**Frequency and mortality of septic shock in Europe and North America: a systematic review and meta-analysis**

Jean-Louis Vincent et al.

**Additional File 1**

## Search strategy

### *Medline and Medline In-Process*

Searched 23/12/15 via OvidSP interface.
Limited to 2005 onwards, no language limits.
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search strategy:
1 septic shock/ (19631)
2 ((seps$ or sept$) adj3 (shock$ or severe or syndrome$)).ti,ab. (25875)
3 ((bacteremic or bacterial or bacteriemic or endotoxic or endotoxine or toxic) adj2 shock).ti,ab. (6661)
4 ("forward failure" adj2 toxic).ti,ab. (0)
5 1 or 2 or 3 or 4 (39398)
6 *Epidemiology/ (9719)
7 epidemiology.fs. (1336638)
8 6 or 7 (1345469)
9 quality-adjusted life years/ or quality of life/ (142229)
10 (sf36 or sf 36 or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. (18820)
11 (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. (1540)
12 (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab. (3542)
13 (sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab. (562)
14 (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab. (359)
15 (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab. (330)
16 "health related quality of life".ti,ab. (27384)
17 (Quality adjusted life or Quality-adjusted-life).ti,ab. (7931)
18 "assessment of quality of life".ti,ab. (1343)
19 (euroqol or euro qol or eq5d or eq 5d).ti,ab. (5479)
20 (hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab. (12836)
21 (hye or hyes).ti,ab. (63)
22 health$ year$ equivalent$.ti,ab. (40)
23 (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab. (1066)
24 (quality time or qwb or quality of well being or "quality of wellbeing" or "index of wellbeing" or "index of well being").ti,ab. (701)
25 (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab. (2348)
26 (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab. (8863)

27 (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab. (4726)
28 15d.ti,ab. (1355)
29 (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab. (283)
30 (utilit$ adj3 ("quality of life" or valu$ or scor$ or measur$ or health or life or estimat$ or elicit$ or disease$)).ti,ab. (8259)
31 (utilities or disutili$).ti,ab. (5010)
32 (Severity Weighted Assessment Tool or SWAT or mSWAT).ti,ab. (402)
33 exp Health Behavior/ (132133)
34 (patient$ adj2 (attitude$ or compliance or "non compliance" or adheren$ or "non adherence" or participation or "non participation" or preference$ or satisf$ or dissatisf$ or toleran$ or intoleran$ or "reported outcome" or "reported outcomes")).ab,ti. (80522)
35 or/9-34 (367715)
36 economics/ (27237)
37 exp "costs and cost analysis"/ (196980)
38 economics, dental/ (1889)
39 exp "economics, hospital"/ (21044)
40 economics, medical/ (9044)
41 economics, nursing/ (3971)
42 economics, pharmaceutical/ (2657)
43 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (541242)
44 (expenditure$ not energy).ti,ab. (21208)
45 (value adj1 money).ti,ab. (28)
46 budget$.ti,ab. (21496)
47 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 (676152)
48 ((energy or oxygen) adj cost).ti,ab. (3195)
49 (metabolic adj cost).ti,ab. (966)
50 ((energy or oxygen) adj expenditure).ti,ab. (19253)
51 48 or 49 or 50 (22612)
52 47 not 51 (671059)
53 exp Employment/ (59564)
54 exp Work/ (15209)
55 Efficiency/ (11965)
56 Absenteeism/ (7756)
57 "Cost of Illness"/ (20490)
58 "Length of Stay"/ (66244)
59 ((employment or employed or employee$ or unemployment or unemployed) adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing)).ti,ab. (1690)
60 (productivity adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing)).ti,ab. (2051)
61 ((long standing or longstanding or long term or longterm or permanent or employee$) adj2 (absence$ or absent$ or ill$ or sick$ or disab$)).ti,ab. (7971)
62 llsi.ti,ab. (11)
63 (cost$ adj2 (illness or disease$ or sickness$)).ti,ab. (3558)
64 (burden$ adj2 (disease$ or illness or sickness$)).ti,ab. (14924)
65 ((social or societ$ or work$ or employe$ or business$ or communit$ or famil$ or carer$ or caregiver$) adj3 (burden$ or consequenc$ or impact$ or problem$ or productivity or sickness or impairment$)).ti,ab. (64832)
66 ((allowance or status or long-term or pension$ or benefit$) adj2 disab$).ti,ab. (8851)
67 ((unable or inability or incapacit$ or incapab$) adj3 work).ti,ab. (1492)
68 budget$ impact$.ti,ab. (732)
69 budget$ implicat$.ti,ab. (44)
70 resource$ use$.ti,ab. (6852)
71 resource$ utili$.ti,ab. (6485)

72 resource$ usage.ti,ab. (239)
73 (length adj2 stay$).ti,ab. (34475)
74 (hospital$ adj2 stay$).ti,ab. (62003)
75 (duration adj2 stay$).ti,ab. (2462)
76 extended stay$.ti,ab. (137)
77 prolonged stay$.ti,ab. (699)
78 ((hospitali?ation or hospitali?ed) adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing)).ti,ab. (4251)
79 economic consequenc$.ti,ab. (2609)
80 or/52-79 (916218)
81 Critical Pathways/ (5192)
82 practice guideline/ (21297)
83 (guideline$ or guidance or ((care or clinical or critical) adj1 pathway$)).ti,ab. (297939)
84 or/81-83 (310152)
85 5 and 8 (3130)
86 5 and 35 (208)
87 5 and 80 (1783)
88 5 and 84 (913)
89 85 or 86 or 87 or 88 (5247)
90 89 not (animals/ not (human/ and animals/)) (5175)
91 90 not (editorial or letter or case reports).pt. (4747)
92 limit 91 to yr="2005 -Current" (3163)
3163 results.

***Embase***
Searched 23/12/15 via OvidSP interface.
Limited to 2005 onwards, no language limits.
Database: Embase <1996 to 2015 Week 51>
Search strategy:
1 septic shock/ (28007)
2 ((seps$ or sept$) adj3 (shock$ or severe or syndrome$)).ti,ab. (31144)
3 ((bacteremic or bacterial or bacteriemic or endotoxic or endotoxine or toxic) adj2 shock).ti,ab. (4448)
4 ("forward failure" adj2 toxic).ti,ab. (0)
5 or/1-4 (44748)
6 *epidemiology/ (23866)
7 *epidemiological data/ (1479)
8 ep.fs. (686321)
9 or/6-8 (709649)
10 quality adjusted life year/ or quality of life index/ (17105)
11 Short Form 12/ or Short Form 20/ or Short Form 36/ or Short Form 8/ (17502)
12 "International Classification of Functioning, Disability and Health"/ or "Ferrans and Powers Quality of Life Index"/ (1677)
13 (sf36 or sf 36 or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. (27627)
14 (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. (1163)
15 (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab. (5424)
16 (sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab. (914)
17 (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab. (295)

18 (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab. (511)
19 "health related quality of life".ti,ab. (36206)
20 (Quality adjusted life or Quality-adjusted-life).ti,ab. (10847)
21 "assessment of quality of life".ti,ab. (1869)
22 (euroqol or euro qol or eq5d$ or eq 5d$).ti,ab. (9628)
23 (hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab. (19034)
24 (hye or hyes).ti,ab. (73)
25 health$ year$ equivalent$.ti,ab. (25)
26 (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab. (1398)
27 (quality time or qwb or "quality of well being" or "quality of wellbeing" or "index of wellbeing" or index of well being).ti,ab. (737)
28 (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab. (2460)
29 (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab. (13752)
30 (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab. (6463)
31 15d.ti,ab. (1821)
32 (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab. (354)
33 (utilit$ adj3 ("quality of life" or valu$ or scor$ or measur$ or health or life or estimat$ or elicit$ or disease$)).ti,ab. (11256)
34 (utilities or disutili$).ti,ab. (6843)
35 (Severity Weighted Assessment Tool or SWAT or mSWAT).ti,ab. (507)
36 "patient attitude"/exp or (patient$ adj2 (attitude$ or compliance or "non compliance" or adheren$ or "non adherence" or participation or "non participation" or preference$ or satisf$ or dissatisf$ or toleran$ or intoleran$ or "reported outcome" or "reported outcomes")).ab,ti. (102459)
37 or/10-36 (206261)
38 health economics/ (17272)
39 exp economic evaluation/ (202530)
40 exp "health care cost"/ (196101)
41 exp pharmacoeconomics/ (141614)
42 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (576790)
43 (expenditure$ not energy).ti,ab. (21702)
44 (value adj2 money).ti,ab. (1435)
45 budget$.ti,ab. (20666)
46 or/38-45 (817477)
47 (metabolic adj cost).ti,ab. (815)
48 ((energy or oxygen) adj cost).ti,ab. (2250)
49 ((energy or oxygen) adj expenditure).ti,ab. (18776)
50 or/47-49 (21261)
51 46 not 50 (813441)
52 exp employment/ (40916)
53 exp work/ (197303)
54 "cost of illness"/ (15399)
55 "length of stay"/ (99592)
56 ((employment or employed or employee$ or unemployment or unemployed) adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing)).ti,ab. (1614)
57 (productivity adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing)).ti,ab. (2401)
58 ((long standing or longstanding or long term or longterm or permanent or employee$) adj2 (absence$ or absent$ or ill$ or sick$ or disab$)).ti,ab. (8459)
59 llsi.ti,ab. (11)

60 (cost$ adj2 (illness or disease$ or sickness$)).ti,ab. (4623)
61 (burden$ adj2 (disease$ or illness or sickness$)).ti,ab. (20518)
62 ((social or societ$ or work$ or employe$ or business$ or communit$ or famil$ or carer$ or caregiver$) adj3 (burden$ or consequenc$ or impact$ or problem$ or productivity or sickness or impairment$)).ti,ab. (69824)
63 ((social or societ$ or work$ or employe$ or business$ or communit$ or famil$ or carer$ or caregiver$) adj3 (burden$ or consequenc$ or impact$ or problem$ or productivity or sickness or impairment$)).ti,ab. (69824)
64 ((allowance or status or long-term or pension$ or benefit$) adj2 disab$).ti,ab. (11494)
65 ((unable or inability or incapacit$ or incapab$) adj3 work).ti,ab. (1370)
66 budget$ impact$.ti,ab. (1920)
67 budget$ implicat$.ti,ab. (53)
68 resource$ use$.ti,ab. (9170)
69 resource$ utili$.ti,ab. (10271)
70 resource$ usage.ti,ab. (317)
71 (length adj2 stay$).ti,ab. (54025)
72 (hospital$ adj2 stay$).ti,ab. (84781)
73 (duration adj2 stay$).ti,ab. (3112)
74 extended stay$.ti,ab. (169)
75 prolonged stay$.ti,ab. (829)
76 ((hospitali?ation or hospitali?ed) adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing)).ti,ab. (6094)
77 economic consequenc$.ti,ab. (2865)
78 or/51-77 (1212529)
79 clinical pathway/ or practice guideline/ or (guideline$ or guidance or ((care or clinical) adj1 pathway$)).ti,ab. (527797)
80 5 and 9 (2278)
81 5 and 37 (278)
82 5 and 78 (4210)
83 5 and 79 (2423)
84 or/80-83 (7991)
85 84 not (animals/ not (human/ and animals/)) (7976)
86 85 not ((editorial or letter or conference or "conference paper" or "conference proceeding" or "conference proceeding article" or "conference proceeding conference paper" or "conference proceeding editorial" or "conference proceeding note" or "conference proceeding review" or "journal conference abstract" or "journal conference paper" or "journal conference review").pt. or case report/) (5073)
87 limit 86 to yr="2005 -Current" (4013)
88 limit 87 to embase (3428)
3428 results.

***Cochrane Library***
Includes Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Cochrane Central Register of Controlled Trials (CENTRAL), Health Technology Assessment Database (HTAD), NHS Economic Evaluations Database (NHSEED).
Searched 23/12/15 online at http://onlinelibrary.wiley.com/cochranelibrary/search/advanced
Search strategy:
#1 MeSH descriptor: [Shock, Septic] this term only (451)
#2 ((seps* or sept* or septicem* or septicaem*) near/3 (shock* or severe or syndrome*)):ti,ab (1570)
#3 ((bacteremic or bacterial or bacteriemic or endotoxic or endotoxine or toxic) near/2 shock):ti,ab (24)
#4 ("forward failure" near/2 toxic):ti,ab (0)
#5 #1 or #2 or #3 or #4 Publication Year from 2005 to 2015 (1013)

1013 total results comprised of 27 from CDSR, 51 from DARE, 895 from CENTRAL, 10 from HTAD, and 25 from NHSEED.

