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PROGNOSTIC FACTORS FOR STREPTOCOCCAL TOXIC SHOCK SYNDROME: SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Objective: To quantify the prognostic effects of demographic and modifiable factors in streptococcal toxic shock syndrome (STSS).

Methods and analysis: We searched MEDLINE and EMBASE from inception to 6 August 2021, along with CINAHL from inception to 16 September 2021 and citations of included studies. Pairs of reviewers screened potentially eligible studies of patients with GAS-induced STSS that quantified the association between at least one prognostic factor and outcome of interest. We performed random-effects meta-analysis after duplicate data extraction and risk of bias assessments. We rated the certainty of evidence using the GRADE approach.

Results: One randomized trial and 39 observational studies were eligible (n=1,914 patients). Low certainty evidence suggests the odds of mortality may be significantly reduced by clindamycin treatment (n=144; odds ratio [OR] 0.14, 95% confidence interval [CI] 0.06 to 0.37) and within clindamycin-treated STSS patients, intravenous immunoglobulin (IVIG) treatment (n=188; OR 0.34, 95% CI 0.15 to 0.75), and increased in patients ≥65 years when compared to patients 18-64 years (n=396; OR 2.37, 95% CI 1.47 to 3.84). We are uncertain whether non-steroidal anti-inflammatory drugs (NSAIDs) increased the odds of mortality (n=50; OR 4.14, 95% CI 1.13 to 15.14; very low certainty). Results failed to show a significant association between any other prognostic factor and outcome combination (very low to low certainty evidence) and no studies quantified the association between a prognostic factor and morbidity post-infection in STSS survivors.

Conclusions: STSS mortality may be modified with clindamycin and within clindamycin-treated patients, IVIG. Future research should focus on morbidity post-infection in STSS survivors.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Strengths of this review include its systematic and explicit search of the literature, capture of a wide breadth of patient-important outcomes within and outside of critical care and the use of meta-analysis to increase statistical power in studying relationships between prognostic factors and outcomes in STSS patients.
- These strengths directly address limitations of a narrative synthesis of STSS prognosis restricted to the critical care setting.
- In the absence of large cohort studies and randomized trials, conclusions for STSS prognosis in this review are limited by very low to low certainty evidence.
- A limitation of the evidence is the lack of long-term outcome data reported, including morbidity post-infection in STSS survivors.

Introduction

Streptococcal toxic shock syndrome (STSS) is an acute and severe life-threatening complication of predominantly invasive group A *Streptococcus* (GAS) infections. STSS is relatively uncommon, but is fatal [1]. Using US data from 2000 to 2004, the Center for Diseases Control and Prevention estimated an annual incidence rate of 0.2 cases per 100,000 people and a fatality rate of 36% [2]. STSS has important consequences for morbidity as well, in which patients may require radical surgical debridement, and patients with organ failure may have permanent respiratory and renal insufficiency [1].

Although extensive multidisciplinary clinical management efforts by intensivists, infectious disease specialists, and surgeons have curbed STSS all-cause mortality [1], data on the natural history of long-term sequelae in surviving patients, such as renal, respiratory and neuropsychiatric complications, are sparse [1-4]. Published studies of prognostic and treatment factors for STSS have consistently focused on associations with all-cause mortality [5-14], with few reporting on outcomes capturing the morbidity post-infection in STSS survivors [7, 12]. Furthermore, a thorough and systematic review to corroborate this evidence is lacking. A narrative review of STSS was limited by the lack of a systematic or explicit search of the literature, it included studies that were only narratively synthesized, and the focus was limited to studies within a critical care setting [1].

Understanding prognosis of STSS is important for patients, clinicians, and healthcare decision makers. We conducted a systematic review to summarize the prognostic and treatment factors, and outcomes of STSS. We aimed to capture a wide breadth of patient-important outcomes with follow up that included both short- and long-term outcomes within and outside of critical care.

Materials and methods

We registered a protocol for the present systematic review and meta-analysis with PROSPERO (CRD42020166961) [15, 16]. We report this systematic review and meta-analysis following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analyses of Observational Studies in Epidemiology (MOOSE) checklists [17, 18]. Decisions regarding criteria for study inclusion, search methods for identification of

studies, data collection, risk of bias, evaluation of the certainty of evidence and analysis were established a priori.

Search strategy and selection criteria

We searched MEDLINE (OVID interface, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, 1946 to 6 August 2021) and EMBASE (OVID interface, 1974 to 6 August 2021) from inception to 6 August 2021, with no restrictions on publication date. We searched the Cumulative Index to Nursing And Allied Health Literature (CINAHL), excluding MEDLINE records, from inception to 16 September 2021. We applied search filters for randomized controlled trials and non-randomized studies (cohort, case-control and case series with at least 2 STSS patients) [19, 20], and tailored search strategies to each database. We restricted included studies to the English language to facilitate screening of full-texts [21, 22] and searched citations of included studies to minimize the risk of failing to include relevant studies.

We included studies of randomized and non-randomized designs that reported the association of at least one prognostic factor of interest on at least one outcome of interest, and compared GAS-induced STSS patients with the prognostic factor of interest (i.e. exposed) to GAS-induced STSS patients without the prognostic factor of interest (i.e. unexposed). Studies of patients with microbiologically confirmed STSS, probable cases of STSS and patients with clinical evidence of STSS as defined by study authors and generally consistent with the below criteria were eligible [3, 23]. Clinical evidence of STSS included hypotension and at least two of the following: renal impairment, coagulopathy, liver function abnormality, acute respiratory distress syndrome, generalized erythematous macular rash (with desquamation), soft-tissue necrosis (including necrotizing fasciitis, myositis or gangrene), or meningitis. Probable cases of STSS were defined as meeting clinical evidence with GAS isolated from a non-sterile site (e.g. throat, sputum, superficial skin lesion) or antigen detected. Confirmed cases of STSS were defined as meeting clinical evidence with GAS isolated from a sterile site (e.g. blood, cerebrospinal fluid, deep tissue specimen taken during surgery) [3, 23]. Demographic, comorbidity, infection, modifiable and process variables were prognostic factors of interest. Informed by clinical expertise in the review team, we selected outcomes based on importance to patients. Further, we aimed to capture the long-term sequelae in patients surviving STSS [1, 2, 4]. We chose the

following outcomes of interest: (time to) mortality, hospital length-of-stay, pediatric (P) intensive care unit (ICU) admission, (P)ICU length-of-stay, mechanical ventilation, duration of mechanical ventilation, (time to) clinical cure/improvement or resolution of shock, change in Sequential Organ Failure Assessment (SOFA) score from baseline, functional status (e.g. physical component summary (PCS) score on the 36-item short form health survey (SF-36)) and health related quality of life (HRQoL). We also extracted on cost outcomes, which are relevant to hospital and patient payees.

We excluded case reports and conference abstracts, and studies in which the population was less than 80% GAS-induced STSS cases (i.e. toxic shock syndrome of bacterial aetiologies other than GAS made up more than 20% of the study population). Because prognostic evidence in STSS patients is scarce [1, 2, 4], we did not apply any restrictions based on analytical method (e.g. conducting an adjusted, multivariable analysis) or sample size.

Using a systematic review software, Rayyan [24], following training and calibration exercises, pairs of reviewers independently screened all titles and abstracts, followed by full-texts of records that were identified as potentially eligible. When necessary, consensus was reached through discussion between the review pair, and arbitration by a senior co-investigator in the absence of consensus.

Data analysis

For each eligible study, pairs of reviewers extracted data independently using a standardized, pilot tested data extraction form. Reviewers collected information on study characteristics (study design as defined by study authors, sample size, country), patient characteristics (age, sex), disease characteristics (confirmed vs probable STSS, presence of necrotizing fasciitis), prognostic factors and outcomes of interest (means or medians and measures of variability for continuous outcomes and the proportion of participants who experienced an event for dichotomous outcomes). If multiple time points were reported for outcomes of interest, we extracted all time points. To minimize risk of confounding associated with prognostic effect estimates on dichotomous outcomes in non-randomized studies, we preferentially extracted adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CI) over proportions

when both were reported. We used the proportions to calculate crude ORs when no adjusted ORs were provided. Reviewers resolved discrepancies by discussion and, when necessary, with adjudication by a third party.

Following training and calibration exercises, reviewers, independently and in duplicate, used a modified version of the Quality in Prognosis Studies (QUIPS) tool to rate each prognostic factor and outcome combination at low, moderate or high risk of bias overall [25]. Based on prespecified sets of questions, we assessed risk of bias across the following domains: participation, attrition, prognostic factor measurement, outcome measurement, confounding, and statistical analysis and reporting. For studies addressing more than one prognostic factor and outcome combination, we reported the highest risk of bias rating among the prognostic factor and outcome combinations within a study for each domain. We rated overall study risk of bias as low if the study was prospective and five or more domains were assessed as low risk of bias, and high if two or more domains were assessed as high risk of bias. All other studies were rated as moderate risk of bias overall. Due to high risk of selection bias and residual confounding, we rated all case series as high risk of bias overall. Reviewer pairs resolved discrepancies by discussion and, when needed, with adjudication by a senior co-investigator.

Pairs of reviewers used a modified version of the grading of recommendations, assessment, development, and evaluation (GRADE) approach to independently assess the certainty of prognostic evidence for each meta-analysed outcome. Criteria for rating the certainty for each prognostic factor and outcome as high, moderate, low, or very low, included considerations of risk of bias, inconsistency, indirectness, size and precision of the association and publication bias [26, 27]. Judgments of imprecision for this systematic review were made using a minimally contextualised approach. This approach considers whether confidence intervals include the null effect. The supplementary file presents detailed guidance on the certainty of the evidence assessment. To facilitate interpretation of the results in which the summary measure was an OR, we used the median event rate in the reference group of studies reporting proportions to calculate baseline risks and subsequently calculated absolute effects. GRADE evidence summaries (Summary of Findings tables) were generated in the MAGIC Authoring and Publication Platform (www.magicapp.org).

When at least two included studies reported on the same prognostic factor and outcome, we conducted DerSimonian and Laird random-effects meta-analyses using the *metafor* package in R version 4.0.4 (R Studio, Boston, MA, USA) [28]. We summarised the effects of prognostic factors on dichotomous outcomes using ORs and corresponding 95% CI, and on continuous outcomes using mean differences and corresponding 95% CI. For prognostic factor and dichotomous outcome combinations in which every patient in the reference arm experienced the outcome, we summarised the effects by directly calculating risk differences and corresponding 95% CI. We set the criterion for statistical significance at alpha = 0.05. Visual inspection of forest plots and the chi-square test were performed to evaluate heterogeneity. We interpreted an I^2 statistic value of 0%-40%, 30%-60%, 50%-90%, or 75%-100% as not likely important, moderate, substantial, or considerable heterogeneity, respectively [29]. When inconsistent magnitudes and directions of summary estimates were observed upon visual inspection of the forest plots, and the chi-square test was significant, we interpreted heterogeneity as more important (i.e. we reported the interpretation corresponding to the higher limit in overlapping I^2 statistic values) [29]. For meta-analyses of continuous outcomes, we imputed means and standard deviations for studies reporting medians and (interquartile) ranges, respectively.

Patient-level data from case-series were aggregated when possible to enable comparative analysis via meta-analysis. We planned to perform regression analyses for studies for which age was reported at the patient level to generate aggregate ORs that could be used in meta-analysis when the study had at least 10 observations for continuous outcomes and 10 events for dichotomous outcomes; however, no study met the sample size or event number requirements. Further, scarcity and variability of data precluded our plan to narratively synthesize the evidence from included studies for which meta-analysis of a prognostic factor and outcome combination was not possible.

The analysis plan included performing subgroup analyses of STSS patients treated with clindamycin vs no clindamycin, STSS patients with necrotizing fasciitis vs without necrotizing fasciitis, age (0 to 17 years old vs 18 to 64 years old vs 65 years old or older), sex (male vs

female) and risk of bias (high vs moderate vs low) when at least two studies were present for each subgroup.

Patient and public involvment

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Results

After screening 25,397 titles and abstracts and 282 full texts, 40 studies that reported on the association between at least one prognostic factor and outcome of interest in STSS patients proved eligible (Figure 1). All but one study (39/40, 98%) were non-randomized. Eligible studies were published between 1989 and 2021, ranged in sample size from 2 to 476, included 1,914 STSS patients in total and were conducted in 22 different countries, most commonly in the United States (15/40, 38%).

Table 1 describes the characteristics of included studies reporting on the association of at least one prognostic factor and outcome of interest. The supplementary data includes additional study characteristics for each study. Of the 40 included studies, 28 (70%) reported on demographic prognostic factors of interest, 5 (13%) medical history of being immunocompromised, 11 (28%) early disease characteristics, and 16 (40%) treatment. Of the dichotomous outcomes, mortality was most commonly reported (35/40, 88%), followed by (P)ICU admission (10/40, 25%), clinical cure or improvement (8/40, 20%) and need for mechanical ventilation (6/40, 15%). Few studies reported on hospital (3/40, 8%) and ICU length-of-stay (2/40, 5%). Two studies reported on time to mortality in days [7, 30]; however, only one reported sufficient data precluding meta-analysis [7]. One study each reported on cost [14], change in SOFA score [7], time to clinical improvement or resolution of shock [7] and duration of mechanical ventilation [10] precluding meta-analysis for these continuous outcomes. No studies quantified the association between a prognostic factor and functional status or health related quality of life outcomes. A multivariable analysis was conducted in two (5%) of the included studies [10, 11]. A total of 19 of the 40 studies were cohort studies (authors reported on at least one comparative analysis), 18 were case series (authors did not report a comparative analysis) and 2 were case-control studies. To meta-

analyse the data, we aggregated the data from the individual patients the case series reported on. Further, we pooled the one randomized study [7] with non-randomized studies in meta-analyses and included patients receiving intravenous or intramuscular IVIG from one non-randomized study [31].

Table 1. Study characteristics. Values are numbers (percentages) of studies unless stated otherwise.

Characteristics	(40 studies, 1914 patients)
Range of publication year	1989 to 2021
Median (IQR) No. of patients	11 (5 to 29)
Geographical region:	
North America	19 (48)
Europe	14 (35)
Central/South America	0 (0)
Asia	3 (7)
Other	4 (10)
Study design:	
Randomized trial	1 (2)
Cohort	19 (48)
Case-control	2 (5)
Case-series	18 (45)
Case definition:	
No. (%) Probable STSS patients	115 (6)
No. (%) Confirmed STSS patients	223 (12)
Prognostic factor type:	
Demographic	28 (70)
Medical history	5 (13)
Early disease	11 (28)
Treatment	16 (40)

IQR=interquartile range
STSS=streptococcal toxic shock syndrome
Medical history included prognostic variable: immunocompromised
Early disease included prognostic variables: necrotizing fasciitis, acute renal failure

The supplementary material includes the forest plots depicting the studies included in the meta-analysis of each prognostic factor-outcome combination. It also includes the list of studies

reporting on prognostic factor-outcome combinations of interest that were not eligible for any meta-analysis, along with the reasons for exclusion from meta-analysis.

Risk of bias in included studies

Table 2 presents the risk of bias assessment of the 40 included studies. The majority of studies were rated as high risk of bias overall owing to residual confounding and lack of adjustment for confounding in statistical analyses (36/40, 90%) [2, 5, 6, 10, 30-61]. Three studies were rated at moderate risk of bias overall [7, 14, 62] and one at low risk of bias overall [11].

Table 2. Risk of bias assessment of included studies.

Author	Study participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Presentation Summary	Overall Risk of Bias
Abuhammour 2004	Low	Low	Low	Low	High	High	High
Adalat 2014	Low	High	High	Low	High	High	High
Al-Ajmi 2012	NA	NA	NA	NA	NA	NA	High
Barnham 2002	NA	NA	NA	NA	NA	NA	High
Bernaldo de Quiros 1997	Low	Low	Low	Low	High	High	High
Brogan 1995	NA	NA	NA	NA	NA	NA	High
Butragueno Laiseca 2017	NA	NA	NA	NA	NA	NA	High
Carapetis 1995	NA	NA	NA	NA	NA	NA	High
Carapetis 2014	Low	Low	Low	Low	High	High	High
Cimolai 1992	NA	NA	NA	NA	NA	NA	High
Cook 2021	Low	Low	Low	Low	High	High	High
Cowan 1994	NA	NA	NA	NA	NA	NA	High
Crum 2004	NA	NA	NA	NA	NA	NA	High
Dahl 2002	NA	NA	NA	NA	NA	NA	High
Darenberg 2003	Low	Moderate	Low	Moderate	Low	Low	Moderate
Donaldson 1993	NA	NA	NA	NA	NA	NA	High
Erdem 2004	NA	NA	NA	NA	NA	NA	High

Eriksson 1999	Low	Low	Low	Low	High	High	High
Forni 1995	NA	NA	NA	NA	NA	NA	High
Fronhoffs 2000	NA	NA	NA	NA	NA	NA	High
Hasegawa 2004	Low	Low	Moderate	Low	High	High	High
Hayata 2021	Low	Low	Low	Low	High	High	High
Huang 2001	NA	NA	NA	NA	NA	NA	High
Kansal 2000	Moderate	Low	Moderate	Low	High	High	High
Kaul 1999	Low	Low	Low	Low	High	High	High
Linder 2017	Low	Moderate	Low	Moderate	High	High	High
Linner 2014	Low	Low	Low	Low	Moderate	Low	Low
Luca-Harari 2009	Low	High	Low	Low	High	High	High
Nelson 2016	Low	Low	Low	Low	High	High	High
O'Loughlin 2007	Low	Low	Low	Low	High	High	High
Page 2011	Low	Low	Low	Low	Moderate	High	Moderate
Safar 2011	Low	Low	Low	Low	High	High	High
Schwartz 1992	NA	NA	NA	NA	NA	NA	High
Shah 2009	Low	High	Low	Low	Moderate	Moderate	Moderate
Sriskandan 2000	Moderate	Moderate	High	Low	High	High	High
Stegmayr 1992	NA	NA	NA	NA	NA	NA	High
Stevens 1989	NA	NA	NA	NA	NA	NA	High
Stockmann 2012	Low	Low	Low	Low	High	High	High
Tagini 2017	NA	NA	NA	NA	NA	NA	High
Zachariadou 2013	Low	Low	Low	Low	High	High	High

NA, Not Applicable because case-series study design and rated at high risk of bias.

Prognostic factors for mortality

Eleven prognostic factors from 31 studies including 1339 patients were eligible for analysis (table 3, supplementary data). Low certainty evidence suggests that treatment with clindamycin antibiotic may reduce the odds of mortality (n=144, OR 0.14, 95% CI 0.06 to 0.37). Within

clindamycin-treated STSS patients, IVIG may also reduce the odds of mortality (n=188, OR 0.34, 95% CI 0.15 to 0.75; low certainty of evidence); however, we are uncertain whether IVIG treatment reduces the odds of mortality in all STSS patients regardless of concurrent clindamycin treatment (n=365, OR 0.37, 95% CI 0.17 to 0.80; very low certainty of evidence). Patients ≥65 years compared to patients 18-64 years may have increased odds of mortality (n=396, OR 2.37, 95% CI 1.47 to 3.84; low certainty of evidence); however, we are less certain whether the same is true for patients ≥65 years compared to patients <18 years (n=136, OR 10.66, 95% CI 1.28 to 88.57; very low certainty of evidence). We are also uncertain whether NSAIDs increase the odds of mortality (n=50, OR 4.14, 95% CI 1.13 to 15.14; very low certainty of evidence). Very low certainty evidence failed to show a significant association with any other prognostic factor and mortality in STSS patients: male vs female (n=76, OR 0.91, 95% CI 0.34 to 2.46), patients <18 years vs patients 18 to 64 years (n=694, OR 0.54, 95% CI 0.15 to 1.94), immunocompromised vs not immunocompromised (n=33, OR 1.65, 95% CI 0.33 to 8.26), necrotizing fasciitis vs no necrotizing fasciitis (n=840, OR 0.81, 95% CI 0.51 to 1.29), acute renal failure vs no acute renal failure (n=91, OR 2.50, 95% CI 0.97 to 6.42), hemodialysis vs no hemodialysis (n=42, OR 1.94, 95% CI 0.22 to 16.99) and any antibiotic vs no antibiotic (n=19, OR 0.48, 95% CI 0.05 to 4.76).

Table 3. Summary of findings for prognostic factor – outcome meta-analyses.

Prognostic factor	Number of patients (studies)	Odds ratio (95% confidence interval)	Absolute effect estimates		GRADE: Certainty of the Evidence
			Risk without prognostic factor	Risk with prognostic factor	
MORTALITY					
Demographic					
Male vs Female	76 (12)	0.91 (0.34 to 2.46)	**250** per 1000	**233** per 1000	**Very low**
			-17 (-148 to 201)		Due to very serious risk of bias and imprecision
<18 vs 18-64 years	694 (5)	0.54 (0.15 to 1.94)	**234** per 1000	**142** per 1000	**Very low**
			-92 (-190 to 138)		Due to very serious risk of bias and imprecision, and serious inconsistency
≥65 vs <18 years	136 (2)	10.66 (1.28 to 88.57)*	**50** per 1000	**359** per 1000	**Very low**
			309 (13 to 773)		Due to very serious risk of bias and serious imprecision
≥65 vs 18–64 years	396 (2)	2.37 (1.47 to 3.84)*	**193** per 1000	**362** per 1000	**Low**
			169 (67 to 286)		Due to very serious risk of bias
Medical history					
Immunocompromised vs Not Immunocompromised	33 (4)	1.65 (0.33 to 8.26)	**438** per 1000	**563** per 1000	**Very low**
			125 (-233 to 428)		Due to very serious risk of bias and imprecision
Early disease					
Acute Renal Failure vs No Acute	91 (4)	2.50 (0.97 to 6.42)	**NA** per 1000	**NA** per 1000	**Very low**

Renal Failure			140 (-60 to 330)		Due to very serious risk of bias and imprecision
Necrotizing Fasciitis vs No Necrotizing Fasciitis	840 (10)	0.81 (0.51 to 1.29)	**347** per 1000	**301** per 1000	**Very low** Due to very serious risk of bias and imprecision
			-46 (-134 to 60)		
Treatment					
IVIG vs No IVIG (all STSS patients)	365 (9)	0.37 (0.17 to 0.80)*	**231** per 1000	**100** per 1000	**Very low** Due to very serious risk of bias and serious imprecision
			-131 (-182 to -37)		
IVIG vs No IVIG (subset of STSS patients treated with clindamycin)	188 (6)	0.34 (0.15 to 0.75)*	**300** per 1000	**127** per 1000	**Low** Due to serious risk of bias and imprecision
			-173 (-240 to -57)		
Any Antibiotic vs No Antibiotic	19 (3)	0.48 (0.05 to 4.76)	**NA** per 1000	**NA** per 1000	**Very low** Due to very serious risk of bias and imprecision
			-120 (-490 to 260)		
Clindamycin vs No Clindamycin Antibiotic	144 (4)	0.14 (0.06 to 0.37)*	**800** per 1000	**359** per 1000	**Low** Due to serious risk of bias and imprecision
			-441 (-606 to -203)		
Hemodialysis vs No Hemodialysis	42 (4)	1.94 (0.22 to 16.99)	**107** per 1000	**189** per 1000	**Very low** Due to very serious risk of bias and imprecision
			82 (-81 to 564)		
NSAIDs vs No NSAIDs	50 (4)	4.14 (1.13 to 15.14)*	**100** per 1000	**315** per 1000	**Very low** Due to very serious risk of bias and serious imprecision
			215 (12 to 527)		
ICU ADMISSION					
Demographic					
Male vs Female	19 (3)	2.87 (0.29 to 28.27)	**NA** per 1000	**NA** per 1000	**Very low** Due to very serious risk of bias and imprecision
			150 (-160 to 450)		
Early disease					
Necrotizing Fasciitis vs No Necrotizing Fasciitis	28 (3)	0.74 (0.12 to 4.48)	**900** per 1000	**869** per 1000	**Very low** Due to very serious risk of bias and imprecision
			-31 (-381 to 76)		
Treatment					
IVIG vs No IVIG (all STSS patients)	156 (3)	1.09 (0.43 to 2.77)	**833** per 1000	**845** per 1000	**Very low** Due to very serious risk of bias and imprecision
			12 (-151 to 100)		
Any Antibiotic vs No Antibiotic	14 (2)	4.60 (0.29 to 72.89)	**500** per 1000	**821** per 1000	**Very low** Due to very serious risk of bias and imprecision
			321 (-275 to 486)		
Hemodialysis vs No Hemodialysis	13 (2)	3.25 (0.21 to 50.35)	**875** per 1000	**958** per 1000	**Very low** Due to very serious risk of bias and imprecision
			83 (-280 to 122)		
NSAIDs vs No NSAIDs	15 (2)	0.86 (0.06 to 12.48)	**NA** per 1000	**NA** per 1000	**Very low** Due to very serious risk of bias and imprecision
			-10 (-430 to 400)		
CLINICAL CURE OR IMPROVEMENT					
Demographic					
Male vs Female	23 (4)	3.33 (0.47 to 23.59)	**875** per 1000	**959** per 1000	**Very low** Due to very serious risk of bias and imprecision
			84 (-108 to 119)		
Early disease					
Necrotizing Fasciitis vs No Necrotizing Fasciitis	24 (2)	0.34 (0.02 to 5.20)	**950** per 1000	**866** per 1000	**Very low** Due to very serious risk of bias and serious imprecision
			-84 (-675 to 40)		
Treatment					
IVIG vs No IVIG (in all STSS patients)	23 (2)	0.27 (0.02 to 3.76)	**NA** per 1000	**NA** per 1000	**Very low** Due to very serious risk of bias and imprecision
			-100 (-350 to 140)		

Hemodialysis vs No Hemodialysis	26 (3)	1.43 (0.15 to 14.08)	**NA** per 1000	**NA** per 1000 50 (-240 to 340)	**Very low** Due to very serious risk of bias and imprecision
NEED FOR MECHANICAL VENTILATION					
Demographic					
Male vs Female	21 (3)	2.09 (0.32 to 13.74)	**NA** per 1000	**NA** per 1000 120 (-200 to 440)	**Very low** Due to very serious risk of bias and imprecision
Early disease					
Acute Renal Failure vs No Acute Renal Failure	20 (2)	1.14 (0.17 to 7.82)	**750** per 1000	**774** per 1000 24 (-412 to 209)	**Very low** Due to very serious risk of bias and imprecision
Necrotizing Fasciitis vs No Necrotizing Fasciitis	31 (3)	3.75 (0.47 to 29.81)	**700** per 1000	**897** per 1000 197 (-177 to 286)	**Very low** Due to very serious risk of bias and imprecision
Treatment					
IVIG vs No IVIG (in all STSS patients)	157 (3)	2.22 (0.78 to 6.32)	**333** per 1000	**526** per 1000 193 (-53 to 426)	**Very low** Due to very serious risk of bias and imprecision
Hemodialysis vs No Hemodialysis	26 (3)	2.05 (0.39 to 10.70)	**500** per 1000	**672** per 1000 172 (-219 to 415)	**Very low** Due to very serious risk of bias and imprecision
DURATION OF HOSPITALIZATION					
Treatment					
IVIG vs no IVIG (all STSS patients)	201 (3)	NA	**NA** per 1000	**NA** per 1000 On average, 5.51 fewer days (17.64 fewer to 6.62 more)	**Low** Due to serious risk of bias and imprecision
DURATION OF INTENSIVE CARE UNIT STAY					
Treatment					
IVIG vs no IVIG (all STSS patients)	131 (2)	NA	**NA** per 1000	**NA** per 1000 On average, 3.80 more days (3.62 fewer to 11.23 more)	**Very low** Due to very serious risk of bias and serious imprecision

*statistical evidence of an association

Prognostic factors for ICU admission

Six prognostic factors from eight studies including 174 patients were eligible for analysis (table 3, supplementary data). We found no statistical evidence of an association between any prognostic factor and ICU admission: male vs female sex (n=19, OR 2.87, 95% CI 0.29 to 28.27), necrotizing fasciitis vs no necrotizing fasciitis (n=28, OR 0.74, 95% CI 0.12 to 4.48), hemodialysis vs no hemodialysis (n=13, OR 3.25, 95% CI 0.21 to 50.35), NSAIDs vs no NSAIDs (n=15, OR 0.86, 95% CI 0.06 to 12.48), IVIG treatment vs no IVIG treatment (n=156, OR 1.09, 95% CI 0.43 to 2.77) and antibiotic treatment vs no antibiotic treatment (n=14, OR 4.60, 95% CI 0.29 to 72.98). The certainty of all ICU admission evidence was very low due to very serious risk of bias and imprecision.

Prognostic factors for clinical cure or improvement

Four prognostic factors from six studies including 38 STSS patients were eligible for analysis (table 3, supplementary data). We found no statistical evidence of an association between any prognostic factor and clinical cure or improvement: male vs female sex (n=23, OR 3.33, 95% CI 0.47 to 23.59), necrotizing fasciitis vs no necrotizing fasciitis (n=24, OR 0.34, 95% CI 0.02 to 5.20), hemodialysis vs no hemodialysis (n=26, OR 1.43, 95% CI 0.15 to 14.08) and IVIG treatment vs no IVIG treatment (n=23, OR 0.27, 95% CI 0.02 to 3.76). The certainty of all clinical cure or improvement evidence was very low due to very serious risk of bias and serious or very serious imprecision.

Prognostic factors for mechanical ventilation

Five prognostic factors from six studies including 170 STSS patients were eligible for analysis (table 3, supplementary data). We found no statistical evidence of an association between any prognostic factor and need for mechanical ventilation: male vs female sex (n=21, OR 2.09, 95% CI 0.32 to 13.74), necrotizing fasciitis vs no necrotizing fasciitis (n=31, OR 3.75, 95% CI 0.47 to 29.81), acute renal failure vs no acute renal failure (n=20, OR 1.14, 95% CI 0.17 to 7.82), hemodialysis vs no hemodialysis (n=26, OR 2.05, 95% CI 0.39 to 10.70) and IVIG treatment vs no IVIG treatment (n=157, OR 2.22, 95% CI 0.78 to 6.32). The certainty of all need for mechanical ventilation evidence was very low due to very serious risk of bias and imprecision.

Prognostics factors for hospital length-of-stay

One prognostic factor from three studies including 201 STSS patients was eligible for analysis (table 3, supplementary data). Low certainty evidence – due to serious risk of bias and imprecision – provides no support for an association between IVIG treatment and hospital length-of-stay, when compared to no IVIG treatment (n=201, MD -5.51 days, 95% CI -17.64 to 6.62).

Prognostic factors for intensive care unit length-of-stay

One prognostic factor from two studies including 131 STSS patients was eligible for analysis (table 3, supplementary data). We are uncertain if IVIG treatment compared to no IVIG

treatment is associated with ICU length-of-stay (n=131, MD 3.80 days, 95% CI -3.62 to 11.23; very low certainty evidence due to very serious risk of bias and serious imprecision).

Subgroup analysis

Sparsity of data precluded our planned subgroup analyses by clindamycin treatment, presence of necrotizing fasciitis and sex (i.e. each subgroup did not have at least two studies). We collapsed the low and moderate risk of bias categories to allow for subgroup analysis by risk of bias (low or moderate vs high). The prognostic factor-outcome combinations for which there was sufficient evidence for subgroup analysis by age or modified risk of bias level were IVIG-mortality and sex-mortality. We found no statistical evidence that the association between IVIG and mortality differed between low or moderate and high risk of bias studies in all STSS patients (p=0.884) and clindamycin-treated STSS patients (p=0.867) or between studies with STSS patients <18 years and patients 18-64 years (p=0.328). We also found no statistical evidence that the association between sex and mortality differed between studies with patients <18 years and patients 18-64 years (p=0.666).

Discussion

This systematic review and meta-analysis provides a comprehensive overview of the prognostic evidence for STSS. Prognostic factors for which there was statistical evidence of an association with mortality in STSS patients were age, clindamycin treatment, IVIG treatment and NSAIDs treatment. Patients ≥65 years compared to patients 18 to 64 years may have increased odds of mortality (low certainty of evidence); however we are uncertain if the same is true for patients ≥65 years compared to patients <18 years (very low certainty of evidence). We are also uncertain whether NSAIDs increase the odds of mortality (very low certainty of evidence). Low certainty evidence suggests the odds of mortality may be reduced by treatment with clindamycin and within clindamycin-treated patients, IVIG. We are highly uncertain whether IVIG reduces mortality in all STSS patients, regardless of clindamycin treatment (very low certainty of evidence). Results failed to show a significant association between all other meta-analyzed prognostic factors and outcomes (table 3). The certainty of STSS prognostic evidence was low or very low due to serious or very serious risk of bias and imprecision concerns.

Strengths of this review include its systematic and explicit search of the literature, capture of a wide breadth of patient-important outcomes within and outside of critical care and the use of meta-analysis to increase statistical power in studying relationships between prognostic factors and outcomes in STSS patients. These strengths directly address limitations of a narrative synthesis of STSS prognosis restricted to the critical care setting [1].

In the absence of large cohort studies and randomized trials, conclusions for STSS prognosis in this review are limited by very low to low certainty evidence. The majority of included studies were non-randomized (39/40, 98%) and small (median sample size was 10 patients), introducing bias from residual confounding and imprecision around pooled summary estimates. Small numbers of events further contributed to the imprecision around summary estimates. With few participants and events, minor changes in the data can cause major changes in the results. In such instances, results can be exaggerated by the presentation of relative effect estimates only. To minimize the risk of misinterpreting results from the inclusion of small studies in our meta-analyses, we calculated an absolute effect estimate for each relative effect estimate (table 3). Further, despite expecting small studies to be more heterogeneous than large studies, we did not find statistical evidence of heterogeneity in any of our 33 meta-analyses and in interpreting the I^2 statistic value, we found not likely important heterogeneity in all but one meta-analysis [63]. Creation of an international registry of STSS patients may improve the credibility of prognostic evidence for STSS. Although we meta-analyzed adjusted odds ratios from included studies when possible, almost all included studies reported crude data (38/40, 95%), precluding adjustment for important confounders. A limitation of the evidence is the lack of long-term outcome data reported. For example, no studies quantified associations between prognostic factors and functional status or health related quality of life outcomes post-infection in STSS survivors. Given the high morbidity associated with STSS [64], future research in STSS prognosis should quantify these patient-important outcomes, facilitating future meta-analyses and providing further insights into STSS prognosis.

Our finding that IVIG treatment may reduce the odds of mortality in STSS patients who receive clindamycin treatment is consistent with a systematic review and meta-analysis of IVIG treatment in clindamycin-treated STSS patients, which found statistical evidence of a decreased risk of mortality in IVIG- and clindamycin-treated STSS patients when compared to only clindamycin-treated STSS patients [64]. For this question relevant to clindamycin-treated STSS

patients, our meta-analysis included one additional non-randomized study, whose small sample size and imprecision contributed to an overall point estimate of greater magnitude [30]. Our findings suggest that treatment regimens of IVIG in adjunct to clindamycin and clindamycin alone may significantly improve STSS prognosis. We found a significant association between a regimen of IVIG regardless of clindamycin treatment and mortality; however, due to very serious risk of bias and serious imprecision, and thus very low certainty evidence, we cannot rule out the possibility that clindamycin treatment may be necessary for STSS patients to benefit from IVIG treatment. Further, only one study reported on IVIG treatment in STSS patients that were not also treated with clindamycin [31]; therefore, our planned subgroup analysis to test if the beneficial effect of IVIG is modified in the absence of clindamycin was precluded. Based on very low certainty evidence, our finding that NSAID treatment is significantly associated with mortality in STSS patients can be explained by clinical and basic science literature, which suggests nonselective NSAIDs mask early signs and symptoms of GAS infection, such as fever, subsequently delaying time to antibiotic treatment – a risk factor for severe sepsis and shock, and mortality [65, 66].

After analyzing 30 different prognostic factor and outcome combinations, we found that age equal to or older than 65 years and treatment with NSAIDs was significantly associated with a worse STSS prognosis and that clindamycin treatment was significantly associated with an improved STSS prognosis. Further, we found that IVIG treatment may reduce the odds of mortality in STSS patients who receive clindamycin treatment, but we are uncertain if this is true for all STSS patients, regardless of clindamycin treatment. These findings support the use of IVIG as an adjunctive treatment in clindamycin-treated STSS patients. Results from very low to low certainty evidence failed to show a significant association between any other factors of interest and STSS prognosis.

Contributors

All authors attest they meet the ICMJE criteria for authorship. All authors have made substantial contributions to the following: (1) the conception and design of the study (Jessica J Bartoszko, Lehana Thabane, Dominik Mertz, Mark Loeb), acquisition of data (Jessica J Bartoszko, Zeyad Elias, Paulina Rudziak, Carson KL Lo), analysis and interpretation of data (Jessica J Bartoszko,

Zeyad Elias, Paulina Rudziak, Carson KL Lo, Mark Loeb); (2) drafting the article and revising it critically for important intellectual content (Jessica J Bartoszko, Lehana Thabane, Dominik Mertz, Mark Loeb), (3) final approval of the version to be submitted (Jessica J Bartoszko, Zeyad Elias, Paulina Rudziak, Carson KL Lo, Lehana Thabane, Dominik Mertz, Mark Loeb).

Declaration of interests

Mark Loeb declares grants or contracts from the World Health Organization, consulting fees from AVIR Pharma, and participating on data safety monitoring or advisory boards for Paladin Labs and Sunovion Pharmaceuticals.

Role of the funding source

There was no funding source for this study.

Data availability statement

Data extracted from individual studies are available upon reasonable request to the corresponding author. All other data relevant to the study are included in the article or uploaded as online supplemental information.

Ethics statement

Patient consent for publication not applicable.

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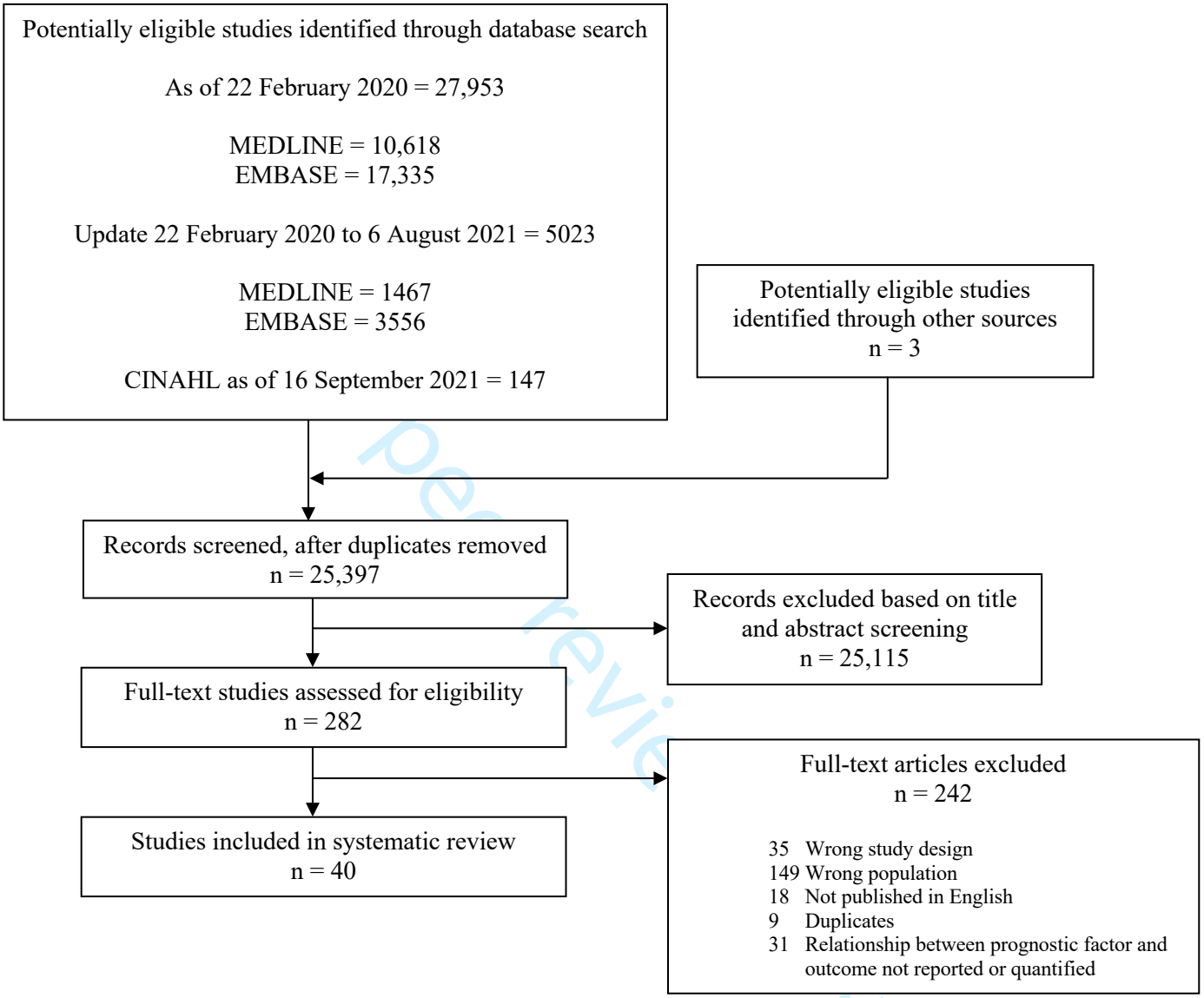
Figure 1. PRISMA flow diagram.



PROGNOSTIC FACTORS FOR STREPTOCOCCAL TOXIC SHOCK SYNDROME: SYSTEMATIC REVIEW AND META-ANALYSIS

Supplementary Material

Table of contents **Page**

Search strategies

1) Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:
---
1 toxic shock syndrome.mp. or exp Shock, Septic/ or STSS.mp. or streptococcal toxic shock syndrome.mp. or necrotizing fasciitis.mp. or exp Fasciitis, Necrotizing/ or septic shock.mp.
2 (group a streptococc* or group A streptococc* or pyogenes or streptococcus pyogenes).mp. or exp Streptococcus pyogenes/
3 exp Cohort Studies/
4 cohort$.tw.
5 controlled clinical trial.pt.
6 epidemiologic methods/
7 limit 6 to yr=1966-1989
8 exp case-control studies/
9 (case$ and control$).tw.
10 (case$ and series).tw.
11 or/3-5,7-10
12 randomized controlled trial.pt.
13 (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
14 (retraction of publication or retracted publication).pt.
15 or/12-14
16 (animals not humans).sh.
17 ((comment or editorial or meta-analysis or practice-guideline or review or letter) not randomized controlled trial).pt.
18 (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not randomized controlled trial.pt.
19 15 not (16 or 17 or 18)
20 animals/ not humans/
21 (1 or 2) and (11 or 19)
22 21 not 20

2) Database: Embase <1974 to 2020 February 03>

Search Strategy:
---
1 toxic shock syndrome.mp. or exp septic shock/ or STSS.mp. or streptococcal toxic shock syndrome.mp. or necrotizing fasciitis.mp. or exp necrotizing fasciitis/ or septic shock.mp. or exp toxic shock syndrome/
2 (group a streptococc* or group A streptococc* or pyogenes or streptococcus pyogenes).mp. or exp Streptococcus pyogenes/ or exp Streptococcus group A/
3 exp cohort analysis/
4 exp longitudinal study/
5 exp prospective study/

6 exp follow up/
7 cohort$.tw.
8 exp case control study/ or (case$ and control$).tw.
9 exp case study/ or (case$ and series).tw.
10 or/3-9
11 (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
12 RETRACTED ARTICLE/
13 or/11-12
14 (animal$ not human$).sh,hw.
15 (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/
16 (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/
17 13 not (14 or 15 or 16)
18 exp animal/
19 exp human/
20 18 not 19
21 (1 or 2) and (10 or 17)
22 21 not 20

GRADE assessment guidance

Based on GRADE guidance for prognostic studies, we start with high certainty evidence for each meta-analysis.

Risk of bias
For each meta-analysis, we downgraded the certainty of the evidence once for risk of bias when studies with moderate or high risk of bias contributed >50% weight to the pooled effect estimates or when studies providing unadjusted estimates contributed >50% weight to the pooled effect estimate (i.e. serious risk of bias). We downgraded the certainty of the evidence twice for risk of bias when studies with moderate or high risk of bias contributed >80% weight to the pooled effect estimates or when studies providing unadjusted estimates contributed >80% weight to the pooled effect estimate (i.e. very serious risk of bias).

Inconsistency
We used visual inspection of the forest plots and the I^2 statistic to assess inconsistency. For visual inspection of the forest plots, we considered the variability in point estimates and confidence interval overlap in relation to the null effect. Further, we downgraded the certainty of the evidence once when there was substantial (I^2 50-90%) heterogeneity and twice when there was considerable (I^2 75-100%) heterogeneity.

Imprecision
We downgraded the certainty of the evidence once for imprecision if:
1) The effect on the patient, or clinical action, would differ depending on whether the upper or the lower boundary of the confidence interval represented the truth, **OR**
2) The 95% CI of the pooled absolute estimate crossed the null effect by less than 50 people per 1000 on one or both sides, **OR**
3) In cases where we had large effects that did not cross the null, we assessed the optimal information size. If the ratio of the upper to the lower limit of the confidence interval of the relative estimate was >3, the optimal information size would never be met; thus, we rated down once for imprecision, **OR**
4) There were fewer than 10 outcome events for each prognostic variable (for dichotomous outcomes, **OR**
5) There were fewer than 100 cases reaching endpoint (for continuous outcomes).
We downgraded the certainty of the evidence twice for imprecision if:
1) The 95% CI of the pooled absolute estimate crossed the null effect by more than 50 people per 1000 on both sides.

Indirectness
We rated down once if the study sample, the prognostic factor, and/or the outcome in the primary studies did not accurately reflect the review question.

Publication bias
We rated down once if:
1) Small studies reported higher rates compared to large studies, suggesting the selective publication of "positive" studies, **OR**

2) The value of the risk/protective factor in predicting the outcome has NOT been repetitively investigated (e.g. only exploratory studies with no external validation, replication or confirmation exist).

References

1. Guyatt GH, Oxman AD, Kunz R, et al. GRADE Guidelines 6. Rating the Quality of Evidence—Imprecision. J Clin Epidemiol 2011; 64(12): 1283–93. https://doi.org/10.1016/j.jclinepi.2011.01.012
2. Huguet A, Hayden JA, Stinson J, et al. Judging the quality of evidence in reviews of prognostic factor research: adapting the GRADE framework. Syst Rev. 2013;2:71. Published 2013 Sep 5. doi:10.1186/2046-4053-2-71

Table of excluded full texts (n=242)

Author, Year	Title	Reason for Exclusion
Hamilton, 2013	Pregnancy-related group a streptococcal infections: Temporal relationships between bacterial acquisition, infection onset, clinical findings, and outcome	Wrong study design
Ichiyama, 1997	Transmission of Streptococcus pyogenes causing toxic shock-like syndrome among family members and confirmation by DNA macrorestriction analysis	Wrong study design
Idubor, 2019	Invasive group a streptococcus infections among residents of multiple nursing Homes-Denver, Colorado, 2017-2018	Wrong study design
Ikebe, 2015	Increased prevalence of group A streptococcus isolates in streptococcal toxic shock syndrome cases in Japan from 2010 to 2012	Wrong study design
Klinker, 1997	Toxic shock syndrome in AIDS	Wrong study design
Langmuir, 1982	Toxic-shock syndrome--an epidemiologist's view	Wrong study design
McIvor, 1982	Treatment of recurrent toxic shock syndrome with oral contraceptive agents	Wrong study design
Pathi, 2013	Prompt recognition and multidisciplinary approach in Group A streptococcal sepsis	Wrong study design
Shah, 2015	Role of intravenous immune globulin in streptococcal toxic shock syndrome and Clostridium difficile infection	Wrong study design
Stallones, 1982	A review of the epidemiologic studies of toxic shock syndrome	Wrong study design
Stevens, 2000	Molecular epidemiology of nga and NAD glycohydrolase/ADP-ribosyltransferase activity among Streptococcus pyogenes causing streptococcal toxic shock syndrome	Wrong study design
Turner, 2015	Emergence of a New Highly Successful Acapsular Group A Streptococcus Clade of Genotype emm89 in the United Kingdom	Wrong study design
Udagawa, 1999	Serious group A streptococcal infection around delivery	Wrong study design
Valiquette, 2006	A survey of physician's attitudes regarding management of severe group A streptococcal infections	Wrong study design
Valiquette, 2009	Assessing the impact of intravenous immunoglobulin in the management of streptococcal toxic shock syndrome: a noble but difficult quest	Wrong study design
Wozniak, 2012	M-protein gene-type distribution and hyaluronic acid capsule in group A Streptococcus clinical isolates in Chile: Association of emm gene markers with csrR alleles	Wrong study design
Anonymous, 1984	Diagnostic bias and toxic shock syndrome	Wrong study design
Blonde, 2017	A prospective multicentric study of severe cutaneous infections in pediatric intensive care: The SCIPIC cohort	Wrong study design
Busowski, 2010	Puerperal group A streptococci (GAS) infection: Reemergence of a dreaded disease - A case series	Wrong study design
Cimolai, 2002	Nonhemolytic Streptococcus pyogenes causing invasive infection	Wrong study design
Clark, 2010	Puerperal group a streptococcal sepsis and proinflammatory immune response	Wrong study design

Dahdi, 2018	Necrotizing soft tissue infection: Microbiological distribution from district region	Wrong study design
Das, 2012	Necrotizing fasciitis in New Zealand - Risk factors, microbiological findings and outcomes in a large case series	Wrong study design
De Zoysa, 2013	Invasive group A streptococcal disease in the UK, 2008-2012 and molecular characterisation of isolates during enhanced surveillance	Wrong study design
Donawa, 1984	Toxic shock syndrome: chronology of state and federal epidemiologic studies and regulatory decision-making	Wrong study design
Figueira, 2013	Peri-ocular necrotising fasciitis: A multicentre retrospective australian series	Wrong study design
Gaensbauer, 2016	Importance of toxic shock syndrome in pediatric septic shock clinical decision-making	Wrong study design
Goldberg, 2015	Group A beta streptococcal infections in children after oral or dental trauma: A case series of 5 patients	Wrong study design
McViety, 2014	Don't forget IGAS: Lessons learnt from review of 2 peak seasons in the north west and North Wales, UK	Wrong study design
Zangara, 2019	Epidemiology, outcomes from treatment, and the spectrum of soft tissue infections over time in hospitalized patients: A populationbased description of inpatients in the state of california	Wrong study design
Arias-Constanti, 2018	Invasive disease by Streptococcus pyogenes: patients hospitalized for 6 years	Wrong population
Hankins, 2008	Factors that affect the clinical course of group A beta-haemolytic streptococcal infections of the hand and upper extremity: a retrospective study	Wrong population
Henrichsen, 1997	Invasive infections caused by Streptococcus pyogenes in Denmark 1990- 1994	Wrong population
Hoge, 1993	The changing epidemiology of invasive group A streptococcal infections and the emergence of streptococcal toxic shock-like syndrome. A retrospective population-based study	Wrong population
Jauregui, 2015	Life- and limb-threatening infections following the use of an external fixator	Wrong population
Kadri, 2017	Impact of Intravenous Immunoglobulin on Survival in Necrotizing Fasciitis With Vasopressor-Dependent Shock: A Propensity Score-Matched Analysis From 130 US Hospitals	Wrong population
Leggiadro, 1993	Group A streptococcal bacteremia in a mid-south children's hospital	Wrong population
Madsen, 2019	Patient's characteristics and outcomes in necrotising soft-tissue infections: results from a Scandinavian, multicentre, prospective cohort study	Wrong population
Mitchell, 2011	A strep in the wrong direction-invasive group a streptococcal disease	Wrong population
Moses, 1995	Group A streptococcus bacteremia at the Hadassah Medical Center in Jerusalem	Wrong population
Mosites, 2017	Use of single-dose azithromycin to control a community outbreak of EMM26.3 group a streptococcus invasive disease-Alaska, 2017	Wrong population
Mosites, 2019	Risk for invasive streptococcal infections among adults experiencing homelessness, anchorage, Alaska, USA, 2002-2015	Wrong population

Mulla, 2007	Clinical and epidemiologic features of invasive group A streptococcal infections in children	Wrong population
Mulla, 2003	Invasive group A streptococcal infections in Florida	Wrong population
Navarro, 1993	A comparison of Streptococcus pyogenes (group A streptococcal) bacteremia at an urban and a suburban hospital. The importance of intravenous drug use	Wrong population
Norton, 2004	Invasive group A streptococcal disease in North Queensland (1996 - 2001)	Wrong population
Nuwayhid, 2007	Blunt Trauma as a Risk Factor for Group A Streptococcal Necrotizing Fasciitis	Wrong population
Oliver, 2019	Invasive group A Streptococcus disease in Australian children: 2016 to 2018 - a descriptive cohort study	Wrong population
Oliver, 2019	Recent trends in invasive group A Streptococcus disease in Victoria	Wrong population
Peterson, 1996	Risk factors for invasive group A streptococcal infections in children with varicella: A case-control study	Wrong population
Rainbow, 2008	Invasive group A streptococcal disease in nursing homes, Minnesota, 1995-2006	Wrong population
Rathore, 1992	Suppurative group A beta-hemolytic streptococcal infections in children	Wrong population
Reingold, 1984	Epidemiology of toxic-shock syndrome, United States, 1960-1984	Wrong population
Reingold, 1989	Risk factors for menstrual toxic shock syndrome: results of a multistate case-control study	Wrong population
Remy, 2019	Septic shock and toxic shock syndrome-two infectious shocks with different immune response	Wrong population
Rudolph, 2016	Epidemiology of invasive group a streptococcal disease in Alaska, 2001 to 2013	Wrong population
Saldana, 2010	Periorbital necrotizing fasciitis: Outcomes using a CT-guided surgical debridement approach	Wrong population
Sarangi, 1995	A nursing home outbreak of group A streptococcal infection: case control study of environmental contamination	Wrong population
Scaber, 2011	Group a streptococcal infections during the seasonal influenza outbreak 2010/11 in South East England	Wrong population
Scheuer, 2018	Rising high rate of invasive group a streptococcus infections among persons experiencing homelessness in San Francisco, 2010-2017	Wrong population
Schlech, 1982	Risk factors for development of toxic shock syndrome. Association with a tampon brand	Wrong population
Schwartz, 1989	Nonmenstrual toxic shock syndrome associated with barrier contraceptives: report of a case-control study	Wrong population
Shands, 1982	Toxic shock syndrome: Case-control studies at the centers for disease control	Wrong population
Sharma, 2019	Real-time whole genome sequencing to control a Streptococcus pyogenes outbreak at a national orthopaedic hospital	Wrong population
Sierra, 2006	Group A streptococcal infections in injection drug users in Barcelona, Spain: Epidemiologic, clinical, and microbiologic analysis of 3 clusters of cases from 2000 to 2003	Wrong population

Simonart, 2004	The importance of serum creatine phosphokinase level in the early diagnosis and microbiological evaluation of necrotizing fasciitis	Wrong population
Smith, 2003	Mass antibiotic treatment for group A streptococcus outbreaks in two long-term care facilities	Wrong population
Spargen, 2011	Proinflammatory immune response and puerperal group a streptococcal sepsis	Wrong population
Steer, 2009	Prospective surveillance of invasive group A streptococcal disease, fiji, 2005-2007	Wrong population
Steer, 2008	High burden of invasive beta-haemolytic streptococcal infections in Fiji	Wrong population
Tanna, 2006	Molecular characterization of clinical isolates of M non-typable group A streptococci from invasive disease cases	Wrong population
Tapiainen, 2016	Invasive Group A Streptococcal Infections in Children: A Nationwide Survey in Finland	Wrong population
Thanert, 2019	Molecular profiling of tissue biopsies reveals unique signatures associated with streptococcal necrotizing soft tissue infections	Wrong population
Theis, 2002	Severe necrotising soft tissue infections in orthopaedic surgery	Wrong population
Thigpen, 2007	Nursing home outbreak of invasive group A streptococcal infections caused by 2 distinct strains	Wrong population
Urbina, 2019	Early identification of patients at high risk of group A streptococcus-associated necrotizing skin and soft tissue infections: a retrospective cohort study	Wrong population
Vasant, 2019	Mass prophylaxis in an outbreak of invasive group A streptococcal disease in a residential aged care facility	Wrong population
Vlaminckx, 2005	Long-term surveillance of invasive group A streptococcal disease in The Netherlands, 1994-2003	Wrong population
Vugia, 1996	Invasive group A streptococcal infections in children with varicella in Southern California	Wrong population
Waldhausen, 1996	Surgical implications of necrotizing fasciitis in children with chickenpox	Wrong population
Watanabe-Ohnishi, 1995	Selective depletion of V beta-bearing T cells in patients with severe invasive group A streptococcal infections and streptococcal toxic shock syndrome. Ontario Streptococcal Study Project	Wrong population
Wheeler, 1991	Outbreak of group A streptococcus septicemia in children: Clinical, epidemiologic, and microbiological correlates	Wrong population
Wilson, 1995	Group A streptococcal necrotizing fasciitis following varicella in children: Case reports and review	Wrong population
Wong, 2019	A Cluster of Pediatric Invasive Group A Streptococcus Disease in Melbourne, Australia, Coinciding with a High-Burden Influenza Season	Wrong population
Yagupsky, 1987	Group A beta-hemolytic streptococcal bacteremia in children	Wrong population
Zerr, 1999	A case-control study of necrotizing fasciitis during primary varicella	Wrong population
Zimbelman, 1999	Improved outcome of clindamycin compared with beta-lactam antibiotic treatment for invasive Streptococcus pyogenes infection	Wrong population

Abraham, 2016	Distribution of emm types of beta hemolytic streptococci associated with necrotizing fascitis: Clinical profile and outcome	Wrong population
Acosta, 2014	Severe Maternal Sepsis in the UK, 2011-2012: A National Case-Control Study	Wrong population
Adams, 2010	Investigation into an outbreak of invasive Group A Streptococcal (iGAS) infection at a general hospital in 2010	Wrong population
Adem, 2009	Identification of invasive streptococcal disease in a pediatric and infant death Cohort-Iowa, 2007-2008	Wrong population
Afifi, 2008	Acute necrotizing fasciitis in Egyptian patients: A case series	Wrong population
Al-Khadidi, 2017	Group A Streptococcal bacteraemia. Experience at King Fahad Medical City in Riyadh, Saudi Arabia	Wrong population
Alva, 2013	Necrotising fasciitis: A series of seven cases	Wrong population
Anonymous, 2007	Summaries for patients. Invasive streptococcal infections in hospitals in Ontario, Canada, 1992 to 2000	Wrong population
Aronoff, 2008	Postpartum invasive group A streptococcal disease in the modern era	Wrong population
Babbar, 2018	Pivotal Role of Preexisting Pathogen-Specific Antibodies in the Development of Necrotizing Soft-Tissue Infections	Wrong population
Babbar, 2016	A serological evaluation of the host immune response during Necrotizing Soft Tissue Infections caused by Streptococcus pyogenes	Wrong population
Babiker, 2019	Impact of adjunctive clindamycin in invasive beta-hemolytic streptococcal infections: A propensity score-matched analysis of 1956 beta-lactam treated patients from 118 us hospitals	Wrong population
Bajpai, 1977	Chemotherapy of acute bone and joint infections	Wrong population
Barnham, 2001	Bacteraemic Streptococcus pyogenes infection in the peri-partum period: now a rare disease and prior carriage by the patient may be important	Wrong population
Basma, 1999	Risk factors in the pathogenesis of invasive group A streptococcal infections: Role of protective humoral immunity	Wrong population
Bauer, 2015	Maternal deaths due to sepsis in the state of Michigan, 1999-2006	Wrong population
Beaudoin, 2014	Invasive group A Streptococcus infections associated with liposuction surgery at outpatient facilities not subject to state or federal regulation	Wrong population
Beigh, 2012	Postoperative complications followed by septoplasty comparison between conventional nasal packing and glove finger pack	Wrong population
Berkley, 1987	The relationship of tampon characteristics to menstrual toxic shock syndrome	Wrong population
Bingol-Kologlu, 2007	Necrotizing fasciitis in children: diagnostic and therapeutic aspects	Wrong population
Bruun, 2013	Necrotizing soft tissue infections caused by Streptococcus pyogenes and Streptococcus dysgalactiae subsp. equisimilis of groups C and G in western Norway	Wrong population
Bruun, 2020	Risk factors and Predictors of Mortality in Streptococcal Necrotizing Soft-Tissue Infections: A Multicenter Prospective Study	Wrong population

