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Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy (Review)

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Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy.
Cochrane Database of Systematic Reviews 2012, Issue 1. Art. No.: CD004386.
DOI: 10.1002/14651858.CD004386.pub3.

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[Intervention Review]

Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy

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Editorial group: Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 7, 2018.

Citation: Gafter-Gvili A, Fraser A, Paul M, Vidal L, Lawrie TA, van de Wetering MD, Kremer LCM, Leibovici L. Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. *Cochrane Database of Systematic Reviews* 2012, Issue 1. Art. No.: CD004386. DOI: 10.1002/14651858.CD004386.pub3.

ABSTRACT

Background

Bacterial infections are a major cause of morbidity and mortality in patients who are neutropenic following chemotherapy for malignancy. Trials have shown the efficacy of antibiotic prophylaxis in reducing the incidence of bacterial infections but not in reducing mortality rates. Our systematic review from 2006 also showed a reduction in mortality.

Objectives

This updated review aimed to evaluate whether there is still a benefit of reduction in mortality when compared to placebo or no intervention.

Search methods

We searched the Cochrane Cancer Network Register of Trials (2011), Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 2, 2011), MEDLINE (1966 to March 2011), EMBASE (1980 to March 2011), abstracts of conference proceedings and the references of identified studies.

Selection criteria

Randomised controlled trials (RCTs) or quasi-RCTs comparing different types of antibiotic prophylaxis with placebo or no intervention, or another antibiotic, to prevent bacterial infections in afebrile neutropenic patients.

Data collection and analysis

Two authors independently appraised the quality of each trial and extracted data from the included trials. Analyses were performed using RevMan 5.1 software.

Main results

One-hundred and nine trials (involving 13,579 patients) that were conducted between the years 1973 to 2010 met the inclusion criteria. When compared with placebo or no intervention, antibiotic prophylaxis significantly reduced the risk of death from all causes (46 trials, 5635 participants; risk ratio (RR) 0.66, 95% CI 0.55 to 0.79) and the risk of infection-related death (43 trials, 5777 participants; RR 0.61, 95%

CI 0.48 to 0.77). The estimated number needed to treat (NNT) to prevent one death was 34 (all-cause mortality) and 48 (infection-related mortality).

Prophylaxis also significantly reduced the occurrence of fever (54 trials, 6658 participants; RR 0.80, 95% CI 0.74 to 0.87), clinically documented infection (48 trials, 5758 participants; RR 0.65, 95% CI 0.56 to 0.76), microbiologically documented infection (53 trials, 6383 participants; RR 0.51, 95% CI 0.42 to 0.62) and other indicators of infection.

There were no significant differences between quinolone prophylaxis and TMP-SMZ prophylaxis with regard to death from all causes or infection, however, quinolone prophylaxis was associated with fewer side effects leading to discontinuation (seven trials, 850 participants; RR 0.37, 95% CI 0.16 to 0.87) and less resistance to the drugs thereafter (six trials, 366 participants; RR 0.45, 95% CI 0.27 to 0.74).

Authors' conclusions

Antibiotic prophylaxis in afebrile neutropenic patients significantly reduced all-cause mortality. In our review, the most significant reduction in mortality was observed in trials assessing prophylaxis with quinolones. The benefits of antibiotic prophylaxis outweighed the harm such as adverse effects and the development of resistance since all-cause mortality was reduced. As most trials in our review were of patients with haematologic cancer, we strongly recommend antibiotic prophylaxis for these patients, preferably with a quinolone. Prophylaxis may also be considered for patients with solid tumours or lymphoma.

PLAIN LANGUAGE SUMMARY

Antibiotics to prevent bacterial infections due to chemotherapy in cancer patients with a low white blood cell count and no fever

For patients receiving chemotherapy, there is an increased risk of infection due to a low white blood cell count (neutropenia) caused by a toxic effect of chemotherapy on the bone marrow. The objective of this review was to establish whether preventive antibiotic therapy (prophylaxis) before the development of fever prevents illness and death in people with a low white blood cell count after chemotherapy and to assess whether certain types of antibiotics are better than others. We included 109 randomised controlled trials conducted between the years 1973 to 2010.

Antibiotic prophylaxis significantly decreased the risk of death when compared to no intervention. We estimated that the number of patients needed to be treated with antibiotics in order to prevent one death from all causes was 34. Antibiotic prophylaxis also decreased the risk of death from infection and the risk of development of fever. Although antibiotic prophylaxis may be associated with unfavourable effects and may encourage new and more resistant infection, this was not shown in existing trials. Recent studies used antibiotics of the quinolone class, which showed fewer adverse events and better outcomes than other classes of antibiotics.

Most studies were limited to haematological cancer patients (mostly leukaemia).

In conclusion, patients with a low white blood count following chemotherapy who received preventive antibiotic treatment in the absence of fever had a reduced risk of dying. This was shown mainly for haematological cancer patients. Antibiotic prophylaxis, preferably from the quinolone class of antibiotics, should be recommended for routine use in these patients.

Summary of findings for the main comparison. Summary of findings: antibiotics versus placebo or no intervention

Antibiotics compared with placebo or no intervention for afebrile neutropenia

Patient or population: patients with afebrile neutropenia induced by chemotherapy

Settings: hospital or outpatient

Intervention: antibiotics

Comparison: placebo or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Antibiotic drug				
All cause mortality	**88 per 1000**	**57 per 1000** (47 to 68)	**RR 0.66 (0.55-0.79)**	5,635 participants (46 trials)	⊕⊕⊕⊕ **high**	I^2 = 20%. NNT to prevent one death from any cause is 34 (95% CI 26-56). The greatest effect was seen in the quinolone prophylaxis subgroup (20 trials, 3,798 participants; RR 0.54 (95% CI 0.40 to 0.74). Test for subgroup differences: I^2= 42%, P=0.16. Quality was not downgraded despite a high risk of bias: (allocation concealment was unclear in most of the trials) because when results of low risk allocation concealment were compared to unclear allocation concealment, they were similar.
Febrile patients and episodes	**607 per 1000**	**486 per 1000** (449 to 528)	**RR 0.80 (0.74-0.87)**	6,658 participants (54 trials)	⊕⊕⊕ **moderate**	NNT to prevent one febrile patient or febrile episode was 7 (95%CI 5-10). Quality was downgraded because of heterogeneity and unit of analysis issues, not because of the high risk of bias (allocation concealment was unclear in most of the trials) as, when results between low risk allocation concealment were compared to unclear allocation concealment, the results were similar.
Bacteraemia	**209 per 1000**	**105 per 1000** (88 to 125)	**RR 0.50 (0.43-0.60)**	6,390 participants (53 trials)	⊕⊕⊕⊕ **high**	This reduction occurred for all subgroups. NNT to prevent bacteraemia is 10 (95% CI 8-12).

	Quality was first downgraded due to a high risk of bias (allocation concealment was unclear in most of the trials) and then upgraded due to large number of participants and large effect (RR 0.50).

*The basis for the **assumed risk** is the median control group risk across studies. 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; **NS**: not significantly different; NNT: number needed to treat

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.

Summary of findings 2. Summary of findings: quinolone prophylaxis compared with TMP-SMZ prophylaxis

Quinolones compared with TMP-SMZ for afebrile neutropenia

Patient or population: cancer patients with afebrile neutropenia following chemotherapy

Settings: hospital or outpatient

Intervention: quinolones

Comparison: TMP-SMZ

Outcomes	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)*	Comments
All cause-mortality	**RR 1.07 (0.66-1.72)**	917 participants (10 trials)	⊕⊕⊕ **moderate**	Quality was downgraded due to imprecision.
Febrile patients and episodes	**RR 0.92 (0.78-1.09)**	931 participants (10 trials)	⊕⊕⊕ **moderate**	Quality was downgraded due heterogeneity.
Bacteraemia	**RR 0.89 (0.56-1.42)**	931 participants (10 trials)	⊕⊕⊕ **moderate**	Quality was downgraded due heterogeneity and imprecision.

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.

*Quality was downgraded to moderate for these outcomes due to a high risk of bias (allocation concealment was unclear in most of the trials).

BACKGROUND

Description of the condition

Patients with cancer are subject to infections as a result of several factors, notably breakdown of normal skin and mucosal barriers, obstruction related to the tumour, alteration of host defences secondary to infiltration of bone marrow, reduced or altered immunoglobulin or cytokine production, or neutropenia related to chemotherapy. Neutropenia, a deficiency in white blood cells, is the most frequently encountered host cell defect in patients with cancer and predicts the development of bacteraemia caused by Gram-positive and Gram-negative bacteria. In the absence of preventive measures, between 48% and 60% of neutropenic patients who become febrile have an established or occult infection, and around 16% to 20% or more of patients with profound neutropenia (neutrophil counts of less than 100/mm^3) have bacteraemia (Bodey 1966; Lucas 1996; Schimpff 1986). During the past two decades there have been changes in the organisms that cause infection. In the 1990s the incidence of Gram-negative infections declined and Gram-positive organisms accounted for 60% to 70% of microbiologically documented infections (EORTC 1990; Hughes 2002). Currently, coagulase-negative staphylococci are the most common blood isolates in most centres, however Gram-negative pathogens are on the rise in some centres (Freifeld 2011).

Description of the intervention

A number of prophylactic strategies have been used in order to reduce the risk of infection during severe neutropenia. Different measures that have been investigated include isolation of the patient, granulocyte transfusions in patients with severe infections (Massey 2009; van de Wetering 2007), active or passive immunisation, and acceleration of granulocyte recovery by administration of granulocyte stimulating growth factors (GSCF) (Frank 2008; Kuderer 2007). However, these are still not enough to reduce infections. Numerous studies since the 1980s, evaluating prophylactic use of antibacterial agents, have shown that the frequency of febrile episodes can be reduced by administering antibiotics during the early afebrile period (Hughes 1990; Kerr 1999). Several prophylactic regimens have been studied in patients with malignancies. Selective intestinal decontamination has been suggested as a method of preventing bacterial infections in these patients. This consists of inhibition of the Gram-negative flora of the gut with preservation of the remaining flora, especially anaerobic bacteria, which is important in maintaining resistance of the gut against intestinal colonisation and overgrowth and extra-intestinal spread of pathogenic bacteria (Verhoef 1993).

Oral nonabsorbable antibiotics (such as polymyxin, neomycin, aminoglycoside, vancomycin) and absorbable antibiotics (quinolones, trimethoprim-sulfamethoxazole (TMP-SMZ)) as well as intravenous antibiotics (ceftriaxone, vancomycin) have been evaluated. The oral nonabsorbable drugs, which were studied in the early trials, have been abandoned due to poor tolerance and low patient compliance.

Studies of prophylaxis with TMP-SMZ have shown a reduced infection rate for TMP-SMZ treated patients when compared with placebo or a different agent (Hughes 1990; Walsh 1994). However, these studies failed to demonstrate a significant difference in mortality. Disadvantages of this regimen include side effects of the sulfamethoxazole component, myelosuppression and prolongation of neutropenia, the emergence of resistant bacteria, fungal overgrowth, *Clostridium difficile* colitis and inadequate coverage of *Pseudomonas aeruginosa*.

Quinolones were first introduced in the 1980s and since then they have become an attractive option for prophylaxis in neutropenic cancer patients. This is due to their broad antimicrobial spectrum (increased activity against Gram-negative bacteria, including *P. aeruginosa*), preservation of the anaerobic flora of the alimentary tract (selective decontamination), high concentration in the faeces, systemic bactericidal activity, good tolerability and lack of myelosuppression (Del Favero 1993; Patrick 1997a). They were proved in published randomised trials to be more effective than placebo, oral nonabsorbable antibiotics or cotrimoxazole in the prevention of Gram-negative infections. However, most of these studies were underpowered to detect an advantage in survival. In addition, some investigators did not show a reduction in the number of febrile episodes in patients receiving quinolones (Bow 1996; de Marie 1993). Moreover, not all studies demonstrate superiority of quinolones against comparable regimens (Donnelly 1992a). Whatever the perceived advantages, the problem of inadequate coverage for Gram-positive bacteria cannot be ignored (Cruciani 1996; Kern 1991). Furthermore, the administration of quinolones has already been associated with the emergence and spread of resistant Staphylococcus-coagulase negative bacteria (Oppenheim 1989). This has led to the addition of agents with increased anti-Gram positive activity to the quinolone-based regimens (penicillin or rifampin) (Kerr 1999). Another potential problem related to the prophylactic use of fluoroquinolones is the reported emergence of quinolone-resistant Gram-negative bacilli (Cometta 1994; Kern 1994).

Why it is important to do this review

When we originally started to work on the review, guidelines existed on antibiotic treatment for fever and neutropenia in cancer patients but the use of antibiotics for afebrile neutropenia was highly controversial and lacked consensus (Hughes 2002), with the exception of the use of TMP-SMZ for all patients at risk of Pneumocystis pneumonia (those with childhood leukaemia, AIDS) regardless of whether they had neutropenia. It was only in cases of profound and prolonged neutropenia that a quinolone plus penicillin or TMP-SMZ might have been recommended.

Although data supported the efficacy of TMP-SMZ and quinolones in reducing the number of infectious episodes, such prophylaxis had not been shown to reduce mortality rates. In addition, there were concerns about adverse effects and the emergence of drug-resistant bacteria. Several meta-analyses have been conducted to assess the efficacy of quinolones for preventing bacterial infections in neutropenic patients (Cruciani 1996; Cruciani 2003; Engels 1998; Rotstein 1997; van de Wetering 2005). They all concluded that quinolone prophylaxis reduces the various infection-related outcomes but not mortality.

Our original systematic review demonstrated a significant reduction in mortality with the use of prophylactic antibiotics (Gafter-Gvili 2005a; Gafter-Gvili 2005b; Leibovici Cancer 2006). This advantage in reducing mortality was not detected in individual studies due to small sample sizes. By updating the review to include new randomised controlled trials (RCTs), we aimed to assess whether the benefit of prophylaxis in terms of a reduction

in mortality was robust and whether the rise in resistance to antibiotics nullifies or reduces the efficiency of prophylaxis.

OBJECTIVES

Our primary objective was to evaluate the effect of antibiotic prophylaxis on mortality and infection in neutropenic patients following chemotherapy.

Our secondary objectives were to assess:

- whether the effectiveness of different antibiotic regimens are similar;
- subgroups of patients and which may benefit most from prophylaxis;
- emergence of quinolone-resistant Gram-negative bacteria;
- adverse effects of the antibiotic regimens.

METHODS

Criteria for considering studies for this review

Types of studies

For the 2005 review, RCTs and quasi-RCTs comparing different types of antibiotic therapy with placebo, no intervention, or with another antibiotic for the prophylaxis of bacterial infections in afebrile neutropenic patients. For the 2011 update, only RCTs identified by the updated search were added. Trials were included irrespective of publication status, language and blinding.

Types of participants

Patients with cancer and neutropenia induced by chemotherapy or following bone marrow transplantation.

Types of interventions

The following medications, used alone or in combination, were considered regardless of the mode of administration (intravenous or oral):

- quinolones (e.g. ciprofloxacin, ofloxacin, norfloxacin, pefloxacin) alone or in combination with gram-positive prophylaxis (penicillin, rifampin, roxythromycin, vancomycin);
- trimethoprim-sulphamethoxazole (TMP-SMZ);
- nonabsorbable oral antibiotics: aminoglycoside (e.g. gentamicin, neomycin, tobramycin), colistin, polymyxin;
- rifampin;
- intravenous cephalosporins (e.g. ceftriaxone);
- intravenous vancomycin;
- other antibiotics.

The control groups received any of the above medications, placebo, or no intervention.

Types of outcome measures

Primary outcomes

- All-cause mortality (at 30 day follow-up or at the end of the follow-up in each study)

Secondary outcomes

Indicators of infection

- Infection-related mortality
- Incidence of febrile patients or febrile episodes
- Clinically documented infection, defined as the presence of symptoms or signs of inflammation at an anatomic site whether pathogens were recovered from the affected site or not
- Microbiologically documented infection, defined as the presence of symptoms or signs of inflammation at an anatomic site where pathogens were recovered from the affected site
- Microbiologically documented infections caused by Gram-positive bacteria
- Microbiologically documented infections caused by Gram-negative bacteria
- Bacteraemia, defined as the recovery of bacteria from one or more blood cultures
- Incidence of superinfection or bacteria resistant to the given antibiotic in at least one of the follow-up cultures
- Incidence of hospital admissions and length of hospital stay
- Duration of fever

Adverse events

- Any serious adverse events that were fatal, life-threatening, or requiring inpatient hospitalisation or prolongation of existing hospitalisation
- Any adverse events that resulted in significant disability or incapacity
- Any important medical events that might not have been immediately life-threatening or result in death or hospitalisation, but might have jeopardised the patient or required intervention to prevent one of the above outcomes. Specifically we attempted to extract data on *Clostridium difficile* associated diarrhea (CDAD)
- Any adverse events that required discontinuation of medication

Search methods for identification of studies

Electronic searches

For the original review, searches were conducted spanning from 1966 to 2005, see Appendix 1. The updated search was performed in March 2011 (from November 2005 to March 2011) and included the following databases: Cochrane Cancer Network Register of Trials, Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 2, 2011), MEDLINE, EMBASE, and the following conference proceedings (2005 to 2010): Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Annual Meetings of the Infectious Diseases Society of America (IDSA) and European Congress of Clinical Microbiology and Infectious Diseases (ECCMID). For the present update, the following conference proceedings were also included: the American Society of Hematology (ASH), the European Society of Hematology (EHA) and the European Society for Bone Marrow and Transplantation (EBMT).

MEDLINE (Appendix 2) was searched and the search strategy adapted for searching the other databases (Appendix 3; Appendix 4).

Searching other resources

The references of all identified studies were inspected for more trials. Additionally, we attempted to contact the first or corresponding author of each included trial and researchers who are active in the field for information regarding unpublished trials or complementary information.

Data collection and analysis

Selection of studies

For the 2005 review (AGG, AF) and the update (AGG, LV), two authors independently assessed the titles and abstracts for inclusion of all the potential studies identified as a result of the search strategy . For potentially relevant articles, or in cases where there was disagreement between the two review authors, the full article was obtained and inspected independently by the two review authors. We resolved any further disagreement through discussion or, if required, we consulted MP.

Data extraction and management

For the 2005 review (AGG, AF) and the 2011 update (AGG, LV), two authors independently extracted the data of included trials to our specifically-designed data extraction form. We resolved discrepancies through discussion or, if required, we consulted MP who then also extracted data. We documented our decisions and, where necessary, we contacted the authors of the trials for clarification. We identified trials by the name of the first author and year in which the trial was first published and ordered them chronologically. We entered data into Review Manager software (RevMan 2008) and checked them for accuracy. The following data were recorded:

(1) Characteristics of trials

- Date, location and setting of trial
- Publication status
- Case definitions used (clinical, serological, bacteriological)
- Sponsor of trial (specified, known or unknown)
- Duration of follow-up

(2) Characteristics of participants

- Number of participants in each group
- Age, gender, nationality
- Underlying malignancy (haematological or solid)
- Neutrophil count below 1000 or 500 or 100/mm^3, in each group
- Percentage of patients with acute leukaemia in each group

(3) Characteristics of interventions

- Type of antibiotic, dose, mode of administration, schedule (started with chemotherapy or at onset of neutropenia), length of follow-up (in months)
- Number of days that the antibiotic prophylaxis was provided

(4) Characteristics of outcome measures

- Whenever possible, the numbers of events previously listed under 'Types of outcome measures' were recorded in each arm of the randomised trials together with the numbers evaluated
- When intention-to-treat (ITT) analysis was not performed by trial authors, we extracted data and performed an available case analysis

For trials which included three arms, the data collection was influenced by the different arms.

In trials in which there was a quinolone versus another antibiotic versus placebo arm, the patients and events in the control arm were divided so as to avoid counting them twice in two different comparisons, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009), that is quinolone versus placebo and the other antibiotic versus placebo.

In the event that two arms contained a quinolone and the third arm was placebo, the patients and events in the quinolone arm were combined (for example an arm of quinolone only, an arm of quinolone plus another antibiotic and an arm of placebo). In the event that two of the arms were of different quinolones (for example quinolone versus quinolone versus placebo or quinolone versus quinolone versus another antibiotic) the patients and events in the quinolone arms were merged and counted in only one comparison (quinolone versus placebo or quinolone versus another antibiotic, respectively).

When information regarding any of the above was unclear, we attempted to contact authors of the original reports for them to provide further details.

Assessment of risk of bias in included studies

See Appendix 1 for the methodology of the original review. For the updated review, AGG and LV independently assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009).

We assessed the following and resolved any disagreement by discussion:

- selection bias (random sequence generation; allocation concealment);
- performance bias (blinding of participants and personnel);
- detection bias (blinding of outcome assessment);
- attrition bias (incomplete outcome data); and
- reporting bias (selective reporting of outcomes).

For further details see Appendix 5.

Measures of treatment effect

Dichotomous data were analysed by calculating the risk ratio (RR) for each trial with the uncertainty in each result being expressed using 95% confidence intervals (CIs). We had planned to analyse continuous data by using the mean and standard deviation (SD) of each trial and calculating the effect size (average mean difference) and the 95% CI, where comparisons in the two groups were normally distributed. However, data could not be combined for days of hospitalisation and fever days as these outcomes were summarised heterogeneously in the various included trials as means or medians without appropriate CIs.

Dealing with missing data

For included studies, we noted levels of attrition. For all outcomes we carried out analyses, as far as possible, on an intention-to-treat

basis, that is we attempted to include all participants randomised to each group in the analysis, and all participants were analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if I^2 was greater than 30%, and if there was a low P value (< 0.10) in the Chi^2 test for heterogeneity. We anticipated inter-trial variation in estimation of morbidity and mortality for trials comparing patients at different risk levels.

Assessment of reporting biases

If there were 10 or more studies in the meta-analysis of the main outcomes, we investigated reporting biases (such as publication bias) using funnel plots. We assessed funnel plot asymmetry visually (Egger 1997). If asymmetry was suggested by a visual assessment we performed exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2008). We used fixed-effect model meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect, that is where trials were examining the same intervention and the trials' populations and methods were judged to be sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects model meta-analysis to produce an overall summary if an average treatment effect across trials was considered clinically meaningful. The random-effects model summary was treated as the average range of possible treatment effects. If the average treatment effect was not clinically meaningful we did not combine trials. If we used random-effects model analyses, the results were presented as the average treatment effect with 95% CI and the estimates of the Chi^2 and I^2 statistics.

Studies were sorted by publication year in the meta-analyses to allow for a visual inspection of trends by year.

Subgroup analysis and investigation of heterogeneity

We subgrouped studies according to the type of antibiotic used, that is:

1. quinolone versus placebo or no intervention;
2. trimethoprim-sulphamethoxazole (TMP-SMZ) versus placebo or no intervention;
3. other systemic antibiotic versus placebo or no intervention;
4. nonabsorbable antibiotic versus placebo or no intervention.

In addition, we assessed the effects of underlying cancer (haematological or solid), timing of prophylaxis initiation (with start of chemotherapy or at onset of neutropenia), type of quinolone, and study year (published before 2000 or thereafter) on results for mortality through subgroup analyses. These analyses were performed only for the comparison of quinolone versus placebo or no treatment, which is the main intervention currently considered in clinical practice.

Sensitivity analysis

Sensitivity analyses were performed by the assessment of bias indicators, namely randomisation (low - A, unclear - B and high - C risk), allocation concealment (low - A, unclear - B risk), and by whether the trials were double blind.

We included four outcomes for sensitivity analysis: mortality, incidence of fever, clinically documented infection and microbiologically documented infection.

RESULTS

Description of studies

Results of the search

For the original review, 162 studies were identified from the search and 101 studies, conducted between the years 1973 to 2005, were included. For the 2011 update, we identified 18 potentially eligible studies. After independent assessment, we included eight of these studies. This makes a total of 109 studies included in the review.

Included studies

Studies were conducted between the years 1973 to 2010 and randomised 13,579 patients. One trial included 111 neutropenic episodes without specifying the number of patients (Gurwith 1979).

Sixty-four studies compared a prophylactic antibiotic given orally or intravenously to placebo or no intervention (Characteristics of included studies).

- Twenty-seven studies compared quinolones to placebo or no intervention, the last published in 2010. Two studies included three arms: in one of the studies there was an additional arm in which patients were given vancomycin (Moreau 1995) and in the other there was an additional arm in which patients were given a quinolone plus vancomycin (Thomas 2000). Of the 27 studies that compared quinolones to placebo, in five of them the quinolone arm also included coverage against Gram-positive bacteria (such as vancomycin, amoxicillin-clavulonic acid or roxythromycin) (Lee 2002; Lalami 2004; Papaiakovou 2010; Thomas 2000; Tjan Heijnen 2001).
- Nineteen studies compared TMP-SMZ to placebo or no intervention. in two of them a macrolide (roxythromycin or erythromycin) was added to the antibiotic regimen (Kramer 1984; Pizzo 1983).
- Eleven studies compared other systemic antibiotics with placebo or no intervention: intravenous vancomycin (five studies), intravenous cefipime (one study), intravenous imipenem (one study), intravenous ceftriaxone (two studies), intravenous teicoplanin (one study), oral amoxicillin-clavulanate (one study).
- Six studies compared oral nonabsorbable antibiotics with placebo or no intervention. The nonabsorbable antibiotics arm used combinations of oral gentamicin, vancomycin, neomycin, polymyxin, colistin, nalidixic acid, bacitracin or kanamycin.

Forty-five studies compared different prophylactic regimens to each other, of which 35 studies compared quinolones to other antibiotics, including nonabsorbable antibiotics, or to each other.

- Ten trials compared quinolones to quinolones plus antibiotics active against Gram-positive pathogens. The antibiotics against Gram-positive pathogens included: penicillin V in two trials, phenethicillin in one trial, amoxicillin-clavulanate in one, vancomycin in two trials, rifampin in three trials and roxythromycin in one.
- Thirteen studies compared quinolones to TMP-SMZ.
- Five studies compared different types of quinolones (ciprofloxacin, ofloxacin, norfloxacin, pefloxacin) in the two study arms. Results for these studies were not part of the meta-analysis and are given separately (Table 1).
- Three studies compared TMP-SMZ to other antibiotics (trimethoprim, penicillin V, TMP-SMZ plus ciprofloxacin) (Bow 1984; Guiot 1992; Murase 1995).
- Twelve studies compared nonabsorbable antibiotics to the combination of nonabsorbable antibiotics and systemic antibiotics (Characteristics of included studies). In eight of the studies, quinolones were the systemic antibiotic. Three studies compared systemic antibiotics to the combination of nonabsorbable antibiotics and systemic antibiotics (Malarme 1981; Nemet 1989; Starke 1982). One study compared two different regimens of nonabsorbable antibiotics (Bender 1979).

Six studies had three arms, thus the total number of comparisons listed above is larger than the number of trials (Arning 1990; Bow 1996; D'Antonio 1994; Malarme 1981; Moreau 1995; Thomas 2000).

Patients and settings

Seventy-six studies included adult patients only. Twenty-six studies included children less than 16 years, 10 exclusively. The other studies did not specify the patients' ages. Most patients had haematological malignancies, mostly acute leukaemia, acute myeloid leukaemia or acute lymphoblastic leukaemia but also lymphoma, chronic myelocytic leukaemia in blast crisis and multiple myeloma.

- Seventy trials included only patients with haematological malignancies.
- Bone marrow transplant patients were included in 33 studies. In 18 of these, more than half of the patients underwent bone marrow transplantation.
- In 13 studies more than 80% of the patients had solid tumours (mostly breast, lung, ovary and germ cell tumours).

Patients were hospitalised for the duration of prophylaxis in 86 studies, both outpatients and inpatients were included in two studies, and 11 studies included only outpatients. The remaining studies did not report on the trial setting.

Prophylaxis was initiated either upon initiation of chemotherapy (87 studies) or when the patient became neutropenic (22 studies). Initiation time was not specified in one study. Prophylaxis was continued until: the peripheral granulocyte count reached greater than 500/mm^3 or greater than 1000/mm^3, the development of fever, remission, or a maximum of six weeks of treatment. Duration was different in several trials: in the Cullen 2005 study prophylaxis was administered during six cycles of chemotherapy, and in each cycle for seven consecutive days just before and during the anticipated period of neutropenia (thus, for a total of 42 days). In two other trials, treatment was prolonged to 40 weeks in one trial and three years in the other (Goorin 1985; van Eys 1987). Both of these studies included pediatric patients with acute lymphoblastic leukaemia (ALL). In the study in which prophylaxis was administered for 40 weeks the patients randomised to prophylaxis received it throughout the whole course of induction, consolidation and maintenance therapy. In the other study prophylaxis was administered throughout the whole course and even after.

In 15 studies the mean duration ranged between 10 to 151 days. In eight studies the median duration ranged between 8 to 37.5 days. Specific treatment duration was not reported in remaining studies.

In 57 studies anti-fungal prophylaxis was administered to both study groups, unrelated to randomisation. The vast majority of studies did not report compliance.

Reporting of outcomes

- Seventy studies, including 7502 participants, reported overall mortality (Characteristics of included studies).
- Seventy-one studies, including 9289 participants, reported infection-related mortality, four of which did not report all-cause mortality. Infection-related mortality was not defined a priori in most of the original trials.
- Eighty-six studies, including 10,002 participants, reported the number of febrile patients or number of febrile episodes. Of these studies, 18 reported only the number of episodes.
- Seventy-nine studies, including 8811 participants, reported the number of clinically documented infections. Ninety-three studies, including 10,922 participants, reported the number of microbiologically documented infections.
- Eighty-seven studies, including 9304 participants, reported the number of episodes of bacteraemia. Sixty-six studies, including 8031 participants, reported the number of episodes of any side effects.
- Sixty-nine studies, including 5271 participants, reported the number of episodes of fungal infection.

Excluded studies

A total of 71 studies were excluded (Characteristics of excluded studies).

The design of 58 of these was incompatible with inclusion criteria: 25 non-randomised trials, 26 review articles, six trials were trials of treatment of febrile neutropenia (Garcia 2000; Gilbert 1994; Karp 1986; Mantovani 1998; Schaison 1991; Takemoto 1990) and one trial assessed Pneumocystis pneumonia prophylaxis in AIDS patients (May 1994).

The randomised trials were excluded for the following reasons:

- peri-procedural (central line insertion) prophylactic antibiotic administration (Ljungman 1997),
- vancomycin solution administration for prevention of catheter infection (Barriga 1997),
- high attrition (EORTC 1982),
- prophylactic antibiotic therapy combined with a protected environment (Lohner 1979),
- prophylactic antibiotic therapy combined with lactobacilli (Ekert 1980),

- the intervention evaluated was granulocyte colony stimulating factor and both arms received prophylactic antibiotics (Timmer-Bonte 2005),
- seven reports were identified as duplicate publications and were considered under their primary references (Bow 1984; Castagnola 2003; Donnelly 1992b; Harousseau 1987; Karp 1987; Sleijfer 1980; Winston 1986).

Risk of bias in included studies

Results are summarised in Figure 1 showing that the large majority of risk of bias items were not described. The method of generating the randomisation sequence was adequate in 33 studies (classified as A, or low risk of bias) (Characteristics of included studies). In two studies generation of randomisation was inadequate (classified as C, or high risk of bias). In one, the randomisation generation was by birth dates (Lange 1984) and in the other by order of admission (Yamada 1993). In the remaining trials it was not clearly described (classified as B, or unclear risk of bias).

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

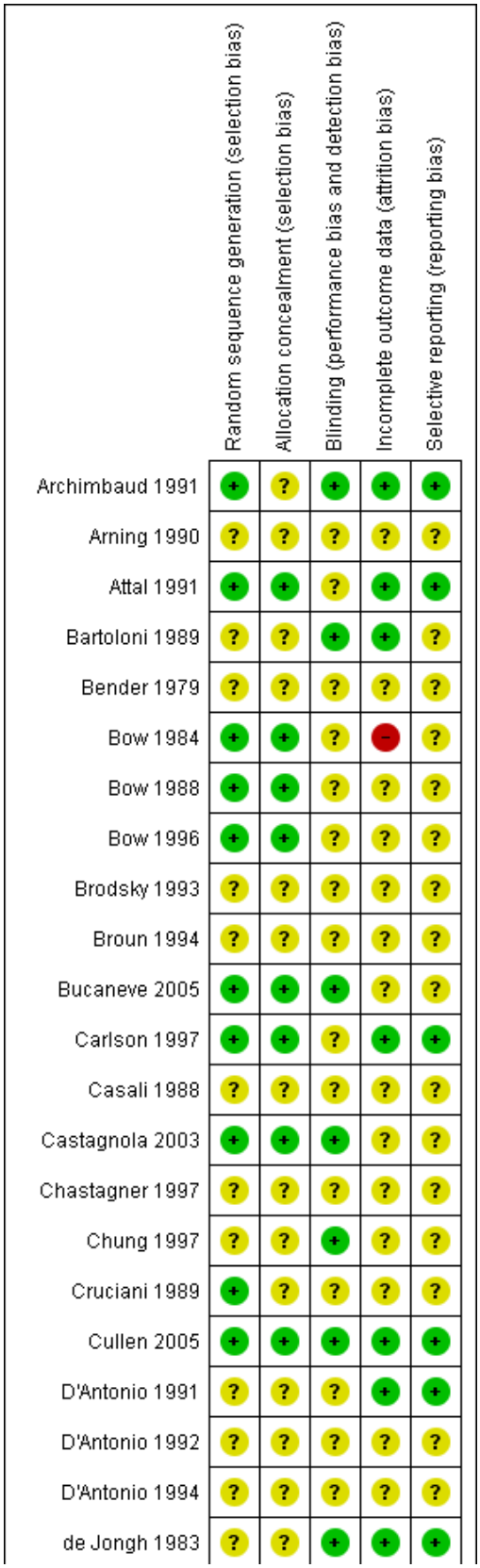


Figure 1. (Continued)

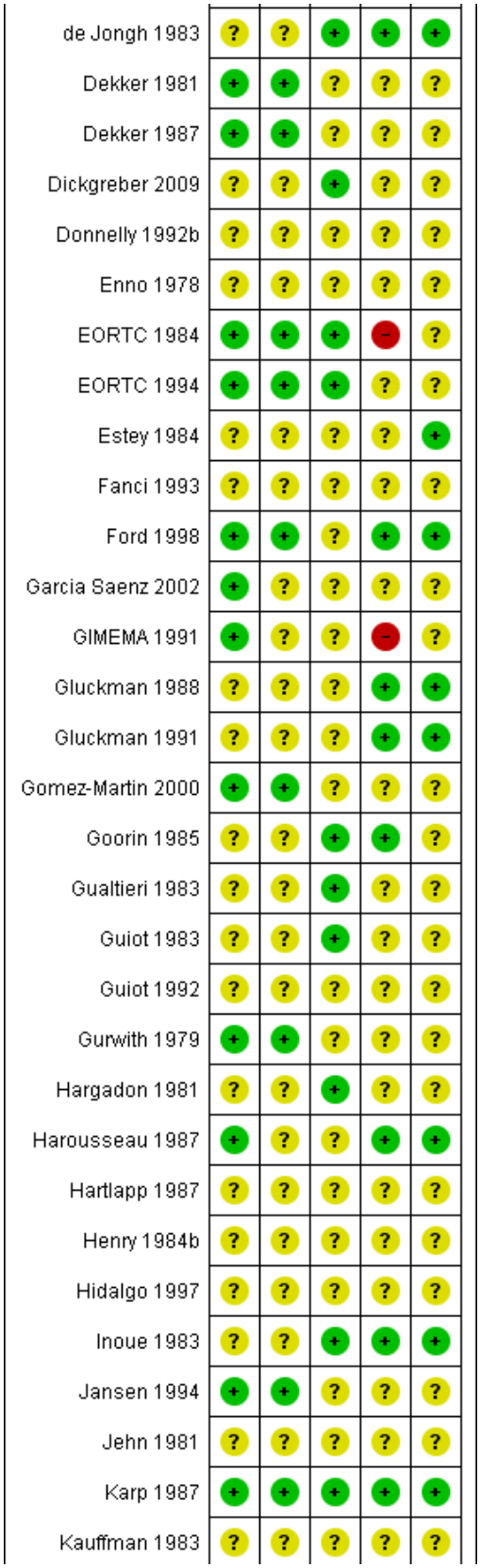


Figure 1. (Continued)

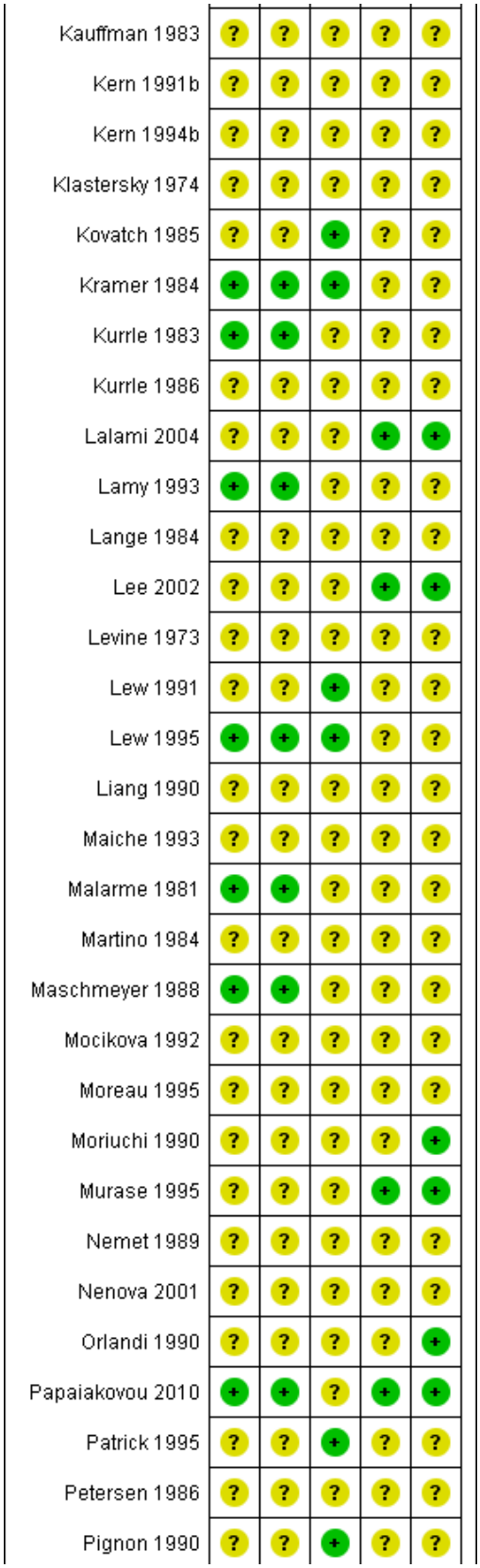
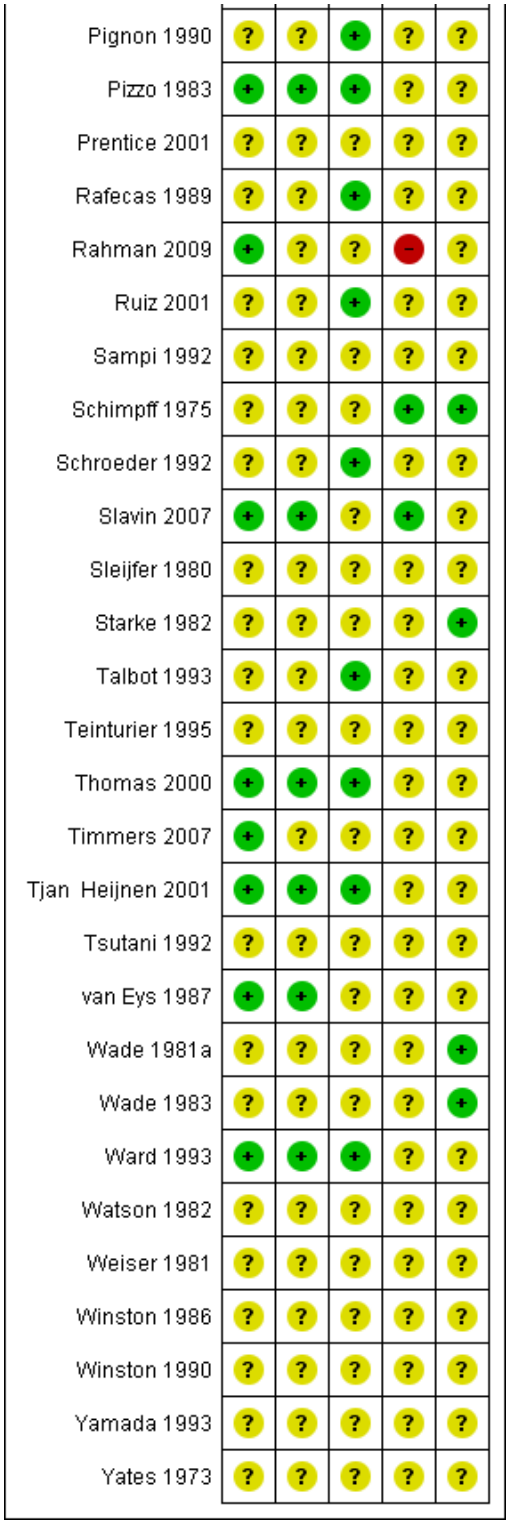


Figure 1. (Continued)



Allocation concealment was adequate (A, low risk) in 27 studies, and seven additional studies used sealed envelopes that were not described as opaque (classified as B). In the remaining studies allocation concealment was not described (also classified as B). Thirty studies were conducted in a double-blinded fashion. All remaining trials were open.

Full intention-to-treat (ITT) analyses for mortality and infection were reported in 24 studies, and for mortality alone in six. In 14 studies the number evaluated was the same as the number randomised, with no mention of loss to follow-up. In the remaining studies ITT analysis was not performed.

Fifty-six studies reported that patients gave their consent to participate in the research. Approval of the ethics committee was reported in 27 of them.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings: antibiotics versus placebo or no intervention; **Summary of findings 2** Summary of findings: quinolone prophylaxis compared with TMP-SMZ prophylaxis

Antibiotic versus placebo or no intervention

Primary outcome

1. All-cause mortality

Antibiotic prophylaxis resulted in a significant reduction in the risk of mortality (46 trials, 5635 participants; RR 0.66, 95% CI 0.55 to 0.79) (Analysis 1.1; Figure 2). NNT to prevent one death from any cause was 34 (95% CI 26 to 56).

Figure 2. Forest plot of comparison: 1 All-cause mortality, prophylaxis vs. placebo/no intervention or other antibiotic, outcome: 1.1 drug vs. placebo/no intervention.

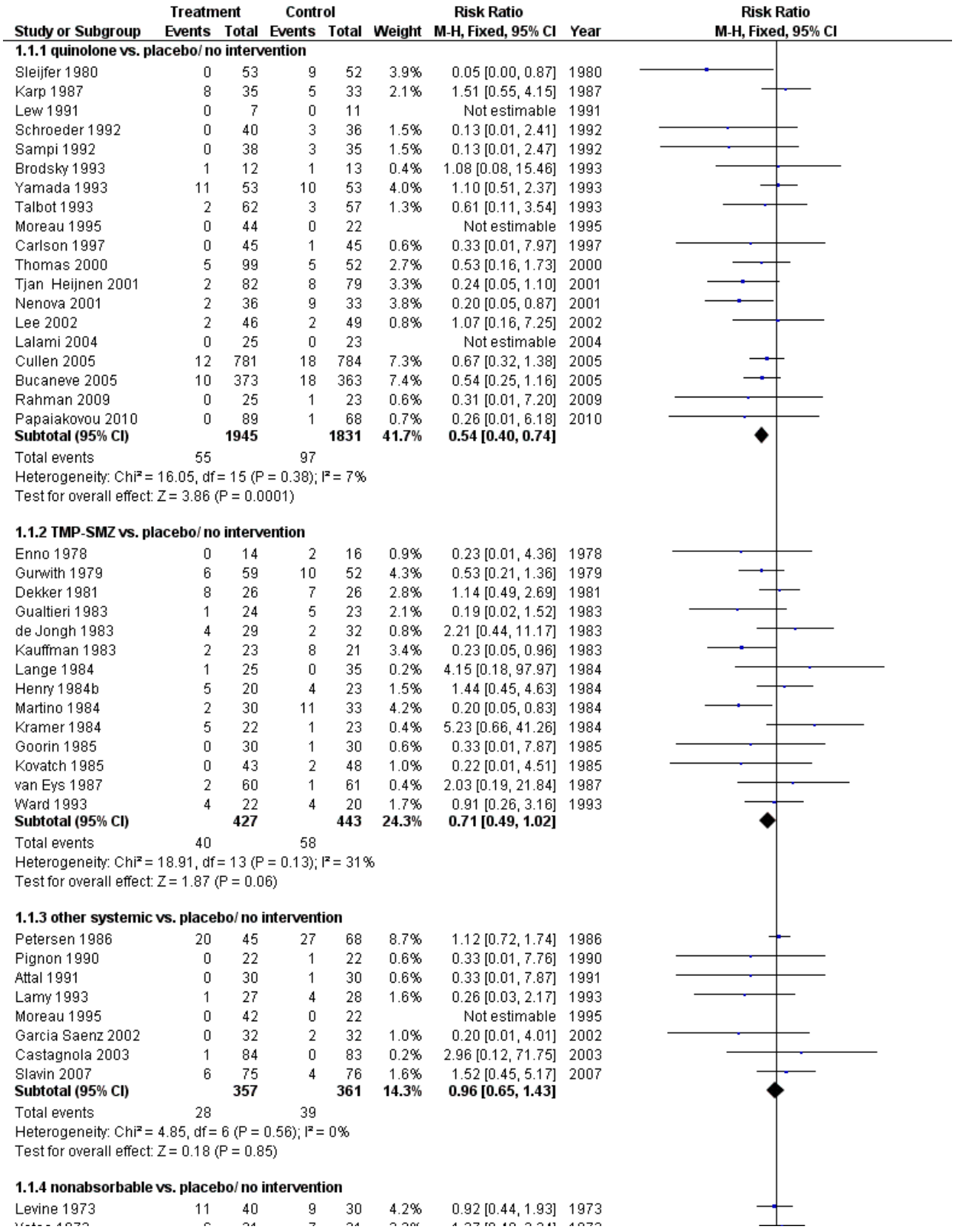
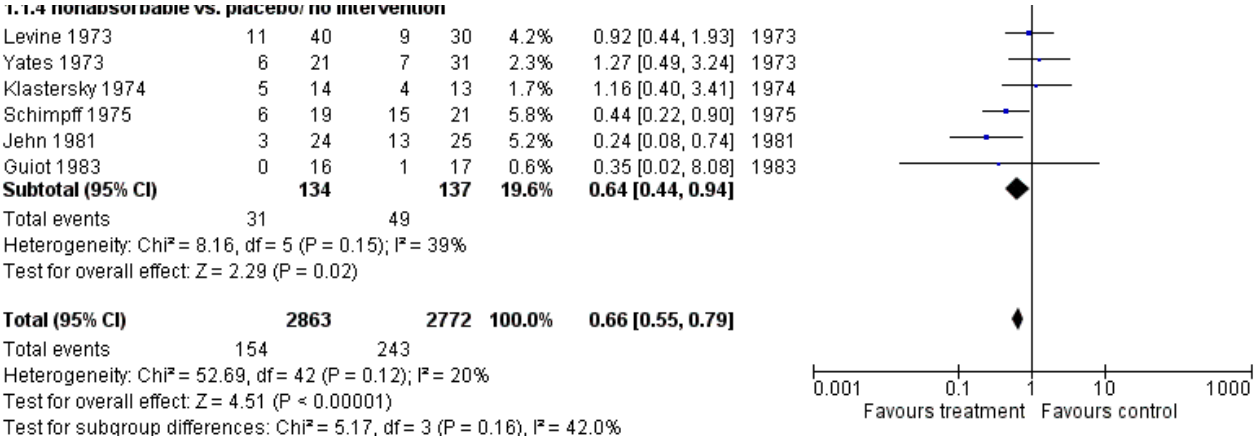


Figure 2. (Continued)



The greatest effect was seen in the quinolone prophylaxis subgroup (19 trials, 3,776 participants; RR 0.54, 95% CI 0.40 to 0.74) although tests for subgroup differences were not significant (I^2 = 42%, P = 0.16).

Results for mortality for this comparison of antibiotic versus placebo or no treatment were not affected by the studies' risk of bias; mortality was significantly lower with antibiotic prophylaxis in adequately randomised, concealed and double-blind trials (Analysis 16.1; Analysis 17.1; Analysis 18.1).

Further to this outcome we performed some exploratory subgroup analyses on the quinolone prophylaxis subgroup, as follows.

Quinolones versus placebo or no treatment

A. All-cause mortality by disease status

Most of the trials included haematological cancer patients, showing an advantage of prophylaxis. In patients with acute leukaemia or patients undergoing haematopoietic cell transplant (mainly allogeneic haematopoietic cell transplantation but also autologous stem cell transplant) quinolone prophylaxis resulted in a significant decrease in mortality (13 trials, 1818 participants; RR 0.57, 95% CI 0.40 to 0.82); NNT to prevent one death from any cause for haematological malignancies was 33 (95% CI 16 to 100). In trials assessing patients with solid cancer or lymphoma the effect was also statistically significant (5 trials, 1940 participants; RR 0.48, 95% CI 0.26 to 0.88) (Analysis 15.1); with a larger NNT of 50 (95% CI 33 to 1000).

The group of patients with solid tumours or lymphoma included tumours of the lung, ovary, breast, testis and other. These were mostly outpatients. Tests for subgroup differences were nonsignificant and the funnel plot was symmetrical.

B. All-cause mortality by type of quinolone

An advantage was seen with all quinolones except for norfloxacin. Levofloxacin reduced all-cause mortality (4 trials, 2349 patients; RR 0.59, 95% CI 0.35 to 0.99) as did ciprofloxacin (8 trials, 726 patients; RR 0.30, 95% CI 0.13 to 0.69) and other quinolones (ofloxacin, pefloxacin or enoxacin) (4 trials, 451 patients; RR, 0.28, 95% CI 0.12 to 0.64). Norfloxacin had no significant effect on all-cause mortality compared with placebo (4 trials, 271 patients; RR 1.03, 95% CI 0.58 to 1.81) (Analysis 15.2). Tests for subgroup differences were significant (I^2 = 67.8%, P = 0.03).

