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[Intervention Review]

Beta-lactam versus beta-lactam-aminoglycoside combination therapy in cancer patients with neutropenia

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ABSTRACT

Background

Continued controversy surrounds the optimal empirical treatment for febrile neutropenia. New broad-spectrum beta-lactams have been introduced as single treatment, and classically, a combination of a beta-lactam with an aminoglycoside has been used.

Objectives

To compare beta-lactam monotherapy versus beta-lactam-aminoglycoside combination therapy for cancer patients with fever and neutropenia.

Search methods

The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, Issue 7, 2012), LILACS (August 2012), MEDLINE and EMBASE (August 2012) and the Database of Abstracts of Reviews of Effects (DARE) (Issue 3, 2012). We scanned references of all included studies and pertinent reviews and contacted the first author of each included trial, as well as the pharmaceutical companies.

Selection criteria

Randomised controlled trials (RCTs) comparing any beta-lactam antibiotic monotherapy with any combination of a beta-lactam and an aminoglycoside antibiotic, for the initial empirical treatment of febrile neutropenic cancer patients. All cause mortality was the primary outcome assessed.

Data collection and analysis

Data concerning all cause mortality, infection related mortality, treatment failure (including treatment modifications), super-infections, adverse effects and study quality measures were extracted independently by two review authors. Risk ratios (RRs) with their 95% confidence intervals (CIs) were estimated. Outcomes were extracted by intention-to-treat (ITT) analysis whenever possible. Individual domains of risk of bias were examined through sensitivity analyses. Published data were complemented by correspondence with authors.

Main results

Seventy-one trials published between 1983 and 2012 were included. All cause mortality was lower with monotherapy (RR 0.87, 95% CI 0.75 to 1.02, without statistical significance). Results were similar for trials comparing the same beta-lactam in both trial arms (11 trials, 1718

episodes; RR 0.74, 95% CI 0.53 to 1.06) and for trials comparing different beta-lactams—usually a broad-spectrum beta-lactam compared with a narrower-spectrum beta-lactam combined with an aminoglycoside (33 trials, 5468 episodes; RR 0.91, 95% CI 0.77 to 1.09). Infection related mortality was significantly lower with monotherapy (RR 0.80, 95% CI 0.64 to 0.99). Treatment failure was significantly more frequent with monotherapy in trials comparing the same beta-lactam (16 trials, 2833 episodes; RR 1.11, 95% CI 1.02 to 1.20), and was significantly more frequent with combination therapy in trials comparing different beta-lactams (55 trials, 7736 episodes; RR 0.92, 95% CI 0.88 to 0.97). Bacterial super-infections occurred with equal frequency, and fungal super-infections were more common with combination therapy. Adverse events were more frequent with combination therapy (numbers needed to harm 4; 95% CI 4 to 5). Specifically, the difference with regard to nephrotoxicity was highly significant. Adequate trial methods were associated with a larger effect estimate for mortality and smaller effect estimates for failure. Nearly all trials were open-label. No correlation was noted between mortality and failure rates and these trials.

Authors' conclusions

Beta-lactam monotherapy is advantageous compared with beta-lactam-aminoglycoside combination therapy with regard to survival, adverse events and fungal super-infections. Treatment failure should not be regarded as the primary outcome in open-label trials, as it reflects mainly treatment modifications.

PLAIN LANGUAGE SUMMARY

Cancer patients with fever and suspected infection can be treated with a single 'new-generation' beta-lactam antibiotic

Cancer chemotherapy or bone marrow transplantation disrupts the immune system, exposing patients to severe infection. The major sign of infection is fever, and the hallmark of damaged immune defences is a decreased white blood cell count. Patients have usually been treated with a combination of two different classes of antibiotics. Evidence shows that treatment with a new single drug (monotherapy), belonging to the beta-lactam class of antibiotics, is associated with better outcomes. Survival is improved when single-drug therapy is used, and side effects, mainly damage to the kidneys, are more frequent with combination therapy.

Summary of findings for the main comparison. beta-lactam monotherapy compared to beta-lactam-aminoglycoside combination therapy for Febrile neutropenic cancer patients

Beta-lactam monotherapy compared with beta-lactam-aminoglycoside combination therapy for febrile neutropenic cancer patients

Patient or population: febrile neutropenic cancer patients.
Settings:
Intervention: beta-lactam monotherapy.
Comparison: beta-lactam-aminoglycoside combination therapy.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Beta-lactam-aminoglycoside combination therapy	Beta-lactam monotherapy				
All cause mortality	**Study population**		**RR 0.87** (0.75 to 1.02)	7186 (44 studies)	⊕⊕⊕⊕ **high**	
	83 per 1000	**72 per 1000** (62 to 85)				
	Moderate					
	68 per 1000	**59 per 1000** (51 to 69)				
Any nephrotoxicity - Ag dosing regimen (Copy)	**Study population**		**RR 0.45** (0.35 to 0.57)	6608 (39 studies)	⊕⊕⊕⊕ **high**	
	57 per 1000	**26 per 1000** (20 to 33)				
	Moderate					
	29 per 1000	**13 per 1000** (10 to 17)				
Treatment failure - same beta-lactam	**Study population**		**RR 1.11** (1.02 to 1.2)	2833 (16 studies)	⊕⊕⊕⊖ **moderate** [1]	
	405 per 1000	**449 per 1000** (413 to 485)				

	Moderate				
	398 per 1000	**442 per 1000** (406 to 478)			
Treatment failure - different beta-lactam	**Study population**		**RR 0.92** (0.88 to 0.97)	7736 (55 studies)	⊕⊕⊝⊝ **low** [1,2,3,4]
	426 per 1000	**392 per 1000** (375 to 413)			
	Moderate				
	432 per 1000	**397 per 1000** (380 to 419)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence:
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Outcome determined mainly by treatment modifications. Poor correlation with all cause mortality, the ultimate target of treating cancer patients.
[2] Differences decreased with low risk of bias regarding allocation concealment.
[3] Differences in effects between published and unpublished trials.
[4] No explanation was provided.&&

BACKGROUND

Cancer patients are prone to infection. Low blood cell count (neutropenia) and disruption of normal barriers to infection, such as skin and mucous membranes, are caused by chemotherapy or underlying malignancy. Both disrupt the normal immune response and predispose patients to infection (Bodey 1966). Pathogens implicated in these infections are Gram-negative bacteria, including *Pseudomonas aeruginosa*, Gram-positive bacteria and fungi (Chow 1991; Hughes 1997). The considerable morbidity and mortality associated with these infections in neutropenic patients led to the routine use of empirical antibiotic treatment, which is given upon suspicion of infection (e.g. fever), before the causative pathogen/s or their susceptibilities are identified (Hughes 1997; Schimpff 1986).

Initial effective empirical treatment for patients with fever and neutropenia consisted of combinations of antibiotics, including double beta-lactam regimens and, more recently, aminoglycoside-beta-lactam combinations (Hughes 1990; Hughes 1997; Schimpff 1971). In the 1980s, third-generation cephalosporins and carbapenems having bactericidal activity against Enterobacteriaceae, *Pseudomonas aeruginosa* and many Gram-positive organisms became available, making monotherapy a reasonable alternative to combination therapy. Neither combination therapy nor monotherapy provides full coverage for the spectrum of infections encountered among neutropenic patients. Notably, resistant Gram-positive bacteria and fungi are left untreated. Nevertheless, current guidelines recommend beta-lactam monotherapy in clinically stable patients (Freifeld 2011; Tam 2011).

An evident advantage of combination therapy over monotherapy is the higher probability that the infecting pathogen will be covered by at least one of the components of the regimen. Furthermore, the interaction between two antibiotics may be synergistic, resulting in enhanced bacterial kill activity compared with the additive activities of the antibiotics when assessed separately (Giamarellou 1984; Giamarellou 1986; Klastersky 1976; Klastersky 1982). Finally, use of combination therapy has been claimed to suppress the emergence of resistant subpopulations of bacteria (Allan 1985; Milatovic 1987; Wade 1989). On the other hand, benefits of monotherapy may include a lower probability of adverse effects and narrower-spectrum treatment, possibly reducing the chance of developing a super-infection with resistant bacteria (Weistein 1985). Adverse effects may be related to administration of aminoglycosides per se (e.g. nephrotoxicity) or to interactions between antibiotic and underlying disease and/or other drugs. Neutropaenic participants not responding to the initial antibiotic regimen will be given modified treatment, which usually includes vancomycin to cover resistant Gram-positive bacteria and/or amphotericin-based preparations or azoles to treat fungal infection (Hughes 1997), thus increasing the chance for adverse events and drug interactions.

Although neutropenia itself is the single most important risk factor for infection, other factors can alter the risk. The probability and severity of infection are inversely proportional to the absolute neutrophil count, and patients with neutrophil counts below 100/mm^3 are at highest risk for severe infection (Bodey 1966; Schimpff 1986). Underlying malignancy may affect outcome. Patients with acute leukaemia and other haematological malignancies have a worse prognosis than solid tumour patients (Rolston 1992; Rossini 1994; Talcott 1992). The severity and nature of the infection (e.g. bacteraemia, Gram-positive and *Pseudomonas aeruginosa* infections, resistant organisms) as well as the patient's age may underlie heterogeneity (Elting 1997; Hann 1997; Rolston 1992). More recent guidelines for empirical treatment of febrile neutropenia have emphasized the importance of risk stratification, both for deciding on the setting of therapy (out-patient versus hospitalisation) and for choosing among empirical antibiotics (monotherapy versus combination therapy) (Freifeld 2011; Tam 2011).

We undertook this systematic review to assess the evidence for combination therapy versus monotherapy in patients with febrile neutropenia in clinical trials. In 2002, the first version of this review was published. Results showed no advantage of combination therapy with regard to all cause mortality, the primary outcome assessed and an increased rate of nephrotoxicity with the combined regimen. Most trials compared a broad-spectrum beta-lactam with an older beta-lactam combined with an aminoglycoside; however comparisons performed to directly assess our research question, that is, trials comparing the same beta-lactam with or without an aminoglycoside, were rare. We called for further studies assessing directly the clinical implications of synergism, and further trials comparing different beta-lactams were discouraged in our recommendations (Paul 2003). In 2008 we updated our systematic review with new evidence that had accumulated since publication of the first version of our review; no significant differences were presented in terms of outcomes or subsequent recommendations. At present we are undertaking to update the review to include new evidence that has accumulated since the previous version.

OBJECTIVES

To compare the effectiveness of beta-lactam monotherapy versus that of beta-lactam-aminoglycoside combination therapy in febrile neutropenic cancer patients. In addition, to compare the effectiveness of the two treatment modalities in the following subgroups of neutropenic participants:

- Participants with an absolute neutrophil count of less than 100/mm^3
- Participants with microbiologically documented infection
- Participants with documented *Pseudomonas aeruginosa* infection
- Bacteraemic participants
- Participants with an underlying haematological malignancy or bone marrow transplantation

The following hypotheses were tested for the comparison between participants treated with beta-lactam monotherapy and those treated with beta-lactam-aminoglycoside combination therapy:

- There is no difference in the number of deaths in febrile neutropenic patients
- There is no difference in the number of deaths in the above subgroups of febrile neutropenic patients
- There is no difference in the number of treatment failures in all febrile neutropenic patients and in the defined subgroups
- There is no difference in the number and severity of adverse effects among all patients

- There is no difference in the rate of resistant colonisation and super-infection among all neutropenic patients

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised trials comparing any beta-lactam antibiotic monotherapy with any combination of a beta-lactam and an aminoglycoside antibiotic, for the treatment of febrile neutropenia in cancer patients. Allocation to these regimens had to occur initially, before administration of any other antibiotics for the specific febrile episode and, empirically, before detection of pathogen/s or their susceptibilities.

Trials with randomly assigned participants with microbiologically documented infection (e.g. *Pseudomonas aeruginosa* infection, Gram-negative bacteraemia) were excluded, as were trials comparing short versus long courses of aminoglycoside treatment, because in both cases randomisation to combination treatment versus monotherapy did not occur empirically (referred to as semi-empirical studies).

Types of participants

Febrile cancer patients with neutropenia, as defined in the study, induced by chemotherapy or bone marrow transplantation. Neonates and preterm babies were excluded.

Types of interventions

The following antibiotic regimens were compared:

- Intravenous beta-lactam antibiotic given as monotherapy, including:
  - Antipseudomonal carboxy-penicillins or ureido-penicillins ± beta-lactamase inhibitor (piperacillin, piperacillin/clavulanate, ticarcillin-clavulanate, azlocilin, mezlocillin)
  - Cephalosporins (ceftazidime, ceftriaxone, cefoperazone, cefoxitin, cefuroxime, cefepime, cefpiramide)
  - Carbapenems (imipenem/cilastatin, meropenem)

Studies comparing the same beta-lactam, with the addition of an aminoglycoside to one arm ('same beta-lactam'), were analysed separately from studies comparing different beta-lactams ('different beta-lactam').

- Combination duotherapy of an intravenous beta-lactam antibiotic (as specified) with one of the following aminoglycosides given intravenously:
  - Gentamicin
  - Tobramycin
  - Amikacin
  - Netilmicin
  - Kanamycin

Types of outcome measures

Primary outcomes

Death at end of follow-up for the infectious episode, up to 30 days (all cause mortality).

Secondary outcomes

- Treatment failure: a composite end point comprising one or more of the following: death; persistence, recurrence or worsening of clinical signs or symptoms of presenting infection; any modification of the assigned empirical antibiotic treatment.
- Infection related mortality, as reported in the study.
- Duration of hospital stay.
- Dropouts before end of study.
- Super-infection: new, persistent or worsening symptoms and/or signs of infection associated with the isolation of a new pathogen (different, or different susceptibilities) or the development of a new site of infection.
- Colonisation: isolation during or after therapy of Gram-negative bacteria resistant to the beta-lactam included in the empirical regimen, without symptoms or signs of infection.

Adverse effects

- Life threatening or associated with permanent disability.
- Serious—requiring discontinuation of therapy.
- Any other.

Search methods for identification of studies

Electronic searches

Relevant randomised trials were identified by searching the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, Issue 7, 2012), LILACS to August 2012, Database of Abstracts of Reviews of Effects (DARE) (Issue 3, 2012) and MEDLINE and EMBASE to August 2012. We conducted a wide search targeting all randomised trials for the treatment of infection in neutropenic patients for this and other systematic reviews conducted by our group. The detailed search strategies for each database are provided in Appendix 1, Appendix 2 and Appendix 3.

Searching other resources

References of all identified studies as well as major reviews were inspected for more studies. We checked the conference proceedings of the Interscience Conference of Antimicrobial Agents and Chemotherapy (ICAAC) 1995 to 2011, the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID 2001 to 2012) and the American Society of Hematology (ASH) 2003 to 2011. Letters, abstracts and unpublished trials were accepted to reduce the influence of publication bias. Additionally, the first or corresponding author of each included study and pharmaceutical companies were contacted for complementary information or information regarding unpublished trials.

Data collection and analysis

Selection of studies

One review author inspected the abstract of each reference identified by the search and applied inclusion criteria. For possibly relevant articles, the full article was obtained and inspected by two review authors.

Data extraction and management

Two review authors independently extracted data from included trials. In cases of disagreement between the two review authors, a third review author extracted the data. In addition the third

review author extracted 10% of the studies, selected randomly. Data extractions were discussed, decisions documented and all authors of included studies contacted for clarification. Justification for excluding studies from the review was also documented. Differences in the data extracted were resolved by discussion. All data were collected on an intention-to-treat (ITT) basis whenever possible.

Assessment of risk of bias in included studies

Trials fulfilling the review inclusion criteria were assessed for risk of bias by two review authors working independently. For the 2012 update, this was done using the criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We primarily assessed the effect of allocation concealment on results, based on the evidence of a strong association between poor allocation concealment and overestimation of effect (Schulz 1995), as defined below:

- Low risk of bias (adequate allocation concealment).
- Moderate risk of bias (uncertainty regarding allocation concealment).
- High risk of bias (inadequate allocation concealment).

In addition to the adequacy of allocation concealment, methods of allocation generation, blinding, incomplete outcome data, selective reporting, the unit of randomisation (patient or febrile episode) and publication status were recorded independently by the two review authors.

Assessment of heterogeneity

Heterogeneity in the results of the trials was initially graphically inspected and assessed by calculating a test of heterogeneity (Chi-square). We anticipated between-trial variation in estimation of morbidity and mortality for studies comparing the same beta-lactam and studies comparing different beta-lactams (Elphick 2001). These were separated when heterogeneity was observed. Further heterogeneity was explored through subgroup analysis, assessing the above-defined patient subgroups (Objectives).

A funnel plot estimating the precision of trials (plots of the log of the risk ratio for efficacy against the sample size) was examined to estimate potential selection bias (such as publication bias) and to assess whether effect estimates are associated with study size.

Adjusted means were calculated and corrected by the inverse of the variance. We searched for the correlation between mortality and treatment failure, to assess the clinical relevance of treatment failure and infection related mortality outcomes in these studies. Correlations were tested for significance using a non-parametric test (Spearman) using the Statistical Package for the Social Sciences (SPSS) version 14.0. Numbers needed to treat or harm were calculated as 1/(CER-CER*RR), where CER is the control event rate and RR is the risk ratio.

Data synthesis

Dichotomous data were analysed by calculating the risk ratio (RR) for each trial with the uncertainty in each result expressed with the use of 95% confidence intervals (CIs). A fixed-effect model was used throughout the review, unless significant heterogeneity was observed ($P < 0.1$ or $I^2 > 50\%$) where the random-effects model was used.

RESULTS

Description of studies

The computerised search strategy identified a large number of randomised trials assessing the treatment of febrile neutropenia —not all of which were relevant for the present review. These were screened for trials assessing beta-lactam-aminoglycoside combination therapy versus beta-lactam monotherapy. Ninety-five publications of RCTs were considered eligible for this review.

Twenty-three publications of 22 trials were excluded (Characteristics of excluded studies). Allocation to monotherapy versus combination therapy was non-random in five studies, randomisation to monotherapy versus combination therapy was semi-empirical in three trials (Bodey 1976; EORTC 1987; Pegram 1989), the comparator regimens were incompatible with our inclusion criteria in nine trials, and non-neutropenic patients were included in three trials (D'Antonio 1992; Fainstein 1983; Hoepelman 1988), in which results for neutropenic patients only could not be extracted. One trial randomly assigned participants to treatment with ticarcillin-clavulanate versus ticarcillin-clavulanate +amikacin; however participants who had undergone bone marrow transplantation were allocated to combination therapy only, over-riding the random allocation (Bru 1986); another trial comparing imipenem versus ceftazidime versus amikacin was excluded, because it was presented as an ongoing study in a conference in 1986, no further publication of the study was found and we were not able to contact the authors (Moreno-Sanchez 1992).

We could not yet obtain the full text of one trial, which is awaiting assessment (Li 1998). Another trial was presented at a conference in 2005 and is listed as ongoing (Bilgir 2005).

Seventy-one trials described in 89 publications are included in the review (Characteristics of included studies; secondary publications are listed under their primary reference). The trials were published between 1983 and 2012. Three trials were added since the previous version of this review, all published between 2007 and 2012. Forty-three trials reported data on all cause mortality and 41 reported on infection related mortality. Data regarding treatment failure were available for all trials. Thirty-one trials contained usable information for super-infections, and 49 trials are included in the adverse event analysis.

Eight included trials, presented in conference proceedings between 1987 and 2002, were published in abstract form only. Supplementary data from the authors were available for two of these (Cornely 2001, Hense 2000). Additional information on trial methods and/or on mortality was available from 24 full-text publications ('unpublished data' in the reference description).

Patient and infection characteristics

Most trials included adult cancer patients. Fourteen trials included only children, and another 14 trials included both adults and children. Most trials included participants with haematological cancer: 35 trials included only patients with haematological malignancies, and in another 32 trials most patients had haematological cancer. Bone marrow transplant patients were excluded from three trials. Patients with septic shock were specifically excluded from four trials; most trials did not refer to patients with septic shock, and in the few trials that did report patients with septic shock, only a few patients were included (1%

to 6% of patients in five trials reporting the number of patients with shock on admission).

The ratio between Gram-negative and Gram-positive bacteria among all included studies was 0.69. The adjusted mean rate of infection caused by Gram-negative bacteria was 11.5% of participants. *Pseudomonas aeruginosa*, a commonly implicated pathogen of febrile neutropenia in the past, was isolated in only 1.7% of included participants, constituting 15.3% of all documented Gram-negative isolates.

Surveillance cultures were performed in nine trials.

Antibiotic regimens

The same beta-lactam was compared in 16 of 71 included trials. In these trials the beta-lactam was ceftazidime (seven trials), piperacillin-tazobactam (four trials), cefepime (three trials), imipenem (two trials—one of which included four arms and assessed both ceftazidime and imipenem) and cefoperazone (one trial). All other trials compared one beta-lactam (usually a new drug) with a narrower-spectrum beta-lactam combined with an aminoglycoside. The most common mono-combi beta-lactam comparison was between a carbapenem and a cephalosporin (18 trials). Other comparisons included cephalosporin-cephalosporin (11 trials), cephalosporin-penicillin (nine trials), carbapenem-penicillin (nine trials), penicillin-cephalosporin (four trials) and penicillin-penicillin (three trials), respectively.

The most commonly tested aminoglycoside was amikacin (43 trials), followed by tobramycin (14 trials), gentamicin (11 trials) and netilmicin (three trials). Aminoglycosides were administered once daily in 16 trials. Aminoglycosides were administered for the duration of treatment in all trials, except Tamura 2004, where amikacin was administered only for the first 3 days of combination therapy.

Treatment duration was reported as means or medians. The mean treatment duration ranged from 7 to 15 days (most commonly 9 days); median treatment duration varied between 4 and 9 days (most commonly 9 days).

Risk of bias in included studies

Adequate allocation concealment, using sealed opaque envelopes or central randomisation, was described in 27 trials (Ahmed 2007; Akova 1999; Alanis 1983; Behre 1998; Cometta 1996; Cornely 2001; De la Camara 1997; Del Favero 2001; De Pauw 1994; Gibson 1989; Gorschluter 2003; Hess 1998; Jimeno 2006; Kinsey 1990; Leyland 1992; Lieschke 1990; Marie 1991; Matsui 1991; Norrby 1987; Novakova 1991; Novakova 1990; Petrilli 1991; Pickard 1983; Tamura 2002; Tamura 2004; Wrzesien-Kus 2001; Yamamura 1997). Allocation generation was adequate in a similar number of studies. These studies used tables of random numbers or computer-generated lists. Allocation concealment was inadequate in two trials describing the randomisation only as consecutive (Corapcioglu 2005; Zengin 2011). Randomisation methods were not described in all other trials. Four trials were double-blinded (Del Favero 2001; Ozyilkan 1999; Schuchter 1988; Wade 1989), four single-blinded (Cometta 1996; Duzova 2001; Leyland 1992; Rolston 1992) and the remainder open-randomised trials.

Intention-to-treat (ITT) analysis was presented in 23 of 68 trials included for treatment failure analysis and in 25 of 47 trials included for mortality analysis. Dropouts were reported by their allocation group in 26 of the 45 trials presenting per protocol analysis for treatment failure, permitting a secondary ITT analysis in which dropouts were assumed to be failures (see later, sensitivity analyses for failure). The number of patients excluded from analysis in studies in which ITT analysis was impossible ranged between 3% and 30% and the median rate of excluded patients was 10%. Twelve trials, mostly presented as conference proceedings, addressed 'treated' or 'evaluated' patients, without specifying a different figure for the number of randomly assigned participants (Agaoglu 2001; Borbolla 2001; Duzova 2001; El Haddad 1995; Esteve 1997; Gaytan-Martinez 2002; Kliasova 2001; Marie 1991; Pegram 1984; Pellegrin 1988; Schuchter 1988; Wade 1987). The analysis presumed for these studies was per-protocol.

A pre-determined, defined follow-up period was available from the publication or through author contact for 14 included trials (Behre 1998; Cometta 1996; De la Camara 1997; Del Favero 2001; Gorschluter 2003; Hess 1998; Kojima 1994; Leyland 1992; Norrby 1987; Ozyilkan 1999; Smith 1990; Tamura 2002; Tamura 2004; Yamamura 1997). Follow-up ranged from 72 hours to 1 month following the end of treatment. The observation time was longer than 1 month in two trials (De la Camara 1997; Ozyilkan 1999), both of which reported the outcomes at 1 month post-therapy. In five trials the time of outcome assessment was described more generally as end of treatment, fever, episode or neutropenia (De Pauw 1994; Erjavec 1994; Lieschke 1990; Matsui 1991; Piguet 1988). Two additional trials reported the average follow-up period of their trials (8 and 14 days) but a fixed time for outcome assessment was not specified (Akova 1999; Rolston 1992).

The unit of randomisation was the patient in 23 of the 71 trials (Characteristics of included studies). Episodes comprised the unit of randomisation in all the other trials, which allowed patient re-entry for recurrent episodes of fever and neutropenia. The number of participating patients was given in 74% of trials analysing episodes, and the mean episode-to-patient ratio in these trials was 1.3 (range 1.02 to 2.07). Trials that allowed repeat randomisation of participants for separate episodes of febrile neutropenia did not adjust their analyses to the 'cluster' effect of episodes within single participants and did not provide an intra-patient correlation estimate to allow for adjusted analyses in the meta-analysis. All trials were included in the main analysis and the effect of episode randomisation was assessed through sensitivity analyses.

Effects of interventions

See: **Summary of findings for the main comparison** beta-lactam monotherapy compared to beta-lactam-aminoglycoside combination therapy for Febrile neutropenic cancer patients

Overall effectiveness

All cause mortality :
All cause mortality was reported in 44 trials, including 7186 episodes. A difference in favour of monotherapy was observed overall (RR 0.87, 95% CI 0.75 to 1.02) (Analysis 1.1). This difference was not statistically significant, but there was no heterogeneity (P = 0.95, I^2 = 0) among trials for this combined effect estimate. Similar results were obtained using the random-effects model (RR 0.88, 95% CI 0.75 to 1.04). Among trials comparing the same beta-lactam, the RR was 0.74 (95% CI 0.53 to 1.06, 11 trials, 1718 episodes). Among trials comparing different beta-lactams, the RR was 0.91

(95% CI 0.77 to 1.09, 33 trials, 5468 episodes). Results were similar for trials comparing same and different beta-lactams with regard to all cause mortality; therefore these trials were combined in all subsequent subgroup and sensitivity analyses for mortality.

No significant differences between monotherapy and combination therapy were observed for the planned subgroups. The trend observed was similar for all comparisons, with RRs favouring monotherapy, with no statistical significance. Moreover, effect estimates favouring monotherapy were larger in subgroups designating participants with a potential worst prognosis:

- Participants with microbiologically documented infection: 13 trials, 1188 episodes, RR 0.81 (95% CI 0.56 to 1.17) (Analysis 4.1).
- Participants with bacteraemia: 14 trials, 676 episodes, RR 0.74 (95% CI 0.46 to 1.18) (Analysis 5.1).
- Participants with microbiologically documented Gram-negative infection: 16 trials, 376 episodes, RR 0.64 (95% CI 0.37 to1.11) (Analysis 6.1).
- Participants with documented *Pseudomonas aeruginosa* infection: 9 trials, 71 episodes, RR 0.87 (95% CI 0.34 to 2.24) (Analysis 7.1).
- Participants with haematological cancer: 22 trials 3463 episodes, RR 0.88 (95% CI 0.68 to 1.13) (Analysis 8.1).
- Participants with severe neutropenia on admission: 6 trials, 737 episodes, RR 0.68 (95% CI 0.37 to 1.24) (Analysis 9.1).

When the analysis was separated by the monotherapy beta-lactam (Analysis 10.1), only piperacillin-tazobactam was associated with significantly improved survival compared with combination therapy (RR 0.62, 95% CI 0.40 to 0.96, 5 trials, 1093 episodes). In studies including only children, the RR was 0.80 (95% CI 0.29 to 1.64), and in trials including only adults, the RR was 0.90 (95% CI 0.75 to 1.09) (Analysis 11.1).

In summary, monotherapy was associated with a trend toward improved survival overall and in all subgroups assessed.

Infection related mortality and treatment failure

Infection related mortality was reported in 41 trials (Analysis 1.2). No deaths related to infection were reported in nine trials (which did not contribute to the meta-analysis). Monotherapy was associated with a significantly lower rate of infection related mortality compared with combination therapy (RR 0.80, 95% CI 0.64 to 0.99). Results were similar for trials comparing same and different beta-lactams. The number of participants needed to treat with monotherapy to prevent one death related to infection was 95 participants, but 95% CIs were large (49 to 1241 participants).

Studies performed in recent years based their definitions for treatment success and failure on recommendations of the Immuncompromised Host Society (Consensus 1990). Treatment failure reported here is the inverse of "success without modification". It should be noted that we defined *treatment failure* more broadly in our protocol as death, lack of clinical improvement or any modification of the assigned empirical antibiotic treatment (see earlier, outcomes). Death judged as unrelated to infection was not included in the consensus definitions for failure. Thus other than infection related deaths, treatment failure reflected mainly treatment modifications in trials that were open-label in the vast majority.

In trials comparing the same beta-lactam, a significant advantage was seen with combination therapy (RR 1.11, 95% CI 1.02 to 1.20) with minor heterogeneity (I^2 = 12%). In trials comparing different beta-lactams, a significant advantage was observed with beta-lactam monotherapy (RR 0.92, 95% CI 0.88 to 0.97, I^2 = 16%) (Analysis 1.3). Results diverged for trials comparing same and different beta-lactams with regard to treatment failure; therefore these data were not pooled for the main and all subsequent analyses of treatment failure.

Subgroup analyses for trials comparing the same beta-lactams (Analysis 4.2; Analysis 5.2; Analysis 6.2; Analysis 7.2; Analysis 8.2; Analysis 9.2) demonstrated significant differences in favour of combination therapy for patients with Gram-negative infection (RR 1.34) and severe neutropenia (RR 1.48). No significant differences were observed for the subgroups of participants with any microbiologically documented infection, *Pseudomonas aeruginosa* infection, bacteraemia and haematological cancer. No specific beta-lactam monotherapy was associated with increased risk for failure (Analysis 10.2). All subgroup analyses for trials comparing the same beta-lactam were limited by the paucity of trials and participants included.

Similar subgroup analyses for trials comparing different beta-lactams showed that the significant advantage associated with monotherapy persisted in all tested subgroups, except for cases of documented *Pseudomonas aeruginosa* infection, severe neutropenia and haematological cancer. Similar RRs in favour of monotherapy were observed with the different specific beta-lactams.

No correlation was noted between rates of treatment failure and all cause or infection related mortality in these studies (r = 0.27, P = 0.11, 38 trials, and r = 0.21, P = 0.27, 30 trials, respectively). As expected, infection related mortality was significantly correlated with all cause mortality (r = 0.63, P < 0.001, 29 trials). No significant correlation was noted between publication year and the RRs for mortality or treatment failure.

Super-infections

Twenty-nine trials, including 4961 episodes, reported on the development of bacterial super infections during and after antibiotic treatment (Analysis 2.1), and 20 trials, including 3437 episodes, reported on fungal super infections (Analysis 2.2). Equivalence was demonstrated with regard to bacterial super infections (RR 1.02, 95% CI 0.87 to 1.19). Fungal super infections developed more frequently in the combination treatment group (RR 0.70, 95% CI 0.49 to 1.00). Data concerning resistant colonisation were scarce. Five trials supplied data regarding any colonisation (Alanis 1983; Cornelissen 1992; Erjavec 1994; Kojima 1994; Norrby 1987), and comparison of colonisation with resistant Gram-negative bacteria was possible in only two studies (Cornelissen 1992; Norrby 1987). In these studies, resistant Gram-negative bacteria were detected in 5 of 152 participants in the monotherapy group versus 1 of 152 in the combination group. Notably, none of the newer trials included in the updated review performed surveillance cultures, nor did they report on colonisation with resistant bacteria.

Adverse events

Adverse events were significantly more frequent in the combination treatment group. The difference was most remarkable when

development of renal failure was compared (RR 0.45, 95% CI 0.35 to 0.57) for any nephrotoxicity (Analysis 3.3) and (RR 0.16, 95% CI 0.05 to 0.49) for severe nephrotoxicity (Analysis 3.4). Nephrotoxicity was more common in the combination therapy than in the monotherapy arm also in studies using a once-daily dosing regimen for the aminoglycoside (RR 0.31, 95% CI 0.15 to 0.63, 8 trials, 1707 participants). In assessment of any adverse effect in all trials and in studies grouped by their monotherapy (Analysis 3.1), an advantage of monotherapy was seen overall (RR 0.87, 95% CI 0.81 to 0.94), and with ceftazidime monotherapy (RR 0.64, 95% CI 0.53 to 0.76). Likewise, discontinuation of study medication due to adverse events occurred more often in the combination group (Analysis 3.2) (RR 0.61, 95% CI 0.40 to 0.93). The number needed to harm with combination therapy was 34 participants (95% CI, 20 to 104) with regard to any adverse event and 31 participants (95% CI, 24 to 42) with regard to nephrotoxicity.

Other outcomes

Duration of hospital stay was non-significantly shorter in the monotherapy group in each of the four trials that reported this outcome: mean 24.8 days (standard deviation (SD) 21 to 31) versus 27.3 days (SD 23 to 56) (De la Camara 1997, data availed through personal correspondence), median 8.6 ± 4 versus 11.8 ± 5.6 (Corapcioglu 2005), mean 9.96 versus 11.93 days (Jimeno 2006) and mean 12.6 ± 5.3 versus 10.6 ± 4.7 (Yildirim 2008) for monotherapy versus combination therapy, respectively. The data were not pooled because variable reporting measures were used.

Selection bias

Funnel plot analyses were undertaken for the two main comparisons: failure and mortality. The funnel plot for mortality was symmetrical (Figure 1). The funnel plots for trials comparing same and different beta-lactams for failure were separated. Among trials comparing the same beta-lactam, the funnel plot was approximately symmetrical (Figure 2); among trials comparing different beta-lactams, an indication that small trials favouring combination therapy are missing may be present (Figure 3).

Figure 1. All cause mortality.

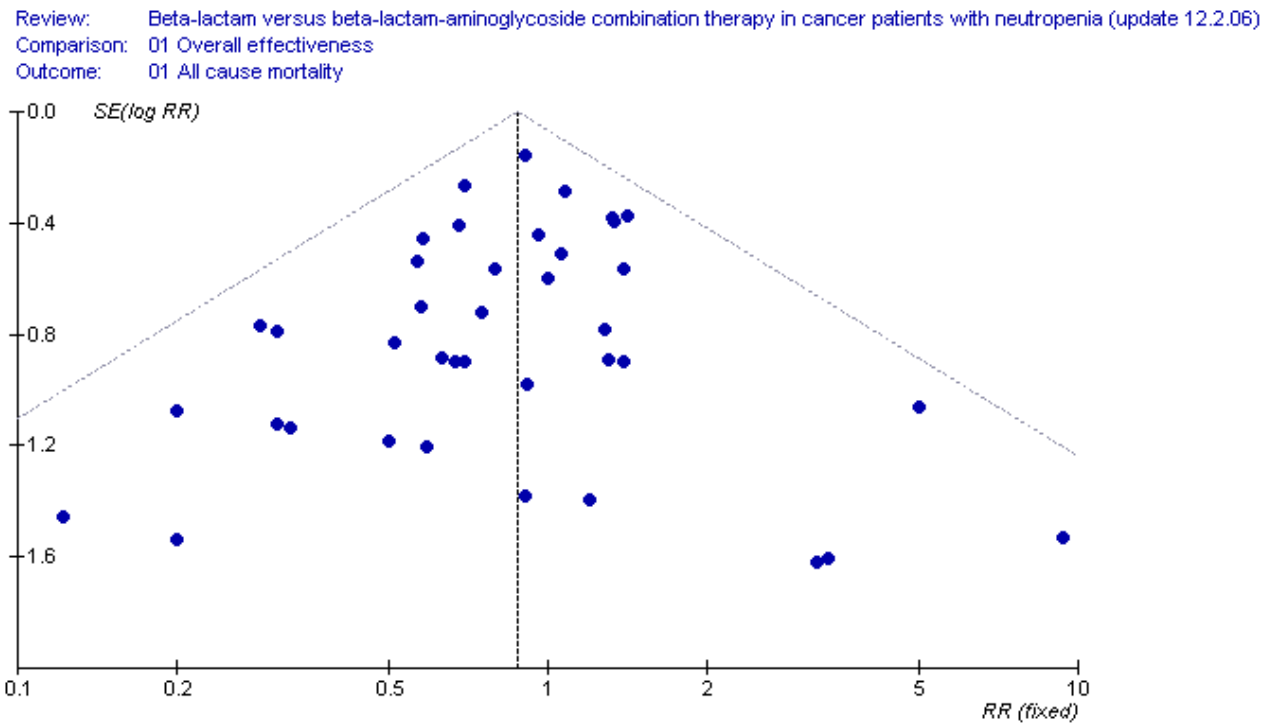


Figure 2. Failure-same BL.

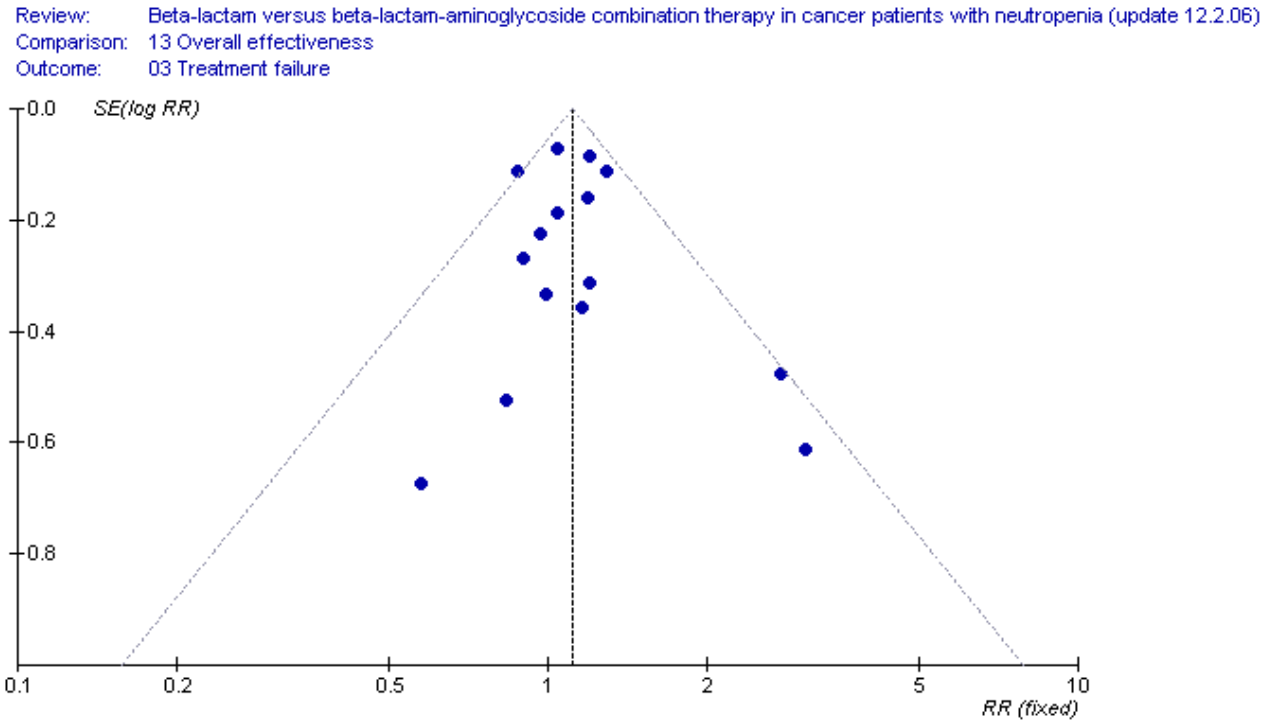
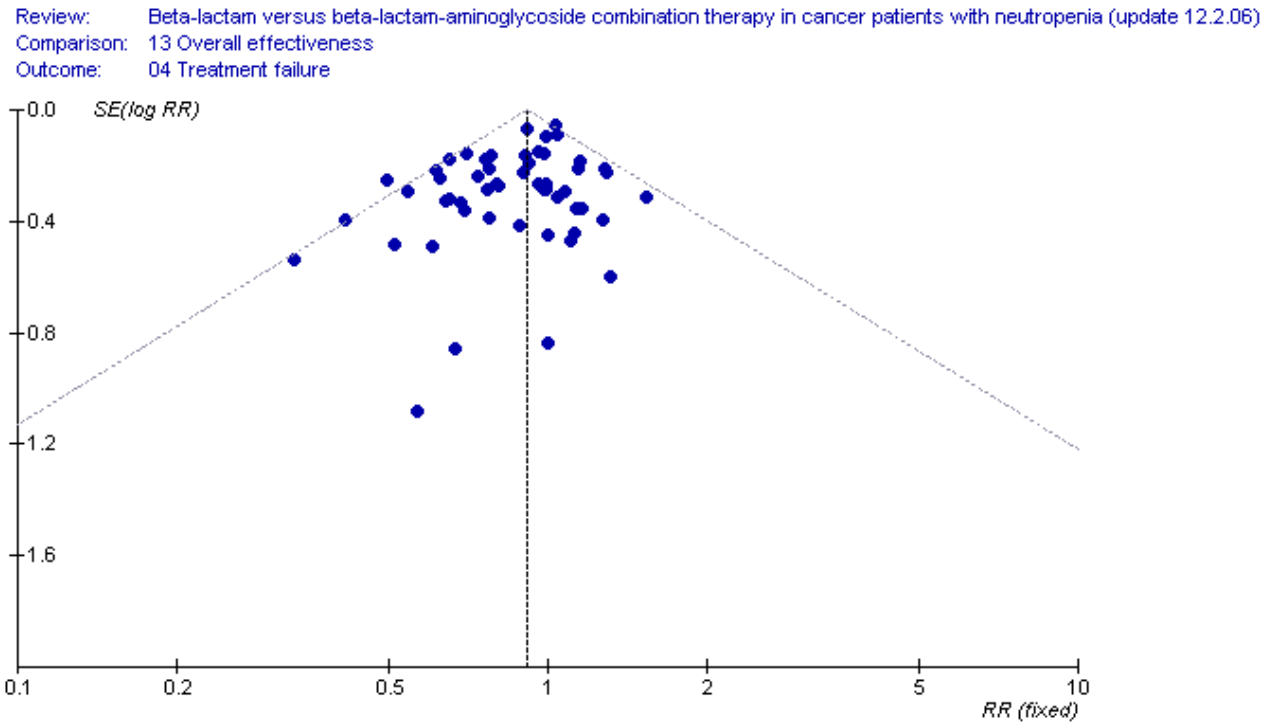


Figure 3. Failure-different BL.



Sensitivity analyses

Sensitivity analyses were performed for the primary outcomes—mortality and failure—to assess the impact of study quality on our results.

For mortality, results from studies with adequate allocation concealment (RR 0.88) were similar to results from studies with unclear allocation concealment (RR 0.87; Analysis 12.1), as were results for trials reporting ITT (RR 0.87) versus efficacy analysis (RR 0.88; Analysis 12.2). The effect size was smaller in trials assessing episodes (RR 0.90) compared with trials assessing participants (RR 0.84), although the 95% CI overlapped (Analysis 12.3). Small and large trials provided similar results, with no study size effect for mortality (comparison 12.5). Unpublished trials and those published only in conference proceedings showed no advantage of monotherapy (RR 1.07, 95% CI 1.07 to 0.72 to 1.59), and trials published in peer reviewed journals showed an advantage of monotherapy (RR 0.84, 95% CI 0.71 to 1.00) (Analysis 12.4).

For failure among trials comparing the same beta-lactams, no significant differences in the pooled effect estimate were observed for the different methodological measures assessed. In an ITT analysis counting all dropouts as failures, the advantage of combination therapy decreased (RR 1.07; Analysis 12.8). Analysis by episodes was associated with a larger effect estimate in favour of combination therapy (RR 1.16; Analysis 12.10). The only double-blinded trial showed similar results for combination therapy versus monotherapy (Del Favero 2001, Analysis 12.11).

Among trials comparing different beta-lactams, adequate allocation concealment was associated with a smaller effect estimate in favour of monotherapy than was seen with unclear methods (RR 0.94 versus RR 0.87, respectively; Analysis 12.6). ITT analysis in the publication was associated with a smaller effect estimate than was seen with efficacy analysis (RR 0.80, 95% CI 0.71 to 0.91 versus RR 0.95, 95% CI 0.88 to 1.01, respectively; Analysis 12.7), and an ITT analysis assuming that all dropouts were failures did not alter results significantly (RR 0.92, 95% CI 0.86 to 0.97; Analysis 12.8). Analysis by episodes was associated with a smaller effect estimate than analysis by participants (RR 0.95 versus RR 0.89; Analysis 12.10). Smaller trials were associated with a significantly larger effect estimate than was noted in the bigger trials (RR 0.75, 95% CI 0.67 to 0.84 versus RR 0.98, 95% CI 0.92 to 1.03; Analysis 12.9), pointing at the same small studies for effects observed in the corresponding funnel plot analysis (Figure 3). No advantage was seen with monotherapy in double-blind trials (Analysis 12.11).

For trials comparing same and different beta-lactams, unpublished trials showed no difference between monotherapy and combination therapy, but published trials showed a significant difference favouring combination therapy for trials comparing the same beta-lactams, and favouring monotherapy for trials comparing different beta-lactams (Analysis 12.12).

DISCUSSION

Seventy one trials that included more than 10,000 participants were analysed to compare beta-lactam monotherapy with beta-lactam-aminoglycoside combination therapy for the empirical treatment of febrile neutropenic cancer patients. The same beta-lactam was compared in 16 trials, but all other trials compared a broad-spectrum beta-lactam with a narrower-spectrum beta-lactam combined with an aminoglycoside. Most of the participants included in these trials were haematological cancer patients. We assessed all cause mortality as the primary outcome.

Monotherapy was associated with a statistically non-significant lower all cause mortality rate at end of follow-up (30 days) (RR 0.87, 95% CI 0.75 to 1.02). Results for trials comparing same and different beta-lactams were similar. Appropriate trial methods (adequate allocation concealment, ITT analysis and analysis by participants) were associated with similar effect estimates in favour of monotherapy, and no small studies effect was observed. Mortality attributed in the primary studies to infection was significantly lower with monotherapy (RR 0.80, 95% CI 0.64 to 0.99).

Treatment failure was assessed as the primary outcome in all included trials. By definition, its main addition on the rather subjective outcome of infection related mortality is treatment modifications (Consensus 1990). Among trials comparing the same beta-lactams, treatment failure was significantly more frequent with monotherapy. This difference likely reflects mainly physicians' tendency for treatment modifications in open trials comparing one antibiotic regimen with a broader-spectrum regimen. Among trials comparing different beta-lactams, a significant advantage was seen with monotherapy. Adequate trial methods were associated with smaller effect estimates for both 'same' and 'different' comparisons. Notably, in the single double-blind trial comparing the same beta-lactams, failure was equal with combination treatment and with monotherapy, and in three double-blind trials assessing different beta-lactams, the RRs were in the opposite direction compared with those in the other trials. We detected a small studies effect for trials comparing different beta-lactams. This may reflect a publication bias related to trials that assessed a newer monotherapy without showing its advantage.

Bacterial super infections occurred with equal frequency with monotherapy and combination therapy. Fungal super-infections were more common with combination therapy. All adverse events were more common with combination therapy, with a highly significant difference for nephrotoxicity. The pooled effect estimate translated to a number needed to harm of 34 participants (95% CI 20 to 104 participants).

To explain the advantage of monotherapy with regard to all cause mortality, several of the secondary outcomes may be used. Infection related mortality was significantly lower with monotherapy, and fungal super infections occurred more frequently with combination treatment. Fungal infections developing during neutropenia are highly lethal (Lin 2001). Thus, the improvement in survival may indeed be infection related. On the other hand, nephrotoxicity associated with combination therapy is a risk factor for subsequent adverse outcomes. Given these results and those of the methodological quality assessment, it is likely that the both mechanisms contribute to an unbiased advantage in overall survival with monotherapy.

Several hypotheses underlie the use of beta-lactam-aminoglycoside combination therapy for patients with neutropenia and suspected infection. Synergism is usually claimed as the major reason for combination therapy. Synergism was assessed most directly in trials comparing the same beta-lactam. We did not detect the beneficial effects of synergism. A wider spectrum of coverage may be the incentive for the addition of

an aminoglycoside depending on local patterns of resistance. Studies included in the review did not supply enough data to allow determination of whether coverage is indeed improved with combination therapy. However, the efficacy of aminoglycosides alone for the treatment of neutropenic patients is doubtful (Bodey 1972; Klastersky 1986); therefore this potential advantage does not seem substantial. Finally, combination therapy is claimed to prevent emergence of resistant pathogens. Development of resistance after antibiotic treatment is difficult to quantify. We intended to extract data regarding colonisation with resistant pathogens following antibiotic treatment, but these data were rarely available. Resistance was therefore indirectly examined through super infections, under the assumption that infection that develops under antibiotic treatment involves resistant pathogens. No difference was noted in the rate of bacterial super infections between monotherapy and combination therapy, and this analysis resulting in an RR close to 1. Fungal super infections developed more frequently with combination therapy, perhaps as a reflection of increased antibiotic spectrum or burden with combination therapy. Thus we could not show an advantage of combination therapy from this aspect.

We chose all cause mortality as the primary outcome, rather than treatment failure or infection related mortality, and have drawn our conclusions from the analysis for all cause mortality. Only a small part of the variance in mortality is explained by infection and its treatment; however, appropriate randomisation should ensure similar distribution of non–infection related risk factors for death between the study groups. Infection related mortality may be prone to bias in that the cause of death is difficult to determine in severely ill cancer patients. Moreover, ignoring deaths due to treatment-related adverse effects and super infections is inappropriate. Early empirical antibiotic treatment is the standard of practice for febrile neutropenic patients because it has been proven to decrease mortality (Hughes 1997; Schimpff 1986). Survival is indeed the objective when an acute infection is treated in cancer patients. Treatment failure indicates mainly modifications of the initial antibiotic regimen, and possibly a longer time to defervescence. The implications of such an outcome are not clear from the clinical point of view. Finally, deaths are objective, but failures cannot be objective when the trials are open. It is important to note that we could demonstrate in this review that assessing treatment failure is probably inappropriate, because no correlation between failure and mortality could be shown.