Busowski, 2013	Puerperal group a streptococcal infections: A case series and discussion	Wrong population
Byer, 2006	Clinical deterioration among patients with fever and erythroderma	Wrong population
Centers for Disease, 1982	Toxic-shock syndrome, United States, 1970-1982	Wrong population
Centers for Disease, 2011	Invasive group A streptococcus in a skilled nursing facility--Pennsylvania, 2009-2010	Wrong population
Chan, 2009	Toxic shock syndrome and rhinosinusitis in children	Wrong population
Chen, 2011	The microbiological profile and presence of bloodstream infection influence mortality rates in necrotizing fasciitis	Wrong population
Chen, 2015	Clinical Characteristics and Risk Factor Analysis for Lower-Extremity Amputations in Diabetic Patients With Foot Ulcer Complicated by Necrotizing Fasciitis	Wrong population
Chen, 2018	Macro- and Microvascular Parameters After Toxic Shock Syndrome	Wrong population
Ching, 2019	Prospective surveillance of pediatric invasive group A Streptococcus infection	Wrong population
Chiobotaru, 1997	Changing epidemiology of invasive Streptococcus pyogenes infections in southern Israel: differences between two ethnic population groups	Wrong population
Christie, 1988	Bacteremia with group A streptococci in childhood	Wrong population
Corona, 2016	Necrotising fasciitis of the extremities: implementation of new management technologies	Wrong population
Daneman, 2007	Surveillance for hospital outbreaks of invasive group a streptococcal infections in Ontario, Canada, 1992 to 2000	Wrong population
Daneman, 2005	Hospital-acquired invasive group A streptococcal infections in Ontario, Canada, 1992-2000	Wrong population
Davies, 1996	Invasive group A streptococcal infections in Ontario, Canada. Ontario Group A Streptococcal Study Group	Wrong population
Davis, 1982	Toxic shock syndrome: a critique of the 1980 Wisconsin case-control study	Wrong population
De Almeida Torres, 2013	Group a streptococcus meningitis in children	Wrong population
Deutscher, 2011	Incidence and severity of invasive Streptococcus pneumoniae, group A Streptococcus, and group B Streptococcus infections among pregnant and postpartum women	Wrong population
Devaney, 2015	Necrotising soft tissue infections: The effect of hyperbaric oxygen on mortality	Wrong population
Dooling, 2013	Investigation of a prolonged Group A Streptococcal outbreak among residents of a skilled nursing facility, Georgia, 2009-2012	Wrong population
Dworkin, 2009	The epidemiology of necrotizing fasciitis including factors associated with death and amputation	Wrong population
Eneli, 2007	Epidemiology and Outcome of Necrotizing Fasciitis in Children: An Active Surveillance Study of the Canadian Paediatric Surveillance Program	Wrong population
Factor, 2005	Risk factors for pediatric invasive group A streptococcal disease	Wrong population
Factor, 2003	Invasive group a streptococcal disease: Risk factors for adults	Wrong population

Fauno Thrane, 2017	Hyperbaric oxygen may only be optional in head and neck necrotizing fasciitis: a retrospective analysis of 43 cases and review of the literature	Wrong population
Fichtenbaum, 1993	Ehrlichiosis presenting as a life-threatening illness with features of the toxic shock syndrome	Wrong population
Flavahan, 2014	Incidence of periorbital necrotising fasciitis in the UK population: A BOSU study	Wrong population
Flores, 2019	Capsule-negative EMM types are an increasing cause of pediatric group a streptococcal infections at a large pediatric hospital in Texas	Wrong population
Frere, 2016	Clinical and Microbiological Characteristics of Invasive Group A Streptococcal Infections Before and After Implementation of a Universal Varicella Vaccine Program	Wrong population
Givner, 1998	Invasive disease due to group A beta-hemolytic streptococci: Continued occurrence in children in North Carolina	Wrong population
Givner, 1991	Apparent increase in the incidence of invasive group A beta-hemolytic streptococcal disease in children	Wrong population
Gooskens, 2005	Streptococcal toxic shock syndrome by an iMLS resistant M type 77 Streptococcus pyogenes in the Netherlands	Wrong population
Gonzalez, 1996	Necrotizing fasciitis of the upper extremity	Wrong population
Lesko, 2001	Invasive group A streptococcal infection and nonsteroidal antiinflammatory drug use among children with primary varicella	Wrong population
Lin, 2013	Group a streptococcal necrotizing fasciitis in the emergency department	Wrong population
Lin, 2015	Early Differentiation of Kawasaki Disease Shock Syndrome and Toxic Shock Syndrome in a Pediatric Intensive Care Unit	Wrong population
Parks, 2019	Elevated risk of invasive group A streptococcal disease and host genetic variation in the human leucocyte antigen locus	Wrong population
Stromberg, 1991	Outbreak of group A streptococcal bacteremia in Sweden: an epidemiologic and clinical study	Wrong population
Haggar, 2012	Clinical and microbiologic characteristics of invasive Streptococcus pyogenes infections in north and south India	Relationship between prognostic factor and outcome not reported or quantified
Laupland, 2000	Invasive group A streptococcal disease in children and association with varicella-zoster virus infection. Ontario Group A Streptococcal Study Group	Relationship between prognostic factor and outcome not reported or quantified
Linnemann, 1986	Increasing incidence of toxic shock syndrome in the 1970s	Relationship between prognostic factor and outcome not reported or quantified
Miday, 1988	Toxic shock syndrome: incidence and geographic distribution from a hospital medical records reporting system	Relationship between prognostic factor and outcome not reported or quantified
Mosites, 2018	Outbreak of Invasive Infections from Subtype emm26.3 Group A Streptococcus among Homeless Adults-Anchorage, Alaska, 2016-2017	Relationship between prognostic factor and outcome not reported or quantified

O'Grady, 2007	The epidemiology of invasive group A streptococcal disease in Victoria, Australia	Relationship between prognostic factor and outcome not reported or quantified
Petitti, 1989	Update through 1985 on the incidence of toxic shock syndrome among members of a prepaid health plan	Relationship between prognostic factor and outcome not reported or quantified
Pilon, 2019	Invasive group A streptococcal infection outbreaks of typeemm118 in a long-term care facility, and of type emm74 in the homeless population, Montreal, Quebec	Relationship between prognostic factor and outcome not reported or quantified
Rantala, 2012	Streptococcus pyogenes bacteraemia, emm types and superantigen profiles	Relationship between prognostic factor and outcome not reported or quantified
Tanner, 1981	Toxic shock syndrome	Relationship between prognostic factor and outcome not reported or quantified
Teatero, 2018	Canada-Wide Epidemic of emm74 Group A Streptococcus Invasive Disease	Relationship between prognostic factor and outcome not reported or quantified
Todd, 1985	Toxic shock syndrome. II. Estimated occurrence in Colorado as influenced by case ascertainment methods	Relationship between prognostic factor and outcome not reported or quantified
Tsai, 2014	Correlation of virulence genes to clinical manifestations and outcome in patients with Streptococcus dysgalactiae subspecies equisimilis bacteremia	Relationship between prognostic factor and outcome not reported or quantified
Vallalta Morales, 2006	Group A streptococcal bacteremia: outcome and prognostic factors	Relationship between prognostic factor and outcome not reported or quantified
Vlaminckx, 2004	Epidemiological features of invasive and noninvasive group A streptococcal disease in the Netherlands, 1992-1996	Relationship between prognostic factor and outcome not reported or quantified
Aydin, 2017	Clinical indications of intravenous immunoglobulin use in pediatric infectious diseases clinic	Relationship between prognostic factor and outcome not reported or quantified
Ben-Abraham, 2002	Invasive group A streptococcal infections in a large tertiary center: epidemiology, characteristics and outcome	Relationship between prognostic factor and outcome not reported or quantified
Bochicchio, 2001	Group A Streptococcus (GAS) soft-tissue infections: a lethal organism on the rise	Relationship between prognostic factor and outcome not reported or quantified
Cancellara, 2016	Multicenter study on invasive Streptococcus pyogenes infections in children in Argentina	Relationship between prognostic factor and

		outcome not reported or quantified
Chen, 2016	Toxic shock syndrome in Australian children	Relationship between prognostic factor and outcome not reported or quantified
Doctor, 1995	Group A beta-hemolytic streptococcal bacteremia: historical overview, changing incidence, and recent association with varicella	Relationship between prognostic factor and outcome not reported or quantified
Eriksson, 2003	Group A streptococcal infections in Sweden: a comparative study of invasive and noninvasive infections and analysis of dominant T28 emm28 isolates	Relationship between prognostic factor and outcome not reported or quantified
Norrby-Teglund, 2003	The treatment of severe group a streptococcal infections	Relationship between prognostic factor and outcome not reported or quantified
Rodriguez-Nunez, 2011	Clinical characteristics of children with group A streptococcal toxic shock syndrome admitted to pediatric intensive care units	Relationship between prognostic factor and outcome not reported or quantified
Snall, 2016	Differential neutrophil responses to bacterial stimuli: Streptococcal strains are potent inducers of heparin-binding protein and resistin-release	Relationship between prognostic factor and outcome not reported or quantified
Eriksson, 1998	Epidemiological and clinical aspects of invasive group A streptococcal infections and the streptococcal toxic shock syndrome	Relationship between prognostic factor and outcome not reported or quantified
Sahli, 2014	Necrotizing fasciitisin in diabetic patients: A report of 14 cases	Not in English
Arnholm, 2004	High-dose immunoglobulin - Life-saving in invasive group a streptococcal infection	Not in English
Caetano, 2010	[S. Pyogenes invasive disease in a paediatric hospital: 1996-2009]	Not in English
Costa Orvay, 2007	[Toxic shock syndrome: experience in a pediatric intensive care unit]	Not in English
Dosil Gallardo, 2009	[Streptococcal toxic shock syndrome: an emerging pathology?]	Not in English
Emmi, 1999	Severe infection from invasive beta-hemolytic streptococcus group A. Three cases of toxic shock observed in resuscitation	Not in English
Faye, 2014	Management of severe invasive group A streptococcal infections	Not in English
Floret, 2001	Clinical aspects of staphylococcal and streptococcal toxinic diseases	Not in English
Hua, 2018	[Streptococcal toxic shock syndrome caused by Streptococcus pyogenes: a retrospective study of 15 pediatric cases]	Not in English
Kach, 1993	[Necrotizing soft tissue infections]	Not in English
Kaul, 1999	Intravenous immunoglobulin therapy for streptococcal toxic shock syndrome--a comparative observational study. The Canadian Streptococcal Study Group	Duplicate
Salinas, 2005	Immunoglobulins in sepsis and septic shock	Not in English

Shands, 1982	Toxic shock syndrome: case-control studies at the Centers for Disease Control	Duplicate
Sierra, 2006	Group A streptococcal infections in injection drug users in Barcelona, Spain: epidemiologic, clinical, and microbiologic analysis of 3 clusters of cases from 2000 to 2003	Duplicate
Urbina, 2019	Early identification of patients at high risk of group A streptococcus-associated necrotizing skin and soft tissue infections: A retrospective cohort study	Duplicate
Vallalta-Morales, 2005	[Streptococcal toxic shock syndrome: ten years' experience at a tertiary hospital]	Not in English
Vasant, 2019	Mass prophylaxis in an outbreak of invasive group A streptococcal disease in a residential aged care facility	Duplicate
Vugia, 1996	Invasive group A streptococcal infections in children with varicella in Southern California	Duplicate
Zachariadou, 2014	Differences in the epidemiology between paediatric and adult invasive Streptococcus pyogenes infections	Duplicate
Bernard, 1995	[Bacterial dermo-hypodermatitis in adults. Incidence and role of streptococcal etiology]	Not in English
Bleton, 1991	Necrotizing fasciitis of the upper limb. 12 cases	Not in English
Bleton, 1991	Necrotising fasciitis of the upper limb. Report of twelve cases	Duplicate
Fan, 2014	[Clinical characteristics and antimicrobial resistance of invasive group A beta-hemolytic streptococcus infection in children]	Not in English
Fica, 2003	Molecular epidemiology of a streptococcus pyogenes related nosocomial outbreak in a burn unit	Not in English
Fredlund, 1990	[Increased frequency of group A hemolytic streptococci. Old age and immune deficiency among the risk factors]	Not in English
Georgiev, 1993	Puerperal streptococcal sepsis	Not in English
Khan, 2003	Treatment of necrotizing fasciitis with quinolones	Wrong population
Frosi, 1999	Necrotizing fasciitis: A serious and uncommon alcohol related disease	Wrong study design
Nedrebo, 2020	Necrotizing Soft Tissue Infections: Case Reports, from the Clinician's Perspectives.	Wrong study design
Reicher, 2021	450 Obstetrically related group a streptococcal infection and predictors for severity - retrospective 12-year cohort study	Wrong study design
Bajpai, 2020	Anti-microbial-resistance and profile of exotoxins of invasive beta-haemolytic-streptococci infections in trauma patients	Wrong population
Adamkova, 2020	Can gram-negative-like biomarker values in Streptococcus pyogenes sepsis negatively influence right choice of initial antibiotic therapy?	Wrong population
Bandi, 2021	Group A streptococcal infections in children	Wrong population
Ceccato, 2020	Use of corticosteroids in patients with severe CAP admitted to ICU, experience in a real-life setting	Wrong population
Tepper, 2021	Long-term safety and tolerability of atogepant following once daily dosing over 1 year for the preventive treatment of migraine	Wrong population

Melo, 2021	Clinical, epidemiological and microbiological features of streptococcus pyogenes invasive infection - 10 year retrospective review	Wrong population
Bringel, 2021	Clinical characteristics and outcomes of children with toxic shock syndrome admitted to a pediatric intensive care unit: A case series	Wrong population
Neff, 2020	Characterisation of clinical manifestations and treatment strategies for invasive beta-haemolytic streptococcal infections in a Swiss tertiary hospital.	Wrong population
Urbina, 2020	Assessing and applying individualized treatment for group A streptococcal necrotizing soft-tissue infection is possible	Wrong population
Bergsten, 2020	Correlation between immunoglobulin dose administered and plasma neutralization of streptococcal superantigens in patients with necrotizing soft tissue infections	Wrong population
Boukthir, 2020	A prospective survey of Streptococcus pyogenes infections in French Brittany from 2009 to 2017: Comprehensive dynamic of new emergent emm genotypes.	Wrong population
Escrihuela-Vidal, 2021	Clinical Features and Outcomes of Streptococcus anginosus Group Infective Endocarditis: A Multicenter Matched Cohort Study.	Wrong population
Babiker, 2021	Effectiveness of adjunctive clindamycin in beta-lactam antibiotic-treated patients with invasive beta-haemolytic streptococcal infections in US hospitals: a retrospective multicentre cohort study.	Wrong population
Cui, 2021	Necrotizing soft tissue infection: clinical characteristics, diagnosis, and management of 32 cases in Beijing.	Wrong population
Link-Gelles, 2020	Characteristics of Intracranial Group A Streptococcal Infections in US Children, 1997-2014.	Wrong population
Peetermans, 2020	Use of Intravenous Immunoglobulins in Patients with Suspected Toxin-Mediated Shock Requiring Extracorporeal Membrane Oxygenation.	Wrong population
Bruun, 2020	Beta-Hemolytic Streptococci and Necrotizing Soft Tissue Infections.	Wrong population
Lima-Setta, 2021	Multisystem inflammatory syndrome in children (MIS-C) during SARS-CoV-2 pandemic in Brazil: a multicenter, prospective cohort study.	Wrong population
Kohler, 2020	Kininogen supports inflammation and bacterial spreading during Streptococccus Pyogenes Sepsis.	Wrong population
Bruun, 2021	Risk Factors and Predictors of Mortality in Streptococcal Necrotizing Soft-tissue Infections: A Multicenter Prospective Study.	Wrong population
Bjorck, 2020	Morbidity and mortality in critically ill patients with invasive group A streptococcus infection: an observational study.	Wrong population
Contou, 2021	Menstrual toxic shock syndrome: a French nationwide multicenter retrospective study.	Wrong population
Billon, 2020	Association of characteristics of tampon use with menstrual toxic shock syndrome in France.	Wrong population
Canetti, 2021	Invasive Group A Streptococcus Infection in Children in Central Israel in 2012-2019	Relationship between prognostic factor and outcome not reported or quantified

Vilhonen, 2020	Group A streptococcal bacteremias in Southwest Finland 2007-2018: epidemiology and role of infectious diseases consultation in antibiotic treatment selection.	Relationship between prognostic factor and outcome not reported or quantified
Thielemans, 2020	Clinical Description and Outcomes of Australian Children With Invasive Group A Streptococcal Disease.	Relationship between prognostic factor and outcome not reported or quantified
Madsen, 2020	Treatment of Necrotizing Soft Tissue Infections: IVIG	Wrong study design
Deniskin, 2019	Clinical Manifestations and Bacterial Genomic Analysis of Group A Streptococcus Strains That Cause Pediatric Toxic Shock Syndrome.	Relationship between prognostic factor and outcome not reported or quantified
Mosites, 2018	Outbreak of Invasive Infections From Subtype emm26.3 Group A Streptococcus Among Homeless Adults-Anchorage, Alaska, 2016-2017.	Relationship between prognostic factor and outcome not reported or quantified
Hasin, 2020	Invasive Group A Streptococcus Infection in Children in Southern Israel Before and After the Introduction of Varicella Vaccine.	Wrong population
Ching, 2019	Prospective Surveillance of Pediatric Invasive Group A Streptococcus Infection.	Wrong population
Loewen, 2017	Epidemiologic features of invasive group A Streptococcus infection in a rural hospital: 6-year retrospective report and literature review.	Wrong population
Bergsten, 2020	Correlation Between Immunoglobulin Dose Administered and Plasma Neutralization of Streptococcal Superantigens in Patients With Necrotizing Soft Tissue Infections.	Wrong population
Kobayashi, 2016	A Cluster of Group A Streptococcal Infections in a Skilled Nursing Facility-the Potential Role of Healthcare Worker Presenteeism.	Wrong population
Adebanjo, 2020	Evaluating Household Transmission of Invasive Group A Streptococcus Disease in the United States Using Population-based Surveillance Data, 2013-2016.	Wrong population
Link-Gelles, 2020	Characteristics of Intracranial Group A Streptococcal Infections in US Children, 1997-2014.	Wrong population
Bruun, 2021	Risk Factors and Predictors of Mortality in Streptococcal Necrotizing Soft-tissue Infections: A Multicenter Prospective Study.	Wrong population
Shah, 2015	Role of intravenous immune globulin in streptococcal toxic shock syndrome and Clostridium difficile infection.	Wrong study design
Hayata, 2021	Nationwide study of mortality and survival in pregnancy-related streptococcal toxic shock syndrome.	Duplicate

Table of additional study characteristics

Study	Study Design	Country	Number of STSS cases	Mean age	% Male	Cardiovascular Disease (%)	Diabetes (%)	Presence of Necrotizing Fasciitis (%)	Probable GAS STSS (%)	Confirmed GAS STSS (%)	Prognostic factor and outcome combination of interest reported
Abuhammour 2004	Cohort	United States	2	9	100	NR	NR	NR	NR	NR	age - clinical cure/improvement^ age - ICU admission^ age - mortality^ any antibiotic - clinical cure/improvement^ any antibiotic - ICU admission any antibiotic - mortality
Adalat 2014	Cohort	United Kingdom, Ireland	29	4 (median)	62	NR	NR	28	38	62	IVIG - mortality
Al-Ajmi 2012	Case-series	Qatar	2	35	0	NR	NR	NR	0	100	age - clinical cure/improvement^ age - ICU admission^ age - mortality^
Barnham 2002	Case-series	England	12	57	64	NR	NR	58	17	83	age - ICU admission^ age - mortality^ any antibiotic - ICU admission any antibiotic - mortality clindamycin - ICU admission^ clindamycin - mortality emm type - ICU admission^ emm type - mortality^ immunocompromised - ICU admission^ immunocompromised - mortality IVIG - ICU admission IVIG - mortality IVIG - time to mortality^ NF - ICU admission NF - mortality NSAIDs - ICU admission NSAIDs - mortality
Bernaldo de Quiros 1997	Cohort	Spain	9	NR	NR	NR	NR	NR	NR	NR	immunocompromised - mortality^

Study	Study Design	Country	Number of STSS cases	Mean age	% Male	Cardiovascular Disease (%)	Diabetes (%)	Presence of Necrotizing Fasciitis (%)	Probable GAS STSS (%)	Confirmed GAS STSS (%)	Prognostic factor and outcome combination of interest reported
Brogan 1995	Case-series	United States	5	6	60	NR	NR	100	60	40	age - clinical cure/improvement^ age - hospital LOS^ age - ICU admission^ age - ICU LOS^ age - mortality^ NSAIDs - clinical cure/improvement^ NSAIDs - hospital LOS^ NSAIDS - ICU admission NSAIDs - ICU LOS^ NSAIDs - mortality sex - clinical cure/improvement sex - hospital LOS^ sex - ICU admission sex - ICU LOS^ sex - mortality
Butragueno Laiseca 2017	Case-series	Spain	13	2	50	NR	NR	15	15	85	acute renal failure - clinical cure/improvement^ acute renal failure - mechanical ventilation acute renal failure - mortality age - clinical cure/improvement^ age - ICU LOS^ age - mechanical ventilation^ age - mortality^ clindamycin - clinical cure/improvement^ clindamycin - ICU LOS^ clindamycin - mechanical ventilation^ clindamycin - mortality hemodialysis - clinical cure/imrpovement hemodialysis - mechanical ventilation hemodialysis - mortality IVIG - clinical cure/improvement IVIG - ICU LOS IVIG - mechanical ventilation IVIG - mortality NF - clinical cure/improvement NF - ICU LOS^ NF - mechanical ventilation NF - mortality
Carapetis 1995	Case-series	Australia	5	NR	NR	NR	NR	NR	NR	NR	age - mortality^

Study	Study Design	Country	Number of STSS cases	Mean age	% Male	Cardiovascular Disease (%)	Diabetes (%)	Presence of Necrotizing Fasciitis (%)	Probable GAS STSS (%)	Confirmed GAS STSS (%)	Prognostic factor and outcome combination of interest reported
Carapetis 2014	Cohort	Australia	37	60	50	NR	NR	100	0	100	age - mortality^ IVIG - mortality sex - mortality
Cimolai 1992	Case-series	Canada	4	8	50	NR	NR	NR	0	100	age - clinical cure/improvement^ age - mortality^ sex - clinical cure/improvement sex - mortality
Cook 2020	Cohort	United States	27	9	44	NR	NR	19	56	44	other - other^
Cowan 1994	Case-series	United States	3	2	67	NR	NR	NR	100	0	age - clinical cure/improvement^ age - ICU admission^ age - ICU LOS^ age - mechanical ventilation^ age - mortality^ sex - clinical cure/improvement sex - ICU admission sex - ICU LOS^ sex - mechanical ventilation sex - mortality
Crum 2004	Case-series	United States	2	24	100	NR	NR	50	0	100	age - clinical cure/improvement^ age - ICU admission^ age - mechanical ventilation^ age - mortality^ hemodialysis - clinical cure/improvement hemodialysis - ICU admission hemodialysis - mechanical ventilation hemodialysis - mortality
Dahl 2002	Case-series	United States	5	53	NR	NR	NR	100	0	100	age - mortality^ immunocompromised - mortality
Darenberg 2003	Randomized trial	Sweden, Norway, Finland, Netherlands	18	52	48	NR	NR	NR	11	89	IVIG - change in SOFA score^ IVIG - mortality IVIG - time to clinical cure/improvement^ IVIG - time to mortality^

Study	Study Design	Country	Number of STSS cases	Mean age	% Male	Cardiovascular Disease (%)	Diabetes (%)	Presence of Necrotizing Fasciitis (%)	Probable GAS STSS (%)	Confirmed GAS STSS (%)	Prognostic factor and outcome combination of interest reported
Donaldson 1993	Case-series	England	5	67	20	NR	NR	100	NR	NR	age - mortality^ any antibiotic - mortality sex - mortality
Erdem 2004	Case-series	United States	3	52	67	NR	NR	100	NR	33	age - mortality^ sex - mortality
Eriksson 1999	Cohort	Sweden	6	46	83	NR	NR	NR	0	100	age - mortality^ emm type - mortality^ sex - mortality
Forni 1995	Case-series	United States	5	54	83	NR	17	50	0	100	acure renal failure - ICU admission^ acute renal failure - mortality age - hospital LOS^ age - ICU admission^ age - mortality^ emm type - ICU admission^ emm type - mortality^ NF - ICU admission NF - mortality
Fronhoffs 2000	Case-series	Germany	7	49	71	14	14	86	86	14	acute renal failure - mechanical ventilation acute renal failure - mortality age - mechanical ventilation^ age - mortality^ immunocompromised - mechanical ventilation^ immunocompromised - mortality NF - mechanical ventilation NF - mortality NSAIDs - mechanical ventilation^ NSAIDs - mortality sex - mechanical ventilation sex - mortality
Hasegawa 2004	Case-control	Japan	66*	Range: 0 to 70	59	NR	18	NR	100	0	acute renal failure - mortality
Hayata 2021	Cohort	Japan	28	NR	0	NR	NR	NR	0	100	age - mortality^ NSAIDs - mortality

Study	Study Design	Country	Number of STSS cases	Mean age	% Male	Cardiovascular Disease (%)	Diabetes (%)	Presence of Necrotizing Fasciitis (%)	Probable GAS STSS (%)	Confirmed GAS STSS (%)	Prognostic factor and outcome combination of interest reported
Huang 2001	Case-series	Taiwan	3	6	100	NR	NR	NR	33	67	age - mortality^
Kansal 2000	Cohort	Canada	28	NR	NR	NR	NR	NR	NR	NR	NF - other^
Kaul 1999	Case-control	Canada	53	57	55	NR	NR	NR	NR	NR	clindamycin - mortality IVIG - duration of mechanical ventilation^ IVIG - hospital LOS IVIG - mortality NF - mortality
Linder 2017	Cohort	United States	10	NR	NR	NR	NR	NR	0	100	immunocompromised - mortality
Linnér 2014	Cohort	Sweden	67	63	42	48	16	28	NR	NR	age - mortality^ clindamycin - mortality IVIG - hospital LOS IVIG - mortality
Luca-Harari 2009	Cohort	Cyprus, Czech Republic, Denmark, Finand, France, Germany, Greece, Italy, Romania, Sweden, United Kingdom	476	NR	NR	NR	NR	NR	NR	NR	emm type - mortality^
Nelson 2016	Cohort	United States	381	NR	NR	NR	NR	19	NR	NR	age - mortality NF - mortality
O'Loughlin 2007	Cohort	United States	309	NR	NR	NR	NR	20	NR	NR	age - mortality NF - mortality
Page 2011	Cohort	Canada	16	NR	NR	NR	NR	NR	NR	NR	other - other^
Safar 2011	Cohort	New Zealand	30	NR	NR	NR	NR	17	0	100	age - mortality NF - mortality
Schwartz 1992	Case-series	United States	8	40	40	NR	NR	NR	0	100	age - mortality^ emm type - mortality^ sex - mortality
Shah 2009	Cohort	United States	192	8	49	NR	NR	NR	NR	NR	IVIG - cost^ IVIG - hospital LOS IVIG - ICU admission IVIG - ICU LOS IVIG - mechanical ventilation IVIG - mortality

Study	Study Design	Country	Number of STSS cases	Mean age	% Male	Cardiovascular Disease (%)	Diabetes (%)	Presence of Necrotizing Fasciitis (%)	Probable GAS STSS (%)	Confirmed GAS STSS (%)	Prognostic factor and outcome combination of interest reported
Sriskandan 2000	Cohort	England	7	NR	NR	NR	NR	NR	NR	NR	other - other^
Stegmayr 1992	Case-series	Sweden	11	42	64	NR	NR	NR	27	73	age - clinical cure/improvement^ age - ICU admission^ age - mechanical ventilation^ age - mortality^ hemodialysis - clinical cure/improvement hemodialysis - ICU admission hemodialysis - mechanical ventilation hemodialysis - mortality IVIG - clinical cure/improvement IVIG - ICU admission IVIG - mechanical ventilation IVIG - mortality NF - clinical cure/improvement NF - ICU admission NF - mechanical ventilation NF - mortality sex - clinical cure/improvement sex - ICU admission sex - mechanical ventilation sex - mortality
Stevens 1989	Case-series	United States	19	41	53	80	5	21	0	100	age - mortality^ emm type - mortality^ hemodialysis - mortality NF - mortality sex - mortality
Stockmann 2012	Cohort	United States	53	30 (median)	NR	58	19	32	NR	NR	age - ICU admission^ age - mortality
Tagini 2017	Case-series	Switzerland	5	18	60	NR	NR	NR	20	80	age - mortality^ emm type - mortality^ sex - mortality
Zachariadou 2013	Cohort	Greece	19	NR	NR	NR	NR	NR	0	100	age - mortality emm type - mortality^

*More than 80% of STSS cases due to group A *Streptococcus*
^Excluded from meta-analysis

NF=necrotizing fasciitis

NSAIDs=non-steroidal anti-inflammatory drugs
ICU=intensive care unit
IVIG=intravenous immunoglobulin
GAS=group A *Streptococcus*
STSS=streptococcal toxic shock syndrome
NR=not reported

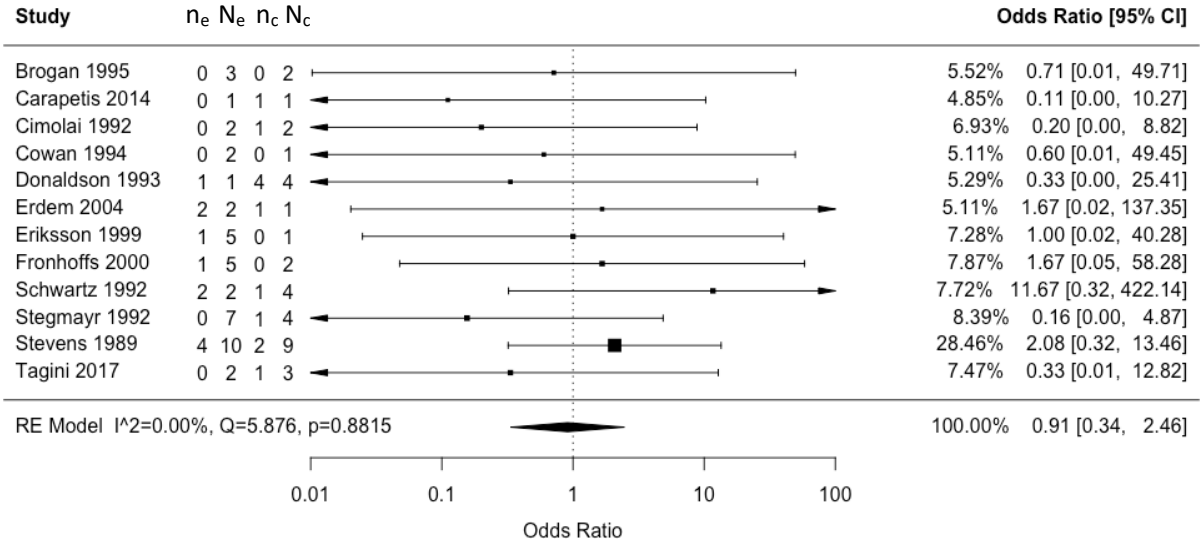
Forest plots

n_e: number of patients with the outcome exposed to or experiencing the prognostic factor (experimental group)
N_e: total number of patients exposed to or experiencing the prognostic factor (experimental group)
n_c: number of patients with the outcome not exposed to or experiencing the prognostic factor (control group)
N_c: total number of patients not exposed to or experiencing the prognostic factor (control group)

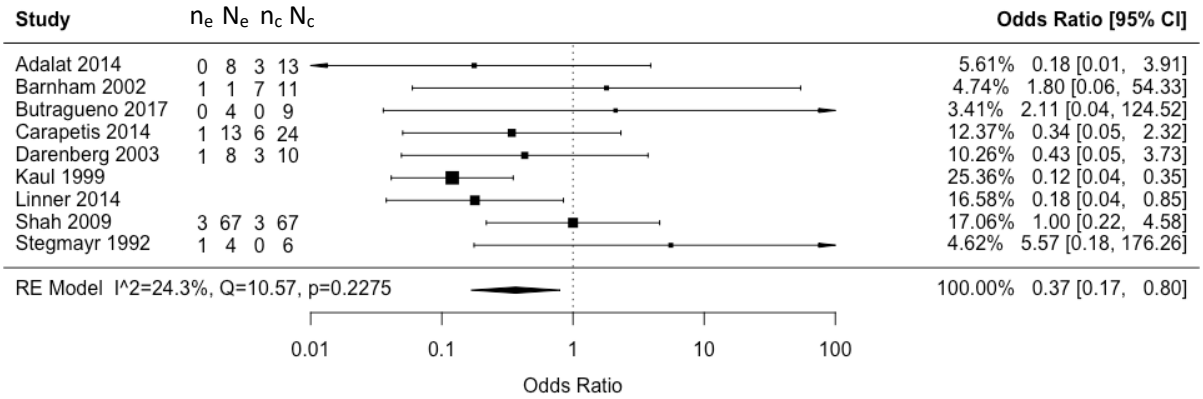
Percentages in forest plots correspond to the percent weight contribution of each study in the meta-analysis.

Mortality

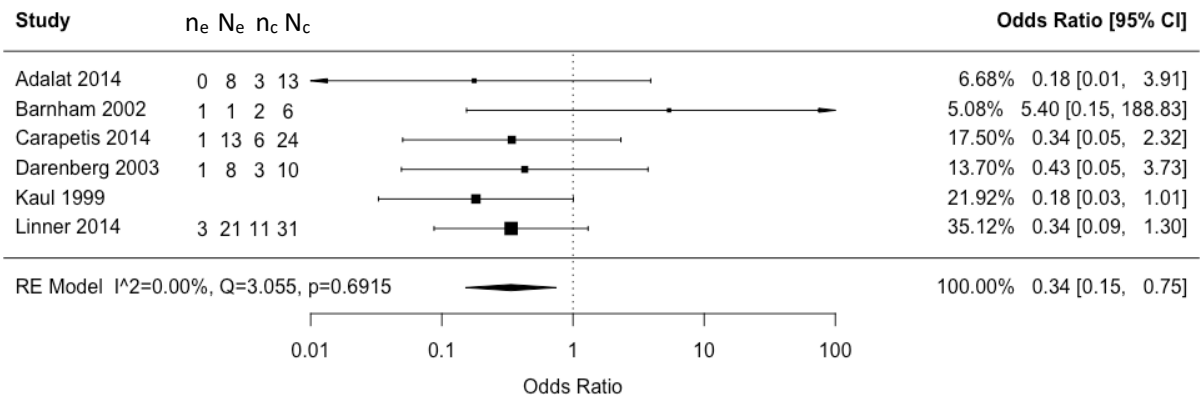
1. Sex: male vs female (reference)



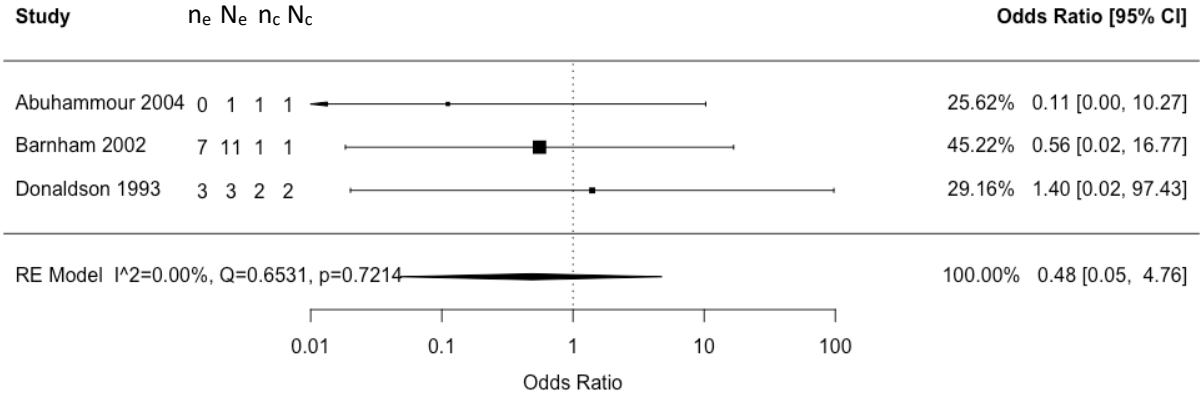
2.A) IVIG in all STSS patients: yes vs no (reference)

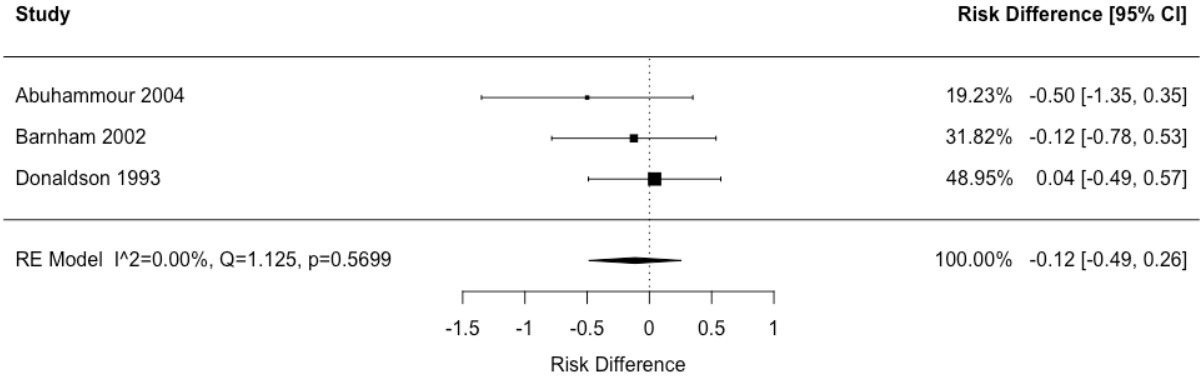


2.B) IVIG in the subset of STSS patients treated with clindamycin: yes vs no (reference)

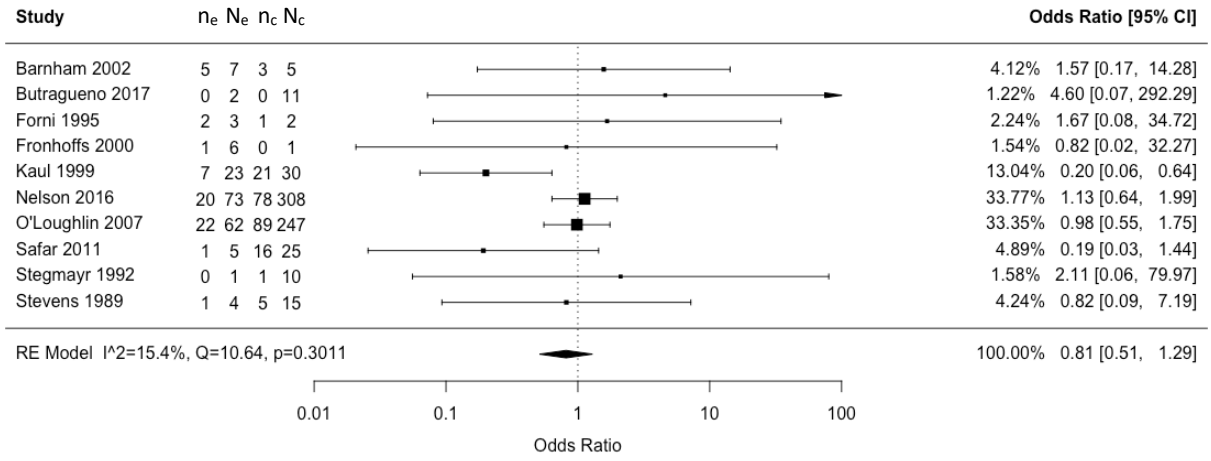


3. Any antibiotic: yes vs no (reference)

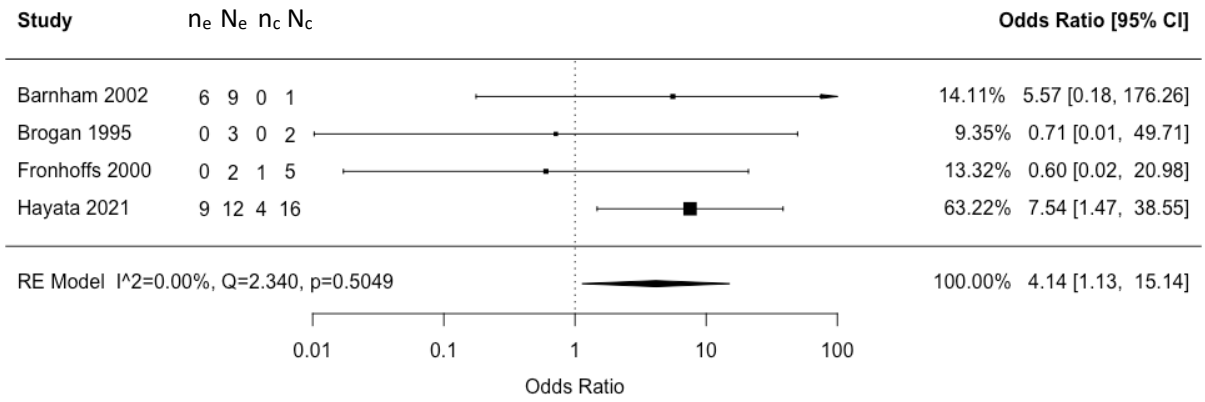




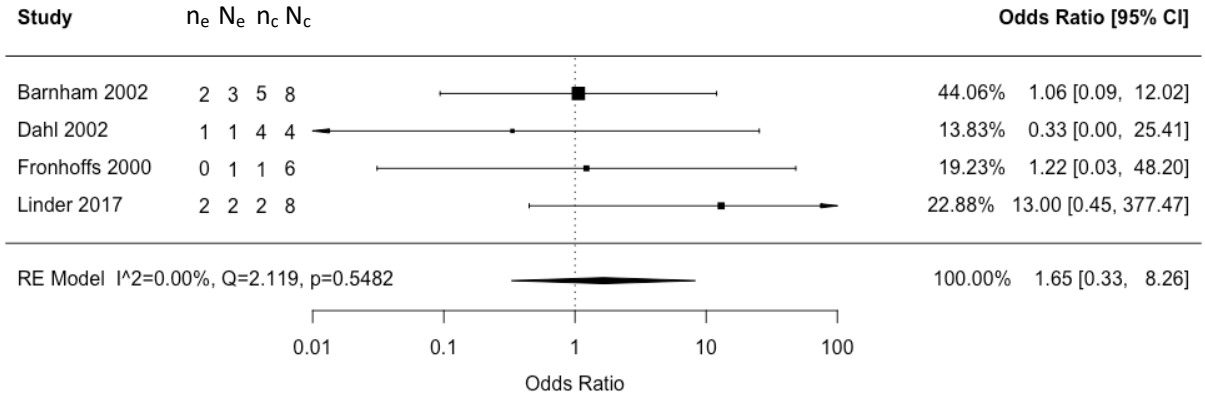
4. Necrotizing fasciitis: yes vs no (reference)



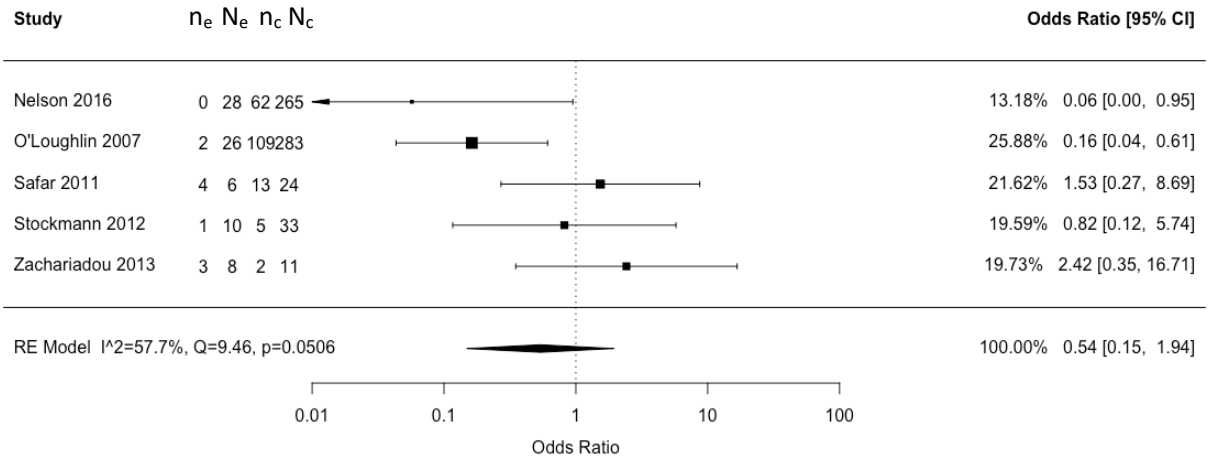
5. NSAIDs: yes vs no (reference)



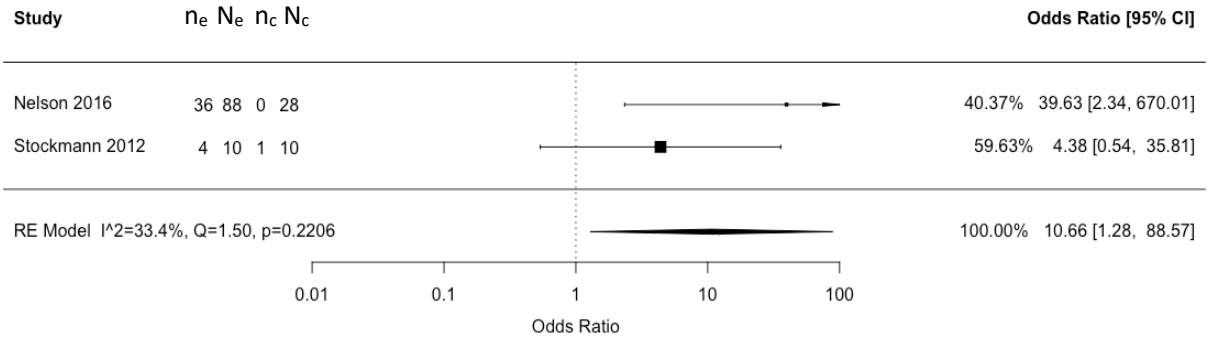
6. Immunocompromised: yes vs no (reference)



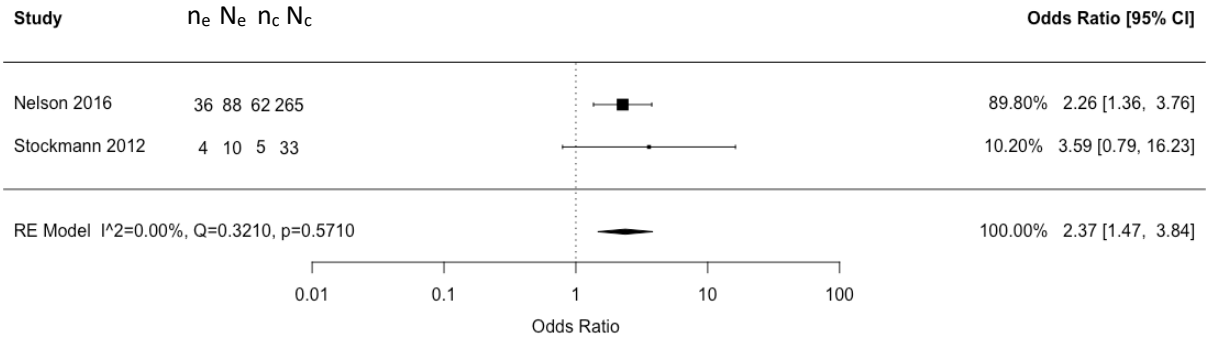
7. Age: <18 years vs 18-64 years (reference)



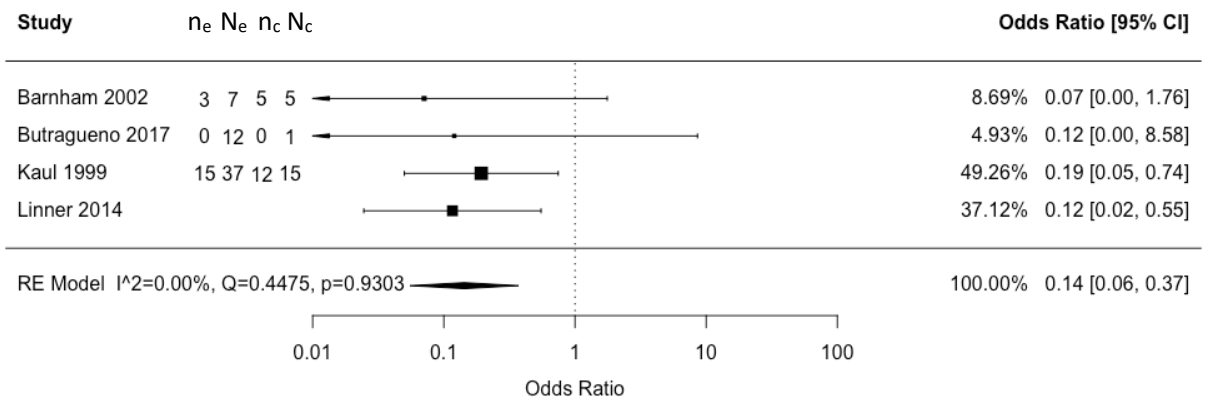
8. Age: ≥65 years vs <18 years (reference)



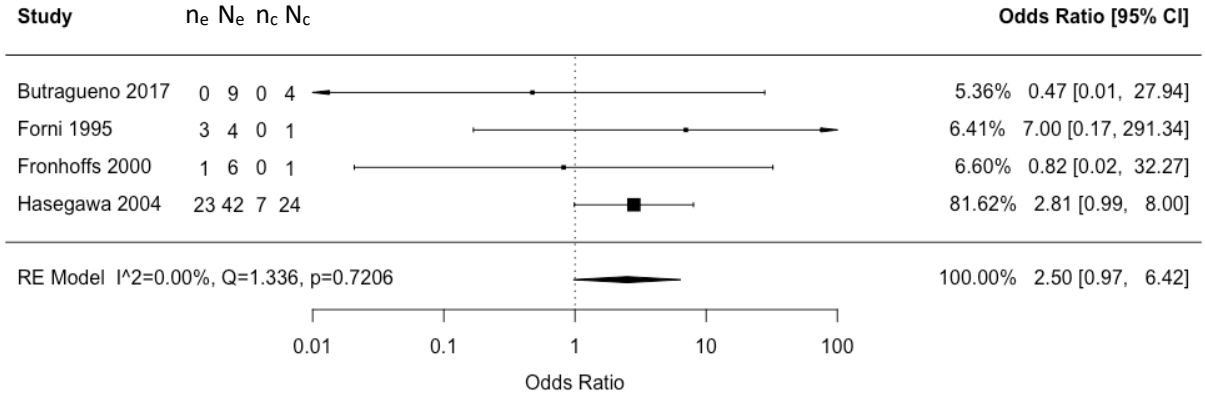
9: Age: ≥65 years vs 18-64 years (reference)

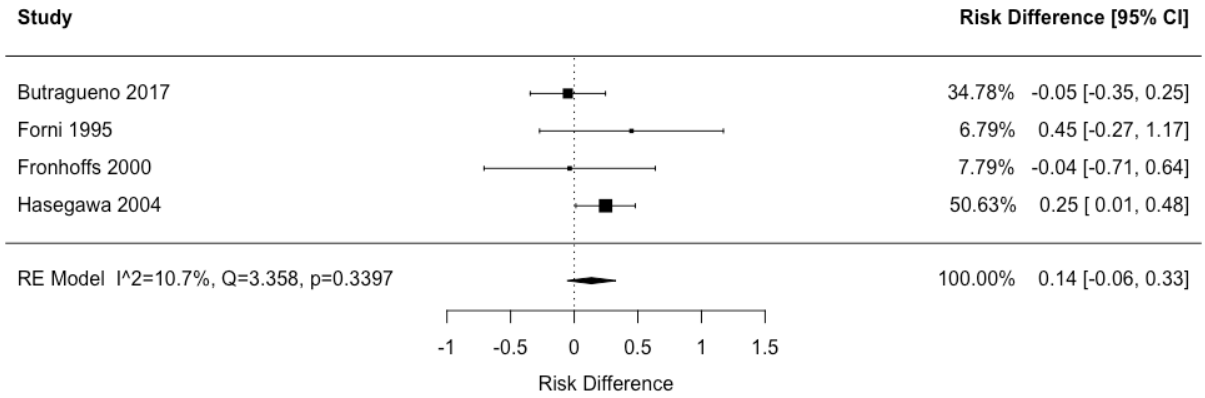


10. Clindamycin antibiotic vs no clindamycin antibiotic (reference)

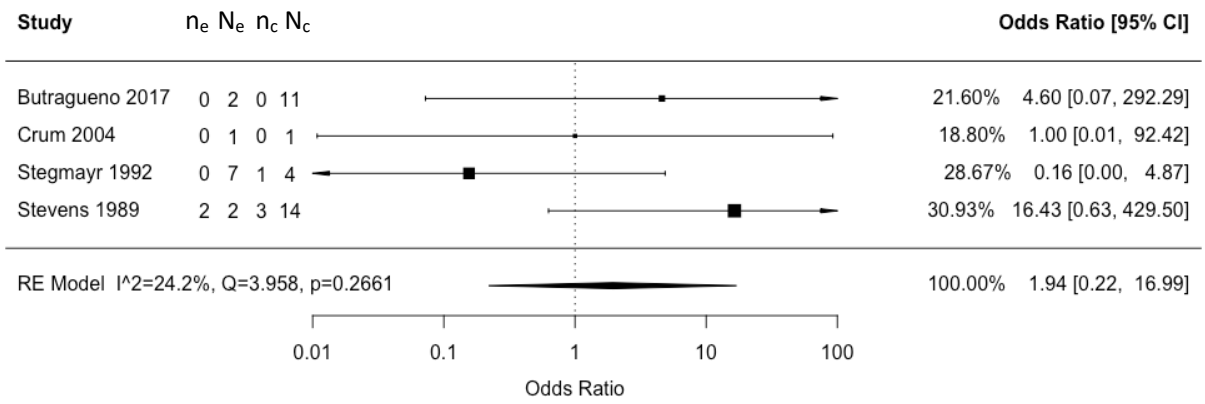


11. Acute renal failure: yes vs no (reference)





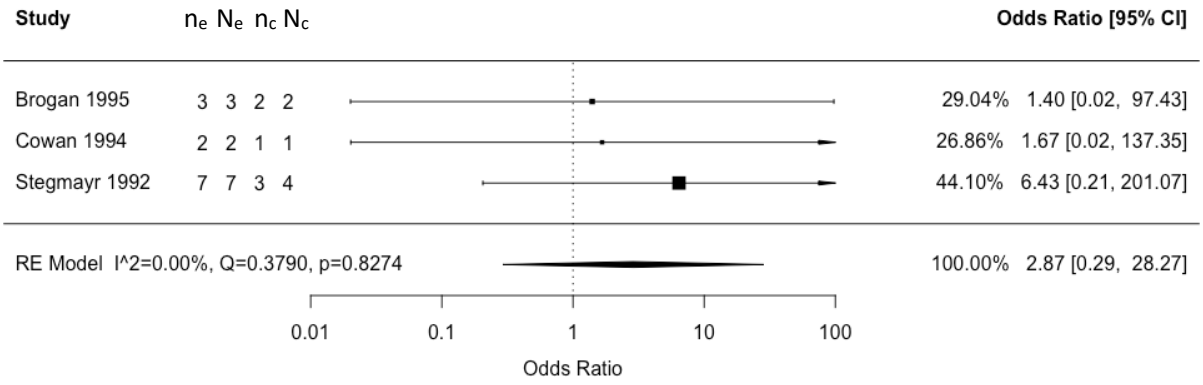
12. Hemodialysis: yes vs no (reference)

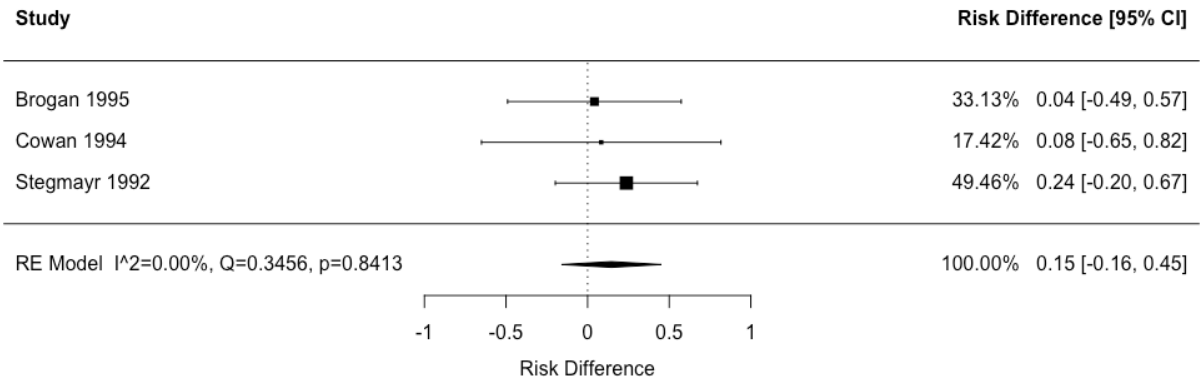


ICU admission

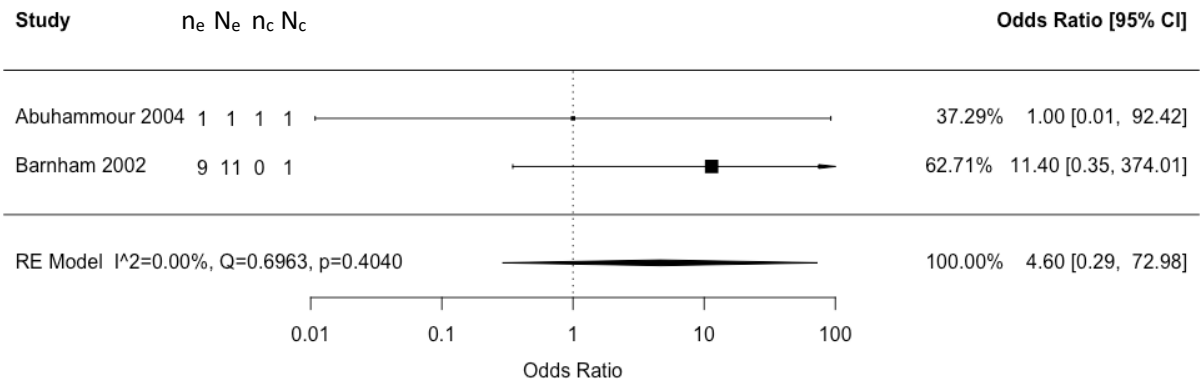
This note pertains to meta-analyses of the outcome ICU admission that include the study Stegmayr 1992. For this study, 10 of 11 STSS patients were admitted to the ICU. Despite no explicit mention of which one patient was not admitted to the ICU, our interpretation of the clinical profiles and patient-level data allowed us to deduce that patient 1 likely did not require ICU admission. We reached out to the corresponding author to confirm if our interpretation was correct, but did not receive a response.

