

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Sepsis-associated mortality in England: an analysis of multiple cause of death data from 2001 to 2010.
<b>AUTHORS</b>	McPherson, Duncan; Griffiths, Clare; Williams, Matthew; Baker, Allan; Klodawski, Ed; Jacobson, Bobbie; Donaldson, Liam

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Vincent, Jean-Louis Erasmus University Hospital, Department of Intensive Care
<b>REVIEW RETURNED</b>	31-Jan-2013

<b>GENERAL COMMENTS</b>	<p>The authors reviewed the causes of death of the UK population to define how many deaths were due to sepsis. Using IDC-10 codes, they concluded that sepsis was involved in between 4.7 and 6.9 % of deaths.</p> <p>These rates are very low, but grossly underestimated, with the crude methodology used.</p> <p>The problem largely lies in the identification of the complex signs and symptoms of sepsis, and especially the organ failure that characterizes it (otherwise it is only an infection).</p> <p>The rate of sepsis is particularly difficult to define outside the hospital.</p> <p>The ethical questions leading to therapeutic limitations are important, and do not transpire in this analysis. Many patients die from sepsis without benefitting from therapeutic efforts. As an example an elderly patient who dies with pneumonia (the old man's friend) may have dehydration responsible for some degree of renal dysfunction and thereby meet the criteria of sepsis.</p>
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<b>REVIEWER</b>	Professor Kevin Rooney National Clinical Lead for Sepsis Healthcare Improvement Scotland Consultant in Anaesthesia & Intensive Care Medicine Professor of Care Improvement NHS Greater Glasgow & Clyde and the University of the West of Scotland
<b>REVIEW RETURNED</b>	27-Mar-2013

<b>GENERAL COMMENTS</b>	<p>This is a very interesting paper which does it 's best to identify the true incidence of Sepsis mortality in England. This is of particular interest as more and more countries and organisations are targeting improvement collaborative against Sepsis. A standardised diagnostic code for Sepsis would help with outcome measures for these initiatives. Unfortunately, it will still be a gross underestimate</p>
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	of the true incidence of Sepsis deaths due to the vast majority of conditions which could trigger the spectrum of illness from Sepsis to Septic Shock, Multiple organ dysfunction and death. A prime example here would be multiple organ dysfunction from a perforated viscus e.g. faecal peritonitis. This is highly unlikely to be coded as a Sepsis death.
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<b>REVIEWER</b>	Jan Bakker MD PhD Chair dept Intensive Care Adults Erasmus MC University Medical Center Rotterdam The Netherlands
<b>REVIEW RETURNED</b>	18-Apr-2013

<b>THE STUDY</b>	The overall study design is limited by the information available. As we have no specific-uniform sepsis coding system in the cause of death system there is no direct solution today. The authors used adequate methodology to make the most out of the available data. Given the above, the patients included in the analysis might not have had sepsis and the cause of death might not have been associated with sepsis at all but the authors have adequately tried to exclude most of these.
<b>RESULTS &amp; CONCLUSIONS</b>	The problem I have with this is that defining sepsis in a patient as a probably or most likely contributing cause of death does not mean that this was a preventable death or an undesirable death . Surely in many patients admitted to the ICU with severe infection the goal of admission is to have these patients survive this infection. However it might be that in patients admitted to a general ward this is not always the case. As the authors compile all in hospital deaths the extrapolation of these sepsis numbers and sepsis mortality to surviving sepsis campaign, early recognition etc. in preventing mortality and saving costs is long fetched and not supported by these data

<b>REVIEWER</b>	Antonio Artigas, Critical Care Department, Sabadell Hospital, Spain.  Not conflicts of interests.
<b>REVIEW RETURNED</b>	22-Apr-2013

<b>THE STUDY</b>	Include references: G.Martin et al. New Engl J Med 2003;348:156-54 D.Angus et al. Crit Care Med 2001;29:1303-10 See comments to the authors.
<b>GENERAL COMMENTS</b>	This is an interesting study on sepsis-associated mortality in England during 2001-2010 years. The authors demonstrated an incidence of 20-28/100,000 population similar to that reported in other epidemiological studies. These patients represent 6.9% of all death and 7% among these were outside hospital. Comments: 1. Mortality rate changes and Co-morbidities Recently mortality rate due to sepsis decreased probably because the impact of the Surviving Sepsis Campaign reporting a mortality rate of 30% in 2012. Early recognition and early treatment produced a progressive decline in mortality as it was demonstrated in this study. How the authors explain the increase in mortality during the first period of the study between 2001-2006? And why the mortality in 2010 did not reached the same value as it was in 2001? The

