Supplementary Online Content

Tan B, Wong JJ-M, Sultana R, et al. Global case fatality trends in pediatric severe sepsis and septic shock: a systematic review and meta-analysis. *JAMA Pediatr*. Published online February 11, 2019. doi:10.1001/jamapediatrics.2018.4839

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Search strategies for databases

Database	Search Strategies	Results obtained as of 10th January 2017
PubMed	Search ((“infant”[MeSH Terms] OR “child”[MeSH Terms] OR “adolescent”[MeSH Terms] OR “Intensive Care Units, Pediatric”[Mesh] OR “Pediatrics”[Mesh] OR “Hospitals, Pediatric”[Mesh]) AND (“mortality”[Subheading] OR “Mortality”[Mesh] OR “Hospital Mortality”[Mesh]) AND (“Systemic Inflammatory Response Syndrome”[Mesh] OR “Sepsis”[Mesh] OR “Shock, Septic”[Mesh] OR “severe sepsis”[All Fields])) Filters: Child: birth-18 years	4279
Web of Science	((“septic shock” NEAR (child OR children OR pedatric* OR paediatric*)) OR (“severe sepsis” NEAR (child OR children OR pediatric* OR paediatric*)) OR (“systemic inflammatory response syndrome” NEAR (child OR children OR pediatric* OR paediatric*)) OR (sepsis NEAR (child OR children OR pediatric* OR paediatric*))) AND “mortality”	843
EMBASE	((‘systemic inflammatory response syndrome’/exp/mj OR ‘sepsis’/exp/mj OR ‘severe sepsis’/exp/mj OR ‘septic shock’/exp/mj) AND ‘mortality’) AND ([adolescent]/lim OR [child]/lim OR [infant]/lim OR [newborn]/lim OR [preschool]/lim OR [school]/lim)	2787
CINAHL	(MH “Sepsis+” OR MH”systemic inflammatory response syndrome+” OR MH “severe sepsis+” OR MH “septic shock+”) AND (MH “mortality+” OR MH “child mortality+”) Narrow by SubjectAge: - child, preschool: 2-5 years Narrow by SubjectAge: - infant: 1-23 months Narrow by SubjectAge: - child: 6-12 years Narrow by SubjectAge: - infant, newborn: birth-1 month Narrow by SubjectAge: - adolescent: 13-18 years Narrow by SubjectAge: - all infant Narrow by SubjectAge: - all child Search modes – Boolean/Phrase	324
Cochrane CENTRAL	([mh “systemic inflammatory response syndrome”] OR [mh “sepsis”] OR “severe sepsis” OR [mh “shock, septic”]) AND [mh “mortality”]	302

eTable 2. Characteristics of included studies conducted in developed countries

Author, Study Year	Description of Study	Continent	N	Mortality
Randomised Controlled Trials				
Rivera, 2014[39]	Two antibiotic guidelines in patients with Rocky Mountain Spotted Fever septic shock	NA	6	20
Nadel, 2003[40]	Drotecogin alfa vs. placebo in severe sepsis	Multi	237	41
Long, 2002[41]	Plasma filtration vs. standard therapy in severe sepsis	AO	23	4
Levin, 2000[42]	Recombinant bactericidal/permeability-increasing protein vs. placebo in meningococcal sepsis	EU, NA	203	12
Derkx, 1993[43]	HA-1A vs. placebo in meningococcal septic shock	EU	137	37
J5 Study Group, 1992[44]	Anti-J5 plasma vs. control plasma in severe infectious purpura	EU	33	12
Prospective Observational Studies				
Alder, 2016[45]	Olfactomedin-4 as marker in septic shock	NA	45	6
Wong, 2016[46]	Pediatric biomarker risk model to stratify mortality risk	NA	195	31
Muszynski, 2014[47]	Early adaptive immune response in septic shock	NA	22	2
Wong, 2014[48]	Temporal pediatric biomarker risk model in complicated shock	NA	180	23
Mickiewicz, 2013[49]	Metabolomics for early diagnosis of septic shock	NA	60	10
Weiss, 2013[6]	Sepsis prevalence, outcomes and therapies in severe sepsis	Multi	567	139
Fitrolaki, 2012[50]	Heat-shock protein as marker in severe sepsis and septic shock	EU	22	2
Wong, 2012[51]	Pediatric sepsis biomarker risk model	NA	139	11
Vila Perez, 2011[52]	Prognostic factors in pediatric sepsis	EU	88	17
Wong, 2011[53]	Gene-expression based classification for septic shock	NA	53	9
Bongers, 2010[54]	ADAMTS13 in severe meningococcal sepsis	EU	65	9
Carcillo, 2010[55]	C-reactive protein and ferritin as marker in severe sepsis	NA	100	8
Deep, 2010[56]	Hemodynamics in fluid-refractory septic shock	EU	36	4
Nowak, 2010[57]	Chemokine (C-C) in predicting septic shock survival	NA	22	2
Zurek, 2010[58]	Procalcitonin as biomarker in SIRS and sepsis	EU	28	5
Wheeler, 2008[59]	Neutrophil gelatinase-associated lipocalin in septic shock	NA	90	11
Wong, 2008[60]	Interleukin-8 as stratification too for septic shock intervention	NA	139	18
Inwald, 2006[61]	Emergency management of severe sepsis	EU	139	24
Wynn, 2006[62]	Developmental age influence in septic shock	NA	180	29
Michalek, 2004[63]	Bactericidal permeability increasing protein in sepsis	EU	45	3

