Online Supplement 1

Incidence and mortality of hospital- and ICU-treated sepsis: results from an updated and expanded systematic review and meta-analysis

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Supplementary Methods

M1. Search strategy

The following search strategy was used in PUBMED and adapted for the other databases.

Pubmed (and adapted for all other databases)

(((sepsis[Title] OR septic*[Title]) AND (Developing Countries*[Title/Abstract] OR Africa*[Title/Abstract] OR Asia*[Title/Abstract] OR Caribbean[Title/Abstract] OR West Ind*[Title/Abstract] OR South America*[Title/Abstract] OR Latin America*[Title/Abstract] OR Central America*[Title/Abstract] OR Afghanistan* OR Albania*[Title/Abstract] OR Algeria*[Title/Abstract] OR Angola*[Title/Abstract] OR Antigua*[Title/Abstract] OR Barbuda*[Title/Abstract] OR Argentina*[Title/Abstract] OR Armenia[Title/Abstract] OR Armenian[Title/Abstract] OR Aruba*[Title/Abstract] OR Azerbaijan*[Title/Abstract] OR Bahrain*[Title/Abstract] OR Bangladesh*[Title/Abstract] OR Barbados*[Title/Abstract] OR Benin*[Title/Abstract] OR Byelarus[Title/Abstract] OR Byelorussian[Title/Abstract] OR Belarus*[Title/Abstract] OR Belorussian[Title/Abstract] OR Belorussia[Title/Abstract] OR Beliz*[Title/Abstract] OR Bhutan*[Title/Abstract] OR Bolivia*[Title/Abstract] OR Bosnia*[Title/Abstract] OR Herzegovina*[Title/Abstract] OR Hercegovina*[Title/Abstract] OR Botswana*[Title/Abstract] OR Brasil*[Title/Abstract] OR Brazil*[Title/Abstract] OR Bulgaria*[Title/Abstract] OR Burkina Faso*[Title/Abstract] OR Burkina Fasso*[Title/Abstract] OR Upper Volta*[Title/Abstract] OR Burundi*[Title/Abstract] OR Urundi*[Title/Abstract] OR Cambodia*[Title/Abstract] OR Khmer Republic*[Title/Abstract] OR Kampuchea*[Title/Abstract] OR Cameroon*[Title/Abstract] OR Cameroons*[Title/Abstract] OR Cameron*[Title/Abstract] OR Cape Verde[Title/Abstract] OR Central African Republic*[Title/Abstract] OR Chad*[Title/Abstract] OR Chile*[Title/Abstract] OR China*[Title/Abstract] OR Colombia*[Title/Abstract] OR Comoros*[Title/Abstract] OR Comoro Island*[Title/Abstract] OR Comores[Title/Abstract] OR Mayotte[Title/Abstract] OR Congo*[Title/Abstract] OR Zaire*[Title/Abstract] OR Costa Rica*[Title/Abstract] OR Cote d'Ivoire[Title/Abstract] OR Ivory Coast[Title/Abstract] OR Croatia*[Title/Abstract] OR Cuba*[Title/Abstract] OR Cyprus*[Title/Abstract] OR Czechoslovakia*[Title/Abstract] OR Czech Republic*[Title/Abstract] OR Czechia*[Title/Abstract] OR Slovakia*[Title/Abstract] OR Slovak Republic*[Title/Abstract] OR Djibouti*[Title/Abstract] OR French Somaliland*[Title/Abstract] OR Dominica*[Title/Abstract] OR Dominican Republic*[Title/Abstract] OR East

Timor*[Title/Abstract] OR East Timur*[Title/Abstract] OR Timor Leste*[Title/Abstract] OR Ecuador*[Title/Abstract] OR Egypt*[Title/Abstract] OR United Arab Republic*[Title/Abstract] OR El Salvador*[Title/Abstract] OR Eritrea*[Title/Abstract] OR Estonia*[Title/Abstract] OR Ethiopia*[Title/Abstract] OR Fiji*[Title/Abstract] OR Gabon*[Title/Abstract] OR Gabonese Republic[Title/Abstract] OR Gambia*[Title/Abstract] OR Gaza*[Title/Abstract] OR Georgia Republic*[Title/Abstract] OR Georgian Republic*[Title/Abstract] OR Ghana*[Title/Abstract] OR Gold Coast*[Title/Abstract] OR Greece[Title/Abstract] OR Grenada*[Title/Abstract] OR Guatemala*[Title/Abstract] OR Guinea*[Title/Abstract] OR Guam*[Title/Abstract] OR Guiana*[Title/Abstract] OR Guyana*[Title/Abstract] OR Haiti*[Title/Abstract] OR Honduras*[Title/Abstract] OR Hungar*[Title/Abstract] OR India OR Maldiv*[Title/Abstract] OR Indonesia*[Title/Abstract] OR Iran*[Title/Abstract] OR Iraq*[Title/Abstract] OR Isle of Man[Title/Abstract] OR Jamaica*[Title/Abstract] OR Jordan*[Title/Abstract] OR Kazakhstan*[Title/Abstract] OR Kazakh*[Title/Abstract] OR Kenya*[Title/Abstract] OR Kiribati*[Title/Abstract] OR Korea*[Title/Abstract] OR Kosovo*[Title/Abstract] OR Kyrgyzstan*[Title/Abstract] OR Kirghizia*[Title/Abstract] OR Kyrgyz Republic*[Title/Abstract] OR Kirghiz*[Title/Abstract] OR Kirgizstan*[Title/Abstract] OR Lao PDR*[Title/Abstract] OR Laos*[Title/Abstract] OR Latvia*[Title/Abstract] OR Lebanon*[Title/Abstract] OR Lesotho*[Title/Abstract] OR Basutoland*[Title/Abstract] OR Liberia*[Title/Abstract] OR Libya*[Title/Abstract] OR Lithuania*[Title/Abstract] OR Macedonia*[Title/Abstract] OR Madagascar*[Title/Abstract] OR Malagasy Republic*[Title/Abstract] OR Malaysia*[Title/Abstract] OR Malaya*[Title/Abstract] OR Malay*[Title/Abstract] OR Sabah*[Title/Abstract] OR Sarawak*[Title/Abstract] OR Malawi*[Title/Abstract] OR Nyasaland OR Mali*[Title/Abstract] OR Malta*[Title/Abstract] OR Marshall Island*[Title/Abstract] OR Mauritania*[Title/Abstract] OR Mauritius*[Title/Abstract] OR Agalega Island*[Title/Abstract] OR Mexico*[Title/Abstract] OR Micronesia*[Title/Abstract] OR Middle East*[Title/Abstract] OR Moldova*[Title/Abstract] OR Moldovia*[Title/Abstract] OR Moldovian*[Title/Abstract] OR Mongolia*[Title/Abstract] OR Montenegro*[Title/Abstract] OR Morocco*[Title/Abstract] OR Ifni*[Title/Abstract] OR Mozambique*[Title/Abstract] OR Myanmar*[Title/Abstract] OR Myanma*[Title/Abstract] OR Burma*[Title/Abstract] OR Namibia*[Title/Abstract] OR Nepal*[Title/Abstract] OR Netherlands Antilles[Title/Abstract] OR New Caledonia*[Title/Abstract] OR Nicaragua*[Title/Abstract] OR Niger*[Title/Abstract] OR Nigeria*[Title/Abstract] OR Northern Mariana Island*[Title/Abstract] OR Oman*[Title/Abstract] OR Muscat OR

