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The Cost of Sepsis Care in the UK

Final Report

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1. INTRODUCTION

The aim of this report is to highlight the considerable costs associated with sepsis in the UK. Sepsis is a potentially life-threatening condition caused by infection from numerous potential sources. In more severe forms it results in hospital admission and the most severe forms require treatment in intensive care. There is a high mortality rate associated with patients with sepsis. This implies significant costs to both the health care system and society more broadly.

Despite the economic and human costs associated with sepsis there are very little data on incidence, care pathways and costs in the UK. The incidence of sepsis may be under-reported as sepsis may be attributed to other conditions such as pneumonia. There is consensus that much more could be done to recognise sepsis at an earlier stage in many cases, and that if this were the case, deaths, complications and the use of hospital resources could be reduced.

In 2016, the National Institute for Health and Care Excellence (NICE) published a guideline which included interventions which aimed to improve diagnosis and management of sepsis. The Guideline Development Group identified that records of prevalence and incidence of sepsis in the UK are not robust and did not carry out cost-effectiveness modelling.

This study has attempted to gather the data and evidence on the cost burden of sepsis that do exist and to use them to develop some estimates of the potential range of the current cost of sepsis in the UK. There are many caveats to the estimates that have been developed but one of the important outputs from this work has been the identification of gaps in evidence and data and recommendations about how these gaps can be potentially filled.

2. METHODS

The study adopted a systematic but pragmatic approach to the work, drawing on the best available evidence. This was derived from two sources:

- A burden of illness literature review designed to identify published academic literature on the costs of sepsis;
- Engagement with key opinion leaders (KOLs) to sense check the approach to costing and provide signposts to other evidence, including any unpublished evidence.

The literature review sought to find evidence on both direct and indirect costs of sepsis. Direct costs included hospital costs of care and ongoing care in the community following discharge, as well as any long-term costs associated with complications and disability caused by sepsis. Indirect costs included loss of productivity as a result of sepsis and the costs of litigation from claims against the health service brought by people with sepsis.

The development of the cost model was dictated by the evidence and data found from the literature reviews, along with any evidence and data that could be added to by the KOLs, including any assumptions or estimates.

It was originally intended to consider the different populations with sepsis (neonates, children, adults, elderly), as well as different types of sepsis (sepsis, severe sepsis, septic shock) and the extent to which evidence and data were applicable across populations and sepsis type. We found that there was simply not enough evidence to be able to estimate the incidence of different types of sepsis in the different populations.

The costing framework considered the direct costs associated with in-hospital treatment for sepsis (e.g. costs of ICU treatment and overall length of hospital stay). Where possible, these costs were broken down by the different populations with sepsis. Results from the initial burden of illness review were used to populate these costs, along with pragmatic searches and sources provided by KOLs to cover any data gaps. The costing framework also considered longer-term costs associated with three separate areas: litigation; lost lifetime productivity resulting from mortality; treatment costs for different post-sepsis complications.

3. RESULTS

The estimated costs of sepsis each year in the UK are £7.76 billion, including approximately £830 million of direct costs. Applying sensitivity analysis to these costs (higher hospital costs and lower estimate of average age of death from sepsis for adults of working age) would give an estimated annual cost of more than £10 billion, including more than £1.1 billion of direct costs. Table 1 summarises the estimated costs.

Table 1: Summary of estimated costs of sepsis (using estimated incidence of 147,000 per year)

		Base case	Low estimate	High estimate
Direct costs	Hospital costs	£819,577,538	£619,934,130	£1,114,746,168
	Complications	£9,180,688	£1,836,138	£18,361,376
	Total	**£828,758,227**	**£621,770,267**	**£1,133,107,544**
Indirect costs	Productivity	£6,770,841,600	£6,770,841,600	£8,751,080,366
	Litigation	£160,274,100	£32,054,830	£320,548,200
	Total	**£6,931,115,700**	**£6,802,896,430**	**£9,071,628,566**
GRAND TOTAL		**£7,759,873,926**	**£7,424,666,697**	**£10,204,736,110**

The lack of clarity about the numbers of patients with sepsis, their disease trajectory and their care pathways mean that it is impossible to provide definitive estimates of changes in costs as a result of improvements in care. It is, however, possible to provide a high level estimate of the potential for reduced costs. If the overall number of admissions for sepsis were reduced by 10%, 20% or 30% due to improvements in care, then the potential annual cost savings to the NHS would be £83 million, £166 million or £249 million respectively. This would also have the effect of reducing lost productivity amongst working age adults. If rates of mortality could be reduced by similar proportions (10%, 20% or 30%), then there is potential for improvements in annual productivity of £672 million, £1,345 million or £2,017 million.

The costs estimated in Table 1 were based on Hospital Episode Statistics (HES) data, extrapolated to the UK population, which estimated incidence of sepsis at 147,000 cases per year. An as yet unpublished study has examined HES data in more detail and indicate that incidence of sepsis in the UK could be as high as 260,000. Applying this level of incidence would increase the estimated costs of sepsis to £11.25 billion per year, with direct costs of almost £1.5 billion. Applying the same sensitivity analysis to these costs would give a higher estimate of £15.63 billion, with almost £2 billion of direct costs relating to sepsis every year (Table 2).

Table 2: Summary of estimated costs of sepsis (using estimated incidence of 260,000 per year)

		Base case	Low estimate	High estimate
Direct costs	Hospital costs	£1,461,794,291	£1,112,244,609	£1,938,286,295
	Complications	£16,753,080	£3,350,616	£33,506,161
	Total	**£1,478,547,371**	**£1,115,595,225**	**£1,971,792,456**
Indirect costs	Productivity	£9,486,432,686	£9,486,432,686	£13,100,069,511
	Litigation	£283,478,000	£56,695,600	£556,956,000
	Total	**£9,769,910,686**	**£9,543,128,286**	**£13,657,025,511**
GRAND TOTAL		**£11,248,458,057**	**£10,658,723,511**	**£15,628,817,967**

This is almost certainly an under-estimate because no change was made to the level of incidence of sepsis in children (10,000). If sepsis incidence in children is higher, then the estimated costs of lost productivity would increase considerably.

If the overall number of admissions for sepsis were reduced by 10%, 20% or 30% due to improvements in care, then under this scenario, the potential annual cost savings to the NHS would be £148 million, £296 million or £444 million respectively. If rates of mortality could be reduced by similar proportions, then there is potential for improvements in annual productivity of £940 million, £1,880 million or £2,820 million.

4. CONCLUSIONS

This paper outlines the estimated costs for care of sepsis in the UK, including both direct hospital treatment costs for sepsis recovery and associated complications, as well as indirect costs of lost productivity and litigation. There are heavy caveats on the reported results due to significant missing data and a lack of clarity around the incidence, prevalence and patient pathways for sepsis in the UK.

It should be noted that the data used to calculate these figures were derived from a variety of sources. This included recent UK population studies but where gaps in the literature were identified, older, or non-UK-based data were used, and in some cases where no alternative was available, assumptions have been used.

There are some significant methodological limitations to this study. Incidence rates of specific subgroups affect the calculation of all of the costs included in this study. However, incidence rates have had to be extrapolated on the basis of proportions observed in small studies and applied to the total estimated number of people who contract sepsis in the UK each year. Where proportionate estimates were not identified from the literature, proxies from different subgroups have been used, for example, the late mortality rate observed in a study of adult ICU patients was applied to children. While every effort has been made to check the appropriateness of such proxies, they may result in inaccurate estimates of subgroup totals, which would have knock-on impacts for subsequent cost calculations.

It is also important to note that the lack of data and evidence meant it was not possible to generate costs for all of the patient subgroups that had been originally planned. In particular, the study team is aware that there are specific issues in relation to neonates and sepsis but there is an absence of data in the numbers of babies affected. The methodology has had, therefore, to adopt a cruder split between adults and children.

Finding data was particularly problematic for many of the model inputs (e.g. length of stay, mortality and rates of complications) relating to sepsis patients who were not admitted to ICU, as many of the literature sources identified included only patients who were admitted to ICU. Given the discrepancy in the total number of patients in the UK thought to be affected by sepsis each year and the number admitted to ICU for sepsis, this indicates roughly two thirds of adults with sepsis are treated exclusively outside of ICU. The lack of data indicates a need for improved reporting of sepsis cases outside of the ICU in order to accurately assess the costs for this subgroup.

Costs for hospital treatment for the initial sepsis episode are not sepsis specific, and instead use the average daily cost of treatment on either ICU, or general wards. Costs of sepsis care on both ICU and general wards are likely to vary extensively for different patients, depending on various indicators of severity such as the number of organs that require support, the necessity to perform amputations, or the presence of septic shock. Due to the absence of data with the required level of detail, and using a conservative approach, average ICU and general ward costs were considered the most appropriate metrics for these estimates. It is worth noting that NHS Reference Costs are lower than US reported costs, partly because US costs relate to reported insurance costs. This is important as direct cost estimates of sepsis in the UK have tended to rely on reported US costs.

