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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-002586
Article Type:	Research
Date Submitted by the Author:	11-Jan-2013
Complete List of Authors:	McPherson, Duncan; Portsmouth Hospitals NHS Trust, Anaesthesia; Imperial College London, Institute of Global Health Innovation Griffiths, Clare; London Health Observatory, Williams, Matthew; Portsmouth Hospitals NHS Trust, Critical Care Medicine Baker, Allan; London Health Observatory, Klodawski, Ed; London Health Observatory, Jacobson, Bobbie; London Health Observatory, Donaldson, Liam; Imperial College London, Institute of Global Health Innovation
Primary Subject Heading:	Public health
Secondary Subject Heading:	Research methods, Intensive care, Infectious diseases, Health policy, Epidemiology
Keywords:	STATISTICS & RESEARCH METHODS, EPIDEMIOLOGY, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Public health < INFECTIOUS DISEASES, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, PUBLIC HEALTH

Sepsis-associated mortality in England: an analysis of multiple cause of death data from 2001 to 2010

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Contents: 2 figures, 4 tables, 1 appendix.

Abstract

Objectives

To quantify mortality associated with sepsis in the whole population of England.

Design

Descriptive statistics of multiple cause of death data.

Setting

England between 2001 and 2010.

Participants

All people whose death was registered in England between 2001 and 2010 and whose certificate contained a sepsis associated International Classification of Diseases, Tenth Revision (ICD-10) code.

Data sources

Multiple cause of death data extracted from Office for National Statistics mortality database.

Statistical methods

Age and sex specific death rates and directly age standardised death rates.

Results

In 2010, 5.1% of deaths in England were definitely associated with sepsis. Adding those that may be associated with sepsis increases this figure to 7.7% of all deaths. Only 8.6% of deaths definitely associated with sepsis in 2010 had a sepsis related condition as the underlying cause of death. 99% of deaths definitely associated with sepsis have one of three ICD-10 codes, A40, A41 and P36, in at least one position on the death

certificate. 7% of deaths definitely associated with sepsis in 2001-10 did not occur in hospital.

Conclusions

Sepsis is a major public health problem in England. In attempting to tackle the problem of sepsis it is not sufficient to rely on hospital based statistics, or methods of intervention, alone. A robust estimate of the burden of sepsis associated mortality in England can be made by identifying deaths with one of three ICD-10 codes in multiple cause of death data. These three codes could be used for future monitoring of the burden of sepsis-associated mortality.

Summary

Article Focus

- A large proportion of patients admitted to critical care units with sepsis die and if sepsis is identified and treated earlier, mortality can be reduced producing cost-effective benefits in terms of life years/quality-adjusted life years gained;
- Assessing sepsis-associated mortality is not straightforward as there are no codes for sepsis in ICD-10 and sepsis-related conditions are often not selected as the underlying cause of death;
- Multiple cause of death data are now available for deaths in the UK and provide a way of determining those that are associated with sepsis.

Key Messages

- In 2001-10, one in twenty deaths in England was associated with sepsis;
- 99% of deaths definitely associated with sepsis include one of three ICD-10 codes, A40, A41 and P36, somewhere on the list of causes of death;
- These deaths occur across a wide range of specialty areas and 15,000 (7%) deaths definitely associated with sepsis in 2001-10 did not occur in hospital; this should prompt a much wider population-based approach to future quality improvement.

Strengths and Limitations

- Multiple Cause of Death data are collected for all deaths, allowing us to count all those whose death is associated with sepsis, not just those who die in hospital, or those for whom septicaemia is the underlying cause;
- Our population estimates are based on the 2001 UK census, which will shortly be updated by the 2011 Census;

- The study relies on the accuracy of coding. There is no specific code for sepsis within ICD-10, which may lead to misclassification of causes. We may have underestimated the true impact of sepsis.

Introduction

Sepsis is defined as systemic inflammatory response syndrome caused by infection.[1] [2] Severe sepsis is sepsis with organ system dysfunction, while septic shock is defined as sepsis with hypotension refractory to fluid resuscitation, leading to inadequate tissue perfusion. These entities lie on a spectrum of diseases culminating with death caused by multiple organ dysfunction.

Twenty seven per cent of intensive care admissions in England and Wales are for severe sepsis and almost half of these patients die in hospital.[3] In 1995-96, in an adult general intensive care unit (ICU) in a UK university hospital, the median cost of treating a patient with sepsis was six times the cost of treating a patient without sepsis. The mortality rate was also significantly higher for the sepsis patients, despite the increased spending, at 53% compared with 29% for non-sepsis patients.[4] More recent studies have found that using integrated sepsis treatment protocols, including those developed by the International Surviving Sepsis Campaign, can be effective at reducing mortality rates.[5-7] Such protocols may increase costs through lengthier ICU stays, but appear cost-effective in terms of life years and quality-adjusted life years gained. Estimates of the incidence of sepsis, and associated mortality, are hard to obtain. Recent estimates suggest that the incidence of severe sepsis in the general population is 38 per 100,000 in Finland[8] and 25 per 100,000 in Spain[9]. However, these estimates are based on administrative in-patient data. It is likely that these underestimate the incidence of sepsis as they only count those admitted to hospital. Using multiple cause of death (MCOD) data it has been estimated that 6% of all deaths in the USA are associated with sepsis.[10]

In 1993, the redevelopment of the Office for National Statistics (ONS) mortality database allowed all the diseases and conditions mentioned on the death certificate to be coded and stored. Up to 15 mentioned causes of death can be coded, in addition to

the underlying and secondary causes of death.[11] MCOD data have been used in England to examine the contribution to mortality of many different diseases and conditions.[12-17] Analysis of mortality by cause of death usually uses the underlying cause of death, which is the "disease or injury which initiated the train of morbid events leading directly to death or the circumstances of the accident or violence which produced the fatal injury."[18] For many patients, sepsis may be part of that causal sequence, but it would not be listed as the underlying cause of death. For example, in cases where sepsis is hospital-acquired, the original reason for hospitalisation would generally be the underlying cause of death. Consequently, examining mortality from sepsis using the underlying cause of death would not identify those deaths as being sepsis-associated.

In this paper MCOD data have been used to estimate the number of deaths in England associated with sepsis.

Methods

Mortality data were obtained from the Office for National Statistics (ONS) mortality database, for the period from 2001 to 2010. As sepsis deaths cannot be directly identified in ICD-10, a list of codes related to sepsis was selected. Using the underlying question, "If this condition appears on the death certificate, what is the chance this person would have had sepsis?" a list of conditions was derived. These were then divided into two categories: those definitely meaning sepsis was involved and those that may mean sepsis was involved. The ICD-10 codes associated with these conditions were identified using the ICD-10 index[19] and online searching tool developed by WHO and the German Institute of Medical Documentation and Information[20]. The first three authors then reviewed the list of codes, by asking the question "If this code was recorded on a death certificate, what is the probability that the deceased had severe sepsis?" If the probability was considered to be more than 50% then the code was included in a candidate list. This candidate list of codes was crosschecked with the Melamed paper[10] and the ICD "List of conditions unlikely to cause death"[21] to ensure that no unlikely codes were included and that no likely codes had been overlooked. The ICD-10 codes that are definitely or maybe associated with sepsis are listed in the Appendix.

Deaths were extracted from the mortality database if they had a mention of any of the identified codes anywhere on the death certificate. Age- and sex-specific rates were calculated using mid-year population estimates for England, published in June 2010, as denominators for the relevant year and, where appropriate, death rates were directly age-standardised using the European Standard Population.

To look at patterns of sepsis-associated mortality, we also examined the underlying cause of death for these deaths, other co-morbidities mentioned on the certificate, and the total number of contributing causes mentioned on the death certificate. We compared these with overall patterns for all deaths in England. We also examined

sepsis-associated mortality by place of death: home, hospital, care home etc. We restricted these analyses to those deaths definitely considered to be sepsis-associated. Deaths under 28 days have a separate death certificate and only mentioned causes are coded for these deaths - an underlying cause of death cannot be selected from them.[22] These deaths were included in the majority of analyses in this study and where they have been excluded this has been noted in the results.

Results

Between 2001 and 2010 there were 226,547 deaths that were definitely directly associated with sepsis in England, 4.7% of all deaths. Adding those that may be related to sepsis increased this to 332,757, 6.9% of all deaths. In 2010 alone, 5.1% of deaths were definitely associated with sepsis, and adding in those deaths that may be related increased that percentage to 7.7%. Figure 1 shows mortality rates for deaths that are definitely and maybe linked to sepsis for each year. For both sexes combined, the rate rose to a peak in 2007 and then declined. Excluding the 'maybe' group brings the peak in mortality forward to 2006. The number of deaths definitely associated with sepsis was also highest in 2006. The number rose from 16,800 in 2001 to a peak of 26,150 in 2006, before decreasing every year to 23,700 in 2010. The remaining analyses in this paper present results only for those deaths definitely associated with sepsis.

In 2010, the percentage of deaths associated with sepsis was higher for females (5.5%) than males (4.8%). However, when directly age-standardised rates were calculated (which take into account differences in the age structures of the population between the sexes) the rate in 2010 was higher for males (29.8 deaths per 100,000 population) than females (24.8 per 100,000). Between 2001 and 2010, the annual death rate for males was 20-28 per cent higher than the rate for females.

Age-specific mortality rates were higher in the very youngest and elderly, with the rate in the under 1s being similar to the rate among those in their 60s (figure 2). At younger ages, the rate declined rapidly after age 1. In 2001-10, the age-specific mortality rate for deaths associated with sepsis in ages 5-14 was less than 1 per 100,000 population for both males and females. Rates then rose with age, with particularly marked increases in the oldest age groups. For both males and females, the rate in the 85+ age group was double the rate for those aged 80-84. The age-specific rate for males was higher than females for deaths under age 5 and for every age group from age 30

onwards. For deaths at age 85 and over, the age-specific rate for men was 822 deaths per 100,000 population, compared to 683 per 100,000 for women.