Pakistan*[Title/Abstract] OR Palau*[Title/Abstract] OR Palestine*[Title/Abstract] OR Panama*[Title/Abstract] OR Paraguay*[Title/Abstract] OR Peru*[Title/Abstract] OR Philippines*[Title/Abstract] OR Philipines*[Title/Abstract] OR Phillipines*[Title/Abstract] OR Phillippines*[Title/Abstract] OR Poland*[Title/Abstract] OR Portugal*[Title/Abstract] OR Puerto Rico*[Title/Abstract] OR Romania*[Title/Abstract] OR Rumania*[Title/Abstract] OR Roumania*[Title/Abstract] OR Russia*[Title/Abstract] OR Russian*[Title/Abstract] OR Rwanda*[Title/Abstract] OR Ruanda*[Title/Abstract] OR Saint Kitts*[Title/Abstract] OR St Kitts*[Title/Abstract] OR Nevis*[Title/Abstract] OR Saint Lucia*[Title/Abstract] OR St Lucia*[Title/Abstract] OR Saint Vincent*[Title/Abstract] OR St Vincent*[Title/Abstract] OR Grenadines*[Title/Abstract] OR Samoa*[Title/Abstract] OR Samoan Island*[Title/Abstract] OR Navigator Island*[Title/Abstract] OR Navigator Island*[Title/Abstract] OR Sao Tome*[Title/Abstract] OR Saudi Arabia*[Title/Abstract] OR Senegal*[Title/Abstract] OR Serbia*[Title/Abstract] OR Montenegro*[Title/Abstract] OR Seychelles*[Title/Abstract] OR Sierra Leone*[Title/Abstract] OR Slovenia*[Title/Abstract] OR Sri Lanka*[Title/Abstract] OR Ceylon*[Title/Abstract] OR Solomon Island*[Title/Abstract] OR Somalia*[Title/Abstract] OR South Africa*[Title/Abstract] OR Sudan*[Title/Abstract] OR Suriname*[Title/Abstract] OR Surinam*[Title/Abstract] OR Swaziland*[Title/Abstract] OR eSwatini*[Title/Abstract] OR Syria*[Title/Abstract] OR Tajikistan*[Title/Abstract] OR Tadzhikistan*[Title/Abstract] OR Tadjikistan*[Title/Abstract] OR Tadzhik*[Title/Abstract] OR Tanzania*[Title/Abstract] OR Thailand*[Title/Abstract] OR Togo*[Title/Abstract] OR Togolese Republic*[Title/Abstract] OR Tonga*[Title/Abstract] OR Trinidad*[Title/Abstract] OR Tobago*[Title/Abstract] OR Tunisia*[Title/Abstract] OR Turk*[Title/Abstract] OR Turkmenistan*[Title/Abstract] OR Turkmen*[Title/Abstract] OR Uganda*[Title/Abstract] OR Ukrain*[Title/Abstract] OR Uruguay*[Title/Abstract] OR USSR*[Title/Abstract] OR Soviet Union*[Title/Abstract] OR Union of Soviet Socialist Republics*[Title/Abstract] OR Uzbekistan*[Title/Abstract] OR Uzbek*[Title/Abstract] OR Vanuatu*[Title/Abstract] OR New Hebrides*[Title/Abstract] OR Venezuela*[Title/Abstract] OR Vietnam*[Title/Abstract] OR Viet Nam*[Title/Abstract] OR West Bank*[Title/Abstract] OR Yemen*[Title/Abstract] OR Yugoslavia*[Title/Abstract] OR Zambia*[Title/Abstract] OR Zimbabw*[Title/Abstract] OR Rhodesia*[Title/Abstract] OR Cook Island*[Title/Abstract] OR Marshall Island*[Title/Abstract] OR Nauru*[Title/Abstract] OR Niue*[Title/Abstract] OR Papua New Guinea*[Title/Abstract] OR Tuvalu*[Title/Abstract] OR Vanuatu*[Title/Abstract]) AND ("1979/01/01"[PDat] : "3000/12/31"[PDat])) OR ((sepsis[Title] OR septic*[Title]) AND

(epidemiolog*[Title] OR incidence[Title] OR burden[Title] OR prevalence[Title]) AND ("2015/05/01"[PDat] : "3000/12/31"[PDat])) NOT "animals"[MeSH:noexp]

M2. Study selection process for the meta-analysis

The study selection and selection of estimates was performed as follows:

(1) If one study applied different sepsis case definition on one data source, e.g. comparing different clinical criteria or ICD-based case abstraction strategies, we preferred
   - Sepsis-3 to sepsis-2 or -1 criteria
   - Explicit to implicit ICD-based definition
   - In case of multiple explicit case definitions, we chose the most conservative estimate

(2) If two or more studies used the same data source or referred to the same population,
   - we included the most recent estimate
   - we allowed partial overlaps, e.g. if two studies used the same database observing sepsis incidence in several years, with just one year overlap

(3) We included the most recent year of observation in the meta-analysis, or the most recent time frame

The following Table provides an overview of the study selection from different studies with overlapping or identical data sources:

Country	Data source	Years reported	Selection
Spain			
Alvaro Meca et al.	Minimum Basic Data Set	2000-2004, 2005-2009, 2010-2013	2010-2013
Bouza et al.	Minimum Basic Data Set	2006,2011	2011
Bouza et al.	Minimum Basic Data Set	2006-2011	excluded
Inigio et al.	Minimum Basic Data Set (Region Madrid)	2001	2001
Ballester et al.	hospital discharge data Valencian hospitals	1995-2004	1995-2004
Yebenes et al.	Catalan Health System (CatSalut) Minimum Basic Data	2012	2012
US			
Stoller et al.	National Inpatient Sample	2008-2012	2008-2012
Lagu et al.	National Inpatient Sample	2003,2007	excluded
Lagu et al.	National Inpatient Sample	2007	excluded
Kumar et al.	National Inpatient Sample	2000,2007	excluded
Dombrovyski et al.	National Inpatient Sample	1993,2003	2003
Gaieski et al.	National Inpatient Sample	2004-2009	2004-2009
Martin et al.	National Hospital Discharge Survey	1979,2000	2000
Danai et al.	National Hospital Discharge Survey	1979-2003	excluded
Taiwan			
Shen et al.	random 1% sample of the national health insurance dataset	1997,2006	excluded
Lee et al.	national health insurance data set	2002-2012	2002-2012
Germany			
Fleischmann et al.	DRG statistics	2007-2013	2013
Fleischmann-Struzek et al.	DRG statistics	2010-2015	2015
Heublein et al.	DRG statistics	2011	2011
UK			
Harrison et al.	ICNARC Database	1996,2004	2004
Padkin et al.	ICNARC Database	1997	1997
Shankar-Hari et al.	ICNARC Database (England)	2011-2015	2011-2015

M3. Detailed description of statistical analyses

This part of the Supplement provides more details about the statistical modelling that we used for the meta-analyses of population-level incidence and mortality rates of hospital-treated and ICU-treated sepsis.

We chose generalized linear mixed models (GLMM) as the general class of models for the meta-analyses of incidence and mortality. The incidence is given by the ratio of the number of incident cases and the number of person-years, which can properly be modelled using Poisson models for count data. The natural logarithm $\ln(p_i)$ of the person-years p_i of the underlying study i are included as an offset variable. The meta-analytic Poisson model can be written as a random intercept model:

$$\begin{aligned}\ln\left(Y_i\right) &= \gamma_i + \ln\left(p_i\right) \\ &= \gamma_0 + u_i + \ln\left(p_i\right)\end{aligned}$$

The dependent variable Y_i is the number of sepsis cases. Hence, the random intercept γ_i is equal to logarithm of the ratio of incident cases and person-years in study i. The expected value $E(\gamma_i)$ of the random intercepts across the studies is γ_0. The variable u_i is the study-specific difference γ_i - γ_0 between the expected value and the random intercept. The systematic between-study variance is $\tau^2 = Var(u_i)$.
Similarly, the meta-analytic logistic model of the mortality can be written as a random intercept model:

$$\begin{aligned}\ln\left(\frac{M_i}{1-M_i}\right) &= \lambda_i \\ &= \lambda_0 + u_i\end{aligned}$$

M_i is the probability of hospital death among patients with sepsis. The logit of the mortality M_i in study i is equal to the random intercept λ_i. The expected value $E(\lambda_i)$ of the random intercepts across the studies is λ_0. Again u_i is the study-specific difference λ_i - λ_0 between the expected value and the random intercept of study i, and the systematic between-study variance is given by $\tau^2 = Var(u_i)$.

The parameters of interest are the expected values $E(\gamma_i) = \gamma_0$ and $E(\lambda_i) = \lambda_0$, as well as the between study variance τ^2 in both models. However, it is important to note that the Poisson model and the logistic model incorporate nonlinear link functions. Hence, the model parameters are on the log-scale or the logit scale. For better interpretation, the model parameters can be back transformed into the natural metric of incident cases per 100.000 person-years or the probability metric in percent. In the case of the Poisson model for the incidence rates the exponential function can be used for back transformation. However, the exponential function $\exp(\lambda_0)$ of the expected value λ_0 of the random intercepts γ_i is not equal to the average of the number of incident cases per person-years across the studies. From the Jensen's inequality follows that $\exp(\lambda_0)$ is smaller than the true average:

$$\exp\left(\gamma_0\right) \le E\left(\frac{\text{incident cases}}{\text{100.000 person years}}\right)$$

This is illustrated in Fig. E1a for the example of the incidence rate of the severe sepsis, which is presented in the main paper. The meta-analytic estimate γ_0 in the Poisson model is ≈ -6.273

(red line in the left graph of Fig. E1a). Using the back transformation $\exp(\gamma_0) \cdot 100.000$ gives the metaanlytic estimate on the scale of numbers of incident cases per 100.000 person-years. However, the distribution of the numbers of incident cases per 100.000 person-years across studies is highly skewed, which implies that the median and the average differ substantially. This is shown in the right graph of Fig. E1a. The back transformed parameter γ_0 (red line) is rather the median than the average (blue line).

