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 Armeniantitle* OR Armenia*[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 Herzegovina*[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 Cameroon*[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...
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 Philippines*[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 Samoa 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 Uzhek*[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 Zimbabwe*[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 | 2009-2004, 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 |
|         | Inigo et al. | Minimum Basic Data Set (Region Madrid) | 2001 | 2001 |
|         | Ballesster et al. | hospital discharge data Valencian hospitals | 1995-2004 | 1995-2004 |
|         | Yeboes et al. | Catalian 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 |
|         | Dombrovsky et al. | National Inpatient Sample | 1993, 2003 | 2003 |
|         | Geierski 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-Brueck et al. | DRG statistics | 2010-2015 | 2015 |
|         | Heubel et al. | DRG statistics | 2011 | 2011 |
| UK      | Harrison et al. | ICNARC Database | 1996, 2004 | 2004 |
|         | Padlon 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:

\[
\ln(Y_i) = \gamma_i + \ln(p_i) \\
= \gamma_0 + u_i + \ln(p_i)
\]

The dependent variable \( Y_i \) is the number of sepsis cases. Hence, the random intercept \( \gamma_i \) 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 \( \gamma_0 \). The variable \( u_i \) is the study-specific difference \( \gamma_i - \gamma_0 \) 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:

\[
\ln\left(\frac{M_i}{1-M_i}\right) = \lambda_i \\
= \lambda_0 + u_i
\]

\( M_i \) 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 \( \lambda_i \). The expected value \( E(\lambda_i) \) of the random intercepts across the studies is \( \lambda_0 \). Again \( u_i \) is the study-specific difference \( \lambda_i - \lambda_0 \) 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 \( \tau^2 \) 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 \( \lambda_0 \) of the random intercepts \( \gamma_i \) 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:

\[
\exp(\gamma_0) \leq E\left(\frac{\text{incident cases}}{100,000 \text{ person years}}\right)
\]

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 \( \gamma_0 \) in the Poisson model is \( \approx -6.273 \).
(red line in the left graph of Fig. E1a). Using the back transformation $\exp(\gamma_0) \cdot 100,000$ gives the metaanalytic 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 $\gamma_0$ (red line) is rather the median than the average (blue line).

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 $1/[1 + \exp(-\lambda_0)] \cdot 100$. 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 $\hat{\lambda}_0$ 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).](image)

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:

\[
\ln(Y_i) = \gamma_0 + u_j + \ln(p_i) + \gamma_A I_{AFRO} + \gamma_P I_{PAHO} + \gamma_W I_{WPRO}
\]

\[
\ln\left(\frac{M_i}{1-M_i}\right) = \gamma_0 + u_j + \lambda_A I_{AFRO} + \lambda_P I_{PAHO} + \lambda_W I_{WPRO}
\]

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

\[
\ln \left( \frac{M_i}{1-M_i} \right) = \lambda_0 + \lambda_1 I_{\text{Sepsis-2}} + \lambda_2 I_{\text{Sepsis-3}} + \lambda_3 I_{\text{imp}} + \lambda_4 I_{\text{exp}}
\]

