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Assessment of global incidence and mortality of hospital-treated sepsis – Current estimates and limitations

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Author contribution

CF and TT performed the literature review and data extraction. AS and PS performed the meta-analyses. CF, KR and CSH drafted the manuscript. NKJA, DCA, KR, CSH, CF and AS revised the manuscript for important intellectual content.

Competing interests

CF was supported by a grant from the Center for Sepsis Control and Care (CSCC). The CSCC is funded by the German Federal Ministry of Education and Research (BMBF), Germany, FKZ: 01EO1002. KR, AS and CSH receive CSCC research grants. KR is unpaid chairman of the Global Sepsis Alliance and shareholder of InflaRx Jena, a University spin-off that develops adjunctive therapies for systemic inflammation. The funding agencies played no role in the study design or analysis of data. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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At a Glance Commentary: Sepsis is a major public health concern, but comprehensive knowledge on sepsis incidence and mortality worldwide is missing. This article provides a systematic overview of epidemiological data on population-level incidence rates and hospital mortality around the world. It includes data from 7 countries on 4 continents over last 36 years. The data were used to generate estimates for hospital-treated sepsis cases in high-income countries. In low- and middle-income countries, however, important knowledge gaps are evident.

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org.

ABSTRACT

Rationale: Reducing the global burden of sepsis, a recognised global health challenge, requires comprehensive data on the incidence and mortality on a global scale.

Objective: To estimate the worldwide incidence and mortality of sepsis and to identify knowledge gaps based on available evidence from observational studies.

Methods: We systematically searched 15 international citation databases for population-level estimates of sepsis incidence rates and fatality in adult populations using consensus criteria and published in the last 36 years.

Main results: The search yielded 1553 reports from 1979 to 2015, of which 45 met our criteria. 27 studies from 7 high-income-countries provided data for meta-analysis. For these countries, the population incidence rate was 288 [95%CI, 215-386, τ=0.55] hospital-treated sepsis cases and 148 [95%CI, 98-226, τ=0.99] hospital-treated severe sepsis cases per 100 000 person-years. Restricted to the last decade, the incidence rate was 437 [95%CI, 334-571, τ=0.38] sepsis and 270 [95%CI, 176-412, τ=0.60] severe sepsis cases per 100 000 person-years. Hospital mortality was 17% for sepsis and 26% for severe sepsis during this period. There were no population-level sepsis incidence estimates from lower-income-countries, which limits the prediction of global cases and deaths. However, a tentative extrapolation from high-income-country data suggests global estimates of 31.5 million sepsis and 19.4 million severe sepsis cases, with potentially 5.3 million deaths annually.

Conclusions: Population-level epidemiological data for sepsis are scarce, and non-existent for low- and middle-income-countries. Our analyses underline the urgent need to implement global strategies to measure sepsis morbidity and mortality – particularly in low- and middle-income-countries.

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INTRODUCTION

Sepsis is the life-threatening condition that arises when the body's response to an infection injures its own tissues and organs. (1, 2) It has been called "one of the oldest and most elusive syndromes in medicine". (3) Despite advances in care, existing epidemiologic studies suggest that sepsis remains a huge burden across all economic regions. In the United States, admissions for sepsis have overtaken those for myocardial infarction and stroke. (4) Sepsis incidence rates are up to 535 cases per 100 000 person-years and rising. (5) In-hospital mortality remains high at 25-30%. (6) However, there is no gold standard of sepsis diagnosis and non-standardized definitions hamper comparability of results from clinical and epidemiological studies. (2) Thus, current sepsis criteria are under revision to overcome the limitation that they don't differentiate between infection and sepsis. (6) Sepsis is also not tracked in the Global Burden of Disease taxonomy. Rather, infections are reported separately, and only neonatal sepsis is reported explicitly. (7) Indeed, controversy remains regarding the true attributable burden of sepsis because of notable differences in both the methods and results of epidemiologic studies, especially those based on administrative data. (8) Reducing the global burden of sepsis, a recognized global health challenge, requires comprehensive data on incidence and mortality on a global scale. Therefore, the principal aim of this systematic review was to summarize existing epidemiological studies of sepsis throughout the world. In addition, we aimed to generate estimates of global incidence and case-fatality rates of sepsis using meta-analyses. To address the expected heterogeneity of the studies, we predefined subgroups for stratification according to the World Bank classification of high-, middle-, and low-income-countries and settings (intensive care unit (ICU), emergency department (ED), or hospital). Some of the results of this study have been previously reported in the form of an abstract. (9)

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METHODS

Search strategy and selection criteria

The literature search and review process followed a protocol designed before data collection. To identify observational epidemiological studies reporting on population-level incidence of sepsis on a global scale, we used three different approaches: a search for published or unpublished literature in regional and international databases, a scan of reference lists for potentially relevant studies, and queries to national experts for regions where no data were found.

We assessed 15 regional and international databases for published or unpublished studies on the sepsis incidence from 01/1979 through 05/2015: PubMed, EMBASE, LILACS, African Index Medicus (AIM), African Healthline, African Journals Online, OpenGREY, MedCarib, Pascal Biomed, Index Medicus for the WHO Eastern Mediterranean Region (IMEMR), IndMed, Web of Science, Index Medicus for South East Asia Region (IMSEAR), Western Pacific Region Index Medicus (WPRIM), and WHOLIS. No language or publication restrictions were applied.
We used the same comprehensive list of search terms for each database and applied it to the title of publications: "(sepsis OR septic*) AND (epidemiology*, incidence, burden OR prevalence)" (*=truncation). Although we focused on incidence rates, the search term "prevalence" was included because sepsis – in the acute setting – is a non-chronic disease that rarely occurs twice in the same individual if the observational time period is sufficiently small.

Studies were considered for inclusion if they reported on sepsis or severe sepsis incidence on a population level within a defined population and period of time. Sepsis or severe sepsis were defined according to the following: ACCP/SCCM consensus criteria, (10, 11) PROWESS-SHOCK

criteria, (12) sepsis-relevant ICD-9/ICD-10 codes, or codes representing both infection and organ dysfunction to identify severe sepsis cases. We excluded studies that were limited to sub-groups of sepsis (e.g. positive blood cultures or specific gram stain), selected patient groups (e.g. cancer patients or paediatric patients), or treatment units (e.g. surgical ICU). Studies that cited incidence without giving details about the method of data collection or inclusion and exclusion criteria were also excluded.

Data compilation

Abstracts were reviewed by one investigator (CF) and those that seemed likely to fulfil the inclusion criteria underwent full-text review and analysis independently by two investigators (CF, TT). Discrepancies were resolved by discussion. Non-English articles were assessed and extracted by native speakers with medical backgrounds. Extracted data included: authors; year of publication; country or countries classified by a) low-income countries, b) middle-income countries, and c) high-income countries according to World Bank country classification of income groups; (13) observation period; observed cases of sepsis or severe sepsis; cases of sepsis or severe sepsis/100 admissions; cases of sepsis or severe sepsis/100 000 person-years; ICU-, hospital-, or 28-day-mortality. In our analysis, sepsis is considered as an umbrella term compiling cases of severe sepsis and septic shock. Likewise, cases of severe sepsis include cases of septic shock. If there was a distinction between sepsis patients and observed sepsis episodes, the number of observed episodes was included for analysis. Thus, we present estimates on sepsis cases (rather than on patients) per 100 000 population. Finally, we classified the studies regarding (A) setting (ICU, ED, or hospital), (B) design (prospective or retrospective), and (C) sepsis definition (clinical consensus criteria or ICD-coding) to perform stratified meta-analyses. We contacted authors, where required, for additional data.

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Statistical analysis

Meta-analysis focused primarily on population-level incidence rates of hospital-treated sepsis or severe sepsis per 100 000 person-years and used all other extracted information for their description. As a secondary objective, we also report meta-analysis estimates for hospital case fatality rates in the included studies if such data were available. Missing population data were requested from the authors or searched in national census databases. We recalculated the population-level incidence rates to reduce additional heterogeneity due to different calculations and standardizations reported in the original publications; nevertheless, the original calculations are also provided. We used information on the relation between observed hospital sepsis cases and annual total of hospitalizations within a nation's population (as provided by the authors) and finally related these numbers to the national population given by census enquiries. ICU data were excluded from meta-analysis due to substantial variations in national ICU capacities that would be expected to be highly correlated with the number of ICU-treated sepsis cases.

There was substantial heterogeneity between the estimates of the underlying studies as expressed by the estimated τ, the estimated square-root of the between-study variance, and I^2, a re-scaled version of this variance that ranges between 0-100%, with larger values indicating more substantial heterogeneity (I^2=100% for all analyses and τ between 0.13 and 0.87 for the incidence rates or τ between 0.21 and 0.58 for the case fatality rates). We present random effects estimates based on the method of Hartung and Knapp, (14) which generates wider confidence intervals compared to standard methods. (15) Balancing between taking care of heterogeneity by stratification and the availability of a considerable number of studies to be meta-analysed to derive a relatively robust estimator, we finally stratified all studies into two subgroups (hospital-treated sepsis and hospital-treated severe sepsis). As some studies applied more restricted or wider criteria to derive their

estimates for hospital-treated severe sepsis, we decided to run two additional sensitivity analyses (minimum and maximum) using these criteria. Studies applying multiple strategies for severe sepsis case identification to one dataset were included in sensitivity analyses according to the strategy used. From these studies, all data rows were included in the combined meta-analysis, to balance the influence from wider and more restrictive definitions. The same analyses were also run separately for the most recent studies (first year of enrolment ≥ 2003; see supplement). All analyses were done using metaprop of the R 3.0.2 package `meta` which provides exact 95% confidence intervals for the incidence rate estimates of the individual studies. For all incidence rate calculations we had to apply an approximation to circumvent computational difficulties (the number of input observations was first divided by 10 and the estimate was afterwards up-scaled by the factor 10 and rounded to the next integer).

