Author's response to reviews

Title: Hospital staff education on severe sepsis/septic shock and hospital mortality: An original hypothesis

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

We send you the new revised version of our manuscript. We hope that it will be suitable for publication. We thank again you and reviewers for the work done and the suggestions given.

ANSWERS TO REVIEWERS

REV 1

Minor comments.
Abstract - method section - line 3. Include learning after "adults"
R: done

P 7 - line 7. You mention a questionnaire to assess learning, but you do not give any results. Even though it is only postcourse values - these data could support your findings (process measurements). If not, then delete the information here.
R: done

I am aware that you were asked to expand the section about the educational program, but could it be shortened without valuable information being lost?
R: To shorten the section on education we moved the part concerning the teamwork activity and the algorithm to be displayed in the working areas.

Discussion - would suggest to delete the first 6 lines (repetition of methods) - start with main findings. In general, mention own findings and then compare with other studies.
R: done

REV 2

Major compulsory revisions
1. In the Results 2nd paragraph (and also in the discussion) you stated: "Age, Charlson index, and percentages of males and of urgent admissions were lower in the period before education than in the other periods. Length of stay in hospital showed a gradual decrease over time. Please clarify, as data does not suggest a significant difference. Please add p values on table 2. Moreover, if it is true that age and comorbidities increased in the after training period, this would have contributed to increase mortality not to decrease it.
R: We added p-values in table 2 and we thank the reviewer for that, because it clarifies to the reader that the three periods are not equivalent, and that’s just the reason why we adjusted mortality.
Please, note that our study involved thousands of patients, so some comparisons of clinically similar values (showing small differences) can be statistically significant.
In the Statistical analysis section we added the following sentence about the tests used for p-values computation:
“F-test (one-way ANOVA) was used to compare means and Chi-Squared test to compare percentages of categorical variables.”

2. As a consequence of this potential equivalence between periods regarding these four variables, it would be nice to have also the unadjusted mortality.
R: We added the unadjusted mortality in table 2: it increases over time, probably because of the increase of age and comorbidities, as the reviewer supposes.

3. In the statistical section authors stated “We excluded data regarding the two months before and after this period in order to include all the patients with known outcomes present in hospital every month, and for each month we computed the mortality for the patients present in the hospital in that month.” I still don’t understand why the months of September and October were withdrawn from the analysis. It seems arbitrary as you do have data on mortality available until October 2009, even if not for a few of the patients. Does the addition of these 2 months will change the linear trend for decreased mortality and the relative risk along the first and second period?
R: The SDO record database collects discharge records monthly. For this reason, at the time of the analysis, we didn’t have data regarding the patients admitted in September and October who were still in hospital in November and we can’t know how many they were. Therefore, we found correct to exclude these two months from the multivariate analysis. However, to satisfy this reviewer, we have fitted also the model including them. The following tables report the results with and without the last two months (September and October 2009).

**Without September and October 2009:**

| Coefficients: | Estimate | Std. Error | z value | Pr(>|z|) | RR |
|---------------|----------|------------|---------|----------|----|
| Time          | 0.001929 | 0.001165   | 1.655   | 0.097874 | 1.02* |
| Period1_of_edu| -0.071667| 0.031989   | -2.240  | 0.025069 | 0.93 |
| Period2_of_edu| -0.115758| 0.046481   | -2.490  | 0.012759 | 0.89 |

* RR of time, which is a continuous variable, is computed with respect to 12 months

**With September and October 2009:**

| Coefficients: | Estimate | Std. Error | z value | Pr(>|z|) | RR |
|---------------|----------|------------|---------|----------|----|
| Time          | 0.002371 | 0.001099   | 2.158   | 0.03091  | 1.03* |
| Period1_of_edu| -0.088477| 0.029655   | -2.984  | 0.00285  | 0.92 |
| Period2_of_edu| -0.133908| 0.044636   | -3.000  | 0.00270  | 0.87 |

* RR of time, which is a continuous variable, is computed with respect to 12 months

As you can see, our findings become stronger in the model including these two months.
To clarify our methodological choice, we have changed the second paragraph of the statistical analysis section as follows:

“We performed a time series analysis, modelling a sequence of data points (dependent variable) measured at successive time instants, spaced at uniform time intervals. Admission data were available from October 2003 to October 2009. We used months as time intervals and the dependent variable was the monthly hospital mortality rate calculated for each of the 69 months from December 2003 to August 2009. We excluded data regarding the two months before this period in order to include all the patients present in hospital every month. For each month we computed the mortality rate for the patients present in hospital in that month. We also excluded data regarding the last two months because our data came from a retrospective discharge dataset, so data regarding the last two months could be incomplete and missing the patients admitted in that period and not yet discharged. The SDO records are collected on an individual patient basis, so we collapsed data into a time series of monthly average values or proportions in order to model the mortality rate trend over time (months).”