Our results are congruent with those of several other analyses of beta-lactam-aminoglycoside combination therapy versus beta-lactam monotherapy, showing no advantage associated with combination therapy. We conducted a similar analysis in non-neutropenic participants with sepsis, showing an advantage of monotherapy in trials comparing different beta-lactams, and no difference in trials comparison the same beta-lactam (Paul 2004; Paul 2006a). In an analysis of all RCTs comparing the same beta-lactam in the combination and monotherapy arms, in both neutropenic and non-neutropenic participants, and including semi-empirical studies, we did not find a significant difference in all cause mortality, but we noted significantly more bacterial super infections and increased renal failure with the addition of aminoglycosides (Marcus 2011). An analysis focusing on the development of resistance did not find an advantage associated with combination therapy (Bliziotis 2005). Finally, an analysis of observational studies focusing on*Pseudomonas aeruginosa* infection (mainly bacteraemia), a pathogen with special relevance to neutropenic cancer patients, did not find an advantage for combination therapy (Vardakas 2013).

The major limitations of this review include the lack of complete data concerning mortality (all cause mortality was available for 44 of 71 included trials, 62%) and the paucity of available data regarding specific patient subgroups, such as those with *Pseuomonas aeruginosa* infection. Other limitations stem from those of the primary studies. Allocation concealment was at low risk of bias in less than 35% of the trials, and nearly all were non-blinded. Many of the trials did not adhere to the principle of ITT analysis, resulting in incomplete data reporting. Most studies used febrile episodes as the unit of randomisation, although recurrent episodes are not independent for any for the outcomes assessed. Finally, follow-up did not seem pre-determined in many of the studies. Reported mortality may have been biased because the time of assessment was not defined in advance. We included trials regardless of their publication status. The differences detected in our review, namely, the advantage of monotherapy with regard to survival and the divergent advantages with regard to failure, existed with larger effect estimates in trials published in peer reviewed journals. The RRs were close to 1 for these outcomes in unpublished trials, mainly conference proceedings. Their inclusion in the meta-analysis tipped the overall RRs toward equivalence.

AUTHORS' CONCLUSIONS

Implications for practice

Monotherapy can be regarded as the standard of care for the empirical treatment of febrile neutropenic patients. The addition of an aminoglycoside does not improve survival. On the contrary, it is associated with significant morbidity incurred mainly through aminoglycoside-associated nephrotoxicity.

The monotherapies assessed in recent years have included imipenem, meropenem, ceftazidime, piperacillin-tazobactam and cefepime. These beta-lactams have also been assessed in head-to-head trials comparing different monotherapies and have shown similar efficacies, but for cefepime this was associated with increased all cause mortality (Paul 2006). Thus, individual centres should select the best matching monotherapy according to local epidemiology and susceptibility patterns.

RCTs do not support an advantage of combination therapy for *Pseudomonas aeruginosa* infection and other more severely ill patient subgroups. However the paucity of data precludes firm conclusions regarding these patient subgroups.

Implications for research

Assessment of new beta-lactams for febrile neutropenia should not be performed by comparison with a narrower-spectrum beta-lactam combined with an aminoglycoside. The results of these trials are uniformly unfavourable for patients. Assessment of new beta-lactam monotherapies should be performed by comparison with established monotherapies for febrile neutropenia. This design can and does show the advantages and disadvantages of specific beta-lactams (Paul 2006).

The need for further trials assessing the addition of an aminoglycoside to the same beta-lactam is doubtful given the results of our review, spanning more than two decades of

clinical trials in febrile neutropenia and without a change in RRs throughout the years. We can foresee such a need if a reduction in aminoglycoside-related adverse effects is expected, or if new data will point toward drug combinations with a marked synergistic effect—much greater than that observed in current studies. Trials targeting specific patient subgroups, such as those with severe sepsis and septic shock, documented *Pseudomonas aeruginosa* infection, etc. are warranted.

Future trials should report all cause mortality. The primary outcome used in these studies should be re-defined because with current definitions, no correlation can be noted between failure and the ultimate outcome: survival. This outcome should be defined in a consensus statement and applied universally to permit comparisons and compilation of different studies. The unit of randomisation should be the patient—not the episode. If recurrent episodes are allowed, results for the first randomisation of each patient should be reported separately, or the analysis should be adjusted to the clustering effect of patient episodes. Length of follow-up should be uniform and should be determined before the study is begun.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Agaoglu 2001

Methods	Randomisation: "systematic sampling". Blinding: single. Intention-to-treat: yes. Interim analysis: none. Exclusions from analysis: 0/82.
Participants	Turkey: 82 children. <18 years with 87 episodes randomly assigned to 3 arms. Underlying haematological cancer in 74/87 episodes. Neutropenia < 1000/mm^3 and fever > 38.5°.
Interventions	Meropenem 20 mg/kg × 3 versus Cefepime 33 mg/kg × 3 + netilmicin 2.5 mg/kg × 2 versus Ceftazidime 33 mg/kg × 3 + amikacin 7.5 mg/kg × 2.
Outcomes	All cause mortality; infection related mortality. Treatment failure. Adverse events.
Notes	Journal publication. No outcomes in subgroups. Additional outcome in study: cost.

Risk of bias

Bias	Authors' judgement	Support for judgement

Agaoglu 2001 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	B—Unclear.
Allocation concealment (selection bias)	Unclear risk	B—Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All episodes included in analysis.

Ahmed 2007

Methods	Randomisation: sealed opaque envelopes drawn at a central phone. Location. Blinding: no information. Intention to treat: possible. Interim analysis: none. Exclusions from analysis: 10/129 episodes. Follow-up period: no information.
Participants	Egygt: 129 episodes among children < 18 years with haematological cancer mainly (80%), neutropenia < 500/mm^3 expected to last > 6 days and fever.
Interventions	Imipenem 20-25 mg/kg × 4 versus Ceftriaxone 100 mg/kg × 1 + amikacin 15 mg/kg × 1.
Outcomes	All cause mortality. Infection related mortality. Treatment failure. Adverse events.
Notes	Journal publication and correspondence with author. Outcome in subgroups: bacteraemia, Gram-negative bacteraemia,*Pseudomonas aeruginosa* bacteraemia, haematological cancer. Additional outcome in study: cost.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central and sealed opaque envelopes.
Allocation concealment (selection bias)	Low risk	A—Adequate.

Ahmed 2007 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	10 patients excluded from analysis.

Akova 1999

Methods	Randomisation: sealed envelopes (opaque not mentioned), containing numbers from a computer-generated list in balanced blocks. Blinding: none. Intention-to-treat: possible. Interim analysis: none. Exclusions from analysis: 12/83 (in study). Follow-up period: mean 14 ± 9 days.
Participants	Turkey: Multicentre. 83 adults > 18 years with cancer, neutropenia < 500/mm^3 and fever. Patients with life expectancy < 24 hours were excluded.
Interventions	Meropenem 1 gr × 3 versus Ceftazidime 2 gr × 3 + amikacin 1 gr × 1.
Outcomes	All cause mortality; infection related mortality. Treatment failure. Adverse events. Dropouts after randomisation.
Notes	Journal publication. No outcomes in subgroups.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A—Adequate.
Allocation concealment (selection bias)	Low risk	A—Adequate.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.

Akova 1999 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	6 patients excluded from analysis.

Alanis 1983

Methods	Randomisation: random selection of sealed envelopes (opaque not mentioned). Blinding: none. Intention-to-treat: no. Interim analysis: none. Exclusions from analysis: 14/108. Follow-up period: no information.
Participants	USA: 108 febrile episodes in 86 cancer patients (9-74 years) with neutropenia < 1000/mm^3 . Included were 3 participants with neutropenia unrelated to malignancy.
Interventions	Moxalactam 50- to 70 mg/kg × 2-3 (max 14 gr/d) versus Nafcillin 30 mg/kg × 6 (max 12 gr/d) + tobramycin 1.7 mg/kg × 3.
Outcomes	Treatment failure. Bacterial and fungal super-infections. Colonisation. Adverse events. Dropouts after randomisation.
Notes	Journal publication. Outcome in subgroups. Bacteraemia, Severe neutropenia.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A—Adequate.
Allocation concealment (selection bias)	Low risk	A—Adequate.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	14 episodes excluded from analysis.

Antmen 2001

Methods	Randomisation: no information. Blinding: no information. Intention-to-treat: yes. Interim analysis: none. Exclusions from analysis: 0/67 episodes. Follow-up period: no information.
Participants	Turkey: 67 febrile episodes in 52 children (11 months-15 years) with haematological cancer mainly and neutropenia < 1000/mm^3 .
Interventions	Meropenem versus ceftazidime + amikacin (no data on doses).
Outcomes	Treatment failure.
Notes	Conference proceeding: no outcomes in subgroups.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B—Unclear.
Allocation concealment (selection bias)	Unclear risk	B—Unclear.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	B—Unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	B—Unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All episodes included in analysis.

Au 1994

Methods	Randomisation: no information. Blinding: no information. Intention-to-treat: no. Interim analysis: none. Exclusions from analysis: 5/56. Follow-up period: no information.
Participants	Singapore: 50 cancer patients > 14 years with neutropenia < 1000/mm^3 and fever > 38°. Patients with life expectancy < 24 hours were excluded.
Interventions	Imipenem/cilastatin 500 mg × 4 versus Ceftriaxone 2 gr × 1 + gentamicin 1 mg/kg × 3.
Outcomes	Treatment failure. Adverse events.

Au 1994 *(Continued)*

Notes	Journal publication. Outcome in subgroups. Documented infections: bacteraemia. Documented Gram-negative and *Pseudomonas* infections.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B — Unclear.
Allocation concealment (selection bias)	Unclear risk	B — Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	6 participants excluded from analysis.

Behre 1998

Methods	Randomisation: pre-formed randomisation lists, provided by study centre. Blinding: none. Intention-to-treat: yes. Interim analysis: none. Exclusions from analysis: 7/78 (for efficacy analysis). Follow-up period: 14 days following end of study medication.
Participants	Germany, multicentre: 78 episodes in 71 adults > 18 years with cancer (excluding allogeneic BMT), neutropenia < 500/mm^3 and fever.
Interventions	Meropenem 1 gr × 3 versus Ceftazidime 2 gr × 3 + amikacin 5-7.5 mg/kg × 2-3.
Outcomes	All cause mortality; infection related mortality. Treatment failure. Adverse events. Dropouts after randomisation.
Notes	Journal publication and author correspondence. Outcomes in subgroups. Documented infections: bacteraemia. Documented Gram-negative and *Pseudomonas* infections.

Risk of bias

Bias	Authors' judgement	Support for judgement

Behre 1998 *(Continued)*

Random sequence generation (selection bias)	Low risk	A—Adequate.
Allocation concealment (selection bias)	Low risk	A—Adequate.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	7 episodes excluded from analysis.

Bezwoda 1985

Methods	Randomisation: no information. Blinding: no information. Intention-to-treat: no. Interim analysis: none. Exclusions from analysis: 3/63. Follow-up period: no information.
Participants	South Africa: 60 adult cancer patients with neutropenia < 1000/mm^3 and fever > 39°.
Interventions	Moxalactam 2 gr × 3 versus cephradine 2 gr × 3 + tobramycin 1.5 mg/kg × 3.
Outcomes	All cause mortality. Treatment failure. Adverse events.
Notes	Journal publication. Trial terminated because of increasing resistance to cephradine. Outcomes in subgroups. Documented infections: documented Gram-negative and *Pseudomonas* infections.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	B—Unclear.
Allocation concealment (selection bias)	Unclear risk	B—Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.

Bezwoda 1985 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	3 participants excluded from analysis.

Borbolla 2001

Methods	Randomisation: no information. Blinding: no information. Intention-to-treat: no information. Interim analysis: none. Exclusions from analysis: no information (the study does not refer to excluded patients, 40 participants included). Follow-up period: no information.
Participants	Mexico: 40 acute leukaemia patients included. Neutropenia < 500/mm^3 and fever > 38° or focal infection.
Interventions	Cefepime 2 gr × 3 versus ceftriaxone 17 mg/kg × 3 + amikacin 15 mg/kg × 1.
Outcomes	Treatment failure. Adverse events.
Notes	Journal publication. Outcomes in subgroups. Haematological cancer patients.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	B—Unclear.
Allocation concealment (selection bias)	Unclear risk	B—Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis.

Cometta 1996

Methods	Randomisation: central computer-generated randomisation using minimisation technique for 2 stratifications: leukaemia or BMT and centre. Blinding: single (assessing committee). Intention-to-treat: no (performed according to study on eligible evaluable patients). Interim analysis: 2. Exclusions from analysis: 76/1034. Follow-up period: 30 days.
Participants	Europe, multicentre: 1034 cancer or BMT patients aged > 3 months with neutropenia < 1000/mm^3, fever and a presumed infection.
Interventions	Meropenem 1 gr × 3 or 20 mg/kg × 3 versus ceftazidime 2 gr × 3 or 35 mg/kg × 3 + amikacin 20 mg/kg × 1.
Outcomes	All cause mortality. Infection related mortality. Treatment failure. Adverse events. Super-infections. Dropouts after randomisation.
Notes	Journal publication. Envelopes used for randomisation in case of computer/connection failure. Outcomes in subgroups. Documented infections: documented Gram-negative, resistant Gram-negative and *Pseudomonas* infections.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A—Adequate.
Allocation concealment (selection bias)	Low risk	A—Adequate.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	76 participants excluded from analyses.

Conte 1996

Methods	Randomisation: no information. Blinding: none. Intention-to-treat: yes.

Conte 1996 *(Continued)*

	Exclusions from analysis: 0/40 episodes. Follow-up period: no information.
Participants	Chile: 40 episodes in 25 participants with haematological cancer and high-risk febrile neutropenia (median count < 100/mm^3).
Interventions	Cefoperazone-sulbactam 3 gr × 2 versus ceftazidime 1 gr × 3 + amikacin 7.5 mg/kg × 2.
Outcomes	All cause mortality. Treatment failure. Adverse events.
Notes	Conference proceedings. Outcomes in subgroups: haematological malignancies. Vitamin K added to cefoperazone-sulbactam group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B—Unclear.
Allocation concealment (selection bias)	Unclear risk	B—Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis.

Corapcioglu 2005

Methods	Randomisation: consecutive with no further details. Blinding: none. Intention-to-treat: no Interim analysis: 0. Exclusions from analysis: 10/60 episodes; follow-up period: not specified.
Participants	Turkey: 60 episodes among 29 children 11 months-17 years, mainly with haematological cancer (74%), with neutropenia < 500/mm^3 or < 1000/mm^3 and expected to decline to < 500/mm^3 within 24-48 hours and fever.
Interventions	Cefepime 50 mg/kg × 3 versus Ceftazidime 50 mg/kg × 3 + amikacin 15 mg/kg × 1.
Outcomes	Infection related mortality. Treatment failure.

Corapcioglu 2005 *(Continued)*

	Adverse events. Dropouts after randomisation.
Notes	Journal publication. No outcomes in subgroups.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	C — Inadequate.
Allocation concealment (selection bias)	High risk	C — Inadequate.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	10 episodes excluded from analysis.

Cornelissen 1992

Methods	Randomisation: no information. Blinding: none. Intention-to-treat: no. Exclusions from analysis: 6/100. Follow-up period: no information.
Participants	Netherlands: 100 episodes in 93 adult cancer patients with neutropenia < 500/mm^3 and fever. Allogeneic BMT patients excluded.
Interventions	Imipenem 500 mg × 4 versus Cefuroxime 1.5 gr × 3 or cephalotin 1 gr × 6 + gentamicin 80 mg × 3.
Outcomes	Treatment failure. Colonisation. Adverse events. Dropouts after randomisation.
Notes	Journal publication. Treatment modification suggested by protocol differs between the two treatment groups. Outcomes in subgroups. Documented infections: Gram-negative, resistant Gram-negative and *Pseudomonas* infections; bacteraemia.

Risk of bias

Cornelissen 1992 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B — Unclear.
Allocation concealment (selection bias)	Unclear risk	B — Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	6 participants excluded from analysis.

Cornely 2001

Methods	Randomisation: block randomisation with a block length of six (3 arms for first randomisation × 2 arms for second randomisation). Consecutively numbered sealed opaque envelopes, non-used envelopes to be returned (envelopes glued to the binding of the CRF). Blinding: none. Intention-to-treat: yes for mortality. Exclusions from analysis: 73/602 participants for failure patients. Follow-up period: up to 42 days (mortality data given up to 30 days).
Participants	MC, Germany: 602 adult participants with high-risk haematological malignancies, neutropenia < 500 mm^3 and fever > 38.5° once or > 38 twice within 24 hours. Randomly assigned to 3 arms.
Interventions	Meropenem 1 gr × 3 versus Cefepime 2 gr × 3 versus Piperacillin-tazobactam 4.5 gr × 3 + aminoglycoside once daily. For the purposes of the meta-analysis, the two monotherapy arms (cefepime and meropenem) were joined.
Outcomes	All cause mortality. Infection related mortality. Treatment failure. Adverse events.
Notes	Conference proceedings: Full methods and results supplied by the author. Outcomes in subgroups: haematological malignancies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A — Computer-generated block randomisation.

Cornely 2001 *(Continued)*

Allocation concealment (selection bias)	Low risk	A—Consecutively numbered sealed opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	73 participants excluded from analysis.

De la Camara 1997

Methods	Randomisation: consecutive computer-generated, concealed by sealed, opaque envelopes, stratified by centre. Blinding: none. Intention-to-treat: possible for mortality. Interim analysis: none. Exclusions from analysis: 29/122 episodes (for failure). Follow-up period: 1 month following end of treatment.
Participants	Spain, multicentre: 122 episodes in 103 participants > 16 years with neutropenia < 500/mm^3 and fever. All participants with underlying haematological malignancy, of which 49% had BMT and an additional 29% acute leukaemia.
Interventions	Meropenem 1 gr × 3 versus Ceftazidime 2 gr × 3 + Amikacin 5-7.5 mg/kg × 2-3.
Outcomes	All cause mortality. Infection related mortality. Treatment failure. Adverse events. Bacterial and fungal super infections. Dropouts after randomisation.
Notes	Journal publication and author correspondence. Outcomes in subgroups. Documented infections: bacteraemia; haematological cancer patients.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A—Adequate.
Allocation concealment (selection bias)	Low risk	A—Adequate.

De la Camara 1997 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	10 participants excluded from analysis.

De Pauw 1983

Methods	Randomisation: no information. Blinding: none. Intention-to-treat: no. Interim analysis: no. Exclusions from analysis: 4/78. Follow-up period: no information.
Participants	Netherlands: 78 haematological or BMT cancer patients > 15 years with neutropenia < 1000/mm^3 and fever.
Interventions	Ceftazidime 2 gr × 3 versus Cefotaxime 2 gr × 4 + gentamicin 80 mg × 3.
Outcomes	Treatment failure. Fungal super infections. Adverse events.
Notes	Journal publication. Surveillance cultures performed. Outcomes in subgroups: Gram-negative and *Pseudomonas* infections; haematological cancer patients.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	B—Unclear.
Allocation concealment (selection bias)	Unclear risk	B—Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias)	High risk	4 participants excluded from analysis.

De Pauw 1983 *(Continued)*

All outcomes

De Pauw 1994

Methods	Randomisation: central in blocks of eight, concealed by sealed envelopes (opaque not mentioned). Blinding: none. Intention-to-treat: no. Interim analysis: no. Exclusions from analysis: 74/1086. Follow-up period: end of treatment.
Participants	Australia, Canada, Europe, multicentre: 968 episodes in 872 participants > 14 years evaluated, with neutropenia < 500/mm^3 and fever. Underlying haematological cancer in 83% of participants.
Interventions	Ceftazidime 2 gr × 3 versus Piperacillin 3-4 gr × 4-6 + Tobramycin 1.7-2 mg/kg × 3. Supplemented as indicated by Vancomycin 1 gr × 2 or Metronidazole 500 × 3-4.
Outcomes	All cause mortality. Infection related mortality. Treatment failure. Super-infections. Adverse events. Dropouts after randomisation.
Notes	Journal publication, conference proceedings and author correspondence. Participants with suspected Gram-positive (n = 113) or anaerobic (n = 71) infections were given vancomycin or metronidazole, respectively, in addition to the randomly allocated antibiotic/s. Outcomes in subgroups. Documented infections: haematological cancer patients.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A—Adequate.
Allocation concealment (selection bias)	Low risk	A—Adequate.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	118 episodes excluded from analysis.

Del Favero 2001

Methods	Randomisation: computer-generated, central, stratified by center and underlying malignancy. Blinding: double, placebo-controlled. Intention-to-treat: possible for failure. Interim analysis: no. Exclusions from analysis: 27/760 (for efficacy analysis and mortality). Follow-up period: 30 days.
Participants	Italy, multicentre: 760 participants > 13 years with neutropenia < 500/mm^3 and fever > 38.5°. Underlying haematological cancer in 81%. of participants, and BMT in 52%.
Interventions	Piperacillin-tazobactam 4.5 gr × 3 versus piperacillin-tazobactam 4.5 gr × 3 + amikacin 7.5 mg/kg × 2.
Outcomes	All cause mortality. Infection related mortality. Treatment failure. Dropouts after randomisation. Adverse events.
Notes	Journal publication. Outcomes in subgroups. Documented infections: bacteraemia. Documented Gram-negative and *Pseudomonas* infections.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A—Adequate.
Allocation concealment (selection bias)	Low risk	A—Adequate.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	27 participants excluded from analysis.

Dincol 1998

Methods	Randomisation: no information. Blinding: none. Intention-to-treat: yes. Interim analysis: no. Exclusions from analysis: none. Follow-up period: end of treatment.

Dincol 1998 *(Continued)*

Participants	Turkey: 150 episodes in 97 cancer patients > 14 years, with neutropenia < 500/mm^3 and fever > 38.5°. Underlying haematological cancer in 43%.
Interventions	Imipenem 500 mg × 4 versus cefoperazone-sulbactam 2 gr × 2 + amikacin 15 mg/kg × 1.
Outcomes	All cause mortality. Infection related mortality. Treatment failure. Adverse events.
Notes	Journal publication and author correspondence. Outcomes in subgroups. Documented infections: bacteraemia. Documented Gram-negative and *Pseudomonas* infections.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A—Adequate.
Allocation concealment (selection bias)	Unclear risk	B—Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All episodes included in analysis.

Doyen 1983

Methods	Randomisation: no information. Blinding: none. Intention-to-treat: possible for mortality. Interim analysis: 1. Exclusions from analysis: 7/104 (for failure). Follow-up period: no information.
Participants	Belgium: 104 episodes in 83 adult haematological cancer with neutropenia < 500/mm^3 and fever > 38°.
Interventions	Ceftazidime 30 mg/kg × 3 versus ceftazidime 30 mg/kg × 3 + amikacin 5 mg/kg × 3.
Outcomes	All cause mortality. Infection related mortality. Treatment failure.

Doyen 1983 *(Continued)*

	Bacterial and fungal super infections.
Notes	Conference proceeding and author correspondence: Study not completed, all randomly assigned participants included in the review. Outcomes in subgroups. Documented infections: bacteraemia; haematological cancer patients. Documented Gram-negative infections.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B — Unclear.
Allocation concealment (selection bias)	Unclear risk	B — Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	7 episodes excluded from analysis.

Duzova 2001

Methods	Randomisation: no information. Blinding: single-blinded. Intention-to-treat: unknown. Interim analysis: no. Exclusions from analysis: no information, 90 episodes included. Follow-up period: no information.
Participants	Turkey: 90 episodes in children < 16 years with lymphomas or solid tumours (leukaemia excluded), with neutropenia < 500/mm^3 and fever > 38.3°.
Interventions	Meropenem 50 mg/kg × 3 versus Piperacillin 200 mg/kg × 4 + Amikaciin 15 mg/kg × 1.
Outcomes	All cause mortality. Infection related mortality. Treatment failure.
Notes	Journal publication and author correspondence. Outcomes in subgroups: haematological cancer patients.

Risk of bias

Duzova 2001 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B — Unclear.
Allocation concealment (selection bias)	Unclear risk	B — Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All episodes included in analysis.

El Haddad 1995

Methods	Randomisation: no information. Blinding: none. Intention-to-treat: no. Interim analysis: no. Exclusions from analysis: unknown, only number of evaluated participants reported. Follow-up period: unknown.
Participants	Egypt: 46 episodes in children < 15 years with leukaemia or lymphoma and neutropenia < 500/mm^3 with fever > 38.5° once or > 38° thrice during 24 hours.
Interventions	Randomization 2:1 to cefoperazone-sulbactam 67 mg/kg × 3 versus Piperacillin 100 mg/kg × 4 + Amikacin 5 mg/kg × 3.
Outcomes	Infection related mortality. Treatment failure. Adverse events.
Notes	Journal publication. Outcomes in subgroups: haematological cancer.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B — Unclear.
Allocation concealment (selection bias)	Unclear risk	B — Unclear.

El Haddad 1995 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	B—Unclear.

Erjavec 1994

Methods	Randomisation: no information. Blinding: none. Intention-to-treat: yes. Interim analysis: no. Exclusions from efficacy and subgroup analysis: 36/179. Follow-up period: resolution of neutropenia.
Participants	Netherlands: 179 episodes in 127 haematological cancer patients > 16 years, with neutropenia < 500/mm^3 and fever.
Interventions	Imipenem 12.5 mg/kg -1gr × 4 versus Cefuroxime 15 mg/kg × 3 + Tobramycin 2 mg/kg × 2 following a loading dose of 2.5 mg/kg.
Outcomes	Treatment failure. Bacterial and fungal super-infections.
Notes	Journal publication. Outcomes in subgroups. Documented infections: documented Gram-negative, *Pseudomonas* and resistant Gram-negative infections; haematological cancer patients.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	B—Unclear.
Allocation concealment (selection bias)	Unclear risk	B—Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.

Erjavec 1994 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	36 episodes excluded from analysis.

Esteve 1997

Methods	Randomisation: no information. Blinding: none. Intention-to-treat: unknown. Interim analysis: unknown. Exclusions analysis: only the number of treated participants reported. Follow-up period: unknown.
Participants	Spain: 85 episodes in 75 haematological cancer patients (excluding bone marrow transplantation) with neutropenia < 1000/mm^3 and fever.
Interventions	Piperacillin-tazobactam 4 gr × 4 versus Piperacillin-tazobactam 4 gr × 4 + Amikacin 15 mg/kg × 1.
Outcomes	All cause mortality. Treatment failure. Adverse events.
Notes	Conference proceeding. Outcomes in subgroups: haematological cancer patients.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	B — Unclear.
Allocation concealment (selection bias)	Unclear risk	B — Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	B — Unclear.

Gaytan-Martinez 2002

Methods	Randomisation: no information. Blinding: none.

Gaytan-Martinez 2002 *(Continued)*

	Intention-to-treat: no. Interim analysis: unknown. Exclusions from analysis: unknown (only number of evaluated episodes reported). Follow-up period: unknown.
Participants	Mexico: 117 evaluated episodes in participants with non-Hodgkin lymphoma or acute leukaemia with neutropenia and fever > 38.3°.
Interventions	Cefepime 2 gr × 2 versus Ceftazidime 2 gr × 3 + Amikacin 1 gr × 1.
Outcomes	Treatment failure.
Notes	Conference proceeding. No outcomes in subgroups.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B — Unclear.
Allocation concealment (selection bias)	Unclear risk	B — Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	B — Unclear.

Gibson 1989

Methods	Randomisation: computer-generated random numbers, concealed by sealed envelopes, which were taken in consecutive order (opaque not mentioned). Blinding: none. Intention-to-treat: yes. Interim analysis: none. Exclusions from analysis: 0. Follow-up period: no information.
Participants	Australia: 102 adults > 14 years. All with underlying haematological malignancy. Neutropenia < 1000/mm^3 and fever or clinically localised site of infection.
Interventions	Ceftazidime 2 gr × 3 versus Azlocillin 4 gr × 4 + Amikacin 5 mg/kg × 3.
Outcomes	All cause mortality. Infection related mortality.

Gibson 1989 *(Continued)*

	Treatment failure.
Notes	Journal publication. Additional empirical treatment with flucloxacillin allowed. Outcomes in subgroups: haematological cancer patients.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A—Adequate.
Allocation concealment (selection bias)	Low risk	A—Adequate.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis.

Gorschluter 2003

Methods	Randomisation: computer-generated, concealed by sealed, opaque envelopes. Blinding: none. Intention-to-treat: modified (performed on all eligible participants). Interim analysis: 2. Exclusions from analysis: 29/212 episodes. Follow-up period: 21 days after treatment initiation.
Participants	Germany: 212 episodes in 130 adults > 18 years. All with underlying haematological malignancy, 90% acute leukaemia. Leukopaenia < 1000/mm^3 or neutropenia < 500/mm^3 and fever > 38.5° (rectal) or > 38° (axillary).
Interventions	Piperacillin-tazobactam 4.5 gr × 3 versus Ceftriaxone 2 gr × 1 + gentamycin 5 mg/kg × 1.
Outcomes	All cause mortality. Infection related mortality. Treatment failure.
Notes	Journal article. Study discontinued at second interim analysis by protocol because of a significant advantage for monotherapy. Outcomes in subgroups. Documented infections: bacteraemia. Documented: Gram-negative, *Pseudomonas* and resistant Gram-negative infections; haematological cancer patients.

Gorschluter 2003 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A — Computer generated lists.
Allocation concealment (selection bias)	Low risk	A — Sealed opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	29 episodes excluded from analysis.

Gribble 1983

Methods	Randomisation: computer-generated, concealment not specified. Blinding: none. Intention-to-treat: no. Interim analysis: none. Exclusions from analysis: 4/54. Follow-up period: 14 days after treatment cessation.
Participants	Canada: 50 episodes in 38 adults > 16 years evaluated. Of these, 30 episodes were in neutropenic participants with neutropenia < 1000/mm^3 and fever > 38.3°.
Interventions	Piperacillin 75 mg/kg × 4 versus Carbenicillin 125 mg/kg × 4 (could be replaced by ticarcillin) + Gentamicin 1.5 mg/kg × 3 (could be replaced by tobramycin).
Outcomes	Treatment failure: super-infections. Adverse events.
Notes	Journal publication. Additional empirical treatment with cloxacillin allowed. Study includes both neutropenic and non-neutropenic participants, and only outcomes that can be separated were extracted. No outcomes in subgroups (for neutropenic participants only).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A — Adequate.

Gribble 1983 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	B—Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	4 participants excluded from analysis.

Hansen 1986

Methods	Randomisation: no information, stratification according to cytotoxic therapy. Blinding: none. Intention-to-treat: no. Interim analysis: none. Exclusions from analysis: 7/40. Follow-up period: no information.
Participants	Denmark: 80 episodes in 70 solid tumour cancer patients with neutropenia < 1500/mm^3 and fever, randomised to 4 arms, of which 2 arms and 40 episodes are included in the review.
Interventions	Latamoxef 2 gr × 3 versus Carbenicillin 10 gr × 3 +gentamicin 80 mg × 3.
Outcomes	Treatment failure: dropouts after randomisation.
Notes	Journal publication. Outcomes in subgroups: severe neutropenia, bacteraemia, documented Gram-negative infections.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	B—Unclear.
Allocation concealment (selection bias)	Unclear risk	B—Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias)	High risk	7 episodes excluded from analysis.

Hansen 1986 *(Continued)*

All outcomes

Hense 2000

Methods	Randomisation: no information. Blinding: none. Intention-to-treat: yes for mortality, possible for failure. Interim analysis: none. Exclusions from analysis: in study 3/87. Follow-up period: no information.
Participants	Germany: 88 adult patients with haematological malignancy, with neutropenia < 500/mm^3 and fever.
Interventions	Meropenem 1 gr × 3 (given either as bolus or infusion—2 arms merged for this review) versus Ceftazidime 2 gr × 3 + Amikacin 5 mg/kg × 3.
Outcomes	All cause mortality. Infection related mortality. Treatment failure: adverse events; dropouts after randomisation.
Notes	Conference proceeding and results from author. Outcomes in subgroups: haematological malignancy.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B—Unclear.
Allocation concealment (selection bias)	Unclear risk	B—Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	3 participants excluded from analysis.

Hess 1998

Methods	Randomisation: consecutively numbered sealed envelopes (opaque not mentioned) in randomly permuted blocks, by 24 hours' service. Blinding: none. Intention-to-treat: no. Interim analysis: none. Exclusions from analysis: 11/107.

Hess 1998 *(Continued)*

	Follow-up period: 30 days after inclusion.
Participants	Switzerland: 107 episodes in 83 cancer patients > 13 years with neutropenia < 500/mm^3 and fever or documented infection without fever.
Interventions	Piperacillin-tazobactam 4.5 gr × 3 versus Ceftazidime 2 gr × 3 + Amikacin 15 mg/kg × 1.
Outcomes	All cause mortality. Infection related mortality. Treatment failure: adverse events; dropouts after randomisation.
Notes	Journal publication. Additional empirical treatment with vancomycin allowed by protocol for non-responders after 48 hours. Discrepancy between tables and text concerning dropouts, disabling analysis by intention-to-treat. Outcomes in subgroups: bacteraemia.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A—Adequate.
Allocation concealment (selection bias)	Low risk	A—Adequate.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	11 episodes excluded from analysis.

Hung 2003

Methods	Randomisation: no information, stratified by haematological malignancy. Blinding: none. Intention-to-treat: no. Interim analysis: none. Exclusions from analysis: 24/100 episodes. Follow-up period: no information.
Participants	China: 76 episodes in 51 children < 14 years with neutropenia < 500/mm^3, fever and suspected infection.
Interventions	Meropenem 40 mg/kg × 3 versus Ceftazidime 50 mg/kg × 3 + Amikacin 5 mg/kg × 3,
Outcomes	All cause mortality.

Hung 2003 *(Continued)*

	Infection related mortality. Treatment failure: adverse events; dropouts after randomisation.
Notes	Journal publication. Outcomes in subgroups: severe neutropenia. Documented infections.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B—Unclear.
Allocation concealment (selection bias)	Unclear risk	B—Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	24 episodes excluded from analysis.

Jacobs 1993

Methods	Randomisation: no information, stratified by centre. Blinding: none. Intention-to-treat: no. Interim analysis: none. Exclusions from analysis: 16/107. Follow-up period: no information.
Participants	USA: multicentre, 107 episodes in 92 children < 18 years treated for cancer with fever > 38° and neutropenia > 500/mm^3.
Interventions	Ceftazidime 50 mg/kg × 3 versus Ceftazidime 50 mg/kg × 3 + Tobramycin 2.5 mg/kg × 3.
Outcomes	Treatment failure: bacterial super-infections; adverse events; dropouts after randomisation.
Notes	Journal publication. Outcomes in subgroups. Documented infections: bacteraemia. Documented Gram-negative and *Pseudomonas* infections.

Risk of bias

Bias	Authors' judgement	Support for judgement

Jacobs 1993 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	B—Unclear.
Allocation concealment (selection bias)	Unclear risk	B—Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	16 episodes excluded from analysis.

Jimeno 2006

Methods	Randomisation: computer-generated, concealed by sealed opaque envelopes. Blinding: none. Intention-to-treat: yes. Interim analysis: study stopped early because cancer treatment protocol changed. Exclusions from analysis: 0/51 episodes. Follow-up period: no information.
Participants	Spain: 51 episodes in 49 adults with solid malignancies treated with high-dose chemotherapy and peripheral blood stem cell support, with fever > 38.3° (or > 38° lasting > 1 hour) and neutropenia < 500/mm^3 .
Interventions	Cefepime 2 gr × 3 versus Ceftazidime 2 gr × 3 + Amikacin 500 mg × 2.
Outcomes	All cause mortality. Infection related mortality. Treatment failure: adverse events; hospitalisation duration.
Notes	Journal publication and correspondence with author. Outcomes in subgroups. Documented infections.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A—Computer generated.
Allocation concealment (selection bias)	Low risk	A—Sealed opaque envelopes.

Jimeno 2006 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All episodes included in analysis.

Kiehl 2001

Methods	Randomisation: no information. Blinding: none. Intention-to-treat: yes. Interim analysis: unknown. Exclusions from analysis: 0/71 participants. Follow-up period: no information.
Participants	Germany: 71 patients following autologous stem cell transplantation with febrile neutropenia.
Interventions	Piperacillin-tazobactam 4.5 gr × 3 versus Piperacillin-tazobactam 4.5 gr × 3 + Netilmicin 5 mg/kg × 1.
Outcomes	Treatment failure.
Notes	Conference proceeding. Outcomes in subgroups: haematological cancer patients.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B—Unclear.
Allocation concealment (selection bias)	Unclear risk	B—Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis.

Kinsey 1990

Methods	Randomisation: no information. Blinding: none. Intention-to-treat: no Interim analysis: none. Exclusions from analysis: 45/205. Follow-up period: no information.
Participants	UK: 205 episodes in 139 haematological cancer patients, aged 9-74 years with neutropenia < 500/mm^3 and fever.
Interventions	Ceftazidime versus ceftazidime + gentamicin (no dosing information).
Outcomes	All cause mortality. Infection related mortality. Treatment failure.
Notes	Journal publication. No outcomes in subgroups. 11 deaths in 45 excluded participants.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B — Unclear.
Allocation concealment (selection bias)	Unclear risk	B — Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	45 episodes excluded from analysis.

Kliasova 2001

Methods	Randomisation: no information. Blinding: none. Intention-to-treat: unknown. Interim analysis: unknown. Exclusions from analysis: only number evaluated provided. Follow-up period: 60 days after treatment.

Kliasova 2001 *(Continued)*

Participants	Russia: 43 episodes in 42 haematological cancer patients > 15 years after bone marrow transplantation, with fever and neutropenia.
Interventions	Meropenem 1 gr × 3 versus Ceftazidime 2 gr × 3 + Amikacin 500 mg × 3.
Outcomes	All cause mortality. Infection related mortality. Treatment failure: adverse events.
Notes	Conference proceeding. Outcomes in subgroups: haematological cancer patients.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B — Unclear.
Allocation concealment (selection bias)	Unclear risk	B — Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	B — Unclear.

Koehler 1990

Methods	Randomisation: no information. Blinding: none. Intention-to-treat: yes. Interim analysis: none. Exclusions from analysis: 0/120 episodes. Follow-up period: no information.
Participants	Poland: 76 children with haematological cancer with 120 episodes of neutropenia <= 1000/mm^3 and fever >= 38° for > 3 hours.
Interventions	Ceftazidime 50 mg/kg × 3 versus Ampicilin or Amoxycillin 100 mg/kg × 3 + Tobramycin 4 mg/kg × 3.
Outcomes	Treatment failure: bacterial and fungal super-infections; adverse events.
Notes	Journal publication. Outcomes in subgroups: haematological cancer.

Koehler 1990 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B—Unclear.
Allocation concealment (selection bias)	Unclear risk	B—Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All episodes included in analysis.

Kojima 1994

Methods	Randomisation: stratified by use of G-CSF, no further information. Blinding: none. Intention-to-treat: no. Interim analysis: none. Exclusions from analysis: 2/70. Follow-up period: 72 hours after completion of treatment.
Participants	Japan: 70 episodes in 60 solid tumour cancer adult patients with neutropenia < 1000/mm^3 and fever. No BMT patients.
Interventions	Imipenem 500 mg × 4 versus Imipenem 500 mg × 4 + Amikacin 200 mg/m^2 × 2.
Outcomes	Treatment failure: adverse events; fungal colonisation; dropouts after randomisation.
Notes	Journal publication and author correspondence. Study terminated prematurely because of excess failures in monotherapy. Outcomes in subgroups: Documented infections: documented Gram-negative and *Pseudomonas* infections.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B—Unclear.
Allocation concealment (selection bias)	Low risk	A—Adequate.

Kojima 1994 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	3 participants excluded from analysis.

Leyland 1992

Methods	Randomisation: generation not specified, concealment by sealed envelopes (opaque not mentioned). Blinding: single (outcome assessor). Intention-to-treat: no. Interim analysis: none. Exclusions from analysis: 96/312. Follow-up period: 14 days.
Participants	UK , multicentre: 312 episodes in 234 adults > 18 years with haematological cancer, neutropenia < 1000/mm^3 and fever.
Interventions	Imipenem 0.5-1 gr × 4 versus Piperacillin 4 gr × 4 + Gentamycin 80 mg/kg × 3.
Outcomes	Overall mortality. Treatment failure: bacterial super-infections; adverse events; dropouts after randomisation.
Notes	Journal publication. Exclusion rate 30.8%, with 3 patients not accounted for. Outcomes in subgroups. Documented infections: bacteraemia. Documented Gram-negative infections: haematological cancer patients.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B—Unclear.
Allocation concealment (selection bias)	Low risk	A—Adequate.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor blinded.

Leyland 1992 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	96 episodes excluded from analysis.

Lieschke 1990

Methods	Randomisation: generated through centre at drug company, concealed by envelopes (sealed or opaque not mentioned). Blinding: none. Intention-to-treat: yes. Interim analysis: 1. Exclusions from analysis: none. Follow-up period: end of fever, infection or neutropenia.
Participants	Australia: 182 episodes in 150 adult febrile neutropenic cancer patients. Neutropenia < 1000/mm^3 and fever > 38°.
Interventions	Imipenem 500 mg × 4 versus Piperacillin 4 gr × 4 + Tobramycin 1 mg/kg × 3.
Outcomes	All cause mortality. Infection related mortality. Treatment failure: bacterial super-infections; adverse events.
Notes	Data from manuscript of unpublished trial supplied by author. Published as an abstract at an interim analysis. No outcomes in subgroups.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B—Unclear.
Allocation concealment (selection bias)	Low risk	A—Adequate.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All episodes included in analysis.

Liu 1989

Methods	Randomisation: no information.

Liu 1989 *(Continued)*

	Blinding: none. Intention-to-treat: no. Interim analysis: none. Exclusions from analysis: 1/28. Follow-up period: no information.
Participants	China: 28 adults > 18 years with cancer, neutropenia < 500/mm^3 and fever. Randomised to 3 treatment arms.
Interventions	Imipenem 500 mg × 4 versus Ceftriaxone 2 gr × 1 + Amikacin 7.5 mg/kg × 2 versus Ceftazidime 2 gr × 3 + Amikacin 7.5 mg/kg × 2.
Outcomes	Treatment failure: bacterial and fungal super-infections; adverse events; dropouts after randomisation.
Notes	Journal publication. Outcomes in subgroups: documented infections.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B—Unclear.
Allocation concealment (selection bias)	Unclear risk	B—Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	1 patient excluded from analysis.

Marie 1991

Methods	Randomisation: "triage a sort" concealed by sealed envelopes (opaque not mentioned). Blinding: none. Intention-to-treat: unknown. Interim analysis: yes. Exclusions from analysis: no information (the study does not refer to excluded participants). Follow-up period: no information.
Participants	France, bi-centre: 146 episodes in adult cancer patients with cancer, neutropenia < 500/mm^3 and fever. Randomised to 3 treatment arms, of which 2 are relevant for the comparison in the review.
Interventions	Ceftazidime 1 gr × 3 versus Ceftazidime 1 gr × 3 + Amikacin 7.5 mg/kg × 2 versus Ceftazidime 1 gr × 3 + Vancomycin 500 mg × 3 (third treatment arm excluded).

Marie 1991 *(Continued)*

Outcomes	Treatment failure: bacterial and fungal super-infections; adverse events.
Notes	Journal publication. No outcomes in subgroups.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A—Adequate.
Allocation concealment (selection bias)	Low risk	A—Adequate.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	B—Unclear.

Matsui 1991

Methods	Randomisation: computer generated, concealed with opaque envelopes. Blinding: single. Intention-to-treat: possible. Interim analysis: none. Exclusions from analysis: 3/101 (in study). Follow-up period: end of treatment.
Participants	Japan: 101 episodes in 98 adults with chemotherapy treated lung cancer, leukopenia < 3000/mm^3 and fever (80% with neutropenia < 1000/mm^3). All participants with clinically or microbiologically documented infection.
Interventions	Imipenem 1 gr × 2 versus Moxalactam 2 gr × 2 + Tobramycin 90 mg × 2.
Outcomes	All cause mortality. Infection related mortality. Treatment failure.
Notes	Journal publication and author correspondence. Outcomes in subgroups. Documented infections: documented Gram-negative and*Pseudomonas* infections; severe neutropenia.

Risk of bias

Bias	Authors' judgement	Support for judgement

Matsui 1991 *(Continued)*

Random sequence generation (selection bias)	Low risk	A—Adequate.
Allocation concealment (selection bias)	Low risk	A—Adequate.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Only patient blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	3 episodes excluded from analysis.

Miller 1993

Methods	Randomisation: no information. Blinding: none. Intention-to-treat: no, modified ITT possible for failure. Interim analysis: none. Exclusions from analysis: 45/131 episodes. Follow-up period: end of treatment.
Participants	USA: 131 episodes in 106 adult patients with haematological or solid cancer from three hospitals, with neutropenia < 500/mm^3 and fever > 38° or a clinically or microbiologically documented source of infection.
Interventions	Imipenem 500 mg × 4 versus Ceftazidime 2 gr × 3 + Tobramycin 1-1.5 mg/kg × 3-4.
Outcomes	All cause mortality. Infection related mortality. Treatment failure: bacterial super-infections; adverse events.
Notes	Journal publication. Outcomes in subgroups. Documented infections: bacteraemia. Documented Gram-negative infections; severe neutropenia.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B—Unclear.
Allocation concealment (selection bias)	Unclear risk	B—Unclear.

Miller 1993 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	45 episodes excluded from analysis.

Morgan 1983

Methods	Randomisation: no information. Blinding: none. Intention-to-treat: no. Interim analysis: none. Exclusions from analysis: 3/50. Follow-up period: no information.
Participants	England: 50 episodes in 34 children < 15 years with malignancy. Neutropenia < 1000/mm^3 and fever.
Interventions	Ceftazidime 30 mg/kg × 3 versus Azlocillin 50 mg/kg × 3 + Tobramycin 2 mg/kg × 3.
Outcomes	All cause mortality. Infection related mortality. Treatment failure: dropouts after randomisation.
Notes	Journal publication. Outcomes in subgroups:*Pseudomonas* infections.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B — Unclear.
Allocation concealment (selection bias)	Unclear risk	B — Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias)	High risk	3 episodes excluded from analysis.

Morgan 1983 *(Continued)*

All outcomes

Norrby 1987

Methods	Randomisation: concealed by sealed envelopes (opaque not mentioned), stratified by centre. No information on allocation generation. Blinding: none. Intention-to-treat: yes. Interim analysis: none. Exclusions from analysis: none. Follow-up period: 7 days after treatment.
Participants	Europe+Canada, multicentre: 210 participants > 16 years with neutropenia < 1000/mm^3 and fever. Participants with high probability of death within 48 hours excluded.
Interventions	Imipenem 1 gr (or 125 mg/kg) × 4 versus Piperacillin 4 gr × 4 (or 75 mg/kg × 4-6) + Amikacin 5-7.5 mg/kg × 2-3.
Outcomes	All cause mortality. Infection related mortality. Treatment failure: bacterial and fungal super-infections; colonisation and resistant colonisation; adverse events.
Notes	Journal publication and author correspondence. Outcomes in subgroups. Documented infections: bacteraemia Documented Gram-negative and *Pseudomonas* infections; severe neutropenia.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B—Unclear.
Allocation concealment (selection bias)	Low risk	A—Adequate.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	Low risk	78 participants excluded from efficacy analysis in study, but ITT analysis also given.

Novakova 1990

Methods	Randomisation: computer-generated allocation with sealed envelope concealment (opaque not mentioned). Blinding: none. Intention-to-treat: possible. Interim analysis: none. Exclusions from analysis: 21/90 (in study). Follow-up period: no information.
Participants	Netherlands: 90 episodes in 83 adult patients > 15 years with neutropenia < 500/mm^3 and fever. All with underlying haematological malignancy.
Interventions	Ceftazidime 2 gr × 3 versus Piperacillin 4 gr × 4 + Amikacin 500 mg × 3.
Outcomes	All cause mortality. Infectionvrelated mortality. Treatment failure: bacterial and fungal super-infections; dropouts after randomisation.
Notes	Journal publication. Outcomes in subgroups: bacteraemia; haematological cancer patients. Participants nursed in reverse isolation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A—Adequate.
Allocation concealment (selection bias)	Low risk	A—Adequate.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	21 episodes excluded from analysis.

Novakova 1991

Methods	Randomisation: computer-generated, concealed by sealed envelopes (opaque not mentioned). Blinding: none. Intention-to-treat: possible. Interim analysis: none. Exclusions from analysis: 21/90 (in study). Follow-up period: no information.
Participants	Netherlands: 90 episodes in 82 adults > 15 years with neutropenia < 1000/mm^3, fever and signs of a local infection. All with underlying haematological malignancy or BMT.

Novakova 1991 *(Continued)*

Interventions	Ceftazidime 2 gr × 3 versus Ceftazidime 2 gr × 3 + Amikacin 500 mg × 3.
Outcomes	All cause mortality. Infection×related mortality. Treatment failure: bacterial and fungal super-infections; dropouts after randomisation.
Notes	Journal publication. Outcomes in subgroups. Documented infections: bacteraemia; haematological cancer patients. Participants nursed in reverse isolation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A—Adequate.
Allocation concealment (selection bias)	Low risk	A—Adequate.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	21 episodes excluded from analysis.

Ozyilkan 1999

Methods	Randomisation: central randomisation with random file number. Blinding: double. Intention-to-treat: yes. Interim analysis: none. Exclusions from analysis: none. Follow-up period: 12 months.
Participants	Turkey: 30 adult cancer patients with neutropenia < 1000/mm^3 and fever. 93% with underlying haematological malignancy.
Interventions	Imipenem 500 mg × 4 versus Cefoperazone-sulbactam 2 gr × 2 + Amikacin 7.5 mg/kg × 2.
Outcomes	All cause mortality. Infection related mortality. Treatment failure: bacterial and fungal super-infections; dropouts after randomisation.
Notes	Journal publication and author correspondence. Outcomes in subgroups.

Ozyilkan 1999 *(Continued)*

	Documented infections.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A—Adequate.
Allocation concealment (selection bias)	Low risk	A—Adequate.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis.

Papachristodoulou 96

Methods	Randomisation: no information. Blinding: none. Intention-to-treat: yes. Interim analysis: unknown (results obtain from conference proceeding). Exclusions from analysis: 0/85 episodes. Follow-up period: no information.
Participants	Greece: 85 episodes in 77 cancer patients with neutropenia <= 1000/mm^3 and fever >= 38°.
Interventions	Ceftazidime 6 gr/day versus Ceftazidime 6 gr/day + Amikacin 1 gr/day.
Outcomes	All cause mortality. Treatment failure.
Notes	Conference proceeding. No outcomes in subgroups.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B—Unclear.
Allocation concealment (selection bias)	Unclear risk	B—Unclear.

Papachristodoulou 96 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All episodes included in analysis.