***Update of epidemiology searches February 2018***

The epidemiology sections of the original searches were re-run from the date of the original searches onwards;

*Medline and Medline In-Process*

Searched 20/02/18 via OvidSP interface.
Limited to 2005 onwards, no language limits.
Limited to records added to database from 23/12/15 (date of previous search) onwards.
Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:

1 septic shock/ (20578)
2 ((seps$ or sept$) adj3 (shock$ or severe or syndrome$)).ti,ab. (29380)
3 ((bacteremic or bacterial or bacteriemic or endotoxic or endotoxine or toxic) adj2 shock).ti,ab. (6935)
4 ("forward failure" adj2 toxic).ti,ab. (0)
5 1 or 2 or 3 or 4 (43239)
6 *Epidemiology/ (9582)
7 epidemiology.fs. (1455855)
8 6 or 7 (1464532)
9 5 and 8 (3558)
10 9 not (animals/ not (human/ and animals/)) (3526)
11 10 not (editorial or letter or case reports).pt. (3285)
12 limit 11 to yr="2005 -Current" (2207)
13 ("20151223" or "20151224" or "20151225" or "20151226" or "20151228" or "20151229" or "20151230" or "20151231" or 2016$ or 2017$ or 2018$).ed. (2093879)
14 12 and 13 (526)

*Embase*

Searched 20/02/18 via OvidSP interface.
Limited to 2005 onwards, no language limits.
Limited to records added to database from 23/12/15 (date of previous search) onwards.
Database: Embase <1996 to 2018 Week 08>
Search Strategy:

1 septic shock/ (35404)
2 ((seps$ or sept$) adj3 (shock$ or severe or syndrome$)).ti,ab. (38557)
3 ((bacteremic or bacterial or bacteriemic or endotoxic or endotoxine or toxic) adj2 shock).ti,ab. (4914)
4 ("forward failure" adj2 toxic).ti,ab. (0)
5 or/1-4 (55133)
6 *epidemiology/ (28307)
7 *epidemiological data/ (1867)
8 ep.fs. (742580)
9 or/6-8 (770558)
10 5 and 9 (2544)
11 10 not (animals/ not (human/ and animals/)) (2535)
12 11 not ((editorial or letter or conference or "conference paper" or "conference proceeding" or "conference proceeding article" or "conference proceeding conference paper" or "conference proceeding editorial" or "conference proceeding note" or "conference proceeding review" or "journal conference abstract" or "journal conference paper" or "journal conference review").pt. or case report/) (2163)

13 limit 12 to yr="2005 -Current" (1578)
14 limit 13 to embase (1284)
15 ("20151223" or "20151224" or "20151225" or "20151226" or "20151227" or "20151228" or "20151229" or "20151230" or "20151231" or 2016$ or 2017$ or 2018$).dc. (3552842)
16 14 and 15 (240)

*Cochrane Library*
Includes Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTAD), NHS Economic Evaluations Database (NHSEED). CENTRAL was not included for this epidemiology update- only reviews, HTA reports, or economic evaluations that might contain epidemiology sections.
Searched 21/02/18 online at http://onlinelibrary.wiley.com/cochranelibrary/search/advanced
Search strategy:
#1 MeSH descriptor: [Shock, Septic] this term only (565)
#2 ((seps* or sept* or septicem* or septicaem*) near/3 (shock* or severe or syndrome*)):ti,ab (2294)
#3 ((bacteremic or bacterial or bacteriemic or endotoxic or endotoxine or toxic) near/2 shock):ti,ab (32)
#4 ("forward failure" near/2 toxic):ti,ab (0)
#5 #1 or #2 or #3 or #4 Publication Year from 2016 to 2018, in Cochrane Reviews (Reviews and Protocols), Other Reviews, Technology Assessments and Economic Evaluations (9)
9 total results comprised of 9 from CDSR.

**Inclusion and exclusion criteria for systematic review of epidemiology of septic shock**

**Inclusion criteria**

(1) Observational studies of frequency of septic shock in an assessed cohort ≥100 patients
(2) Observational studies reporting the mortality of septic shock in an assessed cohort ≥15 patients
(3) Studies published in the last 13 years (2005 – 2018)
(4) Studies reporting information for one of the following countries: USA, Canada and any European country

**Exclusion criteria**

(1) Pediatric patients (aged <15 years) with sepsis/septic shock
(2) Non-observational/interventional studies (RCTs, quasi-RCT)
(3) Studies with frequency /incidence/mortality of septic shock in specific disease groups/special populations (e.g. cancer, obesity, HIV, pregnancy).
(4) Studies in which the aim is to assess the effect of pharmacological interventions
(5) Studies indexed as case reports, editorials and letters
(6) Conference abstracts
(7) Non-human studies
(8) Non-English language publications
(9) Studies published before 2005
(10) Studies reporting information for countries other than USA, Canada and Europe