Wolfler 2004, (Severe Sepsis)[64]	Survey of incidence of and mortality due to sepsis, severe sepsis and septic shock	EU	45	11
Wolfler 2004, (Septic Shock)[64]	Survey of incidence of and mortality due to sepsis, severe sepsis and septic shock	EU	59	30
Fisher, 2002[65]	Clinical spectrum of shock in emergency department	NA	84	4
Goldstein, 2002[66]	Drotecogin alfa in severe sepsis	NA	187	25
Barton, 2000[67]	Pharmacological properties of Drotecogin alfa in sepsis	NA	83	8
Hatherill, 2000[68]	Procalcitonin and cytokine levels in septic shock	EU	75	21
Ten Have, 2000[69]	Heart failure in meningococcal septic shock	EU	27	7
Verhoeven, 2000[70]	Hyperglycemia in meningococcal septic shock	EU	67	10
Ceneviva, 1998[71]	Hemodynamic support in fluid-refractory shock	NA	50	10
de Groof, 1998[72]	Growth hormone/insulin-like growth factor-I axis in meningococcal sepsis	EU	27	8
Krafte-Jacobs, 1998[73]	Increased circulating thrombomodulin in septic shock	NA	22	9
Thiru, 1997[74]	Myocardial cytotoxicity in meningococcal shock	EU	101	5
Emonts, 1996[75]	Thrombin-activatable fibrinolysis inhibitor in shock	EU	96	12
Hatherill, 1996[76]	Adrenal insufficiency in septic shock	EU	33	11
Hatherill, 1996[77]	Gastric tonometry in septic shock	EU	26	7
Leteurtre, 1996[78]	Pediatric risk of mortality and pediatric index of mortality in predicting shock outcome	EU	58	16
Derkx, 1992[79]	Interleukin-10 in initial phase of meningococcal septic shock	EU	25	4
Hazelzet, 1991[80]	Capillary leakage and inflammation in septic shock	EU	52	14
Kornelisse, 1991[81]	Characteristics of meningococcal septic shock	EU	75	16
Leclerc, 1989[82]	Protein C and S in severe infectious purpura	EU	30	7
Leclerc, 1986[83]	Severity scores in meningococcal sepsis and shock	EU	35	13
Carcillo, 1985[84]	Role of early fluid resuscitation in septic shock	NA	34	16
Pollack, 1985[85]	Cardiopulmonary variables in septic shock survivors	NA	42	24
Pollack, 1984[86]	Sequential cardiopulmonary variables in septic shock	NA	32	18
Mercier, 1982[87]	Hemodynamic patterns of meningococcal shock	EU	39	15

Abbreviations: AO = Australia/Oceania, EU = Europe, NA = North America.

eTable 3. Characteristics of included studies conducted in developing countries

Author, Study Year	Description of Study	Continent	N	Mortality
Randomised Controlled Trials				
Ramaswamy, 2013[88]	Dopamine vs. Epinephrine in septic shock	AA	31	18
Ventura, 2011[89]	Dopamine vs. Epinephrine in septic shock	SA	63	13
Chopra, 2007[90]	Hypertonic vs. normal saline in septic shock	AA	30	10
Yildizdas, 2004[91]	Terlipressin as rescue therapy in septic shock	AA	28	20
Santhanam, 2003[92]	Faster vs. slower fluid resuscitation in shock	AA	73	13
Upadhyay, 1999[93]	Crystalloid vs. colloid in septic shock	AA	31	9
Observational Studies				
Naveda, 2016[94]	Positive fluid balance and mortality in paediatric severe sepsis and septic shock	SA	16	63
Wu, 2015[95]	Brain natriuretic peptide levels and cardiac dysfunction in shock	AA	36	7
Bustos B, 2015[96]	Predictive value of calcitonin in suspected sepsis	SA	11	31
Cui, 2015[97]	High- versus standard-volume hemofiltration in children with severe sepsis	AA	24	72
Chen, 2014[98]	Central venous-to-arterial carbon dioxide difference in paediatric septic shock	AA	21	48
Ibrahiem, 2014[99]	Prognostic markers in sepsis	AA	39	8
Li, 2014[100]	Continuous blood purification in treating childhood severe sepsis	AA	9	47
Manzoli, 2014[101]	Suppression of human leukocyte antigen-DR in sepsis	SA	29	7
Rady, 2014[102]	Adrenocortical status in sepsis and septic shock	AF	30	15
Ranjit, 2014[103]	Early norepinephrine in septic shock	AA	41	4
Samransamruakjit, 2014[104]	Interleukin-10 polymorphisms and clinical risk factors in severe sepsis and septic shock	AA	33	7
Yuan, 2014[105]	Impact of continuous blood purifications on T-cell subsets in children with severe sepsis	AA	10	48
Chen, 2013[106]	Fluid accumulation in severe sepsis	AA	202	61
Kaur, 2012[9]	Clinical predictors of mortality in sepsis	AA	50	29
Phumeetam, 2012[107]	Genetic association of tumor necrosis factor-alpha with sepsis and septic shock in pediatric patients	AA	10	23
Jat, 2011[108]	Lactate as predictor of outcome in septic shock	AA	30	15
Raj, 2011[109]	Myocardial dysfunction in septic shock	AA	30	2
Sankar, 2011[110]	Venacaval oxygen saturation monitoring	AA	120	52
Sankar, 2011[111]	Diastolic dysfunction in fluid-refractory shock	AA	56	19
Karim, 2010[112]	ADAMTS-13 deficiency in severe sepsis	AA	80	32
Ranjit, 2010[113]	Multimodal hemodynamic monitoring in shock	AA	48	4
Samransamruakjit (post-implementation cohort), 2010[114]	Clinical outcomes after utilizing surviving sepsis campaign in children with septic shock and prognostic value of plasma N-terminal pro B-type natriuretic peptide	AA	47	9