Pegram 1984

Methods	Randomisation: no information. Blinding: none. Intention-to-treat: unknown. Interim analysis: yes. Exclusions from analysis: no information. Follow-up period: no information.
Participants	USA: 140 episodes in cancer patients. with neutropenia < 1000/mm^3 and fever.
Interventions	Moxalactam 4 gr × 3 versus Ticarcillin 50 mg/kg × 6 + Tobramycin 1.5 mg/kg × 3.
Outcomes	Treatment failure.
Notes	Conference proceeding. Outcomes in subgroups. Documented*Pseudomonas* infections.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	B—Unclear.
Allocation concealment (selection bias)	Unclear risk	B—Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	B—Unclear.

Pellegrin 1988

Methods	Randomisation: allocation by table of 20 numbers; no reference to concealment. Blinding: none. Intention-to-treat: no information. Interim analysis: none. Exclusions from analysis: no information (157 participants evaluated, the study does not refer to the number of randomly assigned participants). Follow-up period: no information.
Participants	France: 157 patients with acute leukaemia newly diagnosed or in first remission, with neutropenia < 500/mm^3 for 21 or more days, and fever. All participants > 16 years. BMT patients excluded.
Interventions	Ceftazidime 2 gr × 2 versus Cefotaxime 2 gr × 2 + Tobramycin 1 mg/kg × 2.
Outcomes	Treatment failure: bacterial and fungal super-infections.
Notes	Journal publication: French language. Outcomes in subgroups Documented infections: bacteraemia; haematological cancer patients. Documented Gram-negative infections. Participants treated in a protected environment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A—Adequate.
Allocation concealment (selection bias)	Unclear risk	B—Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	B—Unclear.

Pereira 2009

Methods	Randomisation: allocation by number list, no reference to concealment. Blinding: none. Intention-to-treat: no. Interim analysis: no.

Pereira 2009 *(Continued)*

	Exclusion from analysis: 5/130 episodes. Follow-up period: not described.
Participants	Brazil: 130 episodes in 57 patients with haematological malignancy all ≤ 18 years. Neutropenia < 500 cells/mm^3 or between 500 and 1000 cells/mm^3 before the nadir of chemotherapy and fever with axillary temperature > 38.0° C or 3 measurements between 37.5° C and 38.0° C.
Interventions	Cefepime 50 mg/kg × 3 versus Ceftriaxone 50 mg/kg × 2 + Amikacin 15 mg/kg × 1.
Outcomes	Treatment failure: infection related mortality; bacterial super-infection.
Notes	Journal publication. Outcome in subgroup: first episode of neutropenic fever. Added AMP-B after 5 days with continued neutropenic fever, vanco for CR-BSI, skin and pulmonary infections and hypotension.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation by number list.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	5 episodes excluded from analysis.

Perez 1995

Methods	Randomisation: allocation by balanced table, no reference to concealment. Blinding: none. Intention-to-treat: yes. Interim analysis: none. Exclusions from analysis: 0/60. Follow-up period: no information.
Participants	Chile: 60 episodes in 52 cancer patients > 16 years, of whom 88% had underlying haematological malignancy. Neutropenia < 500/mm^3 and fever.
Interventions	Imipenem 500 mg × 4 versus Ceftazidime 1-1.5 gr × 4 + Amikacin 7.5 mg/kg × 2.

Perez 1995 *(Continued)*

Outcomes	All cause mortality. Infection related mortality. Treatment failure: bacterial super-infections; dropouts after randomisation.
Notes	Journal publication, Spanish language. Outcomes in subgroups. Documented infections: bacteraemia. Documented Gram-negative infections.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A — Adequate.
Allocation concealment (selection bias)	Unclear risk	B — Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All episodes included in analysis.

Petrilli 2003

Methods	Randomisation: allocation by table of random numbers concealed by sealed opaque envelopes. Blinding: none. Intention-to-treat: no. Interim analysis: none. Exclusions from analysis: 2/138 episodes. Follow-up period: no information.
Participants	Brazil: 138 episodes in 70 children or adolescents with leukaemia or grade III-IV lymphoma, neutropenia < 500/mm^3 (or < 1000/mm^3 expected to decline) and fever.
Interventions	Ticarcillin-clavulanic acid 62.5 mg/kg × 4 versus Ceftriaxone 100 mg/kg × 1 + Amikacin 7.5 mg/kg × 2,
Outcomes	All cause mortality. Infection related mortality; Treatment failure: bacterial super-infections; adverse events; dropouts after randomisation.
Notes	Journal publication. Outcomes in subgroups.

Petrilli 2003 *(Continued)*

	Documented Gram-negative infections: haematological cancer patients; bacteraemia.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	A — Random number table.
Allocation concealment (selection bias)	Low risk	A — Sealed opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	2 episodes excluded from analysis.

Piccart 1984

Methods	Randomisation: no information. Blinding: none. Intention-to-treat: no. Interim analysis: none. Exclusions from analysis: 5/49. Follow-up period: no information.
Participants	Belgium: 154 cancer patients > 17 years randomly assigned, of which 49 patients with neutropenia < 1000/mm^3, and with fever > 38.5° are included in the review.
Interventions	Cefoperazone 6 gr × 2 versus Cefoperazone 2 gr × 2 + Amikacin 500 mg × 2.
Outcomes	All cause mortality (in bacteraemia only). Infection related mortality. Treatment failure: super-infections; dropouts after randomisation.
Notes	Journal publication. Outcomes in subgroups. Documented infections: Gram-negative and resistant Gram-negative infections; haematological cancer patients; severe neutropenia.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B — Unclear.

Piccart 1984 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	B—Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	5 participants excluded from analysis.

Pickard 1983

Methods	Randomisation: random number table supplied by sponsor, concealed by sealed envelopes (opaque not mentioned). Blinding: none. Intention-to-treat: possible for mortality. Interim analysis: 2. Exclusions from analysis: 5/80. Follow-up period: no information.
Participants	USA: 80 episodes in cancer patients > 18 years with neutropenia < 1000/mm^3 and fever.
Interventions	Moxalactam 2-4 gr × 3 versus Ticarcillin 3 gr × 4 + Tobramycin 1.66 mg/kg × 3.
Outcomes	All cause mortality. Treatment failure: bacterial super-infections; adverse events; dropouts after randomisation.
Notes	Author correspondence and conference proceedings. Outcomes in subgroups. Documented infections: documented Gram-negative and *Pseudomonas* infections. Study not by Intention-to-treat but permits re-analysis by Intention-to-treat. Participants nursed in reverse isolation.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A—Adequate.
Allocation concealment (selection bias)	Low risk	A—Adequate.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.

Pickard 1983 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	5 episodes excluded from analysis.

Piguet 1988

Methods	Randomisation: envelope selection (sealed or opaque not mentioned). Blinding: none. Intention-to-treat: no. Interim analysis: none. Exclusions from analysis: 5/174. Follow-up period: until resolution of neutropenia.
Participants	France, multicentre: 169 episodes evaluated in participants > 16 years with underlying haematological malignancy, neutropenia < 1000/mm^3 and fever. BMT patients excluded.
Interventions	Ceftazidime 2 gr × 3 versus Cefotaxime 2 gr × 3 + Amikacin 5 mg/kg × 3.
Outcomes	All cause mortality. Infection related mortality. Treatment failure.
Notes	Journal publication: French language. Outcomes in subgroups. Documented infections: haematological cancer patients.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B — Unclear.
Allocation concealment (selection bias)	Unclear risk	B — Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	5 episodes excluded from analysis.

Rodjer 1987

Methods	Randomisation: by envelope (sealed or opaque not mentioned). Blinding: none. Intention-to-treat: no. Interim analysis: none. Exclusions from analysis: 16/61 for failure; 3/61 for death. Follow-up period: no information.
Participants	Sweden: 61 febrile episodes in 52 immunocompromised cancer patients > 16 years. Neutropenia not part of inclusion criteria, but 70% of included patients were neutropenic < 1000/mm^3.
Interventions	Ceftazidime 1-2 gr × 2-3 versus Cefuroxime 1.5 gr × 2-3 + Tobramycin 1.5 mg/kg × 2-3.
Outcomes	All cause mortality. Treatment failure: bacterial and fungal super-infections.
Notes	Journal publication. Outcomes in subgroups. Documented infections: bacteraemia. Documented Gram-negative and *Pseudomonas* infections.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B — Unclear.
Allocation concealment (selection bias)	Unclear risk	B — Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	3 episodes excluded from analysis.

Rodriguez 1995

Methods	Randomisation: table of random numbers, concealment not specified. Blinding: none. Intention-to-treat: no. Interim analysis: none. Exclusions from analysis: 14/150 participants. Follow-up period: no information.

Rodriguez 1995 *(Continued)*

Participants	Peru: 136 participants > 15 years evaluated, with solid cancer or non-Hodgkin lymphoma, neutropenia < 1000/mm^3 expected to last less than 10 days and fever or suspected infection using specific criteria.
Interventions	Cefotaxime 1 gr × 3 versus Cephalotin 1gr × 4 + Gentamicin 4 mg/kg × 1.
Outcomes	Infection related mortality. Treatment failure.
Notes	Journal publication. Outcomes in subgroups. Documented infections: bacteraemia; *Pseudomonas* infections; severe neutropenia.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A—Table of random numbers.
Allocation concealment (selection bias)	Unclear risk	B—Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	14 participants excluded from analysis.

Rolston 1992

Methods	Randomisation: computer-generated sequence of numbers. Blinding: single (outcome assessor). Intention-to-treat: no. Interim analysis: none. Exclusions from analysis: 158/908. Follow-up period: median 8-9 days.
Participants	USA: 750 episodes in 567 participants > 16 years in 4 arms. 67% underlying haematological malignancy. Neutropenia < 1000/mm^3 and fever or documented infection.
Interventions	Ceftazidime 1 gr × 6 versus Ceftazidime 1 gr × 6 + Amikacin and Imipenem 12.5 mg/kg × 4 versus Imipenem 12.5 mg/kg × 4 + Amikacin. Amikacin given continuously 800 mg/m^2 per day after 200 mg/m^2 loading dose.
Outcomes	Treatment failure: bacterial and fungal super-infections; adverse events.
Notes	Journal publication. Outcomes in subgroups.

Rolston 1992 *(Continued)*

	Documented infections. Documented Gram-negative, resistant Gram-negative and *Pseudomonas* infections; severe neutropenia.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A—Adequate.
Allocation concealment (selection bias)	Unclear risk	B—Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	158 episodes excluded from analysis.

Schuchter 1988

Methods	Randomisation: no information. Blinding: double-blind. Intention-to-treat: unknown (assumed yes). Interim analysis: unknown. Exclusions from analysis: no information. Follow-up period: no information.
Participants	USA: 133 patients following bone marrow transplantation between 2 and 57 years (median, 27 years) with neutropenia < 500/mm^3 and fever > 38.5° once or > 38° more than once during 24 hours..
Interventions	Ceftazidime 50 mg/kg or 2 gr × 3 versus Ticarcillin 45 mg/kg × 6 + Gentamicin 2 mg/kg × 4.
Outcomes	Treatment failure: bacterial and fungal super-infections.
Notes	Conference proceeding. Outcomes in subgroups. Documented infections: haematological cancer patients.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B—Unclear.

Schuchter 1988 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	B—Unclear.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	B—Unclear.

Smith 1990

Methods	Randomisation: no information. Blinding: none. Intention-to-treat: unknown. Interim analysis: none. Exclusions from analysis: no information. Follow-up period: 7 days.
Participants	UK: 100 episodes in 63 children < 16 years old. Neutropenia < 500/mm^3 and fever > 39°.
Interventions	Ceftriaxone 50 mg/kg × 1 versus Azlocillin 75 mg/kg × 3 + Netilmicin 2.5 mg/kg × 3.
Outcomes	All cause mortality. Infection related mortality. Treatment failure.
Notes	Journal publication. No outcomes in subgroups.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B—Unclear.
Allocation concealment (selection bias)	Unclear risk	B—Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.

Smith 1990 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All episodes included in analysis.

Tamura 2002

Methods	Randomisation: table of random numbers concealed with sealed opaque envelopes. Blinding: none. Intention-to-treat: yes for mortality and possible for failure Interim analysis: yes, number not specified, trial stopped when the interim analysis demonstrated that the number of participants was sufficient for analysis. Exclusions from analysis: 12/206 participants for failure. Follow-up period: 30 days.
Participants	Japan, multicentre: 206 adult cancer patients with neutropenia < 1000/mm^3 and fever >= 37.5°. Nearly all patients with haematological cancer.
Interventions	Cefepime 1-2 gr × 2 versus Cefepime 1-2 gr × 2 + Amikacin (28 participants) or Isepamicin (36 participants) or Tobramycin or Netilmicin (12 participants).
Outcomes	All cause mortality. Treatment failure: adverse events; dropouts after randomisation.
Notes	Journal publication and author correspondence. Outcomes in subgroups. Documented infections. An additional arm of carbapenem monotherapy is not included in this review.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A—Adequate.
Allocation concealment (selection bias)	Low risk	A—Adequate.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	12 participants excluded from analysis.

Tamura 2004

Methods	Randomisation: computer-generated, central. Blinding: none. Intention-to-treat: no. Interim analysis: no information. Exclusions from analysis: 12/201 participants. Follow-up period: 30 days.
Participants	Japan, multicentre: 201 haematological cancer patients with neutropenia < 1000/mm^3 and fever >= 37.5°.
Interventions	cefepime 1-2 gr × 2 versus Cefepime 1-2 gr × 2 + Amikacin 100-200 mg × 2.
Outcomes	All cause mortality. Infection related mortality. Treatment failure: adverse events; dropouts after randomisation.
Notes	Journal publication. Outcomes in subgroups: haematological malignancy; bacteraemia.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A — Computer generated.
Allocation concealment (selection bias)	Low risk	A — Central.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	12 participants excluded from analysis.

Wade 1987

Methods	Randomisation: no information. Blinding: double. Intention-to-treat: unknown. Interim analysis: none. Exclusions from analysis: no information. Follow-up period: no information.
Participants	USA: 460 evaluable episodes in cancer patients with neutropenia < 500/mm^3 and fever > 38°.
Interventions	Imipenem 4 gr/qd versus Piperacillin 300 mg/kg/qd + Amikacin 24 mg/kg/qd.

Wade 1987 *(Continued)*

Outcomes	Treatment failure.
Notes	Conference proceeding + review. Outcomes in subgroups. Documented infections. Documented Gram-negative and *Pseudomonas* infections.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B — Unclear.
Allocation concealment (selection bias)	Unclear risk	B — Unclear.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	B — Unclear.

Wrzesien-Kus 2001

Methods	Randomisation: coin toss performed after participants' recruitment into the trial. Blinding: none. Intention-to-treat: yes. Interim analysis: none. Exclusions from analysis: 0/40 participants. Follow-up period: no information.
Participants	Poland: 40 adults with cancer (haematological in 95%), neutropenia <= 1000/mm^3 and fever >= 38°.
Interventions	Cefepime 2 gr × 3 versus Cefepime 2 gr × 3 + Amikacin 500 mg × 2.
Outcomes	All cause mortality. Infection related mortality. Treatment failure.
Notes	Journal publication in Polish. No outcomes in subgroups.

Risk of bias

Bias	Authors' judgement	Support for judgement

Wrzesien-Kus 2001 *(Continued)*

Random sequence generation (selection bias)	Low risk	A—Coin toss.
Allocation concealment (selection bias)	Low risk	A—Performed after patient recruitment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis.

Yamamura 1997

Methods	Randomisation: computer-generated code, concealed by sealed, opaque envelopes. Blinding: none. Intention-to-treat: possible. Interim analysis: none. Exclusions from analysis: 11/111 (in study). Follow-up period: no information.
Participants	USA, multicentre: 111 cancer patients > 18 years. Neutropenia < 1000/mm^3 and fever > 38.5°.
Interventions	Cefepime 2 gr × 3 versus Piperacillin 3 gr × 6 + Gentamicin 1.5 mg/kg × 3.
Outcomes	Treatment failure: bacterial and fungal super-infections; adverse events; dropouts after randomisation.
Notes	Journal publication and author correspondence. Vancomycin addition after 72 hours permitted by protocol, not counted as failure (27 participants). Outcomes in subgroups. Documented infections: bacteraemia. Documented Gram-negative and *Pseudomonas* infections; haematological cancer patients.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A—Adequate.
Allocation concealment (selection bias)	Low risk	A—Adequate.
Blinding of participants and personnel (performance bias)	High risk	Open-label.

Yamamura 1997 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	12 participants excluded from analysis.

Yildirim 2008

Methods	Randomisation: computer-generated random number list. Blinding: open. Intention-to-treat: no. Interim analysis: no. Exclusions from analysis: 12/99 participants. Follow-up period: no information.
Participants	Turkey: 99 episodes in 99 participants with haematological malignancy all ≤ 16. Neutropenia < 500 or < 1000 and expected to decline and fever > 38.5° or 2 measurements > 38°.
Interventions	Imipenem/meropenem 20 mg/kg × 3; Piperacillin-tazobactam 80 mg/kg × 4 + Amikacin 7.5 mg/kg × 2.
Outcomes	Treatment failure: duration of fever; neutropenia; hospitalisation; mortality; need for additional antibiotics or antifungal drugs.
Notes	Journal publication. Added glycopeptide after 72 hours with persistent fever, added AMP-B after 5 days with continued fever and neutropenia. In participants with monotherapy added aminoglycoside after 72 hours with persistent fever. No outcomes in subgroups.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A — Computer-generated random number list.
Allocation concealment (selection bias)	Unclear risk	B — Unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.

Yildirim 2008 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	12 participants excluded from analysis.

Zengin 2011

Methods	Randomisation: no mention. Blinding: open, Intention-to-treat: no, Interim analysis: no. Exclusions from analysis: 7/79 episodes. Follow-up period: no information.
Participants	Turkey: 79 episodes in 43 participants with haematological malignancy all ≤ 19 years. Neutropenia ≤ 500 or ≤ 1000 with decrease to ≤ 500 within 48 hours and fever ≥ 38.5° once or ≥ 8° for longer than 1 hour.
Interventions	Piperacillin-tazobactam 90 mg/kg × 4; Piperacillin-tazobactam 90 mg/kg × 4 + Amikacin 15 mg/kg × 1.
Outcomes	Treatment failure.
Notes	Journal publication. Added teicoplanin after 96 hours with persistent fever, added AMP-B or LipAMP-B or fluconazole after 120 hours with persistent neutropenia and fever. Subgroup analyses: episodes with and without catheter; high-dose cytosine arabinocide in the previous chemotherapy.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No random sequence — participants randomly assigned by presentation.
Allocation concealment (selection bias)	High risk	No concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	7 episodes excluded from analysis.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Berezin 2003	Retrospective comparative study comparing cefepime monotherapy versus ceftriaxone combined with gentamicin or amikacin.
Bodey 1976	The randomisation to beta-lactam versus beta-lactam + aminoglycoside was semi-empirical, after pathogen identification. Empirically the participants all received carbenicillin and cephalotin. Following pathogen isolation, participants with *Pseudomonas* sp. or *Proteus mirabilis* infection (analysed together) were randomly assigned to carbenicillin monotherapy versus carbenicillin-gentamicin combination therapy, and those with other Gram-negative infections were randomly assigned to cephalotin versus cephalotin with gentamicin.
Bru 1986	Study randomly assigned participants to ticarcillin-clavulanate versus ticarcillin-clavulanate + amikacin; however, several problems preclude its inclusion: Participants following bone marrow transplantation were allocated to combination therapy only, over-riding the random allocation; only the number of evaluated episodes is reported, numbers of randomly assigned participants/episodes unknown; number of episodes described in results is larger than the number of evaluable episodes; most results are reported as percentages and the denominator is unknown.
Cetto 1983	Participants with haematological malignancies were randomly assigned to receive cefuroxime or tobramycin plus ampicillin. However, all neutropenic participants also received carbenicillin with both regimens.
D'Antonio 1992	Study included non-neutropenic, haematological cancer patients with altered immune defences.
Drusano 1985	Study includes monotherapy and combination treatment groups compatible with the protocol, but randomisation was not performed between these groups. Non-neutropenic cancer patients received empirically beta-lactam monotherapy, while neutropenic cancer patients were randomly assigned to double beta-lactam combination therapy versus beta-lactam-aminoglycoside combination therapy.
EORTC 1987	Randomisation to monotherapy versus beta-lactam-aminoglycoside combination therapy semi-empirical. Empirically all participants received beta-lactam-aminoglycoside combination therapy. After 3 days, participants were randomly assigned to continue the combination, or to discontinue the aminoglycoside (beta-lactam monotherapy).
Fainstein 1983	Randomized study comparing ceftazidime versus ceftazidime + tobramycin. The study randomly assigned 321 episodes in 253 cancer patients with or without neutropenia. A subgroup of participants with neutropenia and documented infection were analysed separately. The number of neutropenic participants per group is not known, only the denominator for the subgroup of participants with neutropenia and documented infections is given. The outcome assessed in the subgroup is failure but does not include the non–infection related deaths. Author contacted without response.
Hauer 1990	Non-randomised controlled clinical trial.
Hazel 1998	Randomised trial presented as a conference proceeding comparing piperacillin-tazobactam + tobramycin versus imipenem + tobramycin for participants with febrile neutropenia, colonised with ESBL+ Enterobactericeae.
Hoepelman 1988	Study includes data on neutropenic and non-neutropenic participants combined. Data on neutropenic participants are not separated.
Karthaus 1998	Study not randomised: prospective observational design.
Moreno-Sanchez 1992	Randomized trial comparing imipenem versus ceftazidime + amikacin presented in conference. The abstract states that the study is in progress, but no further publications were identified. Results

Study	Reason for exclusion
	in abstract are given for 31 participants, but the number of dropouts is unknown; only evaluable participants are discussed. Author contacted without response.
Moroni 1987	Incompatible comparator regimens: ceftazidime + amikacin versus ceftazidime + vancomycin.
Pegram 1989	Randomisation to monotherapy versus beta-lactam-aminoglycoside combination therapy semi-empirical. Empirically all participants were treated with combination therapy. At 4 days, participants were randomly assigned to continue the combination, or to discontinue the aminoglycoside (beta-lactam monotherapy).
Petrilli 1991	Non-randomised study describing treatment with imipenem and ceftriaxone monotherapy for high-risk and low-risk febrile neutropenic children, respectively.
Pizzo 1986	Randomised trial comparing ceftazidime monotherapy versus double beta-lactam-aminoglycoside combination therapy.
Reilly 1983	Study not randomised: patient groups were studied sequentially.
Sampi 1987	Study compares two combination regimens: cefmenoxime + amikacin versus piperacillin + amikacin.
Sanz 2005	Study not randomised: prospective observational matched cohort study comparing imipenem monotherapy versus piperacillin-tazobactam + amikacin for febrile neutropenia.
Sawae 1996	Study randomly assigned participants to imipenem monotherapy or combination therapy. The combination arm included several different combinations (beta-lactam-aminoglycoside combinations, beta-lactam-beta-lactam combinations and other combinations), but the decision as to which combination therapy the patient received was left to the physician's decision. (Personal communication with author.)
Wrzesien-Kus 2000	Comparison between cefepime and ceftazidime, both combined with amikacin.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Li 1998

Methods	No information
Participants	Febrile neutropenia
Interventions	Ceftazidime and netilmicin
Outcomes	No information
Notes	

Characteristics of ongoing studies *[ordered by study ID]*

Bilgir 2005

Trial name or title	The comparison of imipenem with piperacillin/tazobactam and amikacin combination in participants with haematological malignancies in the treatment of febrile neutropenia.

Bilgir 2005 *(Continued)*

Methods	
Participants	Turkey: 40 participants with haematological malignancies.
Interventions	Imipenem versus piperacillin-tazobactam + amikacin.
Outcomes	Treatment failure and adverse events reported only as percentages, without a denominator per group.
Starting date	Unknown. Results presented in EHA 2005.
Contact information	Dr. O. Bilgir, Okmeydani Hastanesi, Izmir, Turkey.
Notes	Author's address unknown.

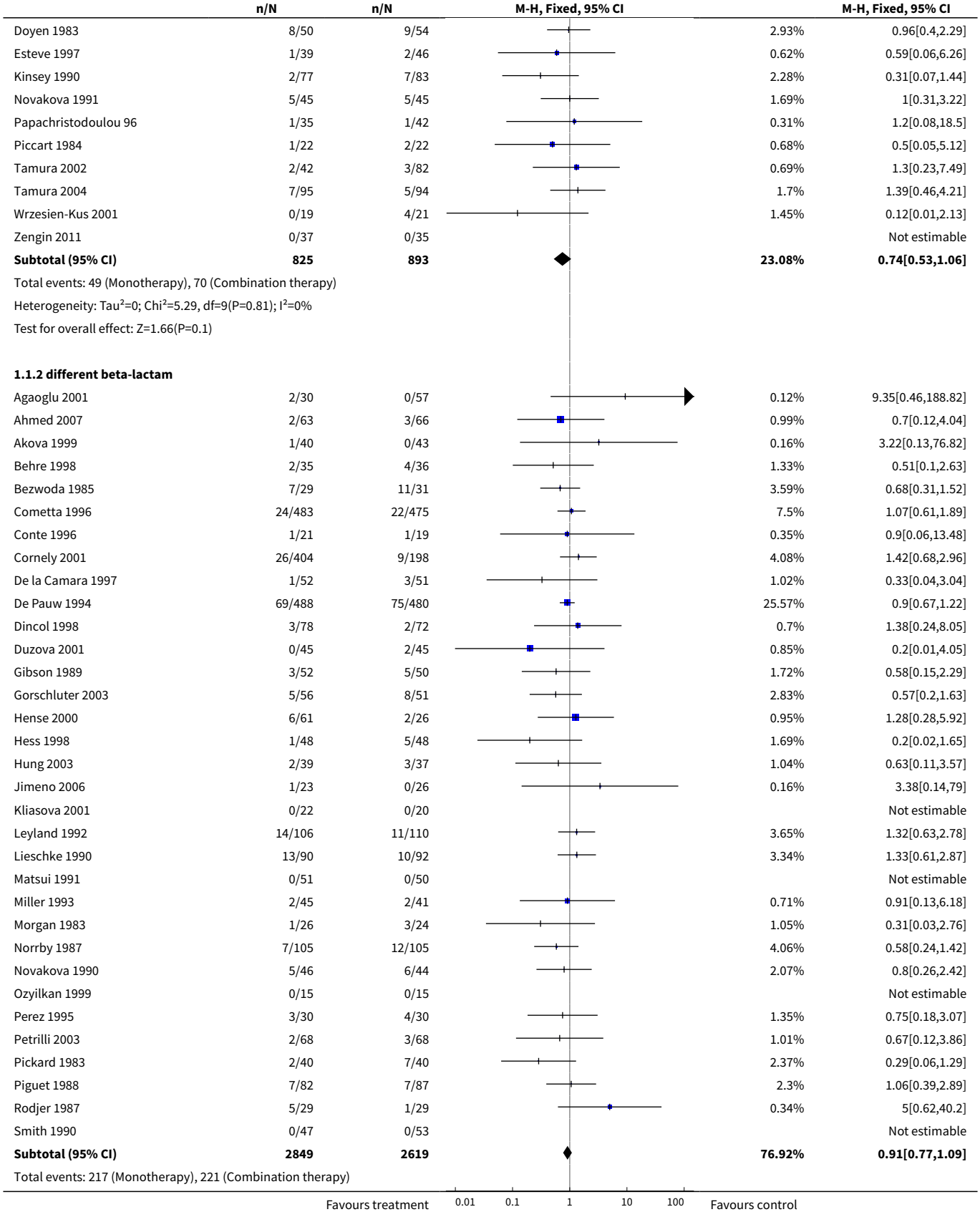
DATA AND ANALYSES

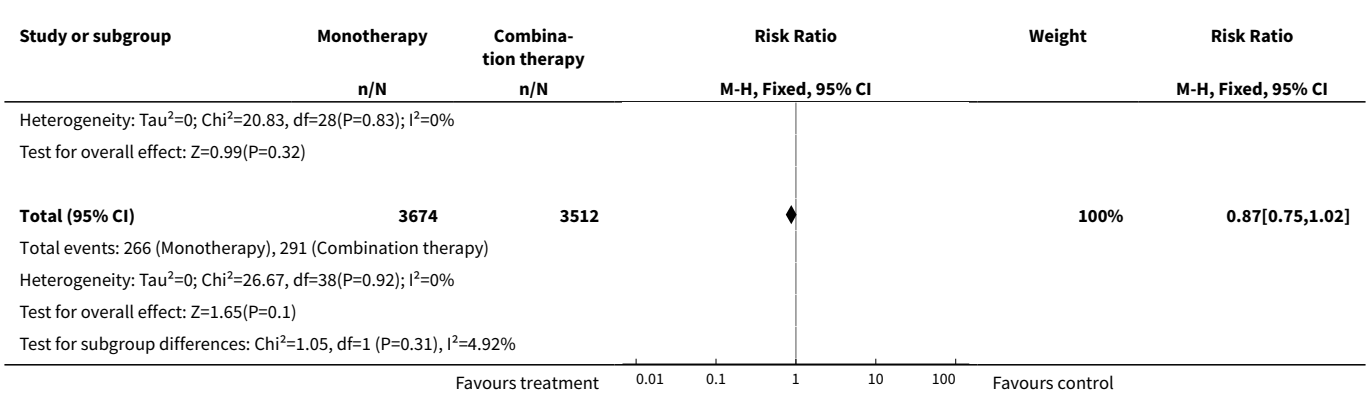
Comparison 1. Overall effectiveness

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All cause mortality	44	7186	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.75, 1.02]
1.1 same beta-lactam	11	1718	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.53, 1.06]
1.2 different beta-lactam	33	5468	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.77, 1.09]
2 Infection-related mortality	41	6872	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.64, 0.99]
2.1 same beta-lactam	8	1403	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.43, 1.10]
2.2 different beta-lactam	33	5469	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.65, 1.06]
3 Treatment failure	71		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 same beta-lactam	16	2833	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [1.02, 1.20]
3.2 different beta-lactam	55	7736	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.88, 0.97]

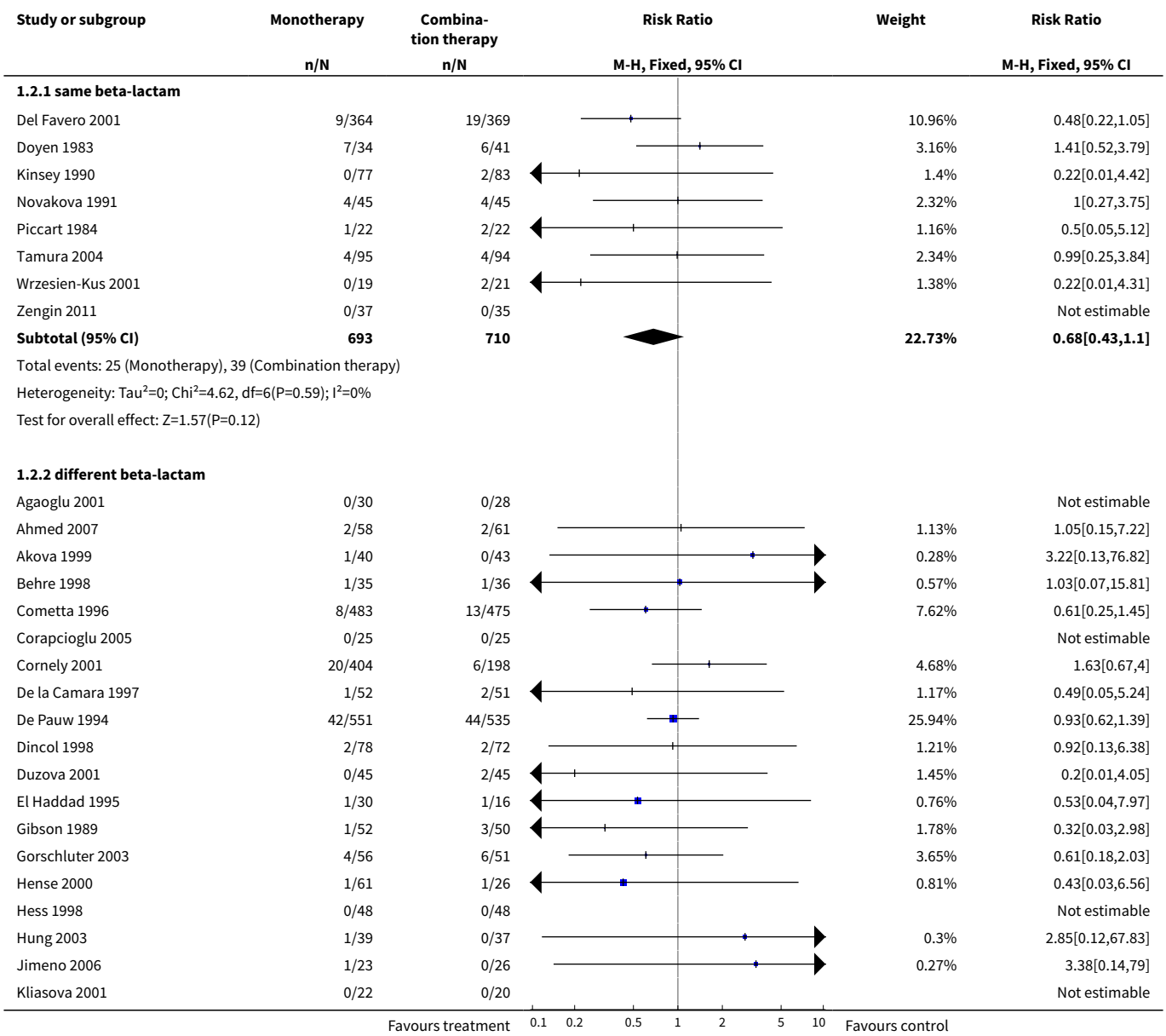
Analysis 1.1. Comparison 1 Overall effectiveness, Outcome 1 All cause mortality.

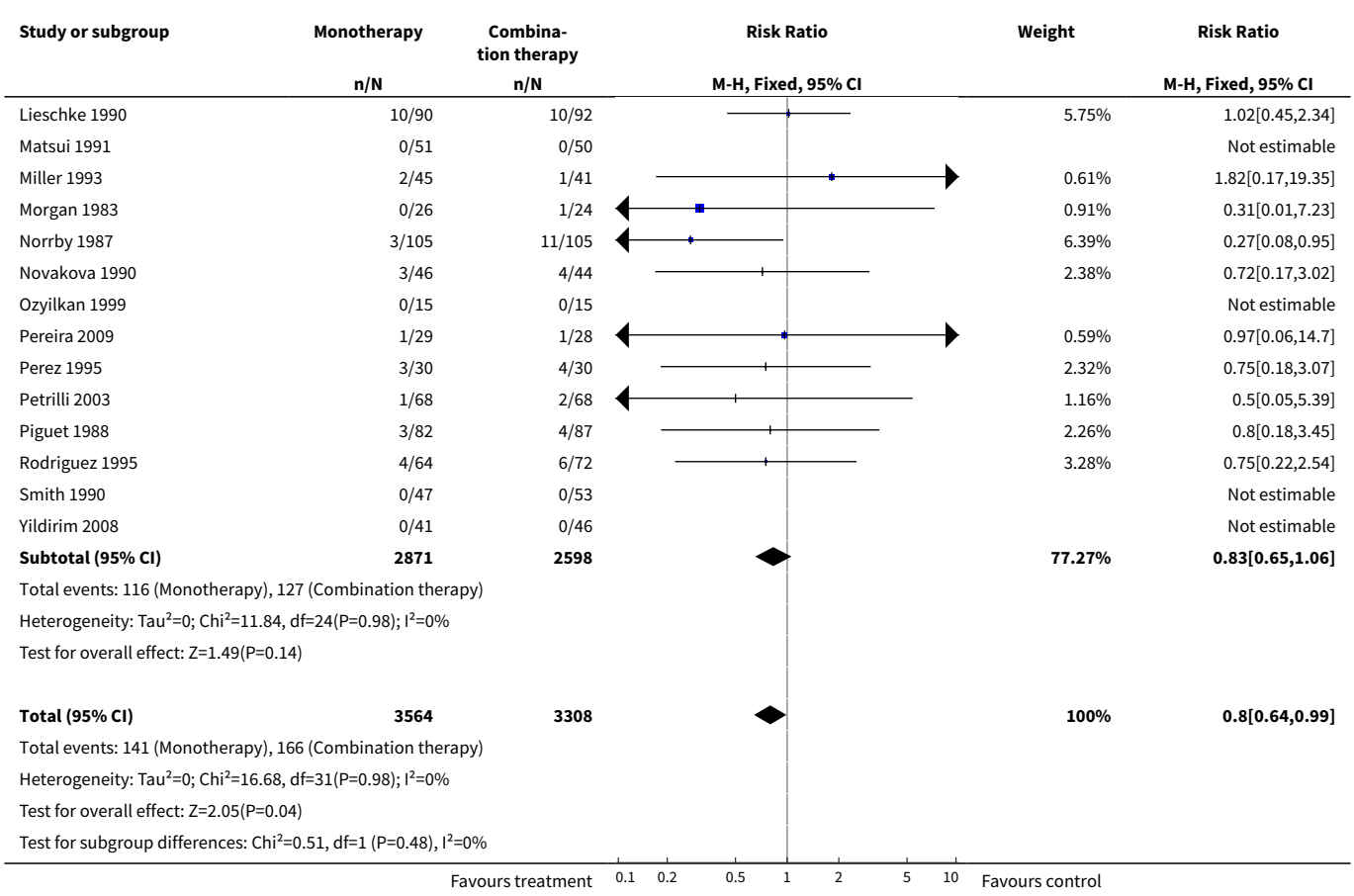
Study or subgroup	Monotherapy n/N	Combination therapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 same beta-lactam					
Del Favero 2001	22/364	32/369		10.74%	0.7[0.41,1.18]



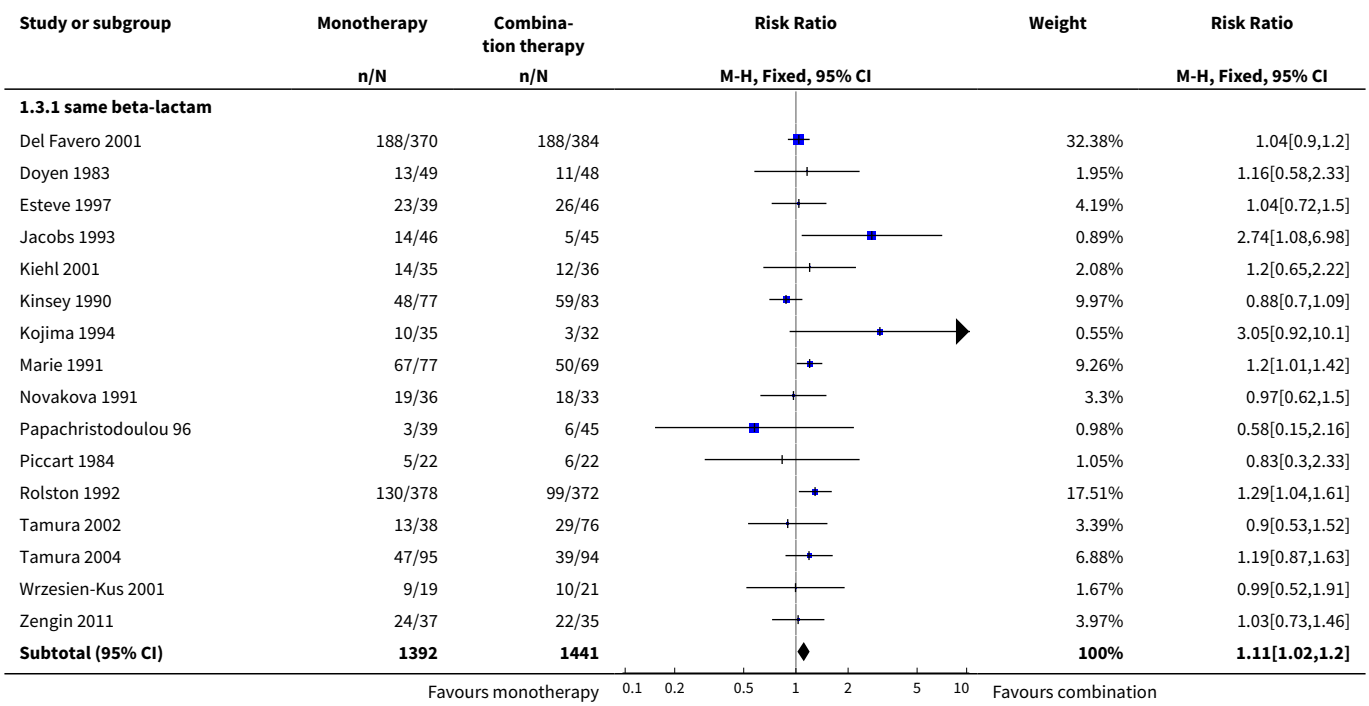


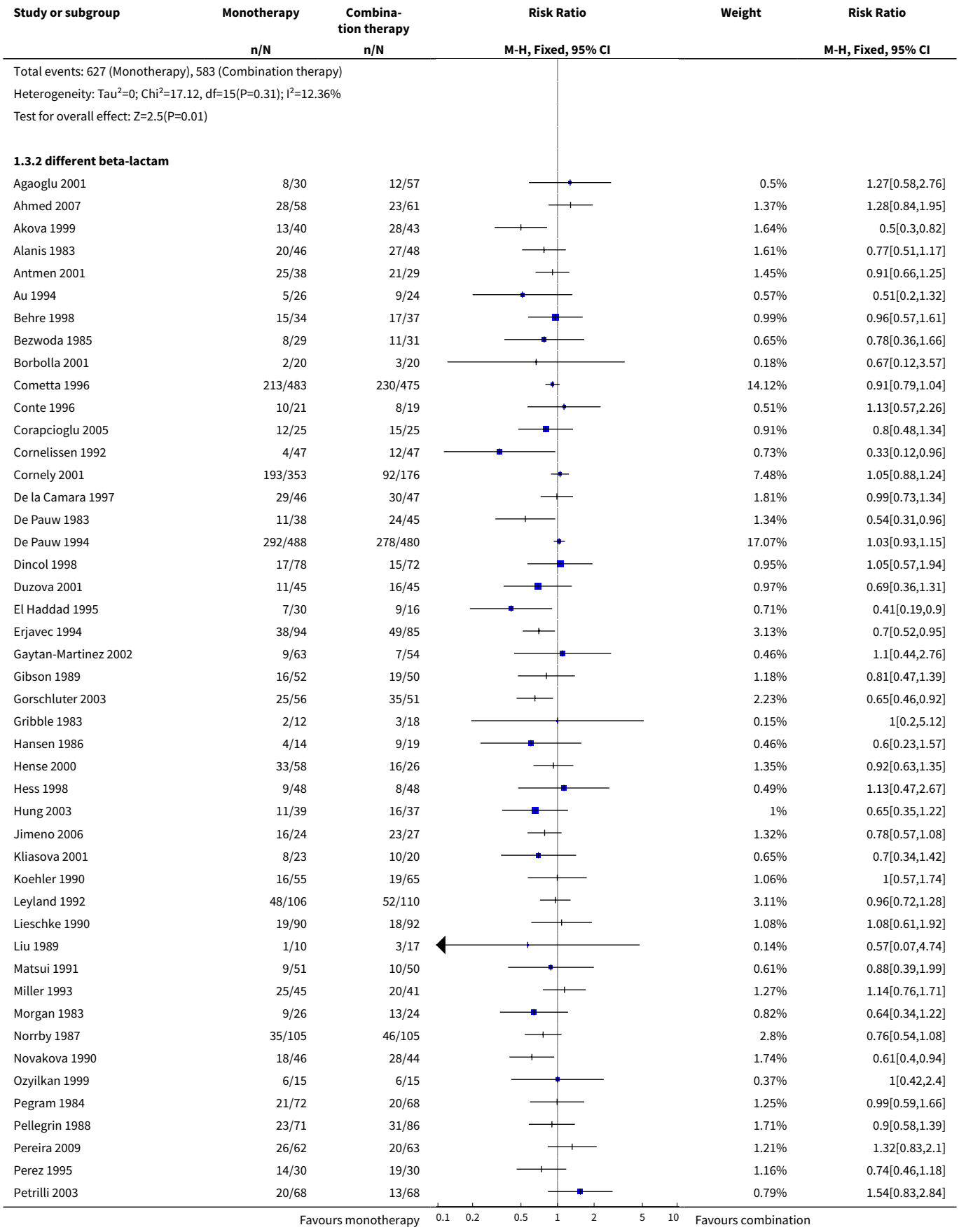
Analysis 1.2. Comparison 1 Overall effectiveness, Outcome 2 Infection-related mortality.

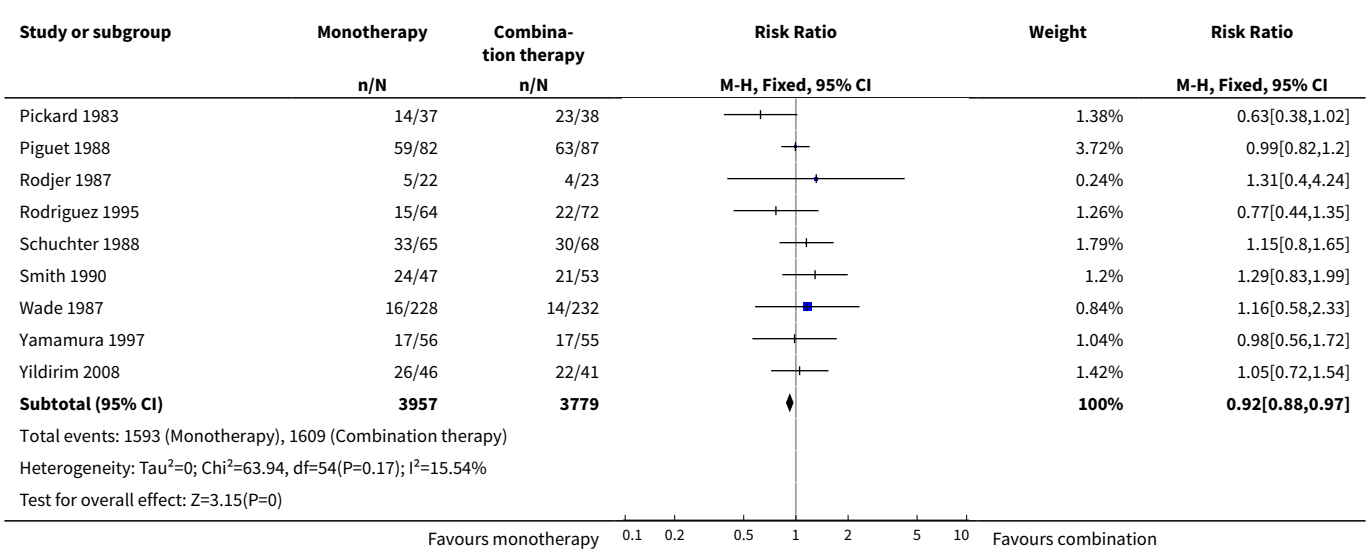




Analysis 1.3. Comparison 1 Overall effectiveness, Outcome 3 Treatment failure.