A number of costs that would be attributable to sepsis were not considered estimable given the current data identified and have, therefore, not been included. For example, no costs of continued drug treatment following hospital discharge have been included and there was no estimate made of the cost of complications associated with children with sepsis. These costs are likely to be significant, potentially up to £3-4 million per child. Similarly, no costs were included in relation to productivity losses from absence due to at-home recovery time, absence due to follow-up, absence of informal carers (e.g. relatives), as well as 'presenteeism' whereby patients returning to work are less productive due to ongoing problems. This is primarily due to an absence of either baseline data on incidence or prevalence, or a lack of evidence in the literature.

In conclusion, despite its limitations, this study has estimated the costs of sepsis care are significant, both in terms of direct costs to the NHS and particularly in relation to productivity costs because of high levels of early mortality associated with sepsis. Improvements in care that could reduce either the incidence of sepsis or mortality associated with sepsis could result in significant cost-savings, as well as obvious quality of life benefits.

The variety of sources required to populate this model and number of assumptions it was necessary to make in order to fill data gaps are indicative of the paucity of information available regarding sepsis care in the UK. This report synthesised the best available data, reports a range of scenarios around uncertain parameters and sought advice from key opinion leaders in its formation. Nevertheless it is likely that the costs, particularly the direct costs, are under-estimated. It is possible that costs are over-estimated, but given the absence of features within the model that we are aware would have cost implications, but which were not considered estimable, such as lost productivity for informal carers, or for follow-up treatment, it is thought that this is unlikely.

Better quality data and an improved understanding of the disease trajectory for sepsis would undoubtedly improve the quality of the costs estimates. It would also enable more useful analyses to be carried out of the cost effectiveness of particular interventions to improve sepsis care.

It is understood that there are initiatives underway to improve the recording of sepsis and clinical coding in hospitals. There is the potential to go further than this and to establish a disease registry for sepsis. This would capture accurate data on the sub-populations with sepsis as well as providing an understanding of the disease trajectory and care pathways for different types of patient.

The following recommendations are made:

- NHS Hospital Trusts in England should adopt new directives on clinical coding for sepsis and these should also be rolled out to the rest of the UK;
- If clinical coding can be improved there may be a possibility of carrying out more robust cost burden analysis using more precise figures in two to three years' time;
- In line with recommendations made by the NICE sepsis Guideline Development Group, The Department of Health or NHS England should consider establishing, or commissioning the establishment of some form of sepsis registry to capture key metrics on people with sepsis.

Acknowledgements

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Section 1: Introduction

1.1 BACKGROUND TO SEPSIS

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] It is a potentially life-threatening condition caused by infection, usually bacterial but also viral or fungal. A UK Parliamentary and Health Service Ombudsman enquiry (2013) [2] and UK National Confidential Enquiry into Patient Outcome and Death (NCEPOD, 2015) [3] have recently highlighted sepsis as being a leading cause of potentially avoidable death [4].

Sepsis can happen to anybody but those most at risk include people with a weakened immune system (due to a medical condition or treatment), patients admitted to hospital with serious illness, the very young or very old and post-operative patients or those with wounds or injuries due to an accident. The potential sources of infection are numerous and sometimes cannot be identified but include pneumonia, appendicitis, peritonitis, urinary tract infection, cholangitis, skin infections, infections after surgery, brain and nervous system infections, 'flu (this is arguable- some experts believe the features leading to organ failure are identical), osteomyelitis and endocarditis.

Early symptoms can include fever, low body temperature, chills, shivering, raised heart beat and rapid breathing. Symptoms of sepsis or septic shock may develop soon after including feeling dizzy or faint, a change in mental state, diarrhoea, nausea and vomiting, slurred speech, severe muscle pain, severe breathlessness, reduced urine production, cold clammy and pale or mottled skin and loss of consciousness.

In the UK, patients diagnosed with sepsis will usually be referred to hospital for further management, through simple tests such as blood tests and clinical evaluation, and treatment. The National Institute for Health and Care Excellence (NICE), the UK Sepsis Trust, NHS England and the Royal Colleges have proposed the use of 'Red Flag' bedside criteria to prompt and empower urgent action. Patients with 'Red Flag' Sepsis and septic shock are referred to the 999 service. Depending on the severity of the case, which may be linked to how early it was detected, some patients might be treated at home with antibiotics [5].

Most patients with Red Flag Sepsis and septic shock are admitted to hospital and some are admitted to the intensive care unit (ICU). The UK Sepsis Trust has until the date of launch of this report estimated that in the UK, about 147,000 people are admitted to hospital with sepsis annually, though has acknowledged that this could be closer to 200,000.[6] New data obtained through a bespoke analysis of Hospital Episode Statistics by the UK Sepsis Trust now suggest a higher figure, which is discussed later in this report. The Sepsis Trust also estimates that, due to problems with vital organs, 44,000 patients die from sepsis each year.

Recovering from sepsis varies depending on the severity of the sepsis, the person's baseline health, duration of hospital stay and whether the patient was admitted to ICU. Time to full recovery varies and some experience long-term problems such as lethargy, muscle weakness, swollen limbs or joint pain, chest pain or breathlessness, insomnia, hair loss, dry/flaking skin and nails, changes in taste, vision and limb sensation, poor appetite, post-sepsis syndrome and repeated infections. There are also potential psychological consequences, such as anxiety or fear, depression, flashbacks, nightmares, insomnia, post-traumatic stress disorder and poor concentration or short-term memory loss.

The Global Sepsis Alliance claims that in the developed world, from 2006 to 2015, the incidence of sepsis increased annually by between 8% and 13% [7]. This is likely due to increased recognition, an aging population, increased use of high-risk interventions and the evolution of more drug-resistant and dangerous varieties of pathogens causing infection. The Global Sepsis Alliance targets a reduction of incidence of sepsis by at least 20%, by 2020, through promoting good practices such as hygiene and hand washing, access to healthcare including vaccination, clean obstetric deliveries, improved sanitation, nutrition and delivery of clean water in low and middle income countries, and by improving uptake of vaccination together with some of the above strategies in high income countries.

Using a figure derived from the European SOAP study, the UK Sepsis Trust estimates that each case of sepsis costs €25,000 to healthcare systems in developed countries, and so for the UK, this means a total annual cost of £2 billion [8, 6]. These costs could potentially be reduced through effective delivery of basic care, such as microbiological sampling and antibiotic delivery within one hour, fluid resuscitation, and risk stratification using serum lactate (or an alternative), which has been explored by previous research [9]. Other non-UK studies have also demonstrated the potential for improvements in care to sepsis patients in developed countries through explored implementation of severe sepsis and septic shock management bundles in the US and an educational program to clinicians in Spain [10, 11].

1.2 NICE GUIDELINE ON SEPSIS

NICE published a guideline on sepsis recognition, assessment and early management in July 2016 [4]. The guideline set out to answer 18 research questions covering care processes including:

- Diagnostic and prognostic (blood tests, signs and symptoms, monitoring, source of infection, scoring tools, creatinine, disseminated intravascular coagulation, lactate);
- Intervention (escalation of care, central venous access, inotropic agents, intravenous fluids, bicarbonates, oxygen, education and training, antimicrobials, early goal directed therapy).

Systematic literature searches were undertaken to identify health economic evidence within published literature relevant to the review questions. The focus of the searches was on evidence of the cost-effectiveness of processes and interventions for sepsis, so they looked for the following study types comparing costs and health consequences of alternative courses of action: cost-utility, cost-effectiveness, cost-benefit and cost-consequences analyses.

The Guideline Development Group (GDG) identified the timing of the use of empirical antibiotics as the highest priority area for original economic modelling. The clinical evidence for this question indicates that early empirical antimicrobials (given <1 hour) result in lower mortality than delayed use. The GDG were confident that any resource implications, and therefore costs, would be offset by the benefits in terms of reduced mortality. The GDG agreed that the cost-effectiveness of interventions could be deduced without the need to model.

An additional lower priority of a pathway approach (the impact of identifying and treating people with sepsis) was also considered for economic modelling. A pathway approach was considered unfeasible due to the large number of unknowns in the epidemiology of sepsis.

The Guideline makes some important points about the changing terminology in relation to sepsis. At the time of development of the guideline terms such as SIRS (systematic inflammatory response syndrome), severe sepsis and septic shock were in use. New terminology suggests using the terms sepsis and septic shock only. In this study we have not differentiated between the different 'types' (severities) of sepsis as, although there is plenty of literature on different severities, the lack of data on incidence and prevalence means that it is not possible to cost them separately.

1.3 STUDY OBJECTIVES

Sepsis generates a high degree of morbidity and mortality but it is not necessarily well understood by all clinicians and the public. In order to raise the profile of sepsis it is important that the cost burden of the disease is estimated. There are no accurate estimates of the costs of sepsis to the UK for a number of reasons, the main one being poor quality data. The NICE GDG identified that records of prevalence and incidence of sepsis in the UK are not robust and decided that carrying out cost-effectiveness modelling was unfeasible as a result.