1. Sex: male vs female (reference)

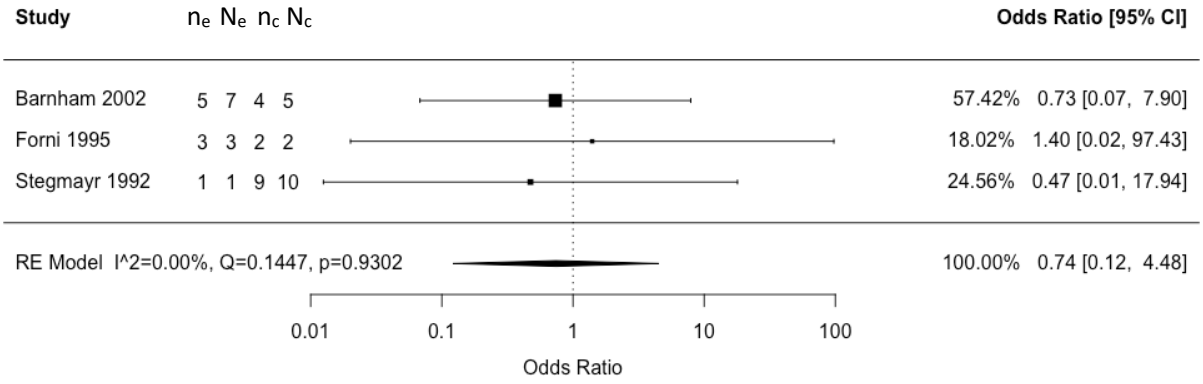




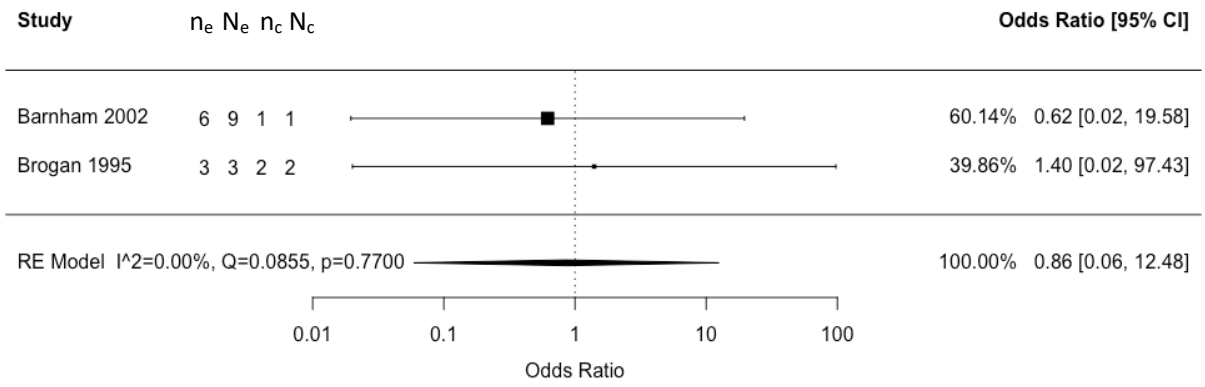
2. Any antibiotic: yes vs no (reference)

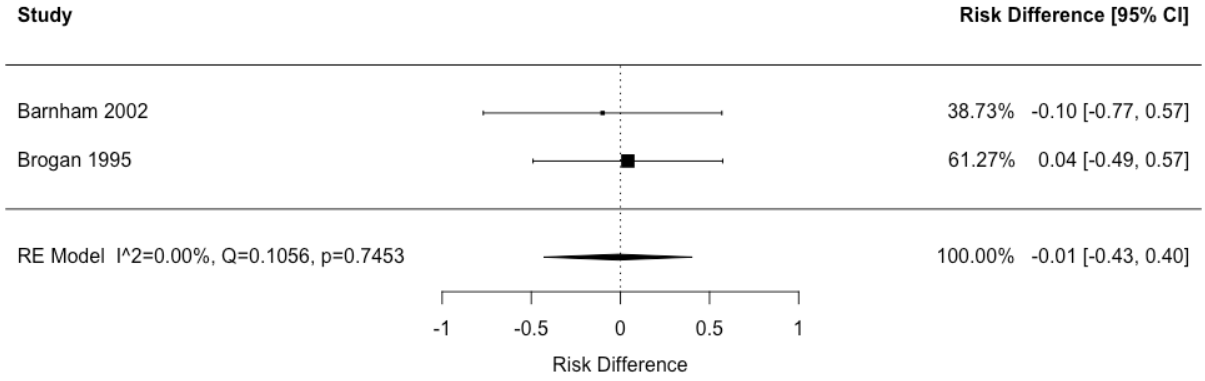


3. Necrotizing fasciitis: yes vs no (reference)

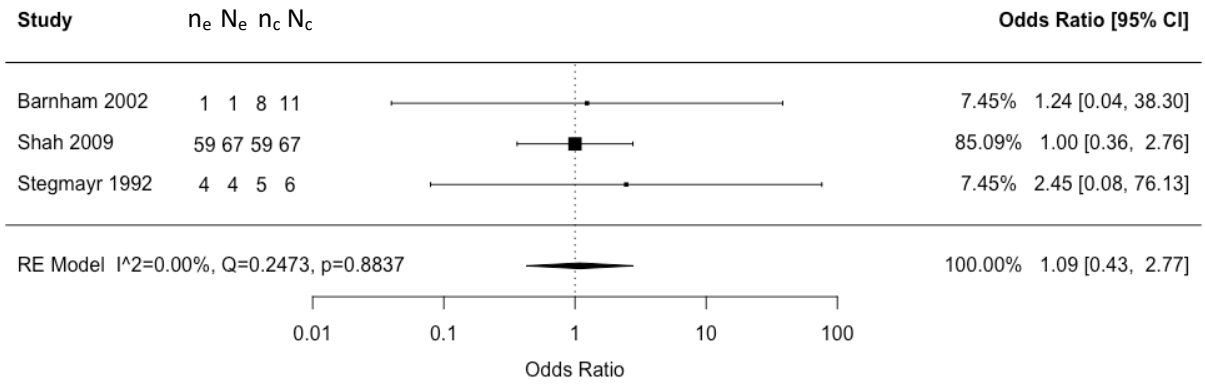


4. NSAIDs: yes vs no (reference)

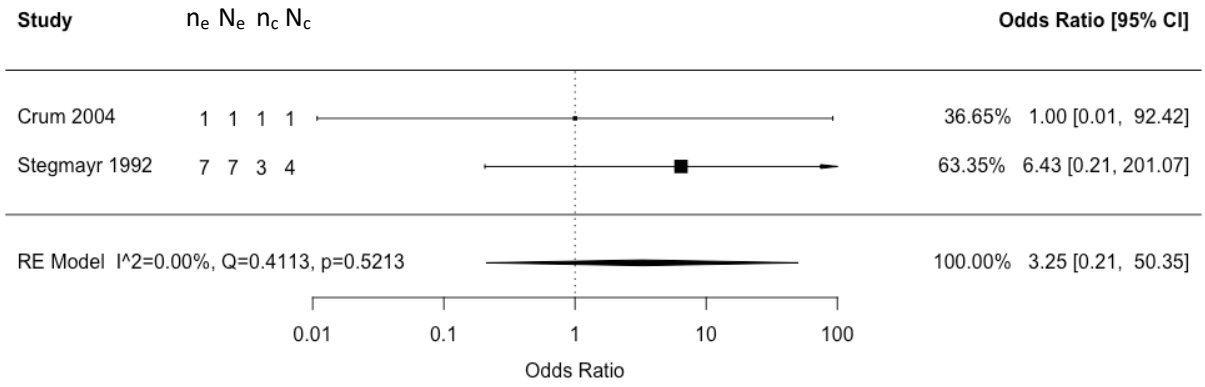




5. IVIG in all STSS patients: yes vs no (reference)

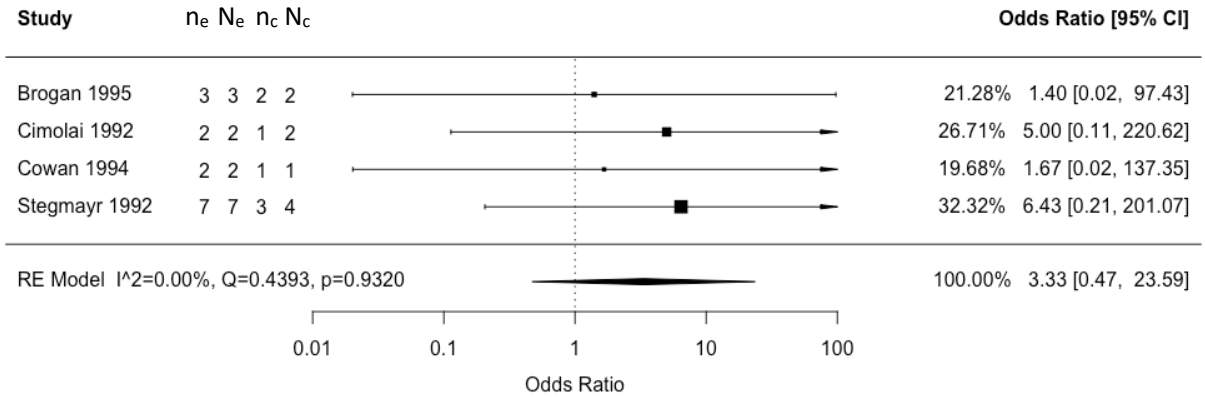


6. Hemodialysis: yes vs no (reference)

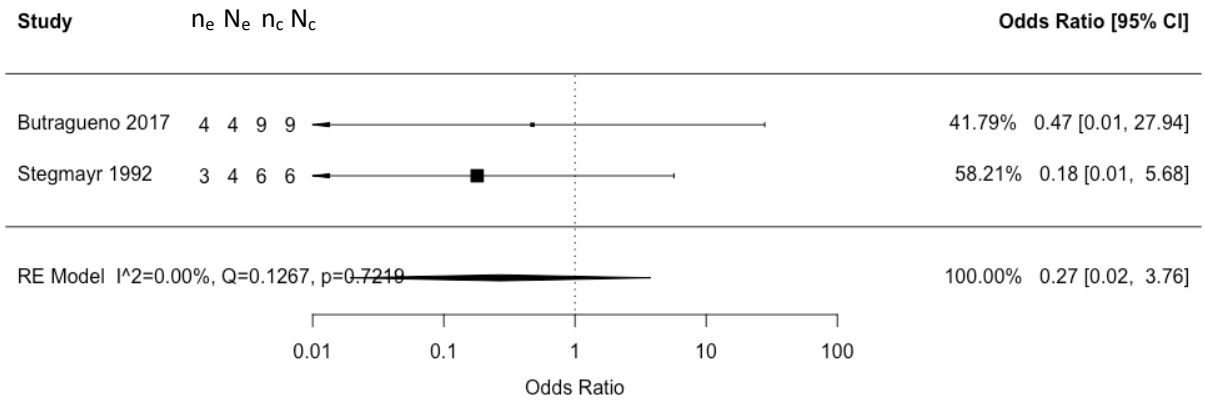


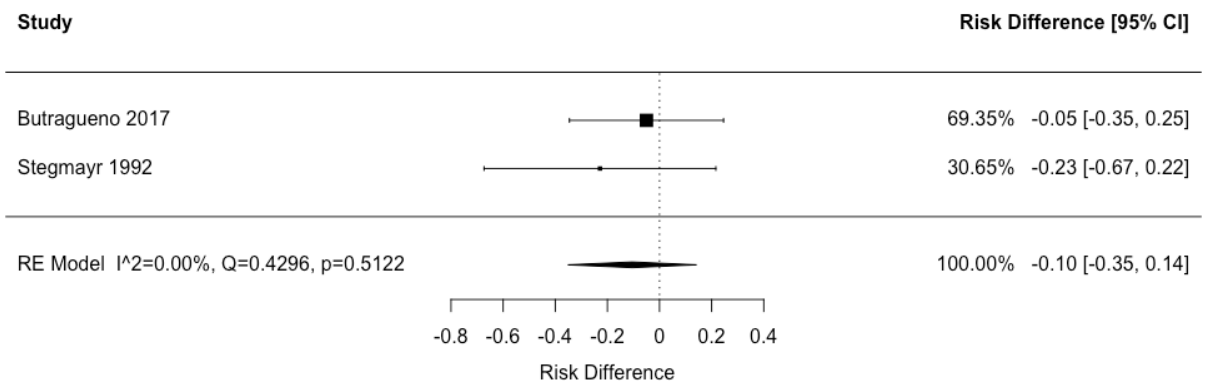
Clinical cure or improvement

1. Sex: male vs female (reference)

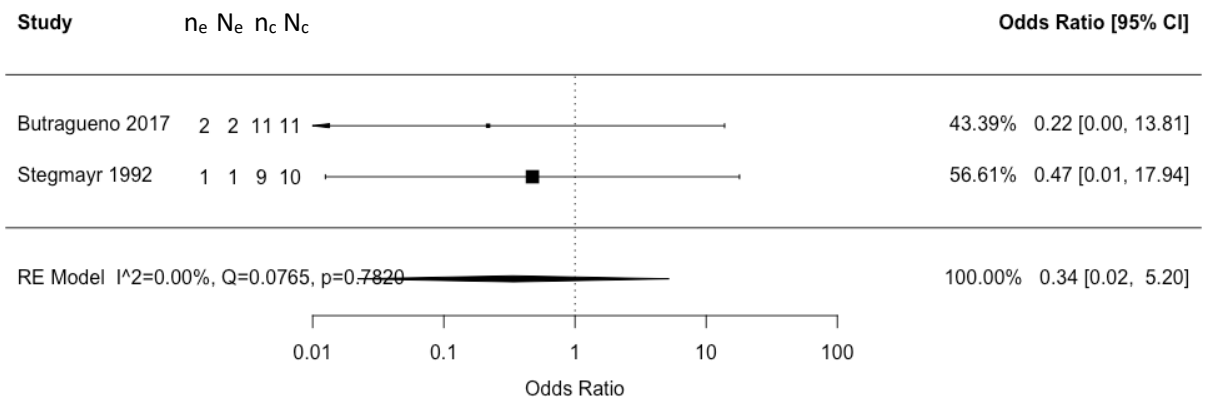


2. IVIG in all STSS patients: yes vs no (reference)

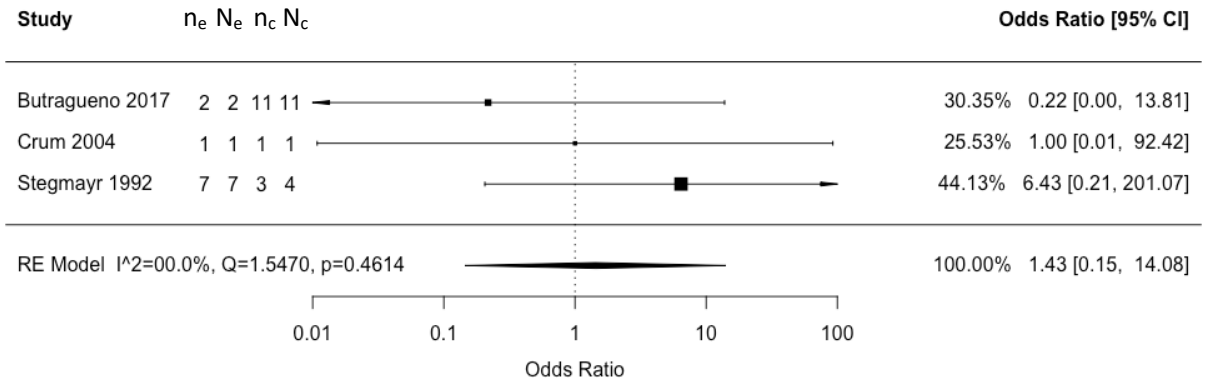


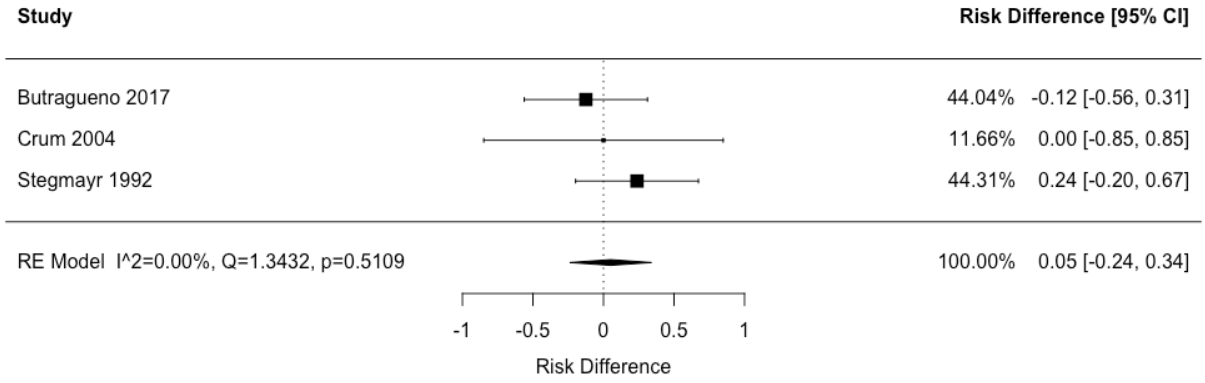


3. Necrotizing fasciitis: yes vs no (reference)



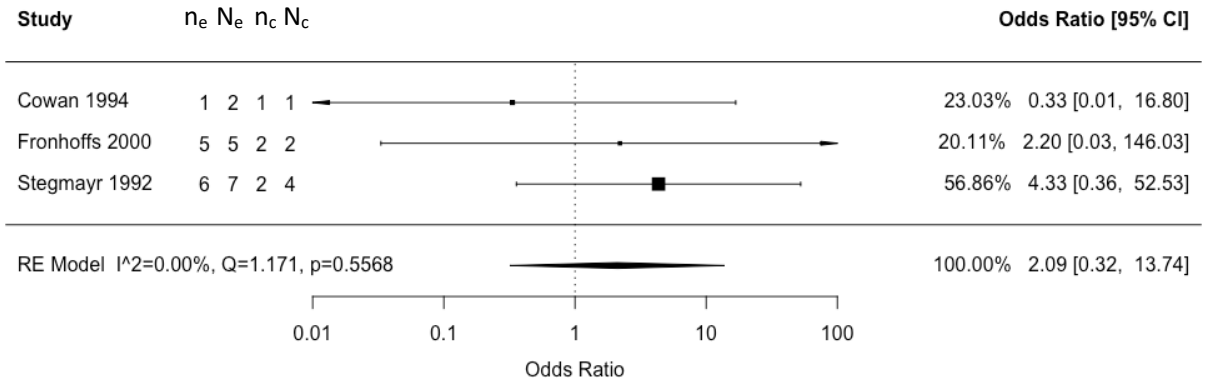
4. Hemodialysis: yes vs no (reference)

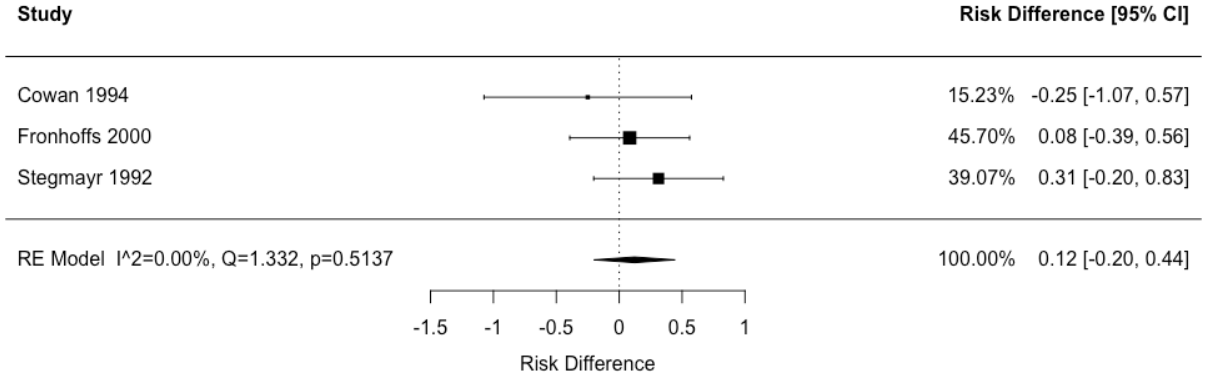




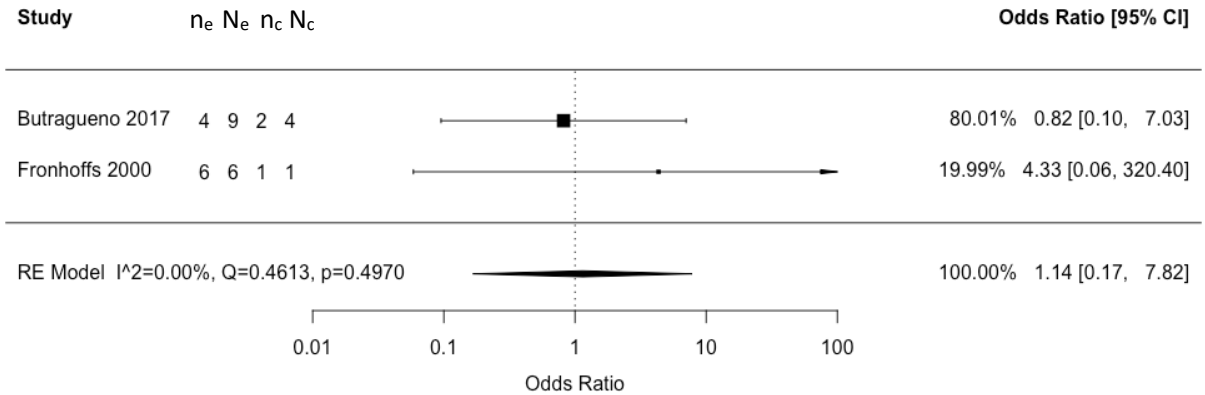
Mechanical ventilation

1. Sex: male vs female (reference)

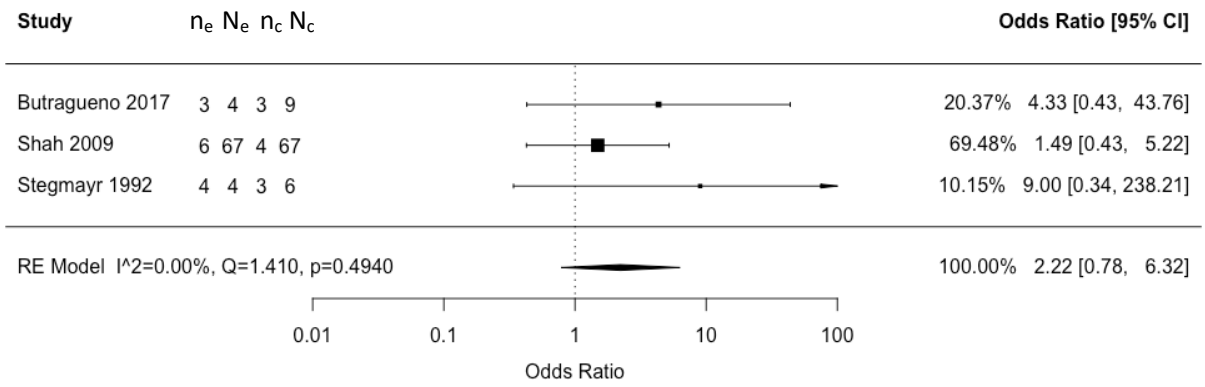




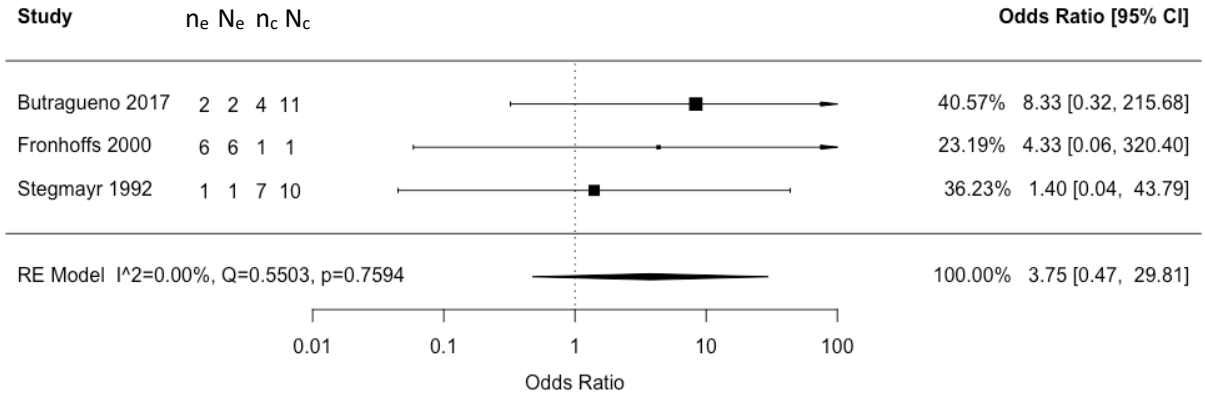
2. Acute renal failure: yes vs no (reference)



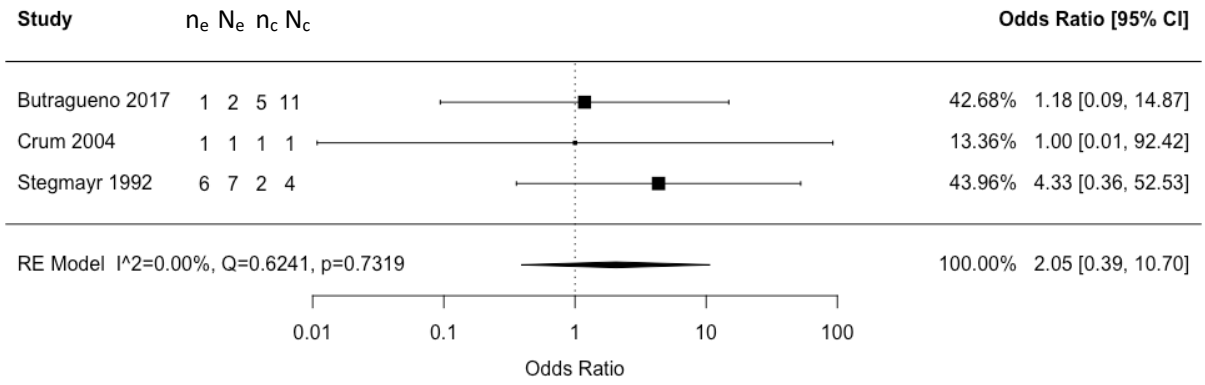
3. IVIG in all STSS patients: yes vs no (reference)



4. Necrotizing fasciitis: yes vs no (reference)

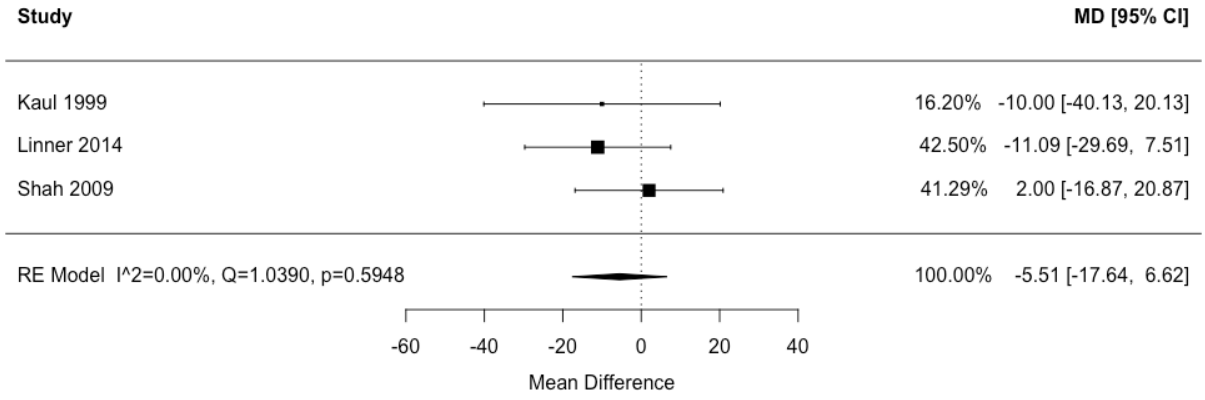


5. Hemodialysis: yes vs no (reference)



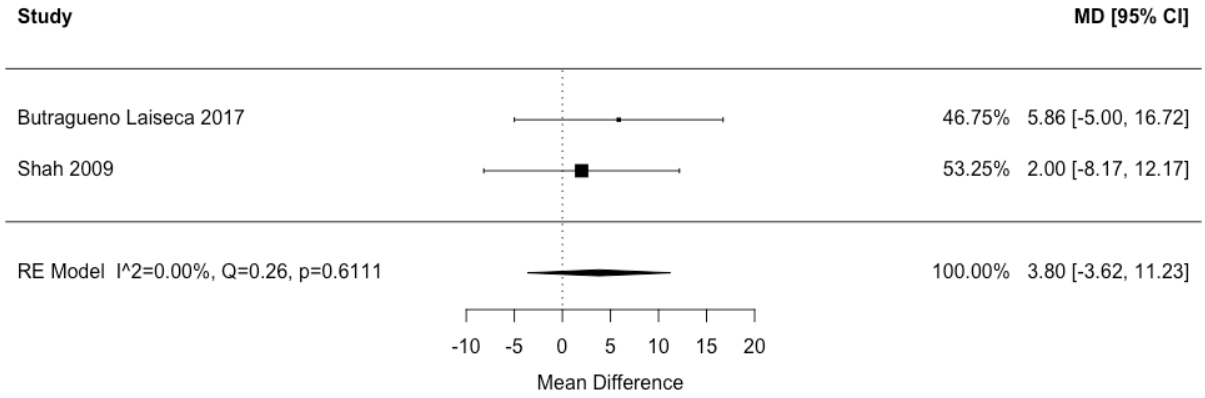
Hospital length-of-stay

1. IVIG: yes vs no (reference)



ICU length-of-stay

1. IVIG: yes vs no (reference)



Description of studies ineligible for meta-analysis by outcome

Mortality

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	4	4	
age	28	5	n=17 case-series with <10 patients, precluding the aggregation of patient-level data; n=6 study population consisted of patients all within same age category
antibiotic	3	3	
clindamycin	4	4	
early hypotension	0	0	
emmtype	7	0	n=7 variability in reporting of molecular characteristics and comparators
hemodialysis	4	4	
immunocompromised	5	4	n=1 insufficient data for meta-analysis (only p value reported)
IVIG in all STSS patients	9	9	
IVIG in clindamycin-treated patients	6	6	
NF	10	10	
NSAIDs	4	4	
sex	12	12	
timetoantibiotic	1	0	Meta-analysis precluded with only one study

(P)ICU admission

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	1	0	Meta-analysis precluded with only one study
age	9	0	n=5 case-series with <10 patients, precluding the aggregation of patient-level data; n=3 study population consisted of patients all within same age category; n=1 eligible for analysis, but meta-analysis precluded with only one study
antibiotic	2	2	
clindamycin	1	0	Meta-analysis precluded with only one study
early hypotension	0	0	
emmtype	2	0	n=2 variability in reporting of molecular characteristics and comparators
hemodialysis	2	2	
immunocompromised	1	0	Meta-analysis precluded with only one study
IVIG in all STSS patients	3	3	
IVIG in clindamycin-treated patients	0	0	
NF	3	3	
NSAIDs	2	2	
sex	3	3	
timetoantibiotic	0	0	

Clinical cure or improvement

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	1	0	Meta-analysis precluded with only one study
age	8	0	n=6 case-series with <10 patients, precluding the aggregation of patient-level data; n=2 study population consisted of patients all within same age category
antibiotic	1	0	Meta-analysis precluded with only one study
clindamycin	1	0	Meta-analysis precluded with only one study
earlyhypotension	0	0	
emmtype	0	0	
hemodialysis	3	3	
immunocompromised	0	0	
IVIG in all STSS patients	2	2	
IVIG in clindamycin-treated patients	0	0	
NF	2	2	
NSAIDs	1	0	Meta-analysis precluded with only one study
sex	4	4	
timetoantibiotic	0	0	

Mechanical ventilation

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	2	2	
age	5	0	n=3 case-series with <10 patients, precluding the aggregation of patient-level data; n=2 study population consisted of patients all within same age category
antibiotic	0	0	
clindamycin	1	0	Meta-analysis precluded with only one study
earlyhypotension	0	0	
emmtype	0	0	
hemodialysis	3	3	
immunocompromised	1	0	Meta-analysis precluded with only one study
IVIG in all STSS patients	3	3	
IVIG in clindamycin-treated patients	0	0	
NF	3	3	
NSAIDs	1	0	Meta-analysis precluded with only one study
sex	3	3	
timetoantibiotic	0	0	

Hospital length-of-stay

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	0	0	
age	2	0	n=2 case-series with <10 patients, precluding the aggregation of patient-level data
antibiotic	0	0	
clindamycin	0	0	
early hypotension	0	0	
emmtype	0	0	
hemodialysis	0	0	
immunocompromised	0	0	
IVIG in all STSS patients	3	3	
IVIG in clindamycin-treated patients	0	0	
NF	0	0	
NSAIDs	1	0	Meta-analysis precluded with only one study
sex	1	0	Meta-analysis precluded with only one study
timetoantibiotic	0	0	

Duration of mechanical ventilation

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	0	0	
age	0	0	
antibiotic	0	0	
clindamycin	0	0	
early hypotension	0	0	
emmtype	0	0	
hemodialysis	0	0	
immunocompromised	0	0	
IVIG in all STSS patients	1	0	Meta-analysis precluded with only one study
IVIG in clindamycin-treated patients	0	0	
NF	0	0	
NSAIDs	0	0	
sex	0	0	
timetoantibiotic	0	0	

ICU length-of-stay

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	0	0	
age	3	0	n=2 case-series with <10 patients, precluding the aggregation of patient-level data; n=1 study population consisted of patients all within same age category
antibiotic	0	0	
clindamycin	1	0	Meta-analysis precluded with only one study
early hypotension	0	0	
emmtype	0	0	
hemodialysis	0	0	
immunocompromised	0	0	
IVIG in all STSS patients	2	2	
IVIG in clindamycin-treated patients	0	0	
NF	1	0	Meta-analysis precluded with only one study
NSAIDs	1	0	Meta-analysis precluded with only one study
sex	2	0	n=1 study with one person in each group > cannot calculate mean; n=1 meta-analysis precluded with only one study
timetoantibiotic	0	0	

Change in SOFA score from baseline

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	0	0	
age	0	0	
antibiotic	0	0	
clindamycin	0	0	
early hypotension	0	0	
emmtype	0	0	
hemodialysis	0	0	
immunocompromised	0	0	
IVIG in all STSS patients	1	0	Meta-analysis precluded with only one study
IVIG in clindamycin-treated patients	0	0	
NF	0	0	
NSAIDs	0	0	
sex	0	0	
timetoantibiotic	0	0	

Functional status

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	0	0	
age	0	0	
antibiotic	0	0	
clindamycin	0	0	
early hypotension	0	0	
emmtype	0	0	
hemodialysis	0	0	
immunocompromised	0	0	
IVIG in all STSS patients	0	0	
IVIG in clindamycin-treated patients	0	0	
NF	0	0	
NSAIDs	0	0	
sex	0	0	
timetoantibiotic	0	0	

Health related quality of life

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	0	0	
age	0	0	
antibiotic	0	0	
clindamycin	0	0	
early hypotension	0	0	
emmtype	0	0	
hemodialysis	0	0	
immunocompromised	0	0	
IVIG in all STSS patients	0	0	
IVIG in clindamycin-treated patients	0	0	
NF	0	0	
NSAIDs	0	0	
sex	0	0	
timetoantibiotic	0	0	

Cost

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	0	0	
age	0	0	
antibiotic	0	0	
clindamycin	0	0	
early hypotension	0	0	
emmtype	0	0	
hemodialysis	0	0	
immunocompromised	0	0	
IVIG in all STSS patients	1	0	Meta-analysis precluded with only one study
IVIG in clindamycin-treated patients	0	0	
NF	0	0	
NSAIDs	0	0	
sex	0	0	
timetoantibiotic	0	0	

Time to mortality

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	0	0	
age	0	0	
antibiotic	0	0	
clindamycin	0	0	
early hypotension	0	0	
emmtype	0	0	
hemodialysis	0	0	
immunocompromised	0	0	
IVIG in all STSS patients	2	0	n=1 study with one person in each group > cannot calculate mean; n=1 meta-analysis precluded with only one study
IVIG in clindamycin-treated patients	2	0	n=1 study with one person in each group > cannot calculate mean; n=1 meta-analysis precluded with only one study
NF	0	0	
NSAIDs	0	0	
sex	0	0	
timetoantibiotic	0	0	

Time to clinical improvement or resolution of shock

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	0	0	
age	0	0	
antibiotic	0	0	
clindamycin	0	0	
early hypotension	0	0	
emmtype	0	0	
hemodialysis	0	0	
immunocompromised	0	0	
IVIG in all STSS patients	1	0	Meta-analysis precluded with only one study
IVIG in clindamycin-treated patients	1	0	Meta-analysis precluded with only one study
NF	0	0	
NSAIDs	0	0	
sex	0	0	
timetoantibiotic	0	0	

MOOSE (Meta-analyses Of Observational Studies in Epidemiology) Checklist

A reporting checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Reporting of Background		
Problem definition		
Hypothesis statement		
Description of Study Outcome(s)		
Type of exposure or intervention used		
Type of study design used		
Study population		
Reporting of Search Strategy		
Qualifications of searchers (eg, librarians and investigators)		
Search strategy, including time period included in the synthesis and keywords		
Effort to include all available studies, including contact with authors		
Databases and registries searched		
Search software used, name and version, including special features used (eg, explosion)		
Use of hand searching (eg, reference lists of obtained articles)		
List of citations located and those excluded, including justification		
Method for addressing articles published in languages other than English		
Method of handling abstracts and unpublished studies		
Description of any contact with authors		
Reporting of Methods		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested		
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)		
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)		
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate		

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results		
Assessment of heterogeneity		
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated		
Provision of appropriate tables and graphics		
Reporting of Results		
Table giving descriptive information for each study included		
Results of sensitivity testing (eg, subgroup analysis)		
Indication of statistical uncertainty of findings		
Reporting of Discussion		
Quantitative assessment of bias (eg, publication bias)		
Justification for exclusion (eg, exclusion of non–English-language citations)		
Assessment of quality of included studies		
Reporting of Conclusions		
Consideration of alternative explanations for observed results		
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)		
Guidelines for future research		
Disclosure of funding source		

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PROGNOSTIC FACTORS FOR STREPTOCOCCAL TOXIC SHOCK SYNDROME: SYSTEMATIC REVIEW AND META-ANALYSIS

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PROGNOSTIC FACTORS FOR STREPTOCOCCAL TOXIC SHOCK SYNDROME: SYSTEMATIC REVIEW AND META-ANALYSIS

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Key words: streptococcal toxic shock syndrome (STSS); systematic review; meta-analysis

Word count: 4320

ABSTRACT

Objective: To quantify the prognostic effects of demographic and modifiable factors in streptococcal toxic shock syndrome (STSS).

Methods and analysis: We searched MEDLINE and EMBASE from inception to 6 August 2021, along with CINAHL from inception to 16 September 2021 and citations of included studies. Pairs of reviewers independently screened potentially eligible studies of patients with GAS-induced STSS that quantified the association between at least one prognostic factor and outcome of interest. We performed random-effects meta-analysis after duplicate data extraction and risk of bias assessments. We rated the certainty of evidence using the GRADE approach.

Results: One randomized trial and 39 observational studies were eligible (n=1,914 patients). We found a statistically significant association between clindamycin treatment and mortality (n=144; odds ratio [OR] 0.14, 95% CI 0.06 to 0.37), but the certainty of evidence was low. Within clindamycin-treated STSS patients, we found a statistically significant association between intravenous immunoglobulin (IVIG) treatment and mortality (n=188; OR 0.34, 95% CI 0.15 to 0.75), but the certainty of evidence was also low. The odds of mortality may increase in patients ≥65 years when compared to patients 18-64 years (n=396; OR 2.37, 95% CI 1.47 to 3.84), but the certainty of evidence was low. We are uncertain whether non-steroidal anti-inflammatory drugs (NSAIDs) increased the odds of mortality (n=50; OR 4.14, 95% CI 1.13 to 15.14; very low certainty). Results failed to show a significant association between any other prognostic factor and outcome combination (very low to low certainty evidence) and no studies quantified the association between a prognostic factor and morbidity post-infection in STSS survivors.

Conclusions: Treatment with clindamycin and within clindamycin-treated patients, IVIG, was each significantly associated with mortality, but the certainty was evidence was low. Future research should focus on morbidity post-infection in STSS survivors.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Strengths of this review include its systematic and explicit search of the literature, capture of a wide breadth of patient-important outcomes within and outside of critical care and the use of meta-analysis to increase statistical power in studying relationships between prognostic factors and outcomes in STSS patients.
- These strengths directly address limitations of an existing narrative synthesis of STSS prognosis restricted to the critical care setting.
- In the absence of large cohort studies and randomized trials, conclusions for STSS prognosis in this review are limited by very low to low certainty evidence.
- A limitation of the evidence is the lack of long-term outcome data reported, including morbidity post-infection in STSS survivors.

Introduction

Streptococcal toxic shock syndrome (STSS) is an acute and severe life-threatening complication of predominantly invasive Group A *Streptococcus* (GAS) infections. STSS is relatively uncommon, but is fatal [1]. Using US data from 2000 to 2004, the Center for Diseases Control and Prevention estimated an annual incidence rate of 0.2 cases per 100,000 people and a fatality rate of 36% [2]. STSS has important consequences for morbidity as well, in which patients may require radical surgical debridement, and patients with organ failure may have permanent respiratory and renal insufficiency [1].

Although extensive multidisciplinary clinical management efforts by intensivists, infectious disease specialists, and surgeons have curbed STSS all-cause mortality [1], data on the natural history of long-term sequelae in surviving patients, such as renal, respiratory and neuropsychiatric complications, are sparse [1-4]. Published studies of prognostic and treatment factors for STSS have consistently focused on associations with all-cause mortality [5-14], with few reporting on outcomes capturing the morbidity post-infection in STSS survivors [7, 12]. Furthermore, a thorough and systematic review to corroborate this evidence is lacking. A narrative review of STSS was limited by the lack of a systematic or explicit search of the literature, it included studies that were only narratively synthesized, and the focus was limited to studies within a critical care setting [1].

Understanding prognosis of STSS is important for patients, clinicians, and healthcare decision makers. We conducted a systematic review to summarize the prognostic and treatment factors, and outcomes of STSS. We aimed to capture a wide breadth of patient-important outcomes with follow up that included both short- and long-term outcomes within and outside of critical care.

Materials and methods

We registered a protocol for the present systematic review and meta-analysis with PROSPERO (CRD42020166961) [15, 16]. We report this systematic review and meta-analysis following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analyses of Observational Studies in Epidemiology (MOOSE) checklists [17, 18]. Decisions regarding criteria for study inclusion, search methods for identification of

studies, data collection, risk of bias, evaluation of the certainty of evidence and analysis were established a priori.

Search strategy and selection criteria

We searched MEDLINE (OVID interface, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, 1946 to 6 August 2021) and EMBASE (OVID interface, 1974 to 6 August 2021) from inception to 6 August 2021, with no restrictions on publication date. We searched the Cumulative Index to Nursing And Allied Health Literature (CINAHL), excluding MEDLINE records, from inception to 16 September 2021. We applied search filters for randomized controlled trials and non-randomized studies (cohort, case-control and case series with at least 2 STSS patients) [19, 20], and tailored search strategies to each database. We restricted included studies to the English language to facilitate screening of full-texts [21, 22] and searched citations of included studies to minimize the risk of failing to include relevant studies.

We included studies of randomized and non-randomized designs that reported the association of at least one prognostic factor of interest on at least one outcome of interest, and compared GAS-induced STSS patients with the prognostic factor of interest (i.e. exposed) to GAS-induced STSS patients without the prognostic factor of interest (i.e. unexposed). Studies of patients with microbiologically confirmed STSS, probable cases of STSS and patients with clinical evidence of STSS as defined by study authors and generally consistent with the below criteria were eligible [3, 23]. Clinical evidence of STSS included hypotension and at least two of the following: renal impairment, coagulopathy, liver function abnormality, acute respiratory distress syndrome, generalized erythematous macular rash (with desquamation), soft-tissue necrosis (including necrotizing fasciitis, myositis or gangrene), or meningitis. Probable cases of STSS were defined as meeting clinical evidence with GAS isolated from a non-sterile site (e.g. throat, sputum, superficial skin lesion) or antigen detected. Confirmed cases of STSS were defined as meeting clinical evidence with GAS isolated from a sterile site (e.g. blood, cerebrospinal fluid, deep tissue specimen taken during surgery) [3, 23]. Demographic, comorbidity, infection, modifiable and process variables were prognostic factors of interest. Informed by clinical expertise in the review team, we selected outcomes based on importance to patients. Further, we aimed to capture the long-term sequelae in patients surviving STSS [1, 2, 4]. We chose the

following outcomes of interest: (time to) mortality, hospital length-of-stay, pediatric (P) intensive care unit (ICU) admission, (P)ICU length-of-stay, mechanical ventilation, duration of mechanical ventilation, (time to) clinical cure/improvement or resolution of shock, change in Sequential Organ Failure Assessment (SOFA) score from baseline, functional status (e.g. physical component summary (PCS) score on the 36-item short form health survey (SF-36)) and health related quality of life (HRQoL). We also extracted on cost outcomes, which are relevant to hospital and patient payees.

We excluded case reports and conference abstracts, and studies in which the population was less than 80% GAS-induced STSS cases (i.e. toxic shock syndrome of bacterial aetiologies other than GAS made up more than 20% of the study population). Because prognostic evidence in STSS patients is scarce [1, 2, 4], we did not apply any restrictions based on analytical method (e.g. conducting an adjusted, multivariable analysis) or sample size.

Using a systematic review software, Rayyan [24], following training and calibration exercises, pairs of reviewers independently screened all titles and abstracts, followed by full-texts of records that were identified as potentially eligible. When necessary, consensus was reached through discussion between the review pair, and arbitration by a senior co-investigator in the absence of consensus.

Data analysis

For each eligible study, pairs of reviewers extracted data independently using a standardized, pilot tested data extraction form. Reviewers collected information on study characteristics (study design as defined by study authors, sample size, country), patient characteristics (age, sex), disease characteristics (confirmed vs probable STSS, presence of necrotizing fasciitis), prognostic factors and outcomes of interest (means or medians and measures of variability for continuous outcomes and the proportion of participants who experienced an event for dichotomous outcomes). If multiple time points were reported for outcomes of interest, we extracted all time points. To minimize risk of confounding associated with prognostic effect estimates on dichotomous outcomes in non-randomized studies, we preferentially extracted adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CI) over proportions

when both were reported. We used the proportions to calculate crude ORs when no adjusted ORs were provided. Reviewers resolved discrepancies by discussion and, when necessary, with adjudication by a senior co-investigator.

Following training and calibration exercises, reviewers, independently and in duplicate, used the Quality in Prognosis Studies (QUIPS) tool to rate each prognostic factor and outcome combination at low, moderate or high risk of bias. Based on prespecified sets of questions, we assessed risk of bias across the following domains: participation, attrition, prognostic factor measurement, outcome measurement, confounding, and statistical analysis and reporting [25]. For studies addressing more than one prognostic factor and outcome combination, we reported the highest risk of bias rating among the prognostic factor and outcome combinations within a study for each domain. In addition to assessing risk of bias at the domain-level as outlined in the QUIPS tool, we applied the following rules to assess risk of bias overall at the study-level. We rated overall study risk of bias as low if the study was prospective and five or more domains were assessed as low risk of bias, and high if two or more domains were assessed as high risk of bias. All other studies were rated as moderate risk of bias overall. Due to high risk of selection bias and residual confounding, we rated all case series as high risk of bias overall. Reviewer pairs resolved discrepancies by discussion and, when needed, with adjudication by a senior co-investigator.

Pairs of reviewers used the grading of recommendations, assessment, development, and evaluation (GRADE) approach to independently assess the certainty of prognostic evidence for each meta-analysed outcome. Criteria for rating the certainty for each prognostic factor and outcome as high, moderate, low, or very low, included considerations of risk of bias, inconsistency, indirectness, size and precision of the association and publication bias [26, 27]. Judgments of imprecision for this systematic review were made using a minimally contextualised approach. This approach considers whether confidence intervals include the null effect. The supplementary file presents the detailed guidance we developed to facilitate the certainty of the evidence assessment in this review. To facilitate interpretation of the results in which the summary measure was an OR, we used the median event rate in the reference group of studies reporting proportions to calculate baseline risks and subsequently calculated absolute effects.

GRADE evidence summaries (Summary of Findings tables) were generated in the MAGIC Authoring and Publication Platform (www.magicapp.org).

When at least two included studies reported on the same prognostic factor and outcome in patients with GAS-induced STSS, we conducted DerSimonian and Laird random-effects meta-analyses using the *metafor* package in R version 4.0.4 (R Studio, Boston, MA, USA) [28]. We summarised the effects of prognostic factors on dichotomous outcomes using ORs and corresponding 95% CI, and on continuous outcomes using mean differences and corresponding 95% CI. For prognostic factor and dichotomous outcome combinations in which every patient in the reference arm experienced the outcome, we summarised the effects by directly calculating risk differences and corresponding 95% CI. We set the criterion for statistical significance at alpha = 0.05. Visual inspection of forest plots and the chi-square test were performed to evaluate heterogeneity. We interpreted an I^2 statistic value of 0%-40%, 30%-60%, 50%-90%, or 75%-100% as not likely important, moderate, substantial, or considerable heterogeneity, respectively [29]. If an I^2 statistic value was within a range of overlapping values (e.g. 80%), we would interpret heterogeneity as more important (e.g. considerable instead of substantial) if we observed inconsistent magnitudes and directions of summary estimates upon visual inspection of the forest plots, and the chi-square test was significant [29]. For meta-analyses of continuous outcomes, we imputed means and standard deviations for studies reporting medians and (interquartile) ranges, respectively [30, 31].

Patient-level data from case-series were aggregated when possible to enable comparative analysis via meta-analysis. We planned to perform a regression analysis for each study for which age was reported at the patient level to generate a study and age category (0 to 17 years old vs 18 to 64 years old vs 65 years old or older) specific OR that could be used in meta-analysis when a study had at least 10 observations for continuous outcomes and 10 events for dichotomous outcomes; however, no study met the sample size or event number requirements. Further, scarcity and variability of data precluded our plan to narratively synthesize the evidence from included studies for which meta-analysis of a prognostic factor and outcome combination was not possible.

The analysis plan included performing subgroup analyses of STSS patients treated with clindamycin vs no clindamycin, STSS patients with necrotizing fasciitis vs without necrotizing fasciitis, age (0 to 17 years old vs 18 to 64 years old vs 65 years old or older), sex (male vs female) and risk of bias (high vs moderate vs low) when at least two studies were present for each subgroup. Because select meta-analyses were limited by small numbers of events, we performed a post-hoc sensitivity analysis using the Peto method for meta-analysis, which is recommended for meta-analysis of rare events [32], and compared the results to those from the DerSimonian and Laird method we applied in this review.

Patient and public involvment

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Results

After screening 25,397 titles and abstracts and 282 full texts, 40 studies that reported on the association between at least one prognostic factor and outcome of interest in STSS patients proved eligible (Figure 1). All but one study (39/40, 98%) were non-randomized. Eligible studies were published between 1989 and 2021, ranged in sample size from 2 to 476, included 1,914 STSS patients in total and were conducted in 22 different countries, most commonly in the United States (15/40, 38%).

Table 1 describes the characteristics of included studies reporting on the association of at least one prognostic factor and outcome of interest. The supplementary data includes additional study characteristics for each study. Of the 40 included studies, 28 (70%) reported on demographic prognostic factors of interest, 5 (13%) medical history of being immunocompromised, 11 (28%) early disease characteristics, and 16 (40%) treatment. Of the dichotomous outcomes, mortality was most commonly reported (35/40, 88%), followed by (P)ICU admission (10/40, 25%), clinical cure or improvement (8/40, 20%) and need for mechanical ventilation (6/40, 15%). Few studies reported on hospital (3/40, 8%) and ICU length-of-stay (2/40, 5%). Two studies reported on time to mortality in days [7, 33]; however, only one reported sufficient data precluding meta-analysis [7]. One study each reported on cost [14], change in SOFA score [7], time to clinical

improvement or resolution of shock [7] and duration of mechanical ventilation [10] precluding meta-analysis for these continuous outcomes. No studies quantified the association between a prognostic factor and functional status or health related quality of life outcomes. A multivariable analysis was conducted in two (5%) of the included studies [10, 11]. A total of 19 of the 40 studies were cohort studies (authors reported on at least one comparative analysis), 18 were case series (authors did not report a comparative analysis) and 2 were case-control studies. To meta-analyse the data, we aggregated the data from the individual patients the case series reported on. Further, we pooled the one randomized study [7] with non-randomized studies in meta-analyses and included patients receiving intravenous or intramuscular IVIG from one non-randomized study [34].

Table 1. Study characteristics. Values are numbers (percentages) of studies unless stated otherwise.

Characteristics	**(40 studies, 1914 patients)**
Range of publication year	1989 to 2021
Median (IQR) No. of patients	11 (5 to 29)
Geographical region:	
North America	19 (48)
Europe	14 (35)
Central/South America	0 (0)
Asia	3 (7)
Other	4 (10)
Study design:	
Randomized trial	1 (2)
Cohort	19 (48)
Case-control	2 (5)
Case-series	18 (45)
Case definition:	
Probable STSS patients	115 (6)
Confirmed STSS patients	223 (12)
Prognostic factor type:	
Demographic	28 (70)
Medical history	5 (13)
Early disease	11 (28)
Treatment	16 (40)

IQR=interquartile range

STSS=streptococcal toxic shock syndrome
Medical history included prognostic variable: immunocompromised
Early disease included prognostic variables: necrotizing fasciitis, acute renal failure

The supplementary material includes the forest plots depicting the studies included in the meta-analysis of each prognostic factor-outcome combination. It also includes the list of studies reporting on prognostic factor-outcome combinations of interest that were not eligible for any meta-analysis, along with the reasons for exclusion from meta-analysis.

Risk of bias in included studies

The supplementary file presents the risk of bias assessment of the 40 included studies. The majority of studies were rated as high risk of bias overall owing to residual confounding and lack of adjustment for confounding in statistical analyses (36/40, 90%) [2, 5, 6, 10, 33-64]. Three studies were rated at moderate risk of bias overall [7, 14, 65] and one at low risk of bias overall [11].

Prognostic factors for mortality

Eleven prognostic factors from 31 studies including 1339 patients were eligible for analysis (table 2, supplementary data). We found a statistically significant association between clindamycin treatment and mortality (figure 2A; n=144; odds ratio [OR] 0.14, 95% CI 0.06 to 0.37), but the certainty of evidence was low. Within clindamycin-treated STSS patients, we found a statistically significant association between intravenous immunoglobulin (IVIG) treatment and mortality (figure 2B; n=188; OR 0.34, 95% CI 0.15 to 0.75), but the certainty of evidence was also low. We are uncertain whether IVIG treatment reduces the odds of mortality in all STSS patients regardless of concurrent clindamycin treatment (n=365, OR 0.37, 95% CI 0.17 to 0.80; very low certainty of evidence). The odds of mortality may increase in patients ≥65 years when compared to patients 18-64 years (n=396; OR 2.37, 95% CI 1.47 to 3.84), but the certainty of evidence was low. We are less certain whether the same is true for patients ≥65 years compared to patients <18 years (n=136, OR 10.66, 95% CI 1.28 to 88.57; very low certainty of evidence). We are also uncertain whether NSAIDs increase the odds of mortality (n=50, OR 4.14, 95% CI 1.13 to 15.14; very low certainty of evidence). Very low certainty evidence failed to show a significant association with any other prognostic factor and mortality in STSS patients:

male vs female (n=76, OR 0.91, 95% CI 0.34 to 2.46), patients <18 years vs patients 18 to 64 years (n=694, OR 0.54, 95% CI 0.15 to 1.94), immunocompromised vs not immunocompromised (n=33, OR 1.65, 95% CI 0.33 to 8.26), necrotizing fasciitis vs no necrotizing fasciitis (n=840, OR 0.81, 95% CI 0.51 to 1.29), acute renal failure vs no acute renal failure (n=91, OR 2.50, 95% CI 0.97 to 6.42), hemodialysis vs no hemodialysis (n=42, OR 1.94, 95% CI 0.22 to 16.99) and any antibiotic vs no antibiotic (n=19, OR 0.48, 95% CI 0.05 to 4.76).

Table 2. Summary of findings for prognostic factor – outcome meta-analyses.

Prognostic factor	Number of patients (studies)	Odds ratio (95% confidence interval)	Absolute effect estimates		GRADE: Certainty of the Evidence
			Risk without prognostic factor	Risk with prognostic factor	
MORTALITY					
Demographic					
Male vs Female	76 (12)	0.91 (0.34 to 2.46)	**250** per 1000	**233** per 1000	**Very low** Due to very serious risk of bias and imprecision
			-17 (-148 to 201)		
<18 vs 18-64 years	694 (5)	0.54 (0.15 to 1.94)	**234** per 1000	**142** per 1000	**Very low** Due to very serious risk of bias and imprecision, and serious inconsistency
			-92 (-190 to 138)		
≥65 vs <18 years	136 (2)	10.66 (1.28 to 88.57)*	**50** per 1000	**359** per 1000	**Very low** Due to very serious risk of bias and serious imprecision
			309 (13 to 773)		
≥65 vs 18–64 years	396 (2)	2.37 (1.47 to 3.84)*	**193** per 1000	**362** per 1000	**Low** Due to very serious risk of bias
			169 (67 to 286)		
Medical history					
Immunocompromised vs Not Immunocompromised	33 (4)	1.65 (0.33 to 8.26)	**438** per 1000	**563** per 1000	**Very low** Due to very serious risk of bias and imprecision
			125 (-233 to 428)		
Early disease					
Acute Renal Failure vs No Acute Renal Failure	91 (4)	2.50 (0.97 to 6.42)	**NA** per 1000	**NA** per 1000	**Very low** Due to very serious risk of bias and imprecision
			140 (-60 to 330)		
Necrotizing Fasciitis vs No Necrotizing Fasciitis	840 (10)	0.81 (0.51 to 1.29)	**347** per 1000	**301** per 1000	**Very low** Due to very serious risk of bias and imprecision
			-46 (-134 to 60)		
Treatment					
IVIG vs No IVIG (all STSS patients)	365 (9)	0.37 (0.17 to 0.80)*	**231** per 1000	**100** per 1000	**Very low** Due to very serious risk of bias and serious imprecision
			-131 (-182 to -37)		
IVIG vs No IVIG (subset of STSS patients treated with clindamycin)	188 (6)	0.34 (0.15 to 0.75)*	**300** per 1000	**127** per 1000	**Low** Due to serious risk of bias and imprecision
			-173 (-240 to -57)		
Any Antibiotic vs No Antibiotic	19 (3)	0.48 (0.05 to 4.76)	**NA** per 1000	**NA** per 1000	**Very low** Due to very serious risk of bias and imprecision
			-120 (-490 to 260)		
Clindamycin vs No Clindamycin Antibiotic	144 (4)	0.14 (0.06 to 0.37)*	**800** per 1000	**359** per 1000	**Low** Due to serious risk of bias and imprecision
			-441 (-606 to -203)		
Hemodialysis vs No Hemodialysis	42 (4)	1.94 (0.22 to 16.99)	**107** per 1000	**189** per 1000	**Very low** Due to very serious risk of bias and imprecision
			82 (-81 to 564)		

NSAIDs vs No NSAIDs	50 (4)	4.14 (1.13 to 15.14)*	**100** per 1000	**315** per 1000	**Very low** Due to very serious risk of bias and serious imprecision
			215 (12 to 527)		
ICU ADMISSION					
Demographic					
Male vs Female	19 (3)	2.87 (0.29 to 28.27)	**NA** per 1000	**NA** per 1000	**Very low** Due to very serious risk of bias and imprecision
			150 (-160 to 450)		
Early disease					
Necrotizing Fasciitis vs No Necrotizing Fasciitis	28 (3)	0.74 (0.12 to 4.48)	**900** per 1000	**869** per 1000	**Very low** Due to very serious risk of bias and imprecision
			-31 (-381 to 76)		
Treatment					
IVIG vs No IVIG (all STSS patients)	156 (3)	1.09 (0.43 to 2.77)	**833** per 1000	**845** per 1000	**Very low** Due to very serious risk of bias and imprecision
			12 (-151 to 100)		
Any Antibiotic vs No Antibiotic	14 (2)	4.60 (0.29 to 72.89)	**500** per 1000	**821** per 1000	**Very low** Due to very serious risk of bias and imprecision
			321 (-275 to 486)		
Hemodialysis vs No Hemodialysis	13 (2)	3.25 (0.21 to 50.35)	**875** per 1000	**958** per 1000	**Very low** Due to very serious risk of bias and imprecision
			83 (-280 to 122)		
NSAIDs vs No NSAIDs	15 (2)	0.86 (0.06 to 12.48)	**NA** per 1000	**NA** per 1000	**Very low** Due to very serious risk of bias and imprecision
			-10 (-430 to 400)		
CLINICAL CURE OR IMPROVEMENT					
Demographic					
Male vs Female	23 (4)	3.33 (0.47 to 23.59)	**875** per 1000	**959** per 1000	**Very low** Due to very serious risk of bias and imprecision
			84 (-108 to 119)		
Early disease					
Necrotizing Fasciitis vs No Necrotizing Fasciitis	24 (2)	0.34 (0.02 to 5.20)	**950** per 1000	**866** per 1000	**Very low** Due to very serious risk of bias and serious imprecision
			-84 (-675 to 40)		
Treatment					
IVIG vs No IVIG (in all STSS patients)	23 (2)	0.27 (0.02 to 3.76)	**NA** per 1000	**NA** per 1000	**Very low** Due to very serious risk of bias and imprecision
			-100 (-350 to 140)		
Hemodialysis vs No Hemodialysis	26 (3)	1.43 (0.15 to 14.08)	**NA** per 1000	**NA** per 1000	**Very low** Due to very serious risk of bias and imprecision
			50 (-240 to 340)		
NEED FOR MECHANICAL VENTILATION					
Demographic					
Male vs Female	21 (3)	2.09 (0.32 to 13.74)	**NA** per 1000	**NA** per 1000	**Very low** Due to very serious risk of bias and imprecision
			120 (-200 to 440)		
Early disease					
Acute Renal Failure vs No Acute Renal Failure	20 (2)	1.14 (0.17 to 7.82)	**750** per 1000	**774** per 1000	**Very low** Due to very serious risk of bias and imprecision
			24 (-412 to 209)		
Necrotizing Fasciitis vs No Necrotizing Fasciitis	31 (3)	3.75 (0.47 to 29.81)	**700** per 1000	**897** per 1000	**Very low** Due to very serious risk of bias and imprecision
			197 (-177 to 286)		
Treatment					
IVIG vs No IVIG (in all STSS patients)	157 (3)	2.22 (0.78 to 6.32)	**333** per 1000	**526** per 1000	**Very low** Due to very serious risk of bias and imprecision
			193 (-53 to 426)		
Hemodialysis vs No Hemodialysis	26 (3)	2.05 (0.39 to 10.70)	**500** per 1000	**672** per 1000	**Very low**

			172 (-219 to 415)		Due to very serious risk of bias and imprecision
DURATION OF HOSPITALIZATION					
Treatment					
IVIG vs no IVIG (all STSS patients)	201 (3)	NA	**NA** per 1000	**NA** per 1000	**Low**
			On average, 5.51 fewer days (17.64 fewer to 6.62 more)		Due to serious risk of bias and imprecision
DURATION OF INTENSIVE CARE UNIT STAY					
Treatment					
IVIG vs no IVIG (all STSS patients)	131 (2)	NA	**NA** per 1000	**NA** per 1000	**Very low**
			On average, 3.80 more days (3.62 fewer to 11.23 more)		Due to very serious risk of bias and serious imprecision

*statistical evidence of an association

Prognostic factors for ICU admission

Six prognostic factors from eight studies including 174 patients were eligible for analysis (table 2, supplementary data). We found no statistical evidence of an association between any prognostic factor and ICU admission: male vs female sex (n=19, OR 2.87, 95% CI 0.29 to 28.27), necrotizing fasciitis vs no necrotizing fasciitis (n=28, OR 0.74, 95% CI 0.12 to 4.48), hemodialysis vs no hemodialysis (n=13, OR 3.25, 95% CI 0.21 to 50.35), NSAIDs vs no NSAIDs (n=15, OR 0.86, 95% CI 0.06 to 12.48), IVIG treatment vs no IVIG treatment (n=156, OR 1.09, 95% CI 0.43 to 2.77) and antibiotic treatment vs no antibiotic treatment (n=14, OR 4.60, 95% CI 0.29 to 72.98). The certainty of all ICU admission evidence was very low due to very serious risk of bias and imprecision.