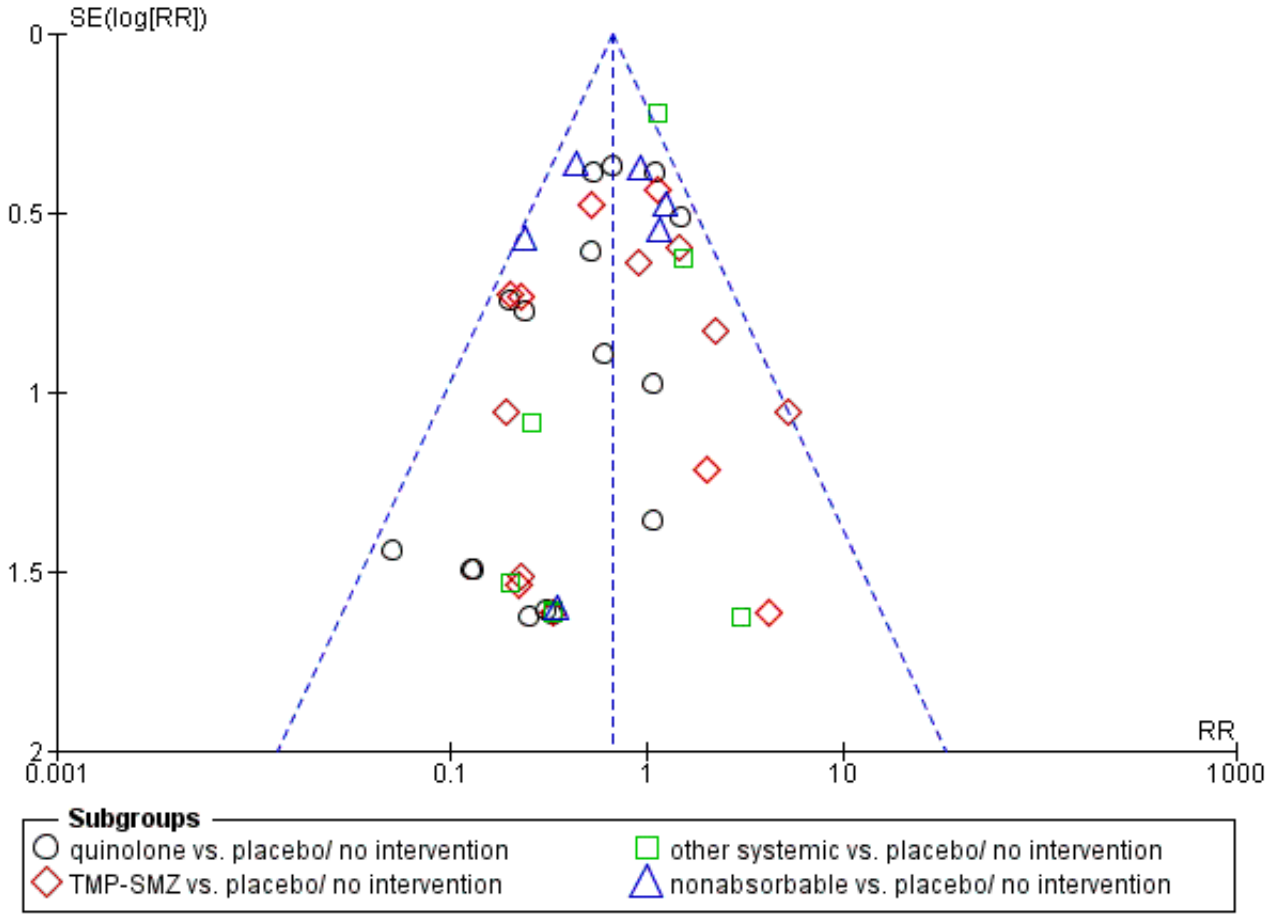
C. All-cause mortality by timing of prophylaxis initiation

Most trials initiated antibiotic prophylaxis with the start of chemotherapy. Results were similar for this set of trials (15 trials, 1947 patients; RR 0.63, 95% CI 0.44 to 0.92); or when prophylaxis was initiated at onset of neutropenia (4 trials, 1829 patients; RR 0.39, 95% CI 0.22 to 0.70) (Analysis 15.3). As shown, the effect was even larger for trials which initiated prophylaxis at the onset of neutropenia, without a statistically significant difference between these subgroups.

D. All-cause mortality by publication years

Finally, we analysed all-cause mortality according to year of publication, that is before 2000 or thereafter. Studies conducted in the last decade (studies published after 2000) showed a larger effect of quinolone prophylaxis on mortality (8 trials, 2879 patients; RR 0.49, 95% CI 0.32 to 0.75) than older studies (conducted before and until 2000) (11 trials, 897 patients; RR 0.61, 95% CI 0.39 to 0.96), without a statistically significant difference between these subgroups (Analysis 15.4). There was no evidence to suggest publication bias in the funnel plot for mortality (Figure 3).

Figure 3. Funnel plot of comparison: 1.1 drug vs. placebo/no intervention for the outcome: All-cause mortality.



Secondary outcomes

2. Infection-related mortality

Antibiotic prophylaxis resulted in a significant reduction in the risk of infection-related death (43 trials, 5777 participants; RR 0.61, 95% CI 0.48 to 0.77) (Analysis 2.1); NNT to prevent one death from infection was 48 (95% CI 34 to 77). This effect was consistent across subgroups with the greatest risk reduction seen in the quinolone prophylaxis subgroup (16 studies, 3733 participants; RR 0.51, 95% CI 0.33 to 0.78). TMP-SMZ was associated with a RR of 0.60 (95% CI 0.41 to 0.87) (Figure 4; Figure 5).

Figure 4. Forest plot of comparison: 2 Infection related mortality, prophylaxis vs. placebo/no intervention or other antibiotic, outcome: 2.1 drug vs. placebo/no intervention.

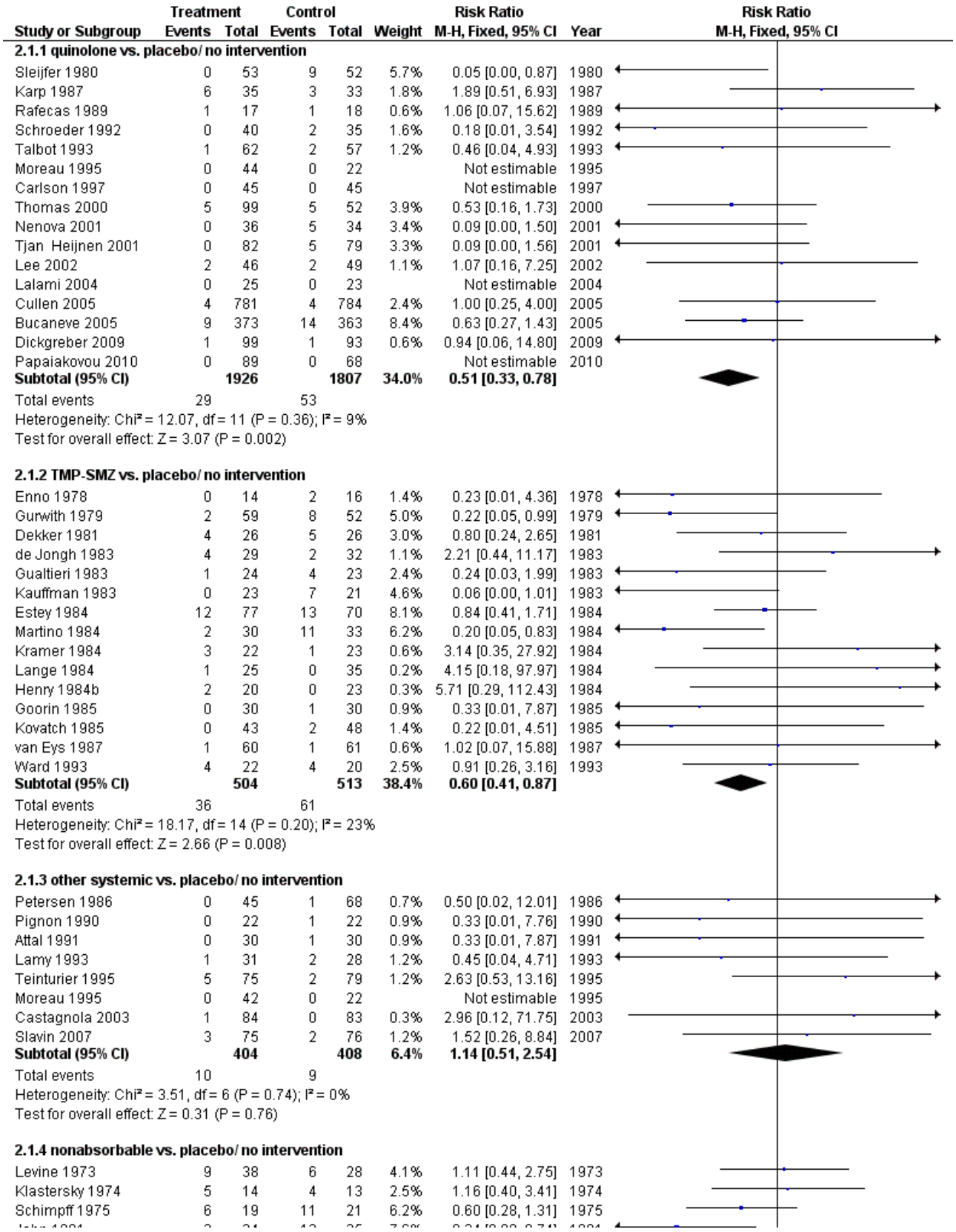


Figure 4. (Continued)

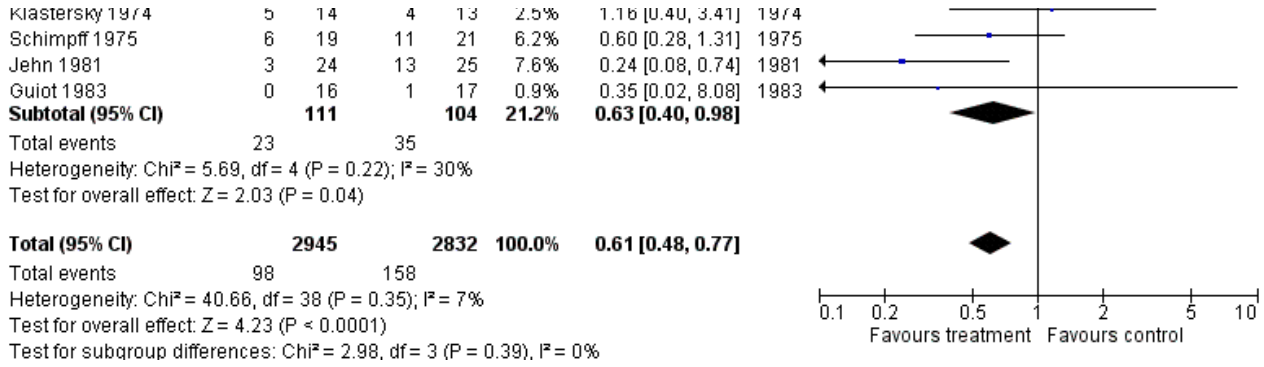
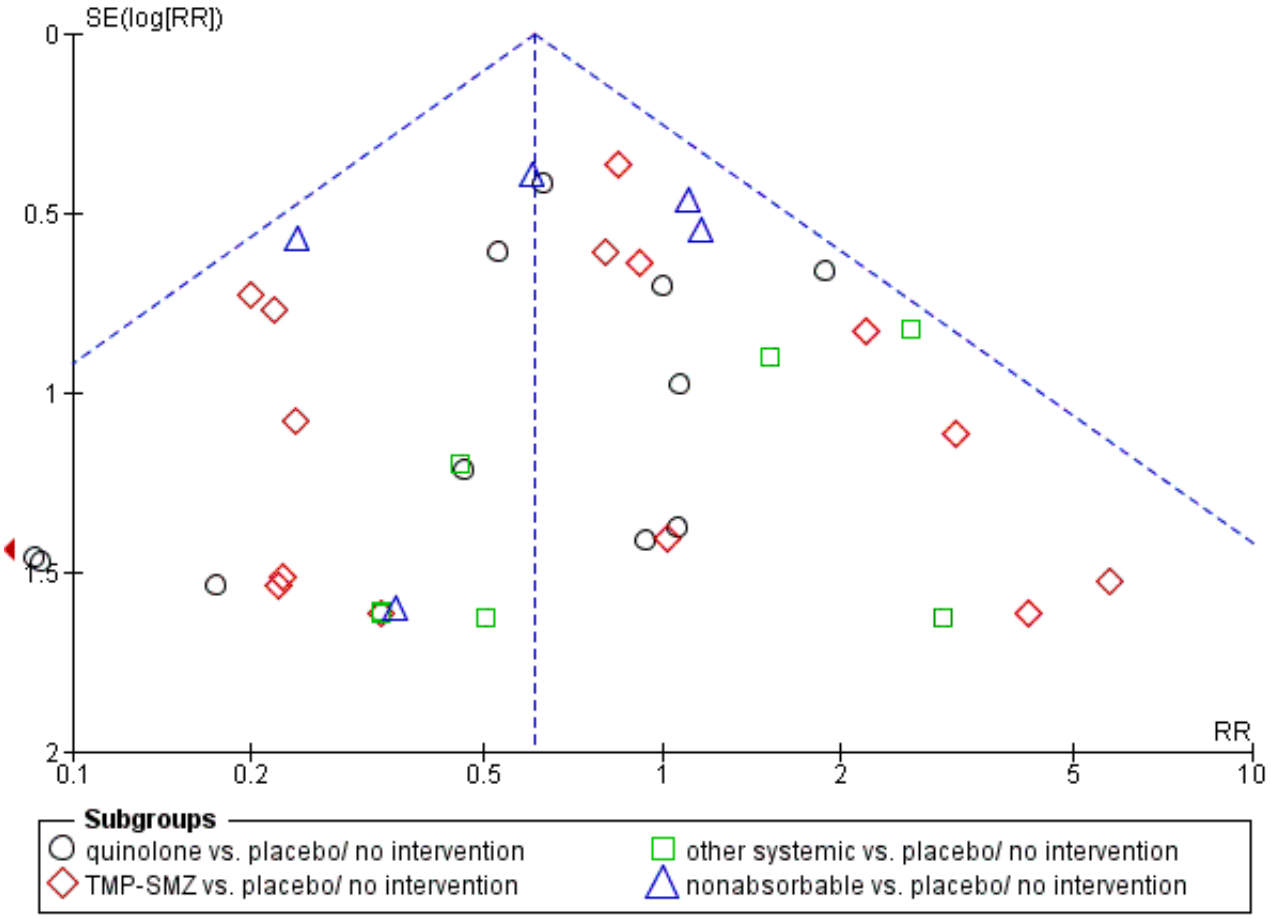


Figure 5. Funnel plot of comparison: 2 Infection related mortality, prophylaxis vs. placebo/no intervention or other antibiotic, outcome: 2.1 drug vs. placebo/no intervention.



3. Febrile episodes

Antibiotic prophylaxis resulted in a significant decrease in the occurrence of fever (54 trials, 6658 participants; RR 0.80, 95% CI 0.74 to 0.87) (Analysis 3.1; Figure 6) when both febrile patients and episodes were included in the analysis (when data on febrile patients were not available, data on febrile episodes were used for the numerator). The NNT to prevent one febrile patient or febrile episode was 7 (95% CI 5 to 10). Data were substantially heterogenous for this outcome, overall and across subgroups (I^2 = 89% and I^2 = 67%, respectively). Quinolones and TMP-SMZ were the only subgroups associated with a reduction in febrile episodes (26 trials, 4205 participants; RR 0.74, 95% CI 0.65 to 0.84; and 16 trials, 1424 participants; RR 0.80, 95% CI 0.69 to 0.92, respectively).

Figure 6. Forest plot of comparison: 3 Febrile patients and febrile episodes, prophylaxis vs. placebo/no intervention or other antibiotic, outcome: 3.1 drug vs. placebo/ no intervention.

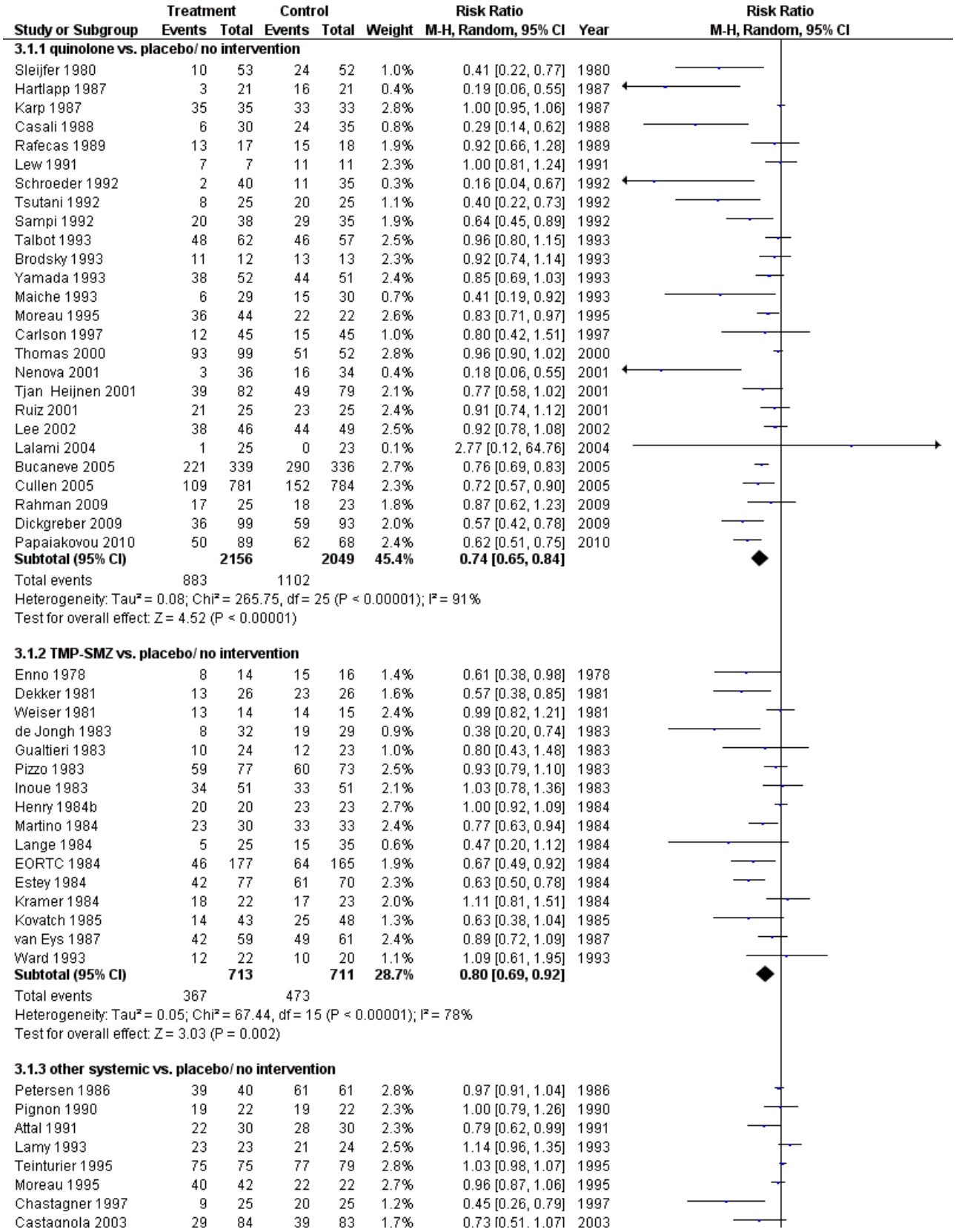
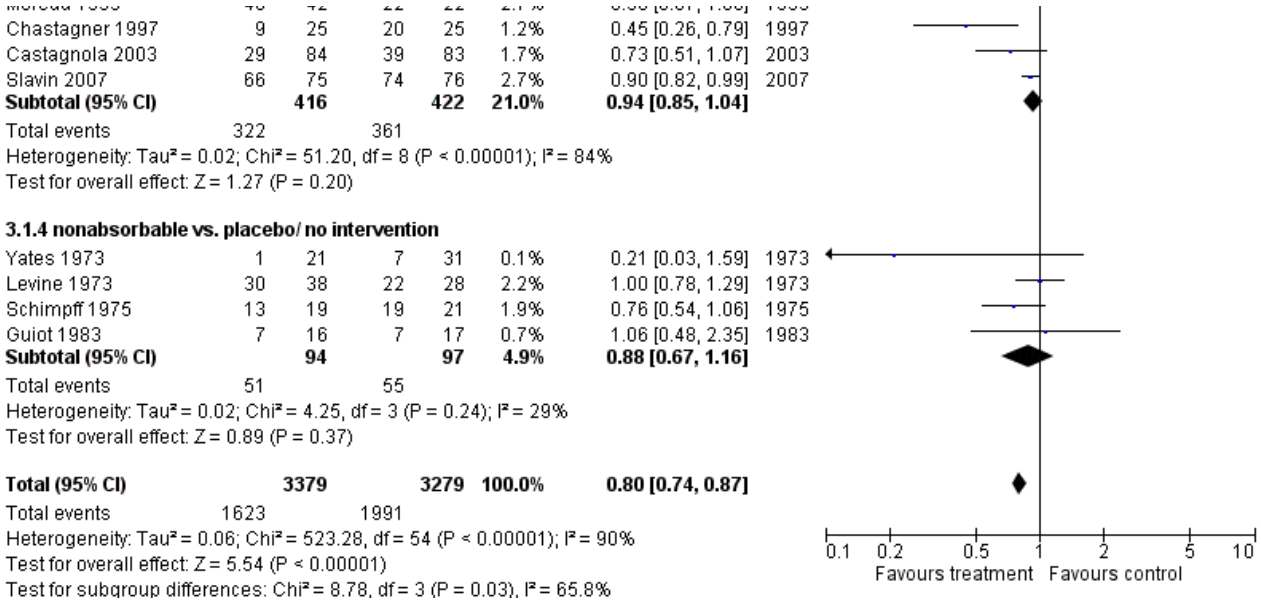


Figure 6. (Continued)



Sensitivity analysis for this outcome showed that results did not differ significantly according to randomisation generation, concealment and blinding (for example Analysis 16.2; Analysis 17.2; Analysis 18.2).

4. Clinically documented infection

Antibiotic prophylaxis resulted in a significant decrease in the occurrence of clinically documented infection (48 trials, 5758 participants; RR 0.65, 95% CI 0.56 to 0.76) (Analysis 4.1).

This reduction occurred for quinolones (21 trials, 3889 participants; RR 0.58, 95% CI 0.44 to 0.76), TMP-SMZ (17 trials, 1229 participants; RR 0.68, 95% CI 0.56 to 0.82) and other systemic antibiotics (five trials, 413 participants; RR 0.48, 95% CI 0.26 to 0.90) but not nonabsorbables.

Sensitivity analysis for this outcome showed that results did not differ significantly according to randomisation generation, concealment and blinding (for example Analysis 16.3; Analysis 17.3; Analysis 18.3).

5. Microbiologically documented infection

Antibiotic prophylaxis resulted in a significant decrease in the occurrence of microbiologically documented infection (53 trials, 6383 participants; RR 0.51, 95% CI 0.42 to 0.62) (Analysis 5.1); NNT to prevent one microbiologically documented infection was 7 (95% CI 6 to 9). This reduction occurred for quinolones (24 trials, 3953 participants; RR 0.46, 95% CI 0.32 to 0.66); TMP-SMZ (17 trials, 1400 participants; RR 0.50, 95% CI 0.38 to 0.65); and other systemic antibiotics (10 trials, 882 participants; RR 0.63, 95% CI 0.45 to 0.87) but not nonabsorbables.

Sensitivity analysis for this microbiologically documented infection showed that results did not differ significantly according to randomisation generation, concealment and blinding (for example Analysis 16.4; Analysis 17.4; Analysis 18.4).

6. Gram-negative infection

Antibiotic prophylaxis resulted in a significant decrease in the occurrence of microbiologically documented Gram-negative infection (44 trials, 5607 participants; RR 0.38, 95% CI 0.28 to 0.52) (Analysis 6.1). This reduction occurred with quinolones (21 trials, 3752 participants; RR 0.30, 95% CI 0.22 to 0.41) and TMP-SMZ (13 trials, 1120 participants; RR 0.40, 95% CI 0.29 to 0.56) but not for other systemic or nonabsorbable antibiotics.

7. Gram-positive infection

Antibiotic prophylaxis resulted in a significant decrease in the occurrence of microbiologically documented Gram-positive infection (45 trials, 5583 participants; RR 0.45, 95% CI 0.34 to 0.59) (Analysis 7.1). This reduction occurred with quinolones (21 trials, 3749 participants; RR 0.33, 95% CI 0.21 to 0.52) and TMP-SMZ (12 trials, 1009 participants; RR 0.37, 95% CI 0.26 to 0.53) but not for nonabsorbable antibiotics. There was a trend towards reduction in the systemic antibiotic subgroup (7 trials, 610 participants; RR 0.59, 95% CI 0.34 to 1.02).

8. Bacteraemia

Antibiotic prophylaxis resulted in a significant decrease in the occurrence of bacteraemia (53 trials, 6390 participants; RR 0.50, 95% CI 0.43 to 0.60) (Analysis 8.1); NNT to prevent bacteraemia was 10 (95% CI 8 to 12).

This reduction occurred for quinolones (22 trials, 3806 participants; RR 0.52, 95% CI 0.40 to 0.69), TMP-SMZ (18 trials, 1511 participants; RR 0.46, 95% CI 0.37 to 0.57), other systemic antibiotics (9 trials, 832 participants; RR 0.40, 95% CI 0.23 to 0.71) and nonabsorbable antibiotics (5 trials, 215 participants; RR 0.64, 95% CI 0.43 to 0.95).

9. Gram-negative bacteraemia

Antibiotic prophylaxis significantly decreased the occurrence of Gram-negative bacteraemia (40 trials, 5328 participants; RR 0.41, 95% CI 0.33 to 0.50) (Analysis 9.1). Overall, the NNT to prevent one episode of Gram-negative bacteraemia was 17 (95% CI 14 to 22).

The reduction occurred with quinolones (15 trials, 3228 participants; RR 0.33, 95% CI 0.24 to 0.45), TMP-SMZ (RR 0.46, 95% CI 0.33 to 0.65) and other systemic antibiotics (8 trials, 791 participants; RR 0.52, 95% CI 0.29 to 0.93).

10. Gram-positive bacteraemia

Antibiotic prophylaxis resulted in a significant decrease in the occurrence of Gram-positive bacteraemia (39 trials, 5265 participants; RR 0.63, 95% CI 0.54 to 0.74) (Analysis 10.1); NNT to prevent one episode of Gram-positive bacteraemia was 24 (95% CI 17 to 36). TMP-SMZ resulted in a significant decrease in the occurrence of Gram-positive bacteraemia (14 trials, 1098 participants; RR 0.38, 95% CI 0.24 to 0.60) as did quinolones (15 trials, 3228 participants; RR 0.70, 95% CI 0.57 to 0.86) and other systemic antibiotics (8 trials, 791 participants; RR 0.63, 95% CI 0.44 to 0.89).

11. Side effects

When compared to placebo or no intervention, prophylactic antibiotics caused more side effects (37 trials, 5103 participants; RR 1.58, 95% CI 1.19 to 2.12) (Analysis 11.1). This occurrence of side effects was significant in the quinolone (17 trials, 3324 participants; RR 1.51, 95% CI 1.12 to 2.04) and TMP-SMZ (13 trials, 1240 participants; RR 1.70, 95% CI 1.12 to 2.59) subgroups only. These were mostly gastrointestinal side effects, including diarrhoea and nausea. *C. difficile*-associated diarrhea specifically was reported on in only in two studies, with no events in one (Carlson 1997) and a similar event rate in the two arms in the other (Talbot 1993). Few other studies reported one to two cases in the antibiotic arm but did not report the number of events in the control arm.

12. Side effects requiring discontinuation

When compared to placebo or no intervention, prophylactic antibiotics caused more side effects requiring discontinuation (18 trials, 2281 participants; RR 2.06, 95% CI 1.32 to 3.19) (Analysis 12.1). This was only significant for the quinolone (8 trials, 1513 participants; RR 2.04, 95% CI 1.10 to 3.81) and TMP-SMZ subgroups (5 trials, 305 participants; RR 3.63, 95% CI 1.32 to 9.98).

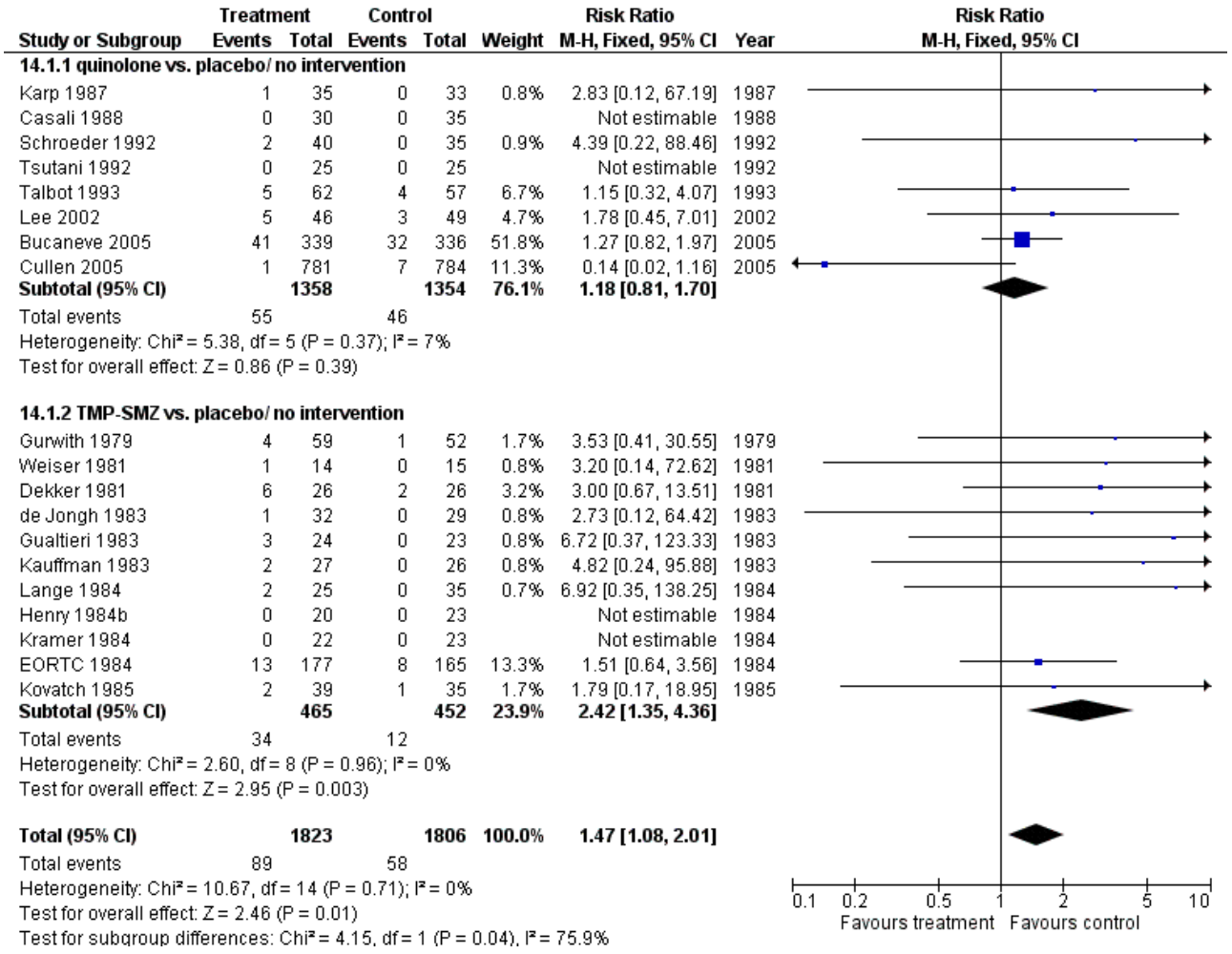
13. Fungal infection

There was no statistically significant difference in the number of episodes of fungal infection when prophylactic antibiotics were compared to placebo (39 trials, 2887 participants; RR 1.04, 95% CI 0.82 to 1.33) (Analysis 13.1).

14. Resistance to antibiotics

For this comparison, the numerator was the number of episodes in which bacilli resistant to the specific drug (quinolones or TMP-SMZ) were grown in cultures during follow-up, and the denominator was the number of patients evaluated. When compared to placebo, participants receiving antibiotics were more likely to harbour resistant bacteria to the specific drug (19 trials, 3629 participants; RR 1.47, 95% CI 1.08 to 2.01) (Analysis 14.1; Figure 7). This applied specifically to the TMP-SMZ subgroup (11 trials, 917 participants; RR 2.42, 95% CI 1.35 to 4.36). With quinolones there was no statistically significant difference between study groups.

Figure 7. Forest plot of comparison: 14 Infection resistant to drug taken, prophylaxis vs. placebo/no intervention or other antibiotic, outcome: 14.1 drug vs. placebo/ no intervention.



15. Hospitalisations and fever days

Data on the number of hospitalisations, length of hospital stay and days of fever were too sparse for meta-analyses.

Antibiotic versus antibiotic

Primary outcome

1. All-cause mortality

There was no significant difference in all cause mortality between participants receiving quinolones compared with TMP-SMZ (10 trials, 917 participants; RR 1.07, 95% CI 0.66 to 1.72) (Analysis 1.2). The last study was conducted in 1995. Ten studies (1474 participants) compared quinolones to quinolones plus prophylactic antibiotics active against Gram-positive pathogens (Analysis 1.3). The addition of an antibiotic against Gram-positive infection yielded no statistical significant difference (RR 1.28, 95% CI 0.69 to 2.38). When nonabsorbable antibiotics were compared to systemic antibiotics, again there was no difference in the risk for mortality in trials conducted between 1983 and 2001 (8 trials, 813 participants; RR 1.06, 95% CI 0.74 to 1.50) (Analysis 1.5). In two trials there was no advantage with the addition of nonabsorbable antibiotics to systemic antibiotic (Analysis 1.6). Six studies compared the different quinolones but no significant statistical differences were found (Table 1; Table 2). These studies were not summarised in a meta-analysis.

Secondary outcomes

2. Infection-related mortality

Eleven studies including 1019 participants compared quinolones with TMP-SMZ. No statistically significant difference was found (RR 0.91, 95% CI 0.54 to 1.54) (Analysis 2.2). Ten studies including 1474 participants compared quinolones to quinolones plus prophylactic antibiotics active against Gram-positive pathogens. The addition of antibiotic against Gram-positive infection yielded no advantage in terms of infection-related mortality (RR 1.01, 95% CI 0.56 to 1.81) (Analysis 2.3). Eleven studies which included 1005 patients compared nonabsorbable antibiotics to systemic antibiotics. For this comparison, there was a significant decrease in infection-related mortality in favour of the systemic antibiotics arm (RR 2.48, 95% CI 1.65 to 3.73) (Analysis 2.5).

3. Febrile episodes

Ten studies including 931 participants compared quinolones with TMP-SMZ, with no statistically significant difference (RR 0.92, 95% CI 0.78 to 1.09) (Analysis 3.2). The addition of an antibiotic

against Gram-positive infection yielded no statistically significant difference either (8 trials, 1375 participants; RR 1.03, 95% CI 0.97 to 1.11) (Analysis 3.3).

4. Clinically documented infection

Ten studies including 931 participants compared quinolones with TMP-SMZ. A statistically significant difference in favour of TMP-SMZ was shown (RR 1.33, 95% CI 1.06 to 1.66) (Analysis 4.2). The addition of an antibiotic against Gram-positive infections yielded no statistically significant difference (7 studies, 1335 patients; RR 0.99, 95% CI 0.69 to 1.42) (Analysis 4.3).

5 to 7. Microbiologically documented infection

Eleven studies including 1019 participants compared quinolones with TMP-SMZ. There was a trend to a reduction in microbiologically documented infection in the quinolone group (RR 0.75, 95% CI 0.56 to 1.01) (Analysis 5.2) and with the addition to quinolones of an antibiotic against Gram-positive infection (RR 0.78, 95% CI 0.55 to 1.11) (Analysis 5.3). There was a clear benefit of systemic antibiotics when compared to nonabsorbable antibiotics (RR 1.49, 95% CI 1.17 to 1.91) (Analysis 5.5).

Quinolones resulted in a significant reduction in Gram-negative infection compared with TMP-SMZ prophylaxis (9 trials, 915 participants; RR 0.21, 95% CI 0.13 to 0.36; Analysis 6.2) but not Gram-positive infections (9 trials, 915 participants; RR 1.01, 95% CI 0.60 to 1.69) (Analysis 7.2). The addition of an antibiotic against Gram-positive infection to quinolones resulted in a significant decrease in documented Gram-positive infection (7 trials, 740 participants; RR 0.40, 95% CI 0.22 to 0.72) (Analysis 7.3).

8 to 10. Bacteraemia

There was no significant difference in bacteraemia when quinolones were compared to TMP-SMZ (10 trials, 931 participants; RR 0.89, 95% CI 0.56 to 1.42) (Analysis 8.2), however, the addition of an antibiotic against Gram-positive infection to quinolones resulted in a significant decrease in bacteraemic episodes (8 trials, 824 participants; RR 0.74, 95% CI 0.56 to 0.97) (Analysis 8.6). There was also a clear benefit of other systemic antibiotics over nonabsorbable ones (10 trials, 716 participants; RR 1.50, 95% CI 1.18 to 1.91) (Analysis 8.5).

Quinolone prophylaxis resulted in a significant reduction in Gram-negative bacteraemia compared to TMP-SMZ prophylaxis (10 trials, 931 participants; RR 0.35, 95% CI 0.13 to 0.93) (Analysis 9.2) but there was no significant difference between them with regard to Gram-positive bacteraemia (10 trials, 931 participants; RR 1.24, 95% CI 0.86 to 1.60) (Analysis 10.2). The addition of an antibiotic against Gram-positive infections to quinolones resulted in a significant reduction in documented Gram-positive bacteraemia (8 trials, 824 participants; RR 0.61, 95% CI 0.44 to 0.83) (Analysis 10.3).

11 to 12. Side effects

When compared to TMP-SMZ, quinolones caused fewer side effects (10 trials, 1027 participants; RR 0.62, 95% CI 0.43 to 0.90) (Analysis 11.2). There was a trend towards increased side effects with the addition to quinolones of an antibiotic against Gram-positive infection (6 trials, 516 participants; RR 2.69, 95% CI 0.78 to 9.27) (Analysis 11.3).

Compared to TMP-SMZ, quinolones caused fewer side effects requiring discontinuation (7 trials, 850 participants; RR 0.37, 95% CI 0.16 to 0.87) (Analysis 12.2). The addition to quinolones of antibiotic against Gram-positive infection significantly increased side effects requiring discontinuation (RR 4.92, 95% CI 1.61 to 15.01) (Analysis 12.3).

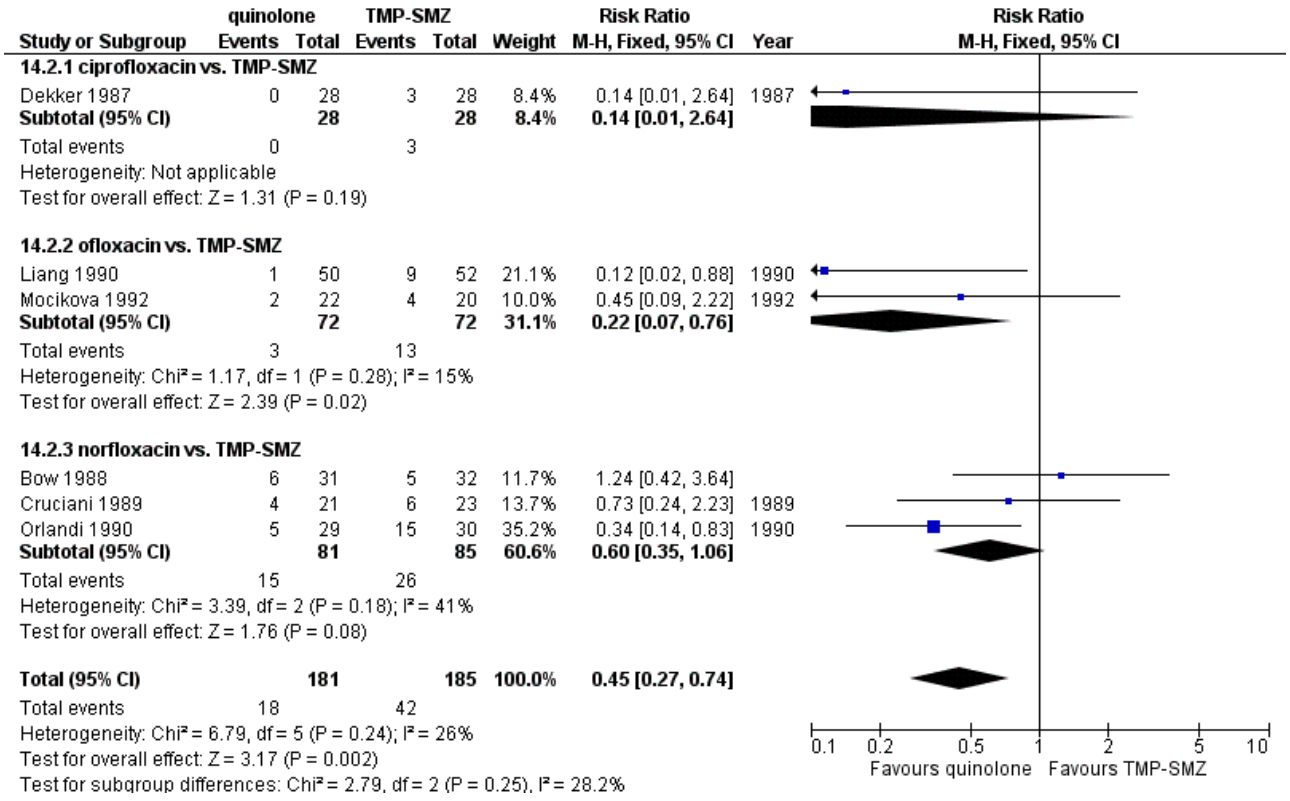
13. Fungal infection

When quinolones were compared to TMP-SMZ, no significant difference was found (10 trials, 789 participants; RR 0.65, 95% CI 0.36 to 1.16) (Analysis 13.2).

14. Resistance to antibiotics

For this comparison the numerator was the number of episodes in which bacilli resistant to the specific drug (quinolones or TMP-SMZ) were grown in cultures, and the denominator was the number of evaluable patients. In studies comparing quinolones to TMP-SMZ, less resistance to quinolones was observed following treatment with quinolones than resistance to TMP-SMZ following treatment with TMP-SMZ (6 trials, 366 participants; RR 0.45, 95% CI 0.27 to 0.74) (Analysis 14.2; Figure 8).

Figure 8. Forest plot of comparison: 14 Infection resistant to drug taken, prophylaxis vs. placebo/no intervention or other antibiotic, outcome: 14.2 quinolone vs. TMP-SMZ.



DISCUSSION

Summary of main results

In studies comparing antibiotic prophylaxis to placebo or no treatment in neutropenic patients, prophylaxis significantly reduced all-cause mortality and infection-related mortality. We estimated the NNT with antibiotic prophylaxis in order to prevent one death from all causes as 34 (95% CI 26 to 56). Prophylaxis significantly reduced febrile episodes. Patients receiving prophylaxis also experienced fewer clinically documented infections, fewer microbiologically documented infections, fewer Gram-negative infections, fewer Gram-positive infections, fewer episodes of bacteraemia, fewer episodes of Gram-negative bacteraemia, and fewer episodes of Gram-positive bacteraemia than patients who did not receive prophylaxis (Summary of findings for the main comparison). Side effects were increased by administration of prophylaxis, as was the development of resistance to the antibiotic regimen concerned.

When quinolones were compared to TMP-SMZ, there was no significant difference in all-cause mortality, febrile episodes or bacteraemia (Summary of findings 2), however Gram-negative infections, Gram-negative bacteraemia and side effects were significantly reduced.

The addition to quinolones of an antibiotic against Gram-positive infection resulted in a significant decrease in the number of bacteraemic episodes, Gram-positive infections, and Gram-positive bacteraemia but an increase in side effects and no reduction in mortality.

Systemic antibiotics were more efficient than nonabsorbable ones in reducing the number of febrile patients, clinically documented infections, microbiologically documented infections, Gram-negative infections, Gram-positive infections, episodes of bacteraemia, episodes of Gram-negative bacteraemia and episodes of Gram-positive bacteraemia; however, side effects were increased.

Overall completeness and applicability of evidence

Overall, most trials included haematological patients and so our results apply mainly to this group. The haematological patients included mainly acute leukaemia and patients undergoing haematopoietic cell transplant. The group of patients with solid tumours or lymphoma was small and clinically heterogenous, including tumours of the lung, ovary, breast, testicular and other.

Our assessment of treatment effect supports quinolones as the prophylaxis of choice since they reduced the risk of death when compared to placebo or no intervention. This reduction occurred for patients with haematological malignancies (acute leukaemia and patients undergoing haematopoietic cell transplantation) and for patients with solid tumours and lymphoma. Quinolones are an attractive option for prophylaxis in neutropenic patients due to their broad antimicrobial spectrum, preservation of the anaerobic flora of the alimentary tract, high concentration in the faeces, systemic bactericidal activity, good tolerability and lack of myelosuppression (Engels 1998).

The majority of patients in the trials in our review were treated with either levofloxacin or ciprofloxacin. All types of quinolones reduced

mortality when compared to placebo or no intervention except for norfloxacin. Furthermore, the efficacy of quinolone prophylaxis did not decrease in studies published in later years, with even a larger effect of quinolone prophylaxis on mortality reported than in older studies (although not statistically significant).

Our study demonstrates that quinolones also reduced the risk of infection-related mortality, fever, clinically documented infections, microbiologically documented infections, Gram-negative infections, Gram-positive infections and bacteraemia when compared to placebo or no intervention. In addition, they reduced the risk for microbiologically documented infections, Gram-negative infections and Gram-negative bacteraemia and had fewer side effects when compared to TMP-SMZ. A frequent misconception is that quinolone prophylaxis increases the incidence of Gram-positive bacteraemia. Our meta-analyses show that Gram-positive bacteraemia is not significantly altered by quinolone prophylaxis.

One of the major concerns raised in regard to treatment with quinolones is the emergence of resistance and outbreaks of infections due to resistant organisms, such as coagulase-negative Staphylococci (Oppenheim 1989) and *E. coli* (Kern 1994). When quinolones were compared to placebo or no intervention in our review there was no significant difference in the number of patients developing infections caused by organisms resistant to quinolones. Because the overall mortality was reduced by prophylaxis, the danger of infection caused by resistant pathogens to a particular patient evidently was much smaller than the gain. In studies in which quinolones were compared to TMP-SMZ, resistance to the quinolone following quinolone treatment was less than resistance to TMP-SMZ following treatment with TMP-SMZ (RR 0.45, 95% CI 0.27 to 0.74). Furthermore, development of resistance to quinolones is not necessarily associated with development of resistance to other antibiotics which are administered for treatment of febrile neutropenia (Gentry 2002).

The addition to quinolones of antibiotics with coverage against Gram-positive pathogens resulted in reduction of microbiologically documented infections, total episodes of bacteraemia and Gram-positive bacteraemia. However, considering the lack of clear benefits in terms of mortality, it is probably not reasonable to recommend the addition of Gram-positive coverage.

Hughes 1977 have shown that TMP-SMZ is highly effective in the prevention of Pneumocystis pneumonia (PCP) among cancer patients at high risk of this infection. Currently identified risk factors for *Pneumocystis jirovecii* infections among cancer patients include prolonged corticosteroid therapy (equivalents of 20 mg prednisolone for over a month); intense chemotherapy, particularly with haematologic malignancies or mediastinal irradiation; and lymphopenia (Hughes 1977; Roblot 2004; Worth 2005). We could not assess the effect of TMP-SMZ or other antibiotics on PCP since the studies included in our review do not report this particular infection among the outcomes assessed. PCP is not included within the fungal infections outcome since its classification within this class succeeded most of these studies. TMP-SMZ prophylaxis should be administered to patients at high risk for PCP. The dosing schedule should follow that used in the studies included in our review (for example daily administration) to gain the survival benefit of TMP-SMZ. The addition of quinolones to TMP-SMZ has not been assessed in enough studies to draw conclusions. Thus, this decision should be based on local susceptibility patterns. We recommend that quinolones be added to TMP-SMZ in locations where the prevalence of Gram-negative bacteria resistant to TMP-SMZ is high.

Combinations of oral nonabsorbable drugs which were studied in early studies have since been abandoned due to poor tolerance and low patient compliance (Hughes 2002). Our results support this, as oral nonabsorbable drugs were less efficient when compared to other regimens. TMP-SMZ was also frequently used, although many centres have stopped its use due to possible prolongation of neutropenia, adverse reactions caused by sulfonamide drugs, development of drug-resistant bacteria and oral candidiasis (Hughes 2002).

All-cause mortality encompasses the personal harm associated with prophylactic antibiotic administration, side effects, and the emergence of resistant micro-organisms. The number needed to treat to prevent one death (34) compares favourably with other interventions well accepted in medical practice. Thus, antibiotic prophylaxis for patients similar to those included in our review is clearly indicated. Even the reduction in the incidence of fever carries important implications, since the occurrence of fever in neutropenic patients prompts additional use of broad-spectrum antibiotics, with the associated drawbacks.

Potential biases in the review process

Several limitations of our analyses should be noted.

- We could obtain data on all-cause mortality for only 47 studies out of 64 studies that compared antibiotic prophylaxis to placebo. Among studies that did not report mortality are some of the larger studies (EORTC 1984; EORTC 1994; GIMEMA 1991).
- Data regarding the time period during which mortality was assessed were scarce and varied among the trials that reported it.
- Many studies in our review are old. However, it seems that the RRs for efficacy and developing infections caused by quinolone-resistant bacteria did not change over the years.
- Length of follow-up may have been too short to detect emergence of resistant bacteria and resistance data were not routinely collected in these studies. To actually assess the risk for resistance development studies must perform surveillance cultures prior to and following antibiotic treatment. None of these studies assessed resistance development.
- Most studies assessed prophylaxis that was started at the onset of chemotherapy (rather than onset of neutropenia). Future studies should assess whether antibiotics started at onset of neutropenia are as effective, to limit unnecessary exposure to antibiotics.
- Most studies were limited to haematological cancer patients. Seventy-nine studies were conducted on inpatients. RRs for mortality obtained for patients with solid cancer or outpatients were not significantly different from those seen for haematological inpatients. However, the latter group of patients was smaller and should be studied further. Moreover, data regarding the specific chemotherapeutic protocols were scarce in the original trials and were not extracted.

Agreements and disagreements with other studies or reviews

Several previous meta-analyses (Cruciani 1996; Cruciani 2003; Engels 1998; Rotstein 1997) have studied the efficacy of various prophylactic regimens compared to placebo or a to a different treatment regimen. All of these reviews demonstrated a reduced incidence of various infection-related outcomes, but none demonstrated a significant effect of prophylaxis on mortality. Another recent meta-analysis included only RCTs which were double blind and compared quinolones to placebo, only in adult patients (Imran 2008). It included eight trials. There was a statistically nonsignificant reduction in mortality with quinolone prophylaxis. These reviews included up to 20 trials while our review, which includes 64 trials comparing prophylaxis versus placebo or no treatment, has the power to detect a significant effect.

Before our original systematic review was published, there was no consensus to recommend antibiotic prophylaxis for afebrile neutropenic patients according to the IDSA guidelines (Hughes 2002). After our publication, several guidelines have changed their recommendation, taking into account the benefit of reduction in mortality. The recent Infectious Disease Society of America guidelines for antibiotic treatment in neutropenic patients with cancer, updated in 2010, now recommend antibiotic prophylaxis (Freifeld 2011). According to the guidelines, quinolone prophylaxis should be considered for high-risk patients with expected durations of prolonged and profound neutropenia (ANC <100 cells/mm^3 for more than 7 days). The First European Conference on Infections in Leukaemia (ECIL1) published their guidelines in July 2007 (Cordonnier 2007). They found quinolone prophylaxis to be effective in preventing bacterial infection and in reducing mortality in acute leukaemia and HSCT recipient afebrile neutropenic patients, and recommended ciprofloxacin or levofloxacin as the drug of choice.