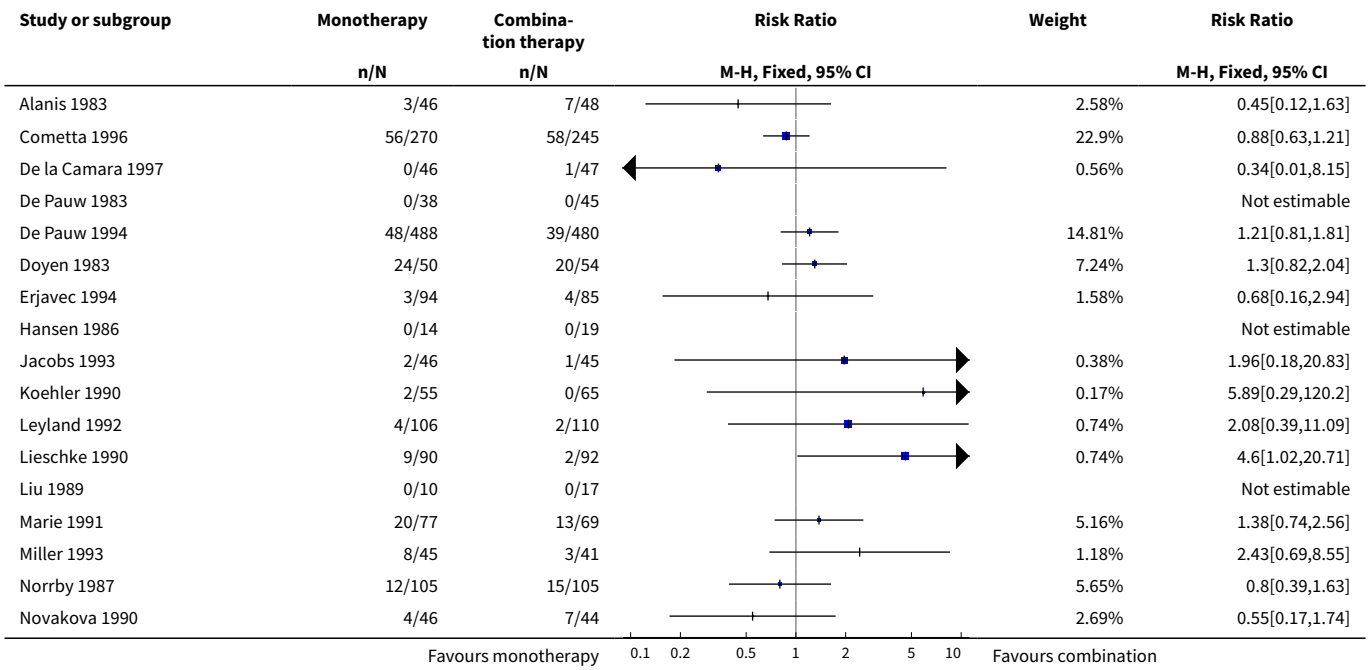


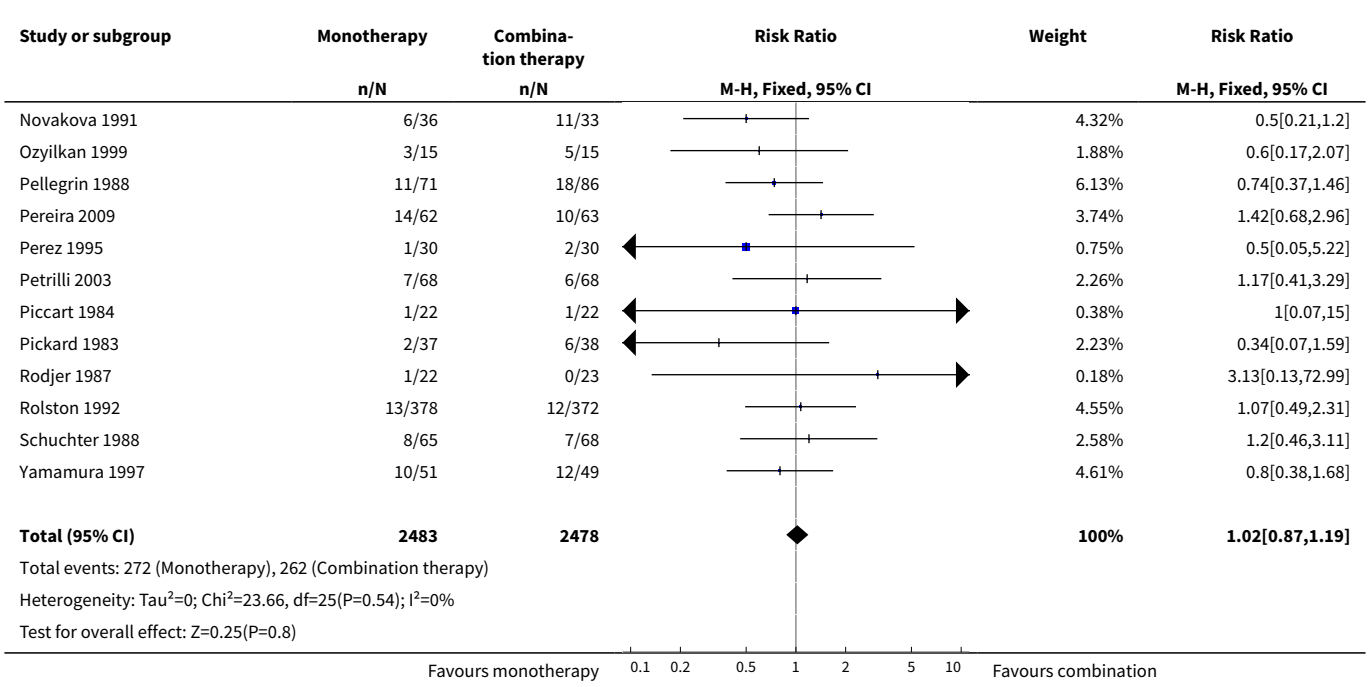


Comparison 2. Superinfections

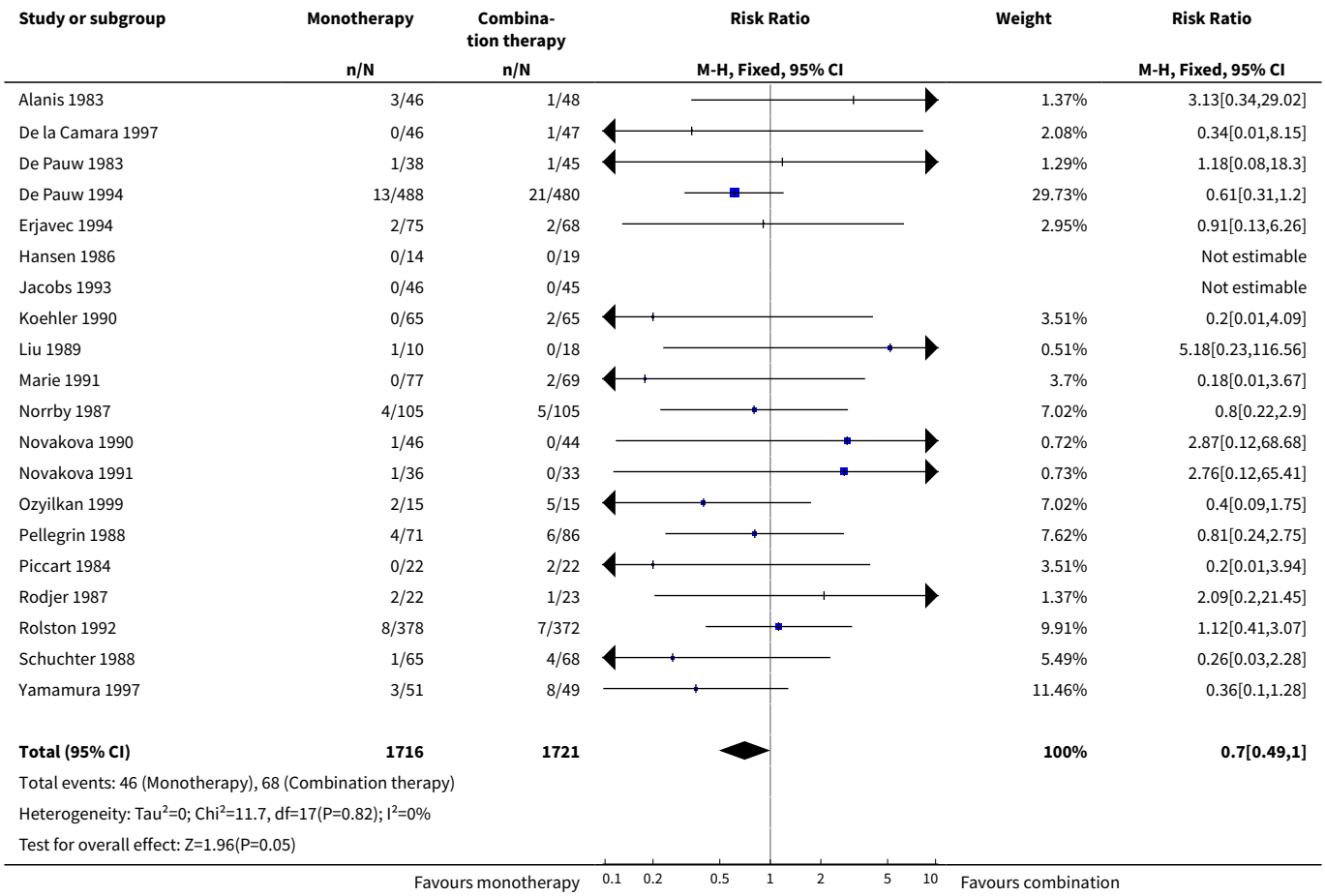
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Bacterial superinfections	29	4961	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.87, 1.19]
2 Fungal superinfections	20	3437	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.49, 1.00]

Analysis 2.1. Comparison 2 Superinfections, Outcome 1 Bacterial superinfections.





Analysis 2.2. Comparison 2 Superinfections, Outcome 2 Fungal superinfections.

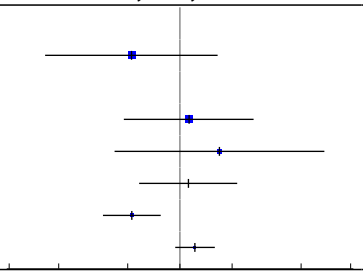


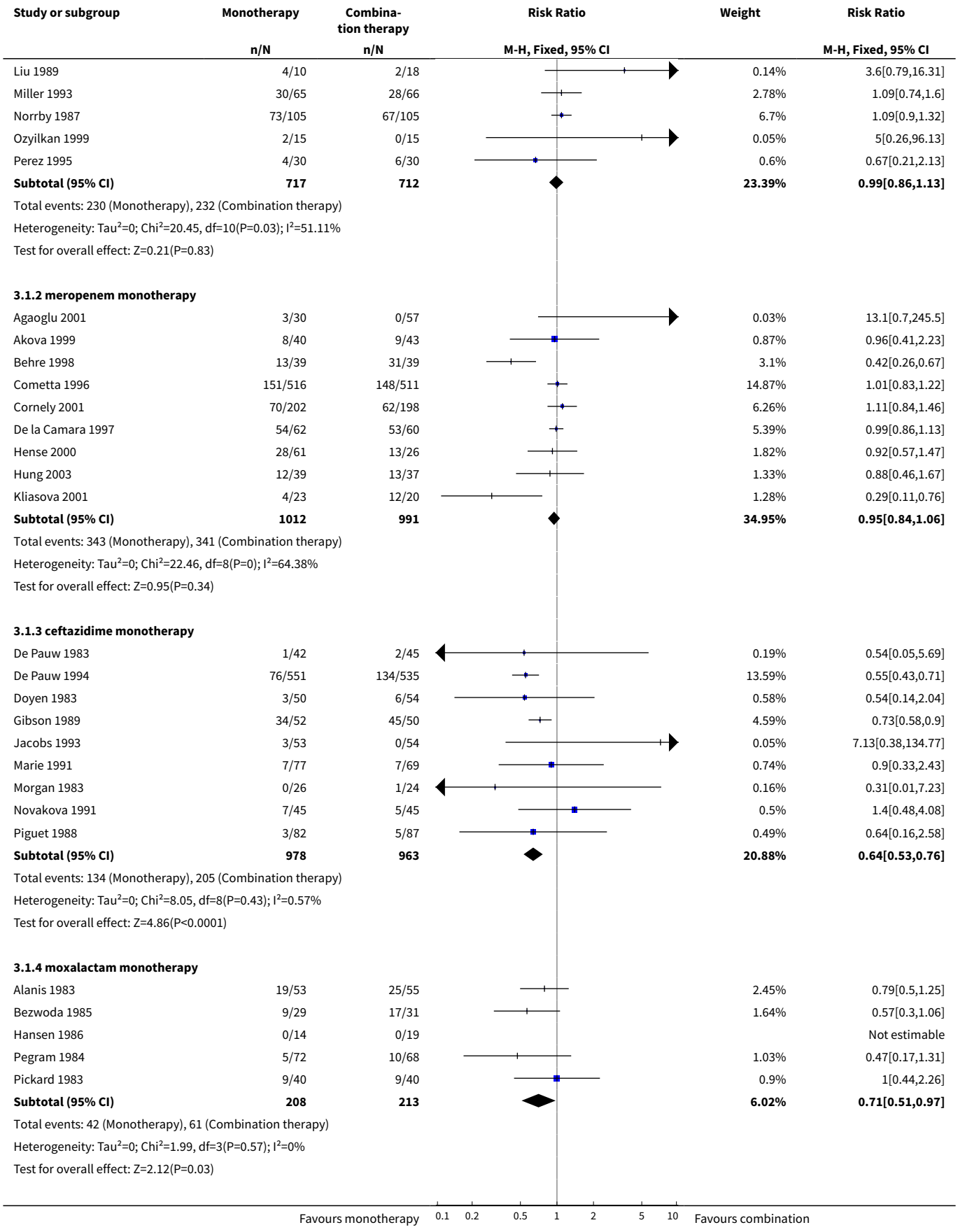
Comparison 3. Adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any adverse event (monotherapy)	49	7412	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.81, 0.94]
1.1 imipenem monotherapy	12	1429	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.86, 1.13]
1.2 meropenem monotherapy	9	2003	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.84, 1.06]
1.3 ceftazidime monotherapy	9	1941	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.53, 0.76]
1.4 moxalactam monotherapy	5	421	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.51, 0.97]
1.5 cefepime monotherapy	8	1079	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.75, 1.17]
1.6 other monotherapy	7	539	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.61, 1.44]
2 Discontinuation due to adverse event	16	4051	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.40, 0.93]
3 Any nephrotoxicity - Ag dosing regimen	39	6608	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.35, 0.57]
3.1 Once daily	8	1707	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.15, 0.63]
3.2 Multiple daily	31	4901	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.36, 0.61]
4 Severe nephrotoxicity - Ag dosing regimen	20	4199	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.05, 0.49]
4.1 Once daily	6	1526	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.03, 1.14]
4.2 Multiple daily	14	2673	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.03, 0.60]

Analysis 3.1. Comparison 3 Adverse events, Outcome 1 Any adverse event (monotherapy).

Study or subgroup	Monotherapy n/N	Combination therapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 imipenem monotherapy					
Ahmed 2007	4/58	8/61		0.78%	0.53[0.17,1.65]
Au 1994	0/26	0/24			Not estimable
Cornelissen 1992	9/47	8/47		0.8%	1.13[0.47,2.66]
Dincol 1998	5/71	3/72		0.3%	1.69[0.42,6.81]
Kojima 1994	13/36	11/34		1.13%	1.12[0.58,2.14]
Leyland 1992	31/164	53/148		5.57%	0.53[0.36,0.77]
Lieschke 1990	55/90	46/92		4.55%	1.22[0.94,1.59]





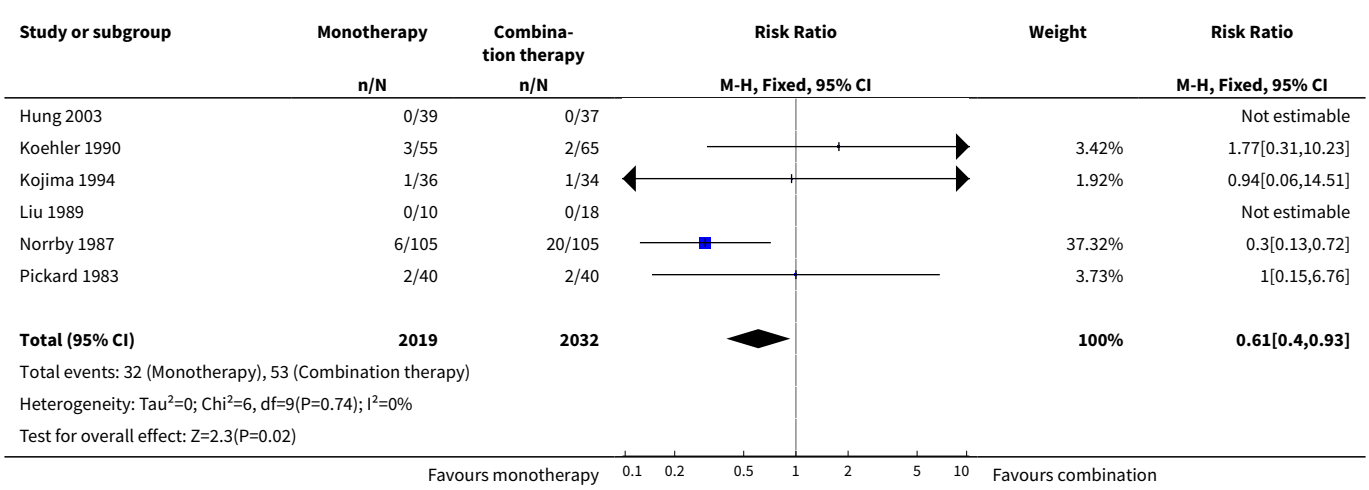
Study or subgroup	Monotherapy n/N	Combination therapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.5 cefepime monotherapy					
Tamura 2002	11/38	12/76		0.8%	1.83[0.89,3.76]
Corapcioglu 2005	0/25	1/25		0.15%	0.33[0.01,7.81]
Cornely 2001	53/202	62/198		6.26%	0.84[0.61,1.14]
Jimeno 2006	2/24	5/27		0.47%	0.45[0.1,2.11]
Tamura 2004	5/95	4/94		0.4%	1.24[0.34,4.46]
Wrzesien-Kus 2001	0/19	0/20			Not estimable
Yamamura 1997	12/56	23/55		2.32%	0.51[0.28,0.92]
Pereira 2009	21/62	11/63		1.09%	1.94[1.02,3.68]
Subtotal (95% CI)	**521**	**558**		**11.49%**	**0.94[0.75,1.17]**
Total events: 104 (Monotherapy), 118 (Combination therapy)					
Heterogeneity: Tau^2=0; Chi^2=14.28, df=6(P=0.03); I^2=58%					
Test for overall effect: Z=0.56(P=0.58)					
3.1.6 other monotherapy					
Conte 1996	1/21	4/19		0.42%	0.23[0.03,1.85]
El Haddad 1995	0/30	0/16			Not estimable
Hess 1998	17/48	15/48		1.5%	1.13[0.64,2]
Petrilli 2003	11/68	10/68		1%	1.1[0.5,2.42]
Piccart 1984	0/25	0/24			Not estimable
Smith 1990	1/47	2/53		0.19%	0.56[0.05,6.02]
Zengin 2011	0/37	1/35		0.15%	0.32[0.01,7.5]
Subtotal (95% CI)	**276**	**263**		**3.26%**	**0.93[0.61,1.44]**
Total events: 30 (Monotherapy), 32 (Combination therapy)					
Heterogeneity: Tau^2=0; Chi^2=2.98, df=4(P=0.56); I^2=0%					
Test for overall effect: Z=0.3(P=0.76)					
Total (95% CI)	**3712**	**3700**		**100%**	**0.87[0.81,0.94]**
Total events: 883 (Monotherapy), 989 (Combination therapy)					
Heterogeneity: Tau^2=0; Chi^2=93.14, df=44(P<0.0001); I^2=52.76%					
Test for overall effect: Z=3.65(P=0)					
Test for subgroup differences: Chi^2=18.5, df=1 (P=0), I^2=72.98%					

Favours monotherapy — Favours combination

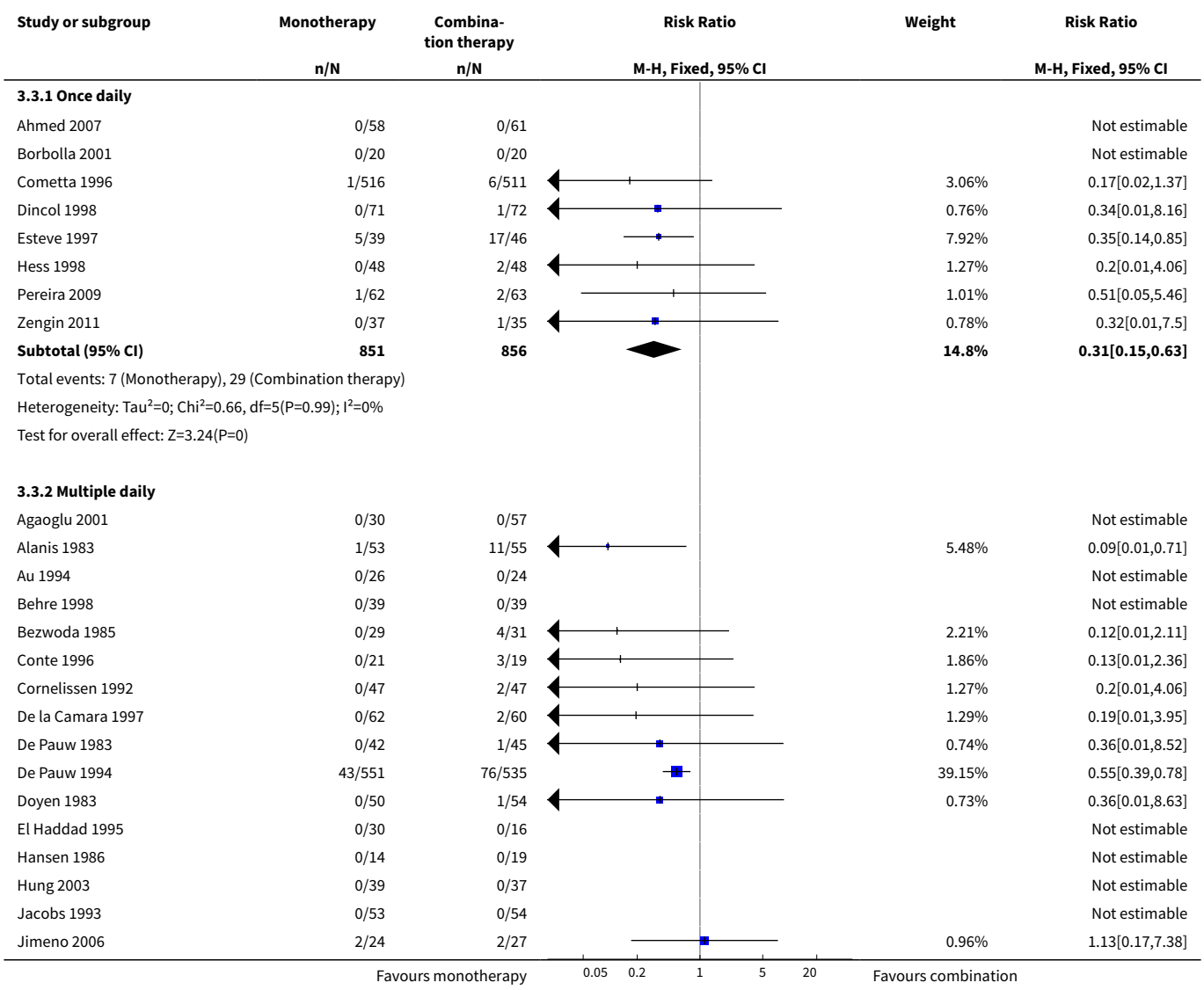
Analysis 3.2. Comparison 3 Adverse events, Outcome 2 Discontinuation due to adverse event.

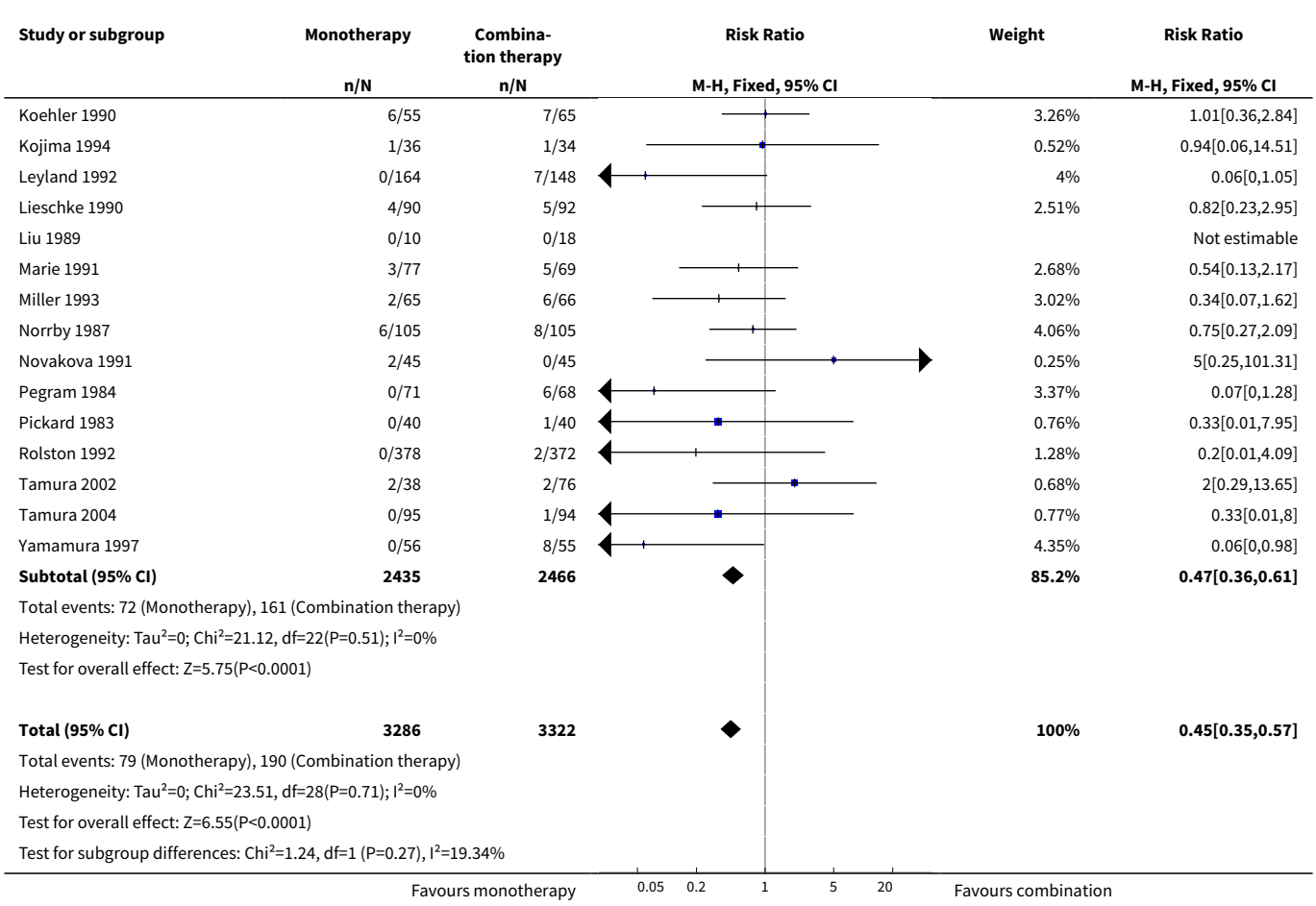
Study or subgroup	Monotherapy n/N	Combination therapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Agaoglu 2001	0/30	0/57			Not estimable
Borbolla 2001	0/20	0/20			Not estimable
Cometta 1996	3/516	5/511		9.37%	0.59[0.14,2.47]
De la Camara 1997	1/62	1/60		1.9%	0.97[0.06,15.12]
De Pauw 1983	0/42	0/45			Not estimable
De Pauw 1994	12/551	16/535		30.29%	0.73[0.35,1.52]
Del Favero 2001	2/364	5/369		9.27%	0.41[0.08,2.08]
Dincol 1998	1/71	1/72		1.85%	1.01[0.06,15.9]
El Haddad 1995	0/30	0/16			Not estimable
Hess 1998	1/48	0/48		0.93%	3[0.13,71.85]

Favours monotherapy — Favours combination

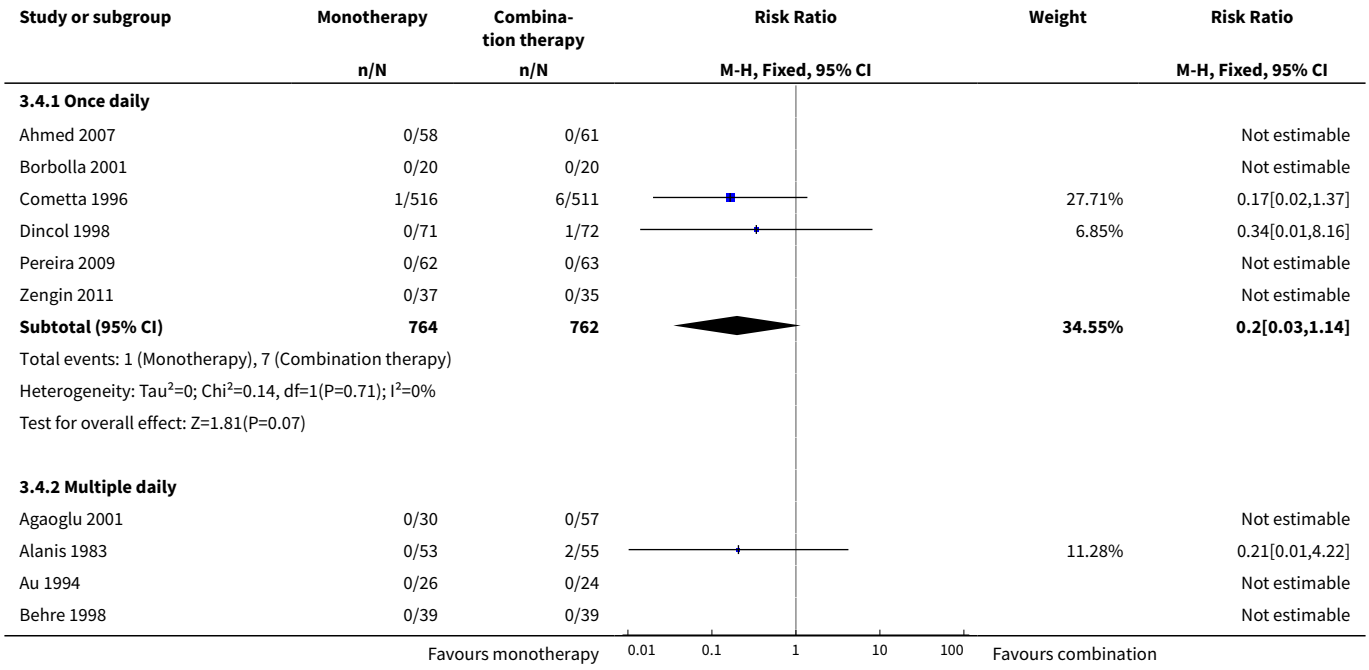


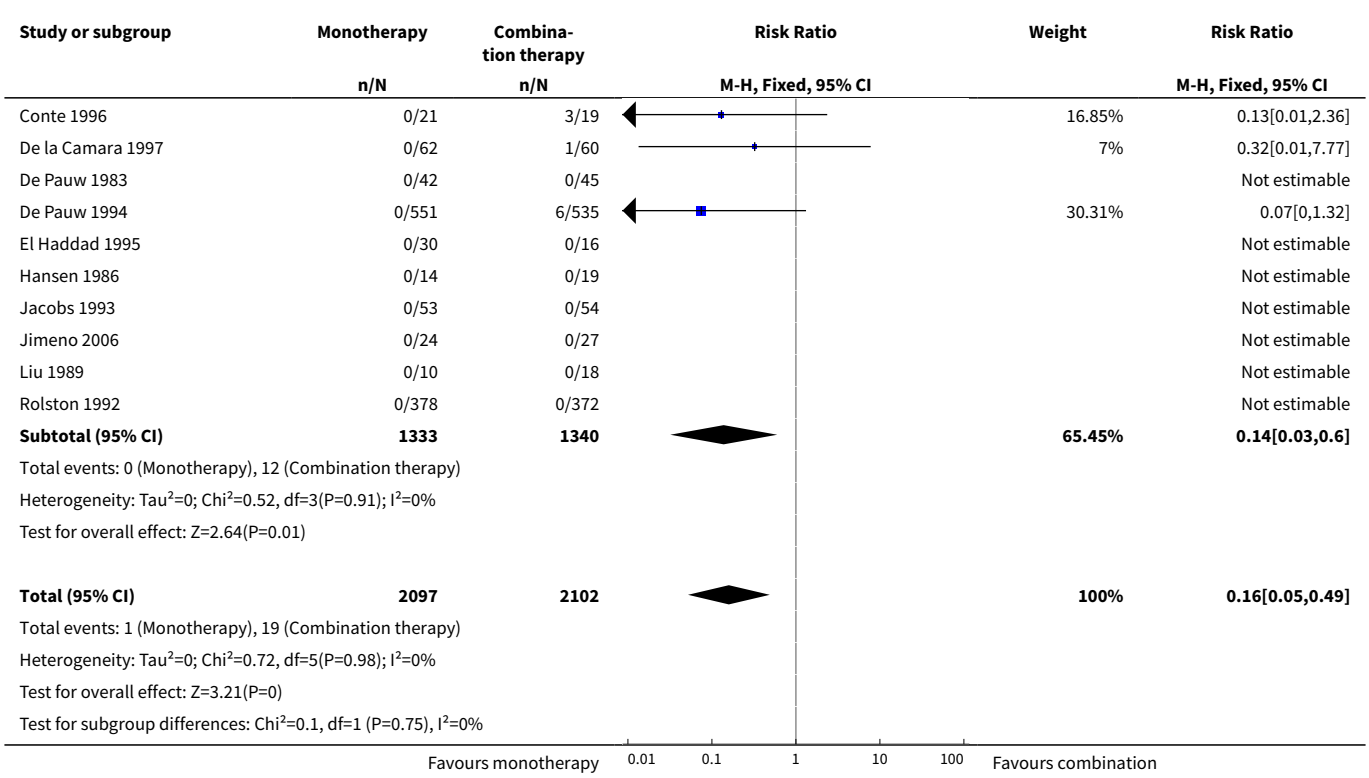
Analysis 3.3. Comparison 3 Adverse events, Outcome 3 Any nephrotoxicity - Ag dosing regimen.





Analysis 3.4. Comparison 3 Adverse events, Outcome 4 Severe nephrotoxicity - Ag dosing regimen.

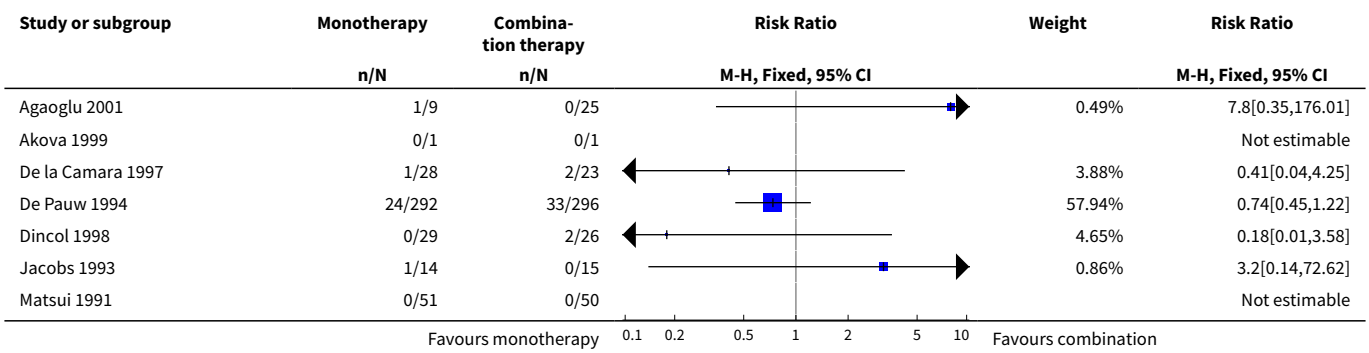




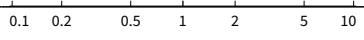
Comparison 4. Documented infections (subgroup analysis)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All cause mortality	13	1188	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.56, 1.17]
2 Treatment failure	35		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 same beta-lactam	8	1043	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.93, 1.19]
2.2 different beta-lactam	27	2740	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.82, 0.95]

Analysis 4.1. Comparison 4 Documented infections (subgroup analysis), Outcome 1 All cause mortality.



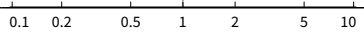
Study or subgroup	Monotherapy n/N	Combination therapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Miller 1993	2/15	0/15		0.88%	5[0.26,96.13]
Norrby 1987	3/58	9/62		15.38%	0.36[0.1,1.25]
Novakova 1991	5/45	5/45		8.84%	1[0.31,3.22]
Ozyilkan 1999	0/10	0/11			Not estimable
Perez 1995	3/20	3/21		5.17%	1.05[0.24,4.61]
Rodjer 1987	3/14	1/12		1.9%	2.57[0.31,21.59]
Total (95% CI)	**586**	**602**		**100%**	**0.81[0.56,1.17]**
Total events: 43 (Monotherapy), 55 (Combination therapy)					
Heterogeneity: Tau^2=0; Chi^2=8.68, df=9(P=0.47); I^2=0%					
Test for overall effect: Z=1.13(P=0.26)					



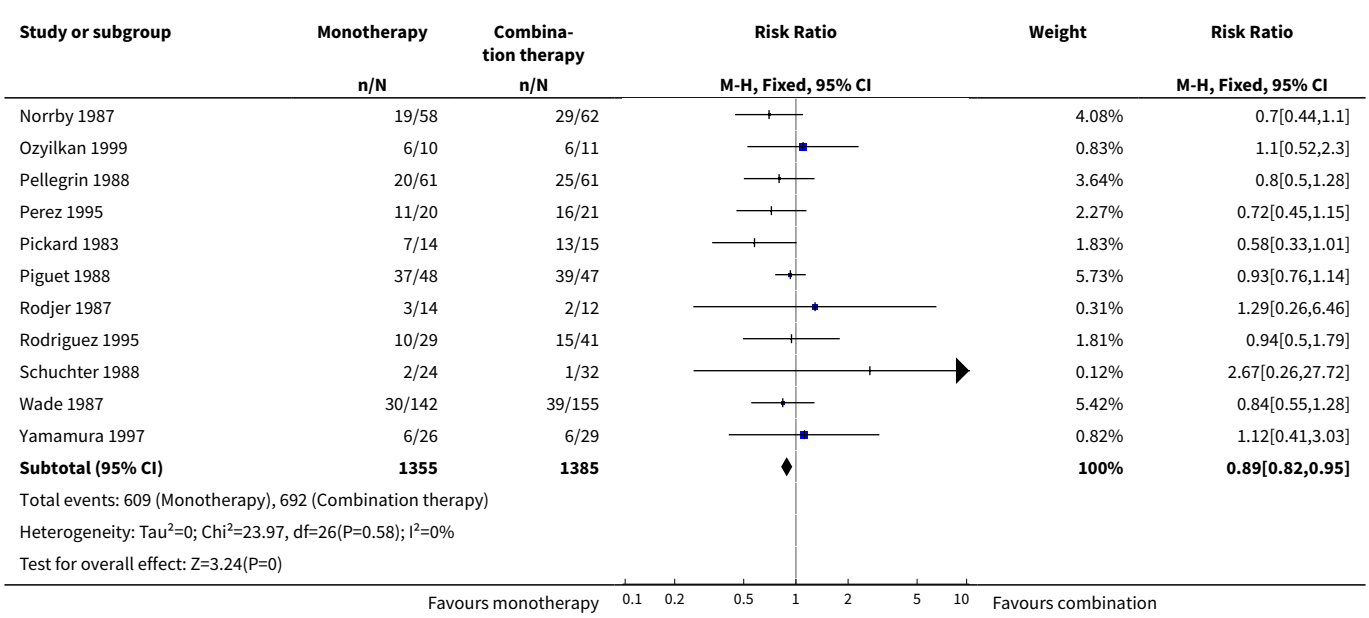
Favours monotherapy — Favours combination

Analysis 4.2. Comparison 4 Documented infections (subgroup analysis), Outcome 2 Treatment failure.

Study or subgroup	Monotherapy n/N	Combination therapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.2.1 same beta-lactam					
Del Favero 2001	120/190	121/181		53.8%	0.94[0.81,1.1]
Doyen 1983	8/45	6/46		2.58%	1.36[0.51,3.62]
Jacobs 1993	3/14	4/15		1.68%	0.8[0.22,2.97]
Kojima 1994	7/29	3/16		1.68%	1.29[0.39,4.3]
Novakova 1991	19/45	18/45		7.81%	1.06[0.64,1.73]
Piccart 1984	3/15	6/16		2.52%	0.53[0.16,1.76]
Rolston 1992	77/172	60/177		25.67%	1.32[1.01,1.72]
Tamura 2002	7/14	13/23		4.27%	0.88[0.47,1.67]
Subtotal (95% CI)	**524**	**519**		**100%**	**1.05[0.93,1.19]**
Total events: 244 (Monotherapy), 231 (Combination therapy)					
Heterogeneity: Tau^2=0; Chi^2=6.89, df=7(P=0.44); I^2=0%					
Test for overall effect: Z=0.78(P=0.44)					
4.2.2 different beta-lactam					
Agaoglu 2001	5/9	8/25		0.62%	1.74[0.77,3.93]
Au 1994	2/5	5/9		0.52%	0.72[0.21,2.44]
Behre 1998	11/15	7/14		1.05%	1.47[0.8,2.69]
Bezwoda 1985	13/29	14/31		1.97%	0.99[0.57,1.74]
Cometta 1996	136/251	145/240		21.56%	0.9[0.77,1.05]
Cornelissen 1992	3/39	12/38		1.77%	0.24[0.07,0.8]
De la Camara 1997	20/28	16/23		2.55%	1.03[0.72,1.47]
De Pauw 1994	176/292	186/296		26.86%	0.96[0.84,1.09]
Erjavec 1994	23/42	30/37		4.64%	0.68[0.49,0.93]
Gorschluter 2003	18/31	21/29		3.16%	0.8[0.55,1.17]
Hung 2003	4/13	7/14		0.98%	0.62[0.23,1.62]
Jimeno 2006	4/6	9/9		1.14%	0.68[0.38,1.2]
Leyland 1992	30/76	24/61		3.87%	1[0.66,1.52]
Liu 1989	1/7	3/8		0.41%	0.38[0.05,2.88]
Matsui 1991	9/51	10/50		1.47%	0.88[0.39,1.99]
Miller 1993	3/15	4/15		0.58%	0.75[0.2,2.79]



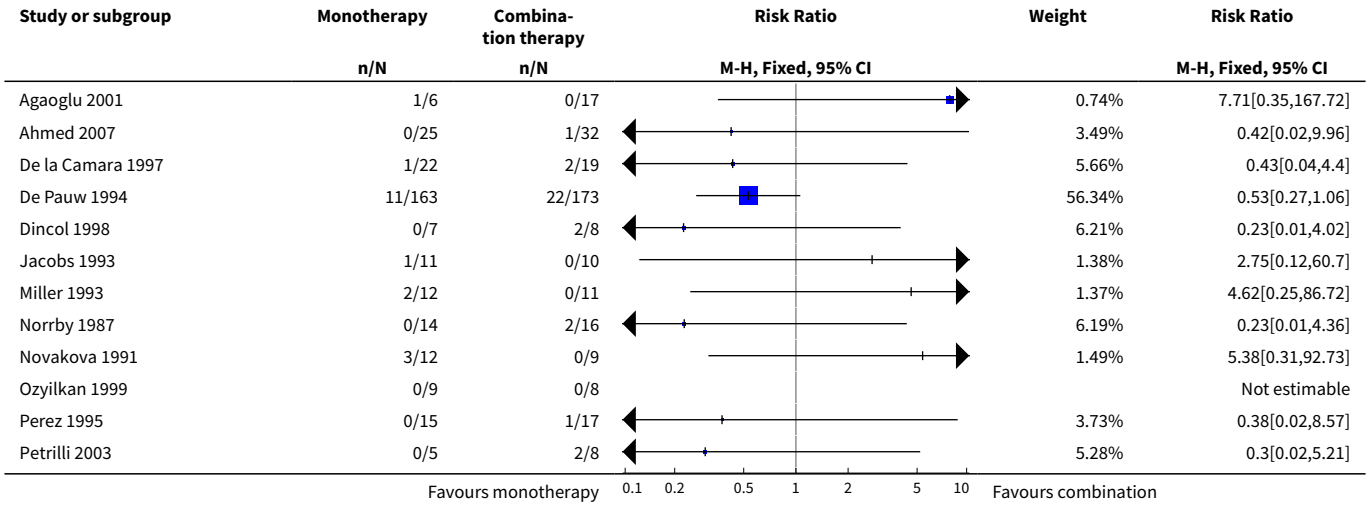
Favours monotherapy — Favours combination

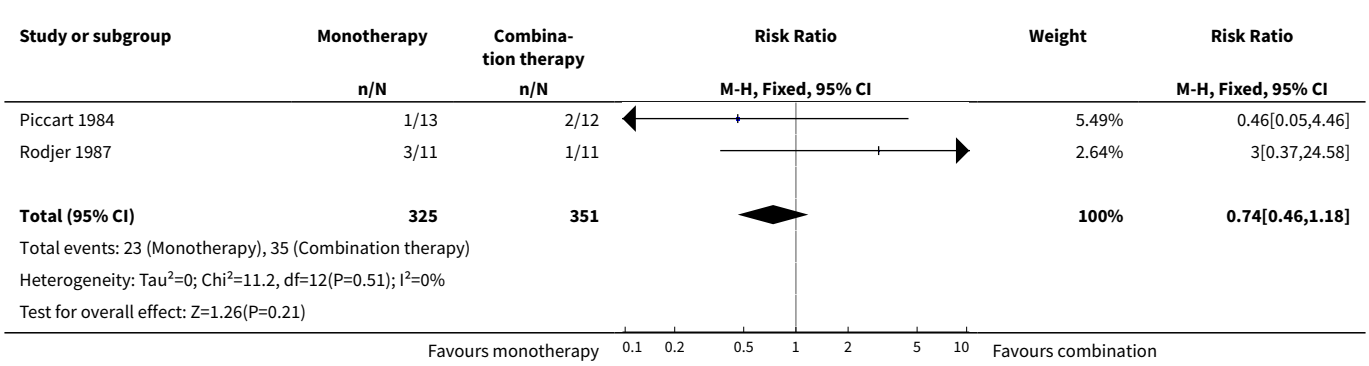


Comparison 5. Bacteraemia (subgroup analysis)

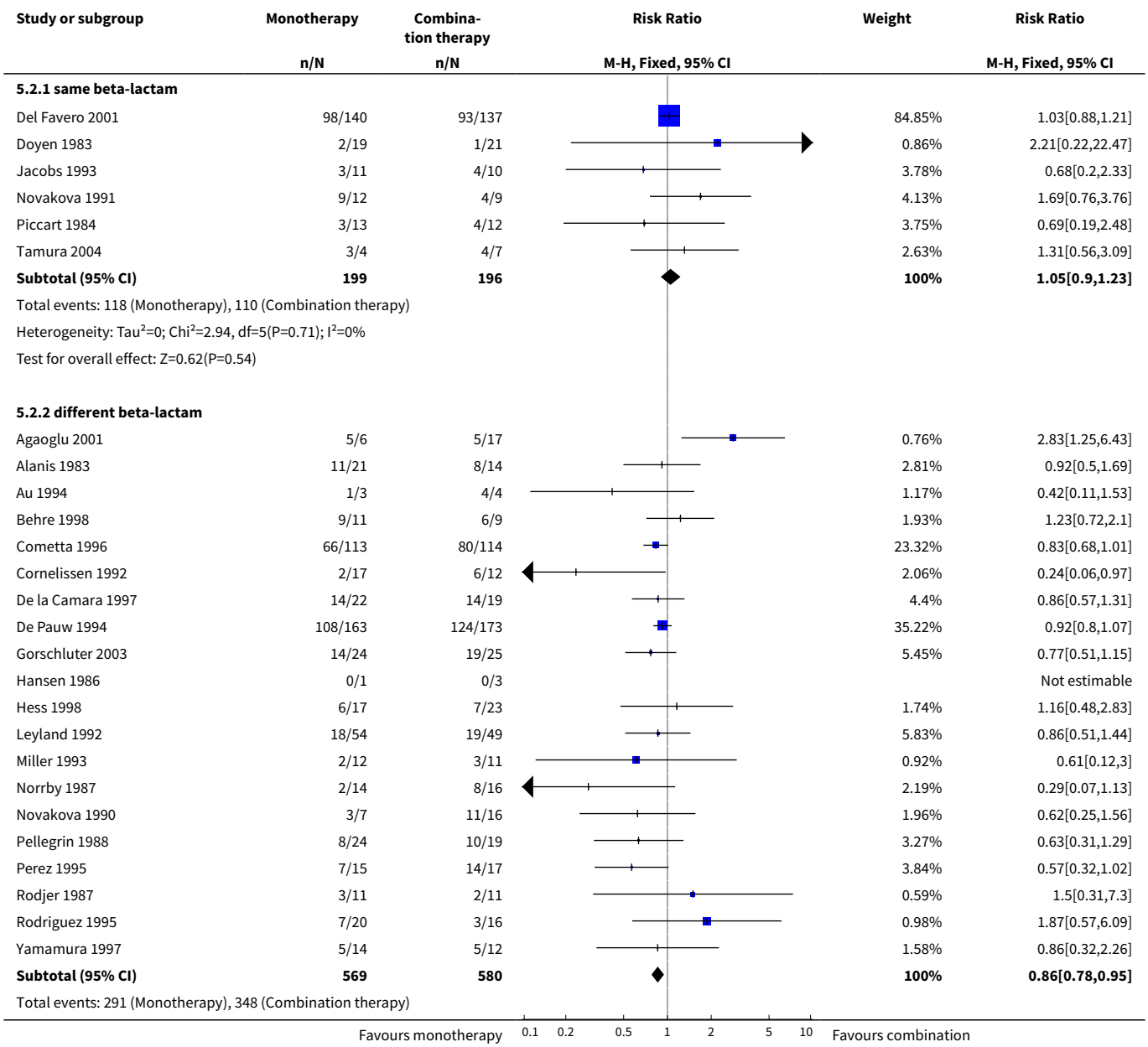
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All cause mortality	14	676	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.46, 1.18]
2 Treatment failure	26		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 same beta-lactam	6	395	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.90, 1.23]
2.2 different beta-lactam	20	1149	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.78, 0.95]

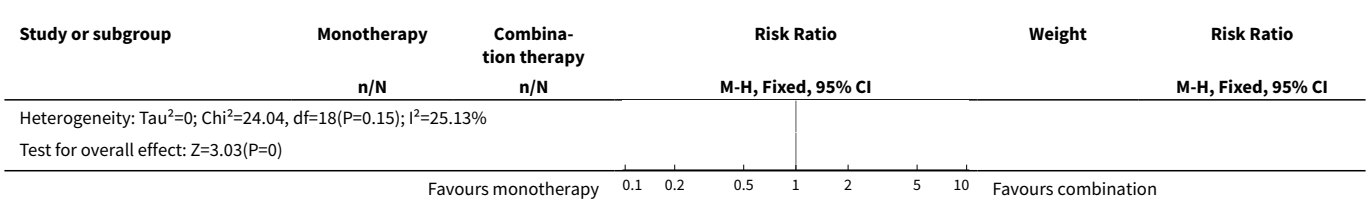
Analysis 5.1. Comparison 5 Bacteraemia (subgroup analysis), Outcome 1 All cause mortality.





Analysis 5.2. Comparison 5 Bacteraemia (subgroup analysis), Outcome 2 Treatment failure.

