Author’s response to reviews


Authors:

Alejandro ÁLVARO-MECA (alejandro.alvaro@urjc.es)

María JIMÉNEZ-SOUS (jimenezsousa@isciii.es)

Dariela MICHELOUD (micheloudary@gmail.com)

Ainhoa SÁNCHEZ-LOPEZ (ainhoasanlopez@gmail.com)

María HEREDIA-RODRÍGUEZ (maria_her_o5@hotmail.com)

Eduardo TAMAYO (eduardo.tamayo@uva.es)

Salvador Resino (sresino@isciii.es)

Version: 1 Date: 07 Sep 2017

Author’s response to reviews:

Reviewer #1: This is a retrospective study to analyze incidence, mortality rate and costs of sepsis during 21st century in Spain. The authors used a MBDS of the National Surveillance System for public hospitals data in Spain.

The major concerns are:

1. MBDS used is a large bank of data with the risk of missing and non-precise information. Is there a quality control of data introduced in the system?

We only have access to the database and we cannot perform quality control, but the Spanish MSSSI perform periodic audits in MBDS with quality controls.

We have added two new sentences:

“Data were obtained from records in the Minimum Basic Data Set (MBDS) of the National Surveillance System for Hospital Data in Spain, provided by the Ministry of Health Social Services and Equality (MSSSI). The MBDS is a clinical and administrative database containing clinical information recorded at the time of hospital discharge, which has an estimated coverage of 92% of hospital discharges registered in hospitals in Spain (84.14% from public hospitals and
15.86% from private hospitals) [27]. The MBDS includes up to 14 discharge diagnoses and up to 20 procedures performed during the hospital stay. The MBDS provides encrypted patient identification numbers (the identification of patients at the individual level is not possible in the MBDS), gender, date of birth, dates of hospital admission and discharge, medical institutions providing the services, the diagnosis and procedure codes according to the International Classification of Diseases 9th Revision, Clinical Modification (ICD-9-CM), as well as the outcome at discharge [28]. The Spanish MSSSI sets standards for record-keeping and performs periodic audits in MBDS.”

2. Algorithm of Angus was used to define sepsis in previous reports but did not coincide with the current definition of sepsis-3. Diagnosis of sepsis is crucial. The authors presumed that Angus methodology, i.e. combination of infection and organ dysfunction based on primary and secondary diagnosis, would not identify patients with sepsis consistent with the new sepsis-3 definition. However, this hypothesis should be validated. The new sepsis-3 definition defines SOFA score-based organ dysfunction differently from sepsis-1 and 2. For example, a platelet count of 100 to 150,000 indicates a SOFA score of 1 for coagulation system, which by no means be identified as organ dysfunction by previous sepsis definitions.

We are grateful for the reviewer's comment. We deleted this reference:

“The algorithm of Angus et al. [4] was used to define sepsis in previous reports [4, 29-31].”

3. The increase incidence seems to be related to the inclusion of less severely ill patients, thus resulting also in a reduction of length of stay and reduction of mortality. The adjusted analysis did not include severity of illness scores. This need to be better addressed in the discussion.

This hypothesis is posed as a possibility, not as a proven fact. Besides, we did not have access to severity of illness scores such as SOFA or APACHE.

We have changed a paragraph in discussion:

“Furthermore, the introduction and improvement of the management of ICD-9 codes may have facilitated coding in medical records similar to MBDS [23]. Namely, as awareness of sepsis has increased during the last decade, the coding practices might have become more inclusive [33]. Thereby, if an increasing number of less sick patients had been included as sepsis patients, the incidence of sepsis could be increased and the mortality could be decreased. However, we have not been able to evaluate this hypothesis through the MBDS and we do not have access to severity of illness scores such as SOFA or APACHE for adjusting the analysis.”
We have changed a sentence in discussion:

“As with other metrics, if an increasing number of less sick patients were diagnosed with sepsis, the CFR could decrease.”

4. It is unexpected the high incidence of urinary infection (19%-23.4%). This seems to be a bias of the data base as it is probably more reliable to report urinary infection than the other sources. This need to be mentioned as a limitation of the study. As we know, urinary sepsis has a lower mortality rates and can have contributed to the rate reported by this study.