Table 1 shows the underlying cause of death for deaths that are definitely sepsis-associated, by chapter of the ICD, and the percentage of each ICD chapter that is sepsis-associated. Deaths with a mention of sepsis are spread across a wide spectrum of ICD chapters. The ICD chapter that accounts for the biggest percentage of sepsis-associated deaths is genitourinary diseases (17.8%). The leading causes of death also account for high percentages, such as respiratory diseases (15.4%), digestive diseases (14.0%), cancer (13.4%) and circulatory diseases (11.5%), while 11.7% of deaths have an underlying cause in the infectious diseases chapter. Almost half of deaths with an underlying cause of infectious disease are associated with sepsis (49.1%). There are wide differences in the percentages in other chapters. Only 1.5% of circulatory disease deaths are associated with sepsis, but for deaths with an underlying cause of skin disease, three-quarters are associated with sepsis (75.7%). Twenty per cent of deaths from diseases originating in the perinatal period also had a sepsis-associated cause of death on the death certificate. However, it must be borne in mind that deaths under 28 days were not included in the analysis of deaths by underlying cause as a different death certificate is used to register these deaths in England (Office for National Statistics 2009).[22]

We also examined the percentage of sepsis-associated deaths where sepsis was also the underlying cause of death. For deaths definitely considered to be sepsis-associated, this was 8.6% in 2010. Of the cases definitely associated with sepsis, 99% contained one of three ICD-10 codes in at least one position on the death certificate: A40 (streptococcal septicaemia), A41 (other septicaemia) and P36 (bacterial sepsis of newborn).

Table 2 shows the total number of causes mentioned on the death certificate for all deaths and for sepsis-associated deaths. Sepsis-associated deaths tend to have more

conditions mentioned than do all deaths. For all deaths, two is the most common number of causes mentioned, whereas for sepsis-associated deaths the most common number is three. Very few sepsis-associated deaths have only one cause of death on the death certificate. This is because 'sepsis' alone is not sufficient detail to allow the death to be registered without reference to a coroner – the certificate must mention the cause of the sepsis for this to be acceptable under law. However, it also seems that overall, sepsis-associated deaths have proportionally more conditions mentioned, as might be expected given the severity of illness amongst these individuals. For sepsis-associated deaths, 23.2% have five or more conditions mentioned, compared with 7.2% of all deaths. Neonatal deaths were excluded from this part of the analysis, because the conditions mentioned on their death certificates include conditions in the mother and in the baby, so they are not directly comparable to those deaths where the deceased was aged 28 days or older.

Many of the chronic conditions known to be associated with sepsis appear on the death certificates of sepsis-associated deaths – 16.8% of certificates mentioned cancer, and 9.4% diabetes (table 3).

Table 4 shows that 93.4% of all sepsis-associated deaths took place in hospital, compared with 55.6% of all deaths. Nearly 7% of sepsis-associated deaths therefore did not take place in hospital. Less than 2% of sepsis-associated deaths occurred in the deceased's own home, compared with nearly 20% of all deaths. Almost 8% of deaths in hospital were associated with sepsis, compared to less than half a percent of deaths that took place in the deceased's own home, hospices, or elsewhere.

Discussion

We have estimated that at least one in twenty of all deaths in England are associated with sepsis. The sepsis-associated death rate has been increasing over the last decade, reaching a peak in 2006. The rate has decreased in more recent years, but not yet to the level in the earlier part of the decade. We have shown that 6.6% of patients with definite severe sepsis die outside of a hospital, indicating that in 2001-10 up to 15,000 deaths associated with sepsis may have been missed if we had only counted deaths in hospital. Sepsis-associated deaths appear to have larger numbers of conditions on their death certificates than do all deaths.

Our study does have some limitations. In using multiple cause of death data, it relies on the accuracy of the recording of causes of death on the death certificate. As a study of sepsis-associated deaths in the US has noted, codes for septicaemia have to be used as a proxy for sepsis in ICD-10. There is a risk that this may lead to misclassification of deaths, and possibly an under-estimation of the burden of sepsis-related mortality.[10] We should also note that our mortality rates were calculated using mid-year population estimates which are based on the 2001 Census. In December 2012, ONS plan to release revised mid-year estimates for England, which will take into account the results of the 2011 Census.

Our estimate of deaths associated with sepsis is similar to that found in the USA using a similar method.[10] Many current estimates of mortality due to sepsis look at patients admitted to hospital and who subsequently die, giving an indication of case fatality. It is estimated that the mortality of patients admitted to critical care units and diagnosed with severe sepsis is 47%.[3] Our study is population-based and therefore gives an indication of the burden of sepsis across the whole population. Most analyses of cause of death data only look at the underlying cause, which identifies the disease or injury that initiated the events leading to death. We have shown, however, that less than

10% of deaths associated with sepsis have it as the underlying cause. To fully account for sepsis-related mortality, it is therefore necessary to examine all the recorded causes of death, as we have done. Although this analysis is more complex than just examining the underlying cause of death, we have shown that just three ICD-10 codes – A40, A41 and P36 – identify 99% of deaths definitely associated with sepsis. These three codes alone could therefore be used for future monitoring and audit of the burden and quality of sepsis care using multiple cause of death data. However, regular review of the ICD-10 codes definitely or possibly associated with sepsis (and the number of deaths with these codes) would be worthwhile as ICD codes are updated. For example, a code for necrotising fasciitis, M72.6, was added by the WHO as an update to ICD-10, but not implemented for coding by ONS until 2011. As the presence of this code on a death certificate may indicate sepsis, this could be considered in future analyses, but counting deaths with one of just the three identified ICD-10 codes would still find the vast majority of sepsis-associated mortality.

Sepsis can no longer be regarded as a niche problem relevant only to the critical care units that treat the most severely affected patients. There is some evidence that recognition of sepsis may be low outside hospitals. For example, patients diagnosed with severe sepsis in one US emergency department were reviewed.[23] Only half of these patients had been transported to hospital by ambulance. In this half of cases, the paramedic had explicitly considered sepsis in only a fifth. For those patients where paramedics had recognised sepsis, there was a significant decrease in time taken to receive antibiotic treatment. By the time patients with sepsis are admitted to critical care, they are very severely unwell and therefore likely to die despite the best efforts of their healthcare team. There is also evidence that treating patients with sepsis earlier and in a more coordinated manner reduces mortality.[24] Therefore, if we could find ways to encourage earlier diagnosis and earlier, coordinated treatment, it is probable that the overall mortality from sepsis could be reduced. The reduction of sepsis related mortality

since 2007 may represent the results of the introduction of changes to identify such patients, e.g. Early Warning Scoring (EWS) systems, Critical Care Outreach, efforts to improve awareness and training (e.g. Surviving Sepsis Campaign). However, we contend there is clearly room for further improvements. There is growing consensus that the clinical treatment of severely ill patients is best done initially in a general way, avoiding over emphasis on identifying the exact cause of sepsis. The most important element of the treatment of sepsis is to recognise that severe illness is present early and rapidly institute appropriate treatment (with targeted but broad spectrum antibiotics and source control) and resuscitation that aims to correct the physiological abnormalities associated with sepsis, whatever the underlying cause. Resuscitation efforts are generic, as many elements of the sepsis syndrome are common whatever the causal pathogen, but are important as part of the "bundle of care" if mortality is to be lowered.

This study provides further evidence that sepsis is a major public health problem in England as well as elsewhere in the world. We hope that this result, and this method of using multiple cause of death data, will form the basis of a more accurate, and ongoing, accounting of the burden of sepsis among the population of England as well as a tool to support audit of the quality of sepsis diagnosis and treatment across the whole healthcare system. Estimating sepsis-associated mortality from multiple cause of death data (rather than estimates based on hospital patients) would also allow more detailed analyses to be undertaken, such as investigating geographic or socio-economic inequalities in these deaths. This would be a profitable area for future research. It also allows a more nuanced debate to take place, which should now involve policy makers, public health services, primary and emergency care providers as well as critical care specialists. Ultimately, having this more detailed picture should enable improved quality of care and more cost-effective use of resources with respect to preventing, identifying and treating sepsis.

Figures

Figure 1. Directly age-standardised rates of death definitely, black, and maybe, grey, associated with sepsis, England 2001-10.

Figure 2. Age specific death rates for males, black, and females, grey, of deaths definitely associated with sepsis, England, 2001-10.

Tables

Table 1. Deaths that are definitely associated with sepsis, by underlying cause of death and comparison with all deaths, occurring in England 2001-10 excluding neonatal deaths.

Table 2. Percentage of deaths with given number of diseases or conditions mentioned on the death certificate in deaths definitely associated with sepsis, excluding neonatal deaths, compared with all deaths in England 2001-10.

Table 3. Co-morbidities mentioned on the death certificates of deaths definitely associated with sepsis, excluding neonatal deaths, in England 2001-10.

Table 4: Deaths definitely associated with sepsis, excluding neonatal deaths, compared with all deaths by place of death in England 2001-10.

Footnotes

Copyright

Contributors

DMcP, CG and MW compiled the list of ICD-10 codes to be searched. AB and EK extracted and tabulated the mortality data and calculated death rates. All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data. All authors took part in drafting the article or revising it critically for important intellectual content and gave final approval of the version to be published. DMcP is the guarantor.

Funding

The departments of the authors funded this study.

Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical Approval

Ethical approval was not required for this study.

Data Sharing

No additional data available. The London Health Observatory holds individual mortality data but these records cannot be shared under the terms of the data access agreement with the Office for National Statistics who provide the data.

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Appendix

ICD-10 codes that are definitely or maybe linked with sepsis.

