**Author's response to reviews**

**Title:** Epidemiology and recent trends of severe sepsis in Spain: a nationwide population-based analysis (2006-2011).

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**Author's response to reviews:** see over
Dear Sir,

Please find enclosed our manuscript entitled "Epidemiology and recent trends of severe sepsis in Spain: a nationwide population-based analysis (2006-2011)".

Recent epidemiological studies have shown a progressive increase in the incidence of severe sepsis while its mortality remains disappointingly high thus making it a challenge for western healthcare systems. Despite this, there is very limited information on the epidemiological characteristics of severe sepsis from a population perspective, particularly in Europe.

To the best of our knowledge this is the first study to provide nationwide population-based representative estimates of the epidemiological characteristics and recent trends of severe sepsis in Spain. The data provided are complementary to recent reports of trends in severe sepsis epidemiology published in the US. This information has significant implications for health system planning and may prove useful to estimate future care requirements. Additionally, it might be useful in other European countries with a population similar to ours.

Funding for this study was provided by the Spanish National I+D Program (grant number STPY 1346/09). The funding body had no further role in study design, data collection, analysis, interpretation, writing of the report, or the decision to submit the paper for publication. I also state that this study did not receive any support from industry or private corporations.

I would like to ask you to evaluate the manuscript for publication in your journal with the understanding that it has been read and approved by all authors.

We should also like to thank the reviewers for their comments, which have helped us improve the text. Indeed, the document has been amended in an attempt to incorporate many of the ideas expressed.

As to the specific comments of the reviewers, we provide point-by-point replies below

**Reviewer #1:**

1. Many of the results mention in hospital mortality, but the method section does not explain how mortality was established: was this from hospital administrative data, cross linking to death certification or other method?

   Hospital mortality was directly taken from the national database this work was based on, as it includes the reason for hospital discharge. The same as occurs with other variables, we assumed it was understood from the study’s design and did not think it needed to be specifically mentioned in the methods section.

2. The European standard population was changed in 2013, have you used the standard in use at the time of data collection, or the one in use at the time of publication?
We used the last report from Eurostat “Revision of the European Standard Population” published in 2013. This document is an update of the European Standard Population (ESP) published in 1976 in light of changes experienced by the European population so as to provide a more current, methodologically sound and widely acceptable basis for the calculation of age standardized rates.

3. A weakness of the study not mentioned is the problem with hospital discharge data not capturing cases that don’t present to hospital McPherson et al, showed that this might be 6.5% of all deaths associated with sepsis, suggesting that the values reported are an underestimate.

We acknowledge the value of this comment regarding the cases that are not hospitalized and have included a specific paragraph in the limitations section:

Lastly, we must recognize that the restriction of the study to hospitalized patients may have introduced a bias, as Linde-Zwirble [42] points out, and our estimates of incidence rates of severe sepsis really correspond to incidence treated. In line with this, the figures of mortality associated to severe sepsis refer to hospitalized cases. A recent publication by McPherson et al that analyses the mortality database from the National Statistics Office using the ICD-10 coding systems, points out that in England, between 2001 and 2010, 93.4% of all deaths associated to sepsis occurred within hospitals, while the remaining 6.6% took place outside hospitals [45]. We do not know whether the same occurs in our country, but it is possible that our estimates are conservative and underestimate the impact of severe sepsis in our population and our health system.

4. If mortality from sepsis is increasing in Spain then this implies that more healthcare resources should be allocated to treating sepsis, an important policy point that is not made clear.

It is true that our data indicate that in the study period, the incidence and mortality rates have increased, which means there is an increase in the number of deaths associated to severe sepsis in our population. Indeed, as we comment in our discussion and conclusions, we believe our data have important implications for planning purposes in the health system, and following your suggestion, we have added a paragraph highlighting this point even more.

We firmly believe that our results can be useful in the design and application of educational and therapeutic programmes to promote the early identification and treatment of patients with severe sepsis that can improve the quality of healthcare and enable a cost-effective use of health resources. At the same time, our data represent a fundamental working basis to evaluate the impact of severe sepsis in our country and estimate future needs.

5. If case fatality is decreasing then the reasons for this need to be explored in detail that would potentially give ideas to how other countries should start treating sepsis. They mention “educative initiatives” and give a reference to a 2008 paper. More detail on this point would be valuable.
Our results suggest that, indeed, the fatality of severe sepsis shows a modest, though significant, descending trend in the study period. The trend observed coincides with that described in countries such as USA but, unfortunately, the design of our study does not allow us to determine what the possible causes are. We can only speculate that maybe the introduction of educational measures to identify and treat these patients early may have contributed to this decreasing trend. Indeed, in the last few years, several international educational campaigns such as Surviving Sepsis Campaign and the application of quality indicators in the management of severe sepsis have been accompanied by a mortality reduction in countries such as the USA. In our country, the reference cited is the one that, in our opinion, covers the effectiveness of one of those educational programmes which is why we included it in our study.