Finally, we extrapolated our estimates to the global scale based on the estimated size of the world population of about 7.2 billion people. (16)

RESULTS

Our search yielded 1 553 abstracts including 24 publications which were identified by hand-searching. Two independent investigators read in full and analysed 129 publications (figure 1). Overall, 45 studies from 18 high-income-countries in North America, Europe, Asia, and Australia met the eligibility criteria, of which 27 contributed to meta-analyses (figure 2). Interrater-agreement (Kappa) for study inclusion was 0.85 (95%CI 0.74-0.93). 30 (67%) of these studies were retrieved by searching MEDLNE, three (7%) by EMBASE, and one (2%) by Web of Science. Another eleven (24%) were identified by hand searching. Two were non-English language publications. Queries to

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experts in China, Russia, and the Middle East yielded no further studies. Two studies provided data from more than one country. Additional data for meta-analysis were obtained from 16 of the approached 33 study authors.

Classification of epidemiological studies on sepsis incidence

The included 45 studies varied in terms of (A) study setting (ICU, ED, or hospital), (B) design (prospective: one-day or period prevalence study, retrospective), and (C) sepsis criteria.

None of the studies based their observations on a population as a whole. Therefore, all results need to be interpreted as incidence rates of *treated* sepsis cases. In the next step, we assessed the results of all studies providing population-level estimates of sepsis incidence rates in the categories of interest to generate meta-analytic estimates on the global burden of hospital treated sepsis cases. Only studies with complete data on nominators and denominators were used for meta-analysis (tables 1 and 2). Because only two studies (17, 18) reported on population-level incidence rates for sepsis patients in EDs, we did not calculate any estimators for this category, but provide data in tables 3 and 4.

Data from 2 prospective and 25 retrospective hospital-based studies from seven countries on four continents were selected for further analysis. Both prospective studies were period prevalence studies and applied consensus criteria (ACCP/SCCM, PROWESS-SHOCK) to identify cases of sepsis or severe sepsis. (19, 20) Retrospective studies (n=25) mainly analysed hospital discharge databases for the number of hospitalizations due to sepsis or severe sepsis based on various ICD code combinations. They generally used three different abstraction approaches to mirror the clinical criteria of sepsis or severe sepsis. 17 studies screened databases for all hospitalizations with ICD-09-CM codes for septicemia, sepsis, or severe sepsis (direct coding strategy). (5, 17, 21-36) In this

context, septicemia was defined as "a systemic disease associated with the presence of pathological microorganisms or toxins in the blood, which can include bacteria, viruses, fungi or other organisms" (ICD-9-CM Official Coding Guidelines). Codes for sepsis and severe sepsis were introduced in 2003 in a revised edition of the ICD-09-CM (26) and demand a code for a systemic infection as well as a code for sepsis or severe sepsis; thus they incorporate the consensus criteria which require a documented or suspected infection instead of a proven septicemia. Another four studies used different ICD-10-CM combinations including codes for septicemia, sepsis, and severe sepsis. (28, 37-39) In this 10th edition, coding for sepsis and severe sepsis was also possible with negative blood cultures, as postulated in the consensus criteria (direct coding strategy). Eight studies selected all hospitalizations with ICD-codes for bacterial, viral, or fungal infection combined with a diagnosis of acute organ dysfunction to identify severe sepsis cases (indirect coding strategy). (28, 30, 32, 40-44)

Estimated population-level incidence rates

Estimates of hospital-treated sepsis incidence rates

17 studies were included (table 1). These were mainly based on comprehensive hospital discharge registers with ICD-coded diagnoses of each patient (direct coding strategy). Worldwide, population incidence for sepsis cases in hospitals ranged from 73.6/100 000 inhabitants in 1979 in the US (27) to 1 180/100 000 inhabitants in 2007/2008 in a mainly indigenous population in Australia's Northern Territory, (20) with an aggregate global estimator of 288 [95% CI, 215-386] sepsis cases per 100 000 person-years (τ=0.55, figure 4 (A)). For the last ten years (2003-2015), this estimator was even higher (437 [95% CI, 334-571] sepsis cases per 100 000 person-years (τ=0.38), see Figure E1 in the online data supplement).

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Estimates of hospital-treated severe sepsis incidence rates

20 studies were included (table 2). Again, the results show a marked heterogeneity; the lowest incidences were found in Northern Europe, ranging from 3 to 49 hospital-treated severe sepsis cases per 100 000 person-years in Sweden (28) and Norway (37). In contrast, a hospital incidence of up to 1 061 severe sepsis cases per 100 000 inhabitants in the US was observed, (32) by mirroring clinical sepsis criteria in ICD-codings. Jointly analysing all included studies, we estimate a population incidence of severe sepsis of 148 [95% CI, 98-226] (τ=0.99) cases per 100 000 person-years (figure 4 (B)). The estimate was larger for more recent investigations (270 [95% CI, 176-412] cases per 100 000 person-years (τ=0.60) for 2003-2015, see Figure E2 in the online data supplement). In sensitivity analyses including studies that applied a restricted severe sepsis definition, these numbers changed to 94 [95% CI, 56-158, τ=0.87] and more recently 183 [95% CI, 112-297, τ=0.31] cases per 100 000 person-years (see Figure E3 in the online data supplement). In studies using wider severe sepsis definitions, we found an aggregate global estimate of 317 [95% CI, 158-634, τ=0.27] and more recently 560 [95% CI, 277-1129, τ=0.13] hospital-treated severe sepsis cases per 100 000 person-years (see Figure E4 in the online data supplement).

Estimated hospital-treated sepsis and severe sepsis case fatality rates

Case fatality rates of hospital-treated cases from 14 studies on sepsis and 18 studies on severe sepsis were analysed. For sepsis, these rates ranged from 5% (20) to 42.5% (21) between 1979 and 2015 resulting in a meta-analytic estimate of 21% [95% CI, 17%-25%] (τ=0.21). For the years 2003-2015 the estimator was 17% [95% CI, 11%-26%] (τ=0.24, see Figure E5 in the online data supplement). For severe sepsis, the estimated case fatality rates for severe sepsis was higher: 28% [95% CI, 24%-

32%] (τ=0.61) from 1979 until 2015. Focussing on the last decade (2003-2015), meta-analysis resulted in a lower estimated case fatality rate of 26% [95% CI, 20%-33%] (τ=0.62, see Figure E6 in the online data supplement) for severe sepsis. For severe sepsis from 1979-2015, depending on the definition, case fatality rates were higher (33% [95% CI, 28%-38%] (τ=0.49)) for a more restricted definition and 22% [95% CI, 16%-30%] (τ=0.58) for a wider definition (see Figures E7, E8 in the online data supplement). For 2003-2015, we found similar estimated case fatality rates of 33% [95% CI, 25%-42%] (τ=0.52) for a more restricted definition and 18% [95% CI, 9%-32%] (τ=0.44) for a wider definition of severe sepsis (see Figures E7, E8 in the online data supplement).

Estimated global sepsis incidence and mortality

High-income-countries only represent 13% of the world's population. Since we aimed to generate estimates on the global burden of sepsis, we need to acknowledge that 87% of the world population has understudied sepsis epidemiology. If we assume that the incidence rates for hospital-treated sepsis and severe sepsis estimated here similarly apply to low- and middle-income-countries, a total annual number of 20.7 million sepsis and 10.7 million severe sepsis cases could be expected based on a global population of 7.2 billion people. Focussing only on data from the last decade, 31.5 million sepsis and 19.4 million severe sepsis cases would be expected to be treated in hospitals around the globe each year. Finally, if the case fatality rates for sepsis and severe sepsis in the hospital setting from the last decade are applied to the estimated global incidence, sepsis may cause or contribute to up to 5.3 million deaths worldwide per annum.

DISCUSSION

A main finding of this systematic review on a global level is that studies on population-level

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incidence and case-fatality rates for sepsis and severe sepsis are scarce, and none exists for low- and middle-income-countries. The available data from high-income-countries are mainly derived from large retrospective database studies for hospitalizations due to sepsis identified by different ICD-coding-strategies. Since for most prospective cohort studies population denominators were not available or predictable, we had to exclude these studies from analyses; however, they reveal that ICU admissions rates for infections and sepsis are comparable throughout the world, even though causative organisms differ remarkably between continents (45, 46) Furthermore, data on population-level incidences of ICU-treated sepsis cases was excluded from meta-analysis because it was expected to be highly dependent on national ICU capacities. In the included studies from high-income-countries, we observed large heterogeneity between single study estimates, which can be related to varying sepsis definitions and other methodological differences among the studies, but also to a differing prevalence of the underlying infections. Results suggest high population-level incidence rates for sepsis and severe sepsis treated in hospitals in high-income-countries compared to other diseases such as myocardial infarction. (47) The intended evaluation of the global burden of sepsis turned out to be limited due to missing reliable population-based data from low- and middle-income-countries. If the incidence and case fatality rates we estimated in this review would also apply to low- and middle-income-countries, tentative extrapolations suggest a global number of more than 31 million sepsis cases and five million deaths from sepsis globally merely in the hospital setting. However, the true incidence and burden of sepsis in these countries remains uncertain due to a lack of information on sepsis epidemiology and may even be higher as infectious diseases are considerably more prevalent in these areas of the world and cause a substantially higher proportion of deaths than in high-income-countries (48): In 2010, lower respiratory tract infections and malaria ranked second and sixth among the leading causes of disability-adjusted life-years