**Figure S1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart for the systematic literature review of septic shock

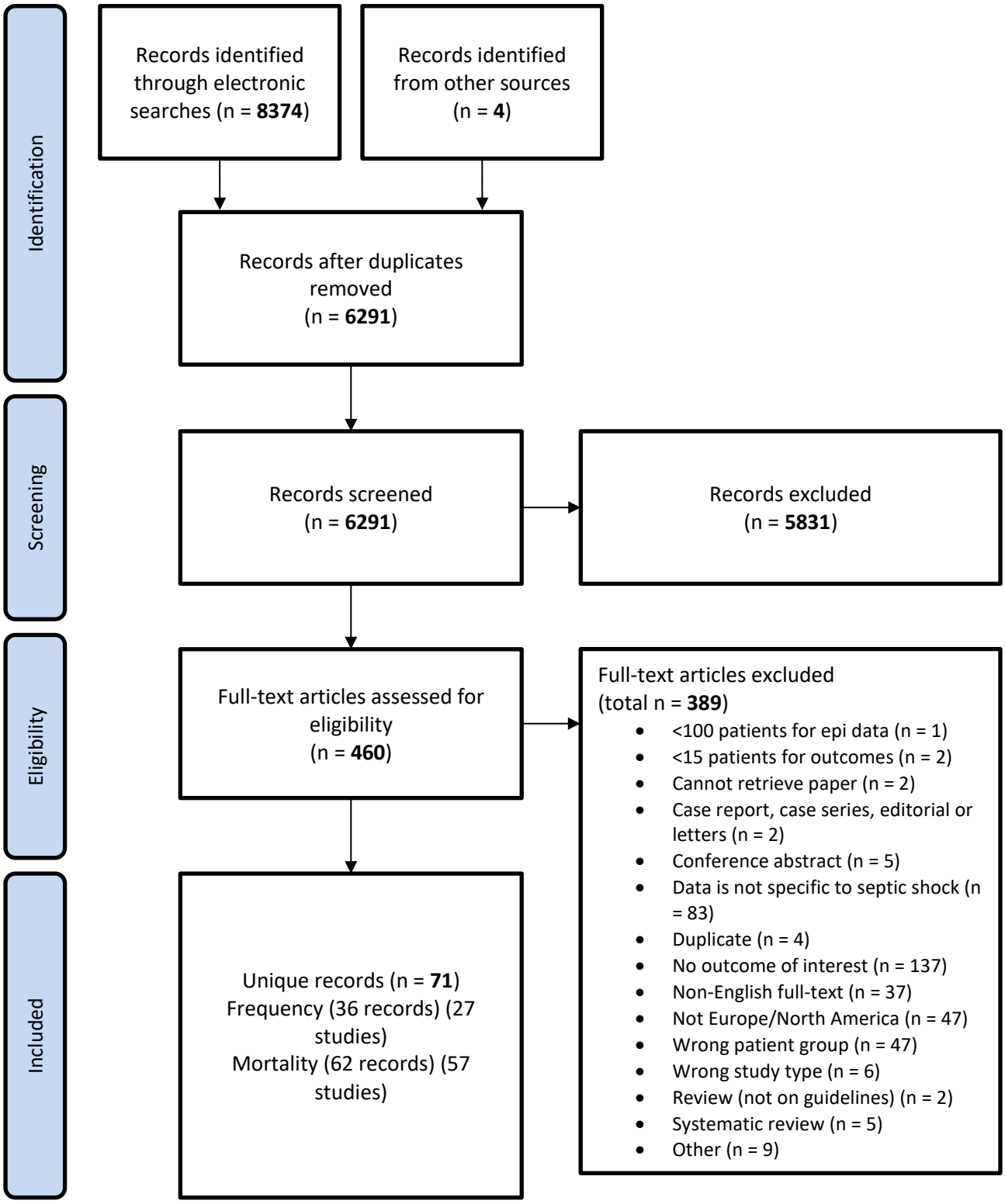

**Table S1**. Summary of included studies reporting septic shock frequency

| | Author, Year [ref] | Time period | No. of centers | Cohort screened | Timepoint for septic shock diagnosis | Frequency: cases/total number screened (%) | Criteria used for diagnosis | Data source |
|---|---|---|---|---|---|---|---|---|
| France | Adrie 2005 [22] | 1997 – 2000 | 6 | All adult admissions hospitalized for more than 48 hours | Anytime during stay | 279/1,698 (16.4) | Not reported | OUTCOMEREA database generated from standardized report forms |
| Canada | Laupland 2005 [23] | 1999 – 2002 | 7 | All adult admissions | At admission | 159/4,845 (3.3) | BSI-associated sepsis requiring vasopressor infusion | Four large regional databases |
| Finland | Varpula 2005 [24] | 1999 – 2002 | 1 | Consecutive admissions | Anytime during stay | 111/1,419 (7.8) | Discharge diagnosis compatible with sepsis and a need for vasopressor support during the first 48 h | ICU clinical data management system (HP CareVue, Palo Alto, Calif., USA) |
| Croatia | Degoricija 2006 [25] | 2000 – 2005 | 1 | Medical patients referred from the emergency department | At admission | 125/5,022 (2.5) | SEPSIS 1/2 | Hospital database |
| | | | | | Anytime during stay | 138/5,022 (2.7) | | |
| Multiple European | SOAP study (Sakr 2006 [27], Vincent 2006 [26], Sprung 2006 [28], Sakr 2007 [32]) | 2002 | 198 | Consecutive adult admissions | At admission | 243/3,147 (7.7) | SEPSIS 1 | Case report forms entered in a central database |
| | | | | | Anytime during stay | 462/3,147 (14.7) | | |
| France | Guidet 2007 [30] | 1998 – 2002 | 35 | Admissions in the CUB-Rea network | Anytime during stay | 4,707/98,015 (4.8) | Not reported | Cub-REA database |
| Germany | Engel 2007 [29], Elke 2008 [34] | 2003 – 2004 | 454 | All patients present on a single day in 310 randomly chosen hospitals | Anytime during stay | Engel: 190/3,877 (4.9)<br>Elke: 184/3,877 (4.7) | SEPSIS 1 (modified) | Case report forms entered into a national central database |
| Finland | Karlsson 2007 [31] | 2004 – 2005 | 25 | Consecutive adult admissions | Anytime during stay | 363/4,500 (8.1) | SEPSIS 1 | Hospital admissions and discharge data |
| Spain | Blanco 2008 [33] | 2002 | 14 | Consecutive admissions (without non-infectious heart problems) | Anytime during stay | 180/2,619 (6.9) | Not reported | Standardized forms entered into a multicenter central database |
| Italy | Malacarne 2008 [35] | 2002 – 2003 | 71 | Consecutive admissions (>48 hrs stay) | Anytime during stay | 224/5,814 (3.9) | SEPSIS 2 | Electronic case record forms entered into a multicenter national database |
| France | Adrie 2009 [36] | 1996 – 2007 | 12 | Consecutive adult admissions hospitalized | Anytime during stay | 674/7,719 (8.7) | SEPSIS 1 | OUTCOMEREA database generated from |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | for more than 24 hours | | | | standardized report forms |
| Germany | Weiss 2009 [38] | 2007 | 1 | Surgical critically ill patients admitted to an adult ICU | Anytime during stay | 162/742 (21.8) | SEPSIS 1 | Standardized electronic case report forms entered into a single center database |
| | | | | | | 205/742 (27.6) | SEPSIS 2 | Standardized electronic case report forms entered into a single center database |
| Portugal | SACiUCI study (Povoa 2009 [37], Cardoso 2010 [39]) | 2004 – 2005 | 17 | Consecutive adult admissions | At admission | Povoa: 458/4,142 (11.1)<br><br>Cardoso: 437/4,142 (10.6) | SEPSIS 1/2 (Povoa)<br>SEPSIS 1 (Cardoso) | Data collected prospectively into a multicenter national database |
| Austria | Wurzinger 2010 [40] | 2003 – 2008 | 1 | Prospectively collected database of admissions | Anytime during stay | 343/2,700 (12.7) | SEPSIS 2 | Institutional database and medical records |
| USA | Moore 2011 [41] | 2007 – 2009 | 1 | Retrospective screen of all admissions | Anytime during stay | 61/4,514 (1.4) | SEPSIS 1 (modified) | General surgical ICU database |
| USA | Plataki 2011 [42] | 2005 – 2007 | 1 | Consecutive adult (>18 years of age) patients admitted to a medical ICU | Anytime during stay | 467/4,893 (9.4) | SEPSIS 1 | Retrospective review of medical records |
| Netherlands | Klein Klouwenberg 2012 [43] | 2009 – 2010 | 1 | All adult admissions (not transferred or elective surgery) | At admission | 98/1,072 (9.1) | Liberal definition: sepsis (≥2 criteria transiently present during a 24 h period of automatic recording) plus refractory hypotension | Clinical data collected prospectively |
| | | | | | | | Restrictive definition: sepsis (≥3 criteria simultaneously present with manual recording at hourly intervals) plus refractory hypotension with other organ system failure | |
| Portugal | Almeida 2013 [44] | 2004 – 2008 | 1 | Consecutive adult admissions | Anytime during stay | 197/1,223 (16.1) | SEPSIS 1 | Clinical data registered prospectively until hospital discharge |
| France | EPISS study (Pavon 2013 [46], Quenot 2013 [47]) | 2009 – 2011 | 14 | Consecutive adult admissions | Anytime during stay | 1,495/10,941 (13.7) | Infection requiring vasopressors despite adequate vascular filling with either metabolic acidosis, oliguria/renal insufficiency or hepatic | Clinical data registered prospectively using standardized electronic case report forms |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | dysfunction | |
| USA | Miller 2013 [45] | 2004 – 2010 | 18 | Consecutive admissions | At admission | 1,426/15,019 (9.5) | SEPSIS 2 | Retrospective chart review and electronic health records |
| Italy | PICU-Network study (Sakr 2013 [48], Sakr 2013 [49]) | 2006 | 24 | All adult patients admitted to a network of 24 ICUs from 17 hospitals during a 180 day period | At admission | 100/3,902 (2.6) | SEPSIS 1 | Electronic case record forms entered into a multicenter regional database |
| | | | | | Anytime during stay | 145/3,902 (3.7) | | |
| Portugal | INFAUCI study Goncalves-Pereira 2014 [50] | 2009 – 2010 | 14 | Consecutive adult admissions | At admission | 856/3,766 (22.7) | SEPSIS 1/2 | Data collected prospectively into a multicenter database |
| France | Tolsma 2014 [51] | 1997 – 2011 | 11 | All patients admitted to ICU OUTCOMEREA database | At admission | 1,094/14,419 (7.6) | Not reported | OUTCOMEREA database generated from standardized report forms |
| France | Chauvet 2015 [52] | 2008 – 2010 | 1 | Consecutive admissions | At admission | 218/962 (22.7) | Not reported | Medical records and ICU observation charts |
| Poland | Kubler 2015 [53] | 2012, 2013 | NR | All patients treated on a single day of questionnaire completion | Anytime during stay | 243/2,258 (10.8) | Surviving Sepsis Campaign 2008 | National survey of ICUs |
| Greece | Papadimitriou-Olivgeris 2016 [55] | 2011 – 2014 | 1 | All adult admissions | At admission | 55/834 (6.6) | SEPSIS 3 | Retrospective chart review of a single center database |
| | | | | | Anytime during stay | 136/834 (16.3) | | |
| Germany | SepNet 2016 [54] | 2013 | 154 | All admissions | At admission | SEPSIS 1: 1,285/11,883 (10.8)<br>SEPSIS 3: 848/11,883 (7.1) | SEPSIS 1&3 | Data collected prospectively |
| Netherlands | van Vught 2016 [56] | 2011 – 2013 | 2 | All consecutive admissions (>48 hrs stay) | At admission | 549/3,168 (17.3) | Shock was defined by the use of noradrenaline for hypotension in a dose of more than 0.1 µg/kg/min during at least 50% of the ICU day | Data collected prospectively |
| UK | Shankar-Hari 2017 [57] | 2011 – 2015 | 189 | Consecutive adult admissions | At admission | SEPSIS 2: 153,257/654,918 | SEPSIS 2&3 | Data collected prospectively into a |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | (23.4)<br><br>SEPSIS 3: 39,262/654,918 (6.0) | | multicenter national database |

*ACCP/SCCM, American College of Chest Physicians/Society of Critical Care Medicine; BSI, bloodstream infection; ED, emergency department; EPISS; EPIdemiology of Septic Shock study; ICD, International classification of Diseases; ICU, intensive care unit; INFAUCI, The Infection on Admission to the ICU study; NR, not reported; PICU-Network, Piedmont Intensive Care Unit Network study; SACiUCI, Portuguese Community-Acquired Sepsis study; SIRS, systemic inflammatory response syndrome; SOAP, Sepsis Occurrence in Acutely Ill Patients study*

**Table S2.** Summary of included studies reporting septic shock mortality outcomes

| Country | Author, year [ref] | Timeframe of data collection | Setting (no. of centers) | Type of ICU | Criteria used | Data source | Cohort screened | Timepoint for septic shock diagnosis | Mortality Deaths/cases, n (%) |
|---|---|---|---|---|---|---|---|---|---|
| Canada | Laupland 2005 [23] | 1999 – 2002 | ICU (7) | Multi disciplinary, cardiovascular | BSI-associated sepsis requiring vasopressor infusion | Four large regional databases | All adult ICU admissions | At admission | 28-day: 81/159 (50.9) |
| Finland | Varpula 2005 [24] | 1999 – 2002 | ICU (1) | Medical-surgical | Discharge diagnosis compatible with sepsis and a need for vasopressor support during the first 48 h | ICU clinical data management system (HP CareVue, Palo Alto, Calif., USA) | Consecutive ICU admissions | Anytime during stay | ICU: 33/111 (29.7)<br>30-day: 36/111 (32.4)<br>48-hr: 12/111 (10.8) |
| Croatia | Degoricija 2006 [25] | 2000 – 2005 | ICU (1) | Medical | SEPSIS 1/2 | Hospital database | Medical ICU patients referred to the ICU from the emergency department | Anytime during stay | ICU: 107/138 (77.5) |
| Canada and USA | Kumar 2006 [58] | Cohort 1: 1999 – 2004<br>Cohort 2: 1989 – 1999<br>Cohort 3: 1999 – 2004 | ICU (14); hospitals (10) | Medical, general surgical, mixed | SEPSIS 1 | Local database where cases were encoded prospectively based on ICU registries and ICD-9 diagnoses | Hospital cohort data in locally developed databases (two Canadian cohorts and one American) | Anytime during stay | Hospital: NR/2731 (56.2) |
| Europe (multiple); SOAP study | Sakr 2006 [27], Vincent 2006 [26], Sprung 2006 [28], Sakr 2007 [32] | 2002 | ICU (198) | Not reported | SEPSIS 1 | Case report forms entered in a central database | Consecutive adult ICU admissions | At admission | ICU: 111/243 (45.7)<br>Hospital: 133/243 (54.7) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Anytime during stay | ICU: 219/462 (47.4)<br>Hospital: 250/462 (54.1) |
| Spain | Esteban 2007 [59] | 2003 | Hospital (3) | Medical-surgical | SEPSIS 1 | Preprinted case report forms prospectively entered in a database until hospital discharge | Consecutive hospital admissions (> 48 hrs stay, not transferred with sepsis) | Anytime during stay | Hospital: 27/59 (45.8)<br>ICU: 19/44 (43.2) |
| Finland | Karlsson 2007 [31] | 2004 – 2005 | ICU (25) | Multidisciplinary | SEPSIS 1 | Hospital admissions and discharge data | Consecutive adult ICU admissions | Anytime during stay | ICU: 19/44 (43.2) |
| Germany | Elke 2008 [34] | 2003 | ICU (454) | Not reported | SEPSIS 1 (modified) | Case report forms entered into a national central database | All ICU patients present on a single day in 310 randomly chosen hospitals | Anytime during stay | Hospital: 110/177 (62.1) |
| Italy | Malacarne 2008 [35] | 2002 – 2003 | ICU (71) | Medical-surgical | SEPSIS 2 | Electronic case record forms entered into a multicenter national database | Consecutive ICU admissions (>48 hrs stay) | Anytime during stay | Hospital: 358/472 (75.8)<br>ICU: 334/472 (70.8) |
| USA | Mikkelsen 2009 [60] | 2005 – 2006 | ED (1) | Not reported | Hypotension (systolic blood pressure <90 mmHg) despite adequate fluid resuscitation or the use of vasoactive agents | Clinical data collected retrospectively from electronic medical records | ED admissions with severe sepsis | At admission | 28-day: 74/196 (37.8) |
| Germany | Weiss 2009 [38] | 2007 | ICU (1) | Surgical | SEPSIS 1 | Standardized electronic case report forms entered into a single center database | Surgical critically ill patients admitted to an adult ICU | Anytime during stay | ICU: 43/162 (26.5) |
| | | | | | SEPSIS 2 | Standardized electronic case report forms entered into a single center database | Surgical critically ill patients admitted to an adult ICU | Anytime during stay | ICU: 45/205 (22.0) |
| Portugal | SACiUCI study (Povoa 2009 [37]; Cardoso 2010 [39]) | 2004 – 2005 | ICU (17) | Medical, mixed | SEPSIS 1 (Cardoso), SEPSIS 1/2 (Povoa) | Data collected prospectively into a multicenter national database | Consecutive adult ICU admissions | At admission | ICU: NR/458 (44)<br>28-day: 191/437 (43.7) |
| Spain | Pestana 2010 [61] | 2003 – 2008 | ICU (NR) | Surgical | SEPSIS 1 | Review of medical records | Consecutive surgical ICU admissions with septic shock | Anytime during stay | ICU: 71/182 (39) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Austria | Wurzinger 2010 [40] | 2003 – 2008 | ICU (1) | Multi disciplinary | SEPSIS 2 | Institutional database and medical records | Prospectively collected database of ICU admissions | Anytime during stay | ICU: 50/301 (16.6)<br>Hospital: 67/301 (22.3) |
| Spain | Castellanos-Ortega 2011 [63] | 2005 – 2010 | ICU (3) | Medical, surgical, transplant, neurology, neurosurgical, trauma | SEPSIS 2 | Not reported | Consecutive adult admissions to medical-surgical ICUs with severe sepsis | At admission | Hospital: 165/546 (30.2) |
| Canada | Chua 2011 [64] | 2006 – 2008 | ICU (1) | Not reported | Not reported | Retrospective chart review | All ICU admissions | At admission | ICU: 52/150 (34.7)<br>Hospital: 66/150 (44.0) |
| USA | Moore 2011 [41] | 2007 – 2009 | ICU (1) | General surgery | SEPSIS 1 (modified) | A general surgical ICU database | Retrospective screen of all admissions | Anytime during stay | Hospital: 22/61 (36.1)<br>ICU: 17/61 (27.9) |
| USA | Plataki 2011 [42] | 2005 – 2007 | ICU (1) | Medical | SEPSIS 1 | Retrospective review of medical records | Consecutive adult patients (>18 years of age) admitted to a medical ICU | Anytime during stay | Hospital: 167/390 (42.8) |
| France | Zahar 2011 [62] | 1996 – 2009 | ICU (12) | Not reported | Sepsis induced hypotension persisting despite adequate fluid resuscitation plus organ dysfunction | OUTCOMEREA database generated from standardized report forms | All patients admitted to ICU OUTCOMEREA database | Anytime during stay | Hospital (community): 215/530 (40.6)<br>Hospital (ICU): 123/232 (53.0)<br>Hospital (nosocomial): 233/480 (48.5) |
| Netherlands | Klein Klouwenberg 2012 [43] | 2009 – 2010 | ICU (1) | Mixed | Liberal definition: sepsis (two or more criteria transiently present during a 24 h period of automatic recording) plus refractory hypotension | Clinical data collected prospectively | All adult ICU admissions (not transferred or elective surgery) | At admission | Hospital: 23/51 (45.1) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Restrictive definition: sepsis (≥ 3 criteria simultaneously present with manual recording at hourly intervals) plus refractory hypotension with other organ system failure | Clinical data collected prospectively | All adult ICU admissions (not transferred or elective surgery) | At admission | Hospital: 28/47 (59.6) |
| Denmark | Smith 2012 [65] | 2009 | ICU (6) | General | SEPSIS 1 | Collected on paper case report forms and entered into an Excel data sheet | Consecutive ICU admissions with septic shock | Anytime during stay | 30-day: 65/164 (39.6) |
| | | | | | | | | | 90-day: 83/164 (50.6) |
| France | EPISS study (Pavon 2013 [46], Quenot 2013 [47]) | 2009 – 2011 | ICU (14) | General | Infection requiring vasopressors despite adequate vascular filling with either metabolic acidosis, oliguria/renal insufficiency or hepatic dysfunction | Clinical data registered prospectively using standardized electronic case report forms | Consecutive adult ICU admissions | Anytime during stay | 28-day: 625/1488 (42) |
| | | | | | | | | | ICU: 587/1488 (39.4) |
| | | | | | | | | | Hospital: 724/1488 (48.7) |
| USA | Miller 2013 [45] | 2004 – 2010 | ICUs (18) | Not reported | SEPSIS 2 | Retrospective chart review and electronic health records | Consecutive ICU admissions | At admission | Hospital: 242/1426 (17) |
| France | Nesseler 2013 [69] | 2008 – 2010 | ICU (1) | Not reported | SEPSIS 1 | Not reported | All patients with a first episode of septic shock that was present upon admission to the ICU or that developed during the course of ICU stay | Anytime during stay | ICU: 26/93 (28) |
| | | | | | | | | | Hospital: 30/93 (32.3) |
| | | | | | | | | | 28-day: 24/93 (25.8) |
| | | | | | | | | | 90-day: 37/93 (39.8) |
| | | | | | | | | | 180-day: 42/93 (45.2) |
| Italy | Sakr 2013 [48] | 2006 | ICU (24) | Mixed medical/ surgical, surgical cardiac, neuro surgical | SEPSIS 1 | Electronic case record forms entered into a multicenter regional database | All adult patients admitted to a network of 24 ICUs from 17 hospitals during a 180 day period | At admission | ICU: 56/100 (56) |
| | | | | | | | | Anytime during stay | ICU: 85/145 (58.6) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Denmark | Storgaard 2013 [66] | 2004 – 2007 | Hospital (1) | Not reported | Infection and failure of ≥ 1 organ and systolic blood pressure ≤ 90 mmHg with no response to adequate volume therapy | Data extracted from 3 population-based registers: the Funen Patient Administrative System, the Danish National Registry of Patients, and the Civil Registration System | Patients hospitalized in one of the medical departments at Odense University Hospital | Anytime during stay | 30-day: 44/103 (42.7)<br>31 days - 4 years: 21/59 (35.6) |
| USA | Walkey 2013 [67] | 2009 | Hospital (up to 1000) | Not reported | SEPSIS 1 | Discharge data from the Nationwide Inpatient Sample database | Admitted through the ED with suspected severe sepsis/septic shock | At admission | Hospital: NR/182,220 (31.4) |
| USA | Whittaker 2013 [68] | 2005 – 2009 | ED (1) | Not reported | SEPSIS 1/2 | Case report forms | Patients admitted through the ED with a diagnosis of severe sepsis/septic shock | At admission | 28-day: 117/321 (36.4) |
| Portugal | Goncalves-Pereira 2014 [50] | 2009 – 2010 | ICU (14) | Not reported | SEPSIS 1/2 | Data collected prospectively into a multicenter database | Consecutive adult ICU admissions | At admission | Hospital: 418/856 (48.8) |
| USA | Lee 2014 [70] | 2007 – 2009 | ICU (1) | Medical | SEPSIS 2 | Previously validated electronic medical database (ICU datamart) | Consecutive adult ICU admissions | Anytime during stay | Hospital: 142/594 (23.9) |
| Denmark | Rosland 2014 [71] | NR | ICU (7) | General | SEPSIS 1 | Entered centrally in a local database from paper case report forms | Consecutive ICU admissions with septic shock | Anytime during stay | 28-day: 102/213 (47.9)<br>90-day: 114/213 (53.5) |
| France | Tolsma 2014 [51] | 1997 – 2011 | ICU (11) | Not reported | Not reported | OUTCOMEREA database generated from standardized report forms | All patients admitted to ICU OUTCOMEREA database | At admission | Day 28: 412/1094 (37.7) |
| France | Chauvet 2015 [52] | 2008 – 2010 | ICU (1) | Not reported | Not reported | Medical records and ICU observation charts | Consecutive ICU admissions | At admission | 28-day: 83/218 (38.1)<br>ICU: 66/218 (30.3) |
| Switzerland | Que 2015 [74] | 2008 – 2012 | ICU (1) | Mixed | SEPSIS 2 | Electronic clinical report forms specifically designed for the study | Prospectively enrolled in the ICU with severe sepsis/septic shock | At admission | Hospital: 38/103 (36.9) |