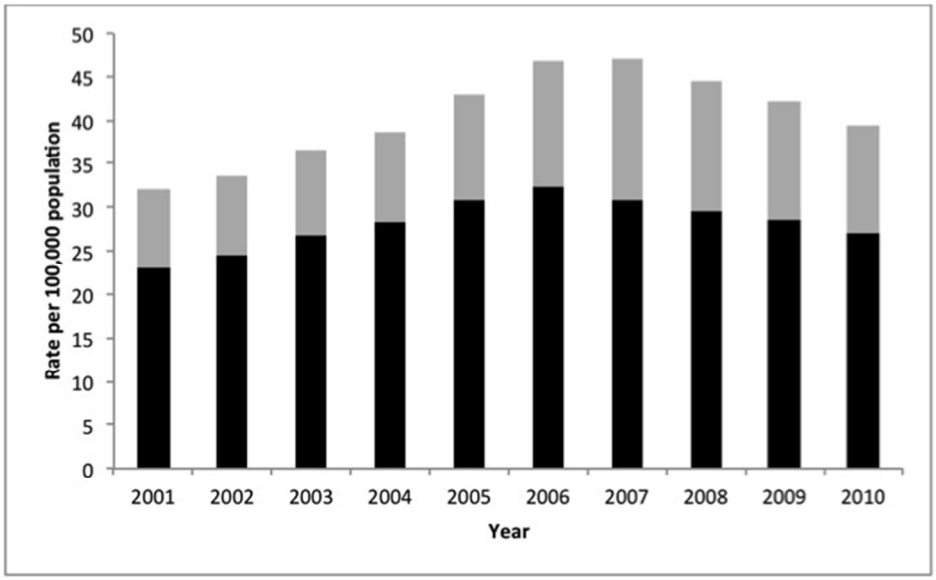

Figure 1. Directly age-standardised rates of death definitely, black, and maybe, grey, associated with sepsis, England 2001-10.
254x190mm (72 x 72 DPI)

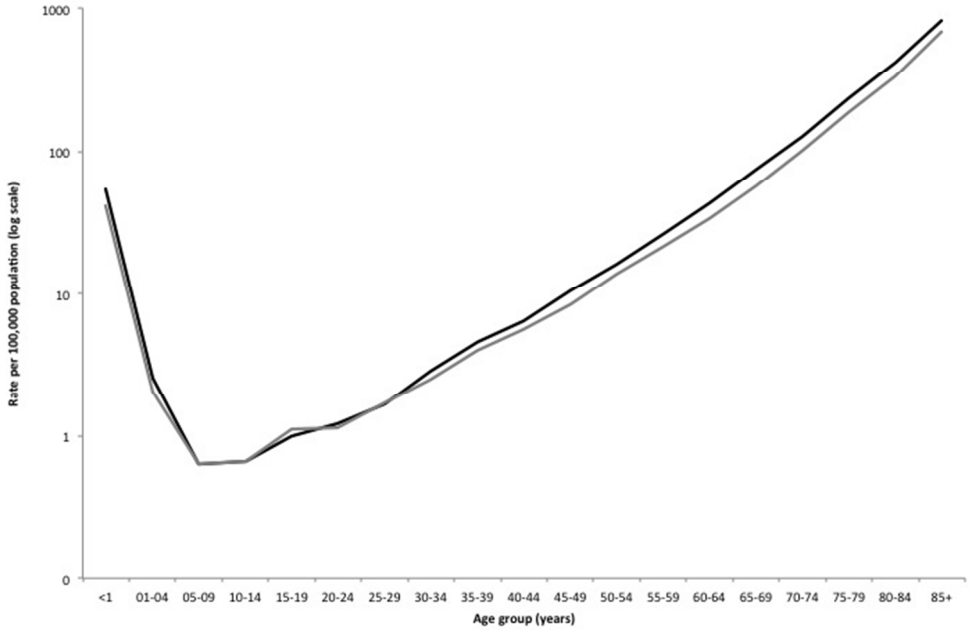

Figure 2. Age specific death rates for males, black, and females, grey, of deaths definitely associated with sepsis, England, 2001-10.
254x190mm (72 x 72 DPI)

Table 1

ICD-10 codes	ICD-10 Chapter	Sepsis deaths	All deaths	Percentage of sepsis associated deaths in chapter	Percentage of all deaths in chapter that are sepsis associated
A00-B99	Infectious diseases	26,296	53,543	11.7	49.1
C00-D48	Neoplasms	30,210	1,307,155	13.4	2.3
D50-D89	Diseases of the blood	1,696	9,610	0.8	17.6
E00-E90	Endocrine diseases	6,995	69,483	3.1	10.1
F00-F99	Mental and behavioural disorders	1,899	150,122	0.8	1.3
G00-G99	Nervous system diseases	3,199	149,773	1.4	2.1
H00-H59	Eye diseases	40	112	0.0	35.7
H60-H95	Ear diseases	53	206	0.0	25.7
I00-I99	Circulatory diseases	25,803	1,708,766	11.5	1.5
J00-J99	Respiratory diseases	34,581	654,960	15.4	5.3
K00-K93	Digestive diseases	31,550	234,960	14.0	13.4
L00-L99	Skin diseases	12,251	16,190	5.5	75.7
M00-M99	Musculoskeletal diseases	5,215	41,617	2.3	12.5
N00-N99	Genitourinary diseases	40,090	96,988	17.8	41.3
O00-O99	Pregnancy	41	429	0.0	9.6
P00-P96	Perinatal period	372	1,958	0.2	19.0
Q00-Q99	Congenital abnormalities	568	11,545	0.3	4.9
R00-R99	Symptoms, signs and abnormal clinical and laboratory findings	17	109,542	0.0	0.0
V01-Y98, U50.9	External causes	3,849	162,139	1.7	2.4
	Total	**224,725**	**4,800,260**	**100.0**	**4.7**

Table 2

Number of causes mentioned	All deaths (%)	Sepsis-associated deaths (%)
1	25.1	1.1
2	35.1	18.8
3	21.9	33.0
4	10.6	23.9
5	4.4	12.8
6	1.7	6.0
7 or more	1.1	4.4

Table 3

	Number of deaths	Percentage of all sepsis associated deaths
Cancer	37,727	16.8
Diabetes	21,086	9.4
Congestive Heart Failure	9,957	4.4
Chronic renal failure	12,611	5.6
Chronic Lower Respiratory Diseases	13,666	6.1
Hypertension	9,375	4.2
Chronic liver disease	6,033	2.7
HIV	298	0.1
Chronic alcohol abuse	3,719	1.7

Table 4

Place of death	Sepsis associated deaths (number [percent])	All deaths (number [percent])	Sepsis associated deaths (% of all deaths in location)
Care Home	10,165 [4.5]	865,755 [18.0]	1.2
Elsewhere	315 [0.1]	96,632 [2.0]	0.3
Home	3,495 [1.5]	915,919 [19.1]	0.4
Hospice	609 [0.3]	232,899 [4.9]	0.3
Hospital	211,695 [93.4]	2,669,925 [55.6]	7.9
Other Communal Establishment	268 [0.1]	19,131 [0.4]	1.4
Total	**226,547 [100]**	**4,800,261 [100]**	**4.7**

Appendix

Association with sepsis	ICD-10 Chapter	ICD-10 codes
Definite	Infectious and parasitic diseases	A02.1, A20.2, A20.7, A21.7, A22.7, A26.7, A32.7, A39.2, A39.4, A40, A41, A42.7, A48.4, B00.7, B37.7
	Pregnancy, childbirth and the puerperium	O85
	Conditions originating in the perinatal period	P36, P37.2
	Symptoms, signs and abnormal clinical and laboratory findings	R57.8
Maybe	Infectious and parasitic diseases	A02.9, A03.9, A04, A20.3, A21.9, A22.8, A22.9, A23.8, A23.9, A24.1, A24.4, A28.2, A28.8, A28.9, A31.0, A32.9, A33, A39.0, A39.1, A39.3, A39.9, A48.0, A49, A54.8, B20.1, B20.7
	Diseases of the eye and adnexa	H44.0
	Diseases of the respiratory system	J80, J95.0
	Diseases of the musculoskeletal system	M72.9
	Diseases of the genitourinary system	N39.0
	Pregnancy, childbirth and the puerperium	O08.0, O08.2, O75.3, O86, O88.3
	Conditions originating in the perinatal period	P22.0
	Symptoms, signs and abnormal clinical and laboratory findings	R02, R50.8, R50.9, R57.9
	Injury, poisoning and certain other consequences of external causes	T80.2, T81.4, T82.6, T82.7, T83.5, T83.6, T84.5, T84.6, T84.7, T85.7, T88.0
	Additional codes used by WHO for new and emerging conditions	U04

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any pre-specified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	N/A

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-11
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	N/A
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(*b*) Report category boundaries when continuous variables were categorized	9-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Sepsis-associated mortality in England: an analysis of multiple cause of death data from 2001 to 2010.

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-002586.R1
Article Type:	Research
Date Submitted by the Author:	23-May-2013
Complete List of Authors:	McPherson, Duncan; Portsmouth Hospitals NHS Trust, Anaesthesia; Imperial College London, Institute of Global Health Innovation Griffiths, Clare; London Health Observatory, Williams, Matthew; Portsmouth Hospitals NHS Trust, Critical Care Medicine Baker, Allan; London Health Observatory, Klodawski, Ed; London Health Observatory, Jacobson, Bobbie; London Health Observatory, Donaldson, Liam; Imperial College London, Institute of Global Health Innovation
Primary Subject Heading:	Public health
Secondary Subject Heading:	Research methods, Intensive care, Infectious diseases, Health policy, Epidemiology
Keywords:	STATISTICS & RESEARCH METHODS, EPIDEMIOLOGY, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Public health < INFECTIOUS DISEASES, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, PUBLIC HEALTH

Sepsis-associated mortality in England: an analysis of multiple cause of death data from 2001 to 2010

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Contents: 2 figures, 4 tables, 1 appendix.

Abstract

Objectives

To quantify mortality associated with sepsis in the whole population of England.

Design

Descriptive statistics of multiple cause of death data.

Setting

England between 2001 and 2010.

Participants

All people whose death was registered in England between 2001 and 2010 and whose certificate contained a sepsis associated International Classification of Diseases, Tenth Revision (ICD-10) code.

Data sources

Multiple cause of death data extracted from Office for National Statistics mortality database.

Statistical methods

Age and sex specific death rates and directly age standardised death rates.