(DALYs), (7) and accounted for 2 652 600 (49) and 854 568 (50) deaths in 2013, respectively. Malaria (51) and viral infections like Dengue (52) are also a major source of systemic infections in low- and middle-income-countries, with a majority of the deaths attributable to sepsis. (53-56) Furthermore, HIV infection, which is also most prevalent in low- and middle-income countries, is associated with a high risk of co-infection and sepsis (52, 57, 58): Mayanja et al. (59) reported 3 240 cases of septicemia per 100 000 person-years in a population of 45.7% HIV-positive individuals, i.e. up to tenfold higher incidence of septicemia than that reported for high-income-countries (this study included only a subgroup of sepsis patients with positive blood cultures and was therefore excluded from meta-analysis). Given the considerably higher prevalence of acute infections that may lead to sepsis in low- and middle-income-countries where studies on the epidemiology of sepsis are missing, any estimates derived from high-income-countries which add hospital-acquired to community-acquired cases may underestimate the true global cumulative incidence of sepsis. Furthermore, we estimated incidence rates based on hospitalized patients only. By searching death registers in the US, Melamed et al. (60) showed that around 13% of sepsis-related deaths occur outside of the hospital environment in nursing homes and residences, even in the US. Finally, the studies we included in our meta-analysis had substantial methodological differences. Prospective and retrospective studies differed enormously in their approach to identify sepsis cases. In clinical practice, SIRS criteria for sepsis definition appear insufficiently precise, with many non-sepsis conditions presenting with SIRS and many severe sepsis patients shown to be SIRS-negative. (61) This diagnostic imprecision contributes to the heterogeneity observed in this meta-analysis and limits comparability of studies. Moreover, clinical consensus criteria and ICD-codes for sepsis changed over time and may be influenced by changes in clinical practice.

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Generally, there is an ongoing controversy about the accuracy of ICD-identification of sepsis cases (8, 28, 30, 62), due to challenges with defining sepsis, severe sepsis, and organ dysfunction in administrative data. The different approaches to mirror clinical sepsis criteria using codes for infection and organ dysfunction for severe sepsis (e.g. Angus et al. – wider case definition (40)), codes for septicemia and sepsis (e.g. Martin et al. – more restricted case definition (25)), or variations of these coding schemes are susceptible to under- or overestimation. (63) As confirmed by sensitivity analyses, these different approaches of ICD case identification add substantially to the heterogeneity observed in our meta-analyses. Chart-based clinical validation of sepsis cases identified through administrative databases revealed severalfold higher incidence rates. (18) These observations are in accordance with several studies, which suggested that in hospital administrative data, septicemia, sepsis, or severe sepsis themselves may not be coded correctly or missed. (64, 65) On the other hand, it was argued that sepsis may be coded too frequently for billing reasons, based on the observation that over the same time period where the sepsis incidence increased, the incidence of pneumonia decreased and the incidence of intra-abdominal infections and urinary tract infections remained unchanged. (8) Most recent representative data from the US however suggest that both sepsis and infection hospitalizations increased in parallel when principal and secondary claims were used for case identification. (66) Likewise, severe sepsis cases requiring mechanical ventilation increased at the same rate as overall sepsis cases. Furthermore, differences hospital admission rates are likely to be related to hospital- and country-specific availability of hospital beds, admission policies, insurance systems and other factors. Data extrapolation to a national level also assumes certainty regarding the correct estimation of the total number of hospitalized or treated patients. Regarding case fatality rates, the interpretation of administrative data is similarly challenging. Our data show decreased sepsis mortality rates in the last decade. The impact of

improved diagnostic measures, an increased awareness, and more accurate ICD-coding for sepsis and severe sepsis, which may lead to a better recognition of milder sepsis cases, is difficult to determine. (62, 67) However, the decline of mortality rates has been shown to be similarly evident in both retrospective register-based studies and multicenter randomized trials. (68) Even though our estimated temporal trends are in line with a recent large Australian cohort, (69) our summary estimates of incidence and case fatality rates may nevertheless be biased and confidence intervals may be too narrow given the heterogeneity among studies. Indeed, some may argue that the studies should not be summarized by meta-analysis techniques at all. But given the systematic and transparent approach and the broad search strategy for a time frame of more than 30 years, we decided that reporting these summaries is more important for the reader than not providing them. Nevertheless, we also included detailed information for each study to enable alternative interpretations.

Aside from these limitations, our review captured a comprehensive number of observational epidemiological studies from high-income-countries, for which we observed and confirmed a high incidence rate for hospital-treated sepsis. The lack of data from low- and middle-income-countries as well as the differences in methodology of studies from high-income-countries highlight the need for additional studies and more consistent methodological approaches. A revision of sepsis definitions by the international community is necessary to pave the way towards comparable sepsis criteria for clinical practice and research, and to allow a more consistent abstraction in ICD coding. Further research on sepsis coding using administrative data seems necessary to derive sensitive and specific sepsis case identifications. Most importantly, more population-based cohort studies are required to generate more accurate estimates on the global burden of sepsis. In conclusion, our

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review underlines the urgent need to implement global strategies to monitor sepsis morbidity and mortality as well as prevention and treatment regimens – especially in low- and middle-income-countries.

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TABLES

Table 1: Population-level incidence rates for hospital treated sepsis cases.

	study duration (days)	population	patients observed	age range	total number of sepsis cases	incidence (per 100 000 person-years)	mean age	hospital mortality (%)	remarks
Prospective studies									
Australia (Davis et al.) (20)									
2007-2008	365	102 854 (ar)	15 963	≥ 15 years	1 191	1180	46.7	5	Period prevalence study in the major hospital for Tropical Northern Territory, Australia (27% Indigenous population)
Spain (Esteban et al.) (19)									
2003	122	573 149	15 852	> 18 years	702 (2 106¶)	367	69	12.8	Period prevalence study, three hospitals in Madrid, Spain, 4-month-period
Retrospective studies									
Norway (Flaatten) (37)									
1999	365	4 461 913	700 107	no neonates	6 665	149	57.9	13.5	Norwegian Patient Registry, all patients admitted in 1999, ICD-10
Spain (Ballester et al.) (21)									
1995-2004	3650	41 677 000 (nc)	23 351 859	all ages	33 767	45-114	55.9-62.4	42.5	Discharge diagnoses in all 26 public hospitals in the Valencian Community, Spain, 10-year-period, ICD-9
US (Seymour et al.) (23)									
2006	365	6 434 047	876 963	≥ 20 years	37 524	580	58-81	18-25	Hospital discharge data from New Jersey from the Healthcare Cost and Utilization Project 2006 State Inpatient Database (SID), ICD-9
US (Buechner et al.) (24)									

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1990	365	1 003 464 (ar)	141 027 (ar)	all ages	1 998	187.7	-	25.5	Discharge diagnoses from all acute hospitals in Rhode Island, ICD-9
2002	365	1 066 034 (ar)	133 494 (ar)	all ages	3 430	287.7	-	23.4	
US (Martin et al.) (25)									
1979	365	224 567 000 (nc)	-	all ages	164 072	82.7	57.4 (1979-84)	27.8	Data from the National Hospital Discharge Survey, 1979-2000, ICD-9
2000	365	281 425 000 (nc)	-	all ages	659 935	240.4	60.8 (1995-2000)	17.9	
US (Hall et al.) (26)									
2000	365	281 425 000 (nc)	-	all ages	621 000	221	-	-	Data from the National Hospital Discharge Survey, 2000 and 2008, ICD-9
2008	365	30 4375 000 (nc)	-	all ages	1 141 000	377	-	17	
US (CDC) (27)									
1979	365	224 567 000 (nc)	-	all ages	164 000	73.6	-	31	Data from the National Hospital Discharge Survey, 1979 and 1987, ICD-9
1987	365	242 289 000 (nc)	-	all ages	425 000	175.9	-	25.3	
Australia (Sundararajan et al.) (39)									
1999	365	4 500 000	3 122 515 (during 4 y)	all ages	33 741 (during 4 y)	166	-	18.4 (during 4 y)	Hospital discharge database study based on the Victorian Admitted Episodes Dataset, Victoria, ICD-10
2003	365			all ages		194	-		
Germany (Heublein et al.) (38)									
2011	365	81 843 700 (nc)	-	all ages	175 051	213¶	67.5	28.6	Hospital discharge data for Germany 2011, ICD-10-coding
US (Dombrovskiy et al.) (22)									
1993	365	257 783 000 (ar)	-	all ages	656 932	255¶	-	-	Hospital discharge database study based on the National Inpatient Sample, ICD-9
2003	365	290 447 644 (ar)	-	all ages	893 762	308¶	-	-	
US (Lagu et al.) (29)									

2003	365	217 068 000 (ar)	31 634 852	≥ 18 years	799 155	368¶	-	-	Data from the Nationwide Inpatient Sample (NIS) 2003-2007, ICD-9
2007	365	227 240 000 (ar)	32 716 306	≥ 18 years	1 115 112	491¶	-	-	
US (Danai et al.) (36)									
1979-2003	9 125	6 384 773 427 (nc)	-	all ages	12 505 082	41.7-48.6	60.1-60.9	20	Data from the National Hospital Discharge Survey, 1979-2003, ICD-9
US (Elixhauser et al.) (34)									
2009	365	306 771 529 (ar)	-	all ages	1 665 400	540	60.3	16.3	Data from the Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS), 2009, ICD-9
US (Sutton and Friedman) (33)									
2005	365	64741527 (ar)	-	≥ 18 years	267 000	492	-	-	Data from the Healthcare Cost and Utilization Project (HCUP), State Inpatient Databases (SID), 2005-10, ICD-9
2010	365	68599514 (ar)	-	≥ 18 years	354 000	651	-	-	
US (Walkey et al.) (5)									
2003	365	290 107 933 (ar)	227 000 000	≥ 18 years	789 410 (ar)	359	-	24	Data from the Nationwide Inpatient Sample (NIS), 2003-2009, ICD-9
2009	365	306 771 529 (ar)		≥ 18 years	1 306 730 (ar)	535	-	19	

