Differences in reported sepsis incidence according to study design: a literature review

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Abstract

Background: Sepsis and severe sepsis are common conditions in hospital settings, and are associated with high rates of morbidity and mortality, but reported incidences vary considerably. In this literature review, we describe the variation in reported population-based incidences of sepsis and severe sepsis. We also examine methodological and demographic differences between studies that may explain this variation.

Methods: We carried out a literature review searching three major databases and reference lists of relevant articles, to identify all original studies reporting the incidence of sepsis or severe sepsis in the general population. Two authors independently assessed all articles, and the final decision to exclude an article was reached by consensus. We extracted data according to predetermined variables, including study country, sepsis definition, and data source. We then calculated descriptive statistics for the reported incidences of sepsis and severe sepsis. The studies were classified according to the method used to identify cases of sepsis or severe sepsis: chart-based (i.e. review of patient charts) or code-based (i.e. predetermined International Classification of Diseases [ICD] codes).

Results: Among 482 articles initially screened, we identified 23 primary publications reporting incidence of sepsis and/or severe sepsis in the general population. The reported incidences ranged from 74 to 1180 per 100,000 person-years and 3 to 1074 per 100,000 person-years for sepsis and severe sepsis, respectively. Most chart-based studies used the Bone criteria (or a modification hereof) and Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study criteria to identify cases of sepsis and severe sepsis. Most code-based studies used ICD-9 codes, but the number of codes used ranged from 1 to more than 1200. We found that the incidence varied according to how sepsis was identified (chart-based vs. code-based), calendar year, data source, and world region.

Conclusion: The reported incidences of sepsis and severe sepsis in the general population varied greatly between studies. Such differences may be attributable to differences in the methods used to collect the data, the study period, or the world region where the study was undertaken. This finding highlights the importance of standardised definitions and acquisition of data regarding sepsis and severe sepsis.

Keywords: Sepsis, Severe sepsis, SIRS, Septicaemia, Method, Incidence, Epidemiology, Review

Background

Sepsis is associated with high rates of morbidity and mortality, accounting for as much as one of every two to three in-hospital deaths [1]. Notably, the mortality rates of sepsis increased during the last decade, which is in contrast to the declining rates of all other major causes of death in the US [2].

Determining the incidence of sepsis is of great interest to both clinicians and public health officials, in order to quantify the burden of the disease [3]. However, estimation of sepsis incidence is difficult, as it depends on the definition of sepsis, the method used to assess the condition, and the underlying population. Until 1992, no consensus existed on the terminology used to describe the presence and severity of sepsis, impairing comparison of studies on sepsis incidence and therapy outcomes [4]. The 1991 American College of Chest Physicians/Society
of Critical Care Medicine (ACCP/SCCM) Consensus Conference addressed this issue, with the aim to create a set of criteria for identifying and assessing the severity of sepsis [5]. The consensus proposal included an introduction of the systemic inflammatory response syndrome (SIRS) criteria for early identification of sepsis, defining sepsis as 2 SIRS criteria in patients with known or suspected infection, and severe sepsis as sepsis associated with organ dysfunction, hypoperfusion, or hypotension (Table 1). Though repeatedly criticised for being too sensitive [6, 7] and of questionable prognostic value [8–10] these easily applied “Bone criteria” remained the clinical standard in many hospital guidelines even after the introduction of internationally agreed-upon, but more comprehensive, criteria [6, 11, 12]. In 2016 the definition of sepsis was updated to categorise sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection (by The Third International Consensus Definitions for Sepsis and Septic Shock) [13].

In this review, we focus on the variation in reported incidences of sepsis and severe sepsis in the general population, and discuss the potential explanations including the use of different definitions or methods to assess sepsis.

Methods

Literature search and study selection

We included original studies with incidences of sepsis or severe sepsis in the general population (in person-years) as an outcome, published before 2016. Consequently, we excluded studies focusing on a specific subgroup of patients (e.g. neonatal sepsis, sepsis caused by a specific microbial agent), as these studies would include only a fraction of the general population as their study population. The number of excluded studies and reasons for exclusion are described in Fig. 1.