Results

In 2010, 5.1% of deaths in England were definitely associated with sepsis. Adding those that may be associated with sepsis increases this figure to 7.7% of all deaths. Only 8.6% of deaths definitely associated with sepsis in 2010 had a sepsis related condition as the underlying cause of death. 99% of deaths definitely associated with sepsis have one of three ICD-10 codes, A40, A41 and P36, in at least one position on the death

certificate. 7% of deaths definitely associated with sepsis in 2001-10 did not occur in hospital.

Conclusions

Sepsis is a major public health problem in England. In attempting to tackle the problem of sepsis it is not sufficient to rely on hospital based statistics, or methods of intervention, alone. A robust estimate of the burden of sepsis associated mortality in England can be made by identifying deaths with one of three ICD-10 codes in multiple cause of death data. These three codes could be used for future monitoring of the burden of sepsis-associated mortality.

Summary

Article Focus

- A large proportion of patients admitted to critical care units with sepsis die and if sepsis is identified and treated earlier, mortality can be reduced producing cost-effective benefits in terms of life years/quality-adjusted life years gained;
- Assessing sepsis-associated mortality is not straightforward as there are no codes for sepsis in ICD-10 and sepsis-related conditions are often not selected as the underlying cause of death;
- Multiple cause of death data are now available for deaths in the UK and provide a way of determining those that are associated with sepsis.

Key Messages

- In 2001-10, one in twenty deaths in England was associated with sepsis based on information recorded on death certificates;
- 99% of deaths definitely associated with sepsis include one of three ICD-10 codes, A40, A41 and P36, somewhere on the list of causes of death;
- These deaths occur across a wide range of specialty areas and 15,000 (7%) deaths definitely associated with sepsis in 2001-10 did not occur in hospital; this should prompt a much wider population-based approach to future quality improvement.

Strengths and Limitations

- Multiple Cause of Death data are collected for all deaths, allowing us to count all those whose death is associated with sepsis, not just those who die in hospital, or those for whom septicaemia is the underlying cause;
- Our population estimates are based on the 2001 UK census, which will shortly be updated by the 2011 Census;

- The study relies on the accuracy of coding. There is no specific code for sepsis within ICD-10, which may lead to misclassification of causes. We may have underestimated the true impact of sepsis.

Introduction

Sepsis is defined as systemic inflammatory response syndrome caused by infection.[1] [2] Severe sepsis is sepsis with organ system dysfunction, while septic shock is defined as sepsis with hypotension refractory to fluid resuscitation, leading to inadequate tissue perfusion. These entities lie on a spectrum of diseases culminating with death caused by multiple organ dysfunction.

Twenty seven per cent of intensive care admissions in England and Wales are for severe sepsis and almost half of these patients die in hospital.[3] In 1995-96, in an adult general intensive care unit (ICU) in a UK university hospital, the median cost of treating a patient with sepsis was six times the cost of treating a patient without sepsis. The mortality rate was also significantly higher for the sepsis patients, despite the increased spending, at 53% compared with 29% for non-sepsis patients.[4] More recent studies have found that using integrated sepsis treatment protocols, including those developed by the International Surviving Sepsis Campaign, can be effective at reducing mortality rates.[5-7] Such protocols may increase costs through lengthier ICU stays, but appear cost-effective in terms of life years and quality-adjusted life years gained. Estimates of the incidence of sepsis, and associated mortality, are hard to obtain. Recent estimates suggest that the incidence of severe sepsis in the general population is 38 per 100,000 in Finland[8] and 25 per 100,000 in Spain[9], while older studies have found rates as high as 240-300 per 100,000 population in the USA.[10, 11]. However, these estimates are based on administrative in-patient data. It is likely that these underestimate the incidence of sepsis as they only count those admitted to hospital. Using multiple cause of death (MCOD) data it has been estimated that 6% of all deaths in the USA are associated with sepsis.[12]

In 1993, the redevelopment of the Office for National Statistics (ONS) mortality database allowed all the diseases and conditions mentioned on the death certificate to

be coded and stored. Up to 15 mentioned causes of death can be coded, in addition to the underlying and secondary causes of death.[13] MCOD data have been used in England to examine the contribution to mortality of many different diseases and conditions.[14-19] Analysis of mortality by cause of death usually uses the underlying cause of death, which is the "disease or injury which initiated the train of morbid events leading directly to death or the circumstances of the accident or violence which produced the fatal injury."[20] For many patients, sepsis may be part of that causal sequence, but it would not be listed as the underlying cause of death. For example, in cases where sepsis is hospital-acquired, the original reason for hospitalisation would generally be the underlying cause of death. Consequently, examining mortality from sepsis using the underlying cause of death would not identify those deaths as being sepsis-associated.

In this paper MCOD data have been used to estimate the number of deaths in England associated with sepsis.

Methods

Mortality data were obtained from the Office for National Statistics (ONS) mortality database, for the period from 2001 to 2010. As sepsis deaths cannot be directly identified in ICD-10, a list of codes related to sepsis was selected. Using the underlying question, "If this condition appears on the death certificate, what is the chance this person would have had sepsis?" a list of conditions was derived. These were then divided into two categories: those definitely meaning sepsis was involved and those that may mean sepsis was involved. The ICD-10 codes associated with these conditions were identified using the ICD-10 index[21] and online searching tool developed by WHO and the German Institute of Medical Documentation and Information[22]. The first three authors then reviewed the list of codes, by asking the question "If this code was recorded on a death certificate, what is the probability that the deceased had severe sepsis?" If the probability was considered to be more than 50% then the code was included in a candidate list. This candidate list of codes was crosschecked with the Melamed paper[12] and the ICD "List of conditions unlikely to cause death"[23] to ensure that no unlikely codes were included and that no likely codes had been overlooked. The ICD-10 codes that are definitely or maybe associated with sepsis are listed in the Appendix.

Deaths were extracted from the mortality database if they had a mention of any of the identified codes anywhere on the death certificate. Age- and sex-specific rates were calculated using mid-year population estimates for England, published in June 2010, as denominators for the relevant year and, where appropriate, death rates were directly age-standardised using the European Standard Population.

To look at patterns of sepsis-associated mortality, we also examined the underlying cause of death for these deaths, other co-morbidities mentioned on the certificate, and the total number of contributing causes mentioned on the death certificate. We compared these with overall patterns for all deaths in England. We also examined

sepsis-associated mortality by place of death: home, hospital, care home etc. We restricted these analyses to those deaths definitely considered to be sepsis-associated. Deaths under 28 days have a separate death certificate and only mentioned causes are coded for these deaths - an underlying cause of death cannot be selected from them.[24] These deaths were included in the majority of analyses in this study and where they have been excluded this has been noted in the results.

Results

Between 2001 and 2010 there were 226,547 deaths that were definitely directly associated with sepsis in England, 4.7% of all deaths. Adding those that may be related to sepsis increased this to 332,757, 6.9% of all deaths. In 2010 alone, 5.1% of deaths were definitely associated with sepsis, and adding in those deaths that may be related increased that percentage to 7.7%. Figure 1 shows mortality rates for deaths that are definitely and maybe linked to sepsis for each year. For both sexes combined, the rate rose to a peak in 2007 and then declined. Excluding the 'maybe' group brings the peak in mortality forward to 2006. The number of deaths definitely associated with sepsis was also highest in 2006. The number rose from 16,800 in 2001 to a peak of 26,150 in 2006, before decreasing every year to 23,700 in 2010. The remaining analyses in this paper present results only for those deaths definitely associated with sepsis.

In 2010, the percentage of deaths associated with sepsis was higher for females (5.5%) than males (4.8%). However, when directly age-standardised rates were calculated (which take into account differences in the age structures of the population between the sexes) the rate in 2010 was higher for males (29.8 deaths per 100,000 population) than females (24.8 per 100,000). Between 2001 and 2010, the annual death rate for males was 20-28 per cent higher than the rate for females.

Age-specific mortality rates were higher in the very youngest and elderly, with the rate in the under 1s being similar to the rate among those in their 60s (figure 2). At younger ages, the rate declined rapidly after age 1. In 2001-10, the age-specific mortality rate for deaths associated with sepsis in ages 5-14 was less than 1 per 100,000 population for both males and females. Rates then rose with age, with particularly marked increases in the oldest age groups. For both males and females, the rate in the 85+ age group was double the rate for those aged 80-84. The age-specific rate for males was significantly higher than females for deaths under age one and for every age group

from age 40 onwards. For deaths at age 85 and over, the age-specific rate for men was 822 deaths per 100,000 population, compared to 683 per 100,000 for women.

Table 1 shows the underlying cause of death for deaths that are definitely sepsis-associated, by chapter of the ICD, and the percentage of each ICD chapter that is sepsis-associated. This does not attempt to identify the cause of sepsis for these deaths, but merely identifies the disease or injury that initiated the train of morbid events leading directly to death. The underlying causes for deaths with a mention of sepsis are spread across a wide spectrum of ICD chapters. The ICD chapter that accounts for the biggest percentage of sepsis-associated deaths is genitourinary diseases (17.8%). The leading causes of death also account for high percentages, such as respiratory diseases (15.4%), digestive diseases (14.0%), cancer (13.4%) and circulatory diseases (11.5%), while 11.7% of deaths have an underlying cause in the infectious diseases chapter. Almost half of deaths with an underlying cause of infectious disease are associated with sepsis (49.1%). There are wide differences in the percentages in other chapters. Only 1.5% of circulatory disease deaths are associated with sepsis, but for deaths with an underlying cause of skin disease, three-quarters are associated with sepsis (75.7%). Twenty per cent of deaths from diseases originating in the perinatal period also had a sepsis-associated cause of death on the death certificate. However, it must be borne in mind that deaths under 28 days were not included in the analysis of deaths by underlying cause as a different death certificate is used to register these deaths in England (Office for National Statistics 2009).[24]

We also examined the percentage of sepsis-associated deaths where sepsis was also the underlying cause of death. For deaths definitely considered to be sepsis-associated, this was 8.6% in 2010. Of the cases definitely associated with sepsis, 99% contained one of three ICD-10 codes in at least one position on the death certificate: A40 (streptococcal septicaemia), A41 (other septicaemia) and P36 (bacterial sepsis of newborn).