Cartaya, 2009[115]	American College of Critical Care Medicine guidelines implementation in pediatric intensive care unit	SA	280	31
Jaramillo-Bustamante (Septic Shock), 2009[8]	Epidemiology of sepsis in pediatric intensive care unit: First Colombian multicentre study	SA	261	14
Jaramillo-Bustamante (Severe Sepsis), 2009[8]	Epidemiology of sepsis in pediatric intensive care unit: First Colombian multicentre study	SA	503	171
Xu, 2009[116]	Multiplex cytokine score for disease severity	AA	111	15
Carmona, 2008[117]	Inflammation, myocardial dysfunction in shock	SA	20	6
Oliveira, 2008[118]	Serum Troponin-I level in sepsis or septic shock	SA	69	23
Samransamruakjit (pre-implementation cohort), 2008[114]	Clinical outcomes after utilizing surviving sepsis campaign in children with septic shock and prognostic value of plasma N-terminal pro B-type natriuretic peptide	AA	66	28
Santolaya, 2005[119]	Predictor of severe sepsis in the first 24 hours	SA	116	12
Lodha, 2004[120]	Thyroid function in sepsis and septic shock	AA	24	12
Onenli-Mungan, 2004[121]	Growth hormone/insulin-like growth factor-I axis in sepsis and septic shock	AA	21	15
Pancera, 2004[122]	Predictive factors in severe sepsis and septic shock among children with cancer			
Samransamruakjit, 2004[123]	Protein C activity and clinical factors in early phase of septic shock and mortality association	AA	67	26
Sarthi, 2004[124]	Adrenal status in septic shock with stimulation	AA	30	15
Casartelli, 2003[125]	Adrenal response in children with septic shock	SA	22	7
Branco, 2002[126]	Glucose level and mortality risk in septic shock	SA	57	28
Pizarro, 2002[127]	Adrenal insufficiency in septic shock	SA	57	26
Singh, 2001[128]	Clinical profile of shock	AA	34	18
Goh, 1995[129]	Sepsis severity and outcome in multiple organ dysfunction syndrome	AA	20	13

Abbreviations: AA = Asia, SA = South America, AF = Africa.

eTable 4. Risk of bias of individual randomized clinical trials

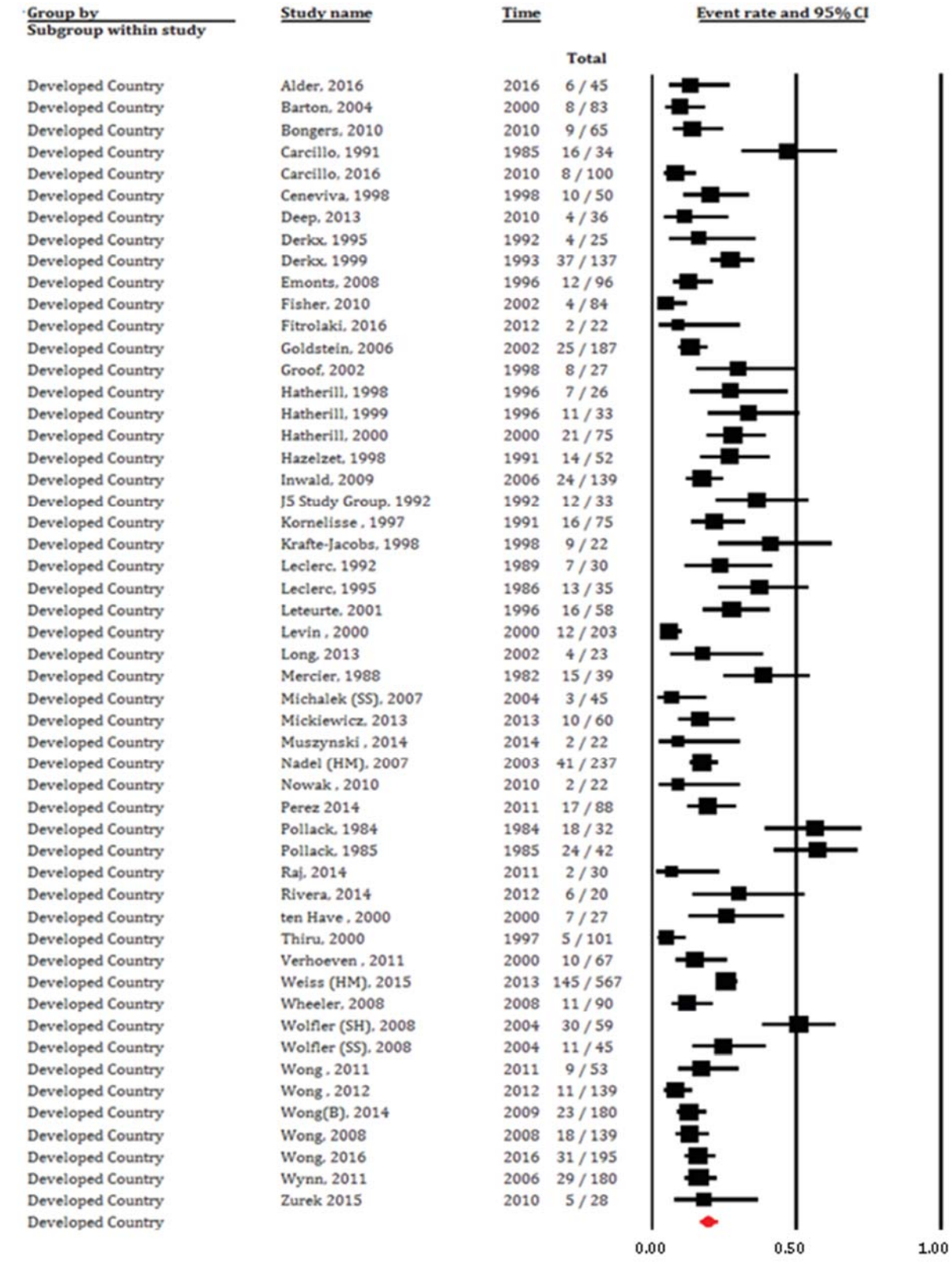
Author & Publication Year	Domains								Overall Risk
	Selection Bias	Performance Bias	Attrition Bias	Detection Bias	Information Bias	Reporting Bias	Statistical Analyses	Confounding Bias	
Ramaswamy, 2016[88]	Low	Low	Low	Low	Unclear	Low	Low	Low	**Low**
Ventura, 2015[89]	Low	Low	Low	Low	Low	Low	Low	Low	**Low**
Rivera, 2014 [39]	High	Low	Unclear	Unclear	Low	Low	Low	Unclear	**Moderate**
Long 2013[41]	High	Low	Low	Low	Low	Low	High	Low	**Moderate**
Chopra 2011[90]	Low	Low	Low	High	Low	High	High	Unclear	**Moderate**
Santhanam 2008[92]	Low	Low	Low	Low	Low	Low	Low	Low	**Low**
Yildiszas 2008[91]	Low	High	Low	High	Low	Low	High	Unclear	**Moderate**
Nadel 2007[10] (28-day mortality)	Low	Low	Low	Low	Low	Low	Unclear	Low	**Low**
Nadel 2007[40] (Hospital mortality)	Low	Low	Low	Low	Low	Low	Unclear	Low	**Low**
Upadhyay 2004[93]	Low	High	Unclear	High	High	Low	High	Unclear	**Moderate**
Levin 2000[42]	Low	Low	Low	Low	Low	Low	Unclear	Low	**Low**
Derkx 1999[43]	Unclear	Low	Low	Unclear	Low	Low	Low	Low	**Moderate**
J5 Study Group[44]	Low	Low	Low	Low	Low	Low	Unclear	Low	**Low**