Prognostic factors for clinical cure or improvement

Four prognostic factors from six studies including 38 STSS patients were eligible for analysis (table 2, supplementary data). We found no statistical evidence of an association between any prognostic factor and clinical cure or improvement: male vs female sex (n=23, OR 3.33, 95% CI 0.47 to 23.59), necrotizing fasciitis vs no necrotizing fasciitis (n=24, OR 0.34, 95% CI 0.02 to 5.20), hemodialysis vs no hemodialysis (n=26, OR 1.43, 95% CI 0.15 to 14.08) and IVIG treatment vs no IVIG treatment (n=23, OR 0.27, 95% CI 0.02 to 3.76). The certainty of all clinical cure or improvement evidence was very low due to very serious risk of bias and serious or very serious imprecision.

Prognostic factors for mechanical ventilation

Five prognostic factors from six studies including 170 STSS patients were eligible for analysis (table 2, supplementary data). We found no statistical evidence of an association between any prognostic factor and need for mechanical ventilation: male vs female sex (n=21, OR 2.09, 95% CI 0.32 to 13.74), necrotizing fasciitis vs no necrotizing fasciitis (n=31, OR 3.75, 95% CI 0.47 to 29.81), acute renal failure vs no acute renal failure (n=20, OR 1.14, 95% CI 0.17 to 7.82), hemodialysis vs no hemodialysis (n=26, OR 2.05, 95% CI 0.39 to 10.70) and IVIG treatment vs no IVIG treatment (n=157, OR 2.22, 95% CI 0.78 to 6.32). The certainty of all need for mechanical ventilation evidence was very low due to very serious risk of bias and imprecision.

Prognostics factors for hospital length-of-stay

One prognostic factor from three studies including 201 STSS patients was eligible for analysis (table 2, supplementary data). Low certainty evidence – due to serious risk of bias and imprecision – provides no support for an association between IVIG treatment and hospital length-of-stay, when compared to no IVIG treatment (n=201, MD -5.51 days, 95% CI -17.64 to 6.62).

Prognostic factors for intensive care unit length-of-stay

One prognostic factor from two studies including 131 STSS patients was eligible for analysis (table 2, supplementary data). We are uncertain if IVIG treatment compared to no IVIG treatment is associated with ICU length-of-stay (n=131, MD 3.80 days, 95% CI -3.62 to 11.23; very low certainty evidence due to very serious risk of bias and serious imprecision).

Subgroup and sensitivity analysis

Sparsity of data precluded our planned subgroup analyses by clindamycin treatment, presence of necrotizing fasciitis and sex (i.e. each subgroup did not have at least two studies). We collapsed the low and moderate risk of bias categories to allow for subgroup analysis by risk of bias (low or moderate vs high). The prognostic factor-outcome combinations for which there was sufficient evidence for subgroup analysis by age or modified risk of bias level were IVIG-mortality and sex-mortality. We found no statistical evidence that the association between IVIG and mortality differed between low or moderate and high risk of bias studies in all STSS patients (p=0.884) and clindamycin-treated STSS patients (p=0.867) or between studies with STSS

patients <18 years and patients 18-64 years (p=0.328). We also found no statistical evidence that the association between sex and mortality differed between studies with patients <18 years and patients 18-64 years (p=0.666). Because results were consistent across Peto, and DerSimonian and Laird methods, our post-hoc sensitivity analysis showed that our meta-analyses based on few events were robust.

Discussion

This systematic review and meta-analysis provides a comprehensive overview of the prognostic evidence for STSS. Prognostic factors for which there was a statistically significant association with mortality in STSS patients were age, clindamycin treatment, IVIG treatment and NSAIDs treatment. Patients ≥65 years compared to patients 18 to 64 years may have increased odds of mortality (low certainty of evidence); however we are uncertain if the same is true for patients ≥65 years compared to patients <18 years (very low certainty of evidence). We are also uncertain whether NSAIDs increase the odds of mortality (very low certainty of evidence). Low certainty evidence suggests the odds of mortality may be reduced by treatment with clindamycin and within clindamycin-treated patients, IVIG. We are highly uncertain whether IVIG reduces mortality in all STSS patients, regardless of clindamycin treatment (very low certainty of evidence). Results failed to show a significant association between all other meta-analyzed prognostic factors and outcomes (table 2). The certainty of STSS prognostic evidence was low or very low due to serious or very serious risk of bias and imprecision concerns.

Strengths of this review include its systematic and explicit search of the literature, capture of a wide breadth of patient-important outcomes within and outside of critical care and the use of meta-analysis to increase statistical power in studying relationships between prognostic factors and outcomes in STSS patients. These strengths directly address limitations of a narrative synthesis of STSS prognosis restricted to the critical care setting [1].

In the absence of large cohort studies and randomized trials, conclusions for STSS prognosis in this review are limited by very low to low certainty evidence. The majority of included studies were non-randomized (39/40, 98%) and small (median sample size was 10 patients), introducing bias from residual confounding and imprecision around pooled summary estimates. Small

numbers of events further contributed to the imprecision around summary estimates and limited the interpretation of our findings. With few participants and events, minor changes in the data can cause major changes in the results. In such instances, results can be exaggerated by the presentation of relative effect estimates only. To minimize the risk of misinterpreting results from the inclusion of small studies in our meta-analyses, we calculated an absolute effect estimate for each relative effect estimate (table 2). Further, despite expecting small studies to be more heterogeneous than large studies, we did not find statistical evidence of heterogeneity in any of our 33 meta-analyses and in interpreting the I^2 statistic value, we found not likely important heterogeneity in all but one meta-analysis [66]. Creation of an international registry of STSS patients may improve the credibility of prognostic evidence for STSS and facilitate the conduct of high-quality cohort studies. Although we meta-analyzed adjusted odds ratios from included studies when possible, almost all included studies reported crude data (38/40, 95%), precluding adjustment for important confounders. A limitation of the evidence is the lack of long-term outcome data reported. For example, no studies quantified associations between prognostic factors and functional status or health related quality of life outcomes post-infection in STSS survivors. Given the high morbidity associated with STSS [67], future research in STSS prognosis should quantify these patient-important outcomes, facilitating future meta-analyses and providing further insights into STSS prognosis.

Our finding that IVIG treatment may reduce the odds of mortality in STSS patients who receive clindamycin treatment is consistent with a systematic review and meta-analysis of IVIG treatment in clindamycin-treated STSS patients, which found statistical evidence of a decreased risk of mortality in IVIG- and clindamycin-treated STSS patients when compared to only clindamycin-treated STSS patients [67]. For this question relevant to clindamycin-treated STSS patients, our meta-analysis included one additional non-randomized study, whose small sample size and imprecision contributed to an overall point estimate of greater magnitude [33]. Our findings suggest that treatment regimens of IVIG in adjunct to clindamycin and clindamycin alone may significantly improve STSS prognosis. We found a significant association between a regimen of IVIG regardless of clindamycin treatment and mortality; however, due to very serious risk of bias and serious imprecision, and thus very low certainty evidence, we cannot rule out the possibility that clindamycin treatment may be necessary for STSS patients to benefit from IVIG

treatment. Further, only one study reported on IVIG treatment in STSS patients that were not also treated with clindamycin [34]; therefore, our planned subgroup analysis to test if the beneficial effect of IVIG is modified in the absence of clindamycin was precluded. Based on very low certainty evidence, our finding that NSAID treatment is significantly associated with mortality in STSS patients can be explained by clinical and basic science literature, which suggests nonselective NSAIDs mask early signs and symptoms of GAS infection, such as fever, subsequently delaying time to antibiotic treatment – a risk factor for severe sepsis and shock, and mortality [68, 69].

After analyzing 30 different prognostic factor and outcome combinations, we found that clindamycin treatment was significantly associated with an improved STSS prognosis. Further, we found that IVIG treatment may reduce the odds of mortality in STSS patients who receive clindamycin treatment, but we are uncertain if this is true for all STSS patients, regardless of clindamycin treatment. Although these findings support the use of IVIG as an adjunctive treatment in clindamycin-treated STSS patients, the certainty of evidence was low due to serious risk of bias and imprecision. Age equal to or older than 65 years and treatment with NSAIDs was significantly associated with a worse STSS prognosis. Results from very low to low certainty evidence failed to show a significant association between any other factors of interest and STSS prognosis.

Contributors

All authors attest they meet the ICMJE criteria for authorship. All authors have made substantial contributions to the following: (1) the conception and design of the study (Jessica J Bartoszko, Lehana Thabane, Dominik Mertz, Mark Loeb), acquisition of data (Jessica J Bartoszko, Zeyad Elias, Paulina Rudziak, Carson KL Lo), analysis and interpretation of data (Jessica J Bartoszko, Zeyad Elias, Paulina Rudziak, Carson KL Lo, Mark Loeb); (2) drafting the article and revising it critically for important intellectual content (Jessica J Bartoszko, Lehana Thabane, Dominik Mertz, Mark Loeb), (3) final approval of the version to be submitted (Jessica J Bartoszko, Zeyad Elias, Paulina Rudziak, Carson KL Lo, Lehana Thabane, Dominik Mertz, Mark Loeb).

Declaration of interests

Mark Loeb declares grants or contracts from the World Health Organization, consulting fees from AVIR Pharma, and participating on data safety monitoring or advisory boards for Paladin Labs and Sunovion Pharmaceuticals.

Role of the funding source

There was no funding source for this study.

Data availability statement

Data extracted from individual studies are available upon reasonable request to the corresponding author. All other data relevant to the study are included in the article or uploaded as online supplemental information.

Ethics statement

Patient consent for publication not applicable.

Figure 1. PRISMA study flow diagram.

Figure 2. Meta-analyses comparing IVIG treatment to no IVIG treatment for the outcome mortality in A) all STSS patients; and B) the subset of STSS patients treated with clindamycin. Please note proportions are blank for study rows where we meta-analyzed adjusted odds ratios instead of crude proportions.

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Figure 1. PRISMA flow diagram.

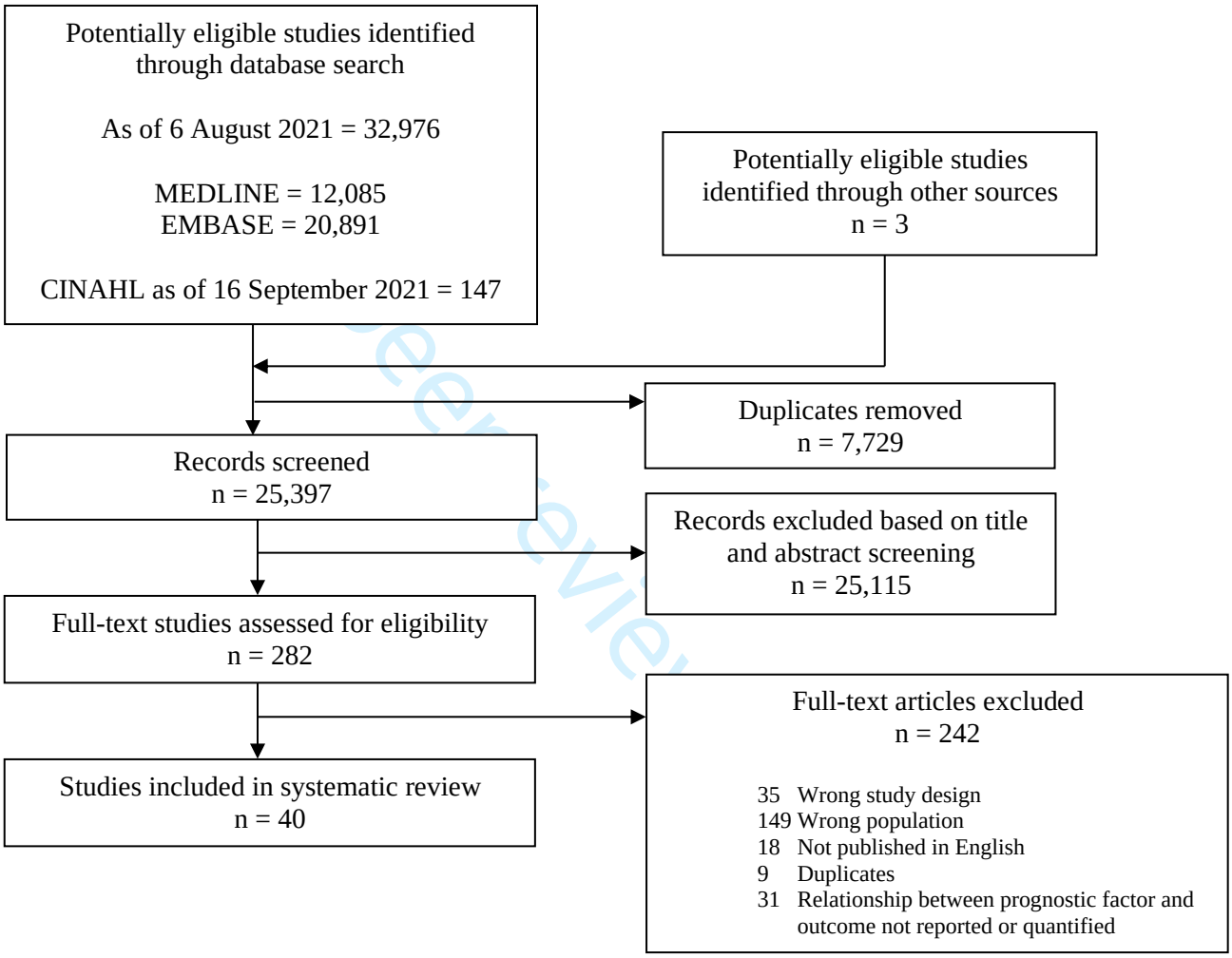
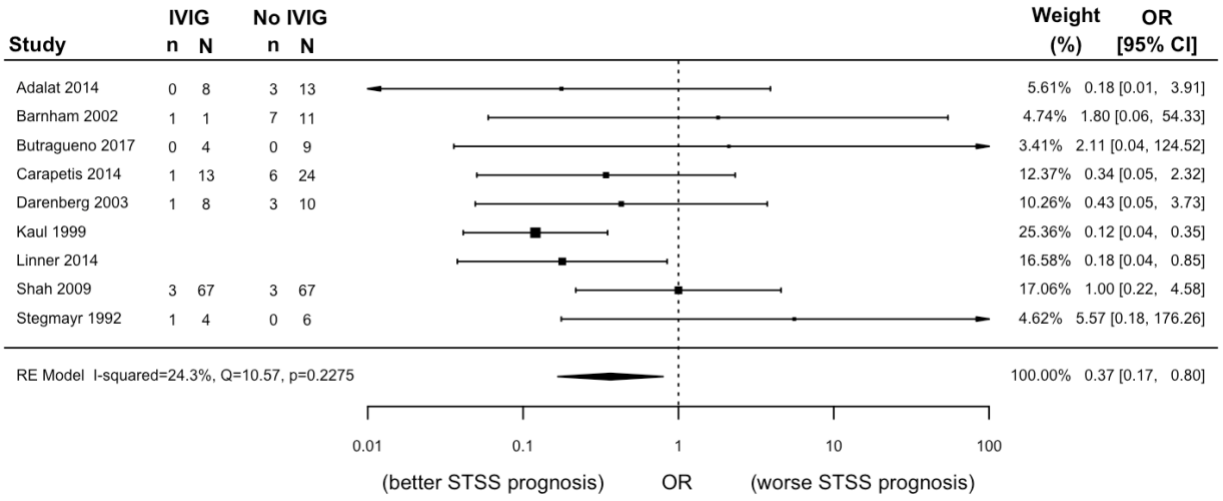
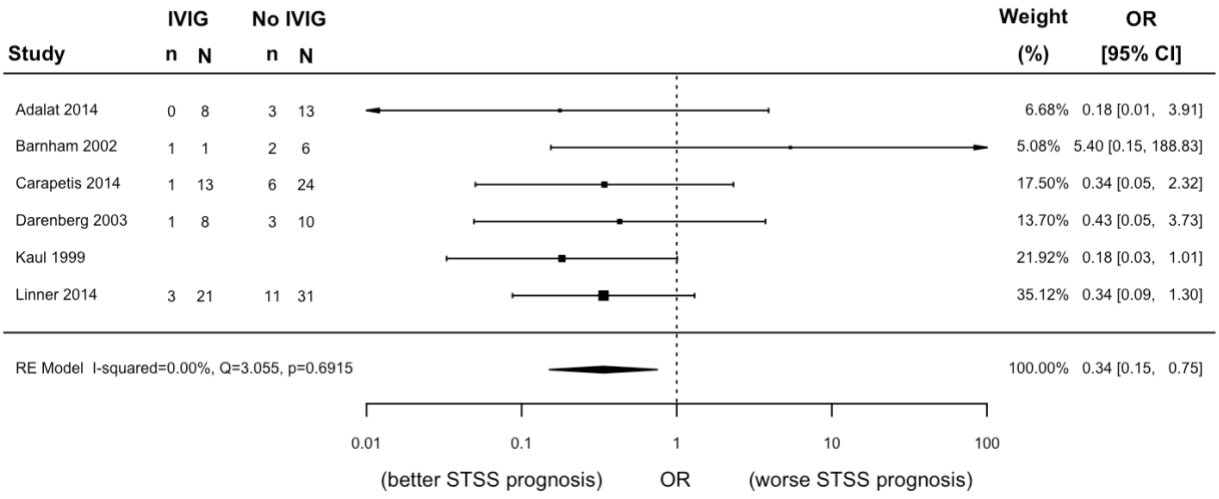


Figure 2. Meta-analyses comparing IVIG treatment to no IVIG treatment for the outcome mortality in A) all STSS patients; and B) the subset of STSS patients treated with clindamycin. Please note proportions are blank for study rows where we meta-analyzed adjusted odds ratios instead of crude proportions.

A)



B)



PROGNOSTIC FACTORS FOR STREPTOCOCCAL TOXIC SHOCK SYNDROME: SYSTEMATIC REVIEW AND META-ANALYSIS

Supplementary Material

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Search strategies

1) Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:
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1 toxic shock syndrome.mp. or exp Shock, Septic/ or STSS.mp. or streptococcal toxic shock syndrome.mp. or necrotizing fasciitis.mp. or exp Fasciitis, Necrotizing/ or septic shock.mp.
2 (group a streptococc* or group A streptococc* or pyogenes or streptococcus pyogenes).mp. or exp Streptococcus pyogenes/
3 exp Cohort Studies/
4 cohort$.tw.
5 controlled clinical trial.pt.
6 epidemiologic methods/
7 limit 6 to yr=1966-1989
8 exp case-control studies/
9 (case$ and control$).tw.
10 (case$ and series).tw.
11 or/3-5,7-10
12 randomized controlled trial.pt.
13 (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
14 (retraction of publication or retracted publication).pt.
15 or/12-14
16 (animals not humans).sh.
17 ((comment or editorial or meta-analysis or practice-guideline or review or letter) not randomized controlled trial).pt.
18 (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not randomized controlled trial.pt.
19 15 not (16 or 17 or 18)
20 animals/ not humans/
21 (1 or 2) and (11 or 19)
22 21 not 20

2) Database: Embase <1974 to 2020 February 03>

Search Strategy:
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1 toxic shock syndrome.mp. or exp septic shock/ or STSS.mp. or streptococcal toxic shock syndrome.mp. or necrotizing fasciitis.mp. or exp necrotizing fasciitis/ or septic shock.mp. or exp toxic shock syndrome/
2 (group a streptococc* or group A streptococc* or pyogenes or streptococcus pyogenes).mp. or exp Streptococcus pyogenes/ or exp Streptococcus group A/
3 exp cohort analysis/
4 exp longitudinal study/
5 exp prospective study/

6 exp follow up/
7 cohort$.tw.
8 exp case control study/ or (case$ and control$).tw.
9 exp case study/ or (case$ and series).tw.
10 or/3-9
11 (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
12 RETRACTED ARTICLE/
13 or/11-12
14 (animal$ not human$).sh,hw.
15 (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/
16 (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/
17 13 not (14 or 15 or 16)
18 exp animal/
19 exp human/
20 18 not 19
21 (1 or 2) and (10 or 17)
22 21 not 20

GRADE assessment guidance

Based on GRADE guidance for prognostic studies, we start with high certainty evidence for each meta-analysis.

Risk of bias
For each meta-analysis, we downgraded the certainty of the evidence once for risk of bias when studies with moderate or high risk of bias contributed >50% weight to the pooled effect estimates or when studies providing unadjusted estimates contributed >50% weight to the pooled effect estimate (i.e. serious risk of bias). We downgraded the certainty of the evidence twice for risk of bias when studies with moderate or high risk of bias contributed >80% weight to the pooled effect estimates or when studies providing unadjusted estimates contributed >80% weight to the pooled effect estimate (i.e. very serious risk of bias).

Inconsistency
We used visual inspection of the forest plots and the I^2 statistic to assess inconsistency. For visual inspection of the forest plots, we considered the variability in point estimates and confidence interval overlap in relation to the null effect. Further, we downgraded the certainty of the evidence once when there was substantial (I^2 50-90%) heterogeneity and twice when there was considerable (I^2 75-100%) heterogeneity.

Imprecision
We downgraded the certainty of the evidence once for imprecision if:
1) The effect on the patient, or clinical action, would differ depending on whether the upper or the lower boundary of the confidence interval represented the truth, **OR**
2) The 95% CI of the pooled absolute estimate crossed the null effect by less than 50 people per 1000 on one or both sides, **OR**
3) In cases where we had large effects that did not cross the null, we assessed the optimal information size. If the ratio of the upper to the lower limit of the confidence interval of the relative estimate was >3, the optimal information size would never be met; thus, we rated down once for imprecision, **OR**
4) There were fewer than 10 outcome events for each prognostic variable (for dichotomous outcomes, **OR**
5) There were fewer than 100 cases reaching endpoint (for continuous outcomes).
We downgraded the certainty of the evidence twice for imprecision if:
1) The 95% CI of the pooled absolute estimate crossed the null effect by more than 50 people per 1000 on both sides.

Indirectness
We rated down once if the study sample, the prognostic factor, and/or the outcome in the primary studies did not accurately reflect the review question.

Publication bias
We rated down once if:
1) Small studies reported higher rates compared to large studies, suggesting the selective publication of "positive" studies, **OR**

2) The value of the risk/protective factor in predicting the outcome has NOT been repetitively investigated (e.g. only exploratory studies with no external validation, replication or confirmation exist).

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2. Huguet A, Hayden JA, Stinson J, et al. Judging the quality of evidence in reviews of prognostic factor research: adapting the GRADE framework. Syst Rev. 2013;2:71. Published 2013 Sep 5. doi:10.1186/2046-4053-2-71

Table of excluded full texts (n=242)

Author, Year	Title	Reason for Exclusion
Hamilton, 2013	Pregnancy-related group a streptococcal infections: Temporal relationships between bacterial acquisition, infection onset, clinical findings, and outcome	Wrong study design
Ichiyama, 1997	Transmission of Streptococcus pyogenes causing toxic shock-like syndrome among family members and confirmation by DNA macrorestriction analysis	Wrong study design
Idubor, 2019	Invasive group a streptococcus infections among residents of multiple nursing Homes-Denver, Colorado, 2017-2018	Wrong study design
Ikebe, 2015	Increased prevalence of group A streptococcus isolates in streptococcal toxic shock syndrome cases in Japan from 2010 to 2012	Wrong study design
Klinker, 1997	Toxic shock syndrome in AIDS	Wrong study design
Langmuir, 1982	Toxic-shock syndrome--an epidemiologist's view	Wrong study design
McIvor, 1982	Treatment of recurrent toxic shock syndrome with oral contraceptive agents	Wrong study design
Pathi, 2013	Prompt recognition and multidisciplinary approach in Group A streptococcal sepsis	Wrong study design
Shah, 2015	Role of intravenous immune globulin in streptococcal toxic shock syndrome and Clostridium difficile infection	Wrong study design
Stallones, 1982	A review of the epidemiologic studies of toxic shock syndrome	Wrong study design
Stevens, 2000	Molecular epidemiology of nga and NAD glycohydrolase/ADP-ribosyltransferase activity among Streptococcus pyogenes causing streptococcal toxic shock syndrome	Wrong study design
Turner, 2015	Emergence of a New Highly Successful Acapsular Group A Streptococcus Clade of Genotype emm89 in the United Kingdom	Wrong study design
Udagawa, 1999	Serious group A streptococcal infection around delivery	Wrong study design
Valiquette, 2006	A survey of physician's attitudes regarding management of severe group A streptococcal infections	Wrong study design
Valiquette, 2009	Assessing the impact of intravenous immunoglobulin in the management of streptococcal toxic shock syndrome: a noble but difficult quest	Wrong study design
Wozniak, 2012	M-protein gene-type distribution and hyaluronic acid capsule in group A Streptococcus clinical isolates in Chile: Association of emm gene markers with csrR alleles	Wrong study design
Anonymous, 1984	Diagnostic bias and toxic shock syndrome	Wrong study design
Blonde, 2017	A prospective multicentric study of severe cutaneous infections in pediatric intensive care: The SCIPIC cohort	Wrong study design
Busowski, 2010	Puerperal group A streptococci (GAS) infection: Reemergence of a dreaded disease - A case series	Wrong study design
Cimolai, 2002	Nonhemolytic Streptococcus pyogenes causing invasive infection	Wrong study design
Clark, 2010	Puerperal group a streptococcal sepsis and proinflammatory immune response	Wrong study design

Dahdi, 2018	Necrotizing soft tissue infection: Microbiological distribution from district region	Wrong study design
Das, 2012	Necrotizing fasciitis in New Zealand - Risk factors, microbiological findings and outcomes in a large case series	Wrong study design
De Zoysa, 2013	Invasive group A streptococcal disease in the UK, 2008-2012 and molecular characterisation of isolates during enhanced surveillance	Wrong study design
Donawa, 1984	Toxic shock syndrome: chronology of state and federal epidemiologic studies and regulatory decision-making	Wrong study design
Figueira, 2013	Peri-ocular necrotising fasciitis: A multicentre retrospective australian series	Wrong study design
Gaensbauer, 2016	Importance of toxic shock syndrome in pediatric septic shock clinical decision-making	Wrong study design
Goldberg, 2015	Group A beta streptococcal infections in children after oral or dental trauma: A case series of 5 patients	Wrong study design
McViety, 2014	Don't forget IGAS: Lessons learnt from review of 2 peak seasons in the north west and North Wales, UK	Wrong study design
Zangara, 2019	Epidemiology, outcomes from treatment, and the spectrum of soft tissue infections over time in hospitalized patients: A populationbased description of inpatients in the state of california	Wrong study design
Arias-Constanti, 2018	Invasive disease by Streptococcus pyogenes: patients hospitalized for 6 years	Wrong population
Hankins, 2008	Factors that affect the clinical course of group A beta-haemolytic streptococcal infections of the hand and upper extremity: a retrospective study	Wrong population
Henrichsen, 1997	Invasive infections caused by Streptococcus pyogenes in Denmark 1990- 1994	Wrong population
Hoge, 1993	The changing epidemiology of invasive group A streptococcal infections and the emergence of streptococcal toxic shock-like syndrome. A retrospective population-based study	Wrong population
Jauregui, 2015	Life- and limb-threatening infections following the use of an external fixator	Wrong population
Kadri, 2017	Impact of Intravenous Immunoglobulin on Survival in Necrotizing Fasciitis With Vasopressor-Dependent Shock: A Propensity Score-Matched Analysis From 130 US Hospitals	Wrong population
Leggiadro, 1993	Group A streptococcal bacteremia in a mid-south children's hospital	Wrong population
Madsen, 2019	Patient's characteristics and outcomes in necrotising soft-tissue infections: results from a Scandinavian, multicentre, prospective cohort study	Wrong population
Mitchell, 2011	A strep in the wrong direction-invasive group a streptococcal disease	Wrong population
Moses, 1995	Group A streptococcus bacteremia at the Hadassah Medical Center in Jerusalem	Wrong population
Mosites, 2017	Use of single-dose azithromycin to control a community outbreak of EMM26.3 group a streptococcus invasive disease-Alaska, 2017	Wrong population
Mosites, 2019	Risk for invasive streptococcal infections among adults experiencing homelessness, anchorage, Alaska, USA, 2002-2015	Wrong population

Mulla, 2007	Clinical and epidemiologic features of invasive group A streptococcal infections in children	Wrong population
Mulla, 2003	Invasive group A streptococcal infections in Florida	Wrong population
Navarro, 1993	A comparison of Streptococcus pyogenes (group A streptococcal) bacteremia at an urban and a suburban hospital. The importance of intravenous drug use	Wrong population
Norton, 2004	Invasive group A streptococcal disease in North Queensland (1996 - 2001)	Wrong population
Nuwayhid, 2007	Blunt Trauma as a Risk Factor for Group A Streptococcal Necrotizing Fasciitis	Wrong population
Oliver, 2019	Invasive group A Streptococcus disease in Australian children: 2016 to 2018 - a descriptive cohort study	Wrong population
Oliver, 2019	Recent trends in invasive group A Streptococcus disease in Victoria	Wrong population
Peterson, 1996	Risk factors for invasive group A streptococcal infections in children with varicella: A case-control study	Wrong population
Rainbow, 2008	Invasive group A streptococcal disease in nursing homes, Minnesota, 1995-2006	Wrong population
Rathore, 1992	Suppurative group A beta-hemolytic streptococcal infections in children	Wrong population
Reingold, 1984	Epidemiology of toxic-shock syndrome, United States, 1960-1984	Wrong population
Reingold, 1989	Risk factors for menstrual toxic shock syndrome: results of a multistate case-control study	Wrong population
Remy, 2019	Septic shock and toxic shock syndrome-two infectious shocks with different immune response	Wrong population
Rudolph, 2016	Epidemiology of invasive group a streptococcal disease in Alaska, 2001 to 2013	Wrong population
Saldana, 2010	Periorbital necrotizing fasciitis: Outcomes using a CT-guided surgical debridement approach	Wrong population
Sarangi, 1995	A nursing home outbreak of group A streptococcal infection: case control study of environmental contamination	Wrong population
Scaber, 2011	Group a streptococcal infections during the seasonal influenza outbreak 2010/11 in South East England	Wrong population
Scheuer, 2018	Rising high rate of invasive group a streptococcus infections among persons experiencing homelessness in San Francisco, 2010-2017	Wrong population
Schlech, 1982	Risk factors for development of toxic shock syndrome. Association with a tampon brand	Wrong population
Schwartz, 1989	Nonmenstrual toxic shock syndrome associated with barrier contraceptives: report of a case-control study	Wrong population
Shands, 1982	Toxic shock syndrome: Case-control studies at the centers for disease control	Wrong population
Sharma, 2019	Real-time whole genome sequencing to control a Streptococcus pyogenes outbreak at a national orthopaedic hospital	Wrong population
Sierra, 2006	Group A streptococcal infections in injection drug users in Barcelona, Spain: Epidemiologic, clinical, and microbiologic analysis of 3 clusters of cases from 2000 to 2003	Wrong population

Simonart, 2004	The importance of serum creatine phosphokinase level in the early diagnosis and microbiological evaluation of necrotizing fasciitis	Wrong population
Smith, 2003	Mass antibiotic treatment for group A streptococcus outbreaks in two long-term care facilities	Wrong population
Spargen, 2011	Proinflammatory immune response and puerperal group a streptococcal sepsis	Wrong population
Steer, 2009	Prospective surveillance of invasive group A streptococcal disease, fiji, 2005-2007	Wrong population
Steer, 2008	High burden of invasive beta-haemolytic streptococcal infections in Fiji	Wrong population
Tanna, 2006	Molecular characterization of clinical isolates of M non-typable group A streptococci from invasive disease cases	Wrong population
Tapiainen, 2016	Invasive Group A Streptococcal Infections in Children: A Nationwide Survey in Finland	Wrong population
Thanert, 2019	Molecular profiling of tissue biopsies reveals unique signatures associated with streptococcal necrotizing soft tissue infections	Wrong population
Theis, 2002	Severe necrotising soft tissue infections in orthopaedic surgery	Wrong population
Thigpen, 2007	Nursing home outbreak of invasive group A streptococcal infections caused by 2 distinct strains	Wrong population
Urbina, 2019	Early identification of patients at high risk of group A streptococcus-associated necrotizing skin and soft tissue infections: a retrospective cohort study	Wrong population
Vasant, 2019	Mass prophylaxis in an outbreak of invasive group A streptococcal disease in a residential aged care facility	Wrong population
Vlaminckx, 2005	Long-term surveillance of invasive group A streptococcal disease in The Netherlands, 1994-2003	Wrong population
Vugia, 1996	Invasive group A streptococcal infections in children with varicella in Southern California	Wrong population
Waldhausen, 1996	Surgical implications of necrotizing fasciitis in children with chickenpox	Wrong population
Watanabe-Ohnishi, 1995	Selective depletion of V beta-bearing T cells in patients with severe invasive group A streptococcal infections and streptococcal toxic shock syndrome. Ontario Streptococcal Study Project	Wrong population
Wheeler, 1991	Outbreak of group A streptococcus septicemia in children: Clinical, epidemiologic, and microbiological correlates	Wrong population
Wilson, 1995	Group A streptococcal necrotizing fasciitis following varicella in children: Case reports and review	Wrong population
Wong, 2019	A Cluster of Pediatric Invasive Group A Streptococcus Disease in Melbourne, Australia, Coinciding with a High-Burden Influenza Season	Wrong population
Yagupsky, 1987	Group A beta-hemolytic streptococcal bacteremia in children	Wrong population
Zerr, 1999	A case-control study of necrotizing fasciitis during primary varicella	Wrong population
Zimbelman, 1999	Improved outcome of clindamycin compared with beta-lactam antibiotic treatment for invasive Streptococcus pyogenes infection	Wrong population

Abraham, 2016	Distribution of emm types of beta hemolytic streptococci associated with necrotizing fascitis: Clinical profile and outcome	Wrong population
Acosta, 2014	Severe Maternal Sepsis in the UK, 2011-2012: A National Case-Control Study	Wrong population
Adams, 2010	Investigation into an outbreak of invasive Group A Streptococcal (iGAS) infection at a general hospital in 2010	Wrong population
Adem, 2009	Identification of invasive streptococcal disease in a pediatric and infant death Cohort-Iowa, 2007-2008	Wrong population
Afifi, 2008	Acute necrotizing fasciitis in Egyptian patients: A case series	Wrong population
Al-Khadidi, 2017	Group A Streptococcal bacteraemia. Experience at King Fahad Medical City in Riyadh, Saudi Arabia	Wrong population
Alva, 2013	Necrotising fasciitis: A series of seven cases	Wrong population
Anonymous, 2007	Summaries for patients. Invasive streptococcal infections in hospitals in Ontario, Canada, 1992 to 2000	Wrong population
Aronoff, 2008	Postpartum invasive group A streptococcal disease in the modern era	Wrong population
Babbar, 2018	Pivotal Role of Preexisting Pathogen-Specific Antibodies in the Development of Necrotizing Soft-Tissue Infections	Wrong population
Babbar, 2016	A serological evaluation of the host immune response during Necrotizing Soft Tissue Infections caused by Streptococcus pyogenes	Wrong population
Babiker, 2019	Impact of adjunctive clindamycin in invasive beta-hemolytic streptococcal infections: A propensity score-matched analysis of 1956 beta-lactam treated patients from 118 us hospitals	Wrong population
Bajpai, 1977	Chemotherapy of acute bone and joint infections	Wrong population
Barnham, 2001	Bacteraemic Streptococcus pyogenes infection in the peri-partum period: now a rare disease and prior carriage by the patient may be important	Wrong population
Basma, 1999	Risk factors in the pathogenesis of invasive group A streptococcal infections: Role of protective humoral immunity	Wrong population
Bauer, 2015	Maternal deaths due to sepsis in the state of Michigan, 1999-2006	Wrong population
Beaudoin, 2014	Invasive group A Streptococcus infections associated with liposuction surgery at outpatient facilities not subject to state or federal regulation	Wrong population
Beigh, 2012	Postoperative complications followed by septoplasty comparison between conventional nasal packing and glove finger pack	Wrong population
Berkley, 1987	The relationship of tampon characteristics to menstrual toxic shock syndrome	Wrong population
Bingol-Kologlu, 2007	Necrotizing fasciitis in children: diagnostic and therapeutic aspects	Wrong population
Bruun, 2013	Necrotizing soft tissue infections caused by Streptococcus pyogenes and Streptococcus dysgalactiae subsp. equisimilis of groups C and G in western Norway	Wrong population
Bruun, 2020	Risk factors and Predictors of Mortality in Streptococcal Necrotizing Soft-Tissue Infections: A Multicenter Prospective Study	Wrong population

Busowski, 2013	Puerperal group a streptococcal infections: A case series and discussion	Wrong population
Byer, 2006	Clinical deterioration among patients with fever and erythroderma	Wrong population
Centers for Disease, 1982	Toxic-shock syndrome, United States, 1970-1982	Wrong population
Centers for Disease, 2011	Invasive group A streptococcus in a skilled nursing facility--Pennsylvania, 2009-2010	Wrong population
Chan, 2009	Toxic shock syndrome and rhinosinusitis in children	Wrong population
Chen, 2011	The microbiological profile and presence of bloodstream infection influence mortality rates in necrotizing fasciitis	Wrong population
Chen, 2015	Clinical Characteristics and Risk Factor Analysis for Lower-Extremity Amputations in Diabetic Patients With Foot Ulcer Complicated by Necrotizing Fasciitis	Wrong population
Chen, 2018	Macro- and Microvascular Parameters After Toxic Shock Syndrome	Wrong population
Ching, 2019	Prospective surveillance of pediatric invasive group A Streptococcus infection	Wrong population
Chiobotaru, 1997	Changing epidemiology of invasive Streptococcus pyogenes infections in southern Israel: differences between two ethnic population groups	Wrong population
Christie, 1988	Bacteremia with group A streptococci in childhood	Wrong population
Corona, 2016	Necrotising fasciitis of the extremities: implementation of new management technologies	Wrong population
Daneman, 2007	Surveillance for hospital outbreaks of invasive group a streptococcal infections in Ontario, Canada, 1992 to 2000	Wrong population
Daneman, 2005	Hospital-acquired invasive group A streptococcal infections in Ontario, Canada, 1992-2000	Wrong population
Davies, 1996	Invasive group A streptococcal infections in Ontario, Canada. Ontario Group A Streptococcal Study Group	Wrong population
Davis, 1982	Toxic shock syndrome: a critique of the 1980 Wisconsin case-control study	Wrong population
De Almeida Torres, 2013	Group a streptococcus meningitis in children	Wrong population
Deutscher, 2011	Incidence and severity of invasive Streptococcus pneumoniae, group A Streptococcus, and group B Streptococcus infections among pregnant and postpartum women	Wrong population
Devaney, 2015	Necrotising soft tissue infections: The effect of hyperbaric oxygen on mortality	Wrong population
Dooling, 2013	Investigation of a prolonged Group A Streptococcal outbreak among residents of a skilled nursing facility, Georgia, 2009-2012	Wrong population
Dworkin, 2009	The epidemiology of necrotizing fasciitis including factors associated with death and amputation	Wrong population
Eneli, 2007	Epidemiology and Outcome of Necrotizing Fasciitis in Children: An Active Surveillance Study of the Canadian Paediatric Surveillance Program	Wrong population
Factor, 2005	Risk factors for pediatric invasive group A streptococcal disease	Wrong population
Factor, 2003	Invasive group a streptococcal disease: Risk factors for adults	Wrong population

Fauno Thrane, 2017	Hyperbaric oxygen may only be optional in head and neck necrotizing fasciitis: a retrospective analysis of 43 cases and review of the literature	Wrong population
Fichtenbaum, 1993	Ehrlichiosis presenting as a life-threatening illness with features of the toxic shock syndrome	Wrong population
Flavahan, 2014	Incidence of periorbital necrotising fasciitis in the UK population: A BOSU study	Wrong population
Flores, 2019	Capsule-negative EMM types are an increasing cause of pediatric group a streptococcal infections at a large pediatric hospital in Texas	Wrong population
Frere, 2016	Clinical and Microbiological Characteristics of Invasive Group A Streptococcal Infections Before and After Implementation of a Universal Varicella Vaccine Program	Wrong population
Givner, 1998	Invasive disease due to group A beta-hemolytic streptococci: Continued occurrence in children in North Carolina	Wrong population
Givner, 1991	Apparent increase in the incidence of invasive group A beta-hemolytic streptococcal disease in children	Wrong population
Gooskens, 2005	Streptococcal toxic shock syndrome by an iMLS resistant M type 77 Streptococcus pyogenes in the Netherlands	Wrong population
Gonzalez, 1996	Necrotizing fasciitis of the upper extremity	Wrong population
Lesko, 2001	Invasive group A streptococcal infection and nonsteroidal antiinflammatory drug use among children with primary varicella	Wrong population
Lin, 2013	Group a streptococcal necrotizing fasciitis in the emergency department	Wrong population
Lin, 2015	Early Differentiation of Kawasaki Disease Shock Syndrome and Toxic Shock Syndrome in a Pediatric Intensive Care Unit	Wrong population
Parks, 2019	Elevated risk of invasive group A streptococcal disease and host genetic variation in the human leucocyte antigen locus	Wrong population
Stromberg, 1991	Outbreak of group A streptococcal bacteremia in Sweden: an epidemiologic and clinical study	Wrong population
Haggar, 2012	Clinical and microbiologic characteristics of invasive Streptococcus pyogenes infections in north and south India	Relationship between prognostic factor and outcome not reported or quantified
Laupland, 2000	Invasive group A streptococcal disease in children and association with varicella-zoster virus infection. Ontario Group A Streptococcal Study Group	Relationship between prognostic factor and outcome not reported or quantified
Linnemann, 1986	Increasing incidence of toxic shock syndrome in the 1970s	Relationship between prognostic factor and outcome not reported or quantified
Miday, 1988	Toxic shock syndrome: incidence and geographic distribution from a hospital medical records reporting system	Relationship between prognostic factor and outcome not reported or quantified
Mosites, 2018	Outbreak of Invasive Infections from Subtype emm26.3 Group A Streptococcus among Homeless Adults-Anchorage, Alaska, 2016-2017	Relationship between prognostic factor and outcome not reported or quantified

O'Grady, 2007	The epidemiology of invasive group A streptococcal disease in Victoria, Australia	Relationship between prognostic factor and outcome not reported or quantified
Petitti, 1989	Update through 1985 on the incidence of toxic shock syndrome among members of a prepaid health plan	Relationship between prognostic factor and outcome not reported or quantified
Pilon, 2019	Invasive group A streptococcal infection outbreaks of typeemm118 in a long-term care facility, and of type emm74 in the homeless population, Montreal, Quebec	Relationship between prognostic factor and outcome not reported or quantified
Rantala, 2012	Streptococcus pyogenes bacteraemia, emm types and superantigen profiles	Relationship between prognostic factor and outcome not reported or quantified
Tanner, 1981	Toxic shock syndrome	Relationship between prognostic factor and outcome not reported or quantified
Teatero, 2018	Canada-Wide Epidemic of emm74 Group A Streptococcus Invasive Disease	Relationship between prognostic factor and outcome not reported or quantified
Todd, 1985	Toxic shock syndrome. II. Estimated occurrence in Colorado as influenced by case ascertainment methods	Relationship between prognostic factor and outcome not reported or quantified
Tsai, 2014	Correlation of virulence genes to clinical manifestations and outcome in patients with Streptococcus dysgalactiae subspecies equisimilis bacteremia	Relationship between prognostic factor and outcome not reported or quantified
Vallalta Morales, 2006	Group A streptococcal bacteremia: outcome and prognostic factors	Relationship between prognostic factor and outcome not reported or quantified
Vlaminckx, 2004	Epidemiological features of invasive and noninvasive group A streptococcal disease in the Netherlands, 1992-1996	Relationship between prognostic factor and outcome not reported or quantified
Aydin, 2017	Clinical indications of intravenous immunoglobulin use in pediatric infectious diseases clinic	Relationship between prognostic factor and outcome not reported or quantified
Ben-Abraham, 2002	Invasive group A streptococcal infections in a large tertiary center: epidemiology, characteristics and outcome	Relationship between prognostic factor and outcome not reported or quantified
Bochicchio, 2001	Group A Streptococcus (GAS) soft-tissue infections: a lethal organism on the rise	Relationship between prognostic factor and outcome not reported or quantified
Cancellara, 2016	Multicenter study on invasive Streptococcus pyogenes infections in children in Argentina	Relationship between prognostic factor and

		outcome not reported or quantified
Chen, 2016	Toxic shock syndrome in Australian children	Relationship between prognostic factor and outcome not reported or quantified
Doctor, 1995	Group A beta-hemolytic streptococcal bacteremia: historical overview, changing incidence, and recent association with varicella	Relationship between prognostic factor and outcome not reported or quantified
Eriksson, 2003	Group A streptococcal infections in Sweden: a comparative study of invasive and noninvasive infections and analysis of dominant T28 emm28 isolates	Relationship between prognostic factor and outcome not reported or quantified
Norrby-Teglund, 2003	The treatment of severe group a streptococcal infections	Relationship between prognostic factor and outcome not reported or quantified
Rodriguez-Nunez, 2011	Clinical characteristics of children with group A streptococcal toxic shock syndrome admitted to pediatric intensive care units	Relationship between prognostic factor and outcome not reported or quantified
Snall, 2016	Differential neutrophil responses to bacterial stimuli: Streptococcal strains are potent inducers of heparin-binding protein and resistin-release	Relationship between prognostic factor and outcome not reported or quantified
Eriksson, 1998	Epidemiological and clinical aspects of invasive group A streptococcal infections and the streptococcal toxic shock syndrome	Relationship between prognostic factor and outcome not reported or quantified
Sahli, 2014	Necrotizing fasciitisin in diabetic patients: A report of 14 cases	Not in English
Arnholm, 2004	High-dose immunoglobulin - Life-saving in invasive group a streptococcal infection	Not in English
Caetano, 2010	[S. Pyogenes invasive disease in a paediatric hospital: 1996-2009]	Not in English
Costa Orvay, 2007	[Toxic shock syndrome: experience in a pediatric intensive care unit]	Not in English
Dosil Gallardo, 2009	[Streptococcal toxic shock syndrome: an emerging pathology?]	Not in English
Emmi, 1999	Severe infection from invasive beta-hemolytic streptococcus group A. Three cases of toxic shock observed in resuscitation	Not in English
Faye, 2014	Management of severe invasive group A streptococcal infections	Not in English
Floret, 2001	Clinical aspects of staphylococcal and streptococcal toxinic diseases	Not in English
Hua, 2018	[Streptococcal toxic shock syndrome caused by Streptococcus pyogenes: a retrospective study of 15 pediatric cases]	Not in English
Kach, 1993	[Necrotizing soft tissue infections]	Not in English
Kaul, 1999	Intravenous immunoglobulin therapy for streptococcal toxic shock syndrome--a comparative observational study. The Canadian Streptococcal Study Group	Duplicate
Salinas, 2005	Immunoglobulins in sepsis and septic shock	Not in English

Shands, 1982	Toxic shock syndrome: case-control studies at the Centers for Disease Control	Duplicate
Sierra, 2006	Group A streptococcal infections in injection drug users in Barcelona, Spain: epidemiologic, clinical, and microbiologic analysis of 3 clusters of cases from 2000 to 2003	Duplicate
Urbina, 2019	Early identification of patients at high risk of group A streptococcus-associated necrotizing skin and soft tissue infections: A retrospective cohort study	Duplicate
Vallalta-Morales, 2005	[Streptococcal toxic shock syndrome: ten years' experience at a tertiary hospital]	Not in English
Vasant, 2019	Mass prophylaxis in an outbreak of invasive group A streptococcal disease in a residential aged care facility	Duplicate
Vugia, 1996	Invasive group A streptococcal infections in children with varicella in Southern California	Duplicate
Zachariadou, 2014	Differences in the epidemiology between paediatric and adult invasive Streptococcus pyogenes infections	Duplicate
Bernard, 1995	[Bacterial dermo-hypodermatitis in adults. Incidence and role of streptococcal etiology]	Not in English
Bleton, 1991	Necrotizing fasciitis of the upper limb. 12 cases	Not in English
Bleton, 1991	Necrotising fasciitis of the upper limb. Report of twelve cases	Duplicate
Fan, 2014	[Clinical characteristics and antimicrobial resistance of invasive group A beta-hemolytic streptococcus infection in children]	Not in English
Fica, 2003	Molecular epidemiology of a streptococcus pyogenes related nosocomial outbreak in a burn unit	Not in English
Fredlund, 1990	[Increased frequency of group A hemolytic streptococci. Old age and immune deficiency among the risk factors]	Not in English
Georgiev, 1993	Puerperal streptococcal sepsis	Not in English
Khan, 2003	Treatment of necrotizing fasciitis with quinolones	Wrong population
Frosi, 1999	Necrotizing fasciitis: A serious and uncommon alcohol related disease	Wrong study design
Nedrebo, 2020	Necrotizing Soft Tissue Infections: Case Reports, from the Clinician's Perspectives.	Wrong study design
Reicher, 2021	450 Obstetrically related group a streptococcal infection and predictors for severity - retrospective 12-year cohort study	Wrong study design
Bajpai, 2020	Anti-microbial-resistance and profile of exotoxins of invasive beta-haemolytic-streptococci infections in trauma patients	Wrong population
Adamkova, 2020	Can gram-negative-like biomarker values in Streptococcus pyogenes sepsis negatively influence right choice of initial antibiotic therapy?	Wrong population
Bandi, 2021	Group A streptococcal infections in children	Wrong population
Ceccato, 2020	Use of corticosteroids in patients with severe CAP admitted to ICU, experience in a real-life setting	Wrong population
Tepper, 2021	Long-term safety and tolerability of atogepant following once daily dosing over 1 year for the preventive treatment of migraine	Wrong population

Melo, 2021	Clinical, epidemiological and microbiological features of streptococcus pyogenes invasive infection - 10 year retrospective review	Wrong population
Bringel, 2021	Clinical characteristics and outcomes of children with toxic shock syndrome admitted to a pediatric intensive care unit: A case series	Wrong population
Neff, 2020	Characterisation of clinical manifestations and treatment strategies for invasive beta-haemolytic streptococcal infections in a Swiss tertiary hospital.	Wrong population
Urbina, 2020	Assessing and applying individualized treatment for group A streptococcal necrotizing soft-tissue infection is possible	Wrong population
Bergsten, 2020	Correlation between immunoglobulin dose administered and plasma neutralization of streptococcal superantigens in patients with necrotizing soft tissue infections	Wrong population
Boukthir, 2020	A prospective survey of Streptococcus pyogenes infections in French Brittany from 2009 to 2017: Comprehensive dynamic of new emergent emm genotypes.	Wrong population
Escrihuela-Vidal, 2021	Clinical Features and Outcomes of Streptococcus anginosus Group Infective Endocarditis: A Multicenter Matched Cohort Study.	Wrong population
Babiker, 2021	Effectiveness of adjunctive clindamycin in beta-lactam antibiotic-treated patients with invasive beta-haemolytic streptococcal infections in US hospitals: a retrospective multicentre cohort study.	Wrong population
Cui, 2021	Necrotizing soft tissue infection: clinical characteristics, diagnosis, and management of 32 cases in Beijing.	Wrong population
Link-Gelles, 2020	Characteristics of Intracranial Group A Streptococcal Infections in US Children, 1997-2014.	Wrong population
Peetermans, 2020	Use of Intravenous Immunoglobulins in Patients with Suspected Toxin-Mediated Shock Requiring Extracorporeal Membrane Oxygenation.	Wrong population
Bruun, 2020	Beta-Hemolytic Streptococci and Necrotizing Soft Tissue Infections.	Wrong population
Lima-Setta, 2021	Multisystem inflammatory syndrome in children (MIS-C) during SARS-CoV-2 pandemic in Brazil: a multicenter, prospective cohort study.	Wrong population
Kohler, 2020	Kininogen supports inflammation and bacterial spreading during Streptococccus Pyogenes Sepsis.	Wrong population
Bruun, 2021	Risk Factors and Predictors of Mortality in Streptococcal Necrotizing Soft-tissue Infections: A Multicenter Prospective Study.	Wrong population
Bjorck, 2020	Morbidity and mortality in critically ill patients with invasive group A streptococcus infection: an observational study.	Wrong population
Contou, 2021	Menstrual toxic shock syndrome: a French nationwide multicenter retrospective study.	Wrong population
Billon, 2020	Association of characteristics of tampon use with menstrual toxic shock syndrome in France.	Wrong population
Canetti, 2021	Invasive Group A Streptococcus Infection in Children in Central Israel in 2012-2019	Relationship between prognostic factor and outcome not reported or quantified

Vilhonen, 2020	Group A streptococcal bacteremias in Southwest Finland 2007-2018: epidemiology and role of infectious diseases consultation in antibiotic treatment selection.	Relationship between prognostic factor and outcome not reported or quantified
Thielemans, 2020	Clinical Description and Outcomes of Australian Children With Invasive Group A Streptococcal Disease.	Relationship between prognostic factor and outcome not reported or quantified
Madsen, 2020	Treatment of Necrotizing Soft Tissue Infections: IVIG	Wrong study design
Deniskin, 2019	Clinical Manifestations and Bacterial Genomic Analysis of Group A Streptococcus Strains That Cause Pediatric Toxic Shock Syndrome.	Relationship between prognostic factor and outcome not reported or quantified
Mosites, 2018	Outbreak of Invasive Infections From Subtype emm26.3 Group A Streptococcus Among Homeless Adults-Anchorage, Alaska, 2016-2017.	Relationship between prognostic factor and outcome not reported or quantified
Hasin, 2020	Invasive Group A Streptococcus Infection in Children in Southern Israel Before and After the Introduction of Varicella Vaccine.	Wrong population
Ching, 2019	Prospective Surveillance of Pediatric Invasive Group A Streptococcus Infection.	Wrong population
Loewen, 2017	Epidemiologic features of invasive group A Streptococcus infection in a rural hospital: 6-year retrospective report and literature review.	Wrong population
Bergsten, 2020	Correlation Between Immunoglobulin Dose Administered and Plasma Neutralization of Streptococcal Superantigens in Patients With Necrotizing Soft Tissue Infections.	Wrong population
Kobayashi, 2016	A Cluster of Group A Streptococcal Infections in a Skilled Nursing Facility-the Potential Role of Healthcare Worker Presenteeism.	Wrong population
Adebanjo, 2020	Evaluating Household Transmission of Invasive Group A Streptococcus Disease in the United States Using Population-based Surveillance Data, 2013-2016.	Wrong population
Link-Gelles, 2020	Characteristics of Intracranial Group A Streptococcal Infections in US Children, 1997-2014.	Wrong population
Bruun, 2021	Risk Factors and Predictors of Mortality in Streptococcal Necrotizing Soft-tissue Infections: A Multicenter Prospective Study.	Wrong population
Shah, 2015	Role of intravenous immune globulin in streptococcal toxic shock syndrome and Clostridium difficile infection.	Wrong study design
Hayata, 2021	Nationwide study of mortality and survival in pregnancy-related streptococcal toxic shock syndrome.	Duplicate

Table of additional study characteristics

Study	Study Design	Country	Number of STSS cases	Mean age	% Male	Cardiovascular Disease (%)	Diabetes (%)	Presence of Necrotizing Fasciitis (%)	Probable GAS STSS (%)	Confirmed GAS STSS (%)	Prognostic factor and outcome combination of interest reported
Abuhammour 2004	Cohort	United States	2	9	100	NR	NR	NR	NR	NR	age - clinical cure/improvement^ age - ICU admission^ age - mortality^ any antibiotic - clinical cure/improvement^ any antibiotic - ICU admission any antibiotic - mortality
Adalat 2014	Cohort	United Kingdom, Ireland	29	4 (median)	62	NR	NR	28	38	62	IVIG - mortality
Al-Ajmi 2012	Case-series	Qatar	2	35	0	NR	NR	NR	0	100	age - clinical cure/improvement^ age - ICU admission^ age - mortality^
Barnham 2002	Case-series	England	12	57	64	NR	NR	58	17	83	age - ICU admission^ age - mortality^ any antibiotic - ICU admission any antibiotic - mortality clindamycin - ICU admission^ clindamycin - mortality emm type - ICU admission^ emm type - mortality^ immunocompromised - ICU admission^ immunocompromised - mortality IVIG - ICU admission IVIG - mortality IVIG - time to mortality^ NF - ICU admission NF - mortality NSAIDs - ICU admission NSAIDs - mortality
Bernaldo de Quiros 1997	Cohort	Spain	9	NR	NR	NR	NR	NR	NR	NR	immunocompromised - mortality^

Study	Study Design	Country	Number of STSS cases	Mean age	% Male	Cardiovascular Disease (%)	Diabetes (%)	Presence of Necrotizing Fasciitis (%)	Probable GAS STSS (%)	Confirmed GAS STSS (%)	Prognostic factor and outcome combination of interest reported
Brogan 1995	Case-series	United States	5	6	60	NR	NR	100	60	40	age - clinical cure/improvement^ age - hospital LOS^ age - ICU admission^ age - ICU LOS^ age - mortality^ NSAIDs - clinical cure/improvement^ NSAIDs - hospital LOS^ NSAIDS - ICU admission NSAIDs - ICU LOS^ NSAIDs - mortality sex - clinical cure/improvement sex - hospital LOS^ sex - ICU admission sex - ICU LOS^ sex - mortality
Butragueno Laiseca 2017	Case-series	Spain	13	2	50	NR	NR	15	15	85	acute renal failure - clinical cure/improvement^ acute renal failure - mechanical ventilation acute renal failure - mortality age - clinical cure/improvement^ age - ICU LOS^ age - mechanical ventilation^ age - mortality^ clindamycin - clinical cure/improvement^ clindamycin - ICU LOS^ clindamycin - mechanical ventilation^ clindamycin - mortality hemodialysis - clinical cure/imrpovement hemodialysis - mechanical ventilation hemodialysis - mortality IVIG - clinical cure/improvement IVIG - ICU LOS IVIG - mechanical ventilation IVIG - mortality NF - clinical cure/improvement NF - ICU LOS^ NF - mechanical ventilation NF - mortality
Carapetis 1995	Case-series	Australia	5	NR	NR	NR	NR	NR	NR	NR	age - mortality^

Study	Study Design	Country	Number of STSS cases	Mean age	% Male	Cardiovascular Disease (%)	Diabetes (%)	Presence of Necrotizing Fasciitis (%)	Probable GAS STSS (%)	Confirmed GAS STSS (%)	Prognostic factor and outcome combination of interest reported
Carapetis 2014	Cohort	Australia	37	60	50	NR	NR	100	0	100	age - mortality^ IVIG - mortality sex - mortality
Cimolai 1992	Case-series	Canada	4	8	50	NR	NR	NR	0	100	age - clinical cure/improvement^ age - mortality^ sex - clinical cure/improvement sex - mortality
Cook 2020	Cohort	United States	27	9	44	NR	NR	19	56	44	other - other^
Cowan 1994	Case-series	United States	3	2	67	NR	NR	NR	100	0	age - clinical cure/improvement^ age - ICU admission^ age - ICU LOS^ age - mechanical ventilation^ age - mortality^ sex - clinical cure/improvement sex - ICU admission sex - ICU LOS^ sex - mechanical ventilation sex - mortality
Crum 2004	Case-series	United States	2	24	100	NR	NR	50	0	100	age - clinical cure/improvement^ age - ICU admission^ age - mechanical ventilation^ age - mortality^ hemodialysis - clinical cure/improvement hemodialysis - ICU admission hemodialysis - mechanical ventilation hemodialysis - mortality
Dahl 2002	Case-series	United States	5	53	NR	NR	NR	100	0	100	age - mortality^ immunocompromised - mortality
Darenberg 2003	Randomized trial	Sweden, Norway, Finland, Netherlands	18	52	48	NR	NR	NR	11	89	IVIG - change in SOFA score^ IVIG - mortality IVIG - time to clinical cure/improvement^ IVIG - time to mortality^

Study	Study Design	Country	Number of STSS cases	Mean age	% Male	Cardiovascular Disease (%)	Diabetes (%)	Presence of Necrotizing Fasciitis (%)	Probable GAS STSS (%)	Confirmed GAS STSS (%)	Prognostic factor and outcome combination of interest reported
Donaldson 1993	Case-series	England	5	67	20	NR	NR	100	NR	NR	age - mortality^ any antibiotic - mortality sex - mortality
Erdem 2004	Case-series	United States	3	52	67	NR	NR	100	NR	33	age - mortality^ sex - mortality
Eriksson 1999	Cohort	Sweden	6	46	83	NR	NR	NR	0	100	age - mortality^ emm type - mortality^ sex - mortality
Forni 1995	Case-series	United States	5	54	83	NR	17	50	0	100	acure renal failure - ICU admission^ acute renal failure - mortality age - hospital LOS^ age - ICU admission^ age - mortality^ emm type - ICU admission^ emm type - mortality^ NF - ICU admission NF - mortality
Fronhoffs 2000	Case-series	Germany	7	49	71	14	14	86	86	14	acute renal failure - mechanical ventilation acute renal failure - mortality age - mechanical ventilation^ age - mortality^ immunocompromised - mechanical ventilation^ immunocompromised - mortality NF - mechanical ventilation NF - mortality NSAIDs - mechanical ventilation^ NSAIDs - mortality sex - mechanical ventilation sex - mortality
Hasegawa 2004	Case-control	Japan	66*	Range: 0 to 70	59	NR	18	NR	100	0	acute renal failure - mortality
Hayata 2021	Cohort	Japan	28	NR	0	NR	NR	NR	0	100	age - mortality^ NSAIDs - mortality

Study	Study Design	Country	Number of STSS cases	Mean age	% Male	Cardiovascular Disease (%)	Diabetes (%)	Presence of Necrotizing Fasciitis (%)	Probable GAS STSS (%)	Confirmed GAS STSS (%)	Prognostic factor and outcome combination of interest reported
Huang 2001	Case-series	Taiwan	3	6	100	NR	NR	NR	33	67	age - mortality^
Kansal 2000	Cohort	Canada	28	NR	NR	NR	NR	NR	NR	NR	NF - other^
Kaul 1999	Case-control	Canada	53	57	55	NR	NR	NR	NR	NR	clindamycin - mortality IVIG - duration of mechanical ventilation^ IVIG - hospital LOS IVIG - mortality NF - mortality
Linder 2017	Cohort	United States	10	NR	NR	NR	NR	NR	0	100	immunocompromised - mortality
Linnér 2014	Cohort	Sweden	67	63	42	48	16	28	NR	NR	age - mortality^ clindamycin - mortality IVIG - hospital LOS IVIG - mortality
Luca-Harari 2009	Cohort	Cyprus, Czech Republic, Denmark, Finand, France, Germany, Greece, Italy, Romania, Sweden, United Kingdom	476	NR	NR	NR	NR	NR	NR	NR	emm type - mortality^
Nelson 2016	Cohort	United States	381	NR	NR	NR	NR	19	NR	NR	age - mortality NF - mortality
O'Loughlin 2007	Cohort	United States	309	NR	NR	NR	NR	20	NR	NR	age - mortality NF - mortality
Page 2011	Cohort	Canada	16	NR	NR	NR	NR	NR	NR	NR	other - other^
Safar 2011	Cohort	New Zealand	30	NR	NR	NR	NR	17	0	100	age - mortality NF - mortality
Schwartz 1992	Case-series	United States	8	40	40	NR	NR	NR	0	100	age - mortality^ emm type - mortality^ sex - mortality
Shah 2009	Cohort	United States	192	8	49	NR	NR	NR	NR	NR	IVIG - cost^ IVIG - hospital LOS IVIG - ICU admission IVIG - ICU LOS IVIG - mechanical ventilation IVIG - mortality

Study	Study Design	Country	Number of STSS cases	Mean age	% Male	Cardiovascular Disease (%)	Diabetes (%)	Presence of Necrotizing Fasciitis (%)	Probable GAS STSS (%)	Confirmed GAS STSS (%)	Prognostic factor and outcome combination of interest reported
Sriskandan 2000	Cohort	England	7	NR	NR	NR	NR	NR	NR	NR	other - other^
Stegmayr 1992	Case-series	Sweden	11	42	64	NR	NR	NR	27	73	age - clinical cure/improvement^ age - ICU admission^ age - mechanical ventilation^ age - mortality^ hemodialysis - clinical cure/improvement hemodialysis - ICU admission hemodialysis - mechanical ventilation hemodialysis - mortality IVIG - clinical cure/improvement IVIG - ICU admission IVIG - mechanical ventilation IVIG - mortality NF - clinical cure/improvement NF - ICU admission NF - mechanical ventilation NF - mortality sex - clinical cure/improvement sex - ICU admission sex - mechanical ventilation sex - mortality
Stevens 1989	Case-series	United States	19	41	53	80	5	21	0	100	age - mortality^ emm type - mortality^ hemodialysis - mortality NF - mortality sex - mortality
Stockmann 2012	Cohort	United States	53	30 (median)	NR	58	19	32	NR	NR	age - ICU admission^ age - mortality
Tagini 2017	Case-series	Switzerland	5	18	60	NR	NR	NR	20	80	age - mortality^ emm type - mortality^ sex - mortality
Zachariadou 2013	Cohort	Greece	19	NR	NR	NR	NR	NR	0	100	age - mortality emm type - mortality^

*More than 80% of STSS cases due to group A *Streptococcus*
^Excluded from meta-analysis

NF=necrotizing fasciitis

NSAIDs=non-steroidal anti-inflammatory drugs
ICU=intensive care unit
IVIG=intravenous immunoglobulin
GAS=group A *Streptococcus*
STSS=streptococcal toxic shock syndrome
NR=not reported

Risk of bias assessment of included studies

Author	Study participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Presentation Summary	Overall Risk of Bias
Abuhammour 2004	Low	Low	Low	Low	High	High	High
Adalat 2014	Low	High	High	Low	High	High	High
Al-Ajmi 2012	NA	NA	NA	NA	NA	NA	High
Barnham 2002	NA	NA	NA	NA	NA	NA	High
Bernaldo de Quiros 1997	Low	Low	Low	Low	High	High	High
Brogan 1995	NA	NA	NA	NA	NA	NA	High
Butragueno Laiseca 2017	NA	NA	NA	NA	NA	NA	High
Carapetis 1995	NA	NA	NA	NA	NA	NA	High
Carapetis 2014	Low	Low	Low	Low	High	High	High
Cimolai 1992	NA	NA	NA	NA	NA	NA	High
Cook 2021	Low	Low	Low	Low	High	High	High
Cowan 1994	NA	NA	NA	NA	NA	NA	High
Crum 2004	NA	NA	NA	NA	NA	NA	High
Dahl 2002	NA	NA	NA	NA	NA	NA	High
Darenberg 2003	Low	Moderate	Low	Moderate	Low	Low	Moderate
Donaldson 1993	NA	NA	NA	NA	NA	NA	High
Erdem 2004	NA	NA	NA	NA	NA	NA	High
Eriksson 1999	Low	Low	Low	Low	High	High	High
Forni 1995	NA	NA	NA	NA	NA	NA	High
Fronhoffs 2000	NA	NA	NA	NA	NA	NA	High
Hasegawa 2004	Low	Low	Moderate	Low	High	High	High
Hayata 2021	Low	Low	Low	Low	High	High	High
Huang 2001	NA	NA	NA	NA	NA	NA	High
Kansal 2000	Moderate	Low	Moderate	Low	High	High	High
Kaul 1999	Low	Low	Low	Low	High	High	High

Linder 2017	Low	Moderate	Low	Moderate	High	High	High
Linner 2014	Low	Low	Low	Low	Moderate	Low	Low
Luca-Harari 2009	Low	High	Low	Low	High	High	High
Nelson 2016	Low	Low	Low	Low	High	High	High
O'Loughlin 2007	Low	Low	Low	Low	High	High	High
Page 2011	Low	Low	Low	Low	Moderate	High	Moderate
Safar 2011	Low	Low	Low	Low	High	High	High
Schwartz 1992	NA	NA	NA	NA	NA	NA	High
Shah 2009	Low	High	Low	Low	Moderate	Moderate	Moderate
Sriskandan 2000	Moderate	Moderate	High	Low	High	High	High
Stegmayr 1992	NA	NA	NA	NA	NA	NA	High
Stevens 1989	NA	NA	NA	NA	NA	NA	High
Stockmann 2012	Low	Low	Low	Low	High	High	High
Tagini 2017	NA	NA	NA	NA	NA	NA	High
Zachariadou 2013	Low	Low	Low	Low	High	High	High

NA, Not Applicable because case-series study design and rated at high risk of bias.