6. **Table 3.** The p values column does not add much information since nearly all differences are statistically significant because the denominators are so large. A better approach would be to give the value and confidence intervals for all values and remove the p-value column.

The suggested changes have been made in Table 3.

7. **Figure 1+2** these would be clearer if they were broken up into separate plots for separate y axes e.g. fig 1a-number of deaths, fig 1b mortality etc. Error bars may help as well, but may be too small to show.

Figures have also been modified according to your advice. Effectively, error bars are too small to show.

**Reviewer #2:**

1. Contribution of ICUS to the total number of admissions for SS
2. Separate analysis of hospital stays with or without ICU admission
3. No information related to centers, number of ICU, presence of intermediate care unit, number of ICU beds, teaching status
4. No scores of severity SAPS, SOFA

Regarding the comments on the absence of ICU data, we would like to point out that we are indeed conscious about the lack of such data but, as specified in the introduction, our study is a national population study set up from a point of view that recognises severe sepsis as an important public health problem and a challenge for health systems. The most recent literature repeatedly indicates that severe sepsis can no longer be considered a problem that affects intensive care units as numerous data show that between 50% and 70% of severe sepsis cases are not taken into those units which limits the extrapolation of that data to the general population. It is from this point of view that our study was planned, a lot more general and trying to overcome the limitations of studies carried out in Intensive Care Units.

On the other hand, although a separate analysis of the cases based on whether or not they were taken into an ICU is indeed interesting, it does not meet the objectives of our study and would require another analysis.
For the same reason and given that it is also a retrospective study, no severity scores such as SOFA or SAPS, designed for and normally used in Intensive Care Units, were included. These scores neither conform to the objectives nor to the methodology of the present study.

At the same time, the design of the study recognises its retrospective character and thus makes it impossible for us to assess the work load.

5. No detailed information regarding the case-mix even if some informations are provided. For example, the percentage of patients with documented infection or positive blood-cultures is low compared to published studies raising concern on coding accuracy and completeness.

Regarding your comment about the percentage of cases with documented infection of positive blood-culture we must mention our complete disagreement. As pointed out in the discussion, our data is in agreement with that from other similar studies that retrospectively analyse population databases and even prospective studies carried out in our country. Therefore, we believe there are no problems with the accuracy and adequacy of the coding, as suggested.

6. The incidence of severe sepsis increased over time but it could be related to several factors besides coding such as changes in case-mix with more patients with cancer, immunosupressive treatments, steroids, aplasia...

The increase in the incidence of severe sepsis appears to be multifactorial. We completely agree with this comment and have thus included this idea in page 10 of the manuscript.

7. No distinction between hospital-acquired infection and community-acquired infection

Although we understand the importance of distinguishing nosocomial from community-acquired infections, this difference does not meet our objectives as our aim was to take a general approach to the severe sepsis problem. Although it is important, there is increasing agreement that patients with severe sepsis must be initially treated in a general way, avoiding the excessive emphasis on identifying the exact cause of sepsis. However, we value your comment in order to design a new study that is more specific and focused on this aspect.

8. No detailed information regarding the treatment received: organ support, antibiotics, other procedures

In the study presented, we refer to specific measures such as the practice of mechanical ventilation and hemodialysis and, indeed, no reference is made to antibiotic treatment. In this line, we must comment that none of the similar studies carried out in the USA mention this either. The most important element in the treatment of these patients is to acknowledge the seriousness and start treatment quickly and early with appropriate, yet broad spectrum, antibiotics, control the source of infection and resuscitation measures with the aim of correcting the physiological
changes associated with severe sepsis, no matter what the cause is. Resuscitation efforts are generic, as many of the septic syndrome elements are common, regardless of the pathogen that causes it.

9. **No definition of ICD-9 codes and organ failure**

Regarding the lack of definition for ICD-9 codes and organ failure, we do not agree with this comment as in the Methods section, a complete description of the codes used is included.

10. **Among surgical patients, it is important to separate planned surgery and urgent surgery.**

With regards to this comment, although we understand the difference pointed out, in order to include this analysis, a vast amount of data analysis would be required, which we consider would be the object of another specific study.

We hope you will find these changes to your liking, and we will look forward to hearing from you.

Yours sincerely,

Carmen Bouza, MD, PhD