AUTHORS' CONCLUSIONS

Implications for practice

These updated findings support antibiotic prophylaxis, preferably with a quinolone where resistance permits, for routine use in neutropenic patients because it reduces mortality. We recommend levofloxacin or ciprofloxacin for this purpose, however the decision to use prophylaxis and the type of drugs, whether a quinolone or a combination of a quinolone and a drug effective against Gram-positive bacteria, should be taken based on the local profile of pathogens in neutropenic patients and their susceptibility to antibiotics.

Prophylaxis is strongly recommended in patients with haematological malignancies, who are usually at higher risk for infection. However, a reduction in mortality was shown for patients with solid tumours or lymphoma as well and therefore these patients are likely to benefit from prophylactic antibiotics. Since studies of these patients were few and they were clinically heterogenous (different diseases), further research is needed to identify which patients with solid tumours or lymphoma may benefit the most.

Centres that implement prophylaxis should institute surveillance measures to monitor quinolone-resistant Gram-negative bacteria, as well as rates of other resistant organisms (vancomycin resistant enterococci (VRE), methicillin resistant *S.aureus* (MRSA) and *Clostridium difficile*.

Implications for research

Current evidence points to an advantage in survival with antibiotic prophylaxis. Therefore, further RCTs comparing prophylaxis to placebo or no intervention are probably not warranted.

Although the evidence in favour of antibiotic prophylaxis is convincing, many of the studies included in the present analysis were of uncertain methodological quality and some of them were quite old. Thus an argument could be made in favour of a contemporary trial evaluating and comparing quinolones that has adequate randomisation, allocation concealment and blinding, and is powered to detect a difference in mortality. However, given that the mortality rates in recent trials of febrile neutropenic patients range between 1% to 8% (Cherif 2004; De Pauw 1994; Giamarellou 2000; Rolston 1992), a RCT powered to demonstrate a difference in mortality due to prophylaxis is probably not feasible since it would require an inordinately large sample size.

Further research should define which patients with solid tumours or lymphoma may benefit from prophylaxis. This could be assessed by conducting RCTs that include patients with a specific malignancy, or according to different chemotherapy protocols. Further studies should determine the advantage of antibiotic prophylaxis in the first chemotherapy cycle versus the next cycles. Data on all-cause mortality should be reported, even if not as a primary outcome. Assessment of resistance development should be carefully planned and performed.

Future studies should assess whether antibiotics started at the onset of neutropenia are as effective as antibiotics started with chemotherapy, to limit unnecessary exposure to antibiotics.

ACKNOWLEDGEMENTS

We thank the Cochrane Gynaecological Cancer Review Group (CGCRG) for their support during the review process. In addition thanks to Jane Hayes for help with the search, and thanks to Clare Jess and Gail Quinn.

We thank the following authors who responded to our request for additional data:

A Casali, AW Dekker, E Estey, R Fanci, C Ford, JA Garcia-Saenz, HFL Guiot, C Harman, J Harousseau, H Heimpel, J Jansen, J Karp, CA Kauffman, J Klastersky, B Kramer, T Lamy, G Maschmeyer, I Nenova, G Prentice, M M Rahman, FJ Rafecas, A Ronald, MA Slavin, X Thomas, J van Eys, T Ward, T Yamada, and SH Zinner.

We thank the CGCRG Co-ordinating Editor Chris Williams and the peer reviewers M Clarke, M Cruciani, K Godfrey, and W Hughes for their helpful comments.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Archimbaud 1991

Methods	Randomisation: a table of random numbers, no data on allocation concealment; Blinding: double blind; Intention to treat: yes; Exclusion from analysis: none (0/150); Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count 500 or death
Participants	France, single centre; 150 afebrile adult patients presenting with neutropenia(<1000) expected to last more than two weeks after intensive chemotherapy for acute leukaemia or BMT for various haematological malignancies; In-patients, reverse isolation
Interventions	Nonabsorbable antibiotics: gentamicin, colistin sulphate, vancomycin (100mg, 3 million U, 800mg - respectively) versus absorbable: pefloxacin, vancomycin (800mg, 800mg)
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Number of febrile patients or episodes; Fever days; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Hospitalization days; Resistance to quinolones; Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No post-randomisation withdrawals
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Arning 1990

Methods	Randomisation: no information (was done for neutropenic episodes,and not patients) Blinding: none; Intention to treat: no; Exclusion from analysis: 6/65 patients, 8/96 neutropenic episodes; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count 500
Participants	Germany, single centre; 65 afebrile adult patients presenting with neutropenia(<1000) after chemotherapy for acute leukaemia; Inpatients, reverse isolation
Interventions	Trimethoprim-sulfamethoxazole + colistin (160/800mg + 2 million units) versus ofloxacin 400mg versus ciprofloxacin 1g
Outcomes	All cause mortality; Infection related death; Number of febrile patients or episodes; Microbiologically documented febrile episodes; Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6/65 patients, 8/96 neutropenic episodes

Attal 1991

Methods	Randomisation: computer-generated sequence unknown to physicians participating in trials, allocation by central randomisation calling a distant data coordinating system; Blinding: none; Intention to treat: yes; Exclusion from analysis: none (0/60); Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count 500 or fever
Participants	France, single centre; 60 patients (adult and children) after BMT for various haematological diseases; Inpatients
Interventions	Intravenous vancomycin (15mg/kg X2/d day) versus no intervention
Outcomes	All cause mortality;

Attal 1991 *(Continued)*

	Infection related death; Number of febrile patients or episodes; Fever days; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated sequence
Allocation concealment (selection bias)	Low risk	Data coordinating system (A - Adequate)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions
Selective reporting (reporting bias)	Low risk	All outcomes reported

Bartoloni 1989

Methods	Randomisation: no information; Blinding: double blind; Intention to treat: unknown; Exclusion from analysis: none; Beginning of prophylaxis: chemotherapy; End of prophylaxis: complete remission or a neutrophil count of 500
Participants	Italy, single centre; 19 adult patients with acute leukaemia or chronic leukaemia in blast crisis undergoing cytotoxic chemotherapy to induce remission; Inpatients
Interventions	Ofloxaxin 300mgX2/d versus trimethoprim-sulphamethoxazole 160/800mg twice daily
Outcomes	No relevant outcomes: the trial evaluates effect of prophylactic antibiotics on the bacterial aerobic flora (nose, gingiva and perineal region)
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)

Bartoloni 1989 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions
Selective reporting (reporting bias)	Unclear risk	No outcomes relevant to this review were reported.

Bender 1979

Methods	Randomisation: no information Blinding: none; Intention to treat: no; Exclusion from analysis: 4/42 patients; Beginning of prophylaxis: chemotherapy; End of prophylaxis: remission, death or 5 weeks
Participants	USA, single centre; 42 patients with acute leukaemia who were undergoing remission chemotherapy; Inpatients
Interventions	Gentamicin 200mgX6, oral vancomycin 500mgX6 and nystatin 5 million units versus gentamicin 200mgX6 and nystatin 5 million units
Outcomes	All cause mortality; Number of febrile patients or episodes; Clinically documented febrile episodes; Microbiologically documented febrile episodes
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4/42 patients excluded from analysis
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

Bow 1984

Methods	Randomisation: central randomisation generated from a computer program, kept in sealed envelopes Blinding: none Intention to treat: no; Exclusion from analysis: 15/75; Beginning of prophylaxis: PMN count < 1000; End of prophylaxis: PMN count 1000 or death
Participants	Canada, single centre; 75 patients with bone marrow failure due to haematological malignancies and neutropenia; Inpatients
Interventions	Trimethoprim 150mgX2/d versus trimethoprim-sulphamethoxazole 160mg/800mg X2/d
Outcomes	All cause mortality; Infection related death; Number of febrile episodes; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Resistance to quinolones
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computer-generated
Allocation concealment (selection bias)	Low risk	sealed envelopes (A - Adequate)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	15/75 excluded from analysis
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

Bow 1988

Methods	Randomisation: central randomisation generated from a computer program, allocations assigned from pharmacies of the participating institutions; Blinding:none Intention to treat: no; Exclusion from analysis: 12/75; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count 1000 or fever
Participants	Canada, multicentre; adult patients with haematological malignancies and cytotoxic induced neutropenia; Inpatients, university hospital
Interventions	Norfloxacin 400mgX2/d versus trimethoprim-sulphamethoxazole 160mg/800mgX2/d

Bow 1988 *(Continued)*

Outcomes	All cause mortality; Infection related death; Number of febrile patients or febrile episodes; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Resistance to quinolones and trimethoprim-sulphamethoxazole
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computer-generated
Allocation concealment (selection bias)	Low risk	pharmacy assigned allocation (A - Adequate)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	12/75 excluded from analysis
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

Bow 1996

Methods	Randomisation: central randomisation, computerized random-number generator, allocations sequentially assigned from a central office; Blinding: none; Intention to treat: no; Exclusion from analysis: 16/127; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count 500 or fever
Participants	Canada, multicentre; adult patients with severe neutropenia receiving cytotoxic therapy for acute leukaemia or BMT; Inpatients
Interventions	Norfloxacin 400mgX2/d, versus ofloxacin 400mg X2/d, versus ofloxacin 400mgX2/d + rifampin 300mgX2/d
Outcomes	All cause mortality; Infection related death; Number of febrile episodes; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Adverse events
Notes	Journal Publication

Risk of bias

Bow 1996 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	sequential allocation from central office (A - Adequate)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	16/127 excluded
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

Brodsky 1993

Methods	Randomisation: no information; Blinding: none; Intention to treat: no; Exclusion from analysis: unknown; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count 500 or fever
Participants	Argentina, single centre; 14 adult patients with severe neutropenia receiving cytotoxic therapy for acute leukaemia; Inpatients
Interventions	Norfloxacin 400mgX2/d or ciprofloxacin 500mgX2 versus no intervention
Outcomes	All cause mortality; Number of febrile episodes; Clinically documented febrile episodes; Microbiologically documented febrile episodes
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blinded
Incomplete outcome data (attrition bias)	Unclear risk	Details not available for the 2011 review update

Brodsky 1993 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

Broun 1994

Methods	Randomisation: no information; Blinding: none; Intention to treat: no; Exclusion from analysis: 3/40; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count 500 or fever
Participants	USA, single centre; adult patients undergoing autologous BMT for haematological or solid tumours; Inpatients
Interventions	Norfloxacin 400mgX3/d versus norfloxacin + penicillin (400mgX3/d, 10 million unitsX6/d)
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Clinically documented febrile episodes; Microbiologically documented febrile episodes
Notes	Journal Publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3/40 excluded
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

Bucaneve 2005

Methods	Randomisation: central, computer-generated Blinding: triple blind; Intention to treat: none; Exclusion from analysis: 22/760; Beginning of prophylaxis: 1-3 days before chemotherapy or reinfusion of stem cells; End of prophylaxis: neutropenia resolution (>1000)

Bucaneve 2005 *(Continued)*

Participants	Italy, multicentre; 760 adult patients with acute leukaemia and solid tumour or lymphoma undergoing autologous blood stem cell transplantation; Inpatients
Interventions	Levofloxacin 500mg X1/d versus placebo
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Infection resistant to quinolones; Adverse events
Notes	Journal publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computer-generated
Allocation concealment (selection bias)	Low risk	central allocation (A - Adequate)
Blinding (performance bias and detection bias) All outcomes	Low risk	triple-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	22/760 excluded
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

Carlson 1997

Methods	Randomisation: central randomisation, computerized random-number table; Blinding:none; Intention to treat: yes; Exclusion from analysis: 0/90; Beginning of prophylaxis: PMN count of 500; End of prophylaxis: PMN count 1000
Participants	USA, multicentre; Patients with ovarian cancer receiving chemotherapy (paclitaxel) and expected to be neutropenic; Outpatients
Interventions	Ciprofloxacin 500mgX2/d versus no intervention
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Microbiologically documented febrile episodes;

Carlson 1997 *(Continued)*

	Hospitalization days; Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Central allocation (A - Adequate)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions
Selective reporting (reporting bias)	Low risk	Analyses by ITT; all expected outcomes reported

Casali 1988

Methods	Randomisation: no information; Blinding: none; Intention to treat: unknown; Exclusion from analysis: unknown Beginning of prophylaxis: PMN count less than 1000 End of prophylaxis: PMN count 1000
Participants	Italy, single centre; 65 cancer patients with solid tumours presenting with neutropenia after chemotherapy; Setting not specified
Interventions	Norfloxacin 400mgX3/d versus no intervention
Outcomes	Number of febrile episodes; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Resistance to quinolones; Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)

Casali 1988 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	ITT not described

Castagnola 2003

Methods	Randomisation: sequentially numbered batches according to a computer-generated randomised list, allocation by central randomisation calling a data coordinating centre; Blinding: triple blind; Intention to treat: no; Exclusion from analysis: 6/173; Beginning of prophylaxis: PMN count less than 500; End of prophylaxis: PMN count 500, maximum 15 days
Participants	Italy, multicentre (16 centres), 173 neutropenic children with cancer (solid or haematological) treated with chemotherapy; Inpatients
Interventions	Amoxicillin/clavulanate 12mg/kgX2/d versus placebo
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Adverse events
Notes	Journal Publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	computer-generated list
Allocation concealment (selection bias)	Low risk	central allocation (A - Adequate)
Blinding (performance bias and detection bias) All outcomes	Low risk	Triple blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6/173 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

Chastagner 1997

Methods	Randomisation: no information; Blinding: none; Intention to treat: none; Exclusion from analysis: 18 Beginning of prophylaxis: PMN count less than 500 End of prophylaxis: PMN count 500
Participants	France, single centre, 68 neutropenic children undergoing induction therapy for acute lymphoblastic leukaemia
Interventions	IV Teicoplanin 10 mg/kg o.d. after initial dosing of 10 mg/kg every 12 hours for 3 doses versus no intervention
Outcomes	Febrile episodes; Microbiologically documented infections
Notes	Abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	no details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	18/68 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

Chung 1997

Methods	Randomisation: no information; Blinding: double blind; Intention to treat: none; Exclusion from analysis: 13 Beginning of prophylaxis: not specified; End of prophylaxis: not specified
Participants	Korea, single centre, 65 neutropenic patients with acute leukaemia undergoing remission induction or consolidation chemotherapy
Interventions	Tosufloxacin 150 mg X2/d versus placebo
Outcomes	Number of febrile episodes; Microbiologically documented infections; Clinically documented infections.

Chung 1997 *(Continued)*

	However, number of episodes for each outcome not specified, and therefore not included in the analysis.
Notes	Abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Low risk	double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	13/65 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

Cruciani 1989

Methods	Randomisation: by an appropriate random-number-table, allocation unknown; Blinding: none; Intention to treat: no; Exclusion from analysis: 5/49; Beginning of prophylaxis: PMN count less than 1000 End of prophylaxis: PMN count 1000
Participants	Italy, single centre; 49 neutropenic children with haematological malignancies (and a few with neuroblastoma); Inpatients
Interventions	Trimethoprim-Sulphamethoxazole 15mg/kgX2/d versus norfloxacin 20mg/kgX2/d
Outcomes	All cause mortality; Infection related death; Number of febrile patients or episodes; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Resistance to quinolones and to trimethoprim-sulphamethoxazole; Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	random number table

Cruciani 1989 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5/49 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

Cullen 2005

Methods	Randomisation: central, computer-generated Blinding: double-blind; Intention to treat: yes; Exclusion from analysis: none; Beginning of prophylaxis: day of anticipated neutropenia as determined by chemotherapy regimen; End of prophylaxis: 7 days per chemotherapy cycle
Participants	UK, multicentre; 1565 adult patients with solid malignancies or lymphoma; Outpatients
Interventions	Levofloxacin 500mgX1/d versus placebo
Outcomes	Infection related death; Number of febrile patients and episodes; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Resistance to quinolones; Adverse events
Notes	Journal publication. Prophylaxis administered for multiple chemotherapy cycles. Results analysed per patient for all cycles

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	computer-generated
Allocation concealment (selection bias)	Low risk	Central allocation (A - Adequate)
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions

Cullen 2005 *(Continued)*

Selective reporting (reporting bias)	Low risk	Analysis by ITT; all expected outcomes reported

D'Antonio 1991

Methods	Randomisation: no information; Blinding: none; Intention to treat: yes; Exclusion from analysis: 0/71; Beginning of prophylaxis: PMN count less than 1000 End of prophylaxis: PMN count 1000
Participants	Italy, single centre; 71 neutropenic adult patients with haematological malignancies; Inpatients
Interventions	Norfloxacin 400mgX2/d versus ofloxacin 400mgX2/d
Outcomes	All cause mortality; Infection related death; Number of febrile patients or febrile episodes; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Resistance to quinolones; Adverse events
Notes	Journal Publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions
Selective reporting (reporting bias)	Low risk	Analysis by ITT; all expected outcomes reported.

D'Antonio 1992

Methods	Randomisation: no information; Blinding: none; Intention to treat: none; Exclusion from analysis: 14/150; Beginning of prophylaxis: PMN count less than 1000 End of prophylaxis: PMN count 1000

D'Antonio 1992 *(Continued)*

Participants	Italy, single centre; neutropenic adult patients (PMN<1000, for more than 10 days); Inpatients
Interventions	Norfloxacin 400mgX2/d versus pefloxacin 400mgX2/d
Outcomes	All cause mortality; Infection related death; Number of febrile patients or febrile episodes; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Resistance to quinolones; Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	14/150 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT; all expected outcomes reported.

D'Antonio 1994

Methods	Randomisation: no information; Blinding: none; Intention to treat: none; Exclusion from analysis: unknown number of patients (data given in neutropenic episodes, 20/255 excluded); Beginning of prophylaxis: PMN count less than 1000 End of prophylaxis: PMN count 1000
Participants	Italy, single centre; neutropenic adult patients undergoing treatment for haematological malignancies; Inpatients
Interventions	Ciprofloxacin 500mgX2/d versus ofloxacin 300mgX2/d versus pefloxacin 400mgX2/d
Outcomes	All cause mortality; Infection related death; Number of febrile episodes; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Resistance to quinolones; Adverse events
Notes	Journal Publication

D'Antonio 1994 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	20/255 neutropenic episodes excluded
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

de Jongh 1983

Methods	Randomisation: no information; Blinding: double blind; Intention to treat: yes; Exclusion from analysis: none; Follow up period: three courses of chemotherapy or adverse effects or withdrawal or death
Participants	USA, single centre; 61 adult patients with newly diagnosed small cell carcinoma of the lung during the initial courses of chemotherapy; Inpatients
Interventions	Trimethoprim-sulfamethoxazole 160mg/800mgX2/d versus placebo
Outcomes	All cause mortality; Infection related death; Number of febrile episodes; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Resistance to quinolones; Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind

de Jongh 1983 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions
Selective reporting (reporting bias)	Low risk	All expected outcomes reported; analysis by ITT

Dekker 1981

Methods	Randomisation: sealed opaque envelopes; Blinding: none; Intention to treat: no; Exclusion from analysis: 6/58; Beginning of prophylaxis: PMN count less than; End of prophylaxis: PMN count of 500
Participants	Netherlands, single centre; 58 adult patients with acute non-lymphocytic leukaemia during remission induction treatment; Inpatients
Interventions	Trimethoprim-sulfamethoxazole 240mg/1200mgX2/d versus no intervention
Outcomes	All cause mortality; Infection related death; Number of febrile episodes; Fever days; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Resistance to trimethoprim-sulphamethoxazole; Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Details not available for the 2011 update
Allocation concealment (selection bias)	Low risk	sealed opaque envelopes (A - Adequate)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6/58 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT. All expected outcomes reported.

Dekker 1987

Methods	Randomisation: sealed opaque envelopes; Blinding: none;

Dekker 1987 *(Continued)*

	Intention to treat: no; Exclusion from analysis: 4/60; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 500
Participants	Netherlands, single centre; 60 adult patients with a first diagnosis or first relapse of acute leukaemia undergoing remission induction treatment; Inpatients
Interventions	Ciprofloxacin 500mgX2/d versus trimethoprim-sulphamethoxazole 160mg/800mgX2/d + colistin 200mgX3
Outcomes	All cause mortality; Infection related death; Number of febrile episodes; Fever days; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Resistance to trimethoprim-sulphamethoxazole; Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Details not available for the 2011 review update
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes (A - Adequate)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4/60 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

Dickgreber 2009

Methods	Randomisation: no information; Blinding: double blind; Intention to treat: not clear; Exclusion from analysis: not clear Beginning of prophylaxis: day 5 after chemotherapy End of prophylaxis: day 11 after chemotherapy
Participants	all patients over the age of 65 with previously untreated advanced non small cell lung carcinoma
Interventions	oral levofloxacin 500mg daily versus placebo
Outcomes	Infection related mortality; Febrile patients; clinically documented infections, adverse events (only grade 3-4 gastrointestinal events)

Dickgreber 2009 *(Continued)*

Notes	Abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Low risk	double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	not clear how many excluded from study
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

Donnelly 1992b

Methods	Randomisation: no information; Blinding: none; Intention to treat: no; Exclusion from analysis: 48/278; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 1000 or 6 weeks
Participants	Netherlands, multicentre (6 centres); 278 adult leukaemic patients expected to be neutropenic for at least one week following chemotherapy; Inpatients
Interventions	Ciprofloxacin 500mgX2/d versus trimethoprim-sulphamethoxazole 960mgX3/d + colistin 200mgX4/d
Outcomes	All cause mortality; Infection related death; Number of febrile episodes; Fever days; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Resistance to trimethoprim-sulphamethoxazole; Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)

Donnelly 1992b *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	48/278 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

Enno 1978

Methods	Randomisation: no information; Blinding: none; Intention to treat: no; Exclusion from analysis: 8/38; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 1000 or fever
Participants	England, single centre; 30 patients over the age 15 with acute leukaemia being treated with chemotherapy; Inpatients
Interventions	Trimethoprim-sulfamethoxazole 160mg/800mgX2/d versus no intervention
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Adverse events
Notes	Journal Publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	8/38 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT.

EORTC 1984

Methods	Randomisation generation by opening consecutively sealed envelopes, allocation by a central randomisation; Blinding: double blind; Intention to treat: no; Exclusion from analysis:203/545; Beginning of prophylaxis: PMN count less than 1000 for at least 6 days End of prophylaxis: resolution of neutropenia
Participants	Europe, multicentre; 545 patients with haematological malignancies or solid tumours expected to be neutropenic for more than 6 days folllowing chemotherapy; Inpatients
Interventions	Trimethoprim-sulfamethoxazole 160mg/800mgX2/d versus placebo
Outcomes	Number of febrile patients; Microbiologically documented febrile episodes; Resistance to trimethoprim-sulphamethoxazole; Adverse events
Notes	Journal publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centrally coordinated randomisation
Allocation concealment (selection bias)	Low risk	sequential sealed envelopes (A - Adequate)
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	High risk	203/545 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

EORTC 1994

Methods	Randomisation: randomisation lists with different codes, allocation by consecutively opening sealed envelopes; Blinding: double blind; Intention to treat: no, yes- only for the mortality outcome; Exclusion from analysis: 15/551; Beginning of prophylaxis: chemotherapy; End of prophylaxis: resolution of neutropenia, fever, the use of IV antibiotics or death
Participants	Europe, multicentre; 551 adult patients with leukaemia, lymphoma or solid tumours undergoing bone marrow transplantation; Inpatients
Interventions	Pefloxacin 400mg2/d + oral penicillin v 500mgX2/d versus pefloxacin 400mg X2/d
Outcomes	All cause mortality; Infection related death;

EORTC 1994 *(Continued)*

	Number of febrile episodes; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	randomisation lists
Allocation concealment (selection bias)	Low risk	Sequential sealed envelopes (A - Adequate)
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	15/551 exclusions
Selective reporting (reporting bias)	Unclear risk	ITT analysis done only for mortality outcome

Estey 1984

Methods	Randomisation: no information; Blinding: none; Intention to treat: yes; Exclusion from analysis: unknown Beginning of prophylaxis: chemotherapy; End of prophylaxis: death or complete remission
Participants	USA, single centre; 147 patients with acute leukaemia undergoing chemotherapy induction treatment; Outpatients or inpatients in standard rooms
Interventions	Trimethoprim-sulfamethoxazole 160mg/800mgX2/d versus no intervention
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Number of febrile episodes; Clinically documented febrile episodes; Microbiologically documented febrile episodes.
Notes	-Journal publication -there were 4 arms:placebo/TMP+SMZ/ ketoconazole/ TMP-SMZ+ketoconazole. We combined them into two groups: placebo and ketoconazole(=placebo) vs TMP-SMZ+-ketoconazole (=TMP-SMZ)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided

Estey 1984 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Exclusions not stated
Selective reporting (reporting bias)	Low risk	Analysis by ITT; all expected outcomes reported.

Fanci 1993

Methods	Randomisation: no information; Blinding: none; Intention to treat: no; Exclusion from analysis: 8/61; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 1000 or fever
Participants	Italy, single centre; 61 adult patients with haematological malignancies designated to receive intensive chemotherapy expected to be neutropenic; Inpatients
Interventions	Ciprofloxacin 500mgX2/d versus ciprofloxacin 500mgX2/d + amoxicillin 1gX1/d
Outcomes	All cause mortality; Infection related death; Number of febrile episodes; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Resistance to quinolones, Adverse events
Notes	Journal publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	8/61 exclusions

Fanci 1993 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

Ford 1998

Methods	Randomisation: a table of random numbers, allocation concealment by sealed opaque envelopes; Blinding: none; Intention to treat: yes; Exclusion from analysis: none (0/84); Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count 500 or the use of systemic antibiotics
Participants	USA, single centre; 84 bone marrow recipients due to haematological malignancies or solid tumours; Inpatients
Interventions	Ciprofloxacin 750mgX2/d and vancomycin versus ciprofloxacin 750mgX2/d
Outcomes	All cause mortality; Infection related death; Fever days; Microbiologically documented febrile episodes; Hospitalization days; Adverse events.
Notes	Journal publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	random number tables
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes (A - Adequate)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions
Selective reporting (reporting bias)	Low risk	Analysis by ITT; all expected outcomes reported

Garcia Saenz 2002

Methods	Randomisation: random number list, allocation concealment: not clear; Blinding: none; Intention to treat: yes, according to chemotherapy cycles Exclusion from analysis:not clear results are reported according to chemotherapy cycles Beginning of prophylaxis: neutropenia End of prophylaxis: neutrophil count >500

Garcia Saenz 2002 *(Continued)*

	This was a randomized trial with a crossover design
Participants	65 adult patients with solid tumors who received prior chemotherapy and were scheduled to receive intensive consolidation chemotherapy with or without autologous stem cell transplant. Malignancies included: ovarian cancer,breast cancer, sarcoma, peripheral neuro-ectodermal tumor, other All inpatients, Hospitalized in single rooms
Interventions	intravenous Imipenem 1gr X2 daily and intravenous vancomycin 1gr X2 daily vs. no prophylaxis (administartion of imipenem when the patient became febrile Cross over: patients received either Imipenem or not after the first cycle of chemotherapy, and then crossed over to receive the opposite
Outcomes	All cause mortality; This was reported per patients after the first cycle of chemotherapy (before the crossover- thus, was usable for the meta-analysis). All other outcomes reported per cycles, after the cross-over - not usable information
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	random number list
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	none
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not available for the 2011 review update
Selective reporting (reporting bias)	Unclear risk	Details not available for the 2011 review update

GIMEMA 1991

Methods	Randomisation: permuted blocks of ten, concealed by sealed envelopes (opaque not mentioned); Blinding:none; Intention to treat: no; Exclusion from analysis: 182/801; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count 1000
Participants	Italy, multicentre; 801 afebrile patients>14 y who had haematologic malignancies or BMT and chemotherapy induced neutropenia(<1000) expected to last >10 d; Inpatients, haematological units in tertiary care or university hospitals, conventional ward or single rooms
Interventions	Norfloxacin 400mgX2 versus ciprofloxacin 500mgX2 + oral vancomycin 250mgX3/d

GIMEMA 1991 *(Continued)*

Outcomes	All cause mortality; Infection related death; Number of febrile patients or episodes; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Infection resistant to quinolones; Adverse events
Notes	Journal publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	randomisation in blocks of ten
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes - opaque not mentioned (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	182/801 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT.

Gluckman 1988

Methods	Randomisation: no information; Blinding: none; Intention to treat: yes; Exclusion from analysis: none (0/65); Beginning of prophylaxis: 8 days before bone marrow transplantation; End of prophylaxis: 15 days after bone marrow transplantation
Participants	France, single centre; 65 patients treated by allogeneic bone marrow transplantation; Inpatients in laminar airflow rooms
Interventions	Pefloxacin 400mg/d and IV penicillin 3 million units/d versus cephalotin, gentamicin and bacitracin 3g, 240mg and 1800IU respectively
Outcomes	All cause mortality; Infection related death; Fever days; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Infection resistant to quinolones
Notes	Journal publication

Risk of bias

Bias	Authors' judgement	Support for judgement

Gluckman 1988 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions
Selective reporting (reporting bias)	Low risk	Anaylsis by ITT. All expected outcomes reported.

Gluckman 1991

Methods	Randomisation: no information; Blinding: none; Intention to treat: yes; Exclusion from analysis: none (0/44); Beginning of prophylaxis: 8 days before bone marrow transplantation; End of prophylaxis: 15 days after bone marrow transplantation
Participants	France, single centre; 44 patients undergoing bone marrow transplantation for leukaemia or aplastic anaemia; Inpatients in laminar airflow rooms
Interventions	Oral vancomycin 450mg/d, tobramycin 450mg/d and colistin 4.5 million units daily (divided in nine capsules) versus ofloxacin 200mgX2/d and amoxicillin 1gX2/d
Outcomes	All cause mortality; Infection related death; Fever days; Microbiologically documented febrile episodes; Adverse events.
Notes	Journal publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions

Gluckman 1991 *(Continued)*

Selective reporting (reporting bias)	Low risk	Anaylsis by ITT. All expected outcomes reported.

Gomez-Martin 2000

Methods	Randomisation: consecutively drawn, sealed envelopes (opaque not mentioned); Blinding:none; Intention to treat: no; Exclusion from analysis: 7/130; Beginning of prophylaxis: 10 days before bone marrow transplantation; End of prophylaxis: PMN count 500 or fever
Participants	Spain, multicentre; 130 patients undergoing high dose chemotherapy with peripheral stem cell transplantation; Inpatients in private rooms
Interventions	Ciprofloxacin 500mgX3/d versus ciprofloxacin 500mgX3/d + rifampin 300mgX2/d
Outcomes	All cause mortality; Infection related death; febrile patients; Fever days; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Infection resistant to quinolone; Hospitalization days; Adverse events.
Notes	Journal publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Details not available for the 2011 review update
Allocation concealment (selection bias)	Low risk	Sequential sealed envelopes (A - Adequate)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	7/130 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT; all expected outcomes reported.

Goorin 1985

Methods	Randomisation: no information; Blinding:double blind; Intention to treat: no; Exclusion from analysis: 1/60; Beginning of prophylaxis: chemotherapy; End of prophylaxis: 40 weeks

Goorin 1985 *(Continued)*

Participants	USA, single centre; 61 newly diagnosed children with acute lymphoblastic leukaemia expected to receive intensive chemotherapy; Inpatients
Interventions	Trimethoprim-sulfamethoxazole 80mg/400mg X2/d versus placebo
Outcomes	All cause mortality; Infection related death; Number of febrile episodes; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Hospitalization days; Number of hospitalisations
Notes	Journal publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	1/61 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

Gualtieri 1983

Methods	Randomisation: no information; Blinding: double blind; Intention to treat: no; Exclusion from analysis: 19/66; Beginning of prophylaxis: PMN count less than 1000 End of prophylaxis: PMN count of 1000
Participants	USA, single centre; 66 adult patients with haematological malignancies and neutropenia; Inpatients
Interventions	Trimethoprim-sulfamethoxazole 160mg/800mg X2/d versus placebo
Outcomes	All cause mortality; Infection related death; Number of febrile episodes; Fever days; Clinically documented febrile episodes; Microbiologically documented febrile episode; Infection resistant to trimethoprim-sulphamethoxazole; Adverse events.
Notes	Journal publication

Gualtieri 1983 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	19/66 exclusions
Selective reporting (reporting bias)	Unclear risk	high attrition

Guiot 1983

Methods	Randomisation: no information; Blinding: double blind; intention to treat: no; Exclusion from analysis: 9/42; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 500
Participants	Netherlands, single centre; 42 adult patients with acute leukaemia undergoing induction chemotherapy; Inpatients
Interventions	Neomycin, amphotericin, nalidixic acid, polymyxin in doses of 250mgX4/d, 250mgX4/d, 1gX2/d, 100mgX4/d respectively versus placebo
Outcomes	All cause mortality; Infection related death; Number of febrile patients or febrile episodes; Fever days; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Adverse events.
Notes	Journal publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias)	Low risk	Double blind

Guiot 1983 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	9/42 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

Guiot 1992

Methods	Randomisation: randomly drawn, envelopes containing lots coded for one of the two types of prophylaxis (opaque not mentioned); Blinding: none; Intention to treat: no; Exclusion from analysis: unknown (data given in episodes); Follow up period: 14 days, from beginning of chemotherapy
Participants	Netherlands, single centre; 48 patients undergoing aggressive antileukaemic therapy; Inpatients in single rooms
Interventions	IV Penicillin G 4 million units/d versus IV trimethoprim-sulphamethoxazole 160mg/800mg X2/d
Outcomes	All cause mortality; Infection related death; Number of febrile episodes; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Infection resistant to trimethoprim-sulphamethoxazole; Adverse events
Notes	Journal publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	randomly drawn envelopes
Allocation concealment (selection bias)	Unclear risk	envelopes not stated as opaque (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

Gurwith 1979

Methods	Randomisation: by a table of random numbers, allocation concealment by an independent pharmacy; Blinding: none; Intention to treat: unknown (randomisation and follow up according to neutropenic episodes, not patients); Exclusion from analysis: exclusion of patients unknown (no episodes excluded); Beginning of prophylaxis: PMN count less than 1000 End of prophylaxis: PMN count of 1000
Participants	Canada, single centre; granulocytopenic patients due to various malignancies (36% haematological malignancies), (a total of 111 neutropenic episodes); Inpatients
Interventions	Trimethoprim-sulfamethoxazole 160mg/800mg X2/d versus no intervention
Outcomes	All cause mortality; Infection related death; Fever days; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Resistance to trimethoprim-sulphamethoxazole; Adverse events.
Notes	Journal publication In the beginning - there was the nonabsorbable group which received: nystatin 1mil X4, neomycin 500mg X4, polymyxin 50mg X4, chlorhexidine. After 4 months it was discontinued because of poor acceptance. Also, all patients were hospitalised

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	random number table
Allocation concealment (selection bias)	Low risk	pharmacy allocation (A - Adequate)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not available for the 2011 review update
Selective reporting (reporting bias)	Unclear risk	The non-absorbable group was discontinued due to poor acceptance

Hargadon 1981

Methods	Randomisation: no information; Blinding: double blind; Intention to treat: no; Exclusion from analysis: none; Follow up period: 5-6 weeks, from beginning of chemotherapy
Participants	USA, single centre; 8 patients with small cell carcinoma of lung undergoing induction chemotherapy and 8 patients with leukaemia undergoing re induction; Setting not specified
Interventions	for lung cancer patients: trimethoprim-sulphamethoxazole 160mg/800mg X2/d versus placebo;

Hargadon 1981 *(Continued)*

	for leukaemic patients: gentamicin liquid 200mg + nystatin tablets (4 million units) and nystatin suspension 1 million unit, all X6/d versus trimethoprim-sulphamethoxazole 160mg/800mg X2/d + nystatin suspension 1 million units X6/d
Outcomes	No relevant outcomes: the trial evaluates effect of prophylactic antibiotics on rectal flora
Notes	Journal publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not available for the 2011 review update
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT. No relevant outcomes

Harousseau 1987

Methods	Randomisation: random table of numbers, allocation concealed by envelopes; Blinding: none; Intention to treat: yes; Exclusion from analysis: none (0/41); Beginning of prophylaxis: PMN count less than 500 End of prophylaxis: PMN count 500
Participants	France, single centre; 64 neutropenic patients with haematological malignancies (and neuroblastoma) undergoing bone marrow transplantation; Inpatients
Interventions	IV ceftriaxone 2gX1/d versus no intervention
Outcomes	Number of febrile episodes; Fever days; Microbiologically documented febrile episodes
Notes	Journal publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	random number tables

Harousseau 1987 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	allocation by envelopes not stated as sealed/opaque (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions/attrition
Selective reporting (reporting bias)	Low risk	Analysis by ITT.

Hartlapp 1987

Methods	Randomisation: no information; Blinding: none; Intention to treat: unknown; Exclusion from analysis: unknown; Beginning of prophylaxis: 7 days after chemotherapy; End of prophylaxis: 10 days
Participants	Germany, single centre; 42 patients with metastatic testicular germ cell tumours after cytostatic treatment; Outpatients
Interventions	Ofloxacin 200mgX2/d versus no intervention
Outcomes	Number of febrile patients; Microbiologically documented febrile episodes; Adverse events.
Notes	Journal publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not available for the 2011 review update
Selective reporting (reporting bias)	Unclear risk	Details not available for the 2011 review update

Henry 1984b

Methods	Randomisation: no information; Blinding: none; Intention to treat: yes; Exclusion from analysis: none (0/43); Beginning of prophylaxis: PMN count less than 1000; End of prophylaxis: PMN count of 1000
Participants	USA, single centre; 43 adult patients with newly diagnosed and relapsed acute leukaemia undergoing remission induction or reinduction chemotherapy; Outpatients
Interventions	Trimethoprim-sulfamethoxazole 160mg/800mgX2/d versus no intervention
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Fever days; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Infection resistance to trimethoprim-sulphamethoxazole; Adverse events.
Notes	Journal publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No exclusions
Selective reporting (reporting bias)	Unclear risk	Details not available for the 2011 review update

Hidalgo 1997

Methods	Randomisation: no information; Blinding: none; Intention to treat: unknown; Exclusion from analysis: unknown; Beginning of prophylaxis: 2 days before peripheral stem cell transplantation; End of prophylaxis: PMN count of 500 or fever
Participants	Spain, single centre; 40 patients, most with solid malignancies, undergoing high dose chemotherapy with peripheral stem cell transplantation; Inpatients
Interventions	Ciprofloxacin 500mgX3/d versus ciprofloxacin 500mgX3/d + rifampin 300mgX2/d
Outcomes	All cause mortality;

Hidalgo 1997 *(Continued)*

	Infection related death; Febrile patients; Fever days; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Infection resistant to quinolones; Hospitalization days; Adverse events.
Notes	Journal publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not available for the 2011 review update
Selective reporting (reporting bias)	Unclear risk	Details not available for the 2011 review update

Inoue 1983

Methods	Randomisation: no information; Blinding: double blind; Intention to treat: yes; Exclusion from analysis: 0/102; Beginning of prophylaxis: chemotherapy End of prophylaxis: end of chemotherapy (2-8.5 months)
Participants	Japan, multicentre; 102 children with acute leukaemia undergoing chemotherapy; Outpatients
Interventions	Trimethoprim-sulfamethoxazole 0.025g/kX2/d versus placebo
Outcomes	Febrile patients; Fever days; Clinically documented febrile episodes; Microbiologically documented febrile episodes.
Notes	Journal publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias)	Low risk	Double blind

Inoue 1983 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions
Selective reporting (reporting bias)	Low risk	Analysis by ITT. All outcomes reported.

Jansen 1994

Methods	Randomisation: a table of random numbers, concealment in white envelopes stored in boxes Blinding: none; Intention to treat: no; Exclusion from analysis: 9/105; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 500
Participants	USA, single centre; 105 adult patients undergoing bone marrow transplantation or aggressive chemotherapy for acute leukaemia or blast crisis of chronic leukaemia; Inpatients
Interventions	Ciprofloxacin 500mgX2/d versus neomycin 250mgX4/d + polymyxin 100mgX4/d + nalidixic acid 1gX2/d
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Adverse events.
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	random number table
Allocation concealment (selection bias)	Low risk	opaque envelopes (A - Adequate)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	9/105 exclusions
Selective reporting (reporting bias)	Unclear risk	Details not available for the 2011 review update

Jehn 1981

Methods	Randomisation: no information;

Jehn 1981 *(Continued)*

	Blinding: none; Intention to treat: unknown; Exclusion from analysis: unknown; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 1000
Participants	Germany, single centre; 49 adult patients with acute leukaemia undergoing chemotherapy; Inpatients in conventional wards
Interventions	Neomycin, colistin (500mg, 1.5 million units respectively) versus no intervention
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Clinically documented febrile episodes; Microbiologically documented febrile episodes
Notes	-Journal Publication -there were originally 3 treatment groups:nonabsorbable antibiotics,regular ward without antibiotics, strict isolation+nonabsorbable antibiotics. Only group1 and 2 were included

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not available for the 2011 review update
Selective reporting (reporting bias)	Unclear risk	The nonabsorbable group was not reported

Karp 1987

Methods	Randomisation: by a random number table, allocation by a central pharmacy; Blinding: double blind; intention to treat: yes; Exclusion from analysis: none (0/68); Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 500
Participants	USA, single centre; 68 adult patients with acute leukaemia and chemotherapy-induced neutropenia; Inpatients
Interventions	Norfloxacin 400mgX2/d versus placebo
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Microbiologically documented febrile episodes; Infection resistant to quinolone;

Karp 1987 *(Continued)*

	Adverse events.
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	random number table
Allocation concealment (selection bias)	Low risk	allocation by pharmacy (A - Adequate)
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions
Selective reporting (reporting bias)	Low risk	ITT analysis; all outcomes reported.

Kauffman 1983

Methods	Randomisation: no information; Blinding:none; Intention to treat: no; Exclusion from analysis: 11/55; Beginning of prophylaxis: chemotherapy; End of prophylaxis: duration of chemotherapy and discharge from hospital
Participants	USA, multicentre; 55 patients over the age of 16 with haematological malignancies or solid tumours who were to be given high dose chemotherapy resulting in severe neutropenia; Inpatients
Interventions	trimethoprim-sulphamethoxazole 80mg/400mgX2/d versus no intervention
Outcomes	All cause mortality; Infection related death; Fever days; Number of febrile episodes; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Infection resistant to trimethoprim-sulphamethoxazole; Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided

Kauffman 1983 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	11/55 excluded
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT; 20% excluded from analysis

Kern 1991b

Methods	Randomisation: no information; Blinding:none; Intention to treat: no; Exclusion from analysis: 32/160; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 1000 or termination of chemotherapy
Participants	Germany, Single centre; 160 patients with acute leukaemia who received aggressive cytotoxic chemotherapy; Inpatients
Interventions	Ofloxacin 200mgX3/d versus trimethoprim-sulphamethoxazole 960mgX3/d
Outcomes	All cause mortality; Infection related death; Number of febrile patients or episodes; Fever days; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Adverse events
Notes	Journal Publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	32/160 exclusions

Kern 1991b *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT; all expected outcomes reported

Kern 1994b

Methods	Randomisation: no information; Blinding:none; Intention to treat: no; Exclusion from analysis: 10/141; Beginning of prophylaxis: chemotherapy; End of prophylaxis: development of fever
Participants	Germany, Single centre; 141 afebrile patients>16 y who had acute leukaemia and received bone marrow transplantation and chemotherapy; Inpatients, most patients in standard rooms, bone marrow transplant patients in private rooms
Interventions	Roxythromycin 150 mgX2 + ofloxacin 200 mgX3 versus ofloxacin 200 mg X3
Outcomes	All cause mortality; Infection related death; Number of febrile patients or febrile episodes; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Infection resistant to quinolones; Adverse events.
Notes	Journal Publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	10/141 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT; all expected outcomes reported

Klastersky 1974

Methods	Randomisation: no information; Blinding: none; Intention to treat: no; Exclusion from analysis: unknown;

Klastersky 1974 *(Continued)*

	Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 1000
Participants	France, single centre; 43 patients with haematological malignancies undergoing cytotoxic therapy
Interventions	neomycin, bacitracin, kanamycin, polymyxin, nystatin (3.5g,10000 units, 3g, 850mg, 1 million units respectively) versus no prophylaxis
Outcomes	All cause mortality; Infection related death; number of febrile episodes; clinically documented febrile episode; microbiologically documented febrile episode;
Notes	-Journal Publication -there were originally 3 treatment groups: isolation+nonabsorbable antibiotics,nonabsorbable antibiotics alone, regular ward without prophylaxis. Only groups 2 and 3 were included

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not available for the 2011 review update
Selective reporting (reporting bias)	Unclear risk	Only two out of three allocation groups were reported

Kovatch 1985

Methods	Randomisation: no information; Blinding: double blind; Intention to treat: no; Exclusion from analysis: 17/91; Beginning of prophylaxis: chemotherapy; End of prophylaxis: remission of leukaemia or infection or 60 days
Participants	USA, single centre; 91 infants, children and adolescents with haematological malignancies or solid tumours, during intensive chemotherapy treatment; Inpatients
Interventions	Trimethoprim-sulfamethoxazole 3mg/kgX2/d versus placebo
Outcomes	All cause mortality; Infection related death; Number of febrile patients or febrile episodes; Clinically documented febrile episodes;

Kovatch 1985 *(Continued)*

	Microbiologically documented febrile episodes; Infection resistant to trimethoprim-sulphamethoxazole; Adverse events.
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Low risk	double blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	17/91 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not ITT

Kramer 1984

Methods	Randomisation: by a randomisation list prepared by the pharmacy, allocation concealment by a pharmacy; Blinding:triple blind; Intention to treat: no; Exclusion from analysis: 21/66; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 500 or development of febrile neutropenia
Participants	USA, single centre; 66 adult cancer patients (haematological and solid malignancies, mostly lung) receiving cytotoxic chemotherapy expected to result in significant neutropenia; Inpatients in private rooms with reverse isolation (patients in whom prolonged marrow suppression was anticipated) or outpatients
Interventions	Trimethoprim-sulfamethoxazole 320mg/1600mgX2/d + erythromycin 1gX2/d versus placebo
Outcomes	All cause mortality; Infection related death; Number of febrile episodes; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement

Kramer 1984 *(Continued)*

Random sequence generation (selection bias)	Low risk	list prepared by pharmacy
Allocation concealment (selection bias)	Low risk	allocation concealed by pharmacy (A - Adequate)
Blinding (performance bias and detection bias) All outcomes	Low risk	Triple blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	21/66 excluded
Selective reporting (reporting bias)	Unclear risk	High exclusion/attrition

Kurrle 1983

Methods	Randomisation: computer generated, allocation by central randomisation from a remote centre; Blinding: none; Intention to treat: no (ITT only for mortality); Exclusion from analysis: 22/100; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 1000
Participants	Germany, single centre; 100 patients with acute leukaemia during remission induction chemotherapy; Inpatients
Interventions	Trimethoprim-sulfamethoxazole 160mg/800mgX3/d + polymyxin 100mgX4/d + nystatin (6 million units /d (divided by four) versus nalidixic acid 1gX4/d, neomycin 250mgX4/d, polymyxin 100mgX4/d and nystatin (6 million units /d (divided by four)
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Fever days; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Adverse events
Notes	Journal Publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	computer generated
Allocation concealment (selection bias)	Low risk	central coordinated allocation (A - Adequate)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind

Kurrle 1983 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	22/100 exclusions
Selective reporting (reporting bias)	Unclear risk	ITT analysis done only for mortality

Kurrle 1986

Methods	Randomisation: no information; Blinding: none; Intention to treat: no (ITT only for outcome of mortality); Exclusion from trial:15/155; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN of 1000
Participants	Germany, single centre; 155 adult patients with a diagnosis of acute leukaemia undergoing remission induction chemotherapy; Inpatients in conventional ward
Interventions	Oral nonabsorbable antibiotics: colistin 200mgX4/d + neomycin 250mgX4/d versus trimethoprim-sulphamethoxazole 160mg/800mgX3/d and neomycin 250mgX4/d
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Fever days; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	15/155 exclusions
Selective reporting (reporting bias)	Unclear risk	ITT analysis only for outcome of mortality

Lalami 2004

Methods	Randomisation: unclear, allocation unclear; Blinding: none; Intention to treat: yes

Lalami 2004 *(Continued)*

	Exclusion from analysis:no exclusions, 0/48; Beginning of prophylaxis: 48 hours after completion of chemotherapy; End of prophylaxis: PMN count of 2000
Participants	Belgium (Brussels) and Athens, multicenter centre; adult patients (age >18 years old) treated by chemotherapy for solid tumours who presented with a previous episode of febrile neutropenia after a previous chemotherapy cycle, patients were scheduled for another cycle of the same chemotherapy. All patients also received granulocyte-colony stimulating factor
Interventions	ciprofloxacin 500mg X2 daily and amoxicillin+clavulonic acid 500mg X3 daily vs. no prophylaxis
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Fever days; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Bacteremia Adverse events (reported only according to grades, not entered into the meta-analysis)
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	unclear
Allocation concealment (selection bias)	Unclear risk	unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	no exclusions
Selective reporting (reporting bias)	Low risk	ITT analysis, all prespecified outcomes reported

Lamy 1993

Methods	Randomisation: table of random numbers, allocation concealment by sealed and opaque envelopes; Blinding: none; Intention to treat: no, ITT only for mortality outcome; Exclusion from analysis: 9/59; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 500

Lamy 1993 *(Continued)*

Participants	France, single centre; 59 adult patients mostly with haematological malignancies undergoing induction chemotherapy, chemo-consolidation or bone marrow transplantation and a few with solid tumours undergoing autologous bone marrow transplantation; Inpatients in laminar airflow rooms
Interventions	IV vancomycin 15mg/kg twice daily versus no intervention
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Fever days; Microbiologically documented febrile episodes; Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	random number tables
Allocation concealment (selection bias)	Low risk	sealed opaque envelopes (A - Adequate)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	9/59 excluded
Selective reporting (reporting bias)	Unclear risk	ITT analysis only for mortality outcome

Lange 1984

Methods	Randomisation: according to birth dates, allocation concealment unknown; Blinding:none; Intention to treat: no; Exclusion from analysis: 7/67; Beginning of prophylaxis: chemotherapy; End of prophylaxis: not specified
Participants	USA, single centre; 67 children with acute lymphoblastic leukaemia during remission induction therapy; Outpatients
Interventions	Trimethoprim-sulfamethoxazole 5mg/kg, 25mg/kg respectively X2/d versus no intervention
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Adverse events
Notes	Journal Publication

Lange 1984 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	quasi-randomisation according to birth dates
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	7/67 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT; all expected outcomes reported

Lee 2002

Methods	Randomisation: no information; Blinding: none; Intention to treat: yes; Exclusion from analysis: none, 0/95 Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 500 or fever
Participants	Korea, single centre; 95 patients with acute myeloid leukaemia receiving chemotherapy; Inpatients
Interventions	Ciprofloxacin 250mgX2/d, roxythromycin 150mgX2/d, fluconazole 50mg/d versus no intervention
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Infection resistant to quinolones; Hospitalization days
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind

Lee 2002 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions
Selective reporting (reporting bias)	Low risk	Analysis by ITT. All expected outcomes reported.