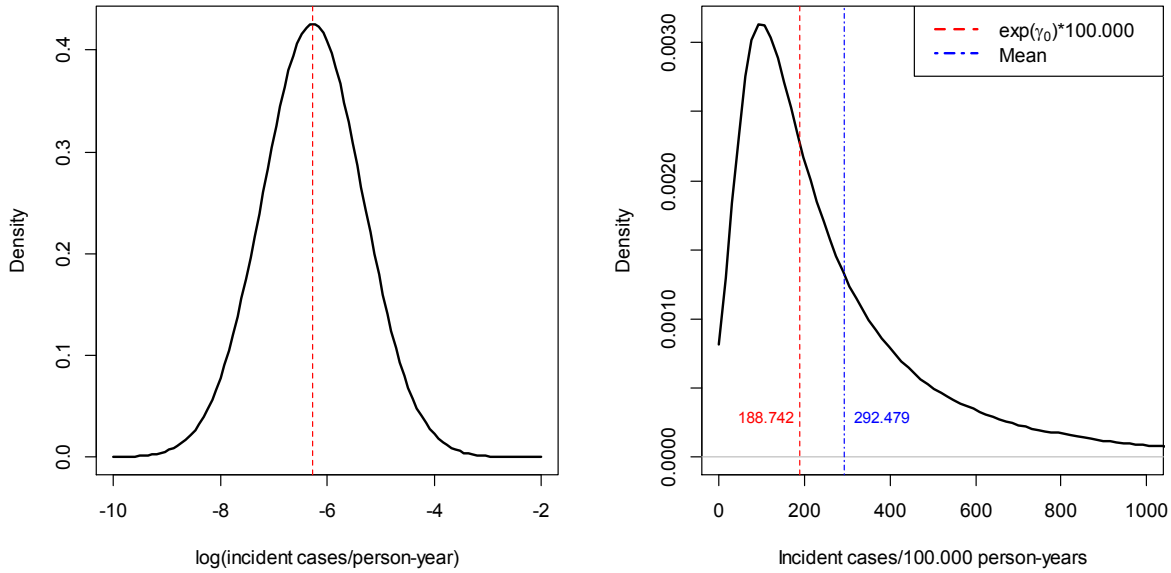


Figure E1a: Distributions of the random intercepts on the log scale (left) and the number of incident cases per 100.000 person years (right).

Given these differences we decided to present both, the commonly reported estimate $\exp(\gamma_0) \cdot 100.000$ as well as an estimate of the average of the number of incident cases per 100.000 person-years, which can be approximated by the integral:

$$E\left(\frac{\text{incident cases}}{100.000 \text{ person years}}\right) = 100.000 \cdot \int_{\mathbb{R}} \exp(\gamma_i)\, d\gamma_i$$

The integral is over the distribution of the random intercepts, which are commonly assumed to follow a normal distribution $\gamma_i \sim N(\gamma_0, \tau)$ in GLMMs. The integral cannot be derived analytically, but can be approximated by means of numerical integration. We used Gauss-Hermite quadrature with 25 nodes.

The problem is essentially the same in logistic models. Using the logistic distribution function, the meta-analytic estimate of the percentage of death among sepsis cases is $1/[1 + \exp(-\lambda_i)] \cdot 100$. However, Jensen's inequality implies

$$\frac{1}{\exp(-\lambda_0)} \leq E(M_i).$$

This is also be exemplified using the estimates of the meta-analysis of mortality of the sepsis, which is also reported in the main paper. The estimate of the average random intercept λ_0 is ≈

-1.013 (left graph of Figure E1b). Back transformation by means of the logistic distribution function gives an estimated mortality of 26.645% (right graph of Figure E1b). This is slightly lower than the model-implied average mortality rate, which is 27.602%.

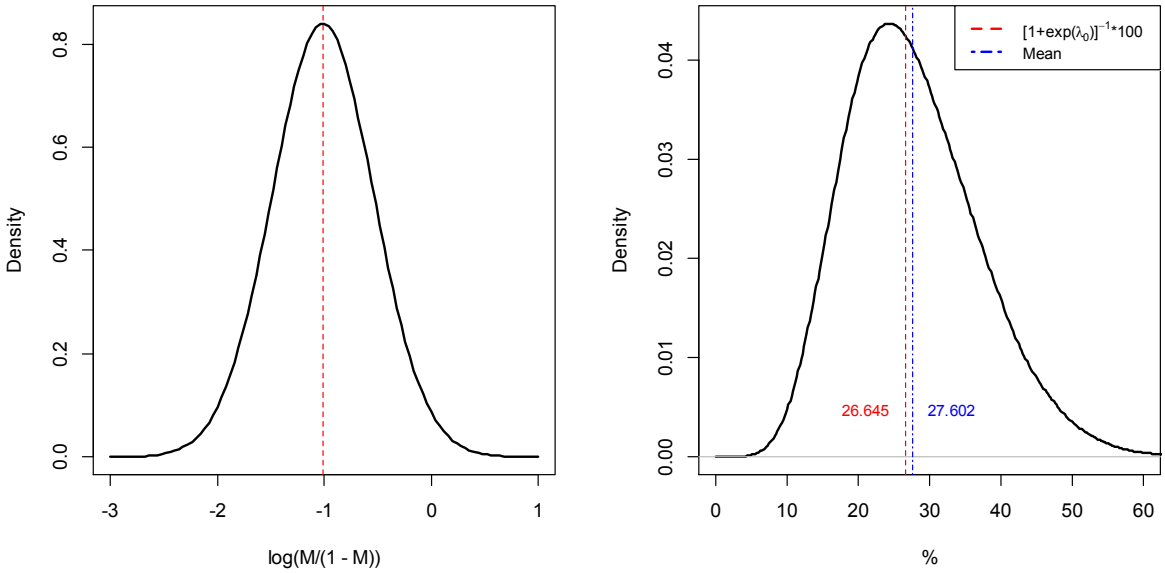


Figure E1b: Distributions of the random intercepts on the logit metric (left) and the mortality in % (right).

The average can be approximated using the integral:

$$E(M_i) = 100 \cdot \int_{\mathbb{R}} \frac{1}{1+\exp(-\lambda_i)} d\lambda_i$$

The integral is over the distribution of the random intercepts in the meta-analytic logistic regression model. According to the model assumptions in GLMMs a normal distribution $\lambda_i \sim N(\lambda_0, \tau)$ is assumed. Again, the integral cannot be derived analytically. Therefore, it is approximated using Gauss-Hermite quadrature with 25 nodes.

In order to analyse differences in incidence and mortality rates across WHO regions we extended the meta-analytic random intercepts model to a meta-regression model by including predictors at the study level. The resulting meta-analytic Poisson model and logistic model are given by:

$$\ln(Y_i) = \underbrace{\gamma_0 + u_i}_{\gamma_i} + \ln(p_i) + \gamma_A I_{AFRO} + \gamma_P I_{PAHO} + \gamma_W I_{WPRO}$$

$$\ln\left(\frac{M_i}{1-M_i}\right) = \underbrace{\lambda_0 + u_i}_{\lambda_i} + \lambda_A I_{AFRO} + \lambda_P I_{PAHO} + \lambda_W I_{WPRO}$$

The dummy variables I_{AFRO}, I_{PAHO} and I_{WPRO} indicate the region of the study population. The EURO region was chosen as the reference region. The random intercepts in both models were assumed be follow a normal distribution within the WHO regions with $\gamma_i \sim N(\gamma_0, \tau)$ and $\lambda_i \sim N(\lambda_0, \tau)$. Based on these models an omnibus test was conducted which tested the Null hypothesis of no differences in incidence or mortality rates between all WHO regions. An *F*-Test according to Knapp and Hartung (1) was used. Post-hoc comparisons between all pairs

of regions were conducted based on the general linear hypothesis. The *p*-values were adjusted for multiple testing based on the approach proposed by Hothorn et al. (2). The results of the subgroup analyses are presented in Table E8. The point estimates of the incidence and mortality rates for each WHO region are presented Table E6.