The dummy variables \( I_{\text{Sepsis-2}}, I_{\text{Sepsis-3}}, I_{\text{imp}}, \) and \( I_{\text{exp}} \) 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 |
| Study             | Year, Location | Time Period | Population  | Case Identification | Median Age (Years) | Cases | Deaths | Case Fatality Rate (%) | Study Details                                                                 |
|-------------------|----------------|-------------|-------------|---------------------|--------------------|-------|--------|------------------------|--------------------------------------------------------------------------------|
| Bouza, 2016, Spain (5) | 2006-2011 | - ≥18 years | 277,024,827 † | 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) | 2008-2012 | >18 years | 308,745,538 | National Inpatient Sample, case identification: explicit septicemia, bacteremia, fungemia + organ dysfunction ICD codes |
| Knoop, 2017, Norway (8) | 2011-2012 | All ages | 9,906,175 | Nationwide administrative data base, case identification: explicit ICD-10 sepsis or infection + organ dysfunction codes |
| Rhee, 2017, US (9) | 2014 | Adult | 318,386,421 | Electronic health records of 409 academic, community, and federal hospital, sepsis definition: sepsis-3 |
| Fleischmann-Struzek, 2018, Germany (10) | 2010-2015 | All ages | 81,751,602 82,175,684 | 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) | 2010-2015 | All ages | 81,751,602 82,175,684 | Nationwide administrative data base, case identification: implicit ICD-10 coding strategy (infection and organ dysfunction) |
| Study | Year, Country (ID) | Year Range | Total Population | Admission Age Range | Total Cases | Rate per 100,000 | Rate per 100,000 | Study Duration | Case Identification Methodology |
|-------|--------------------|------------|-----------------|--------------------|-------------|----------------|----------------|----------------|--------------------------------|
| Kim, 2019, Korea (11) | 365 (2005) | 825,502 | ≥15 years | 2,194 | 453 | 27 (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 | All ages | 11,067 | - | - | - | Private health plans’ electronic claims, sepsis definition: sepsis-1 |
| Zhou, 2017, China (13) | 730 (2012-2014) | 128,695 | ≥18 years | 498 | 194 | 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 | All ages | 230,112,717 | 1,259,578 | 639 | 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 | All ages | 18,133,338 | 1,15,421 | 138 | - | Nationwide administrative data base, case identification: explicit ICD-10 sepsis codes |
| Álvaro-Meca, 2018, Spain (16) | 1,825 (2000-2004) | 207,799,359 | All ages | 686,062 | 330 | 19* 18* | Nationwide administrative data base, case identification: implicit ICD-9 coding strategy (infection and organ dysfunction) |
| Study | Country | Year(s) | Total | Cases | Median | Study Details |
|-------|---------|---------|-------|-------|--------|---------------|
| 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 |
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                        |         |
| Herran-Monge, 2017, Spain (23) | 150 | 2,025,248 | 1,874             | ≥ 18 years | 231                         | 31                                    | 67       | 37                        |         |
| Kübler, 2015, Poland (24) | 1 (2012) 1 (2013) | 38,533,000 38,496,000 | 1,398 860 | All ages | 364 191                     | 69 60                                 | -        | -                         |         |
| Machado, 2017, Brazil (25) | 1 (2014) | 144,483,698† | 2,632             | ≥ 18 years | 794                         | 290                                   | 66       | 56                        |         |
| Author, year                                      | Study period | Population | Median Age | Case definition | Sepsis definition | Study Design | Median Age | 95% CI | Study Details                                                                                                                                 |
|--------------------------------------------------|--------------|------------|------------|-----------------|------------------|--------------|------------|--------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Bertullo, 2016, Uruguay (26)                     | 2011-2012    | 800,000    | ≥ 18 years | 153             | 19*               | Prospective, multicenter study, 5 ICUs, sepsis definition: sepsis-1 | 55         |         |                                                                                                                                           |