Levine 1973

Methods	Randomisation: no information; Blinding: none; Intention to treat: no; Exclusion from analysis: 4/70; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 750 or remission
Participants	USA, single centre; 70 patients with acute leukaemia, between 15 and 65 years of age scheduled to receive remission induction chemotherapy; Inpatients in conventional ward
Interventions	Nonabsorbable antibiotics: gentamicin, vancomycin and nystatin (dosage not specified in text) versus no intervention
Outcomes	All cause mortality; Infection related death; Clinically documented febrile episodes; Microbiologically documented febrile episodes
Notes	Journal Publication The trial compares three groups: gr 1 - protected environment, gr 2 - oral nonabsorbable, gr 3 - placebo. gr 1 was excluded from our study, since it examines a different intervention

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4/70 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

Lew 1991

Methods	Randomisation: generation unclear, allocation not specified; Blinding: double blind;

Lew 1991 *(Continued)*

	Intention to treat: no; Exclusion from analysis:8/26; Beginning of prophylaxis: chemotherapy; End of prophylaxis: Fever or PMN count of 500
Participants	USA, single centre; 26 oncology patients (mostly acute leukaemia and lymphoma but also solid malignancies) receiving chemotherapy, of whom 25 received bone marrow transplantation; Inpatients in private rooms
Interventions	Ciprofloxacin 750mgX2/d versus placebo
Outcomes	All cause mortality; Infection related death; Febrile patients; Fever days; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	8/26 exclusions
Selective reporting (reporting bias)	Unclear risk	High exclusion rate. No ITT analysis.

Lew 1995

Methods	Randomisation: generation unclear, allocation by a remote pharmacy; Blinding: double blind; Intention to treat: no; Exclusion from analysis:22/167; Beginning of prophylaxis: chemotherapy; End of prophylaxis: Fever or PMN count of 400
Participants	USA, single centre; 67 adult patients about to undergo bone marrow transplantation for the treatment of haematological (64%) and solid malignancies; Inpatients in private rooms
Interventions	Ciprofloxacin 750mgX2/d versus trimethoprim-sulphamethoxazole 160mg/800mgX2/d
Outcomes	All cause mortality; Infection related death; Febrile patients, Clinically documented febrile episodes; Microbiologically documented febrile episodes; Infection resistant to quinolones;

Lew 1995 *(Continued)*

	Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	randomisation and allocation by pharmacy
Allocation concealment (selection bias)	Low risk	done centrally by pharmacy (A - Adequate)
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	22/167 exclusions
Selective reporting (reporting bias)	Unclear risk	No ITT analysis

Liang 1990

Methods	Randomisation: no information; Blinding:none; Intention to treat: no; Exclusion from analysis: 8/110; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 500 or development of side effects
Participants	Hong Kong, single centre; 110 patients with haematological malignancies undergoing cytotoxic chemotherapy; Inpatients, university hospital
Interventions	Ofloxacin 300mgX2/d versus trimethoprim-sulphamethoxazole 80mg/400mgX2/d
Outcomes	Infection related death; Febrile patients; Microbiologically documented febrile episodes; Infection resistant to quinolones; Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias)	Unclear risk	Not blind

Liang 1990 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	8/110 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

Maiche 1993

Methods	Randomisation: no information; Blinding: none; Intention to treat: unknown; Exclusion from analysis: unknown; Beginning of prophylaxis: chemotherapy; End of prophylaxis: development of fever
Participants	Finland, single centre; 59 patients with haematological and solid tumours, who have had a previous infection following chemotherapy; Inpatients in standard ward rooms
Interventions	Ofloxacin 200mgX2/d or ciprofloxacin 750mgX2/d versus no intervention (both groups received GCSF)
Outcomes	Febrile episodes; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Adverse events
Notes	Journal Publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not available for the 2011 review update
Selective reporting (reporting bias)	Unclear risk	ITT analysis and exclusions not described

Malarme 1981

Methods	Randomisation: no information on generation, but concealment by a remote pharmacy providing the capsules; Blinding: triple blind; Intention to treat: unknown;

Malarme 1981 *(Continued)*

	Exclusion from analysis: unknown; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 1000, side effects or death
Participants	Belgium, single centre; 63 adult patients with leukaemia, lymphoma or solid tumours receiving chemotherapy; Inpatients in single rooms
Interventions	Oral vancomycin 500mg + gentamIcin 160mg + nystatin 2million units, all X3/d versus trimethoprim-sulphamethoxazole 80mg/400mgX3/d + nystatin 2million unitsX3/d versus vancomycin + trimethoprim-sulphamethoxazole + gentamIcin + nystatin (all in the same dosages)
Outcomes	Number of febrile episodes; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Adverse events
Notes	Journal Publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Pharmacy coordinated
Allocation concealment (selection bias)	Low risk	pharmacy allocation (A - Adequate)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Triple blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not available for the 2011 review update
Selective reporting (reporting bias)	Unclear risk	ITT analysis and exclusions not described.

Martino 1984

Methods	Randomisation: randomisation by a casual choice of packages containing the indication for prophylaxis or not, allocation concealment not specified; Blinding: none; Intention to treat: unknown; Exclusion from analysis: unknown; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 500
Participants	Italy, single centre; 63 adult patients with acute leukaemia undergoing cytostatic treatment; Inpatients
Interventions	Trimethoprim-sulfamethoxazole 160mg/800mgX2/d versus no intervention
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Number of febrile episodes; Microbiologically documented febrile episodes; Adverse events

Martino 1984 *(Continued)*

Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	quasi randomisation
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not available for the 2011 review update
Selective reporting (reporting bias)	Unclear risk	ITT and exclusions not described

Maschmeyer 1988

Methods	Randomisation: allocation concealment by central randomisation Blinding: none; Intention to treat: no; Exclusion from analysis: 3/51; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 1000 or adverse events
Participants	Germany, single centre; 51 adult patients with acute leukaemia undergoing aggressive remission induction chemotherapy; Inpatients in standard ward rooms
Interventions	Ciprofloxacin 500mgX2/d versus ciprofloxacin 250mgX2/d versus norfloxacin 200mgX2/d versus norfloxacin 400mg X2/d
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centrally coordinated randomisation
Allocation concealment (selection bias)	Low risk	centrally coordinated (A - Adequate)
Blinding (performance bias and detection bias)	Unclear risk	Not blind

Maschmeyer 1988 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3/51 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

Mocikova 1992

Methods	Randomisation: no information; Blinding: none; Intention to treat: unknown; Exclusion from analysis: unknown; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 500
Participants	Country not stated, single centre; 42 patients undergoing induction treatment for acute leukaemia; Setting not specified
Interventions	Ofloxacin 200mgx2/d versus trimethoprim-sulphamethoxazole 1440mgX2/d
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Clinically documented febrile episodes; Microbiologically documented febrile episodes; infection resistant to quinolones and trimethoprim-sulphamethoxazole
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not available for the 2011 review update
Selective reporting (reporting bias)	Unclear risk	ITT and exclusions not described.

Moreau 1995

Methods	Randomisation: no information; Blinding: none; Intention to treat: unknown;

Moreau 1995 *(Continued)*

	Exclusion from analysis: unknown; Beginning of prophylaxis: chemotherapy; End of prophylaxis: fever
Participants	France, single centre; 130 patients treated for haematological malignancies with prolonged aplasia>14 days; Inpatients in laminar airflow rooms
Interventions	IV ciprofloxacin 200mgX2/d plus amoxicillin-clavulanic acid 1gX3/d versus IV vancomycin 1gX2/d versus no intervention
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Fever days; Microbiologically documented febrile episodes
Notes	Abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not available for the 2011 review update
Selective reporting (reporting bias)	Unclear risk	ITT and exclusions not described

Moriuchi 1990

Methods	Randomisation: no information; Blinding: none; Intention to treat: yes; Exclusion from analysis:none; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 1000
Participants	Japan, single centre; 24 patients receiving intensive chemotherapy for acute non-lymphocytic leukaemia; Inpatients
Interventions	Ciprofloxacin 600mgX3/d versus polymyxin B 300mgX3/d
Outcomes	Number of febrile episodes; Fever days; Clinically documented febrile episodes; Microbiologically documented febrile episodes
Notes	Journal Publication - in Japanese

Risk of bias

Moriuchi 1990 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not available for the 2011 review update
Selective reporting (reporting bias)	Low risk	Analysis by ITT; no exclusions

Murase 1995

Methods	Randomisation: consecutively drawn, sealed envelopes, opaque not specified; Blinding: no; Intention to treat: yes; Exclusion from analysis:0/53; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 1000
Participants	Japan, single centre; 53 patients with haematological malignancies receiving chemotherapy;
Interventions	Trimethoprim-sulfamethoxazole 80mg/400mgX3/d versus trimethoprim-sulphamethoxazole 80mg/400mgX3/d + ciprofloxacin 200mgX3/d
Outcomes	Number of febrile episodes; Fever days; Microbiologically documented febrile episodes; Adverse events.
Notes	Journal Publication - in Japanese

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	sequential sealed envelopes, not stated as opaque (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions

Murase 1995 *(Continued)*

Selective reporting (reporting bias)	Low risk	Analysis by ITT

Nemet 1989

Methods	Randomisation: no information; Blinding:none; Intention to treat: unknown; Exclusion from analysis: unknown; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 1000
Participants	Yugoslavia, single centre; 40 adult patients with acute leukaemia receiving intensive chemotherapy expected to produce profound and prolonged neutropenia; Inpatients in reverse isolation rooms
Interventions	Norfloxacin 400mgX2/d + trimethoprim-sulphamethoxazole 80mg/800mg X2/d versus gentamicin 120mgX4 plus trimethoprim-sulfamethoxazole 80mg/800mgX2/d
Outcomes	All cause mortality; Infection related death; Number of febrile patients or episodes; Microbiologically documented febrile episodes; Adverse events
Notes	Journal Publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not available for the 2011 review update
Selective reporting (reporting bias)	Unclear risk	Exclusions and ITT not described

Nenova 2001

Methods	Randomisation: no information; Blinding: none; Intention to treat: no; Exclusion from analysis:1/70; Beginning of prophylaxis: PMN count less than 1000 End of prophylaxis: PMN count of 1000 or fever

Nenova 2001 *(Continued)*

Participants	Bulgaria, single centre; 70 adult patients with haematologic malignancies undergoing chemotherapy; Inpatients
Interventions	Ciprofloxacin 500mgX2/d (20 patients), pefloxacin or enoxacin or norfloxacin versus no intervention
Outcomes	All cause mortality; Infection related death; Number of febrile episodes; Cinically documented febrile episodes; Microbiologically documented febrile episodes
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1/70 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

Orlandi 1990

Methods	Randomisation: no information; Blinding:none; Intention to treat: yes; Exclusion from analysis: unknown; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 1000
Participants	Italy, single centre; 60 adult patients with leukaemia undergoing chemotherapy treatment resulting in neutropenia; Inpatients
Interventions	Norfloxacin 400mgX2/d versus trimethoprim-sulphamethoxazole 160mg/800mgX2/d
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Fever days; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Infection resistant to quinolones and trimethoprim-sulphamethoxazole; Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement

Orlandi 1990 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not available for the 2011 review update
Selective reporting (reporting bias)	Low risk	Analysis by ITT; all outcomes reported

Papaiakovou 2010

Methods	Randomisation: computer generated, allocation concealment: central randomisation; Blinding: none; Intention to treat: yes Exclusion from analysis:no exclusions, 0/157; Beginning of prophylaxis: chemotherapy (day 0 of autologous stem cell transplant); End of prophylaxis: neutropenia resolution
Participants	Single center, Greece (Athens); adult patients undergoing high dose chemotherapy (HDT) +autologous stem cell transplant. Malignancies included: Multiple Myeloma 79.6%, epithelial ovarian cancer,germ cell tumor, other All inpatients All received granulocyte-colony stimulating factors
Interventions	oral ciprofloxacin 500mg X2 daily and intravenous vancomycin 1gr X2 daily vs. no prophylaxis
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Fever days; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Gram negative and Gram positive Microbiologically documented febrile episodes; Bacteremia Gram negative and Gram positive Bacteremia Fungal infection Hospitalizations Adverse events
Notes	Journal Publication
Risk of bias	

Papaiakovou 2010 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computer generated
Allocation concealment (selection bias)	Low risk	central randomisation
Blinding (performance bias and detection bias) All outcomes	Unclear risk	no blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	no exclusions
Selective reporting (reporting bias)	Low risk	ITT, all outcomes reported

Patrick 1995

Methods	Randomisation: no information; Blinding:double blind; Intention to treat: unknown; Exclusion from analysis: unknown; Beginning of prophylaxis: one week prior to bone marrow transplantation (BMT); End of prophylaxis: PMN count of 500
Participants	USA, single centre; 48 children with leukaemia (23) or solid tumours (25) undergoing bone marrow transplantation
Interventions	Ciprofloxacin 10 mg/kg /x2/d for 10 days (orally) and then 7.5 mg/kg X2/d (IV) versus placebo
Outcomes	Microbiologically documented febrile episodes
Notes	Abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (D - Not used)
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not available for the 2011 review update

Patrick 1995 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	ITT analysis and exclusions not described; abstract only, insufficient information

Petersen 1986

Methods	Randomisation: no information; Blinding: none; Intention to treat: no; Exclusion from analysis:21/122; Beginning of prophylaxis: PMN count less than 500 End of prophylaxis: PMN count of 500 or bone marrow engraftment or death
Participants	USA, single centre; 122 patients with haematological malignancies undergoing bone marrow transplantation; Inpatients in laminar airflow rooms
Interventions	IV vancomycin 2g/d + ticarcillin 300mg/kg/d + tobramycin 3-5mg/kg/d versus no intervention (all received oral nonabsorbable antibiotic as well)
Outcomes	All cause mortality; Infection related death; Number of febrile episodes; Clinically documented febrile episodes; Microbiologically documented febrile episodes
Notes	Journal Publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	21/122 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

Pignon 1990

Methods	Randomisation: no information; Blinding: double blind; Intention to treat: unknown; Exclusion from analysis:unknown; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 500 or fever

Pignon 1990 *(Continued)*

Participants	France, single centre; 44 patients with various haematological malignancies treated by intensive chemotherapy inducing a prolonged neutropenia; Inpatients in conventional rooms or laminar airflow rooms
Interventions	IV ceftriaxone 2g X1/d versus placebo
Outcomes	Number of febrile episodes; Fever days; Clinically documented febrile episodes; Microbiologically documented febrile episodes
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not available for the 2011 review update
Selective reporting (reporting bias)	Unclear risk	ITT and exclusions not described

Pizzo 1983

Methods	Randomisation: a balanced randomised block design kept in the pharmacy, antibiotics dispensed by a central pharmacist; Blinding: triple blind; Intention to treat: no; Exclusion from analysis: 21/150 Beginning of prophylaxis: chemotherapy; End of prophylaxis: fever or PMN count of 500
Participants	USA, single centre; 150 patients (children and adults) with haematological or solid tumours receiving chemotherapy; Inpatients for induction- chemotherapy, outpatients for maintenance
Interventions	Trimethoprim-sulfamethoxazole 5mg/kg X2/d + erythromycin 15mg/kg X2/d versus placebo
Outcomes	Number of first febrile episode.
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	blocked randomisation

Pizzo 1983 *(Continued)*

Allocation concealment (selection bias)	Low risk	Pharmacy allocated (A - Adequate)
Blinding (performance bias and detection bias) All outcomes	Low risk	Triple blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	21/150 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

Prentice 2001

Methods	Randomisation: no information; Blinding: none; Intention to treat: no; Exclusion from analysis: 22/150 Beginning of prophylaxis: chemotherapy; End of prophylaxis:PMN count of 1000 or 30 days
Participants	England, single centre; 150 patients receiving cytotoxic chemotherapy for treatment of haematological malignancies or undergoing intensive chemotherapy prior to bone marrow transplantation; Inpatients in private rooms
Interventions	Ciprofloxacin 500mgX2/d + colistin 1.5 million unitsX2/d versus neomycin 500mgX2/d + colistin 1.5 million unitsX2/d
Outcomes	All cause mortality; Infection related death; Number of febrile patients or febrile episodes; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Adverse events
Notes	Journal Publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	22/150 exclusions
Selective reporting (reporting bias)	Unclear risk	ITT analysis not described

Rafecas 1989

Methods	Randomisation: not clear;allocation concealment not clear Blinding: double blind; Intention to treat: no; Exclusion from analysis: 5/40; Beginning of prophylaxis: chemotherapy (or once chemotherp-indused emesis resolved); End of prophylaxis: resolution of neutropenia (neutrophil count >500)
Participants	Spain; 40 adult patients with acute leukaemia undergoing aggressive chemotherapyt;70% of evaluable patients were hospitalized
Interventions	ciprofloxacin 500mgX2daily versus placebo
Outcomes	Infection-related mortality; Number of febrile episodes; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Gram negative and Gram positive Microbiologically documented febrile episodes fever days Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	unclear randomisation
Allocation concealment (selection bias)	Unclear risk	unclear allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	double blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5/40 excluded
Selective reporting (reporting bias)	Unclear risk	not ITT

Rahman 2009

Methods	Randomisation: table of random numbers;allocation concealment not clear Blinding: the trial was only single blinded; Intention to treat: no; Exclusion from analysis: 32/80;(the randomisation in this trial was conducted when patients with acute leukaemia at risk for chemotherapy-induced neutropenia were included. 80 were randomized. Then,

Rahman 2009 *(Continued)*

	only those who became neutropenic were included for analysis. Thus, 32 were excluded after randomisation) Beginning of prophylaxis: chemotherapy; End of prophylaxis: resolution of neutropenia
Participants	Bangladesh, single centre; 80 adult patients with acute leukaemia during remission induction treatment;All Inpatients
Interventions	levofloxacin 500mg daily versus placebo
Outcomes	All cause mortality; Number of febrile patients; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Gram negative and Gram positive Microbiologically documented febrile episodes Bacteremia Gram negative and Gram positive bacteraemia
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	table of random numbers
Allocation concealment (selection bias)	Unclear risk	not clear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Exclusion from analysis: 32/80 (more than 30%);(the randomisation in this trial was conducted when patients with acute leukaemia at risk for chemotherapy-induced neutropenia were included. 80 were randomized. Then, only those who became neutropenic were included for analysis. Thus, 32 were excluded after randomisation)
Selective reporting (reporting bias)	Unclear risk	analysis not by ITT

Ruiz 2001

Methods	Randomisation: no information; Blinding: double blind; Intention to treat: unknown; Exclusion from analysis: unknown; Beginning of prophylaxis: 5 days before autologous peripheral blood stem cell transplantation (A-PBSC); End of prophylaxis: fever
Participants	Spain, single centre, 50 patients undergoing autologous peripheral blood stem cell transplantation (A-PBSC) for various malignancies

Ruiz 2001 *(Continued)*

Interventions	Ofloxacin 200mg X2/d versus placebo
Outcomes	Number of febrile episodes; Clinically or microbiologically documented infections; Adverse events
Notes	Abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	exclusions not described
Selective reporting (reporting bias)	Unclear risk	ITT not described; insufficient information

Sampi 1992

Methods	Randomisation: by envelopes; blinding: none; Intention to treat: no; Exclusion from analysis: unknown; Beginning of prophylaxis: chemotherapy; End of prophylaxis: resolution of neutropenia
Participants	Japan, single centre; 73 patients with acute leukaemia receiving consolidation therapy or autologous bone marrow transplantation; Inpatients, some in laminar airflow rooms
Interventions	Norfloxacin 200mgX4/d versus no intervention
Outcomes	All cause mortality; Number of febrile patients; fever days; Clinically documented febrile episodes; Microbiologically documented febrile episodes
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	Envelopes used but not stated as sealed/opaque (B - Unclear)
Blinding (performance bias and detection bias)	Unclear risk	Not blind

Sampi 1992 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not available for the 2011 review update
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT and exclusions not stated.

Schimpff 1975

Methods	Randomisation: no information; Blinding: none; Intention to treat: yes; Exclusion from analysis: none Beginning of prophylaxis: chemotherapy; End of prophylaxis: remission or death
Participants	USA, single centre; 40 patients with acute leukaemia undergoing induction chemotherapy; Inpatients in conventional rooms
Interventions	Nonabsorbable antibiotics: gentamicin, vancomycin and nystatin versus no intervention
Outcomes	All cause mortality; Infection related mortality; Number of febrile patients; Clinically documented febrile episodes; Microbiologically documented febrile episodes
Notes	Journal Publication The trial compares three groups: group 1 - protected environment with antibiotics, group 2 - oral non-absorbable antibiotics, grouo 3 - no intervention. group 1 was excluded from our analysis, since it examines a different intervention

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	no exclusions
Selective reporting (reporting bias)	Low risk	Analysis by ITT

Schroeder 1992

Methods	Randomisation: no information; Blinding: double blind;

Schroeder 1992 *(Continued)*

	Intention to treat: no; Exclusion from analysis:5/80; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 500
Participants	Germany, single centre; 80 patients with solid tumours, who had undergone aggressive chemotherapy and in whom granulocytes had fallen to below 500; Outpatients
Interventions	Ofloxacin 200mgX2/d versus placebo
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Hospitalization days; Number of hospitalisations; Adverse events
Notes	Journal Publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5/80 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

Slavin 2007

Methods	Randomisation: computer generated, allocation concealment: sealed and opaque envelopes; Blinding: none; Intention to treat: no Exclusion from analysis:2/153 excluded after randomisation, but this is explained: in one consent withdrawn before drug administered, in the second failure of transplant before drug Beginning of prophylaxis: chemotherapy (day 0 of autologous stem cell transplant); End of prophylaxis: neutropenia resolution
Participants	Two adult bone marrow transplant centers in Australia adult patients undergoing high dose chemotherapy (HDT) + stem cell transplant: autologous 48%, allogeneic 52% Malignancies included: Almost 100% haematological malignancies-NHL,AML,ALL,CML,MM,Hodgkins,other hemato; also 4% in antibiotic group and 7% in control -solid malignancies: breast,sarcoma,germ cell tumour

Slavin 2007 *(Continued)*

	All inpatients hospitalised in HEPA filter rooms
Interventions	intravenous cefipime 1g X2 daily vs. no prophylaxis (the same antibiotic administered as empiric therapy when the patient became febrile)
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Microbiologically documented febrile episodes; Gram negative and Gram positive Microbiologically documented febrile episodes; Bacteremia Gram negative and Gram positive Bacteremia Hospitalizations Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computer generated
Allocation concealment (selection bias)	Low risk	sealed and opaque envelopes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	no blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	two excluded
Selective reporting (reporting bias)	Unclear risk	not ITT (only 2 excluded), all outcomes reported

Sleijfer 1980

Methods	Randomisation: no information; Blinding: none;Intention to treat: no; Exclusion from analysis: 8/113 Beginning of prophylaxis: PMN count less than 1000; End of prophylaxis: PMN count of 1000 or death
Participants	Netherlands, single centre; 113 patients with haematological malignancies undergoing chemotherapy; Inpatients
Interventions	Nalidixic acid 2gX4/d or Trimethoprim-sulfamethoxazole 160/800mgX3/d or polymyxin 200mgX4/d versus no intervention
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Clinically documented febrile episodes; Microbiologically documented febrile episodes

Sleijfer 1980 *(Continued)*

Notes	-Journal Publication - prophylaxis was administered according to microbiological surveillance cultures. 35 patients received nalidixic acid, 18 patients received TMP-SMZ

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	8/113 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

Starke 1982

Methods	Randomisation: no information; Blinding: none; Intention to treat: yes; Exclusion from analysis: 0/43 Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 500
Participants	England, single centre; 43 patients undergoing treatment for acute leukaemia; Inpatients in single rooms with reverse isolation
Interventions	Trimethoprim-sulfamethoxazole 40mg/800mg2/d versus trimethoprim-sulphamethoxazole 40mg/800mgX2/d plus framycetin 500mgX4/d + colistin 1.5 million unitsX4/d
Outcomes	All cause mortality; Infection related death; Number of febrile episodes; Fever days; Microbiologically documented febrile episodes; Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)

Starke 1982 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not available for the 2011 review update
Selective reporting (reporting bias)	Low risk	Analysis by ITT; No exclusions

Talbot 1993

Methods	Randomisation: no information; Blinding: double blind; Intention to treat: yes; Exclusion from analysis: none, excluded from trial 23/119 Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 500 for 7 days or PMN count of 1000 or 6 weeks
Participants	USA, multicentre; 119 adult patients with acute leukaemia treated with chemotherapy
Interventions	Enoxacin 200mgX2/d versus placebo
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Clinically documented febrile episode; Microbiologically documented febrile episodes; Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	23/119 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis by ITT

Teinturier 1995

Methods	Randomisation: no information; Blinding: none; Intention to treat: no;

Teinturier 1995 *(Continued)*

	Exclusion from analysis: 1/155 Beginning of prophylaxis: 5 days before bone marrow transplantation; End of prophylaxis: one day after bone marrow transplantation
Participants	France, single centre; 155 patients with various malignancies undergoing bone marrow transplantation; Inpatients
Interventions	IV vancomycin 10mg/kg X4/d versus no intervention
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Microbiologically documented febrile episodes; Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not available for the 2011 review update
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT; all expected outcomes reported.

Thomas 2000

Methods	Randomisation: a table of random numbers, sealed and opaque envelopes for allocation concealment; Blinding: double blind; Intention to treat: no; Exclusion from analysis: 11/162 Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 500
Participants	France, single centre; 152 patients with haematological malignancies undergoing induction chemotherapy or consolidation or bone marrow transplantation or solid malignancies undergoing autologous bone marrow transplantation; Inpatients
Interventions	Pefloxacin 200mgX4/d versus pefloxacin 200mgX4/d + oral vancomycin 200mgX4/d versus placebo
Outcomes	All cause mortality; Number of febrile patients; Fever days; Clinically documented infection; Microbiologically documented febrile episodes
Notes	Journal Publication

Risk of bias

Thomas 2000 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	random number table
Allocation concealment (selection bias)	Low risk	sealed opaque envelopes (A - Adequate)
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	11/162 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

Timmers 2007

Methods	Randomisation and concealment: randomisation according to sealed envelopes, opaque not mentioned (A/B); Blinding: none; Intention to treat: no Exclusion from analysis:3 exclusions, 3/245; (3 excluded but this is explained: 1 withdrew consent,another erroneously enrolled twice, 1 died on randomisation day) Beginning of prophylaxis: chemotherapy End of prophylaxis: neutropenia resolution>500
Participants	Single center, Netherlands 100% patients with haematological malignancies-ALL,AML,MM,Lymphoma,MDS,and other The following underwent stem cell transplant: cipro plus phenethicillin arm: 83.3% autologous, 16.7%allogeneic levofloxacin arm:86%autologous, 14%allogeneic All inpatients
Interventions	oral ciprofloxacin 500mg X2 daily plus phenethicillin 250mgX4 daily vs. levofloxacin
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Fever days; Clinically documented febrile episodes; Microbiologically documented febrile episodes; Bacteremia Gram negative and Gram positive Bacteremia Infection resistance to quinolones Adverse events

Timmers 2007 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'Randomised'
Allocation concealment (selection bias)	Unclear risk	sealed envelopes, opaque not mentioned (A/B);
Blinding (performance bias and detection bias) All outcomes	Unclear risk	none
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 excluded from 245
Selective reporting (reporting bias)	Unclear risk	not ITT, only 3 excluded, all outcomes reported

Tjan Heijnen 2001

Methods	Randomisation: generation not specified, central randomisation; Blinding: double blind Intention to treat: no; Exclusion from analysis:2/163; Beginning of prophylaxis: chemotherapy; End of prophylaxis: fever, death or side effects
Participants	Europe, multicentre; 163 adult patients with small cell lung cancer undergoing intensive chemotherapy; Outpatients
Interventions	Ciprofloxacin 750mgX2/d + roxythromycin 150mgX2/d versus placebo
Outcomes	All cause mortality; Infection related death; Number of febrile patients or febrile episodes; Fever days; Clinically documented infection; Microbiologically documented febrile episodes; number of Hospitalizations; Hospitalization days; Infection resistant to quinolones; Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation centrally coordinated
Allocation concealment (selection bias)	Low risk	centrally coordinated (A - Adequate)
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind

Tjan Heijnen 2001 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2/163 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT but all expected outcomes reported

Tsutani 1992

Methods	Randomisation: no information; Blinding: none; Intention to treat: no; Exclusion from analysis: unknown; Beginning of prophylaxis: PMN count less than 500; End of prophylaxis: PMN count of 1500 or fever
Participants	Japan, single centre; 22 patients with haematological malignancies during post remission chemotherapy; Inpatients
Interventions	Ofloxacin 300mgX2 versus no intervention
Outcomes	Number of febrile episodes; Clinically documented infection; Microbiologically documented febrile episodes
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not available for the 2011 review update
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT; exclusions not stated

van Eys 1987

Methods	Randomisation: central randomisation with institutional balancing; Blinding: none; Intention to treat: no; Exclusion from analysis: 6/126 Beginning of prophylaxis: chemotherapy; End of prophylaxis: 3 years or relapse of leukaemia
Participants	USA, multicentre; 126 children with lymphocytic leukaemia undergoing induction chemotherapy; Setting not specified

van Eys 1987 *(Continued)*

Interventions	Trimethoprim-sulfamethoxazole 4mg/kg/d versus no intervention
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Clinically documented infection; Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation
Allocation concealment (selection bias)	Low risk	Central allocation (A - Adequate)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6/126 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not ITT

Wade 1981a

Methods	Randomisation: no information; Blinding: none; Intention to treat: yes; Exclusion from analysis: none 0/53; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 1000, remission or death
Participants	USA, single centre; 53 adult patients with acute leukaemia undergoing induction chemotherapy; Inpatients or outpatients
Interventions	Trimethoprim-sulfamethoxazole 160mg/800mg versus oral gentamIcin 200mgX4
Outcomes	All cause mortality; Infection related death; Number of febrile episodes; Clinically documented infection; Microbiologically documented febrile episodes; Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)

Wade 1981a *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not available for the 2011 review update
Selective reporting (reporting bias)	Low risk	ITT analysis; all expected outcomes reported. No exclusions

Wade 1983

Methods	Randomisation: no information; Blinding: none; Intention to treat: yes; Exclusion from analysis: none 0/62; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 1000, remission or death
Participants	USA, single centre; 62 adult patients with acute leukaemia undergoing induction chemotherapy; Outpatients
Interventions	Trimethoprim-sulfamethoxazole 160mg/800mg versus nalidixic acid 1gX4/d
Outcomes	All cause mortality; Infection related death; Number of febrile patients or febrile episodes; Clinically documented infection; Microbiologically documented febrile episodes; Adverse events
Notes	Journal Publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not available for the 2011 review update
Selective reporting (reporting bias)	Low risk	Analysis by ITT; all expected outcomes reported; no exclusions

Ward 1993

Methods	Randomisation: no information on generation, central randomisation; Blinding: double blind; Intention to treat: no; Exclusion from analysis: none 9/51; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 1000
Participants	USA, multicentre (11 centres); 51 adult neutropenic patients undergoing chemotherapy for acute leukaemia; Inpatients in private rooms with reverse isolation
Interventions	Trimethoprim-sulfamethoxazole 160mg/800mg versus placebo
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Clinically documented infection; Microbiologically documented febrile episodes; Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation
Allocation concealment (selection bias)	Low risk	Centrally coordinated allocation (A - Adequate)
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	9/51 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

Watson 1982

Methods	Randomisation: no information; Blinding: none; Intention to treat: no; Exclusion from analysis: 12/100; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 500,discharge from isolation, withdrawal or death
Participants	England, single centre; 100 patients with acute leukaemia undergoing remission induction or allogeneic bone marrow transplantation; Inpatients in private rooms with reverse isolation
Interventions	Trimethoprim-sulfamethoxazole 160mg/800mgX2/d versus neomycin 500mgX2/d + colistin 1.5 million unitsX2/d 500mgX2
Outcomes	All cause mortality; Infection related death; Number of febrile patients; Clinically documented infection; Microbiologically documented febrile episodes; Adverse events

Watson 1982 *(Continued)*

Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	12/100 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT but all expected outcomes reported

Weiser 1981

Methods	Randomisation: no information; Blinding: none; Intention to treat: unknown; Exclusion from analysis: unknown; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 1000
Participants	USA, single centre; 29 adult patients with acute leukaemia in their first remission and undergoing consolidation chemotherapy; Outpatients
Interventions	Trimethoprim-sulfamethoxazole 160mg/800mgX2/d versus no intervention
Outcomes	Number of febrile episodes; Fever days; Clinically documented infection; Microbiologically documented febrile episodes; Number of hospitalisations; Hospitalization days; Infection resistant to trimethoprim-sulphamethoxazole
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind

Weiser 1981 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not available for the 2011 review update
Selective reporting (reporting bias)	Unclear risk	ITT and exclusions not described

Winston 1986

Methods	Randomisation: no information; Blinding: none; Intention to treat: unknown; Exclusion from analysis: unknown; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 1000 or death
Participants	USA, single centre; 66 adult patients with haematologic malignancies undergoing chemotherapy; Inpatients
Interventions	Norfloxacin 400mg X3/d versus oral vancomycin 400mgX3/d + polymyxin 100mg X3/d
Outcomes	Infection related death; Number of febrile patients or episodes; Clinically documented infection; Microbiologically documented febrile episodes; Infection resistant to quinolones; Adverse events
Notes	Journal Publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not available for the 2011 review update
Selective reporting (reporting bias)	Unclear risk	ITT and exclusions not described

Winston 1990

Methods	Randomisation: no information; Blinding: none; Intention to treat: unknown; Exclusion from analysis: unknown; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 750 or death or withdrawal from trial

Winston 1990 *(Continued)*

Participants	USA, single centre; 62 adult patients with haematologic malignancies undergoing chemotherapy; Inpatients
Interventions	Ofloxacin 400mgX3/d versus oral vancomycin 400mgX3/d + polymyxin 100mgX3/d
Outcomes	Infection related death; Number of febrile patients or episodes; Fever days; Clinically documented infection; Microbiologically documented febrile episodes; Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not available for the 2011 review update
Selective reporting (reporting bias)	Unclear risk	ITT and exclusions not described

Yamada 1993

Methods	Randomisation: generation by order of admission, no information on allocation; Blinding: none; Intention to treat: no; Exclusion from analysis: 5/111; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 1000 or fever
Participants	Japan, single centre; 111 adult patients with acute leukaemia receiving cytotoxic chemotherapy; Inpatients
Interventions	Norfloxacin 200mgX2/d or X4/d versus no intervention
Outcomes	All cause mortality; Number of febrile patients or episodes; Fever days; Clinically documented infection; Microbiologically documented febrile episodes; Adverse events
Notes	Journal Publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	quasi randomisation

Yamada 1993 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5/111 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT

Yates 1973

Methods	Randomisation: no information; Blinding: none; Intention to treat: no; Exclusion from analysis: 15/67; Beginning of prophylaxis: chemotherapy; End of prophylaxis: PMN count of 500, severe side effects or death
Participants	USA, single centre; 67 adult patients with haematologic malignancies undergoing chemotherapy; Inpatients in conventional ward with reverse isolation
Interventions	Nonabsorbable antibiotics: gentamicin,vancomycin and nystatin versus no intervention
Outcomes	All cause mortality; Number of febrile patients
Notes	-Journal Publication -there were originally 4 treatment groups: regular ward, regular ward + nonabsorbable, total isolation without nonabsorbable,total isolation with nonabsorbable . Only group 1 and 2 are included

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided (B - Unclear)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	15/67 exclusions
Selective reporting (reporting bias)	Unclear risk	Analysis not by ITT; high exclusion rate

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

Study	Reason for exclusion
Barriga 1997	Use of vancomycin solution for prevention of catheter infection, not all patients neutropenic
Bunn 2001	Not a randomised controlled trial
Capdevila 1997	Not a randomised controlled trial
Corrado 1988	A review article
Craig 2007	A prospective cohort trial regarding prophylaxis with quinolones, not a randomised controlled trial
Cruciani 2000b	A review article
Davis 1998	A review article
Del Favero 1989	A review article
Del Favero 1993	A review article
Delarive 2000	A review article
Donnelly 1997	A review article
Ekert 1980	A trial comparing prophylactic antibiotic therapy with prophylactic antibiotic and another intervention- lactobacilli
Engerval 1996a	A review article
Engervall 1996b	Not a randomised controlled trial
EORTC 1982	A high percentage of dropouts (53%, 40 patients out of 75 which were randomised were excluded)
Fernndez-Aviles 2010	A trial of ceftriaxone prophylaxis, but not randomised
Figueredo 1985	In this trial the intervention was high dose or low dose chemotherapy. Only the arm which was randomised to high dose chemotherapy received prophylactic antibiotics
Frampton 1996	A review article
Garcia 2000	A randomised controlled trial of treatment of febrile neutropenia, and not of prophylaxis
Giamarellou 1995	A review article
Gilbert 1994	Not a randomised controlled trial, compared to a historical control
Guiot 1981	A prospective clinical trial of antibiotic prophylaxis, not RCT
Haahr 1997	A review article
Hallbk 2010	A cohort study of autologous transplant patients who received prophylaxis, not a randomised trial
Henry 1984a	A review article
Horvathova 1998	Not a randomised controlled trial, analysis of cases with bacteraemia only

Study	Reason for exclusion
Imrie 1995	Not a randomised controlled trial, compared to a historical control
Karp 1986	A randomised controlled trial of treatment of febrile neutropenia, and not of prophylaxis
Kerr 1999b	A review article
Klastersky 1996	A review article
Krupova 1998	A review article
Ljungman 1997	A randomised controlled trial of antibiotic prophylaxis which is only periprocedural (central line insertion). The antibiotic coverage, the outcomes and the time frame are different
Lohner 1979	A trial comparing prophylactic antibiotic therapy with prophylactic antibiotic therapy combined with a protected environment
Maltezou 1999	Not a randomised controlled trial
Maltezou 1999 (a)	Not a randomised controlled trial
Mantovani 1998	A trial of febrile neutropenia
Marchetti 2002	A review article
Martino 1998	A review article
Maschmeyer 1990	A review article
May 1994	A randomised trial for prophylaxis of PCP in HIV patients, not neutropenic cancer patients
Menichetti 1989	A trial of consecutive patients, not RCT
Mihaylov 2007	A review article
Minenko 2004	Not a randomised controlled trial, in this trial moxifloxacin was compared to historical controls treated with ciprofloxacin.
Patrick 1997	A review article
Persson 2000	Not a randomised controlled trial
Pivkova 2005	A comparative study of 35 patients receiving high dose VP16 and undergoing autologous transplant. The comparison is between three options:no antibiotic prophylactic regimens, vancomycin or ciprofloxacin and amoxicillin-clavulonic acid. However, it is not randomised
Reuter 2005	Not an RCT, a prospective observational study
Risi 1998	A review article
Schaison 1991	A study of febrile neutropenia
Solano 2005	Not a randomised trial - a prospective study of prophylaxis compared with historical controls
Spanik 1998	A retrospective trial

Study	Reason for exclusion
Takemoto 1990	A randomised controlled trial but for febrile neutropenia
Timmer-Bonte 2005	A randomised controlled trial, but the intervention was granulocyte colony-stimulating factor and both arms received prophylactic antibiotics
Tjan Heijnen 2002	A letter relating to another trial
Tunkel 2002	A review article
Van De Leur 1995	A study which evaluates antibiotic concentration in faeces, but not in neutropenics, not a RCT
Viscoli 2001	A review article
Viscoli 1998	A review article
Viscoli 2002	A review article
von Baum 2006	Controlled before and after observational study of prophylaxis but not randomised
von Minckwitz 2008	This study compared four consecutive cohort studies of patients receiving chemotherapy for breast cancer, it was not randomised. The 4 methods of neutropenia prophylaxis administered were : ciprofloxacin alone vs figrastim vs. pegfilgratim vs pegfilgradtim+ciprofloxacin
Wade 1981	A retrospective study
Wilson 1982	A case report of two cases of failure of TMP-SMZ prophylaxis
Zinner 1999	A review article

DATA AND ANALYSES

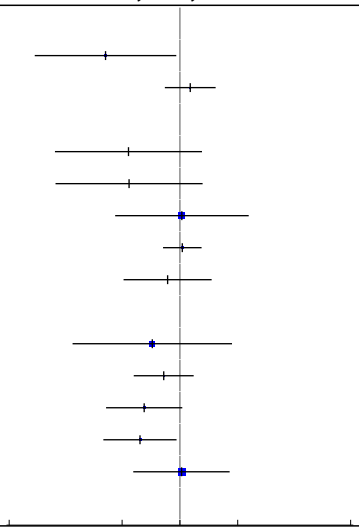
Comparison 1. All-cause mortality, prophylaxis versus placebo or no intervention or other antibiotic

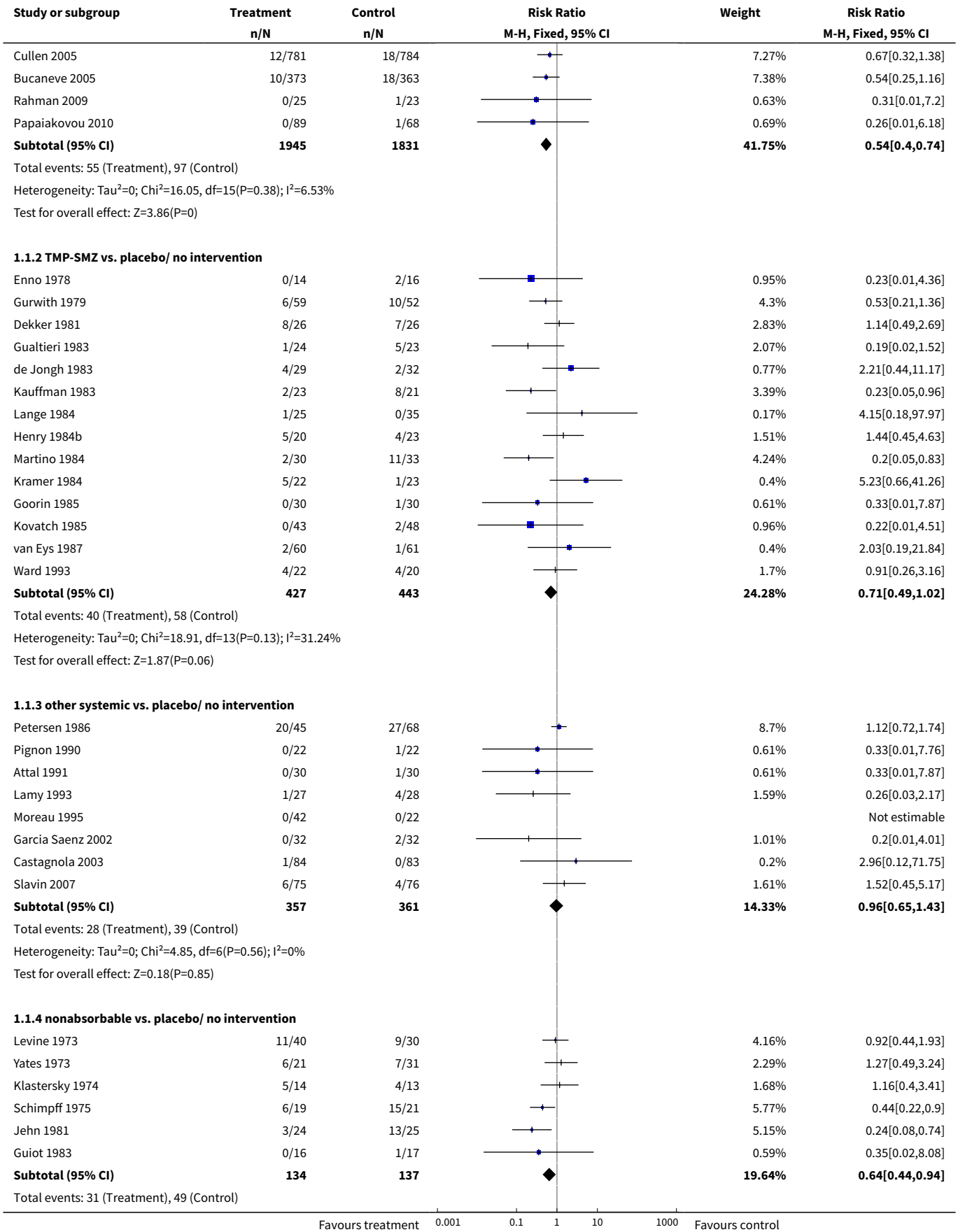
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 drug vs. placebo/no intervention	46	5635	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.55, 0.79]
1.1 quinolone vs. placebo/ no intervention	19	3776	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.40, 0.74]
1.2 TMP-SMZ vs. placebo/ no intervention	14	870	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.49, 1.02]
1.3 other systemic vs. placebo/ no intervention	8	718	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.65, 1.43]
1.4 nonabsorbable vs. placebo/ no intervention	6	271	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.44, 0.94]

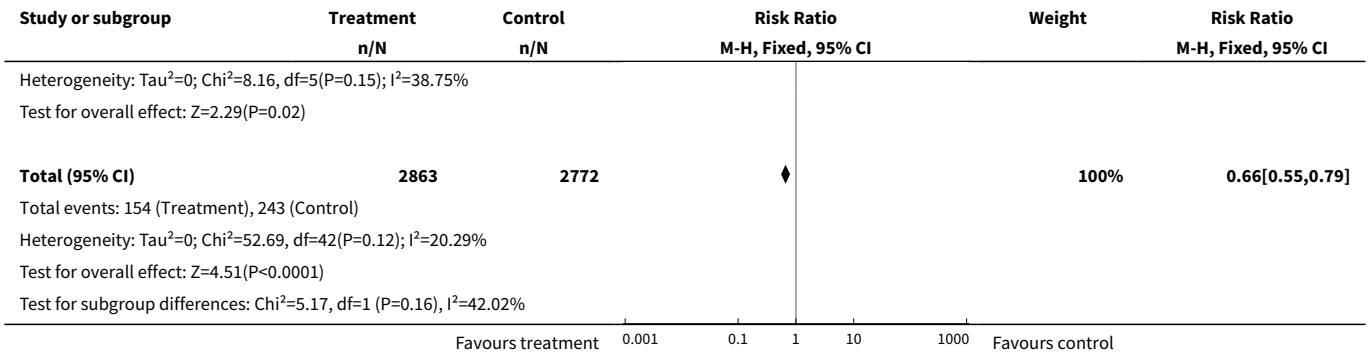
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 quinolone vs. TMP-SMZ	10	917	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.66, 1.72]
2.1 ciprofloxacin vs. TMP-SMZ	3	431	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [0.91, 4.69]
2.2 ofloxacin vs. TMP-SMZ	3	258	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.32, 1.77]
2.3 norfloxacin vs. TMP-SMZ	3	166	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.23, 2.99]
2.4 nalidixic acid vs. TMP-SMZ	1	62	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.15, 1.83]
3 quinolone+other vs. quinolone	9	1375	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.69, 2.38]
3.1 rifampin	3	274	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.25, 8.28]
3.2 vanco	1	84	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 penicillins	4	886	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.56, 2.28]
3.4 roxi	1	131	Risk Ratio (M-H, Fixed, 95% CI)	3.14 [0.34, 29.42]
4 TMP-SMZ vs. other	2	135	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.53, 2.89]
5 nonabsorbable vs. systemic	8	813	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.74, 1.50]
6 systemic + nonabsorbable vs systemic	2	83	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.34, 2.38]

Analysis 1.1. Comparison 1 All-cause mortality, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 1 drug vs. placebo/no intervention.