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|---|---|---|---|---|---|---|---|---|---|
| Europe (multiple) | Rhodes 2015 [73] | 2013 | ED/ICU (NR) | Not reported | SEPSIS 2 | Clinical data registered prospectively using standardized electronic case report forms | Consecutive admissions to the ED or ICU with severe sepsis/septic shock | At admission to ED<br><br>Anytime during ICU stay | 30-day (East Europe): 21/43 (48.8)<br><br>30-day (West Europe): 59/218 (27.1) |
| Spain | Suberviola Canas 2015 [72] | 2005 – 2010 | ICU (1) | Not reported | SEPSIS 2 | Data collected prospectively | All adult ICU admissions with septic shock | At admission | ICU: 92/342 (26.9)<br><br>Hospital: 123/342 (36.0) |
| Finland | Ala-Kokko 2016 [75] | 2011 – 2012 | ICU (17) | Not reported | SEPSIS 1 | Data collected prospectively into a multicenter national database | All adult ICU admissions (>24 hrs stay expected) | At admission | 90-day: 61/178 (34.3) |
| Spain | Bouza 2016 [10] | 2006 – 2001 | Hospital (NR) | Not reported | Not reported | Data collected retrospectively from a national database | All hospitalized adult patients | Anytime during stay | Hospital: 50993/93380 (54.6) |
| USA | Bruns 2016 [76] | 2009 – 2012 | ED (1) | Not reported | Not reported | Retrospective chart review of a single center database | Consecutive ED admissions | At admission | Hospital: 72/166 (43.4) |
| France | Contou 2016 [77] | 2014 – 2015 | ICU (10) | Not reported | SEPSIS 1 | Data collected prospectively | All consecutive ICU admissions with suspected septic shock | At admission | ICU (early confirmed septic shock): 139/374 (37.2) |
| USA | Drumheller 2016 [78] | 2005 – 2009 | ED (1) | Not reported | Arterial hypotension (systolic blood pressure <90 mm Hg) despite adequate fluid resuscitation (> | Data collected retrospectively from ED visit logs and electronic medical records | Patients admitted through the ED with severe sepsis and septic shock | Not reported | Hospital: 57/208 (27.4) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1500mL) or use of vasopressors | | | | |
| USA | Jones 2016 [79] | 2012 – 2013 | Hospital (6) | Not reported | Not reported | Data collected retrospectively from national databases | Hospitalized adult patients with a diagnosis of sepsis | Anytime during stay | Hospital: NR/1683 (36.4) |
| Italy | Mazzone 2016 [80] | 2012 | Hospital (31) | Not reported | SEPSIS 2 | Data collected prospectively until hospital discharge | Consecutive hospitalized patients with an objective diagnosis of sepsis | At admission | Hospital: 2/17 (11.8) |
| Greece | Papadimitriou-Olivgeris 2016 [55] | 2011 – 2014 | ICU (1) | General | SEPSIS 3 | Retrospective chart review of a single center database | All adult ICU admissions | Anytime during stay | ICU: 47/55 (85.5) |
| Germany | SepNet 2016 [54] | 2013 | ICU (133) | Not reported | SEPSIS 1&3 | Data collected prospectively | All ICU admissions | At admission | Hospital mortality<br>SEPSIS-1: 530/1224 (43.3)<br>SEPSIS-3: 412/810 (50.9)<br><br>ICU mortality<br>SEPSIS-1: 473/1268 (37.3)<br>SEPSIS-3: 371/838 (44.3) |
| USA | Adams 2017 [81] | 2010 – 2014 | ICU (2) | Not reported | Per physician diagnosis | Retrospective chart review | Consecutive adult ICU admissions | Anytime during stay | All-cause: 160/308 (51.9) |
| Spain and France | Andaluz-Ojeda 2017 [82] | 2013 – 2016 | ICU (2) | Not reported | SEPSIS 2 | Data collected prospectively | Consecutive adult ICU admissions with severe sepsis/septic shock | Anytime during stay | 28-day: 87/239 (36.4) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| USA | Beesley 2017 [83] | 2006 – 2013 | ICU (3) | Not reported | SEPSIS 1 (modified) | Review of medical records | Adult ICU admissions with septic shock requiring vasopressor therapy | At admission | 28-day: 435/1554 (28.0) |
| USA | Henning 2017 [84] | 2012 – 2013 | ED (1) | Not reported | Systolic blood pressure <90 mm Hg after ≥ 1L IV fluids, new vasopressor requirement, or systolic blood pressure <90 mm Hg and IV fluids held for concern of fluid overload | Institutional database and medical records | All consecutive adult ED admissions with suspected infection | At admission | Hospital: 79/378 (20.9) |
| France | Jamme 2017 [85] | 2008 – 2015 | ICU (1) | Medical | SEPSIS 2 | Retrospective chart review | All adult ICU admissions with septic shock diagnosed within 48 hrs | At admission (48 hours) | 3-day: 113/801 (14.1)<br>ICU: 299/801 (37.3)<br>Hospital: 331/801 (41.3) |
| USA | Kadri 2017 [86] | 2005 – 2014 | Hospital (27) | Not reported | SEPSIS 1/2 | Retrospective chart review of a multicenter national database | All hospitalized adult patients | Anytime during stay | Hospital mortality Septic Shock Surveillance Definition: 51,507/99,312 (51.9)<br>Hospital mortality ICD-9 Code for Septic Shock: 34,665/82,350 (42.1) |
| USA | Liu 2017 [87] | 2010 – 2013 | ED (21) | Not reported | SEPSIS 2 (modified) | Data collected retrospectively from national databases | Adult patients hospitalized through the ED with a diagnosis of sepsis | At admission | Hospital:1215/4,668 (26.0) |
| USA | Marik 2017 [88] | 2013 | ICU (500) | Not reported | Not reported | Retrospective chart review of a multicenter national database | All adult non-surgical ICU patients admitted from the ED with severe sepsis/septic shock and parenteral antibiotics on day 1 | At admission | Hospital: NR/14531 (32.6) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Netherlands | Ong 2017 [89] | 2011 – 2014 | ICU (2) | Mixed | Presence of sepsis plus the use of noradrenaline for hypotension in a dose of >0.1 µg/kg/min for more than 12 hours during the first 3 days in the ICU | Data collected prospectively | Consecutive adult ICU admissions with septic shock | At admission | ICU: 81/329 (24.6) |
| USA | Saqib 2017 [90] | 2003 – 2011 | Hospital (NR) | Not reported | Not reported | Data collected retrospectively from a multicenter national database | Hospitalized patients with septic shock | At admission | Hospital mortality May: NR/118808 (39.6)<br>Hospital mortality July: NR /119798 (38.6) |
| USA | Schuetz 2017 [91] | 2011 – 2014 | ED/ICU (13) | Not reported | SIRS Criteria I + II and state of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes | Data collected prospectively | Adult patients with severe sepsis/septic shock treated in the ICU or admitted from the ED/other wards | At admission | 28-day all-cause: 54/299 (18.1) |
| UK | Shankar-Hari 2017 [57] | 2011 – 2015 | ICU (189) | Adult general | SEPSIS 2&3 | Data collected prospectively into a multicenter national database | Consecutive adult ICU admissions | At admission | ICU mortality SEPSIS 2: 39294/153257 (25.6) SEPSIS 3: 18338/39262 (46.7)<br>Hospital mortality SEPSIS 2: 49656/153257 (32.4) SEPSIS 3: 20457/39262 (52.1) |

*ACCP/SCCM, American College of Chest Physicians/Society of Critical Care Medicine; BSI, bloodstream infection; ED, emergency department; EPISS, EPIdemiology of Septic Shock study; ICD, International classification of Diseases; ICU, intensive care unit; NR, not reported; SACiUCI, Portuguese Community-Acquired Sepsis study; SIRS, systemic inflammatory response syndrome; US, United States of America; SOAP, Sepsis Occurrence in Acutely Ill Patients study*