Forest plots

n_e: number of patients with the outcome exposed to or experiencing the prognostic factor (experimental group)
N_e: total number of patients exposed to or experiencing the prognostic factor (experimental group)
n_c: number of patients with the outcome not exposed to or experiencing the prognostic factor (control group)
N_c: total number of patients not exposed to or experiencing the prognostic factor (control group)

Percentages in forest plots correspond to the percent weight contribution of each study in the meta-analysis.

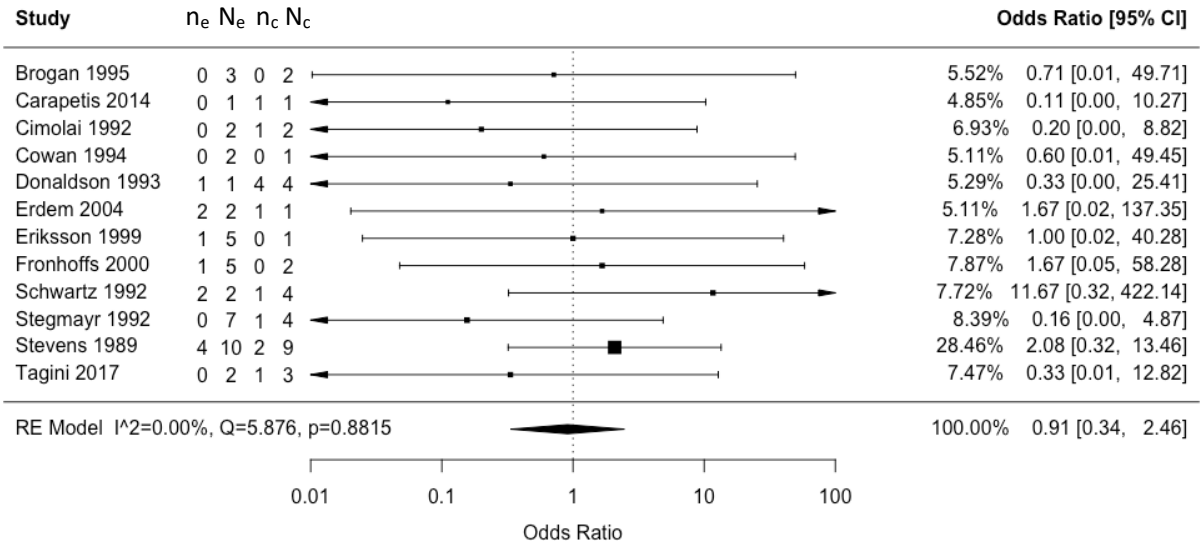
For mortality, ICU admission and need for mechanical ventilation outcomes, an odds ratio greater than 1 corresponds with a worse STSS prognosis and an odds ratio less than 1 corresponds with a better STSS prognosis.

For clinical cure or improvement outcome, an odds ratio greater than 1 corresponds with a better STSS prognosis and an odds ratio less than 1 corresponds with a worse STSS prognosis.

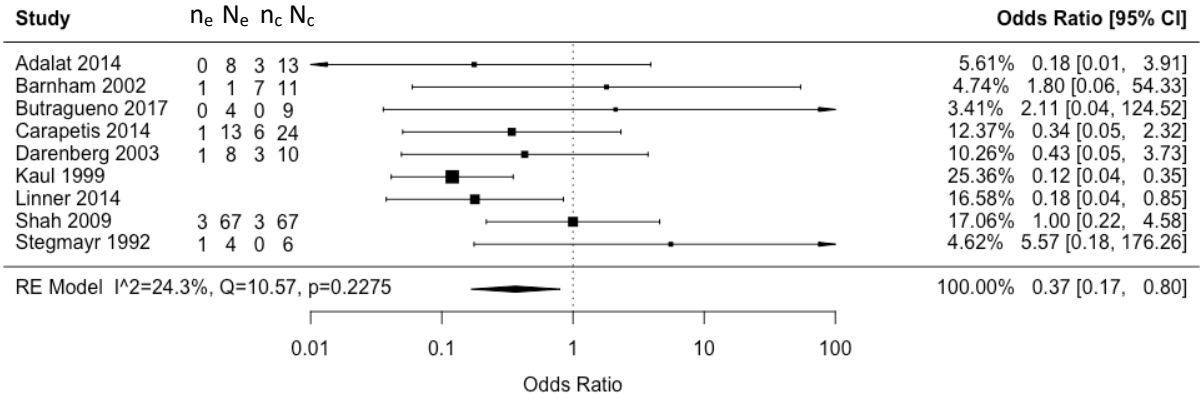
For duration of hospitalization and ICU stay outcomes, a mean difference greater than 1 corresponds with a worse STSS prognosis and a mean difference less than 1 corresponds with a better STSS prognosis.

Mortality

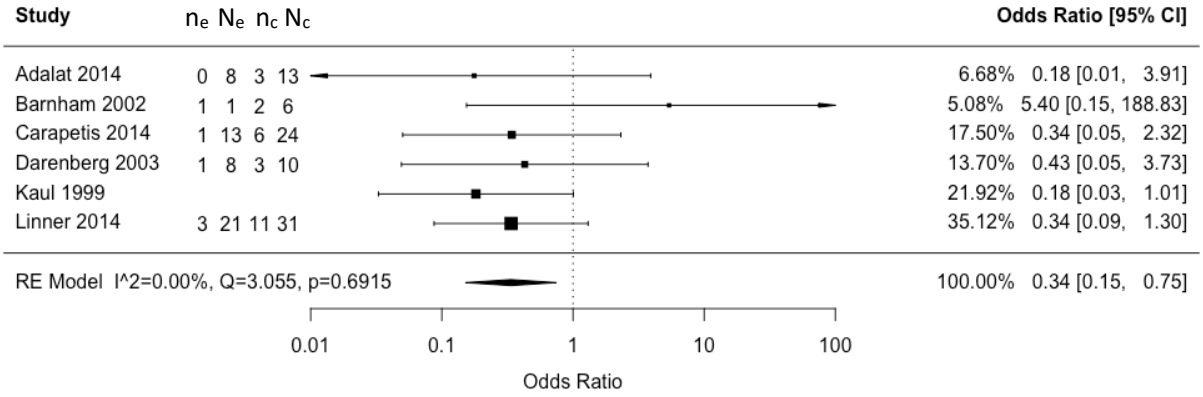
1. Sex: male vs female (reference)



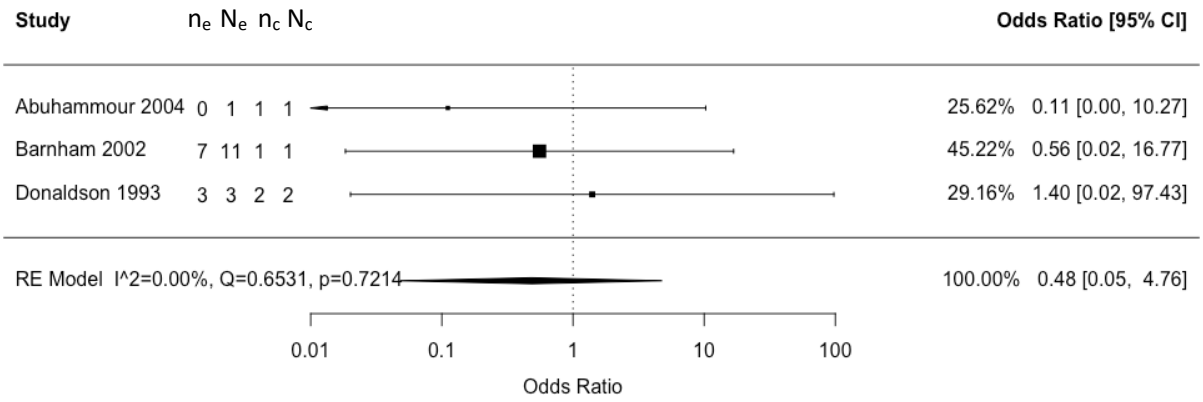
2.A) IVIG in all STSS patients: yes vs no (reference)

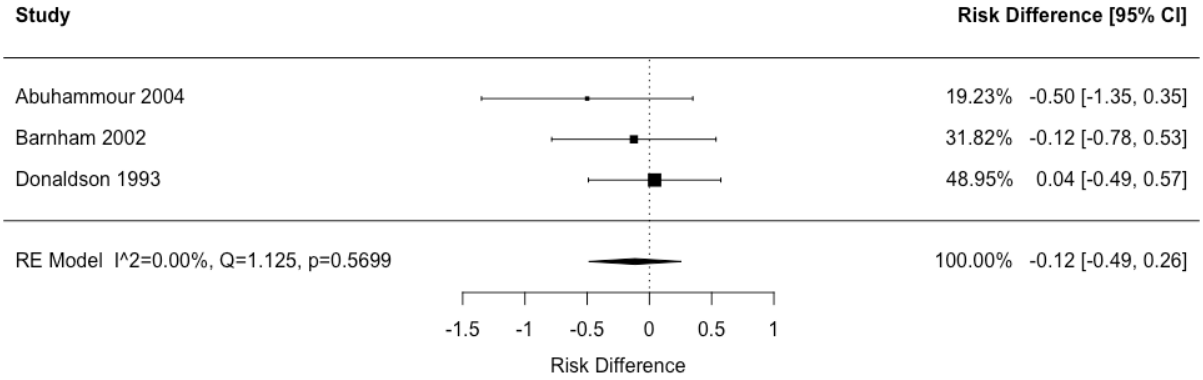


2.B) IVIG in the subset of STSS patients treated with clindamycin: yes vs no (reference)

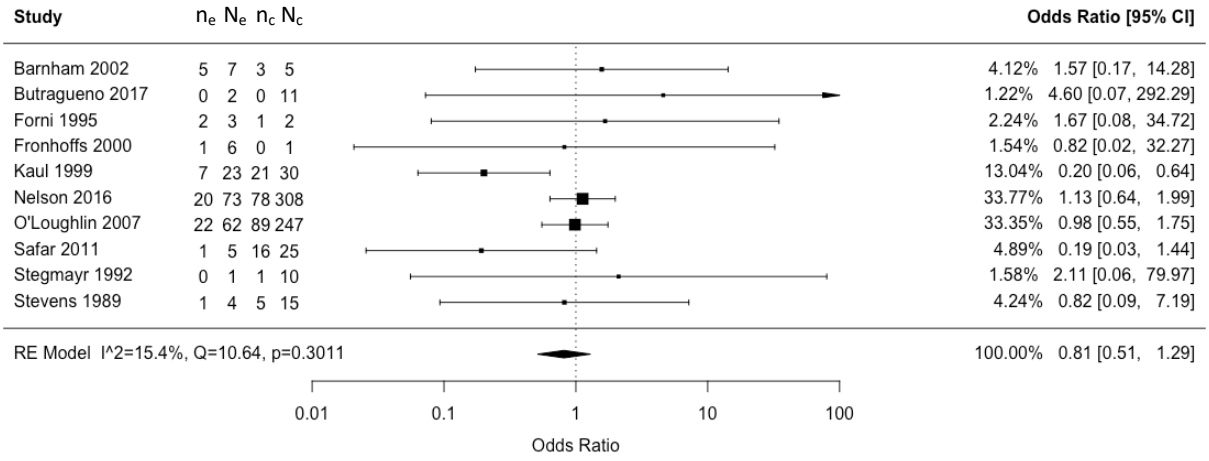


3. Any antibiotic: yes vs no (reference)

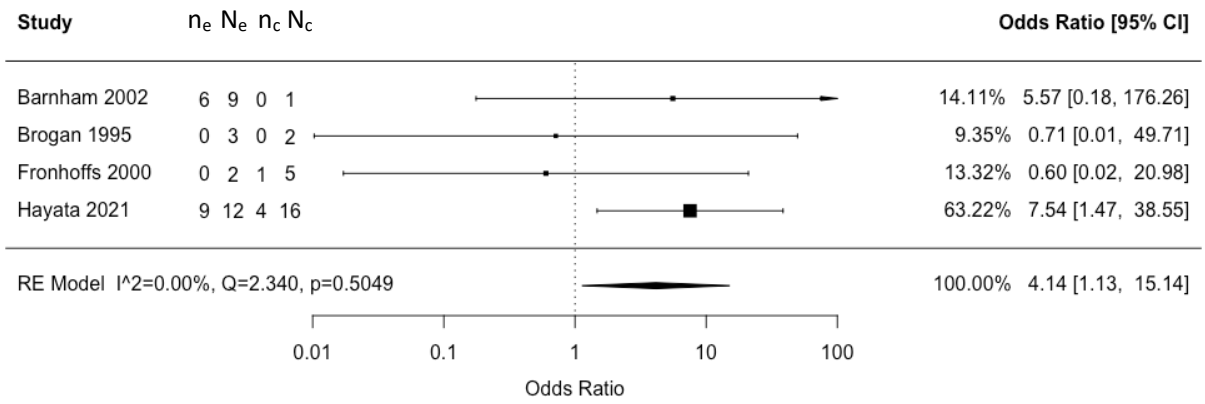




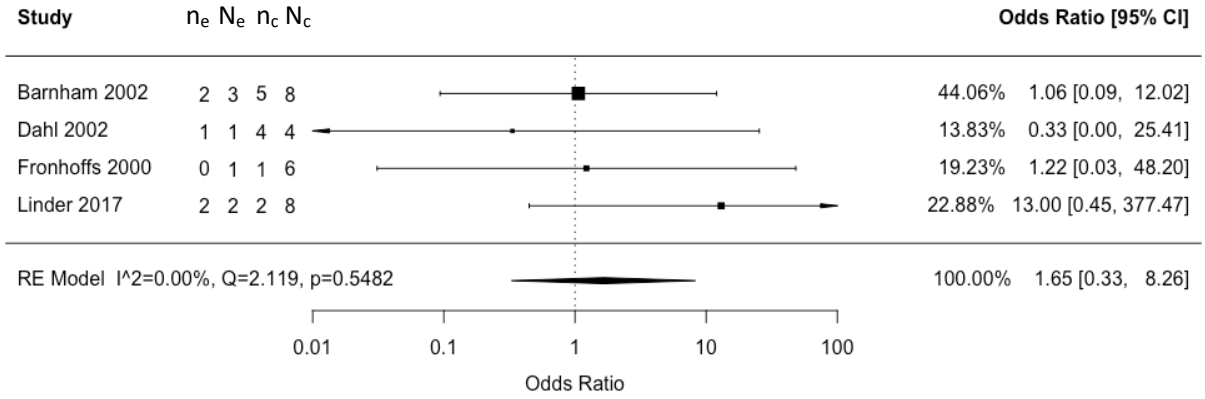
4. Necrotizing fasciitis: yes vs no (reference)



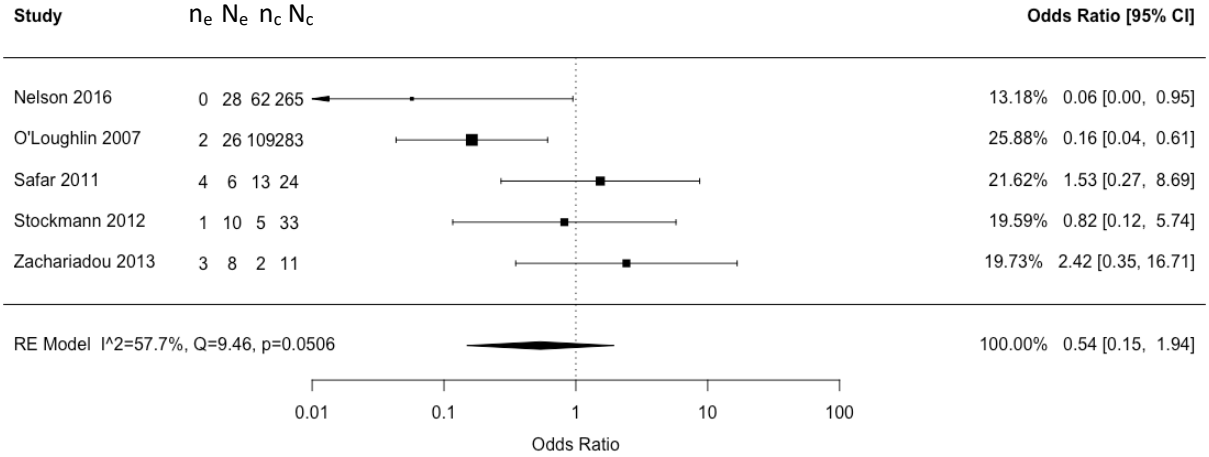
5. NSAIDs: yes vs no (reference)



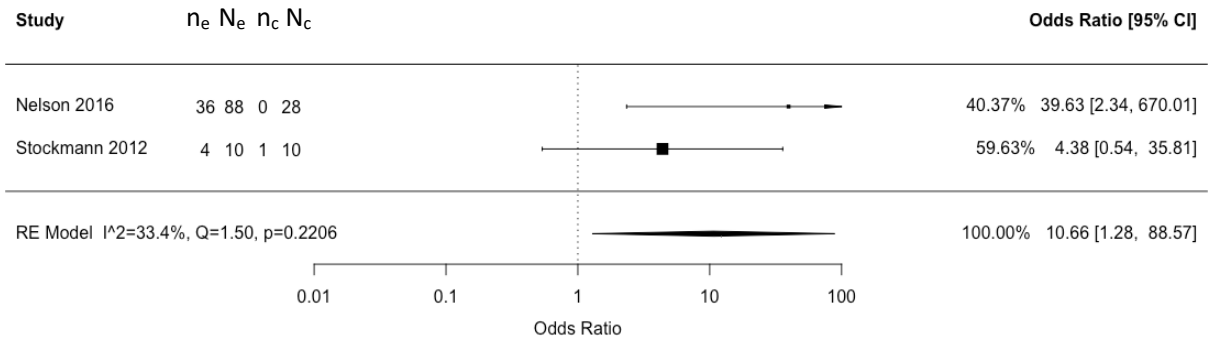
6. Immunocompromised: yes vs no (reference)



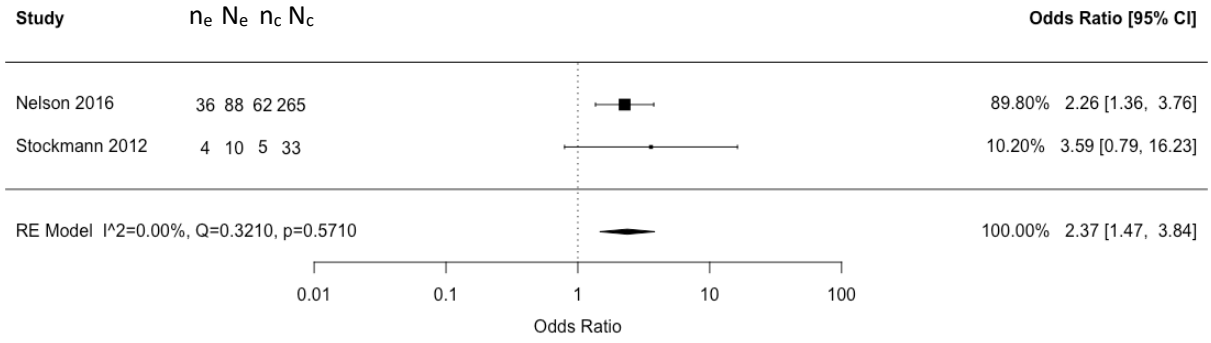
7. Age: <18 years vs 18-64 years (reference)



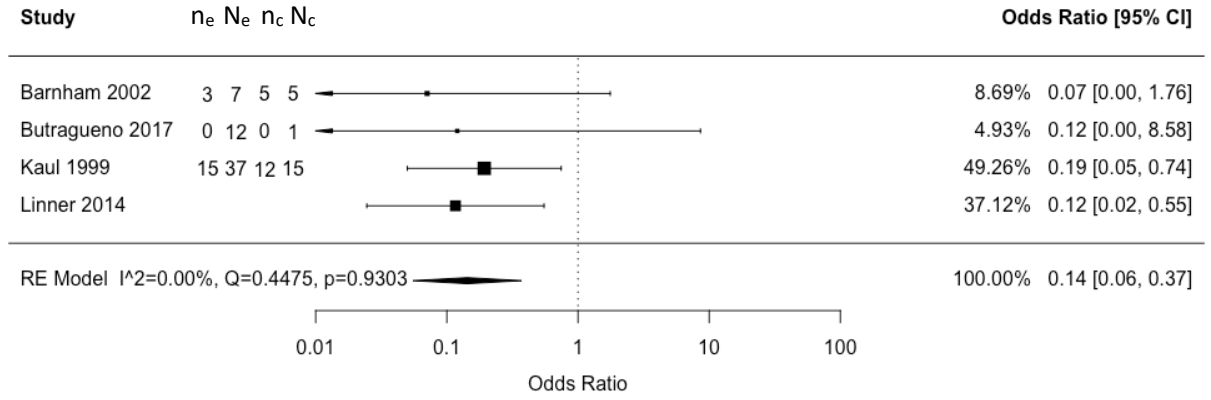
8. Age: ≥65 years vs <18 years (reference)



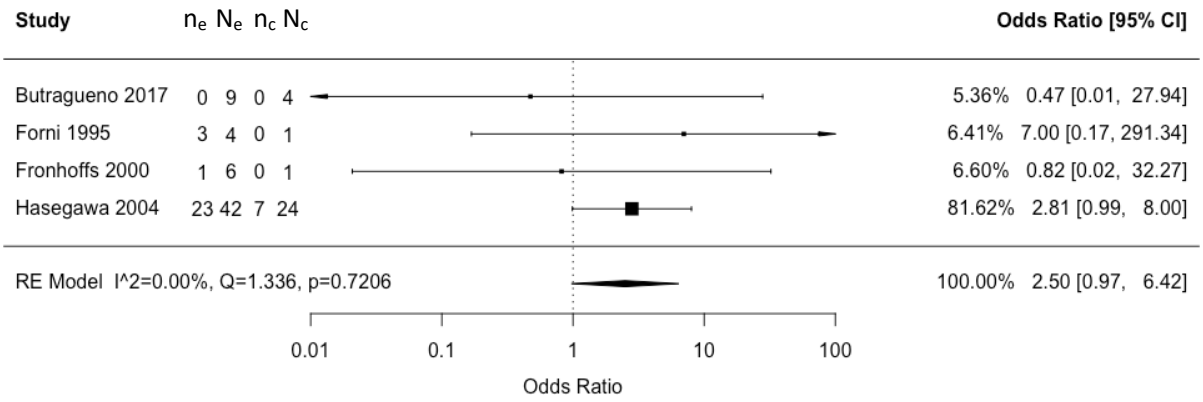
9: Age: ≥65 years vs 18-64 years (reference)

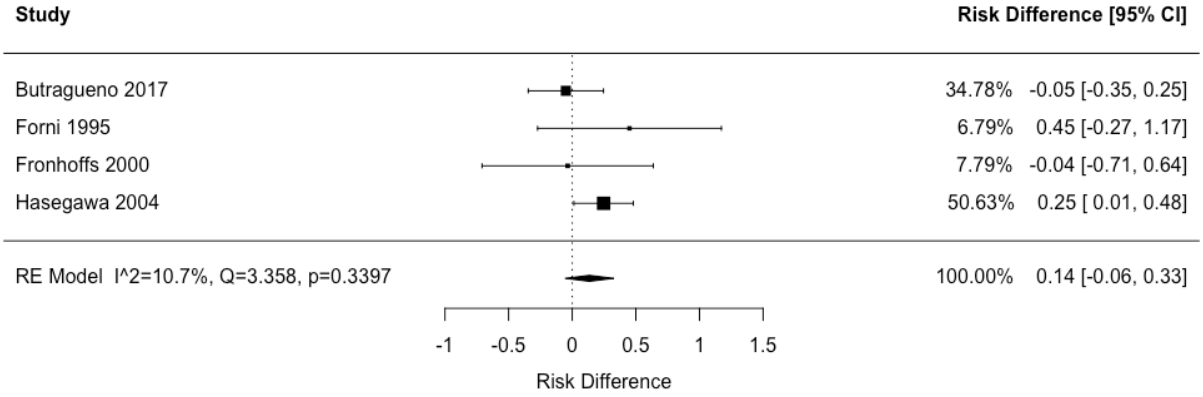


10. Clindamycin antibiotic vs no clindamycin antibiotic (reference)

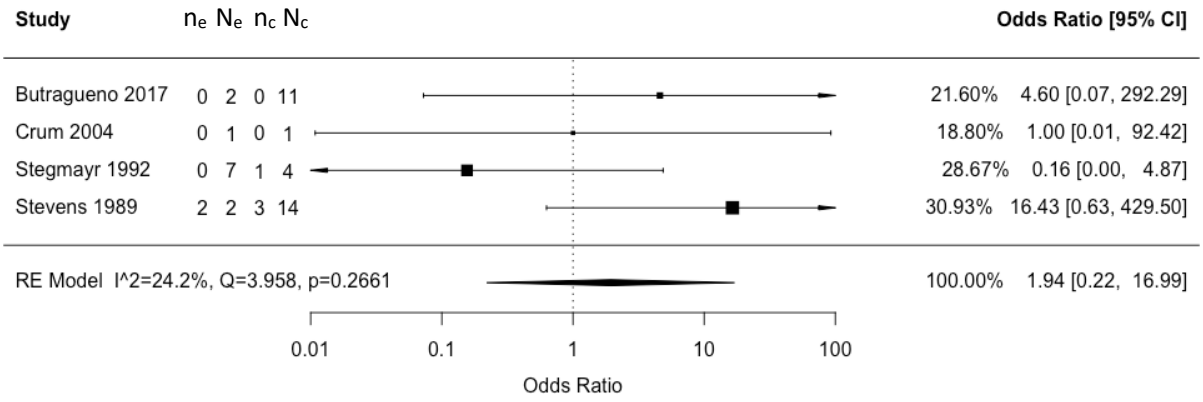


11. Acute renal failure: yes vs no (reference)





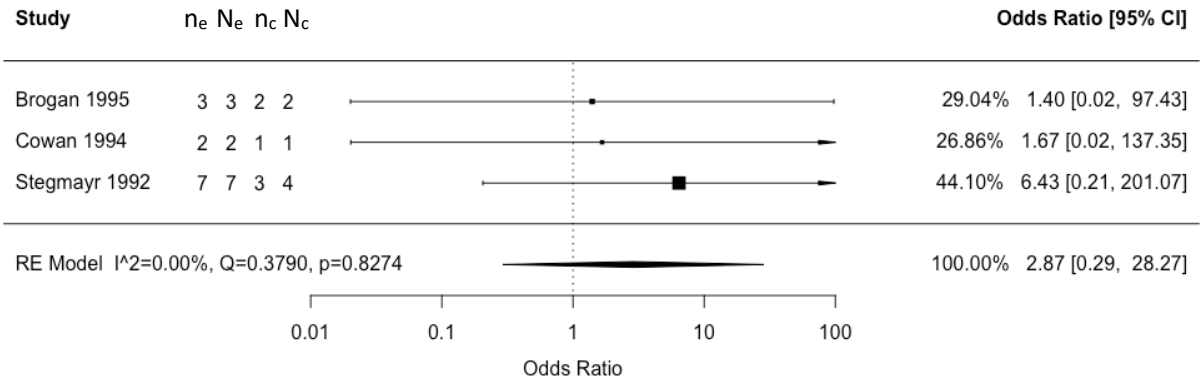
12. Hemodialysis: yes vs no (reference)

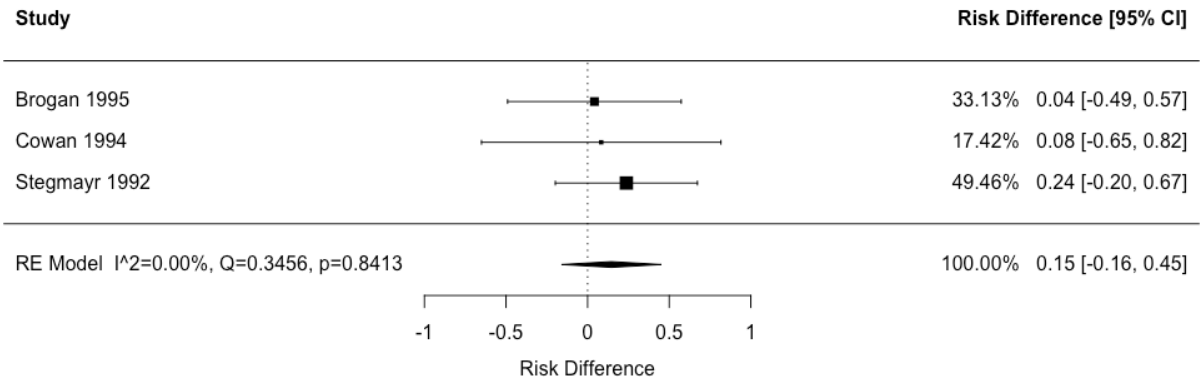


ICU admission

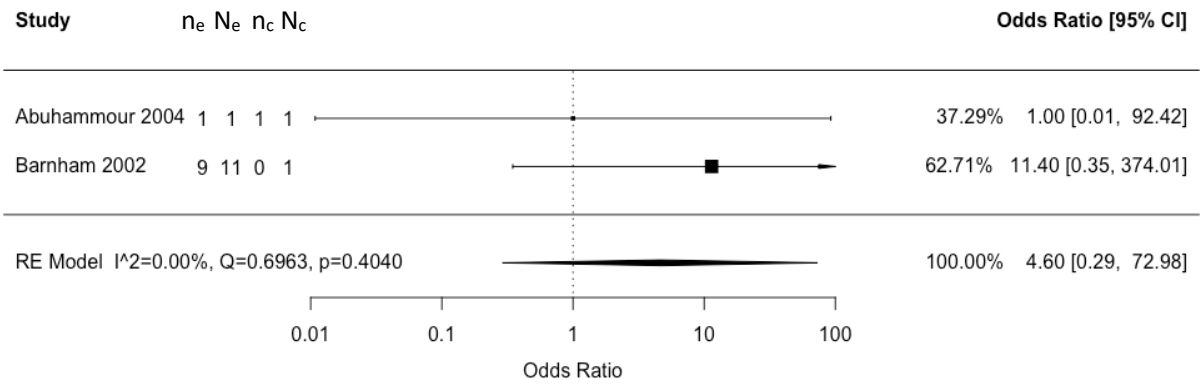
This note pertains to meta-analyses of the outcome ICU admission that include the study Stegmayr 1992. For this study, 10 of 11 STSS patients were admitted to the ICU. Despite no explicit mention of which one patient was not admitted to the ICU, our interpretation of the clinical profiles and patient-level data allowed us to deduce that patient 1 likely did not require ICU admission. We reached out to the corresponding author to confirm if our interpretation was correct, but did not receive a response.

1. Sex: male vs female (reference)

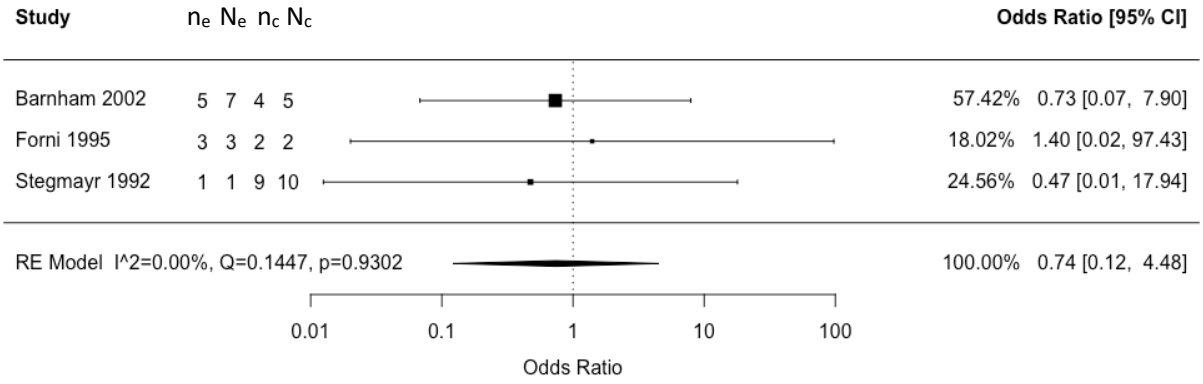




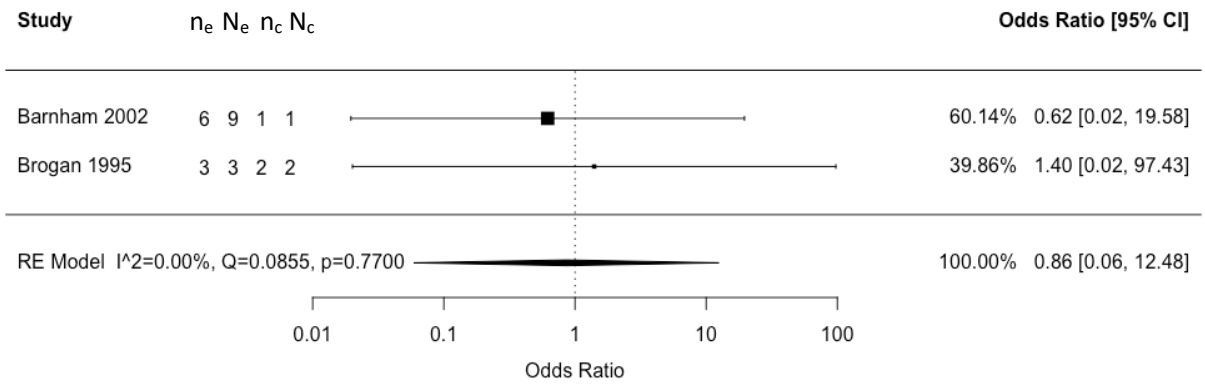
2. Any antibiotic: yes vs no (reference)

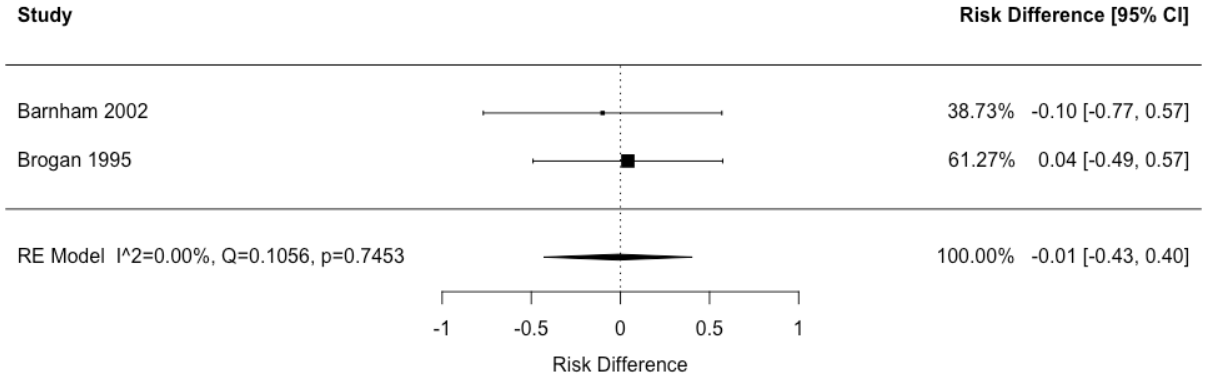


3. Necrotizing fasciitis: yes vs no (reference)

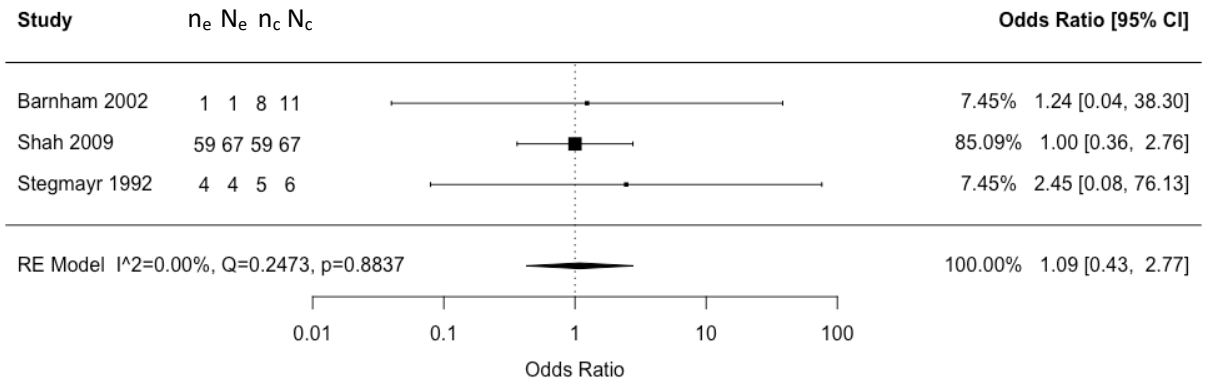


4. NSAIDs: yes vs no (reference)

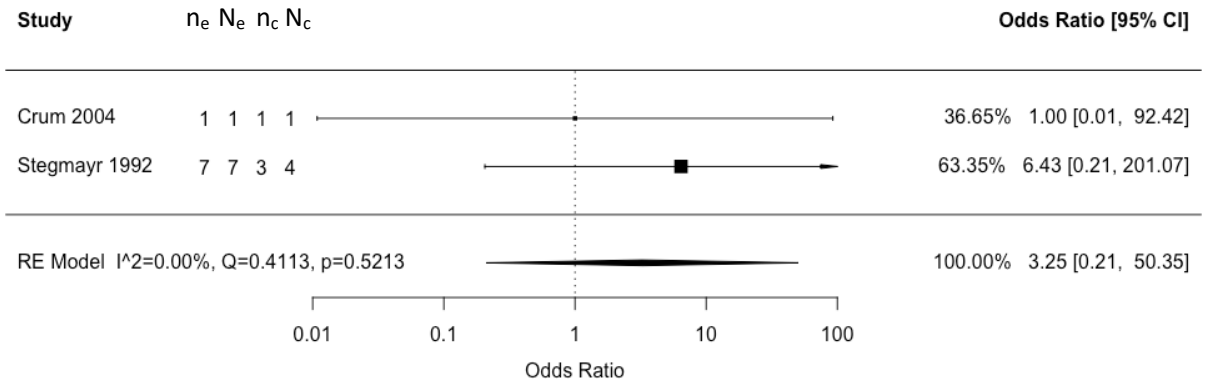




5. IVIG in all STSS patients: yes vs no (reference)

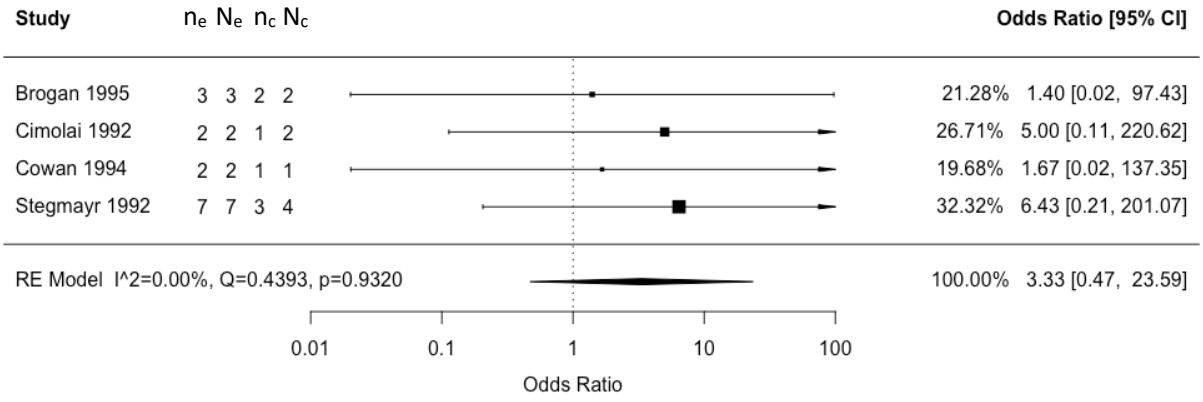


6. Hemodialysis: yes vs no (reference)

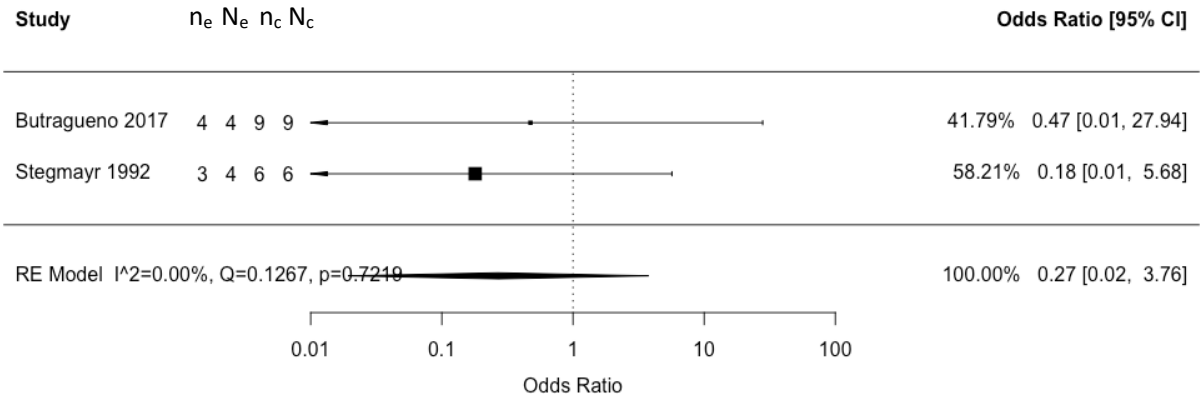


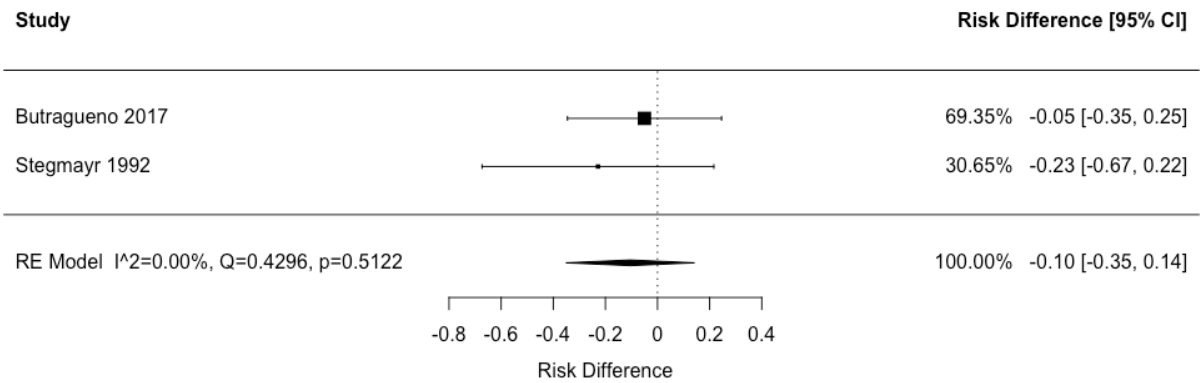
Clinical cure or improvement

1. Sex: male vs female (reference)

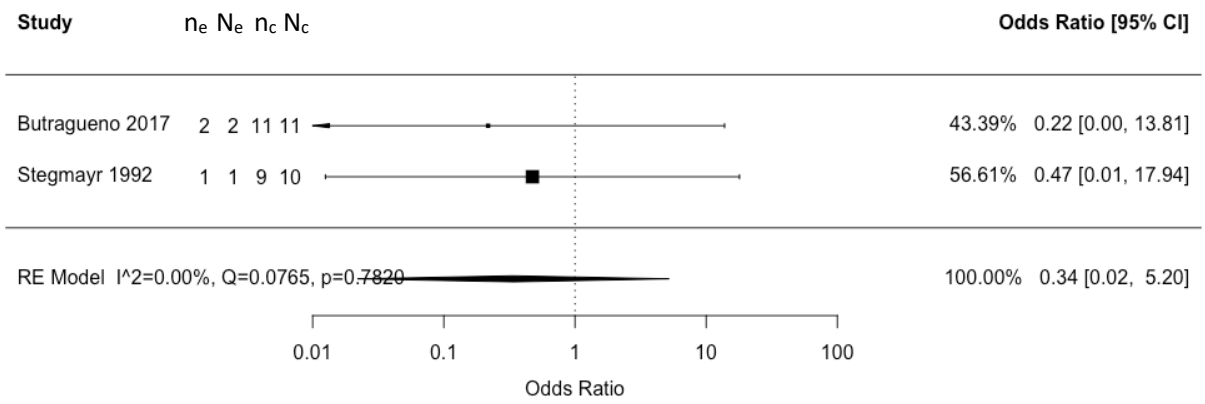


2. IVIG in all STSS patients: yes vs no (reference)

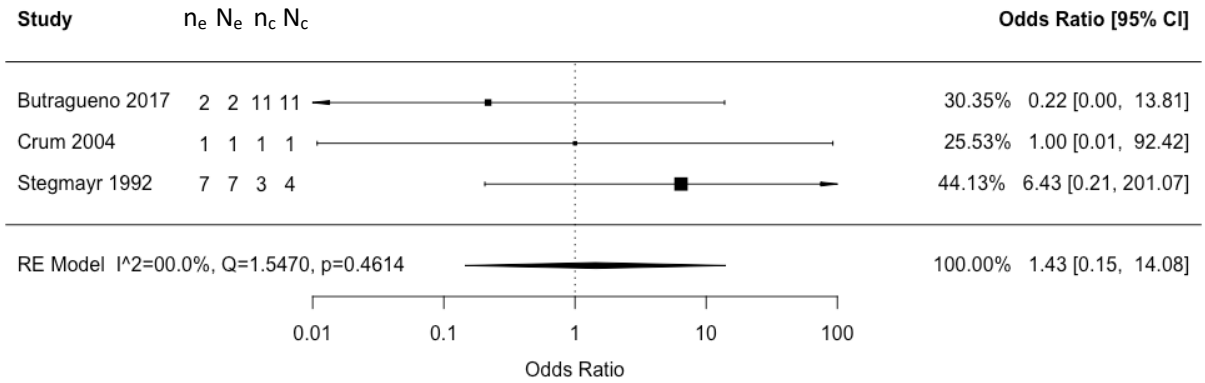


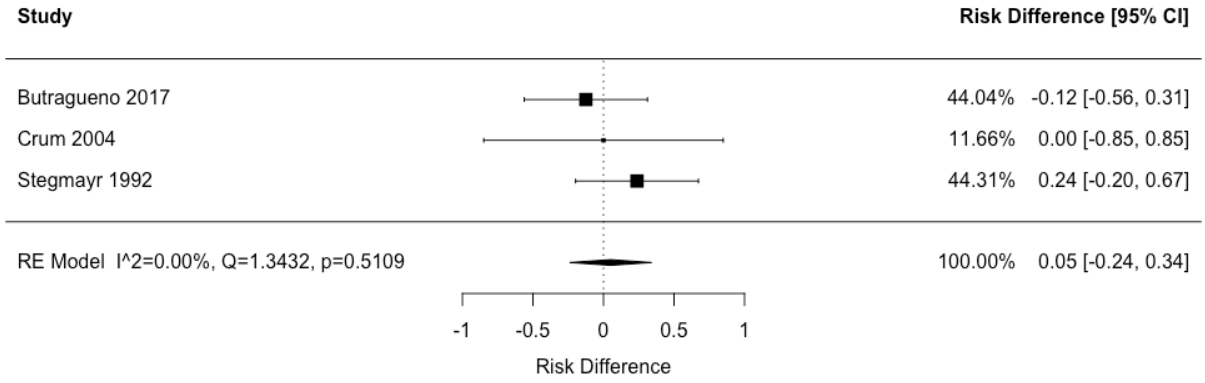


3. Necrotizing fasciitis: yes vs no (reference)



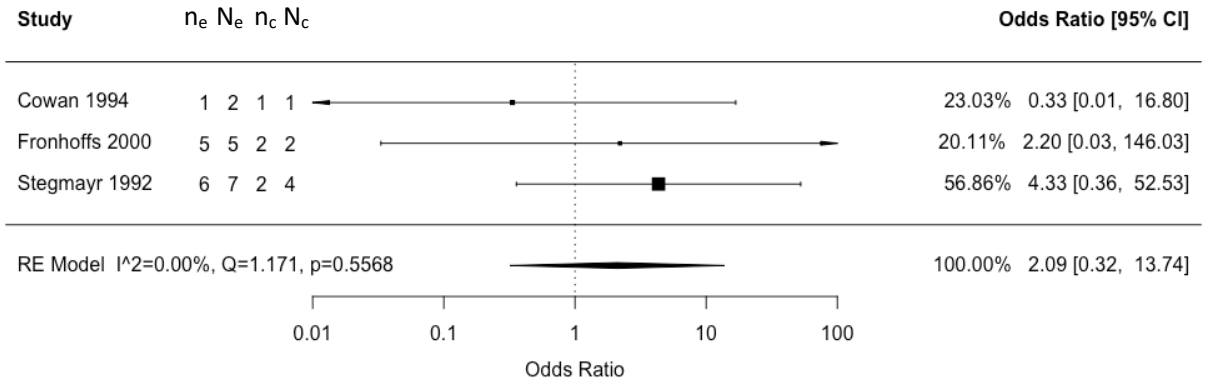
4. Hemodialysis: yes vs no (reference)

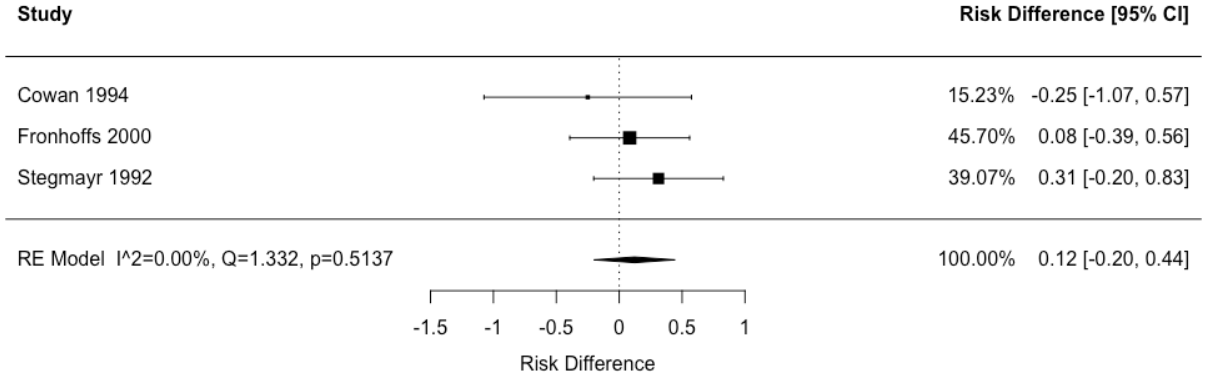




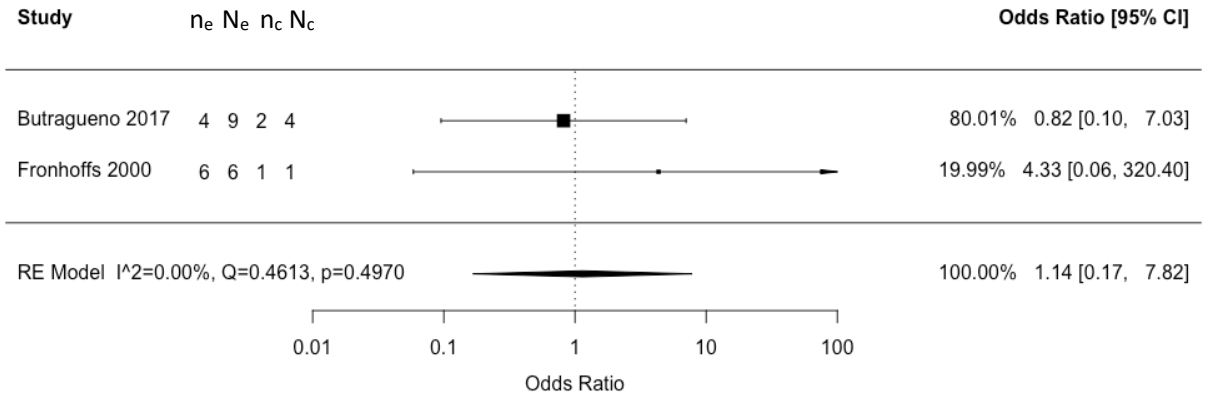
Mechanical ventilation

1. Sex: male vs female (reference)

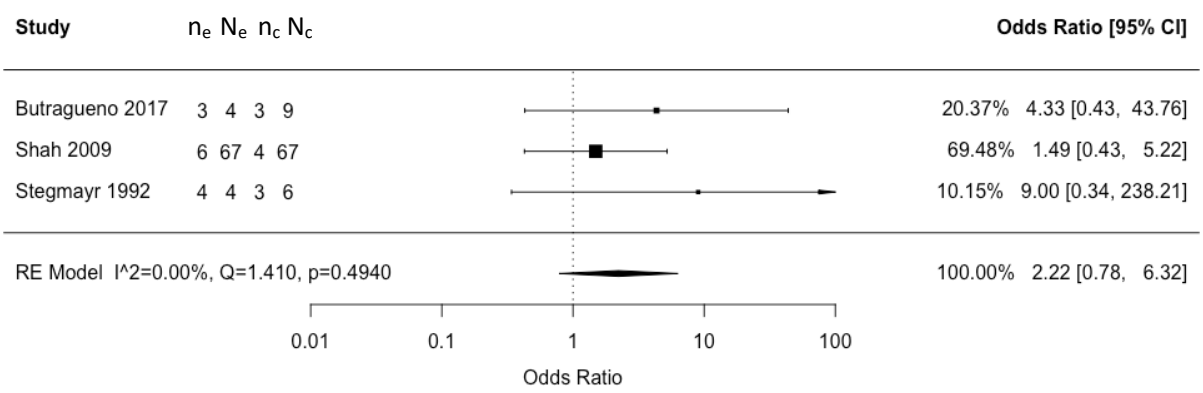




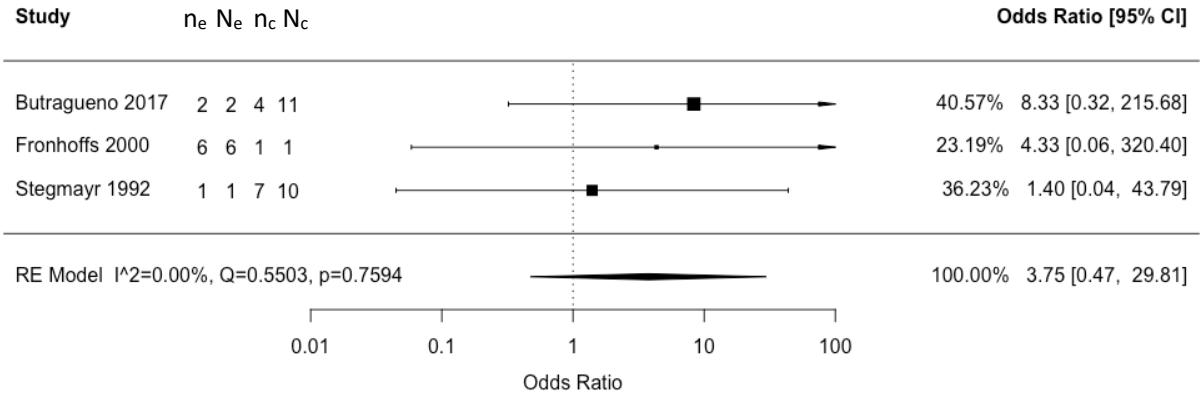
2. Acute renal failure: yes vs no (reference)