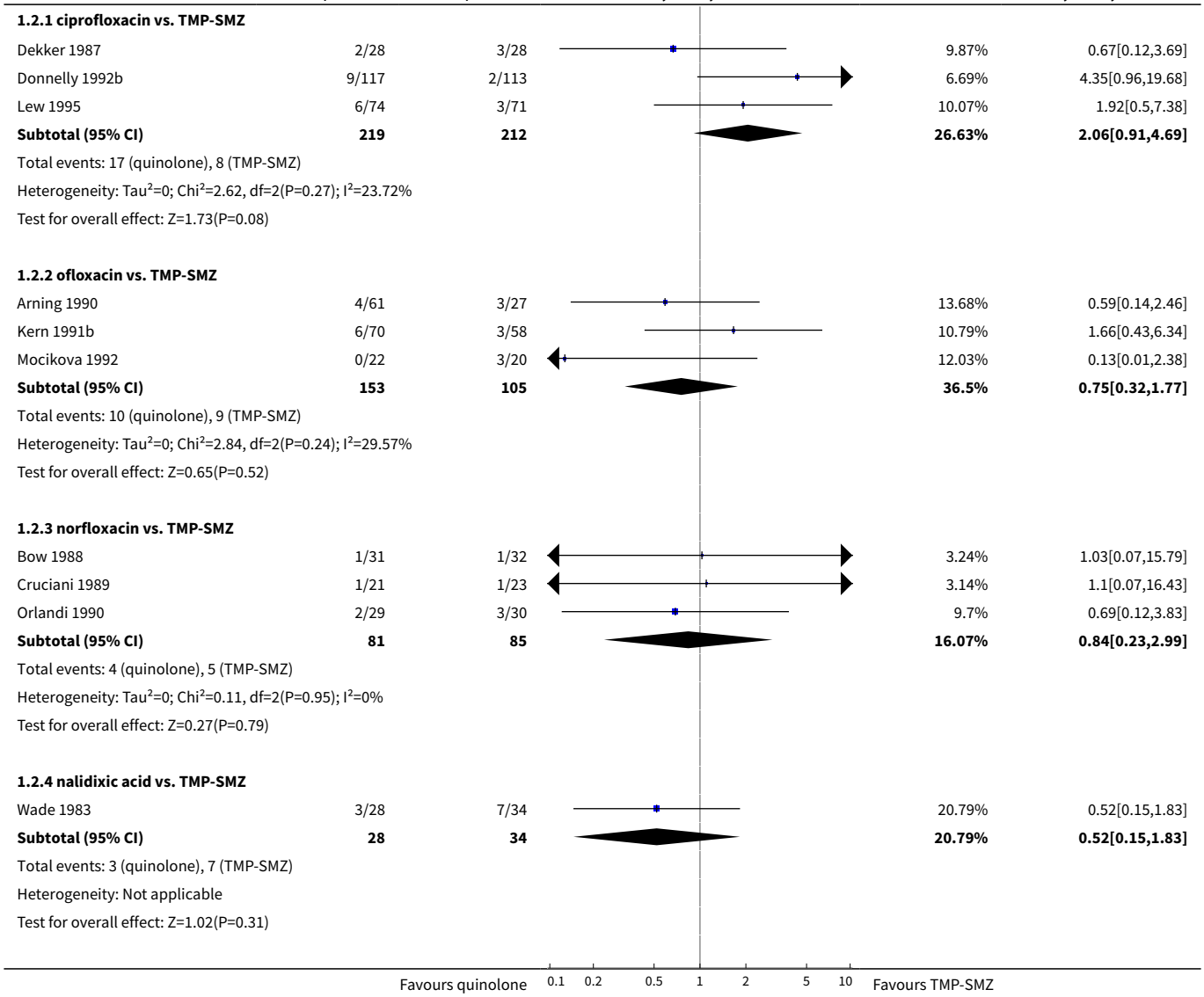
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 quinolone vs. placebo/ no intervention					
Sleijfer 1980	0/53	9/52		3.88%	0.05[0,0.87]
Karp 1987	8/35	5/33		2.08%	1.51[0.55,4.15]
Lew 1991	0/7	0/11			Not estimable
Schroeder 1992	0/40	3/36		1.49%	0.13[0.01,2.41]
Sampi 1992	0/38	3/35		1.47%	0.13[0.01,2.47]
Brodsky 1993	1/12	1/13		0.39%	1.08[0.08,15.46]
Yamada 1993	11/53	10/53		4.05%	1.1[0.51,2.37]
Talbot 1993	2/62	3/57		1.27%	0.61[0.11,3.54]
Moreau 1995	0/44	0/22			Not estimable
Carlson 1997	0/45	1/45		0.61%	0.33[0.01,7.97]
Thomas 2000	5/99	5/52		2.65%	0.53[0.16,1.73]
Tjan Heijnen 2001	2/82	8/79		3.3%	0.24[0.05,1.1]
Nenova 2001	2/36	9/33		3.8%	0.2[0.05,0.87]
Lee 2002	2/46	2/49		0.78%	1.07[0.16,7.25]
Lalami 2004	0/25	0/23			Not estimable

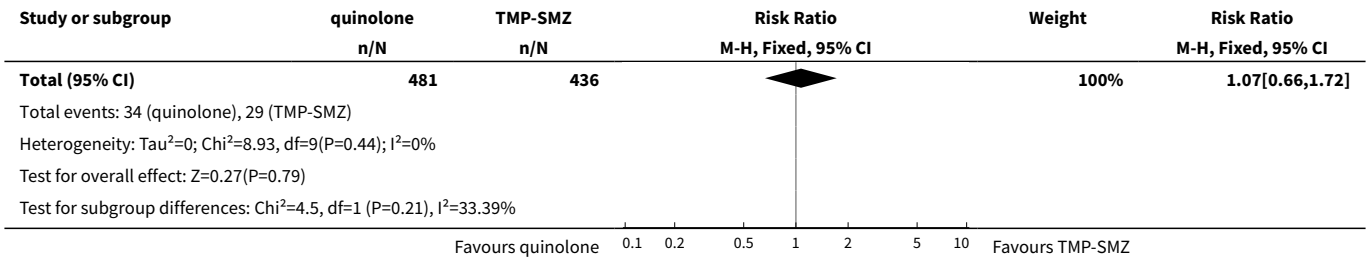




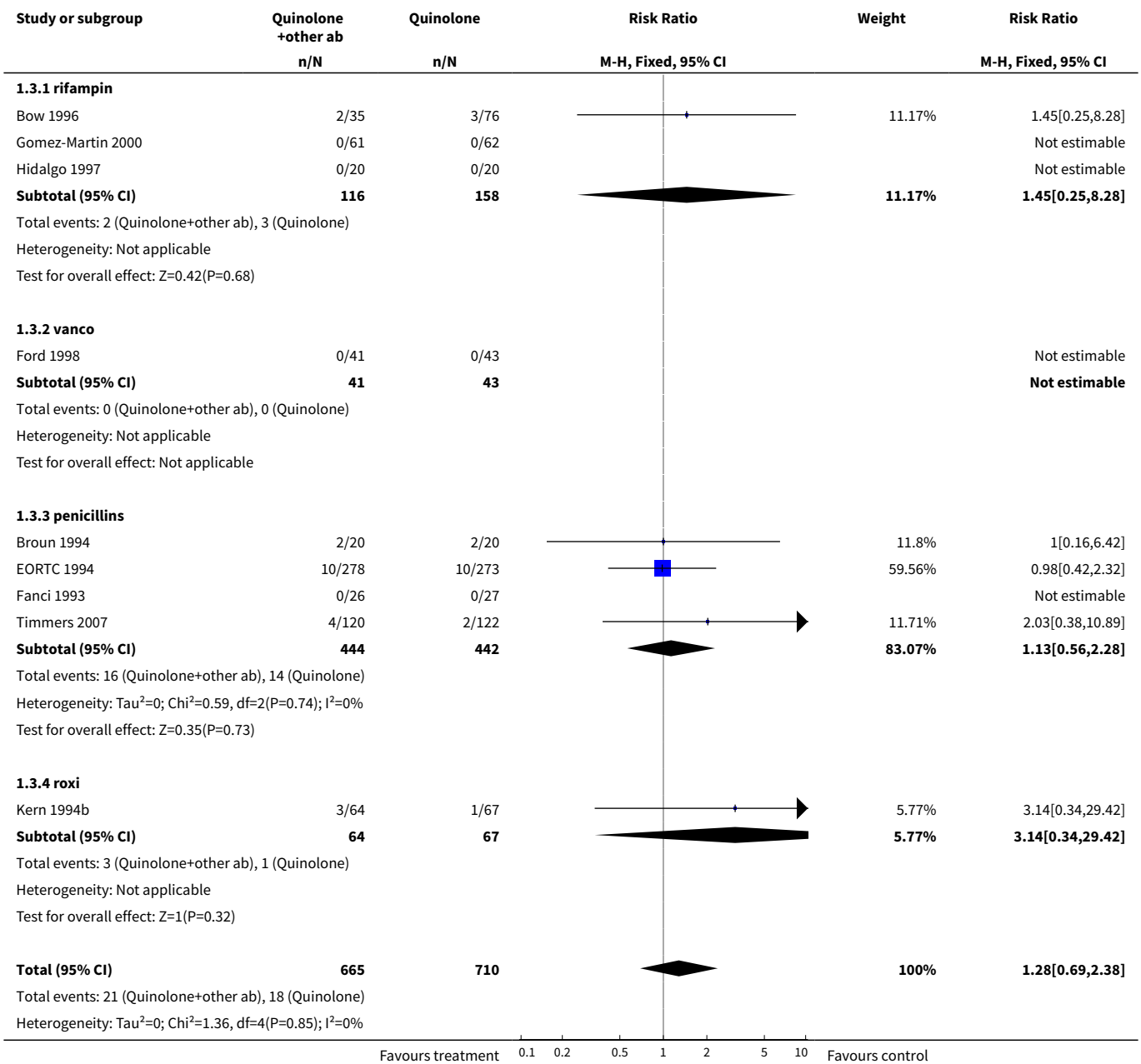


Analysis 1.2. Comparison 1 All-cause mortality, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 2 quinolone vs. TMP-SMZ.

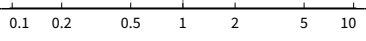




Analysis 1.3. Comparison 1 All-cause mortality, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 3 quinolone+other vs. quinolone.



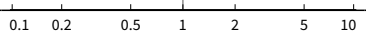
Study or subgroup	Quinolone +other ab n/N	Quinolone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=0.79(P=0.43)					
Test for subgroup differences: Chi²=0.75, df=1 (P=0.69), I²=0%					



Favours treatment Favours control

Analysis 1.4. Comparison 1 All-cause mortality, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 4 TMP-SMZ vs. other.

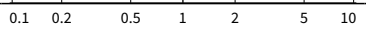
Study or subgroup	TMP-SMZ n/N	other antibiotics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bow 1984	8/34	6/26		86.44%	1.02[0.4,2.58]
Guiot 1992	3/40	1/35		13.56%	2.63[0.29,24.1]
Total (95% CI)	**74**	**61**		**100%**	**1.24[0.53,2.89]**
Total events: 11 (TMP-SMZ), 7 (other antibiotics)					
Heterogeneity: Tau²=0; Chi²=0.61, df=1(P=0.44); I²=0%					
Test for overall effect: Z=0.49(P=0.62)					



Favours treatment Favours control

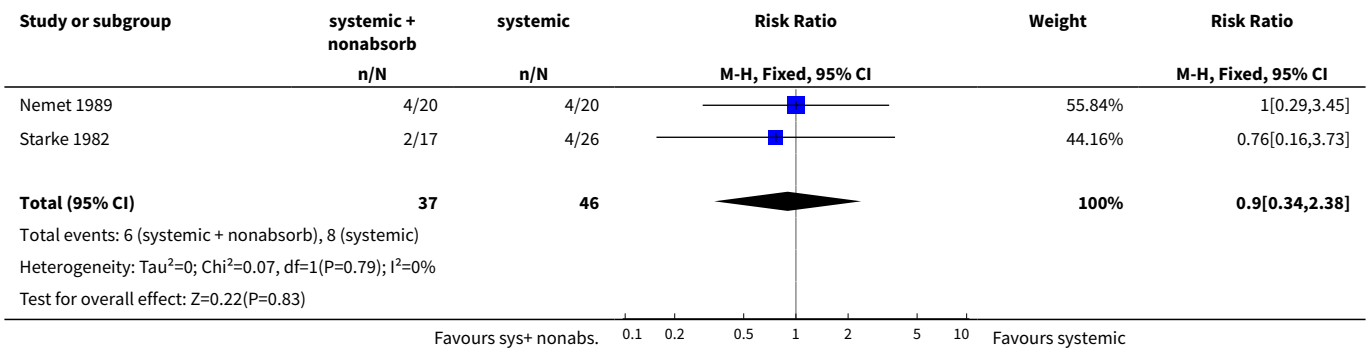
Analysis 1.5. Comparison 1 All-cause mortality, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 5 nonabsorbable vs. systemic.

Study or subgroup	nonabsorbable n/N	systemic n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Archimbaud 1991	13/74	10/76		19.24%	1.34[0.62,2.85]
Gluckman 1991	3/22	9/22		17.55%	0.33[0.1,1.07]
Jansen 1994	5/33	7/63		9.38%	1.36[0.47,3.97]
Kurrle 1983	5/42	7/40		13.98%	0.68[0.24,1.97]
Kurrle 1986	12/77	11/74		21.87%	1.05[0.49,2.23]
Prentice 2001	2/73	1/75		1.92%	2.05[0.19,22.17]
Wade 1981a	8/26	4/27		7.65%	2.08[0.71,6.07]
Watson 1982	5/48	4/41		8.41%	1.07[0.31,3.72]
Total (95% CI)	**395**	**418**		**100%**	**1.06[0.74,1.5]**
Total events: 53 (nonabsorbable), 53 (systemic)					
Heterogeneity: Tau²=0; Chi²=6.83, df=7(P=0.45); I²=0%					
Test for overall effect: Z=0.3(P=0.76)					



nonabsorbable systemic

Analysis 1.6. Comparison 1 All-cause mortality, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 6 systemic + nonabsorbable vs systemic.



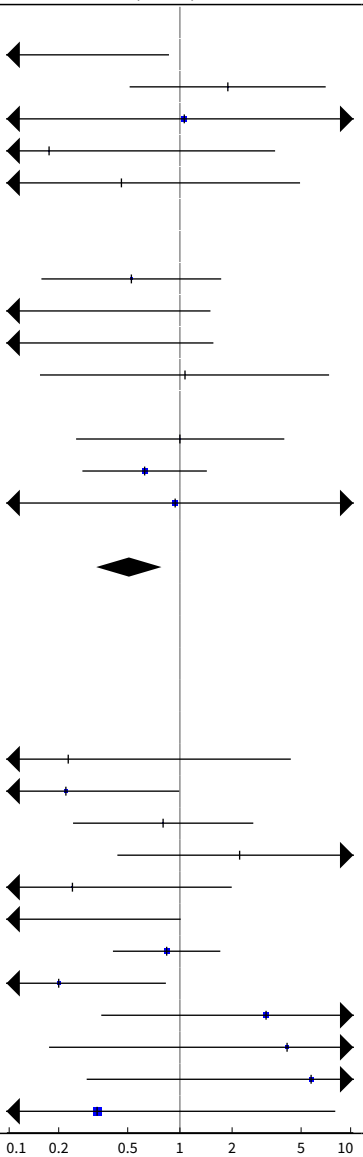
Comparison 2. Infection related mortality, prophylaxis versus placebo or no intervention or other antibiotic

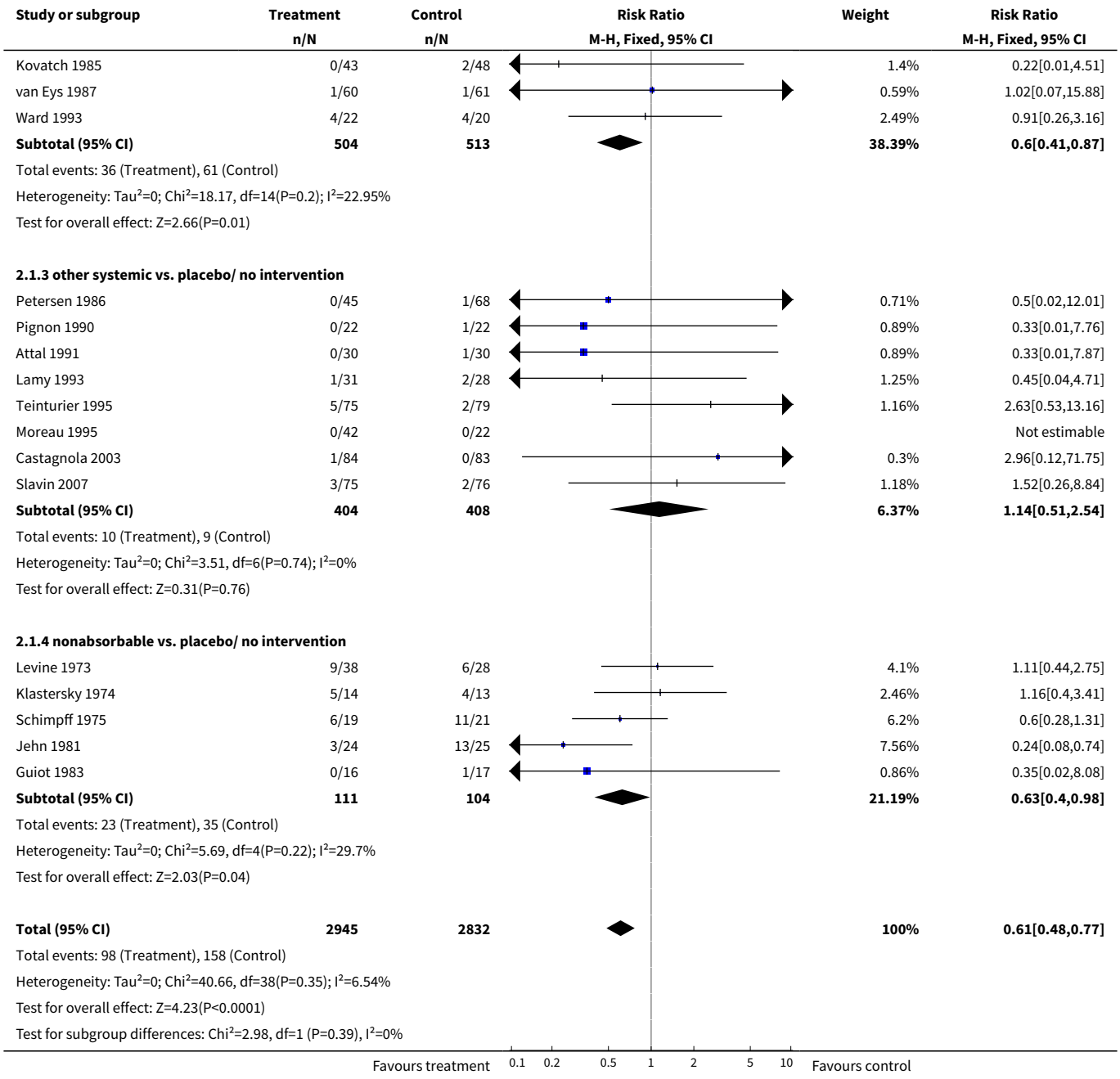
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 drug vs. placebo/no intervention	43	5777	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.48, 0.77]
1.1 quinolone vs. placebo/ no intervention	16	3733	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.33, 0.78]
1.2 TMP-SMZ vs. placebo/ no intervention	15	1017	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.41, 0.87]
1.3 other systemic vs. placebo/ no intervention	8	812	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.51, 2.54]
1.4 nonabsorbable vs. placebo/ no intervention	5	215	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.40, 0.98]
2 quinolone vs. TMP-SMZ	11	1019	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.54, 1.54]
2.1 ciprofloxacin vs. TMP-SMZ	3	431	Risk Ratio (M-H, Fixed, 95% CI)	3.32 [0.81, 13.56]
2.2 ofloxacin vs. TMP-SMZ	4	360	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.30, 1.51]
2.3 norfloxacin vs. TMP-SMZ	3	166	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.23, 2.99]
2.4 nalidixic acid vs. TMP-SMZ	1	62	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.15, 1.83]
3 quinolone+other vs. quinolone	9	1375	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.56, 1.81]
3.1 rifampin	3	274	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.10, 11.58]
3.2 vanco	1	84	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.16, 2.47]
3.3 penicillins	4	886	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.52, 2.16]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.4 roxi	1	131	Risk Ratio (M-H, Fixed, 95% CI)	2.09 [0.19, 22.53]
4 TMP-SMZ vs. other	2	135	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.40, 2.82]
5 nonabsorbable vs. systemic	11	1005	Risk Ratio (M-H, Fixed, 95% CI)	2.48 [1.65, 3.73]
6 systemic + nonabsorbable vs systemic	2	83	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.23, 3.24]

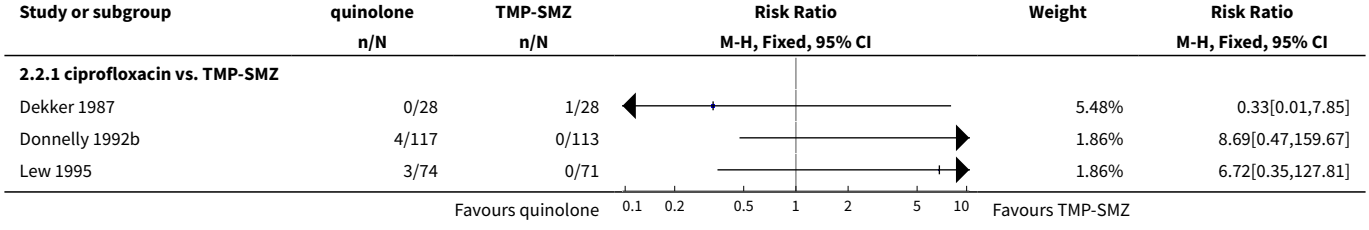
Analysis 2.1. Comparison 2 Infection related mortality, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 1 drug vs. placebo/no intervention.

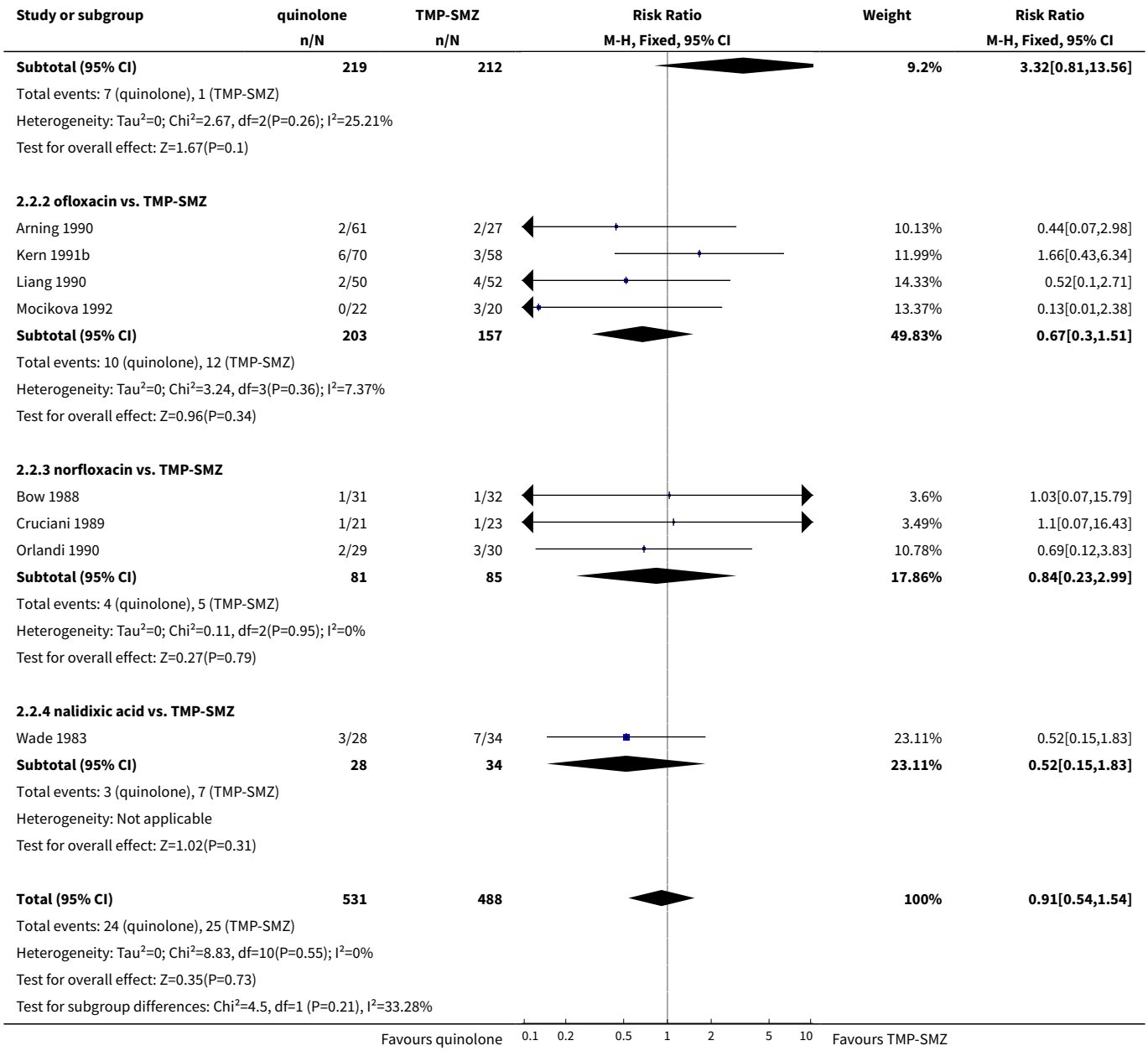
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 quinolone vs. placebo/ no intervention					
Sleijfer 1980	0/53	9/52		5.69%	0.05[0,0.87]
Karp 1987	6/35	3/33		1.83%	1.89[0.51,6.93]
Rafecas 1989	1/17	1/18		0.58%	1.06[0.07,15.62]
Schroeder 1992	0/40	2/35		1.58%	0.18[0.01,3.54]
Talbot 1993	1/62	2/57		1.24%	0.46[0.04,4.93]
Moreau 1995	0/44	0/22			Not estimable
Carlson 1997	0/45	0/45			Not estimable
Thomas 2000	5/99	5/52		3.89%	0.53[0.16,1.73]
Nenova 2001	0/36	5/34		3.36%	0.09[0,1.5]
Tjan Heijnen 2001	0/82	5/79		3.32%	0.09[0,1.56]
Lee 2002	2/46	2/49		1.15%	1.07[0.16,7.25]
Lalami 2004	0/25	0/23			Not estimable
Cullen 2005	4/781	4/784		2.37%	1[0.25,4]
Bucaneve 2005	9/373	14/363		8.42%	0.63[0.27,1.43]
Dickgreber 2009	1/99	1/93		0.61%	0.94[0.06,14.8]
Papaiakovou 2010	0/89	0/68			Not estimable
Subtotal (95% CI)	**1926**	**1807**		**34.05%**	**0.51[0.33,0.78]**
Total events: 29 (Treatment), 53 (Control)					
Heterogeneity: Tau^2=0; Chi^2=12.07, df=11(P=0.36); I^2=8.84%					
Test for overall effect: Z=3.07(P=0)					
2.1.2 TMP-SMZ vs. placebo/ no intervention					
Enno 1978	0/14	2/16		1.39%	0.23[0.01,4.36]
Gurwith 1979	2/59	8/52		5.05%	0.22[0.05,0.99]
Dekker 1981	4/26	5/26		2.97%	0.8[0.24,2.65]
de Jongh 1983	4/29	2/32		1.13%	2.21[0.44,11.17]
Gualtieri 1983	1/24	4/23		2.42%	0.24[0.03,1.99]
Kauffman 1983	0/23	7/21		4.65%	0.06[0,1.01]
Estey 1984	12/77	13/70		8.08%	0.84[0.41,1.71]
Martino 1984	2/30	11/33		6.22%	0.2[0.05,0.83]
Kramer 1984	3/22	1/23		0.58%	3.14[0.35,27.92]
Lange 1984	1/25	0/35		0.25%	4.15[0.18,97.97]
Henry 1984b	2/20	0/23		0.28%	5.71[0.29,112.43]
Goorin 1985	0/30	1/30		0.89%	0.33[0.01,7.87]



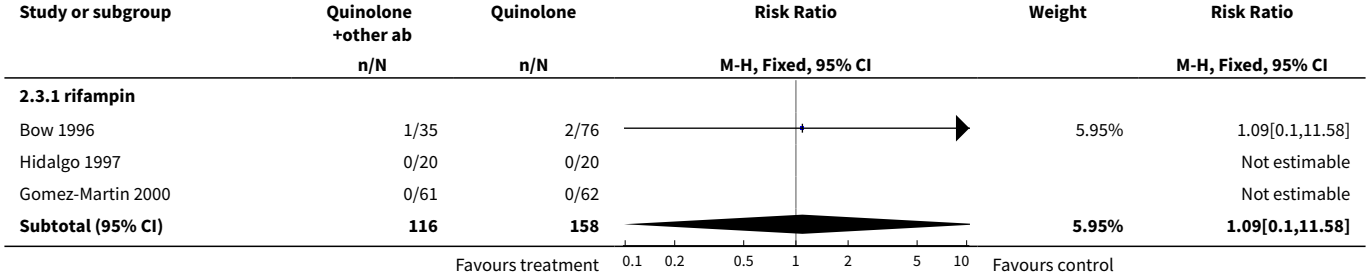


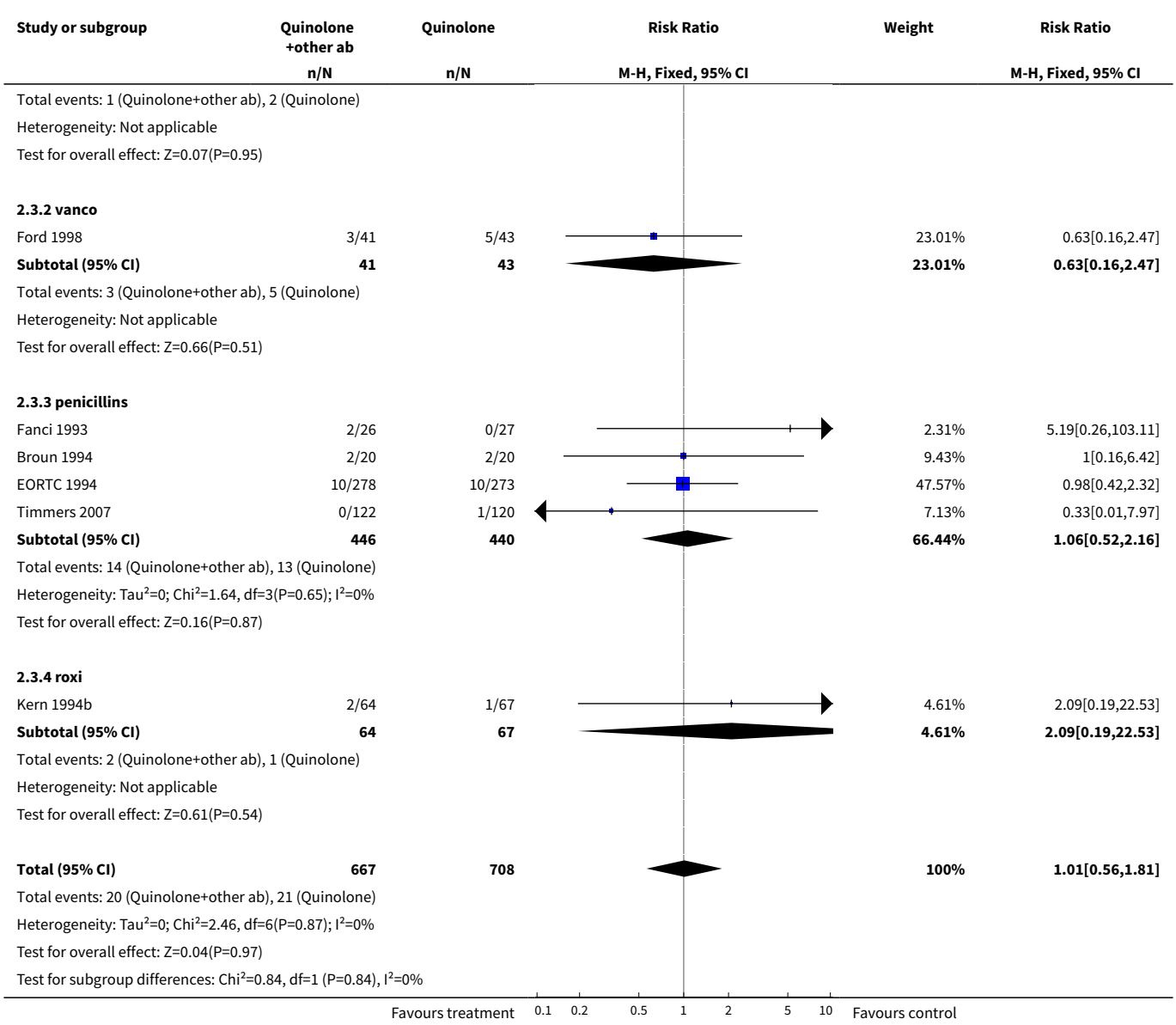
Analysis 2.2. Comparison 2 Infection related mortality, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 2 quinolone vs. TMP-SMZ.



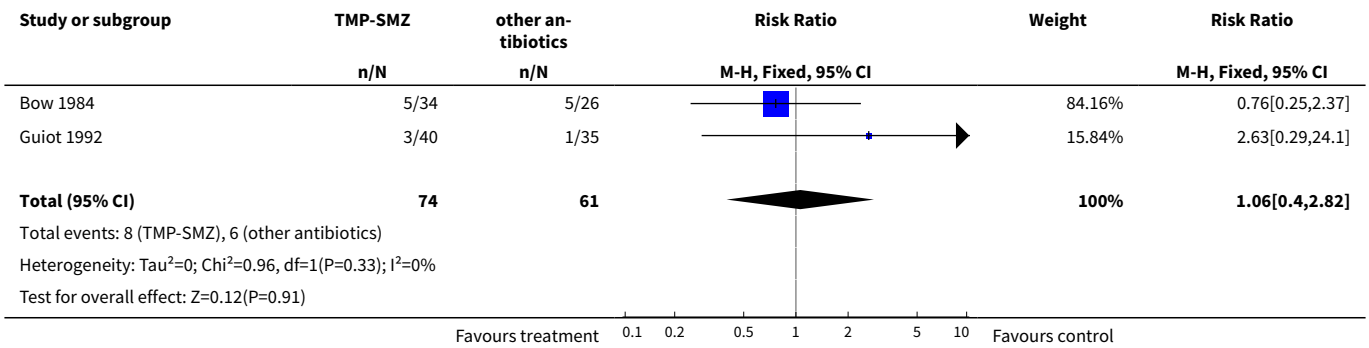


Analysis 2.3. Comparison 2 Infection related mortality, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 3 quinolone+other vs. quinolone.

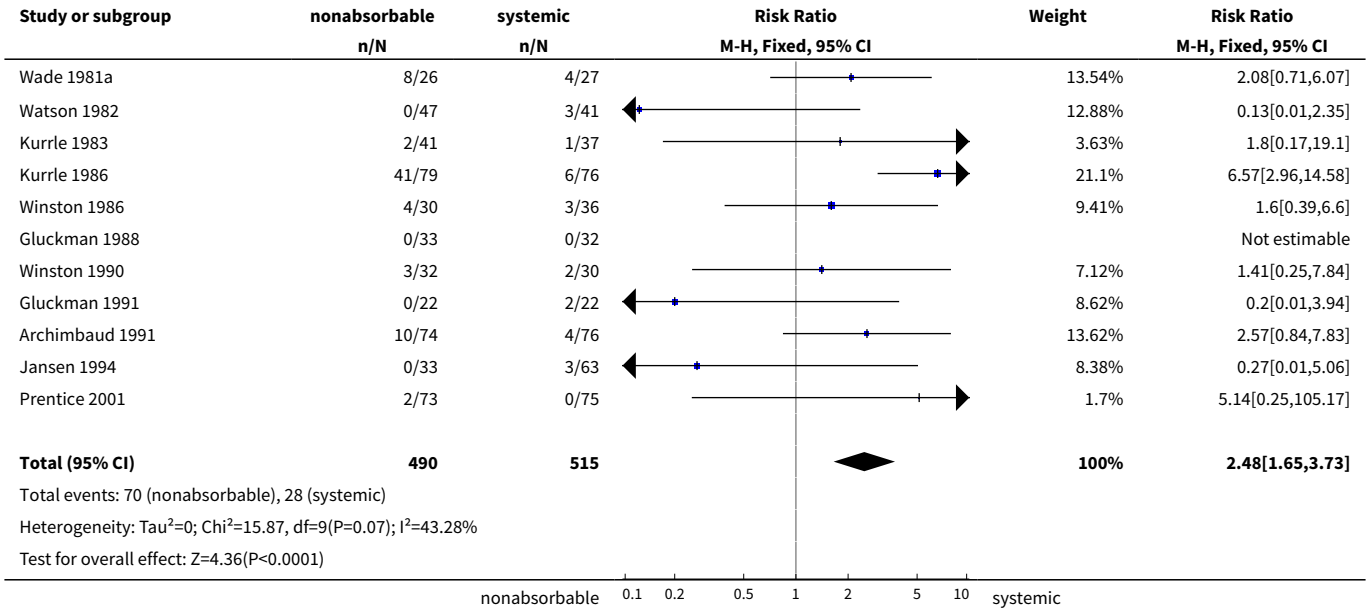




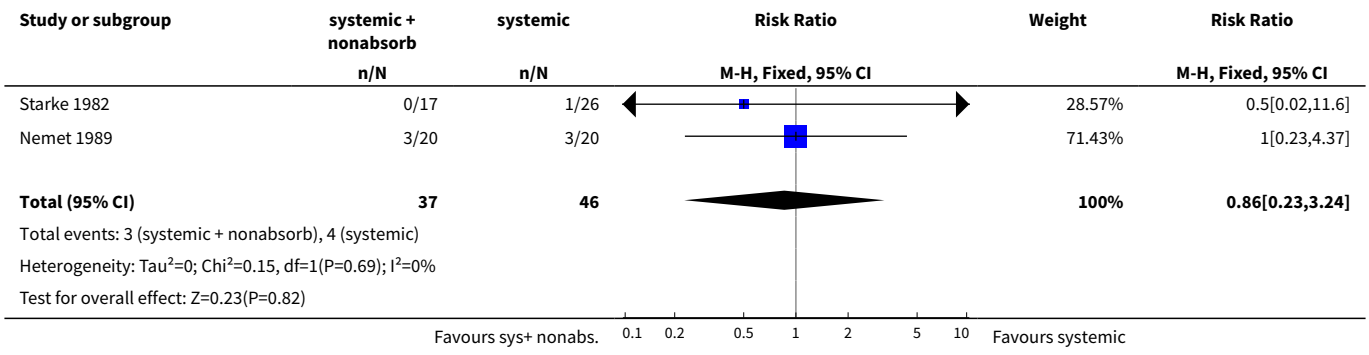
Analysis 2.4. Comparison 2 Infection related mortality, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 4 TMP-SMZ vs. other.



Analysis 2.5. Comparison 2 Infection related mortality, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 5 nonabsorbable vs. systemic.



Analysis 2.6. Comparison 2 Infection related mortality, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 6 systemic + nonabsorbable vs systemic.



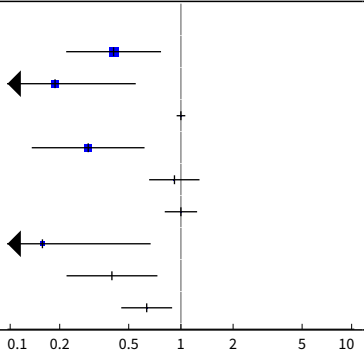
Comparison 3. Febrile patients and febrile episodes, prophylaxis versus placebo or no intervention or other antibiotic

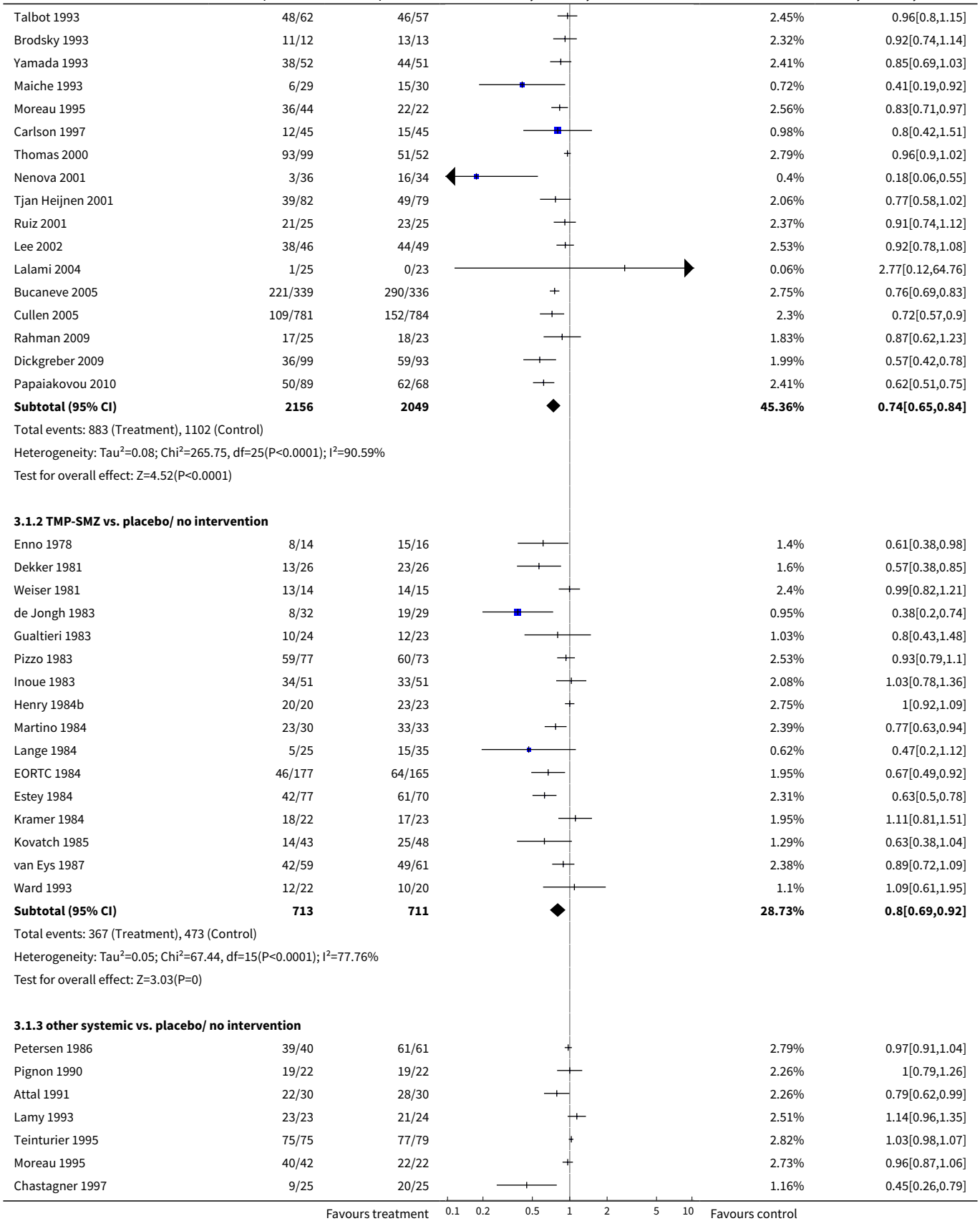
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 drug vs. placebo/ no intervention	54	6658	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.74, 0.87]
1.1 quinolone vs. placebo/ no intervention	26	4205	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.65, 0.84]

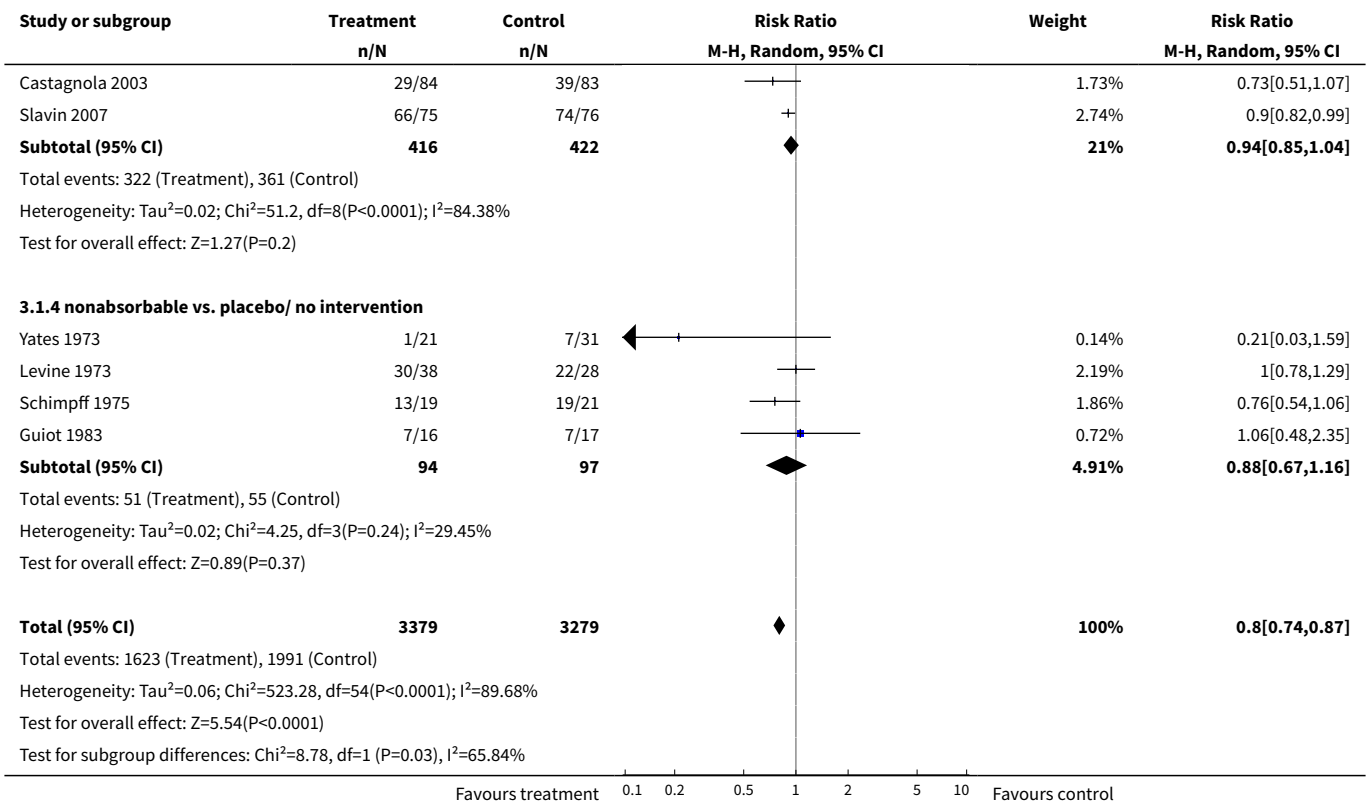
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 TMP-SMZ vs. placebo/ no intervention	16	1424	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.69, 0.92]
1.3 other systemic vs. placebo/ no intervention	9	838	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.85, 1.04]
1.4 nonabsorbable vs. placebo/ no intervention	4	191	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.67, 1.16]
2 quinolone vs. TMP-SMZ	10	931	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.78, 1.09]
2.1 ciprofloxacin vs. TMP-SMZ	3	431	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.96, 1.23]
2.2 ofloxacin vs. TMP-SMZ	3	272	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.50, 1.04]
2.3 norfloxacin vs. TMP-SMZ	3	166	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.54, 1.26]
2.4 nalidixic acid vs. TMP-SMZ	1	62	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.99, 1.77]
3 quinolone+other vs. quinolone	8	1276	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.97, 1.11]
3.1 rifampin	3	274	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.84, 1.05]
3.2 penicillins	4	871	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.97, 1.16]
3.3 roxi	1	131	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.86, 1.39]
4 TMP-SMZ vs. other	2	89	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.64, 1.31]
5 nonabsorbable vs. systemic	8	808	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.99, 1.13]
6 systemic + nonabsorbable vs systemic	2	103	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.72, 1.20]

Analysis 3.1. Comparison 3 Febrile patients and febrile episodes, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 1 drug vs. placebo/ no intervention.

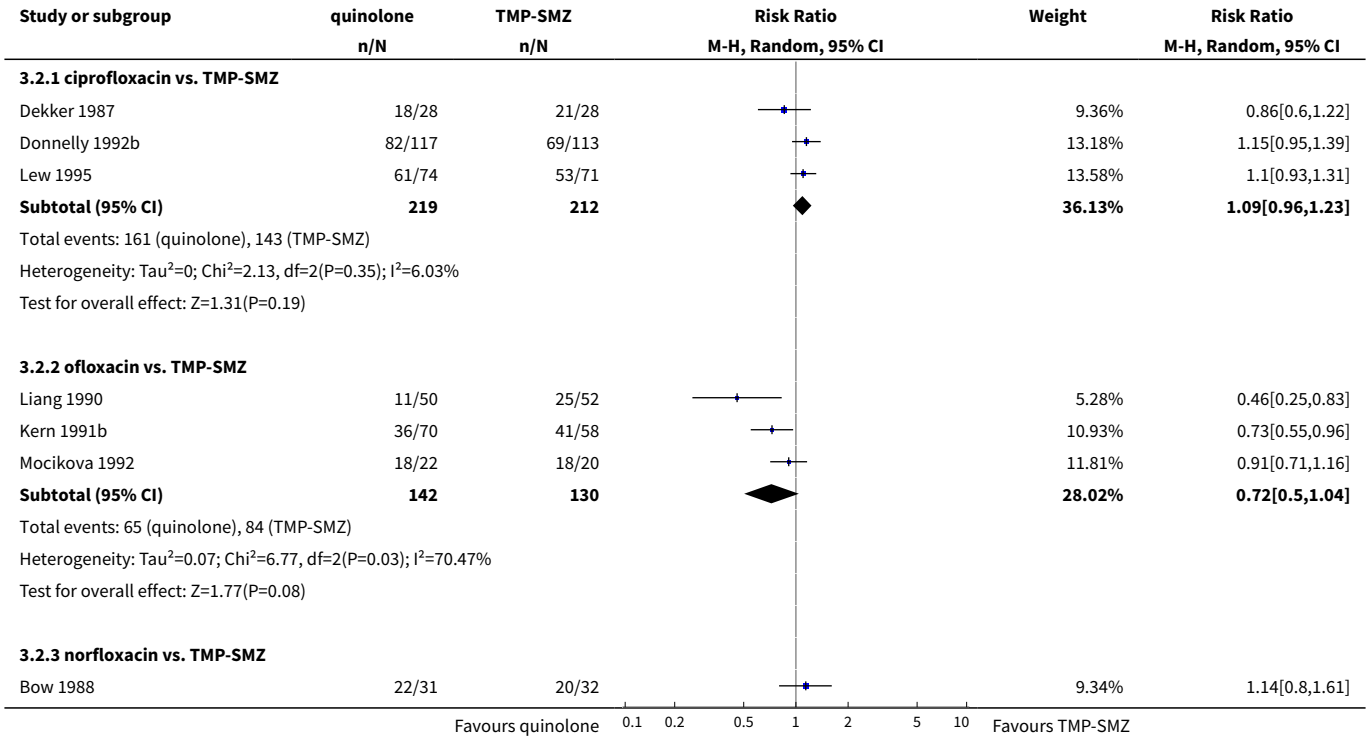
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 quinolone vs. placebo/ no intervention					
Sleijfer 1980	10/53	24/52		1%	0.41[0.22,0.77]
Hartlapp 1987	3/21	16/21		0.44%	0.19[0.06,0.55]
Karp 1987	35/35	33/33		2.8%	1[0.95,1.06]
Casali 1988	6/30	24/35		0.78%	0.29[0.14,0.62]
Rafecas 1989	13/17	15/18		1.87%	0.92[0.66,1.28]
Lew 1991	7/7	11/11		2.34%	1[0.81,1.24]
Schroeder 1992	2/40	11/35		0.27%	0.16[0.04,0.67]
Tsutani 1992	8/25	20/25		1.05%	0.4[0.22,0.73]
Sampi 1992	20/38	29/35		1.86%	0.64[0.45,0.89]

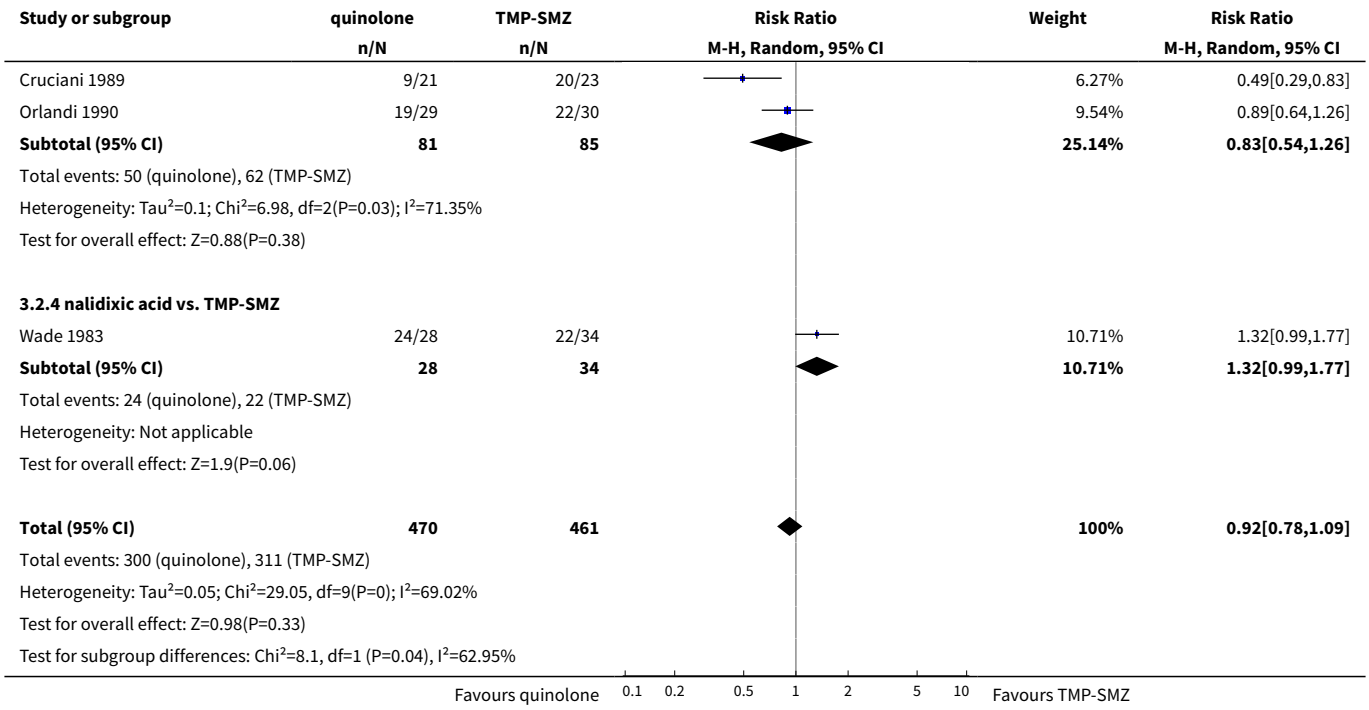




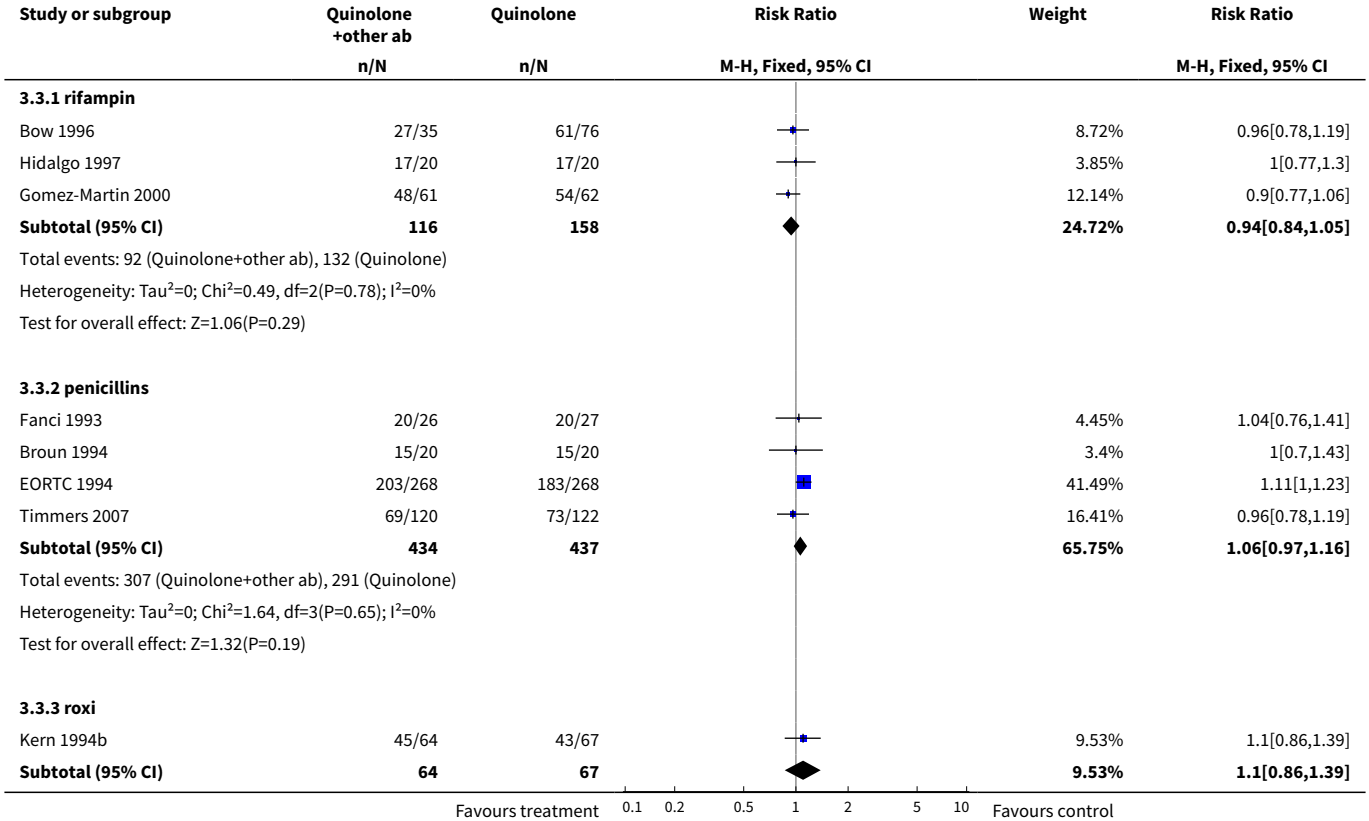


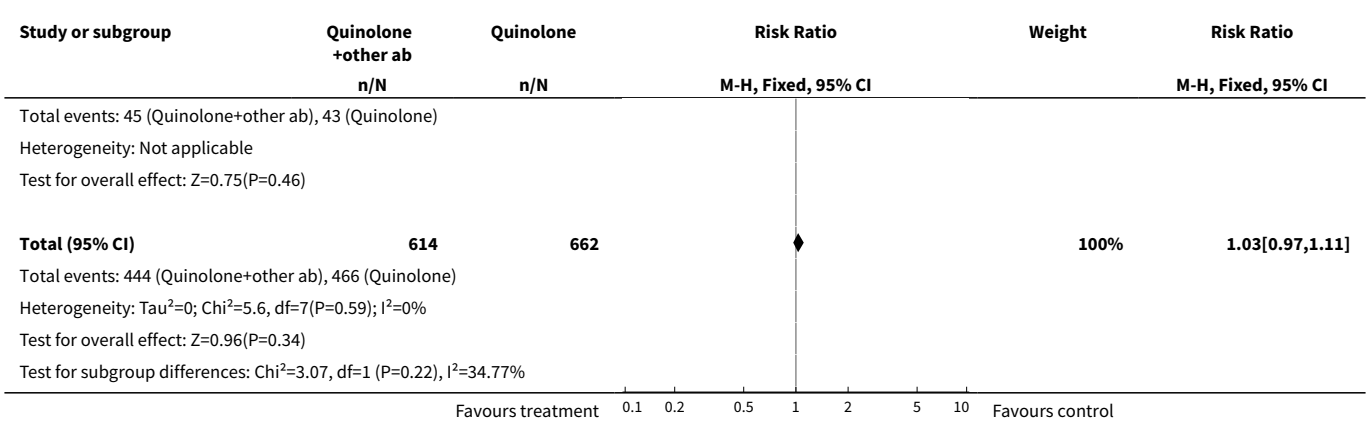
Analysis 3.2. Comparison 3 Febrile patients and febrile episodes, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 2 quinolone vs. TMP-SMZ.