We have changed a paragraph in discussion:

“Secondly, due to the use of the administrative databases, the inaccuracy in differentiating the etiology of the diseases and the reporting of organ dysfunction could have engendered a confusion bias. For example, we found an unexpected high incidence of urinary infection and low incidence of cardiovascular dysfunction, possibly due to a bias in diagnosis report because may be probably more reliable to report urinary infection than cardiovascular dysfunction or the other sources. In this context, grouping of ICD-9-CM codes into comorbidities, organ dysfunction, and site of infection (SDC - Appendixes 1-4) may have been the best approach to solve this issue, considering that we have not used the ICD-9 code 995.9x (sepsis or severe sepsis) nor 785.52 (septic shock) due to these codes are highly problematic. Furthermore, we did not have data of the potential accuracy of the Spanish MBDS for sepsis related diagnosis, which it could be a significant limitation.”

5. It is also unexpected the low incidence of cardiovascular dysfunction (10.2%) and this suggests that the data collection was not appropriate. Registering renal and respiratory dysfunctions seems to be more accurate.

We have changed a paragraph in discussion:

“Secondly, due to the use of the administrative databases, the inaccuracy in differentiating the etiology of the diseases and the reporting of organ dysfunction could have engendered a confusion bias. For example, we found an unexpected high incidence of urinary infection and low incidence of cardiovascular dysfunction, possibly due to a bias in diagnosis report because may be probably more reliable to report urinary infection than cardiovascular dysfunction or the other sources. In this context, grouping of ICD-9-CM codes into comorbidities, organ dysfunction, and site of infection (SDC - Appendixes 1-4) may have been the best approach to solve this issue, considering that we have not used the ICD-9 code 995.9x (sepsis or severe sepsis) nor 785.52 (septic shock) due to these codes are highly problematic. Furthermore, we did not have data of the potential accuracy of the Spanish MBDS for sepsis related diagnosis, which it could be a significant limitation.”
sepsis) nor 785.52 (septic shock) due to these codes are highly problematic. Furthermore, we did not have data of the potential accuracy of the Spanish MBDS for sepsis related diagnosis, which it could be a significant limitation.”

6. Mortality adjustment was based only in age and the authors did not include other important non-modifiable factors as co-morbidities, severity of illness, gender. What was the mortality in patients without co-morbidities?

We had described in M&M that “The incidence and mortality were standardized by age by direct method using as population reference the whole population in Spain (National Statistics Institute; http://www.ine.es/). Thus, the number of events was used as numerator and the denominator was the number of persons at risk by age group.”

This is a standard method to calculate the incidence and mortality when both may change with the age. It is not the statistic adjustment that may be performed to calculate an adjusted risk by logistic regression or Cox regression.

It is not possible to do a similar analysis with comorbidities because we do not have comorbidities in the general population.

7. Cost were calculated using DRG extracted from MBDS and adjusted by the inflation. DRG is not a precise method to determine the costs of ICU patients.

We have added a new paragraph in discussion:

“Fourthly, DRG system was the only viable method to calculate sepsis costs through the MBDS. DRGs may not be a precise method to determine the costs, particularly in ICU patients, because different conditions in a DRG may have widely varying costs and different levels of intensity of care cannot (without adjustment) be distinguished within a DRG. However, DRG system is readily available and provides a uniform methodology to get a common currency of hospital activity, which might be applied in all hospitals of a National Health System.”

8. Referral population: The population in Spain may vary according to the number of foreign habitants that can develop a sepsis and treated in a public hospital. Private hospitals may attend a large proportion of septic patients. How this was considered by the authors?

Private hospitals may also attend a large proportion of septic patients. We have added a new paragraph in discussion:
“Fifthly, regarding to referral population, the population in Spain may vary according to the number of foreign habitants that may develop a sepsis and be treated in a public hospital. Besides, private hospitals may also attend a large proportion of septic patients. However, we did not have data of these two assumptions and could not be considered for the analysis.”

Moreover, we updated a sentence in M&M:

“The MBDS is a clinical and administrative database containing clinical information recorded at the time of hospital discharge, which has an estimated coverage of 92% of hospital discharges registered in hospitals in Spain (84.14% from public hospitals and 15.86% from private hospitals) [27].”

9. Finally it could be interesting to include some information on the regional differences of sepsis patients in Spain.

We added a new Table 2.