| Azkárate, 2015, Spain (27)                       | 2008-2013    | 700,000    | Not specified | 1,136           | 27*               | Prospective observational study, single center, sepsis definition: sepsis-2 | 62-65      | 18*     |                                                                                                                                           |
| Almirall, 2016, Spain (28)                       | 2002-2011    | 180,000    | >16 years  | 917             | 52 (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 | 65         | 19.7    |                                                                                                                                           |
| Rhee, 2017, US (9)                               | 2014         | 318,386,421#  | 94,956     | 292*            | -                | Electronic health records of 409 academic, community, and federal hospital, sepsis definition: sepsis-3 | -          | -       |                                                                                                                                           |
| Fleischmann-Struzek, 2018, Germany (10)         | 2010         | 81,751,602 82,175,684 | 49,584     | 61              | 68               | Nationwide administrative data base, case identification: explicit ICD-10 sepsis codes The 2015 estimate was included in the meta-analysis. | 49         | 45      |                                                                                                                                           |
| Fleischmann-                                   | 2010         | 81,751,602  | 17,433,8  | 197,956         | 242*            | Nationwide administrative data base, case identification: implicit | -          | -       |                                                                                                                                           |
| Authors, Year, Location | Study Period | Number (Year) | Age | Number of Patients | Code Definition | ICUs | Year | Methodology |
|--------------------------|--------------|---------------|-----|--------------------|----------------|------|------|-------------|
| Struzek, 2018, Germany (10) | 365 (2015) | 82,175,684 | All ages | 289,183 | ICD-10 sepsis codes (infection and organ dysfunction codes) | | | |
| Shankar-Hari, 2017, UK (29) | 1,825 (2011-2015) | 215,281,300# | Adults | 197,724 (210,560 extrapolated for all ICUs) | National ICU database, sepsis definition: sepsis-2 | 102 | 63 | 31 |
| Shankar-Hari, 2017, UK (29) | 1,825 (2011-2015) | 215,281,300# | Adults | 197,142 (209,948 extrapolated for all ICUs) | National ICU database, sepsis definition: sepsis-3 | 102 | 63 | 32 |
| Zhou, 2017, China (13) | 730 (2012-2014) | 128,695 | ≥18 years | 191 | Patient chart review, all public hospitals in Yuetan Subdistrict, Beijing, sepsis definition: sepsis-1 | 74* | - | - |
| Kim, 2019, Korea (11) | 365 (2005) 365 (2012) | 825,502 863,820 | ≥15 years | 747 1,208 | National sample cohort, case identification: implicit ICD-10 coding strategy + prescription of antibiotics (infection and organ dysfunction) | 91* 140* | - | - |
| Yebenes, 2017, Spain (30) | 1,825 (2008-2012) | 38,009,065 | All ages | 23,236 | Administrative data base in the region of Catalonia, case identification: implicit ICD-10 coding strategy (infection and organ dysfunction) | 61* | - | - |
| Study                                           | Population Size | Study Population Size | Age Group | Cases | Incidence | Database/Identification Method                                                                 |
|------------------------------------------------|-----------------|-----------------------|-----------|-------|-----------|------------------------------------------------------------------------------------------------|
| Huggan, 2019, New Zealand (17)                 | 1,825 (2007-2012) | 403,368               | All ages  | 278   | 14*       | 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