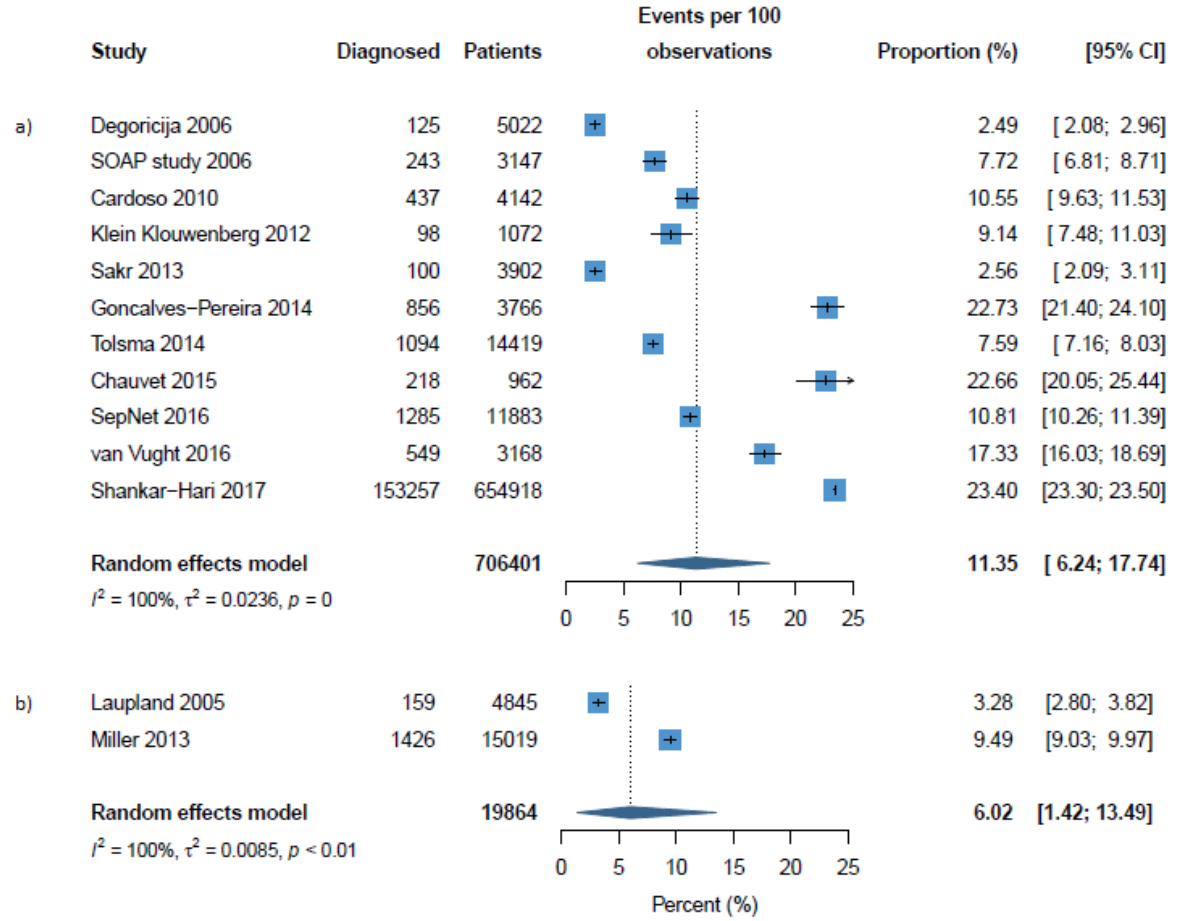
**Table S3.** Quality assessment of frequency studies using the Joanna Briggs Institute tool

| Question | Yes (%) | No (%) | Unclear (%) |
|---|---|---|---|
| Was the sample frame appropriate to address the target population? | 26 (74.3) | 6 (17.1) | 3 (8.6) |
| Were study participants sampled in an appropriate way? | 30 (85.7) | 1 (2.9) | 4 (11.4) |
| Was the sample size adequate? | 35 (100) | 0 | 0 |
| Were the study subjects and the setting described in detail? | 26 (74.3) | 8 (22.9) | 1 (2.9) |
| Was the data analysis conducted with sufficient coverage of the identified sample? | 33 (94.3) | 0 | 1 (5.7) |
| Were valid methods used for the identification of the condition? | 25 (71.4) | 4 (11.4) | 5 (17.1) |
| Was the condition measured in a standard, reliable way for all participants? | 21 (60) | 1 (2.9) | 13 (37.1) |
| Was there appropriate statistical analysis, i.e. in relation to calculating frequency? | 27 (77.1) | 4 (11.4) | 4 (11.4) |
| Was the response rate adequate, and if not, was the low response rate managed appropriately? | 25 (71.4) | 0 | 9 (28.6) |

**Table S4.** Quality assessment of mortality studies using a modified Joanna Briggs Institute tool for the assessment of case series

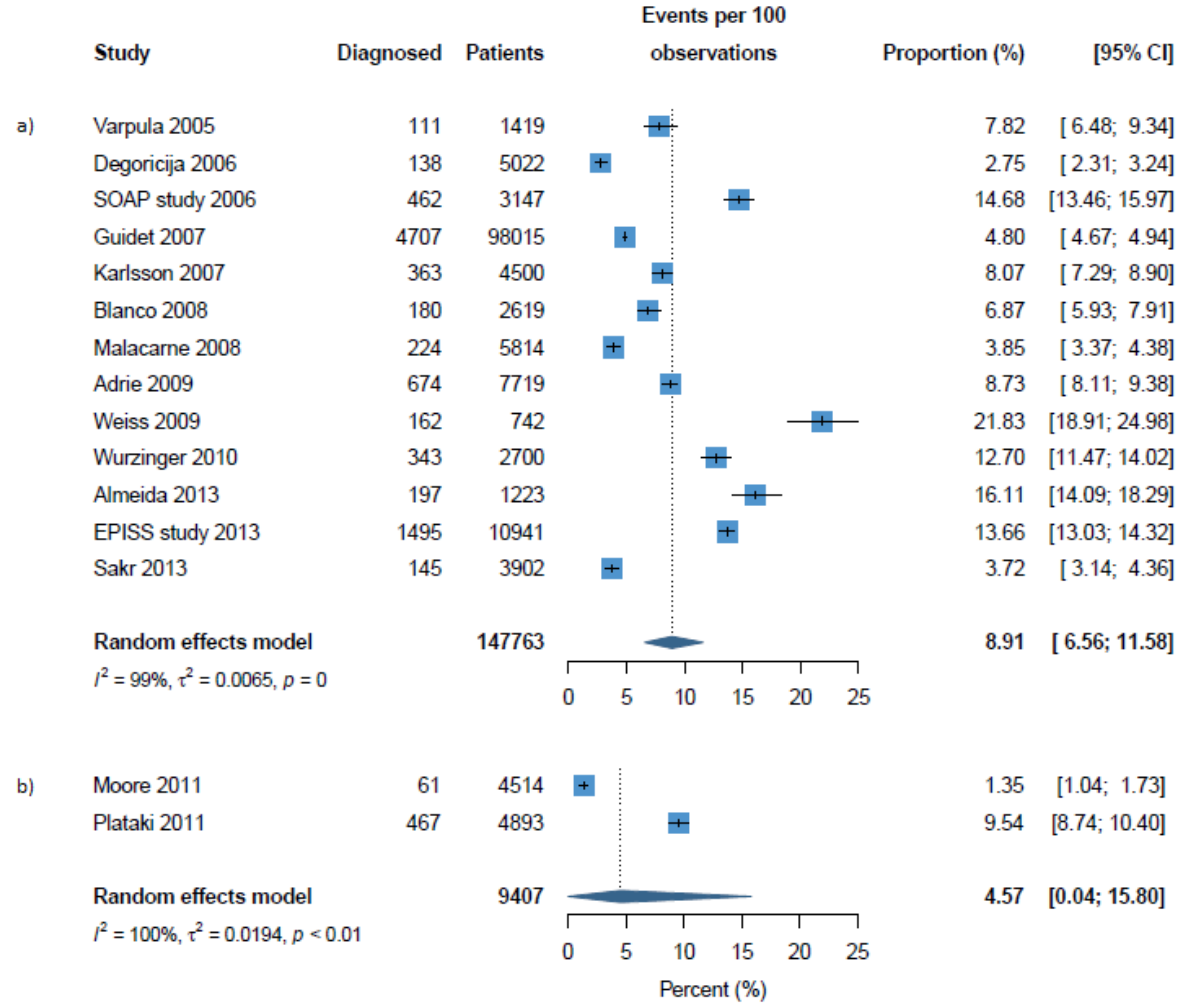
| Question | Yes (%) | No (%) | Unclear (%) |
|---|---|---|---|
| Were there clear criteria for inclusion in the case series? | 54 (94.7) | 3 (5.3) | 0 |
| Was the condition measured in a standard, reliable way for all septic shock patients included in the case series? | 33 (57.9) | 2 (3.5) | 22 (37.9) |
| Were valid methods used for the identification of the condition for all septic shock patients included in the case series? | 35 (61.4) | 7 (12.3) | 15 (25.9) |
| Did the case series have consecutive inclusion of septic shock patients? | 43 (75.4) | 8 (14.0) | 6 (10.3) |
| Did the case series have complete inclusion of septic shock patients? | 28 (49.1) | 22 (38.6) | 7 (12.1) |
| Was there clear reporting of the demographics of the septic shock patients in the study? | 32 (56.1) | 25 (43.9) | 0 (0) |
| Was there clear reporting of the clinical information of the septic shock patients in the study? | 36 (63.2) | 21 (36.8) | 0 (0) |
| Was the mortality of cases clearly reported? | 49 (86.0) | 8 (14.0) | 0 (0) |
| Was there clear reporting of the presenting site(s)/clinic(s) demographic information? | 33 (57.9) | 20 (35.1) | 4 (6.9) |
| Was statistical analysis appropriate to calculate septic shock mortality? | 50 (87.7) | 6 (10.5) | 1 (1.7) |

**Figure S2.** Random effects meta-analysis of studies frequency of septic shock in European (panel a) and North American (panel b) cohorts of patients admitted to the intensive care unit and diagnosed at admission



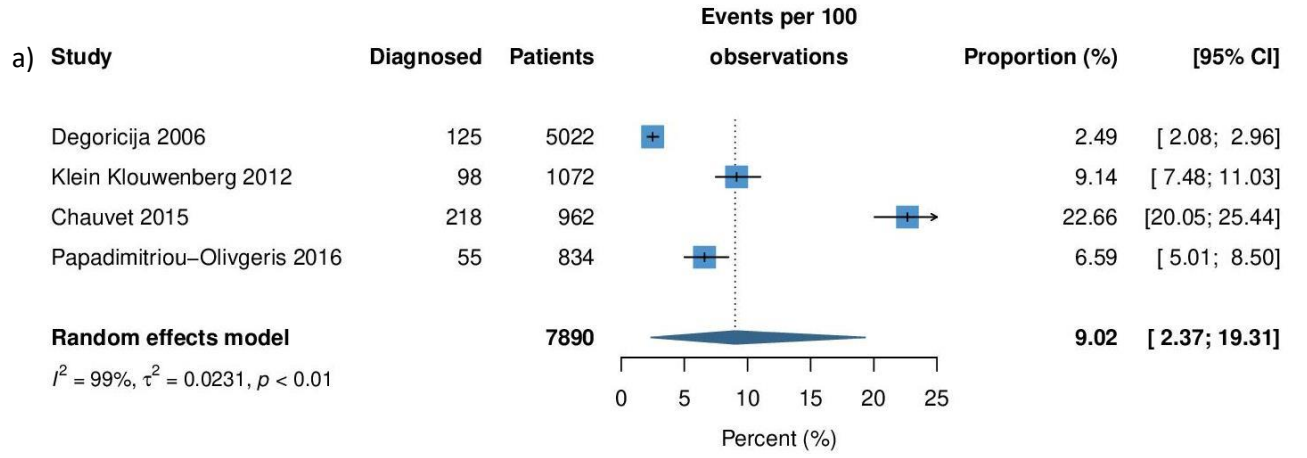

The forest plots contain exact 95% confidence intervals, and specific studies are weighted using the inverse-variance method. The pooled summaries are obtained using the Freeman–Tukey double arcsine transformation and the DerSimonian–Laird method estimates between-study variance.