The same procedure was used to analyze the potential dependence of incidence and mortality rates from different sepsis case definitions that were applied in the included studies (clinical criteria (sepsis-1, -2 or -3) vs. ICD-case identification (implicit or explicit case identification)). The meta-regression models were specified as

$$\ln\left(Y_i\right) = \underbrace{\gamma_0 + u_i}_{\gamma_i} + \ln\left(p_i\right) + \gamma_2 I_{Sepsis-2} + \gamma_3 I_{Sepsis-3} + \gamma_{imp} I_{imp} + \gamma_{\exp} I_{\exp}$$

$$\ln\left(\frac{M_i}{1-M_i}\right) = \underbrace{\lambda_0 + u_i}_{\lambda_i} + \lambda_2 I_{Sepsis-2} + \lambda_3 I_{Sepsis-3} + \lambda_{imp} I_{imp} + \lambda_{\exp} I_{\exp}$$

The dummy variables $I_{Sepsis\text{-}2}$, $I_{Sepsis\text{-}3}$, I_{imp}, and I_{exp} indicate the sepsis case definitions that were used in the study. The clinical sepsis definition Sepsis-1 served as the reference method. The random intercepts in both models were assumed to follow a normal distribution within each sepsis case definition with $\gamma_i \sim N(\gamma_0, \tau)$ and $\lambda_i \sim N(\lambda_0, \tau)$. The Null hypothesis of independence of incidence or mortality rates from the sepsis case definitions was tested with an *F*-Test proposed by Knapp and Hartung (1). Pairwise post-hoc comparisons between all sepsis case definitions were conducted based on the general linear hypothesis with adjusted *p*-values for multiple testing. The results are shown in Table E9. The point estimates of the incidence and mortality rates according to the different sepsis case definitions are presented Table E7.

Note that the Forest plots presented in the paper and the Supplement contain not only point estimates of incidence and mortality rates from the single studies, but also 95% confidence intervals. In the case of incidence rates 95% Poisson-CIs are reported and 95% Wilson score intervals for mortality rates.

For the meta-analytic estimates of the overall incidence and mortality rate, we report the model-based confidence intervals as well as the 95% prediction intervals for future studies. The latter does not quantify the accuracy of the overall estimate obtained by a meta-analysis. The prediction interval is meaningful regarding a single study in the future, which is representative for the studies that were included in the meta-analysis. In our case, it is the range in which the estimated incidence rate or mortality rate from a new single study can be expected with the probability of $p = 0.95$, given that the new study is representative for the studies included in the meta-analysis.

Supplementary Tables

Table E1: Overview on the included studies on hospital-treated sepsis incidence

Author, publication year, country	**study duration in days (years covered)**	**population**	**patients observed**	**age range**	**total number of sepsis cases**	**incidence (per 100 000 person-years)**	**mean age**	**hospital case fatality (%)**	**remarks**
Prospective studies									
Todorovic, 2019, Denmark (3)	548 (2013-2015)	37,870	3,615	≥16 years	287	719	-	13.5 (sepsis with organ dysfunction), 75 (septic shock)	Prospective observational study, single center, sepsis definition: sepsis-1 Data on community-acquired sepsis only, thus not included in the meta-analysis
Retrospective studies									
Mellhammar, 2016, Sweden (4)	**4 (2015)**	**1,275,753**	**563**	**≥18 years**	**109**	**780**	**Median 80**	**17**	**Patient chart review, multi center study in 2 regions of Sweden, sepsis definition: sepsis-3** **This estimate was included in the meta-analysis.**
Mellhammar, 2016, Sweden (4)	4 (2015)	1,275,753	563	≥18 years	96	687	Median 78	20	Patient chart review, multi center study in 2 regions of Sweden, sepsis definition: sepsis-2

Bouza, 2016, Spain (5)	2 190 (2006-2011)	277,024,827 †	-	≥18 years	138,517	61	71	55	Nationwide administrative data base, case identification: explicit ICD-9 sepsis codes Identical data source as Bouza et al. 2014 (6), thus not included in the meta-analysis.
Stoller, 2016, US (7)	**1825 (2008-2012)**	**308,745,538**	**-**	**>18 years**	**6,067,789**	**393***	**69**	**22 (2008) – 17 (2012)§**	**National Inpatient Sample, case identification: explicit septicemia, bacteremia, fungemia + organ dysfunction ICD codes**
Knoop, 2017, Norway (8)	**730 (2011-2012)**	**9,906,175**	**1,767,535**	**All ages**	**18,460**	**140**	**73**	**26**	**Nationwide administrative data base, case identification: explicit ICD-10 sepsis or infection + organ dysfunction codes**
Rhee, 2017, US (9)	**365 (2014)**	**318,386,421 #**	**2,901,019**	**Adult**	**173,690**	**534***	**Median 62**	**15**	**Electronic health records of 409 academic, community, and federal hospital, sepsis definition: sepsis-3**
Fleischmann-Struzek, 2018, Germany (10)	365 (2010) **365 (2015)**	81,751,602 **82,175,684**	17,433,846 **18,664,877**	**All ages**	87,973 **136,542**	108 **158**	69 **70**	48 **42**	**Nationwide administrative data base, case identification: explicit ICD-10 sepsis codes** **The 2015 estimate was included in the meta-analysis.**
Fleischmann-Struzek, 2018, Germany (10)	365 (2010) 365 (2015)	81,751,602 82,175,684	17,433,846 18,664,877	All ages	770,258 1,166,061	942 1,336	67 70	19 17	Nationwide administrative data base, case identification: implicit ICD-10 coding strategy (infection and organ dysfunction)

Kim, 2019, Korea (11)	365 (2005) **365 (2012)**	825,502 **863,820**	**-**	**≥15 years**	2,194 **3,915**	265 **453**	**-**	27 (6 months) **32 (6 months)**	**National sample cohort, case identification: implicit ICD-10 coding strategy (infection and organ dysfunction) + prescription of antibiotics**
Marques, 2007, Brazil (12)	**365 (2005-2006)**	**5,200,000**	**5,200,000**	**All ages**	**11,067**	**212**	**-**	**-**	**Private health plans' electronic claims, sepsis definition: sepsis-1**
Zhou, 2017, China (13)	**730 (2012-2014)**	**128,695**	**21,191**	**≥18 years**	**498**	**194**	**Median 66**	**26§ (only sepsis without organ dysfunction)**	**Patient chart review, all public hospitals in Yuetan Subdistrict, Beijing, sepsis definition: sepsis-1, 2012 Surviving Sepsis Campaign guidelines**
Lee, 2017, Taiwan (14)	**4,015 (2002-2012)**	**230,112,717**	**230,112,717**	**All ages**	**1,259,578**	**639**	**68-70**	**23 (2002) -18 (2012)§**	**Nationwide administrative data base, case identification: implicit ICD-9 coding strategy (infection and organ dysfunction)**
Fleischmann, 2016, Germany (15)	**365 (2013)**	**80,767,463**	**18,133,338**	**All ages**	**115,421**	**138**	**-**	**43.6**	**Nationwide administrative data base, case identification: explicit ICD-10 sepsis codes**
Álvaro-Meca, 2018, Spain (16)	1,825 (2000-2004) **1,460 (2010-2013)**	207,799,359 # **186,658,379 #**		**All ages**	686,062 **976,176**	330 **455**	68 **71**	19* **18***	**Nationwide administrative data base, case identification: implicit ICD-9 coding strategy (infection and organ dysfunction)**

Huggan, 2019, New Zealand (17)	**1,825 (2007-2012)**	**403,368**	**209,730**	**All ages**	**1,643**	**82***	**Median 38**	**19**	**Administrative data base of hospitals in the Waikato region of New Zealand, case identification: implicit ICD-10 coding strategy (infection and organ dysfunction)**
Goodwin, 2016, US (18)	**365 (2010)**	**3,400,939**	**339,670**	**≥20 years**	**24,395**	**717***	**-**	**18***	**Administrative data base of nonfederal hospitals in South Carolina, case identification: explicit ICD-9 sepsis codes**
Dupuis 2017, France (19)	2,190 (2009-2014)	309,535,931 †	25,444,627	Adults	421,699 (septic shock only)	136 (septic shock only)	-	40 (septic shock only)	Nationwide administrative data base, case identification: ICD-10 septic shock codes or vasopressor use + infection codes, only data on septic shock, thus not included in the meta-analysis
De Miguel Yanes, 2015, Spain (20)	1825 (2008-2012)	192,997,924 †	16,598,511	≥18 years	88,092 (septic shock only)	46* (septic shock only)	-	52* (septic shock only)	Nationwide administrative data base, multi center, case identification: explicit ICD-9 septic shock codes, only data on septic shock, thus not included in the meta-analysis
Lorencio, 2018, Spain (21)	365 (2005) 365 (2016)	-	-	All ages	224,396 (all years)	160 390	-	26 17	Administrative data base in the region of Catalonia, case identification: implicit ICD-9 sepsis coding strategy (infection and organ dysfunction) Data partly included in other publication, missing population denominator, thus not included in

									meta-analysis

Bold letters highlight the studies or estimates that were included in the meta-analysis.