eTable 5. Risk of bias of individual observational studies

Author & Publication Year	Domains			Overall Risk
	Selection	Comparability	Outcome: Mortality	
Alder, 2016[45]	Low	Low	Low	**Low**
Carcillo, 2016[55]	Low	High	Low	**Moderate**
Chen, 2016[106]	Low	High	Low	**Moderate**
Fitrolaki, 2016[50]	Low	High	Low	**Moderate**
Ibrahiem, 2016[99]	Low	High	Low	**Moderate**
Lin, 2016[130]	High	High	Low	**Moderate**
Manzoli, 2016[101]	Low	High	Low	**Moderate**
Naveda, 2016[94]	Low	High	Low	**Moderate**
Ranjit, 2016[103]	Low	Low	Low	**Low**
Wong, 2016[46]	Low	Low	Low	**Low**
Bustos B, 2015[96]	Low	High	Low	**Moderate**
Cui, 2015[97]	Low	High	Low	**Moderate**
Weiss, 2015 (Hospital mortality)[6]	Low	High	Low	**Low**
Weiss, 2015 (PICU mortality)[6]	Low	High	Low	**Moderate**
Wu, 2015[95]	Low	High	Low	**Moderate**
Zurek, 2015[58]	Low	Low	Low	**Low**
Carmona, 2014[117]	Low	High	Low	**Moderate**
Cartaya, 2014[115]	Low	High	Low	**Moderate**
Chen, 2014[98]	Low	High	Low	**Moderate**
Kaur, 2014[9]	Low	High	Low	**Moderate**
Li, 2014[100]	Low	High	Low	**Moderate**
Muszynski, 2014[47]	Low	Low	Low	**Low**
Rady, 2014[102]	Low	Low	Low	**Low**
Raj, 2014[109]	Low	High	Low	**Moderate**
Ranjit, 2014[113]	Low	High	Low	**Moderate**
Samransamruakjit, 2014[104]	Low	Low	Low	**Low**
Samransamruakjit(B), 2014[11404]	Low	High	Low	**Moderate**
Sankar, 2014[110]	Low	Low	Low	**Low**
Sankar(B), 2014[111]	Low	High	Low	**Moderate**
Vila Perez, 2014[52]	Low	High	Low	**Moderate**
Wong, 2014[48]	Low	High	Low	**Moderate**
Yuan, 2014[105]	Low	High	Low	**Moderate**
Deep, 2013[56]	Low	High	Low	**Moderate**
Karim, 2013[112]	Low	High	Low	**Moderate**
Mickiewicz, 2013[49]	Low	Low	Low	**Low**
Xu, 2013[116]	Low	Low	Low	**Low**
Bagci, 2012[131]	Low	High	Low	**Moderate**
Jaramillo-Bustamante, 2012[8]	Low	High	Low	**Moderate**
Phumeetham, 2012[107]	Low	High	Low	**Moderate**
Wong, 2012[51]	Low	High	Low	**Moderate**
Jat, 2011[108]	Low	High	Low	**Moderate**
Verhoeven, 2011[70]	Low	High	Low	**Moderate**
Wong, 2011[53]	Low	High	Low	**Moderate**
Wynn, 2011[62]	Low	Low	Low	**Low**