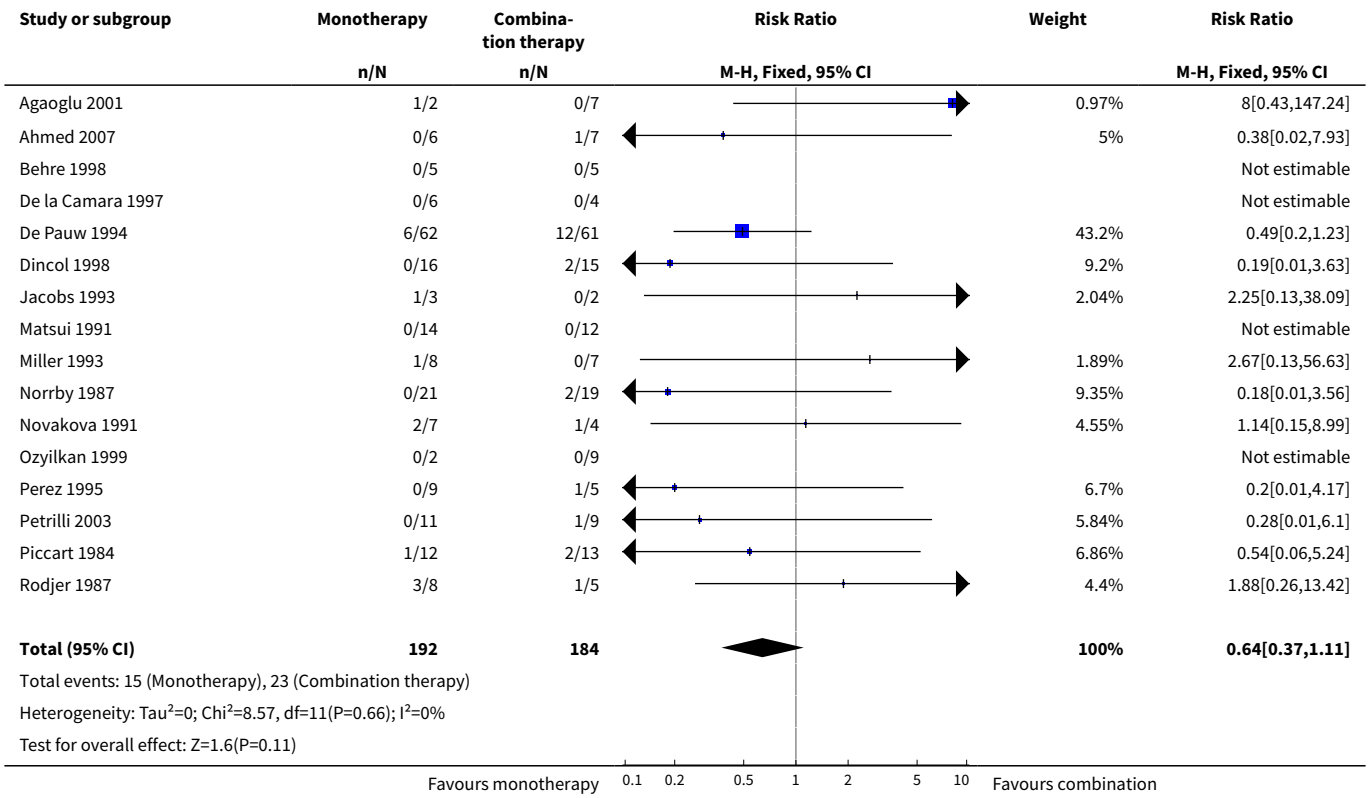




Comparison 6. Gram-negative infections (subgroup analysis)

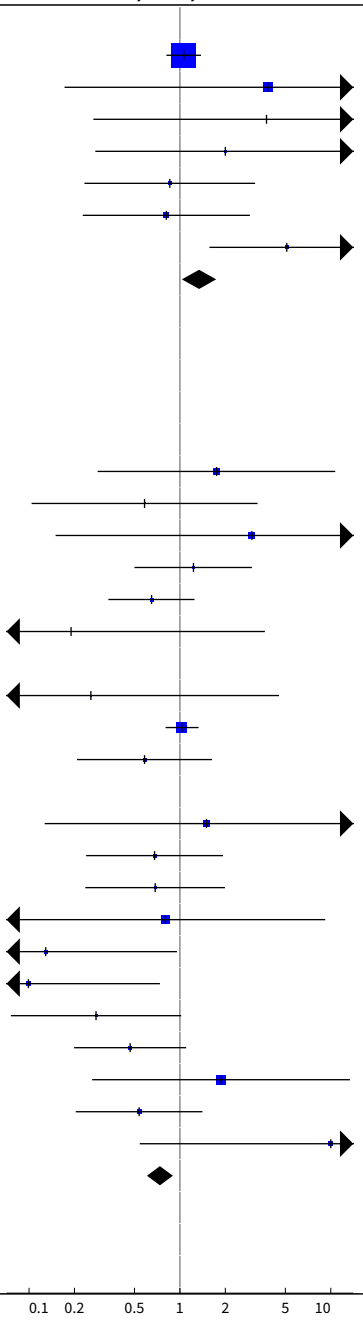
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All cause mortality	16	376	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.37, 1.11]
2 Treatment failure	29		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 same beta-lactam	7	261	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [1.03, 1.74]
2.2 different beta-lactam	22	603	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.60, 0.90]

Analysis 6.1. Comparison 6 Gram-negative infections (subgroup analysis), Outcome 1 All cause mortality.



Analysis 6.2. Comparison 6 Gram-negative infections (subgroup analysis), Outcome 2 Treatment failure.

Study or subgroup	Monotherapy n/N	Combination therapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.2.1 same beta-lactam					
Del Favero 2001	36/51	34/51		75%	1.06[0.81,1.38]
Doyen 1983	1/10	0/13		0.97%	3.82[0.17,84.9]
Jacobs 1993	2/3	0/2		1.26%	3.75[0.27,52.64]
Kojima 1994	5/20	1/8		3.15%	2[0.27,14.55]
Novakova 1991	3/7	2/4		5.62%	0.86[0.23,3.15]
Piccart 1984	3/12	4/13		8.47%	0.81[0.23,2.91]
Rolston 1992	11/28	3/39		5.53%	5.11[1.57,16.63]
Subtotal (95% CI)	**131**	**130**		**100%**	**1.34[1.03,1.74]**
Total events: 61 (Monotherapy), 44 (Combination therapy)					
Heterogeneity: Tau²=0; Chi²=10.26, df=6(P=0.11); I²=41.49%					
Test for overall effect: Z=2.19(P=0.03)					
6.2.2 different beta-lactam					
Agaoglu 2001	1/2	2/7		0.7%	1.75[0.29,10.74]
Au 1994	1/3	4/7		1.89%	0.58[0.1,3.27]
Behre 1998	1/5	0/5		0.39%	3[0.15,59.89]
Bezwoda 1985	7/16	5/14		4.2%	1.23[0.5,3]
Cometta 1996	11/37	11/24		10.51%	0.65[0.34,1.25]
Cornelissen 1992	0/6	1/3		1.5%	0.19[0.01,3.66]
De la Camara 1997	0/6	0/4			Not estimable
De Pauw 1983	0/6	2/8		1.72%	0.26[0.01,4.54]
De Pauw 1994	42/62	40/61		31.77%	1.03[0.8,1.33]
Erjavec 1994	3/9	8/14		4.93%	0.58[0.21,1.63]
Gorschluter 2003	0/1	0/1			Not estimable
Hansen 1986	1/4	1/6		0.63%	1.5[0.13,17.67]
Leyland 1992	5/27	6/22		5.21%	0.68[0.24,1.93]
Matsui 1991	4/14	5/12		4.24%	0.69[0.24,1.99]
Miller 1993	1/5	1/4		0.88%	0.8[0.07,9.18]
Norrby 1987	1/21	7/19		5.79%	0.13[0.02,0.96]
Pellegrin 1988	1/29	8/23		7.03%	0.1[0.01,0.74]
Perez 1995	2/9	4/5		4.05%	0.28[0.08,1.02]
Pickard 1983	4/11	7/9		6.07%	0.47[0.2,1.1]
Rodjer 1987	3/8	1/5		0.97%	1.88[0.26,13.42]
Wade 1987	4/18	12/29		7.24%	0.54[0.2,1.41]
Yamamura 1997	2/7	0/15		0.26%	10[0.54,184.55]
Subtotal (95% CI)	**306**	**297**		**100%**	**0.74[0.6,0.9]**
Total events: 94 (Monotherapy), 125 (Combination therapy)					
Heterogeneity: Tau²=0; Chi²=26.4, df=19(P=0.12); I²=28.02%					
Test for overall effect: Z=3.01(P=0)					



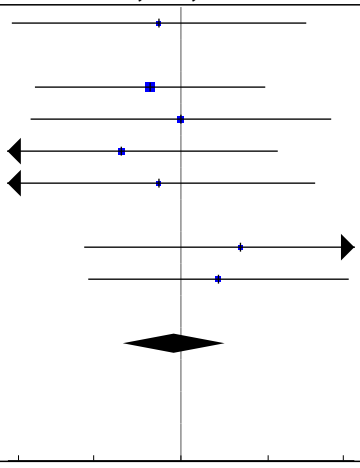
Comparison 7. Pseudomonas infections (subgroup analysis)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All cause mortality	9	71	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.34, 2.24]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Treatment failure	16		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 same beta-lactam	3	49	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.90, 2.22]
2.2 different beta-lactam	13	99	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.60, 1.31]

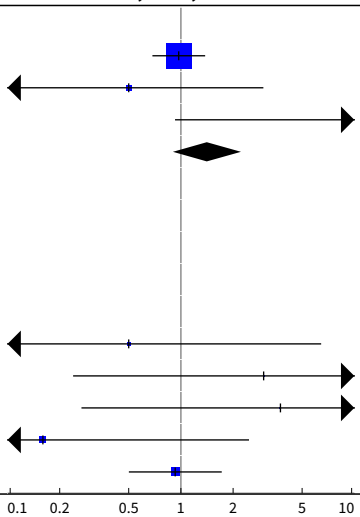
Analysis 7.1. Comparison 7 Pseudomonas infections (subgroup analysis), Outcome 1 All cause mortality.

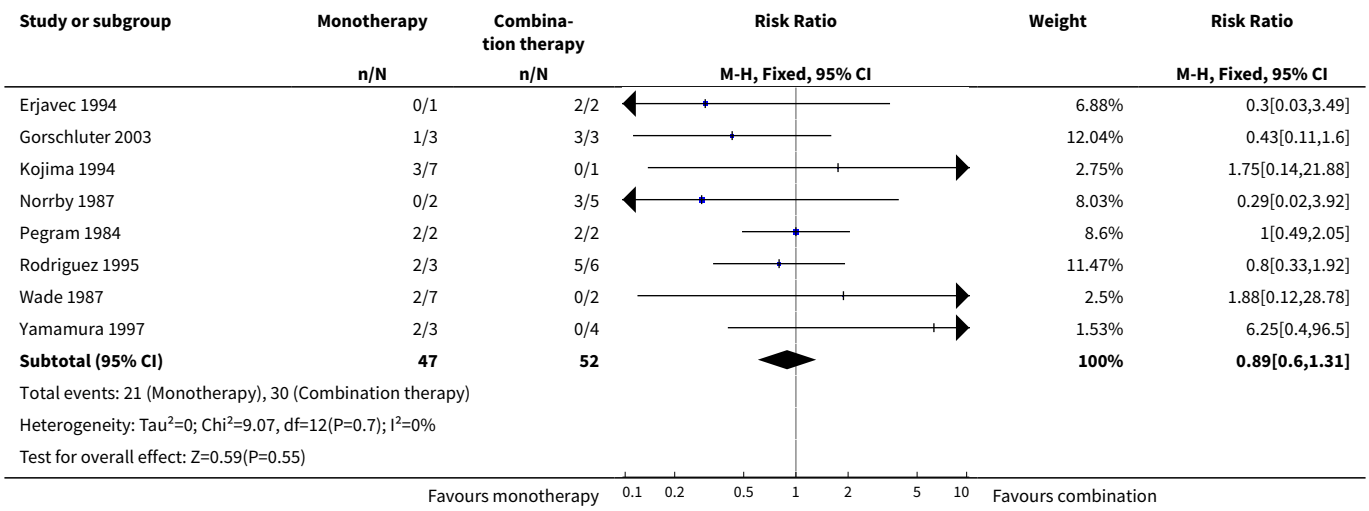
Study or subgroup	Monotherapy n/N	Combination therapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ahmed 2007	0/1	1/3		13.09%	0.67[0.04,10.05]
Behre 1998	0/1	0/1			Not estimable
De Pauw 1994	1/10	3/17		29.09%	0.57[0.07,4.74]
Dincol 1998	0/1	1/5		9.82%	1[0.06,15.99]
Gorschluter 2003	0/3	1/3		19.64%	0.33[0.02,5.97]
Norrby 1987	0/2	1/5		13.09%	0.67[0.04,11.94]
Ozyilkan 1999	0/1	0/3			Not estimable
Piccart 1984	1/3	0/3		6.55%	3[0.17,53.71]
Rodriguez 1995	1/3	1/6		8.73%	2[0.18,22.06]
Total (95% CI)	**25**	**46**		**100%**	**0.87[0.34,2.24]**
Total events: 3 (Monotherapy), 8 (Combination therapy)					
Heterogeneity: Tau^2=0; Chi^2=1.83, df=6(P=0.93); I^2=0%					
Test for overall effect: Z=0.28(P=0.78)					



Analysis 7.2. Comparison 7 Pseudomonas infections (subgroup analysis), Outcome 2 Treatment failure.

Study or subgroup	Monotherapy n/N	Combination therapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
7.2.1 same beta-lactam					
Del Favero 2001	6/7	15/17		78.27%	0.97[0.69,1.38]
Piccart 1984	1/3	2/3		17.89%	0.5[0.08,2.99]
Rolston 1992	5/8	0/11		3.83%	14.67[0.93,232.44]
Subtotal (95% CI)	**18**	**31**		**100%**	**1.41[0.9,2.22]**
Total events: 12 (Monotherapy), 17 (Combination therapy)					
Heterogeneity: Tau^2=0; Chi^2=8.47, df=2(P=0.01); I^2=76.39%					
Test for overall effect: Z=1.5(P=0.13)					
7.2.2 different beta-lactam					
Au 1994	0/1	2/4		4.92%	0.5[0.04,6.44]
Behre 1998	1/1	0/1		1.72%	3[0.24,37.67]
Bezwoda 1985	2/3	0/2		1.97%	3.75[0.27,52.64]
De Pauw 1983	0/4	2/3		9.56%	0.16[0.01,2.47]
De Pauw 1994	6/10	11/17		28.03%	0.93[0.5,1.72]

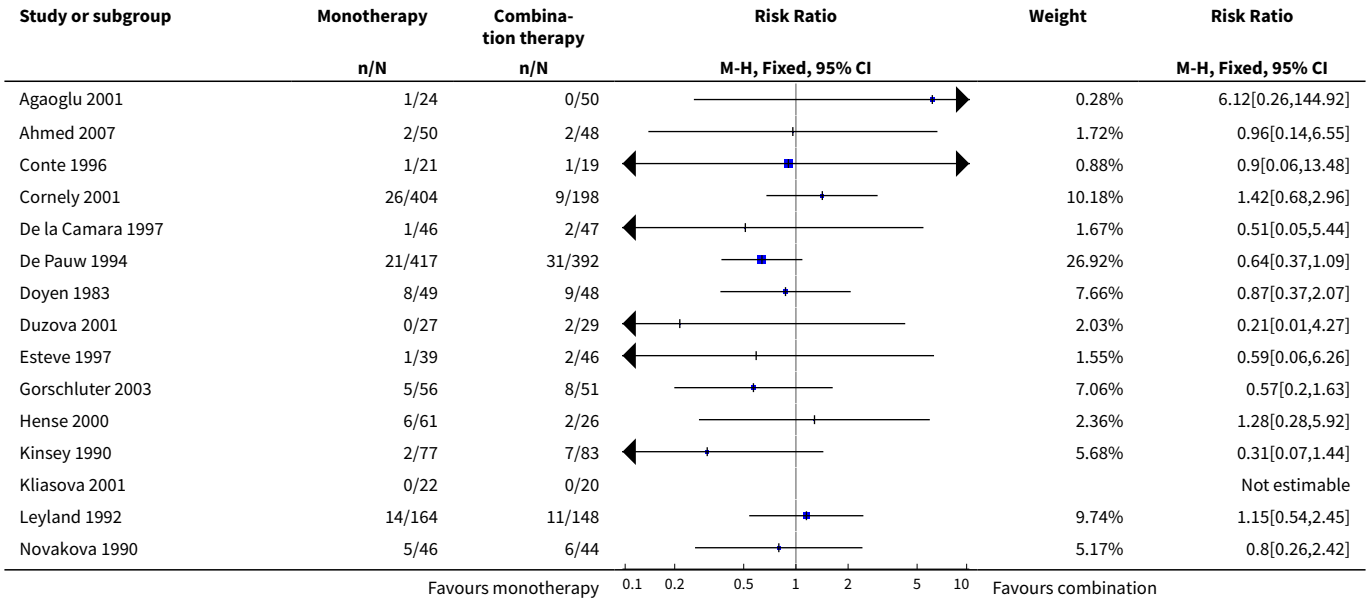


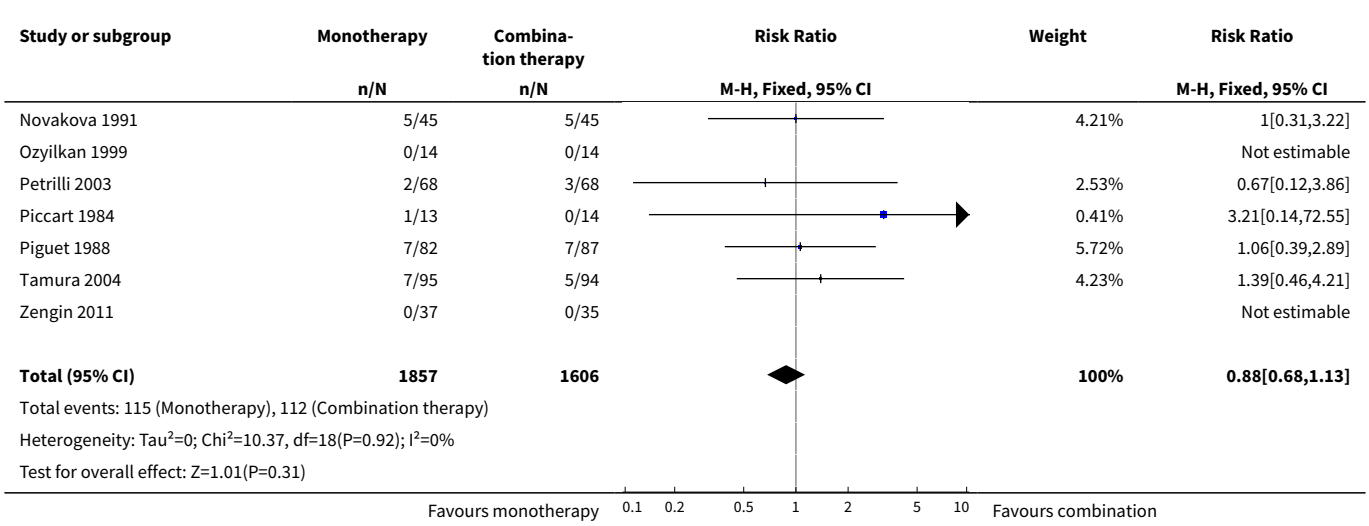


Comparison 8. Haematological cancer patients (subgroup analysis)

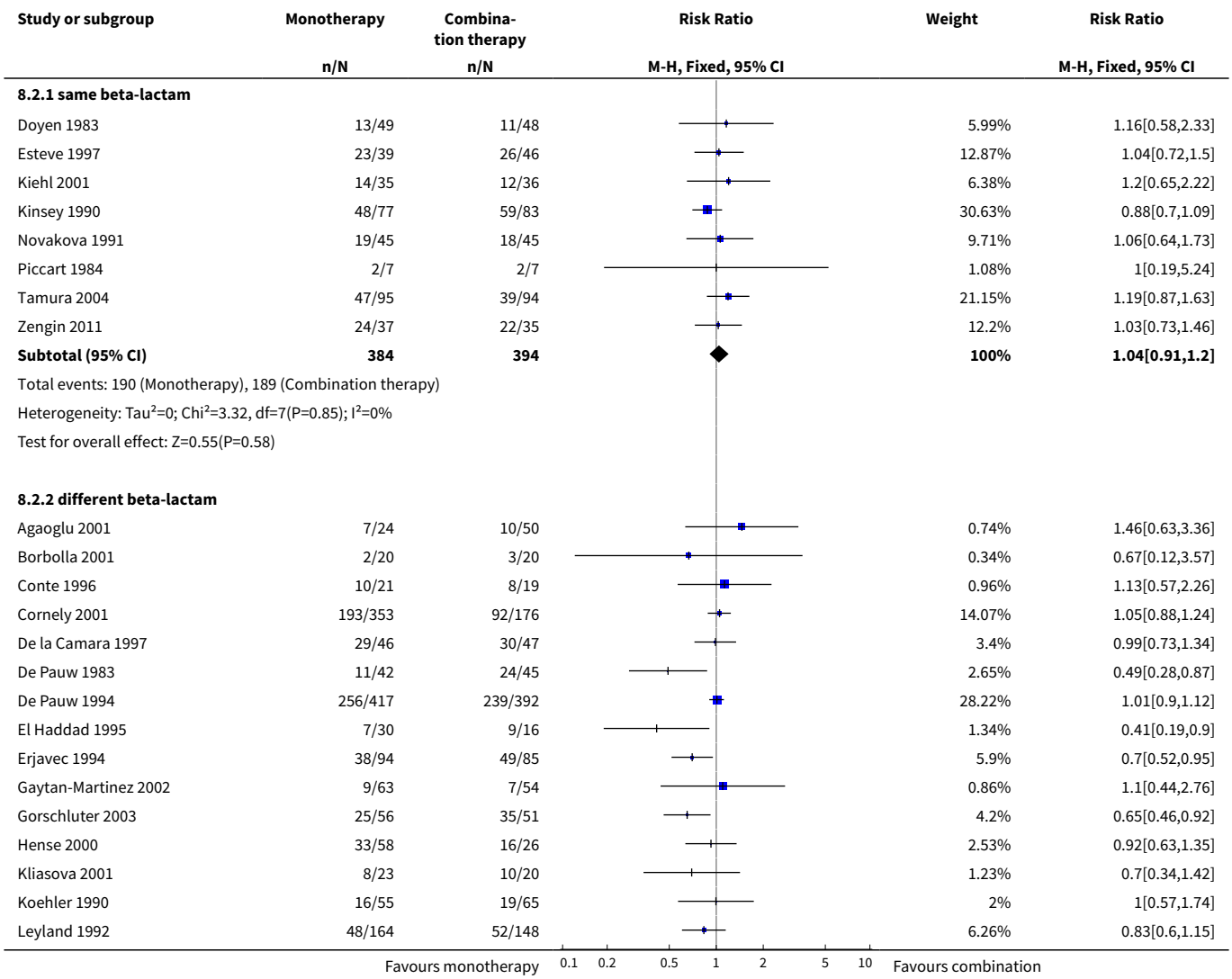
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All cause mortality	22	3463	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.68, 1.13]
2 Treatment failure	32		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 same beta-lactam	8	778	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.91, 1.20]
2.2 different beta-lactam	24	3671	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.88, 1.01]

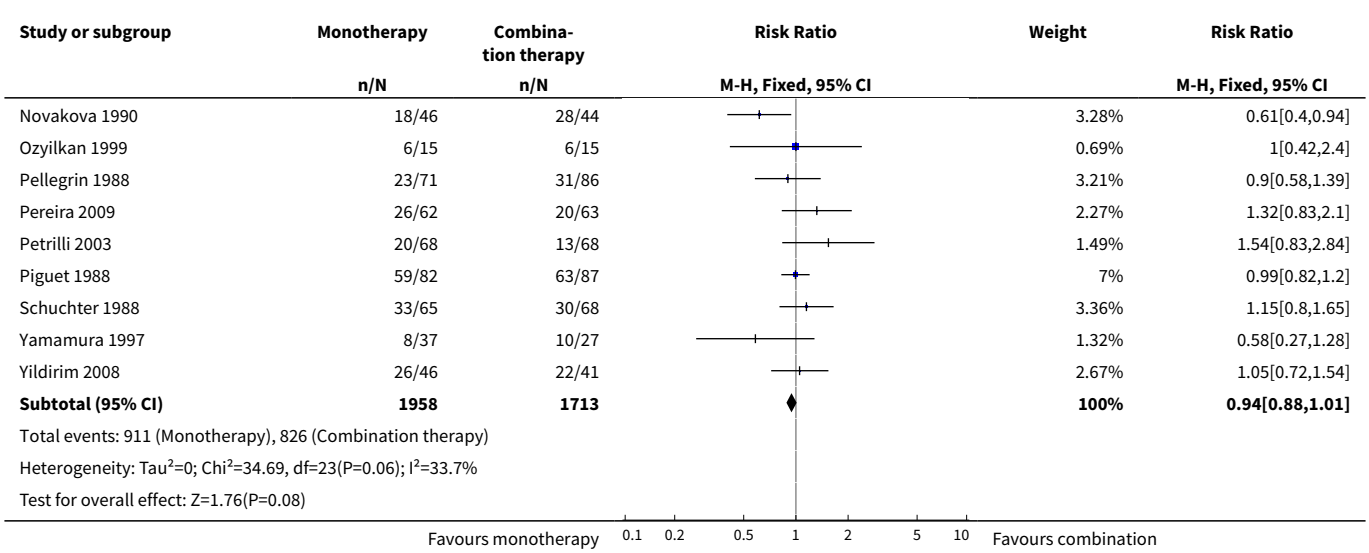
Analysis 8.1. Comparison 8 Haematological cancer patients (subgroup analysis), Outcome 1 All cause mortality.





Analysis 8.2. Comparison 8 Haematological cancer patients (subgroup analysis), Outcome 2 Treatment failure.

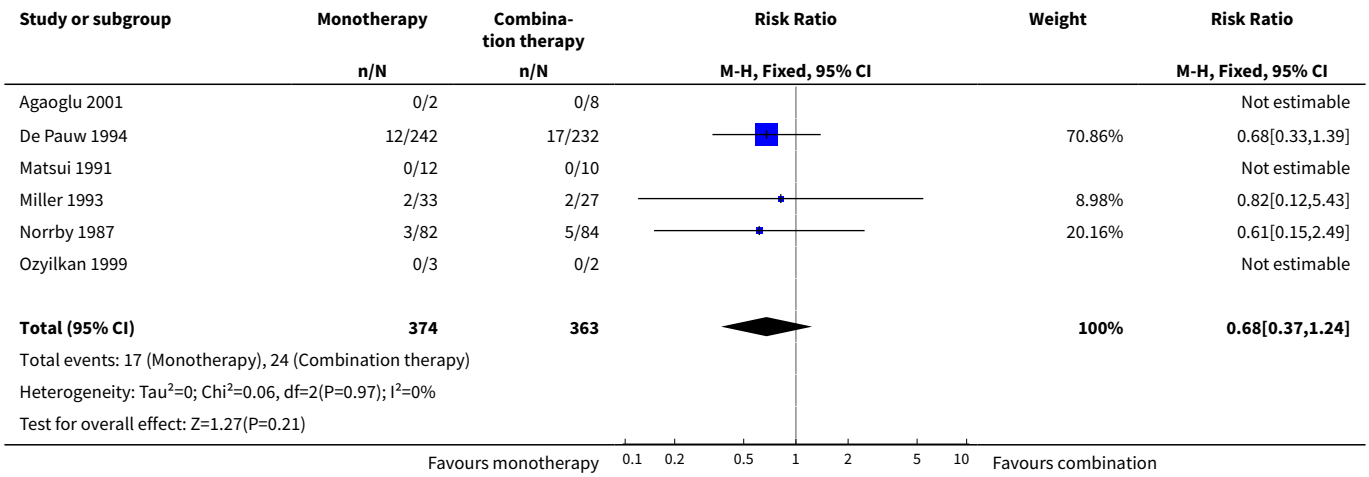




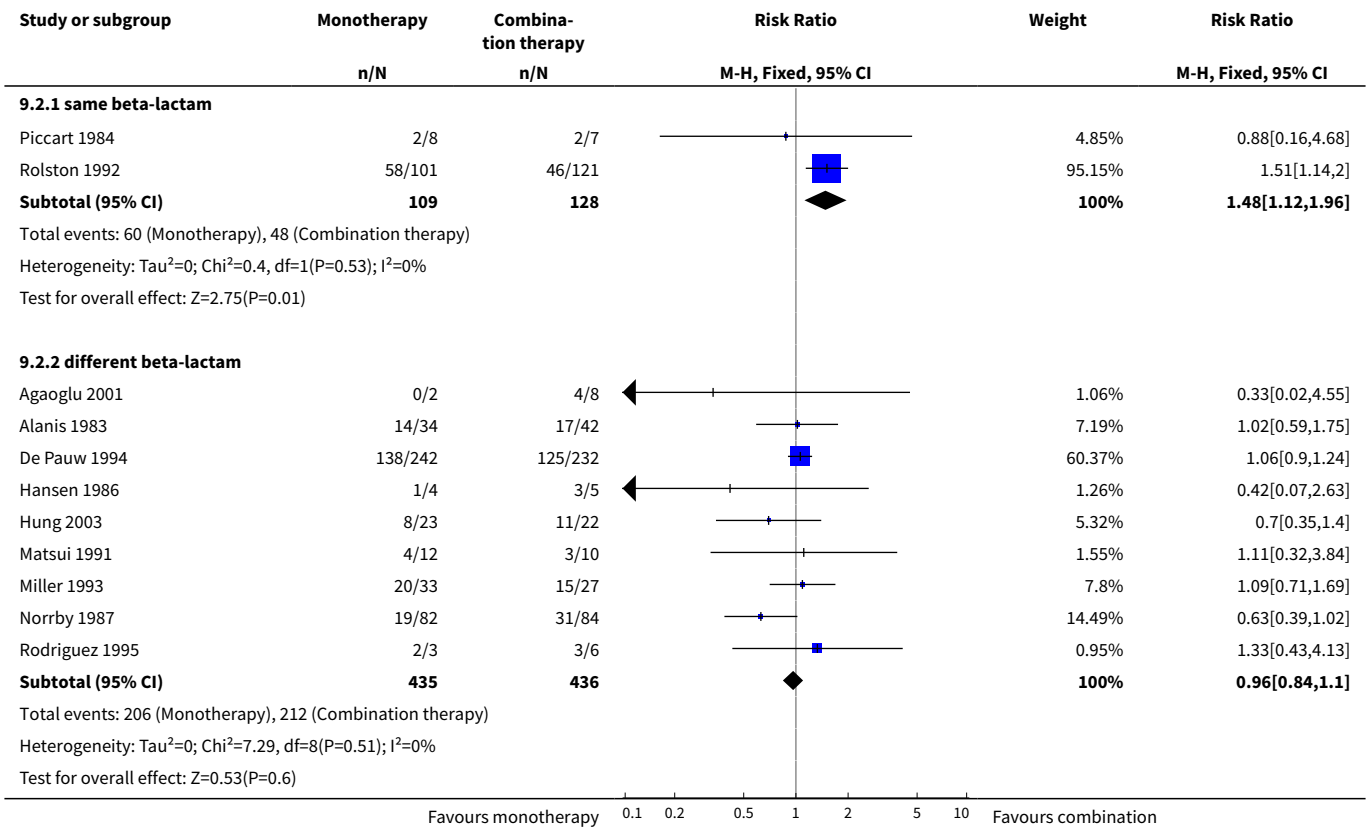
Comparison 9. Severe neutropenia (subgroup analysis)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All cause mortality	6	737	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.37, 1.24]
2 Treatment failure	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 same beta-lactam	2	237	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [1.12, 1.96]
2.2 different beta-lactam	9	871	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.84, 1.10]

Analysis 9.1. Comparison 9 Severe neutropenia (subgroup analysis), Outcome 1 All cause mortality.



Analysis 9.2. Comparison 9 Severe neutropenia (subgroup analysis), Outcome 2 Treatment failure.



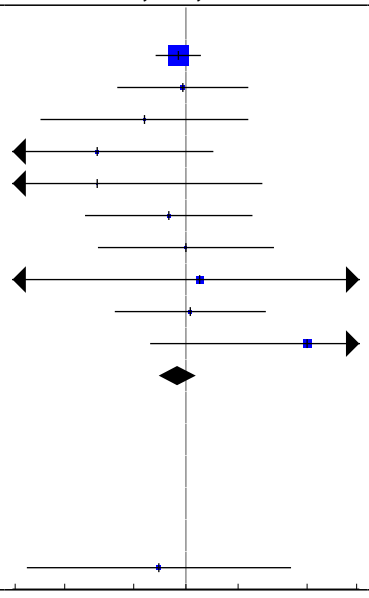
Comparison 10. Monotherapy

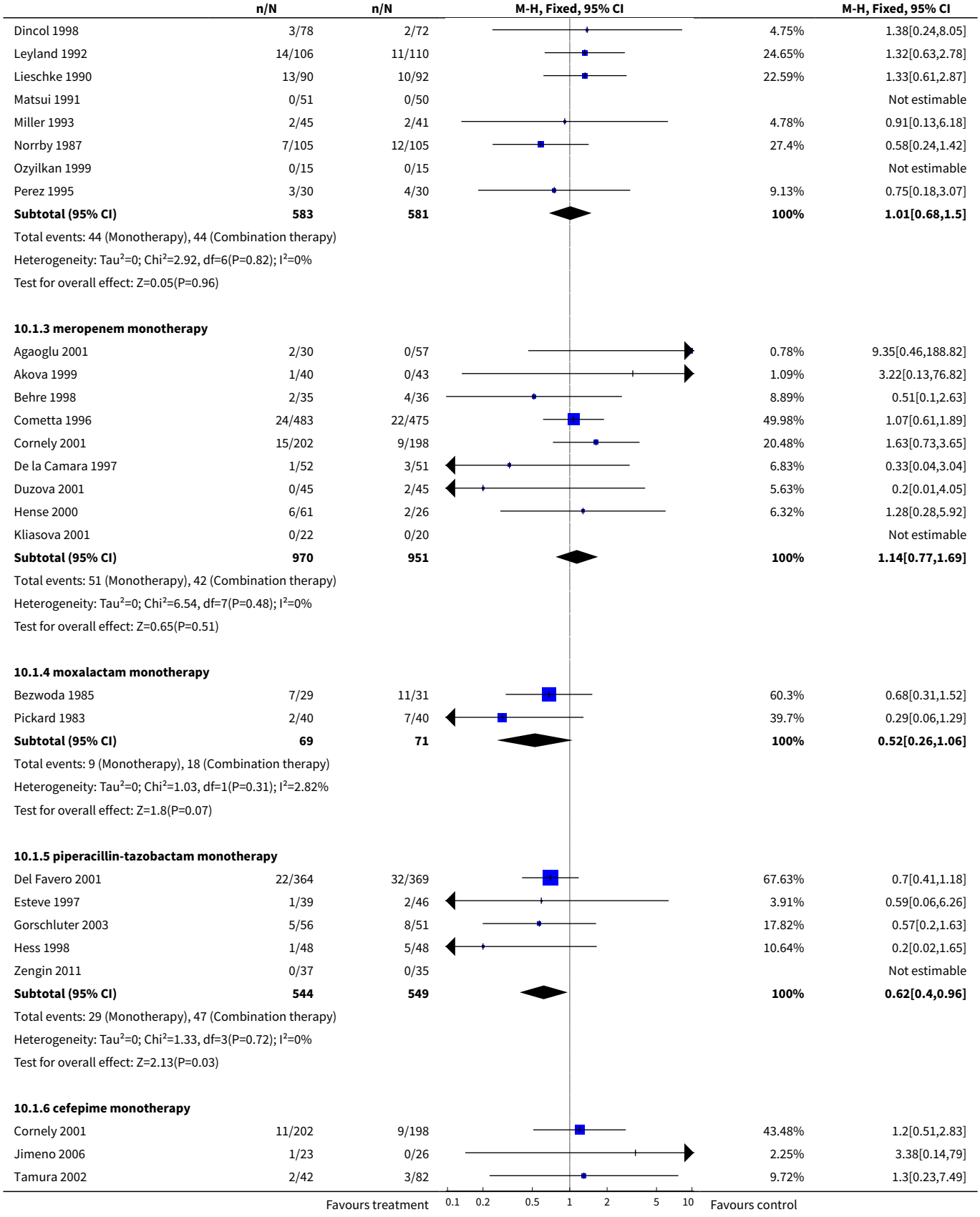
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All cause mortality	43		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 ceftazidime monotherapy	10	1868	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.70, 1.14]
1.2 imipenem monotherapy	9	1164	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.68, 1.50]
1.3 meropenem monotherapy	9	1921	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.77, 1.69]
1.4 moxalactam monotherapy	2	140	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.26, 1.06]
1.5 piperacillin-tazobactam monotherapy	5	1093	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.40, 0.96]
1.6 cefepime monotherapy	5	802	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.61, 1.93]
1.7 other monotherapy	4	320	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.19, 2.25]
2 Treatment failure	65		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 same BL - ceftazidime	6	647	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.94, 1.23]
2.2 same BL - imipenem	1	67	Risk Ratio (M-H, Fixed, 95% CI)	3.05 [0.92, 10.10]
2.3 same BL - piperacillin-tazobactam	3	911	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.92, 1.18]
2.4 same BL - cefepime	3	343	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.84, 1.39]
2.5 same BL - other monotherapy	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.30, 2.33]
2.6 different BL - ceftazidime	10	1917	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.89, 1.05]
2.7 different BL - imipenem	14	1964	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.78, 1.01]
2.8 different BL - meropenem	8	1542	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.79, 0.98]
2.9 different BL - moxalactam	5	402	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.60, 0.99]
2.10 different BL - piperacillin-tazobactam	2	203	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.53, 1.02]
2.11 different BL - cefepime	5	377	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.77, 1.22]
2.12 different BL - other	7	575	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.83, 1.28]

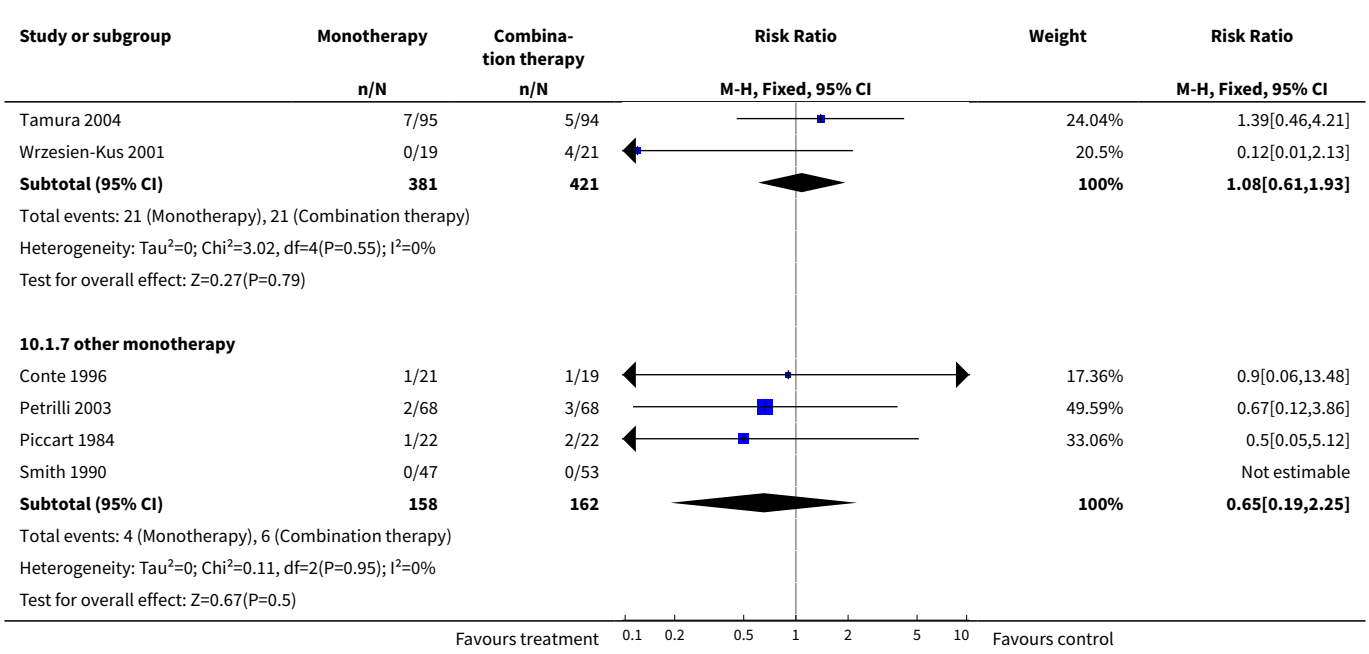
Analysis 10.1. Comparison 10 Monotherapy, Outcome 1 All cause mortality.

Study or subgroup	Monotherapy n/N	Combination therapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
10.1.1 ceftazidime monotherapy					
De Pauw 1994	69/488	75/480		63.51%	0.9[0.67,1.22]
Doyen 1983	8/50	9/54		7.27%	0.96[0.4,2.29]
Gibson 1989	3/52	5/50		4.28%	0.58[0.15,2.29]
Kinsey 1990	2/77	7/83		5.66%	0.31[0.07,1.44]
Morgan 1983	1/26	3/24		2.62%	0.31[0.03,2.76]
Novakova 1990	5/46	6/44		5.15%	0.8[0.26,2.42]
Novakova 1991	5/45	5/45		4.2%	1[0.31,3.22]
Papachristodoulou 96	1/35	1/42		0.76%	1.2[0.08,18.5]
Piguet 1988	7/82	7/87		5.71%	1.06[0.39,2.89]
Rodjer 1987	5/29	1/29		0.84%	5[0.62,40.2]
Subtotal (95% CI)	**930**	**938**		**100%**	**0.89[0.7,1.14]**
Total events: 106 (Monotherapy), 119 (Combination therapy)					
Heterogeneity: $Tau^2=0$; $Chi^2=6.02$, df=9(P=0.74); $I^2=0\%$					
Test for overall effect: Z=0.94(P=0.35)					
10.1.2 imipenem monotherapy					
Ahmed 2007	2/63	3/66		6.69%	0.7[0.12,4.04]

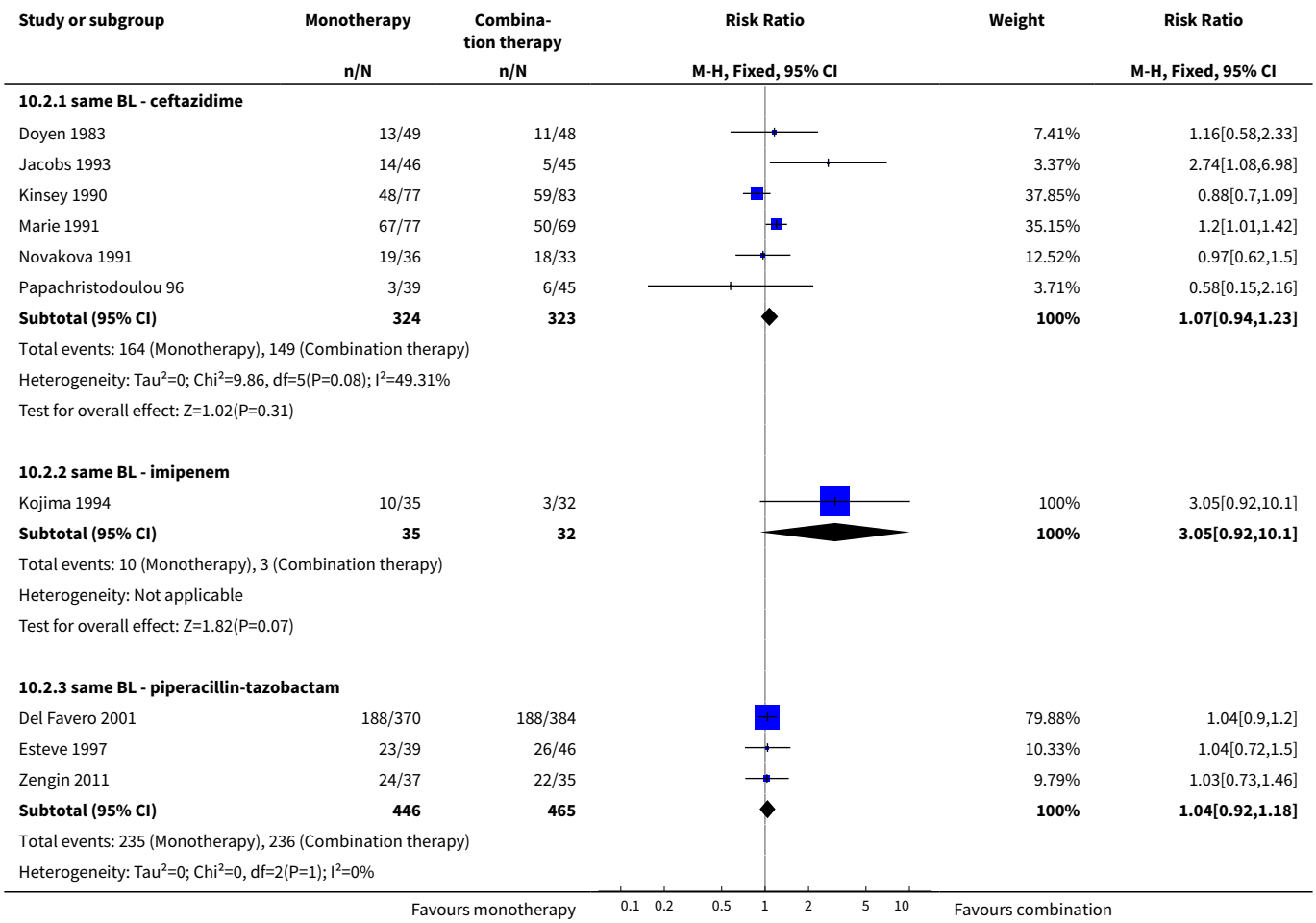


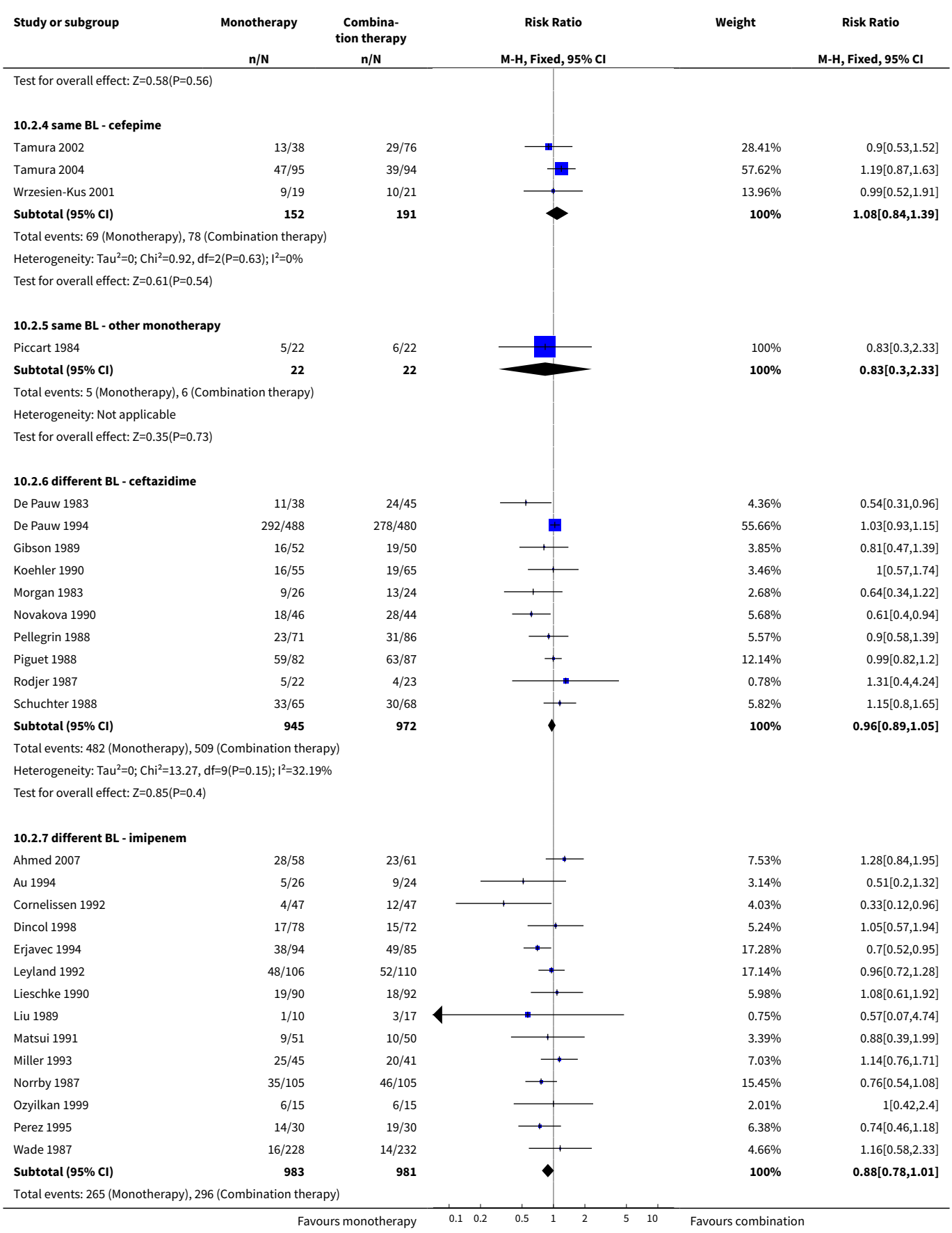


Study or subgroup	Monotherapy n/N	Combination therapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dincol 1998	3/78	2/72		4.75%	1.38[0.24,8.05]
Leyland 1992	14/106	11/110		24.65%	1.32[0.63,2.78]
Lieschke 1990	13/90	10/92		22.59%	1.33[0.61,2.87]
Matsui 1991	0/51	0/50			Not estimable
Miller 1993	2/45	2/41		4.78%	0.91[0.13,6.18]
Norrby 1987	7/105	12/105		27.4%	0.58[0.24,1.42]
Ozyilkan 1999	0/15	0/15			Not estimable
Perez 1995	3/30	4/30		9.13%	0.75[0.18,3.07]
Subtotal (95% CI)	**583**	**581**		**100%**	**1.01[0.68,1.5]**
Total events: 44 (Monotherapy), 44 (Combination therapy)					
Heterogeneity: Tau²=0; Chi²=2.92, df=6(P=0.82); I²=0%					
Test for overall effect: Z=0.05(P=0.96)					
10.1.3 meropenem monotherapy					
Agaoglu 2001	2/30	0/57		0.78%	9.35[0.46,188.82]
Akova 1999	1/40	0/43		1.09%	3.22[0.13,76.82]
Behre 1998	2/35	4/36		8.89%	0.51[0.1,2.63]
Cometta 1996	24/483	22/475		49.98%	1.07[0.61,1.89]
Cornely 2001	15/202	9/198		20.48%	1.63[0.73,3.65]
De la Camara 1997	1/52	3/51		6.83%	0.33[0.04,3.04]
Duzova 2001	0/45	2/45		5.63%	0.2[0.01,4.05]
Hense 2000	6/61	2/26		6.32%	1.28[0.28,5.92]
Kliasova 2001	0/22	0/20			Not estimable
Subtotal (95% CI)	**970**	**951**		**100%**	**1.14[0.77,1.69]**
Total events: 51 (Monotherapy), 42 (Combination therapy)					
Heterogeneity: Tau²=0; Chi²=6.54, df=7(P=0.48); I²=0%					
Test for overall effect: Z=0.65(P=0.51)					
10.1.4 moxalactam monotherapy					
Bezwoda 1985	7/29	11/31		60.3%	0.68[0.31,1.52]
Pickard 1983	2/40	7/40		39.7%	0.29[0.06,1.29]
Subtotal (95% CI)	**69**	**71**		**100%**	**0.52[0.26,1.06]**
Total events: 9 (Monotherapy), 18 (Combination therapy)					
Heterogeneity: Tau²=0; Chi²=1.03, df=1(P=0.31); I²=2.82%					
Test for overall effect: Z=1.8(P=0.07)					
10.1.5 piperacillin-tazobactam monotherapy					
Del Favero 2001	22/364	32/369		67.63%	0.7[0.41,1.18]
Esteve 1997	1/39	2/46		3.91%	0.59[0.06,6.26]
Gorschluter 2003	5/56	8/51		17.82%	0.57[0.2,1.63]
Hess 1998	1/48	5/48		10.64%	0.2[0.02,1.65]
Zengin 2011	0/37	0/35			Not estimable
Subtotal (95% CI)	**544**	**549**		**100%**	**0.62[0.4,0.96]**
Total events: 29 (Monotherapy), 47 (Combination therapy)					
Heterogeneity: Tau²=0; Chi²=1.33, df=3(P=0.72); I²=0%					
Test for overall effect: Z=2.13(P=0.03)					
10.1.6 cefepime monotherapy					
Cornely 2001	11/202	9/198		43.48%	1.2[0.51,2.83]
Jimeno 2006	1/23	0/26		2.25%	3.38[0.14,79]
Tamura 2002	2/42	3/82		9.72%	1.3[0.23,7.49]

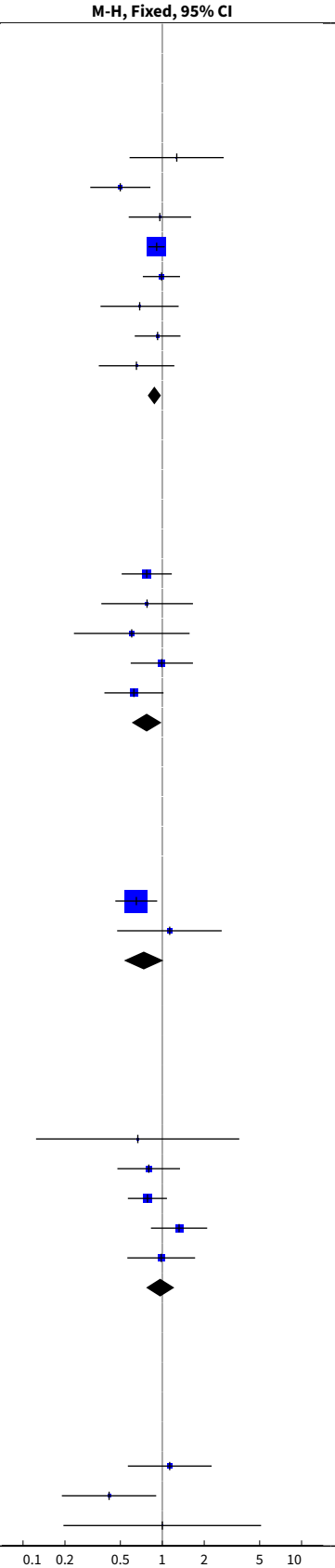


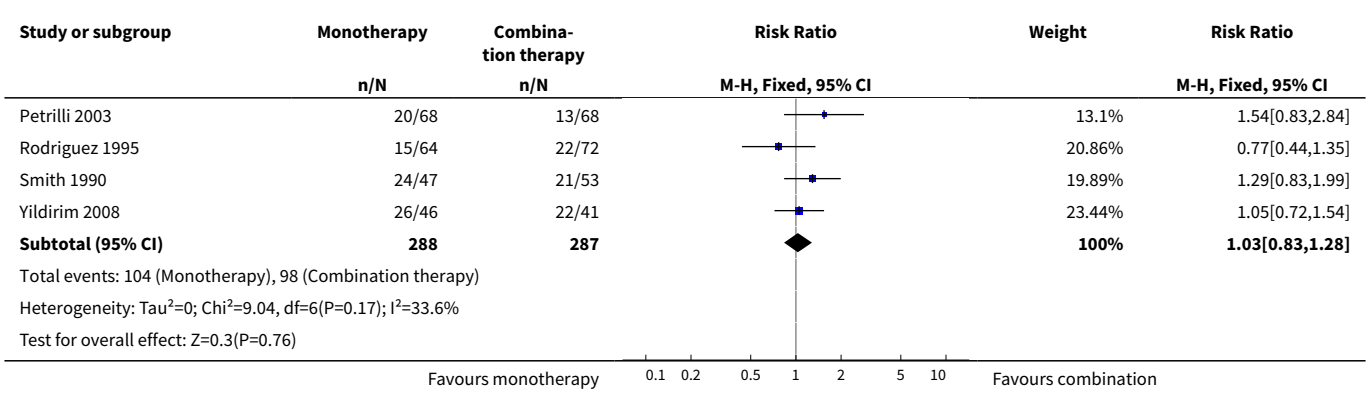
Analysis 10.2. Comparison 10 Monotherapy, Outcome 2 Treatment failure.