* recalculated based on the cases and population as provided in the publication and searched in national census registries or based on sepsis deaths and cases

searched in national census registries

† data provided by the author

§ case fatality estimates not included in meta-analysis

Table E2: Overview on the included studies on ICU-treated sepsis incidence

years	study duration (days)	population	patients observed	age range	total number of sepsis cases	incidence (per 100 000 person-years)	mean age	hospital case fatality (%)	remarks
Prospective studies									
Author, year									
Nzarora, 2016, Rwanda (22)	**426 (2013-2014)**	**13,741,172#**	**504**	**≥ 16 years**	**220**	**2***	**-**	**71**	**Prospective cohort study, two study centers, sepsis definition: sepsis-1**
Herran-Monge, 2017, Spain (23)	**150**	**2,025,248**	**1,874**	**≥ 18 years**	**231**	**31**	**67**	**37**	**Prospective, multicenter, observational study, 11 ICUs, sepsis definition: sepsis-2**
Kübler, 2015, Poland (24)	1 (2012) **1 (2013)**	38,533,000 **38,496,000**	1,398 **860**	All ages	364 **191**	69 **60**	-	-	**Questionnaire sent to ICUs, multicenter, surviving sepsis campaign guidelines (Dellinger 2008)**
Machado, 2017, Brazil (25)	**1 (2014)**	**144,483,698†**	**2,632**	**≥ 18 years**	**794**	**290**	**66**	**56**	**Prospective, multicenter study, 227 ICUs, sepsis definition: sepsis-1**

Bertullo, 2016, Uruguay (26)	**365 (2011-2012)**	**800,000**	**1,834**	**≥ 18 years**	**153**	**19***	**Median 68**	**55**	**Prospective, multicenter study, 5 ICUs, sepsis definition: sepsis-1**
Azkárate, 2015, Spain (27)	**2,190 (2008-2013)**	**700,000**	**-**	**Not specified**	**1,136**	**27***	**62-65**	**18***	**Prospective observational study, single center, sepsis definition: sepsis-2**
Almirall, 2016, Spain (28)	**3,285 (2002-2011)**	**180,000**	**-**	**>16 years**	**917 (community acquired sepsis)**	**52 (community acquired sepsis)**	**65**	**19.7 (community acquired sepsis)**	**Prospective observational study, single-center, sepsis definition: sepsis definition not specified, limited to community-acquired sepsis cases, thus we excluded the study from the meta-analysis**
Retrospective studies									
Author, year									
Rhee, 2017, US (9)	**365 (2014)**	**318,386,421#**	**2,901,019**	**Adults**	**94,956**	**292***	**-**	**-**	**Electronic health records of 409 academic, community, and federal hospital, sepsis definition: sepsis-3**
Fleischmann-Struzek, 2018, Germany (10)	365 (2010) **365 (2015)**	81,751,602 **82,175,684**	17,433,846 **18,664,877**	All ages	49,584 **73,419**	61 **86**	68 **68**	49 **45**	Nationwide administrative data base, case identification: explicit ICD-10 sepsis codes The 2015 estimate was included in the meta-analysis.
Fleischmann-	365 (2010)	81,751,602	17,433,846 18,664	All ages	197,956	242* 352*	- -	- -	Nationwide administrative data base, case identification: implicit

Struzek, 2018, Germany (10)	365 (2015)	82,175,684	,877		289,183				ICD-10 sepsis codes (infection and organ dysfunction codes)
Shankar-Hari, 2017, UK (29)	1,825 (2011-2015)	215,281,300#	654,918	Adults	197,724 (210,560 extrapolated for all ICUs)	102	63	31	National ICU database, sepsis definition: sepsis-2
Shankar-Hari, 2017, UK (29)	**1,825 (2011-2015)**	215,281,300#	**654918**	**Adults**	**197,142** (209,948 extrapolated for all ICUs)	**102**	**63**	**32**	**National ICU database, sepsis definition: sepsis-3** **This estimate was included in the meta-analysis.**
Zhou, 2017, China (13)	**730 (2012-2014)**	**128,695**	**21,191**	**≥18 years**	**191**	**74***	**-**	**-**	**Patient chart review, all public hospitals in Yuetan Subdistrict, Beijing, sepsis definition: sepsis-1**
Kim, 2019, Korea (11)	365 (2005) **365 (2012)**	825,502 **863,820**	-	≥15 years	747 **1,208**	91* **140***	-	-	**National sample cohort, case identification: implicit ICD-10 coding strategy + prescription of antibiotics (infection and organ dysfunction)**
Yebenes, 2017, Spain (30)	**1,825 (2008-2012)**	**38,009,065**	**4,761,726**	**All ages**	**23,236**	**61***			**Administrative data base in the region of Catalonia, case identification: implicit ICD-10 coding strategy (infection and**

									organ dysfunction)
Huggan, 2019, New Zealand (17)	**1,825 (2007-2012)**	**403,368**	**209,730**	**All ages**	**278**	**14***		**34**	**Administrative data base of hospitals in the Waikato region of New Zealand, case identification: implicit ICD-10 coding strategy (infection and organ dysfunction)**

Bold letters highlight the studies or estimates that were included in the meta-analysis.

*recalculated based on the cases and population as provided in the publication and searched in national census registries or based on sepsis deaths and cases

searched in national census registries

Table E3: Overview on the included studies on ED-treated sepsis incidence

years	**study duration (days)**	**population**	**patients observed**	**age range**	**total number of sepsis cases**	**incidence (per 100 000 person-years)**	**mean age**	**hospital case fatality (%)**	**remarks**
Retrospective studies									
Author, year									
Cowan, 2015, UK (31)	14 (2013)	194,000	1,763	≥18 years	38	511	-	-	Patient chart review, single center, sepsis definition: sepsis-2
Vakkalanka, 2019, US (32)	3,285 (2005-2013)	3,035,354†	-	Not specified	154,019	707	-	-	State-wide hospital administrative database, sepsis case identification: implicit sepsis ICD-9 codes (infection and organ dysfunction codes)
Yu, 2018, Taiwan (33)	4,380 (2001-2012)	253,000,000		All ages	493,397	237 (2002) - 370 (2012)	-	21	Nationwide health insurance database, case identification: implicit sepsis-9 codes

† data provided by the author

Table E4: Risk of bias of the included studies

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
Rhee et al.	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Low Risk
Nzarora et al.	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	High risk
Marques et al.	No (High Risk)	Yes (Low Risk)	Unknown	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Unknown	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	High Risk
Lorencio et al.	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	High Risk
Lee et al.	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Moderate Risk
Kim et al.	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Moderate Risk
Dupuis et al.	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Moderate Risk
Yebenes et al.	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	High Risk
Fleischmann-Struzek et al	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Moderate Risk
Zhou et al.	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	High risk
Vakkalanka et al.	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Unknown	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	High Risk
Shankar-Hari et al.	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Low Risk
Machado et al.	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	No (High risk)	Yes (Low Risk)	Moderate Risk
Bertullo et al.	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	High risk
Yu et al.	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Moderate Risk
Herrán-Monge et al.	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	High risk
Goodwin et al.	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	High Risk
Cowan et al.	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	High Risk
De Miguel Yanes et al.	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Moderate Risk
Azkárate et al.	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	High Risk
Knoop et al.	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Moderate Risk
Stoller et al.	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Moderate Risk
Kübler et al.	Unknown	Yes (Low Risk)	No (High Risk)	Unknown	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	No (High risk)	Yes (Low Risk)	High Risk
Huggan et al.	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	High Risk
Mellhammar et al.	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	High Risk
Bouza et al.	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Moderate Risk
Álvaro-Meca et al.	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Moderate Risk
Fleischmann et al.	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	No (High Risk)	Yes (Low Risk)	Yes (Low Risk)	Yes (Low Risk)	Moderate Risk