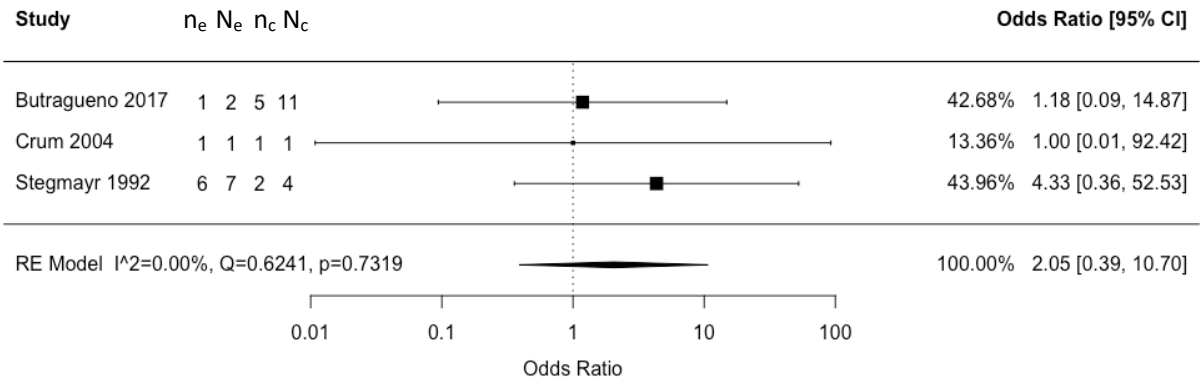
3. IVIG in all STSS patients: yes vs no (reference)



4. Necrotizing fasciitis: yes vs no (reference)

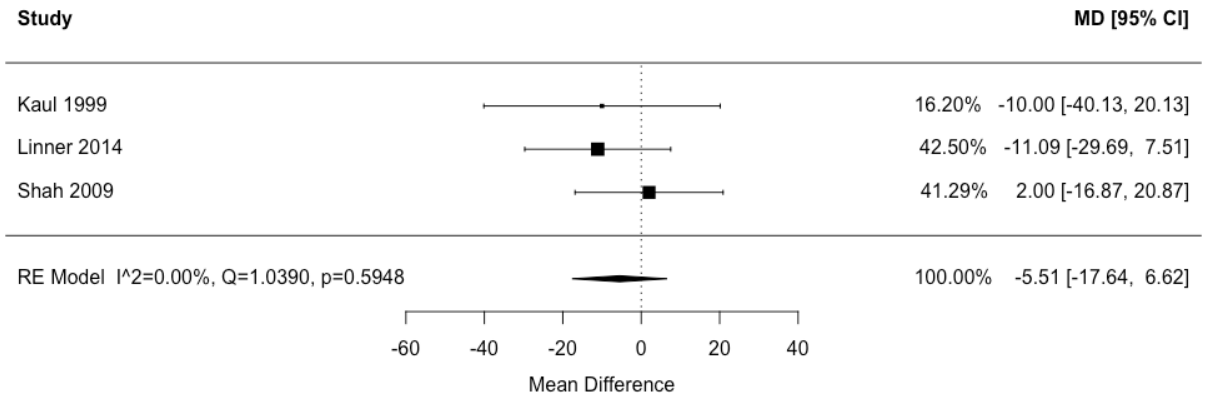


5. Hemodialysis: yes vs no (reference)



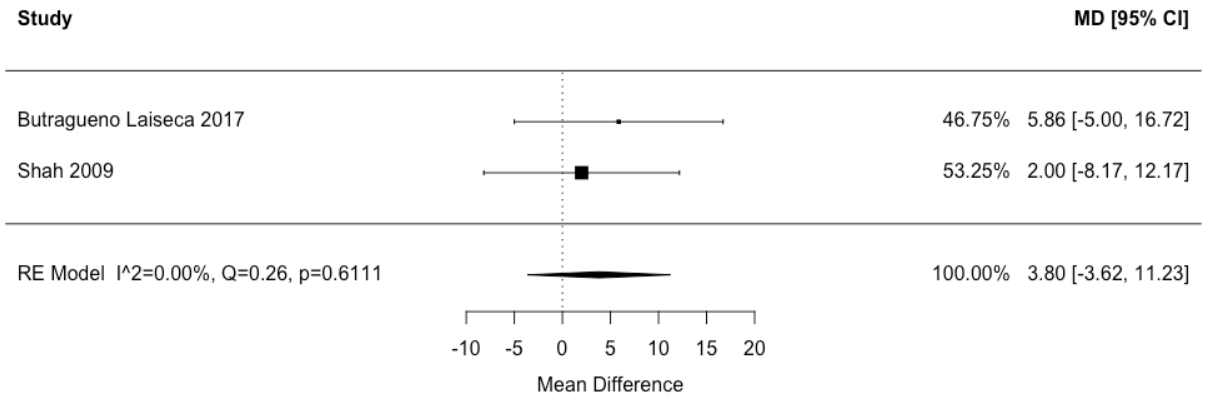
Hospital length-of-stay

1. IVIG: yes vs no (reference)



ICU length-of-stay

1. IVIG: yes vs no (reference)



Description of studies ineligible for meta-analysis by outcome

Mortality

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	4	4	
age	28	5	n=17 case-series with <10 patients, precluding the aggregation of patient-level data; n=6 study population consisted of patients all within same age category
antibiotic	3	3	
clindamycin	4	4	
early hypotension	0	0	
emmtype	7	0	n=7 variability in reporting of molecular characteristics and comparators
hemodialysis	4	4	
immunocompromised	5	4	n=1 insufficient data for meta-analysis (only p value reported)
IVIG in all STSS patients	9	9	
IVIG in clindamycin-treated patients	6	6	
NF	10	10	
NSAIDs	4	4	
sex	12	12	
timetoantibiotic	1	0	Meta-analysis precluded with only one study

(P)ICU admission

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	1	0	Meta-analysis precluded with only one study
age	9	0	n=5 case-series with <10 patients, precluding the aggregation of patient-level data; n=3 study population consisted of patients all within same age category; n=1 eligible for analysis, but meta-analysis precluded with only one study
antibiotic	2	2	
clindamycin	1	0	Meta-analysis precluded with only one study
early hypotension	0	0	
emmtype	2	0	n=2 variability in reporting of molecular characteristics and comparators
hemodialysis	2	2	
immunocompromised	1	0	Meta-analysis precluded with only one study
IVIG in all STSS patients	3	3	
IVIG in clindamycin-treated patients	0	0	
NF	3	3	
NSAIDs	2	2	
sex	3	3	
timetoantibiotic	0	0	

Clinical cure or improvement

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	1	0	Meta-analysis precluded with only one study
age	8	0	n=6 case-series with <10 patients, precluding the aggregation of patient-level data; n=2 study population consisted of patients all within same age category
antibiotic	1	0	Meta-analysis precluded with only one study
clindamycin	1	0	Meta-analysis precluded with only one study
earlyhypotension	0	0	
emmtype	0	0	
hemodialysis	3	3	
immunocompromised	0	0	
IVIG in all STSS patients	2	2	
IVIG in clindamycin-treated patients	0	0	
NF	2	2	
NSAIDs	1	0	Meta-analysis precluded with only one study
sex	4	4	
timetoantibiotic	0	0	

Mechanical ventilation

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	2	2	
age	5	0	n=3 case-series with <10 patients, precluding the aggregation of patient-level data; n=2 study population consisted of patients all within same age category
antibiotic	0	0	
clindamycin	1	0	Meta-analysis precluded with only one study
earlyhypotension	0	0	
emmtype	0	0	
hemodialysis	3	3	
immunocompromised	1	0	Meta-analysis precluded with only one study
IVIG in all STSS patients	3	3	
IVIG in clindamycin-treated patients	0	0	
NF	3	3	
NSAIDs	1	0	Meta-analysis precluded with only one study
sex	3	3	
timetoantibiotic	0	0	

Hospital length-of-stay

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	0	0	
age	2	0	n=2 case-series with <10 patients, precluding the aggregation of patient-level data
antibiotic	0	0	
clindamycin	0	0	
early hypotension	0	0	
emmtype	0	0	
hemodialysis	0	0	
immunocompromised	0	0	
IVIG in all STSS patients	3	3	
IVIG in clindamycin-treated patients	0	0	
NF	0	0	
NSAIDs	1	0	Meta-analysis precluded with only one study
sex	1	0	Meta-analysis precluded with only one study
timetoantibiotic	0	0	

Duration of mechanical ventilation

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	0	0	
age	0	0	
antibiotic	0	0	
clindamycin	0	0	
early hypotension	0	0	
emmtype	0	0	
hemodialysis	0	0	
immunocompromised	0	0	
IVIG in all STSS patients	1	0	Meta-analysis precluded with only one study
IVIG in clindamycin-treated patients	0	0	
NF	0	0	
NSAIDs	0	0	
sex	0	0	
timetoantibiotic	0	0	

ICU length-of-stay

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	0	0	
age	3	0	n=2 case-series with <10 patients, precluding the aggregation of patient-level data; n=1 study population consisted of patients all within same age category
antibiotic	0	0	
clindamycin	1	0	Meta-analysis precluded with only one study
early hypotension	0	0	
emmtype	0	0	
hemodialysis	0	0	
immunocompromised	0	0	
IVIG in all STSS patients	2	2	
IVIG in clindamycin-treated patients	0	0	
NF	1	0	Meta-analysis precluded with only one study
NSAIDs	1	0	Meta-analysis precluded with only one study
sex	2	0	n=1 study with one person in each group > cannot calculate mean; n=1 meta-analysis precluded with only one study
timetoantibiotic	0	0	

Change in SOFA score from baseline

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	0	0	
age	0	0	
antibiotic	0	0	
clindamycin	0	0	
early hypotension	0	0	
emmtype	0	0	
hemodialysis	0	0	
immunocompromised	0	0	
IVIG in all STSS patients	1	0	Meta-analysis precluded with only one study
IVIG in clindamycin-treated patients	0	0	
NF	0	0	
NSAIDs	0	0	
sex	0	0	
timetoantibiotic	0	0	

Functional status

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	0	0	
age	0	0	
antibiotic	0	0	
clindamycin	0	0	
early hypotension	0	0	
emmtype	0	0	
hemodialysis	0	0	
immunocompromised	0	0	
IVIG in all STSS patients	0	0	
IVIG in clindamycin-treated patients	0	0	
NF	0	0	
NSAIDs	0	0	
sex	0	0	
timetoantibiotic	0	0	

Health related quality of life

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	0	0	
age	0	0	
antibiotic	0	0	
clindamycin	0	0	
early hypotension	0	0	
emmtype	0	0	
hemodialysis	0	0	
immunocompromised	0	0	
IVIG in all STSS patients	0	0	
IVIG in clindamycin-treated patients	0	0	
NF	0	0	
NSAIDs	0	0	
sex	0	0	
timetoantibiotic	0	0	

Cost

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	0	0	
age	0	0	
antibiotic	0	0	
clindamycin	0	0	
early hypotension	0	0	
emmtype	0	0	
hemodialysis	0	0	
immunocompromised	0	0	
IVIG in all STSS patients	1	0	Meta-analysis precluded with only one study
IVIG in clindamycin-treated patients	0	0	
NF	0	0	
NSAIDs	0	0	
sex	0	0	
timetoantibiotic	0	0	

Time to mortality

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	0	0	
age	0	0	
antibiotic	0	0	
clindamycin	0	0	
early hypotension	0	0	
emmtype	0	0	
hemodialysis	0	0	
immunocompromised	0	0	
IVIG in all STSS patients	2	0	n=1 study with one person in each group > cannot calculate mean; n=1 meta-analysis precluded with only one study
IVIG in clindamycin-treated patients	2	0	n=1 study with one person in each group > cannot calculate mean; n=1 meta-analysis precluded with only one study
NF	0	0	
NSAIDs	0	0	
sex	0	0	
timetoantibiotic	0	0	

Time to clinical improvement or resolution of shock

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	0	0	
age	0	0	
antibiotic	0	0	
clindamycin	0	0	
early hypotension	0	0	
emmtype	0	0	
hemodialysis	0	0	
immunocompromised	0	0	
IVIG in all STSS patients	1	0	Meta-analysis precluded with only one study
IVIG in clindamycin-treated patients	1	0	Meta-analysis precluded with only one study
NF	0	0	
NSAIDs	0	0	
sex	0	0	
timetoantibiotic	0	0	

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4-9
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	4-9
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	4-9
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4-9
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4-9
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4-9
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4-9
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	4-9
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	4-9
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	4-9
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	4-9
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	4-9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	4-9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	4-9
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	4-9
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	4-9
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	4-9

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	9-17
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	9-17
Study characteristics	17	Cite each included study and present its characteristics.	9-17
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	9-17
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	9-17
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	9-17
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	9-17
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	9-17
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	9-17
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	9-17
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	9-17
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	17-19
	23b	Discuss any limitations of the evidence included in the review.	17-19
	23c	Discuss any limitations of the review processes used.	17-19
	23d	Discuss implications of the results for practice, policy, and future research.	17-19
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	4
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	20
Competing interests	26	Declare any competing interests of review authors.	20
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	21

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PRISMA 2020 Checklist

10.1136/bmj.n71

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MOOSE (Meta-analyses Of Observational Studies in Epidemiology) Checklist

A reporting checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Reporting of Background		
Problem definition		
Hypothesis statement		
Description of Study Outcome(s)		
Type of exposure or intervention used		
Type of study design used		
Study population		
Reporting of Search Strategy		
Qualifications of searchers (eg, librarians and investigators)		
Search strategy, including time period included in the synthesis and keywords		
Effort to include all available studies, including contact with authors		
Databases and registries searched		
Search software used, name and version, including special features used (eg, explosion)		
Use of hand searching (eg, reference lists of obtained articles)		
List of citations located and those excluded, including justification		
Method for addressing articles published in languages other than English		
Method of handling abstracts and unpublished studies		
Description of any contact with authors		
Reporting of Methods		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested		
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)		
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)		
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate		

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results		
Assessment of heterogeneity		
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated		
Provision of appropriate tables and graphics		
Reporting of Results		
Table giving descriptive information for each study included		
Results of sensitivity testing (eg, subgroup analysis)		
Indication of statistical uncertainty of findings		
Reporting of Discussion		
Quantitative assessment of bias (eg, publication bias)		
Justification for exclusion (eg, exclusion of non–English-language citations)		
Assessment of quality of included studies		
Reporting of Conclusions		
Consideration of alternative explanations for observed results		
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)		
Guidelines for future research		
Disclosure of funding source		

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PROGNOSTIC FACTORS FOR STREPTOCOCCAL TOXIC SHOCK SYNDROME: SYSTEMATIC REVIEW AND META-ANALYSIS

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PROGNOSTIC FACTORS FOR STREPTOCOCCAL TOXIC SHOCK SYNDROME: SYSTEMATIC REVIEW AND META-ANALYSIS

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Key words: streptococcal toxic shock syndrome (STSS); systematic review; meta-analysis

Word count: 4320

ABSTRACT

Objectives: To quantify the prognostic effects of demographic and modifiable factors in streptococcal toxic shock syndrome (STSS).

Design: Systematic review and meta-analysis.

Data sources: MEDLINE, EMBASE and CINAHL from inception to 19 September 2022, along with citations of included studies.

Eligibility criteria: Pairs of reviewers independently screened potentially eligible studies of patients with GAS-induced STSS that quantified the association between at least one prognostic factor and outcome of interest.

Data extraction and synthesis: We performed random-effects meta-analysis after duplicate data extraction and risk of bias assessments. We rated the certainty of evidence using the GRADE approach.

Results: One randomized trial and 40 observational studies were eligible (n=1,918 patients). We found a statistically significant association between clindamycin treatment and mortality (n=144; odds ratio [OR] 0.14, 95% CI 0.06 to 0.37), but the certainty of evidence was low. Within clindamycin-treated STSS patients, we found a statistically significant association between intravenous immunoglobulin (IVIG) treatment and mortality (n=188; OR 0.34, 95% CI 0.15 to 0.75), but the certainty of evidence was also low. The odds of mortality may increase in patients ≥65 years when compared to patients 18-64 years (n=396; OR 2.37, 95% CI 1.47 to 3.84), but the certainty of evidence was low. We are uncertain whether non-steroidal anti-inflammatory drugs (NSAIDs) increased the odds of mortality (n=50; OR 4.14, 95% CI 1.13 to 15.14; very low certainty). Results failed to show a significant association between any other prognostic factor and outcome combination (very low to low certainty evidence) and no studies quantified the association between a prognostic factor and morbidity post-infection in STSS survivors.

Conclusions: Treatment with clindamycin and within clindamycin-treated patients, IVIG, was each significantly associated with mortality, but the certainty of evidence was low. Future research should focus on morbidity post-infection in STSS survivors.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Strengths of this review include its systematic and explicit search of the literature, capture of a wide breadth of patient-important outcomes within and outside of critical care and the use of meta-analysis to increase statistical power in studying relationships between prognostic factors and outcomes in STSS patients.
- These strengths directly address limitations of an existing narrative synthesis of STSS prognosis restricted to the critical care setting.
- In the absence of large cohort studies and randomized trials, conclusions for STSS prognosis in this review are limited by very low to low certainty evidence.
- A limitation of the evidence is the lack of long-term outcome data reported, including morbidity post-infection in STSS survivors.

Introduction

Streptococcal toxic shock syndrome (STSS) is an acute and severe life-threatening complication of predominantly invasive Group A *Streptococcus* (GAS) infections. STSS is relatively uncommon, but is fatal [1]. Using US data from 2000 to 2004, the Center for Diseases Control and Prevention estimated an annual incidence rate of 0.2 cases per 100,000 people and a fatality rate of 36% [2]. STSS has important consequences for morbidity as well, in which patients may require radical surgical debridement, and patients with organ failure may have permanent respiratory and renal insufficiency [1].

Although extensive multidisciplinary clinical management efforts by intensivists, infectious disease specialists, and surgeons have curbed STSS all-cause mortality [1], data on the natural history of long-term sequelae in surviving patients, such as renal, respiratory and neuropsychiatric complications, are sparse [1-4]. Published studies of prognostic and treatment factors for STSS have consistently focused on associations with all-cause mortality [5-14], with few reporting on outcomes capturing the morbidity post-infection in STSS survivors [7, 12]. Furthermore, a thorough and systematic review to corroborate this evidence is lacking. A narrative review of STSS was limited by the lack of a systematic or explicit search of the literature, it included studies that were only narratively synthesized, and the focus was limited to studies within a critical care setting [1].

Understanding prognosis of STSS is important for patients, clinicians, and healthcare decision makers. We conducted a systematic review to summarize the prognostic and treatment factors, and outcomes of STSS. We aimed to capture a wide breadth of patient-important outcomes with follow up that included both short- and long-term outcomes within and outside of critical care.

Materials and methods

We registered a protocol for the present systematic review and meta-analysis with PROSPERO (CRD42020166961) [15, 16]. We report this systematic review and meta-analysis following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analyses of Observational Studies in Epidemiology (MOOSE) checklists [17, 18]. Decisions regarding criteria for study inclusion, search methods for identification of

studies, data collection, risk of bias, evaluation of the certainty of evidence and analysis were established a priori.

Search strategy and selection criteria

We searched MEDLINE (OVID interface, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, 1946 to 19 September 2022), EMBASE (OVID interface, 1974 to 19 September 2022) and the Cumulative Index to Nursing And Allied Health Literature (CINAHL) from inception to 19 September 2022, with no restrictions on publication date. We applied search filters for randomized controlled trials and non-randomized studies (cohort, case-control and case series with at least 2 STSS patients) [19, 20], and tailored search strategies to each database. We restricted included studies to the English language to facilitate screening of full-texts [21, 22] and searched citations of included studies to minimize the risk of failing to include relevant studies.

We included studies of randomized and non-randomized designs that reported the association of at least one prognostic factor of interest on at least one outcome of interest, and compared GAS-induced STSS patients with the prognostic factor of interest (i.e. exposed) to GAS-induced STSS patients without the prognostic factor of interest (i.e. unexposed). Studies of patients with microbiologically confirmed STSS, probable cases of STSS and patients with clinical evidence of STSS as defined by study authors and generally consistent with the below criteria were eligible [3, 23]. Clinical evidence of STSS included hypotension and at least two of the following: renal impairment, coagulopathy, liver function abnormality, acute respiratory distress syndrome, generalized erythematous macular rash (with desquamation), soft-tissue necrosis (including necrotizing fasciitis, myositis or gangrene), or meningitis. Probable cases of STSS were defined as meeting clinical evidence with GAS isolated from a non-sterile site (e.g. throat, sputum, superficial skin lesion) or antigen detected. Confirmed cases of STSS were defined as meeting clinical evidence with GAS isolated from a sterile site (e.g. blood, cerebrospinal fluid, deep tissue specimen taken during surgery) [3, 23]. Demographic, comorbidity, infection, modifiable and process variables were prognostic factors of interest. Informed by clinical expertise in the review team, we selected outcomes based on importance to patients. Further, we aimed to capture the long-term sequelae in patients surviving STSS [1, 2, 4]. We chose the

following outcomes of interest: (time to) mortality, hospital length-of-stay, pediatric (P) intensive care unit (ICU) admission, (P)ICU length-of-stay, mechanical ventilation, duration of mechanical ventilation, (time to) clinical cure/improvement or resolution of shock, change in Sequential Organ Failure Assessment (SOFA) score from baseline, functional status (e.g. physical component summary (PCS) score on the 36-item short form health survey (SF-36)) and health related quality of life (HRQoL). We also extracted on cost outcomes, which are relevant to hospital and patient payees.

We excluded case reports and conference abstracts, and studies in which the population was less than 80% GAS-induced STSS cases (i.e. toxic shock syndrome of bacterial aetiologies other than GAS made up more than 20% of the study population). Because prognostic evidence in STSS patients is scarce [1, 2, 4], we did not apply any restrictions based on analytical method (e.g. conducting an adjusted, multivariable analysis) or sample size.

Using a systematic review software, Rayyan [24], following training and calibration exercises, pairs of reviewers independently screened all titles and abstracts, followed by full-texts of records that were identified as potentially eligible. When necessary, consensus was reached through discussion between the review pair, and arbitration by a senior co-investigator in the absence of consensus.

Data analysis

For each eligible study, pairs of reviewers extracted data independently using a standardized, pilot tested data extraction form. Reviewers collected information on study characteristics (study design as defined by study authors, sample size, country), patient characteristics (age, sex), disease characteristics (confirmed vs probable STSS, presence of necrotizing fasciitis), prognostic factors and outcomes of interest (means or medians and measures of variability for continuous outcomes and the proportion of participants who experienced an event for dichotomous outcomes). If multiple time points were reported for outcomes of interest, we extracted all time points. To minimize risk of confounding associated with prognostic effect estimates on dichotomous outcomes in non-randomized studies, we preferentially extracted adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CI) over proportions

when both were reported. We used the proportions to calculate crude ORs when no adjusted ORs were provided. Reviewers resolved discrepancies by discussion and, when necessary, with adjudication by a senior co-investigator.

Following training and calibration exercises, reviewers, independently and in duplicate, used the Quality in Prognosis Studies (QUIPS) tool to rate each prognostic factor and outcome combination at low, moderate or high risk of bias. Based on prespecified sets of questions, we assessed risk of bias across the following domains: participation, attrition, prognostic factor measurement, outcome measurement, confounding, and statistical analysis and reporting [25]. For studies addressing more than one prognostic factor and outcome combination, we reported the highest risk of bias rating among the prognostic factor and outcome combinations within a study for each domain. In addition to assessing risk of bias at the domain-level as outlined in the QUIPS tool, we applied the following rules to assess risk of bias overall at the study-level. We rated overall study risk of bias as low if the study was prospective and five or more domains were assessed as low risk of bias, and high if two or more domains were assessed as high risk of bias. All other studies were rated as moderate risk of bias overall. Due to high risk of selection bias and residual confounding, we rated all case series as high risk of bias overall. Reviewer pairs resolved discrepancies by discussion and, when needed, with adjudication by a senior co-investigator.

Pairs of reviewers used the grading of recommendations, assessment, development, and evaluation (GRADE) approach to independently assess the certainty of prognostic evidence for each meta-analysed outcome. Criteria for rating the certainty for each prognostic factor and outcome as high, moderate, low, or very low, included considerations of risk of bias, inconsistency, indirectness, size and precision of the association and publication bias [26, 27]. Judgments of imprecision for this systematic review were made using a minimally contextualised approach. This approach considers whether confidence intervals include the null effect. Further, the terminology used to report GRADE ratings (e.g. low certainty evidence) is based on published GRADE guidance [28, 29]. The supplementary file presents the detailed guidance we developed to facilitate the certainty of the evidence assessment in this review. To facilitate interpretation of the results in which the summary measure was an OR, we used the median

event rate in the reference group of studies reporting proportions to calculate baseline risks and subsequently calculated absolute effects. GRADE evidence summaries (Summary of Findings tables) were generated in the MAGIC Authoring and Publication Platform (www.magicapp.org).

When at least two included studies reported on the same prognostic factor and outcome in patients with GAS-induced STSS, we conducted DerSimonian and Laird random-effects meta-analyses using the *metafor* package in R version 4.0.4 (R Studio, Boston, MA, USA) [30]. We summarised the effects of prognostic factors on dichotomous outcomes using ORs and corresponding 95% CI, and on continuous outcomes using mean differences and corresponding 95% CI. For prognostic factor and dichotomous outcome combinations in which every patient in the reference arm experienced the outcome, we summarised the effects by directly calculating risk differences and corresponding 95% CI. We set the criterion for statistical significance at alpha = 0.05. Visual inspection of forest plots and the chi-square test were performed to evaluate heterogeneity. We interpreted an I^2 statistic value of 0%-40%, 30%-60%, 50%-90%, or 75%-100% as not likely important, moderate, substantial, or considerable heterogeneity, respectively [31]. If an I^2 statistic value was within a range of overlapping values (e.g. 80%), we would interpret heterogeneity as more important (e.g. considerable instead of substantial) if the meta-analysis contained few studies, we observed inconsistent magnitudes and directions of summary estimates upon visual inspection of the forest plots, or the chi-square test was significant [31]. For meta-analyses of continuous outcomes, we imputed means and standard deviations for studies reporting medians and (interquartile) ranges, respectively [32, 33].

Patient-level data from case-series were aggregated when possible to enable comparative analysis via meta-analysis. We planned to perform a regression analysis for each study for which age was reported at the patient level to generate a study and age category (0 to 17 years old vs 18 to 64 years old vs 65 years old or older) specific OR that could be used in meta-analysis when a study had at least 10 observations for continuous outcomes and 10 events for dichotomous outcomes; however, no study met the sample size or event number requirements. Further, scarcity and variability of data precluded our plan to narratively synthesize the evidence from included studies for which meta-analysis of a prognostic factor and outcome combination was not possible.

The analysis plan included performing subgroup analyses of STSS patients treated with clindamycin vs no clindamycin, STSS patients with necrotizing fasciitis vs without necrotizing fasciitis, age (0 to 17 years old vs 18 to 64 years old vs 65 years old or older), sex (male vs female) and risk of bias (high vs moderate vs low) when at least two studies were present for each subgroup. Because select meta-analyses were limited by small numbers of events, we performed a post-hoc sensitivity analysis using the Peto method for meta-analysis, which is recommended for meta-analysis of rare events [34], and compared the results to those from the DerSimonian and Laird method we applied in this review.

Patient and public involvment

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Results

After screening 27,321 titles and abstracts, and 305 full texts, 41 studies that reported on the association between at least one prognostic factor and outcome of interest in STSS patients proved eligible (Figure 1). All but one study (40/41, 98%) were non-randomized. Eligible studies were published between 1989 and 2021, ranged in sample size from 2 to 476, included 1,918 STSS patients in total and were conducted in 22 different countries, most commonly in the United States (15/41, 37%).

Table 1 describes the characteristics of included studies reporting on the association of at least one prognostic factor and outcome of interest. The supplementary data includes additional study characteristics for each study. Of the 41 included studies, 29 (71%) reported on demographic prognostic factors of interest, 5 (12%) medical history of being immunocompromised, 11 (27%) early disease characteristics, and 16 (39%) treatment. Of the dichotomous outcomes, mortality was most commonly reported (36/41, 88%), followed by (P)ICU admission (10/41, 24%), clinical cure or improvement (8/41, 20%) and need for mechanical ventilation (6/41, 15%). Few studies reported on hospital (3/41, 7%) and ICU length-of-stay (2/41, 5%). Two studies reported on time to mortality in days [7, 35]; however, only one reported sufficient data precluding meta-

analysis [7]. One study each reported on cost [14], change in SOFA score [7], time to clinical improvement or resolution of shock [7] and duration of mechanical ventilation [10] precluding meta-analysis for these continuous outcomes. No studies quantified the association between a prognostic factor and functional status or health related quality of life outcomes. A multivariable analysis was conducted in two (5%) of the included studies [10, 11]. A total of 19 of the 41 studies were cohort studies (authors reported on at least one comparative analysis), 19 were case series (authors did not report a comparative analysis) and 2 were case-control studies. To meta-analyse the data, we aggregated the data from the individual patients the case series reported on. Further, we pooled the one randomized study [7] with non-randomized studies in meta-analyses and included patients receiving intravenous or intramuscular IVIG from one non-randomized study [36].

Table 1. Study characteristics. Values are numbers (percentages) of studies unless stated otherwise.

Characteristics	**(41 studies, 1918 patients)**
Range of publication year	1989 to 2021
Median (IQR) No. of patients	11 (5 to 29)
Geographical region:	
North America	19 (46)
Europe	14 (34)
Central/South America	0 (0)
Asia	4 (10)
Other	4 (10)
Study design:	
Randomized trial	1 (2)
Cohort	19 (46)
Case-control	2 (5)
Case-series	19 (46)
Case definition:	
Probable STSS patients	115 (6)
Confirmed STSS patients	227 (12)
Prognostic factor type:	
Demographic	29 (71)
Medical history	5 (12)
Early disease	11 (27)
Treatment	16 (39)

IQR=interquartile range
STSS=streptococcal toxic shock syndrome
Medical history included prognostic variable: immunocompromised
Early disease included prognostic variables: necrotizing fasciitis, acute renal failure

The supplementary material includes the forest plots depicting the studies included in the meta-analysis of each prognostic factor-outcome combination. It also includes the list of studies reporting on prognostic factor-outcome combinations of interest that were not eligible for any meta-analysis, along with the reasons for exclusion from meta-analysis.

Risk of bias in included studies

The supplementary file presents the risk of bias assessment of the 41 included studies. The majority of studies were rated as high risk of bias overall owing to residual confounding and lack of adjustment for confounding in statistical analyses (37/41, 90%) [2, 5, 6, 10, 35-67]. Three studies were rated at moderate risk of bias overall [7, 14, 68] and one at low risk of bias overall [11].

Prognostic factors for mortality

Eleven prognostic factors from 32 studies including 1343 patients were eligible for analysis (table 2, supplementary data). We found a statistically significant association between clindamycin treatment and mortality (figure 2A; n=144; odds ratio [OR] 0.14, 95% CI 0.06 to 0.37), but the certainty of evidence was low. Within clindamycin-treated STSS patients, we found a statistically significant association between intravenous immunoglobulin (IVIG) treatment and mortality (figure 2B; n=188; OR 0.34, 95% CI 0.15 to 0.75), but the certainty of evidence was also low. We are uncertain whether IVIG treatment reduces the odds of mortality in all STSS patients regardless of concurrent clindamycin treatment (n=365, OR 0.37, 95% CI 0.17 to 0.80; very low certainty of evidence). The odds of mortality may increase in patients ≥65 years when compared to patients 18-64 years (n=396; OR 2.37, 95% CI 1.47 to 3.84), but the certainty of evidence was low. We are less certain whether the same is true for patients ≥65 years compared to patients <18 years (n=136, OR 10.66, 95% CI 1.28 to 88.57; very low certainty of evidence). We are also uncertain whether NSAIDs increase the odds of mortality (n=50, OR 4.14, 95% CI 1.13 to 15.14; very low certainty of evidence). Very low certainty evidence failed

to show a significant association with any other prognostic factor and mortality in STSS patients: male vs female (n=80, OR 0.95, 95% CI 0.36 to 2.52), patients <18 years vs patients 18 to 64 years (n=694, OR 0.54, 95% CI 0.15 to 1.94), immunocompromised vs not immunocompromised (n=33, OR 1.65, 95% CI 0.33 to 8.26), necrotizing fasciitis vs no necrotizing fasciitis (n=840, OR 0.81, 95% CI 0.51 to 1.29), acute renal failure vs no acute renal failure (n=91, OR 2.50, 95% CI 0.97 to 6.42), hemodialysis vs no hemodialysis (n=42, OR 1.94, 95% CI 0.22 to 16.99) and any antibiotic vs no antibiotic (n=19, OR 0.48, 95% CI 0.05 to 4.76).

Table 2. Summary of findings for prognostic factor – outcome meta-analyses.

Prognostic factor	Number of patients (studies)	Odds ratio (95% confidence interval)	Absolute effect estimates		GRADE: Certainty of the Evidence
			Risk without prognostic factor	Risk with prognostic factor	
MORTALITY					
Demographic					
Male vs Female	80 (13)	0.95 (0.36 to 2.52)	**250** per 1000	**241** per 1000	**Very low**
			-9 (-143 to 207)		Due to very serious risk of bias and imprecision
<18 vs 18-64 years	694 (5)	0.54 (0.15 to 1.94)	**234** per 1000	**142** per 1000	**Very low**
			-92 (-190 to 138)		Due to very serious risk of bias and imprecision, and serious inconsistency
≥65 vs <18 years	136 (2)	10.66 (1.28 to 88.57)*	**50** per 1000	**359** per 1000	**Very low**
			309 (13 to 773)		Due to very serious risk of bias and serious imprecision
≥65 vs 18–64 years	396 (2)	2.37 (1.47 to 3.84)*	**193** per 1000	**362** per 1000	**Low**
			169 (67 to 286)		Due to very serious risk of bias
Medical history					
Immunocompromised vs Not Immunocompromised	33 (4)	1.65 (0.33 to 8.26)	**438** per 1000	**563** per 1000	**Very low**
			125 (-233 to 428)		Due to very serious risk of bias and imprecision
Early disease					
Acute Renal Failure vs No Acute Renal Failure	91 (4)	2.50 (0.97 to 6.42)	**NA** per 1000	**NA** per 1000	**Very low**
			140 (-60 to 330)		Due to very serious risk of bias and imprecision
Necrotizing Fasciitis vs No Necrotizing Fasciitis	840 (10)	0.81 (0.51 to 1.29)	**347** per 1000	**301** per 1000	**Very low**
			-46 (-134 to 60)		Due to very serious risk of bias and imprecision
Treatment					
IVIG vs No IVIG (all STSS patients)	365 (9)	0.37 (0.17 to 0.80)*	**231** per 1000	**100** per 1000	**Very low**
			-131 (-182 to -37)		Due to very serious risk of bias and serious imprecision
IVIG vs No IVIG (subset of STSS patients treated with clindamycin)	188 (6)	0.34 (0.15 to 0.75)*	**300** per 1000	**127** per 1000	**Low**
			-173 (-240 to -57)		Due to serious risk of bias and imprecision
Any Antibiotic vs No Antibiotic	19 (3)	0.48 (0.05 to 4.76)	**NA** per 1000	**NA** per 1000	**Very low**
			-120 (-490 to 260)		Due to very serious risk of bias and imprecision
Clindamycin vs No Clindamycin Antibiotic	144 (4)	0.14 (0.06 to 0.37)*	**800** per 1000	**359** per 1000	**Low**
			-441 (-606 to -203)		Due to serious risk of bias and imprecision
Hemodialysis vs No Hemodialysis	42 (4)	1.94 (0.22 to 16.99)	**107** per 1000	**189** per 1000	**Very low**

			82 (-81 to 564)		Due to very serious risk of bias and imprecision
NSAIDs vs No NSAIDs	50 (4)	4.14 (1.13 to 15.14)*	**100** per 1000	**315** per 1000	**Very low**
			215 (12 to 527)		Due to very serious risk of bias and serious imprecision
ICU ADMISSION					
Demographic					
Male vs Female	19 (3)	2.87 (0.29 to 28.27)	**NA** per 1000	**NA** per 1000	**Very low**
			150 (-160 to 450)		Due to very serious risk of bias and imprecision
Early disease					
Necrotizing Fasciitis vs No Necrotizing Fasciitis	28 (3)	0.74 (0.12 to 4.48)	**900** per 1000	**869** per 1000	**Very low**
			-31 (-381 to 76)		Due to very serious risk of bias and imprecision
Treatment					
IVIG vs No IVIG (all STSS patients)	156 (3)	1.09 (0.43 to 2.77)	**833** per 1000	**845** per 1000	**Very low**
			12 (-151 to 100)		Due to very serious risk of bias and imprecision
Any Antibiotic vs No Antibiotic	14 (2)	4.60 (0.29 to 72.89)	**500** per 1000	**821** per 1000	**Very low**
			321 (-275 to 486)		Due to very serious risk of bias and imprecision
Hemodialysis vs No Hemodialysis	13 (2)	3.25 (0.21 to 50.35)	**875** per 1000	**958** per 1000	**Very low**
			83 (-280 to 122)		Due to very serious risk of bias and imprecision
NSAIDs vs No NSAIDs	15 (2)	0.86 (0.06 to 12.48)	**NA** per 1000	**NA** per 1000	**Very low**
			-10 (-430 to 400)		Due to very serious risk of bias and imprecision
CLINICAL CURE OR IMPROVEMENT					
Demographic					
Male vs Female	23 (4)	3.33 (0.47 to 23.59)	**875** per 1000	**959** per 1000	**Very low**
			84 (-108 to 119)		Due to very serious risk of bias and imprecision
Early disease					
Necrotizing Fasciitis vs No Necrotizing Fasciitis	24 (2)	0.34 (0.02 to 5.20)	**950** per 1000	**866** per 1000	**Very low**
			-84 (-675 to 40)		Due to very serious risk of bias and serious imprecision
Treatment					
IVIG vs No IVIG (in all STSS patients)	23 (2)	0.27 (0.02 to 3.76)	**NA** per 1000	**NA** per 1000	**Very low**
			-100 (-350 to 140)		Due to very serious risk of bias and imprecision
Hemodialysis vs No Hemodialysis	26 (3)	1.43 (0.15 to 14.08)	**NA** per 1000	**NA** per 1000	**Very low**
			50 (-240 to 340)		Due to very serious risk of bias and imprecision
NEED FOR MECHANICAL VENTILATION					
Demographic					
Male vs Female	21 (3)	2.09 (0.32 to 13.74)	**NA** per 1000	**NA** per 1000	**Very low**
			120 (-200 to 440)		Due to very serious risk of bias and imprecision
Early disease					
Acute Renal Failure vs No Acute Renal Failure	20 (2)	1.14 (0.17 to 7.82)	**750** per 1000	**774** per 1000	**Very low**
			24 (-412 to 209)		Due to very serious risk of bias and imprecision
Necrotizing Fasciitis vs No Necrotizing Fasciitis	31 (3)	3.75 (0.47 to 29.81)	**700** per 1000	**897** per 1000	**Very low**
			197 (-177 to 286)		Due to very serious risk of bias and imprecision
Treatment					
IVIG vs No IVIG (in all STSS patients)	157 (3)	2.22 (0.78 to 6.32)	**333** per 1000	**526** per 1000	**Very low**
			193 (-53 to 426)		Due to very serious risk of bias and imprecision

Hemodialysis vs No Hemodialysis	26 (3)	2.05 (0.39 to 10.70)	**500** per 1000	**672** per 1000	**Very low** Due to very serious risk of bias and imprecision
			172 (-219 to 415)		
DURATION OF HOSPITALIZATION					
Treatment					
IVIG vs no IVIG (all STSS patients)	201 (3)	NA	**NA** per 1000	**NA** per 1000	**Low** Due to serious risk of bias and imprecision
			On average, 5.51 fewer days (17.64 fewer to 6.62 more)		
DURATION OF INTENSIVE CARE UNIT STAY					
Treatment					
IVIG vs no IVIG (all STSS patients)	131 (2)	NA	**NA** per 1000	**NA** per 1000	**Very low** Due to very serious risk of bias and serious imprecision
			On average, 3.80 more days (3.62 fewer to 11.23 more)		

*statistical evidence of an association

Prognostic factors for ICU admission

Six prognostic factors from eight studies including 174 patients were eligible for analysis (table 2, supplementary data). We found no statistical evidence of an association between any prognostic factor and ICU admission: male vs female sex (n=19, OR 2.87, 95% CI 0.29 to 28.27), necrotizing fasciitis vs no necrotizing fasciitis (n=28, OR 0.74, 95% CI 0.12 to 4.48), hemodialysis vs no hemodialysis (n=13, OR 3.25, 95% CI 0.21 to 50.35), NSAIDs vs no NSAIDs (n=15, OR 0.86, 95% CI 0.06 to 12.48), IVIG treatment vs no IVIG treatment (n=156, OR 1.09, 95% CI 0.43 to 2.77) and antibiotic treatment vs no antibiotic treatment (n=14, OR 4.60, 95% CI 0.29 to 72.98). The certainty of all ICU admission evidence was very low due to very serious risk of bias and imprecision.

Prognostic factors for clinical cure or improvement

Four prognostic factors from six studies including 38 STSS patients were eligible for analysis (table 2, supplementary data). We found no statistical evidence of an association between any prognostic factor and clinical cure or improvement: male vs female sex (n=23, OR 3.33, 95% CI 0.47 to 23.59), necrotizing fasciitis vs no necrotizing fasciitis (n=24, OR 0.34, 95% CI 0.02 to 5.20), hemodialysis vs no hemodialysis (n=26, OR 1.43, 95% CI 0.15 to 14.08) and IVIG treatment vs no IVIG treatment (n=23, OR 0.27, 95% CI 0.02 to 3.76). The certainty of all clinical cure or improvement evidence was very low due to very serious risk of bias and serious or very serious imprecision.

Prognostic factors for mechanical ventilation

Five prognostic factors from six studies including 170 STSS patients were eligible for analysis (table 2, supplementary data). We found no statistical evidence of an association between any prognostic factor and need for mechanical ventilation: male vs female sex (n=21, OR 2.09, 95% CI 0.32 to 13.74), necrotizing fasciitis vs no necrotizing fasciitis (n=31, OR 3.75, 95% CI 0.47 to 29.81), acute renal failure vs no acute renal failure (n=20, OR 1.14, 95% CI 0.17 to 7.82), hemodialysis vs no hemodialysis (n=26, OR 2.05, 95% CI 0.39 to 10.70) and IVIG treatment vs no IVIG treatment (n=157, OR 2.22, 95% CI 0.78 to 6.32). The certainty of all need for mechanical ventilation evidence was very low due to very serious risk of bias and imprecision.

Prognostics factors for hospital length-of-stay

One prognostic factor from three studies including 201 STSS patients was eligible for analysis (table 2, supplementary data). Low certainty evidence – due to serious risk of bias and imprecision – provides no support for an association between IVIG treatment and hospital length-of-stay, when compared to no IVIG treatment (n=201, MD -5.51 days, 95% CI -17.64 to 6.62).

Prognostic factors for intensive care unit length-of-stay

One prognostic factor from two studies including 131 STSS patients was eligible for analysis (table 2, supplementary data). We are uncertain if IVIG treatment compared to no IVIG treatment is associated with ICU length-of-stay (n=131, MD 3.80 days, 95% CI -3.62 to 11.23; very low certainty evidence due to very serious risk of bias and serious imprecision).

Subgroup and sensitivity analysis

Sparsity of data precluded our planned subgroup analyses by clindamycin treatment, presence of necrotizing fasciitis and sex (i.e. each subgroup did not have at least two studies). We collapsed the low and moderate risk of bias categories to allow for subgroup analysis by risk of bias (low or moderate vs high). The prognostic factor-outcome combinations for which there was sufficient evidence for subgroup analysis by age or modified risk of bias level were IVIG-mortality and sex-mortality. We found no statistical evidence that the association between IVIG and mortality differed between low or moderate and high risk of bias studies in all STSS patients

(p=0.884) and clindamycin-treated STSS patients (p=0.867) or between studies with STSS patients <18 years and patients 18-64 years (p=0.328). We also found no statistical evidence that the association between sex and mortality differed between studies with patients <18 years and patients 18-64 years (p=0.666). Because results were consistent across Peto, and DerSimonian and Laird methods, our post-hoc sensitivity analysis applying the Peto method supported our main results.

Discussion

This systematic review and meta-analysis provides a comprehensive overview of the prognostic evidence for STSS. Prognostic factors for which there was a statistically significant association with mortality in STSS patients were age, clindamycin treatment, IVIG treatment and NSAIDs treatment. Patients ≥65 years compared to patients 18 to 64 years may have increased odds of mortality (low certainty of evidence); however we are uncertain if the same is true for patients ≥65 years compared to patients <18 years (very low certainty of evidence). We are also uncertain whether NSAIDs increase the odds of mortality (very low certainty of evidence). Low certainty evidence suggests the odds of mortality may be reduced by treatment with clindamycin and within clindamycin-treated patients, IVIG. We are highly uncertain whether IVIG reduces mortality in all STSS patients, regardless of clindamycin treatment (very low certainty of evidence). Results failed to show a significant association between all other meta-analyzed prognostic factors and outcomes (table 2). The certainty of STSS prognostic evidence was low or very low due to serious or very serious risk of bias and imprecision concerns.

Strengths of this review include its systematic and explicit search of the literature, capture of a wide breadth of patient-important outcomes within and outside of critical care and the use of meta-analysis to increase statistical power in studying relationships between prognostic factors and outcomes in STSS patients. These strengths directly address limitations of a narrative synthesis of STSS prognosis restricted to the critical care setting [1].

In the absence of large cohort studies and randomized trials, conclusions for STSS prognosis in this review are limited by very low to low certainty evidence. The majority of included studies were non-randomized (40/41, 98%) and small (median sample size was 11 patients), introducing

bias from residual confounding and imprecision around pooled summary estimates. Small numbers of events further contributed to the imprecision around summary estimates and limited the interpretation of our findings. With few participants and events, minor changes in the data can cause major changes in the results. In such instances, results can be exaggerated by the presentation of relative effect estimates only. To minimize the risk of misinterpreting results from the inclusion of small studies in our meta-analyses, we calculated an absolute effect estimate for each relative effect estimate (table 2). Further, despite expecting small studies to be more heterogeneous than large studies, we did not find statistical evidence of heterogeneity in any of our 33 meta-analyses and in interpreting the I^2 statistic value, we found not likely important heterogeneity in all but one meta-analysis [69]. Creation of an international registry of STSS patients may improve the credibility of prognostic evidence for STSS and facilitate the conduct of high-quality cohort studies. Although we meta-analyzed adjusted odds ratios from included studies when possible, almost all included studies reported crude data (39/41, 95%), precluding adjustment for important confounders. A limitation of the evidence is the lack of long-term outcome data reported. For example, no studies quantified associations between prognostic factors and functional status or health related quality of life outcomes post-infection in STSS survivors. Given the high morbidity associated with STSS [70], future research in STSS prognosis should quantify these patient-important outcomes, facilitating future meta-analyses and providing further insights into STSS prognosis.

Our finding that IVIG treatment may reduce the odds of mortality in STSS patients who receive clindamycin treatment is consistent with a systematic review and meta-analysis of IVIG treatment in clindamycin-treated STSS patients, which found statistical evidence of a decreased risk of mortality in IVIG- and clindamycin-treated STSS patients when compared to only clindamycin-treated STSS patients [70]. For this question relevant to clindamycin-treated STSS patients, our meta-analysis included one additional non-randomized study, whose small sample size and imprecision contributed to an overall point estimate of greater magnitude [35]. Our findings suggest that treatment regimens of IVIG in adjunct to clindamycin and clindamycin alone may significantly improve STSS prognosis. We found a significant association between a regimen of IVIG regardless of clindamycin treatment and mortality; however, due to very serious risk of bias and serious imprecision, and thus very low certainty evidence, we cannot rule out the

possibility that clindamycin treatment may be necessary for STSS patients to benefit from IVIG treatment. Further, only one study reported on IVIG treatment in STSS patients that were not also treated with clindamycin [36]; therefore, our planned subgroup analysis to test if the beneficial effect of IVIG is modified in the absence of clindamycin was precluded. Based on very low certainty evidence, our finding that NSAID treatment is significantly associated with mortality in STSS patients can be explained by clinical and basic science literature, which suggests nonselective NSAIDs mask early signs and symptoms of GAS infection, such as fever, subsequently delaying time to antibiotic treatment – a risk factor for severe sepsis and shock, and mortality [71, 72].

After analyzing 30 different prognostic factor and outcome combinations, we found that clindamycin treatment was significantly associated with an improved STSS prognosis. Further, we found that IVIG treatment may reduce the odds of mortality in STSS patients who receive clindamycin treatment, but we are uncertain if this is true for all STSS patients, regardless of clindamycin treatment. Although these findings support the use of IVIG as an adjunctive treatment in clindamycin-treated STSS patients, the certainty of evidence was low due to serious risk of bias and imprecision. Age equal to or older than 65 years and treatment with NSAIDs were significantly associated with a worse STSS prognosis. Results from very low to low certainty evidence failed to show a significant association between any other factors of interest and STSS prognosis.

Contributors

All authors attest they meet the ICMJE criteria for authorship. All authors have made substantial contributions to the following: (1) the conception and design of the study (Jessica J Bartoszko, Lehana Thabane, Dominik Mertz, Mark Loeb), acquisition of data (Jessica J Bartoszko, Zeyad Elias, Paulina Rudziak, Carson KL Lo), analysis and interpretation of data (Jessica J Bartoszko, Zeyad Elias, Paulina Rudziak, Carson KL Lo, Mark Loeb); (2) drafting the article and revising it critically for important intellectual content (Jessica J Bartoszko, Lehana Thabane, Dominik Mertz, Mark Loeb), (3) final approval of the version to be submitted (Jessica J Bartoszko, Zeyad Elias, Paulina Rudziak, Carson KL Lo, Lehana Thabane, Dominik Mertz, Mark Loeb).

Declaration of interests

Mark Loeb declares grants or contracts from the World Health Organization, consulting fees from AVIR Pharma, and participating on data safety monitoring or advisory boards for Paladin Labs and Sunovion Pharmaceuticals.

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Data availability statement

Data extracted from individual studies are available upon reasonable request to the corresponding author. All other data relevant to the study are included in the article or uploaded as online supplemental information.

Ethics statement

Patient consent for publication not applicable.

Figure 1. PRISMA study flow diagram.

Figure 2. Meta-analyses comparing IVIG treatment to no IVIG treatment for the outcome mortality in A) all STSS patients; and B) the subset of STSS patients treated with clindamycin. Please note proportions are blank for study rows where we meta-analyzed adjusted odds ratios instead of crude proportions.

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Figure 1. PRISMA study flow diagram.

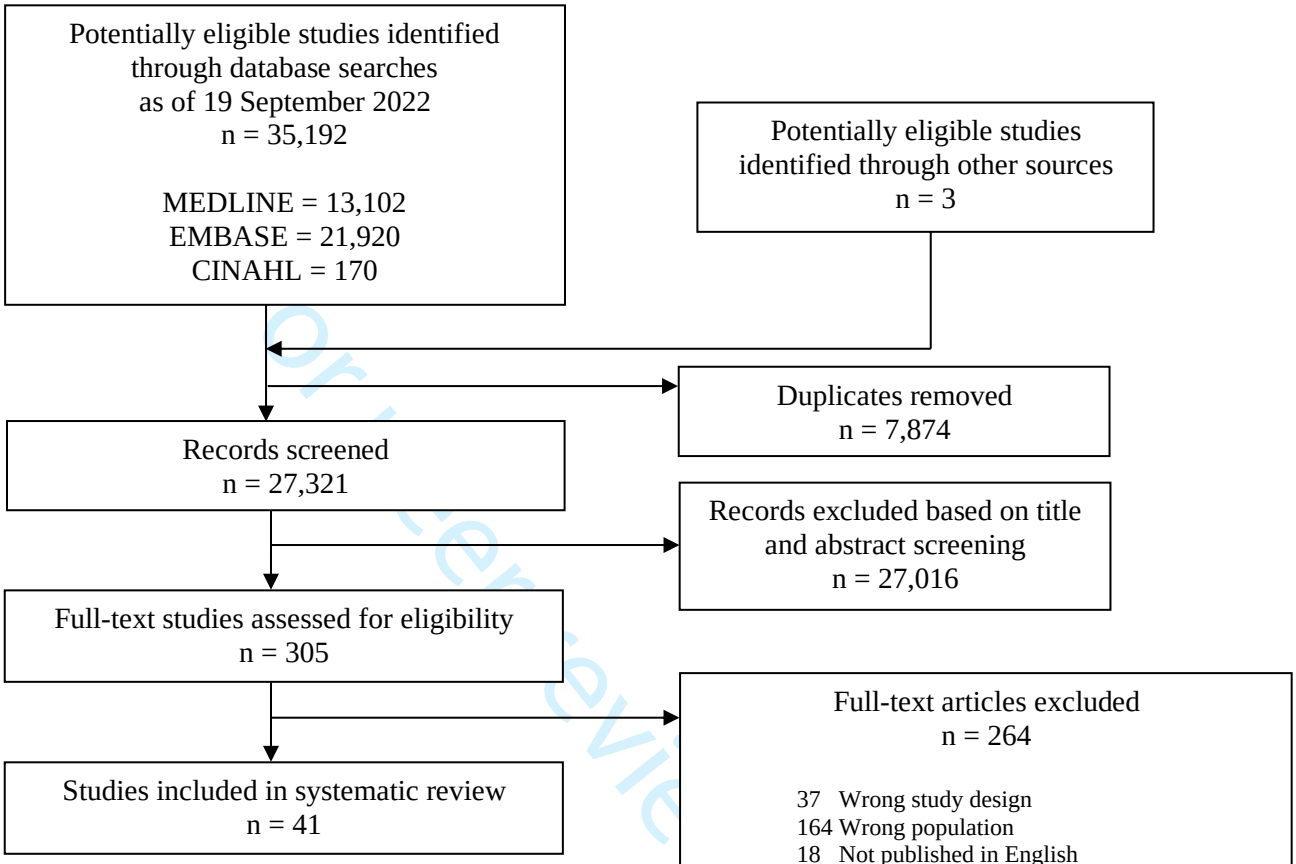
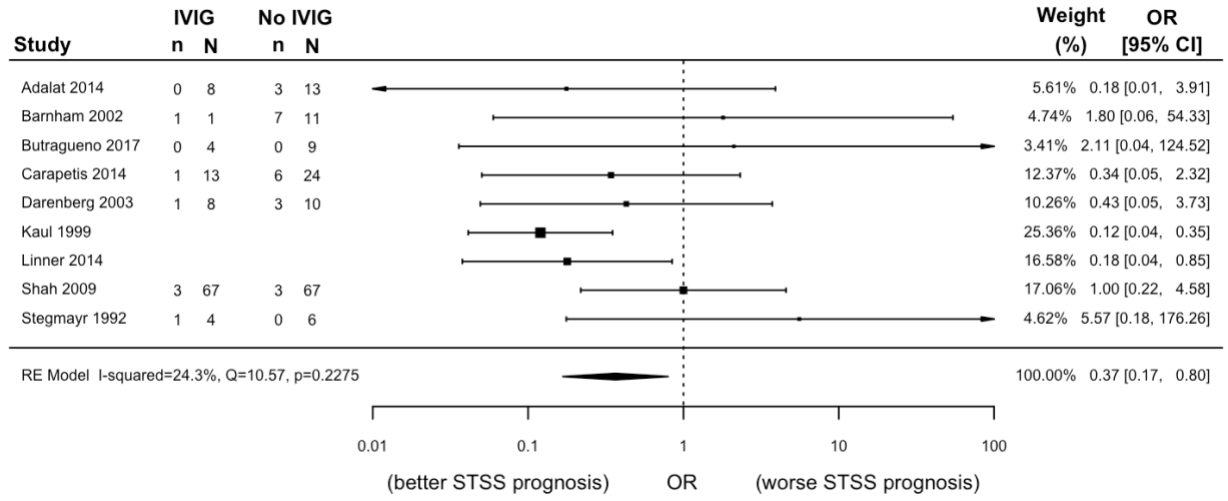
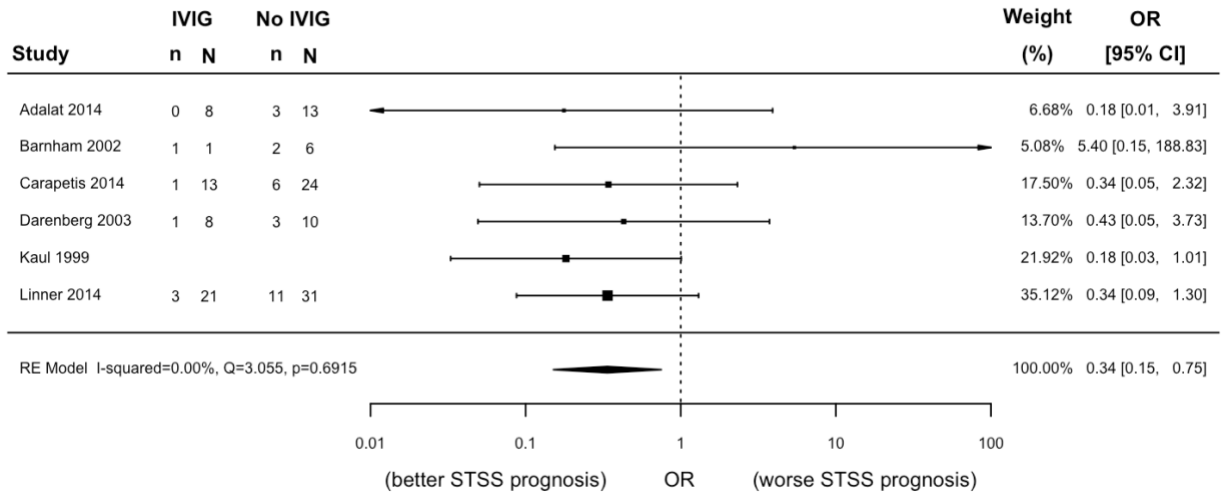


Figure 2. Meta-analyses comparing IVIG treatment to no IVIG treatment for the outcome mortality in A) all STSS patients; and B) the subset of STSS patients treated with clindamycin. Please note proportions are blank for study rows where we meta-analyzed adjusted odds ratios instead of crude proportions.

A)



B)



PROGNOSTIC FACTORS FOR STREPTOCOCCAL TOXIC SHOCK SYNDROME: SYSTEMATIC REVIEW AND META-ANALYSIS

Supplementary Material

Table of contents **Page**

Search strategies

1) Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

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1 toxic shock syndrome.mp. or exp Shock, Septic/ or STSS.mp. or streptococcal toxic shock syndrome.mp. or necrotizing fasciitis.mp. or exp Fasciitis, Necrotizing/ or septic shock.mp.
2 (group a streptococc* or group A streptococc* or pyogenes or streptococcus pyogenes).mp. or exp Streptococcus pyogenes/
3 exp Cohort Studies/
4 cohort$.tw.
5 controlled clinical trial.pt.
6 epidemiologic methods/
7 limit 6 to yr=1966-1989
8 exp case-control studies/
9 (case$ and control$).tw.
10 (case$ and series).tw.
11 or/3-5,7-10
12 randomized controlled trial.pt.
13 (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
14 (retraction of publication or retracted publication).pt.
15 or/12-14
16 (animals not humans).sh.
17 ((comment or editorial or meta-analysis or practice-guideline or review or letter) not randomized controlled trial).pt.
18 (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not randomized controlled trial.pt.
19 15 not (16 or 17 or 18)
20 animals/ not humans/
21 (1 or 2) and (11 or 19)
22 21 not 20

2) Database: Embase <1974 to 2020 February 03>

Search Strategy:

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1 toxic shock syndrome.mp. or exp septic shock/ or STSS.mp. or streptococcal toxic shock syndrome.mp. or necrotizing fasciitis.mp. or exp necrotizing fasciitis/ or septic shock.mp. or exp toxic shock syndrome/
2 (group a streptococc* or group A streptococc* or pyogenes or streptococcus pyogenes).mp. or exp Streptococcus pyogenes/ or exp Streptococcus group A/
3 exp cohort analysis/
4 exp longitudinal study/
5 exp prospective study/

6 exp follow up/
7 cohort$.tw.
8 exp case control study/ or (case$ and control$).tw.
9 exp case study/ or (case$ and series).tw.
10 or/3-9
11 (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
12 RETRACTED ARTICLE/
13 or/11-12
14 (animal$ not human$).sh,hw.
15 (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/
16 (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/
17 13 not (14 or 15 or 16)
18 exp animal/
19 exp human/
20 18 not 19
21 (1 or 2) and (10 or 17)
22 21 not 20

GRADE assessment guidance

Based on GRADE guidance for prognostic studies, we start with high certainty evidence for each meta-analysis.