| Author, year             | years (study duration days) | population patients observed | population age range | total number of sepsis cases | incidence (per 100 000 person-years) | mean age | hospital case fatality (%) | Remarks |
|--------------------------|-----------------------------|------------------------------|----------------------|-------------------------------|--------------------------------------|----------|---------------------------|---------|
| Cowan, 2015, UK (31)    | 14 (2013)                   | 194,000                      | 1,763                | ≥18 years                     | 38                                   | 511      | -                         | -       |
| 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       | Nationwid health insurance database, case identification: implicit sepsis-9 codes |

† data provided by the author
Table E4: Risk of bias of the included studies

| Study                        | (1) | (2) | (3) | (4) | (5) | (6) | (7) | (8) | (9) | (10) | (11) |
|------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|
| Rhee et al.                  | Yes | Low | Yes | Low | Low | Yes | Low | Low | Low | Low | Low |
| Nazor et al.                 | No  | High| Yes | Low | Low | Yes | Low | Low | Low | Low | Low |
| Marques et al.               | No  | High| Yes | Low | Low | Yes | Low | Low | Low | Low | Low |
| Lorenzo et al.               | No  | High| Yes | Low | Low | Yes | Low | Low | Low | Low | Low |
| Lee et al.                   | Yes | Low | Yes | Low | Low | Yes | Low | No  | High| Yes | Low |
| Kim et al.                   | Yes | Low | Yes | Low | Low | Yes | Low | No  | High| Yes | Low |
| Dupuis et al.                | Yes | Low | Yes | Low | Low | Yes | Low | No  | High| Yes | Low |
| Yeboah et al.                | No  | High| Yes | Low | Low | Yes | Low | Yes | Low | Low | Low |
| Fleischmann-Struzek et al.   | Yes | Low | Yes | Low | Low | Yes | Low | Yes | Low | Low | Low |
| Zhou et al.                  | No  | High| Yes | Low | Low | Yes | Low | Low | Low | Low | Low |
| Vaikkalanka et al.           | No  | High| Yes | Low | Low | Yes | Low | Low | Low | Low | Low |
| Shankar-Hari et al.          | Yes | Low | Yes | Low | Low | Yes | Low | Low | Low | Low | Low |
| Machado et al.               | Yes | Low | Yes | Low | Low | Yes | Low | Low | Low | Low | Low |
| Bertullo et al.              | No  | High| Yes | Low | Low | Yes | Low | Low | Low | Low | Low |
| Yu et al.                    | Yes | Low | Yes | Low | Low | Yes | Low | Low | Low | Low | Low |
| Herrán-Monge et al.          | No  | High| Yes | Low | Low | Yes | Low | Low | Low | Low | Low |
| Goodwin et al.               | No  | High| Yes | Low | Low | Yes | Low | Low | Low | Low | Low |
| Cowan et al.                 | No  | High| Yes | Low | Low | Yes | Low | Low | Low | Low | Low |
| De Miguel Yanes et al.       | Yes | Low | Yes | Low | Low | Yes | Low | Low | Low | Low | Low |
| Azkarte et al.               | No  | High| Yes | Low | Low | Yes | Low | No  | High| Yes | Low |
| Knoop et al.                 | Yes | Low | Yes | Low | Low | Yes | Low | No  | High| Yes | Low |
| Stoller et al.               | Yes | Low | Yes | Low | Low | Yes | Low | No  | High| Yes | Low |
| Kühler et al.                | Unknown| Yes | Low | No  | High| Yes | Low | Low | Low | Yes | Low |
| Huggan et al.                | No  | High| Yes | Low | Low | Yes | Low | No  | High| Yes | Low |
| Mehlemann et al.             | No  | High| Yes | Low | Low | Yes | Low | Low | Low | Low | Low |
| Bouza et al.                 | Yes | Low | Yes | Low | Low | Yes | Low | No  | High| Yes | Low |
| Álvaro-Meca et al.           | Yes | Low | Yes | Low | Low | Yes | Low | No  | High| Yes | Low |
| Fleischmann et al.           | Yes | Low | Yes | Low | Low | Yes | Low | No  | High| Yes | Low |

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      | 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 |
| (information on coverage as described in the publication) |                                                                                                                                 |
| representative inpatient samples (weighted national projections) | US NIS – Stoller et al., Lagu et al. 2012a/b, Kumar et al., Dombrovskiy et al., Gaiski 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.                                                                                                                                                                   |
| Hospital Type Description                                                                 | Locations and Methods                                                                 |
|------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| 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(γ₀)*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(-λ₀)]*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] | - |
|                         | back transformed incidence rate (Exp(γ0) * 100.000) | estimated mean of the incidence rates per 100.000 person years | back transformed mortality rate (1/[1 + exp(-λ0)]) * 100.000 | estimated mean of the mortality rate in % |
|-------------------------|------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|-----------------------------------------|
| 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: \( \exp(\gamma_0) \times 100.000 \).

** 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: \( 1/[1 + \exp(-\lambda_0)] \times 100 \).

+ 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 Differences on the log(event/person-year) scale | Mortality Differences on the logit scale | p     |
|------------------|----------------------------------------------------------|-----------------------------------------|-------|
| **Hospital-treated Sepsis** |                                                          |                                         |       |
| Omnibus test: F(df1 = 2, df2 = 25) = 2.993, p = 0.068; τ = 0.850 | Omnibus test: 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** |                                                          |                                         |       |
| Omnibus test: F(df1 = 3, df2 = 30) = 11.682, p = < .001; τ = 0.699 | Omnibus test: 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 Differences on the log(event/person-year) scale | Mortality Differences on the logit scale |  
|---------------------|----------------------------------------------------------|----------------------------------------|
|                     |  
| **Hospital-treated Sepsis**  
| Omnibustest: $F(df1 = 3, df2 = 24) = 3.013, p = 0.0498; \tau = 0.814$ |  
| 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: $F(df1 = 4, df2 = 29) = 1.968, p = 0.126; \tau = 0.899$ |  
| 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 |