We searched PubMed (search string (((“Sepsis/epidemiology” [Mesh]) AND (“sepsis” [Title OR “septicaemia” [Title]]) AND “incidence” [Title/Abstract]) AND “english” [Language]), EMBASE (search string ‘sepsis/exp OR ‘sepsis’ AND (‘epidemiology’/exp OR ‘epidemiology’ OR ‘incidence’/exp OR ‘incidence’) AND [english]/lim) and Cochrane Library (search string #1: MeSH descriptor: Sepsis explode all trees and with qualifier(s): [Epidemiology – EP] + #2: (“sepsis”:ti or “septicaemia:ti”) + #3: “incidence”:ti,ab).

The title and abstract of the resulting articles were screened and categorised according to predefined criteria if excluded (see section Availability of data and materials). All included articles – along with additional articles found in reference lists – were retrieved, read in full and excluded according to the same criteria (see Fig. 1). Two authors (SEM and AHE) performed all rounds independently; the final decision to exclude an article was reached by consensus.

Data were extracted from each study according to a predetermined list of variables (see section Availability of data and materials). If a study reported several incidences – e.g. for different years or applying different methodologies – each incidence measure was registered as an observation. We adapted a widely used terminology to categorise the studies according to method used to identify sepsis or severe sepsis: 1. “chart-based” including studies that identified patients by review of patient charts and 2. “code-based” including studies that identified patients using diagnostic codes [3, 14–16]. To examine regional differences in incidence of sepsis and severe sepsis each study was categorised according to World Bank region [17].

Data management and descriptive statistics were performed using R [18]. In order to examine the heterogeneity that gives rise to the differences in incidence as well as possible interactions, we produced a number of box-plots based on crude data to allow for a visual evaluation of some of the factors that influence the reported incidence. Further, we present detailed tables that allow the reader to compare the included studies. The data set, along with the R-code and codebook, are freely available (see section Availability of data and materials).

International Classification of Diseases (ICD)

In the code-based studies, ICD codes were used to identify cases from discharge databases without specific information on physiological parameters. Implementation of the tenth revision of the ICD coding system (ICD-10) started in 1994 [19], but actual implementation dates vary among countries and was finally completed in the US as of October 1, 2015 [20]. Consequently, ICD-10 data was used in only two studies [21, 22]. A table with the full lists of specific sepsis codes in the ICD-9 and ICD-10 coding systems are provided as an additional file (see Additional file 1).

Below is a brief summary of the development of the guidelines used; Table 1 offers a detailed comparison of sepsis, severe sepsis, septic shock and multiple organ dysfunction syndrome.