Table 2 shows the total number of causes mentioned on the death certificate for all deaths and for sepsis-associated deaths. Sepsis-associated deaths tend to have more conditions mentioned than do all deaths. For all deaths, two is the most common number of causes mentioned, whereas for sepsis-associated deaths the most common number is three. Very few sepsis-associated deaths have only one cause of death on the death certificate. This is because 'sepsis' alone is not sufficient detail to allow the death to be registered without reference to a coroner – the certificate must mention the cause of the sepsis for this to be acceptable under law. However, it also seems that overall, sepsis-associated deaths have proportionally more conditions mentioned, as might be expected given the severity of illness amongst these individuals. For sepsis-associated deaths, 23.2% have five or more conditions mentioned, compared with 7.2% of all deaths. Neonatal deaths were excluded from this part of the analysis, because the conditions mentioned on their death certificates include conditions in the mother and in the baby, so they are not directly comparable to those deaths where the deceased was aged 28 days or older.

Many of the chronic conditions known to be associated with sepsis appear on the death certificates of sepsis-associated deaths – 16.8% of certificates mentioned cancer, and 9.4% diabetes (table 3).

Table 4 shows that 93.4% of all sepsis-associated deaths took place in hospital, compared with 55.6% of all deaths. Nearly 7% of sepsis-associated deaths therefore did not take place in hospital. Less than 2% of sepsis-associated deaths occurred in the deceased's own home, compared with nearly 20% of all deaths. Almost 8% of deaths in hospital were associated with sepsis, compared to less than half a percent of deaths that took place in the deceased's own home, hospices, or elsewhere.

Discussion

Using the information recorded on death certificates for the whole population, we have estimated that at least one in twenty of all deaths in England are associated with sepsis. The sepsis-associated death rate has been increasing over the last decade, reaching a peak in 2006. The rate has decreased in more recent years, but not yet to the level in the earlier part of the decade. This was an observational study but now that this trend in sepsis-related deaths has been identified, it would be a worthwhile research exercise to investigate further why rates have changed over time. We have shown that 6.6% of patients with definite severe sepsis die outside of a hospital, indicating that in 2001-10 up to 15,000 deaths associated with sepsis may have been missed if we had only counted deaths in hospital. Sepsis-associated deaths appear to have larger numbers of conditions on their death certificates than do all deaths.

Our study does have some limitations. In using multiple cause of death data, it relies on the accuracy of the recording of causes of death on the death certificate. As a study of sepsis-associated deaths in the US has noted, codes for septicaemia have to be used as a proxy for sepsis in ICD-10. There is a risk that this may lead to misclassification of deaths, and possibly an under-estimation of the burden of sepsis-related mortality.[12] We should also note that our mortality rates were calculated using mid-year population estimates which are based on the 2001 Census. In December 2012, ONS plan to release revised mid-year estimates for England, which will take into account the results of the 2011 Census.

Our estimate of deaths associated with sepsis is similar to that found in the USA using a similar method.[12] Many current estimates of mortality due to sepsis look at patients admitted to hospital and who subsequently die, giving an indication of case fatality. It is estimated that the mortality of patients admitted to critical care units and diagnosed with severe sepsis is 47%.[3] Our study is population-based and therefore gives

an indication of the burden of sepsis across the whole population. Most analyses of cause of death data only look at the underlying cause, which identifies the disease or injury that initiated the events leading to death. We have shown, however, that less than 10% of deaths associated with sepsis have it as the underlying cause. To fully account for sepsis-related mortality, it is therefore necessary to examine all the recorded causes of death, as we have done. Although this analysis is more complex than just examining the underlying cause of death, we have shown that just three ICD-10 codes – A40, A41 and P36 – identify 99% of deaths definitely associated with sepsis. These three codes alone could therefore be used for future monitoring and audit of the burden and quality of sepsis care using multiple cause of death data. However, regular review of the ICD-10 codes definitely or possibly associated with sepsis (and the number of deaths with these codes) would be worthwhile as ICD codes are updated. For example, a code for necrotising fasciitis, M72.6, was added by the WHO as an update to ICD-10, but not implemented for coding by ONS until 2011. As the presence of this code on a death certificate may indicate sepsis, this could be considered in future analyses, but counting deaths with one of just the three identified ICD-10 codes would still find the vast majority of sepsis-associated mortality.

Sepsis can no longer be regarded as a niche problem relevant only to the critical care units that treat the most severely affected patients. There is some evidence that recognition of sepsis may be low outside hospitals. For example, patients diagnosed with severe sepsis in one US emergency department were reviewed.[25] Only half of these patients had been transported to hospital by ambulance. In this half of cases, the paramedic had explicitly considered sepsis in only a fifth. For those patients where paramedics had recognised sepsis, there was a significant decrease in time taken to receive antibiotic treatment. By the time patients with sepsis are admitted to critical care, they are very severely unwell and therefore likely to die despite the best efforts of their healthcare team. There is also evidence that treating patients with sepsis earlier

and in a more coordinated manner reduces mortality.[26] Therefore, if we could find ways to encourage earlier diagnosis and earlier, coordinated treatment, it is probable that the overall mortality from sepsis could be reduced. The reduction of sepsis related mortality since 2007 may represent the results of the introduction of changes to identify such patients, e.g. Early Warning Scoring (EWS) systems, Critical Care Outreach, efforts to improve awareness and training (e.g. Surviving Sepsis Campaign). However, we contend there is clearly room for further improvements. There is growing consensus that the clinical treatment of severely ill patients is best done initially in a general way, avoiding over emphasis on identifying the exact cause of sepsis. The most important element of the treatment of sepsis is to recognise that severe illness is present early and rapidly institute appropriate treatment (with targeted but broad spectrum antibiotics and source control) and resuscitation that aims to correct the physiological abnormalities associated with sepsis, whatever the underlying cause. Resuscitation efforts are generic, as many elements of the sepsis syndrome are common whatever the causal pathogen, but are important as part of the "bundle of care" if mortality is to be lowered.

Despite the potential for underestimation, this study has demonstrated that sepsis is associated with 1 in 20 deaths and therefore provides further evidence that sepsis is a major public health problem in England as well as elsewhere in the world. While there is no perfect solution to the question of how levels of sepsis-related mortality should be estimated, we hope that this result, and this method of using multiple cause of death data, will form the basis of future accounting of the burden of sepsis among the whole population of England. These results could also support audit of the quality of sepsis diagnosis and treatment across the whole healthcare system. Estimating sepsis-associated mortality from multiple cause of death data (rather than estimates based on hospital patients) would also allow more detailed analyses to be undertaken, such as investigating geographic or socio-economic inequalities in these deaths. This would be a profitable area for future research. It also allows a more nuanced debate to take place,

which should now involve policy makers, public health services, primary and emergency care providers as well as critical care specialists. Ultimately, having this more detailed picture should enable improved quality of care and more cost-effective use of resources with respect to preventing, identifying and treating sepsis.

Figures

Figure 1. Directly age-standardised rates of death definitely, dark grey, and maybe, light grey, associated with sepsis, England 2001-10, with 95% confidence interval for the rate.

Figure 2. Age specific death rates for males, dark grey, and females, light grey, of deaths definitely associated with sepsis, England, 2001-10, with 95% confidence interval for the rate.

Tables

Table 1. Deaths that are definitely associated with sepsis, by underlying cause of death and comparison with all deaths, occurring in England 2001-10 excluding neonatal deaths.

Table 2. Percentage of deaths with given number of diseases or conditions mentioned on the death certificate in deaths definitely associated with sepsis, excluding neonatal deaths, compared with all deaths in England 2001-10.

Table 3. Co-morbidities mentioned on the death certificates of deaths definitely associated with sepsis, excluding neonatal deaths, in England 2001-10.

Table 4: Deaths definitely associated with sepsis, excluding neonatal deaths, compared with all deaths by place of death in England 2001-10.

Footnotes

Copyright

Contributors

DMcP, CG and MW compiled the list of ICD-10 codes to be searched. AB and EK extracted and tabulated the mortality data and calculated death rates. All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data. All authors took part in drafting the article or revising it critically for important intellectual content and gave final approval of the version to be published. DMcP is the guarantor.

Funding

The departments of the authors funded this study.

Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical Approval

Ethical approval was not required for this study.

Data Sharing

No additional data available. The London Health Observatory holds individual mortality data but these records cannot be shared under the terms of the data access agreement with the Office for National Statistics who provide the data.

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Appendix

ICD-10 codes that are definitely or maybe linked with sepsis.

Table 1

ICD-10 codes	ICD-10 Chapter	Sepsis deaths	All deaths	Percentage of sepsis associated deaths in chapter	Percentage of all deaths in chapter that are sepsis associated
A00-B99	Infectious diseases	26,296	53,543	11.7	49.1
C00-D48	Neoplasms	30,210	1,307,155	13.4	2.3
D50-D89	Diseases of the blood	1,696	9,610	0.8	17.6
E00-E90	Endocrine diseases	6,995	69,483	3.1	10.1
F00-F99	Mental and behavioural disorders	1,899	150,122	0.8	1.3
G00-G99	Nervous system diseases	3,199	149,773	1.4	2.1
H00-H59	Eye diseases	40	112	0.0	35.7
H60-H95	Ear diseases	53	206	0.0	25.7
I00-I99	Circulatory diseases	25,803	1,708,766	11.5	1.5
J00-J99	Respiratory diseases	34,581	654,960	15.4	5.3
K00-K93	Digestive diseases	31,550	234,960	14.0	13.4
L00-L99	Skin diseases	12,251	16,190	5.5	75.7
M00-M99	Musculoskeletal diseases	5,215	41,617	2.3	12.5
N00-N99	Genitourinary diseases	40,090	96,988	17.8	41.3
O00-O99	Pregnancy	41	429	0.0	9.6
P00-P96	Perinatal period	372	1,958	0.2	19.0
Q00-Q99	Congenital abnormalities	568	11,545	0.3	4.9
R00-R99	Symptoms, signs and abnormal clinical and laboratory findings	17	109,542	0.0	0.0
V01-Y98, U50.9	External causes	3,849	162,139	1.7	2.4
	Total	**224,725**	**4,800,260**	**100.0**	**4.7**