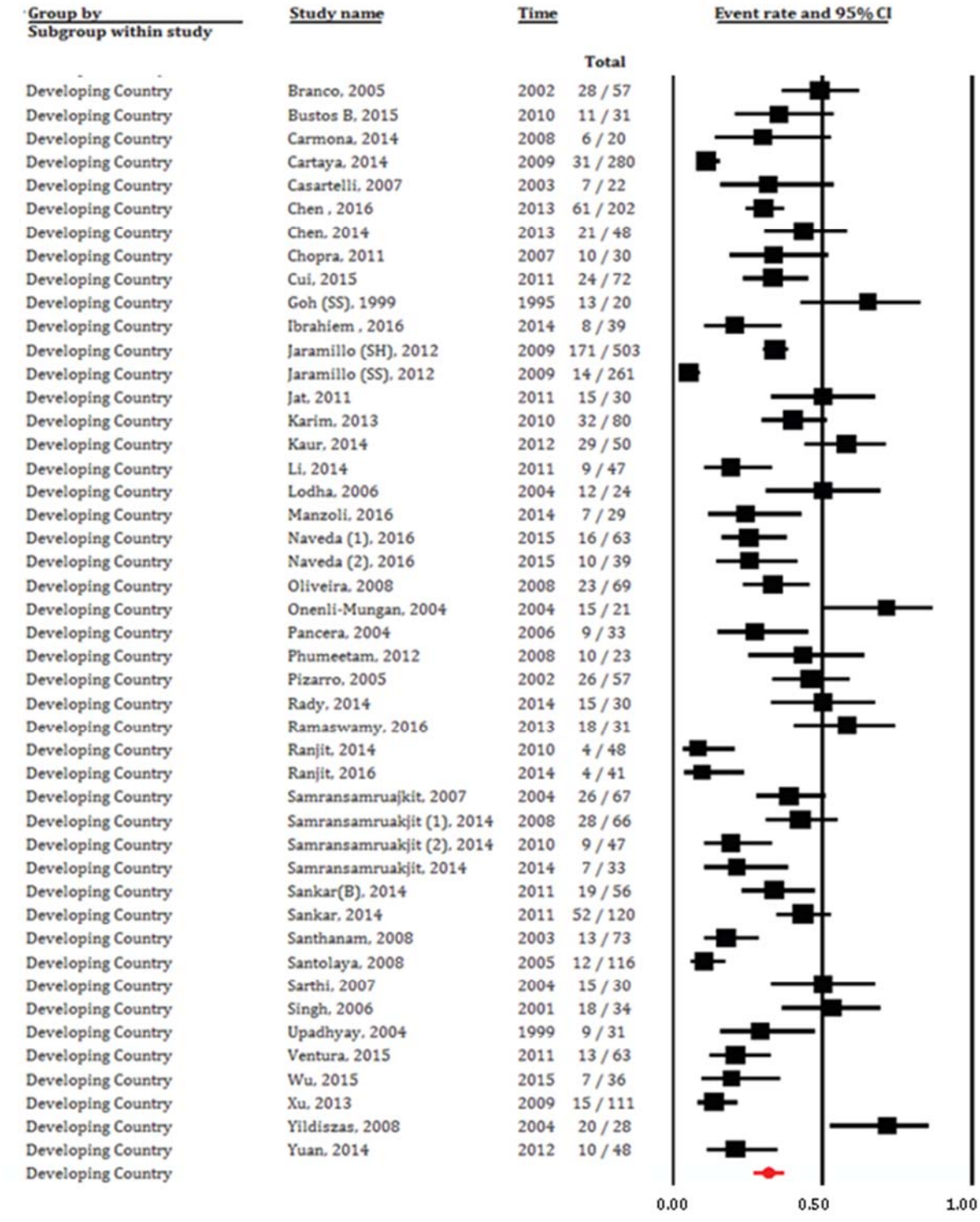
Bongers, 2010[54]	Low	High	Low	**Moderate**
Fisher, 2010[65]	Low	High	Low	**Moderate**
Nowak, 2010[57]	Low	High	Low	**Moderate**
Inwald, 2009[61]	Low	High	Low	**Moderate**
Emonts, 2008[75]	Low	Low	Low	**Low**
Oliveira, 2008[132]	Low	High	Low	**Moderate**
Santolaya, 2008[119]	Low	High	Low	**Moderate**
Wheeler, 2008[59]	Low	Low	Low	**Low**
Wolfler, 2008[64]	Low	High	Low	**Moderate**
Wong, 2008[60]	Low	High	Low	**Moderate**
Casartelli, 2007[125]	Low	Low	Low	**Low**
Michalek, 2007[63]	Low	Low	Low	**Low**
Samransamruakjit, 2007[123]	Low	High	Low	**Moderate**
Sarthi, 2007[124]	Low	High	Low	**Moderate**
Goldstein, 2006[66]	Low	High	Low	**Moderate**
Lodha, 2006[133]	Low	Low	Low	**Low**
Singh, 2006[128]	Low	High	Low	**Moderate**
Branco, 2005[126]	Low	Low	Low	**Low**
Pizarro, 2005[127]	Low	Low	Low	**Low**
Barton, 2004[67]	Low	High	Low	**Moderate**
Onenli-Mungan, 2004[121]	Low	Low	Low	**Low**
Pancera, 2004[122]	Low	High	Low	**Moderate**
de Groof, 2002[72]	Low	High	Low	**Moderate**
Leteurte, 2001[134]	Low	High	Low	**Moderate**
Hatherill, 2000[68]	Low	High	Low	**Moderate**
ten Have, 2000[69]	Low	High	Low	**Moderate**
Thiru, 2000[74]	Low	Low	Low	**Low**
Goh, 1999[129]	Low	High	Low	**Moderate**
Hatherill, 1999[76]	Low	Low	Low	**Low**
Ceneviva, 1998[71]	Low	High	Low	**Moderate**
Hatherill, 1998[77]	Low	High	Low	**Moderate**
Hazelzet, 1998[80]	Low	High	Low	**Moderate**
Krafte-Jacobs, 1998[73]	Low	Low	Low	**Low**
Kornelisse, 1997[81]	Low	High	Low	**Moderate**
Derkx, 1995[79]	Low	High	Low	**Moderate**
Leclerc, 1995[83]	Low	High	Low	**Moderate**
Leclerc, 1992[82]	Low	High	Low	**Moderate**
Carcillo, 1991[84]	Low	High	Low	**Moderate**
Mercier, 1988[87]	Low	High	Low	**Moderate**
Pollack, 1985[85]	Low	High	Low	**Moderate**
Pollack, 1984[86]	Low	High	Low	**Moderate**

eFigure 1. Cumulative forest plot of case fatality rates from studies conducted in developed countries



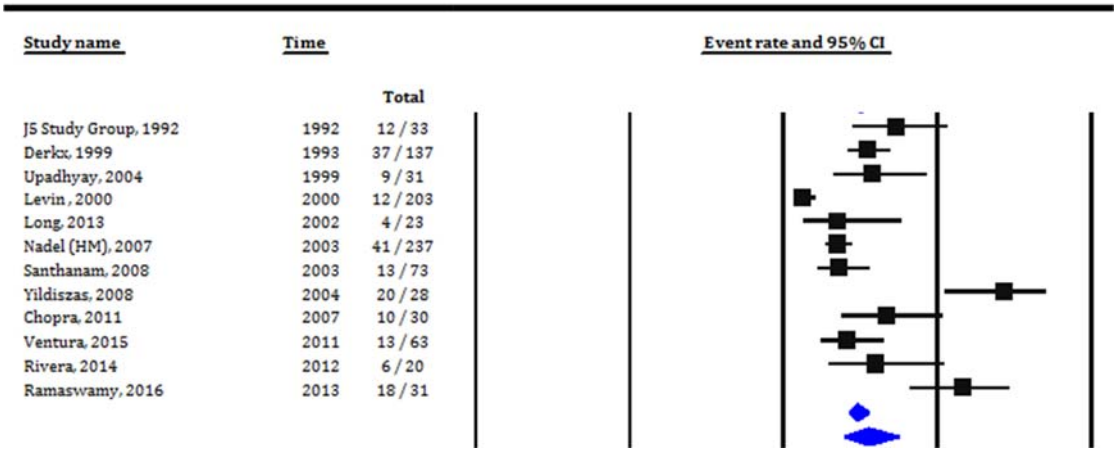
Heterogeneity: $Tau^2 = 0{\cdot}365$, df = 51, $I^2 = 80{\cdot}5$

eFigure 2. Cumulative forest plot of case fatality rates from studies conducted in developing countries