Risk of bias

For each meta-analysis, we downgraded the certainty of the evidence once for risk of bias when studies with moderate or high risk of bias contributed >50% weight to the pooled effect estimates or when studies providing unadjusted estimates contributed >50% weight to the pooled effect estimate (i.e. serious risk of bias). We downgraded the certainty of the evidence twice for risk of bias when studies with moderate or high risk of bias contributed >80% weight to the pooled effect estimates or when studies providing unadjusted estimates contributed >80% weight to the pooled effect estimate (i.e. very serious risk of bias).

Inconsistency

We used visual inspection of the forest plots and the I^2 statistic to assess inconsistency. For visual inspection of the forest plots, we considered the variability in point estimates and confidence interval overlap in relation to the null effect. Further, we downgraded the certainty of the evidence once when there was substantial (I^2 50-90%) heterogeneity and twice when there was considerable (I^2 75-100%) heterogeneity.

Imprecision

We downgraded the certainty of the evidence once for imprecision if:

1) The effect on the patient, or clinical action, would differ depending on whether the upper or the lower boundary of the confidence interval represented the truth, **OR**

2) The 95% CI of the pooled absolute estimate crossed the null effect by less than 50 people per 1000 on one or both sides, **OR**

3) In cases where we had large effects that did not cross the null, we assessed the optimal information size. If the ratio of the upper to the lower limit of the confidence interval of the relative estimate was >3, the optimal information size would never be met; thus, we rated down once for imprecision, **OR**

4) There were fewer than 10 outcome events for each prognostic variable (for dichotomous outcomes, **OR**

5) There were fewer than 100 cases reaching endpoint (for continuous outcomes).

We downgraded the certainty of the evidence twice for imprecision if:

1) The 95% CI of the pooled absolute estimate crossed the null effect by more than 50 people per 1000 on both sides.

Indirectness

We rated down once if the study sample, the prognostic factor, and/or the outcome in the primary studies did not accurately reflect the review question.

Publication bias

We rated down once if:

1) Small studies reported higher rates compared to large studies, suggesting the selective publication of "positive" studies, **OR**

2) The value of the risk/protective factor in predicting the outcome has NOT been repetitively investigated (e.g. only exploratory studies with no external validation, replication or confirmation exist).

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2. Huguet A, Hayden JA, Stinson J, et al. Judging the quality of evidence in reviews of prognostic factor research: adapting the GRADE framework. Syst Rev. 2013;2:71. Published 2013 Sep 5. doi:10.1186/2046-4053-2-71

Table of excluded full texts (n=264)

Author, Year	Title	Reason for Exclusion
Hamilton, 2013	Pregnancy-related group a streptococcal infections: Temporal relationships between bacterial acquisition, infection onset, clinical findings, and outcome	Wrong study design
Ichiyama, 1997	Transmission of Streptococcus pyogenes causing toxic shock-like syndrome among family members and confirmation by DNA macrorestriction analysis	Wrong study design
Idubor, 2019	Invasive group a streptococcus infections among residents of multiple nursing Homes-Denver, Colorado, 2017-2018	Wrong study design
Ikebe, 2015	Increased prevalence of group A streptococcus isolates in streptococcal toxic shock syndrome cases in Japan from 2010 to 2012	Wrong study design
Klinker, 1997	Toxic shock syndrome in AIDS	Wrong study design
Langmuir, 1982	Toxic-shock syndrome--an epidemiologist's view	Wrong study design
McIvor, 1982	Treatment of recurrent toxic shock syndrome with oral contraceptive agents	Wrong study design
Pathi, 2013	Prompt recognition and multidisciplinary approach in Group A streptococcal sepsis	Wrong study design
Shah, 2015	Role of intravenous immune globulin in streptococcal toxic shock syndrome and Clostridium difficile infection	Wrong study design
Stallones, 1982	A review of the epidemiologic studies of toxic shock syndrome	Wrong study design
Stevens, 2000	Molecular epidemiology of nga and NAD glycohydrolase/ADP-ribosyltransferase activity among Streptococcus pyogenes causing streptococcal toxic shock syndrome	Wrong study design
Turner, 2015	Emergence of a New Highly Successful Acapsular Group A Streptococcus Clade of Genotype emm89 in the United Kingdom	Wrong study design
Udagawa, 1999	Serious group A streptococcal infection around delivery	Wrong study design
Valiquette, 2006	A survey of physician's attitudes regarding management of severe group A streptococcal infections	Wrong study design
Valiquette, 2009	Assessing the impact of intravenous immunoglobulin in the management of streptococcal toxic shock syndrome: a noble but difficult quest	Wrong study design
Wozniak, 2012	M-protein gene-type distribution and hyaluronic acid capsule in group A Streptococcus clinical isolates in Chile: Association of emm gene markers with csrR alleles	Wrong study design
Anonymous, 1984	Diagnostic bias and toxic shock syndrome	Wrong study design
Blonde, 2017	A prospective multicentric study of severe cutaneous infections in pediatric intensive care: The SCIPIC cohort	Wrong study design
Busowski, 2010	Puerperal group A streptococci (GAS) infection: Reemergence of a dreaded disease - A case series	Wrong study design
Cimolai, 2002	Nonhemolytic Streptococcus pyogenes causing invasive infection	Wrong study design
Clark, 2010	Puerperal group a streptococcal sepsis and proinflammatory immune response	Wrong study design

Dahdi, 2018	Necrotizing soft tissue infection: Microbiological distribution from district region	Wrong study design
Das, 2012	Necrotizing fasciitis in New Zealand - Risk factors, microbiological findings and outcomes in a large case series	Wrong study design
De Zoysa, 2013	Invasive group A streptococcal disease in the UK, 2008-2012 and molecular characterisation of isolates during enhanced surveillance	Wrong study design
Donawa, 1984	Toxic shock syndrome: chronology of state and federal epidemiologic studies and regulatory decision-making	Wrong study design
Figueira, 2013	Peri-ocular necrotising fasciitis: A multicentre retrospective australian series	Wrong study design
Gaensbauer, 2016	Importance of toxic shock syndrome in pediatric septic shock clinical decision-making	Wrong study design
Goldberg, 2015	Group A beta streptococcal infections in children after oral or dental trauma: A case series of 5 patients	Wrong study design
McViety, 2014	Don't forget IGAS: Lessons learnt from review of 2 peak seasons in the north west and North Wales, UK	Wrong study design
Zangara, 2019	Epidemiology, outcomes from treatment, and the spectrum of soft tissue infections over time in hospitalized patients: A populationbased description of inpatients in the state of california	Wrong study design
Arias-Constanti, 2018	Invasive disease by Streptococcus pyogenes: patients hospitalized for 6 years	Wrong population
Hankins, 2008	Factors that affect the clinical course of group A beta-haemolytic streptococcal infections of the hand and upper extremity: a retrospective study	Wrong population
Henrichsen, 1997	Invasive infections caused by Streptococcus pyogenes in Denmark 1990- 1994	Wrong population
Hoge, 1993	The changing epidemiology of invasive group A streptococcal infections and the emergence of streptococcal toxic shock-like syndrome. A retrospective population-based study	Wrong population
Jauregui, 2015	Life- and limb-threatening infections following the use of an external fixator	Wrong population
Kadri, 2017	Impact of Intravenous Immunoglobulin on Survival in Necrotizing Fasciitis With Vasopressor-Dependent Shock: A Propensity Score-Matched Analysis From 130 US Hospitals	Wrong population
Leggiadro, 1993	Group A streptococcal bacteremia in a mid-south children's hospital	Wrong population
Madsen, 2019	Patient's characteristics and outcomes in necrotising soft-tissue infections: results from a Scandinavian, multicentre, prospective cohort study	Wrong population
Mitchell, 2011	A strep in the wrong direction-invasive group a streptococcal disease	Wrong population
Moses, 1995	Group A streptococcus bacteremia at the Hadassah Medical Center in Jerusalem	Wrong population
Mosites, 2017	Use of single-dose azithromycin to control a community outbreak of EMM26.3 group a streptococcus invasive disease-Alaska, 2017	Wrong population
Mosites, 2019	Risk for invasive streptococcal infections among adults experiencing homelessness, anchorage, Alaska, USA, 2002-2015	Wrong population

Mulla, 2007	Clinical and epidemiologic features of invasive group A streptococcal infections in children	Wrong population
Mulla, 2003	Invasive group A streptococcal infections in Florida	Wrong population
Navarro, 1993	A comparison of Streptococcus pyogenes (group A streptococcal) bacteremia at an urban and a suburban hospital. The importance of intravenous drug use	Wrong population
Norton, 2004	Invasive group A streptococcal disease in North Queensland (1996 - 2001)	Wrong population
Nuwayhid, 2007	Blunt Trauma as a Risk Factor for Group A Streptococcal Necrotizing Fasciitis	Wrong population
Oliver, 2019	Invasive group A Streptococcus disease in Australian children: 2016 to 2018 - a descriptive cohort study	Wrong population
Oliver, 2019	Recent trends in invasive group A Streptococcus disease in Victoria	Wrong population
Peterson, 1996	Risk factors for invasive group A streptococcal infections in children with varicella: A case-control study	Wrong population
Rainbow, 2008	Invasive group A streptococcal disease in nursing homes, Minnesota, 1995-2006	Wrong population
Rathore, 1992	Suppurative group A beta-hemolytic streptococcal infections in children	Wrong population
Reingold, 1984	Epidemiology of toxic-shock syndrome, United States, 1960-1984	Wrong population
Reingold, 1989	Risk factors for menstrual toxic shock syndrome: results of a multistate case-control study	Wrong population
Remy, 2019	Septic shock and toxic shock syndrome-two infectious shocks with different immune response	Wrong population
Rudolph, 2016	Epidemiology of invasive group a streptococcal disease in Alaska, 2001 to 2013	Wrong population
Saldana, 2010	Periorbital necrotizing fasciitis: Outcomes using a CT-guided surgical debridement approach	Wrong population
Sarangi, 1995	A nursing home outbreak of group A streptococcal infection: case control study of environmental contamination	Wrong population
Scaber, 2011	Group a streptococcal infections during the seasonal influenza outbreak 2010/11 in South East England	Wrong population
Scheuer, 2018	Rising high rate of invasive group a streptococcus infections among persons experiencing homelessness in San Francisco, 2010-2017	Wrong population
Schlech, 1982	Risk factors for development of toxic shock syndrome. Association with a tampon brand	Wrong population
Schwartz, 1989	Nonmenstrual toxic shock syndrome associated with barrier contraceptives: report of a case-control study	Wrong population
Shands, 1982	Toxic shock syndrome: Case-control studies at the centers for disease control	Wrong population
Sharma, 2019	Real-time whole genome sequencing to control a Streptococcus pyogenes outbreak at a national orthopaedic hospital	Wrong population
Sierra, 2006	Group A streptococcal infections in injection drug users in Barcelona, Spain: Epidemiologic, clinical, and microbiologic analysis of 3 clusters of cases from 2000 to 2003	Wrong population

Simonart, 2004	The importance of serum creatine phosphokinase level in the early diagnosis and microbiological evaluation of necrotizing fasciitis	Wrong population
Smith, 2003	Mass antibiotic treatment for group A streptococcus outbreaks in two long-term care facilities	Wrong population
Spargen, 2011	Proinflammatory immune response and puerperal group a streptococcal sepsis	Wrong population
Steer, 2009	Prospective surveillance of invasive group A streptococcal disease, fiji, 2005-2007	Wrong population
Steer, 2008	High burden of invasive beta-haemolytic streptococcal infections in Fiji	Wrong population
Tanna, 2006	Molecular characterization of clinical isolates of M non-typable group A streptococci from invasive disease cases	Wrong population
Tapiainen, 2016	Invasive Group A Streptococcal Infections in Children: A Nationwide Survey in Finland	Wrong population
Thanert, 2019	Molecular profiling of tissue biopsies reveals unique signatures associated with streptococcal necrotizing soft tissue infections	Wrong population
Theis, 2002	Severe necrotising soft tissue infections in orthopaedic surgery	Wrong population
Thigpen, 2007	Nursing home outbreak of invasive group A streptococcal infections caused by 2 distinct strains	Wrong population
Urbina, 2019	Early identification of patients at high risk of group A streptococcus-associated necrotizing skin and soft tissue infections: a retrospective cohort study	Wrong population
Vasant, 2019	Mass prophylaxis in an outbreak of invasive group A streptococcal disease in a residential aged care facility	Wrong population
Vlaminckx, 2005	Long-term surveillance of invasive group A streptococcal disease in The Netherlands, 1994-2003	Wrong population
Vugia, 1996	Invasive group A streptococcal infections in children with varicella in Southern California	Wrong population
Waldhausen, 1996	Surgical implications of necrotizing fasciitis in children with chickenpox	Wrong population
Watanabe-Ohnishi, 1995	Selective depletion of V beta-bearing T cells in patients with severe invasive group A streptococcal infections and streptococcal toxic shock syndrome. Ontario Streptococcal Study Project	Wrong population
Wheeler, 1991	Outbreak of group A streptococcus septicemia in children: Clinical, epidemiologic, and microbiological correlates	Wrong population
Wilson, 1995	Group A streptococcal necrotizing fasciitis following varicella in children: Case reports and review	Wrong population
Wong, 2019	A Cluster of Pediatric Invasive Group A Streptococcus Disease in Melbourne, Australia, Coinciding with a High-Burden Influenza Season	Wrong population
Yagupsky, 1987	Group A beta-hemolytic streptococcal bacteremia in children	Wrong population
Zerr, 1999	A case-control study of necrotizing fasciitis during primary varicella	Wrong population
Zimbelman, 1999	Improved outcome of clindamycin compared with beta-lactam antibiotic treatment for invasive Streptococcus pyogenes infection	Wrong population

Abraham, 2016	Distribution of emm types of beta hemolytic streptococci associated with necrotizing fascitis: Clinical profile and outcome	Wrong population
Acosta, 2014	Severe Maternal Sepsis in the UK, 2011-2012: A National Case-Control Study	Wrong population
Adams, 2010	Investigation into an outbreak of invasive Group A Streptococcal (iGAS) infection at a general hospital in 2010	Wrong population
Adem, 2009	Identification of invasive streptococcal disease in a pediatric and infant death Cohort-Iowa, 2007-2008	Wrong population
Afifi, 2008	Acute necrotizing fasciitis in Egyptian patients: A case series	Wrong population
Al-Khadidi, 2017	Group A Streptococcal bacteraemia. Experience at King Fahad Medical City in Riyadh, Saudi Arabia	Wrong population
Alva, 2013	Necrotising fasciitis: A series of seven cases	Wrong population
Anonymous, 2007	Summaries for patients. Invasive streptococcal infections in hospitals in Ontario, Canada, 1992 to 2000	Wrong population
Aronoff, 2008	Postpartum invasive group A streptococcal disease in the modern era	Wrong population
Babbar, 2018	Pivotal Role of Preexisting Pathogen-Specific Antibodies in the Development of Necrotizing Soft-Tissue Infections	Wrong population
Babbar, 2016	A serological evaluation of the host immune response during Necrotizing Soft Tissue Infections caused by Streptococcus pyogenes	Wrong population
Babiker, 2019	Impact of adjunctive clindamycin in invasive beta-hemolytic streptococcal infections: A propensity score-matched analysis of 1956 beta-lactam treated patients from 118 us hospitals	Wrong population
Bajpai, 1977	Chemotherapy of acute bone and joint infections	Wrong population
Barnham, 2001	Bacteraemic Streptococcus pyogenes infection in the peri-partum period: now a rare disease and prior carriage by the patient may be important	Wrong population
Basma, 1999	Risk factors in the pathogenesis of invasive group A streptococcal infections: Role of protective humoral immunity	Wrong population
Bauer, 2015	Maternal deaths due to sepsis in the state of Michigan, 1999-2006	Wrong population
Beaudoin, 2014	Invasive group A Streptococcus infections associated with liposuction surgery at outpatient facilities not subject to state or federal regulation	Wrong population
Beigh, 2012	Postoperative complications followed by septoplasty comparison between conventional nasal packing and glove finger pack	Wrong population
Berkley, 1987	The relationship of tampon characteristics to menstrual toxic shock syndrome	Wrong population
Bingol-Kologlu, 2007	Necrotizing fasciitis in children: diagnostic and therapeutic aspects	Wrong population
Bruun, 2013	Necrotizing soft tissue infections caused by Streptococcus pyogenes and Streptococcus dysgalactiae subsp. equisimilis of groups C and G in western Norway	Wrong population
Bruun, 2020	Risk factors and Predictors of Mortality in Streptococcal Necrotizing Soft-Tissue Infections: A Multicenter Prospective Study	Wrong population

Busowski, 2013	Puerperal group a streptococcal infections: A case series and discussion	Wrong population
Byer, 2006	Clinical deterioration among patients with fever and erythroderma	Wrong population
Centers for Disease, 1982	Toxic-shock syndrome, United States, 1970-1982	Wrong population
Centers for Disease, 2011	Invasive group A streptococcus in a skilled nursing facility--Pennsylvania, 2009-2010	Wrong population
Chan, 2009	Toxic shock syndrome and rhinosinusitis in children	Wrong population
Chen, 2011	The microbiological profile and presence of bloodstream infection influence mortality rates in necrotizing fasciitis	Wrong population
Chen, 2015	Clinical Characteristics and Risk Factor Analysis for Lower-Extremity Amputations in Diabetic Patients With Foot Ulcer Complicated by Necrotizing Fasciitis	Wrong population
Chen, 2018	Macro- and Microvascular Parameters After Toxic Shock Syndrome	Wrong population
Ching, 2019	Prospective surveillance of pediatric invasive group A Streptococcus infection	Wrong population
Chiobotaru, 1997	Changing epidemiology of invasive Streptococcus pyogenes infections in southern Israel: differences between two ethnic population groups	Wrong population
Christie, 1988	Bacteremia with group A streptococci in childhood	Wrong population
Corona, 2016	Necrotising fasciitis of the extremities: implementation of new management technologies	Wrong population
Daneman, 2007	Surveillance for hospital outbreaks of invasive group a streptococcal infections in Ontario, Canada, 1992 to 2000	Wrong population
Daneman, 2005	Hospital-acquired invasive group A streptococcal infections in Ontario, Canada, 1992-2000	Wrong population
Davies, 1996	Invasive group A streptococcal infections in Ontario, Canada. Ontario Group A Streptococcal Study Group	Wrong population
Davis, 1982	Toxic shock syndrome: a critique of the 1980 Wisconsin case-control study	Wrong population
De Almeida Torres, 2013	Group a streptococcus meningitis in children	Wrong population
Deutscher, 2011	Incidence and severity of invasive Streptococcus pneumoniae, group A Streptococcus, and group B Streptococcus infections among pregnant and postpartum women	Wrong population
Devaney, 2015	Necrotising soft tissue infections: The effect of hyperbaric oxygen on mortality	Wrong population
Dooling, 2013	Investigation of a prolonged Group A Streptococcal outbreak among residents of a skilled nursing facility, Georgia, 2009-2012	Wrong population
Dworkin, 2009	The epidemiology of necrotizing fasciitis including factors associated with death and amputation	Wrong population
Eneli, 2007	Epidemiology and Outcome of Necrotizing Fasciitis in Children: An Active Surveillance Study of the Canadian Paediatric Surveillance Program	Wrong population
Factor, 2005	Risk factors for pediatric invasive group A streptococcal disease	Wrong population
Factor, 2003	Invasive group a streptococcal disease: Risk factors for adults	Wrong population

Fauno Thrane, 2017	Hyperbaric oxygen may only be optional in head and neck necrotizing fasciitis: a retrospective analysis of 43 cases and review of the literature	Wrong population
Fichtenbaum, 1993	Ehrlichiosis presenting as a life-threatening illness with features of the toxic shock syndrome	Wrong population
Flavahan, 2014	Incidence of periorbital necrotising fasciitis in the UK population: A BOSU study	Wrong population
Flores, 2019	Capsule-negative EMM types are an increasing cause of pediatric group a streptococcal infections at a large pediatric hospital in Texas	Wrong population
Frere, 2016	Clinical and Microbiological Characteristics of Invasive Group A Streptococcal Infections Before and After Implementation of a Universal Varicella Vaccine Program	Wrong population
Givner, 1998	Invasive disease due to group A beta-hemolytic streptococci: Continued occurrence in children in North Carolina	Wrong population
Givner, 1991	Apparent increase in the incidence of invasive group A beta-hemolytic streptococcal disease in children	Wrong population
Gooskens, 2005	Streptococcal toxic shock syndrome by an iMLS resistant M type 77 Streptococcus pyogenes in the Netherlands	Wrong population
Gonzalez, 1996	Necrotizing fasciitis of the upper extremity	Wrong population
Lesko, 2001	Invasive group A streptococcal infection and nonsteroidal antiinflammatory drug use among children with primary varicella	Wrong population
Lin, 2013	Group a streptococcal necrotizing fasciitis in the emergency department	Wrong population
Lin, 2015	Early Differentiation of Kawasaki Disease Shock Syndrome and Toxic Shock Syndrome in a Pediatric Intensive Care Unit	Wrong population
Parks, 2019	Elevated risk of invasive group A streptococcal disease and host genetic variation in the human leucocyte antigen locus	Wrong population
Stromberg, 1991	Outbreak of group A streptococcal bacteremia in Sweden: an epidemiologic and clinical study	Wrong population
Haggar, 2012	Clinical and microbiologic characteristics of invasive Streptococcus pyogenes infections in north and south India	Relationship between prognostic factor and outcome not reported or quantified
Laupland, 2000	Invasive group A streptococcal disease in children and association with varicella-zoster virus infection. Ontario Group A Streptococcal Study Group	Relationship between prognostic factor and outcome not reported or quantified
Linnemann, 1986	Increasing incidence of toxic shock syndrome in the 1970s	Relationship between prognostic factor and outcome not reported or quantified
Miday, 1988	Toxic shock syndrome: incidence and geographic distribution from a hospital medical records reporting system	Relationship between prognostic factor and outcome not reported or quantified
Mosites, 2018	Outbreak of Invasive Infections from Subtype emm26.3 Group A Streptococcus among Homeless Adults-Anchorage, Alaska, 2016-2017	Relationship between prognostic factor and outcome not reported or quantified

O'Grady, 2007	The epidemiology of invasive group A streptococcal disease in Victoria, Australia	Relationship between prognostic factor and outcome not reported or quantified
Petitti, 1989	Update through 1985 on the incidence of toxic shock syndrome among members of a prepaid health plan	Relationship between prognostic factor and outcome not reported or quantified
Pilon, 2019	Invasive group A streptococcal infection outbreaks of typeemm118 in a long-term care facility, and of type emm74 in the homeless population, Montreal, Quebec	Relationship between prognostic factor and outcome not reported or quantified
Rantala, 2012	Streptococcus pyogenes bacteraemia, emm types and superantigen profiles	Relationship between prognostic factor and outcome not reported or quantified
Tanner, 1981	Toxic shock syndrome	Relationship between prognostic factor and outcome not reported or quantified
Teatero, 2018	Canada-Wide Epidemic of emm74 Group A Streptococcus Invasive Disease	Relationship between prognostic factor and outcome not reported or quantified
Todd, 1985	Toxic shock syndrome. II. Estimated occurrence in Colorado as influenced by case ascertainment methods	Relationship between prognostic factor and outcome not reported or quantified
Tsai, 2014	Correlation of virulence genes to clinical manifestations and outcome in patients with Streptococcus dysgalactiae subspecies equisimilis bacteremia	Relationship between prognostic factor and outcome not reported or quantified
Vallalta Morales, 2006	Group A streptococcal bacteremia: outcome and prognostic factors	Relationship between prognostic factor and outcome not reported or quantified
Vlaminckx, 2004	Epidemiological features of invasive and noninvasive group A streptococcal disease in the Netherlands, 1992-1996	Relationship between prognostic factor and outcome not reported or quantified
Aydin, 2017	Clinical indications of intravenous immunoglobulin use in pediatric infectious diseases clinic	Relationship between prognostic factor and outcome not reported or quantified
Ben-Abraham, 2002	Invasive group A streptococcal infections in a large tertiary center: epidemiology, characteristics and outcome	Relationship between prognostic factor and outcome not reported or quantified
Bochicchio, 2001	Group A Streptococcus (GAS) soft-tissue infections: a lethal organism on the rise	Relationship between prognostic factor and outcome not reported or quantified
Cancellara, 2016	Multicenter study on invasive Streptococcus pyogenes infections in children in Argentina	Relationship between prognostic factor and

		outcome not reported or quantified
Chen, 2016	Toxic shock syndrome in Australian children	Relationship between prognostic factor and outcome not reported or quantified
Doctor, 1995	Group A beta-hemolytic streptococcal bacteremia: historical overview, changing incidence, and recent association with varicella	Relationship between prognostic factor and outcome not reported or quantified
Eriksson, 2003	Group A streptococcal infections in Sweden: a comparative study of invasive and noninvasive infections and analysis of dominant T28 emm28 isolates	Relationship between prognostic factor and outcome not reported or quantified
Norrby-Teglund, 2003	The treatment of severe group a streptococcal infections	Relationship between prognostic factor and outcome not reported or quantified
Rodriguez-Nunez, 2011	Clinical characteristics of children with group A streptococcal toxic shock syndrome admitted to pediatric intensive care units	Relationship between prognostic factor and outcome not reported or quantified
Snall, 2016	Differential neutrophil responses to bacterial stimuli: Streptococcal strains are potent inducers of heparin-binding protein and resistin-release	Relationship between prognostic factor and outcome not reported or quantified
Eriksson, 1998	Epidemiological and clinical aspects of invasive group A streptococcal infections and the streptococcal toxic shock syndrome	Relationship between prognostic factor and outcome not reported or quantified
Sahli, 2014	Necrotizing fasciitisin in diabetic patients: A report of 14 cases	Not in English
Arnholm, 2004	High-dose immunoglobulin - Life-saving in invasive group a streptococcal infection	Not in English
Caetano, 2010	[S. Pyogenes invasive disease in a paediatric hospital: 1996-2009]	Not in English
Costa Orvay, 2007	[Toxic shock syndrome: experience in a pediatric intensive care unit]	Not in English
Dosil Gallardo, 2009	[Streptococcal toxic shock syndrome: an emerging pathology?]	Not in English
Emmi, 1999	Severe infection from invasive beta-hemolytic streptococcus group A. Three cases of toxic shock observed in resuscitation	Not in English
Faye, 2014	Management of severe invasive group A streptococcal infections	Not in English
Floret, 2001	Clinical aspects of staphylococcal and streptococcal toxinic diseases	Not in English
Hua, 2018	[Streptococcal toxic shock syndrome caused by Streptococcus pyogenes: a retrospective study of 15 pediatric cases]	Not in English
Kach, 1993	[Necrotizing soft tissue infections]	Not in English
Kaul, 1999	Intravenous immunoglobulin therapy for streptococcal toxic shock syndrome--a comparative observational study. The Canadian Streptococcal Study Group	Duplicate
Salinas, 2005	Immunoglobulins in sepsis and septic shock	Not in English

Shands, 1982	Toxic shock syndrome: case-control studies at the Centers for Disease Control	Duplicate
Sierra, 2006	Group A streptococcal infections in injection drug users in Barcelona, Spain: epidemiologic, clinical, and microbiologic analysis of 3 clusters of cases from 2000 to 2003	Duplicate
Urbina, 2019	Early identification of patients at high risk of group A streptococcus-associated necrotizing skin and soft tissue infections: A retrospective cohort study	Duplicate
Vallalta-Morales, 2005	[Streptococcal toxic shock syndrome: ten years' experience at a tertiary hospital]	Not in English
Vasant, 2019	Mass prophylaxis in an outbreak of invasive group A streptococcal disease in a residential aged care facility	Duplicate
Vugia, 1996	Invasive group A streptococcal infections in children with varicella in Southern California	Duplicate
Zachariadou, 2014	Differences in the epidemiology between paediatric and adult invasive Streptococcus pyogenes infections	Duplicate
Bernard, 1995	[Bacterial dermo-hypodermatitis in adults. Incidence and role of streptococcal etiology]	Not in English
Bleton, 1991	Necrotizing fasciitis of the upper limb. 12 cases	Not in English
Bleton, 1991	Necrotising fasciitis of the upper limb. Report of twelve cases	Duplicate
Fan, 2014	[Clinical characteristics and antimicrobial resistance of invasive group A beta-hemolytic streptococcus infection in children]	Not in English
Fica, 2003	Molecular epidemiology of a streptococcus pyogenes related nosocomial outbreak in a burn unit	Not in English
Fredlund, 1990	[Increased frequency of group A hemolytic streptococci. Old age and immune deficiency among the risk factors]	Not in English
Georgiev, 1993	Puerperal streptococcal sepsis	Not in English
Khan, 2003	Treatment of necrotizing fasciitis with quinolones	Wrong population
Frosi, 1999	Necrotizing fasciitis: A serious and uncommon alcohol related disease	Wrong study design
Nedrebo, 2020	Necrotizing Soft Tissue Infections: Case Reports, from the Clinician's Perspectives.	Wrong study design
Reicher, 2021	450 Obstetrically related group a streptococcal infection and predictors for severity - retrospective 12-year cohort study	Wrong study design
Bajpai, 2020	Anti-microbial-resistance and profile of exotoxins of invasive beta-haemolytic-streptococci infections in trauma patients	Wrong population
Adamkova, 2020	Can gram-negative-like biomarker values in Streptococcus pyogenes sepsis negatively influence right choice of initial antibiotic therapy?	Wrong population
Bandi, 2021	Group A streptococcal infections in children	Wrong population
Ceccato, 2020	Use of corticosteroids in patients with severe CAP admitted to ICU, experience in a real-life setting	Wrong population
Tepper, 2021	Long-term safety and tolerability of atogepant following once daily dosing over 1 year for the preventive treatment of migraine	Wrong population

Melo, 2021	Clinical, epidemiological and microbiological features of streptococcus pyogenes invasive infection - 10 year retrospective review	Wrong population
Bringel, 2021	Clinical characteristics and outcomes of children with toxic shock syndrome admitted to a pediatric intensive care unit: A case series	Wrong population
Neff, 2020	Characterisation of clinical manifestations and treatment strategies for invasive beta-haemolytic streptococcal infections in a Swiss tertiary hospital.	Wrong population
Urbina, 2020	Assessing and applying individualized treatment for group A streptococcal necrotizing soft-tissue infection is possible	Wrong population
Bergsten, 2020	Correlation between immunoglobulin dose administered and plasma neutralization of streptococcal superantigens in patients with necrotizing soft tissue infections	Wrong population
Boukthir, 2020	A prospective survey of Streptococcus pyogenes infections in French Brittany from 2009 to 2017: Comprehensive dynamic of new emergent emm genotypes.	Wrong population
Escrihuela-Vidal, 2021	Clinical Features and Outcomes of Streptococcus anginosus Group Infective Endocarditis: A Multicenter Matched Cohort Study.	Wrong population
Babiker, 2021	Effectiveness of adjunctive clindamycin in beta-lactam antibiotic-treated patients with invasive beta-haemolytic streptococcal infections in US hospitals: a retrospective multicentre cohort study.	Wrong population
Cui, 2021	Necrotizing soft tissue infection: clinical characteristics, diagnosis, and management of 32 cases in Beijing.	Wrong population
Link-Gelles, 2020	Characteristics of Intracranial Group A Streptococcal Infections in US Children, 1997-2014.	Wrong population
Peetermans, 2020	Use of Intravenous Immunoglobulins in Patients with Suspected Toxin-Mediated Shock Requiring Extracorporeal Membrane Oxygenation.	Wrong population
Bruun, 2020	Beta-Hemolytic Streptococci and Necrotizing Soft Tissue Infections.	Wrong population
Lima-Setta, 2021	Multisystem inflammatory syndrome in children (MIS-C) during SARS-CoV-2 pandemic in Brazil: a multicenter, prospective cohort study.	Wrong population
Kohler, 2020	Kininogen supports inflammation and bacterial spreading during Streptococccus Pyogenes Sepsis.	Wrong population
Bruun, 2021	Risk Factors and Predictors of Mortality in Streptococcal Necrotizing Soft-tissue Infections: A Multicenter Prospective Study.	Wrong population
Bjorck, 2020	Morbidity and mortality in critically ill patients with invasive group A streptococcus infection: an observational study.	Wrong population
Contou, 2021	Menstrual toxic shock syndrome: a French nationwide multicenter retrospective study.	Wrong population
Billon, 2020	Association of characteristics of tampon use with menstrual toxic shock syndrome in France.	Wrong population
Canetti, 2021	Invasive Group A Streptococcus Infection in Children in Central Israel in 2012-2019	Relationship between prognostic factor and outcome not reported or quantified

Vilhonen, 2020	Group A streptococcal bacteremias in Southwest Finland 2007-2018: epidemiology and role of infectious diseases consultation in antibiotic treatment selection.	Relationship between prognostic factor and outcome not reported or quantified
Thielemans, 2020	Clinical Description and Outcomes of Australian Children With Invasive Group A Streptococcal Disease.	Relationship between prognostic factor and outcome not reported or quantified
Madsen, 2020	Treatment of Necrotizing Soft Tissue Infections: IVIG	Wrong study design
Deniskin, 2019	Clinical Manifestations and Bacterial Genomic Analysis of Group A Streptococcus Strains That Cause Pediatric Toxic Shock Syndrome.	Relationship between prognostic factor and outcome not reported or quantified
Mosites, 2018	Outbreak of Invasive Infections From Subtype emm26.3 Group A Streptococcus Among Homeless Adults-Anchorage, Alaska, 2016-2017.	Relationship between prognostic factor and outcome not reported or quantified
Hasin, 2020	Invasive Group A Streptococcus Infection in Children in Southern Israel Before and After the Introduction of Varicella Vaccine.	Wrong population
Ching, 2019	Prospective Surveillance of Pediatric Invasive Group A Streptococcus Infection.	Wrong population
Loewen, 2017	Epidemiologic features of invasive group A Streptococcus infection in a rural hospital: 6-year retrospective report and literature review.	Wrong population
Bergsten, 2020	Correlation Between Immunoglobulin Dose Administered and Plasma Neutralization of Streptococcal Superantigens in Patients With Necrotizing Soft Tissue Infections.	Wrong population
Kobayashi, 2016	A Cluster of Group A Streptococcal Infections in a Skilled Nursing Facility-the Potential Role of Healthcare Worker Presenteeism.	Wrong population
Adebanjo, 2020	Evaluating Household Transmission of Invasive Group A Streptococcus Disease in the United States Using Population-based Surveillance Data, 2013-2016.	Wrong population
Link-Gelles, 2020	Characteristics of Intracranial Group A Streptococcal Infections in US Children, 1997-2014.	Wrong population
Bruun, 2021	Risk Factors and Predictors of Mortality in Streptococcal Necrotizing Soft-tissue Infections: A Multicenter Prospective Study.	Wrong population
Shah, 2015	Role of intravenous immune globulin in streptococcal toxic shock syndrome and Clostridium difficile infection.	Wrong study design
Hayata, 2021	Nationwide study of mortality and survival in pregnancy-related streptococcal toxic shock syndrome.	Duplicate
Fernandez-Galilea, 2022	Clindamycin but not Intravenous Immunoglobulins reduces mortality in a retrospective cohort of critically ill patients with bacteremic Group A Streptococcal infections.	Wrong population
Heil, 2021	Role of Clindamycin Versus Linezolid for Serious Group A Streptococcal Infections	Wrong population
Nanduri, 2022	Challenges in Surveillance for Streptococcal Toxic Shock Syndrome: Active Bacterial Core Surveillance, United States, 2014-2017.	Wrong study design

Hamada, 2022	Association between adjunct clindamycin and in-hospital mortality in patients with necrotizing soft tissue infection due to group A Streptococcus: a nationwide cohort study.	Wrong population
Fay, 2021	Patterns of Antibiotic Nonsusceptibility Among Invasive Group A Streptococcus Infections,ÄîUnited States, 2006,Äì2017.	Relationship between prognostic factor and outcome not reported or quantified
Horn, 2021	Outcomes of Œ≤-Hemolytic Streptococcal Necrotizing Skin and Soft-tissue Infections and the Impact of Clindamycin Resistance.	Relationship between prognostic factor and outcome not reported or quantified
Contou, 2022	Menstrual Toxic Shock Syndrome: A French Nationwide Multicenter Retrospective Study.	Wrong population
Valenciano, 2021	Invasive Group A Streptococcal Infections Among People Who Inject Drugs and People Experiencing Homelessness in the United States, 2010,Äì2017.	Relationship between prognostic factor and outcome not reported or quantified
Jutras, 2021	Intravenous Immunoglobulin Use In Critically Ill Children.	Wrong population
Metcalf, 2022	Cluster Transmission Drives Invasive Group A Streptococcus Disease Within the United States and Is Focused on Communities Experiencing Disadvantage.	Wrong population
Dunne, 2022	Increasing Incidence of Invasive Group A Streptococcus Disease, Idaho, USA, 2008-2019.	Relationship between prognostic factor and outcome not reported or quantified
VanZeeland, 2022	Public health response following an iGAS outbreak in a residential aged care facility in Queensland.	Wrong population
Barisiene, 2021	Lithuanian tertiary pediatric centre experience of multi-system inflammatory syndrome in children (MIS-C): clinical cases study	Wrong population
Silvestre, 2022	Toxic shock syndrome: diagnosis and management.	Wrong study design
Nabarro, 2022	Invasive Group A Streptococcus Outbreaks Associated with Home Healthcare, England, 2018-2019.	Wrong population
Nagata, 2022	Necrotizing fasciitis of the extremities in high and low Charlson Comorbidity Index: A multi-center retrospective cohort study.	Wrong population
deNeergaard, 2022	Invasive streptococcal infection can lead to the generation of cross-strain opsonic antibodies	Wrong population
Pershing, 2021	Pediatric Group A Streptococcal Peritonitis: A Single-Center Eleven Patient Case Series	Wrong population
Nawijn, 2021	Incidence and mortality of necrotizing fasciitis in The Netherlands: the impact of group A Streptococcus.	Wrong population
Sahin, 2022	Clinical and Laboratory Features of Invasive Group A Streptococcal Infections: 8 Years Experience.	Wrong population
Thean, 2020	The epidemiology and clinical course of invasive staphylococcus aureus and group a streptococcus infections in Fiji: A prospective study	Wrong population

Hayata, 2021	Nationwide study of mortality and survival in pregnancy-related streptococcal toxic shock syndrome	Duplicate

Table of additional study characteristics

Study	Study Design	Country	Number of STSS cases	Mean age	% Male	Cardiovascular Disease (%)	Diabetes (%)	Presence of Necrotizing Fasciitis (%)	Probable GAS STSS (%)	Confirmed GAS STSS (%)	Prognostic factor and outcome combination of interest reported
Abuhammour 2004	Cohort	United States	2	9	100	NR	NR	NR	NR	NR	age - clinical cure/improvement^ age - ICU admission^ age - mortality^ any antibiotic - clinical cure/improvement^ any antibiotic - ICU admission any antibiotic - mortality
Adalat 2014	Cohort	United Kingdom, Ireland	29	4 (median)	62	NR	NR	28	38	62	IVIG - mortality
Al-Ajmi 2012	Case-series	Qatar	2	35	0	NR	NR	NR	0	100	age - clinical cure/improvement^ age - ICU admission^ age - mortality^
Barnham 2002	Case-series	England	12	57	64	NR	NR	58	17	83	age - ICU admission^ age - mortality^ any antibiotic - ICU admission any antibiotic - mortality clindamycin - ICU admission^ clindamycin - mortality emm type - ICU admission^ emm type - mortality^ immunocompromised - ICU admission^ immunocompromised - mortality IVIG - ICU admission IVIG - mortality IVIG - time to mortality^ NF - ICU admission NF - mortality NSAIDs - ICU admission NSAIDs - mortality
Bernaldo de Quiros 1997	Cohort	Spain	9	NR	NR	NR	NR	NR	NR	NR	immunocompromised - mortality^

Study	Study Design	Country	Number of STSS cases	Mean age	% Male	Cardiovascular Disease (%)	Diabetes (%)	Presence of Necrotizing Fasciitis (%)	Probable GAS STSS (%)	Confirmed GAS STSS (%)	Prognostic factor and outcome combination of interest reported
Brogan 1995	Case-series	United States	5	6	60	NR	NR	100	60	40	age - clinical cure/improvement^ age - hospital LOS^ age - ICU admission^ age - ICU LOS^ age - mortality^ NSAIDs - clinical cure/improvement^ NSAIDs - hospital LOS^ NSAIDS - ICU admission NSAIDs - ICU LOS^ NSAIDs - mortality sex - clinical cure/improvement sex - hospital LOS^ sex - ICU admission sex - ICU LOS^ sex - mortality
Butragueno Laiseca 2017	Case-series	Spain	13	2	50	NR	NR	15	15	85	acute renal failure - clinical cure/improvement^ acute renal failure - mechanical ventilation acute renal failure - mortality age - clinical cure/improvement^ age - ICU LOS^ age - mechanical ventilation^ age - mortality^ clindamycin - clinical cure/improvement^ clindamycin - ICU LOS^ clindamycin - mechanical ventilation^ clindamycin - mortality hemodialysis - clinical cure/imrpovement hemodialysis - mechanical ventilation hemodialysis - mortality IVIG - clinical cure/improvement IVIG - ICU LOS IVIG - mechanical ventilation IVIG - mortality NF - clinical cure/improvement NF - ICU LOS^ NF - mechanical ventilation NF - mortality
Carapetis 1995	Case-series	Australia	5	NR	NR	NR	NR	NR	NR	NR	age - mortality^

Study	Study Design	Country	Number of STSS cases	Mean age	% Male	Cardiovascular Disease (%)	Diabetes (%)	Presence of Necrotizing Fasciitis (%)	Probable GAS STSS (%)	Confirmed GAS STSS (%)	Prognostic factor and outcome combination of interest reported
Carapetis 2014	Cohort	Australia	37	60	50	NR	NR	100	0	100	age - mortality^ IVIG - mortality sex - mortality
Cimolai 1992	Case-series	Canada	4	8	50	NR	NR	NR	0	100	age - clinical cure/improvement^ age - mortality^ sex - clinical cure/improvement sex - mortality
Cook 2020	Cohort	United States	27	9	44	NR	NR	19	56	44	other - other^
Cowan 1994	Case-series	United States	3	2	67	NR	NR	NR	100	0	age - clinical cure/improvement^ age - ICU admission^ age - ICU LOS^ age - mechanical ventilation^ age - mortality^ sex - clinical cure/improvement sex - ICU admission sex - ICU LOS^ sex - mechanical ventilation sex - mortality
Crum 2004	Case-series	United States	2	24	100	NR	NR	50	0	100	age - clinical cure/improvement^ age - ICU admission^ age - mechanical ventilation^ age - mortality^ hemodialysis - clinical cure/improvement hemodialysis - ICU admission hemodialysis - mechanical ventilation hemodialysis - mortality
Dahl 2002	Case-series	United States	5	53	NR	NR	NR	100	0	100	age - mortality^ immunocompromised - mortality
Darenberg 2003	Randomized trial	Sweden, Norway, Finland, Netherlands	18	52	48	NR	NR	NR	11	89	IVIG - change in SOFA score^ IVIG - mortality IVIG - time to clinical cure/improvement^ IVIG - time to mortality^

Study	Study Design	Country	Number of STSS cases	Mean age	% Male	Cardiovascular Disease (%)	Diabetes (%)	Presence of Necrotizing Fasciitis (%)	Probable GAS STSS (%)	Confirmed GAS STSS (%)	Prognostic factor and outcome combination of interest reported
Donaldson 1993	Case-series	England	5	67	20	NR	NR	100	NR	NR	age - mortality^ any antibiotic - mortality sex - mortality
Erdem 2004	Case-series	United States	3	52	67	NR	NR	100	NR	33	age - mortality^ sex - mortality
Eriksson 1999	Cohort	Sweden	6	46	83	NR	NR	NR	0	100	age - mortality^ emm type - mortality^ sex - mortality
Forni 1995	Case-series	United States	5	54	83	NR	17	50	0	100	acure renal failure - ICU admission^ acute renal failure - mortality age - hospital LOS^ age - ICU admission^ age - mortality^ emm type - ICU admission^ emm type - mortality^ NF - ICU admission NF - mortality
Fronhoffs 2000	Case-series	Germany	7	49	71	14	14	86	86	14	acute renal failure - mechanical ventilation acute renal failure - mortality age - mechanical ventilation^ age - mortality^ immunocompromised - mechanical ventilation^ immunocompromised - mortality NF - mechanical ventilation NF - mortality NSAIDs - mechanical ventilation^ NSAIDs - mortality sex - mechanical ventilation sex - mortality
Hasegawa 2004	Case-control	Japan	66*	Range: 0 to 70	59	NR	18	NR	100	0	acute renal failure - mortality
Hayata 2021	Cohort	Japan	28	NR	0	NR	NR	NR	0	100	age - mortality^ NSAIDs - mortality

Study	Study Design	Country	Number of STSS cases	Mean age	% Male	Cardiovascular Disease (%)	Diabetes (%)	Presence of Necrotizing Fasciitis (%)	Probable GAS STSS (%)	Confirmed GAS STSS (%)	Prognostic factor and outcome combination of interest reported
Huang 2001	Case-series	Taiwan	3	6	100	NR	NR	NR	33	67	age - mortality^
Kansal 2000	Cohort	Canada	28	NR	NR	NR	NR	NR	NR	NR	NF - other^
Kaul 1999	Case-control	Canada	53	57	55	NR	NR	NR	NR	NR	clindamycin - mortality IVIG - duration of mechanical ventilation^ IVIG - hospital LOS IVIG - mortality NF - mortality
Linder 2017	Cohort	United States	10	NR	NR	NR	NR	NR	0	100	immunocompromised - mortality
Linnér 2014	Cohort	Sweden	67	63	42	48	16	28	NR	NR	age - mortality^ clindamycin - mortality IVIG - hospital LOS IVIG - mortality
Luca-Harari 2009	Cohort	Cyprus, Czech Republic, Denmark, Finand, France, Germany, Greece, Italy, Romania, Sweden, United Kingdom	476	NR	NR	NR	NR	NR	NR	NR	emm type - mortality^
Nelson 2016	Cohort	United States	381	NR	NR	NR	NR	19	NR	NR	age - mortality NF - mortality
O'Loughlin 2007	Cohort	United States	309	NR	NR	NR	NR	20	NR	NR	age - mortality NF - mortality
Page 2011	Cohort	Canada	16	NR	NR	NR	NR	NR	NR	NR	other - other^
Safar 2011	Cohort	New Zealand	30	NR	NR	NR	NR	17	0	100	age - mortality NF - mortality
Schwartz 1992	Case-series	United States	8	40	40	NR	NR	NR	0	100	age - mortality^ emm type - mortality^ sex - mortality
Shah 2009	Cohort	United States	192	8	49	NR	NR	NR	NR	NR	IVIG - cost^ IVIG - hospital LOS IVIG - ICU admission IVIG - ICU LOS IVIG - mechanical ventilation IVIG - mortality

Study	Study Design	Country	Number of STSS cases	Mean age	% Male	Cardiovascular Disease (%)	Diabetes (%)	Presence of Necrotizing Fasciitis (%)	Probable GAS STSS (%)	Confirmed GAS STSS (%)	Prognostic factor and outcome combination of interest reported
Sriskandan 2000	Cohort	England	7	NR	NR	NR	NR	NR	NR	NR	other - other^
Stegmayr 1992	Case-series	Sweden	11	42	64	NR	NR	NR	27	73	age - clinical cure/improvement^ age - ICU admission^ age - mechanical ventilation^ age - mortality^ hemodialysis - clinical cure/improvement hemodialysis - ICU admission hemodialysis - mechanical ventilation hemodialysis - mortality IVIG - clinical cure/improvement IVIG - ICU admission IVIG - mechanical ventilation IVIG - mortality NF - clinical cure/improvement NF - ICU admission NF - mechanical ventilation NF - mortality sex - clinical cure/improvement sex - ICU admission sex - mechanical ventilation sex - mortality
Stevens 1989	Case-series	United States	19	41	53	80	5	21	0	100	age - mortality^ emm type - mortality^ hemodialysis - mortality NF - mortality sex - mortality
Stockmann 2012	Cohort	United States	53	30 (median)	NR	58	19	32	NR	NR	age - ICU admission^ age - mortality
Tagini 2017	Case-series	Switzerland	5	18	60	NR	NR	NR	20	80	age - mortality^ emm type - mortality^ sex - mortality
Torimitsu 2021	Case-series	Japan	4	NR	75	NR	50	25	0	100	sex - mortality
Zachariadou 2013	Cohort	Greece	19	NR	NR	NR	NR	NR	0	100	age - mortality emm type - mortality^

*More than 80% of STSS cases due to group A *Streptococcus*
^Excluded from meta-analysis

NF=necrotizing fasciitis

NSAIDs=non-steroidal anti-inflammatory drugs
ICU=intensive care unit
IVIG=intravenous immunoglobulin
GAS=group A *Streptococcus*
STSS=streptococcal toxic shock syndrome
NR=not reported

Risk of bias assessment of included studies

Author	Study participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Presentation Summary	Overall Risk of Bias
Abuhammour 2004	Low	Low	Low	Low	High	High	High
Adalat 2014	Low	High	High	Low	High	High	High
Al-Ajmi 2012	NA	NA	NA	NA	NA	NA	High
Barnham 2002	NA	NA	NA	NA	NA	NA	High
Bernaldo de Quiros 1997	Low	Low	Low	Low	High	High	High
Brogan 1995	NA	NA	NA	NA	NA	NA	High
Butragueno Laiseca 2017	NA	NA	NA	NA	NA	NA	High
Carapetis 1995	NA	NA	NA	NA	NA	NA	High
Carapetis 2014	Low	Low	Low	Low	High	High	High
Cimolai 1992	NA	NA	NA	NA	NA	NA	High
Cook 2021	Low	Low	Low	Low	High	High	High
Cowan 1994	NA	NA	NA	NA	NA	NA	High
Crum 2004	NA	NA	NA	NA	NA	NA	High
Dahl 2002	NA	NA	NA	NA	NA	NA	High
Darenberg 2003	Low	Moderate	Low	Moderate	Low	Low	Moderate
Donaldson 1993	NA	NA	NA	NA	NA	NA	High
Erdem 2004	NA	NA	NA	NA	NA	NA	High
Eriksson 1999	Low	Low	Low	Low	High	High	High
Forni 1995	NA	NA	NA	NA	NA	NA	High
Fronhoffs 2000	NA	NA	NA	NA	NA	NA	High
Hasegawa 2004	Low	Low	Moderate	Low	High	High	High
Hayata 2021	Low	Low	Low	Low	High	High	High
Huang 2001	NA	NA	NA	NA	NA	NA	High
Kansal 2000	Moderate	Low	Moderate	Low	High	High	High
Kaul 1999	Low	Low	Low	Low	High	High	High

Linder 2017	Low	Moderate	Low	Moderate	High	High	High
Linner 2014	Low	Low	Low	Low	Moderate	Low	Low
Luca-Harari 2009	Low	High	Low	Low	High	High	High
Nelson 2016	Low	Low	Low	Low	High	High	High
O'Loughlin 2007	Low	Low	Low	Low	High	High	High
Page 2011	Low	Low	Low	Low	Moderate	High	Moderate
Safar 2011	Low	Low	Low	Low	High	High	High
Schwartz 1992	NA	NA	NA	NA	NA	NA	High
Shah 2009	Low	High	Low	Low	Moderate	Moderate	Moderate
Sriskandan 2000	Moderate	Moderate	High	Low	High	High	High
Stegmayr 1992	NA	NA	NA	NA	NA	NA	High
Stevens 1989	NA	NA	NA	NA	NA	NA	High
Stockmann 2012	Low	Low	Low	Low	High	High	High
Tagini 2017	NA	NA	NA	NA	NA	NA	High
Torimitsu 2021	NA	NA	NA	NA	NA	NA	High
Zachariadou 2013	Low	Low	Low	Low	High	High	High

NA, Not Applicable because case-series study design and rated at high risk of bias.

Forest plots

n_e: number of patients with the outcome exposed to or experiencing the prognostic factor (experimental group)
N_e: total number of patients exposed to or experiencing the prognostic factor (experimental group)
n_c: number of patients with the outcome not exposed to or experiencing the prognostic factor (control group)
N_c: total number of patients not exposed to or experiencing the prognostic factor (control group)

Percentages in forest plots correspond to the percent weight contribution of each study in the meta-analysis.

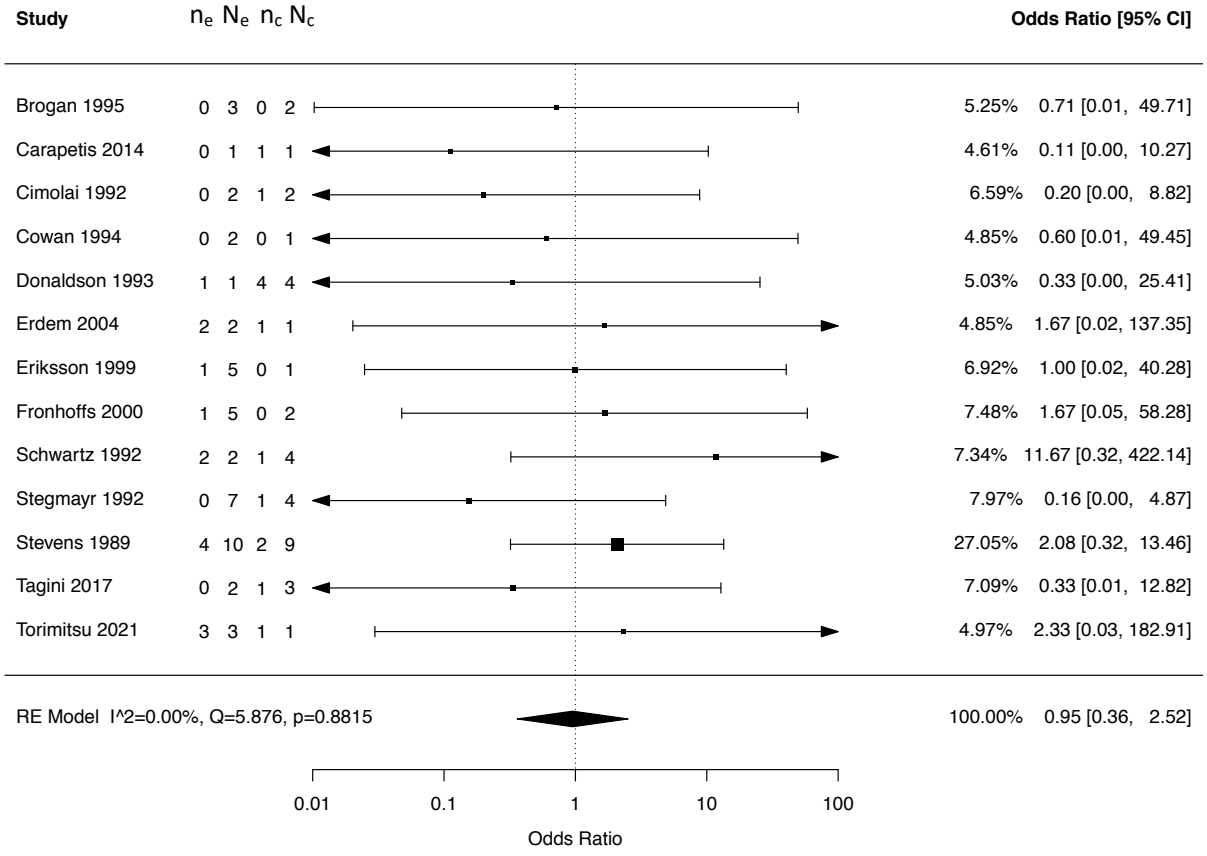
For mortality, ICU admission and need for mechanical ventilation outcomes, an odds ratio greater than 1 corresponds with a worse STSS prognosis and an odds ratio less than 1 corresponds with a better STSS prognosis.

For clinical cure or improvement outcome, an odds ratio greater than 1 corresponds with a better STSS prognosis and an odds ratio less than 1 corresponds with a worse STSS prognosis.

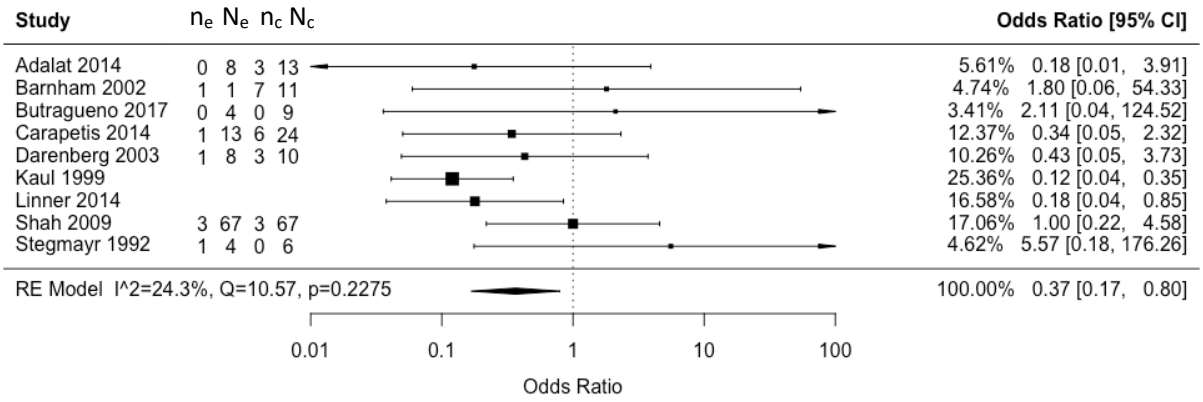
For duration of hospitalization and ICU stay outcomes, a mean difference greater than 1 corresponds with a worse STSS prognosis and a mean difference less than 1 corresponds with a better STSS prognosis.