The linear trend in figure 2 seems highly influenced by the drop in mortality on August 2009.

R: The drop of adjusted mortality on August 2009 is similar to that observed in August of the other years. Note that the August drop is always present, and similar year by year: it shows the relative risk of death in August compared with December, which is the reference month. Moreover, the linear trend in the figure is not influenced by the drop in August 2009, because the addition of September and October reduced the relative risk along the first and second period further (as shown in the previous tables).

Although the drop in mortality after the initial training phase is supported by the 25% of training, it would be difficult to explain that a mortality significantly reduced when the percentage of educated staff increased from 25 to 30%, as I already stated in my previous comments.

R: There is no statistically significant difference between first and second period of education: they are both significantly different from the period before education (in a different measure, that is RR 0.93 and RR 0.89) but they are not significantly different one from another. In fact the 95% CI for the two Relative Risks overlap one with the other (0.87-0.99 and 0.81-0.98). Another way to see this is to fit another model, with one of the two period of education as the reference period, and look at the p-value of the other education period: we did it and there is no statistically significant difference between the two periods.

Please report the results with September and October

R: done.

and the number of patients for whom mortality is not available in these two months.

R: For those patients the problem is that we completely miss the patients: they were still in hospital when we extracted data (November 2009) so they were absent from the SDO discharge database. We can’t know how many they are.
4. Figure also suggests that mortality started to drop on August and not October 2007. And we are aware that any intervention usually have a delay in its impact on outcome. Thus, do the authors have an explanation for this drop in mortality BEFORE the intervention started?

R: The drop in August is identical to the August drops in the years before, also if it seems to be the time where the trend of mortality starts falling.

Figure 2 shows estimated mortality (calculated point by point for the 69 time instants) according to the Poisson model where Charlson score, age, LOS and percentage of Urgent admissions are kept fixed at their mean value, while the other variables included in the analysis (linear time trend, months, first education period, second education period) change. The indented line graphically represents the combined effects of these variables according to their estimated coefficients. Since the month of August has a negative coefficient (-0.058), whether the month of July has a positive one (0.114), every August the trend falls down in the picture. Note that the August drop is always identical year after year: it shows the relative risk of death in August compared with December, which is the reference month.

5. Discussion

5.1 The writing of the third paragraph could be improved. What do you mean with first, second and third? Are these the reasons to justify your finding of decreased mortality, to justify why training only 30% of the staff had results in changes?

R: The aim of the third paragraph was to EXPLAIN that other unmeasured factors may have influenced the level of education of our hospital clinical staff both quantitatively (the first two points, that is the education started in selected wards and the education individually performed by staff members) and qualitatively (as effect of the composition of the Multidisciplinary Sepsis Teams). To clarify the paragraph (now second of the discussion), as required by the reviewer, we have modified it as follows:

"Our educational project on SS/SS involved only 30% of the hospital clinical staff, but other unmeasured factors may have influenced the number of educated staff in the wards and units involved in the analysis of mortality. Firstly, the education started involving the staff of emergency departments, ICUs and larger wards, which were also those included in the study and with higher mortality. The lower percentages of educated staff found in larger hospitals should be due to the lack of education of the staffing for specialised wards with very low mortality (for example allergology, endocrinology, rheumatology), because they were not involved in this phase of the educational project. As a consequence, the percentage of the educated hospital staff is certainly underestimated for the wards/units included in the present analysis. Secondly, some spread of the Surviving Sepsis Campaign guidelines happened before starting the present project and was strengthened by the publication of the updated version of the Surviving Sepsis Campaign [10]. We don't have any measure of this spread but our time series analysis started long before. Moreover, the Multidisciplinary Sepsis Teams consisted of senior staff who acted as tutors for the problem based learning used in the education of our target staff, and this may have facilitated the learning of our well experienced (we excluded residents and medical students) hospital staff [28]."