This study has attempted to gather the data and evidence on the cost burden of sepsis that do exist and to use them to develop some estimates of the potential range of the current cost of sepsis in the UK. There are many caveats to the estimates that have been developed but one of the important outputs from this work has been the identification of gaps in evidence and data and recommendations about how these gaps can be potentially filled.

The original objectives of the project were:

- To research the current annual economic cost of sepsis in the UK through a burden of illness literature review to support The Whitewater Charitable Trust's understanding of the economic costs of sepsis;
- To develop a model which projects the future UK cost of sepsis given improvements in prevention and care pathways.

The first objective has been carried out using a pragmatic literature review and information gathered from key opinion leaders (KOLs). Through the evidence gathered from the literature review, it has become apparent that the second objective can only be achieved in a limited form, i.e. estimates of a range of the potential current costs of sepsis, rather than an accurate model to predict the likely future costs based on improvements in care.

Section 2: Methodology

2.1 METHODOLOGICAL APPROACH AND LIMITATIONS

The project aims to quantify the cost of the burden of care for sepsis in the UK and understand the potential to reduce the cost through improvements in prevention and care pathways. The project has had limitations in terms of timescales and funding, with the aim being to produce a draft report by mid-February 2017.

York Health Economics Consortium (YHEC) has adopted a systematic but pragmatic approach to the work, drawing on the best available evidence. This was derived from two sources:

- A burden of illness literature review designed to identify published academic literature on the costs of sepsis;
- Engagement with KOLs to sense check our approach to costing and provide signposts to other evidence, including any unpublished evidence.

The literature review has sought to find evidence on both direct and indirect costs of sepsis. Direct costs include hospital costs of care and ongoing care in the community following discharge, as well as any long-term costs associated with complications and disability caused by sepsis. Indirect costs include loss of productivity as a result of sepsis and the costs of litigation from claims against the health service brought by people with sepsis.

We identified a number of KOLs who have been engaged throughout the project. A Steering Group was also established including the sponsors of the project.

2.2 LITERATURE SEARCH METHODOLOGY

Literature searches were undertaken to identify UK studies reporting economic costs in patients with sepsis. Following comments received from KOLs and the Steering Group, the searches were run in the week commencing 12 December 2016. Two searches were run to find economic papers, one using a UK filter to find the most appropriate and relevant studies, and the other without the filter to find all studies regardless of geography.

The draft strategy was developed in MEDLINE (Ovid interface). The strategy was devised using a combination of subject indexing terms and free text search terms in the title, abstract and keyword heading word fields.

The MEDLINE strategy comprised 3 concepts:

1. Sepsis;
2. Economic costs;
3. UK studies.

The search concepts were combined as follows: sepsis AND economic costs AND UK studies.

The search terms for the sepsis concept were identified through scanning background literature, browsing database thesauri and use of the PubMed PubReminer tool (http://hgserver2.amc.nl/cgi-bin/miner/miner2.cgi). The terms included synonyms / variant terms / associated terms for sepsis, urosepsis, post-anginal sepsis / fusobacterium necrophorum sepsis (Lemierre syndrome), sepsis syndrome (Systemic Inflammatory Response Syndrome), candida sepsis (candidaemia), fungal sepsis (fungaemia), meningococcal sepsis / neisseria meningitidis sepsis (meningococcaemia), MRSA sepsis (MRSA infection) and staphylococcal sepsis (staphylococcal bacteraemia).

The search terms for the economic costs concept were based on the search filter developed by the University of York Centre for Reviews and Dissemination (CRD) for retrieval of economic evaluations for inclusion in the NHS Economic Evaluation Database. The CRD terms were enriched by the inclusion of additional economics and cost-related terms, reflecting the wider scope of this review.

The strategy used the NICE UK search filter to restrict to UK studies. This validated filter was developed by the NICE guidance Information Services team for use in Ovid MEDLINE to retrieve publications with a UK setting.

The strategy excluded animal studies using a standard algorithm. The strategy also excluded some publication types which were unlikely to yield study reports (news, comment, editorial, letter, case reports) and records with the phrase ‘case report’ in the title field. The strategy was restricted to studies published in English from 2007 to date in order to identify current data.

The draft strategy was included in the project protocol which was reviewed by the research team and the UK Sepsis Trust team, though the latter did not choose to influence search strategy. The final agreed strategy was peer reviewed independently by another information specialist to check for errors in spellings, syntax and line combinations. The final strategy as run in Ovid MEDLINE is shown in Appendix 1.

The literature search was conducted in a range of relevant bibliographic databases containing published literature. The databases searched are shown in Table 2.1. The final agreed MEDLINE search strategy was adapted suitably to perform efficiently in the other databases. Full details of all bibliographic database search strategies will be provided in the final report.

Table 2.1: Databases searched

Database	Interface / URL
Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present	OvidSP
Embase	OvidSP
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library / Wiley
Database of Abstracts of Reviews of Effects (DARE)	Cochrane Library / Wiley
Health Technology Assessment Database (HTA)	Cochrane Library / Wiley
NHS Economic Evaluation Database (NHS EED)	Cochrane Library / Wiley
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library / Wiley
PubMed	http://www.ncbi.nlm.nih.gov/pubmed
EconLit	OvidSP
Health Management Information Consortium Database (HMIC)	OvidSP

In addition to the searches of bibliographic databases we conducted a number of supplementary search activities. These activities were designed to complement the bibliographic database searches and aimed to identify additional eligible publications not retrieved by the database searches, (for example, studies not included in the databases). The activities included:

- Checking the reference lists of any identified relevant reviews for eligible studies;
- Conducting pragmatic, targeted searches using the Google Advanced search interface;
- Contact with experts.

The results of the bibliographic database searches were transferred into an EndNote library and de-duplicated using several algorithms. The de-duplicated references were held in a separate EndNote Library duplicates database for checking if required.

2.3 LITERATURE SEARCH RESULTS

The database searches identified 2,332 records (Table 2.2). Following deduplication 1,763 records were assessed for relevance, of which 88 were Cochrane Reviews and 452 were conference abstracts. These have been reviewed using the inclusion and exclusion criteria and the initial title and abstract selection identified 20 records, with 6 ultimately being eligible for data extraction.

Table 2.2: Literature search results

Resource	Records identified
Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present	545
Embase	1,090
Cochrane Central Register of Controlled Trials (CENTRAL)	157
Database of Abstracts of Reviews of Effects (DARE)	69
Health Technology Assessment Database (HTA)	19
NHS Economic Evaluation Database (NHS EED)	140
Cochrane Database of Systematic Reviews (CDSR)	100
PubMed	121
EconLit	4
Health Management Information Consortium Database (HMIC)	83
Reference list checking	4
TOTAL	**2,332**
TOTAL AFTER DE-DUPLICATION	**1,763**

A narrative synthesis of the eligible database studies is provided at Appendix B.

The studies identified through the burden of illness literature review contain some useful data, particularly in relation to hospital stay due to sepsis. The results are much more limited in terms of data in relation to:

- Longer-term complications and disability associated with sepsis;
- Indirect costs such as reduced productivity caused by sepsis;
- Litigation costs associated with sepsis.

Subsequent to the burden of illness review some further pragmatic searches were carried out to find evidence relating to these measures and also in relation to the incidence of sepsis. The results of these searches are listed at Appendix C. In addition to this, KOLs were asked for lists of additional papers, published and unpublished, in order to try to fill any evidence gaps.

2.4 COST MODELLING APPROACH

The development of the cost model has been dictated by the evidence and data we found from the literature reviews, along with any evidence and data that could be added to by the KOLs, including any assumptions or estimates.

We intended to consider the different populations with sepsis (neonates, children, adults, elderly), as well as different types of sepsis (sepsis, severe sepsis, septic shock) and the extent to which evidence and data were applicable across populations and sepsis type. We found that there was simply not enough evidence to be able to estimate the incidence of different types of sepsis in the different populations.

The costing framework considered the direct costs associated with in-hospital treatment for sepsis (e.g. costs of ICU treatment and overall length of hospital stay). Where possible, these costs were broken down by the different populations with sepsis. Results from the initial burden of illness review were used to populate these costs, along with pragmatic searches and sources provided by KOLs to cover any data gaps.

The cost framework also considered longer-term costs associated with three separate areas:

- Litigation;
- Lost lifetime productivity resulting from mortality;
- Treatment costs for different post-sepsis complications.

Where available, these costs have been broken down by population.

Section 3: Estimated Costs

3.1 MODEL INPUTS

In estimating the costs of sepsis to the UK, direct treatment costs and indirect costs have been considered.

Direct costs include costs relating to the initial treatment of sepsis, as well as costs relating to the treatment of complications that result from sepsis. Costs for the initial treatment of sepsis have been based on finding the product of the number of patients in hospital with sepsis, their average length of stay in different ward types, and the average cost per day of care in ICU and general wards. For the costs relating to treatment for complications occurring following an episode of sepsis average costs of treatment have been combined with estimated incidence.

Indirect costs are those relating to lost productivity and litigation costs as a result of sepsis. Lost productivity has been considered both for in-hospital loss of earnings, as well as for loss of lifetime earnings resulting from early mortality. Lost productivity relating to hospital treatment has been calculated by finding the product of the numbers of adults of working age in hospital with sepsis, their average hospital length of stay, and the average daily salary for the UK.