	<p>authors should analyze the influence and changes of co-morbidities during the study period, and indicate the statistical differences of mortality in Fig. 1.</p> <p>2. Mortality rate, age and gender Mortality rate increased according to the age of patients. &gt; 14 years old as it was described previously by other authors. A separate analysis is necessary among adult patients (&gt;16-18 years old). What was the mortality rate in septic population with and without co-morbidities at different ages (Fig. 2)?</p> <p>It has been reported previously a higher incidence and mortality among males with sepsis adjusted by confounding factors. Please indicate the statistical difference of mortality between males and females at different age intervals in Fig. 2.</p> <p>3. Mortality and Causes of Sepsis What was the mortality rate according to the cause of sepsis adjusted by age? Genitourinary diseases represents 17.8% of sepsis associated death and 41.3% of all death sepsis related. It has been described that mortality rate of urinary tract sepsis is lower compared to pulmonary or abdominal sepsis. How can you explain this discrepancy in your results?</p> <p>Minor Comments</p> <p>Page 10: 20-28 per cent should be 20-28/100,000 population.</p>
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### VERSION 1 – AUTHOR RESPONSE

Prof JL Vincent

We identified that 1 in 20 deaths in England are definitely associated with sepsis. From a public health perspective we would contend that this not a small figure (even though it may be an underestimate) and that the burden of sepsis-related mortality is worthy of monitoring and further analysis. This is many more deaths than are associated with many other diseases.

Whether or not therapeutic limitations have been put in place, or were appropriate, is not relevant to whether or not the death was associated with sepsis.

Professor Kevin Rooney

We agree that a standard code for sepsis would be immensely helpful in monitoring sepsis mortality, although we have found that 99 per cent of deaths definitely associated with sepsis contained one of three ICD-10 codes in at least one position on the death certificate. It is of note that the WHO revised the description of two of these three codes in the latest version of ICD-10. In ICD-10 version 2010, code A40 is described as 'streptococcal sepsis' whereas in ICD-10 version 2008 (and earlier versions) it was described as 'streptococcal septicaemia'. Similarly, code A41 is now described as 'other sepsis' in version 2010, whereas it had been 'other septicaemia' in earlier versions.

Jan Bakker MD PhD

We haven't claimed that sepsis-associated deaths are preventable or undesirable, merely attempted to count them.

We have not compiled in-hospital deaths, but rather all deaths. We have not attempted to measure case fatality for all sepsis deaths or claimed that the reductions in fatality achieved by in-hospital based treatments can simply be extrapolated to other settings. We have quoted other authorities that earlier treatment is effective, and hope that by raising awareness among a more general medical audience, including BMJ Open readers, this may be facilitated.

Antonio Artigas

Thank you for the references, we have added these into the manuscript.

Ours is an observational study, and now that we have identified the trend in sepsis related deaths it would, indeed, be a worthwhile future research exercise to try to understand why the trend changed as it did.

We have altered figures 1 and 2 to include confidence intervals and changed the text to reflect this better.

The chart of sepsis-related mortality by age shows there isn't really a rationale for having a separate analysis just for adults. Examining co-morbidities by age is beyond the scope of this paper, though it could be examined in future research. However, it should be noted that what is analysed is not strictly co-morbidity, it is simply one of two things – other diseases or conditions mentioned on the death certificate, or the underlying cause of death for sepsis-related deaths. Our paper makes it clear that almost all of these deaths will have something other than sepsis also recorded on the death certificate.

Table 1 refers to underlying cause of death by chapter. That is that 41.3% of those whose underlying cause of death was genitourinary had sepsis. This is not the same as saying that 41.3% of those with genitourinary sepsis died. That would be the case fatality, which we are not able to calculate from this data.

On page 10 we do mean the standardized rate is 20-28% higher for males. The absolute difference in standardized rate was 5.0 per 100,000 population in 2010.

#### References

1. Brock A, Baker A, Griffiths C, Jackson G, Fegan G and Marshall D. (2006) Suicide trends and geographical variations in the United Kingdom, 1991–2004. *Health Statistics Quarterly* 31, 6-22.
2. Baker A and Rooney C (2003) Recent trends in alcohol-related mortality, and the impact of ICD-10 on the monitoring of these deaths in England and Wales. *Health Statistics Quarterly* 17, p5–14.