Hoy Risk of Bias Assessment

1. Was the study's target population a close representation of the national population in relation to relevant variables? (low/high risk of bias)

2. Was the sampling frame a true or close representation of the target population? (low/high risk of bias)

3. Was some form of random selection used to select the sample, OR was a census undertaken? (low/high risk of bias)

4. Was the likelihood of nonresponse bias minimal?(low/high risk of bias)

5. Were data collected directly from the subjects (as opposed to a proxy)? (low/high risk of bias)

6. Was an acceptable case definition used in the study? (low/high risk of bias)

7. Was the study instrument that measured the parameter of interest shown to have validity and reliability? (low/high risk of bias)

8. Was the same mode of data collection used for all subjects? (low/high risk of bias)

9. Was the length of the shortest prevalence period for the parameter of interest appropriate? (low/high risk of bias)

10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? (low/high risk of bias)

11. Summary item on the overall risk of study bias (low/moderate/high risk of bias)

Table E5: Data sources and coverage of data sources of the included studies

Data source	Studies
nation-wide or regional registries of inpatients (information on coverage as described in the publication)	Norway – Knoop et al. – all hospitalizations, Flaatten et al. – all hospitalizations; US – Goodwin et al. – discharges from non-federal hospitals in South Carolina, Angus et al. – seven state hospital discharge database; Sweden – Wilhelms et al. – all hospitalizations, Australia – Sundararajan et al. – all hospitalizations, Spain – Yebenes 2015/2017 – CatSalut, full coverage, China – Zhou et al. – all hospitalizations of residents in Yuetan Subdistrict based on home address, Germany – Fleischmann-Struzek et al., Fleischmann et al., Heublein et al.: complete database except for military or prison hospitals as well as psychiatric facilities; Spain – Álvaro-Meca – approx. 92% coverage, Bouza 2015/2016 -97% coverage, Inigo et al., Ballester et al., US – Barnato et al., excluded Veteran Admissions and military hospitals
representative inpatient samples (weighted national projections)	US NIS – Stoller et al., Lagu et al. 2012a/b, Kumar et al., Dombrovskiy et al., Gaieski et al., US National Hospital Discharge Survey (NDHS) – Martin et al., Danai et al.
representative population sample	South Korea – Kim et al.
random population sample	Taiwan – Shen et al.
other population-based registries	Sweden - Mellhammar et al. - antibiotic surveillance tool
ICU sample with population-at risk given in the paper or provided by the author	Brazil – Machado et al. (national extrapolations according to sepsis incidence per ICU bed-days/national occupied ICU bed-days), Finland - Karlsson et al., Germany – Engel et al. (national extrapolations according to ICU admissions in the study sample/national ICU admissions), Uruguay – Bertullo et al., The Netherlands – van Gestel et al. (national extrapolation according to ICU bed in the study sample/ICU bed capacity in the Netherlands), Spain - Herran-Monge, Blanco et al., Slovak republic - Zahorec et al. (national extrapolation according to ICU admissions in the study sample/national ICU admissions), Poland – Kübler et al. 2007/2015 (national extrapolations according to ICU beds in the study sample/national ICU bed capacity), Italy – Sakr et al., Australia/New Zealand – Finfer et al. (national extrapolation according to ICU admission in the study sample/national ICU admissions)
Single ICU with population-at-risk given in the paper	Spain - Azkárate et al.

single or multiple hospital(s) with population-at risk given in the paper	Australia - Davis et al., Spain – Esteban et al., US - Rhee et al. (national weighted incidence was estimated by projecting study hospital case counts into stratifications of US hospitals by region, size, and teaching status)
all hospitals in a region with population-at-risk given in the paper	Spain – Ballester et al.
all ICUs in a country with population at risk given in the paper or searched in national census registries	Slovenia – Beovic, Rwanda – Nzarora et al., Iceland – Vesteinsdottir et al.
ICU databases/registries	UK – Shankar-Hari et al. (national extrapolation of sepsis admissions in the sample to all ICUs in England), Padkin et al (national extrapolation of sepsis admissions in the sample to 235 ICUs in England and Wales), Harrison et al. (national extrapolation of sepsis admissions in the sample to 240 ICUs in England, Wales and Northern Ireland), France - Guidet et al. (national extrapolation according to ICU bed capacity in the study sample/ICU bed capacity in France), Brun-Buisson et al. (national extrapolation of incidence rates after adjustment for the type of hospital and ICU)
screening of the defined population for hospitalizations with sepsis	Brazil – Marques et al. population sample of health insurance holders of a private health plan, New Zealand – Huggan et al. - publically funded healthcare program
screening of the nearly entire populations for hospitalizations with sepsis	Taiwan – Lee et al., 99.7% coverage

Supplement Table E6: Random effects estimators for sepsis incidence rates per 100.000 person-years and case fatality in % according to WHO region.

WHO regions / number of studies	**Incidence rate**		**Mortality**	
	Estimate*	Approximated Mean**	Estimate§	Approximated Mean+
Hospital-treated Sepsis				
EURO (*n*=13/12)	124.421[78.415, 197.417]	178.505 [112.5014, 283.232]	30.117 [25.1432, 35.606]	30.852 [25.974, 36.181]
PAHO (*n* = 9/6)	289.359 [166.185, 503.828]	415.139 [238.423, 722.836]	22.108 [16.710, 28.650]	22.968 [17.55, 29.419]
WPRO (*n* = 6/7)	245.419 [124.291, 484.593]	352.099 [178.318, 695.240]	24.27685 [17.204, 33.095]	25.118 [18.053, 33.749]
ICU-treated Sepsis				
EURO (*n* = 21/11)	52.450 [38.888, 70.742]	66.943 [49.633, 90.289]	40.423 [34.944, 46.152]	40.737 [35.412, 46.281]
AFRO (*n* = 1/1)	1.598 [0.404, 6.321]	-	76.009 [58.540, 87.669]	-
PAHO (*n* = 5/4)	138.865 [75.208, 256.404]	177.236 [95.989, 327.252]	42.6964 [33.697, 52.207]	42.939 [34.195, 52.133]
WPRO (*n* = 7/3)	71.612 [42.560, 120.495]	91.397 [54.319, 153.787]	34.609 [25.387, 45.153]	35.085 [26.033, 45.316]

* Back transformed incidence rate using the exponential function with the average random intercept: $\exp(\gamma_0)*100.000$.

** Estimated mean of the incidence rates per 100.000 person years based on numerical integration using Gauss-Hermite quadrature.

§ Back transformed mortality rate using the logistic distribution function with the average random intercept: $1/[1 +\exp(-\lambda_0)]*100$.

+ Estimated mean of the mortality rate in % based on numerical integration using Gauss-Hermite quadrature.

Supplement Table E7: Random effects estimators for sepsis incidence rates per 100.000 person-years and case fatality in % depending on sepsis case definitions.

Sepsis case definition / number of studies	**Incidence rate**		**Mortality**	
	Estimate*	Approximated Mean**	Estimate*	Approximated Mean**
Hospital-treated Sepsis				
Sepsis-1 (*n* = 4/2)	168.402 [75.860, 373.838]	234.514 [105.641, 520.600]	22.097 [13.540, 33.936]	22.821 [14.201, 34.468]
Sepsis-2 (*n* = 0/0)	-	-	-	-
Sepsis-3 (*n* = 2/2)	645.152 [209.090, 1990.632]	898.427 [291.175, 2772.116]	15.892 [9.435, 25.523]	16.592 [9.979, 26.220]
Explicit (*n* = 13/10)	128.589 [82.646, 200.070]	179.070 [115.091, 278.615]	31.665 [26.598, 37.209]	32.253[27.280, 37.649]
Implicit (*n* = 9/8)	263.056 [154.509, 447.862]	366.327 [215.166, 623.684]	24.668 [19.909, 30.135]	25.374 [20.637, 30.756]
ICU-treated Sepsis				
Sepsis-1 (*n* = 19/12)	45.641 [30.456, 68.396]	68.341 [45.603, 102.415]	46.648 [40.341, 53.064]	46.795 [40.751, 52.930]
Sepsis-2 (*n* = 3/1)	35.443 [12.802, 98.125]	53.0713 [19.170, 146.928]	36.191 [18.725, 58.267]	-
Sepsis-3 (*n* = 2/1)	167.523 [48.386, 580.007]	250.841 [72.450, 868.476]	29.1791 [14.856, 49.314]	-
Explicit (*n* = 3/2)	58.276 [21.078, 161.123]	87.261 [31.561, 241.258]	38.772 [25.632, 53.778]	39.244 [26.473, 53.613]
Implicit (*n* = 7/3)	102.681 [52.707, 200.040]	153.750 [78.921, 299.529]	32.524 [22.574, 44.349]	33.209 [23.449, 44.595]
ICU-treated Sepsis without Rwanda				
Sepsis-1 (*n* = 18/11)	54.973 [39.996, 75.559]	69.595 [50.634, 95.656]	43.877 [38.802, 49.084]	44.039[39.088, 49.109]
Sepsis-2 (*n* = 3/1)	35.464 [16.272, 77.293]	44.896 [20.600, 97.850]	36.19324 [21.774, 53.617	-