The 1991 ACCP/SCCM Consensus Conference guidelines

In 1992 Bone et al. proposed a standardised definition of sepsis [5]. This included an introduction of the four SIRS criteria: 1. Temperature >38 °C or <36 °C; 2. heart rate >90 beats per minute; 3. respiratory rate >20 breaths per minute or PaCO2 <32 mmHg; and 4. white blood cell count >12,000/cu mm, <4,000/cu mm, or >10 % immature (band) forms. According to this, systemic inflammatory response syndrome (SIRS) was defined as at least two SIRS criteria, and sepsis was defined as (suspected) infection and at least two SIRS criteria. In addition it was suggested that use of the term “septicaemia” should
| Sepsis definition | Bone et al., 1992 (Sepsis-1) | Levy et al., 2003 (Sepsis-2) | Dellinger et al., 2013 | Singer et al., 2016 (Sepsis-3) |
|-------------------|-------------------------------|-----------------------------|------------------------|-------------------------------|
|                    | Infection, documented or suspected, and at least 2 of the following (SIRS criteria): | Infection, documented or suspected, and some of the following: | Suspected or documented infection and an acute increase of ≥2 SOFA points (a proxy for organ dysfunction) |
| General parameters | Core temperature | >38°C or <36°C | >38.3°C or <36°C | – |
|                   | Heart rate | >90 bpm | >90 bpm or >2 SD above the normal value for age | – |
|                   | Tachypnea | >20 breaths per minute or PaCO₂ <32 mmHg | No specification | – |
|                   | Mental status | – | Altered mental status | – |
|                   | Significant edema or positive fluid balance | – | >20 mL/kg over 24 hrs | – |
|                   | Hyperglycemia in the absence of diabetes | – | Plasma glucose >120 mg/dL or >7.7 mM/L | – |
|                   | Inflammatory parameters | White blood cell count | >12,000/cu mm (leukocytosis) or <4,000/cu mm (leukopenia) or >10% immature (bands) forms | – |
|                   | | Plasma C reactive protein | – | Normal white blood cell count with >10% immature forms |
|                   | | Plasma procalcitonin | – | >2 SD above the normal value |
|                   | Hemodynamic parameters | Arterial hypotension | SBP <90 mmHg or MAP <70 | MAP or administration of vasopressors (μg/kg/min) |
|                   | | | or SBP decrease >40 mmHg in adults or <2 SD below normal for age | MAP < 70 mm/Hg |
|                   | | | | dop ≤ 5 or doB (any dose) |
|                   | | | | Mop > 5 or epi ≤ 0.1 or nor ≤ 0.1 |
|                   | | | | dop > 15 or epi > 0.1 or nor > 0.1 |
|                   | | | | SOFA score: 13-14 1 |
|                   | | | | 10-12 2 |
|                   | | | | 6-9 3 |
|                   | | | | <6 4 |
|                   | Mental status | – | Altered mental status | – |
|                   | Significant edema or positive fluid balance | – | >20 mL/kg over 24 hrs | – |
|                   | Hyperglycemia in the absence of diabetes | – | Plasma glucose >120 mg/dL or >7.7 mM/L | – |
|                   | Inflammatory parameters | White blood cell count | >12,000/cu mm (leukocytosis) or <4,000/cu mm (leukopenia) or >10% immature (bands) forms | – |
|                   | | Plasma C reactive protein | – | Normal white blood cell count with >10% immature forms |
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|                   | Hemodynamic parameters | Arterial hypotension | SBP <90 mmHg or MAP <70 | MAP or administration of vasopressors (μg/kg/min) |
|                   | | | or SBP decrease >40 mmHg in adults or <2 SD below normal for age | MAP < 70 mm/Hg |
|                   | | | | dop ≤ 5 or doB (any dose) |
|                   | | | | Mop > 5 or epi ≤ 0.1 or nor ≤ 0.1 |
|                   | | | | dop > 15 or epi > 0.1 or nor > 0.1 |
|                   | | | | SOFA score: 13-14 1 |
|                   | | | | 10-12 2 |
|                   | | | | 6-9 3 |
|                   | | | | <6 4 |

Table 1 Criteria proposed to define sepsis and severe sepsis; comparison of guidelines

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| Organ dysfunction parameters | Criteria |
|-------------------------------|----------|
| Mixed venous oxygen saturation | >70% |
| Cardiac index | >3.5 L/min/m² |
| Arterial hypoxemia | PaO₂/FIO₂ <300 |

| Table 1 Criteria proposed to define sepsis and severe sepsis; comparison of guidelines (Continued) |
|-------------------------------|----------|
| Acute oliguria | Urine output <0.5 mL/kg/hr or 45 mmol/L for at least 2 hrs |
| Creatinine increase | >0.5 mg/dL |
| Coagulation abnormalities | INR >1.5 or aPTT >60 s |
| Ileus | Absent bowel sounds |
| Thrombocytopenia | Platelet count <100 x 10³/L |
| Hyperbilirubinemia | Plasma total bilirubin >4 mg/dL or 70 mmol/L |
| Tissue perfusion parameters | Hyperlactatemia | >1 mmol/L |
| SOFA score: PaO₂/FIO₂: |
| <400 | 1 |
| <300 | 2 |
| <200 and mechanically ventilated | 3 |
| <100 and mechanically ventilated | 4 |
| Creatinine (mg/dL) [μmol/L]: |
| 1.2–1.9 [110-170] | 1 |
| 2.0–3.4 [171-299] | 2 |
| 3.5–4.9 [300-440] | 3 |
| > 5.0 (> 440) (or < 200 mL/d) | 4 |
| Platelets x 10³/μL: |
| < 150 | 1 |
| < 100 | 2 |
| < 50 | 3 |
| < 20 | 4 |
| Bilirubin (mg/dL) [μmol/L]: |
| 1.2–1.9 (> 20-32] | 1 |
| 2.0–5.9 [33-101] | 2 |
| 6.0–11.9 [102-204] | 3 |
| > 12.0 (> 204] | 4 |
| Table 1 Criteria proposed to define sepsis and severe sepsis; comparison of guidelines (Continued) |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Capillary refill | Decreased capillary refill or mottling | – |
| Severe sepsis definition | Bone et al., 1992 | Dellinger et al., 2013 | Singer et al., 2016 |
| Hypoperfusion | Sepsis associated with but not limited to | – | Any of the below thought to be due to the infection | – |
| | Hypotension (sepsis-induced), in the absence of other causes | Systolic blood pressure < 90 mmHg or A reduction of ≥ 40 mmHg from baseline. | As defined for sepsis | – |
| Lactate | Lactic acidosis | Lactate above upper limit of laboratory normal | – | – |
| Organ failure | Kidney injury | Oliguria | As defined for sepsis but | Creatinine > 2 mg/dL (176.8 μmol/L) |
| | Acute lung injury | – | – | – |
| | Pneumonia not the infectious source: PaO₂/FIO₂ < 250 or Pneumonia the infectious source: PaO₂/FIO₂ < 200 | – | – | – |
| Liver injury | – | – | As defined for sepsis but | Bilirubin > 2 mg/dL (34.2 μmol/L) |
| Mental status | Acute alteration | – | – | – |
| Septic shock | Hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities, as listed above. | Hypotension not reversed with fluid resuscitation. | Sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥65 mmHg and having a serum lactate level >2 mmol/L (18mg/dL) despite adequate volume resuscitation. | – |
| Multiple organ dysfunction syndrome (MODS) | Altered organ dysfunction in an acutely ill patient such that homeostasis cannot be maintained without intervention. | – | – | – |
be avoided. We will refer to this definition as the “Bone criteria”.