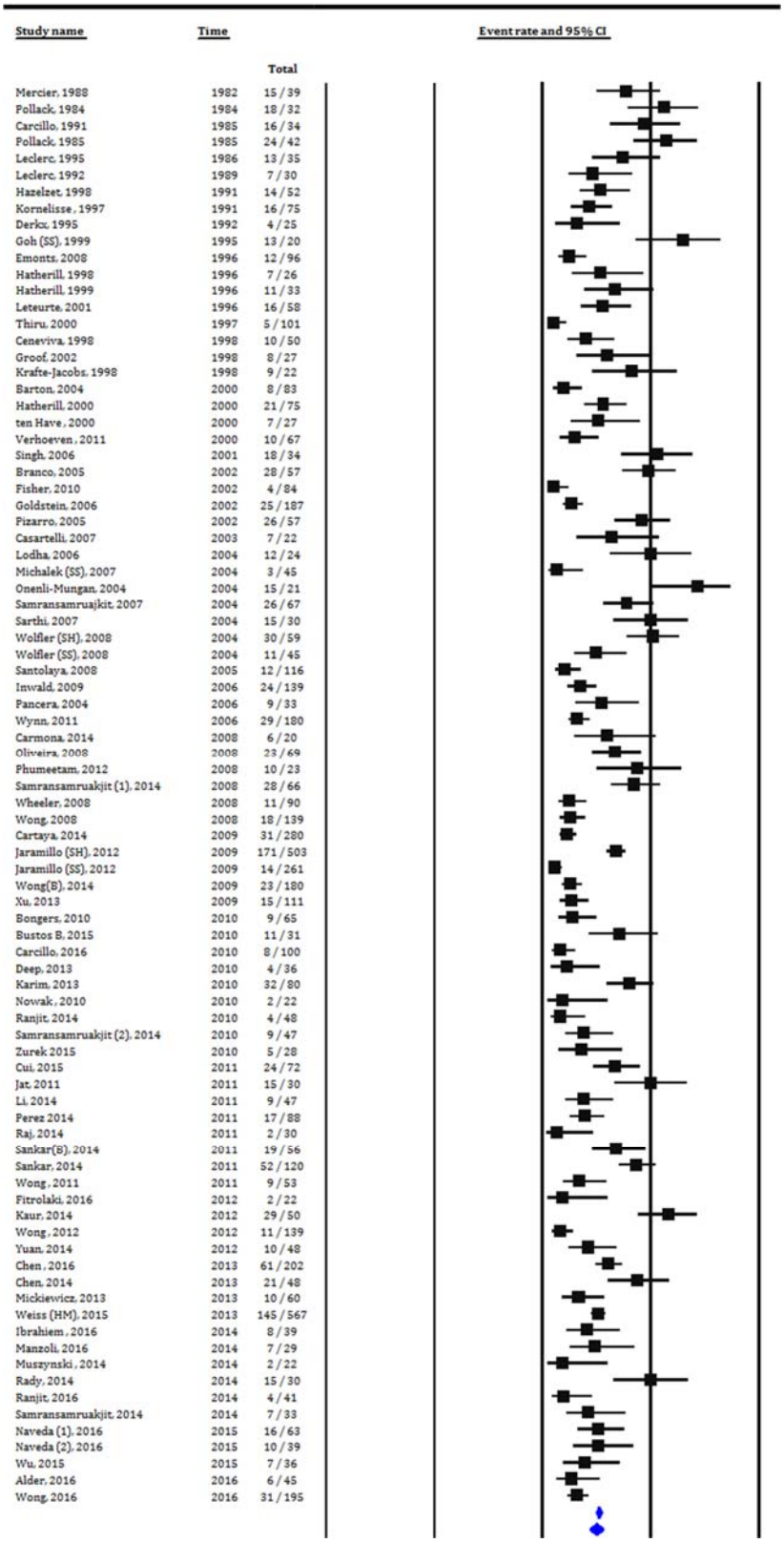
Heterogeneity: $Tau^2 = 0{\cdot}469$, df = 45, $I^2 = 85.3$

eFigure 3. Forest plot of case fatality rates from randomized clinical trials



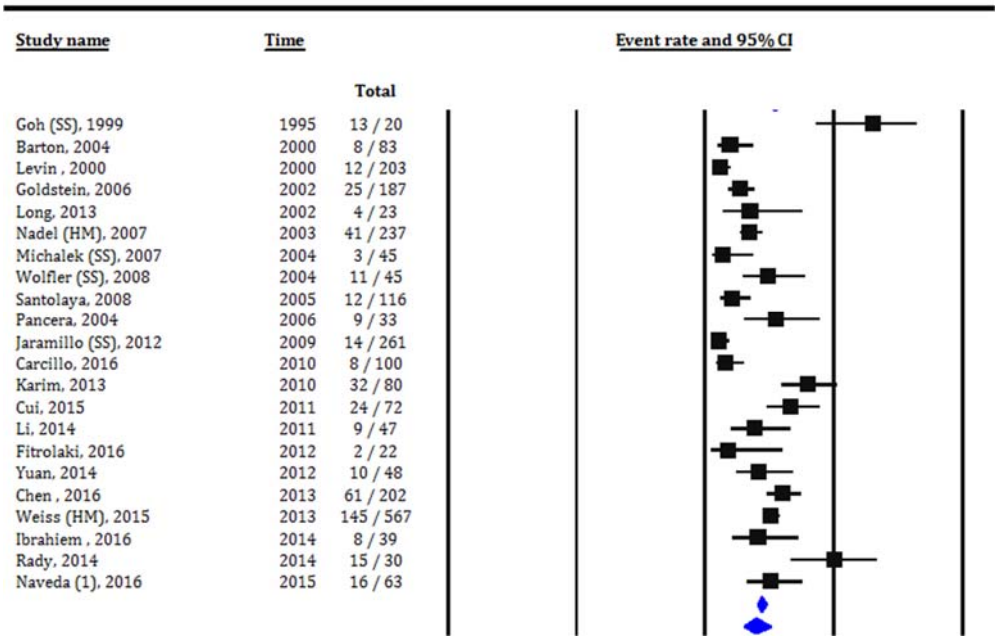
Heterogeneity: $Tau^2 = 0{\cdot}630$, df = 11, $I^2 = 86{\cdot}9$