Study or subgroup	Monotherapy n/N	Combination therapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=14.44, df=13(P=0.34); I²=9.98%					
Test for overall effect: Z=1.86(P=0.06)					
10.2.8 different BL - meropenem					
Agaoglu 2001	8/30	12/57		2.25%	1.27[0.58,2.76]
Akova 1999	13/40	28/43		7.34%	0.5[0.3,0.82]
Behre 1998	15/34	17/37		4.43%	0.96[0.57,1.61]
Cometta 1996	213/483	230/475		63.08%	0.91[0.79,1.04]
De la Camara 1997	29/46	30/47		8.07%	0.99[0.73,1.34]
Duzova 2001	11/45	16/45		4.35%	0.69[0.36,1.31]
Hense 2000	33/58	16/26		6.01%	0.92[0.63,1.35]
Hung 2003	11/39	16/37		4.47%	0.65[0.35,1.22]
Subtotal (95% CI)	**775**	**767**		**100%**	**0.88[0.79,0.98]**
Total events: 333 (Monotherapy), 365 (Combination therapy)					
Heterogeneity: Tau²=0; Chi²=8.27, df=7(P=0.31); I²=15.34%					
Test for overall effect: Z=2.36(P=0.02)					
10.2.9 different BL - moxalactam					
Alanis 1983	20/46	27/48		30.04%	0.77[0.51,1.17]
Bezwoda 1985	8/29	11/31		12.09%	0.78[0.36,1.66]
Hansen 1986	4/14	9/19		8.68%	0.6[0.23,1.57]
Pegram 1984	21/72	20/68		23.39%	0.99[0.59,1.66]
Pickard 1983	14/37	23/38		25.8%	0.63[0.38,1.02]
Subtotal (95% CI)	**198**	**204**		**100%**	**0.77[0.6,0.99]**
Total events: 67 (Monotherapy), 90 (Combination therapy)					
Heterogeneity: Tau²=0; Chi²=1.89, df=4(P=0.76); I²=0%					
Test for overall effect: Z=2.06(P=0.04)					
10.2.10 different BL - piperacillin-tazobactam					
Gorschluter 2003	25/56	35/51		82.08%	0.65[0.46,0.92]
Hess 1998	9/48	8/48		17.92%	1.13[0.47,2.67]
Subtotal (95% CI)	**104**	**99**		**100%**	**0.74[0.53,1.02]**
Total events: 34 (Monotherapy), 43 (Combination therapy)					
Heterogeneity: Tau²=0; Chi²=1.41, df=1(P=0.23); I²=29.27%					
Test for overall effect: Z=1.83(P=0.07)					
10.2.11 different BL - cefepime					
Borbolla 2001	2/20	3/20		3.91%	0.67[0.12,3.57]
Corapcioglu 2005	12/25	15/25		19.57%	0.8[0.48,1.34]
Jimeno 2006	16/24	23/27		28.25%	0.78[0.57,1.08]
Pereira 2009	26/62	20/63		25.89%	1.32[0.83,2.1]
Yamamura 1997	17/56	17/55		22.38%	0.98[0.56,1.72]
Subtotal (95% CI)	**187**	**190**		**100%**	**0.97[0.77,1.22]**
Total events: 73 (Monotherapy), 78 (Combination therapy)					
Heterogeneity: Tau²=0; Chi²=4.05, df=4(P=0.4); I²=1.31%					
Test for overall effect: Z=0.3(P=0.77)					
10.2.12 different BL - other					
Conte 1996	10/21	8/19		8.46%	1.13[0.57,2.26]
El Haddad 1995	7/30	9/16		11.83%	0.41[0.19,0.9]
Gribble 1983	2/12	3/18		2.42%	1[0.2,5.12]

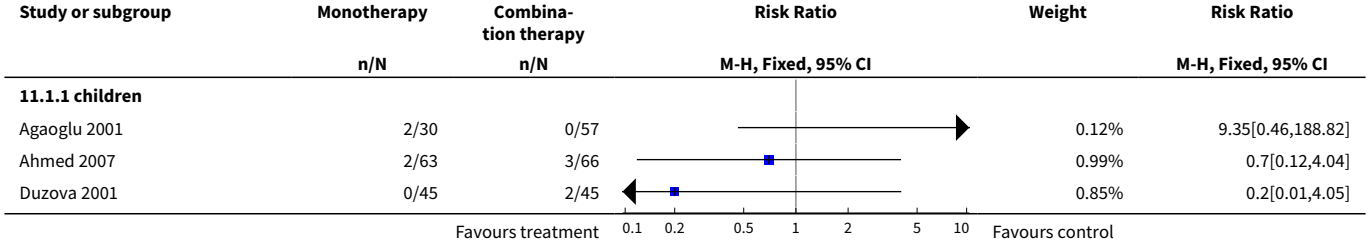


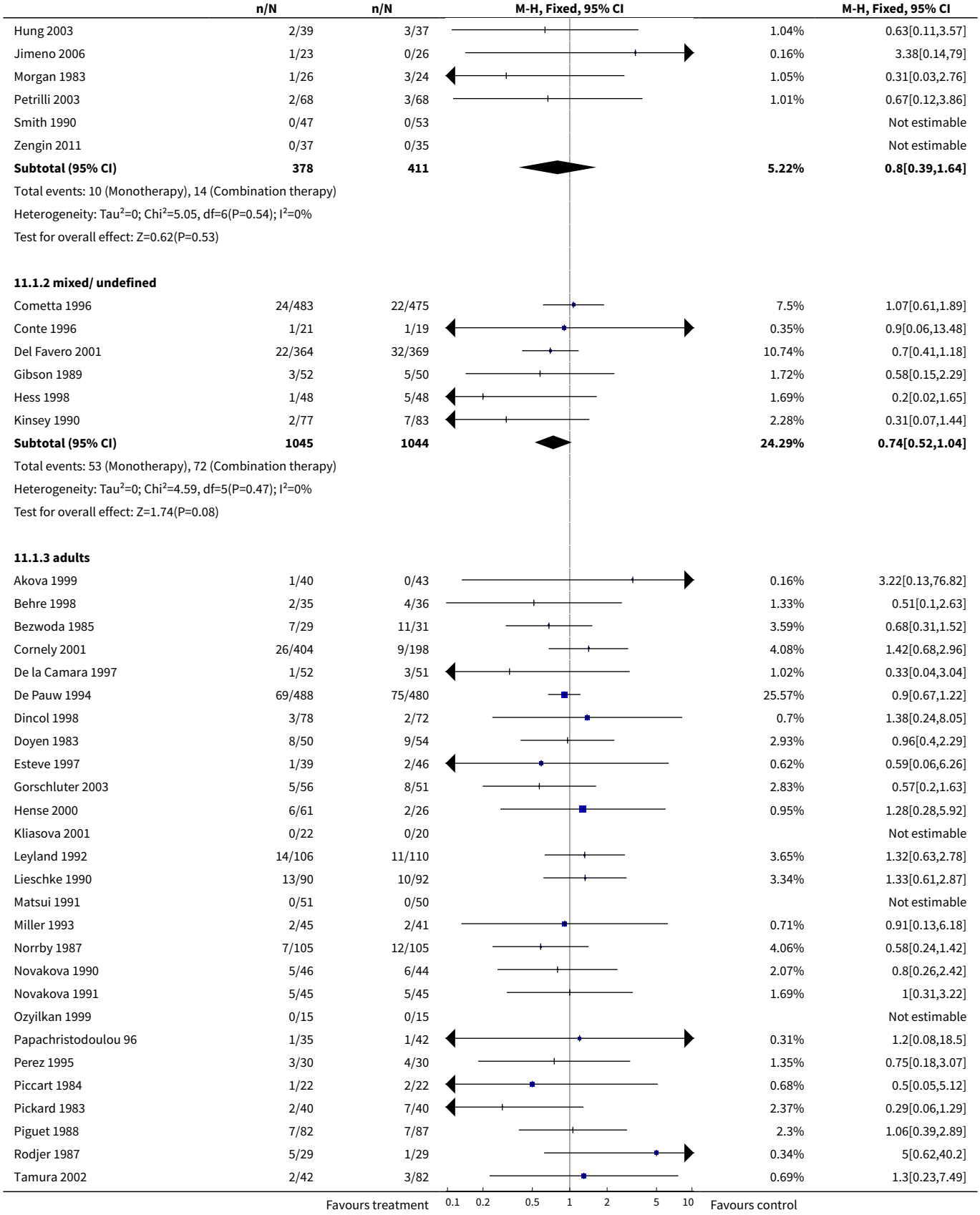


Comparison 11. Adults vs. children

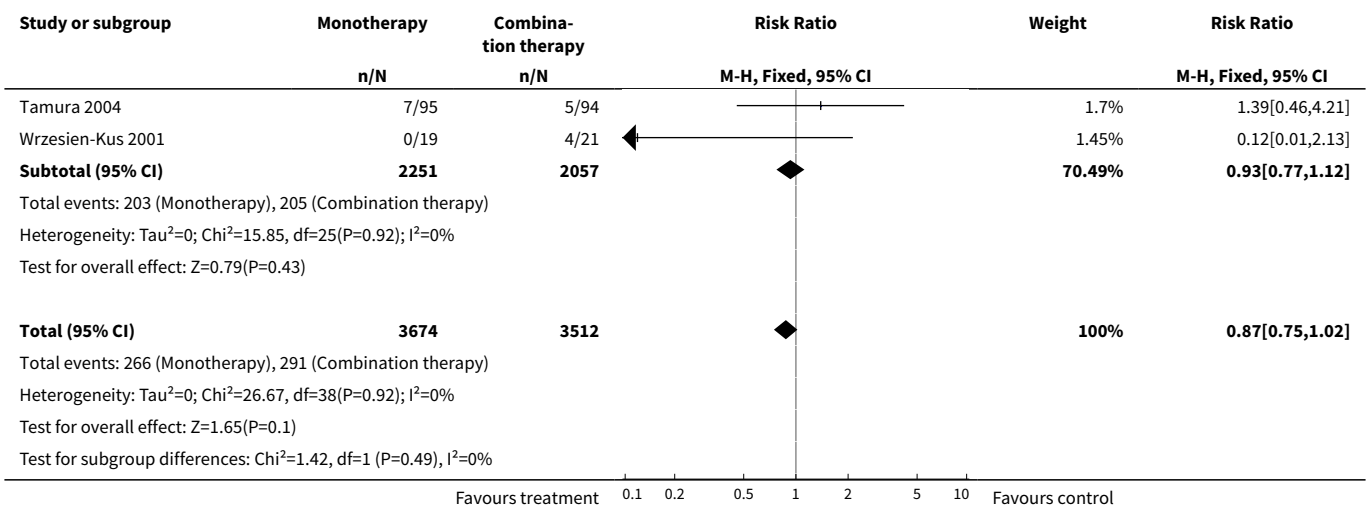
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All cause mortality	44	7186	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.75, 1.02]
1.1 children	9	789	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.39, 1.64]
1.2 mixed/ undefined	6	2089	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.52, 1.04]
1.3 adults	29	4308	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.77, 1.12]
2 Treatment failure	68		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 same BL - children	2	163	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.95, 1.90]
2.2 same BL - mixed	3	985	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.90, 1.14]
2.3 same BL - adults	11	1685	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [1.04, 1.32]
2.4 different BL - children	12	1086	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.87, 1.18]
2.5 different BL - mixed/ undefined	11	2263	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.83, 1.04]
2.6 different BL - adults	29	4160	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.85, 0.96]

Analysis 11.1. Comparison 11 Adults vs. children, Outcome 1 All cause mortality.

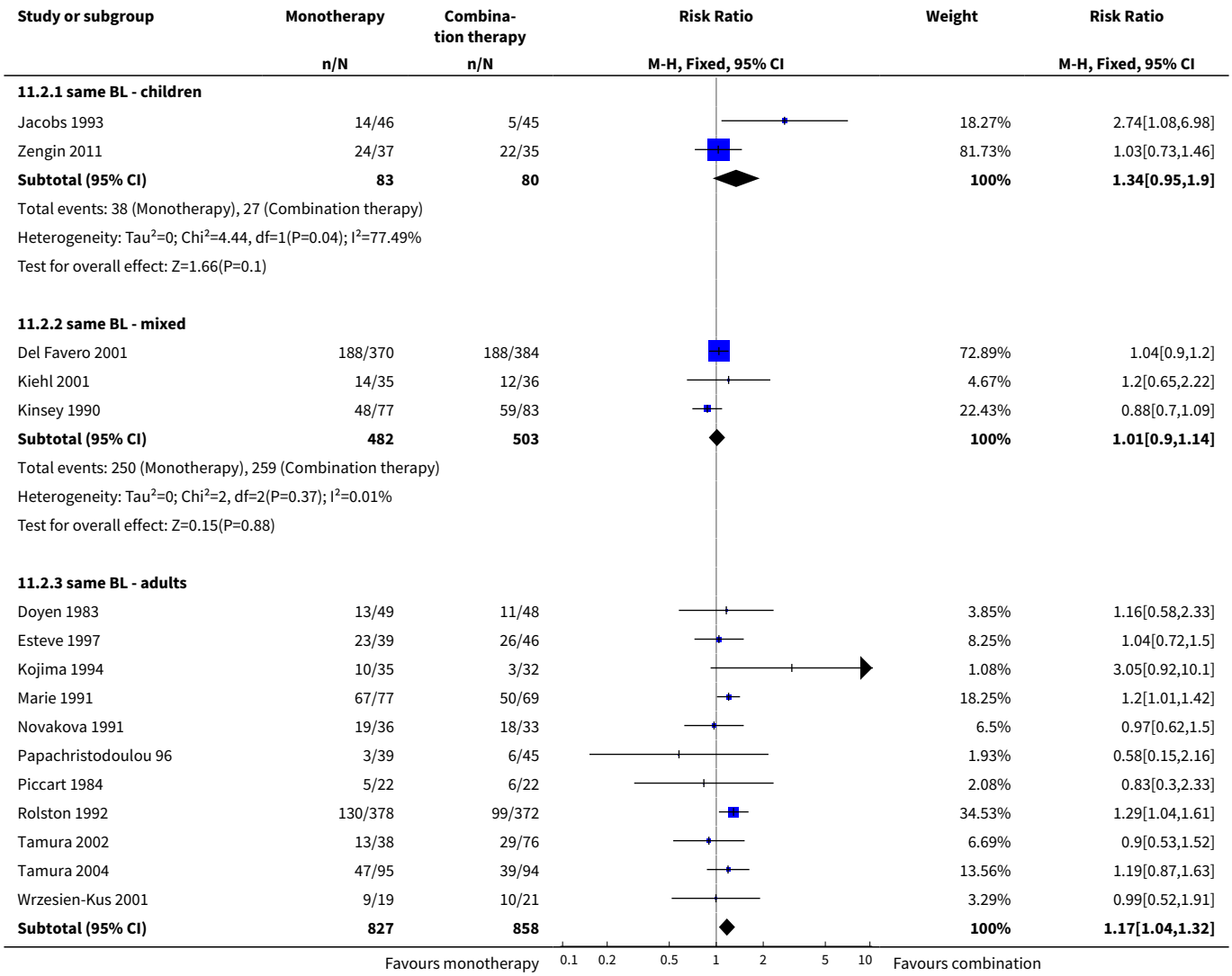


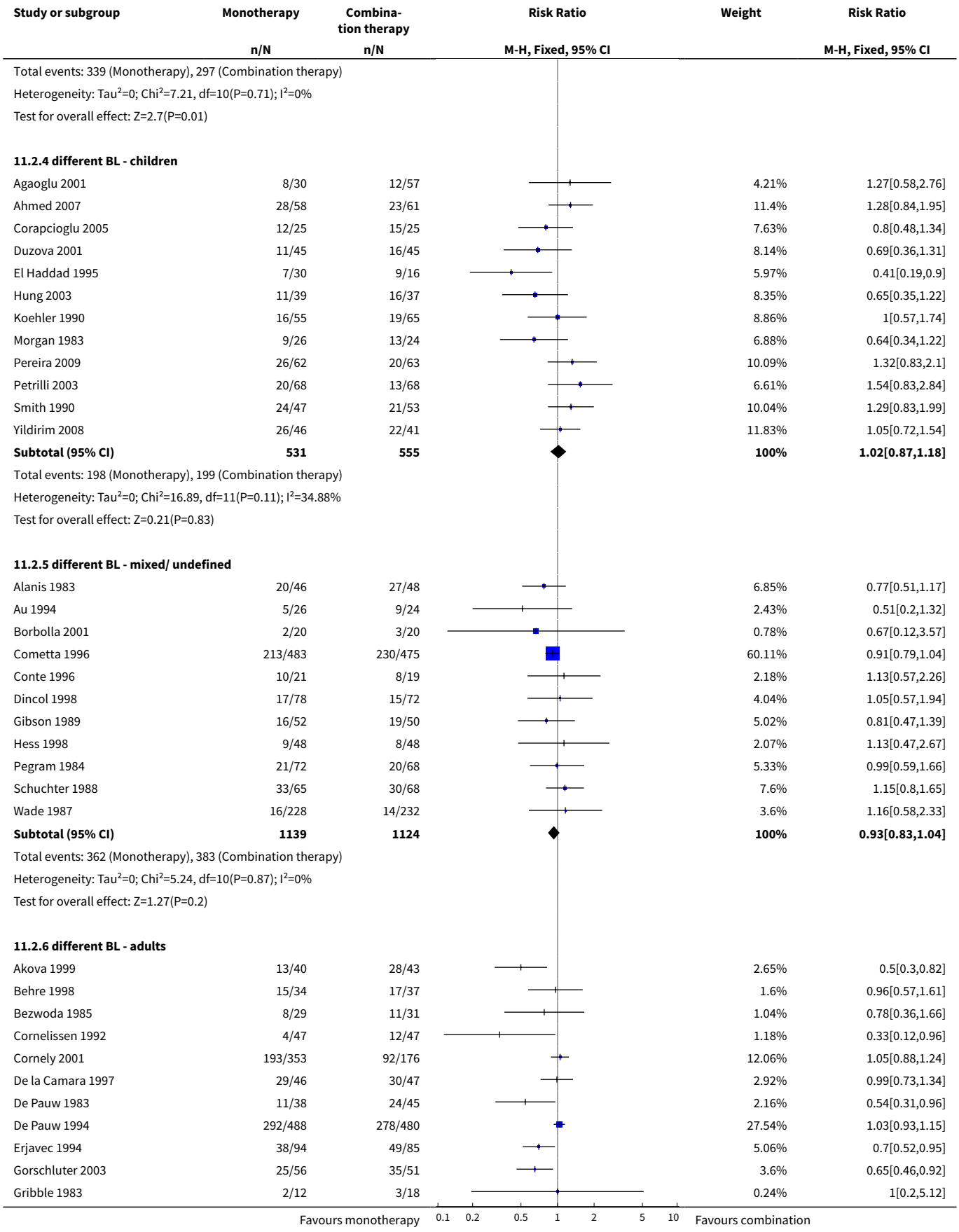


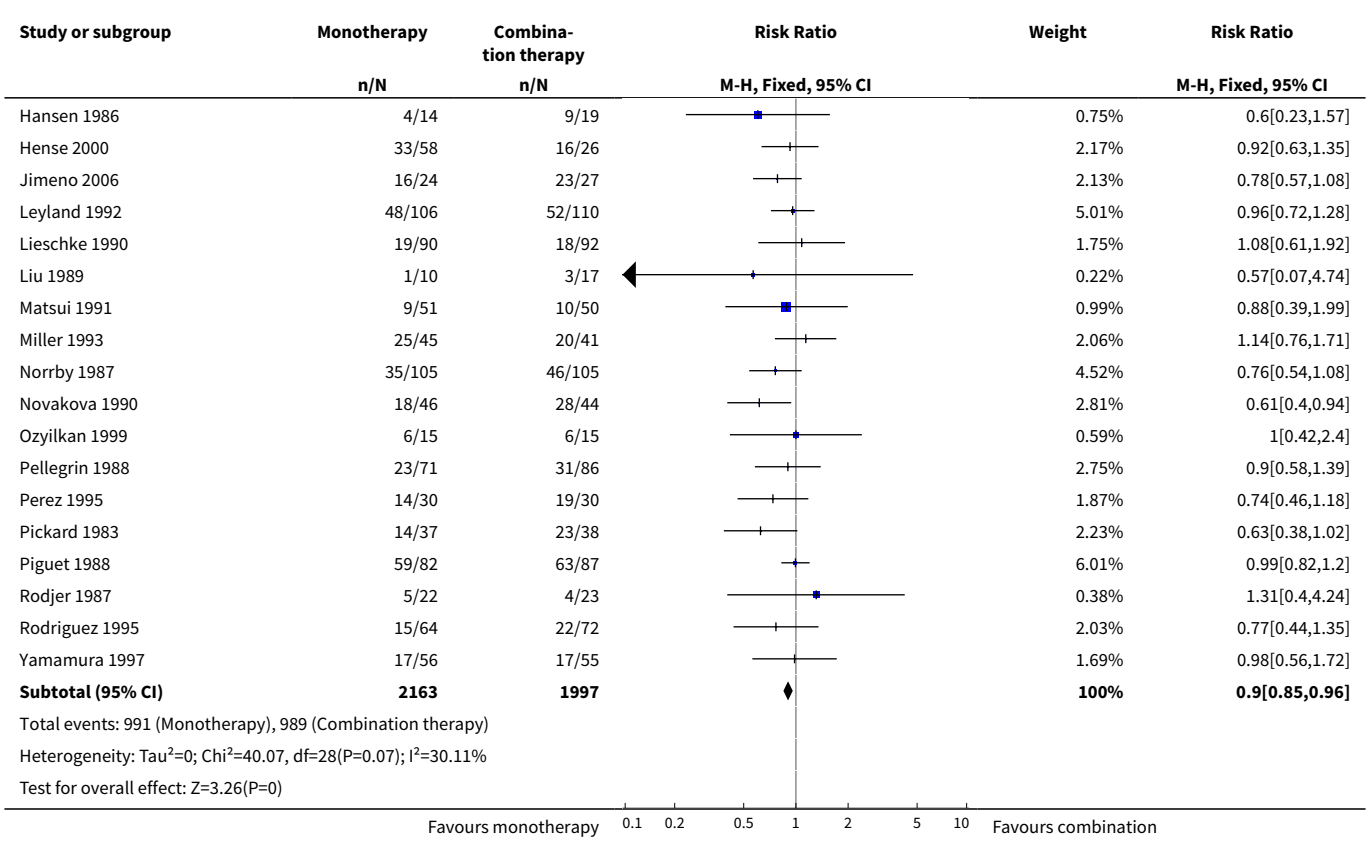
Study or subgroup	Monotherapy n/N	Combination therapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Hung 2003	2/39	3/37		1.04%	0.63[0.11,3.57]
Jimeno 2006	1/23	0/26		0.16%	3.38[0.14,79]
Morgan 1983	1/26	3/24		1.05%	0.31[0.03,2.76]
Petrilli 2003	2/68	3/68		1.01%	0.67[0.12,3.86]
Smith 1990	0/47	0/53			Not estimable
Zengin 2011	0/37	0/35			Not estimable
Subtotal (95% CI)	**378**	**411**		**5.22%**	**0.8[0.39,1.64]**
Total events: 10 (Monotherapy), 14 (Combination therapy)					
Heterogeneity: Tau²=0; Chi²=5.05, df=6(P=0.54); I²=0%					
Test for overall effect: Z=0.62(P=0.53)					
11.1.2 mixed/ undefined					
Cometta 1996	24/483	22/475		7.5%	1.07[0.61,1.89]
Conte 1996	1/21	1/19		0.35%	0.9[0.06,13.48]
Del Favero 2001	22/364	32/369		10.74%	0.7[0.41,1.18]
Gibson 1989	3/52	5/50		1.72%	0.58[0.15,2.29]
Hess 1998	1/48	5/48		1.69%	0.2[0.02,1.65]
Kinsey 1990	2/77	7/83		2.28%	0.31[0.07,1.44]
Subtotal (95% CI)	**1045**	**1044**		**24.29%**	**0.74[0.52,1.04]**
Total events: 53 (Monotherapy), 72 (Combination therapy)					
Heterogeneity: Tau²=0; Chi²=4.59, df=5(P=0.47); I²=0%					
Test for overall effect: Z=1.74(P=0.08)					
11.1.3 adults					
Akova 1999	1/40	0/43		0.16%	3.22[0.13,76.82]
Behre 1998	2/35	4/36		1.33%	0.51[0.1,2.63]
Bezwoda 1985	7/29	11/31		3.59%	0.68[0.31,1.52]
Cornely 2001	26/404	9/198		4.08%	1.42[0.68,2.96]
De la Camara 1997	1/52	3/51		1.02%	0.33[0.04,3.04]
De Pauw 1994	69/488	75/480		25.57%	0.9[0.67,1.22]
Dincol 1998	3/78	2/72		0.7%	1.38[0.24,8.05]
Doyen 1983	8/50	9/54		2.93%	0.96[0.4,2.29]
Esteve 1997	1/39	2/46		0.62%	0.59[0.06,6.26]
Gorschluter 2003	5/56	8/51		2.83%	0.57[0.2,1.63]
Hense 2000	6/61	2/26		0.95%	1.28[0.28,5.92]
Kliasova 2001	0/22	0/20			Not estimable
Leyland 1992	14/106	11/110		3.65%	1.32[0.63,2.78]
Lieschke 1990	13/90	10/92		3.34%	1.33[0.61,2.87]
Matsui 1991	0/51	0/50			Not estimable
Miller 1993	2/45	2/41		0.71%	0.91[0.13,6.18]
Norrby 1987	7/105	12/105		4.06%	0.58[0.24,1.42]
Novakova 1990	5/46	6/44		2.07%	0.8[0.26,2.42]
Novakova 1991	5/45	5/45		1.69%	1[0.31,3.22]
Ozyilkan 1999	0/15	0/15			Not estimable
Papachristodoulou 96	1/35	1/42		0.31%	1.2[0.08,18.5]
Perez 1995	3/30	4/30		1.35%	0.75[0.18,3.07]
Piccart 1984	1/22	2/22		0.68%	0.5[0.05,5.12]
Pickard 1983	2/40	7/40		2.37%	0.29[0.06,1.29]
Piguet 1988	7/82	7/87		2.3%	1.06[0.39,2.89]
Rodjer 1987	5/29	1/29		0.34%	5[0.62,40.2]
Tamura 2002	2/42	3/82		0.69%	1.3[0.23,7.49]



Analysis 11.2. Comparison 11 Adults vs. children, Outcome 2 Treatment failure.







Comparison 12. Sensitivity analysis (outcome in parenthesis)

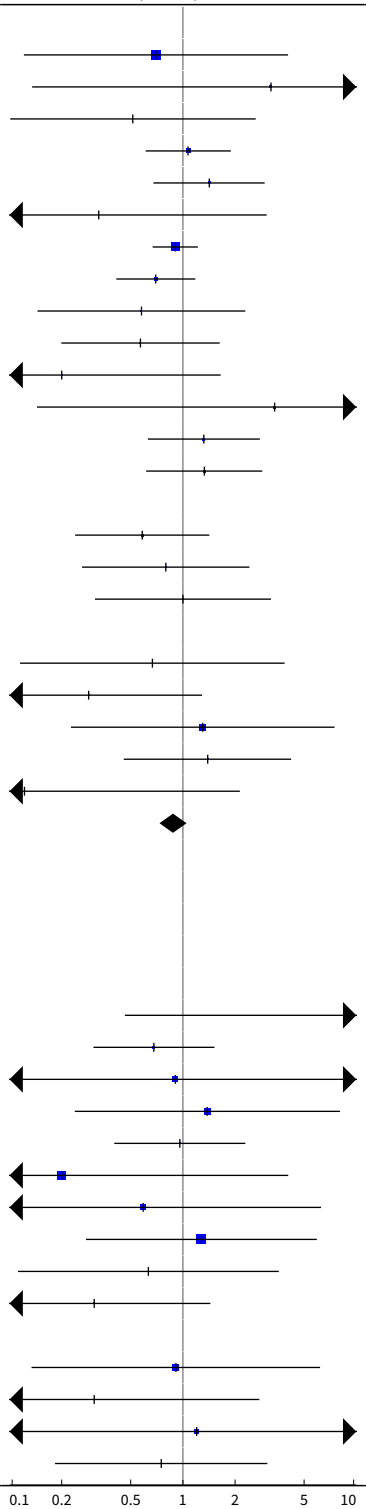
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Allocation concealment (mortality)	44	7186	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.75, 1.02]
1.1 A	24	5489	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.73, 1.05]
1.2 B	19	1625	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.61, 1.24]
1.3 C	1	72	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Intention-to-treat vs. efficacy analysis (mortality)	44	7186	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.75, 1.02]
2.1 efficacy analysis	20	4432	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.73, 1.06]
2.2 intention-to-treat analysis	24	2754	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.66, 1.15]
3 Unit of randomisation (mortality)	44	7186	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.75, 1.02]
3.1 patient analysis	19	3711	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.66, 1.08]
3.2 episode analysis	25	3475	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.73, 1.11]

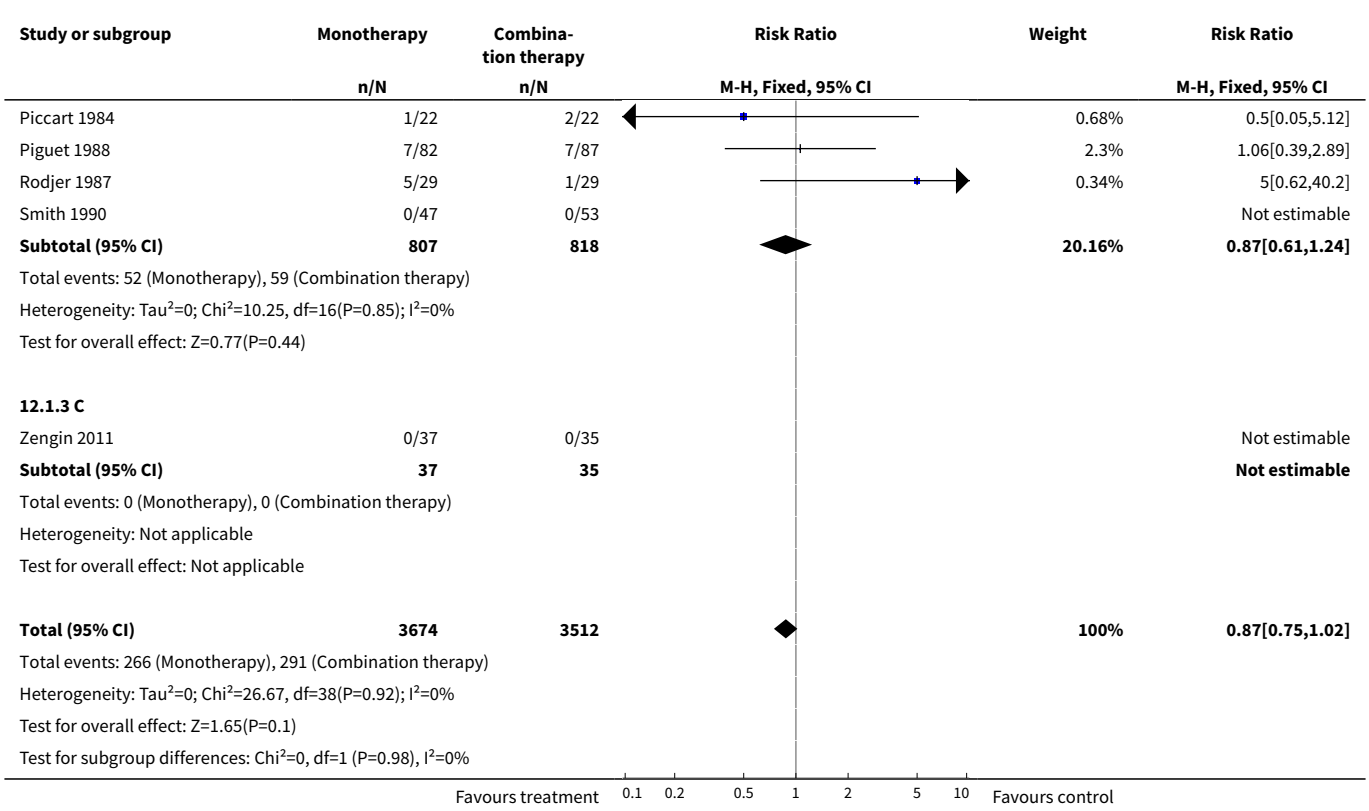
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Publication status (mortality)	43	7110	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.75, 1.03]
4.1 jounal publication	34	5811	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.71, 1.00]
4.2 other publication or un-published	9	1299	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.72, 1.59]
5 Trial size (mortality)	44	7186	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.75, 1.02]
5.1 number randomised>median 94p	19	5438	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.75, 1.07]
5.2 number randomised<median 94p	25	1748	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.55, 1.11]
6 Allocation concealment (failure)	69	10357	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.93, 1.01]
6.1 same beta-lactam - A	6	1310	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.99, 1.22]
6.2 same beta-lactam - B	9	1451	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.99, 1.30]
6.3 same beta-lactam - C	1	72	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.73, 1.46]
6.4 different beta-lactam - A	21	4422	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.88, 1.00]
6.5 different beta-lactam - B	31	3052	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.79, 0.96]
6.6 different beta-lactam - C	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.8 [0.48, 1.34]
7 Intention to treat vs. efficacy analysis (failure)	70		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 same BL - efficacy analysis	12	1884	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.98, 1.26]
7.2 same BL - ITT analysis	4	949	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.91, 1.19]
7.3 different BL - efficacy analysis	38	6010	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.88, 1.01]
7.4 different BL - ITT analysis	16	1659	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.71, 0.91]
8 Intention to treat vs. efficacy analysis, assuming dropouts=failures (failure)	68		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 same BL - efficacy analysis	5	1238	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.02, 1.29]
8.2 same BL - ITT analysis	10	1590	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.96, 1.19]
8.3 different BL - efficacy analysis	20	3037	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.89, 1.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.4 different BL - ITT analysis	33	4922	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.86, 0.97]
9 Trial size (failure)	70		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 same BL no. randomised>median	7	2210	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [1.01, 1.21]
9.2 same BL no. randomised<median	9	623	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.94, 1.39]
9.3 different BL no. randomised>median	28	6032	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.92, 1.03]
9.4 different BL no. randomised<median	26	1637	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.67, 0.84]
10 Unit of randomisation (failure)	71		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 same beta-lactam - patient	6	1212	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.93, 1.19]
10.2 same beta-lactam - episode	10	1621	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [1.04, 1.30]
10.3 different beta-lactam - patient	20	3137	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.82, 0.96]
10.4 different beta-lactam - episode	36	4656	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.89, 1.01]
11 Blinding (failure)	71		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 same beta-lactam - double blind	1	754	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.90, 1.20]
11.2 same beta-lactam - other	15	2079	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [1.04, 1.26]
11.3 different beta-lactam - double blind	3	623	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.83, 1.55]
11.4 different beta-lactam - other	52	7113	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.87, 0.96]
12 Publication status (failure)	71		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 same beta-lactam - journal publication	12	2496	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [1.02, 1.21]
12.2 same beta-lactam - other	4	337	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.79, 1.41]
12.3 different beta-lactam - journal publication	44	5866	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.86, 0.96]
12.4 different beta-lactam - other	11	1870	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.89, 1.12]

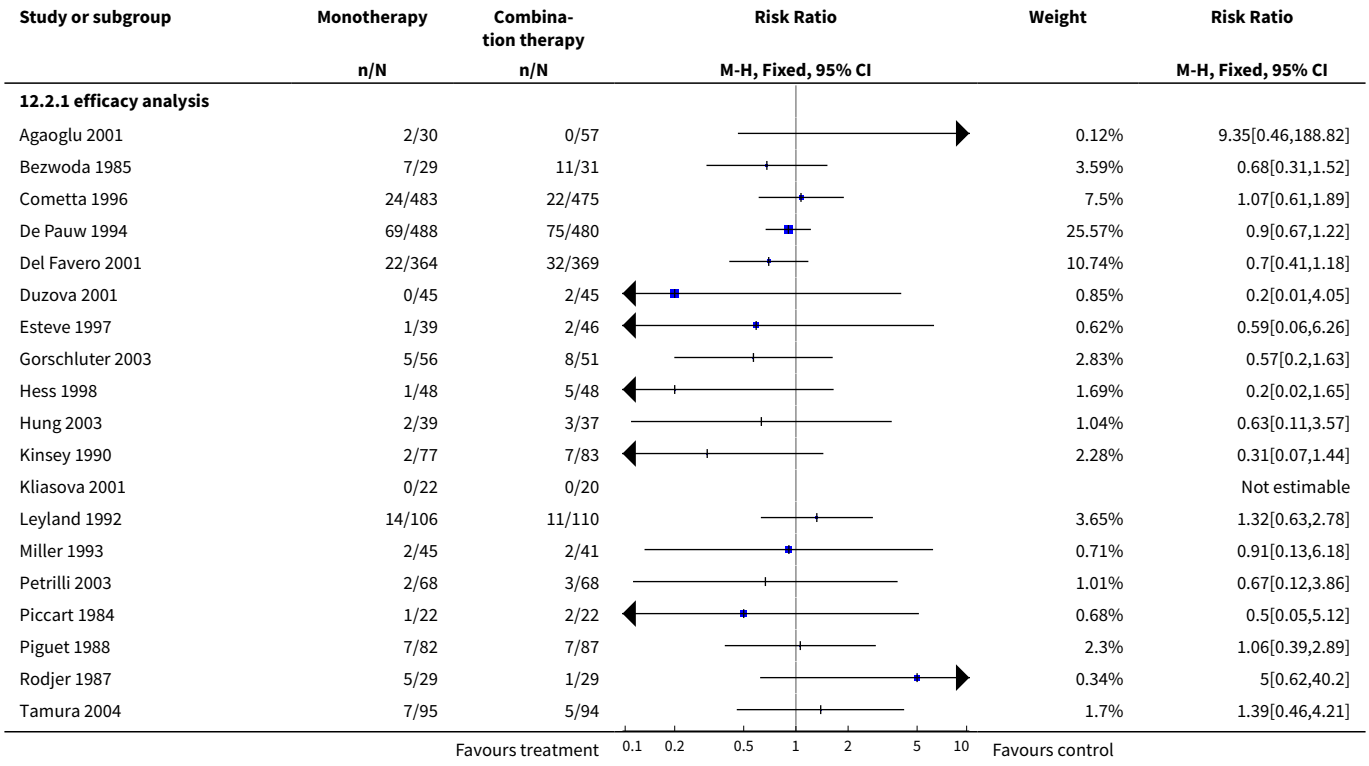
Analysis 12.1. Comparison 12 Sensitivity analysis (outcome in parenthesis), Outcome 1 Allocation concealment (mortality).

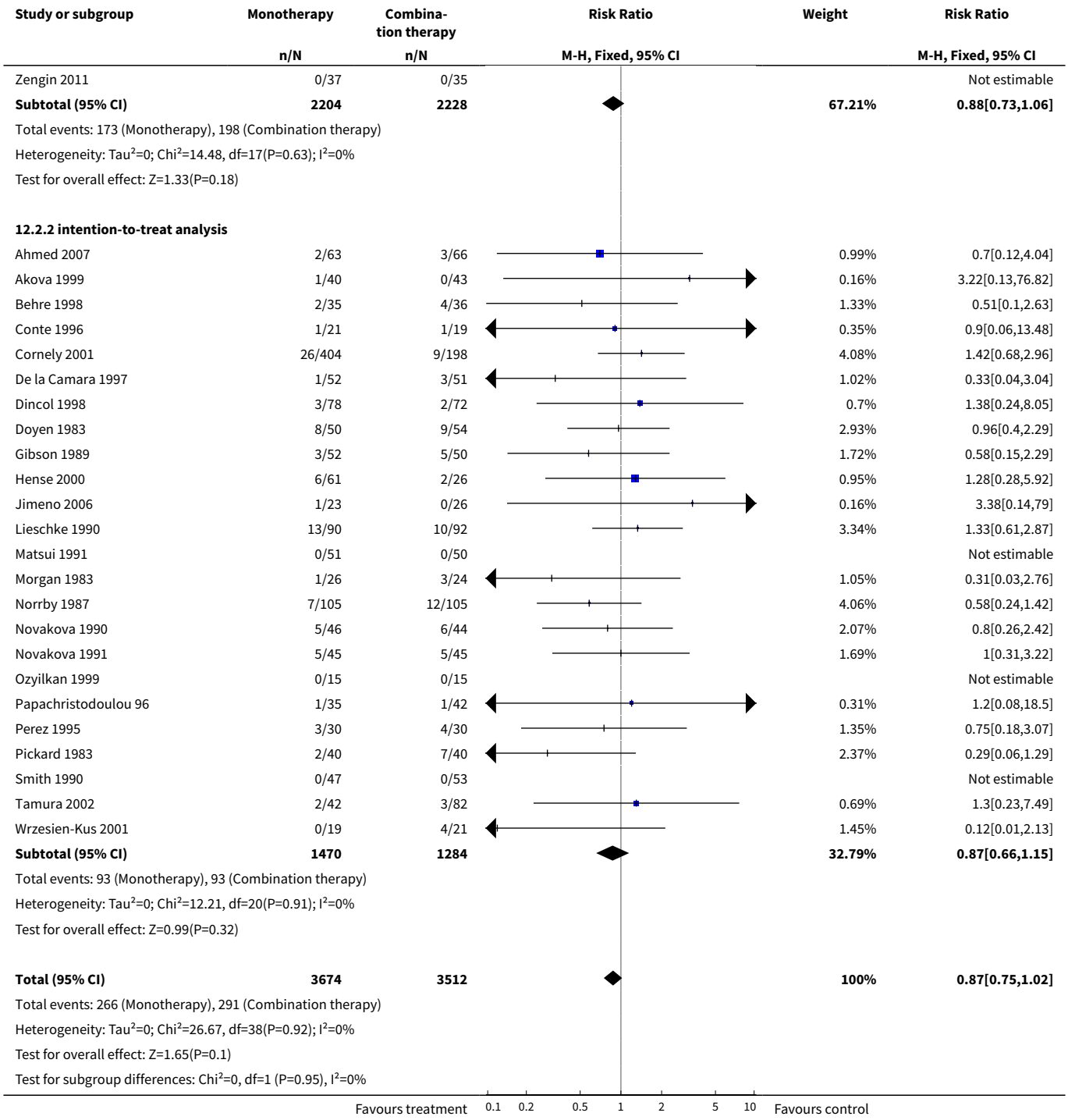
Study or subgroup	Monotherapy n/N	Combination therapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
12.1.1 A					
Ahmed 2007	2/63	3/66		0.99%	0.7[0.12,4.04]
Akova 1999	1/40	0/43		0.16%	3.22[0.13,76.82]
Behre 1998	2/35	4/36		1.33%	0.51[0.1,2.63]
Cometta 1996	24/483	22/475		7.5%	1.07[0.61,1.89]
Cornely 2001	26/404	9/198		4.08%	1.42[0.68,2.96]
De la Camara 1997	1/52	3/51		1.02%	0.33[0.04,3.04]
De Pauw 1994	69/488	75/480		25.57%	0.9[0.67,1.22]
Del Favero 2001	22/364	32/369		10.74%	0.7[0.41,1.18]
Gibson 1989	3/52	5/50		1.72%	0.58[0.15,2.29]
Gorschluter 2003	5/56	8/51		2.83%	0.57[0.2,1.63]
Hess 1998	1/48	5/48		1.69%	0.2[0.02,1.65]
Jimeno 2006	1/23	0/26		0.16%	3.38[0.14,79]
Leyland 1992	14/106	11/110		3.65%	1.32[0.63,2.78]
Lieschke 1990	13/90	10/92		3.34%	1.33[0.61,2.87]
Matsui 1991	0/51	0/50			Not estimable
Norrby 1987	7/105	12/105		4.06%	0.58[0.24,1.42]
Novakova 1990	5/46	6/44		2.07%	0.8[0.26,2.42]
Novakova 1991	5/45	5/45		1.69%	1[0.31,3.22]
Ozyilkan 1999	0/15	0/15			Not estimable
Petrilli 2003	2/68	3/68		1.01%	0.67[0.12,3.86]
Pickard 1983	2/40	7/40		2.37%	0.29[0.06,1.29]
Tamura 2002	2/42	3/82		0.69%	1.3[0.23,7.49]
Tamura 2004	7/95	5/94		1.7%	1.39[0.46,4.21]
Wrzesien-Kus 2001	0/19	4/21		1.45%	0.12[0.01,2.13]
Subtotal (95% CI)	**2830**	**2659**		**79.84%**	**0.88[0.73,1.05]**
Total events: 214 (Monotherapy), 232 (Combination therapy)					
Heterogeneity: Tau^2=0; Chi^2=16.41, df=21(P=0.75); I^2=0%					
Test for overall effect: Z=1.47(P=0.14)					
12.1.2 B					
Agaoglu 2001	2/30	0/57		0.12%	9.35[0.46,188.82]
Bezwoda 1985	7/29	11/31		3.59%	0.68[0.31,1.52]
Conte 1996	1/21	1/19		0.35%	0.9[0.06,13.48]
Dincol 1998	3/78	2/72		0.7%	1.38[0.24,8.05]
Doyen 1983	8/50	9/54		2.93%	0.96[0.4,2.29]
Duzova 2001	0/45	2/45		0.85%	0.2[0.01,4.05]
Esteve 1997	1/39	2/46		0.62%	0.59[0.06,6.26]
Hense 2000	6/61	2/26		0.95%	1.28[0.28,5.92]
Hung 2003	2/39	3/37		1.04%	0.63[0.11,3.57]
Kinsey 1990	2/77	7/83		2.28%	0.31[0.07,1.44]
Kliasova 2001	0/22	0/20			Not estimable
Miller 1993	2/45	2/41		0.71%	0.91[0.13,6.18]
Morgan 1983	1/26	3/24		1.05%	0.31[0.03,2.76]
Papachristodoulou 96	1/35	1/42		0.31%	1.2[0.08,18.5]
Perez 1995	3/30	4/30		1.35%	0.75[0.18,3.07]



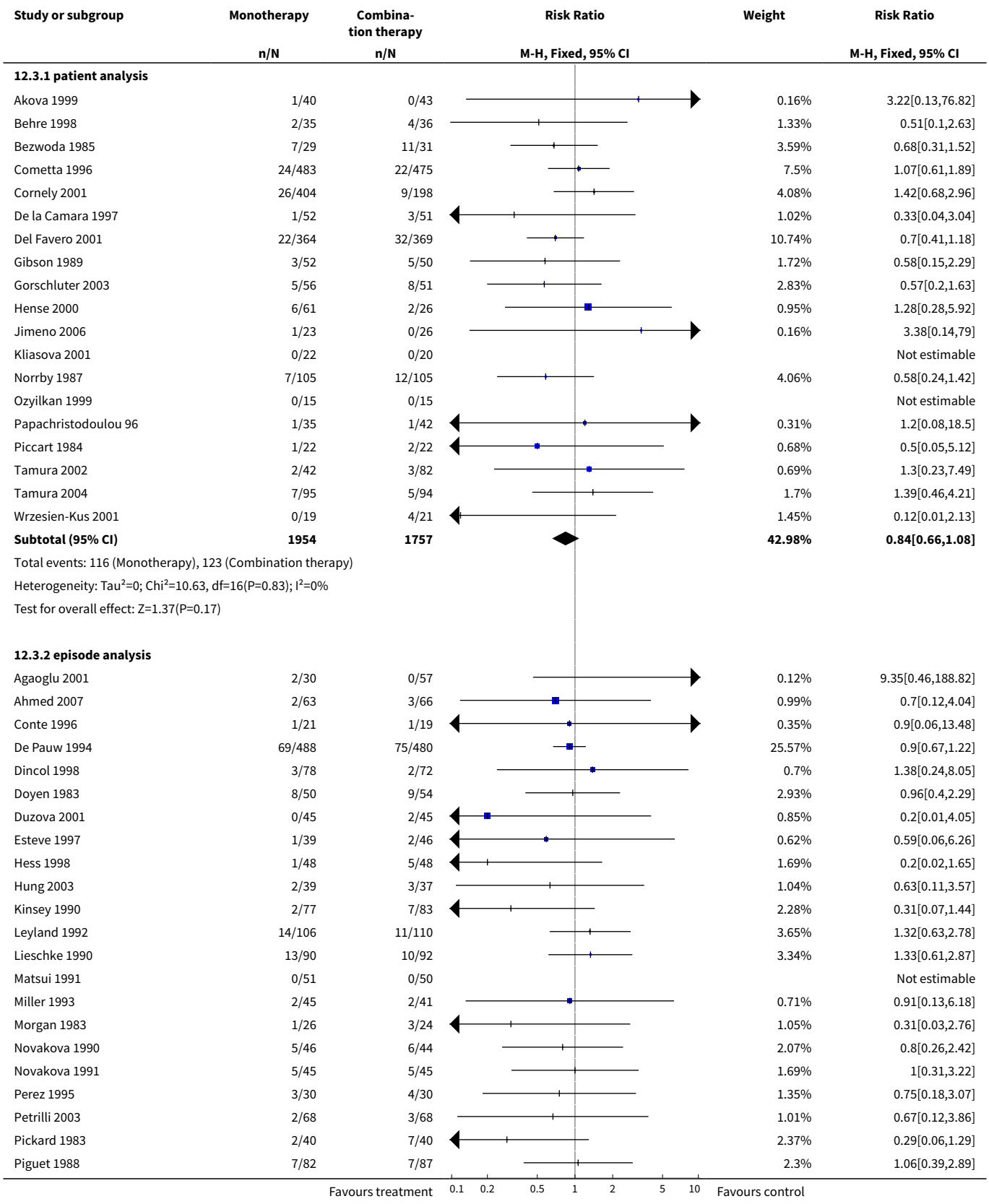


Analysis 12.2. Comparison 12 Sensitivity analysis (outcome in parenthesis), Outcome 2 Intention-to-treat vs. efficacy analysis (mortality).