We Added a paragraph in Results:

“Regional differences of sepsis epidemiology in Spain

Values of sepsis incidence and sepsis-related mortality throughout regions (autonomous communities) of Spain were not uniform (p<0.001; Table 2). When the follow-up was stratified by calendar periods (Table 2), values of sepsis incidence increased significantly in all regions, except in Cantabria; and values of mortality increased significantly in all regions, except in Cantabria, Ceuta and La Rioja (Table 2).”

We Added a paragraph in Discussion:

“The adjusted rates of incidence and mortality also increased, and although their values were not uniform throughout regions (autonomous communities) of Spain, these rate values increased significantly in most regions when the follow-up was stratified by calendar periods.”

Reviewer #2: This is an interesting, well-written, and methodologically sound paper. It adds important information to the field of sepsis epidemiology. The dataset used is very impressive, with excellent coverage of public hospital admissions. I have the following comments:

1. I found at least one paper on a very similar topic using the same dataset (Bouza et al, "Epidemiology and recent trends of severe sepsis in Spain," BMC Infectious Diseases 2014), but this analysis covers a larger time period and uses perhaps a superior method of
identifying sepsis cases. Despite the fact that the two papers cover the same time period with the same dataset, research objectives, and outcomes of interest, the conclusions are quite different. It would be helpful for the authors to compare their findings to those of others with similar work in the Discussion section, highlighting possible reasons for these different findings.

We added a new paragraph:

“It should be noted a paper on a very similar topic using the same dataset and other similar criterion of Angus et al. [24]. Incidence and mortality rate values in our article were higher than in the Bouza's article, whereas CFR values were higher in the latter article [24]. However, the trend of incidence, mortality and CFR were similar in both studies. Moreover, our analysis covers a broader period of time (2000-2013), which includes the years in which the impact of the economic crisis was stronger, and an analysis of hospital resource expenditures and associated costs related to sepsis. These two details make the findings and conclusions are different from those described in the Bouza's article [24].”

2. In Background, on line 10, the authors state that sepsis "is the main cause of death among hospitalized patients." I reviewed the cited studies, and found no evidence to support this claim. Please clarify.

We changed the sentence and updated references:

“On the one hand, Sepsis affects millions of people around the world each year and is the main cause of death among critically ill patients [4-6].”


3. In Background, on line 12, the authors state that "around 3% of patients admitted to hospital have sepsis, and half of these patients are treated in the intensive care unit." This should be clarified to reflect that these data are from a single US study which is quite old. The reason
this is important is that the proportion of patients with sepsis who are treated in the intensive care unit vs acute care wards varies dramatically depending upon resource availability.

We changed the paragraph:

“The incidence of sepsis varies across the world. The incidence of severe sepsis has been estimated around 300 cases per 100,000 population in the United States (US), and half of these patients were treated in the intensive care unit (ICU) [4]. The incidence of severe sepsis in Sweden in 2005 was 430/100,000 population [7]. Moreover, in clinical cohort studies in ICU have been found incidence of sepsis of 11.8% in Australia and New Zealand [8], 14.6% in France [9], 27.1% in the United Kingdom [10], and 30% in the SOAP study [5], that included 198 European ICUs. In most developed countries, sepsis has progressively increased during the last decades [6].”

4. In Background, on line 29, "Information" should be changed to "information," and "…impact of the economic crisis on critical care unit." should be changed to "…impact of the economic crisis on critical care utilization."

The sentence has been changed:

“However, there is growing evidence about the impact of economic crisis on hospital care utilization after 2008 [15-17], but there is not information about the impact of the economic crisis on critical care utilization.”

5. In Materials and Methods section "study design and data source," on line 5, the "." Should be removed after the word "study".

We apologize for the mistake. We remove the "."

6. In Materials and Methods section "study variables," on line 45, the authors should clarify that they adapted the Angus criteria, also using methods from Shen and Bateman as described in Appendix 1.

We have changed a paragraph in Materials and Methods section "study variables.