Table 2

Number of causes mentioned	All deaths (%)	Sepsis-associated deaths (%)
1	25.1	1.1
2	35.1	18.8
3	21.9	33.0
4	10.6	23.9
5	4.4	12.8
6	1.7	6.0
7 or more	1.1	4.4

Table 3

	Number of deaths	Percentage of all sepsis associated deaths
Cancer	37,727	16.8
Diabetes	21,086	9.4
Congestive Heart Failure	9,957	4.4
Chronic renal failure	12,611	5.6
Chronic Lower Respiratory Diseases	13,666	6.1
Hypertension	9,375	4.2
Chronic liver disease	6,033	2.7
HIV	298	0.1
Chronic alcohol abuse	3,719	1.7

Table 4

Place of death	Sepsis associated deaths (number [percent])	All deaths (number [percent])	Sepsis associated deaths (% of all deaths in location)
Care Home	10,165 [4.5]	865,755 [18.0]	1.2
Elsewhere	315 [0.1]	96,632 [2.0]	0.3
Home	3,495 [1.5]	915,919 [19.1]	0.4
Hospice	609 [0.3]	232,899 [4.9]	0.3
Hospital	211,695 [93.4]	2,669,925 [55.6]	7.9
Other Communal Establishment	268 [0.1]	19,131 [0.4]	1.4
Total	**226,547 [100]**	**4,800,261 [100]**	**4.7**

Sepsis-associated mortality in England: an analysis of multiple cause of death data from 2001 to 2010

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Contents: 2 figures, 4 tables, 1 appendix.

Abstract

Objectives

To quantify mortality associated with sepsis in the whole population of England.

Design

Descriptive statistics of multiple cause of death data.

Setting

England between 2001 and 2010.

Participants

All people whose death was registered in England between 2001 and 2010 and whose certificate contained a sepsis associated International Classification of Diseases, Tenth Revision (ICD-10) code.

Data sources

Multiple cause of death data extracted from Office for National Statistics mortality database.

Statistical methods

Age and sex specific death rates and directly age standardised death rates.

Results

In 2010, 5.1% of deaths in England were definitely associated with sepsis. Adding those that may be associated with sepsis increases this figure to 7.7% of all deaths. Only 8.6% of deaths definitely associated with sepsis in 2010 had a sepsis related condition as the underlying cause of death. 99% of deaths definitely associated with sepsis have one of three ICD-10 codes, A40, A41 and P36, in at least one position on the death

certificate. 7% of deaths definitely associated with sepsis in 2001-10 did not occur in hospital.

Conclusions

Sepsis is a major public health problem in England. In attempting to tackle the problem of sepsis it is not sufficient to rely on hospital based statistics, or methods of intervention, alone. A robust estimate of the burden of sepsis associated mortality in England can be made by identifying deaths with one of three ICD-10 codes in multiple cause of death data. These three codes could be used for future monitoring of the burden of sepsis-associated mortality.

Summary

Article Focus

- A large proportion of patients admitted to critical care units with sepsis die and if sepsis is identified and treated earlier, mortality can be reduced producing cost-effective benefits in terms of life years/quality-adjusted life years gained;
- Assessing sepsis-associated mortality is not straightforward as there are no codes for sepsis in ICD-10 and sepsis-related conditions are often not selected as the underlying cause of death;
- Multiple cause of death data are now available for deaths in the UK and provide a way of determining those that are associated with sepsis.

Key Messages

- In 2001-10, one in twenty deaths in England was associated with sepsis based on information recorded on death certificates;
- 99% of deaths definitely associated with sepsis include one of three ICD-10 codes, A40, A41 and P36, somewhere on the list of causes of death;
- These deaths occur across a wide range of specialty areas and 15,000 (7%) deaths definitely associated with sepsis in 2001-10 did not occur in hospital; this should prompt a much wider population-based approach to future quality improvement.

Strengths and Limitations

- Multiple Cause of Death data are collected for all deaths, allowing us to count all those whose death is associated with sepsis, not just those who die in hospital, or those for whom septicaemia is the underlying cause;
- Our population estimates are based on the 2001 UK census, which will shortly be updated by the 2011 Census;

- The study relies on the accuracy of coding. There is no specific code for sepsis within ICD-10, which may lead to misclassification of causes. We may have underestimated the true impact of sepsis.

Introduction

Sepsis is defined as systemic inflammatory response syndrome caused by infection.[1] [2] Severe sepsis is sepsis with organ system dysfunction, while septic shock is defined as sepsis with hypotension refractory to fluid resuscitation, leading to inadequate tissue perfusion. These entities lie on a spectrum of diseases culminating with death caused by multiple organ dysfunction.

Twenty seven per cent of intensive care admissions in England and Wales are for severe sepsis and almost half of these patients die in hospital.[3] In 1995-96, in an adult general intensive care unit (ICU) in a UK university hospital, the median cost of treating a patient with sepsis was six times the cost of treating a patient without sepsis. The mortality rate was also significantly higher for the sepsis patients, despite the increased spending, at 53% compared with 29% for non-sepsis patients.[4] More recent studies have found that using integrated sepsis treatment protocols, including those developed by the International Surviving Sepsis Campaign, can be effective at reducing mortality rates.[5-7] Such protocols may increase costs through lengthier ICU stays, but appear cost-effective in terms of life years and quality-adjusted life years gained. Estimates of the incidence of sepsis, and associated mortality, are hard to obtain. Recent estimates suggest that the incidence of severe sepsis in the general population is 38 per 100,000 in Finland[8] and 25 per 100,000 in Spain[9], while older studies have found rates as high as 240-300 per 100,000 population in the USA.[10, 11]. However, these estimates are based on administrative in-patient data. It is likely that these underestimate the incidence of sepsis as they only count those admitted to hospital. Using multiple cause of death (MCOD) data it has been estimated that 6% of all deaths in the USA are associated with sepsis.[12~~10~~]

In 1993, the redevelopment of the Office for National Statistics (ONS) mortality database allowed all the diseases and conditions mentioned on the death certificate to

be coded and stored. Up to 15 mentioned causes of death can be coded, in addition to the underlying and secondary causes of death.[13~~11~~] MCOD data have been used in England to examine the contribution to mortality of many different diseases and conditions.[14-19 ~~12-17~~] Analysis of mortality by cause of death usually uses the underlying cause of death, which is the "disease or injury which initiated the train of morbid events leading directly to death or the circumstances of the accident or violence which produced the fatal injury."[20~~18~~] For many patients, sepsis may be part of that causal sequence, but it would not be listed as the underlying cause of death. For example, in cases where sepsis is hospital-acquired, the original reason for hospitalisation would generally be the underlying cause of death. Consequently, examining mortality from sepsis using the underlying cause of death would not identify those deaths as being sepsis-associated.

In this paper MCOD data have been used to estimate the number of deaths in England associated with sepsis.

Methods

Mortality data were obtained from the Office for National Statistics (ONS) mortality database, for the period from 2001 to 2010. As sepsis deaths cannot be directly identified in ICD-10, a list of codes related to sepsis was selected. Using the underlying question, "If this condition appears on the death certificate, what is the chance this person would have had sepsis?" a list of conditions was derived. These were then divided into two categories: those definitely meaning sepsis was involved and those that may mean sepsis was involved. The ICD-10 codes associated with these conditions were identified using the ICD-10 index[21~~19~~] and online searching tool developed by WHO and the German Institute of Medical Documentation and Information[22~~20~~]. The first three authors then reviewed the list of codes, by asking the question "If this code was recorded on a death certificate, what is the probability that the deceased had severe sepsis?" If the probability was considered to be more than 50% then the code was included in a candidate list. This candidate list of codes was crosschecked with the Melamed paper[12~~10~~] and the ICD "List of conditions unlikely to cause death"[23~~21~~] to ensure that no unlikely codes were included and that no likely codes had been overlooked. The ICD-10 codes that are definitely or maybe associated with sepsis are listed in the Appendix.

Deaths were extracted from the mortality database if they had a mention of any of the identified codes anywhere on the death certificate. Age- and sex-specific rates were calculated using mid-year population estimates for England, published in June 2010, as denominators for the relevant year and, where appropriate, death rates were directly age-standardised using the European Standard Population.

To look at patterns of sepsis-associated mortality, we also examined the underlying cause of death for these deaths, other co-morbidities mentioned on the certificate, and the total number of contributing causes mentioned on the death certificate. We

compared these with overall patterns for all deaths in England. We also examined sepsis-associated mortality by place of death: home, hospital, care home etc. We restricted these analyses to those deaths definitely considered to be sepsis-associated. Deaths under 28 days have a separate death certificate and only mentioned causes are coded for these deaths - an underlying cause of death cannot be selected from them.[24~~22~~] These deaths were included in the majority of analyses in this study and where they have been excluded this has been noted in the results.

Results

Between 2001 and 2010 there were 226,547 deaths that were definitely directly associated with sepsis in England, 4.7% of all deaths. Adding those that may be related to sepsis increased this to 332,757, 6.9% of all deaths. In 2010 alone, 5.1% of deaths were definitely associated with sepsis, and adding in those deaths that may be related increased that percentage to 7.7%. Figure 1 shows mortality rates for deaths that are definitely and maybe linked to sepsis for each year. For both sexes combined, the rate rose to a peak in 2007 and then declined. Excluding the 'maybe' group brings the peak in mortality forward to 2006. The number of deaths definitely associated with sepsis was also highest in 2006. The number rose from 16,800 in 2001 to a peak of 26,150 in 2006, before decreasing every year to 23,700 in 2010. The remaining analyses in this paper present results only for those deaths definitely associated with sepsis.

In 2010, the percentage of deaths associated with sepsis was higher for females (5.5%) than males (4.8%). However, when directly age-standardised rates were calculated (which take into account differences in the age structures of the population between the sexes) the rate in 2010 was higher for males (29.8 deaths per 100,000 population) than females (24.8 per 100,000). Between 2001 and 2010, the annual death rate for males was 20-28 per cent higher than the rate for females.