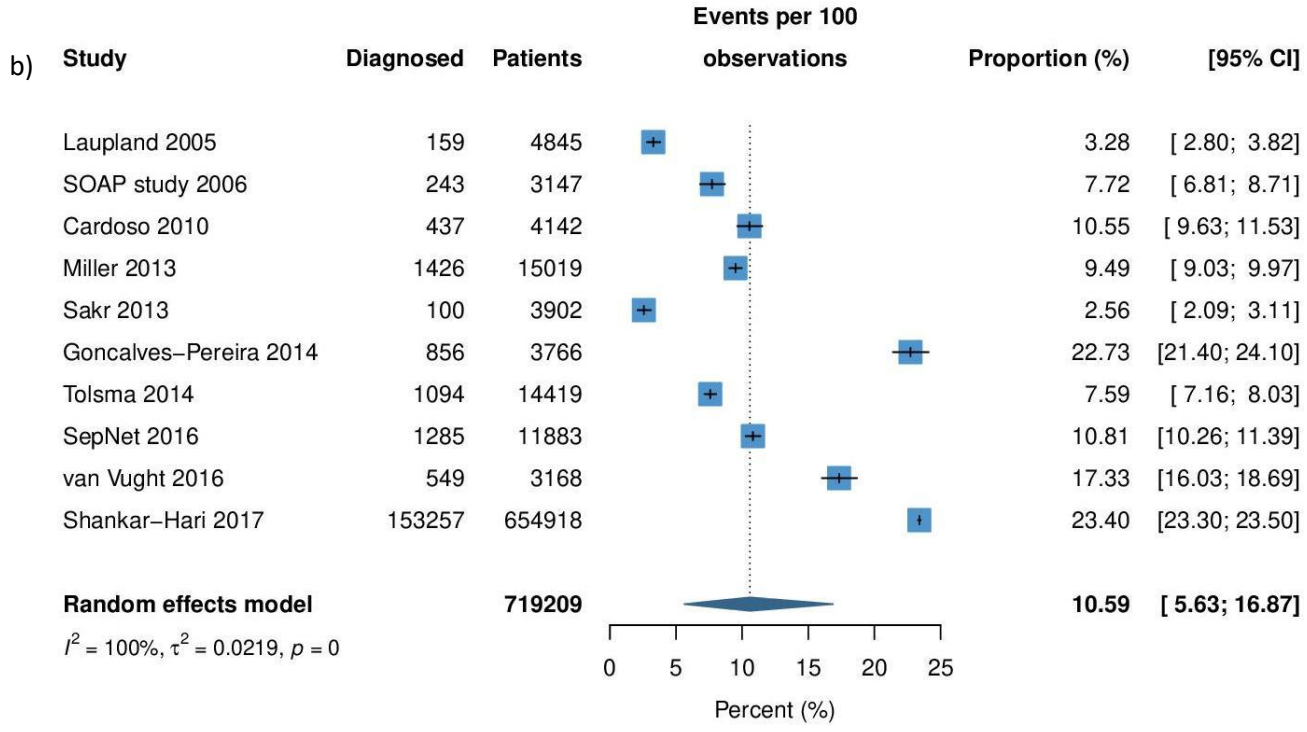
**Figure S3.** Random effects meta-analysis of studies reporting frequency of septic shock in European (panel a) and North American (panel b) cohorts of patients admitted to the intensive care unit and diagnosed at any time during the ICU stay




The forest plots contain exact 95% confidence intervals, and specific studies are weighted using the inverse-variance method. The pooled summaries are obtained using the Freeman–Tukey double arcsine transformation and the DerSimonian–Laird method estimates between-study variance.

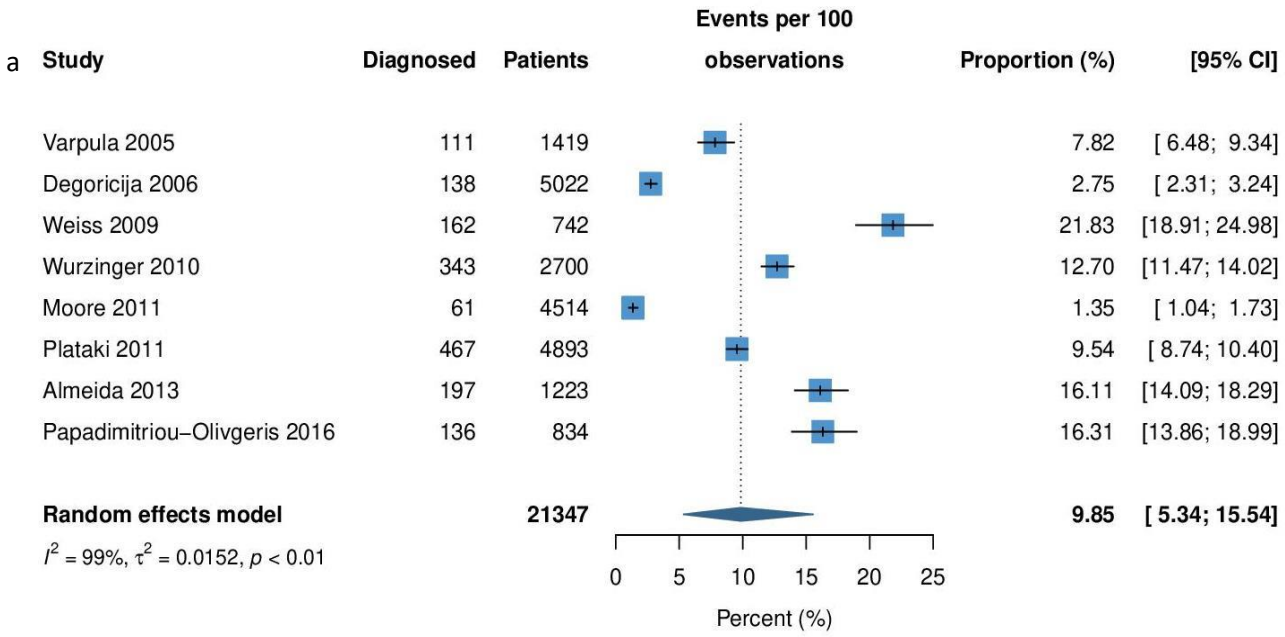
**Figure S4.** Random effects meta-analysis of single center (panel a) and multicenter (panel b) studies reporting frequency of septic shock on admission to the intensive care unit

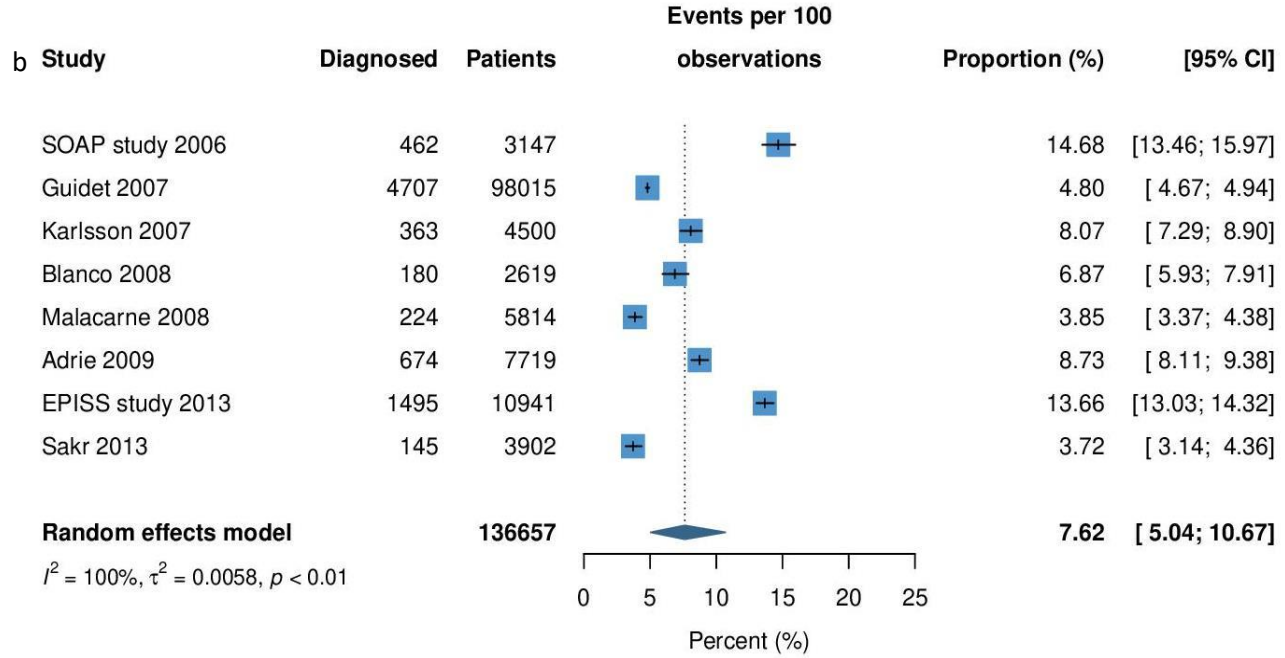



The forest plots contain exact 95% confidence intervals, and specific studies are weighted using the inverse-variance method. The pooled summaries are obtained using the Freeman–Tukey double arcsine transformation and the DerSimonian–Laird method estimates between-study variance.

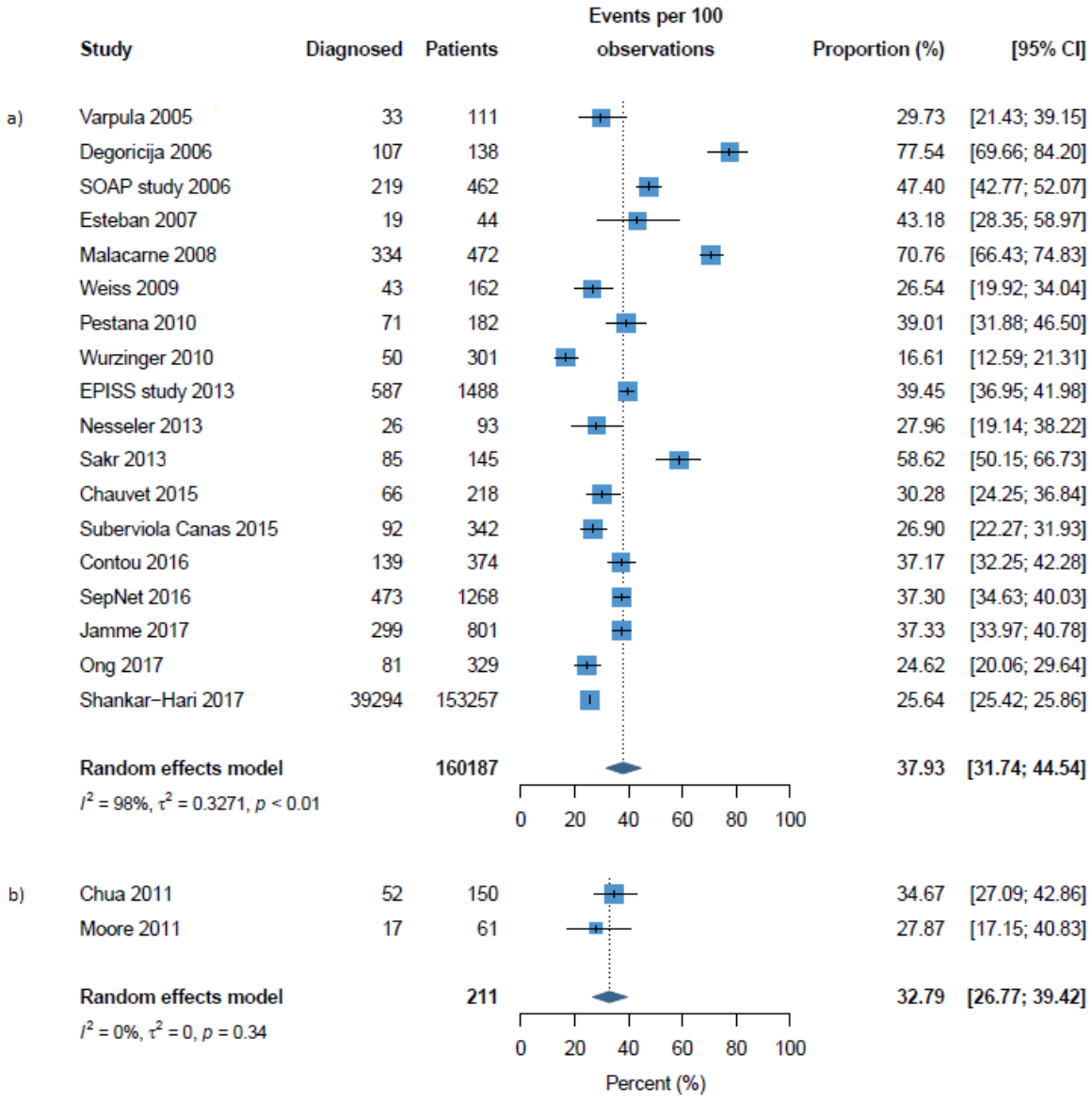
**Figure S5.** Random effects meta-analysis of single center (panel a) and multicenter (panel b) studies reporting frequency of septic shock diagnosed at any time during the ICU stay