Omnibustest: $F(df1 = 3, df2 = 18) = 3.203, p = 0.048; \tau = 0.397$
| Comparison                  | Mean [CI]                 | p-value (df2) | τ  | p-value (df2) |
|----------------------------|---------------------------|--------------|----|--------------|
| 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: \(F(df1 = 4, df2 = 28) = 2.602, p = 0.057; \tau = 0.687\)  
Omnibustest: \(F(df1 = 4, df2 = 13) = 1.801, p = 0.189; \tau = 0.336\)

| Comparison                  | Mean [CI]                 | p-value (df2) | τ  | p-value (df2) |
|----------------------------|---------------------------|--------------|----|--------------|
| 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
Figure E3: Random effects meta-analysis estimators for the mortality of (A) hospital-treated sepsis, and (B) ICU-treated sepsis in the past decade

| Publication (first year of obs.) | Fatality (%) | 95% CI       |
|----------------------------------|--------------|--------------|
| Alvaro-Meca, 2018 (2010)         | 17.799       | [17.723; 17.875] |
| Goodwin, 2016 (2010)             | 17.786       | [17.312; 18.271] |
| Bouza, 2008 (2011)               | 40.199       | [39.769; 40.631] |
| Heublein, 2013 (2011)            | 42.800       | [42.474; 43.128] |
| Knoop, 2017 (2011)               | 26.403       | [25.668; 27.151] |
| Kim, 2019 (2012)                 | 31.750       | [30.310; 33.225] |
| Yebehes, 2014 (2012)             | 19.700       | [19.156; 20.554] |
| Fleischmann, 2016 (2013)         | 43.622       | [43.336; 43.908] |
| Rhee, 2017 (2014)                | 15.004       | [14.837; 15.173] |
| Fleischmann–Struzek, 2018 (2015) | 41.654       | [41.393; 41.916] |
| Melhammar, 2016 (2015)           | 17.431       | [11.453; 25.627] |

**Random effects model**

**Prediction interval**

27.352 [21.240; 34.452]

[9.268; 58.117]
| Publication (first year of obs.) | Fatality (%) | 95% CI |
|---------------------------------|-------------|--------|
| Vesteinsdottir, 2011 (2008)     | 29.665      | [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, 2010 (2010)            | 75.909      | [69.045; 81.004] |
| 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]** |
References

1. Knapp G, Hartung J. Improved tests for a random effects meta-regression with a single covariate. *Statistics in medicine* 2003; 22: 2693-2710.

2. Hothorn T, Bretz F, Westfall P. Simultaneous inference in general parametric models. *Biom J* 2008; 50: 346-363.

3. Todorovic Markovic M, Pedersen C, Gottfredsson M, Todorovic Mitic M, Gaini S. Epidemiology of community-acquired sepsis in the Faroe Islands - a prospective observational study. *Infect Dis (Lond)* 2019; 51: 38-49.

4. Mellhammar L, Wullt S, Lindberg A, Lanbeck P, Christensson B, Linder A. Sepsis Incidence: A Population-Based Study. *Open forum infectious diseases* 2016; 3: ofw207.

5. Bouza C, Lopez-Cuadrado T, Amate-Blanco JM. Use of explicit ICD9-CM codes to identify adult severe sepsis: impacts on epidemiological estimates. *Crit Care* 2016; 20: 313.

6. Bouza C, Lopez-Cuadrado T, Saz-Parkinson Z, Amate-Blanco JM. Epidemiology and recent trends of severe sepsis in Spain: a nationwide population-based analysis (2006-2011). *BMC infectious diseases* 2014; 14: 3863.

7. Stoller J, Halpin L, Weis M, Aplin B, Qu W, Georgescu C, Nazral M. Epidemiology of severe sepsis: 2008-2012. *Journal of critical care* 2016; 31: 58-62.

8. Knoop ST, Skrede S, Langeland N, Flaatten HK. Epidemiology and impact on all-cause mortality of sepsis in Norwegian hospitals: A national retrospective study. *PloS one* 2017; 12: e0187990.