Mortality

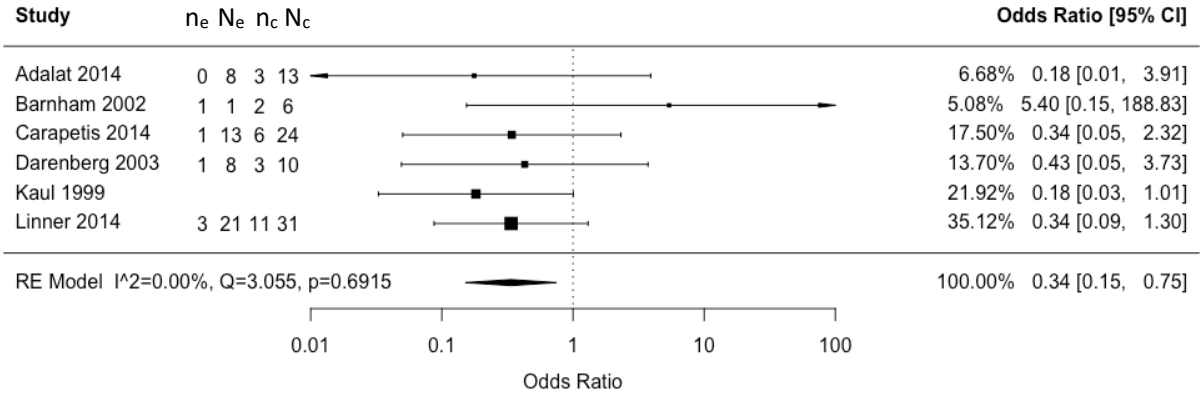
1. Sex: male vs female (reference)



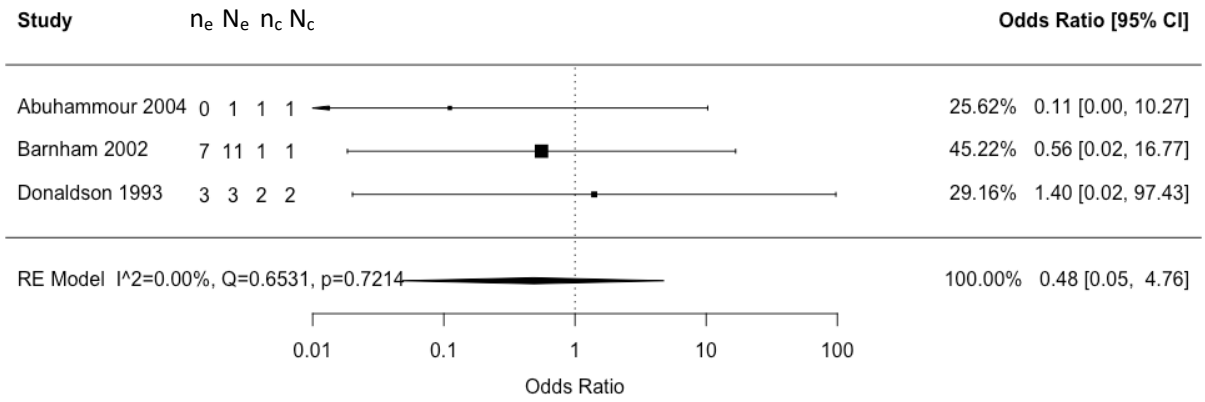
2.A) IVIG in all STSS patients: yes vs no (reference)

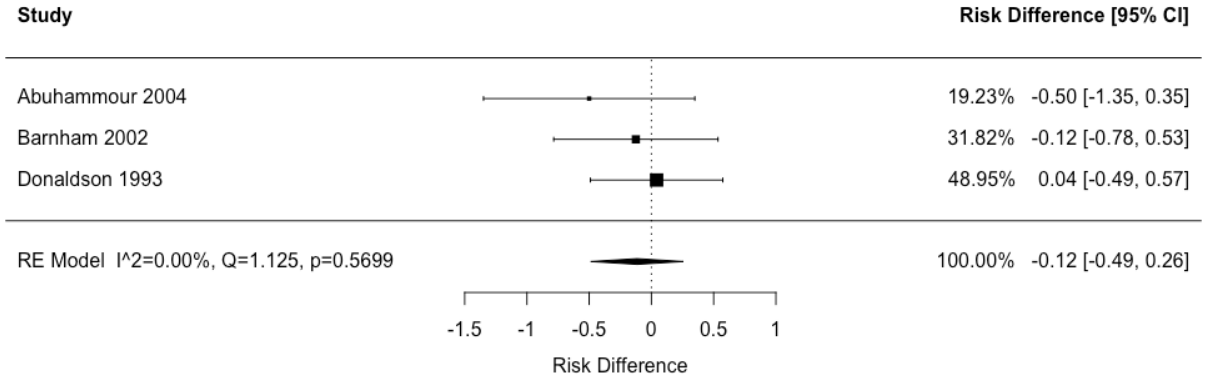


2.B) IVIG in the subset of STSS patients treated with clindamycin: yes vs no (reference)

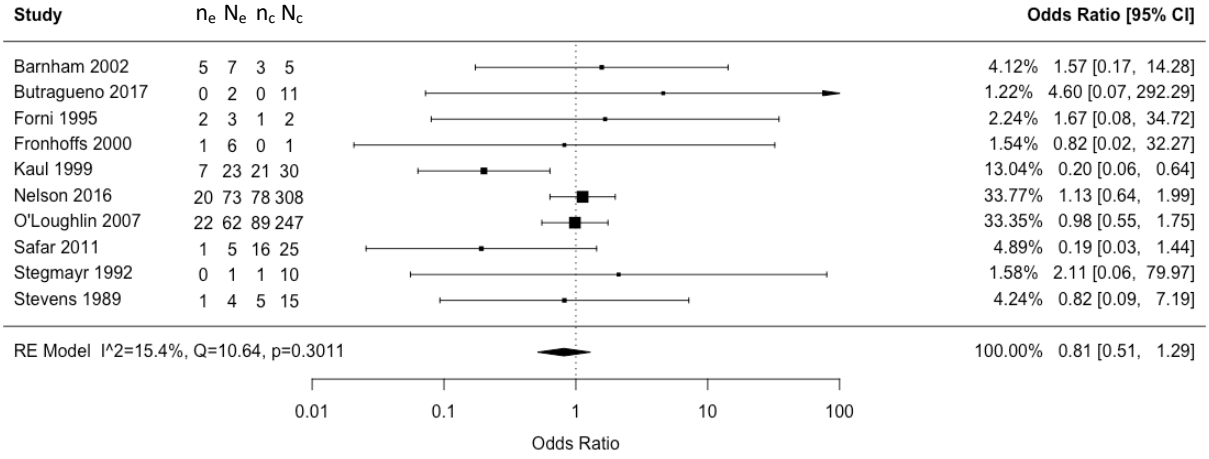


3. Any antibiotic: yes vs no (reference)

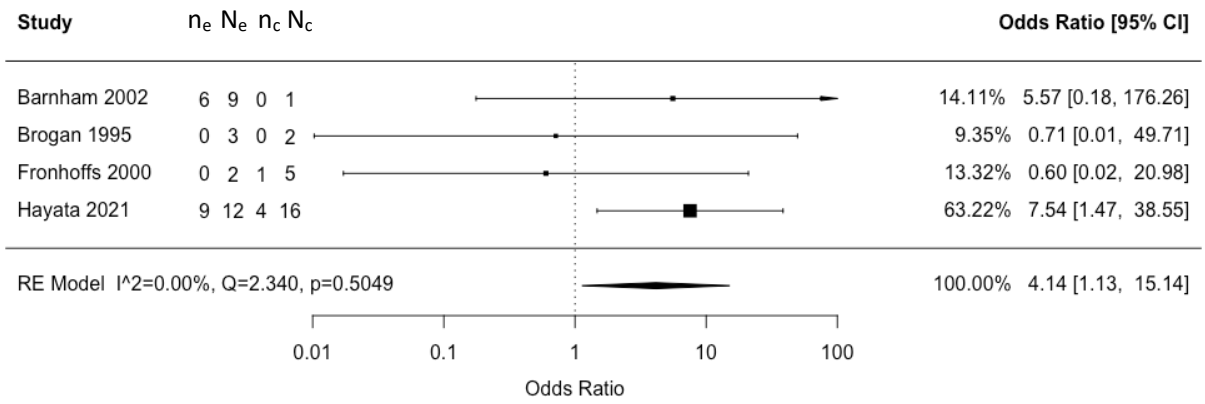




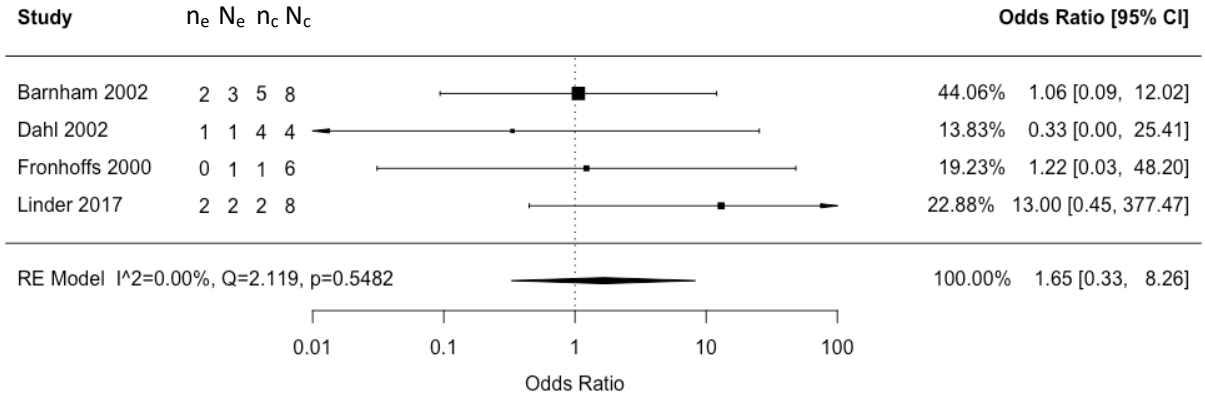
4. Necrotizing fasciitis: yes vs no (reference)



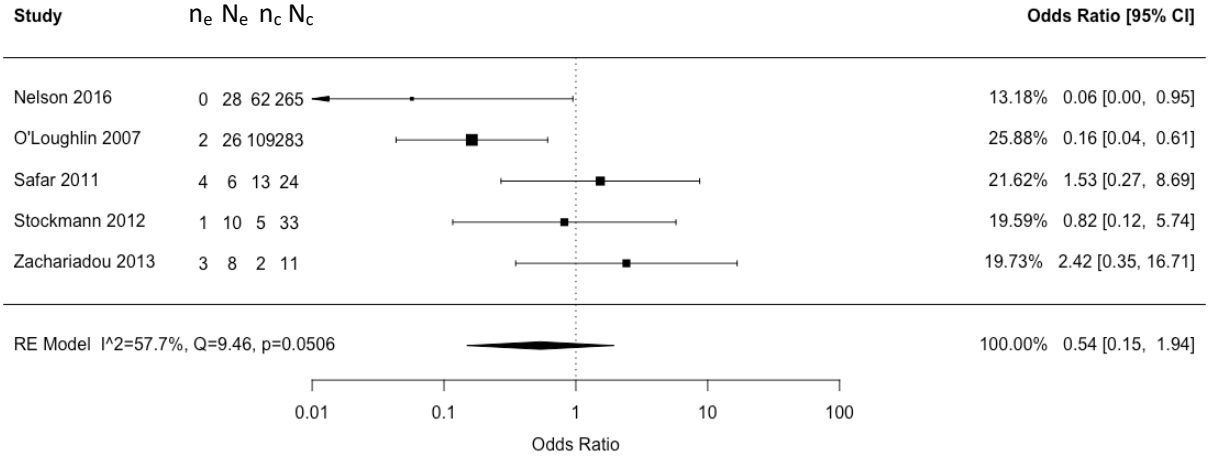
5. NSAIDs: yes vs no (reference)



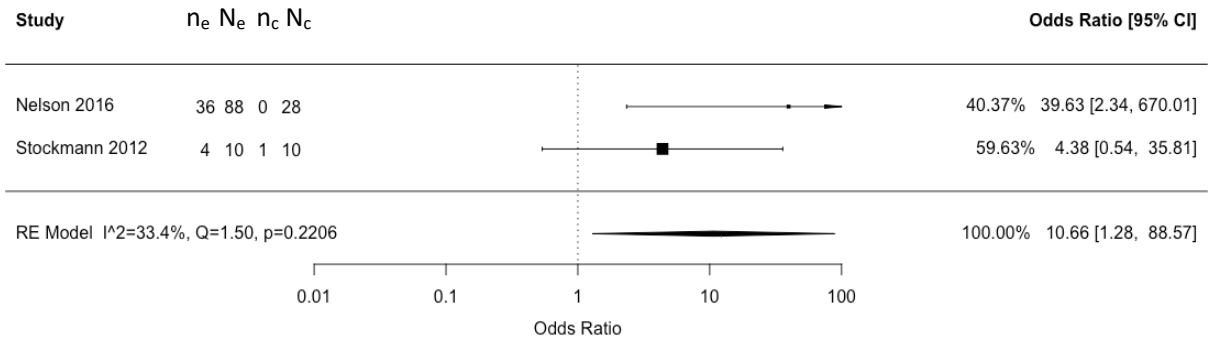
6. Immunocompromised: yes vs no (reference)



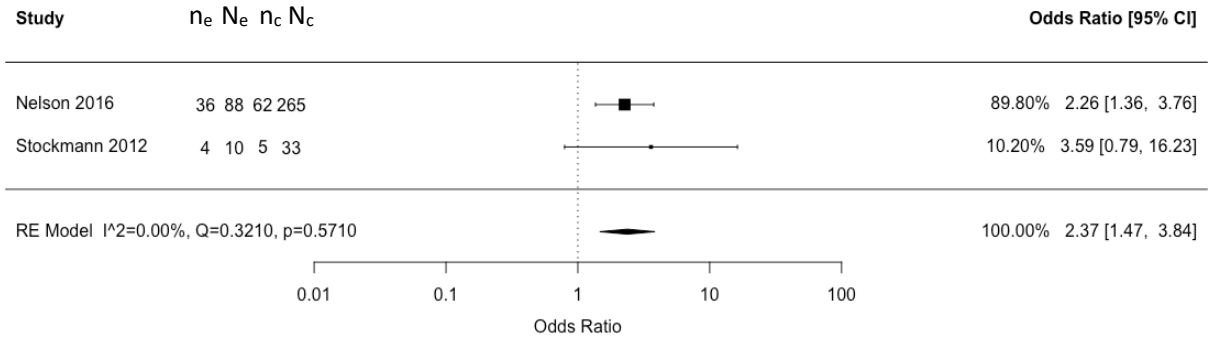
7. Age: <18 years vs 18-64 years (reference)



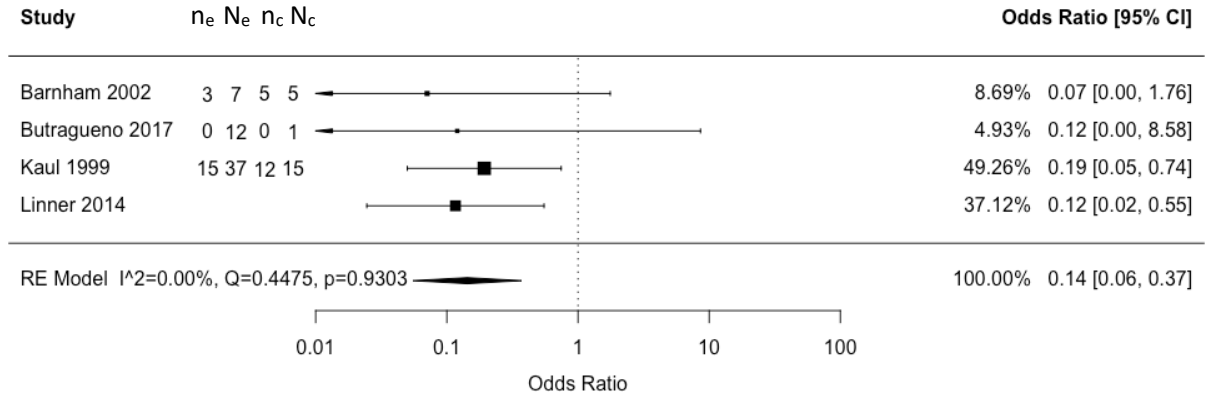
8. Age: ≥65 years vs <18 years (reference)



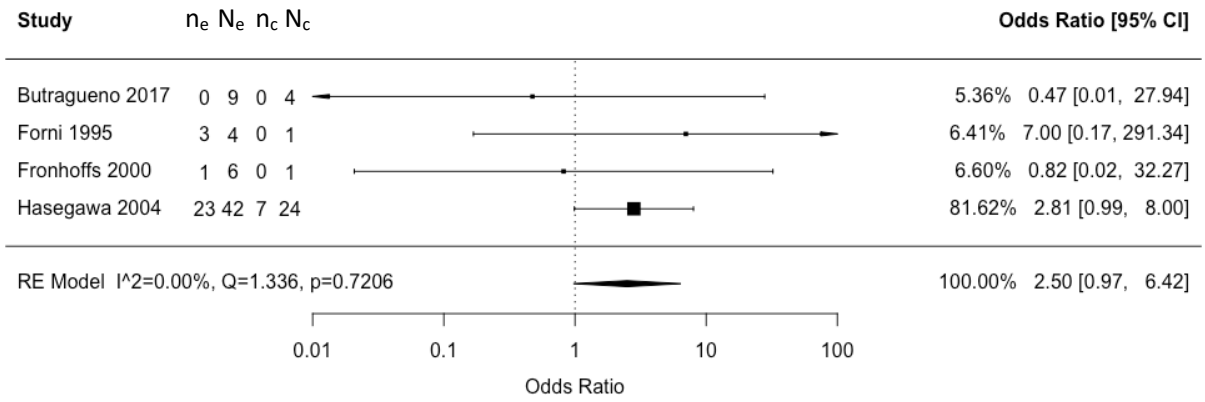
9: Age: ≥65 years vs 18-64 years (reference)

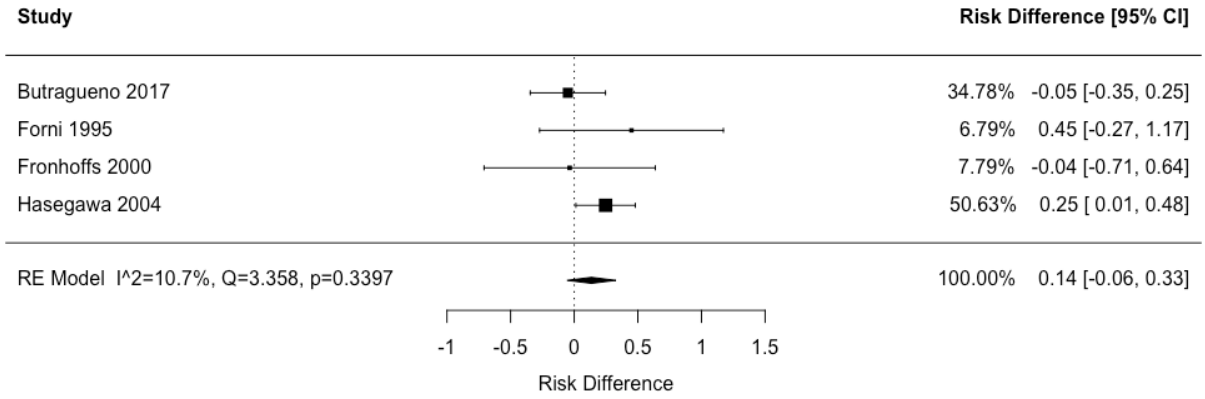


10. Clindamycin antibiotic vs no clindamycin antibiotic (reference)

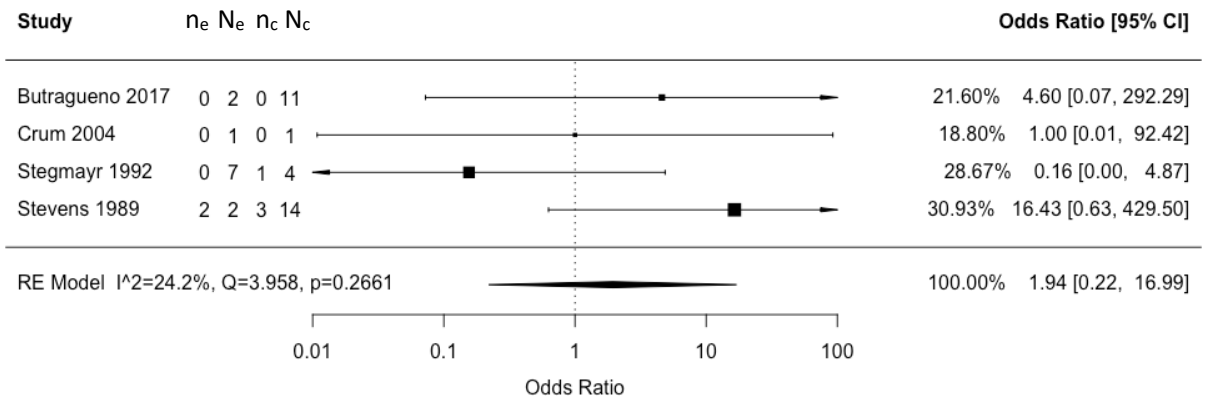


11. Acute renal failure: yes vs no (reference)





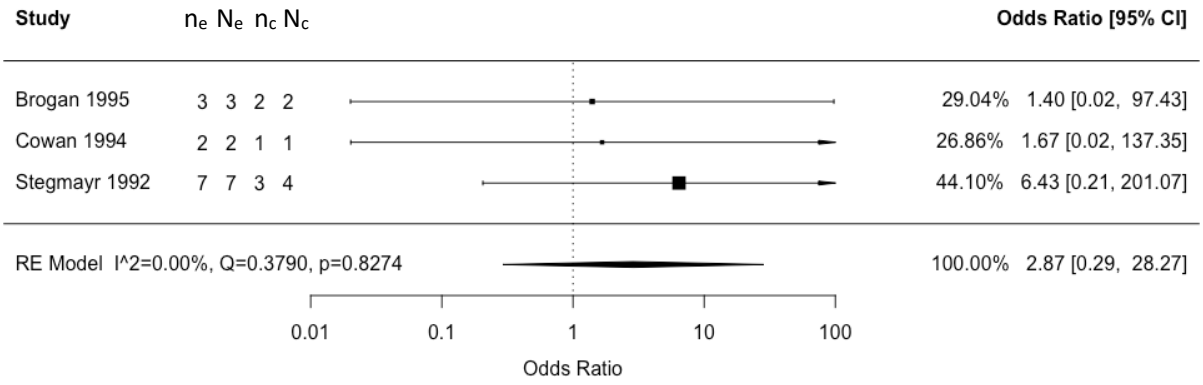
12. Hemodialysis: yes vs no (reference)

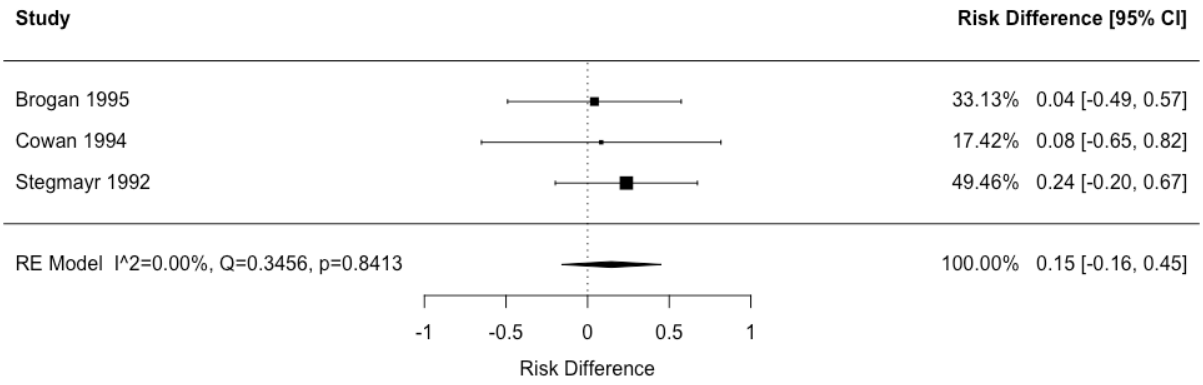


ICU admission

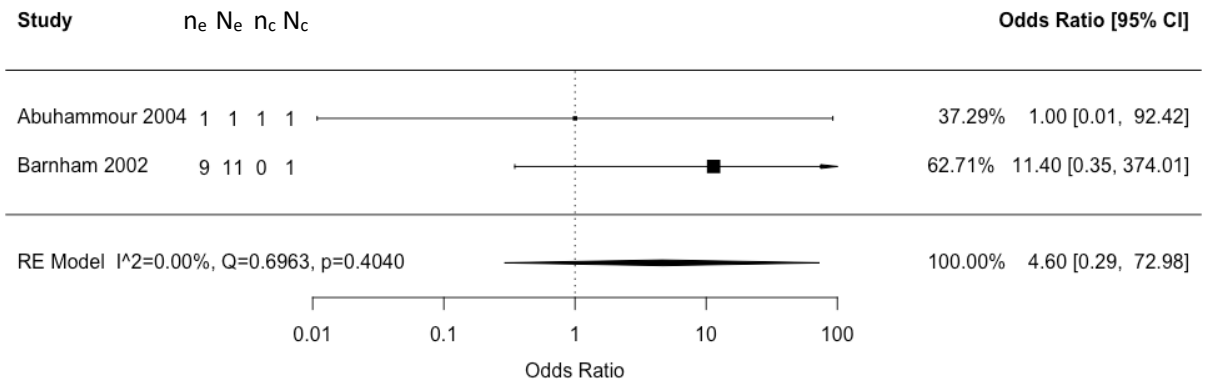
This note pertains to meta-analyses of the outcome ICU admission that include the study Stegmayr 1992. For this study, 10 of 11 STSS patients were admitted to the ICU. Despite no explicit mention of which one patient was not admitted to the ICU, our interpretation of the clinical profiles and patient-level data allowed us to deduce that patient 1 likely did not require ICU admission. We reached out to the corresponding author to confirm if our interpretation was correct, but did not receive a response.

1. Sex: male vs female (reference)

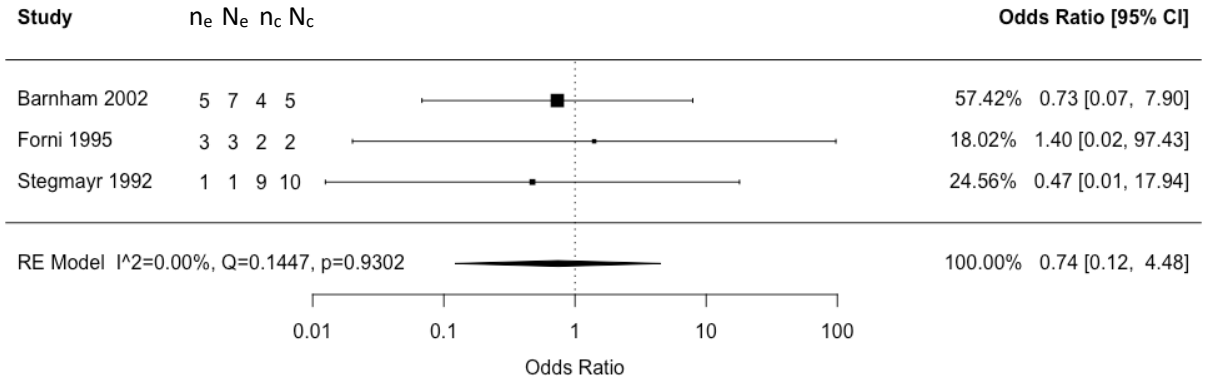




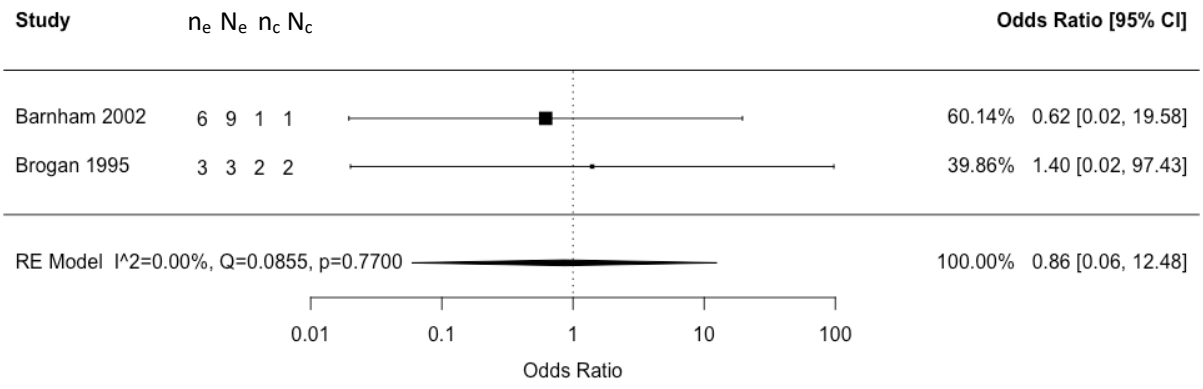
2. Any antibiotic: yes vs no (reference)

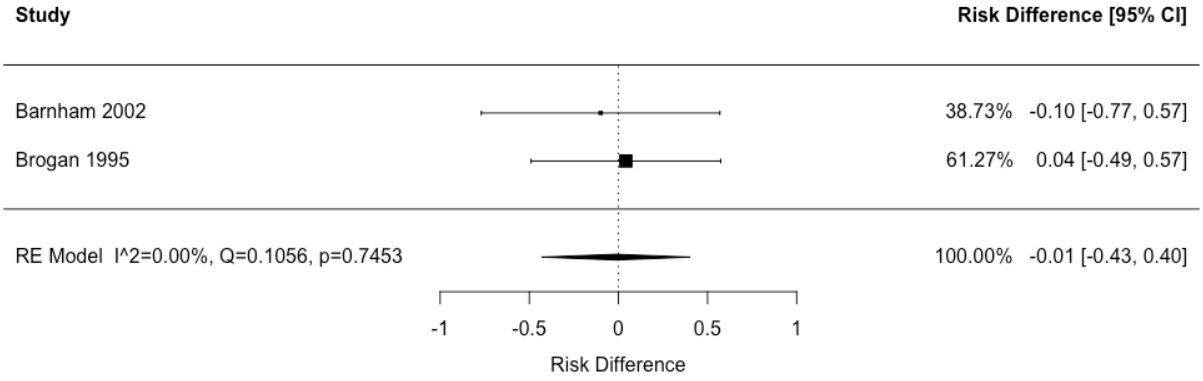


3. Necrotizing fasciitis: yes vs no (reference)

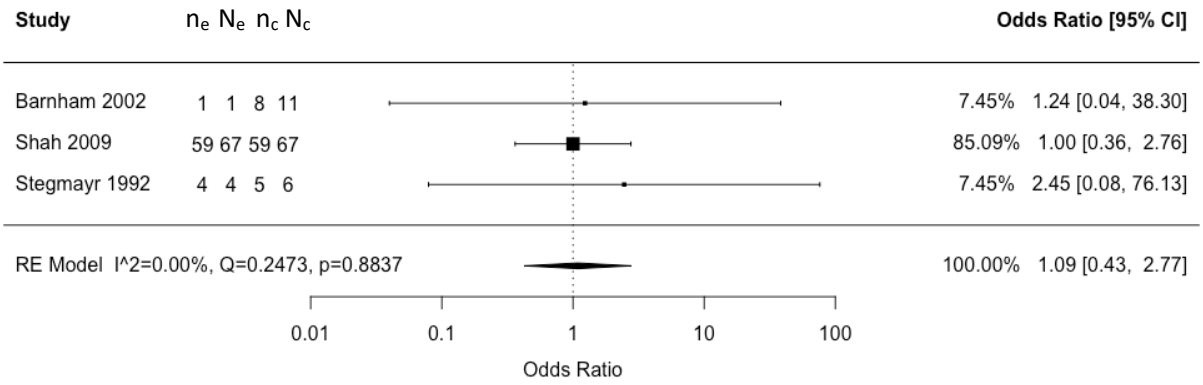


4. NSAIDs: yes vs no (reference)

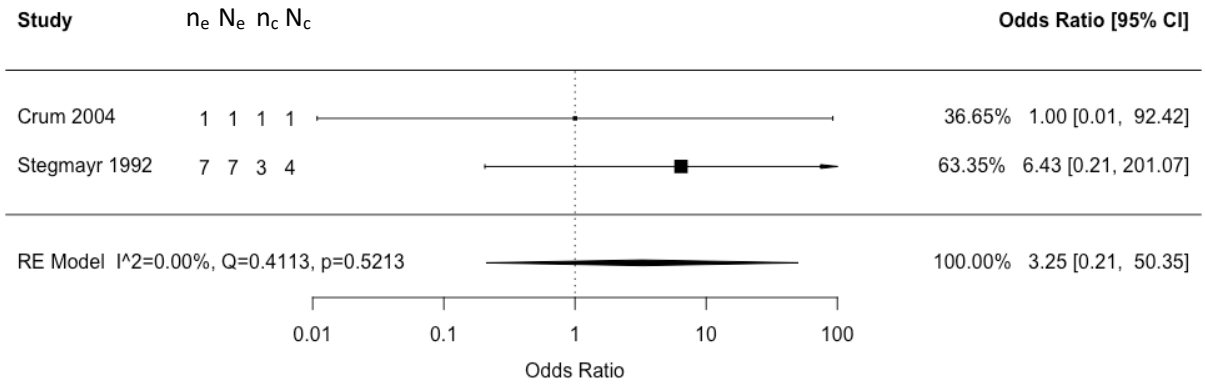




5. IVIG in all STSS patients: yes vs no (reference)

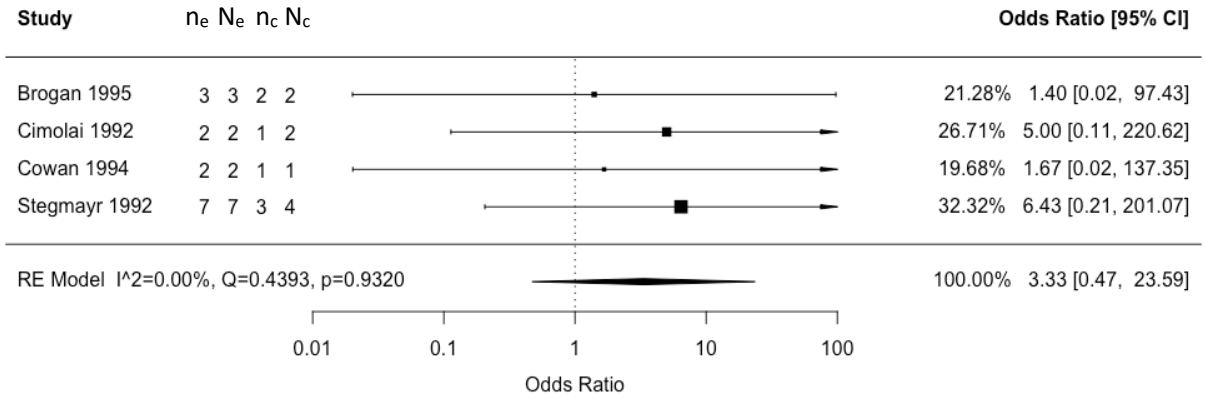


6. Hemodialysis: yes vs no (reference)

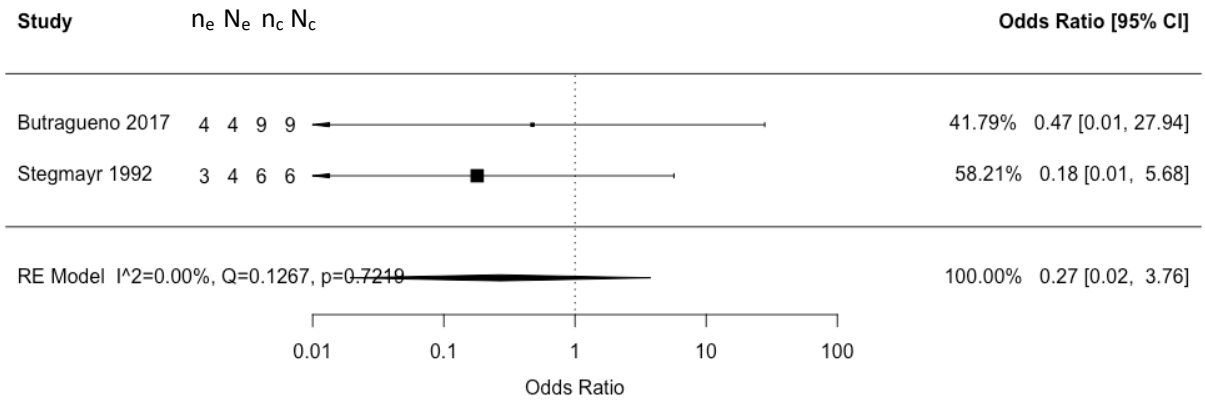


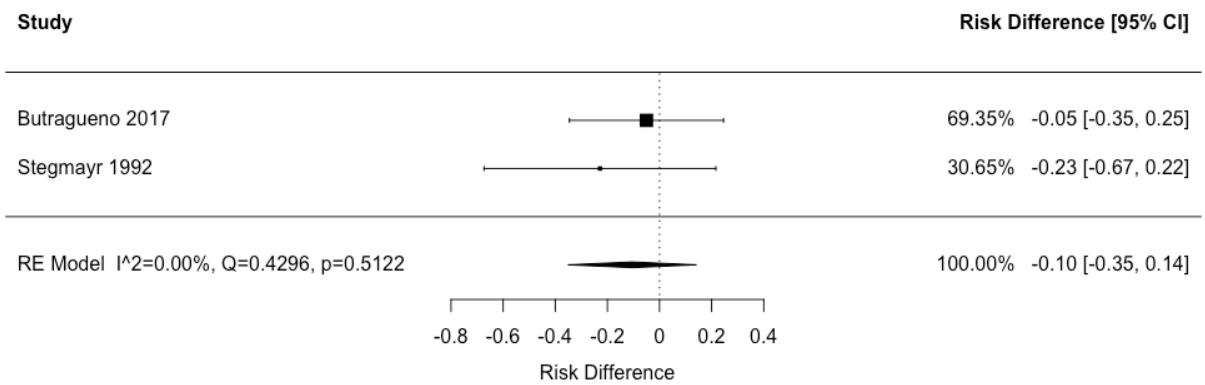
Clinical cure or improvement

1. Sex: male vs female (reference)

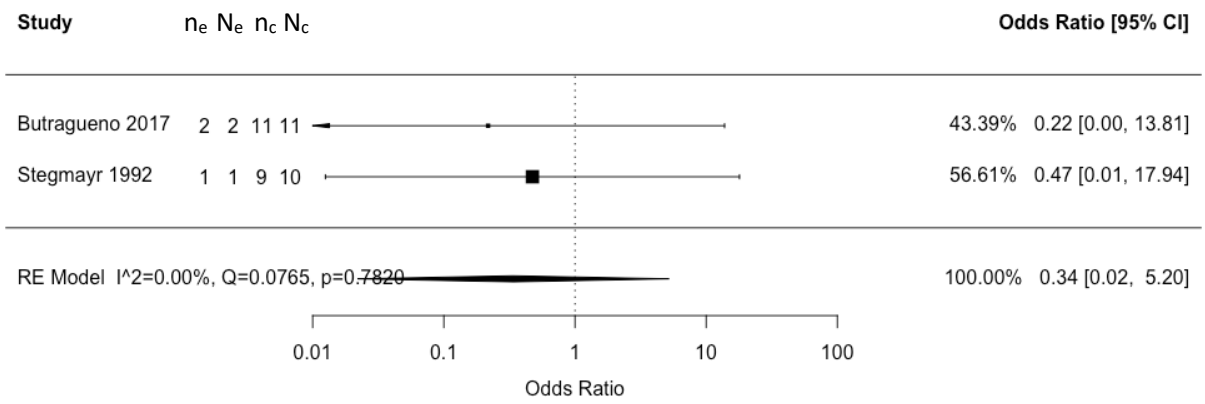


2. IVIG in all STSS patients: yes vs no (reference)

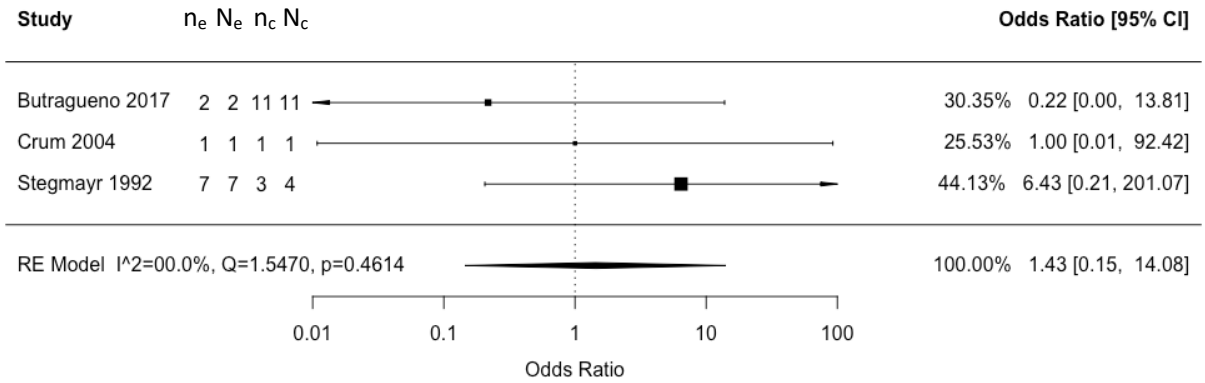


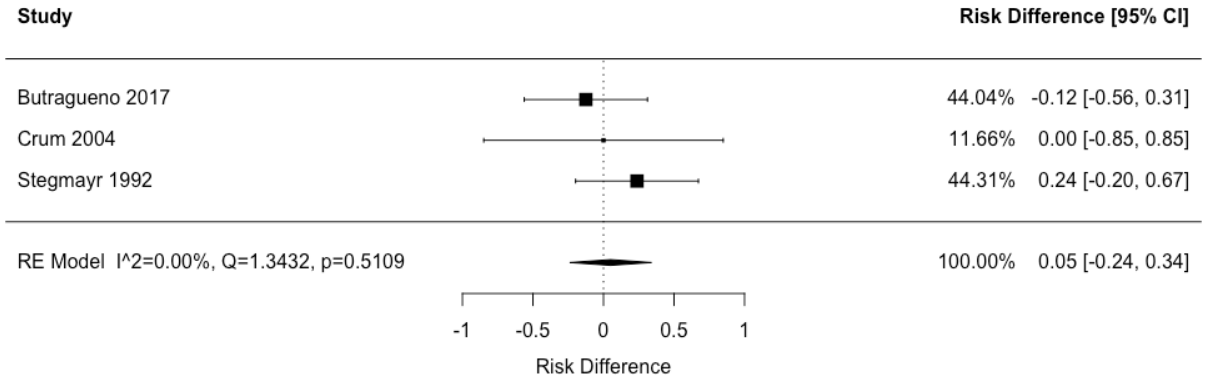


3. Necrotizing fasciitis: yes vs no (reference)



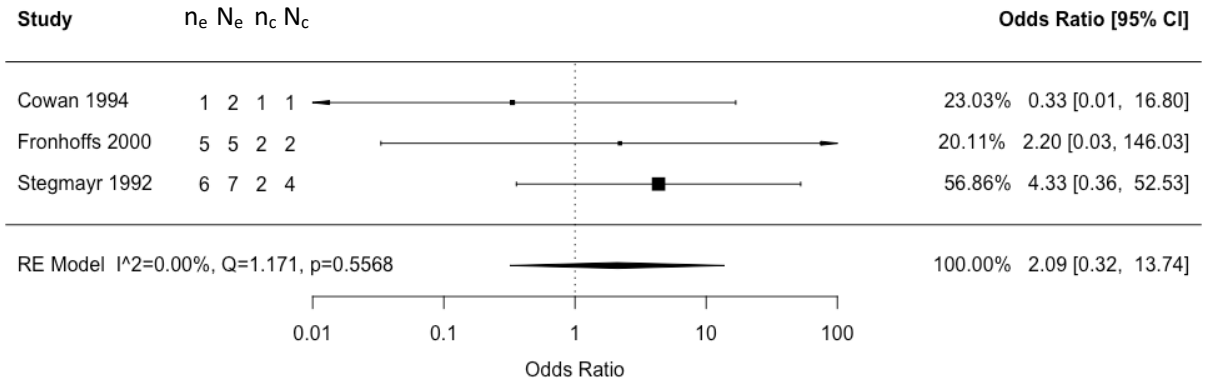
4. Hemodialysis: yes vs no (reference)

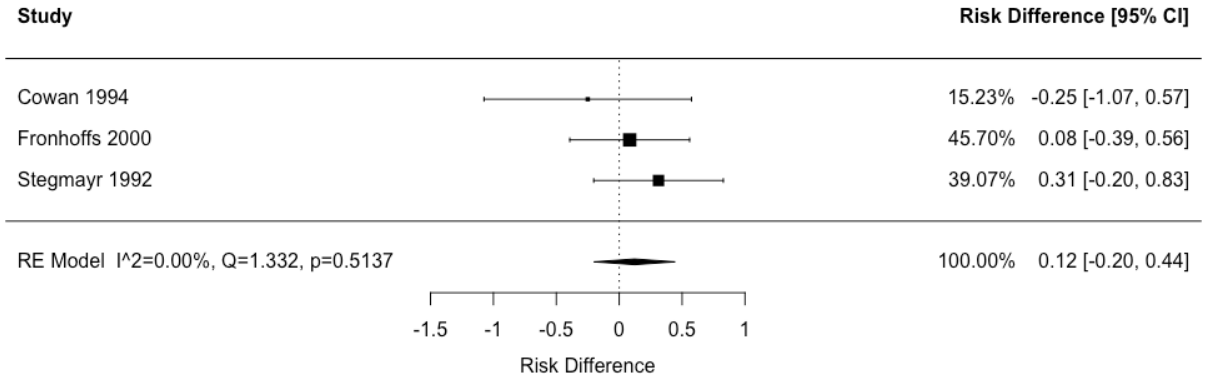




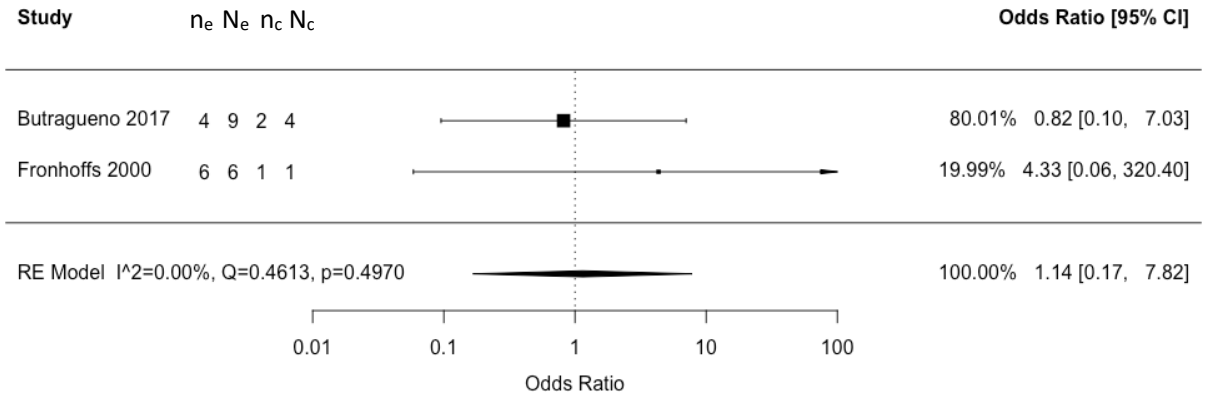
Mechanical ventilation

1. Sex: male vs female (reference)

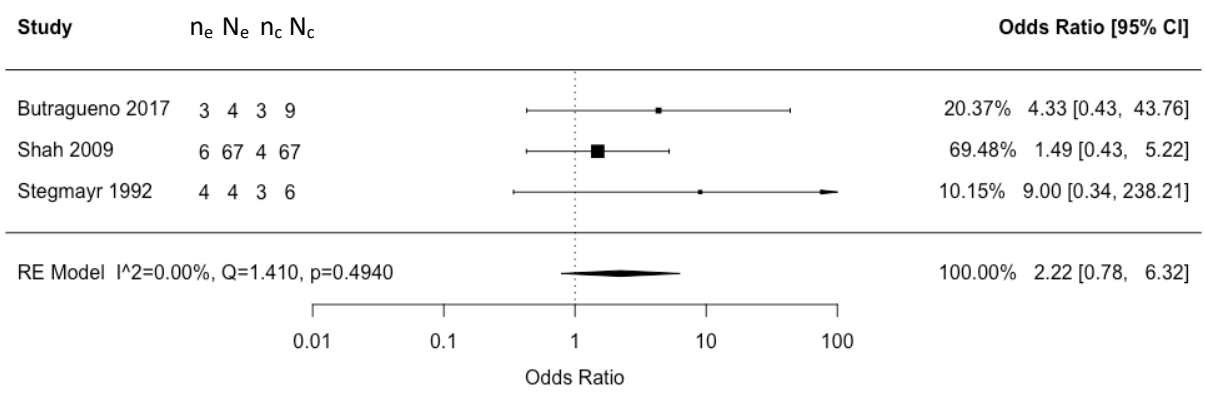




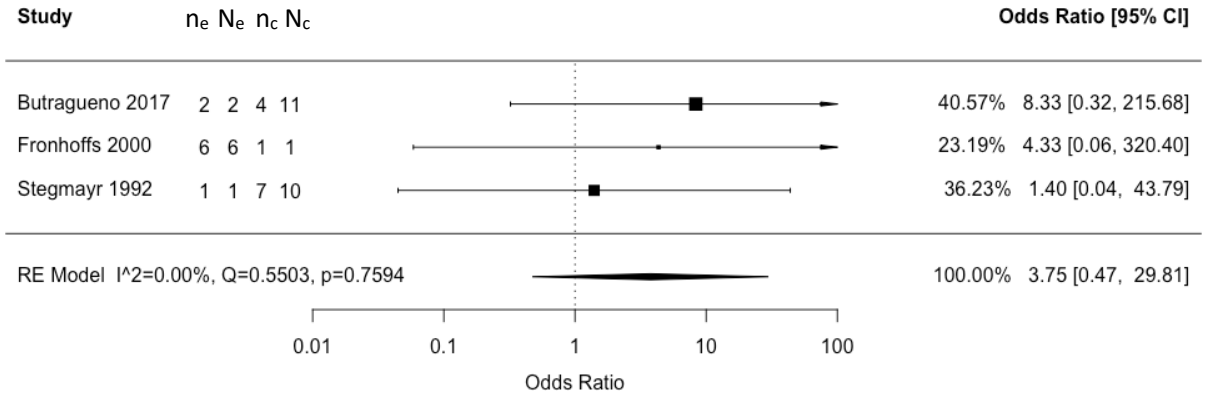
2. Acute renal failure: yes vs no (reference)



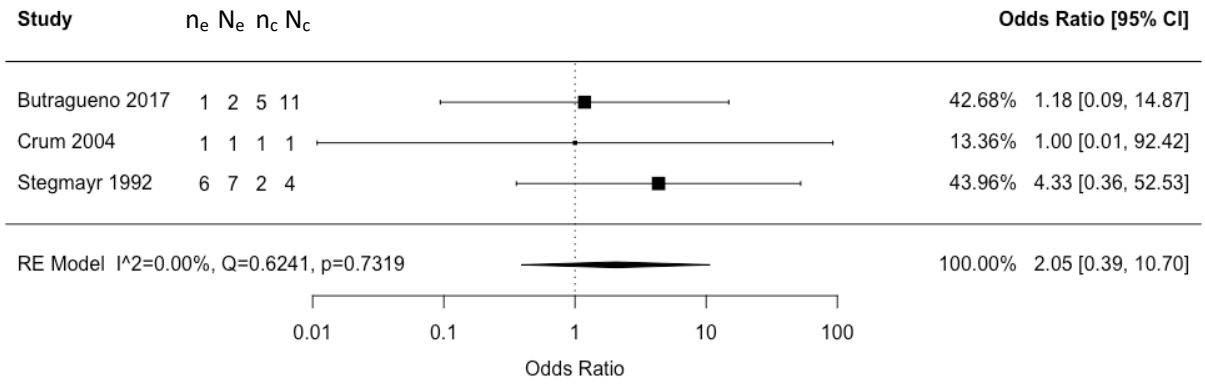
3. IVIG in all STSS patients: yes vs no (reference)



4. Necrotizing fasciitis: yes vs no (reference)

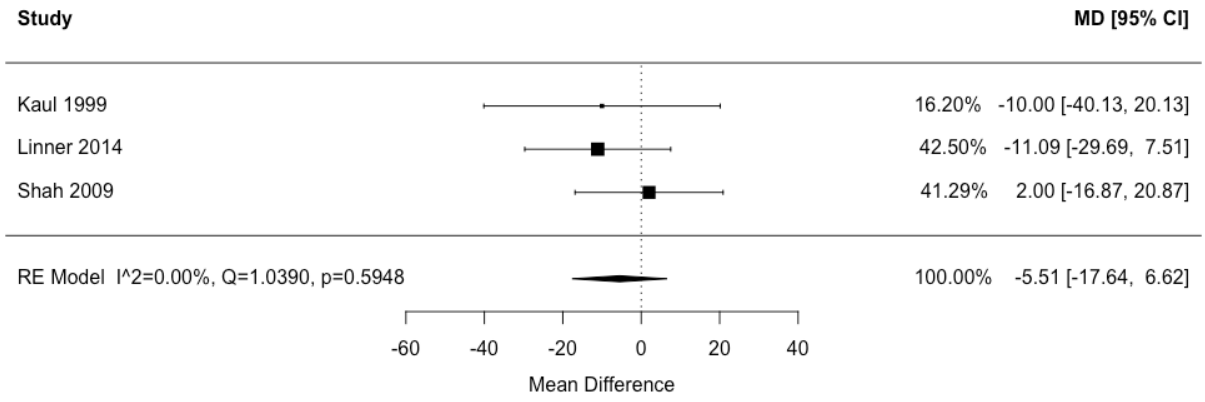


5. Hemodialysis: yes vs no (reference)



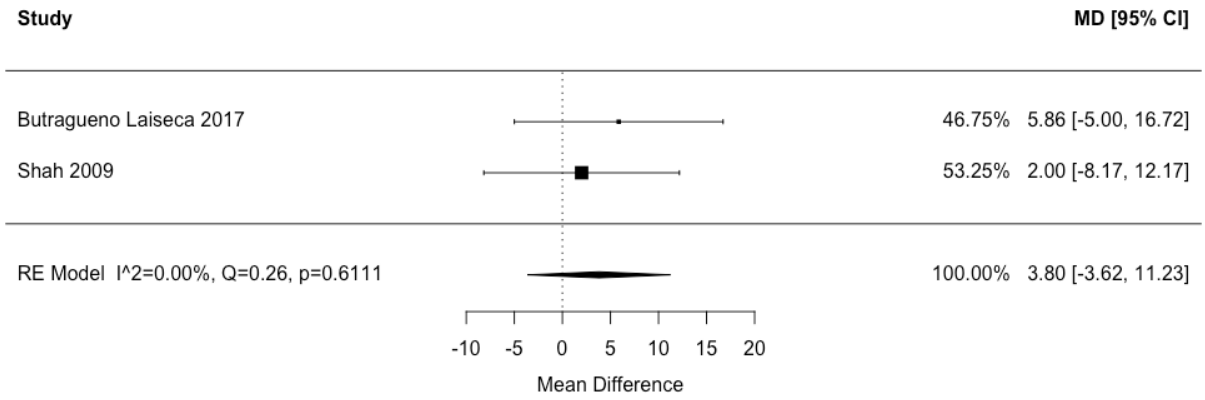
Hospital length-of-stay

1. IVIG: yes vs no (reference)



ICU length-of-stay

1. IVIG: yes vs no (reference)



Description of studies ineligible for meta-analysis by outcome

Mortality

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	4	4	
age	28	5	n=17 case-series with <10 patients, precluding the aggregation of patient-level data; n=6 study population consisted of patients all within same age category
antibiotic	3	3	
clindamycin	4	4	
early hypotension	0	0	
emmtype	7	0	n=7 variability in reporting of molecular characteristics and comparators
hemodialysis	4	4	
immunocompromised	5	4	n=1 insufficient data for meta-analysis (only p value reported)
IVIG in all STSS patients	9	9	
IVIG in clindamycin-treated patients	6	6	
NF	10	10	
NSAIDs	4	4	
sex	12	12	
timetoantibiotic	1	0	Meta-analysis precluded with only one study

(P)ICU admission

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	1	0	Meta-analysis precluded with only one study
age	9	0	n=5 case-series with <10 patients, precluding the aggregation of patient-level data; n=3 study population consisted of patients all within same age category; n=1 eligible for analysis, but meta-analysis precluded with only one study
antibiotic	2	2	
clindamycin	1	0	Meta-analysis precluded with only one study
early hypotension	0	0	
emmtype	2	0	n=2 variability in reporting of molecular characteristics and comparators
hemodialysis	2	2	
immunocompromised	1	0	Meta-analysis precluded with only one study
IVIG in all STSS patients	3	3	
IVIG in clindamycin-treated patients	0	0	
NF	3	3	
NSAIDs	2	2	
sex	3	3	
timetoantibiotic	0	0	

Clinical cure or improvement

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	1	0	Meta-analysis precluded with only one study
age	8	0	n=6 case-series with <10 patients, precluding the aggregation of patient-level data; n=2 study population consisted of patients all within same age category
antibiotic	1	0	Meta-analysis precluded with only one study
clindamycin	1	0	Meta-analysis precluded with only one study
earlyhypotension	0	0	
emmtype	0	0	
hemodialysis	3	3	
immunocompromised	0	0	
IVIG in all STSS patients	2	2	
IVIG in clindamycin-treated patients	0	0	
NF	2	2	
NSAIDs	1	0	Meta-analysis precluded with only one study
sex	4	4	
timetoantibiotic	0	0	

Mechanical ventilation

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	2	2	
age	5	0	n=3 case-series with <10 patients, precluding the aggregation of patient-level data; n=2 study population consisted of patients all within same age category
antibiotic	0	0	
clindamycin	1	0	Meta-analysis precluded with only one study
earlyhypotension	0	0	
emmtype	0	0	
hemodialysis	3	3	
immunocompromised	1	0	Meta-analysis precluded with only one study
IVIG in all STSS patients	3	3	
IVIG in clindamycin-treated patients	0	0	
NF	3	3	
NSAIDs	1	0	Meta-analysis precluded with only one study
sex	3	3	
timetoantibiotic	0	0	

Hospital length-of-stay

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	0	0	
age	2	0	n=2 case-series with <10 patients, precluding the aggregation of patient-level data
antibiotic	0	0	
clindamycin	0	0	
early hypotension	0	0	
emmtype	0	0	
hemodialysis	0	0	
immunocompromised	0	0	
IVIG in all STSS patients	3	3	
IVIG in clindamycin-treated patients	0	0	
NF	0	0	
NSAIDs	1	0	Meta-analysis precluded with only one study
sex	1	0	Meta-analysis precluded with only one study
timetoantibiotic	0	0	

Duration of mechanical ventilation

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	0	0	
age	0	0	
antibiotic	0	0	
clindamycin	0	0	
early hypotension	0	0	
emmtype	0	0	
hemodialysis	0	0	
immunocompromised	0	0	
IVIG in all STSS patients	1	0	Meta-analysis precluded with only one study
IVIG in clindamycin-treated patients	0	0	
NF	0	0	
NSAIDs	0	0	
sex	0	0	
timetoantibiotic	0	0	

ICU length-of-stay

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	0	0	
age	3	0	n=2 case-series with <10 patients, precluding the aggregation of patient-level data; n=1 study population consisted of patients all within same age category
antibiotic	0	0	
clindamycin	1	0	Meta-analysis precluded with only one study
early hypotension	0	0	
emmtype	0	0	
hemodialysis	0	0	
immunocompromised	0	0	
IVIG in all STSS patients	2	2	
IVIG in clindamycin-treated patients	0	0	
NF	1	0	Meta-analysis precluded with only one study
NSAIDs	1	0	Meta-analysis precluded with only one study
sex	2	0	n=1 study with one person in each group > cannot calculate mean; n=1 meta-analysis precluded with only one study
timetoantibiotic	0	0	

Change in SOFA score from baseline

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	0	0	
age	0	0	
antibiotic	0	0	
clindamycin	0	0	
early hypotension	0	0	
emmtype	0	0	
hemodialysis	0	0	
immunocompromised	0	0	
IVIG in all STSS patients	1	0	Meta-analysis precluded with only one study
IVIG in clindamycin-treated patients	0	0	
NF	0	0	
NSAIDs	0	0	
sex	0	0	
timetoantibiotic	0	0	

Functional status

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	0	0	
age	0	0	
antibiotic	0	0	
clindamycin	0	0	
early hypotension	0	0	
emmtype	0	0	
hemodialysis	0	0	
immunocompromised	0	0	
IVIG in all STSS patients	0	0	
IVIG in clindamycin-treated patients	0	0	
NF	0	0	
NSAIDs	0	0	
sex	0	0	
timetoantibiotic	0	0	

Health related quality of life

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	0	0	
age	0	0	
antibiotic	0	0	
clindamycin	0	0	
early hypotension	0	0	
emmtype	0	0	
hemodialysis	0	0	
immunocompromised	0	0	
IVIG in all STSS patients	0	0	
IVIG in clindamycin-treated patients	0	0	
NF	0	0	
NSAIDs	0	0	
sex	0	0	
timetoantibiotic	0	0	

Cost

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	0	0	
age	0	0	
antibiotic	0	0	
clindamycin	0	0	
early hypotension	0	0	
emmtype	0	0	
hemodialysis	0	0	
immunocompromised	0	0	
IVIG in all STSS patients	1	0	Meta-analysis precluded with only one study
IVIG in clindamycin-treated patients	0	0	
NF	0	0	
NSAIDs	0	0	
sex	0	0	
timetoantibiotic	0	0	

Time to mortality

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	0	0	
age	0	0	
antibiotic	0	0	
clindamycin	0	0	
early hypotension	0	0	
emmtype	0	0	
hemodialysis	0	0	
immunocompromised	0	0	
IVIG in all STSS patients	2	0	n=1 study with one person in each group > cannot calculate mean; n=1 meta-analysis precluded with only one study
IVIG in clindamycin-treated patients	2	0	n=1 study with one person in each group > cannot calculate mean; n=1 meta-analysis precluded with only one study
NF	0	0	
NSAIDs	0	0	
sex	0	0	
timetoantibiotic	0	0	

Time to clinical improvement or resolution of shock

Prognostic factor of interest	N reporting	N analyzed	Reasons for exclusion from meta-analysis
acute renal failure	0	0	
age	0	0	
antibiotic	0	0	
clindamycin	0	0	
early hypotension	0	0	
emmtype	0	0	
hemodialysis	0	0	
immunocompromised	0	0	
IVIG in all STSS patients	1	0	Meta-analysis precluded with only one study
IVIG in clindamycin-treated patients	1	0	Meta-analysis precluded with only one study
NF	0	0	
NSAIDs	0	0	
sex	0	0	
timetoantibiotic	0	0	

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4-9
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	4-9
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	4-9
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4-9
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4-9
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4-9
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4-9
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	4-9
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	4-9
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	4-9
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	4-9
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	4-9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	4-9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	4-9
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	4-9
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	4-9
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	4-9

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	9-17
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	9-17
Study characteristics	17	Cite each included study and present its characteristics.	9-17
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	9-17
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	9-17
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	9-17
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	9-17
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	9-17
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	9-17
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	9-17
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	9-17
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	17-19
	23b	Discuss any limitations of the evidence included in the review.	17-19
	23c	Discuss any limitations of the review processes used.	17-19
	23d	Discuss implications of the results for practice, policy, and future research.	17-19
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	4
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	20
Competing interests	26	Declare any competing interests of review authors.	20
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	21

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi:

PRISMA 2020 Checklist

10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

MOOSE (Meta-analyses Of Observational Studies in Epidemiology) Checklist

A reporting checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Reporting of Background		
Problem definition		
Hypothesis statement		
Description of Study Outcome(s)		
Type of exposure or intervention used		
Type of study design used		
Study population		
Reporting of Search Strategy		
Qualifications of searchers (eg, librarians and investigators)		
Search strategy, including time period included in the synthesis and keywords		
Effort to include all available studies, including contact with authors		
Databases and registries searched		
Search software used, name and version, including special features used (eg, explosion)		
Use of hand searching (eg, reference lists of obtained articles)		
List of citations located and those excluded, including justification		
Method for addressing articles published in languages other than English		
Method of handling abstracts and unpublished studies		
Description of any contact with authors		
Reporting of Methods		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested		
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)		
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)		
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate		

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results		
Assessment of heterogeneity		
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated		
Provision of appropriate tables and graphics		
Reporting of Results		
Table giving descriptive information for each study included		
Results of sensitivity testing (eg, subgroup analysis)		
Indication of statistical uncertainty of findings		
Reporting of Discussion		
Quantitative assessment of bias (eg, publication bias)		
Justification for exclusion (eg, exclusion of non–English-language citations)		
Assessment of quality of included studies		
Reporting of Conclusions		
Consideration of alternative explanations for observed results		
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)		
Guidelines for future research		
Disclosure of funding source		

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.