Lost productivity relating to mortality has been calculated for adults of working age, as well as for all children. For adults of working age, mortality related lost productivity has been calculated by finding the product of the numbers of adults of working age who die (including both in-hospital and late mortality attributable to sepsis), the number of years between their average age within the working-age population and retirement age (assumed to be 65 years), and the average yearly salary for the UK. For children, the value has been calculated by finding the product of the numbers of children below the age of 18 who die (including both in-hospital and late mortality attributable to sepsis), the numbers of years of an average working lifetime, and the average yearly salary for the UK.

Litigation costs have been calculated by finding the product of the average cost of litigation claims and the average proportion of sepsis cases that result in litigation.

3.2 INCIDENCE AND PREVALENCE ESTIMATES AND MORTALITY DATA

As the NICE GDG found, there are no reliable estimates of incidence and prevalence of sepsis. The UK Sepsis Trust has until the date of launch of this report estimated that in the UK, about 147,000 people are admitted to hospital with sepsis annually, based on HES data for England and extrapolated to the UK population. The UK Sepsis Trust also historically has estimated that 10,000 children per year have sepsis, so this implies an adult population with sepsis of 137,000.

Shankar-Hari et al estimated that 36,100 adult patients with sepsis were treated in England in ICU [12]. This paper reported diagnostic data from the hierarchical Intensive Care National Audit and Research Centre (ICNARC) coding method and care needs to be applied in using these data as they apply to the first 24 hours following admission to ICU. Extrapolated to the UK population, the data estimates imply that 43,027 adult patients are treated annually for sepsis during their first 24 hours in ICU. On that basis, it has been assumed that the remaining 93,973 adults in the estimated population were treated for sepsis in hospital without needing ICU treatment, though this is likely to be an underestimate. Applying the same estimates to children with sepsis would mean that 3,141 children would be treated annually in ICU and 6,859 would be treated in hospital without needing ICU treatment.

Shankar-Hari's paper also provided age ranges for patients with sepsis in ICU. Around 56% were over 65, equating to 24,298 people. Using this evidence it is possible to extrapolate 18,730 people in ICU with sepsis of working age annually.

Reported data on mortality related to sepsis are not robust due to acknowledged weaknesses in recording sepsis as a reason for mortality. The UK Sepsis Trust has estimated mortality from sepsis to be around 30% [6]. Applied to the total estimate of 147,000 people with sepsis in the UK, this would imply around 44,100 deaths attributable to sepsis annually.

There are some more robust estimates of sepsis-related mortality specific to patients in ICU. Shankar-Hari reported an in-hospital mortality rate for adults in ICU of 32.1%, implying that 13,812 people die each year in ICU from sepsis [12]. For children, excluding newborns, Weiss et al. estimated a 25% mortality rate for patients in ICU [13]. Applied to the estimated population of children in ICU with sepsis (3,141), this would imply an additional 785 deaths from children in ICU annually.

3.3 DIRECT COST ESTIMATES

3.3.1 Hospital Costs

Hospital costs were estimated based on the incidence numbers estimated in Section 3.1, multiplied by length of stay and a unit cost. The unit cost of ICU per day, £1,307.26, has been extracted as a weighted average from NHS Reference Costs for 2015/16. This is given added credence by a 2012 costing study by Tan which estimated the daily cost of ICU at £1,227, inflated to 2015/16 prices using the Hospital and Community Health Services Index [14, 15]. Levy (2012) provides values of median hospital lengths of stay for ICU patients with severe sepsis and septic shock in Europe as 22.8 days, with the stay in ICU being 7.8 days [16].

The costs of ICU treatment for adults are, therefore, estimated at 43,027 x 7.8 x £1,307.26 = £438,730,313. If the lower point estimate of Tan's ICU costs is used (£1,036) the overall cost reduces to £347,692,582 and if the higher point estimate of Tan's costs is used (£1,796), the overall cost increases to £602,756,638.
The additional 15 days spent in hospital by patients who have been in ICU with sepsis would be costed at £272.60, based on the weighted average excess bed day NHS Reference Cost for people with sepsis using the following HRG codes: WJ05A; WJ05B; WJ06A; WJ06B; WJ06C;WJ06D; WJ06E; WJ06F; WJ06G; WJ06H; WJ06J. The estimated cost of the additional hospital stay for adult sepsis patients in ICU is, therefore, 43,027 x 15 x £272.60 = £175,937,403. The lower and upper quartile unit NHS Reference Costs for bed days are £199.85 and £317.36 respectively. Applying these costs to the calculation would give a lower estimate of £128,984,189 and a higher estimate of £204,825,731.

It is assumed that the remaining 93,973 adults would be treated in hospital but not ICU. In the absence of specific data on the length of stay of non-ICU patients in hospital it has been assumed that they would stay for 6.4 days. This is based on the weighted average length of stay for the HRG codes associated with sepsis in NHS Reference Costs. Applying the same unit cost per day, the estimated costs of sepsis patients who do not require ICU treatment is: 93,973 x 6.4 x £272.60 = £163,949,055. Applying the upper and lower quartile unit NHS Reference Costs gives a lower estimate of £120,195,225 and a higher estimate of £190,868,936.

For children, we do not have any specific data on the split between neonates and other children. In the absence of more specific data the current (at the date of publication) UK Sepsis Trust estimate of 10,000 children per year with sepsis has been used- following this report the estimate is likely to be higher. The weighted average excess bed day NHS Reference Cost for children with sepsis is £1,670.80, using the following HRG codes: XB01Z; XB02Z; XB03Z; XB04Z; XB05Z; XB06Z; XB07Z; XB08Z; XB09Z. The highest cost (XB01Z) relates to Advanced Critical Care 5 and is £5,440 per day, while the lowest cost (XB09Z) is £870 per day.

Paul (2012) reports the average length of hospital stay for children with sepsis in paediatric ICU (PICU) is 9.23 days, of which 6.25 days were in PICU [17]. For the 3,141 children in ICU with sepsis, the estimated cost of ICU treatment is, therefore, 3,141 x 6.25 x £1,670.80 = £32,799,893. Using the highest and lowest PICU unit costs for bed days gives a range of costs from £106,794,000 (3,141 x 6.25 x £5,440) to £17,079,188 (3,141 x 6.25 x £870).

It has been assumed that the remaining days (2.98) of the average length of stay would be spent in general wards and the same daily costs have been assumed as for adult patients. The estimate cost for the rest of the stay for children with sepsis who are treated in PICU would therefore be 3,141 x 2.98 x £272.60 = £2,551,585. The range of costs, using the upper and lower quartile NHS Reference Costs would be £1,870,632 (3,141 x 2.98 x £199.85) and £2,970,547 (3,141 x 2.98 x £317.36).

For the children who are not admitted to PICU but who are in hospital with sepsis, the same costs can be assumed. In the absence of evidence or data from NHS Reference Costs, it has been assumed that children not requiring PICU treatment would require a three day stay. The estimate cost would be, therefore, 6,859 x 3 x £272.60 = £5,609,290. The range of costs would be £4,112,313 (6,859 x 3 x £199.85) to £6,530,317 (6,859 x 3 x £317.36).

The estimated total costs of hospital care for sepsis in the UK are around £820 million per year (Table 3.1). Based on point estimates from literature a range of cost can be observed between £620 million and £1,115 million, shown as high and low scenarios in Table 3.1. It should also be noted that these costs are based on the estimates of sepsis incidence derived from the UK Sepsis Trust.

Table 3.1: Estimated annual costs of sepsis care in hospital

Patient types	Hospital care setting	Estimated annual cost	Sensitivity (low)	Sensitivity (high)
Adults	ICU	£614,667,716	£476,676,771	£807,582,368
	General	£163,949,055	£120,195,226	£190,868,936
	Total	**£778,616,771**	**£596,871,997**	**£998,451,305**
Children	ICU	£35,351,478	£18,949,819	£109,764,547
	General	£5,609,290	£4,112,313	£6,530,317
	Total	**£40,960,768**	**£23,062,133**	**£116,294,864**
Overall Total		**£819,577,539**	**£619,934,130**	**£1,114,746,168**

There are a number of areas of uncertainty in this estimate, the greatest of which is the incidence of sepsis treated in hospital. We are also uncertain about the average lengths of stay in hospital of patients with sepsis who do not require treatment in ICU and it has been assumed that these cases are less severe and, therefore, require fewer hospital resources.

3.3.2 Post-Sepsis Complication Costs

Given the uncertainty in defining the hospital costs of treatment for sepsis, it is even more difficult to estimate the ongoing costs of sepsis following the acute phase. This is difficult for two principle reasons:

- Incidence rates are difficult to estimate accurately but prevalence rates are even less readily available. This makes it extremely difficult to estimate how many people in the UK are living with complications associated with sepsis;
- Even if prevalence rates were accurately recorded, it is also difficult to understand the extent to which people who have had sepsis require ongoing care for some time following their acute sepsis phase.