International Sepsis Definitions Conference modifications
In 2003, the first Surviving Sepsis Campaign was published [6]. In an effort to increase the clinical utility, the diagnostic criteria were expanded to include other parameters, among these inflammatory, hemodynamic and tissue perfusion. It was emphasised that none of these new criteria were specific for sepsis. The latest campaign edition published in 2012 contained only minor revisions, and thus these expanded criteria have remained the recommended clinical standard [3]. However, a revised international definition of sepsis criteria has recently been published [13], in which the SIRS criteria are replaced by the sepsis-related organ failure assessment (SOFA) score [23].
Results
Our search identified 467 articles of which 430 were excluded after screening (see Fig. 1). An additional 12 articles were identified from the reference lists of the included articles, of which five were excluded after going through the abstracts. Of 44 articles read in full 21 were excluded: 10 articles did not provide sepsis or severe sepsis incidence on a person-year basis [15, 24–32], eight articles did not report sepsis or severe sepsis incidence as an outcome [33–40], two articles reported sepsis or severe sepsis incidence for a subgroup of patients [41, 42] and one article did not use a relevant design to compute sepsis and severe sepsis incidences [43]. Thus, we included a total of 23 articles: 11 chart-based and 12 code-based studies. Summaries of the included studies can be found in Tables 2 and 3.

Chart-based studies
Nine studies [44–52] screened patients according to pre-defined criteria for sepsis and/or severe sepsis; two studies [53, 54] analysed previously collected data. One chart-based study on severe sepsis reported incidences for several years. Most chart-based studies used the Bone criteria (or a modification hereof) and Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study criteria to identify cases of sepsis and severe sepsis (Table 2). For organ dysfunction definitions, adaptations of the PROWESS study criteria [55] were the most frequently used (see Additional file 2 for a detailed description).

Code-based studies
Three code-based studies applied different algorithms to the same data set [16, 22, 56] while three and six code-based studies reported several years’ observations of sepsis and severe sepsis incidences, respectively [22, 56–63] (Table 3).

Most code-based studies used ICD-9, though there was great diversity in what and how many codes were used, ranging from 1 to more than 1200 (see Additional file 3).

Three code-based studies used the Bone criteria for validation: Angus et al. and Shen et al. [14, 56] used the combination of ICD codes defined in their methods applied to an alternate cohort and a randomly selected database sample, respectively, while Martin et al. [63] compared only the ICD-9 codes specific for septicemia to a chart-based method. In general, there was a high degree of agreement between patients identified using ICD codes and patients identified by the Bone criteria, respectively. However, Angus et al. did find that their ICD codes generated higher incidences than what was found for the reference cohort using clinical and physiologic data [14].

Sepsis and severe sepsis incidence in the general population
Overall, we found great variation in incidence both between and across methods used to identify sepsis and severe sepsis, ranging from 74 to 1180 per 100,000 person-years and 3 to 1074 per 100,000 person-years, respectively. The incidence of both sepsis and severe sepsis increased over time (Fig. 2). When stratifying on method used to identify sepsis, we found that chart-based studies in general reported a higher incidence of sepsis than the code-based studies, whereas the opposite was the case for severe sepsis. There was a great diversity in what and how many codes were used, ranging from 1 to more than 1200 (see Additional file 3).