Age-specific mortality rates were higher in the very youngest and elderly, with the rate in the under 1s being similar to the rate among those in their 60s (figure 2). At younger ages, the rate declined rapidly after age 1. In 2001-10, the age-specific mortality rate for deaths associated with sepsis in ages 5-14 was less than 1 per 100,000 population for both males and females. Rates then rose with age, with particularly marked increases in the oldest age groups. For both males and females, the rate in the 85+ age group was double the rate for those aged 80-84. The age-specific rate for males was significantly higher than females for deaths under age one~~5~~ and for every age group

from age 40~~30~~ onwards. For deaths at age 85 and over, the age-specific rate for men was 822 deaths per 100,000 population, compared to 683 per 100,000 for women.

Table 1 shows the underlying cause of death for deaths that are definitely sepsis-associated, by chapter of the ICD, and the percentage of each ICD chapter that is sepsis-associated. This does not attempt to identify the cause of sepsis for these deaths, but merely identifies the disease or injury that initiated the train of morbid events leading directly to death. The underlying causes for d~~D~~eaths with a mention of sepsis are spread across a wide spectrum of ICD chapters. The ICD chapter that accounts for the biggest percentage of sepsis-associated deaths is genitourinary diseases (17.8%). The leading causes of death also account for high percentages, such as respiratory diseases (15.4%), digestive diseases (14.0%), cancer (13.4%) and circulatory diseases (11.5%), while 11.7% of deaths have an underlying cause in the infectious diseases chapter. Almost half of deaths with an underlying cause of infectious disease are associated with sepsis (49.1%). There are wide differences in the percentages in other chapters. Only 1.5% of circulatory disease deaths are associated with sepsis, but for deaths with an underlying cause of skin disease, three-quarters are associated with sepsis (75.7%). Twenty per cent of deaths from diseases originating in the perinatal period also had a sepsis-associated cause of death on the death certificate. However, it must be borne in mind that deaths under 28 days were not included in the analysis of deaths by underlying cause as a different death certificate is used to register these deaths in England (Office for National Statistics 2009).~~2422~~

We also examined the percentage of sepsis-associated deaths where sepsis was also the underlying cause of death. For deaths definitely considered to be sepsis-associated, this was 8.6% in 2010. Of the cases definitely associated with sepsis, 99% contained one of three ICD-10 codes in at least one position on the death certificate: A40 (streptococcal septicaemia), A41 (other septicaemia) and P36 (bacterial sepsis of newborn).

Table 2 shows the total number of causes mentioned on the death certificate for all deaths and for sepsis-associated deaths. Sepsis-associated deaths tend to have more conditions mentioned than do all deaths. For all deaths, two is the most common number of causes mentioned, whereas for sepsis-associated deaths the most common number is three. Very few sepsis-associated deaths have only one cause of death on the death certificate. This is because 'sepsis' alone is not sufficient detail to allow the death to be registered without reference to a coroner – the certificate must mention the cause of the sepsis for this to be acceptable under law. However, it also seems that overall, sepsis-associated deaths have proportionally more conditions mentioned, as might be expected given the severity of illness amongst these individuals. For sepsis-associated deaths, 23.2% have five or more conditions mentioned, compared with 7.2% of all deaths. Neonatal deaths were excluded from this part of the analysis, because the conditions mentioned on their death certificates include conditions in the mother and in the baby, so they are not directly comparable to those deaths where the deceased was aged 28 days or older.

Many of the chronic conditions known to be associated with sepsis appear on the death certificates of sepsis-associated deaths – 16.8% of certificates mentioned cancer, and 9.4% diabetes (table 3).

Table 4 shows that 93.4% of all sepsis-associated deaths took place in hospital, compared with 55.6% of all deaths. Nearly 7% of sepsis-associated deaths therefore did not take place in hospital. Less than 2% of sepsis-associated deaths occurred in the deceased's own home, compared with nearly 20% of all deaths. Almost 8% of deaths in hospital were associated with sepsis, compared to less than half a percent of deaths that took place in the deceased's own home, hospices, or elsewhere.

Discussion

Using the information recorded on death certificates for the whole population, weWe have estimated that at least one in twenty of all deaths in England are associated with sepsis. The sepsis-associated death rate has been increasing over the last decade, reaching a peak in 2006. The rate has decreased in more recent years, but not yet to the level in the earlier part of the decade. This was an observational study but now that this trend in sepsis-related deaths has been identified, it would be a worthwhile research exercise to investigate further why rates have changed over time. We have shown that 6.6% of patients with definite severe sepsis die outside of a hospital, indicating that in 2001-10 up to 15,000 deaths associated with sepsis may have been missed if we had only counted deaths in hospital. Sepsis-associated deaths appear to have larger numbers of conditions on their death certificates than do all deaths.

Our study does have some limitations. In using multiple cause of death data, it relies on the accuracy of the recording of causes of death on the death certificate. As a study of sepsis-associated deaths in the US has noted, codes for septicaemia have to be used as a proxy for sepsis in ICD-10. There is a risk that this may lead to misclassification of deaths, and possibly an under-estimation of the burden of sepsis-related mortality.[12~~10~~] We should also note that our mortality rates were calculated using mid-year population estimates which are based on the 2001 Census. In December 2012, ONS plan to release revised mid-year estimates for England, which will take into account the results of the 2011 Census.

Our estimate of deaths associated with sepsis is similar to that found in the USA using a similar method.[12~~10~~] Many current estimates of mortality due to sepsis look at patients admitted to hospital and who subsequently die, giving an indication of case fatality. It is estimated that the mortality of patients admitted to critical care units and diagnosed with severe sepsis is 47%.[3] Our study is population-based and therefore gives

an indication of the burden of sepsis across the whole population. Most analyses of cause of death data only look at the underlying cause, which identifies the disease or injury that initiated the events leading to death. We have shown, however, that less than 10% of deaths associated with sepsis have it as the underlying cause. To fully account for sepsis-related mortality, it is therefore necessary to examine all the recorded causes of death, as we have done. Although this analysis is more complex than just examining the underlying cause of death, we have shown that just three ICD-10 codes – A40, A41 and P36 – identify 99% of deaths definitely associated with sepsis. These three codes alone could therefore be used for future monitoring and audit of the burden and quality of sepsis care using multiple cause of death data. However, regular review of the ICD-10 codes definitely or possibly associated with sepsis (and the number of deaths with these codes) would be worthwhile as ICD codes are updated. For example, a code for necrotising fasciitis, M72.6, was added by the WHO as an update to ICD-10, but not implemented for coding by ONS until 2011. As the presence of this code on a death certificate may indicate sepsis, this could be considered in future analyses, but counting deaths with one of just the three identified ICD-10 codes would still find the vast majority of sepsis-associated mortality.

Sepsis can no longer be regarded as a niche problem relevant only to the critical care units that treat the most severely affected patients. There is some evidence that recognition of sepsis may be low outside hospitals. For example, patients diagnosed with severe sepsis in one US emergency department were reviewed.[25][23] Only half of these patients had been transported to hospital by ambulance. In this half of cases, the paramedic had explicitly considered sepsis in only a fifth. For those patients where paramedics had recognised sepsis, there was a significant decrease in time taken to receive antibiotic treatment. By the time patients with sepsis are admitted to critical care, they are very severely unwell and therefore likely to die despite the best efforts of their healthcare team. There is also evidence that treating patients with sepsis earlier

and in a more coordinated manner reduces mortality.[26][24] Therefore, if we could find ways to encourage earlier diagnosis and earlier, coordinated treatment, it is probable that the overall mortality from sepsis could be reduced. The reduction of sepsis related mortality since 2007 may represent the results of the introduction of changes to identify such patients, e.g. Early Warning Scoring (EWS) systems, Critical Care Outreach, efforts to improve awareness and training (e.g. Surviving Sepsis Campaign). However, we contend there is clearly room for further improvements. There is growing consensus that the clinical treatment of severely ill patients is best done initially in a general way, avoiding over emphasis on identifying the exact cause of sepsis. The most important element of the treatment of sepsis is to recognise that severe illness is present early and rapidly institute appropriate treatment (with targeted but broad spectrum antibiotics and source control) and resuscitation that aims to correct the physiological abnormalities associated with sepsis, whatever the underlying cause. Resuscitation efforts are generic, as many elements of the sepsis syndrome are common whatever the causal pathogen, but are important as part of the "bundle of care" if mortality is to be lowered.

Despite the potential for underestimation, this study has demonstrated that sepsis is associated with 1 in 20 deaths and therefore ~~This study~~ provides further evidence that sepsis is a major public health problem in England as well as elsewhere in the world. While there is no perfect solution to the question of how levels of sepsis-related mortality should be estimated, we~~We~~ hope that this result, and this method of using multiple cause of death data, will form the basis of ~~a more accurate, and ongoing,~~future accounting of the burden of sepsis among the whole population of England. These results could also ~~as well as a tool to~~ support audit of the quality of sepsis diagnosis and treatment across the whole healthcare system. Estimating sepsis-associated mortality from multiple cause of death data (rather than estimates based on hospital patients) would also allow more detailed analyses to be undertaken, such as investigating

geographic or socio-economic inequalities in these deaths. This would be a profitable area for future research. It also allows a more nuanced debate to take place, which should now involve policy makers, public health services, primary and emergency care providers as well as critical care specialists. Ultimately, having this more detailed picture should enable improved quality of care and more cost-effective use of resources with respect to preventing, identifying and treating sepsis.

Figures

Figure 1. Directly age-standardised rates of death definitely, dark grey~~black~~, and maybe, light grey, associated with sepsis, England 2001-10, with 95% confidence interval for the rate.

Figure 2. Age specific death rates for males, dark grey~~black~~, and females, light grey, of deaths definitely associated with sepsis, England, 2001-10, with 95% confidence interval for the rate.

Tables

Table 1. Deaths that are definitely associated with sepsis, by underlying cause of death and comparison with all deaths, occurring in England 2001-10 excluding neonatal deaths.