There are likely to be two types of costs associated with ongoing care following the acute phase of sepsis: costs of treatment of complications and the costs of routine follow up care. No evidence on the latter have been found during the literature review and so, in order to maintain a conservative approach to costing, no additional costs have been factored in for routine follow up of patients with sepsis.

For post-sepsis complications some evidence was obtained from the NCEPOD report which provided complication rates for sepsis patients who had been in ICU and who are discharged alive [3]. Of the estimated 43,027 adult patients in ICU with sepsis, it has been assumed that 13,812 will die before discharge, by applying evidence from the Shankar-Hari paper [12]. The NCEPOD report estimates that 21.5% of ICU sepsis patients discharged alive have some form of complication. This equates to 6,281 patients per year. Table 3.2 provides details of the complication rates and estimated annual numbers of patients with complications.

Table 3.2: Rates of complications in ICU patients post-sepsis

Complication	Rate (%)	Estimated no. patients with complications
Worsened physical function	53.5	3,361
Worsened cognitive state	19.7	1,237
Impaired kidney function	14.1	886
Post-sepsis syndrome	5.6	352
Wound problems	5.6	352
Chronic pain	12.7	798
Amputation	8.5	534
Tracheostomy	4.2	264
Post-traumatic stress disorder (PTSD)	9.9	622
Atrial fibrillation	4.2	264
Sepsis recurrence	2.8	176
Weight loss	2.8	176
Depression	2.8	176
Muscle weakness	2.8	176

It is not straightforward to estimate the ongoing costs of these complications because some of them relate to a number of complex conditions for which it is not possible to identify unit costs. Some of the complications are too vague, for example, ‘worsened physical function’ to allow a unit cost to be developed. This type of complication could require a variety of follow up interventions both in hospital and community settings from a range of different health professionals.

To ensure a conservative approach, therefore, only a small number of more specific complications have been costed (kidney function; amputation; PTSD; depression). In order to cost these complications, the estimated numbers of patients with a complication were multiplied by a suitable unit cost. One of the key limitations in this approach is a lack of data on the median survival of sepsis patients discharged with complications. In the absence of any values from literature, it is has been assumed that median survival for these patients could be five years, with a range from one year to ten years.

For impaired kidney function it can be assumed that patients will require treatment for chronic kidney disease (CKD) or renal failure. A paper by Kerr provides an estimate of the cost of CKD to the NHS in England, giving an average annual cost of £801 per patient [18]. Applied to the number of patients estimated to have renal problems following sepsis, the annual costs per year would be £709,509, with a five year cost of £3,547,544 and a ten year cost of £7,095,089.

The ongoing annual costs of amputation are reported in the NICE Type 2 diabetes guideline health economics appendix as £767 [19]. If those costs are applied to the number of patients estimated to have an amputation following sepsis, the annual costs per year would be £409,537, with a five year cost of £2,047,684 and a ten year cost of £4,095,368.

The NICE guideline on depression suggests an average cost of anti-depressant treatment of £481 (uprated from 2010 prices) [20]. If those costs are applied to the number of patients estimated to have depression following sepsis, the annual costs per year would be £84,595, with a five year cost of £422,977 and a ten year cost of £845,955.

The NICE guideline on PTSD suggests an average cost of PTSD treatment of £1,017 (uprated from 2005 prices) [21]. If those costs are applied to the number of patients estimated to have PTSD following sepsis, the annual costs per year would be £632,496, with a five year cost of £3,162,482 and a ten year cost of £6,324,965.

Table 3.3 summarises the potential costs of complications relating to sepsis. There are no data on the rates of post-sepsis complications for children so no estimates of those potential costs have been included.

Table 3.3: Estimates of costs of complications associated with sepsis

Complication	1-year cost	5-year cost	10-year cost
Impaired kidney function	£709,509	£3,547,544	£7,095,089
Amputation	£409,537	£2,047,684	£4,095,368
Depression	£84,595	£422,977	£845,955
PTSD	£632,496	£3,162,482	£6,324,965
Total	**£1,836,138**	**£9,180,688**	**£18,361,376**

3.4 INDIRECT COST ESTIMATES

3.4.1 Productivity Costs

Productivity costs were estimated both for in-hospital lost productivity to cover days lost while patients were hospitalised, and for lost productivity due to early mortality.

3.4.1.1 In-hospital lost productivity

Specifically, estimates for in-hospital lost productivity were generated by multiplying the incidence estimate of the number of adults of working age by average length of stay and average daily salary.

A total of 59,636 working age adults are estimated to be hospitalised due to sepsis each year. This was calculated by applying the proportion of adults aged under-65, observed in the study by Shankar-Hari (2016) to be 43.5%, to the total adult incidence of sepsis [12]. An average length of stay of 11.55 days was calculated by averaging the median total number of days of hospitalisation for ICU-admitted sepsis patients observed in Levy (2012) [16], and the assumed length of stay for sepsis patients not admitted to ICU, and weighted by the number of sepsis patients in each group. The average daily salary of £67.86 was calculated as the average UK weekly salary (excluding bonuses) divided by 7 as cited in the most recent Office of National Statistics (ONS) report [22].

The costs of lost in-hospital productivity, therefore, are estimated at £46,742,535 (59,636 x 11.55 x £67.86). This cost is conservative as it does not include lost productivity due to recovery and rehabilitation time at home following hospitalisation.

3.4.1.2 Mortality related lost productivity

Costs for lost productivity due to early mortality were summed for adults at working age and children. For adults at working age, the cost was estimated by adding the number of in-hospital and post-discharge mortalities in the working age population, and multiplying this figure by the average working years remaining and average yearly salary.

It was estimated that a total of 7,818 sepsis-related deaths occur in hospital each year in adults of working age. This is based on applying the mortality rate of 19.9% observed in this age group in Shankar Hari (2016) [12] to the estimate of the number of adults of working age in ICU with sepsis, plus a 10% mortality rate applied to the estimate of the number of adults of working age not admitted to ICU. A further 8,343 adults of working age were estimated to die post-discharge following sepsis, on the basis of applying the mortality rate of 16.1% observed in another study by Shankar-Hari et al. [23] to the number of adults at working age still living at discharge (i.e. the total minus in-hospital mortality). This sums to a total of 16,161 sepsis-related deaths in adults of working age.

The average number of working years remaining was calculated by finding the difference between the average age at death within the working-age adult population with sepsis and retirement age (65 years). The average age at death within the working-age adult population was estimated at 56.89 years, resulting in an average of 8.11 working years remaining. This estimate of age at death was calculated from categorical data included in the NCEPOD sepsis report [3] by generating an average using the central number presented within each age category (e.g. 25 for the age group 21-30) as the average age, and weighting it by the number of deaths in each age category up to retirement age.

An alternative source of data collected in the USA [24] and estimated using the same technique suggested an average age at death from sepsis of 51.94, which would result in an average of 13.06 working years remaining. The average yearly salary of £24,768 was estimated by multiplying the average UK weekly salary (excluding bonuses) as cited in the most recent ONS report [22], by 52.

It was assumed that for all children who died as a result of sepsis, a full lifetime of productivity would be lost, estimated at 47 years (the years between 18 and 65). Therefore, the sum of total number of paediatric in-hospital and post-discharge sepsis-related deaths was multiplied by the average yearly salary and 47 years. It was estimated that a total of 2,988 children die each year as a result of sepsis. This includes an estimated 785 children admitted to PICU, applying the mortality rate of 25% observed in Weiss (2015) [13], to the estimated number of children admitted to PICU with sepsis, as well as an estimated 857 children not admitted to PICU, applying a 12.5% mortality rate to the estimated number of children with sepsis not admitted to PICU. This is based on the range of mortality rates for non-severe sepsis reported in Martin et al. (2012) [25]. In addition, the post-discharge mortality rate of 16.1% observed in adult ICU populations in Shankar-Hari [23] was applied to the number of children living at discharge, to generate an estimate of a further 1,346 paediatric deaths.

Costs resulting from lost-productivity relating to early mortality were, therefore, estimated at £3,245,611,260 for adults (16,161 x 8.11 x £24,768), and £3,478,487,805 for children (2,988 x 47 x £24,768), totalling £6,724,099,065. As has been noted, there is some uncertainty as to the average age at death from sepsis within the working age adult population. Using the alternative estimate of 51.94 years, this increases the adult productivity loss to £5,225,884,241(16,161 x 13.06 x £24,768), and the total to £8,704,372,046.

These two types of productivity loss combine to produce an estimate of total productivity loss between £6,771 million and £8,751 million annually. Table 3.4 summarises these estimates.

Table 3.4: Estimated annual lost productivity due to sepsis

Patient types	Productivity lost	Estimated annual cost (low)	Estimated annual cost (high)
Adults	In-hospital	£46,742,535	£46,742,535
	Mortality (low)	£3,245,611,260	
	Mortality (high)		£5,225,884,241
Children	Mortality	£3,478,487,805	£3,478,487,805
Overall total		**£6,770,841,600**	**£8,751,114,580**

3.4.2 Litigation

Costs of litigation were estimated by multiplying the average litigation cost by the number of litigation cases. The average litigation cost of £21,806 was estimated as the median value observed in litigation cases in the domain of 'infection' reported in Pascall (2015) [26]. No data were identified that were specific to sepsis litigation nor were there any records of the proportion of people with sepsis who claim damages as a result. An assumption was made that the number of litigation costs could be 5% of the total number of cases of sepsis in the UK each year, totalling 7,350. The estimated costs of litigation would, therefore, be £21,806 x 7,350 = £160,274,100.