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Discussion
In this literature review, we found that the reported incidence of sepsis and severe sepsis in the general population varied greatly between the included studies. We compared the methods used and the demographic characteristics of the studied populations. We found that the variation may in part be attributable to whether a chart-based or a code-based method was used, differences in the criteria used for identifying cases of sepsis or severe sepsis within these groups, year of incidence measure, and the World Bank region in which the study was conducted.

In most chart-based studies on severe sepsis incidence, cases were identified in ICUs only. Such selection might introduce bias towards a lower incidence because patients that fulfill the criteria for severe sepsis but did not need ICU care were excluded. Indeed, these studies did on average find a lower incidence of severe sepsis than studies with other inclusion criteria. However, the chart-based study by Karlsson et al. [50] included admissions to both ICUs and other hospital wards, and still found an incidence of severe sepsis in adults much lower than what was found within a similar time period in the code-based studies of Dombrovskiy et al. [60] and Kumar et al. [62]. This indicates that other factors play an important role for the observed differences in incidence between chart- and code-based studies, and the question is whether these very...
| Country/region | Setting | Study population | Study duration | Exclusion criteria | Sepsis inclusion criteria | Organ failure inclusion criteria | Calendar year | Sepsis incidence 100,000 person yrs⁻¹ | Severe sepsis incidence 100,000 person yrs⁻¹ |
|---------------|---------|------------------|----------------|-------------------|--------------------------|-------------------------------|---------------|-----------------------------------|---------------------------------|
| Padkin, 2003 | England, Wales and Northern Ireland | 91 ICUs | 1995–2000 | <16 years, readmissions, sepsis not present within 24 h from admission | PROWESS | Modified PROWESS | 1997¹ | 51 | 77 |
| Finfer, 2004 | Australia and New Zealand | 23 ICUs | 3 months | <15 years | Bone criteria | SOFA score ≥3 | 1999 | 1001 | 95 |
| Brun-Buisson, 2004 | France | 206 ICUs | 2 weeks | <16 years, readmissions, sepsis not present within 24 h from admission | Bone criteria | Modified PROWESS | 2001 | 1996; 2003 | 46; 66 |
| Harrison, 2006 | England, Wales and Northern Ireland | 172 ICUs | 10 year | <18 years | Bone criteria | MODS score >2 | 2003 | 1999; 2003 | 104 |
| Esteban, 2007 | Madrid, Spain | 3 hospitals | 4 months | <18 years, readmissions | Bone criteria | SOFA score ≥3 | 2003 | 2003 | 38 |
| Karlsson, 2007 | Finland | 24 ICUs/11 hospitals | 4 months/4 days | <18 years, readmissions, sepsis not present on admission | Bone criteria | Modified PROWESS | 2005 | 2005 | 25 |
| Blanco, 2008 | Castilla y León Region, Spain | 11 ICUs | 6 months | <18 years, sepsis not present within 24 h from admission, transferred with diagnosis of severe sepsis | Bone criteria | Modified Bone criteria | 2002 | 2002 | 48 |
| Vesteinsdottir, 2011 | Iceland | 3 ICUs | 1 year | <15 years | PROWESS | PROWESS | 2009 | 2009 | 130 |
| Davis, 2011 | Northern territory, Australia | 1 hospital | 1 year | <15 years, severe sepsis not present within 24 h from admission, immediately preceding hospitalisation | Bone criteria | Bone criteria | 2008 | 2008 | 50 |
| Nygard, 2014 | Norway | 3 ICUs | 1 year | <15 years, readmissions, immediately preceding hospitalisation | Bone criteria | Bone criteria | 2011 | 2011 | 457 |
| Henriksen, 2015 | Denmark | 1 ED | 1 year | – | Bone criteria | Protocol specified criteria | – | – | – |