Legend: Data are from the published study, unless indicated by (ar) – data supplied by the author, (nc) – national census, or ¶ – recalculated

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Table 2: Population-level incidence rates for hospital treated severe sepsis cases.

	study duration (days)	population	patients observed	age range	total number of severe sepsis cases	incidence (per 100 000 person-years)	mean age	hospital mortality (%)	remarks
Prospective studies									
Australia (Davis et al.) (20)									
2007-2008	365	102 854 (ar)	15 963	≥ 15 years	194 (ar)	188¶	-	17.1	Period prevalence study in the major hospital for Tropical Northern Territory, Australia (27% Indigenous population)
Spain (Esteban et al.) (19)									
2003	122	573 149	15 852	> 18 years	199 (597¶)	104	-	28	Period prevalence study, three hospitals in Madrid, 4-month-period
Retrospective studies									
Norway (Flaatten) (37)									
1999	365	4 461 913	700 107	no neonatals	3 683	83¶	57.9 (severe sepsis)	27 (severe sepsis)	Norwegian Patient Registry, all patients admitted in 1999, ICD-10
Taiwan (Shen et al.) (42)									
1997	365	191 510 (ar)	191 510 (ar)	all ages	300 (ar)	153	-	30.8	National Health Insurance Research Database, 99% of in- and outpatient data of the population, ICD-9
2006	365	210 127 (ar)	210 127 (ar)	all ages	662 (ar)	359	-		
Spain (Inigo et al.) (41)									
2001	365	5 423 384	537 223	all ages	6 968	141	62.5	33	Minimum Basic Hospital Data Set from the Region of Madrid in 2001, ICD-9

US (Angus et al.) (40)									
1995	365	63 497 167	6 621 559	all ages	192 980	300	63.8	28.6	Hospital discharge databases from all nonfederal hospitals (n = 847) in seven U.S. States, ICD-9-coding
US (Kumar et al.) (31)									
2000	365	209 130 000 (nc)	30 330 303	≥ 18 years	300 270	143	-	39.6	Data from the Nationwide Inpatient Sample (NIS), ICD-9
2007	365	227 240 000 (nc)	32 845 588	≥ 18 years	781 725	343	-	27.3	
US (Dombrovskiy et al.) (22)									
1993	365	257 783 000 (ar)	-	all ages	168 239	64.7	-	45.0	Hospital discharge database study based on the National Inpatient Sample 1993-2003, ICD-9
2003	365	290 447 644 (ar)	-	all ages	391 544	134.6	-	37.7	
US (Lagu et al.) (29)									
2003	365	217 068 000 (ar)	31 634 852	≥ 18 years	415 280	200	-	37	Data from the Nationwide Inpatient Sample (NIS) 2003-2007, ICD-9
2007	365	227 240 000 (ar)	32 716 306	≥ 18 years	711 736	300	-	29	
Australia (Sundararajan et al.) (39)									
1999-2003	1 460	4 500 000	3 122 515 (during 4 y)	all ages	13 297 (during 4 y)	65-76	-	31.1	Hospital discharge database study based on the Victorian Admitted Episodes Dataset, Victoria, Australia, ICD-10
Germany (Heublein et al.) (38)									
2011	365	81 843 700 (nc)	-	all ages	87 901	107	69.4 (severe sepsis)	42.8 (severe sepsis)	Hospital discharge data for Germany 2011, ICD-10

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US (Gaieski et al.) (30)									
2004-2009	2190	1 355 961 219 (nc)	196 096 962	>18 years	12 267 065	905	-	-	Nationwide Inpatient Sample (NIS), 2004-2009, ICD-9
2004-2009	2190	1 355 961 219 (nc)	196 096 962	> 18 years	13 980 089	1031	-	-	
2004-2009	2190	1 355 961 219 (nc)	196 096 962	> 18 years	4 067 836	300	-	14.7	
2004-2009	2190	1 355 961 219 (nc)	196 096 962	> 18 years	5 001 750	369	-	29.9	
Sweden (Wilhelms et al.) (28)									
1987-2005	6935	166 737 000 (nc)	-	all ages	44 744	10-35	-	22.1	Swedish hospital discharge database, 1987-2005, ICD-9 + ICD-10
1987-2005	6935	166 737 000 (nc)	-	all ages	32 649	26-43	-	22.4	
1987-2005	6935	166 737 000 (nc)	-	all ages	15 045	3-13	-	29.2	
US (Barnato et al.) (43)									
2001	365	71 102 655	8 940 278	all ages	282 292	397	-	24.6	Hospital discharge datasets from seven US states in 2001, ICD-9
US (Lagu et al.) (32)									
2007	365	227 240 000 (ar)	32 716 306	≥ 18 years	2 513 425	1061	-	14.1	Data from the Nationwide Inpatient Sample (NIS) 2007, ICD-9
2007	365	227 240 000 (ar)	32 716 306	≥ 18 years	1 801 689	761	-	8.2	
US (Martin et al.) (25)									
1979	365	224 567 000 (nc)	-	all ages	31 338¶	14¶	-	-	National Hospital Discharge Survey, 1979-2000, ICD-9
2000	365	281 425 000 (nc)	-	all ages	256 033¶	91¶	-	-	

US (Danai et al.) (36)									
1979-2003	9125	6 384 773 427 (nc)	-	all ages	3 831 394	13-15	-	37	Data from the National Hospital Discharge Survey, 1979-2003, ICD-9
Spain (Ballester et al.) (21)									
1995-2004	3650	41 677 000 (nc)	23 351 859	all ages	17 834	43¶	-	-	Discharge diagnoses in all 26 public hospitals in the Valencian Community, Spain, 10-year-period, ICD-9
Spain (Bouza et al.) (35)									
2006	365	44 708 937 (ar)	22 070 672 (during 6 y)	all ages	28 579	64	62.7	45.4	National Hospital Discharge Registry, 2006-2011, ICD-9
2011	365	47 190 493 (ar)		all ages	49 782	106	67.6	40.2	
Spain (Yebenes et al.)									
2008	365	7 364 000 (nc)	4 761 726 (during 5 y)	all ages	12 809	174¶	69	23.7	Administrative Registry of Minimum Basic dataset of Acute-care Hospitals (CMBD-HA), 2008-2012, ICD-9
2012	365	7 571 000 (nc)		all ages	20 228	267¶	73	19.7	

Legend:

Data are from the published study, unless indicated by (ar) – data supplied by the author or (nc) – national census

¶ recalculated

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Table 3: Population-level incidence rates for sepsis and severe sepsis cases treated in the emergency department (ED)

	study duration (days)	population	patients observed	age range	total number of sepsis cases	incidence (per 100 000 person-years)	mean age	Hospital mortality (%)	remarks
Sepsis									
Prospective studies									
Denmark (Henriksen et al.) (18)									
2010-2011	365	235 598	8 358	≥ 15 years	1 713	731	72 (median)	-	
Retrospective studies									
US (Strehlow et al.) (17)									
1992-2001	3650	-	712 000 000	adults	2 800 000	140	-	-	
Severe sepsis									
Prospective studies									
Denmark (Henriksen et al.) (18)									
2010-2011	365	235 598	8 358	≥ 15 years	1 071	265	-	-	

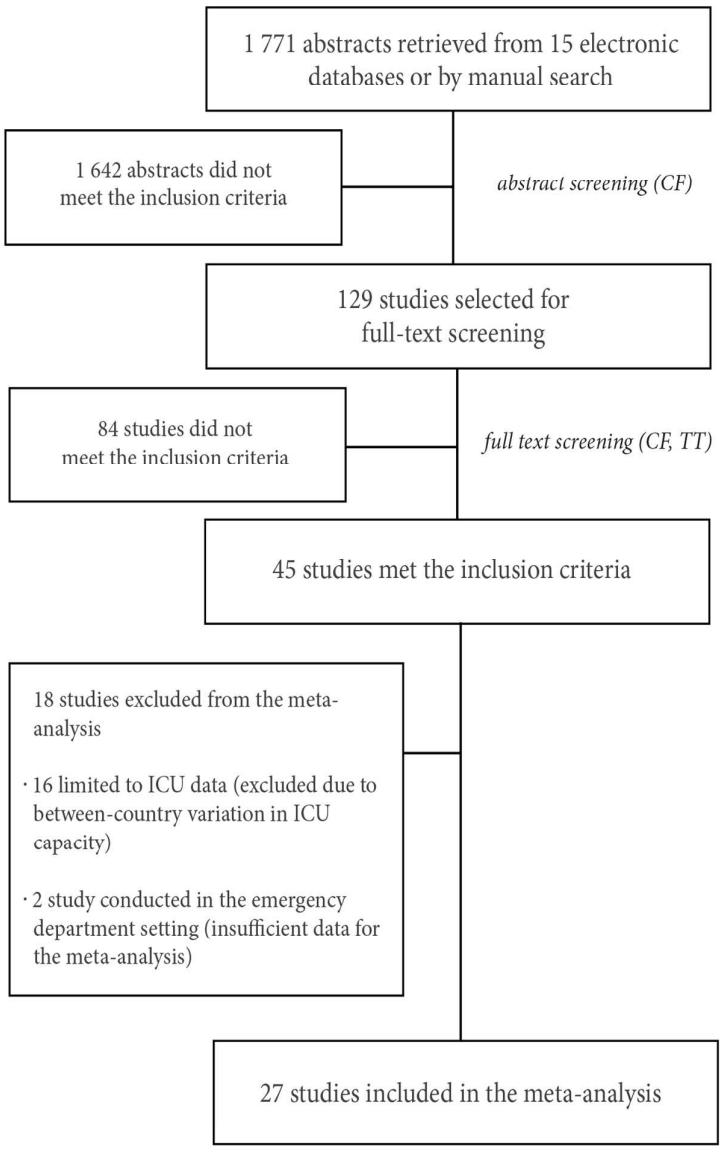

Figure 1: Flowchart of study selection for the systematic review and meta-analyses on global sepsis incidence and mortality