Table 2. Percentage of deaths with given number of diseases or conditions mentioned on the death certificate in deaths definitely associated with sepsis, excluding neonatal deaths, compared with all deaths in England 2001-10.

Table 3. Co-morbidities mentioned on the death certificates of deaths definitely associated with sepsis, excluding neonatal deaths, in England 2001-10.

Table 4: Deaths definitely associated with sepsis, excluding neonatal deaths, compared with all deaths by place of death in England 2001-10.

Footnotes

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Contributors

DMcP, CG and MW compiled the list of ICD-10 codes to be searched. AB and EK extracted and tabulated the mortality data and calculated death rates. All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data. All authors took part in drafting the article or revising it critically for important intellectual content and gave final approval of the version to be published. DMcP is the guarantor.

Funding

The departments of the authors funded this study.

Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical Approval

Ethical approval was not required for this study.

Data Sharing

No additional data available. The London Health Observatory holds individual mortality data but these records cannot be shared under the terms of the data access agreement with the Office for National Statistics who provide the data.

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~~23.~~25. Studnek JR, Artho MR, Garner CL, et al. The impact of emergency medical services on the ED care of severe sepsis. Am J of Emerg Med 2010; 30: 51-6.

~~24.~~26. Levy MM, Dellinger RP, Townsend SR, et al. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targetting severe sepsis. Crit Care Med 2010; 38: 367-74.

Appendix

ICD-10 codes that are definitely or maybe linked with sepsis.

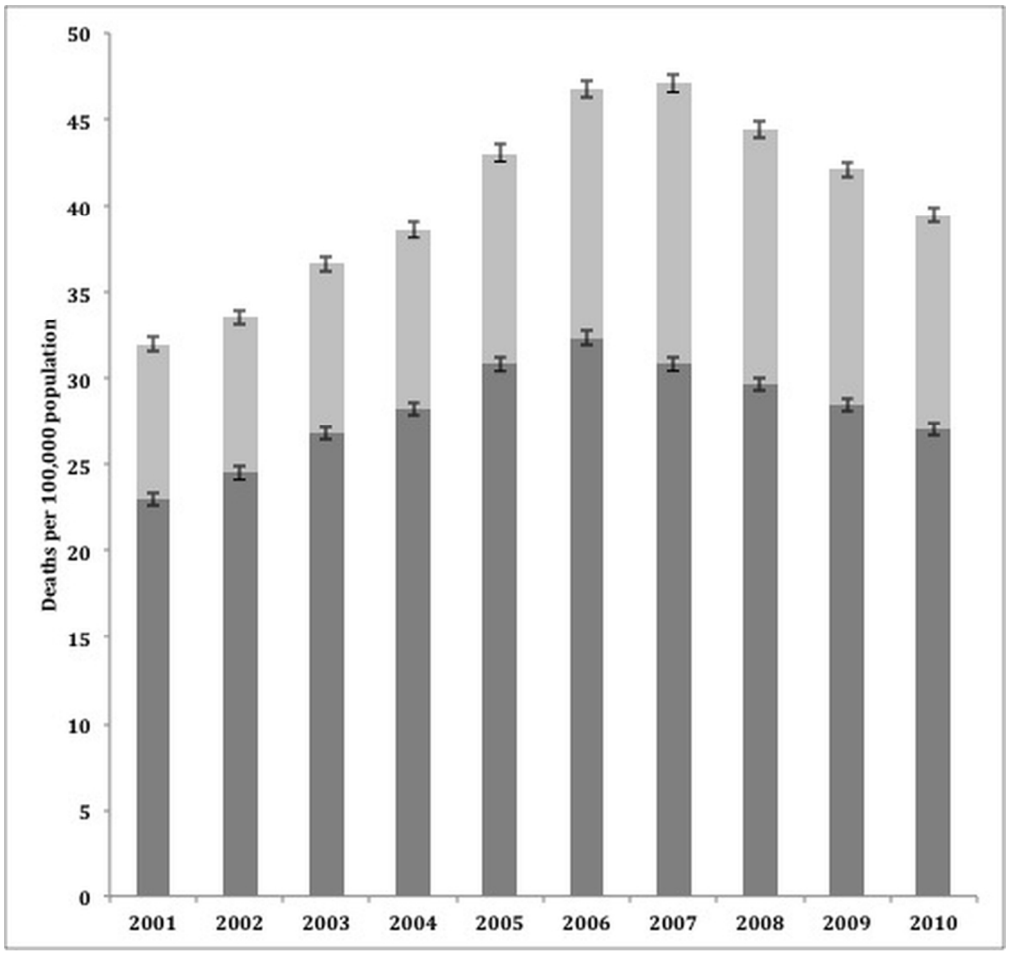

Figure 1. Directly age-standardised rates of death definitely, dark grey, and maybe, light grey, associated with sepsis, England 2001-10, with 95% confidence interval for the rate.
95x90mm (300 x 300 DPI)

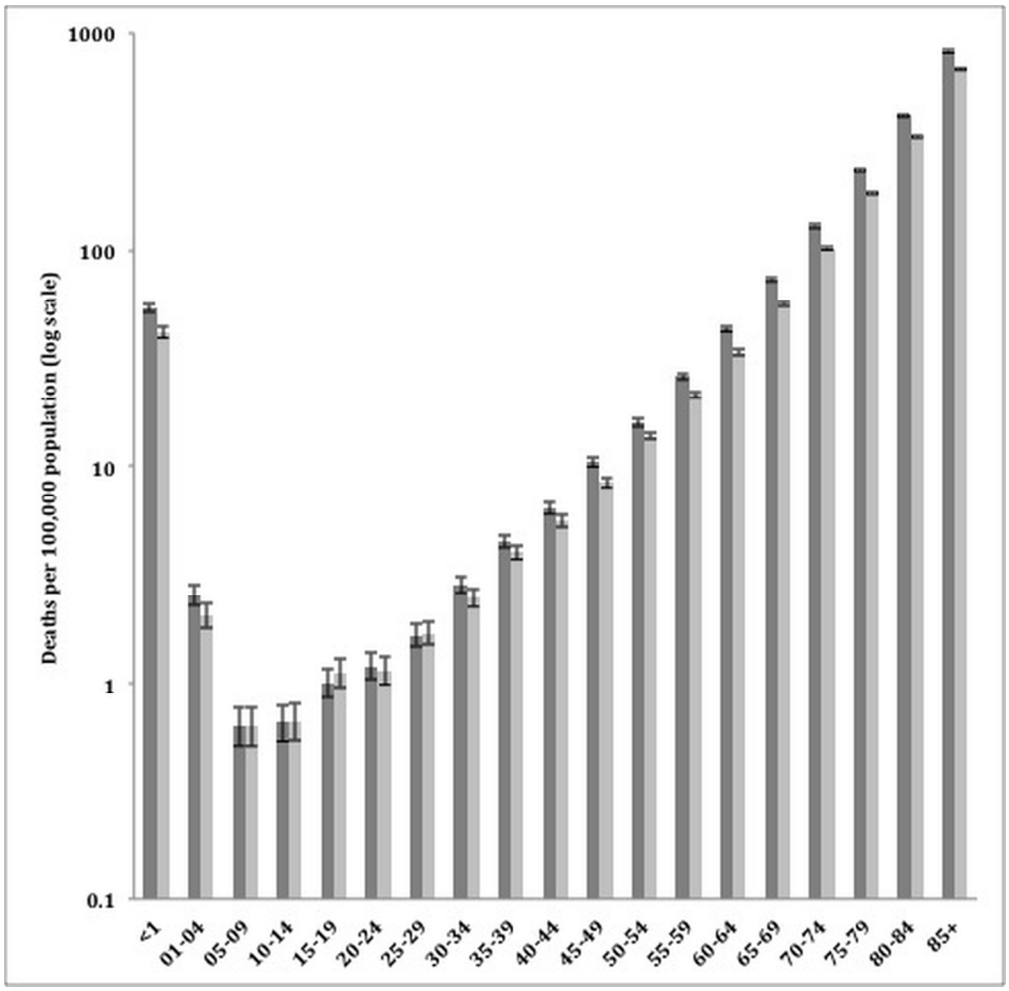

Figure 2. Age specific death rates for males, dark grey, and females, light grey, of deaths definitely associated with sepsis, England, 2001-10, with 95% confidence interval for the rate.
91x90mm (300 x 300 DPI)

Appendix

Association with sepsis	ICD-10 Chapter	ICD-10 codes
Definite	Infectious and parasitic diseases	A02.1, A20.2, A20.7, A21.7, A22.7, A26.7, A32.7, A39.2, A39.4, A40, A41, A42.7, A48.4, B00.7, B37.7
	Pregnancy, childbirth and the puerperium	O85
	Conditions originating in the perinatal period	P36, P37.2
	Symptoms, signs and abnormal clinical and laboratory findings	R57.8
Maybe	Infectious and parasitic diseases	A02.9, A03.9, A04, A20.3, A21.9, A22.8, A22.9, A23.8, A23.9, A24.1, A24.4, A28.2, A28.8, A28.9, A31.0, A32.9, A33, A39.0, A39.1, A39.3, A39.9, A48.0, A49, A54.8, B20.1, B20.7
	Diseases of the eye and adnexa	H44.0
	Diseases of the respiratory system	J80, J95.0
	Diseases of the musculoskeletal system	M72.9
	Diseases of the genitourinary system	N39.0
	Pregnancy, childbirth and the puerperium	O08.0, O08.2, O75.3, O86, O88.3
	Conditions originating in the perinatal period	P22.0
	Symptoms, signs and abnormal clinical and laboratory findings	R02, R50.8, R50.9, R57.9
	Injury, poisoning and certain other consequences of external causes	T80.2, T81.4, T82.6, T82.7, T83.5, T83.6, T84.5, T84.6, T84.7, T85.7, T88.0
	Additional codes used by WHO for new and emerging conditions	U04

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any pre-specified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	N/A

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-11
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	N/A
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(*b*) Report category boundaries when continuous variables were categorized	9-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.