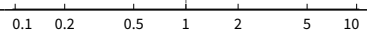


Analysis 12.3. Comparison 12 Sensitivity analysis (outcome in parenthesis), Outcome 3 Unit of randomisation (mortality).



Study or subgroup	Monotherapy n/N	Combination therapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
12.3.1 patient analysis					
Akova 1999	1/40	0/43		0.16%	3.22[0.13,76.82]
Behre 1998	2/35	4/36		1.33%	0.51[0.1,2.63]
Bezwoda 1985	7/29	11/31		3.59%	0.68[0.31,1.52]
Cometta 1996	24/483	22/475		7.5%	1.07[0.61,1.89]
Cornely 2001	26/404	9/198		4.08%	1.42[0.68,2.96]
De la Camara 1997	1/52	3/51		1.02%	0.33[0.04,3.04]
Del Favero 2001	22/364	32/369		10.74%	0.7[0.41,1.18]
Gibson 1989	3/52	5/50		1.72%	0.58[0.15,2.29]
Gorschluter 2003	5/56	8/51		2.83%	0.57[0.2,1.63]
Hense 2000	6/61	2/26		0.95%	1.28[0.28,5.92]
Jimeno 2006	1/23	0/26		0.16%	3.38[0.14,79]
Kliasova 2001	0/22	0/20			Not estimable
Norrby 1987	7/105	12/105		4.06%	0.58[0.24,1.42]
Ozyilkan 1999	0/15	0/15			Not estimable
Papachristodoulou 96	1/35	1/42		0.31%	1.2[0.08,18.5]
Piccart 1984	1/22	2/22		0.68%	0.5[0.05,5.12]
Tamura 2002	2/42	3/82		0.69%	1.3[0.23,7.49]
Tamura 2004	7/95	5/94		1.7%	1.39[0.46,4.21]
Wrzesien-Kus 2001	0/19	4/21		1.45%	0.12[0.01,2.13]
Subtotal (95% CI)	**1954**	**1757**		**42.98%**	**0.84[0.66,1.08]**
Total events: 116 (Monotherapy), 123 (Combination therapy)					
Heterogeneity: Tau^2=0; Chi^2=10.63, df=16(P=0.83); I^2=0%					
Test for overall effect: Z=1.37(P=0.17)					
12.3.2 episode analysis					
Agaoglu 2001	2/30	0/57		0.12%	9.35[0.46,188.82]
Ahmed 2007	2/63	3/66		0.99%	0.7[0.12,4.04]
Conte 1996	1/21	1/19		0.35%	0.9[0.06,13.48]
De Pauw 1994	69/488	75/480		25.57%	0.9[0.67,1.22]
Dincol 1998	3/78	2/72		0.7%	1.38[0.24,8.05]
Doyen 1983	8/50	9/54		2.93%	0.96[0.4,2.29]
Duzova 2001	0/45	2/45		0.85%	0.2[0.01,4.05]
Esteve 1997	1/39	2/46		0.62%	0.59[0.06,6.26]
Hess 1998	1/48	5/48		1.69%	0.2[0.02,1.65]
Hung 2003	2/39	3/37		1.04%	0.63[0.11,3.57]
Kinsey 1990	2/77	7/83		2.28%	0.31[0.07,1.44]
Leyland 1992	14/106	11/110		3.65%	1.32[0.63,2.78]
Lieschke 1990	13/90	10/92		3.34%	1.33[0.61,2.87]
Matsui 1991	0/51	0/50			Not estimable
Miller 1993	2/45	2/41		0.71%	0.91[0.13,6.18]
Morgan 1983	1/26	3/24		1.05%	0.31[0.03,2.76]
Novakova 1990	5/46	6/44		2.07%	0.8[0.26,2.42]
Novakova 1991	5/45	5/45		1.69%	1[0.31,3.22]
Perez 1995	3/30	4/30		1.35%	0.75[0.18,3.07]
Petrilli 2003	2/68	3/68		1.01%	0.67[0.12,3.86]
Pickard 1983	2/40	7/40		2.37%	0.29[0.06,1.29]
Piguet 1988	7/82	7/87		2.3%	1.06[0.39,2.89]

Study or subgroup	Monotherapy n/N	Combination therapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Rodjer 1987	5/29	1/29		0.34%	5[0.62,40.2]
Smith 1990	0/47	0/53			Not estimable
Zengin 2011	0/37	0/35			Not estimable
Subtotal (95% CI)	**1720**	**1755**		**57.02%**	**0.9[0.73,1.11]**
Total events: 150 (Monotherapy), 168 (Combination therapy)					
Heterogeneity: Tau^2=0; Chi^2=15.82, df=21(P=0.78); I^2=0%					
Test for overall effect: Z=1(P=0.32)					
Total (95% CI)	**3674**	**3512**		**100%**	**0.87[0.75,1.02]**
Total events: 266 (Monotherapy), 291 (Combination therapy)					
Heterogeneity: Tau^2=0; Chi^2=26.67, df=38(P=0.92); I^2=0%					
Test for overall effect: Z=1.65(P=0.1)					
Test for subgroup differences: Chi^2=0.17, df=1 (P=0.68), I^2=0%					

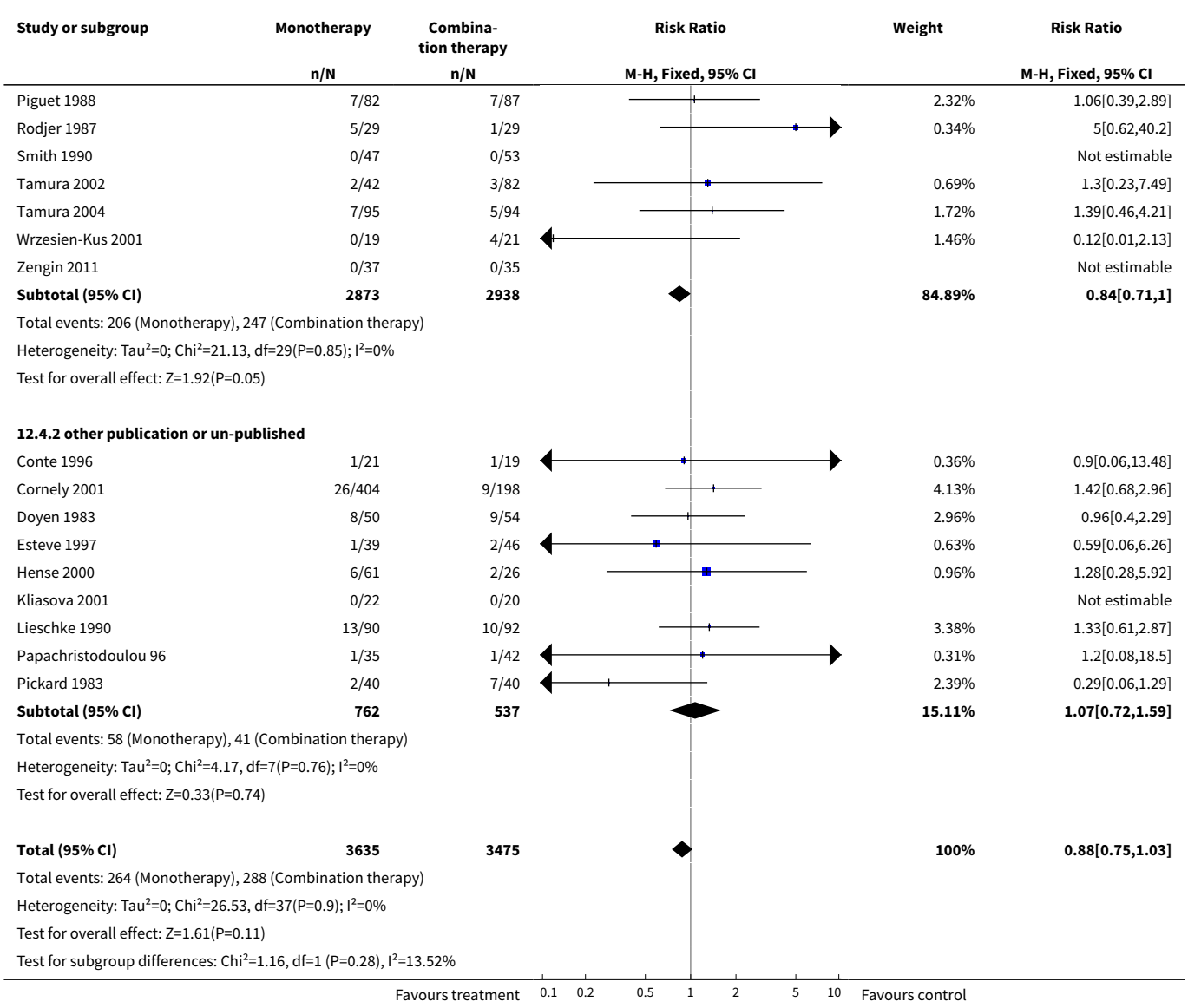


Favours treatment — Favours control

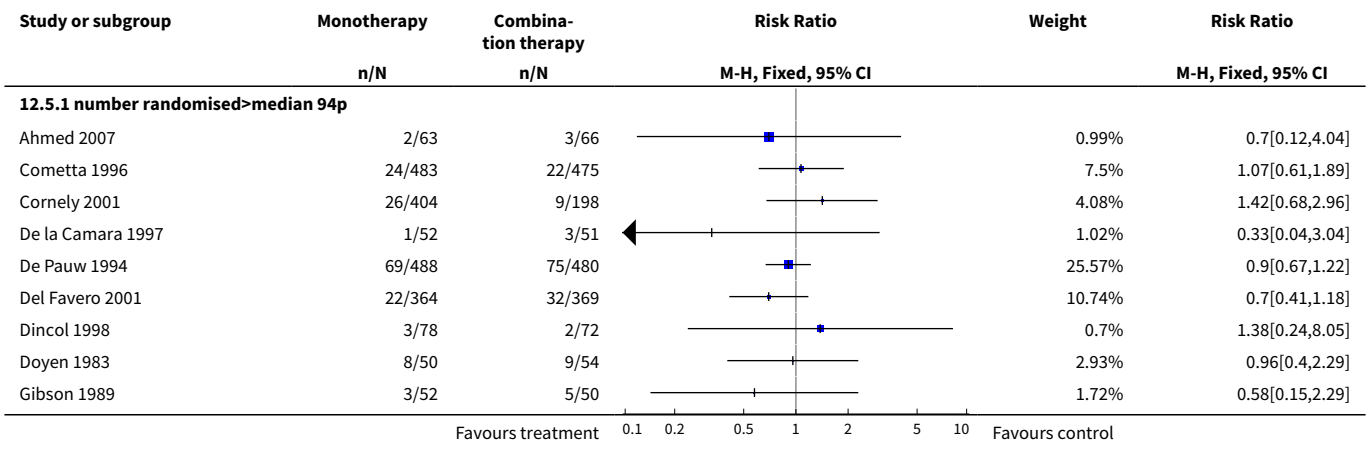
Analysis 12.4. Comparison 12 Sensitivity analysis (outcome in parenthesis), Outcome 4 Publication status (mortality).

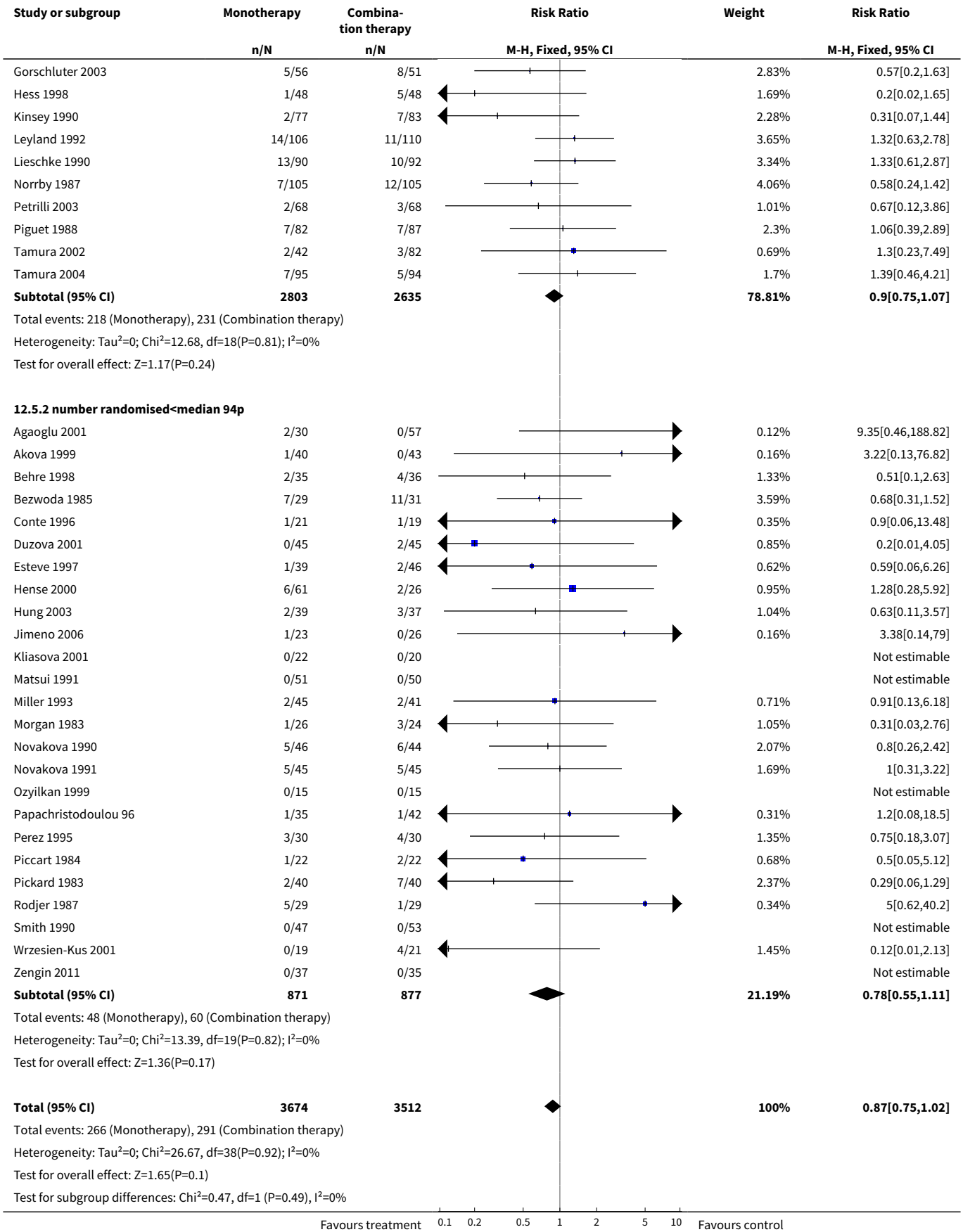
Study or subgroup	Monotherapy n/N	Combination therapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
12.4.1 jounal publication					
Agaoglu 2001	2/30	0/57		0.12%	9.35[0.46,188.82]
Ahmed 2007	2/63	3/66		1%	0.7[0.12,4.04]
Akova 1999	1/40	0/43		0.16%	3.22[0.13,76.82]
Behre 1998	2/35	4/36		1.35%	0.51[0.1,2.63]
Bezwoda 1985	7/29	11/31		3.63%	0.68[0.31,1.52]
Cometta 1996	24/483	22/475		7.58%	1.07[0.61,1.89]
De la Camara 1997	1/52	3/51		1.03%	0.33[0.04,3.04]
De Pauw 1994	69/488	75/480		25.83%	0.9[0.67,1.22]
Del Favero 2001	22/364	32/369		10.86%	0.7[0.41,1.18]
Dincol 1998	3/78	2/72		0.71%	1.38[0.24,8.05]
Duzova 2001	0/45	2/45		0.85%	0.2[0.01,4.05]
Gibson 1989	3/52	5/50		1.74%	0.58[0.15,2.29]
Gorschluter 2003	5/56	8/51		2.86%	0.57[0.2,1.63]
Hess 1998	1/48	5/48		1.71%	0.2[0.02,1.65]
Jimeno 2006	1/23	0/26		0.16%	3.38[0.14,79]
Kinsey 1990	2/77	7/83		2.3%	0.31[0.07,1.44]
Leyland 1992	14/106	11/110		3.69%	1.32[0.63,2.78]
Matsui 1991	0/51	0/50			Not estimable
Miller 1993	2/45	2/41		0.72%	0.91[0.13,6.18]
Morgan 1983	1/26	3/24		1.07%	0.31[0.03,2.76]
Norrby 1987	7/105	12/105		4.1%	0.58[0.24,1.42]
Novakova 1990	5/46	6/44		2.1%	0.8[0.26,2.42]
Novakova 1991	5/45	5/45		1.71%	1[0.31,3.22]
Ozyilkan 1999	0/15	0/15			Not estimable
Perez 1995	3/30	4/30		1.37%	0.75[0.18,3.07]
Petrilli 2003	2/68	3/68		1.02%	0.67[0.12,3.86]
Piccart 1984	1/22	2/22		0.68%	0.5[0.05,5.12]

Favours treatment — Favours control



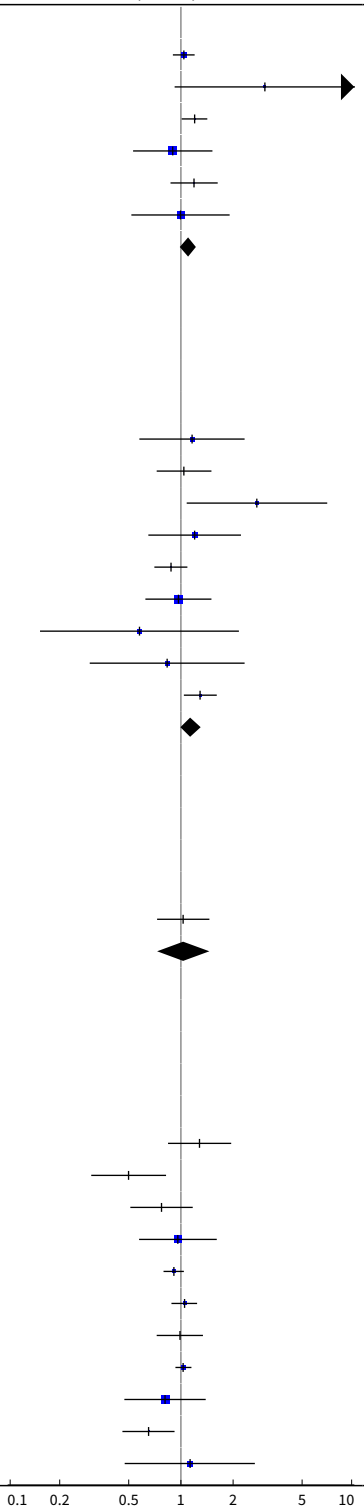
Analysis 12.5. Comparison 12 Sensitivity analysis (outcome in parenthesis), Outcome 5 Trial size (mortality).

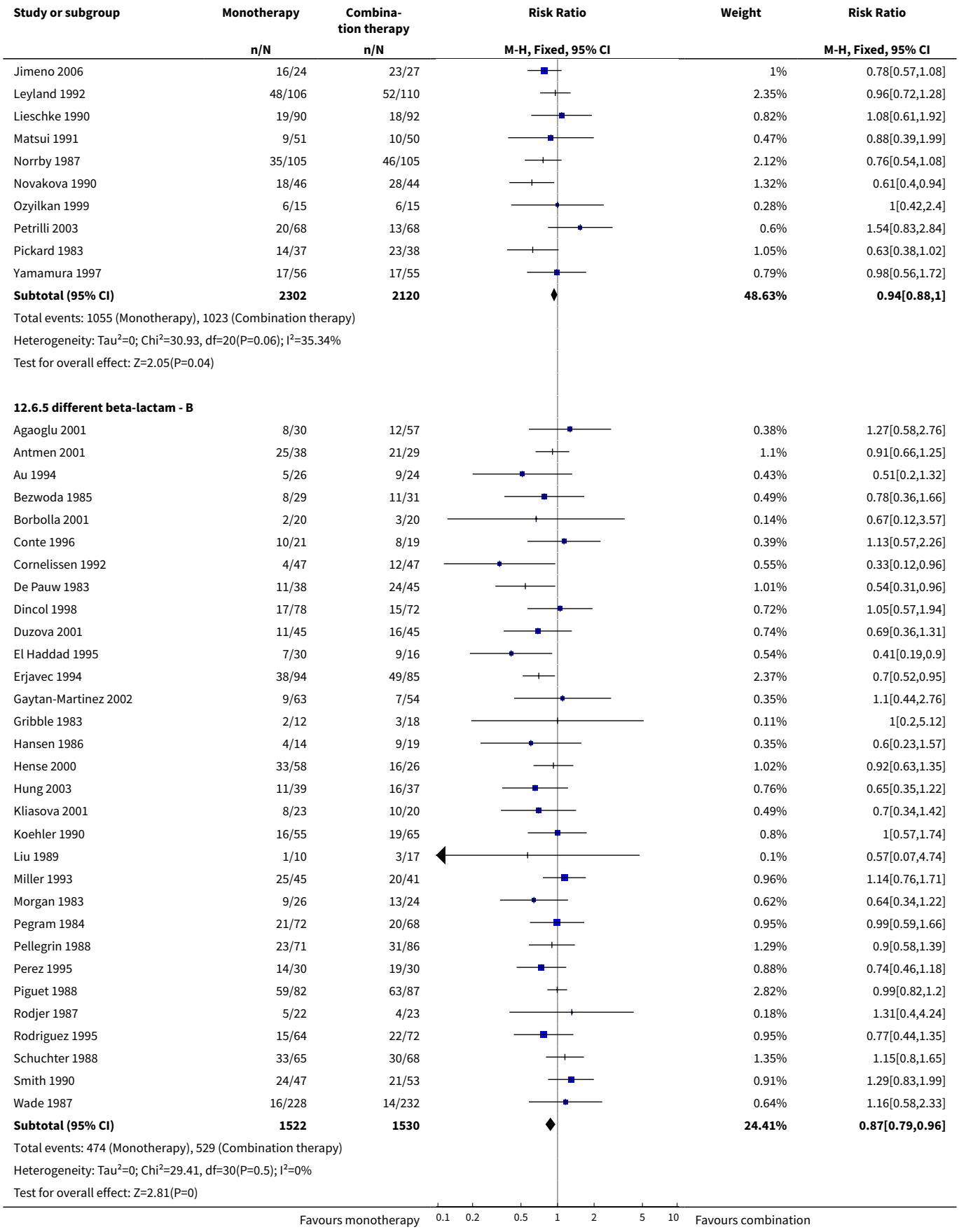


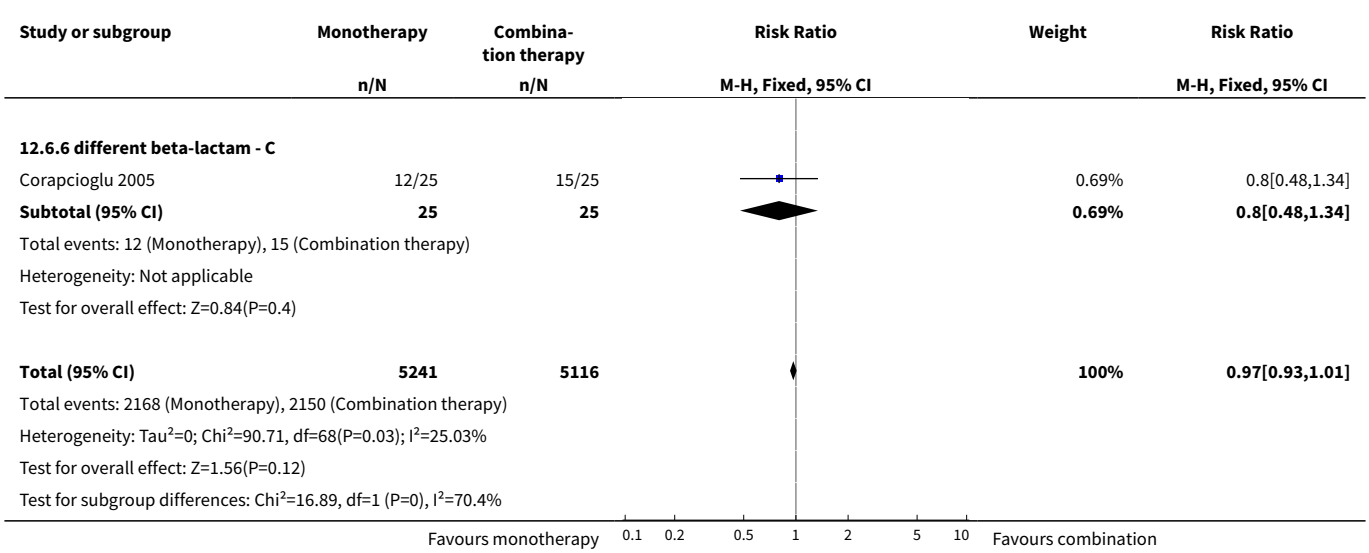


Analysis 12.6. Comparison 12 Sensitivity analysis (outcome in parenthesis), Outcome 6 Allocation concealment (failure).

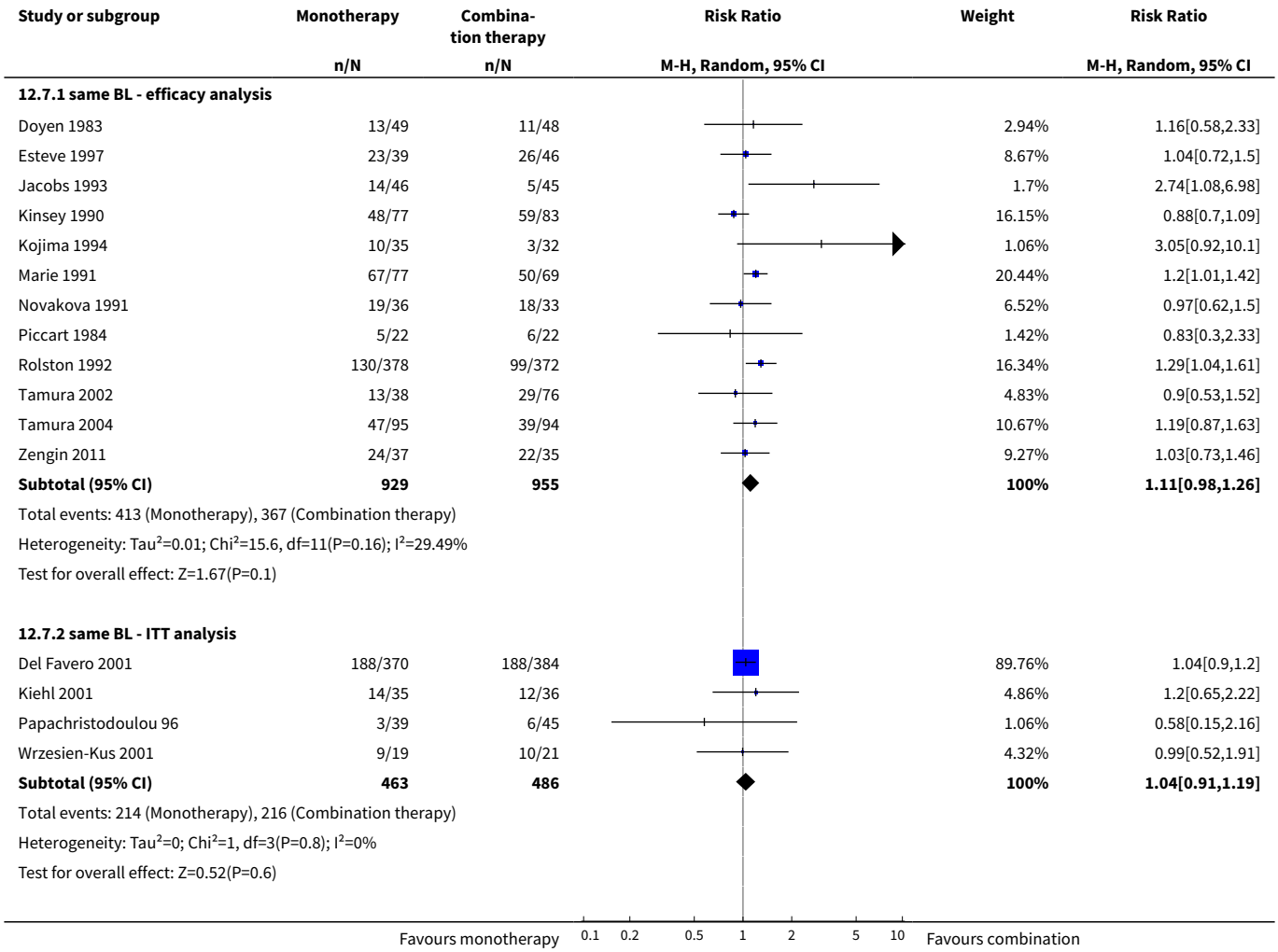
Study or subgroup	Monotherapy n/N	Combination therapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
12.6.1 same beta-lactam - A					
Del Favero 2001	188/370	188/384		8.51%	1.04[0.9,1.2]
Kojima 1994	10/35	3/32		0.14%	3.05[0.92,10.1]
Marie 1991	67/77	50/69		2.43%	1.2[1.01,1.42]
Tamura 2002	13/38	29/76		0.89%	0.9[0.53,1.52]
Tamura 2004	47/95	39/94		1.81%	1.19[0.87,1.63]
Wrzesien-Kus 2001	9/19	10/21		0.44%	0.99[0.52,1.91]
Subtotal (95% CI)	**634**	**676**		**14.22%**	**1.1[0.99,1.22]**
Total events: 334 (Monotherapy), 319 (Combination therapy)					
Heterogeneity: Tau^2=0; Chi^2=5.4, df=5(P=0.37); I^2=7.45%					
Test for overall effect: Z=1.69(P=0.09)					
12.6.2 same beta-lactam - B					
Doyen 1983	13/49	11/48		0.51%	1.16[0.58,2.33]
Esteve 1997	23/39	26/46		1.1%	1.04[0.72,1.5]
Jacobs 1993	14/46	5/45		0.23%	2.74[1.08,6.98]
Kiehl 2001	14/35	12/36		0.55%	1.2[0.65,2.22]
Kinsey 1990	48/77	59/83		2.62%	0.88[0.7,1.09]
Novakova 1991	19/36	18/33		0.87%	0.97[0.62,1.5]
Papachristodoulou 96	3/39	6/45		0.26%	0.58[0.15,2.16]
Piccart 1984	5/22	6/22		0.28%	0.83[0.3,2.33]
Rolston 1992	130/378	99/372		4.6%	1.29[1.04,1.61]
Subtotal (95% CI)	**721**	**730**		**11.01%**	**1.13[0.99,1.3]**
Total events: 269 (Monotherapy), 242 (Combination therapy)					
Heterogeneity: Tau^2=0; Chi^2=12.08, df=8(P=0.15); I^2=33.79%					
Test for overall effect: Z=1.85(P=0.06)					
12.6.3 same beta-lactam - C					
Zengin 2011	24/37	22/35		1.04%	1.03[0.73,1.46]
Subtotal (95% CI)	**37**	**35**		**1.04%**	**1.03[0.73,1.46]**
Total events: 24 (Monotherapy), 22 (Combination therapy)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.18(P=0.86)					
12.6.4 different beta-lactam - A					
Ahmed 2007	28/58	23/61		1.03%	1.28[0.84,1.95]
Akova 1999	13/40	28/43		1.24%	0.5[0.3,0.82]
Alanis 1983	20/46	27/48		1.22%	0.77[0.51,1.17]
Behre 1998	15/34	17/37		0.75%	0.96[0.57,1.61]
Cometta 1996	213/483	230/475		10.69%	0.91[0.79,1.04]
Cornely 2001	193/353	92/176		5.66%	1.05[0.88,1.24]
De la Camara 1997	29/46	30/47		1.37%	0.99[0.73,1.34]
De Pauw 1994	292/488	278/480		12.92%	1.03[0.93,1.15]
Gibson 1989	16/52	19/50		0.89%	0.81[0.47,1.39]
Gorschluter 2003	25/56	35/51		1.69%	0.65[0.46,0.92]
Hess 1998	9/48	8/48		0.37%	1.13[0.47,2.67]

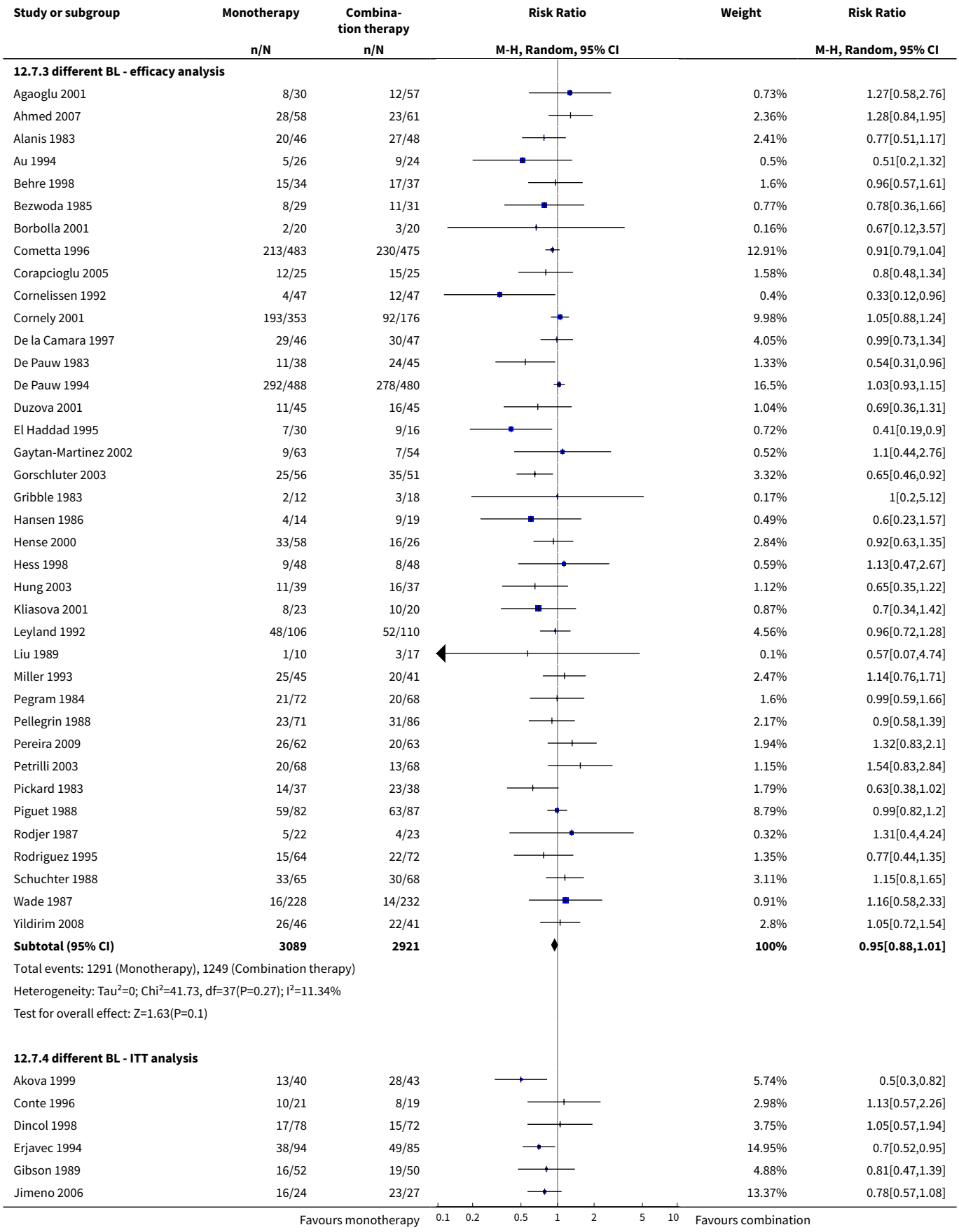




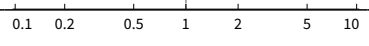


Analysis 12.7. Comparison 12 Sensitivity analysis (outcome in parenthesis), Outcome 7 Intention to treat vs. efficacy analysis (failure).





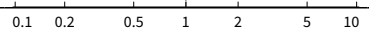
Study or subgroup	Monotherapy n/N	Combination therapy n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Koehler 1990	16/55	19/65		4.54%	1[0.57,1.74]
Lieschke 1990	19/90	18/92		4.3%	1.08[0.61,1.92]
Matsui 1991	9/51	10/50		2.17%	0.88[0.39,1.99]
Morgan 1983	9/26	13/24		3.44%	0.64[0.34,1.22]
Norrby 1987	35/105	46/105		11.7%	0.76[0.54,1.08]
Novakova 1990	18/46	28/44		7.87%	0.61[0.4,0.94]
Ozyilkan 1999	6/15	6/15		1.86%	1[0.42,2.4]
Perez 1995	14/30	19/30		6.43%	0.74[0.46,1.18]
Smith 1990	24/47	21/53		7.5%	1.29[0.83,1.99]
Yamamura 1997	17/56	17/55		4.54%	0.98[0.56,1.72]
Subtotal (95% CI)	**830**	**829**		**100%**	**0.8[0.71,0.91]**
Total events: 277 (Monotherapy), 339 (Combination therapy)					
Heterogeneity: Tau^2=0; Chi^2=15.16, df=15(P=0.44); I^2=1.06%					
Test for overall effect: Z=3.56(P=0)					



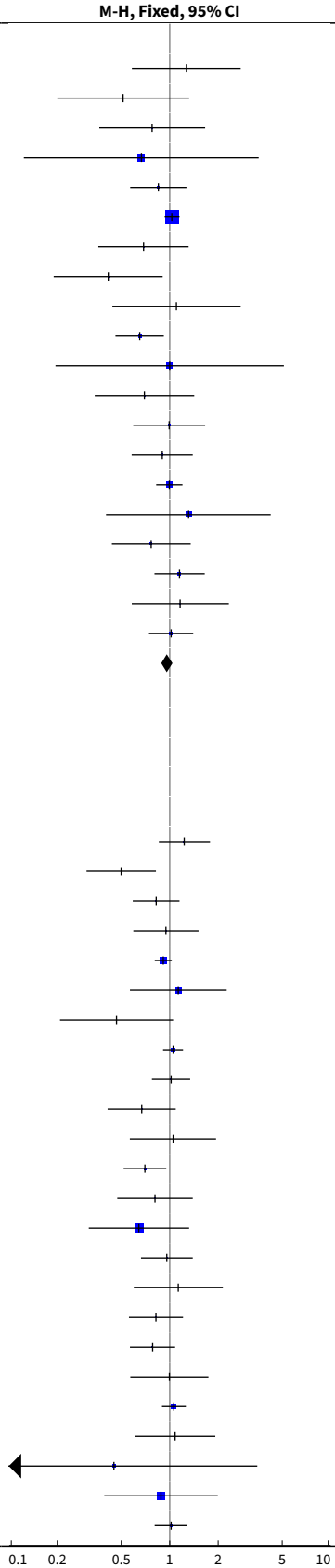
Favours monotherapy — Favours combination

Analysis 12.8. Comparison 12 Sensitivity analysis (outcome in parenthesis), Outcome 8 Intention to treat vs. efficacy analysis, assuming dropouts=failures (failure).

Study or subgroup	Monotherapy n/N	Combination therapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
12.8.1 same BL - efficacy analysis					
Doyen 1983	13/49	11/48		4.55%	1.16[0.58,2.33]
Esteve 1997	23/39	26/46		9.77%	1.04[0.72,1.5]
Kinsey 1990	48/77	59/83		23.25%	0.88[0.7,1.09]
Marie 1991	67/77	50/69		21.59%	1.2[1.01,1.42]
Rolston 1992	130/378	99/372		40.85%	1.29[1.04,1.61]
Subtotal (95% CI)	**620**	**618**		**100%**	**1.15[1.02,1.29]**
Total events: 281 (Monotherapy), 245 (Combination therapy)					
Heterogeneity: Tau^2=0; Chi^2=7.32, df=4(P=0.12); I^2=45.34%					
Test for overall effect: Z=2.2(P=0.03)					
12.8.2 same BL - ITT analysis					
Del Favero 2001	188/370	188/384		54.58%	1.04[0.9,1.2]
Jacobs 1993	21/53	14/54		4.1%	1.53[0.87,2.68]
Kiehl 2001	14/35	12/36		3.5%	1.2[0.65,2.22]
Kojima 1994	11/36	5/34		1.52%	2.08[0.81,5.36]
Novakova 1991	28/45	30/45		8.87%	0.93[0.69,1.27]
Papachristodoulou 96	3/39	6/45		1.65%	0.58[0.15,2.16]
Piccart 1984	8/25	8/24		2.41%	0.96[0.43,2.15]
Tamura 2002	17/42	35/82		7.01%	0.95[0.61,1.48]
Tamura 2004	52/100	46/101		13.54%	1.14[0.86,1.52]
Wrzesien-Kus 2001	9/19	10/21		2.81%	0.99[0.52,1.91]
Subtotal (95% CI)	**764**	**826**		**100%**	**1.07[0.96,1.19]**
Total events: 351 (Monotherapy), 354 (Combination therapy)					
Heterogeneity: Tau^2=0; Chi^2=5.93, df=9(P=0.75); I^2=0%					
Test for overall effect: Z=1.18(P=0.24)					

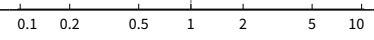


Favours monotherapy — Favours combination



Study or subgroup	Monotherapy n/N	Combination therapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
12.8.3 different BL - efficacy analysis					
Agaoglu 2001	8/30	12/57		1.33%	1.27[0.58,2.76]
Au 1994	5/26	9/24		1.5%	0.51[0.2,1.32]
Bezwoda 1985	8/29	11/31		1.7%	0.78[0.36,1.66]
Borbolla 2001	2/20	3/20		0.48%	0.67[0.12,3.57]
Corapcioglu 2005	17/30	20/30		3.21%	0.85[0.57,1.27]
De Pauw 1994	292/488	278/480		44.93%	1.03[0.93,1.15]
Duzova 2001	11/45	16/45		2.56%	0.69[0.36,1.31]
El Haddad 1995	7/30	9/16		1.88%	0.41[0.19,0.9]
Gaytan-Martinez 2002	9/63	7/54		1.21%	1.1[0.44,2.76]
Gorschluter 2003	25/56	35/51		5.87%	0.65[0.46,0.92]
Gribble 1983	2/12	3/18		0.38%	1[0.2,5.12]
Kliasova 2001	8/23	10/20		1.71%	0.7[0.34,1.42]
Pegram 1984	21/72	20/68		3.3%	0.99[0.59,1.66]
Pellegrin 1988	23/71	31/86		4.49%	0.9[0.58,1.39]
Piguet 1988	59/82	63/87		9.8%	0.99[0.82,1.2]
Rodjer 1987	5/22	4/23		0.63%	1.31[0.4,4.24]
Rodriguez 1995	15/64	22/72		3.32%	0.77[0.44,1.35]
Schuchter 1988	33/65	30/68		4.7%	1.15[0.8,1.65]
Wade 1987	16/228	14/232		2.22%	1.16[0.58,2.33]
Yildirim 2008	30/49	30/50		4.76%	1.02[0.74,1.4]
Subtotal (95% CI)	**1505**	**1532**		**100%**	**0.96[0.89,1.04]**
Total events: 596 (Monotherapy), 627 (Combination therapy)					
Heterogeneity: Tau^2=0; Chi^2=18.67, df=19(P=0.48); I^2=0%					
Test for overall effect: Z=1.08(P=0.28)					
12.8.4 different BL - ITT analysis					
Ahmed 2007	33/63	28/66		2.34%	1.23[0.86,1.78]
Akova 1999	13/40	28/43		2.3%	0.5[0.3,0.82]
Alanis 1983	27/53	34/55		2.85%	0.82[0.59,1.15]
Behre 1998	18/39	19/39		1.62%	0.95[0.59,1.51]
Cometta 1996	248/518	271/516		23.19%	0.91[0.81,1.03]
Conte 1996	10/21	8/19		0.72%	1.13[0.57,2.26]
Cornelissen 1992	7/50	15/50		1.28%	0.47[0.21,1.05]
Cornely 2001	244/404	114/198		13.07%	1.05[0.91,1.21]
De la Camara 1997	35/52	33/50		2.87%	1.02[0.77,1.34]
De Pauw 1983	15/42	24/45		1.98%	0.67[0.41,1.09]
Dincol 1998	17/78	15/72		1.33%	1.05[0.57,1.94]
Erjavec 1994	38/94	49/85		4.4%	0.7[0.52,0.95]
Gibson 1989	16/52	19/50		1.65%	0.81[0.47,1.39]
Hansen 1986	6/16	14/24		0.96%	0.64[0.31,1.32]
Hense 2000	36/61	16/26		1.92%	0.96[0.66,1.39]
Hess 1998	15/54	13/53		1.12%	1.13[0.6,2.14]
Hung 2003	24/52	27/48		2.4%	0.82[0.56,1.21]
Jimeno 2006	16/24	23/27		1.85%	0.78[0.57,1.08]
Koehler 1990	16/55	19/65		1.49%	1[0.57,1.74]
Leyland 1992	106/164	90/148		8.08%	1.06[0.9,1.26]
Lieschke 1990	19/90	18/92		1.52%	1.08[0.61,1.92]
Liu 1989	1/10	4/18		0.24%	0.45[0.06,3.5]
Matsui 1991	9/51	10/50		0.86%	0.88[0.39,1.99]
Miller 1993	45/65	45/66		3.81%	1.02[0.81,1.28]

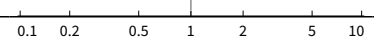
Study or subgroup	Monotherapy n/N	Combination therapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Morgan 1983	9/26	13/24		1.15%	0.64[0.34,1.22]
Norrby 1987	35/105	46/105		3.93%	0.76[0.54,1.08]
Novakova 1990	18/46	28/44		2.44%	0.61[0.4,0.94]
Ozyilkan 1999	6/15	6/15		0.51%	1[0.42,2.4]
Perez 1995	14/30	19/30		1.62%	0.74[0.46,1.18]
Petrilli 2003	21/69	14/69		1.2%	1.5[0.83,2.7]
Pickard 1983	17/40	25/40		2.14%	0.68[0.44,1.05]
Smith 1990	24/47	21/53		1.69%	1.29[0.83,1.99]
Yamamura 1997	17/56	17/55		1.46%	0.98[0.56,1.72]
Subtotal (95% CI)	**2582**	**2340**		**100%**	**0.92[0.86,0.97]**
Total events: 1175 (Monotherapy), 1125 (Combination therapy)					
Heterogeneity: Tau^2=0; Chi^2=41.28, df=32(P=0.13); I^2=22.48%					
Test for overall effect: Z=2.92(P=0)					



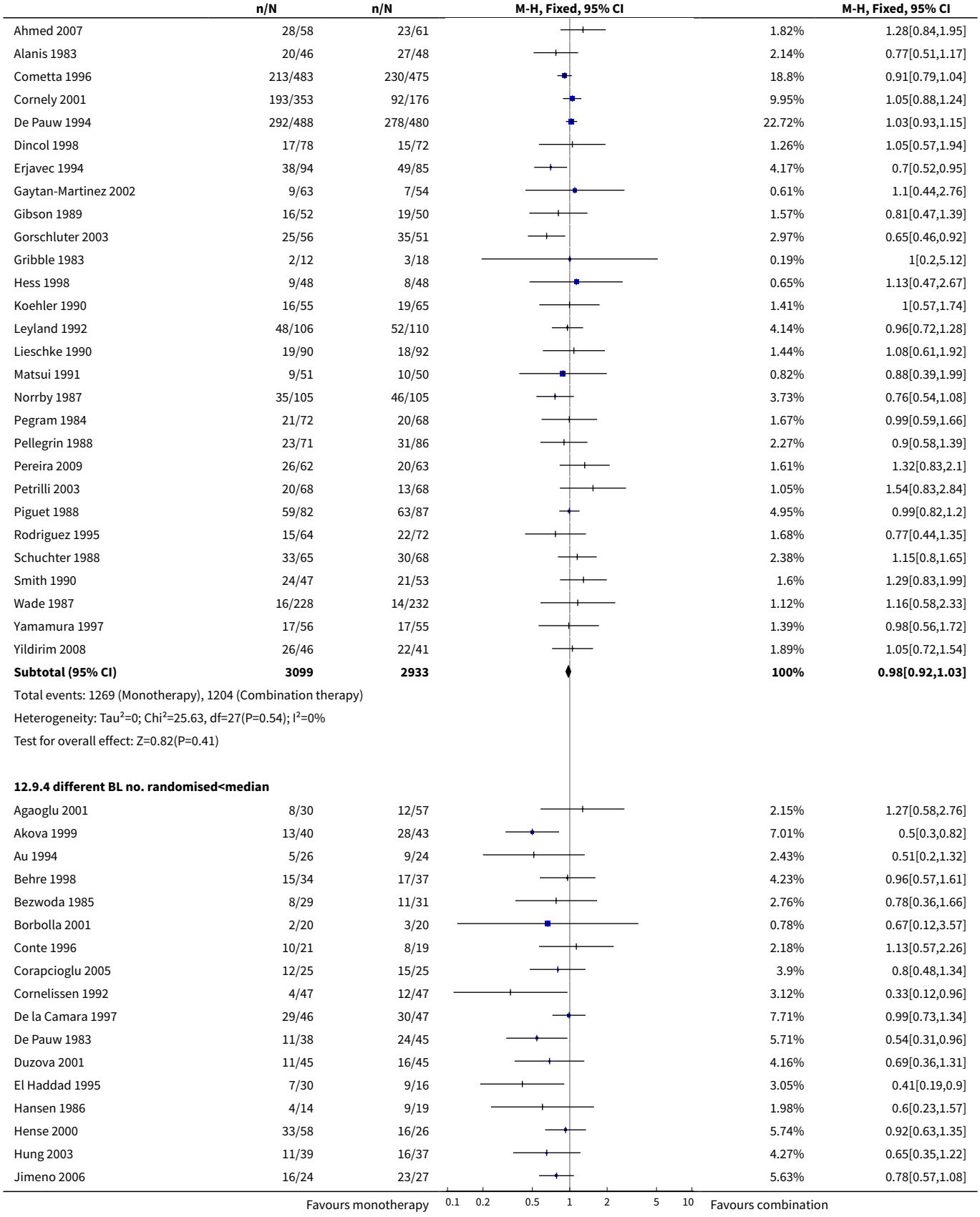
Favours monotherapy — Favours combination

Analysis 12.9. Comparison 12 Sensitivity analysis (outcome in parenthesis), Outcome 9 Trial size (failure).