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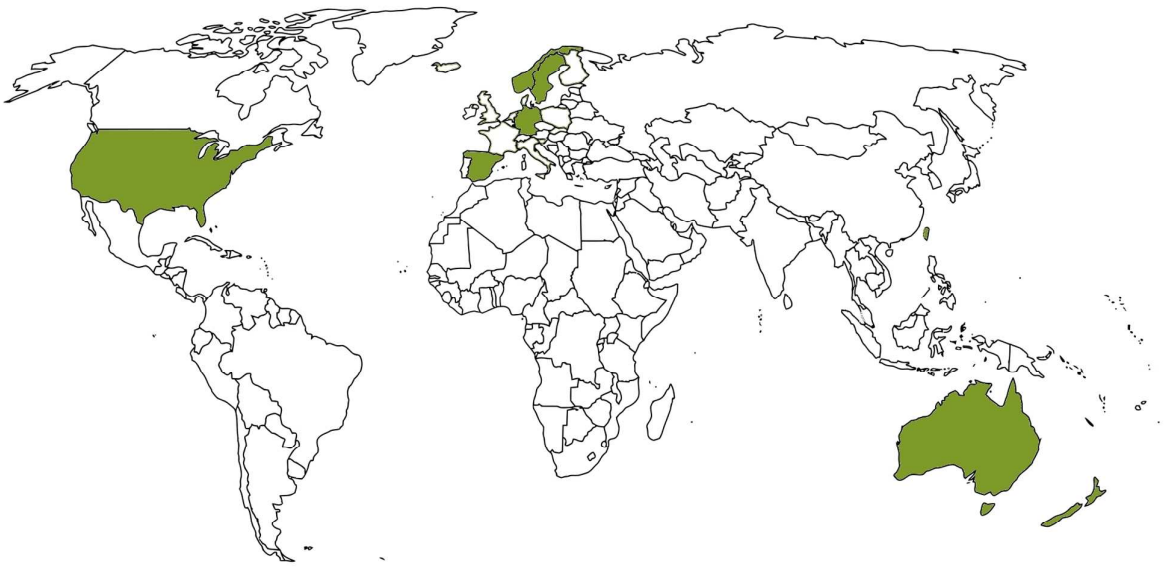

Figure 2: World map of included studies on sepsis and severe sepsis that present population-level incidence rates on hospital-treated sepsis and severe sepsis (USA, Germany, Australia, Taiwan, Norway, Spain, Sweden). Note that only studies on hospital-treated sepsis and severe sepsis were included in the meta-analysis.

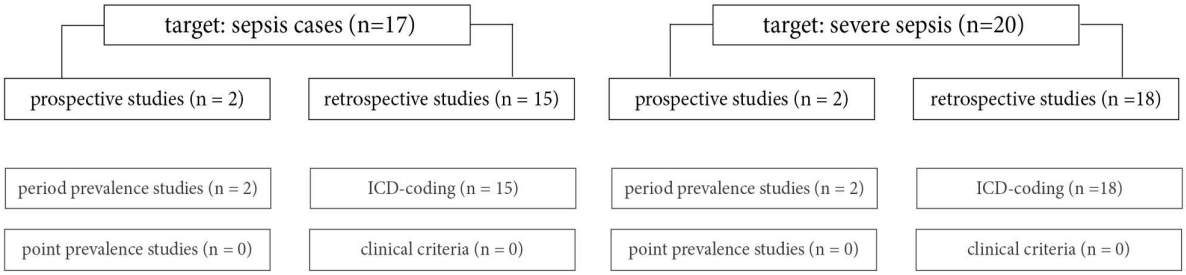

Figure 3: Framework for the classification of all epidemiological studies on hospital-treated sepsis and severe sepsis from 27 articles that were included for meta-analysis (note that studies could be counted more than once if they targeted both sepsis and severe).

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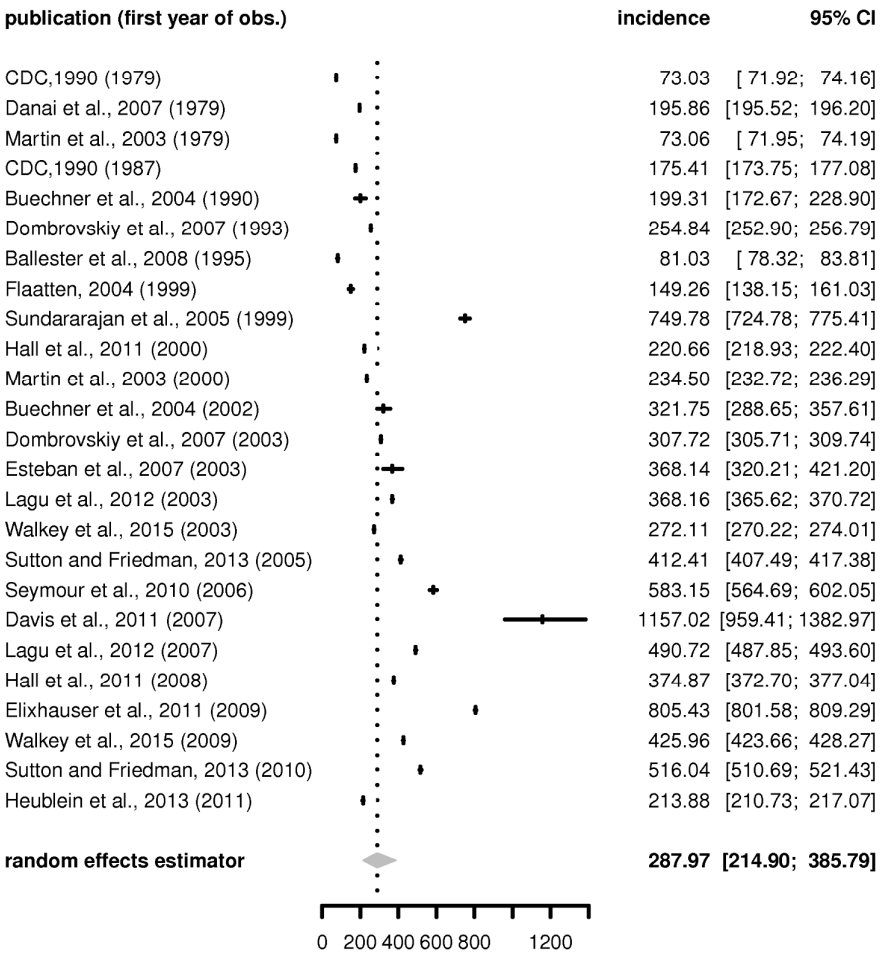
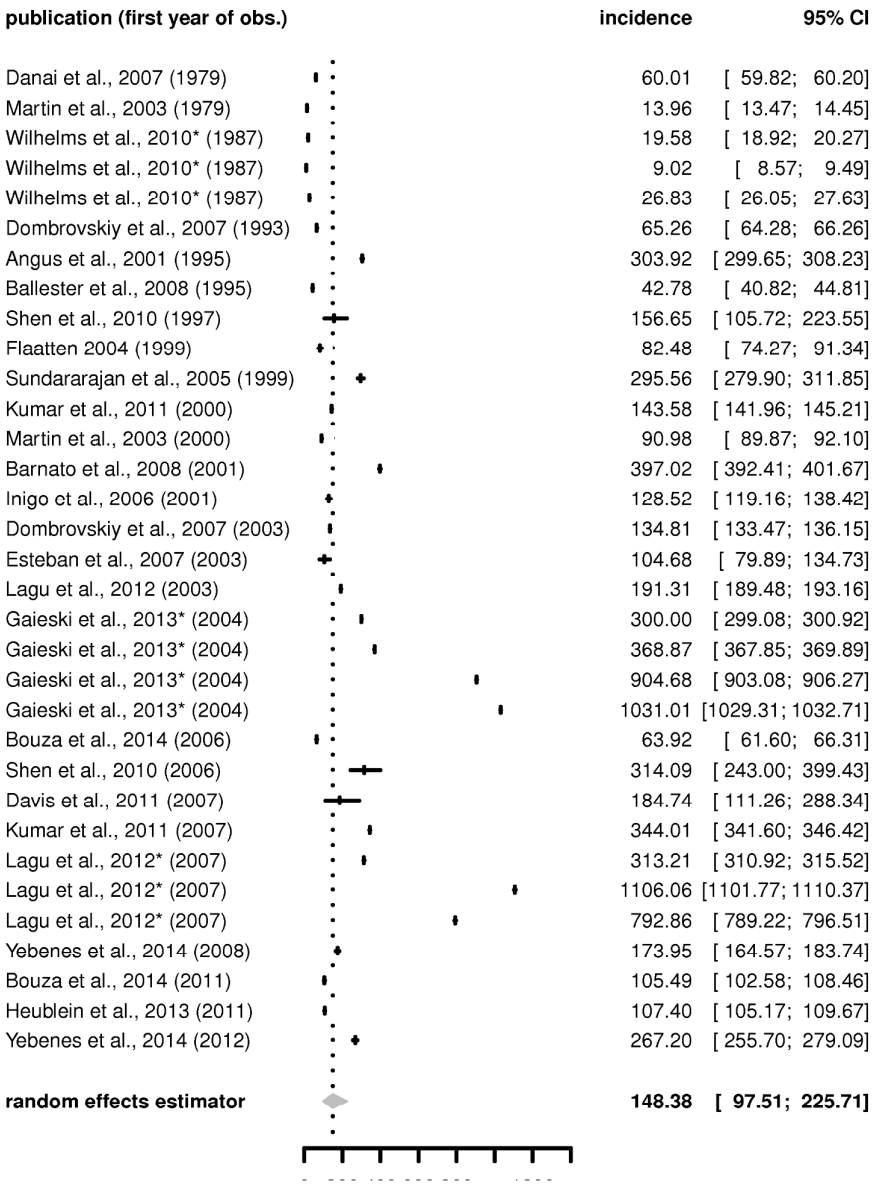


(A)



(B)

Figure 4: Population-level incidence rates per 100 000 person-years with 95% confidence intervals (CI) and a summarizing random effects estimator, (A) hospital-treated sepsis cases, (B) hospital-treated severe sepsis cases. Note that we applied approximations (details see Statistical analyses) to derive the estimates in (A) and (B).