eFigure 4. Forest plot of case fatality rates from observational studies



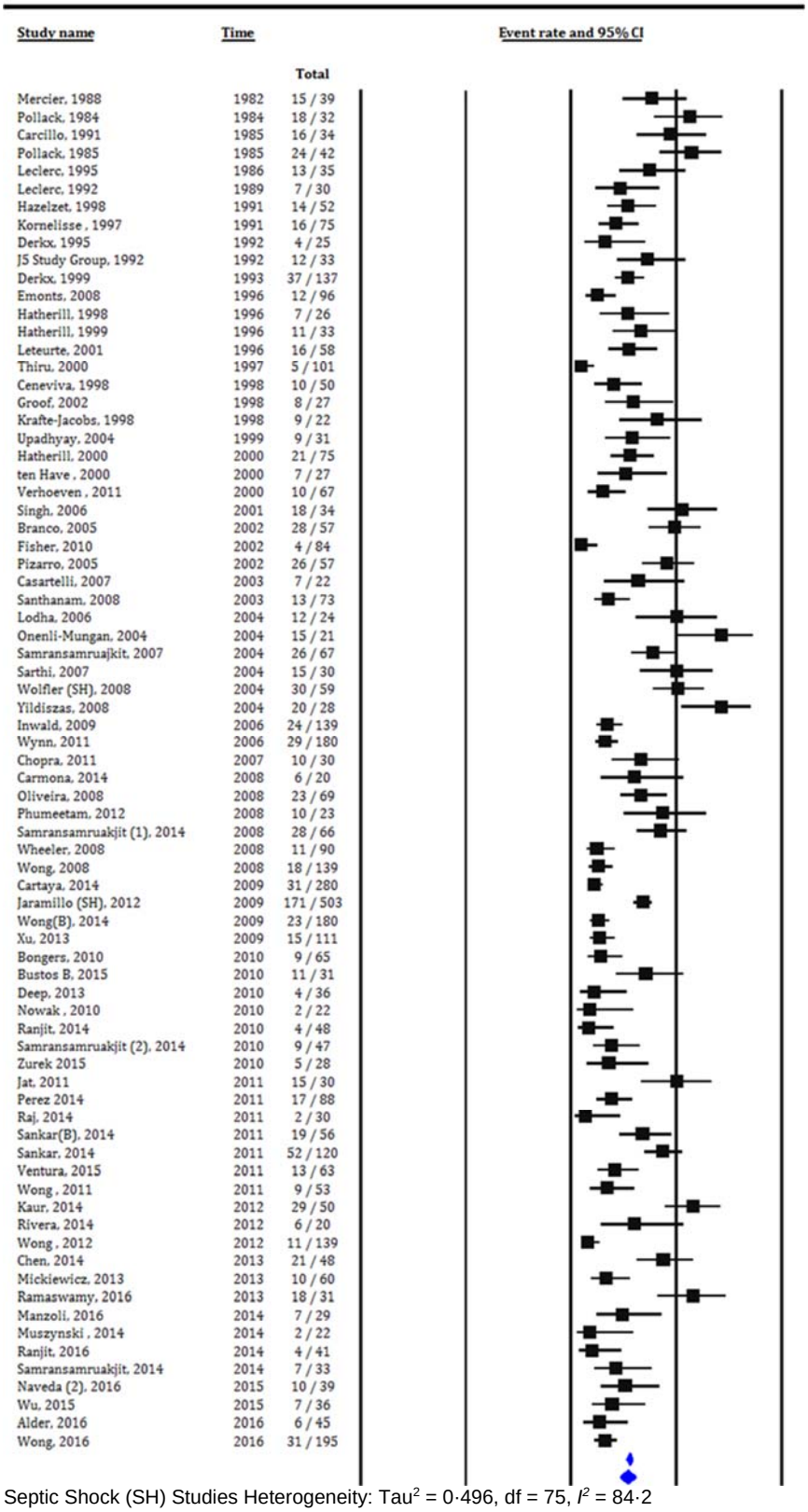
Heterogeneity: $Tau^2 = 0{\cdot}482$, df = 85, $I^2 = 85{\cdot}4$

eFigure 5. Forest plot of case fatality rates from studies with severe sepsis populations