9. Rhee C, Dantes R, Epstein L, Murphy DJ, Seymour CW, Iwashyna TJ, Kadri SS, Angus DC, Danner RL, Fiore AE, Jernigan JA, Martin GS, Septimus E, Warren DK, Karcz A, Chan C, Menchaca JT, Wang R, Gruber S, Klompas M, Program CDCPE. Incidence and Trends of Sepsis in US Hospitals Using Clinical vs Claims Data, 2009-2014. *JAMA : the journal of the American Medical Association* 2017; 318: 1241-1249.

10. Fleischmann-Struzek C, Mikolajetz A, Schwarzkopf D, Cohen J, Hartog C, Pletz M, Gastmeier P, Reinhart K. Challenges in Assessing the Burden of Sepsis and Understanding the Inequalities of Sepsis Outcomes between National Health Systems - Secular Trends in Sepsis and Infection Incidence and Mortality in Germany *Intensive care medicine* 2018; 44: 1826-1835.

11. Kim J, Kim K, Lee H, Ahn S. Epidemiology of sepsis in Korea: a population-based study of incidence, mortality, cost and risk factors for death in sepsis. *Clin Exp Emerg Med* 2019; 6: 49-63.

12. Marques AC, Janiszewski M, Houlis D. Analysis of incidence, resource use and costs of severe sepsis in Brazil and the economic impact of drotrecogin-alfa activated. *Value in Health* 2007; May-Jun: A162-A162.

13. Zhou J, Tian H, Du X, Xi X, An Y, Duan M, Weng L, Du B, for China Critical Care Clinical Trials G. Population-Based Epidemiology of Sepsis in a Subdistrict of Beijing. *Critical care medicine* 2017; 45: 1168-1176.

14. Lee CC, Yo CH, Lee MG, Tsai KC, Lee SH, Chen YS, Lee WC, Hsu TC, Lee SH, Chang SS. Adult sepsis - A nationwide study of trends and outcomes in a population of 23 million people. *The Journal of infection* 2017; 75: 409-419.

15. Fleischmann C, Thomas-Rueddel DO, Hartmann M, Hartog CS, Welte T, Heublein S, Heublein S, Dennler U, Reinhart K. Hospital Incidence and Mortality Rates of Sepsis. *Deutsches Arzteblatt international* 2016; 113: 159-166.

16. Alvaro-Meca A, Jimenez-Sousa MA, Micheloud D, Sanchez-Lopez A, Heredia-Rodriguez M, Tamayo E, Resino S, Group of Biomedical Research in Critical Care M. Epidemiological trends of sepsis in the twenty-first century (2000-2013): an
analysis of incidence, mortality, and associated costs in Spain. *Popul Health Metr* 2018; 16: 4.

17. Huggan PJ, Bell A, Waetford J, Obertova Z, Lawrenson R. Evidence of High Mortality and Increasing Burden of Sepsis in a Regional Sample of the New Zealand Population. *Open forum infectious diseases* 2017; 4: ofx106.

18. Goodwin AJ, Nadig NR, McElligott JT, Simpson KN, Ford DW. Where You Live Matters: The Impact of Place of Residence on Severe Sepsis Incidence and Mortality. *Chest* 2016; 150: 829-836.

19. Dupuis C, Boudalma L, Ruckly S, Perozziello A, Mourvillier B, Bailly S, Sonneville R, Timsit J-F. Septic shock in France from 2009 to 2014: Incidence, outcome, and associated costs of care. *Annals of Intensive Care* 2017; 7: 32-33.

20. de Miguel-Yanes JM, Mendez-Bailon M, Jimenez-Garcia R, Hernandez-Barrera V, Perez-Farinos N, Lopez-de-Andres A. Trends in sepsis incidence and outcomes among people with or without type 2 diabetes mellitus in Spain (2008-2012). *Diabetes Res Clin Pract* 2015; 110: 266-275.

21. Lorencio C, Yébenes JC, Gonzalez Londoño J, Cleriès M, Vela E, Espinosa L, Ruiz JC, Rodriguez A, Esteban E, Ferrer R, Artigas A. Incidence and mortality of multiple organ failure (MOF) in septic patients. An 11 year review in Catalonia. *Intensive Care Medicine Experimental* 2018; 6.