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* Studies that use multiple severe sepsis identification strategies in administrative data. They were considered in sensitivity analysis according to the identification strategy and included in the combined meta-analysis to balance wider and more restricted severe sepsis definitions.

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Online Data Supplement

Assessment of global sepsis incidence and mortality – Current estimates and limitations

This supplement forms part of the original submission.

We post it as supplied by the authors.

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On behalf of the International Forum of Acute Care Trialists

*Derek Angus and Konrad Reinhart have equally contributed to the paper

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Search strategies

PUBMED

Search strategy: (Sepsis OR septic*) AND (Incidence OR Prevalence OR epidemiolog* OR burden)

Active limitations: Publication Date from 1979 to 2015, Species: Human, Field: Title

EMBASE

Search strategy: (SEPSIS OR SEPTIC?)/TI AND (INCIDENCE OR PREVALENCE OR EPIDEMIOLOG? OR BURDEN)/TI

Active limitations: Publication Date from 1979 to 2015, Species: Human, Field: Title

LILACS

Search strategy: (sepsis or septic$) and (incidence or prevalence or epidemiology or burden or epidemiological)

Active limitations: Field: Title

African Index Medicus (AIM)

Search strategy: sepsis AND epidemiologic$, sepsis AND incidence, sepsis AND burden, sepsis AND prevalence, septic$ AND epidemiolog$, septic$ AND incidence, septic$ AND burden, septic$ AND prevalence, sepsis

Active limitations: -

African healthline

Search strategy: see AIM

African Journals Online (AJOL)

Search strategy: see AIM

OpenGREY

Search strategy: see AIM

Pascal Biomed

Search strategy: sepsis AND epidemiologic*, sepsis AND incidence, sepsis AND burden, sepsis AND prevalence, septic* AND epidemiolog*, septic* AND incidence, septic* AND burden, septic* AND prevalence

Active limitations: Titel

IMEMR

Search strategy: (sepsis OR septic$) [Title] and (incidence OR prevalence OR epidemiolog$ OR burden) [Title]

Active limitations: Title

IndMed

Search strategy: ((sepsis:title OR:title septic$:title)) AND ((incidence:title OR:title epidemiologic$:title OR:title prevalence:title OR:title burden:title)) and single word combinations, see AIM

Active limitations: Title

Web of Science

AJRCCM Articles in Press. Published on 28-September-2015 as 10.1164/rccm.201504-0781OC

Search strategy: Title=((Sepsis OR septic*)) AND Title=((Incidence OR Prevalence OR epidemiolog* OR burden))

Active limitations: Timespan=1979-2015., Search language=English

IMSEAR

Search strategy: sepsis AND epidemiologic*, sepsis AND incidence, sepsis AND burden, sepsis AND prevalence, septic* AND epidemiolog*, septic* AND incidence, septic* AND burden, septic* AND prevalence

Active limitations: Title

WPRIM

Search strategy: sepsis AND epidemiologic*, sepsis AND incidence, sepsis AND burden, sepsis AND prevalence, septic* AND epidemiolog*, septic* AND incidence, septic* AND burden, septic* AND prevalence

Active limitations: Title

WHOLIS

Search strategy: sepsis AND epidemiologic*, sepsis AND incidence, sepsis AND burden, sepsis AND prevalence, septic* AND epidemiolog*, septic* AND incidence, septic* AND burden, septic* AND prevalence

Active limitations: Title

Information from study authors

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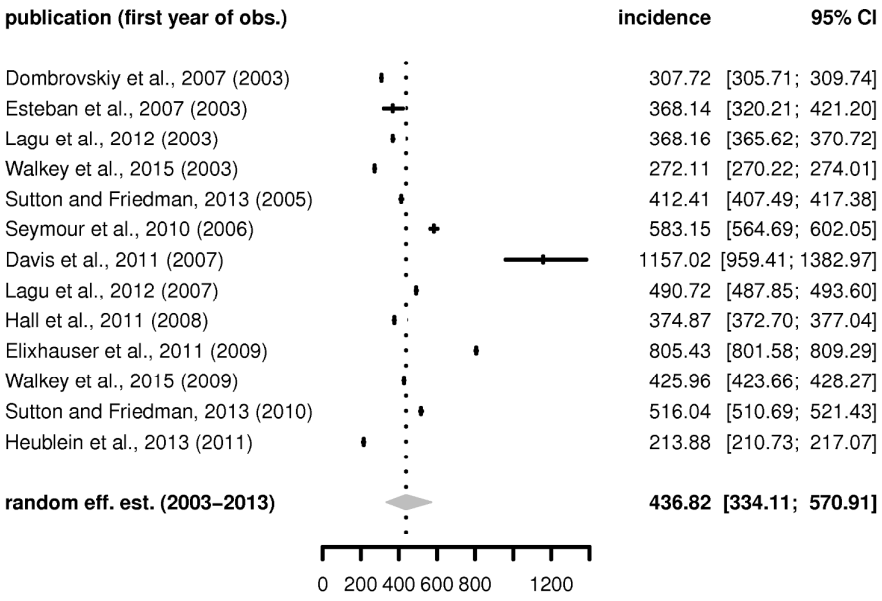

Figure E1: Population-level incidence rates of hospital-treated sepsis cases per 100 000 person-years with 95% confidence intervals (CI) and a summarizing random effects estimator (2003-2015).

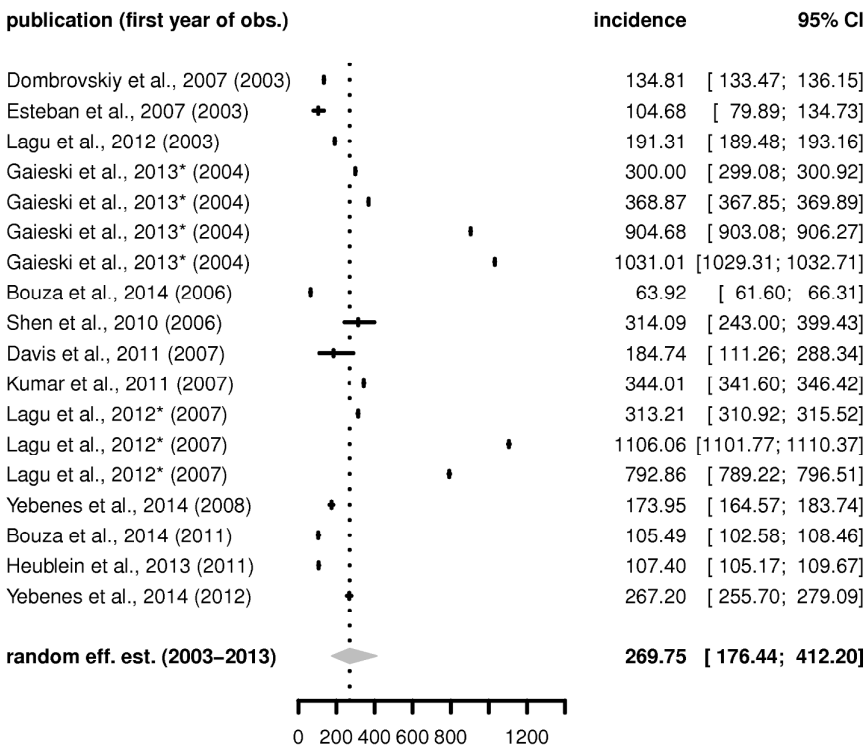

Figure E2: Population-level incidence rates of hospital-treated severe sepsis cases per 100 000 person-years with 95% confidence intervals (CI) and a summarizing random effects estimator (2003-2015).

