Author’s response to reviews

Title: Relationship between adverse drug reactions to antibacterial agents and the Klebsiella pneumoniae carbapenemase-producing (KPC) Klebsiella pneumoniae outbreak: insight from a pharmacovigilance study.

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RESPONSE TO REVIEWERS

PHAT-D-19-00225 entitled “Relationship between adverse drug reactions to antibacterial agents and the Klebsiella pneumoniae carbapenemase-producing (KPC) Klebsiella pneumoniae outbreak: insight from a pharmacovigilance study” by Gatti et al.

Dear Dr Yayan,

We would like to thank you for the opportunity to resubmit a revised version of this manuscript. We appreciated the reviewers’ constructive comments. All have been incorporated in the revision.

Our point-by-point responses are provided below.

Best regards

Emanuel Raschi

Q= QUERY; A= ANSWER

Turhan Dost (Reviewer #1)

Q1: “The manuscript entitled "Relationship between adverse drug reactions to antibacterial agents and the Klebsiella pneumoniae carbapenemase-producing (KPC) Klebsiella pneumoniae outbreak: insight from a pharmacovigilance study" is a comprehensive pharmacovigilance study about adverse reactions belonging to drugs used in the treatment of Klebsiella pneumoniae carbapenemase-producing (KPC) Klebsiella pneumoniae.
Microbiological and pharmacovigilance data of different therapies are reviewed and compared in this study. Although no new safety signals emerge with the use of ceftazidime-avibactam, it should not be ignored that its use is new and there may be increase in ADRs”.

A1: We fully agree with the reviewer. We are aware that ceftazidime-avibactam is a novel antibiotic characterized by growing use, thus making monitoring of spontaneous reports a useful tool to promptly detect potential unexpected safety signals. Although ceftazidime-avibactam belongs to the well-known antibacterial beta-lactams class, typically characterized by large therapeutic window, clinicians should not overlook the potential occurrence of rare idiosyncratic adverse reactions, as discussed in the Discussion section (lines 26-27, page 11 and lines 1-2, page 12).

Muhammad Aamir (Reviewer #2)

Minor corrections Abstract

Q1: 1. Change the very first sentence.

A1: We rephrased this sentence (“The management of Klebsiella pneumoniae carbapenemase producing (KPC) infections represents a major challenge”).

Q2: 2. Rephrase the sentence written in line number 49.

A2: The sentence (“Unexpected safety signals were not detected for both older and newer antibacterial agents”) was rephrased (“Unexpected safety signals involving selected antibiotics were not detected”).

Q3: 3. Conclusion should reflect your results and then your suggestion regarding problem

A3: We modified the conclusions in line with our results and our suggestion.

Mukaddes Gümüştekin (Reviewer #3)

“Pharmacovigilance and spontaneous reporting are really important and physicians' awareness is low. Therefore, I think that this study may increase the awareness of physicians on this subject. Manuscript is well-written and clear. However, the study contains some minor flaws related to the methodology and the results of the paper”.

Q1: “Although the reasons for the comparison of Italy and UK data are stated in the later sections of the text, it is appropriate to specify in the abstract and introduction”.


A1: We agree with the reviewer and incorporated this suggestion into the revised version of the manuscript, both in the abstract (Lines 6-8, Page 2) and in the introduction (Lines 26-28, Page 4 and Lines 4-5, Page 5).

Q2: “While the Italy data covers seven years in terms of 1998-2008 period and that tigecycline data covers three or four years may pose a problem in comparing the data and interpreting the statistical analyses correctly. Therefore, an additional statistical review would be appropriate”.

A2: We thank the reviewer for this comment, which allows us to fully explain the analyses. We are aware that the AIFA database includes spontaneous reports covering only seven years (2002-2008), while reports retrieved in UK and FAERS SRSs also cover the previous three years (1999-2008). In order to make a reliable comparison, we have normalized data calculating the mean reports per year for the different antibiotics in each SRS. In this way, we obtained data expressing an equal amount and directly comparable using the t-test for unpaired data. Similar statistical analyses were performed in order to compare the tigecycline data (Method section, Lines 23-26, Page 7).