminating it all together.

As noted above in the response to the editor, to make Table 3 easier to interpret, we have split it into 3 tables, with Pre-index utilization data becoming a supplemental e table (eTable 7), and index hospitalization and post hospitalization data provided separately. In addition, the lines that provided “mean (SD) events per patient” has been eliminated, and more clear terms substituted for the term “per treated patient”.

4. It was not clear to me if this study was driven by a pharmaceutical company. If so, the exact role of that company should be explained.

Author affiliations make it clear that MedImmune employees played key roles in this study and that the funding for the study was provided by MedImmune. For clarity, however, a sentence was amended as follows, line 65-68, and 2 relevant references were added: This retrospective observational cohort study of administrative claims data from the HealthCore Integrated Research Environment for service dates from 01/01/2006 through 11/30/2012 was developed to assess costs and outcomes of *S. aureus* and *P. aeruginosa* pneumonia in ICU patients to guide the development of monoclonal antibodies designed to prevent these illnesses [19,20].

5. There is no data on antibiotic susceptibility nor on the use of appropriate antibiotic therapy. Again, this would have added valuable data to the study making it of more interest.

We agree that it would have been interesting to evaluate antibiotic usage and susceptibility in this analysis. Unfortunately, insurance claims databases, such as HealthCore, do not contain information on susceptibility to antibiotics. Additionally, the data do not permit analysis of indication for or timing of antibiotic use, so this suggested analysis is not possible or appropriate within the current data set. The absence of resistance data or of use of appropriate antibiotics does not affect the value of the data in our paper.

Thank you for the opportunity to submit our manuscript and our responses to reviewers’ comment to *BMC Health Services Research*. We appreciate your consideration of our manuscript.

Sincerely,