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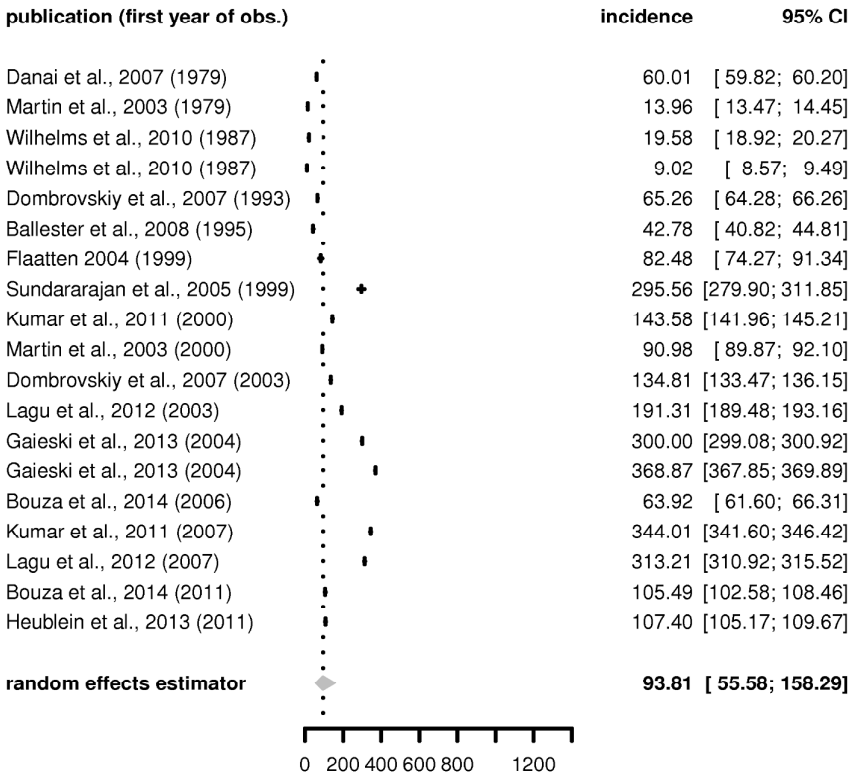
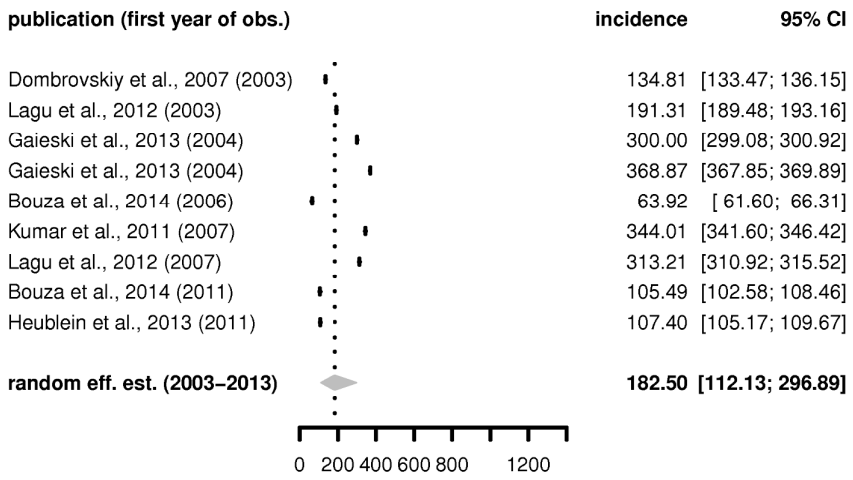


(A)



(B)

Figure E3: Population-level incidence rates of hospital-treated severe sepsis cases (restricted definition) per 100 000 person-years with 95% confidence intervals (CI) and a summarizing random effects estimator, (A) 1979-2015, (B) 2003-2015

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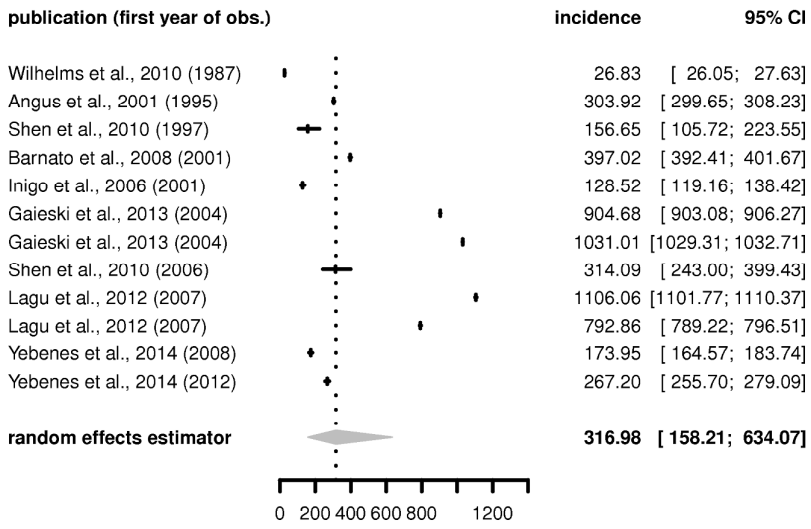

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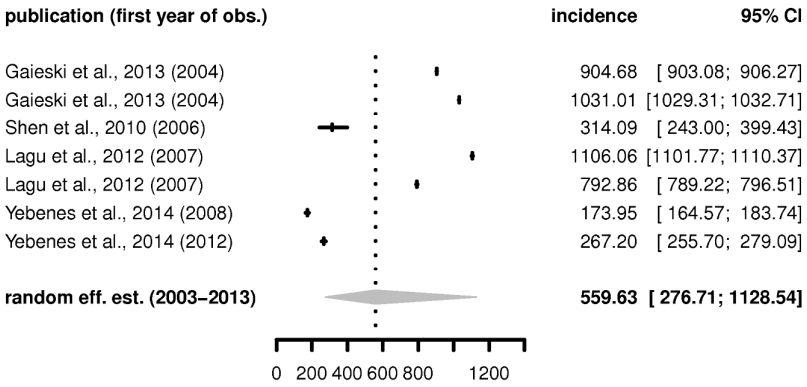
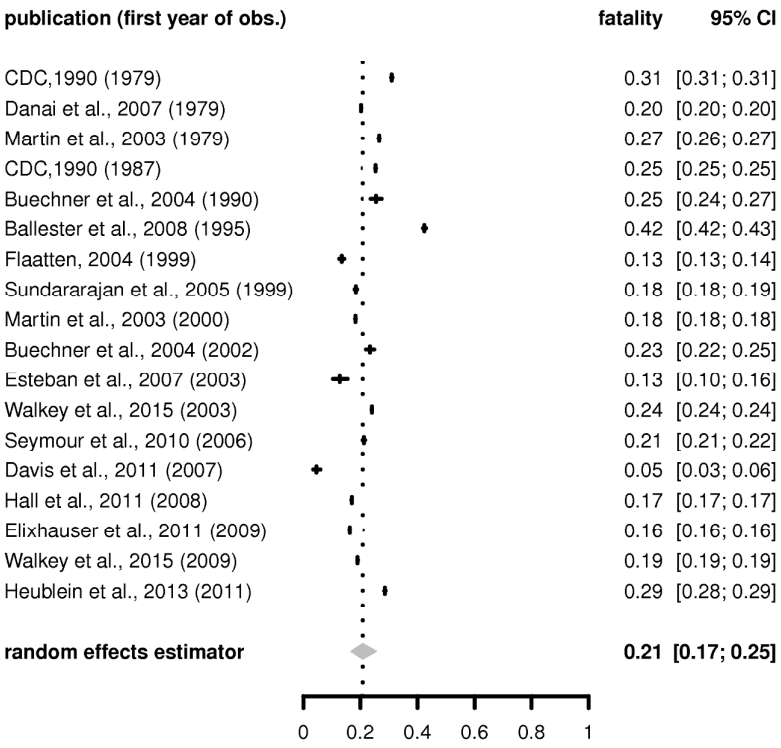


(B)

Figure E4: Population-level incidence rates of hospital-treated severe sepsis cases (wider definition) per 100 000 person-years with 95% confidence intervals (CI) and a summarizing random effects estimator, (A) 1979-2015, (B) 2003-2015



(A)

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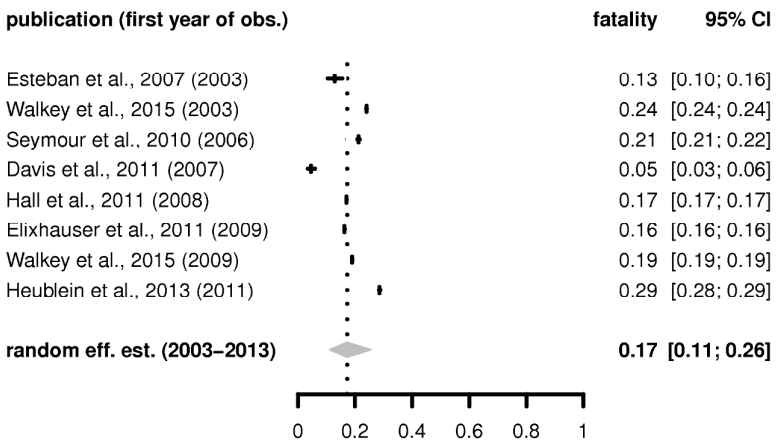
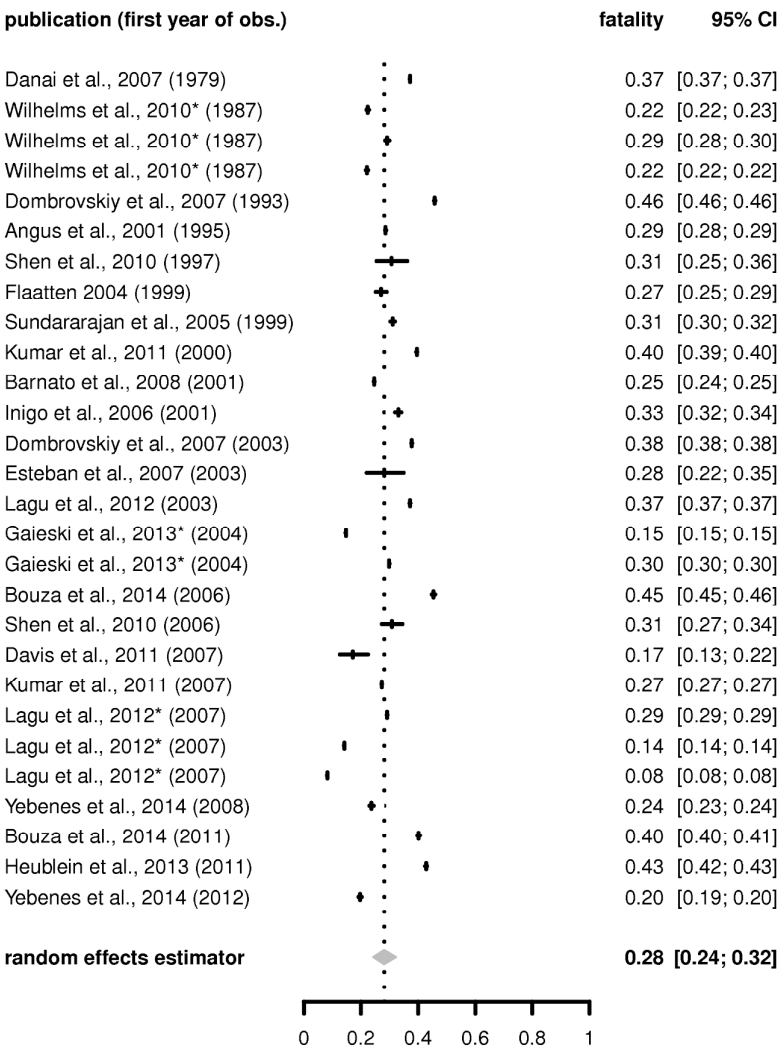