Characteristics of chart based studies of sepsis and severe sepsis incidence extrapolated to the general population. 1) If study is conducted in two consecutive calendar years the last year is reported. 2) If full data were not available for 1997, the closest full year’s data were used. Abbreviations: –, not calculated; ED, emergency department; hrs, hours; ICU, intensive care unit; MODS, multiple organ dysfunction syndrome; NA, not available; PROWESS, Protein C Worldwide Evaluation in Severe Sepsis; SOFA, sequential organ failure assessment; yrs, years old.
| Country/Region | Coding system | Data source | Study population | Number of cases (sepsis/severe sepsis) | Exclusion criteria | Internal validation | Calendar year | Sepsis incidence 100,000 person yrs⁻¹ | Severe sepsis incidence 100,000 person yrs⁻¹ |
|---------------|---------------|-------------|------------------|----------------------------------------|-------------------|---------------------|--------------|--------------------------------------|------------------------------------------|
| CDC, 1990     | ICD-9         | NHDS        | NA               | NA/192,980                             | <1 year           | No                  | 1979; 1987   | 74; 176                               | –                                        |
| Angus, 2001   | ICD-9         | Constructed database | NA             | NA/192,980                             | Presence of severe sepsis, Previous episode of severe sepsis, Neonate sepsis | Yes                  | 1979; 2000   | 1999 – 2002                           | 135 – 208                               |
| Martin, 2003  | ICD-10        | NPR         | 700,107          | 24,765 - 30,081/8096 – 13,453          | <18 years         | Yes                  | 1995 – 2002  | 83; 240                               | –                                        |
| Flaatten, 2004 | ICD-9         | NHDS        | NA               | NA/7531/NA                            | <18 years         | No                  | 1999 – 2003  | 199; 2003                             | 65 – 135                                |
| Dombrovskiy, 2005 | ICD-9     | NHDS        | NA               | NA/5258/NA                            | <18 years         | Yes                  | 1997 – 2006  | 83; 275                               | 135; 213                                |
| Esper, 2006   | ICD-9         | New Jersey SID | NA             | NA/7531/NA                            | <18 years         | No                  | 2003 – 2006  | 10; 35; 25                            | 135; 213                                |
| Dombrovskiy, 2007 | ICD-9       | SHDR        | NA               | NA/12512/NA                           | <18 years         | No                  | 2005 – 2007  | 10; 35; 25                            | 135; 213                                |
| Shen, 2010    | ICD-9         | NIS         | NA               | NA/12512/NA                           | <18 years         | No                  | 2006 – 2008  | 10; 35; 25                            | 135; 213                                |
| Wilhelms, 2010 | ICD-9/10      | NHIRD       | 201,657         | NA/40,856 - 116,749                   | <18 years         | No                  | 1997 – 2005  | 201,657                               | 40,856 - 116,749                       |
| Kumar, 2011   | ICD-9         | NIS         | 2,024,793        | NA/192,980                             | <18 years         | No                  | 1997 – 2005  | 2024,793                              | NA/192,980                             |
| Lagu, 2012    | ICD-9         | NIS         | NA               | NA/192,980                             | <18 years         | No                  | 1997 – 2005  | 2,024,793                             | NA/192,980                             |
| Chen, 2013    | ICD-9         | Taiwan      | NA               | NA/192,980                             | <18 years         | No                  | 1997 – 2005  | 2,024,793                             | NA/192,980                             |

Characteristics of code based studies of sepsis and severe sepsis incidence extrapolated to the general population. i) Age-standardized to fit the population distribution in the 2000 U.S. consensus. ii) Method validated by Martin et al. iii) Age-standardized using 2000 world population reported by WHO as standard. iv) No exclusion criteria. v) Exclusion criteria as stated. vi) Discharge diagnoses were classified according to ICD-9 until the end of 1996. These were translated into ICD-10 for the methods of Angus et al. and Martin et al. vii) Using the method proposed in Angus et al., Flaaten et al. (time of incidence measure: 1997; 2005) and Martin et al., respectively. viii) Using the method proposed in Angus et al. and Dombrovskiy et al., respectively. Abbreviations: –, not calculated; SHDR Swedish hospital discharge register, NA not available, NHDS national hospital discharge survey (USA), NHIRD national health insurance research (Taiwan), NIS nationwide inpatient sample (USA), NPR Norwegian patient register; yrs, years
different approaches are even comparable. Wilhelms et al. [22] addressed this by applying the methods of Angus et al., Flatten, and Martin et al. [14, 21, 63] to the same database. Notably, Wilhelms found that the methods identified very different patient cohorts with little overlap, questioning whether the ICD codes correspond to the clinical definition of severe sepsis. As mentioned previously, Angus et al. did indeed find that their criteria generated higher incidences than the Bone criteria, but most of the code-based studies did not explore the clinical characteristics of identified cases, even though many codes not specific for sepsis were used. In a US study by Gaieski et al. [15], the methods of Angus et al., Wang et al., Dombrovskiy et al., and Martin et al. [2, 14, 59, 63], were all applied to a cohort identified using the Nationwide Inpatient Sample (NIS) database, which was also used in...
The increase found in both sepsis and severe sepsis incidence over the years could be due to an actual increase caused by factors such as increasing prevalences of comorbidities in the general population, a change in the population demographics with more elderly, use of intravenous accesses or other predisposing factors for sepsis. However, an increased clinical and political awareness of sepsis, as pursued by the Surviving Sepsis campaigns, or perhaps a change in coding practice could also lead to higher estimates [64]. Probably, the increase in reported incidences is caused by a combination of several or all of these. As recently suggested, an automatic epidemiological surveillance system based on electronic health records for patients with sepsis, may give better estimates for both sepsis incidence and mortality [65].