22. Nzorora J, Beach ML, Riviello ED, Twagirumugabe T. Epidemiology And Outcomes Of Sepsis In Two Intensive Care Units In Rwanda. *American journal of respiratory and critical care medicine* 2016; 193.

23. Herran-Monge R, Muriel-Bombin A, Garcia-Garcia MM, Merino-Garcia PA, Martinez-Barrios M, Andaluz D, Ballesteros JC, Domínguez-Berrot AM, Moradillo-González S, Macías S, Alvarez-Martínez B, Fernandez-Calavia MJ, Tarancon C, Villar J, Blanco J. Epidemiology and Changes in Mortality of Sepsis After the Implementation of Surviving Sepsis Campaign Guidelines. *Journal of intensive care medicine* 2019; 34: 740-750.

24. Kubler A, Adamik B, Ciszewicz-Adamiczka B, Ostrowska E. Severe sepsis in intensive care units in Poland--a point prevalence study in 2012 and 2013. *Anaesthesiol Intensive Ther* 2015; 47: 315-319.

25. Machado FR, Cavalcanti AB, Bozza FA, Ferreira EM, Angotti Carrara FS, Sousa JL, Caixeta N, Salomao R, Angus DC, Pontes Azevedo LC, Investigators S, Latin American Sepsis Institute N. The epidemiology of sepsis in Brazilian intensive care units (the Sepsis PREvalence Assessment Database, SPREAD): an observational study. *The Lancet infectious diseases* 2017; 17: 1180-1189.

26. Bertullo M, Carbone N, Brandes M, Silva M, Meiss H, Tejera D, Deicas A, Buroni M, Gerez J, Limongi G, Cancela M, Hurtado J. Epidemiología, diagnóstico y tratamiento de la sepsis severa en Uruguay: un estudio multicéntrico prospectivo. *Rev méd Urug* 2016; 32: 178-189.

27. Azkarate I, Choperena G, Salas E, Sebastian R, Lara G, Elosegui I, Barrutia L, Eguibar I, Salaberría R. Epidemiology and prognostic factors in severe sepsis/septic shock. Evolution over six years. *Medicina intensiva / Sociedad Española de Medicina Intensiva y Unidades Coronarias* 2016; 40: 18-25.

28. Almirall J, Guell E, Capdevila JA, Campins L, Palomera E, Martinez R, Miro G, de la Torre MC, Solsoma M, Yebenes JC. [Epidemiology of community-acquired severe sepsis. A population-based study]. *Med Clin (Barc)* 2016; 147: 139-143.

29. Shankar-Hari M, Harrison DA, Rubenfeld GD, Rowan K. Epidemiology of sepsis and septic shock in critical care units: comparison between sepsis-2 and sepsis-3
populations using a national critical care database. *British journal of anaesthesia* 2017; 119: 626-636.

30. Yebenes JC, Ruiz JC, Ferrer R, Artigas A, Lorencio C, Rodriguez A, Nuvials X, Martin-Loeches I, Bordeje L, Bosch A, Cleries M. Trends in incidence and hospital outcomes among patients with severe sepsis in catalonia during the 2008-2012 period. *Intensive Care Medicine, (September 2014) Vol 40, No 1, Supp SUPPL 1, pp S152 Abstract Number: 0537 2014.*

31. Cowan SL, Holland JA, Kane AD, Frost I, Boyle AA. The burden of sepsis in the Emergency Department: an observational snapshot. *Eur J Emerg Med* 2015; 22: 363-365.

32. Vakkalanka JP, Harland KK, Swanson MB, Mohr NM. Clinical and epidemiological variability in severe sepsis: an ecological study. *J Epidemiol Community Health* 2018; 72: 741-745.

33. Yu CW, Chang SS, Lai CC, Wu JY, Yen DW, Lee MG, Yeh CC, Chung JY, Lin YJ, Lee CC. Epidemiology of Emergency Department Sepsis: A National Cohort Study Between 2001 and 2012. *Shock* 2019; 51: 619-624.