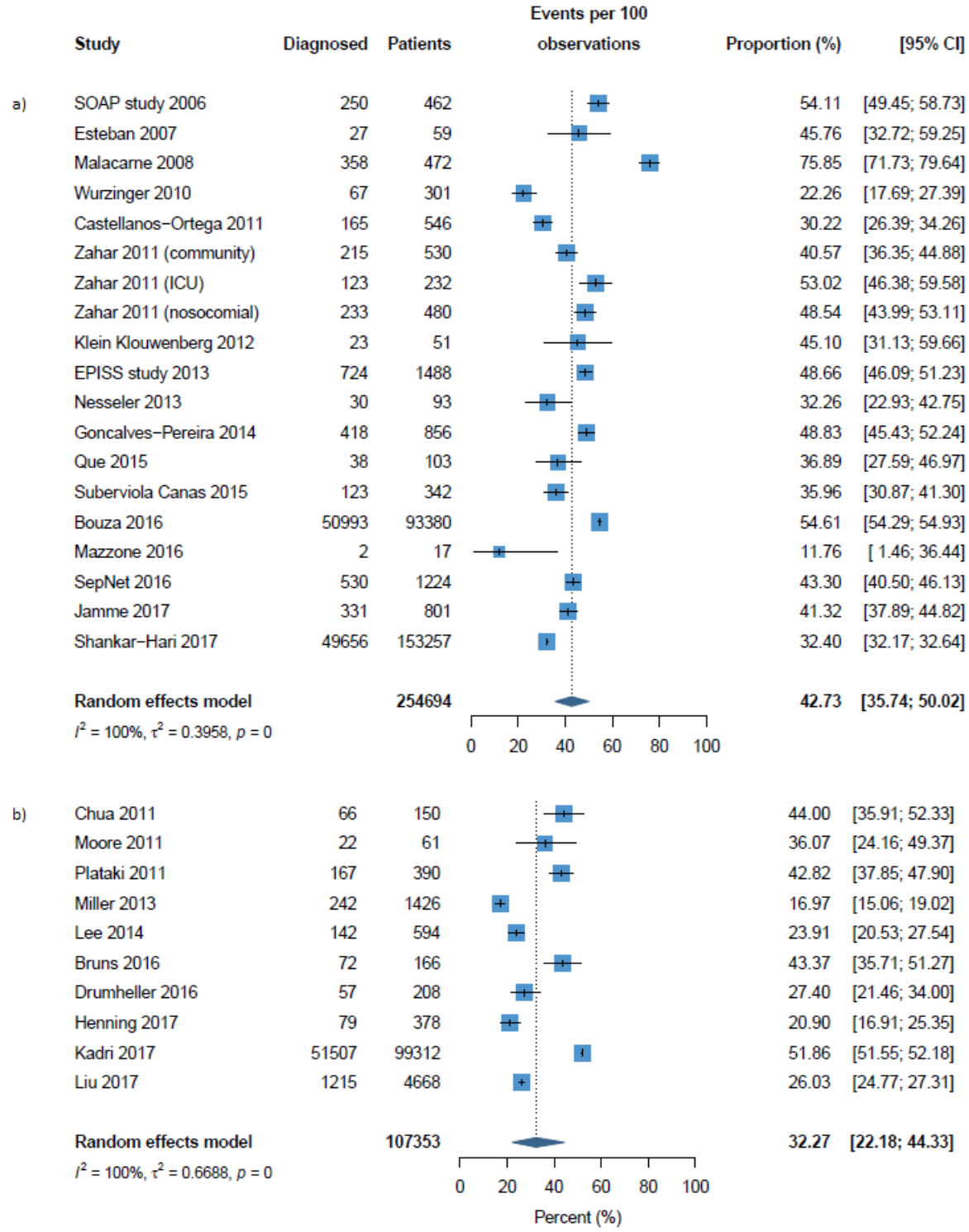

The forest plots contain exact 95% confidence intervals, and specific studies are weighted using the inverse-variance method. The pooled summaries are obtained using the Freeman–Tukey double arcsine transformation and the DerSimonian–Laird method estimates between-study variance.

**Figure S6.** Random effects meta-analysis of studies reporting ICU mortality of septic shock patients in Europe (panel a) and North America (panel b)



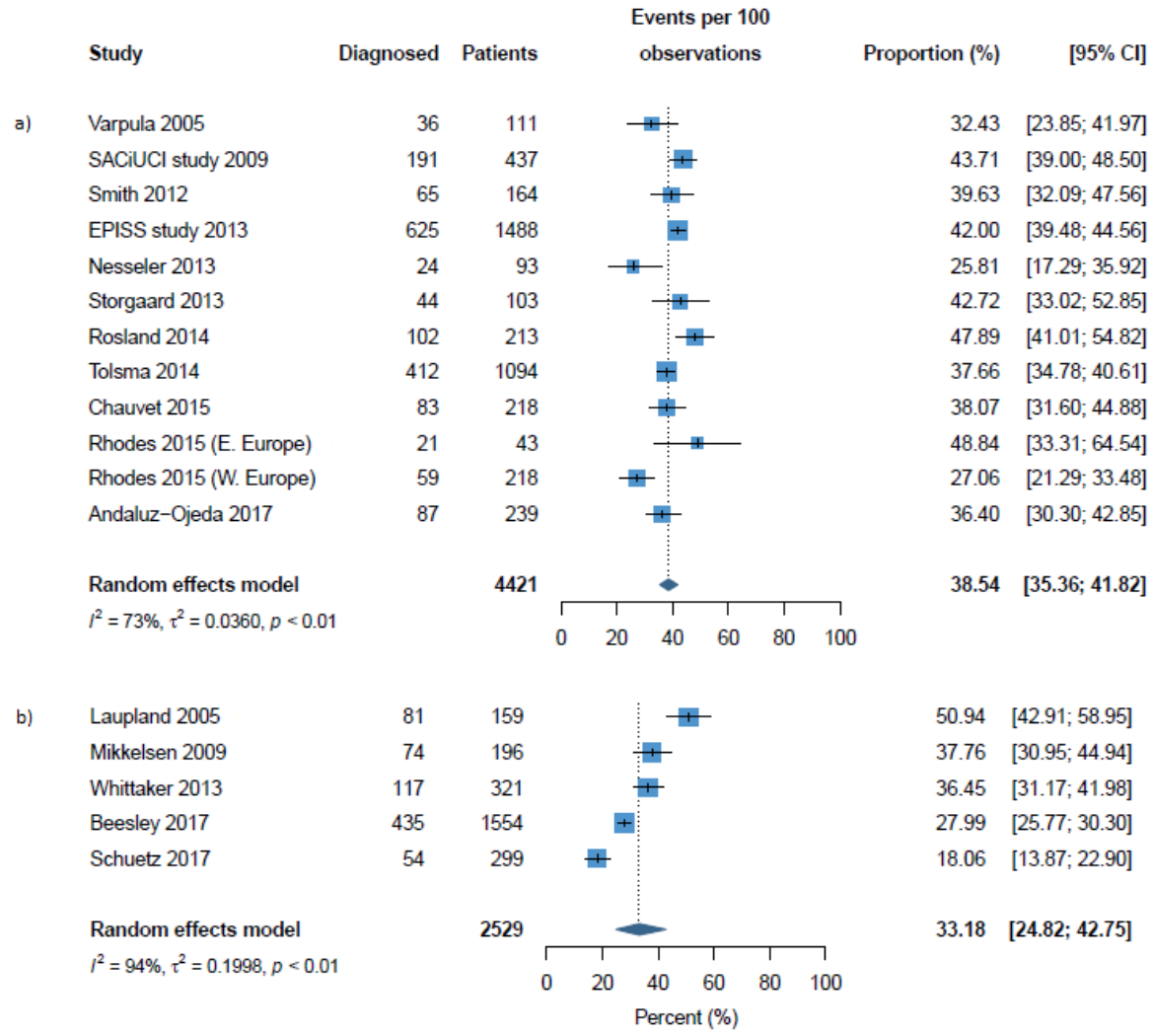

The forest plots contain exact 95% confidence intervals, and specific studies are weighted using the inverse-variance method. The pooled summaries are obtained using the logit transformation and the DerSimonian–Laird method estimates between-study variance.

**Figure S7.** Random effects meta-analysis of studies reporting hospital mortality of septic shock patients in Europe (panel a) and North America (panel b)



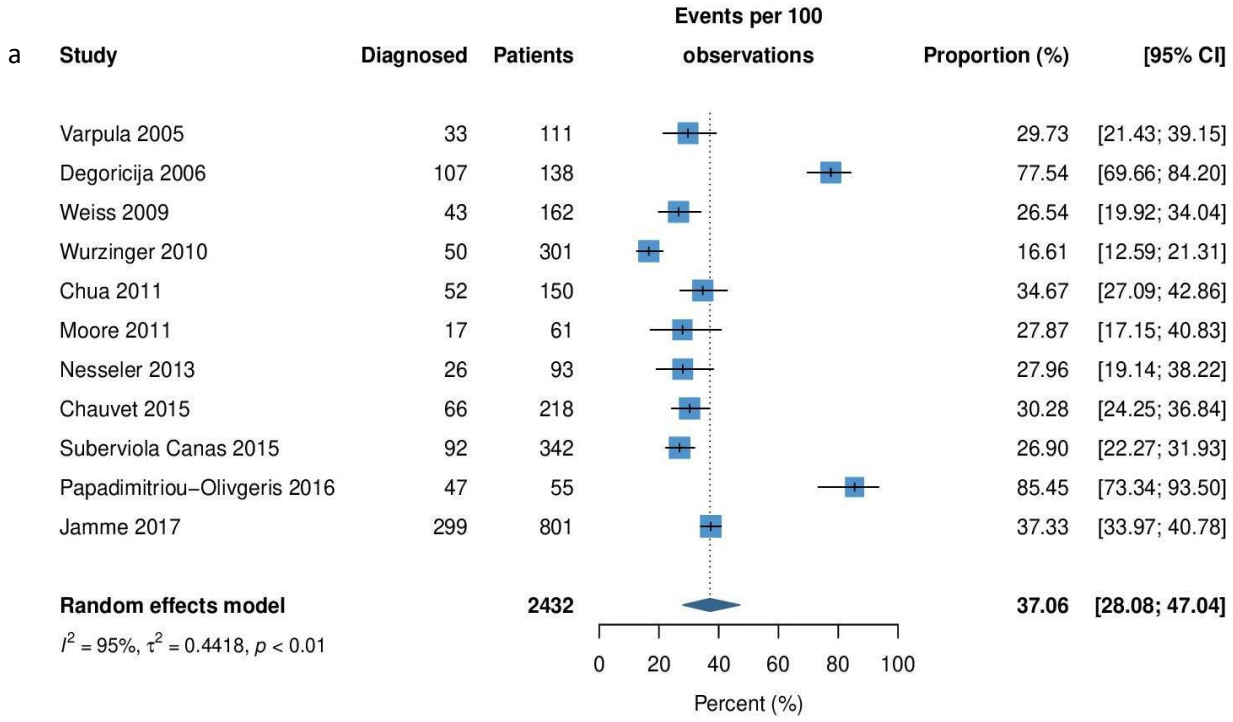

The forest plots contain exact 95% confidence intervals, and specific studies are weighted using the inverse-variance method. The pooled summaries are obtained using the logit transformation and the DerSimonian–Laird method estimates between-study variance.