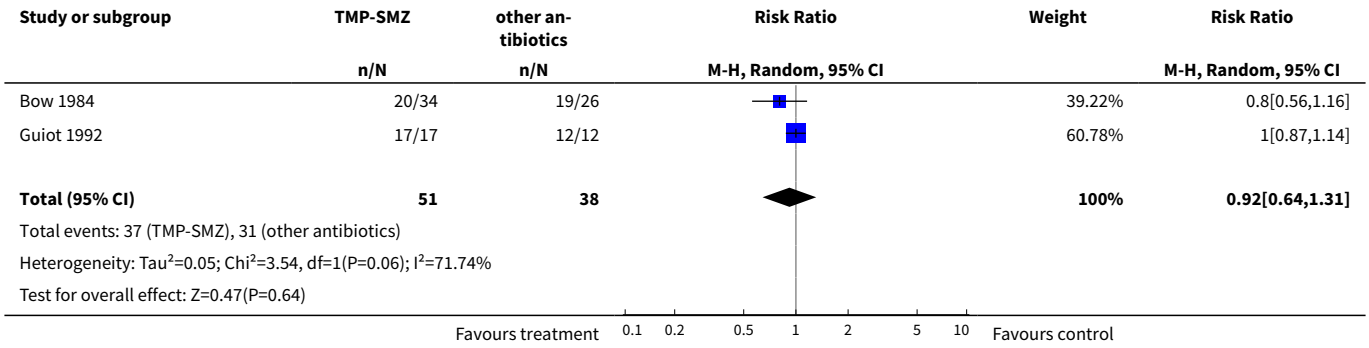


Analysis 3.3. Comparison 3 Febrile patients and febrile episodes, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 3 quinolone+other vs. quinolone.

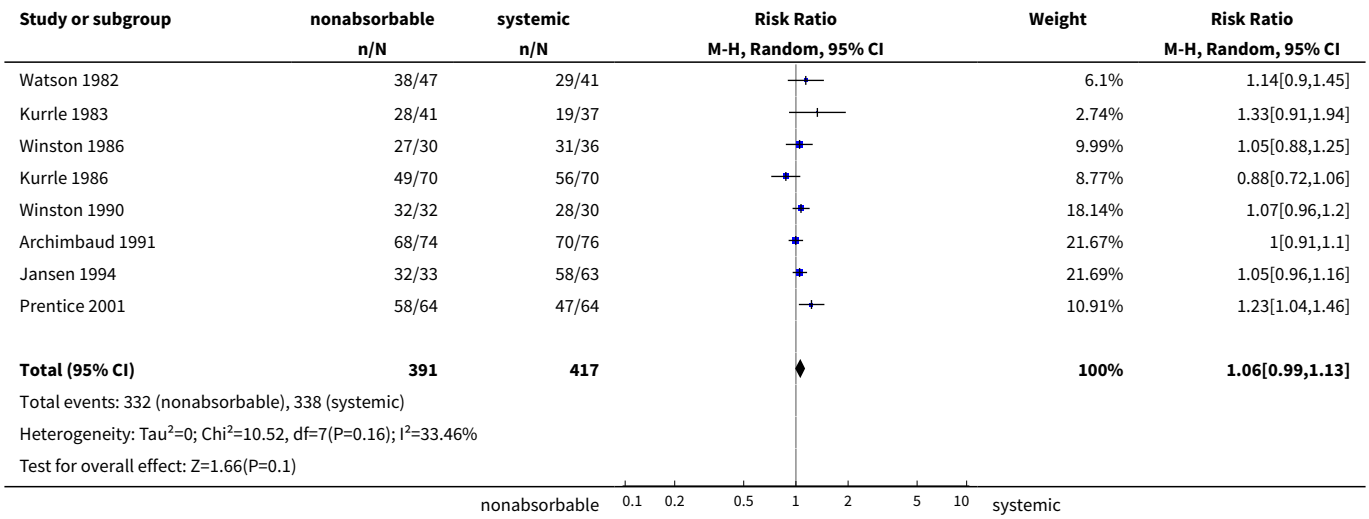




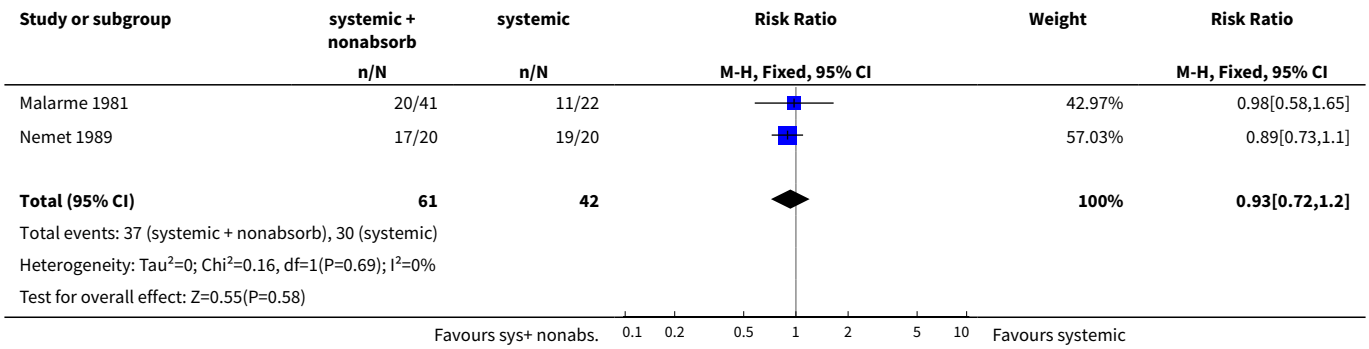
Analysis 3.4. Comparison 3 Febrile patients and febrile episodes, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 4 TMP-SMZ vs. other.



Analysis 3.5. Comparison 3 Febrile patients and febrile episodes, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 5 nonabsorbable vs. systemic.



Analysis 3.6. Comparison 3 Febrile patients and febrile episodes, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 6 systemic + nonabsorbable vs systemic.



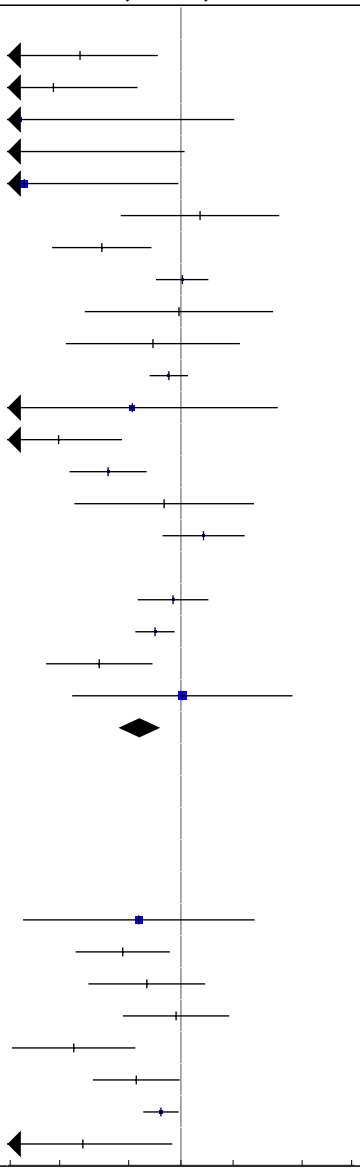
Comparison 4. Clinically documented infection, prophylaxis versus placebo or no intervention or other antibiotic

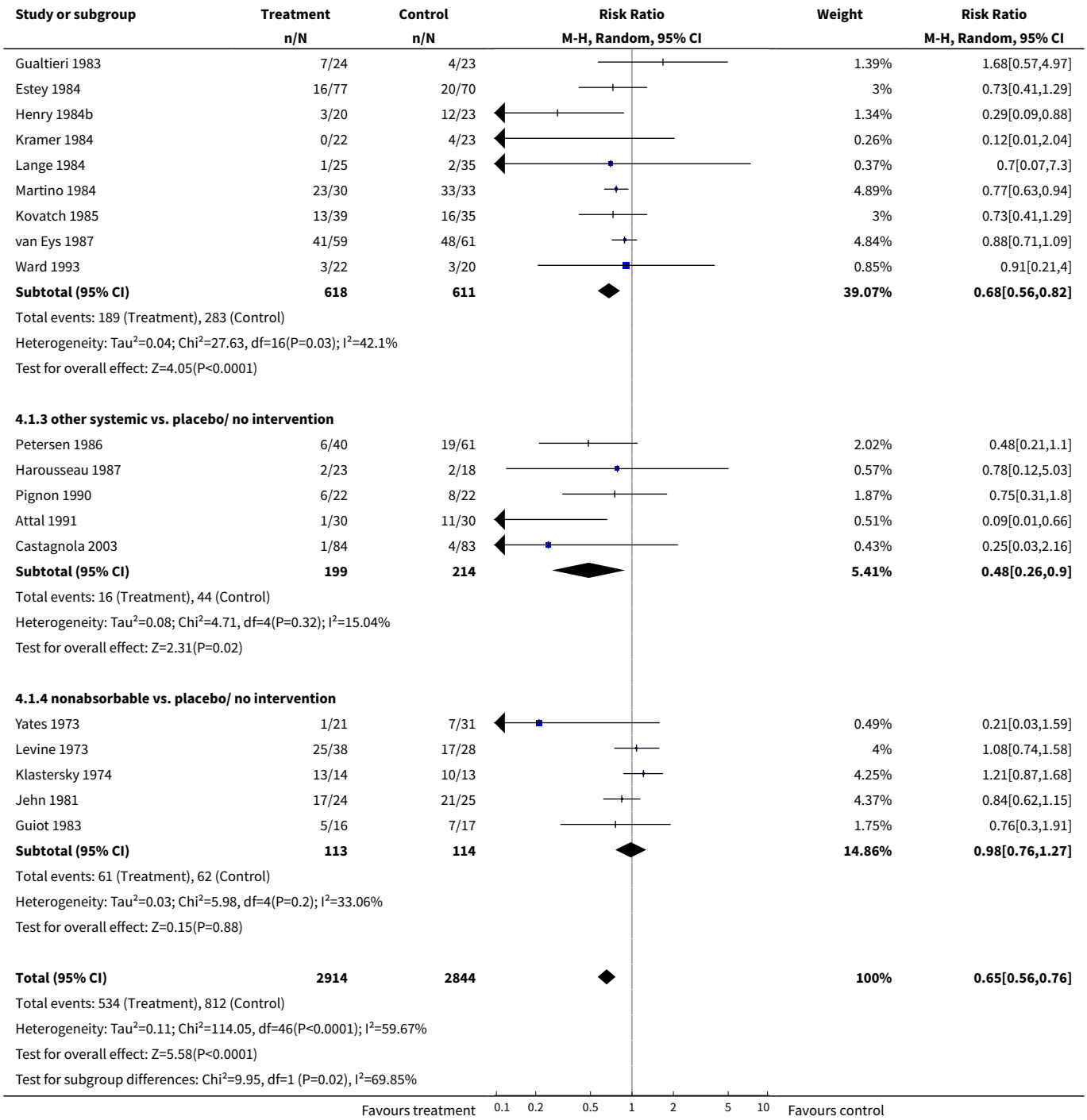
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 drug vs. placebo/ no intervention	48	5758	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.56, 0.76]
1.1 quinolone vs. placebo/ no intervention	21	3889	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.44, 0.76]
1.2 TMP-SMZ vs. placebo/ no intervention	17	1229	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.56, 0.82]
1.3 other systemic vs. placebo/ no intervention	5	413	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.26, 0.90]
1.4 nonabsorbable vs. placebo/ no intervention	5	227	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.76, 1.27]
2 quinolone vs. TMP-SMZ	10	931	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [1.06, 1.66]
2.1 ciprofloxacin vs. TMP-SMZ	3	431	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [1.01, 1.92]
2.2 ofloxacin vs. TMP-SMZ	3	272	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.68, 1.66]
2.3 norfloxacin vs. TMP-SMZ	3	166	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.44, 1.83]
2.4 nalidixic acid vs. TMP-SMZ	1	62	Risk Ratio (M-H, Fixed, 95% CI)	2.32 [1.36, 3.94]
3 quinolone+other vs. quinolone	7	1236	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.69, 1.42]
3.1 rifampin	3	274	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.32, 3.36]
3.2 penicillins	3	831	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.59, 1.16]
3.3 roxi	1	131	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.83, 1.71]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 TMP-SMZ vs. other	2	152	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.56, 2.07]
5 nonabsorbable vs. systemic	10	862	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.89, 1.49]
6 systemic + nonabsorbable vs systemic	1	63	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.25, 1.15]

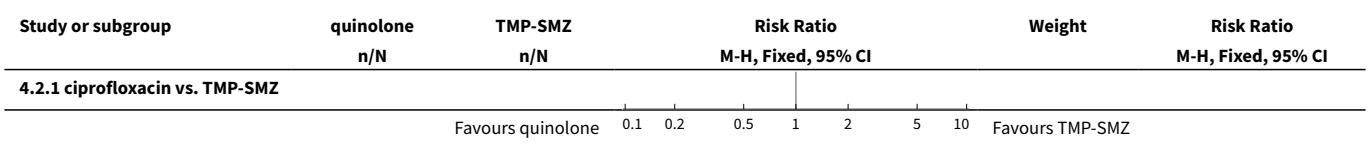
Analysis 4.1. Comparison 4 Clinically documented infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 1 drug vs. placebo/ no intervention.

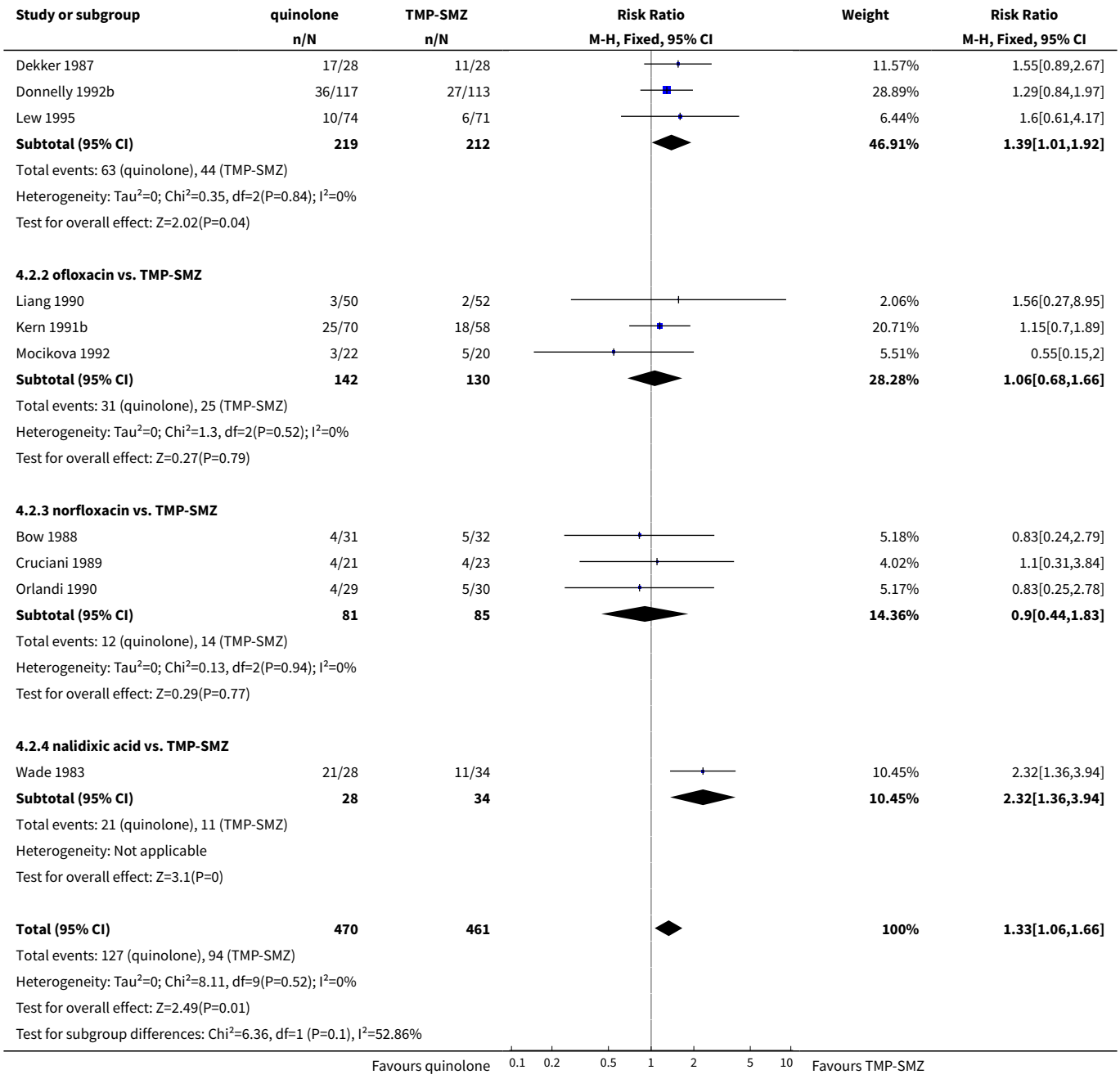
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 quinolone vs. placebo/ no intervention					
Sleijfer 1980	4/53	15/52		1.49%	0.26[0.09,0.74]
Casali 1988	3/30	19/35		1.34%	0.18[0.06,0.56]
Rafecas 1989	0/17	4/18		0.26%	0.12[0.01,2.03]
Lew 1991	0/7	10/11		0.29%	0.07[0,1.05]
Schroeder 1992	1/40	7/35		0.48%	0.13[0.02,0.97]
Sampi 1992	7/38	5/35		1.46%	1.29[0.45,3.69]
Tsutani 1992	7/25	20/25		2.62%	0.35[0.18,0.68]
Yamada 1993	29/52	28/51		4.16%	1.02[0.72,1.44]
Brodsky 1993	3/10	4/13		1.12%	0.98[0.28,3.4]
Maiche 1993	4/29	6/30		1.26%	0.69[0.22,2.19]
Talbot 1993	38/62	41/57		4.64%	0.85[0.66,1.1]
Thomas 2000	2/99	2/52		0.53%	0.53[0.08,3.62]
Nenova 2001	5/36	24/34		1.98%	0.2[0.08,0.46]
Tjan Heijnen 2001	15/82	38/79		3.29%	0.38[0.23,0.63]
Ruiz 2001	4/25	5/25		1.21%	0.8[0.24,2.64]
Lee 2002	19/46	15/49		3.13%	1.35[0.78,2.33]
Lalami 2004	0/25	0/23			Not estimable
Bucaneve 2005	30/339	33/336		3.5%	0.9[0.56,1.44]
Cullen 2005	84/781	119/784		4.61%	0.71[0.55,0.92]
Dickgreber 2009	9/99	25/93		2.43%	0.34[0.17,0.69]
Papaiakovou 2010	4/89	3/68		0.87%	1.02[0.24,4.4]
Subtotal (95% CI)	**1984**	**1905**		**40.66%**	**0.58[0.44,0.76]**
Total events: 268 (Treatment), 423 (Control)					
Heterogeneity: Tau^2=0.19; Chi^2=57.14, df=19(P<0.0001); I^2=66.75%					
Test for overall effect: Z=3.91(P<0.0001)					
4.1.2 TMP-SMZ vs. placebo/ no intervention					
Enno 1978	2/14	4/16		0.8%	0.57[0.12,2.66]
Gurwith 1979	11/59	21/52		2.75%	0.46[0.25,0.86]
Dekker 1981	7/26	11/26		2.18%	0.64[0.29,1.38]
Weiser 1981	7/14	8/15		2.43%	0.94[0.46,1.9]
Kauffman 1983	5/27	20/26		2.05%	0.24[0.11,0.55]
Pizzo 1983	14/77	24/73		2.98%	0.55[0.31,0.98]
Inoue 1983	33/51	43/51		4.74%	0.77[0.61,0.97]
de Jongh 1983	3/32	10/29		1.21%	0.27[0.08,0.89]



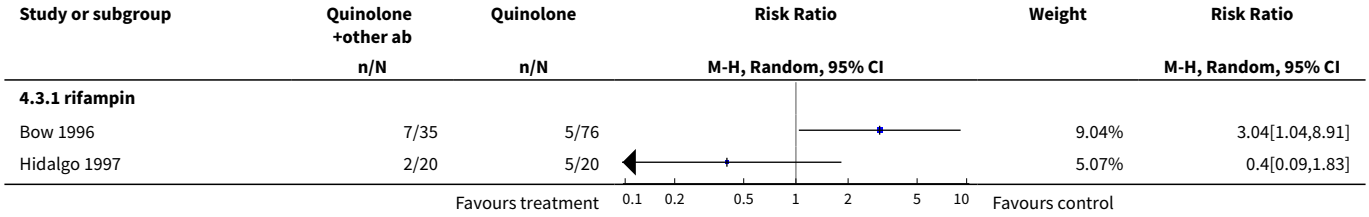


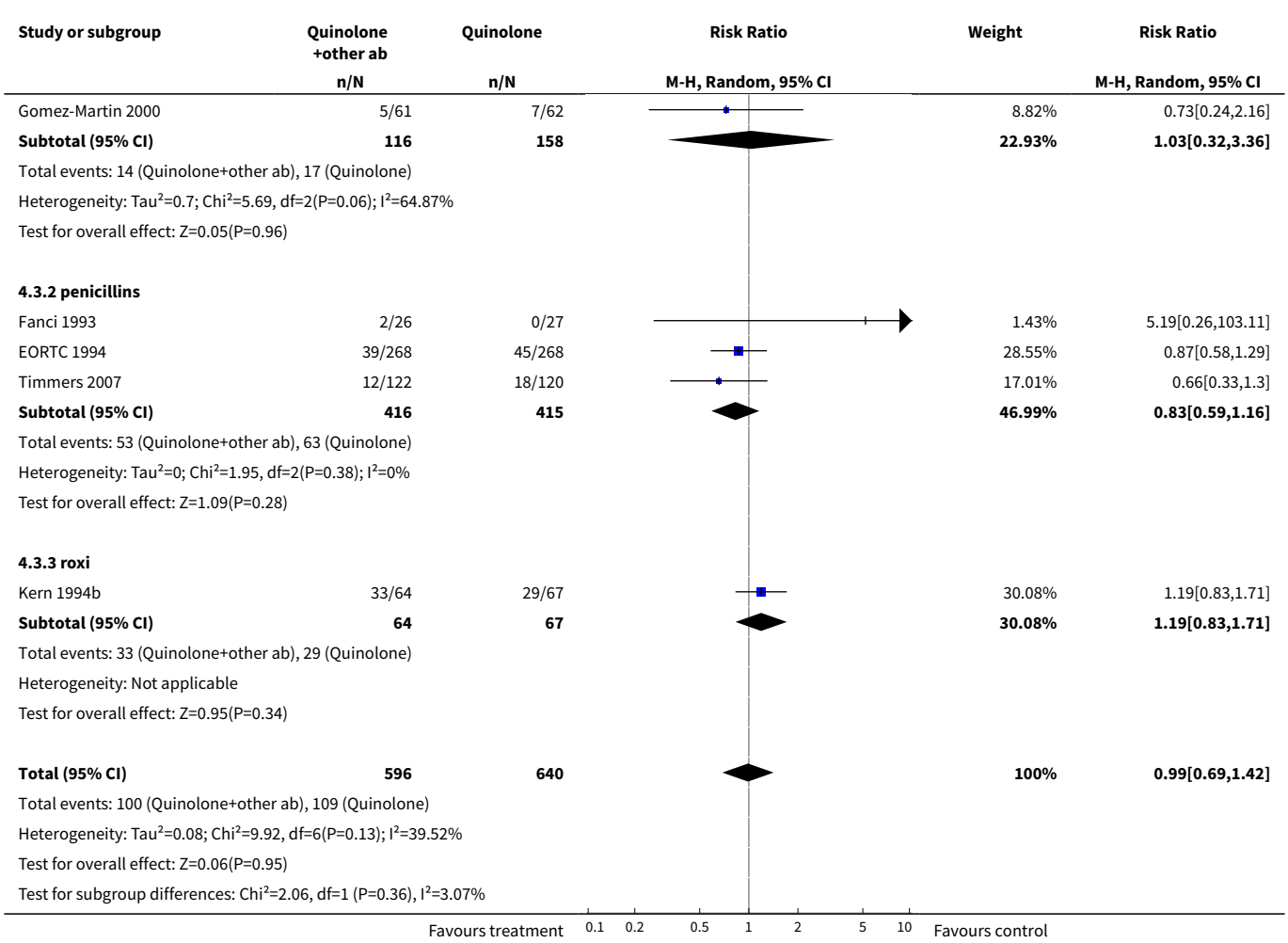
Analysis 4.2. Comparison 4 Clinically documented infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 2 quinolone vs. TMP-SMZ.



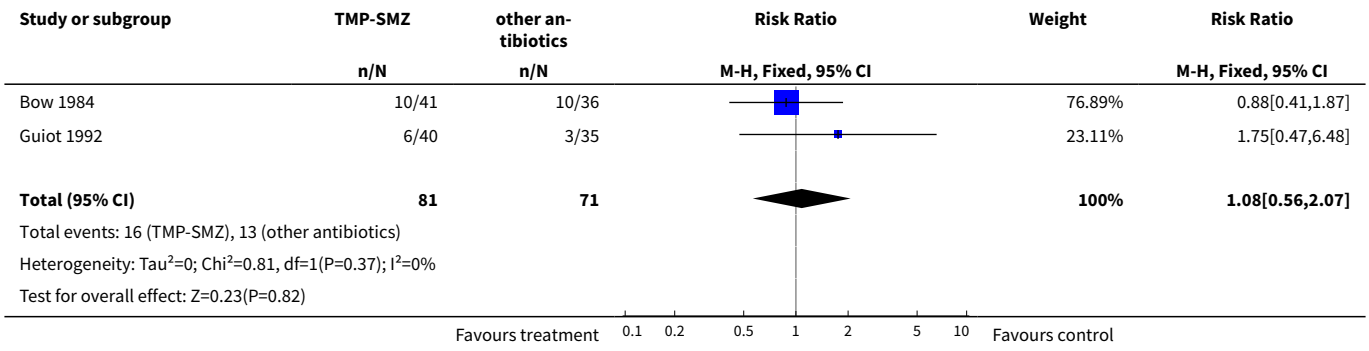


Analysis 4.3. Comparison 4 Clinically documented infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 3 quinolone+other vs. quinolone.

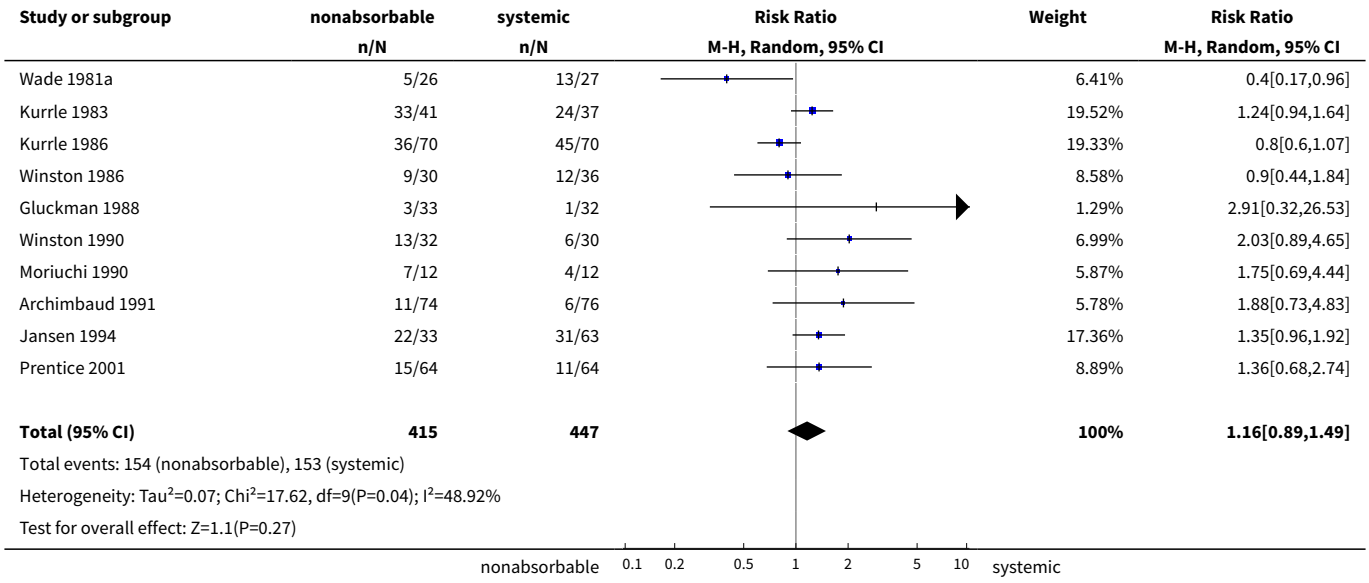




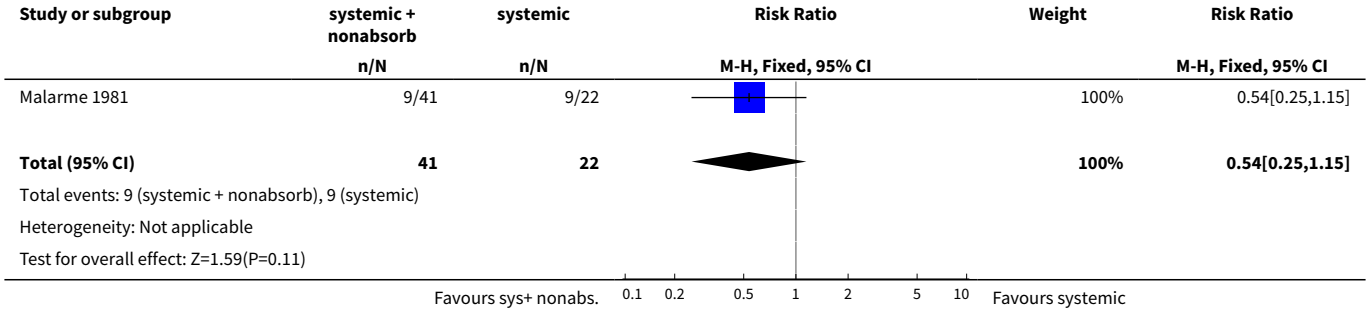
Analysis 4.4. Comparison 4 Clinically documented infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 4 TMP-SMZ vs. other.



Analysis 4.5. Comparison 4 Clinically documented infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 5 nonabsorbable vs. systemic.



Analysis 4.6. Comparison 4 Clinically documented infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 6 systemic + nonabsorbable vs systemic.



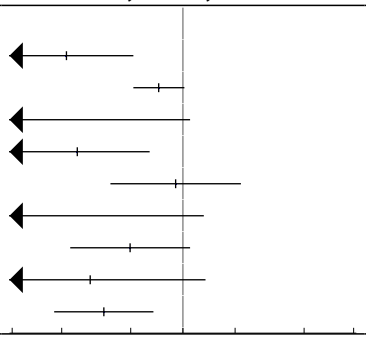
Comparison 5. Microbiologically documented infection, prophylaxis versus placebo or no intervention or other antibiotic

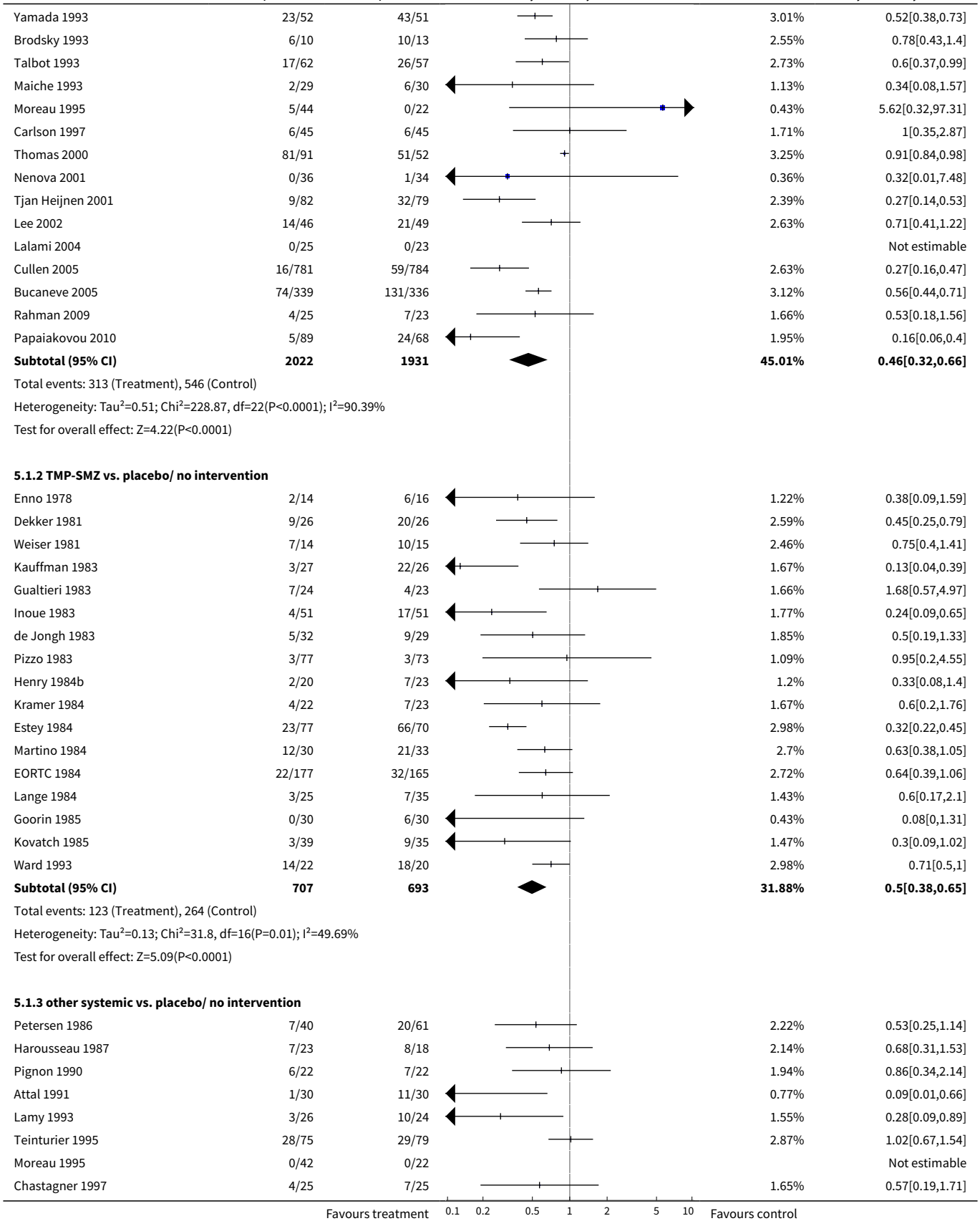
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 drug vs. placebo/ no intervention	53	6383	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.42, 0.62]
1.1 quinolone vs. placebo/ no intervention	24	3953	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.32, 0.66]
1.2 TMP-SMZ vs. placebo/ no intervention	17	1400	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.38, 0.65]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 other systemic vs. placebo/ no intervention	10	882	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.45, 0.87]
1.4 nonabsorbable vs. placebo/ no intervention	3	148	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.25, 2.09]
2 quinolone vs. TMP-SMZ	11	1019	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.56, 1.01]
2.1 ciprofloxacin vs. TMP-SMZ	4	519	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.44, 1.10]
2.2 ofloxacin vs. TMP-SMZ	3	272	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.24, 1.21]
2.3 norfloxacin vs. TMP-SMZ	3	166	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.55, 1.31]
2.4 nalidixic acid vs. TMP-SMZ	1	62	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.82, 1.80]
3 quinolone+other vs. quinolone	9	1360	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.55, 1.11]
3.1 rifampin	3	274	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.21, 0.84]
3.2 penicillins	4	871	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.49, 1.50]
3.3 roxi	1	131	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.58, 1.38]
3.4 vancomycin	1	84	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.48, 1.87]
4 TMP-SMZ vs. other	3	205	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.71, 1.96]
5 nonabsorbable vs. systemic	9	712	Risk Ratio (M-H, Random, 95% CI)	1.49 [1.17, 1.91]
6 systemic + nonabsorbable vs systemic	2	103	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.01, 2.65]

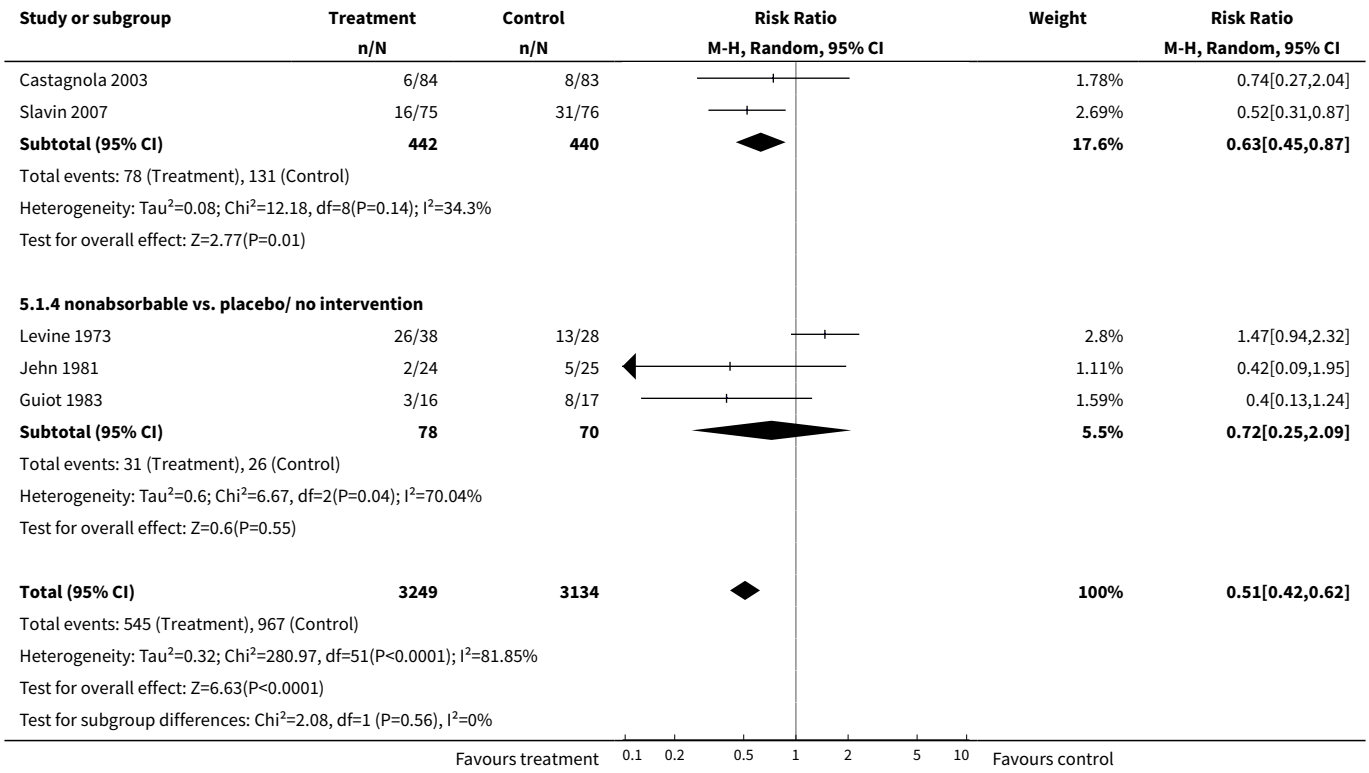
Analysis 5.1. Comparison 5 Microbiologically documented infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 1 drug vs. placebo/ no intervention.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.1.1 quinolone vs. placebo/ no intervention					
Sleijfer 1980	5/53	23/52		1.99%	0.21[0.09,0.52]
Karp 1987	20/35	26/33		2.99%	0.73[0.52,1.02]
Hartlapp 1987	0/21	7/21		0.44%	0.07[0,1.1]
Casali 1988	4/30	19/35		1.86%	0.25[0.09,0.64]
Rafecas 1989	6/17	7/18		2.03%	0.91[0.38,2.16]
Lew 1991	0/7	8/11		0.47%	0.09[0.01,1.32]
Sampi 1992	7/38	13/35		2.15%	0.5[0.22,1.1]
Schroeder 1992	2/40	6/35		1.12%	0.29[0.06,1.35]
Tsutani 1992	7/25	20/25		2.41%	0.35[0.18,0.68]