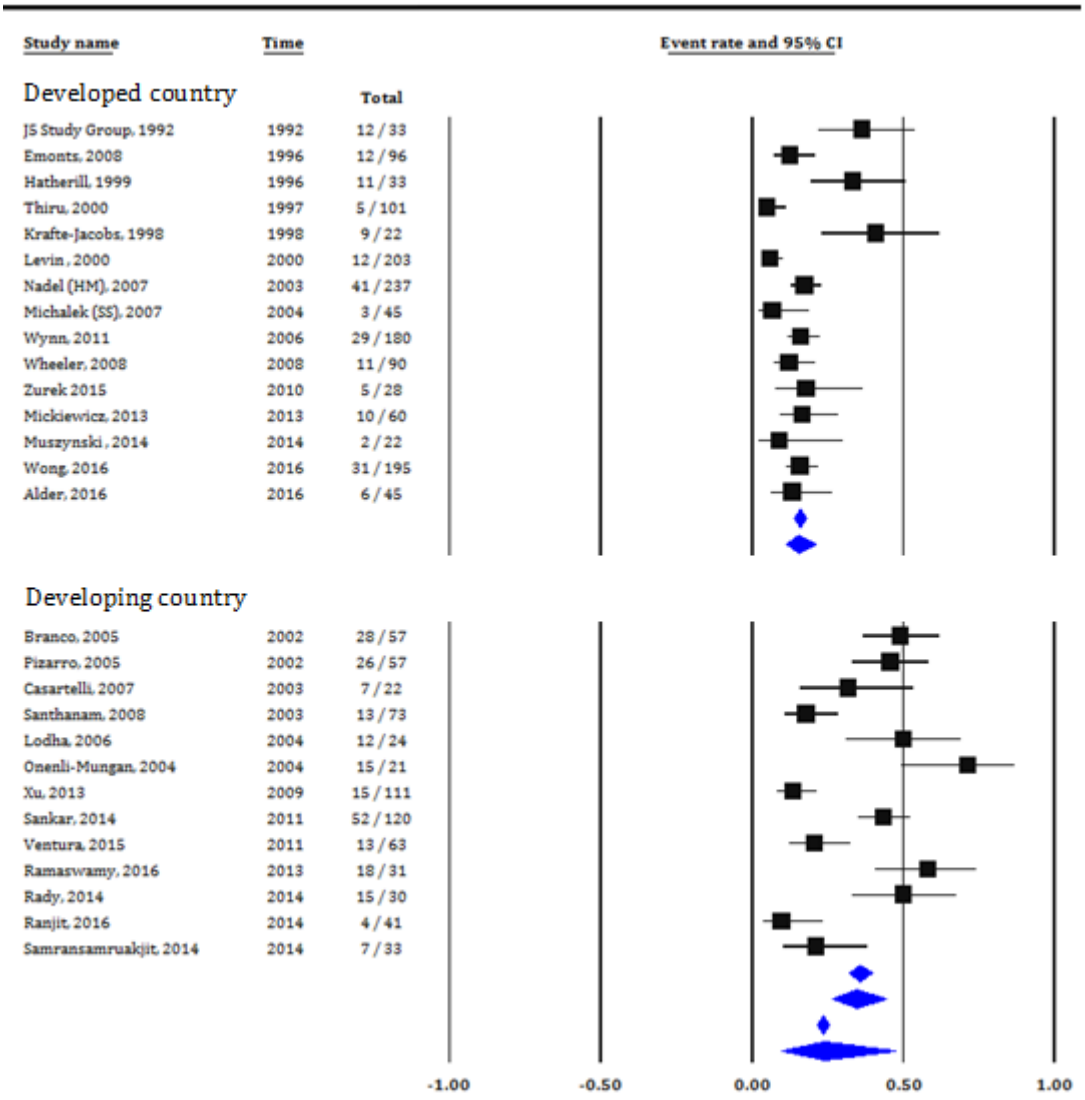
Severe Sepsis (SS) Studies Heterogeneity: Tau^2 = 0·458, df = 21, I^2 = 87·2q

eFigure 6. Forest plot of case fatality rates from studies with septic shock populations



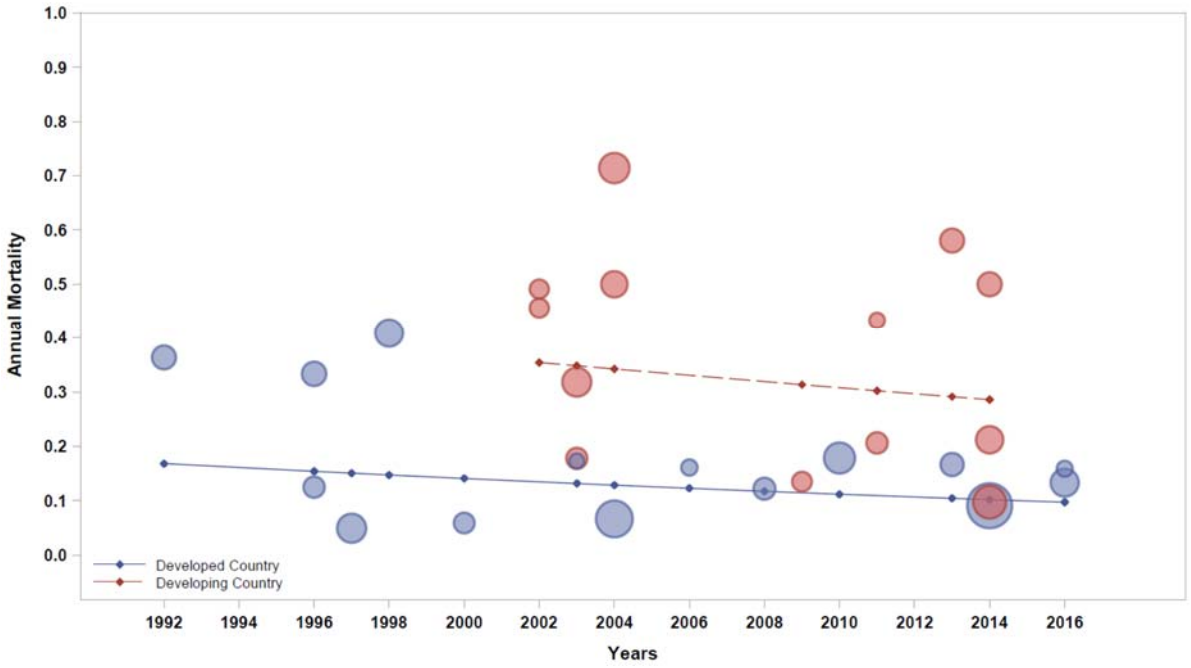
Septic Shock (SH) Studies Heterogeneity: $Tau^2 = 0{\cdot}496$, df = 75, $I^2 = 84{\cdot}2$

eFigure 7. Forest plot of case fatality rates from high-quality studies with low risk of bias



Risk of bias assessed by Cochrane Risk of Bias or Newcastle-Ottawa Scale, stratified by socioeconomic status of country

eFigure 8. Time-trend of pooled weighted mortality rates from 1982 to 2016 (by year of study) for high-quality studies with low risk of bias



Risk of bias assessed by Cochrane Risk of Bias or Newcastle-Ottawa Scale. Adjusted by socioeconomic status of country. The size of the bubble is proportional to the total number of patients recruited in the corresponding study.

eReferences.

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