When stratifying on World Bank region, we found a variation in incidences of both sepsis and severe sepsis. Remarkably, the incidence of sepsis was generally lower in the North America region compared to Europe & Central Asia, whereas the opposite was the case for severe sepsis. These differences may arise from differences in coding practice and the related economic incentive, and access to hospital and ICU care. The study by Wilhelms et al. [22] supports this observation: When reproducing the studies by Angus et al. [14] and Martin et al. [63] on a Swedish cohort they find remarkably lower incidences than was reported for the studies set in North America.

The relatively low number of studies on sepsis and severe sepsis incidence after stratifying on code-based or chart-based studies limits our review. Also, the great heterogeneity of the included studies, such as the number and type of codes used to define sepsis and severe sepsis in the code-based studies, may not only give rise to major differences in outcome but also impedes direct comparison, as the studies differs from each other by several variables.

The importance of reaching a greater consistency in the definition of sepsis and severe sepsis used in epidemiological studies has been commented by Singer et al. [13], following the third international sepsis definition consensus conference, and recommendations are given for both clinical identification of sepsis as well as ICD coding. If these recommendations are successfully implemented worldwide, this may offer a more simple and intuitive approach to diagnosis of sepsis and septic shock. This approach, together with the proposed recommendations for registration of the condition, may not only lead to a more prompt recognition of sepsis, but also enable a higher consistency for epidemiological studies reporting sepsis incidence.

### Conclusion

The reported incidence of sepsis and severe sepsis in the general population varies greatly between studies. In this literature review, we present a detailed systematic examination of all original studies reporting the incidence of sepsis or severe sepsis in the general population as a main outcome. We find that the methods used differ between the studies to a degree that greatly hampers the inference about any variable’s impact on the incidence. This highlights the importance of standardised definitions and acquisition of data regarding sepsis and severe sepsis.

### Additional files

- **Additional file 1:** The specific ICD codes for sepsis in the 9th and 10th revision. (PDF 69 kb)
- **Additional file 2:** Comparison of the different criteria used to define organ dysfunction in the chart-based studies. (PDF 120 kb)
- **Additional file 3:** The ICD-9 codes used in the included studies (except study by Flaatten in which ICD-10 codes were used). (PDF 139 kb)
- **Additional file 4:** Boxplot of the incidence of sepsis stratified by protocol used to identify cases and on data source. (PDF 6 kb)
- **Additional file 5:** Boxplot of the incidence of severe sepsis stratified by protocol used to identify cases and on data source. (PDF 10 kb)

### Abbreviations

ACCP/SCCM: American College of Chest Physicians/Society of Critical Care Medicine; ICD: International Classification of Diseases; ICU: Intensive care unit; PROWESS: Protein C Worldwide Evaluation in Severe Sepsis; SIRS: Systemic inflammatory response syndrome

### Availability of data and materials

The dataset supporting the conclusions of this article together with codebook and the R-code is available in the GitHub repository https://github.com/eiset/SepsisIncidence.git.

### Authors' contributions

SEM and AHE contributed equally to all parts of the research project and in drafting the manuscript as co-first authors. All authors made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data. KKS and CFC contributed in revising the manuscript; given final approval of the version to be published. All authors take public responsibility for appropriate portions of the content; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscripts.

### Competing interests

The authors declare that they have no competing interests.

### Consent for publications

Not applicable.

### Ethics approval and consent to participate

Not applicable.
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