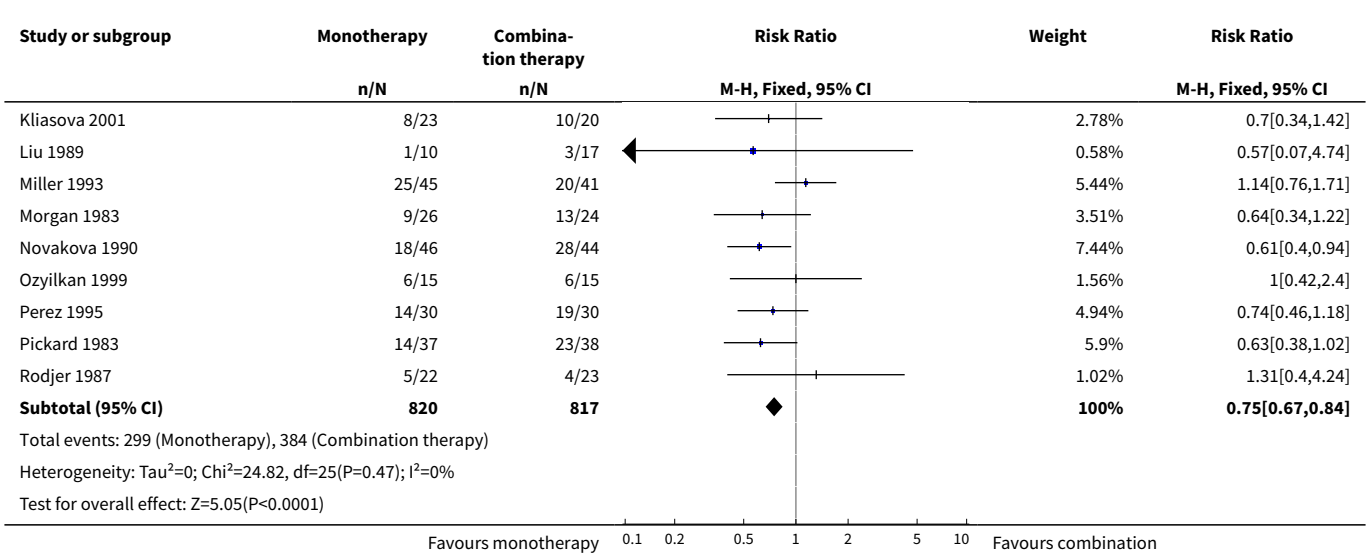
Study or subgroup	Monotherapy n/N	Combination therapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
12.9.1 same BL no. randomised>median					
Del Favero 2001	188/370	188/384		39.81%	1.04[0.9,1.2]
Doyen 1983	13/49	11/48		2.4%	1.16[0.58,2.33]
Kinsey 1990	48/77	59/83		12.25%	0.88[0.7,1.09]
Marie 1991	67/77	50/69		11.38%	1.2[1.01,1.42]
Rolston 1992	130/378	99/372		21.53%	1.29[1.04,1.61]
Tamura 2002	13/38	29/76		4.17%	0.9[0.53,1.52]
Tamura 2004	47/95	39/94		8.46%	1.19[0.87,1.63]
Subtotal (95% CI)	**1084**	**1126**		**100%**	**1.1[1.01,1.21]**
Total events: 506 (Monotherapy), 475 (Combination therapy)					
Heterogeneity: Tau^2=0; Chi^2=8.64, df=6(P=0.19); I^2=30.58%					
Test for overall effect: Z=2.11(P=0.04)					
12.9.2 same BL no. randomised<median					
Esteve 1997	23/39	26/46		22.44%	1.04[0.72,1.5]
Jacobs 1993	14/46	5/45		4.75%	2.74[1.08,6.98]
Kiehl 2001	14/35	12/36		11.13%	1.2[0.65,2.22]
Kojima 1994	10/35	3/32		2.95%	3.05[0.92,10.1]
Novakova 1991	19/36	18/33		17.66%	0.97[0.62,1.5]
Papachristodoulou 96	3/39	6/45		5.24%	0.58[0.15,2.16]
Piccart 1984	5/22	6/22		5.64%	0.83[0.3,2.33]
Wrzesien-Kus 2001	9/19	10/21		8.93%	0.99[0.52,1.91]
Zengin 2011	24/37	22/35		21.26%	1.03[0.73,1.46]
Subtotal (95% CI)	**308**	**315**		**100%**	**1.14[0.94,1.39]**
Total events: 121 (Monotherapy), 108 (Combination therapy)					
Heterogeneity: Tau^2=0; Chi^2=8.66, df=8(P=0.37); I^2=7.67%					
Test for overall effect: Z=1.37(P=0.17)					
12.9.3 different BL no. randomised>median					



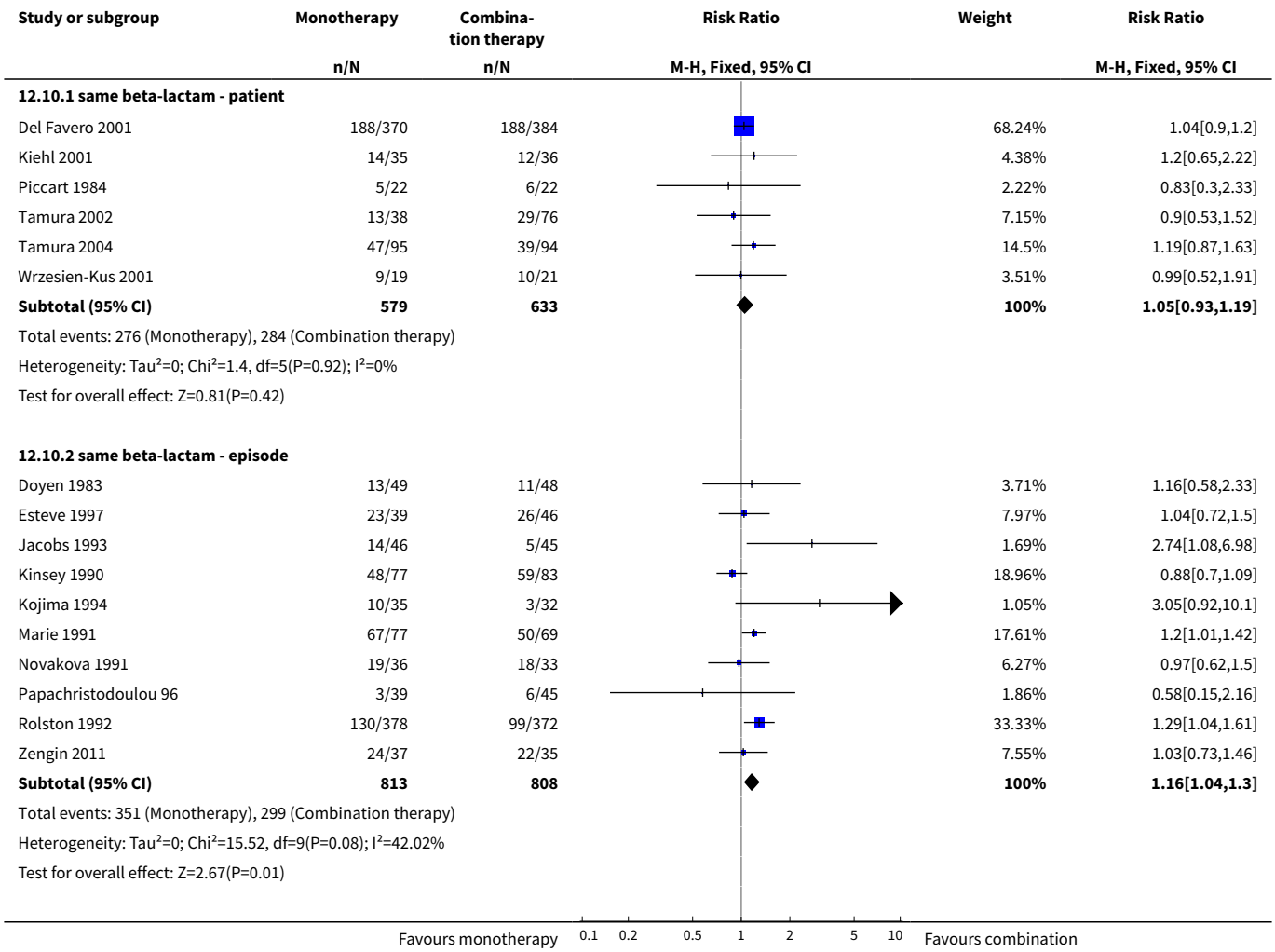
Favours monotherapy — Favours combination

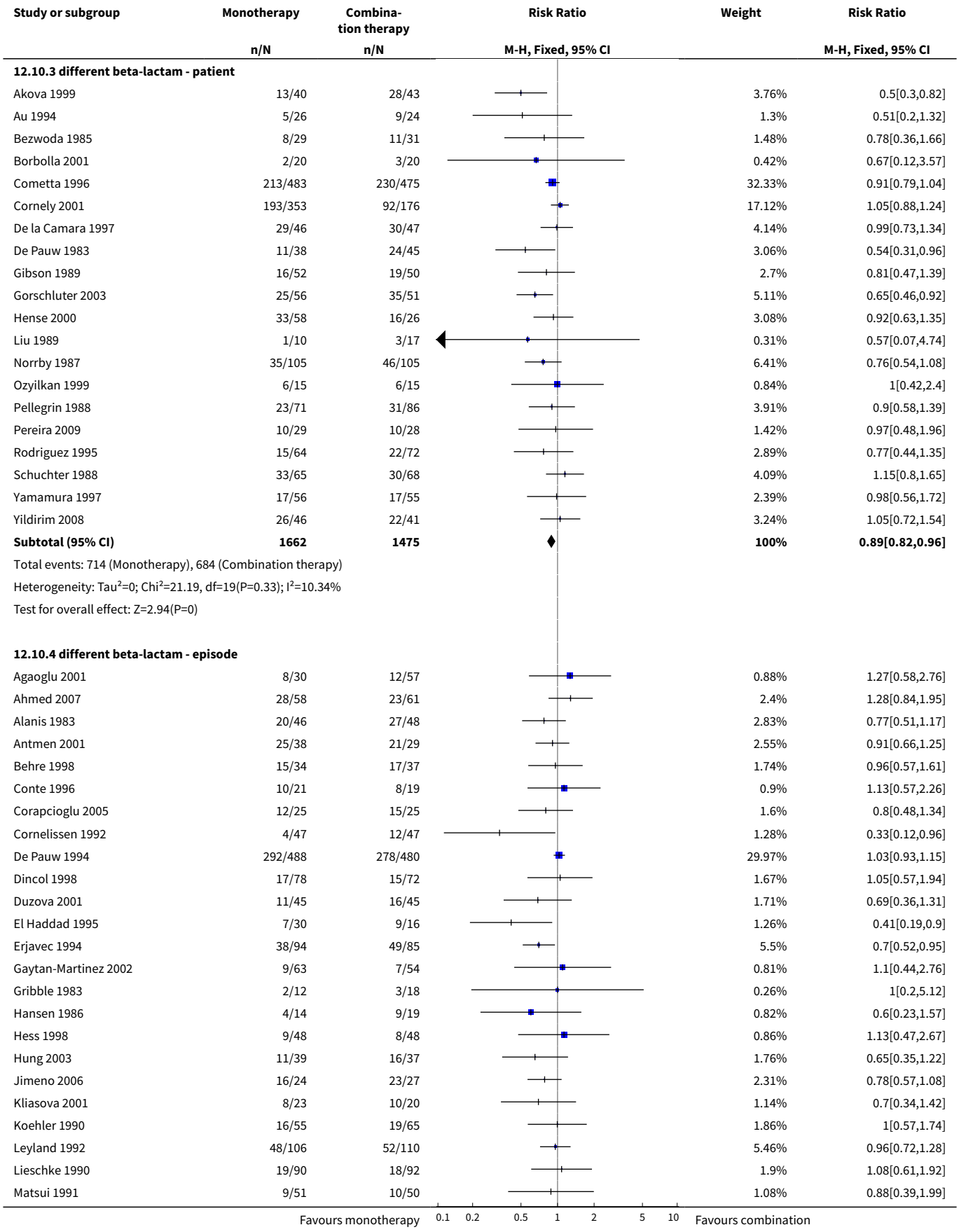


Study or subgroup	Monotherapy n/N	Combination therapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ahmed 2007	28/58	23/61		1.82%	1.28[0.84,1.95]
Alanis 1983	20/46	27/48		2.14%	0.77[0.51,1.17]
Cometta 1996	213/483	230/475		18.8%	0.91[0.79,1.04]
Cornely 2001	193/353	92/176		9.95%	1.05[0.88,1.24]
De Pauw 1994	292/488	278/480		22.72%	1.03[0.93,1.15]
Dincol 1998	17/78	15/72		1.26%	1.05[0.57,1.94]
Erjavec 1994	38/94	49/85		4.17%	0.7[0.52,0.95]
Gaytan-Martinez 2002	9/63	7/54		0.61%	1.1[0.44,2.76]
Gibson 1989	16/52	19/50		1.57%	0.81[0.47,1.39]
Gorschluter 2003	25/56	35/51		2.97%	0.65[0.46,0.92]
Gribble 1983	2/12	3/18		0.19%	1[0.2,5.12]
Hess 1998	9/48	8/48		0.65%	1.13[0.47,2.67]
Koehler 1990	16/55	19/65		1.41%	1[0.57,1.74]
Leyland 1992	48/106	52/110		4.14%	0.96[0.72,1.28]
Lieschke 1990	19/90	18/92		1.44%	1.08[0.61,1.92]
Matsui 1991	9/51	10/50		0.82%	0.88[0.39,1.99]
Norrby 1987	35/105	46/105		3.73%	0.76[0.54,1.08]
Pegram 1984	21/72	20/68		1.67%	0.99[0.59,1.66]
Pellegrin 1988	23/71	31/86		2.27%	0.9[0.58,1.39]
Pereira 2009	26/62	20/63		1.61%	1.32[0.83,2.1]
Petrilli 2003	20/68	13/68		1.05%	1.54[0.83,2.84]
Piguet 1988	59/82	63/87		4.95%	0.99[0.82,1.2]
Rodriguez 1995	15/64	22/72		1.68%	0.77[0.44,1.35]
Schuchter 1988	33/65	30/68		2.38%	1.15[0.8,1.65]
Smith 1990	24/47	21/53		1.6%	1.29[0.83,1.99]
Wade 1987	16/228	14/232		1.12%	1.16[0.58,2.33]
Yamamura 1997	17/56	17/55		1.39%	0.98[0.56,1.72]
Yildirim 2008	26/46	22/41		1.89%	1.05[0.72,1.54]
Subtotal (95% CI)	**3099**	**2933**		**100%**	**0.98[0.92,1.03]**
Total events: 1269 (Monotherapy), 1204 (Combination therapy)					
Heterogeneity: Tau^2=0; Chi^2=25.63, df=27(P=0.54); I^2=0%					
Test for overall effect: Z=0.82(P=0.41)					
12.9.4 different BL no. randomised<median					
Agaoglu 2001	8/30	12/57		2.15%	1.27[0.58,2.76]
Akova 1999	13/40	28/43		7.01%	0.5[0.3,0.82]
Au 1994	5/26	9/24		2.43%	0.51[0.2,1.32]
Behre 1998	15/34	17/37		4.23%	0.96[0.57,1.61]
Bezwoda 1985	8/29	11/31		2.76%	0.78[0.36,1.66]
Borbolla 2001	2/20	3/20		0.78%	0.67[0.12,3.57]
Conte 1996	10/21	8/19		2.18%	1.13[0.57,2.26]
Corapcioglu 2005	12/25	15/25		3.9%	0.8[0.48,1.34]
Cornelissen 1992	4/47	12/47		3.12%	0.33[0.12,0.96]
De la Camara 1997	29/46	30/47		7.71%	0.99[0.73,1.34]
De Pauw 1983	11/38	24/45		5.71%	0.54[0.31,0.96]
Duzova 2001	11/45	16/45		4.16%	0.69[0.36,1.31]
El Haddad 1995	7/30	9/16		3.05%	0.41[0.19,0.9]
Hansen 1986	4/14	9/19		1.98%	0.6[0.23,1.57]
Hense 2000	33/58	16/26		5.74%	0.92[0.63,1.35]
Hung 2003	11/39	16/37		4.27%	0.65[0.35,1.22]
Jimeno 2006	16/24	23/27		5.63%	0.78[0.57,1.08]



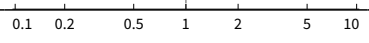
Analysis 12.10. Comparison 12 Sensitivity analysis (outcome in parenthesis), Outcome 10 Unit of randomisation (failure).





Study or subgroup	Monotherapy n/N	Combination therapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
12.10.3 different beta-lactam - patient					
Akova 1999	13/40	28/43		3.76%	0.5[0.3,0.82]
Au 1994	5/26	9/24		1.3%	0.51[0.2,1.32]
Bezwoda 1985	8/29	11/31		1.48%	0.78[0.36,1.66]
Borbolla 2001	2/20	3/20		0.42%	0.67[0.12,3.57]
Cometta 1996	213/483	230/475		32.33%	0.91[0.79,1.04]
Cornely 2001	193/353	92/176		17.12%	1.05[0.88,1.24]
De la Camara 1997	29/46	30/47		4.14%	0.99[0.73,1.34]
De Pauw 1983	11/38	24/45		3.06%	0.54[0.31,0.96]
Gibson 1989	16/52	19/50		2.7%	0.81[0.47,1.39]
Gorschluter 2003	25/56	35/51		5.11%	0.65[0.46,0.92]
Hense 2000	33/58	16/26		3.08%	0.92[0.63,1.35]
Liu 1989	1/10	3/17		0.31%	0.57[0.07,4.74]
Norrby 1987	35/105	46/105		6.41%	0.76[0.54,1.08]
Ozyilkan 1999	6/15	6/15		0.84%	1[0.42,2.4]
Pellegrin 1988	23/71	31/86		3.91%	0.9[0.58,1.39]
Pereira 2009	10/29	10/28		1.42%	0.97[0.48,1.96]
Rodriguez 1995	15/64	22/72		2.89%	0.77[0.44,1.35]
Schuchter 1988	33/65	30/68		4.09%	1.15[0.8,1.65]
Yamamura 1997	17/56	17/55		2.39%	0.98[0.56,1.72]
Yildirim 2008	26/46	22/41		3.24%	1.05[0.72,1.54]
Subtotal (95% CI)	**1662**	**1475**		**100%**	**0.89[0.82,0.96]**
Total events: 714 (Monotherapy), 684 (Combination therapy)					
Heterogeneity: Tau^2=0; Chi^2=21.19, df=19(P=0.33); I^2=10.34%					
Test for overall effect: Z=2.94(P=0)					
12.10.4 different beta-lactam - episode					
Agaoglu 2001	8/30	12/57		0.88%	1.27[0.58,2.76]
Ahmed 2007	28/58	23/61		2.4%	1.28[0.84,1.95]
Alanis 1983	20/46	27/48		2.83%	0.77[0.51,1.17]
Antmen 2001	25/38	21/29		2.55%	0.91[0.66,1.25]
Behre 1998	15/34	17/37		1.74%	0.96[0.57,1.61]
Conte 1996	10/21	8/19		0.9%	1.13[0.57,2.26]
Corapcioglu 2005	12/25	15/25		1.6%	0.8[0.48,1.34]
Cornelissen 1992	4/47	12/47		1.28%	0.33[0.12,0.96]
De Pauw 1994	292/488	278/480		29.97%	1.03[0.93,1.15]
Dincol 1998	17/78	15/72		1.67%	1.05[0.57,1.94]
Duzova 2001	11/45	16/45		1.71%	0.69[0.36,1.31]
El Haddad 1995	7/30	9/16		1.26%	0.41[0.19,0.9]
Erjavec 1994	38/94	49/85		5.5%	0.7[0.52,0.95]
Gaytan-Martinez 2002	9/63	7/54		0.81%	1.1[0.44,2.76]
Gribble 1983	2/12	3/18		0.26%	1[0.2,5.12]
Hansen 1986	4/14	9/19		0.82%	0.6[0.23,1.57]
Hess 1998	9/48	8/48		0.86%	1.13[0.47,2.67]
Hung 2003	11/39	16/37		1.76%	0.65[0.35,1.22]
Jimeno 2006	16/24	23/27		2.31%	0.78[0.57,1.08]
Kliasova 2001	8/23	10/20		1.14%	0.7[0.34,1.42]
Koehler 1990	16/55	19/65		1.86%	1[0.57,1.74]
Leyland 1992	48/106	52/110		5.46%	0.96[0.72,1.28]
Lieschke 1990	19/90	18/92		1.9%	1.08[0.61,1.92]
Matsui 1991	9/51	10/50		1.08%	0.88[0.39,1.99]

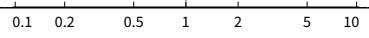
Study or subgroup	Monotherapy n/N	Combination therapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Miller 1993	25/45	20/41		2.24%	1.14[0.76,1.71]
Morgan 1983	9/26	13/24		1.45%	0.64[0.34,1.22]
Novakova 1990	18/46	28/44		3.06%	0.61[0.4,0.94]
Pegram 1984	21/72	20/68		2.2%	0.99[0.59,1.66]
Pereira 2009	26/62	20/63		2.12%	1.32[0.83,2.1]
Perez 1995	14/30	19/30		2.03%	0.74[0.46,1.18]
Petrilli 2003	20/68	13/68		1.39%	1.54[0.83,2.84]
Pickard 1983	14/37	23/38		2.43%	0.63[0.38,1.02]
Piguet 1988	59/82	63/87		6.54%	0.99[0.82,1.2]
Rodjer 1987	5/22	4/23		0.42%	1.31[0.4,4.24]
Smith 1990	24/47	21/53		2.11%	1.29[0.83,1.99]
Wade 1987	16/228	14/232		1.48%	1.16[0.58,2.33]
Subtotal (95% CI)	**2324**	**2332**		**100%**	**0.95[0.89,1.01]**
Total events: 889 (Monotherapy), 935 (Combination therapy)					
Heterogeneity: Tau²=0; Chi²=41.75, df=35(P=0.2); I²=16.18%					
Test for overall effect: Z=1.6(P=0.11)					



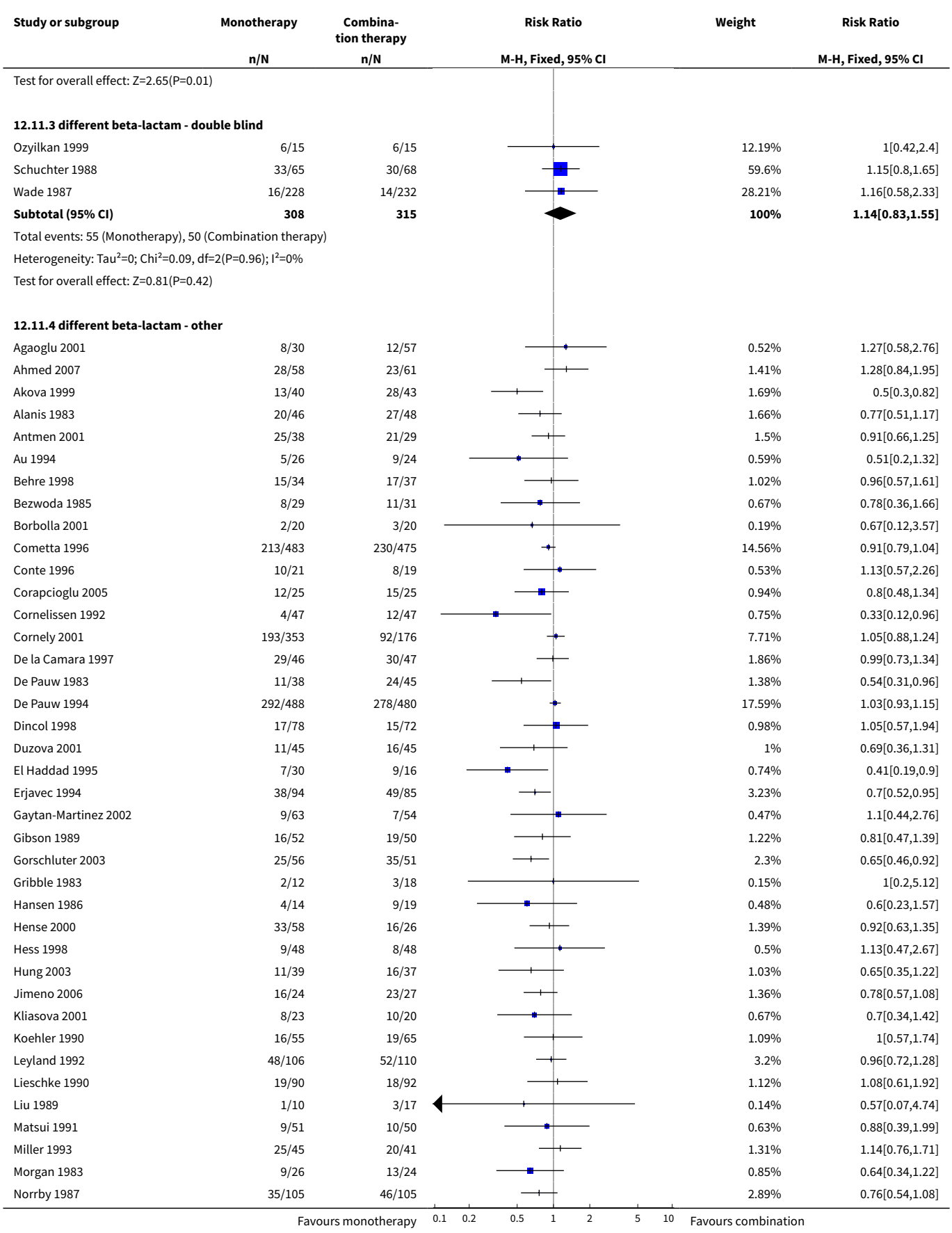
Favours monotherapy — Favours combination

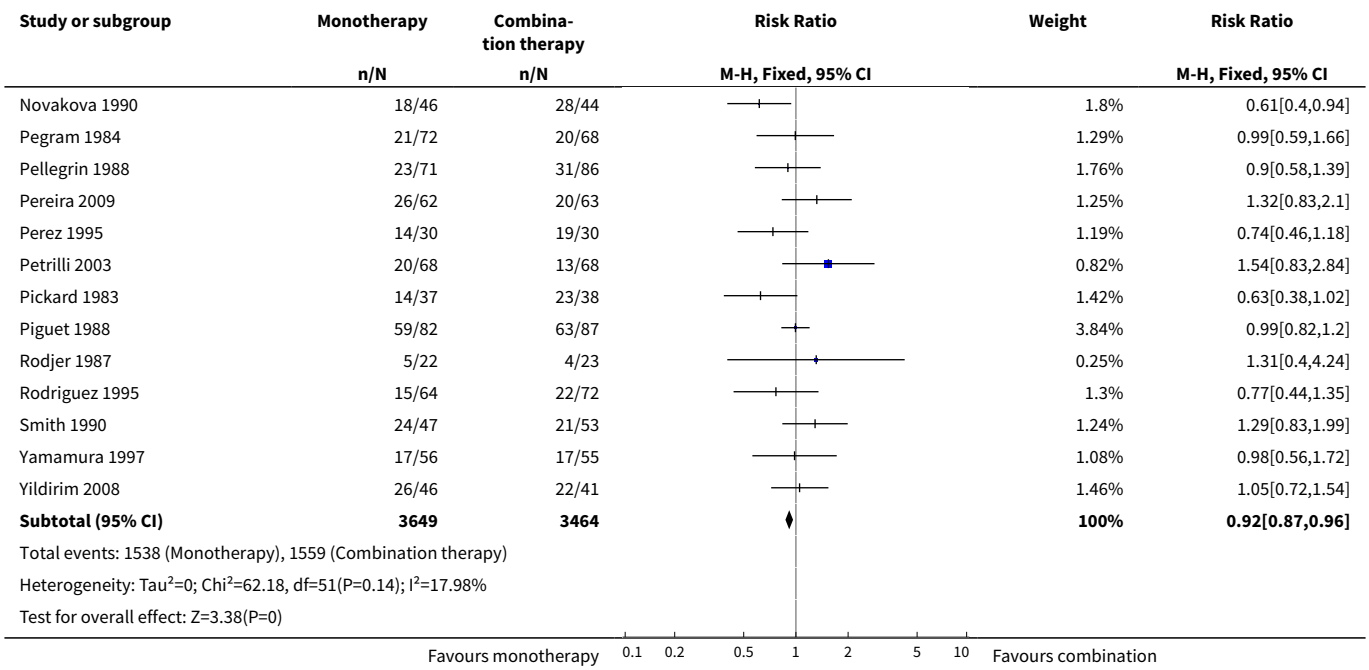
Analysis 12.11. Comparison 12 Sensitivity analysis (outcome in parenthesis), Outcome 11 Blinding (failure).

Study or subgroup	Monotherapy n/N	Combination therapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
12.11.1 same beta-lactam - double blind					
Del Favero 2001	188/370	188/384		100%	1.04[0.9,1.2]
Subtotal (95% CI)	**370**	**384**		**100%**	**1.04[0.9,1.2]**
Total events: 188 (Monotherapy), 188 (Combination therapy)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.51(P=0.61)					
12.11.2 same beta-lactam - other					
Doyen 1983	13/49	11/48		2.88%	1.16[0.58,2.33]
Esteve 1997	23/39	26/46		6.19%	1.04[0.72,1.5]
Jacobs 1993	14/46	5/45		1.31%	2.74[1.08,6.98]
Kiehl 2001	14/35	12/36		3.07%	1.2[0.65,2.22]
Kinsey 1990	48/77	59/83		14.74%	0.88[0.7,1.09]
Kojima 1994	10/35	3/32		0.81%	3.05[0.92,10.1]
Marie 1991	67/77	50/69		13.69%	1.2[1.01,1.42]
Novakova 1991	19/36	18/33		4.87%	0.97[0.62,1.5]
Papachristodoulou 96	3/39	6/45		1.45%	0.58[0.15,2.16]
Piccart 1984	5/22	6/22		1.56%	0.83[0.3,2.33]
Rolston 1992	130/378	99/372		25.9%	1.29[1.04,1.61]
Tamura 2002	13/38	29/76		5.02%	0.9[0.53,1.52]
Tamura 2004	47/95	39/94		10.18%	1.19[0.87,1.63]
Wrzesien-Kus 2001	9/19	10/21		2.47%	0.99[0.52,1.91]
Zengin 2011	24/37	22/35		5.87%	1.03[0.73,1.46]
Subtotal (95% CI)	**1022**	**1057**		**100%**	**1.14[1.04,1.26]**
Total events: 439 (Monotherapy), 395 (Combination therapy)					
Heterogeneity: Tau²=0; Chi²=16.6, df=14(P=0.28); I²=15.68%					

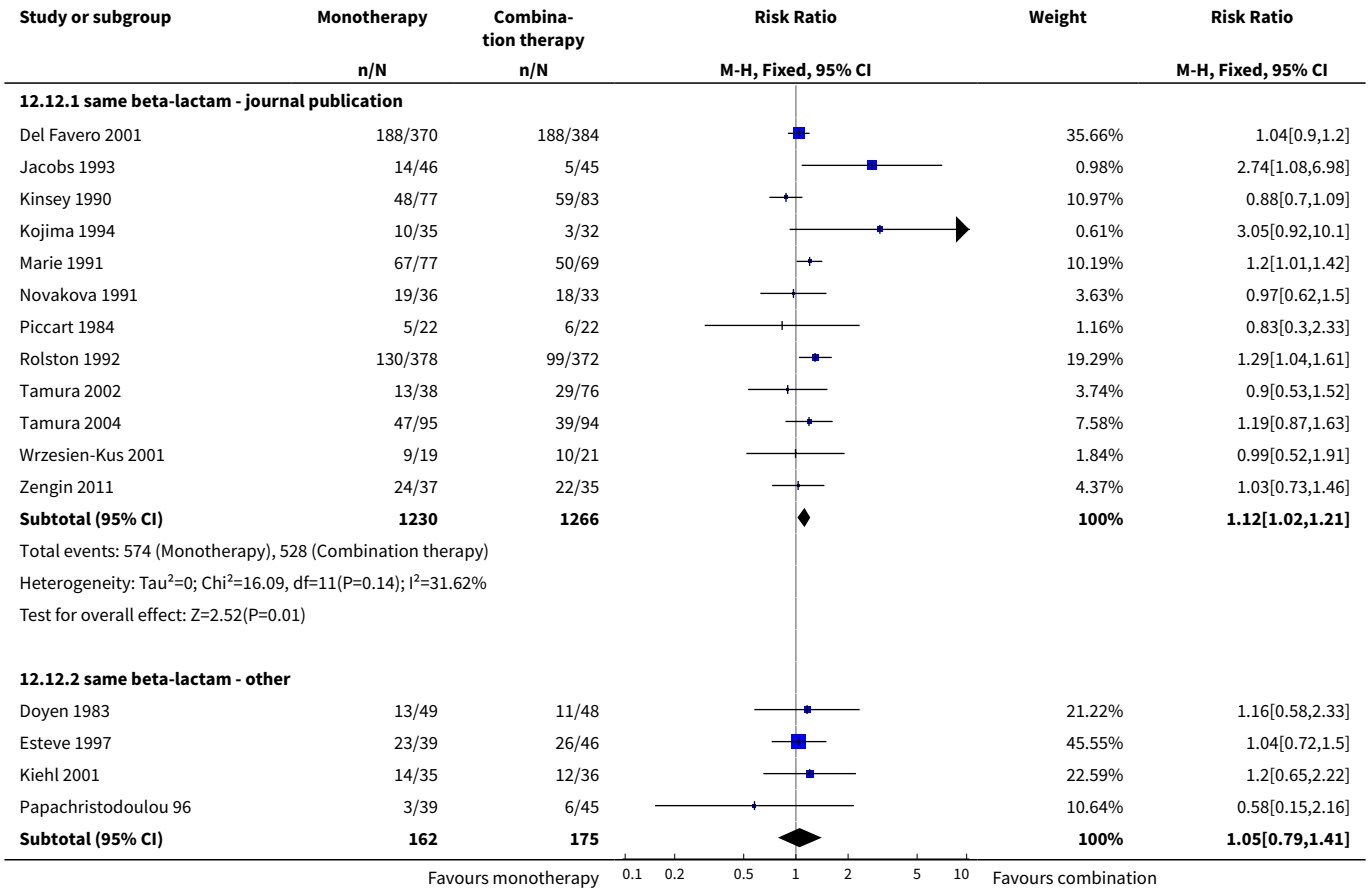


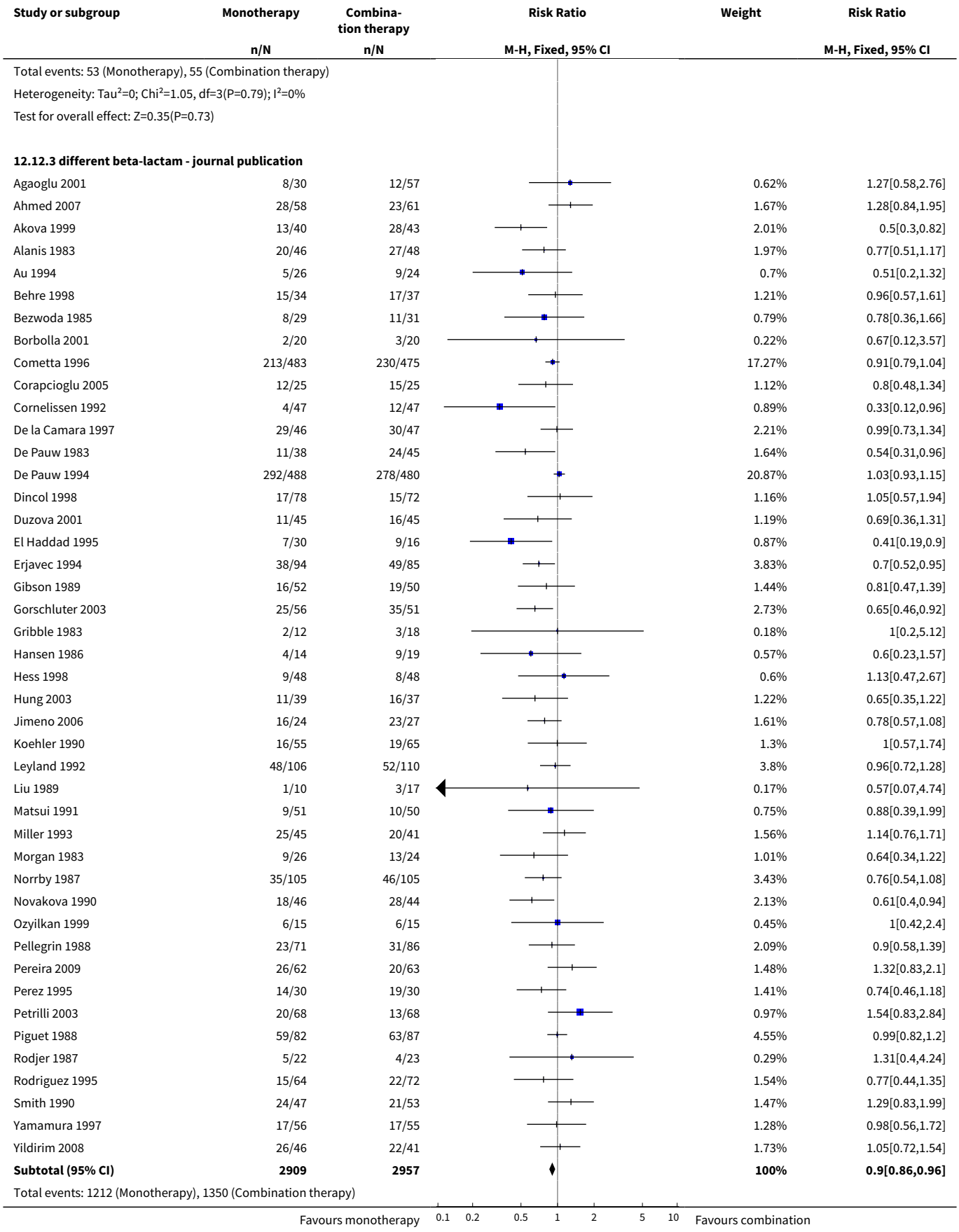
Favours monotherapy — Favours combination

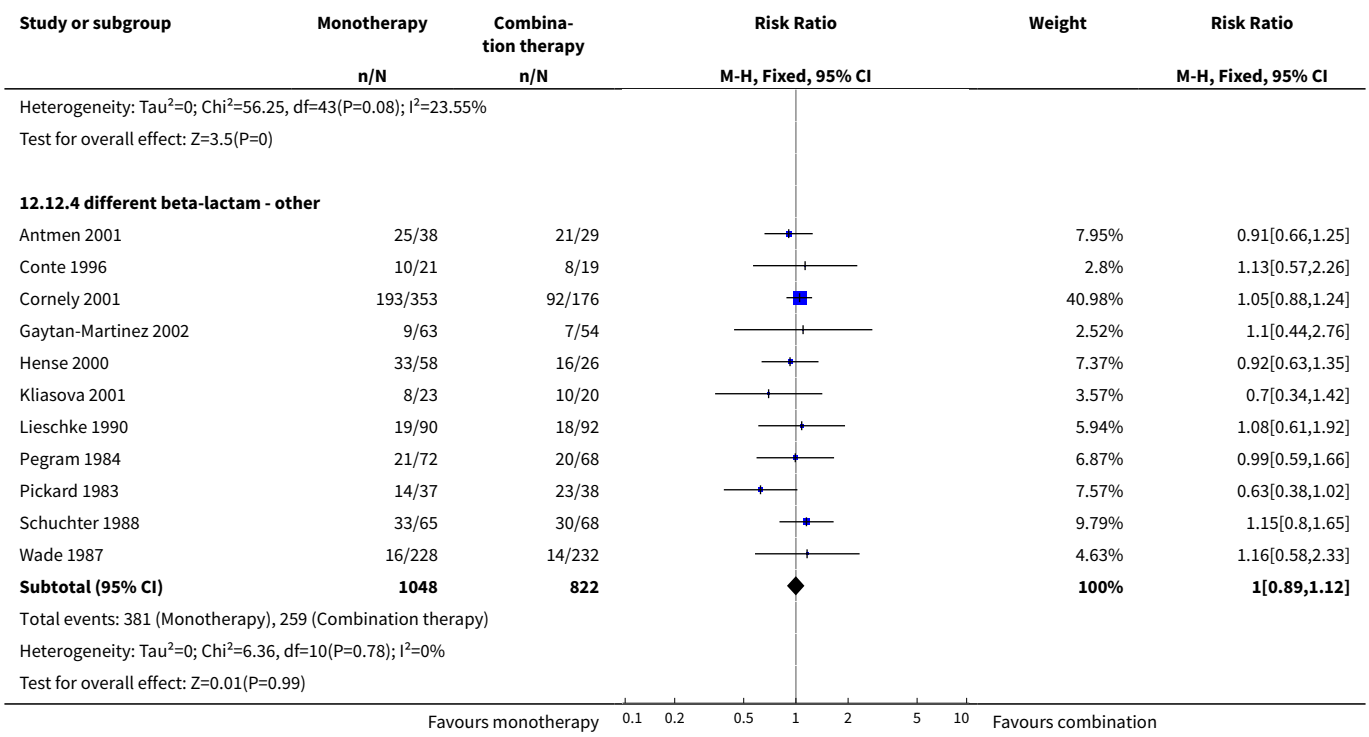




Analysis 12.12. Comparison 12 Sensitivity analysis (outcome in parenthesis), Outcome 12 Publication status (failure).







APPENDICES

Appendix 1. MEDLINE search strategy

Medline Ovid

1 exp Neoplasms/
2 Bone Marrow Transplantation/
3 (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinoma* or adenocarcinoma* or leukemia* or leukaemia* or bone marrow transplant*).mp.
4 1 or 2 or 3
5 exp Agranulocytosis/
6 (agranulocytosis or neutropen* or neutropaen* or granulocytopen* or granulocytopaen* or granulopen* or granulopaen*).mp.
7 5 or 6
8 exp beta-Lactams/
9 exp Anti-Bacterial Agents/
10 (beta-lactam* or antibiotic* or antimicrob* or anti-microb* or antibacteria* or anti-bacteria*).mp.
11 8 or 9 or 10
12 exp Aminoglycosides/
13 (aminoglycoside* or gentamicin or gentamycin or amikacin or amikacyn or tobramicin or tobramycin or kanamicin or kanamycin or netilmicin or netilmycin).mp.
14 12 or 13
15 4 and 7 and 11 and 14
16 randomized controlled trial.pt.
17 controlled clinical trial.pt.
18 randomized.ab
19 placebo.ab.
20 drug therapy.fs.
21 randomly.ab.
22 trial.ab.
23 groups.ab.
24 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23

25 15 and 24

key:

mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier, pt=publication type, ab=abstract, sh=subject heading, ti=title

Appendix 2. EMBASE search strategy

Embase Ovid

1 exp neoplasm/
2 exp bone marrow transplantation/
3 (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinoma* or adenocarcinoma* or leukemia* or leukaemia* or bone marrow transplant*).mp.
4 1 or 2 or 3
5 agranulocytosis/
6 exp neutropenia/
7 (agranulocytosis or neutropen* or neutropaen* or granulocytopen* or granulocytopaen* or granulopen* or granulopaen*).mp.
8 5 or 6 or 7
9 exp antiinfective agent/
10 (beta-lactam* or antibiotic* or antimicrob* or anti-microb* or antibacterial* or anti-bacteria*).mp.
11 9 or 10
12 exp aminoglycoside antibiotic agent/
13 (aminoglycoside* or gentamicin or gentamycin or amikacin or amikacyn or tobramicin or tobramycin or kanamicin or kanamycin or netilmicin or netilmycin).mp.
14 12 or 13
15 4 and 8 and 11 and 14
16 crossover procedure/
17 double-blind procedure/
18 randomized controlled trial/
19 single-blind procedure/
20 random*.mp.
21 factorial*.mp.
22 (crossover* or cross over* or cross-over*).mp.
23 placebo*.mp.
24 (double* adj blind*).mp.
25 (singl* adj blind*).mp.
26 assign*.mp.
27 allocat*.mp.
28 volunteer*.mp.
29 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30 15 and 29

key

[mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

Appendix 3. CENTRAL search strategy

CENTRAL/DARE

#1 MeSH descriptor Neoplasms explode all trees
#2 MeSH descriptor Bone Marrow Transplantation, this term only
#3 (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinoma* or adenocarcinoma* or leukemia* or leukaemia* or bone marrow transplant*)
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Agranulocytosis explode all trees
#6 (agranulocytosis or neutropen* or neutropaen* or granulocytopen* or granulocytopaen* or granulopen* or granulopaen*)
#7 (#5 OR #6)
#8 MeSH descriptor beta-Lactams explode all trees

#9 MeSH descriptor Anti-Bacterial Agents explode all trees
#10 beta-lactam* or antibiotic* or antimicrob* or anti-microb* or antibacterial* or anti-bacteria*
#11 (#8 OR #9 OR #10)
#12 MeSH descriptor Aminoglycosides explode all trees
#13 (aminoglycoside* or gentamicin or gentamycin or amikacin or amikacyn or tobramicin or tobramycin or kanamicin or kanamycin or netilmicin or netilmycin)
#14 (#12 OR #13)
#15 (#4 AND #7 AND #11 AND #14)

WHAT'S NEW

Date	Event	Description
21 September 2016	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 2, 2001
Review first published: Issue 2, 2002

Date	Event	Description
11 February 2015	Amended	Contact details updated.
26 February 2014	Amended	Contact details updated.
7 June 2013	New citation required but conclusions have not changed	No change to conclusions.
10 April 2013	New search has been performed	Three new trials identified.
7 November 2007	New search has been performed	New studies found and included or excluded: 01/06/07. Addition of infection-related mortality as a protocol-defined outcome. Search updated and expanded the search of conference proceedings (ECCMID, ASH). Deleted the limitation on inclusion of trials with >30% dropouts and assessed the effect of dropouts through sensitivity analyses. The comparisons of 'same' and 'different' beta-lactams separated throughout the review for the analysis of treatment failure. Re-wrote results, discussion and implications for further practice and research.
17 April 2003	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Mical Paul performed the search and article retrieval; applied inclusion and exclusion criteria; performed quality assessment and data extraction; contacted authors; analysed results and wrote the review. Yaakov Dickstein conducted the search for the 2012 update, extracted the data from new trials, entered data into RevMan and wrote the review for the 2012 update. Karla Soares-Weiser applied inclusion and exclusion criteria; performed data extraction; analysed results—all for the previous version of the review and commented on all drafts and

final version of the review. Simona Grozinsky-Glasberg assisted with search; retrieved articles; applied inclusion and exclusion criteria and assisted in data extraction — all for the previous version of the review. Leonard Leibovici performed search; applied inclusion and exclusion criteria; performed data extraction; assisted with author correspondence; analysed results; assisted in writing the review and commented on all drafts and final version of the review.

DECLARATIONS OF INTEREST

None known.

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- Tel-Aviv University, Sackler Faculty of Medicine, Israel.

External sources

- EU 5th Framework: TREAT project (grant number: 1999-11459), Not specified.

INDEX TERMS

Medical Subject Headings (MeSH)

Aminoglycosides [adverse effects] [*therapeutic use]; Anti-Bacterial Agents [*therapeutic use]; Cause of Death; Combined Modality Therapy [adverse effects] [methods]; Neoplasms [*complications]; Neutropenia [*drug therapy] [mortality]; Randomized Controlled Trials as Topic; beta-Lactams [*therapeutic use]

MeSH check words

Adult; Child; Humans