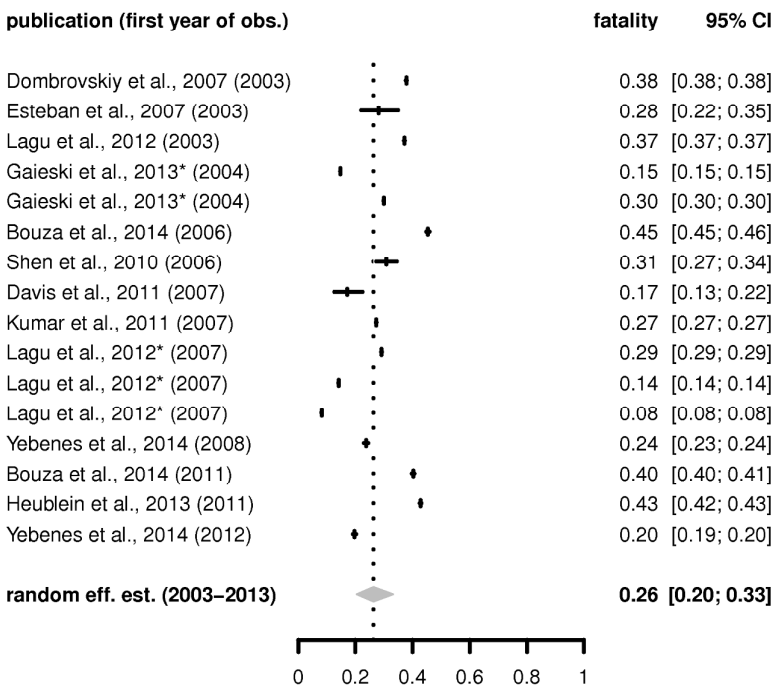
(B)

Figure E5: Case fatality rates of hospital-treated sepsis cases with 95% confidence intervals (CI) and a summarizing random effects estimator, (A) from 1979 to 2015, (B) from 2003 to 2015.



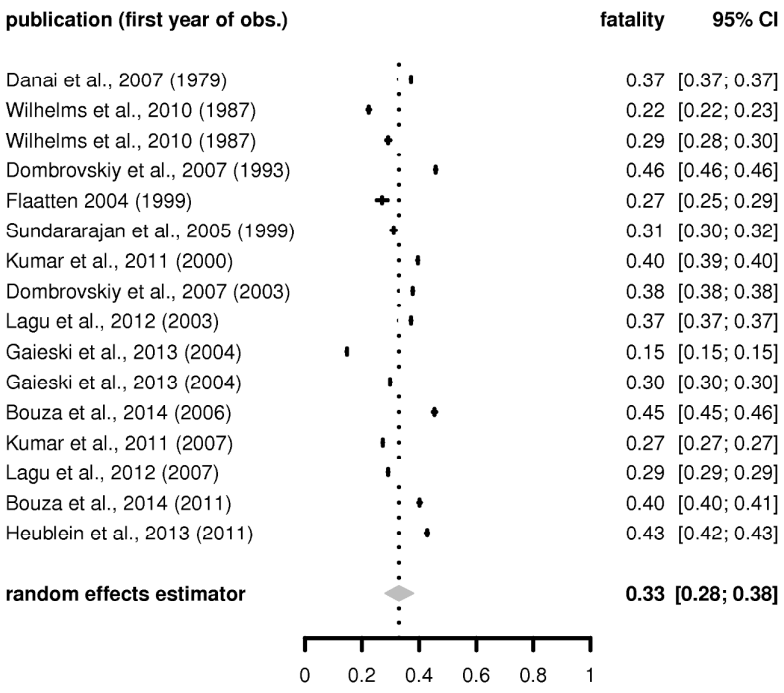
(A)

AJRCCM Articles in Press. Published on 28-September-2015 as 10.1164/rccm.201504-0781OC

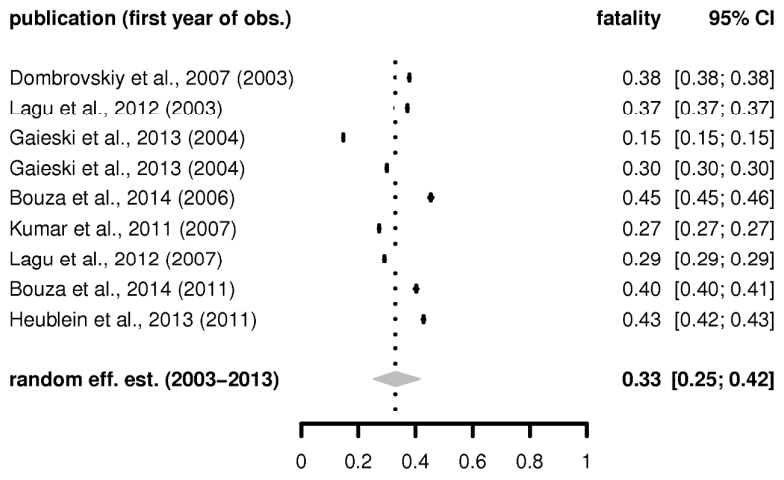


(B)

Figure E6: Case fatality rates of hospital-treated severe sepsis cases with 95% confidence intervals (CI) and a summarizing random effects estimator, (A) from 1979 to 2015, (B) from 2003 to 2015.



(A)



(B)

Figure E7: Case fatality rates of hospital-treated severe sepsis cases (restricted definition) with 95% confidence intervals (CI) and a summarizing random effects estimator, (A) from 1979 to 2015, (B) from 2003 to 2015.

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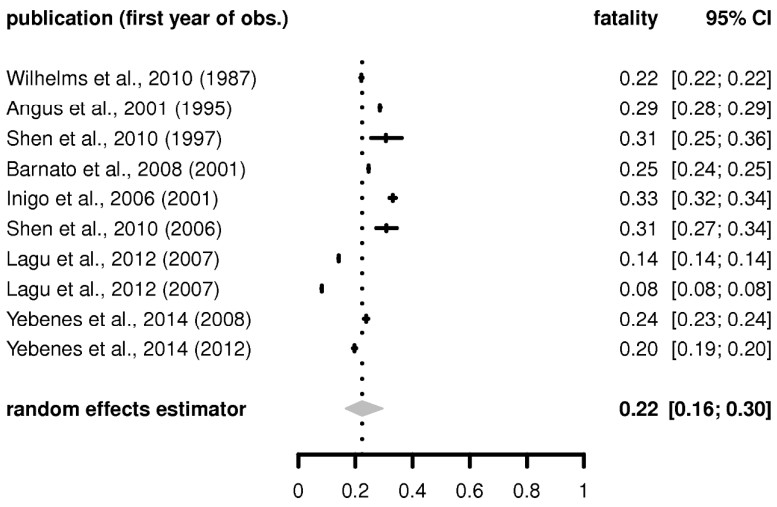
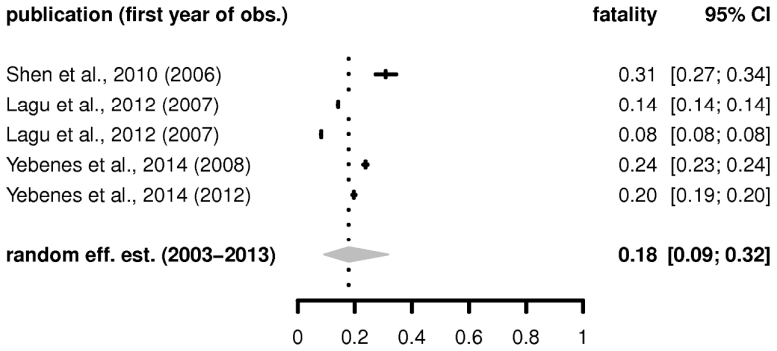


(A)



(B)

Figure E8: Case fatality rates of hospital-treated severe sepsis cases (wider definition) with 95% confidence intervals (CI) and a summarizing random effects estimator, (A) from 1979 to 2015, (B) from 2003 to 2015.