Applying alternative value to the rates of litigation cases would result in a lower cost of £32,054,830 (1%) and a higher cost of £320,548,200 (10%).

3.4.3 Total Indirect Costs

Including both lost productivity and litigation costs, we estimate the indirect costs associated with sepsis to be between £6,931,115,700 and £9,071,628,566. These costs do not include more difficult to measure indirect costs, such as those resulting from 'presenteeism' productivity losses after return to work, absenteeism for post-discharge follow-up treatments, or lost productivity of informal carers who need to give up work to look after relatives.

3.5 POTENTIAL IMPACT OF IMPROVEMENTS IN CARE FOR SEPSIS

The estimated costs of sepsis each year in the UK are £7.76 billion, including approximately £830 million of direct costs. Applying sensitivity analysis to these costs (higher hospital costs and lower estimate of average age of death from sepsis for adults of working age) would give an estimated annual cost of more than £10 billion, including more than £1.1 billion of direct costs. Table 3.5 summarises the estimated costs.

Table 3.5: Summary of estimated costs of sepsis (using estimated incidence of 147,000 per year)

		Base case	Low estimate	High estimate
Direct costs	Hospital costs	£819,577,538	£619,934,130	£1,114,746,168
	Complications	£9,180,688	£1,836,138	£18,361,376
	Total	**£828,758,227**	**£621,770,267**	**£1,133,107,544**
Indirect costs	Productivity	£6,770,841,600	£6,770,841,600	£8,751,080,366
	Litigation	£160,274,100	£32,054,830	£320,548,200
	Total	**£6,931,115,700**	**£6,802,896,430**	**£9,071,628,566**
GRAND TOTAL		**£7,759,873,926**	**£7,424,666,697**	**£10,204,736,110**

The review of literature and existing UK data on sepsis for this study draws similar conclusions to the NICE GDG opinion, i.e. that the modelling of cost improvements in relation to changes in sepsis care cannot be done robustly. The lack of clarity about the numbers of patients with sepsis, their disease trajectory and their care pathways mean that it is impossible to provide definitive estimates of changes in costs as a result of improvements in care.

There are, however, two ways of demonstrating the potential for cost improvements through better sepsis care: by examining the numbers of bed days that could potentially be reduced if the number of sepsis admissions was reduced, and by examining the impact on productivity costs if mortality rates were reduced.

If the overall number of admissions for sepsis were reduced by 10%, 20% or 30% due to improvements in care, then the potential annual cost savings to the NHS would be £83 million, £166 million or £249 million respectively. This would also have the effect of reducing lost productivity amongst working age adults.

If rates of mortality could be reduced by similar proportions, then there is potential for improvements in annual productivity of £672 million, £1,345 million or £2,017 million.

Another source of avoidable mortality arises from reducing avoidable sepsis deterioration in hospital.[27] This has not been quantified in this report but could also contribute to significant cost reduction through better management of sepsis.

3.6 SCENARIO ANALYSIS

There is considerable uncertainty around the incidence data for sepsis in the UK. Ongoing research into HES data by an independent group of data analysts has examined the codes directly consistent with a clinical diagnosis of sepsis (A41.0; A41.5; A41.9; R57.2; P36.9) for 2015/16. Unpublished results indicate 218,255 coded episodes of sepsis in England for that year. Extrapolated to the rest of the UK, assuming similar incidence in the other countries, the annual incidence of sepsis in the UK may be as high as 260,000.

This estimate exceeds the estimate made in a US epidemiological study which placed the incidence of sepsis at 300 episodes per 100,000 population per annum [28]. However, it is consistent with the incidence of sepsis reported in a Spanish multi-centre study which gave an incidence of 367 cases per 100,000 population [29].

Applying this level of incidence would increase the estimated costs of sepsis to £11.25 billion per year, with direct costs of almost £1.5 billion. Applying the same sensitivity analysis to these costs would give a higher estimate of £15.63 billion, with almost £2 billion of direct costs relating to sepsis every year (Table 3.6).

Table 3.6: Summary of estimated costs of sepsis (using estimated incidence of 260,000 per year)

		Base case	Low estimate	High estimate
Direct costs	Hospital costs	£1,461,794,291	£1,112,244,609	£1,938,286,295
	Complications	£16,753,080	£3,350,616	£33,506,161
	Total	**£1,478,547,371**	**£1,115,595,225**	**£1,971,792,456**
Indirect costs	Productivity	£9,486,432,686	£9,486,432,686	£13,100,069,511
	Litigation	£283,478,000	£56,695,600	£556,956,000
	Total	**£9,769,910,686**	**£9,543,128,286**	**£13,657,025,511**
GRAND TOTAL		**£11,248,458,057**	**£10,658,723,511**	**£15,628,817,967**

This is almost certainly an under-estimate because no change was made to the level of incidence of sepsis in children (10,000). If sepsis incidence in children is higher, then the estimated costs of lost productivity would increase considerably.

For the base case scenario for this higher level of incidence, if the overall number of admissions for sepsis were reduced by 10%, 20% or 30% due to improvements in care, then the potential annual cost savings to the NHS would be £148 million, £296 million or £444 million respectively. This would also have the effect of reducing lost productivity amongst working age adults. If rates of mortality could be reduced by similar proportions, then there is potential for improvements in annual productivity of £940 million, £1,880 million or £2,820 million.

Section 4: Discussion

4.1 SUMMARY

This paper outlines the estimated costs for care of sepsis in the UK, including both direct hospital treatment costs for sepsis recovery and associated complications, as well as indirect costs of lost productivity and litigation. There are heavy caveats on the reported results due to significant missing data and a lack of clarity around the incidence, prevalence and patient pathways for sepsis in the UK.

With these limitations in mind, our calculations suggest that the estimated annual cost of sepsis in the UK is around £7.42 billion at the most conservative end of the spectrum, and may be as high as £10.2 billion. These figures comprise roughly 10% direct treatment costs, and 90% indirect costs.

The base case indicated an overall cost of £7.76 billion, made up of direct costs to the NHS of £830 million and indirect costs of £6.93 billion. The lack of clarity on incidence, prevalence and care pathways for sepsis mean that it is difficult to provide an estimate of the potential cost reduction that could accrue from improved care but a simple calculation shows that a 10% reduction in cases of sepsis would potentially save £83 million of hospital care costs and a 10% reduction in mortality would improve productivity by £672 million.

It should be noted that the data used to calculate these figures were derived from a variety of sources. This included recent UK population studies but where gaps in the literature were identified, older, or non-UK-based data were used, and in some cases where no alternative was available, assumptions have been used.

4.2 STUDY LIMITATIONS

There are some significant methodological limitations to this study. Attention to specific points has been drawn in the Estimated Costs section and this section explores more general limitations that affect the estimates calculated.

Incidence rates of specific subgroups affect the calculation of all of the costs included in this study. However, incidence rates have had to be extrapolated on the basis of proportions observed in small studies and applied to the total estimated number of people who contract sepsis in the UK each year. Where proportionate estimates were not identified from the literature, proxies from different subgroups have been used, for example, the late mortality rate observed in a study of adult ICU patients was applied to children. While every effort has been made to check the appropriateness of such proxies, they may result in inaccurate estimates of subgroup totals, which would have knock-on impacts for subsequent cost calculations.

It is also important to note that the lack of data and evidence meant it was not possible to generate costs for all of the patient subgroups that had been originally planned. In particular, the study team is aware that there are specific issues in relation to neonates and sepsis but there is an absence of data in the numbers of babies affected. The methodology has had, therefore, to adopt a cruder split between adults and children.

Finding data was particularly problematic for many of the model inputs (e.g. length of stay, mortality and rates of complications) relating to sepsis patients who were not admitted to ICU, as many of the literature sources identified included only patients who were admitted to ICU. Given the discrepancy in the total number of patients in the UK thought to be affected by sepsis each year and the number admitted to ICU for sepsis, this indicates roughly two thirds of adults with sepsis are treated exclusively outside of ICU. While it may be the case that patients not transferred to ICU are less severe, observations such as that in Esteban et al. (2007) [30] which reported that in three hospitals in Madrid, only one third of severe sepsis patients were transferred to ICU, appear to contradict this theory. The lack of data indicates a need for improved reporting of sepsis cases outside of the ICU in order to accurately assess the costs for this subgroup.