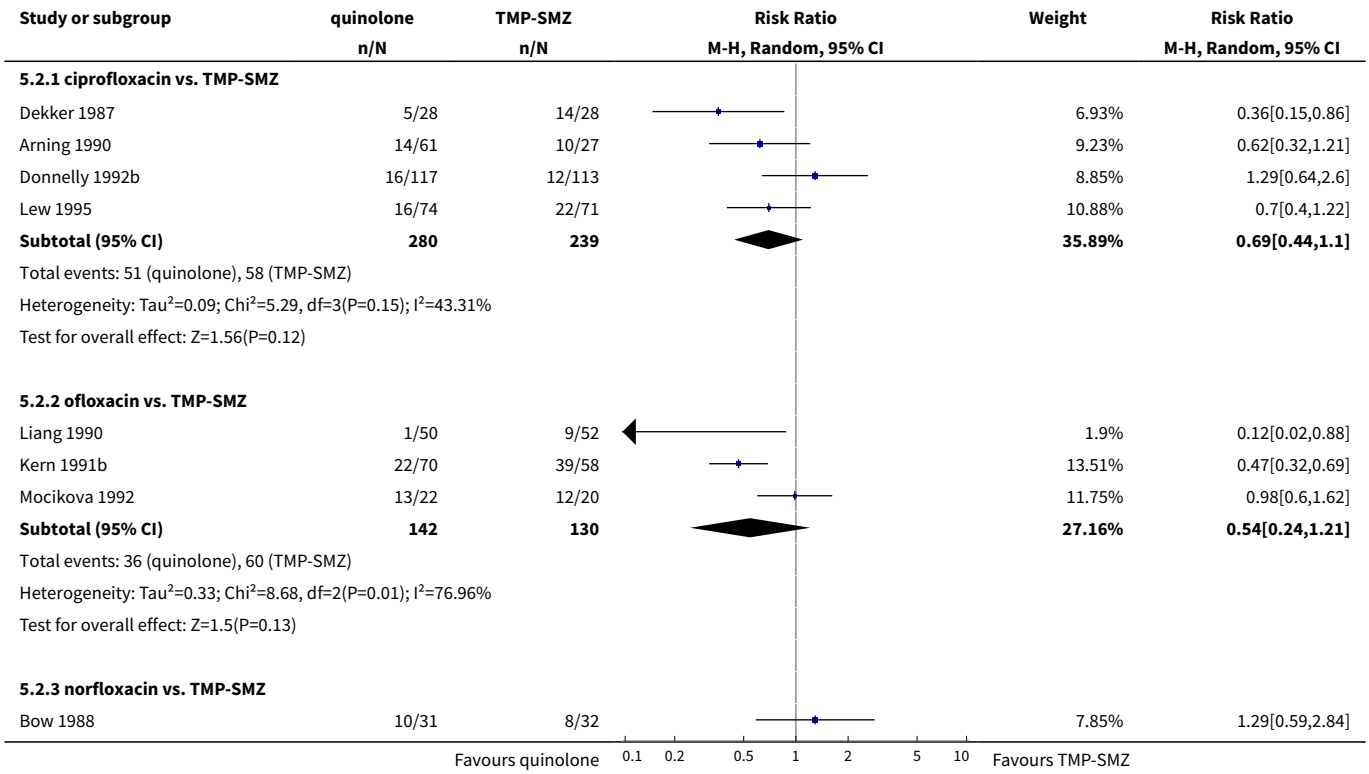


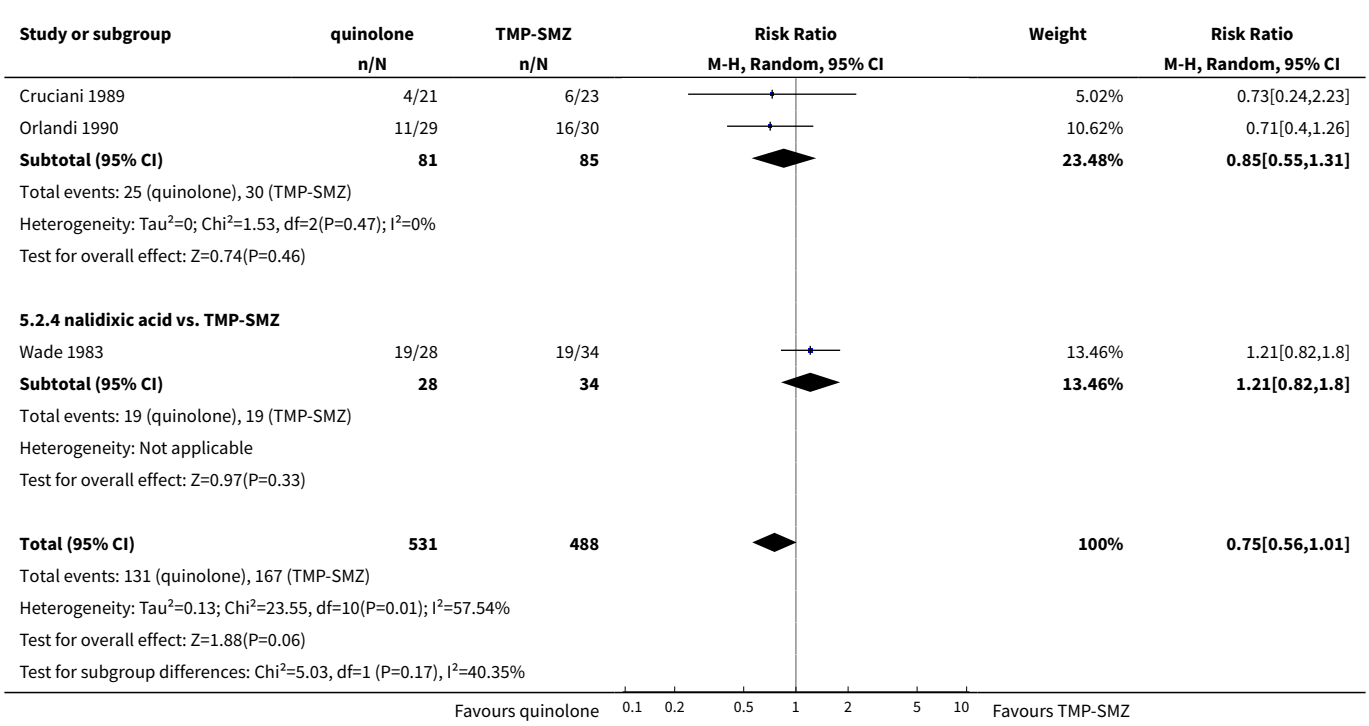


Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Yamada 1993	23/52	43/51		3.01%	0.52[0.38,0.73]
Brodsky 1993	6/10	10/13		2.55%	0.78[0.43,1.4]
Talbot 1993	17/62	26/57		2.73%	0.6[0.37,0.99]
Maiche 1993	2/29	6/30		1.13%	0.34[0.08,1.57]
Moreau 1995	5/44	0/22		0.43%	5.62[0.32,97.31]
Carlson 1997	6/45	6/45		1.71%	1[0.35,2.87]
Thomas 2000	81/91	51/52		3.25%	0.91[0.84,0.98]
Nenova 2001	0/36	1/34		0.36%	0.32[0.01,7.48]
Tjan Heijnen 2001	9/82	32/79		2.39%	0.27[0.14,0.53]
Lee 2002	14/46	21/49		2.63%	0.71[0.41,1.22]
Lalami 2004	0/25	0/23			Not estimable
Cullen 2005	16/781	59/784		2.63%	0.27[0.16,0.47]
Bucaneve 2005	74/339	131/336		3.12%	0.56[0.44,0.71]
Rahman 2009	4/25	7/23		1.66%	0.53[0.18,1.56]
Papaiakovou 2010	5/89	24/68		1.95%	0.16[0.06,0.4]
Subtotal (95% CI)	**2022**	**1931**		**45.01%**	**0.46[0.32,0.66]**
Total events: 313 (Treatment), 546 (Control)					
Heterogeneity: Tau^2=0.51; Chi^2=228.87, df=22(P<0.0001); I^2=90.39%					
Test for overall effect: Z=4.22(P<0.0001)					
5.1.2 TMP-SMZ vs. placebo/ no intervention					
Enno 1978	2/14	6/16		1.22%	0.38[0.09,1.59]
Dekker 1981	9/26	20/26		2.59%	0.45[0.25,0.79]
Weiser 1981	7/14	10/15		2.46%	0.75[0.4,1.41]
Kauffman 1983	3/27	22/26		1.67%	0.13[0.04,0.39]
Gualtieri 1983	7/24	4/23		1.66%	1.68[0.57,4.97]
Inoue 1983	4/51	17/51		1.77%	0.24[0.09,0.65]
de Jongh 1983	5/32	9/29		1.85%	0.5[0.19,1.33]
Pizzo 1983	3/77	3/73		1.09%	0.95[0.2,4.55]
Henry 1984b	2/20	7/23		1.2%	0.33[0.08,1.4]
Kramer 1984	4/22	7/23		1.67%	0.6[0.2,1.76]
Estey 1984	23/77	66/70		2.98%	0.32[0.22,0.45]
Martino 1984	12/30	21/33		2.7%	0.63[0.38,1.05]
EORTC 1984	22/177	32/165		2.72%	0.64[0.39,1.06]
Lange 1984	3/25	7/35		1.43%	0.6[0.17,2.1]
Goorin 1985	0/30	6/30		0.43%	0.08[0,1.31]
Kovatch 1985	3/39	9/35		1.47%	0.3[0.09,1.02]
Ward 1993	14/22	18/20		2.98%	0.71[0.5,1]
Subtotal (95% CI)	**707**	**693**		**31.88%**	**0.5[0.38,0.65]**
Total events: 123 (Treatment), 264 (Control)					
Heterogeneity: Tau^2=0.13; Chi^2=31.8, df=16(P=0.01); I^2=49.69%					
Test for overall effect: Z=5.09(P<0.0001)					
5.1.3 other systemic vs. placebo/ no intervention					
Petersen 1986	7/40	20/61		2.22%	0.53[0.25,1.14]
Harousseau 1987	7/23	8/18		2.14%	0.68[0.31,1.53]
Pignon 1990	6/22	7/22		1.94%	0.86[0.34,2.14]
Attal 1991	1/30	11/30		0.77%	0.09[0.01,0.66]
Lamy 1993	3/26	10/24		1.55%	0.28[0.09,0.89]
Teinturier 1995	28/75	29/79		2.87%	1.02[0.67,1.54]
Moreau 1995	0/42	0/22			Not estimable
Chastagner 1997	4/25	7/25		1.65%	0.57[0.19,1.71]

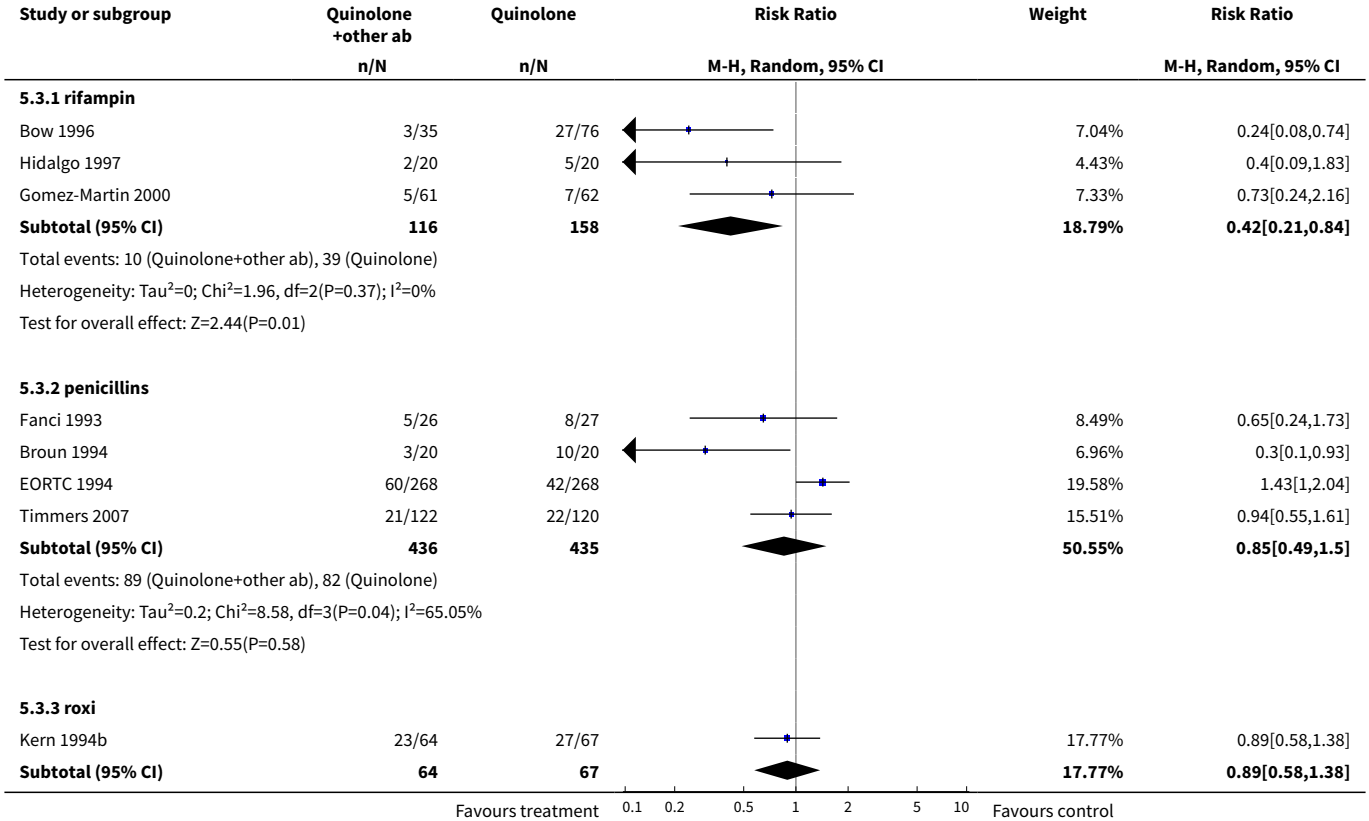


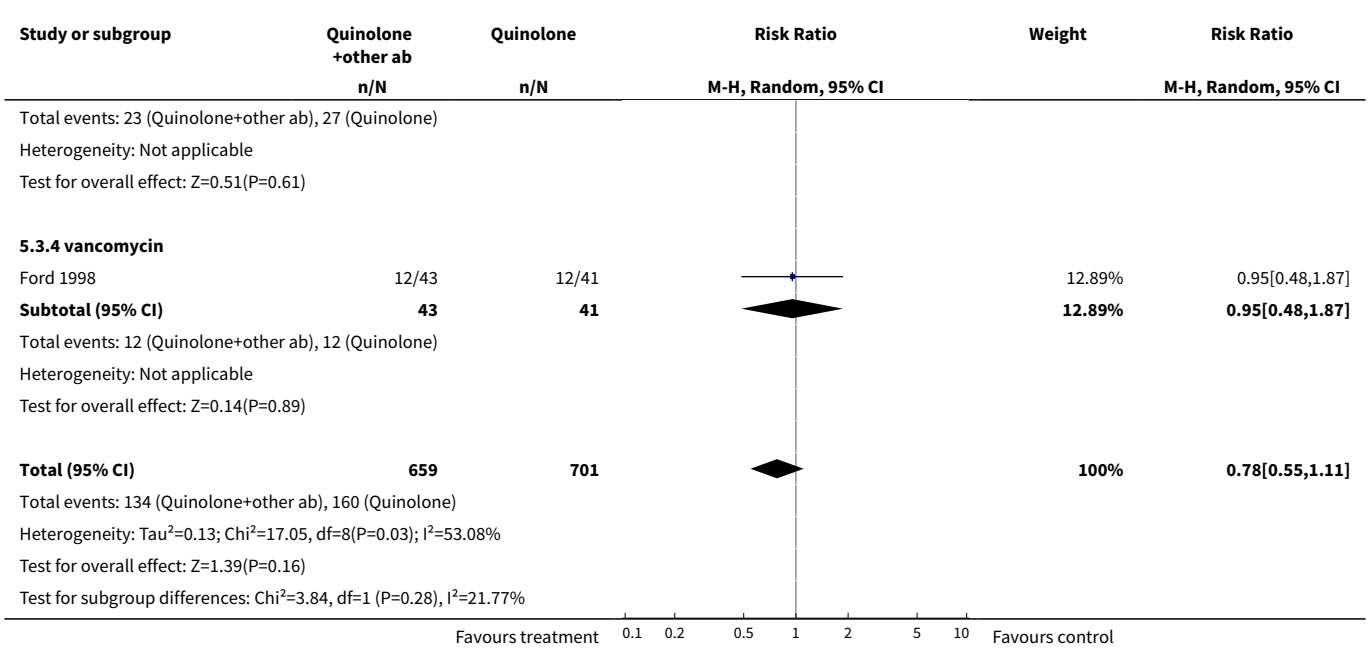
Analysis 5.2. Comparison 5 Microbiologically documented infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 2 quinolone vs. TMP-SMZ.



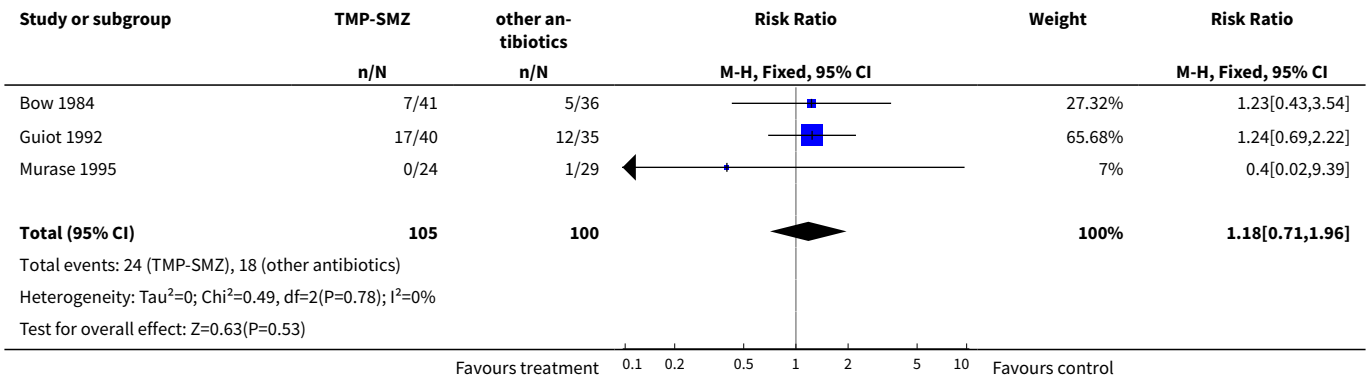


Analysis 5.3. Comparison 5 Microbiologically documented infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 3 quinolone+other vs. quinolone.

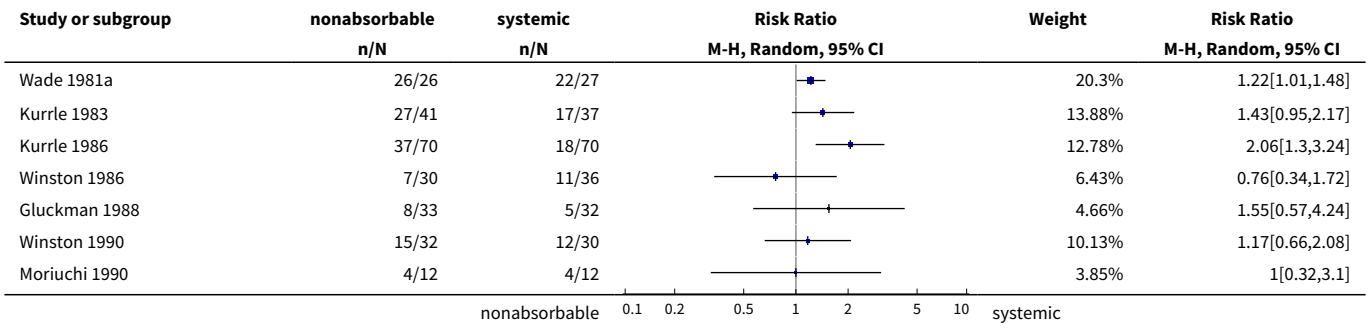


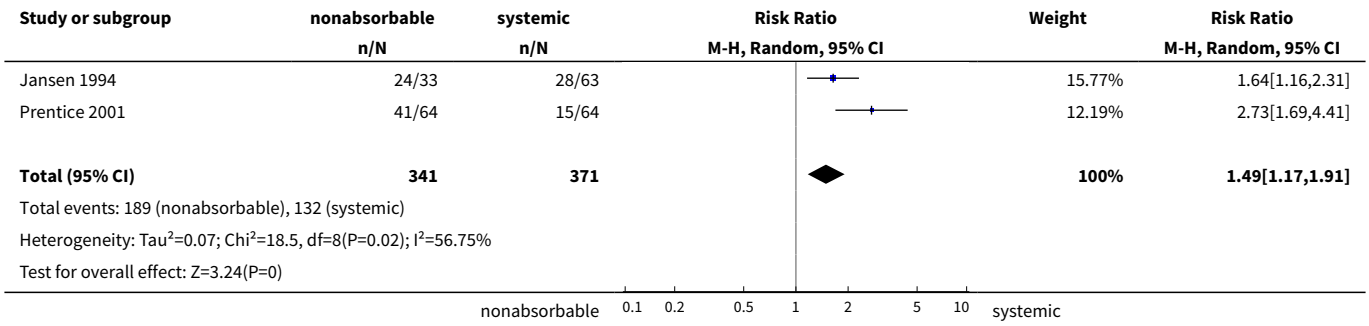


Analysis 5.4. Comparison 5 Microbiologically documented infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 4 TMP-SMZ vs. other.

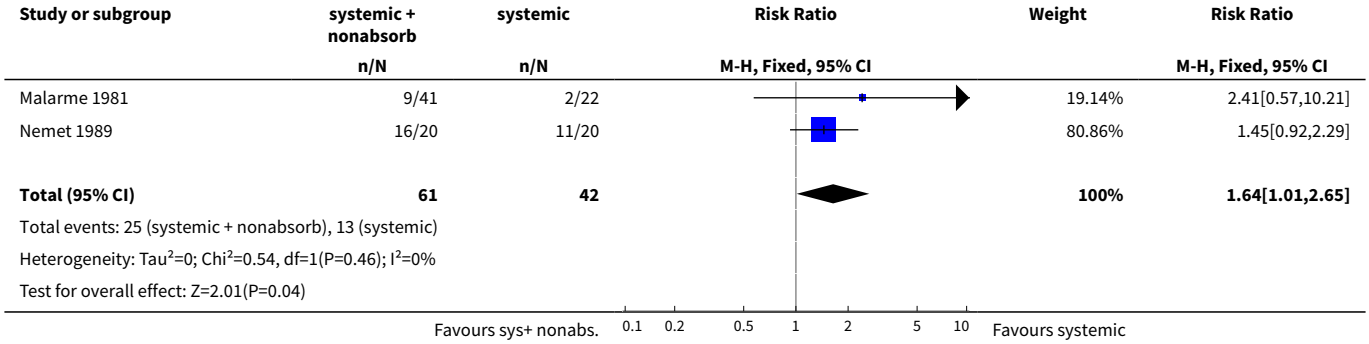


Analysis 5.5. Comparison 5 Microbiologically documented infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 5 nonabsorbable vs. systemic.





Analysis 5.6. Comparison 5 Microbiologically documented infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 6 systemic + nonabsorbable vs systemic.



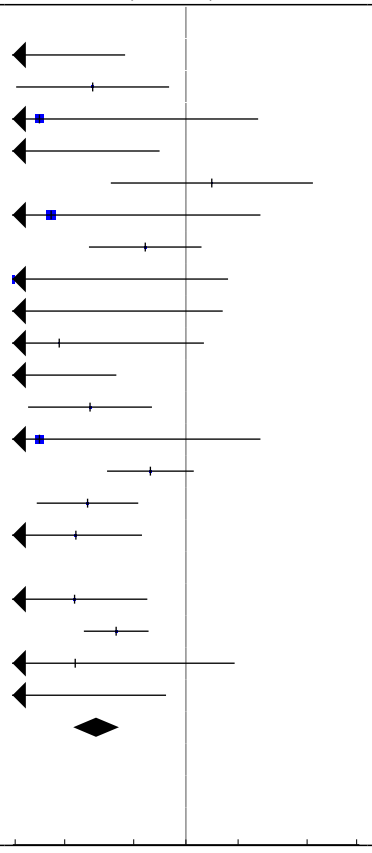
Comparison 6. Gram-negative infection, prophylaxis versus placebo or no intervention or other antibiotic

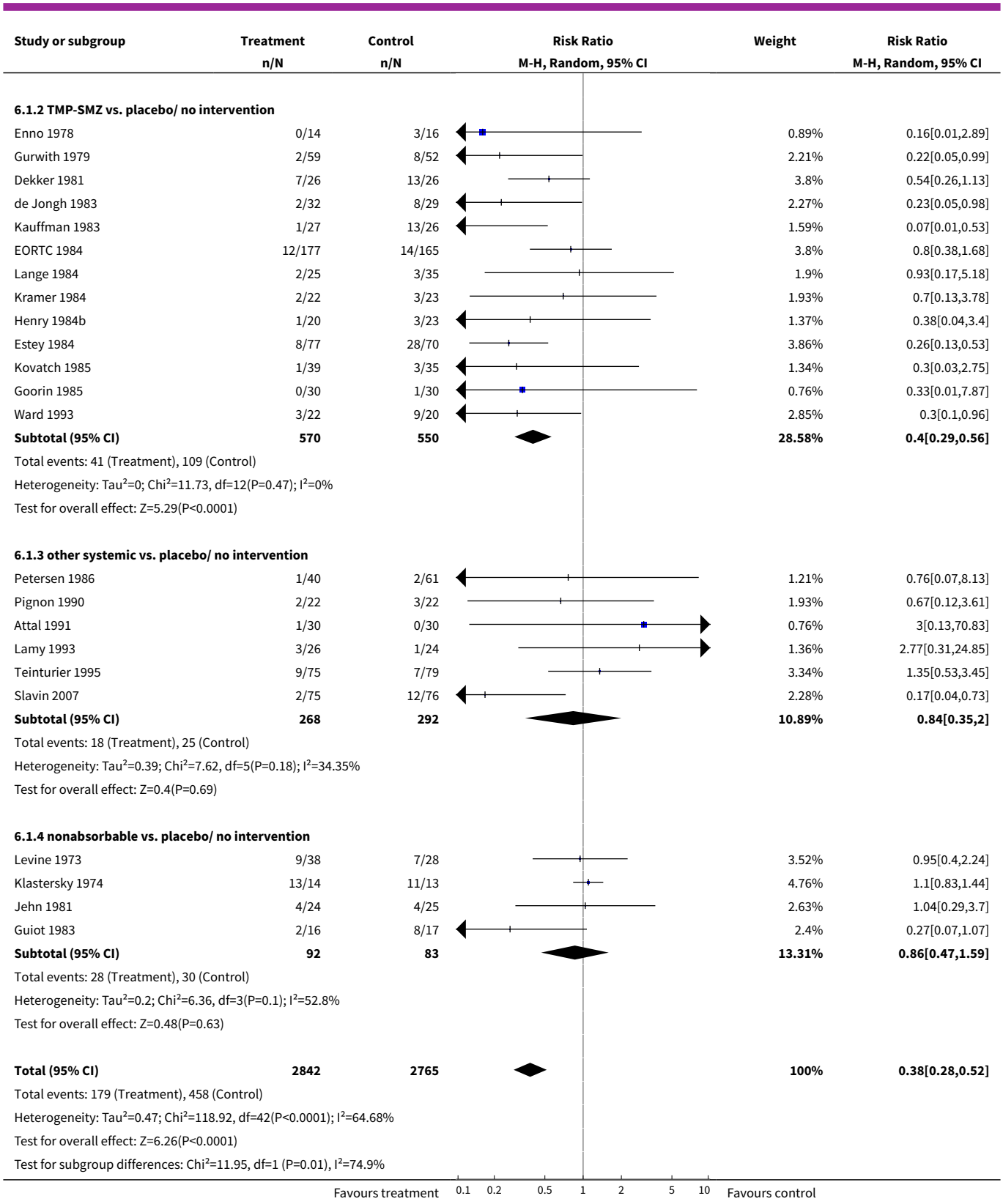
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 drug vs. placebo/ no intervention	44	5607	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.28, 0.52]
1.1 quinolone vs. placebo/ no intervention	21	3752	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.22, 0.41]
1.2 TMP-SMZ vs. placebo/ no intervention	13	1120	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.29, 0.56]
1.3 other systemic vs. placebo/ no intervention	6	560	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.35, 2.00]
1.4 nonabsorbable vs. placebo/ no intervention	4	175	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.47, 1.59]
2 quinolone vs. TMP-SMZ	9	915	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.13, 0.36]
2.1 ciprofloxacin vs. TMP-SMZ	4	519	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.03, 0.43]
2.2 ofloxacin vs. TMP-SMZ	2	230	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.05, 0.35]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 norfloxacin vs. TMP-SMZ	3	166	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.22, 0.93]
3 quinolone+other vs. quinolone	7	740	Risk Ratio (M-H, Fixed, 95% CI)	2.58 [1.21, 5.52]
3.1 rifampin	3	274	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.29, 3.14]
3.2 penicillins	3	335	Risk Ratio (M-H, Fixed, 95% CI)	6.37 [1.16, 35.01]
3.3 roxi	1	131	Risk Ratio (M-H, Fixed, 95% CI)	4.19 [0.92, 18.98]
4 TMP-SMZ vs. other	3	205	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.41, 3.70]
5 nonabsorbable vs. systemic	11	950	Risk Ratio (M-H, Fixed, 95% CI)	2.15 [1.54, 3.00]
6 systemic + nonabsorbable vs systemic	2	103	Risk Ratio (M-H, Fixed, 95% CI)	2.90 [1.05, 8.02]

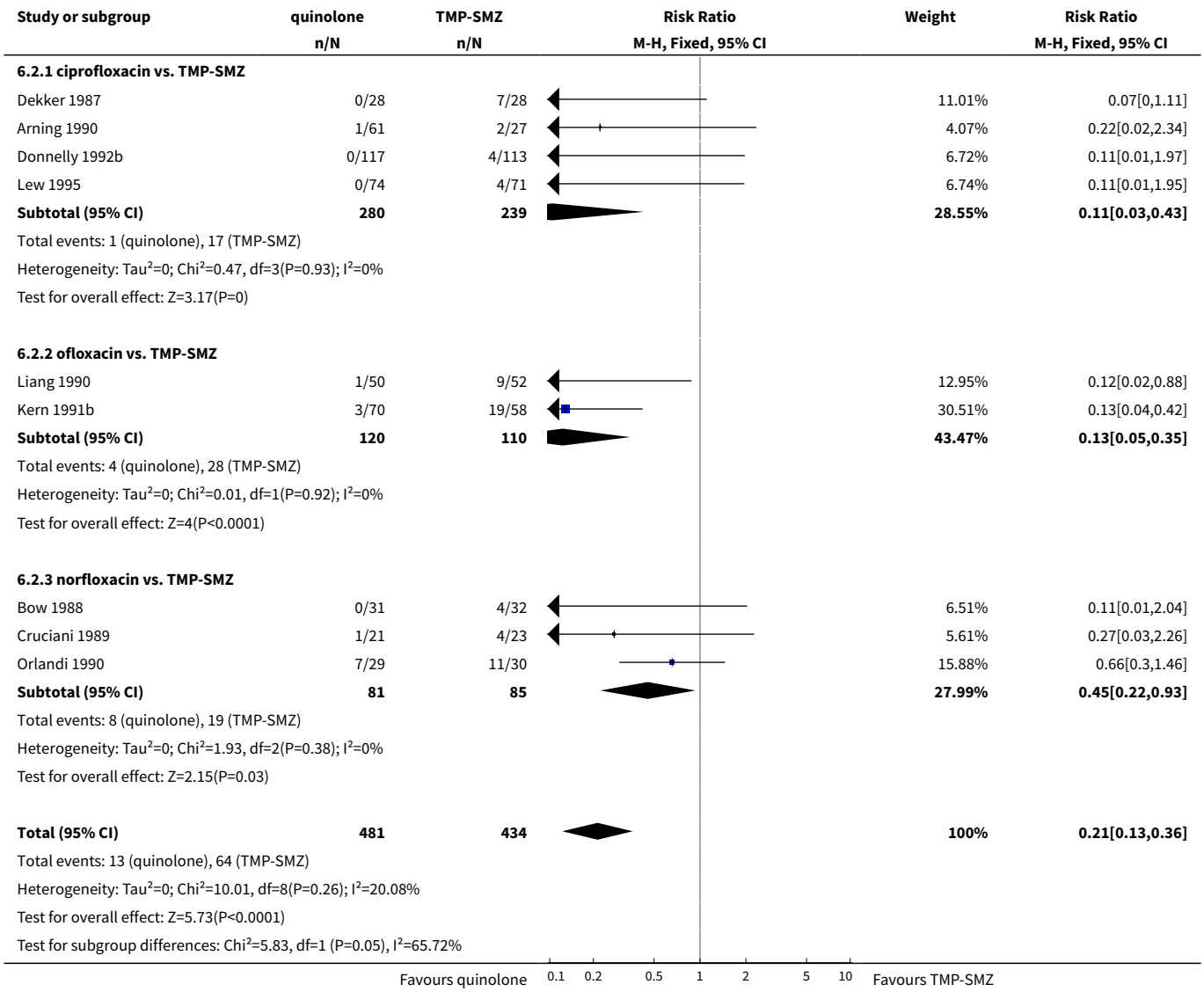
Analysis 6.1. Comparison 6 Gram-negative infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 1 drug vs. placebo/ no intervention.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 quinolone vs. placebo/ no intervention					
Sleijfer 1980	2/53	18/52		2.37%	0.11[0.03,0.45]
Karp 1987	4/35	13/33		3.16%	0.29[0.11,0.8]
Hartlapp 1987	0/21	3/21		0.88%	0.14[0.01,2.61]
Casali 1988	1/30	12/35		1.57%	0.1[0.01,0.7]
Rafecas 1989	4/17	3/18		2.49%	1.41[0.37,5.4]
Lew 1991	0/7	4/11		0.94%	0.17[0.01,2.69]
Tsutani 1992	7/25	12/25		3.78%	0.58[0.28,1.23]
Schroeder 1992	0/40	4/35		0.89%	0.1[0.01,1.75]
Maiche 1993	0/29	5/30		0.91%	0.09[0.01,1.63]
Brodsky 1993	1/10	7/13		1.63%	0.19[0.03,1.27]
Talbot 1993	2/62	19/57		2.36%	0.1[0.02,0.4]
Yamada 1993	6/52	21/51		3.61%	0.28[0.12,0.64]
Carlson 1997	0/45	3/45		0.86%	0.14[0.01,2.69]
Thomas 2000	19/99	16/52		4.19%	0.62[0.35,1.11]
Tjan Heijnen 2001	9/82	32/79		3.97%	0.27[0.14,0.53]
Lee 2002	5/46	23/49		3.48%	0.23[0.1,0.56]
Lalami 2004	0/25	0/23			Not estimable
Cullen 2005	5/781	22/784		3.27%	0.23[0.09,0.6]
Bucaneve 2005	26/339	65/336		4.5%	0.4[0.26,0.61]
Rahman 2009	1/25	4/23		1.43%	0.23[0.03,1.91]
Papaiakovou 2010	0/89	8/68		0.91%	0.05[0,0.77]
Subtotal (95% CI)	**1912**	**1840**		**47.22%**	**0.3[0.22,0.41]**
Total events: 92 (Treatment), 294 (Control)					
Heterogeneity: Tau^2=0.11; Chi^2=26.75, df=19(P=0.11); I^2=28.97%					
Test for overall effect: Z=7.69(P<0.0001)					

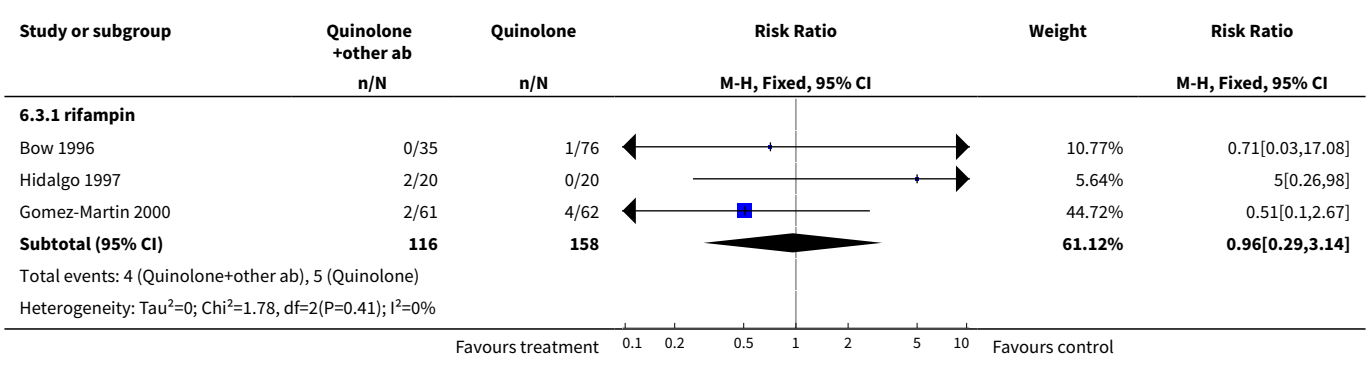


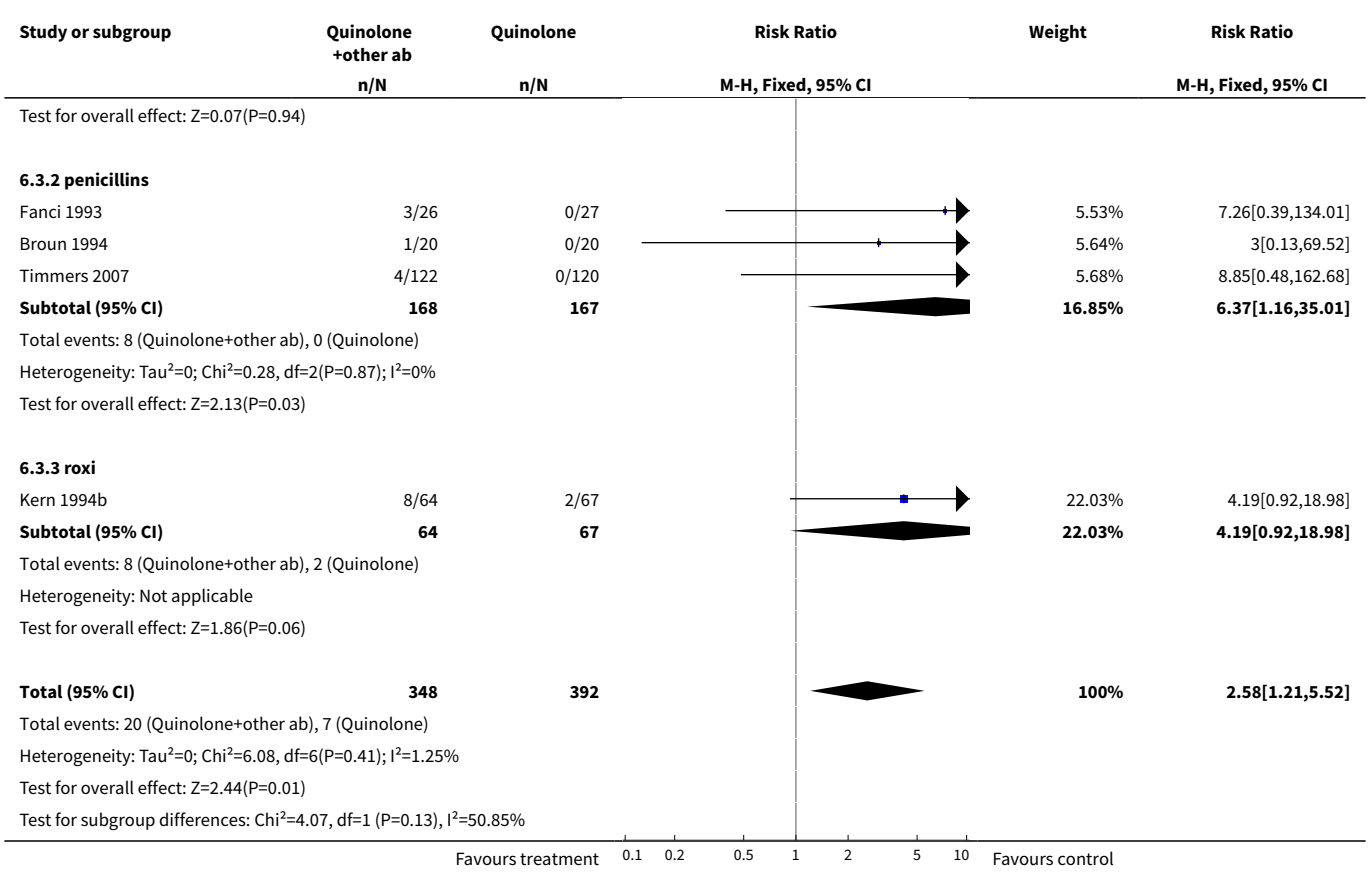


Analysis 6.2. Comparison 6 Gram-negative infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 2 quinolone vs. TMP-SMZ.

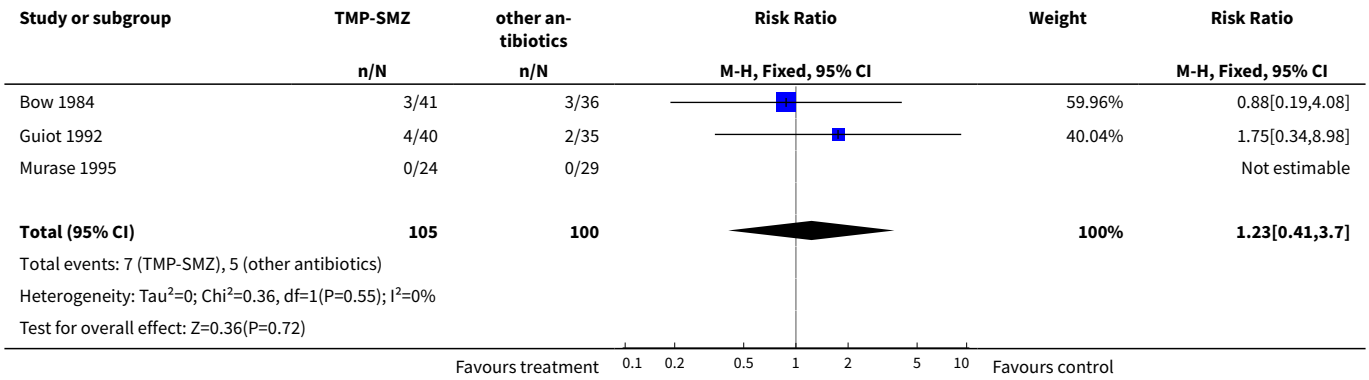


Analysis 6.3. Comparison 6 Gram-negative infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 3 quinolone+other vs. quinolone.



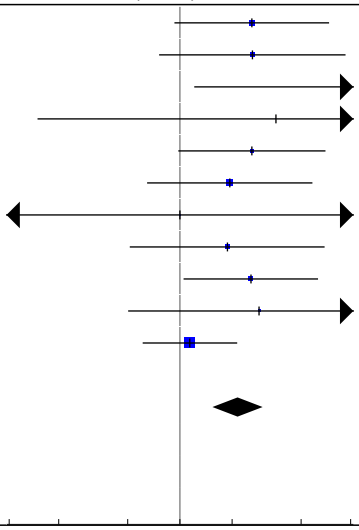


Analysis 6.4. Comparison 6 Gram-negative infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 4 TMP-SMZ vs. other.



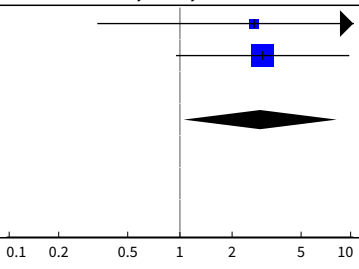
Analysis 6.5. Comparison 6 Gram-negative infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 5 nonabsorbable vs. systemic.

Study or subgroup	nonabsorbable n/N	systemic n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Wade 1981a	10/26	4/27		9.11%	2.6[0.93,7.25]
Watson 1982	9/47	3/41		7.44%	2.62[0.76,9.02]
Kurrle 1983	10/41	1/37		2.44%	9.02[1.21,67.15]
Winston 1986	1/30	0/36		1.06%	3.58[0.15,84.81]
Kurrle 1986	13/70	5/70		11.6%	2.6[0.98,6.91]
Gluckman 1988	8/33	4/32		9.43%	1.94[0.65,5.81]
Moriuchi 1990	1/12	1/12		2.32%	1[0.07,14.21]
Winston 1990	6/32	3/30		7.19%	1.88[0.51,6.83]
Archimbaud 1991	15/74	6/76		13.74%	2.57[1.05,6.26]
Jansen 1994	3/33	2/63		3.19%	2.86[0.5,16.3]
Prentice 2001	16/64	14/64		32.49%	1.14[0.61,2.14]
Total (95% CI)	**462**	**488**		**100%**	**2.15[1.54,3]**
Total events: 92 (nonabsorbable), 43 (systemic)					
Heterogeneity: Tau^2=0; Chi^2=6.97, df=10(P=0.73); I^2=0%					
Test for overall effect: Z=4.48(P<0.0001)					



Analysis 6.6. Comparison 6 Gram-negative infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 6 systemic + nonabsorbable vs systemic.

Study or subgroup	systemic + nonabsorb n/N	systemic n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Malarme 1981	5/41	1/22		30.26%	2.68[0.33,21.55]
Nemet 1989	9/20	3/20		69.74%	3[0.95,9.48]
Total (95% CI)	**61**	**42**		**100%**	**2.9[1.05,8.02]**
Total events: 14 (systemic + nonabsorb), 4 (systemic)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.93); I^2=0%					
Test for overall effect: Z=2.06(P=0.04)					



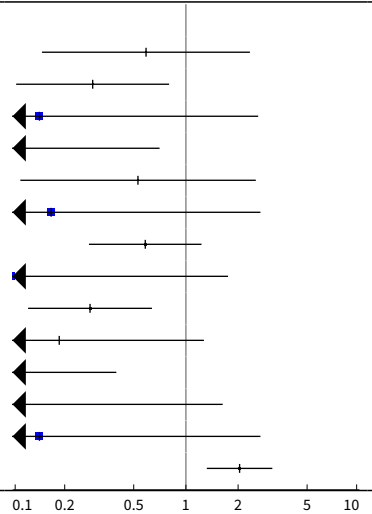
Comparison 7. Gram-positive infection, prophylaxis versus placebo or no intervention or other antibiotic

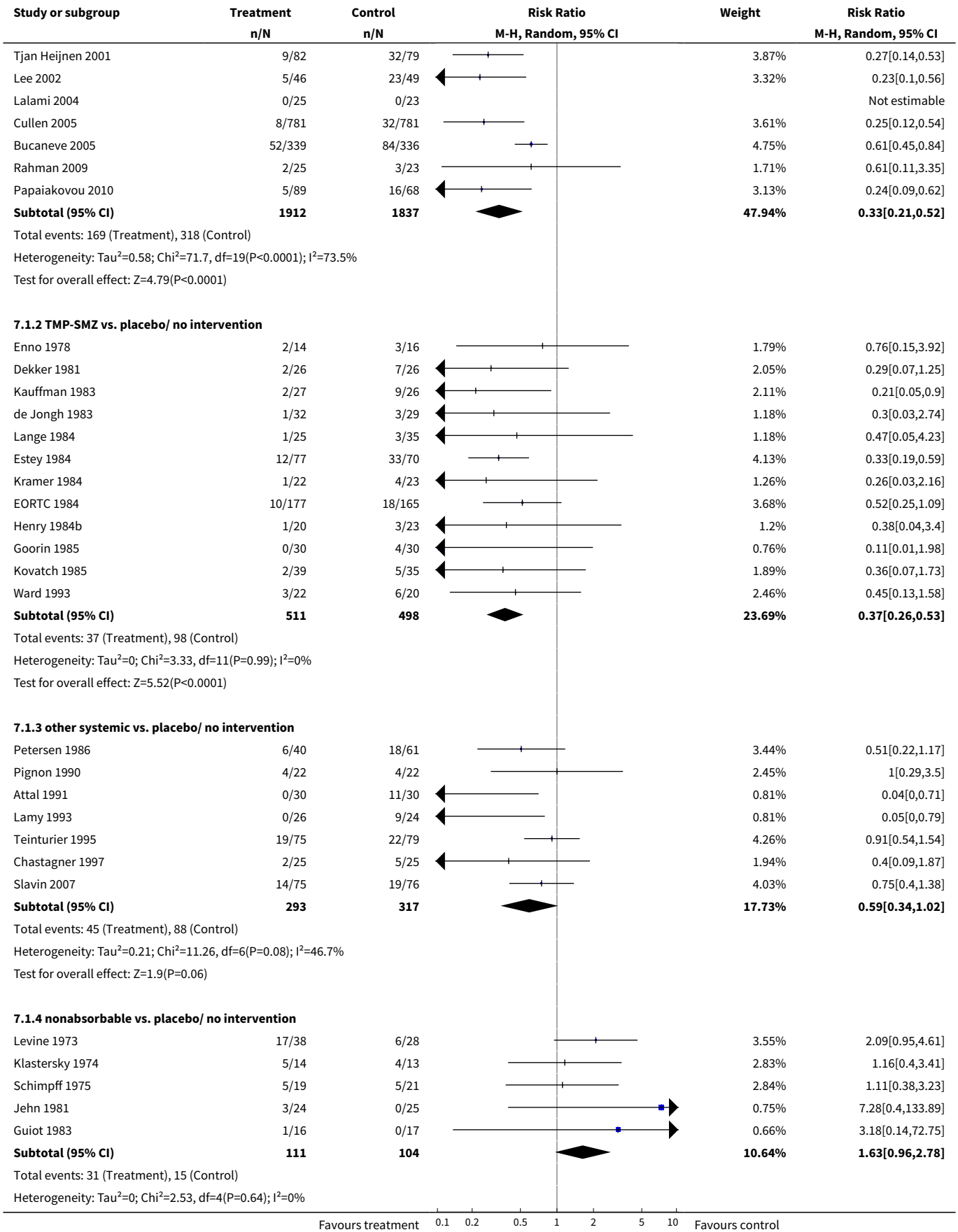
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 drug vs. placebo/ no intervention	45	5583	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.34, 0.59]
1.1 quinolone vs. placebo/ no intervention	21	3749	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.21, 0.52]
1.2 TMP-SMZ vs. placebo/ no intervention	12	1009	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.26, 0.53]

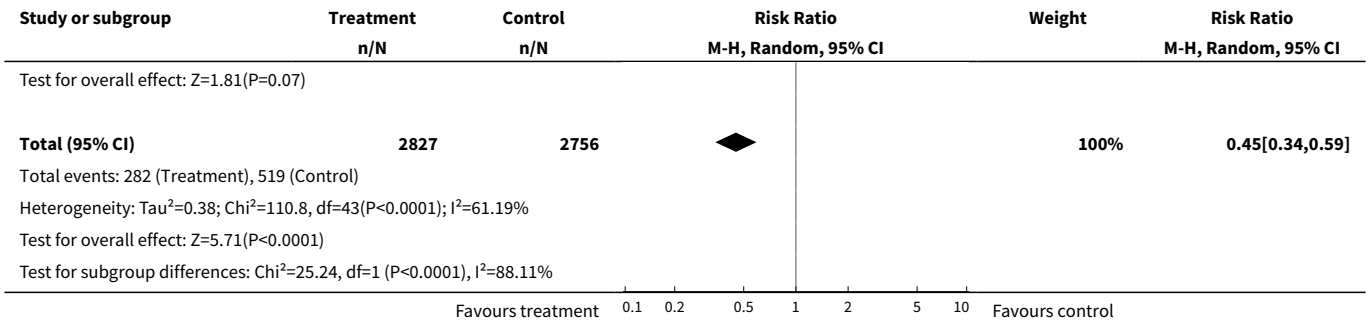
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 other systemic vs. placebo/ no intervention	7	610	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.34, 1.02]
1.4 nonabsorbable vs. placebo/ no intervention	5	215	Risk Ratio (M-H, Random, 95% CI)	1.63 [0.96, 2.78]
2 quinolone vs. TMP-SMZ	9	915	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.60, 1.69]
2.1 ciprofloxacin vs. TMP-SMZ	4	519	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.43, 1.80]
2.2 ofloxacin vs. TMP-SMZ	2	230	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.37, 1.17]
2.3 norfloxacin vs. TMP-SMZ	3	166	Risk Ratio (M-H, Random, 95% CI)	2.07 [0.62, 6.85]
3 quinolone+other vs. quinolone	7	740	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.22, 0.72]
3.1 rifampin	3	274	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.06, 0.38]
3.2 penicillins	3	335	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.33, 1.15]
3.3 roxi	1	131	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.28, 0.99]
4 TMP-SMZ vs. other	3	205	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.53, 2.03]
5 nonabsorbable vs. systemic	10	800	Risk Ratio (M-H, Random, 95% CI)	1.55 [1.06, 2.28]
6 systemic + nonabsorbable vs systemic	2	103	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.49, 2.25]

Analysis 7.1. Comparison 7 Gram-positive infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 1 drug vs. placebo/ no intervention.