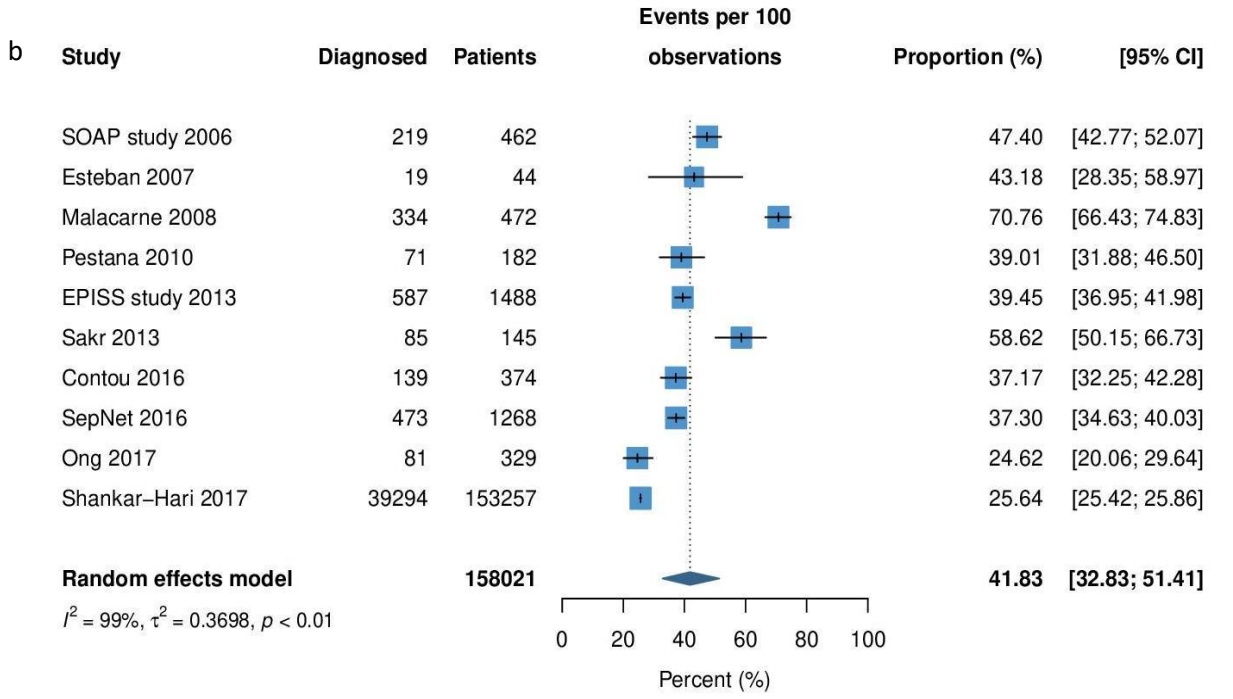
**Figure S8.** Random effects meta-analysis of studies reporting mortality at 28 / 30 days in septic shock patients in Europe (panel a) and North America (panel b)




The forest plots contain exact 95% confidence intervals, and specific studies are weighted using the inverse-variance method. The pooled summaries are obtained using the logit transformation and the DerSimonian–Laird method estimates between-study variance.

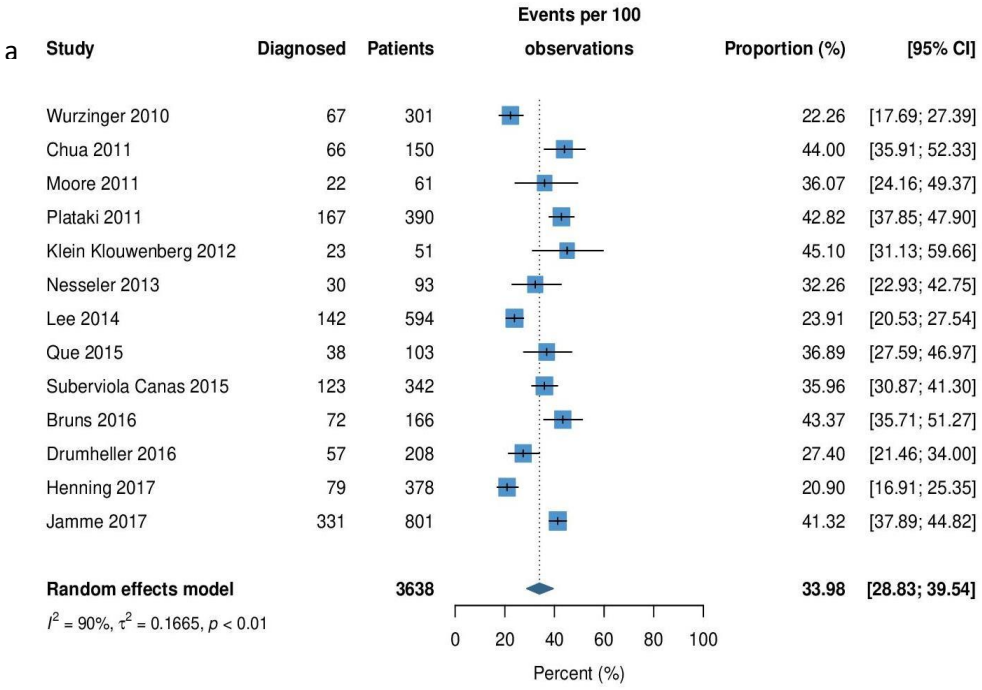
**Figure S9.** Random effects meta-analysis of single center (panel a) and multicenter (panel b) studies reporting ICU mortality in septic shock patients

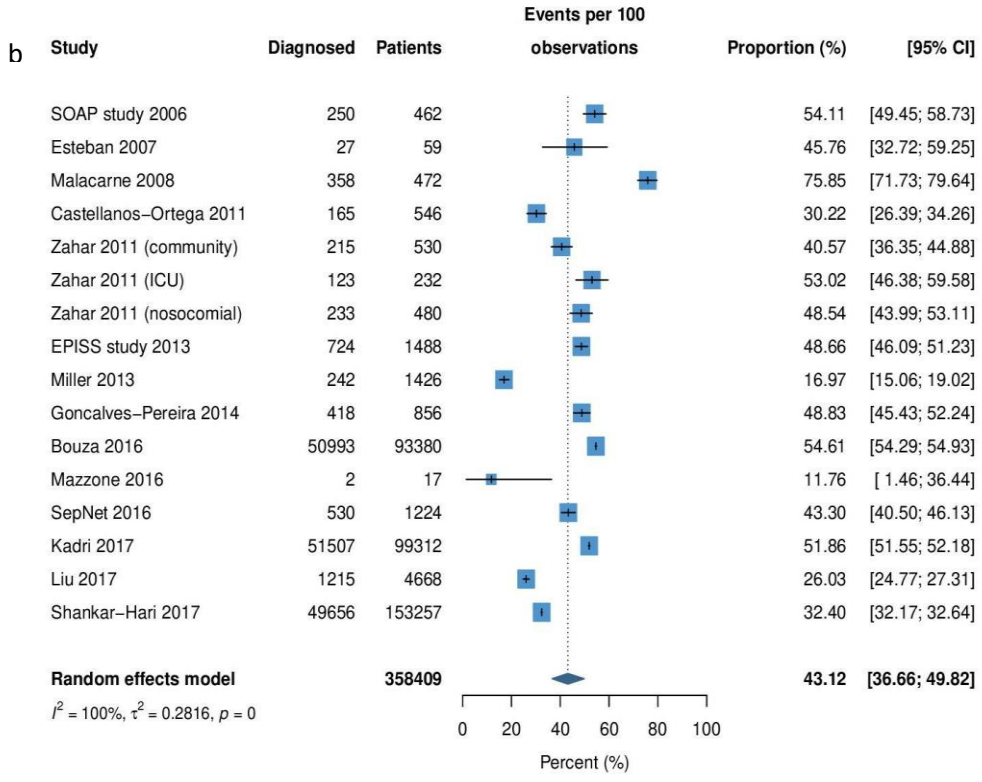



The forest plots contain exact 95% confidence intervals, and specific studies are weighted using the inverse-variance method. The pooled summaries are obtained using the logit transformation and the DerSimonian–Laird method estimates between-study variance.

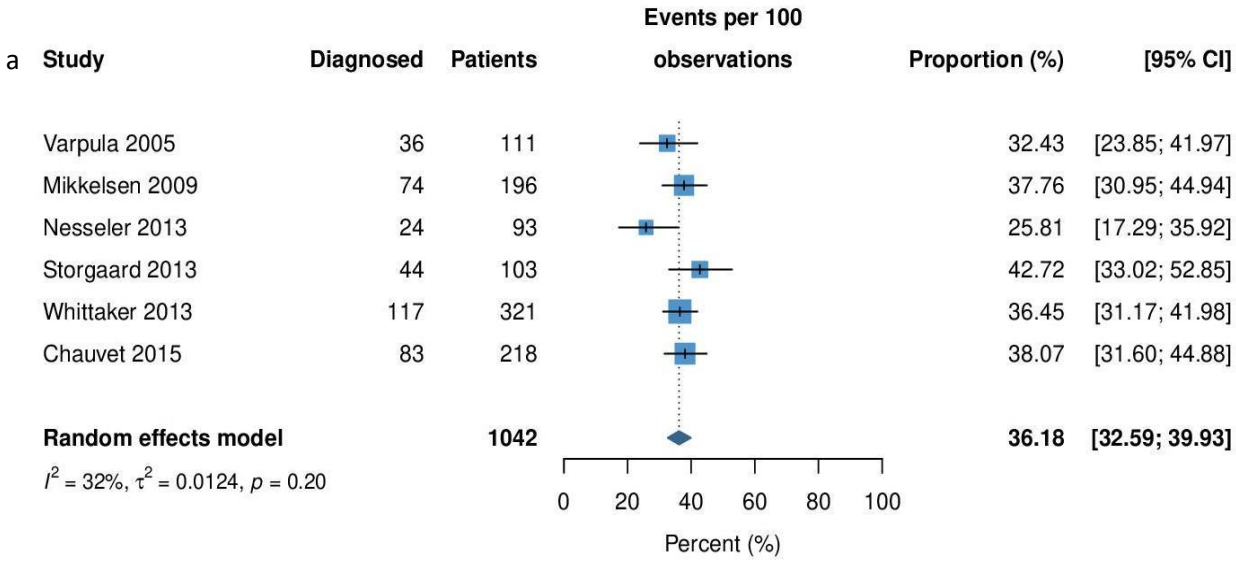
**Figure S10.** Random effects meta-analysis of single center (panel a) and multicenter (panel b) studies reporting hospital mortality in septic shock patients

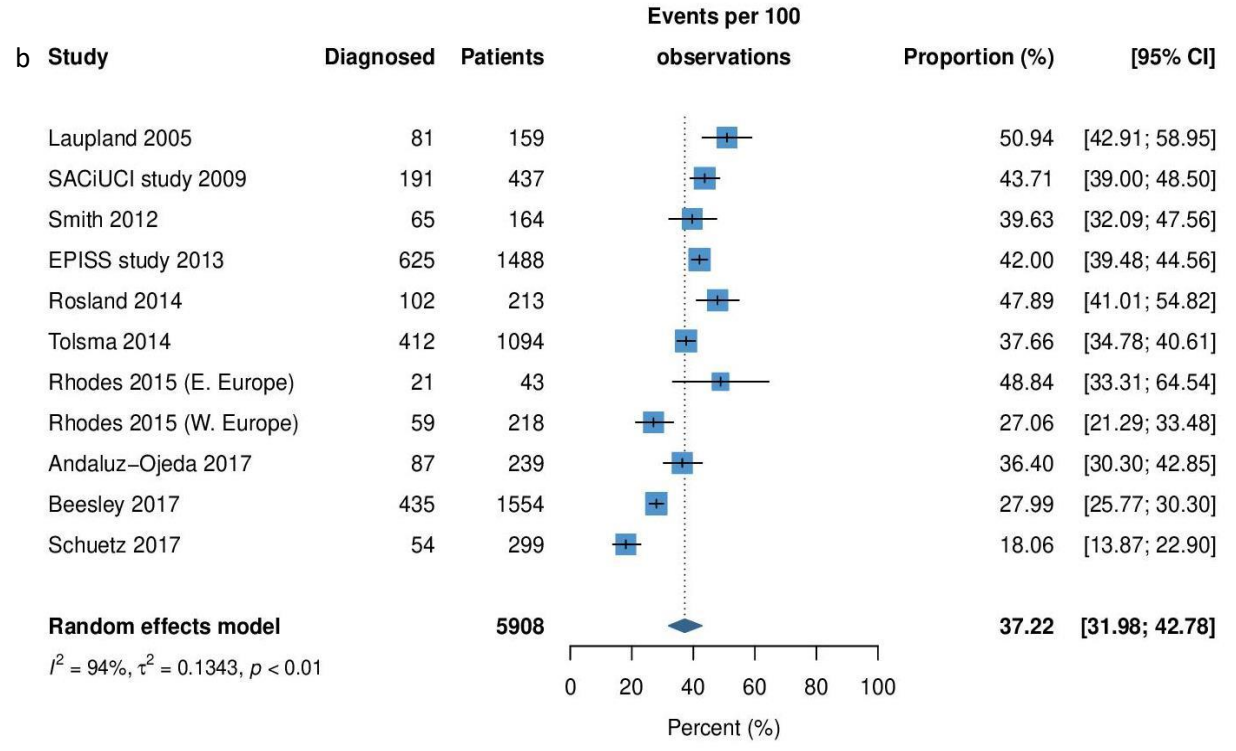



The forest plots contain exact 95% confidence intervals, and specific studies are weighted using the inverse-variance method. The pooled summaries are obtained using the logit transformation and the DerSimonian–Laird method estimates between-study variance.

**Figure S11.** Random effects meta-analysis of single center (panel a) and multicenter (panel b) studies reporting 28/30-day mortality in septic shock patients




The forest plots contain exact 95% confidence intervals, and specific studies are weighted using the inverse-variance method. The pooled summaries are obtained using the logit transformation and the DerSimonian–Laird method estimates between-study variance.