Costs for hospital treatment for the initial sepsis episode are not sepsis specific, and instead use the average daily cost of treatment on either ICU, or general wards. Costs of sepsis care on both ICU and general wards are likely to vary extensively for different patients, depending on various indicators of severity such as the number of organs that require support, the necessity to perform amputations, or the presence of septic shock. Due to the absence of data with the required level of detail, and using a conservative approach, average ICU and general ward costs were considered the most appropriate metrics for these estimates. It is worth noting that NHS Reference Costs are lower than US reported costs, partly because US costs relate to reported insurance costs. This is important as direct cost estimates of sepsis in the UK have tended to rely on reported US costs.

A number of costs that would be attributable to sepsis were not considered estimable given the current data identified and have, therefore, not been included. For example, no costs of continued drug treatment following hospital discharge have been included and there was no estimate made of the cost of complications associated with children with sepsis. These costs are likely to be significant, potentially up to £3-4 million per child.[31] Similarly, no costs were included in relation to productivity losses from absence due to at-home recovery time, absence due to follow-up, absence of informal carers (e.g. relatives), as well as ‘presenteeism’ whereby patients returning to work are less productive due to ongoing problems. This is primarily due to an absence of either baseline data on incidence or prevalence, or a lack of evidence in the literature.

4.3 CONCLUSIONS

In conclusion, despite its limitations, this study has estimated the costs of sepsis care are significant, both in terms of direct costs to the NHS and particularly in relation to productivity costs because of high levels of early mortality associated with sepsis. Improvements in care that could reduce either the incidence of sepsis or mortality associated with sepsis could result in significant cost-savings, as well as obvious quality of life benefits.

The variety of sources required to populate this model and number of assumptions it was necessary to make in order to fill data gaps are indicative of the paucity of information available regarding sepsis care in the UK. This report synthesised the best available data, reports a range of scenarios around uncertain parameters and sought advice from key opinion leaders in its formation. Nevertheless it is likely that the costs, particularly the direct costs, are under-estimated. It is possible that costs are over-estimated, but given the absence of features within the model that we are aware would have cost implications, but which were not considered estimable, such as lost productivity for informal carers, or for follow-up treatment, it is thought that this is unlikely.

Better quality data and an improved understanding of the disease trajectory for sepsis would undoubtedly improve the quality of the costs estimates. It would also enable more useful analyses to be carried out of the cost effectiveness of particular interventions to improve sepsis care.

It is understood that there are initiatives underway to improve the recording of sepsis and clinical coding in hospitals. There is the potential to go further than this and to establish a disease registry for sepsis. This would capture accurate data on the sub-populations with sepsis as well as providing an understanding of the disease trajectory and care pathways for different types of patient.

4.4 RECOMMENDATIONS

NHS Hospital Trusts in England should adopt new directives on clinical coding for sepsis and these should also be rolled out to the rest of the UK.

If clinical coding can be improved there may be a possibility of carrying out more robust cost burden analysis using more precise figures in two to three years' time.

In line with recommendations made by the NICE sepsis Guideline Development Group, The Department of Health or NHS England should consider establishing, or commissioning the establishment of some form of sepsis registry to capture key metrics on people with sepsis.

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APPENDIX A

Search Strategy for Ovid MEDLINE

Search strategy for Ovid MEDLINE

1	exp Systemic Inflammatory Response Syndrome/ (116450)
2	(sepsis$ or septic$ or sepses or postsepsis$ or postseptic$).ti,ab,kf. (132800)
3	(pyoh?emi$ or py?emi$).ti,ab,kf. (223)
4	Bacterial Infections/ and bl.fs. (4901)
5	blood-borne pathogens/ (3021)
6	((blood or bloodstream) adj3 (poison$ or pathogen$)).ti,ab,kf. (2997)
7	(systemic inflammatory response syndrome$ or SIRS).ti,ab,kf. (6738)
8	(bacter?emi$ or bacill?emi$).ti,ab,kf. (29517)
9	Lemierre Syndrome/ (205)
10	(lemierre$ or necrobacillos$).ti,ab,kf. (812)
11	(fusobacterium adj2 necrophorum).ti,ab,kf. (850)
12	exp Neisseria meningitidis/ (9436)
13	(neisseria adj2 meningitid$).ti,ab,kf. (7985)
14	meningococc?emi$.ti,ab,kf. (812)
15	urosepsis$.ti,ab,kf. (1010)
16	(fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$).ti,ab,kf. (32081)
17	endotox?emi$.ti,ab,kf. (8975)
18	((bacterial or endotoxi$ or toxi$) adj3 shock$).ti,ab,kf. (10185)
19	toxic forward failure$.ti,ab,kf. (0)
20	Staphylococcal Infections/ and Methicillin-Resistant Staphylococcus aureus/ (7205)
21	(methicillin resistant staphylococcus aureus infection$ or MRSA infection$).ti,ab,kf. (4130)
22	or/1-21 (264843)
23	Economics/ (28596)
24	exp "costs and cost analysis"/ (217017)
25	Economics, Dental/ (1917)
26	exp economics, hospital/ (23030)
27	Economics, Medical/ (9389)
28	Economics, Nursing/ (4000)
29	Economics, Pharmaceutical/ (2804)
30	(economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab,kf. (654020)
31	(expenditure$ not energy).ti,ab,kf. (25117)
32	value for money.ti,ab,kf. (1372)
33	budget$.ti,ab,kf. (24771)
34	or/23-33 (787687)
35	((energy or oxygen) adj cost).ti,ab,kf. (3661)
36	(metabolic adj cost).ti,ab,kf. (1211)
37	((energy or oxygen) adj expenditure).ti,ab,kf. (23003)
38	or/35-37 (26942)
39	34 not 38 (781715)
40	exp Budgets/ (13597)
41	exp models, economic/ (13060)
42	"Value of Life"/ (5942)
43	ec.fs. (399092)
44	Income/ (26755)
45	Remuneration/ (200)
46	"Salaries and Fringe Benefits"/ (15231)
47	exp "Fees and Charges"/ (30222)
48	(expens$ or earning$ or salar$ or wage$1 or pay or pays or paid or paying or payment$1 or income$1 or remunerat$ or financ$ or money or monetary or fee or fees or charg$).ti,ab,kf. (595152)
49	or/39-48 (1401476)
50	exp Great Britain/ (362414)
51	(national health service* or nhs*).ti,ab,in. (143510)
52	(english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab. (30429)
53	(gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in. (1827760)

54	(bath or "bath's" or ((birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachusetts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in. (1191312)
55	(bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's" or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in. (44313)
56	(aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in. (172310)
57	(armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in. (20379)
58	or/50-57 (2305365)
59	(exp africa/ or exp americas/ or exp antarctic regions/ or exp arctic regions/ or exp asia/ or exp australia/ or exp oceania/) not (exp great britain/ or europe/) (2656726)
60	58 not 59 (2211953)
61	22 and 49 and 60 (1128)
62	exp animals/ not humans/ (4669484)
63	(news or comment or editorial or letter or case reports).pt. or case report.ti. (3521168)
64	61 not (62 or 63) (969)
65	limit 64 to (english language and yr="2007 -Current") (629)
66	remove duplicates from 65 (545)
Key to Ovid symbols and commands	
$	Unlimited right-hand truncation symbol
*	Unlimited right-hand truncation symbol
$N	Limited right-hand truncation - restricts the number of characters following the word to N
?	Wildcard symbol wild card character stands for zero or one characters within a word or at the end of a word
ti,ab,kf.	Searches are restricted to the Title, Abstract, or Keyword Heading Word fields
adjN	Retrieves records that contain terms (in any order) within a specified number (N) of words of each other
/	Searches are restricted to the Subject Heading field
exp	The subject heading is exploded
pt.	Search is restricted to the publication type field
or/1-21	Combines sets 1 to 21 using OR

APPENDIX B

Narrative Synthesis of Eligible Studies in the Burden of Illness Review

Narrative synthesis of eligible studies

Andersson is a conference abstract reporting the findings of a costing study of septic shock in 2012-2013 in England, Wales and Northern Ireland. The total cost was reported as around £293.2 million.

This comprised critical care (£1,044 per day per patient for 7.6 days totalling £175.2 million), admission to post-unit discharge location (£240 per day per patient for 23.3 days totalling about £80.9 million), renal support (£285 per day per person for 5.4 days totalling £6.8 million) and advanced respiratory support (£285 per day per patient for 7.7 days totalling £30.3 million).

Chin is a cost analysis study aiming to determine whether significant bacteraemia is an appropriate marker for sepsis and to assess how accurately patients with sepsis are coded and the financial implications where there is miscoding. Of 54 patients studied in June 2015, 50 were retroactively defined as having sepsis, severe sepsis or septic shock which meant the hospital had an underpayment of £20,779.

Marlow reports 2-year outcomes from a RCT of prophylaxis with granulocyte-macrophage colony-stimulating factor (GM-CSF) in very preterm small-for-gestational age (SGA) babies with neonatal sepsis.

Mean hospital health and social care costs (2007-2008) ranged from £50,464 to £56,339. Mean follow-up care costs (hospital inpatient and outpatient service use, surgeries performed, investigative tests, medications and community health and social care resource use) was reported for 0-6 months (range £3,771 to £5,321), 6-12 months (£2,349 to £2,698), 12-18 months (£1,837 to £1,948) and 18-24 months (£1,753 to £1,963).