Sepsis-3 (n = 2/1)	167.531 [64.699, 433.802]	212.089 [81.907, 549.179]	29.179 [17.573, 44.327]	-
Explicit (n = 3/2)	58.2806 [26.788, 126.796]	73.781 [33.913, 160.519]	38.780 [28.433, 50.249]	39.067 [28.909, 50.243]
Implicit (n = 7/3)	103.084 [61.882, 171.717]	130.500 [78.341, 217.388]	32.505 [24.616, 41.530]	32.920 [25.130, 41.751]

[*] Back transformed incidence rate using the exponential function with the average random intercept: $\exp(\gamma_0)*100.000$.

[**] Estimated mean of the incidence rates per 100.000 person years based on numerical integration using Gauss-Hermite quadrature.

[§] Back transformed mortality rate using the logistic distribution function with the average random intercept: $1/[1 +\exp(-\lambda_0)]*100$.

[+] Estimated mean of the mortality rate in % based on numerical integration using Gauss-Hermite quadrature.

Supplement Table E8: Omnibus test and adjusted pairwise tests for differences in incidence rate and mortality between WHO regions.

	Incidence		Mortality	
	Differences on the log(event/person-year) scale	*p*	Differences on the logit scale	*p*
Hospital-treated Sepsis				
Omnibustest: F(df1 = 2, df2 = 25) = 2.993, *p* = 0.068; τ = 0.850			Omnibustest: F(df1 = 2, df2 = 19) = 2.035, *p* = 0.158; τ = 0.4336	
PAHO - EURO	0.8440 [-0.01723, 1.70523]	0.0564	-0.4176 [-0.92696, 0.09171]	0.132
WPRO - EURO	0.6793 [-0.30188, 1.66048]	0.2357	-0.2958 [-0.89221, 0.30058]	0.474
WPRO - PAHO	-0.1647 [-1.21250, 0.88310]	0.9277	0.1218 [-0.54053, 0.78415]	0.902
ICU-treated Sepsis				
Omnibustest: F(df1 = 3, df2 = 30) = 11.682, *p* = < .001; τ = 0.699			Omnibustest: F(df1 = 3, df2 = 15) = 5.0169, p = 0.013; τ = 0.381	
AFRO - EURO	-3.4914 [-5.30443, -1.67840]	< 0.001	1.54107 [0.45185, 2.63029]	0.002
PAHO - EURO	0.9736 [0.09473, 1.85255]	0.0234	0.09362 [-0.48672, 0.67396]	0.975
WPRO - EURO	0.3114 [-0.46168, 1.08447]	0.7222	-0.24841 [-0.89545, 0.39862]	0.752
WPRO - AFRO	3.8028 [1.90868, 5.69693]	< 0.001	-1.78948 [-2.98199, -0.59697]	< 0.001
WPRO - PAHO	-0.6622 [-1.69812, 0.37362]	0.3482	-0.34203 [-1.09868, 0.41462]	0.645
PAHO - AFRO	4.4651 [2.52536, 6.40475]	< 0.001	-1.44745 [-2.60514, -0.28976]	0.008

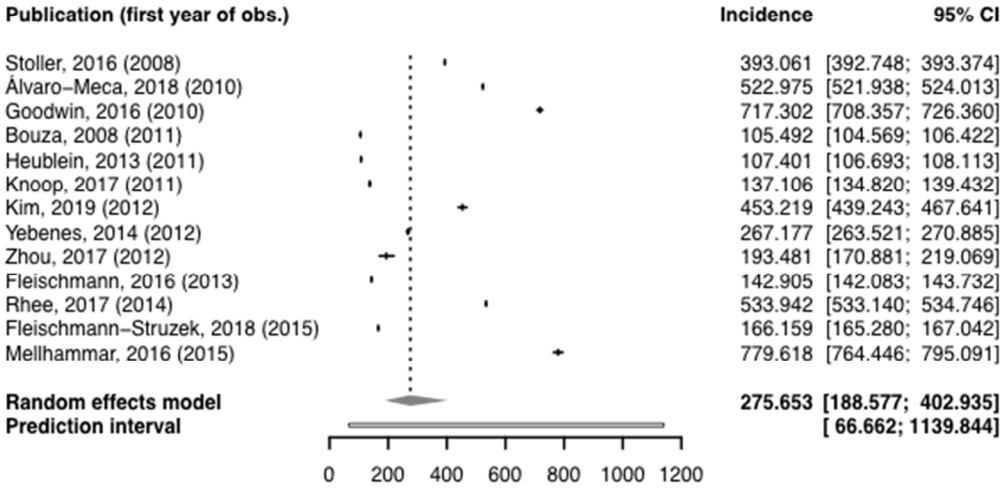
Supplement Table E9: Omnibus test and adjusted pairwise tests for differences in incidence rate and mortality rates between studies with different sepsis case definitions.

	Incidence		Mortaliy	
	Differences on the log(event/person-year) scale	*p*	Differences on the logit scale	*p*
Hospital-treated Sepsis				
Omnibustest: $F(df1 = 3, df2 = 24) = 3.013$, $p = 0.0498$; $\tau = 0.814$			Omnibustest: $F(df1 = 3, df2 = 18) = 3.203$, $p = 0.048$; $\tau = 0.397$	
Sepsis-3 - Sepsis-1	1.343 [-0.449, 3.136]	0.214	-0.406 [-1.495, 0.682]	0.769
Explicit - Sepsis-1	-0.270 [-1.454, 0.914]	0.935	0.491 [-0.341, 1.323]	0.423
Implicit - Sepsis-1	0.446 [-0.800, 1.692]	0.791	0.144 [-0.704, 0.991]	0.972
Implicit - Explicit	0.716 [-0.183, 1.615]	0.169	-0.347 [-0.825, 0.131]	0.240
Implicit - Sepsis-3	-0.897 [-2.516, 0.722]	0.479	0.550 [-0.299, 1.399]	0.339
Explicit - Sepsis-3	-1.613 [-3.186, -0.040]	0.042	0.898 [0.063, 1.731]	0.029
ICU-treated Sepsis				
Omnibustest: $F(df1 = 4, df2 = 29) = 1.968$, $p = 0.126$; $\tau = 0.899$			Omnibustest: $F(df1 = 4, df2 = 14) = 1.676$, $p = 0.211$; $\tau = 0.439$	
Sepsis-2 - Sepsis-1	-0.253 [-1.762, 1.257]	0.991	-0.433 [-1.721, 0.855]	0.886
Sepsis-3 - Sepsis-1	1.300 [-0.498, 3.099]	0.274	-0.752 [-1.985, 0.481]	0.447
Explicit - Sepsis-1	0.244 [-1.263, 1.752]	0.992	-0.323 [-1.231, 0.585]	0.864
Implicit - Sepsis-1	0.811 [-0.264, 1.885]	0.234	-0.596 [-1.372, 0.181]	0.218
Sepsis-3 - Sepsis-2	1.553 [-0.659, 3.766]	0.303	-0.320 [-2.031, 1.392]	0.986