“Sepsis was defined by the presence of an infection-associated diagnosis and organ dysfunction according to the criteria of Angus et al. [4], adapted by other authors. We selected all acute-care hospitalizations with ICD-9-CM codes for both a bacterial or fungal infectious process (ICD-9-CM codes used by Angus et al. [4]; see Supplementary Digital Content (SDC) - Appendix 1) and
a diagnosis of acute organ dysfunction (ICD-9-CM codes used by Angus et al. [4]. Furthermore, we also included ICD-9-CM codes used by Dombrovskiy et al. [7], Shen et al. [26]; see SDC - Appendix 2).”

We reordered the numeration of appendixes 1 & 2.

Appendix 1. International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes for bacterial and fungal infections.


Besides, in appendix 2, we changed the reference of Bateman [1] by Dombrovskiy et al. [2]


7. In the first page of the Discussion section, on line 7, the word "cases" should be added after "the percentage of sepsis…".

We added the word "cases" after "the percentage of sepsis…".

“In our study, the percentage of sepsis cases and in-hospital sepsis-related deaths,…”

8. The authors spend considerable time mentioning the possible biases and limitations of their paper due to issues of ICD-9 coding for sepsis. However, as I understand their methods, they did not actually use ICD-9 code 995.9x for sepsis or severe sepsis, nor 785.52 for septic shock. I think this is actually one of the strengths of their paper, as these codes are highly problematic. Lines 25-34 and 46-52 seem to suggest that this paper used sepsis-specific ICD-9 codes to identify patients. If this is the case, the methods section needs to be edited to reflect this. If it is not the case, the discussion section should be clarified.

We did not use the ICD-9 code 995.9x for sepsis or severe sepsis, nor 785.52 for septic shock. We changed two paragraphs in discussion:
“Additionally, the mortality trends identified using administrative data seem to be similar to those identified in clinical trial participants, and support the use of ICD-9 data, integrated into the Angus algorithm, to monitor mortality trends in patients with sepsis [28].”

“In this context, grouping of ICD-9-CM codes into comorbidities, organ dysfunction, and site of infection (SDC - Appendixes 1-4) may have been the best approach to solve this issue, considering that we have not used the ICD-9 code 995.9x for sepsis or severe sepsis, nor 785.52 for septic shock due to these codes are highly problematic.”

9. In the second page of the Discussion section, on line 10, the statement "the reduction of LOHS leads to a faster return to normal life…" is not supported by the data. Patients may be discharged with high degrees of disability and perhaps not even going home but to a nursing facility. This statement should be removed.

We changed the sentence:

“The reduction of LOHS might lead to a faster recovery and a reduction of costs and hospital resources. However, patients may be also discharged with high degrees of disability, and perhaps, not even going home but to a nursing facility.”

10. In the second page of the Discussion section, the sentences on lines 26-34 are poorly written and need to be revised.

We changed the paragraph

From

“Furthermore, the introduction and improvement of the management of ICD-9 codes may facilitate its coding in medical records [23]; namely, that as awareness of sepsis increases, the coding practices become more inclusive [33]. Thereby, if an increasing number of less sick patients were included as sepsis patients, the incidences of sepsis and mortality could increase.”

To

“Furthermore, the introduction and improvement of the management of ICD-9 codes may have facilitated coding in medical records similar to MBDS [23]. Namely, as awareness of sepsis has increased during the last decade, the coding practices might have been become more inclusive [33]. Thereby, if an increasing number of less sick patients had been included as patients with sepsis, the incidence of sepsis and mortality could be increased. However, we have not been able to evaluate this hypothesis through the MBDS and we do not have access to severity of illness scores such as SOFA or APACHE for adjusting the analysis.”
11. In the third page of the Discussion section, line 6, the authors should clarify that they modified the Angus criteria.

We changed the sentence:

“Our study was performed according to a similar criterion to that used by Angus et al. [4], which was only modified to update the codes of acute organ dysfunction with ICD-9-CM codes used by Dombrovskiy et al. [7] and Shen et al. [26].”

12. In Table 1, the sub-categories for "acute organ dysfunction" and "site of infection" should be reordered alphabetically or in order of highest to lowest frequency.

We have reordered alphabetically the sub-categories for "acute organ dysfunction" and "site of infection".

13. In Figure 1, the title is clear but the left and right Y-axes need to be re-labelled to clarify that these are proportions of those patients admitted to the hospital. Additionally, the word "severe" should be completely removed from this figure, as it is confusing and not mentioned elsewhere in the paper.

The Figure 1 has been changed according to the suggestion of reviewer.