Mouncey was a cost effectiveness analysis assessing the effectiveness of the 6-hour early goal-directed therapy (EGDT) resuscitation protocol for patients with early septic shock, in England. It reports a range of 2012 hospital costs, including summary costs for monitoring and consumables, blood products, drugs, staff time, emergency department admission, critical care unit admission, general medical beds and re-admission costs. It also provided unit costs for numerous items within each of these mostly sourced from NHS reference costs, PSSRU or the BNF.

Total costs for up to 90 days ranged from £11,424 to £12,414, and mostly comprised of critical care unit and general medical bed costs, as well as in-hospital, outpatient and community costs.

Soares was a Health Technology Assessment which conducted a review of cost effectiveness studies for intravenous immunoglobulin (IVIG) in sepsis (severe sepsis and septic shock). IVIG cost £54,901 and standard care was £45,593. Cost input parameters were also reported.

Zia Sadique was a cost effectiveness analysis assessing the effectiveness of Drotrecogin alfa in routine practice for adult patients with severe sepsis and multiple organ systems failure. Its effectiveness data is from England, Wales and Northern Ireland and it reports a range of 2010-2011 hospital costs, including for drug, ICU, bed and readmission costs, both for the intervention and control groups. It also reports data by number of organ systems failing ('2', '3 to 5' or '2 to 5').

Overall, lifetime costs for patients with 2 to 5 organ systems failing were £36,048 for the intervention group and £18,432 for the control group. ICU costs ranged from £8,806 to £22,853. Hospital costs ranged from £3,967 to £5,933. ICU readmission costs ranged from £914 to £2,152. Hospital readmission costs ranged from £1,652 to £2,823.

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APPENDIX C

Results of Pragmatic Searches

Incidence

The Sepsis Trust reports incidence of sepsis for 2013/14 as being just under 123,000 for England. This appears to correspond with Hospital Episode Statistics (HES) data from NHS Digital that shows a total of 122,822 finished discharge episodes (FDE) for the year. The data from NHS Digital also provide the rate of growth in incidence of sepsis over the previous five years. These data could be used to extrapolate incidence of sepsis across the rest of the UK using population statistics.

The data include many different ICD10 codes for sepsis but these are not differentiated:

- A02.1 Salmonella sepsis;
- A20.7 Septicaemic plague;
- A21.7 Generalized tularaemia;
- A22.7 Anthrax sepsis;
- A26.7 Erysipelothrix sepsis;
- A28.0 Pasteurellosis;
- A28.2 Extraintestinal yersiniosis;
- A32.7 Listerial sepsis;
- A39.2 Acute meningococcaemia;
- A39.3 Chronic meningococcaemia;
- A39.4 Meningococcaemia, unspecified;
- A40.- Streptococcal sepsis;
- A41.- Other sepsis;
- A42.7 Actinomycotic sepsis;
- B37.7 Candidal sepsis;
- O85.X Puerperal sepsis;
- P36.- Bacterial sepsis of newborn.

There is potential for under-reporting of sepsis in HES data due to poor recording of sepsis in patient records and miscoding. YHEC will, therefore, vary the rates of estimated sepsis to demonstrate the impact if the rate of sepsis is higher than reported. We have also sourced other data on incidence, including papers such as *Hall* (2011) and *Martin* (2012). We will use these papers to calculate an estimate of the incidence of sepsis in the UK population based on reported rates of sepsis and population data.

Mortality rates are also reported by The Sepsis Trust, derived from a 2015 paper by NCEPOD, which gives a mortality rate of 30%. *Martin* (2012) also provides data on mortality rates. We will need to use these data to estimate the numbers of people with sepsis who die each year. Depending on whether the data are differentiated we may be able to provide some granularity to the estimates, i.e. whether there are different rates of incidence and mortality in different patient populations (neonates, children, adults).

Given the apparent levels of uncertainty in the data and evidence, it will be important to use a range of incidence and mortality estimates.

Longer-term complications

We have found some studies that refer to longer term complications and disability as a result of sepsis. The Sepsis Trust refer to:

- Post-sepsis syndrome (PSS) defined as the "group of long term problems that some patients who have experienced severe sepsis can suffer during their rehabilitation period". The website identifies the following potential long term consequences, as part of PSS: lethargy, muscle weakness, swollen limbs or joint pain, chest pain or breathlessness, insomnia, hair loss, dry/flaking skin and nails, changes in taste, vision and limb sensation, poor appetite, post-sepsis syndrome and repeated infections;
- Potential psychological consequences: anxiety or fear, depression, flashbacks, nightmares, insomnia, post-traumatic stress disorder (PTSD) and poor concentration or short-term memory loss;
- Problems with organs: kidneys, heart, brain, lungs;
- A small percentage of people suffer recurring infection: either a mild version of original sepsis, or infection in different area of the body. Antibiotics are the usual the treatment.

Iwashyna (2012): Population burden of long-term survivorship after severe sepsis in older Americans is a US study of adults age 65+. Around three quarters had functional disability and around one-sixth had moderate to severe cognitive impairment. No costs were applied.

Boer (2008): Factors associated with post-traumatic stress symptoms in a prospective cohort of patients after abdominal sepsis: a nomogram. Dutch study of survivors of abdominal sepsis (for at least 12 months). 28% of patients have moderate PTSD symptom scores and 10% have high scores.

Lopes (2010): Research article Long-term risk of mortality after acute kidney injury in patients with sepsis: a contemporary analysis. Portuguese study of 454 patients, excluding renal transplant and chronic kidney disease patients.

Prescott (2016): Late mortality after sepsis: propensity matched cohort study. US study of mortality after sepsis (i.e. after discharge) - absolute increase in late mortality compared to: adults not in hospital (22.1%), patients admitted with non-sepsis infection (10.4%), and patients admitted with sterile inflammatory conditions (16.2%). Mortality remained higher for at least 2 years relative to adults not in hospital.

Davydow (2012): Depressive symptoms in spouses of older patients with severe sepsis. US study showing the prevalence of substantial depressive symptoms in wives and husbands of patients with severe sepsis increased at the time of severe sepsis. The increase in depression was not explained by bereavement.

Indirect costs

We have found one review that refers to indirect costs and a number of other studies that may also be useful.

Tiru, B., et al. (2015). "The Economic and Humanistic Burden of Severe Sepsis." This was a review of the burden of severe sepsis, including costs. It reported initial inpatient costs represent only 30% of the total cost and are related to severity and length of stay, whereas lost productivity and other indirect medical costs following hospitalization account for the majority of the economic burden of sepsis. Indirect costs were broken down by: productivity loss (absenteeism, mortality and early retirement) and healthcare expenditure (after hospital discharge). The paper cites two studies, one German and one Swiss and then extrapolates these to estimate a USA cost.

On healthcare expenditure the paper reported that most costs occur after hospital discharge and that these mostly are accounted for by subsequent admissions. Survivors of severe sepsis spent nine more days in a health care facility in the following year, compared with survivors of non-sepsis hospitalisations. Only 20% of severe sepsis survivors were not hospitalised in the following year.

Chalupka, A. N. and D. Talmor (2012). "The economics of sepsis." The study is not available freely but its abstract says that it reviews costs of sepsis and its management in the US, including "indirect costs of the burden of illness imposed by sepsis".

Schmid A, et al. (2004). "Burden of illness imposed by severe sepsis in Switzerland." This is the same Swiss study referenced by Tiru.

Burchardi and Schneider (2004). "Economic aspects of severe sepsis: a review of intensive care unit costs, cost of illness and cost effectiveness of therapy." This paper is also not freely available, but it seconds the estimate in the Tiru paper in the abstract, stating that direct costs make up only 20-30% of the total cost of illness from severe sepsis, with the biggest contributor being lost productivity due to early mortality.

Other costs

We have found no specific evidence on the costs of litigation in relation to sepsis.

In relation to sepsis in neonates, we have found a number of potentially useful papers.

Wolfler (2008). "Incidence of and mortality due to sepsis, severe sepsis and septic shock in Italian Pediatric Intensive Care Units: a prospective national survey". Italian study based on children in ICU, which is stratified by sepsis, severe sepsis and septic shock. Of 320 children with sepsis-related diagnosis, 216 were allocated to sepsis, 45 to severe and 59 to septic shock. It also provides mortality data by each group.

Hartman (2013). “Trends in the Epidemiology of Pediatric Severe Sepsis”. The full text was not available, but the abstract gives a paediatric rate of sepsis for USA as 0.89 cases per 1,000 population in 2005. Between 1995 and 2005, severe sepsis in newborns doubled from 4.5 to 9.7 cases per 1,000 births. In non-newborn infants there are 2.25 cases per 1,000, and the rate is 0.23-0.52 per 1,000 in children 1-19 years of age.

SPROUT Study, Weiss (2015). “Global Epidemiology of Pediatric Severe Sepsis: The Sepsis Prevalence, Outcomes, and Therapies Study”. This is a large multinational study showing the prevalence of severe sepsis in paediatric ICU is 8.2%. Mortality was 25% and did not differ by age.

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