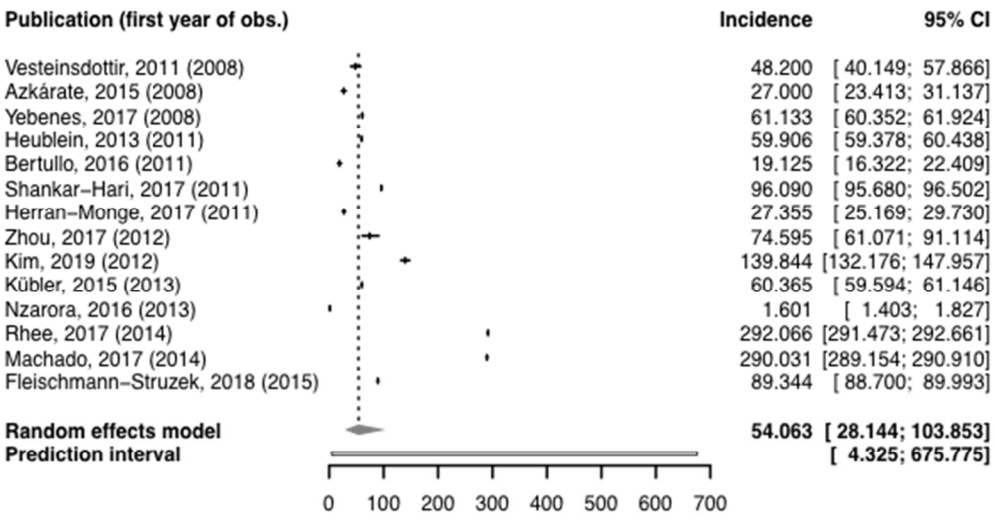
Sepsis-3 - Implicit	0.490 [-1.452, 2.431]	0.957	-0.157 [-1.526, 1.212]	0.998
Sepsis-3 - Explicit	1.056 [-1.155, 3.267]	0.682	-0.430 [-1.877, 1.018]	0.924
Sepsis-2 - Implicit	-1.064 [-2.740, 0.613]	0.408	0.163 [-1.256, 1.581]	0.998
Sepsis-2 - Explicit	-0.497 [-2.480, 1.485]	0.958	-0.110 [-1.605, 1.384]	1.000
Implicit - Explicit	0.566 [-1.109, 2.242]	0.884	-0.273 [-1.358, 0.812]	0.958
ICU-treated Sepsis without Rwanda				
Omnibustest: F(df1 = 4, df2 = 28) = 2.602, p = 0.057; τ = 0.687			Omnibustest: F(df1 = 4, df2 = 13) = 1.801, p = 0.189; τ = 0.336	
Sepsis-2 - Sepsis-1	-0.438 [-1.597, 0.721]	0.836	-0.321 [-1.341, 0.700]	0.909
Sepsis-3 - Sepsis-1	1.114 [-0.267, 2.496]	0.177	-0.641 [-1.591, 0.310]	0.345
Explicit - Sepsis-1	0.058 [-1.098, 1.215]	1.000	-0.210 [-0.914, 0.493]	0.923
Implicit - Sepsis-1	0.629[-0.200, 1.457]	0.229	-0.485 [-1.092, 0.123]	0.185
Sepsis-3 - Sepsis-2	1.553 [-0.141, 3.247]	0.090	-0.320 [-1.654, 1.014]	0.964
Sepsis-3 - Implicit	0.486 [-1.002, 1.973]	0.897	-0.156 [-1.208, 0.896]	0.994
Sepsis-3 - Explicit	1.056 [-0.636, 2.748]	0.426	-0.430 [-1.540, 0.680]	0.822
Sepsis-2 - Implicit	-1.067 [-2.350, 0.216]	0.153	0.164 [-0.952, 1.279]	0.994
Sepsis-2 - Explicit	-0.497 [-2.013, 1.019]	0.896	-0.110 [-1.281, 1.060]	0.999
Implicit - Explicit	0.570 [-0.711, 1.851]	0.737	-0.274 [-1.109, 0.561]	0.895

Supplementary Figures

Figure E2: Random effects meta-analysis estimators for the incidence of (A) hospital-treated sepsis, and (B) ICU-treated sepsis per 100,000 person-years in the past decade

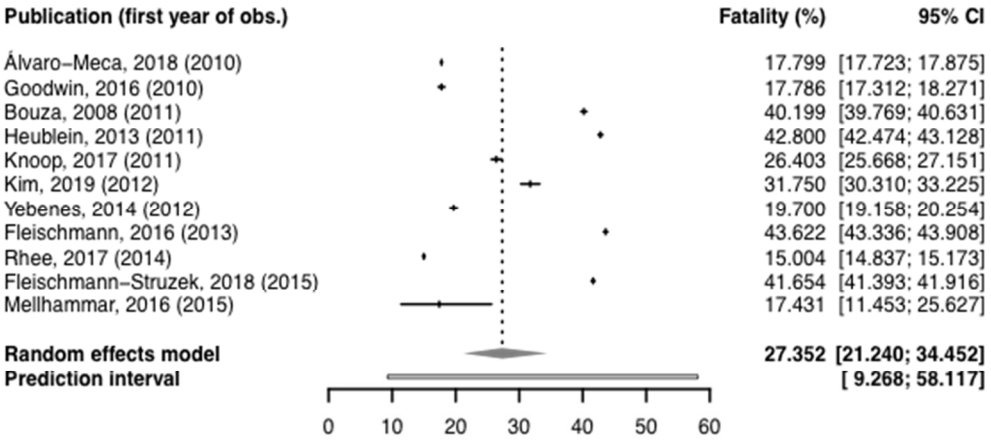


(A)

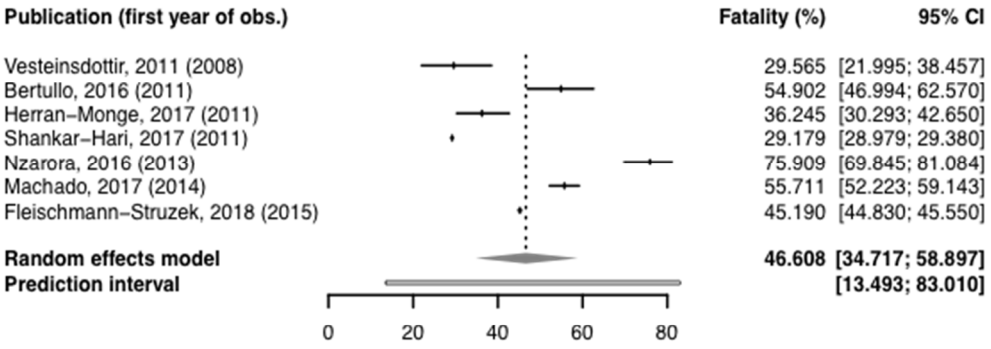

Publication (first year of obs.)
Incidence
95% CI
Vesteinsdottir, 2011 (2008) 48.200 [40.149; 57.866]
Azkárate, 2015 (2008) 27.000 [23.413; 31.137]
Yebenes, 2017 (2008) 61.133 [60.352; 61.924]
Heublein, 2013 (2011) 59.906 [59.378; 60.438]
Bertullo, 2016 (2011) 19.125 [16.322; 22.409]
Shankar−Hari, 2017 (2011) 96.090 [95.680; 96.502]
Herran−Monge, 2017 (2011) 27.355 [25.169; 29.730]
Zhou, 2017 (2012) 74.595 [61.071; 91.114]
Kim, 2019 (2012) 139.844 [132.176; 147.957]
Kübler, 2015 (2013) 60.365 [59.594; 61.146]
Nzarora, 2016 (2013) 1.601 [1.403; 1.827]
Rhee, 2017 (2014) 292.066 [291.473; 292.661]
Machado, 2017 (2014) 290.031 [289.154; 290.910]
Fleischmann−Struzek, 2018 (2015) 89.344 [88.700; 89.993]
Random effects model 54.063 [28.144; 103.853]
Prediction interval [4.325; 675.775]
0 100 200 300 400 500 600 700

(B)

Figure E3: Random effects meta-analysis estimators for the mortality of (A) hospital-treated sepsis, and (B) ICU-treated sepsis in the past decade



(A)


Publication (first year of obs.)
Fatality (%)
95% CI
Vesteinsdottir, 2011 (2008)
29.565 [21.995; 38.457]
Bertullo, 2016 (2011)
54.902 [46.994; 62.570]
Herran−Monge, 2017 (2011)
36.245 [30.293; 42.650]
Shankar−Hari, 2017 (2011)
29.179 [28.979; 29.380]
Nzarora, 2016 (2013)
75.909 [69.845; 81.084]
Machado, 2017 (2014)
55.711 [52.223; 59.143]
Fleischmann−Struzek, 2018 (2015)
45.190 [44.830; 45.550]
Random effects model
46.608 [34.717; 58.897]
Prediction interval
[13.493; 83.010]
0
20
40
60
80

(B)

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