5.2 As many of the issues raised in my first comments were not properly solved, I
strongly suggest authors to emphasize them in the new limitations paragraph:
a. Limited information to characterize the population, as all adjustments were
done only using four variables
b. No data about the compliance with treatment guidelines or any type of
performance measurement to indicate training really results in change in sepsis
bundles or in any other quality indicators. I respectfully disagree with the authors
when they cited Ferrer study to justify that this is not a relevant information. To
address quality indicators is relevant to justify any outcome measurement.
c. Although the authors argued in favor of keeping in the analysis data from
2003, I am not convinced that this is not a source of bias. So, this should be add
as a potential limitation as it could have compromise the ability to associate the
reduction in mortality with your intervention, even with the adjusted analysis.
d. 30% of training still seems a low target which still compromise the ability to
associate training with mortality reduction.

R: The following paragraph has been added in the last page of the discussion:
"There are other weaknesses of the study. Firstly, limited information to characterize
the population was available, so the hospital mortality was adjusted using only four patient-
related variables, also if the linear time trend took into account for each month all
modifications occurred over the previous time and seasonality. Secondly, we don't have
any data about the compliance with treatment guidelines or any quality indicators
assessing the change in processes of care as training result. Thirdly, someone could
argue that the long period considered in the time series analysis could have compromise
the ability to associate the reduction in mortality with education, but the first version of the
Surviving Sepsis Campaign was published in March 2004, so we expected some effect of
the natural spread of the Campaign. Finally, 30% of trained staff may be a low target to
associate training with mortality reduction, but results of education may depend not only on
quantity but also on quality of education, as well as on other factors difficult to measure
like educational activities individually performed by staff members and leadership of
tutors."

Minor essential

Table 2 - The numbers of patients, male patients and urgent admissions can not
be reported with decimals, please correct the mistake.
R: The number of patients are in thousand, and they are reported according to the rules of
English notation (with comma as usually done for numbers of six or more digits) . The
number of patients included in the period before education is 276,541 (two hundred
seventy six thousand five hundred and forty one).

The conclusion in summary should be change to a more appropriate one, as in
the text.

R: Now the conclusion of the abstract is the same as in the text
"Our hypothesis that a program educating hospital staff to early detection and treatment of
severe sepsis/septic shock may affect the outcome of all hospital patients is original, but it
has to be corroborated by other experiences."
Some articles that would be worthy in the discussion and not discussed.1-5


R: The study has been discussed in Page 15, first paragraph, second and subsequent lines:
"Nevertheless sufficient evidence of adverse events like hospital mortality and ICU admission already exists; there is a need now for strategies to prevent or reduce them [34]."


R: thank for the abstract. We have found the study just published, so we have reported it (Carr GE, Yuen TC, McConville JF, Kress JP, VandenHoek TL, Hall JB, Edelson DP; American Heart Association's Get With the Guidelines-Resuscitation (National Registry of CPR) Investigators. In-Hospital cardiac arrest among patients with coexisting pneumonia: a report from the American heart association's get with the guidelines - resuscitation program. Chest 2012,141:1528-36).

The study has been discussed in Page 14, second paragraph, third and subsequent sentences:
" A recently published study on retrospective cardiac arrest registry data has compared in-hospital cardiac arrests occurred within 72 h of hospital admission in patients with (4,453) and without (32,645) preexisting pneumonia [32]. Only 36.5% of the patients with and 30% of those without preexisting pneumonia were receiving mechanical ventilation and only 33.3% of the patients with and 28.8% of those without preexisting pneumonia were receiving infusions of vasoactive drugs prior to cardiac arrest. These results show that more than half of the cardiac arrests occurred in the lack of overt shock and respiratory failure, suggesting the need of early recognition of clinical deterioration in patients with and without sepsis [32]."


R: thank for the copy of the paper included in the comments.

In the discussion, it has been presented in page 11, first paragraph, two sentences before the last as follows:
" Moreover, a recent multicenter study using both before-and-after and concurrent analyses assessed the in-hospital mortality effect of "GENeralized Early Sepsis Intervention Strategies" in community and tertiary care settings [25]. The patients with severe sepsis and septic shock receiving the 6-h resuscitation bundle via a sepsis team or sepsis order sets experience a significant reduction in mortality [25]"
R: sorry for forgetting to reference this relevant paper. It has been done.

R: The study has been discussed in Page 14, last paragraph, sentence before the last: "Moreover, it has long been shown that, in comparison with the patients developing septic shock in the ICU, those developing septic shock in general ward receive intravenous fluid boluses and vasoactive agents with clinically important delay [33]."