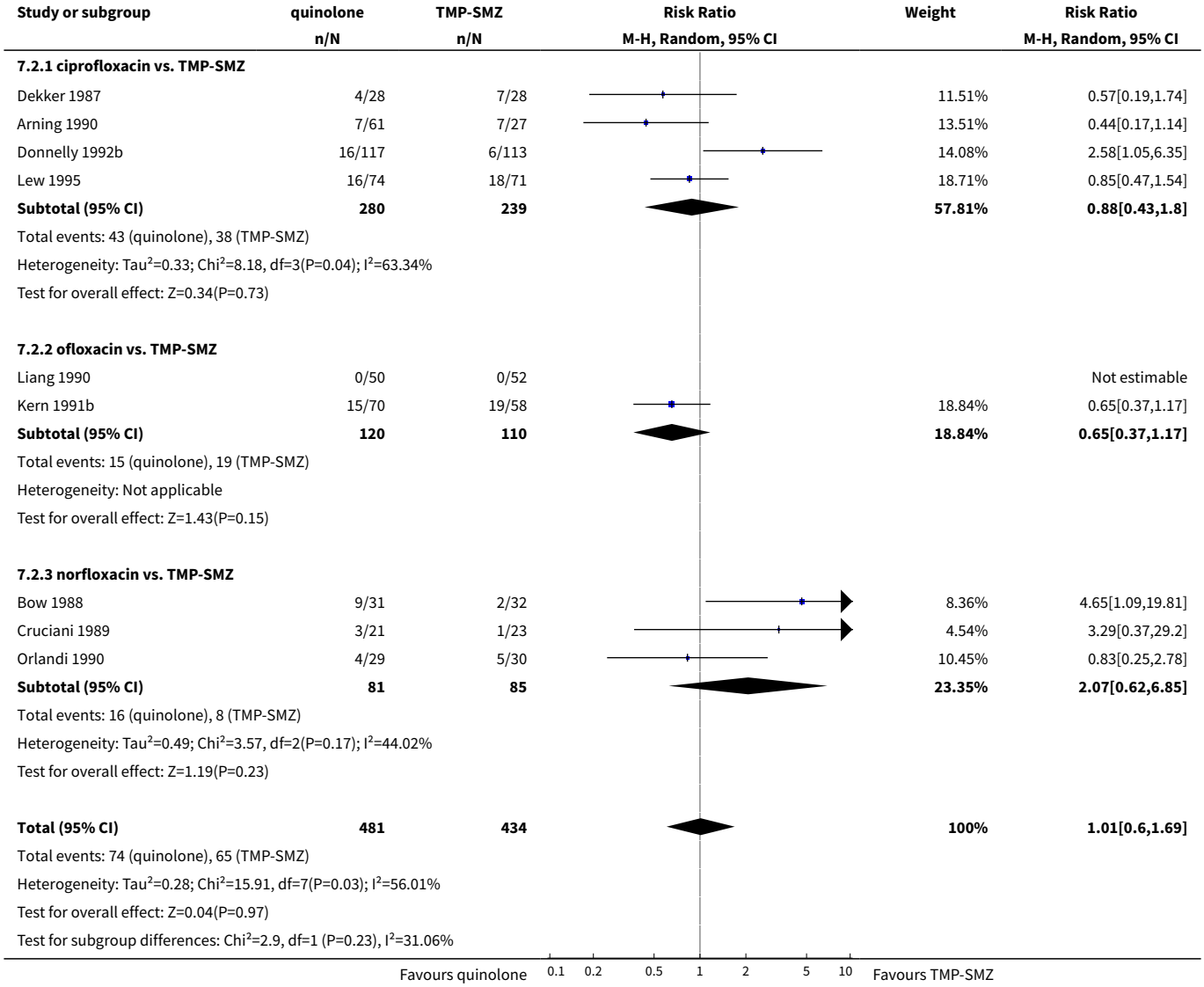
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
7.1.1 quinolone vs. placebo/ no intervention					
Sleijfer 1980	3/53	5/52		2.21%	0.59[0.15,2.34]
Karp 1987	4/35	13/33		2.98%	0.29[0.11,0.8]
Hartlapp 1987	0/21	3/21		0.75%	0.14[0.01,2.61]
Casali 1988	1/30	12/35		1.38%	0.1[0.01,0.7]
Rafecas 1989	2/17	4/18		1.91%	0.53[0.11,2.53]
Lew 1991	0/7	4/11		0.81%	0.17[0.01,2.69]
Tsutani 1992	7/25	12/25		3.66%	0.58[0.28,1.23]
Schroeder 1992	0/40	4/35		0.76%	0.1[0.01,1.75]
Yamada 1993	6/52	21/51		3.47%	0.28[0.12,0.64]
Brodsky 1993	1/10	7/13		1.44%	0.19[0.03,1.27]
Talbot 1993	2/62	19/57		2.15%	0.1[0.02,0.4]
Maiche 1993	0/29	5/30		0.78%	0.09[0.01,1.63]
Carlson 1997	0/45	3/45		0.74%	0.14[0.01,2.69]
Thomas 2000	62/99	16/52		4.48%	2.04[1.32,3.15]





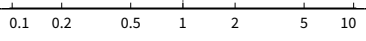


Analysis 7.2. Comparison 7 Gram-positive infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 2 quinolone vs. TMP-SMZ.



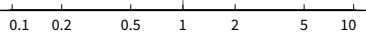
Analysis 7.3. Comparison 7 Gram-positive infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 3 quinolone+other vs. quinolone.

Study or subgroup	Quinolone +other ab n/N	Quinolone n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
7.3.1 rifampin					
Bow 1996	2/35	41/76		11.41%	0.11[0.03,0.41]
Hidalgo 1997	0/20	5/20		3.81%	0.09[0.01,1.54]
Gomez-Martin 2000	2/61	8/62		10.04%	0.25[0.06,1.15]
Subtotal (95% CI)	**116**	**158**		**25.26%**	**0.15[0.06,0.38]**
Total events: 4 (Quinolone+other ab), 54 (Quinolone)					
Heterogeneity: Tau^2=0; Chi^2=0.88, df=2(P=0.64); I^2=0%					
Test for overall effect: Z=3.94(P<0.0001)					
7.3.2 penicillins					
Fanci 1993	6/26	9/27		17.53%	0.69[0.29,1.67]
Broun 1994	2/20	10/20		11.17%	0.2[0.05,0.8]
Timmers 2007	26/122	32/120		24.53%	0.8[0.51,1.26]
Subtotal (95% CI)	**168**	**167**		**53.24%**	**0.61[0.33,1.15]**
Total events: 34 (Quinolone+other ab), 51 (Quinolone)					
Heterogeneity: Tau^2=0.14; Chi^2=3.54, df=2(P=0.17); I^2=43.44%					
Test for overall effect: Z=1.53(P=0.13)					
7.3.3 roxi					
Kern 1994b	11/64	22/67		21.5%	0.52[0.28,0.99]
Subtotal (95% CI)	**64**	**67**		**21.5%**	**0.52[0.28,0.99]**
Total events: 11 (Quinolone+other ab), 22 (Quinolone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.99(P=0.05)					
Total (95% CI)	**348**	**392**		**100%**	**0.4[0.22,0.72]**
Total events: 49 (Quinolone+other ab), 127 (Quinolone)					
Heterogeneity: Tau^2=0.32; Chi^2=14.75, df=6(P=0.02); I^2=59.31%					
Test for overall effect: Z=3.05(P=0)					
Test for subgroup differences: Chi^2=6.39, df=1 (P=0.04), I^2=68.69%					



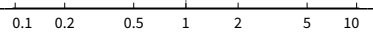
Analysis 7.4. Comparison 7 Gram-positive infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 4 TMP-SMZ vs. other.

Study or subgroup	TMP-SMZ n/N	other antibiotics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bow 1984	2/41	2/36		16.27%	0.88[0.13,5.92]
Guiot 1992	12/40	9/35		73.32%	1.17[0.56,2.43]
Murase 1995	0/24	1/29		10.41%	0.4[0.02,9.39]
Total (95% CI)	**105**	**100**		**100%**	**1.04[0.53,2.03]**
Total events: 14 (TMP-SMZ), 12 (other antibiotics)					
Heterogeneity: Tau^2=0; Chi^2=0.48, df=2(P=0.79); I^2=0%					
Test for overall effect: Z=0.11(P=0.91)					



Analysis 7.5. Comparison 7 Gram-positive infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 5 nonabsorbable vs. systemic.

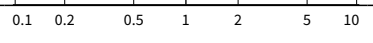
Study or subgroup	nonabsorbable n/N	systemic n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Wade 1981a	9/26	5/27		8.99%	1.87[0.72,4.84]
Watson 1982	26/47	11/41		13.92%	2.06[1.17,3.64]
Kurrle 1983	17/41	16/37		14.65%	0.96[0.57,1.61]
Kurrle 1986	16/70	11/70		12.12%	1.45[0.73,2.91]
Winston 1986	6/30	11/36		9.9%	0.65[0.27,1.56]
Gluckman 1988	7/33	1/32		3.03%	6.79[0.88,52.1]
Moriuchi 1990	3/12	2/12		4.49%	1.5[0.3,7.43]
Winston 1990	9/32	9/30		10.99%	0.94[0.43,2.04]
Jansen 1994	21/33	25/63		16.42%	1.6[1.08,2.39]
Prentice 2001	25/64	2/64		5.5%	12.5[3.09,50.59]
Total (95% CI)	**388**	**412**		**100%**	**1.55[1.06,2.28]**
Total events: 139 (nonabsorbable), 93 (systemic)					
Heterogeneity: Tau^2=0.19; Chi^2=21.51, df=9(P=0.01); I^2=58.17%					
Test for overall effect: Z=2.24(P=0.03)					



nonabsorbable systemic

Analysis 7.6. Comparison 7 Gram-positive infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 6 systemic + nonabsorbable vs systemic.

Study or subgroup	systemic + nonabsorb n/N	systemic n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Malarme 1981	4/41	1/22		13.99%	2.15[0.26,18.05]
Nemet 1989	7/20	8/20		86.01%	0.88[0.39,1.95]
Total (95% CI)	**61**	**42**		**100%**	**1.05[0.49,2.25]**
Total events: 11 (systemic + nonabsorb), 9 (systemic)					
Heterogeneity: Tau^2=0; Chi^2=0.63, df=1(P=0.43); I^2=0%					
Test for overall effect: Z=0.13(P=0.89)					



Favours sys+ nonabs. Favours systemic

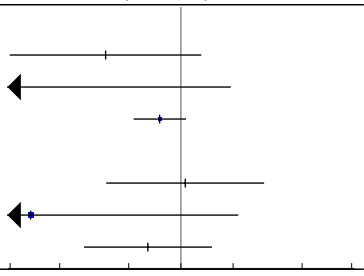
Comparison 8. Bacteraemia, prophylaxis versus placebo or no intervention or other antibiotic

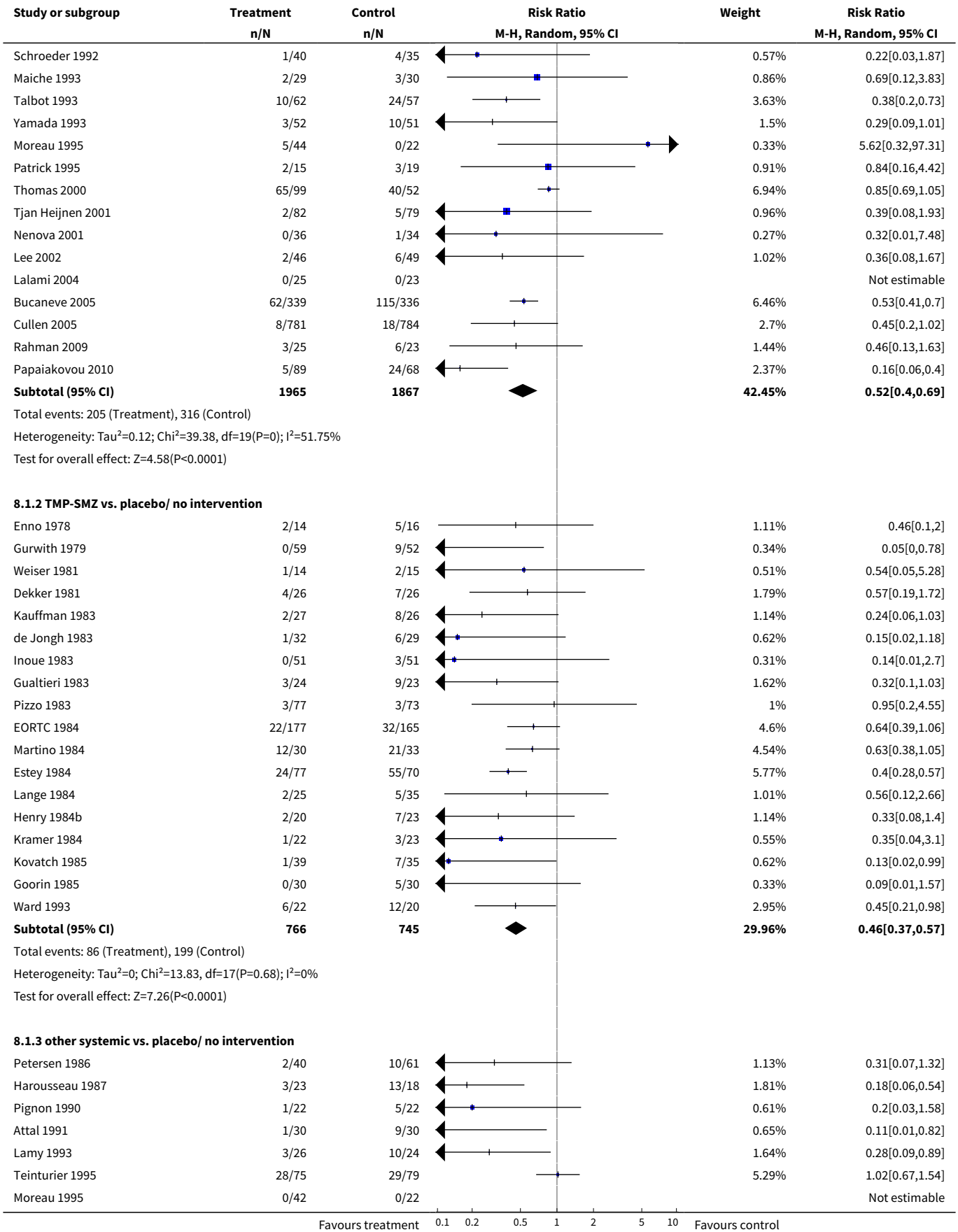
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 drug vs. placebo/ no intervention	53	6390	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.43, 0.60]
1.1 quinolone vs. placebo/ no intervention	22	3832	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.40, 0.69]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 TMP-SMZ vs. placebo/ no intervention	18	1511	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.37, 0.57]
1.3 other systemic vs. placebo/ no intervention	9	832	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.23, 0.71]
1.4 nonabsorbable vs. placebo/ no intervention	5	215	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.43, 0.95]
2 quinolone vs. TMP-SMZ	10	931	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.56, 1.42]
2.1 ciprofloxacin vs. TMP-SMZ	3	431	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.53, 2.62]
2.2 ofloxacin vs. TMP-SMZ	3	272	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.24, 0.82]
2.3 norfloxacin vs. TMP-SMZ	3	166	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.80, 2.42]
2.4 Nalidixic acid vs. TMP-SMZ	1	62	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.61, 3.07]
3 systemic + nonabsorbable vs systemic	2	106	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.38, 5.24]
4 TMP-SMZ vs. other	3	205	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.80, 2.69]
5 nonabsorbable vs. systemic	10	716	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [1.18, 1.91]
6 quinolone+other vs. quinolone	8	824	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.56, 0.97]
6.1 rifampin	3	274	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.15, 0.66]
6.2 penicillins	3	335	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.54, 1.23]
6.3 roxi	1	131	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.64, 1.91]
6.4 vancomycin	1	84	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.48, 1.87]

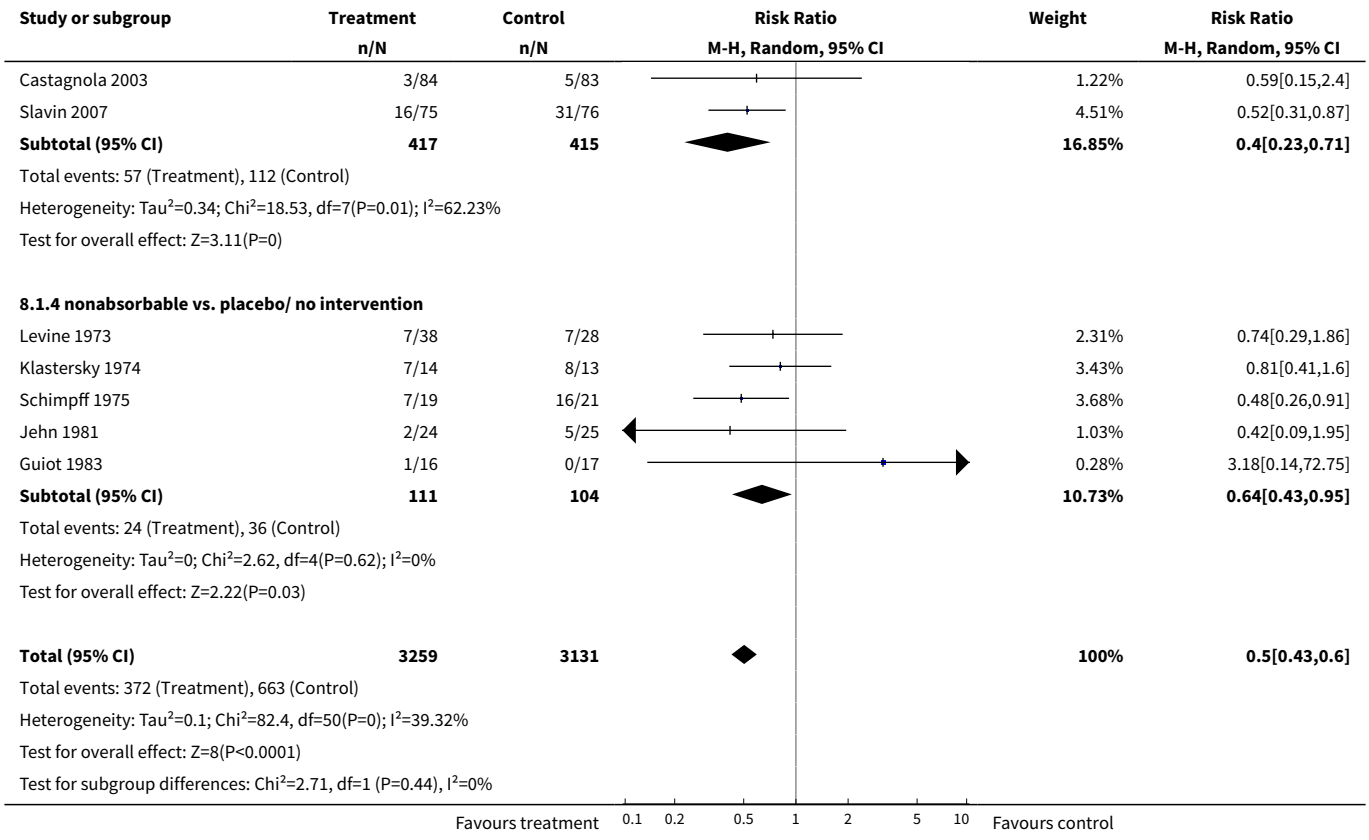
Analysis 8.1. Comparison 8 Bacteraemia, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 1 drug vs. placebo/ no intervention.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
8.1.1 quinolone vs. placebo/ no intervention					
Sleijfer 1980	3/53	8/52		1.43%	0.37[0.1,1.31]
Hartlapp 1987	0/21	4/21		0.33%	0.11[0.01,1.94]
Karp 1987	20/35	25/33		5.84%	0.75[0.53,1.07]
Casali 1988	0/30	0/35			Not estimable
Rafecas 1989	5/17	5/18		1.93%	1.06[0.37,3.02]
Lew 1991	0/7	5/11		0.36%	0.14[0.01,2.14]
Sampi 1992	7/38	10/35		2.6%	0.64[0.28,1.51]

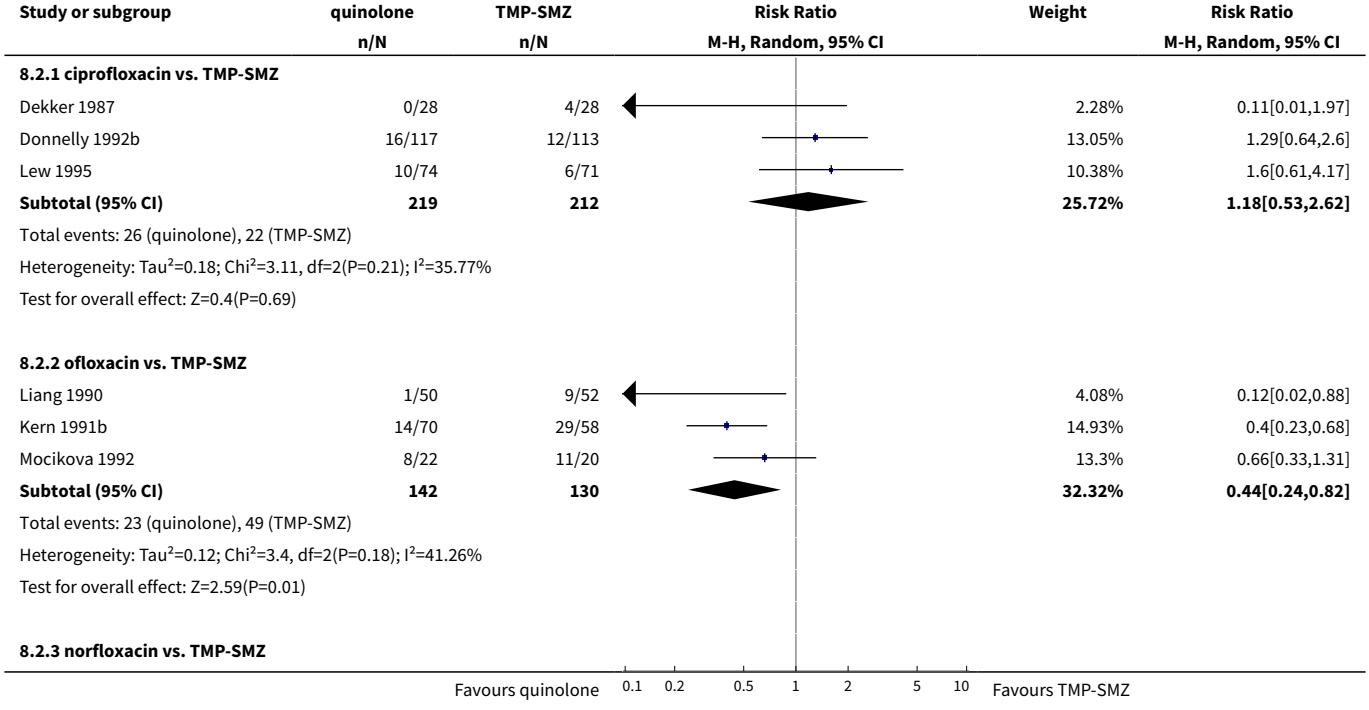


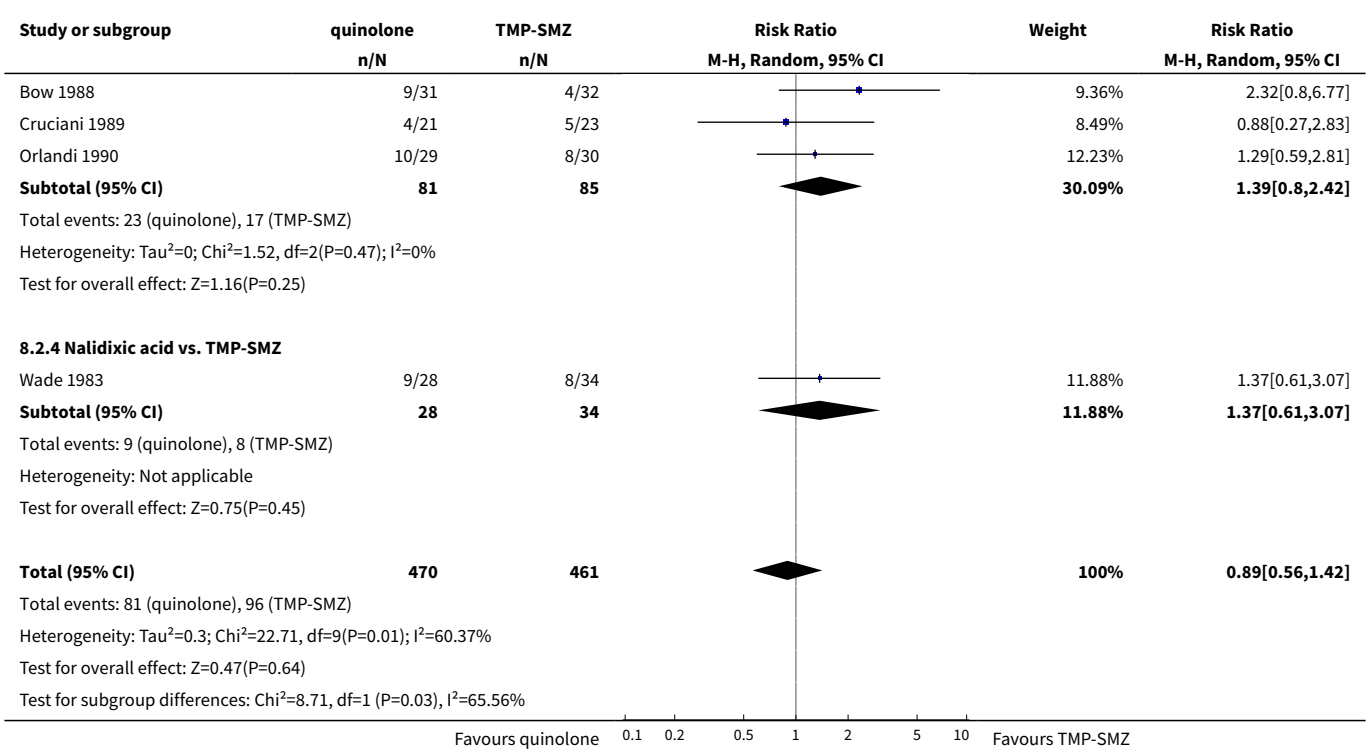


Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Schroeder 1992	1/40	4/35		0.57%	0.22[0.03,1.87]
Maiche 1993	2/29	3/30		0.86%	0.69[0.12,3.83]
Talbot 1993	10/62	24/57		3.63%	0.38[0.2,0.73]
Yamada 1993	3/52	10/51		1.5%	0.29[0.09,1.01]
Moreau 1995	5/44	0/22		0.33%	5.62[0.32,97.31]
Patrick 1995	2/15	3/19		0.91%	0.84[0.16,4.42]
Thomas 2000	65/99	40/52		6.94%	0.85[0.69,1.05]
Tjan Heijnen 2001	2/82	5/79		0.96%	0.39[0.08,1.93]
Nenova 2001	0/36	1/34		0.27%	0.32[0.01,7.48]
Lee 2002	2/46	6/49		1.02%	0.36[0.08,1.67]
Lalami 2004	0/25	0/23			Not estimable
Bucaneve 2005	62/339	115/336		6.46%	0.53[0.41,0.7]
Cullen 2005	8/781	18/784		2.7%	0.45[0.2,1.02]
Rahman 2009	3/25	6/23		1.44%	0.46[0.13,1.63]
Papaiakovou 2010	5/89	24/68		2.37%	0.16[0.06,0.4]
Subtotal (95% CI)	**1965**	**1867**		**42.45%**	**0.52[0.4,0.69]**
Total events: 205 (Treatment), 316 (Control)					
Heterogeneity: Tau^2=0.12; Chi^2=39.38, df=19(P=0); I^2=51.75%					
Test for overall effect: Z=4.58(P<0.0001)					
8.1.2 TMP-SMZ vs. placebo/ no intervention					
Enno 1978	2/14	5/16		1.11%	0.46[0.1,2]
Gurwith 1979	0/59	9/52		0.34%	0.05[0,0.78]
Weiser 1981	1/14	2/15		0.51%	0.54[0.05,5.28]
Dekker 1981	4/26	7/26		1.79%	0.57[0.19,1.72]
Kauffman 1983	2/27	8/26		1.14%	0.24[0.06,1.03]
de Jongh 1983	1/32	6/29		0.62%	0.15[0.02,1.18]
Inoue 1983	0/51	3/51		0.31%	0.14[0.01,2.7]
Gualtieri 1983	3/24	9/23		1.62%	0.32[0.1,1.03]
Pizzo 1983	3/77	3/73		1%	0.95[0.2,4.55]
EORTC 1984	22/177	32/165		4.6%	0.64[0.39,1.06]
Martino 1984	12/30	21/33		4.54%	0.63[0.38,1.05]
Estey 1984	24/77	55/70		5.77%	0.4[0.28,0.57]
Lange 1984	2/25	5/35		1.01%	0.56[0.12,2.66]
Henry 1984b	2/20	7/23		1.14%	0.33[0.08,1.4]
Kramer 1984	1/22	3/23		0.55%	0.35[0.04,3.1]
Kovatch 1985	1/39	7/35		0.62%	0.13[0.02,0.99]
Goorin 1985	0/30	5/30		0.33%	0.09[0.01,1.57]
Ward 1993	6/22	12/20		2.95%	0.45[0.21,0.98]
Subtotal (95% CI)	**766**	**745**		**29.96%**	**0.46[0.37,0.57]**
Total events: 86 (Treatment), 199 (Control)					
Heterogeneity: Tau^2=0; Chi^2=13.83, df=17(P=0.68); I^2=0%					
Test for overall effect: Z=7.26(P<0.0001)					
8.1.3 other systemic vs. placebo/ no intervention					
Petersen 1986	2/40	10/61		1.13%	0.31[0.07,1.32]
Harousseau 1987	3/23	13/18		1.81%	0.18[0.06,0.54]
Pignon 1990	1/22	5/22		0.61%	0.2[0.03,1.58]
Attal 1991	1/30	9/30		0.65%	0.11[0.01,0.82]
Lamy 1993	3/26	10/24		1.64%	0.28[0.09,0.89]
Teinturier 1995	28/75	29/79		5.29%	1.02[0.67,1.54]
Moreau 1995	0/42	0/22			Not estimable

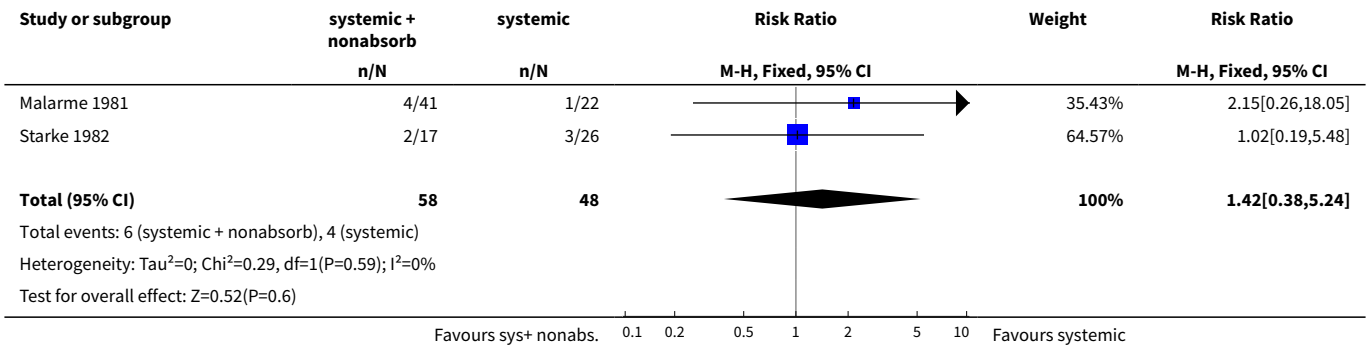


Analysis 8.2. Comparison 8 Bacteraemia, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 2 quinolone vs. TMP-SMZ.

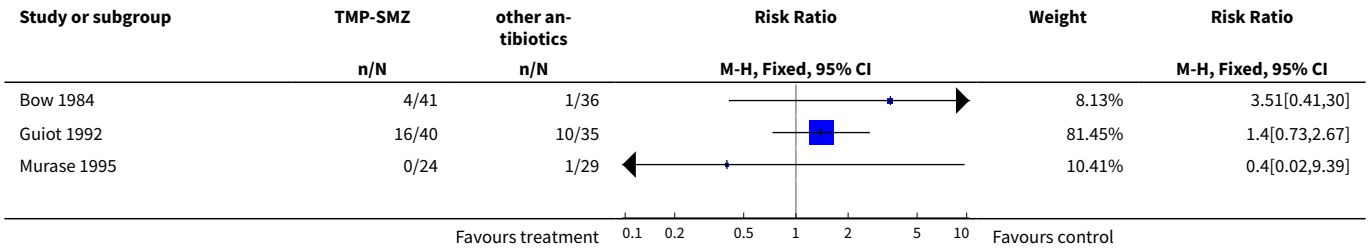


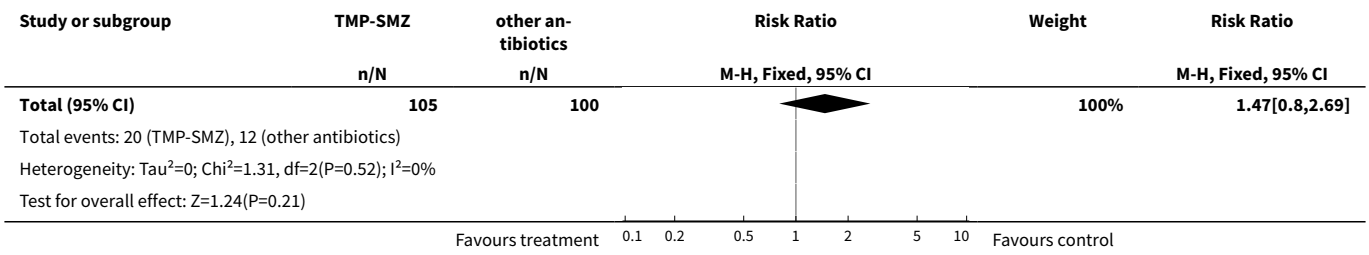


Analysis 8.3. Comparison 8 Bacteraemia, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 3 systemic + nonabsorbable vs systemic.

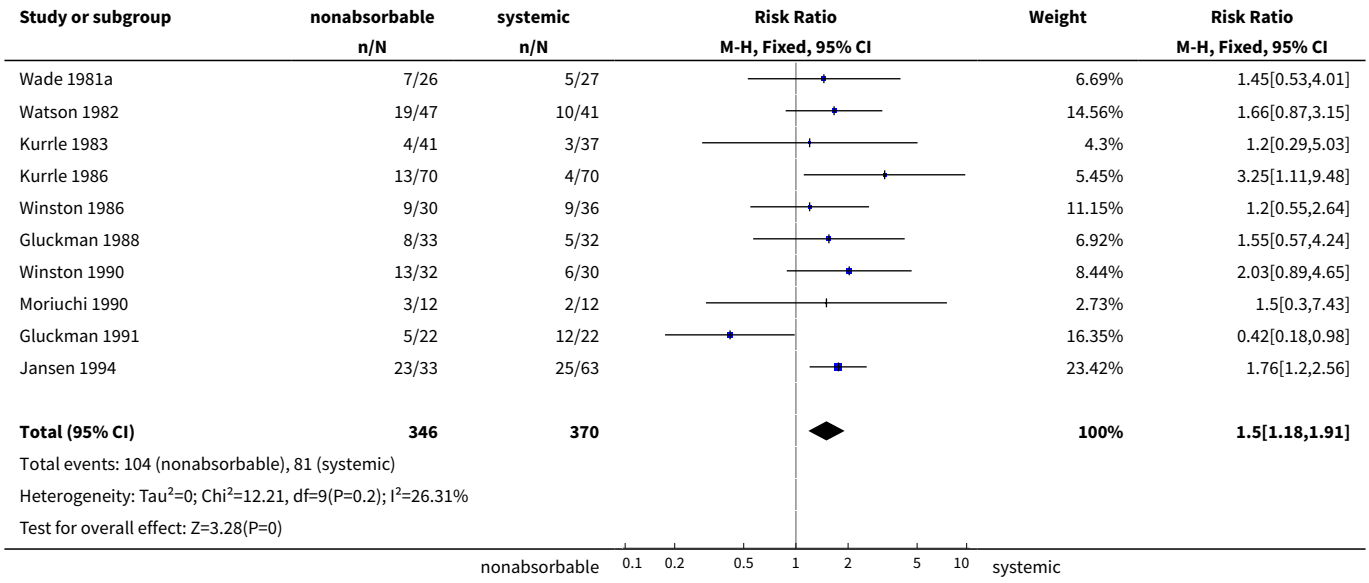


Analysis 8.4. Comparison 8 Bacteraemia, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 4 TMP-SMZ vs. other.

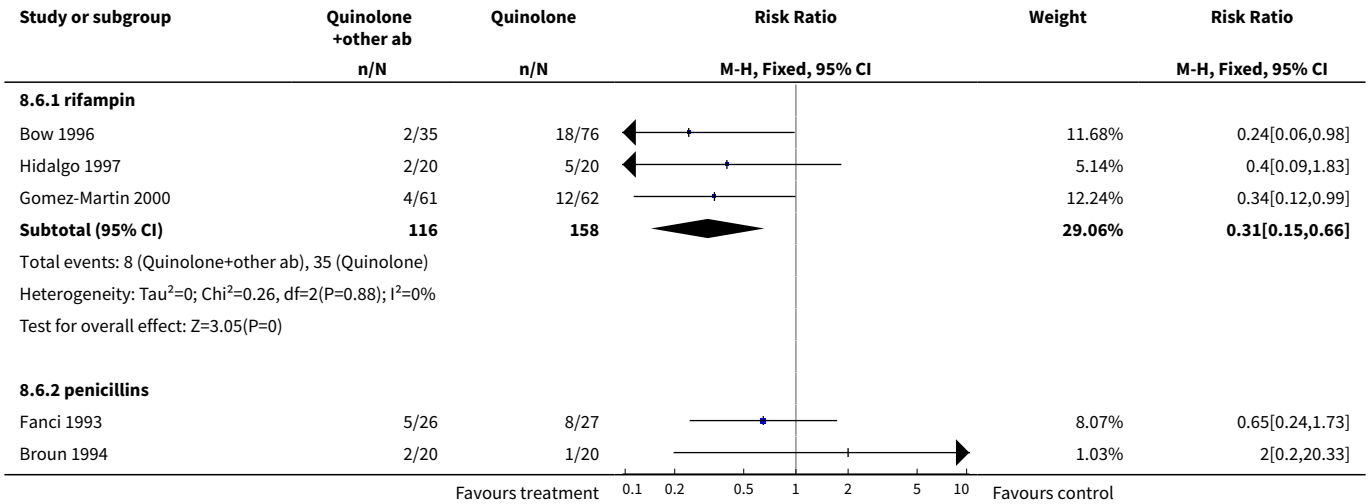


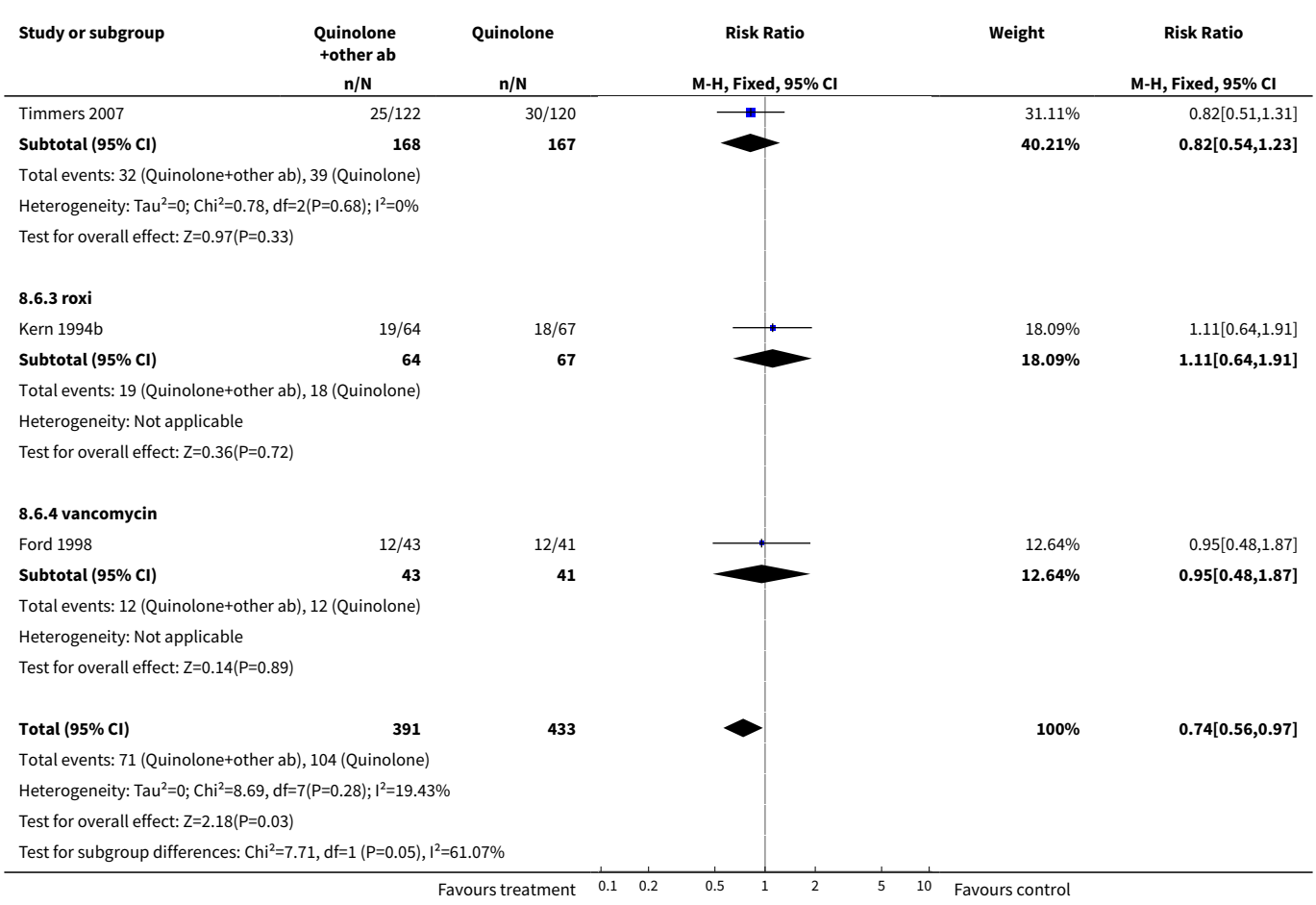


Analysis 8.5. Comparison 8 Bacteraemia, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 5 nonabsorbable vs. systemic.



Analysis 8.6. Comparison 8 Bacteraemia, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 6 quinolone+other vs. quinolone.





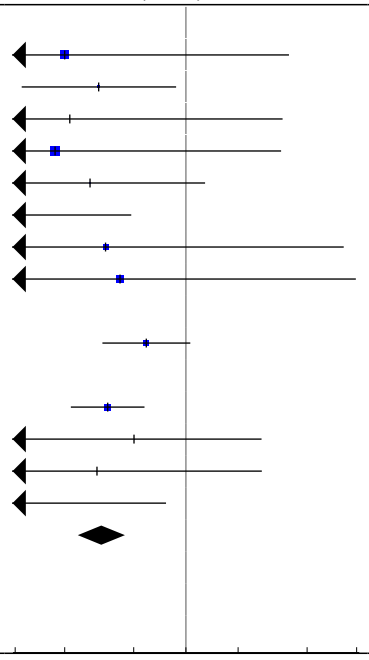
Comparison 9. Gram-negative bacteraemia, prophylaxis versus placebo or no intervention or other antibiotic

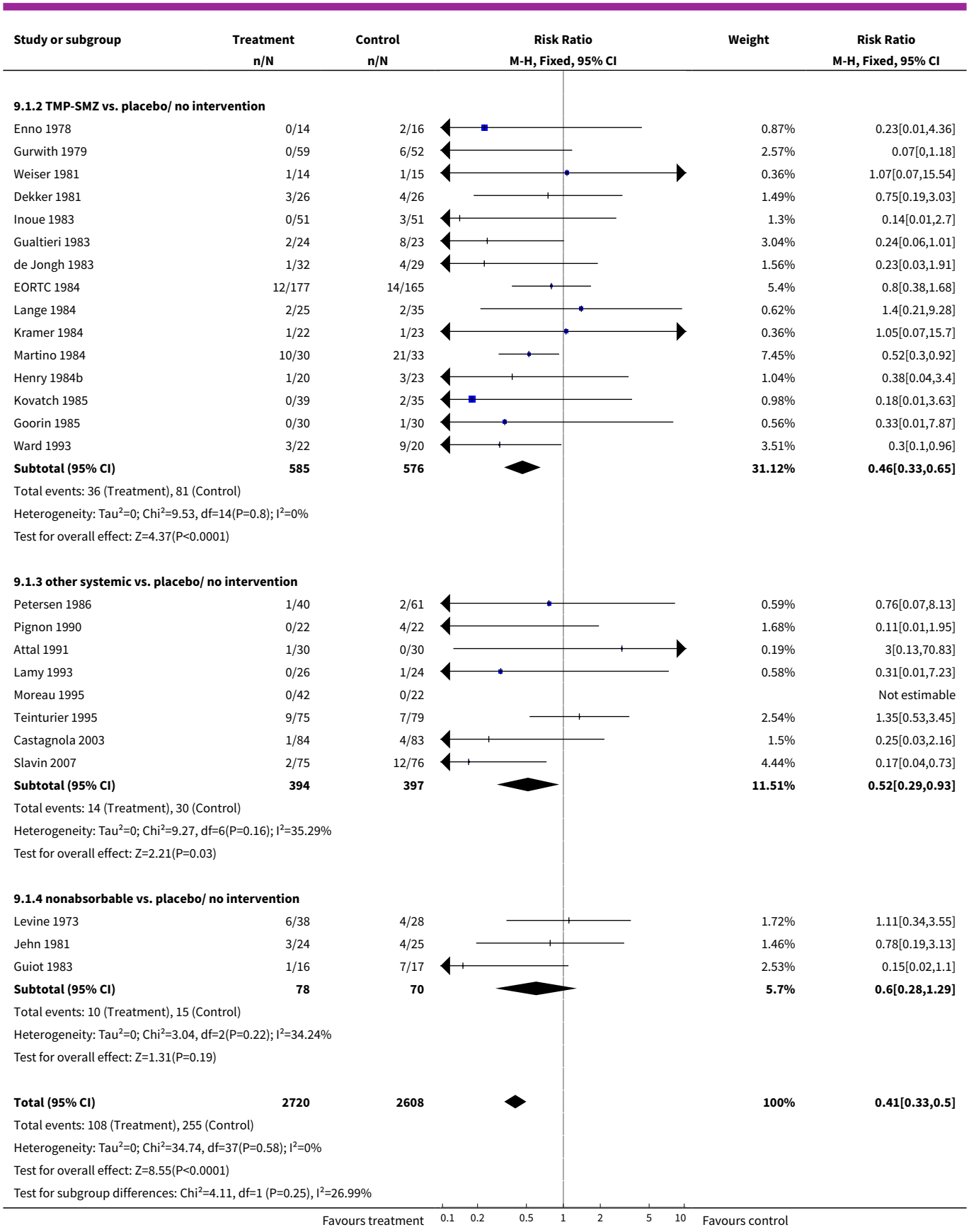
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 drug vs. placebo/ no intervention	40	5328	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.33, 0.50]
1.1 quinolone vs. placebo/ no intervention	15	3228	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.24, 0.45]
1.2 TMP-SMZ vs. placebo/ no intervention	15	1161	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.33, 0.65]
1.3 other systemic vs. placebo/ no intervention	8	791	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.29, 0.93]
1.4 nonabsorbable vs. placebo/ no intervention	3	148	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.28, 1.29]
2 quinolone vs. TMP-SMZ	10	931	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.13, 0.93]
2.1 ciprofloxacin vs. TMP-SMZ	3	431	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.03, 0.84]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 ofloxacin vs. TMP-SMZ	3	272	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.03, 1.35]
2.3 norfloxacin vs. TMP-SMZ	3	166	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.29, 1.56]
2.4 Nalidixic acid vs. TMP-SMZ	1	62	Risk Ratio (M-H, Random, 95% CI)	10.86 [0.61, 193.50]
3 quinolone+other vs. quinolone	8	824	Risk Ratio (M-H, Fixed, 95% CI)	2.30 [1.11, 4.78]
3.1 rifampin	3	274	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.29, 3.14]
3.2 penicillins	3	335	Risk Ratio (M-H, Fixed, 95% CI)	5.05 [0.90, 28.44]
3.3 roxi	1	131	Risk Ratio (M-H, Fixed, 95% CI)	8.38 [1.08, 65.08]
3.4 vancomycin	1	84	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.14, 6.46]
4 TMP-SMZ vs. other	3	205	Risk Ratio (M-H, Fixed, 95% CI)	3.80 [0.66, 21.74]
5 nonabsorbable vs. systemic	10	842	Risk Ratio (M-H, Fixed, 95% CI)	2.70 [1.63, 4.49]
6 systemic + nonabsorbable vs systemic	2	106	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.14, 5.83]

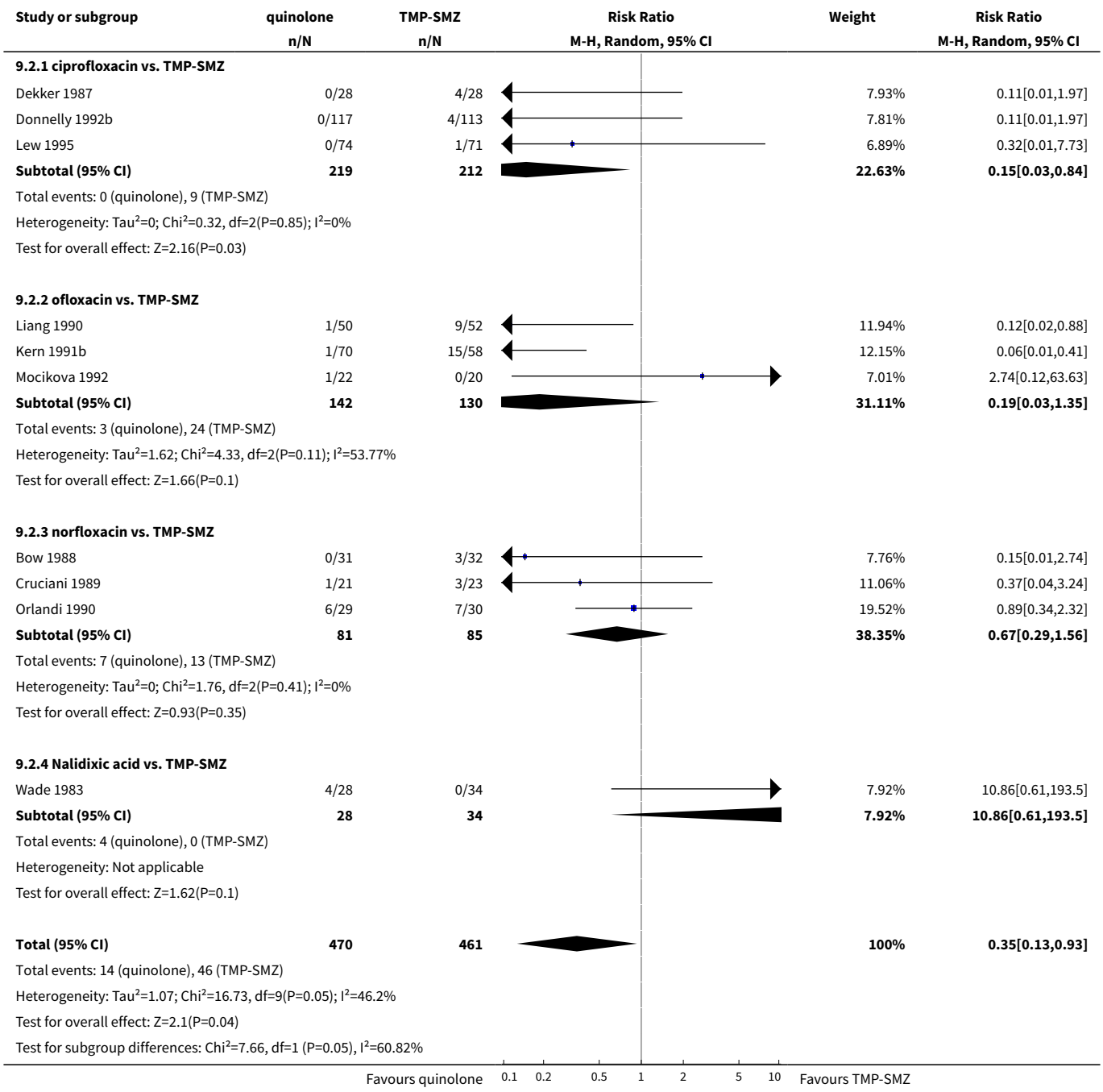
Analysis 9.1. Comparison 9 Gram-negative bacteraemia, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 1 drug vs. placebo/ no intervention.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
9.1.1 quinolone vs. placebo/ no intervention					
Hartlapp 1987	0/21	2/21		0.93%	0.2[0.01,3.93]
Karp 1987	4/35	12/33		4.6%	0.31[0.11,0.88]
Lew 1991	0/7	3/11		1.04%	0.21[0.01,3.61]
Schroeder 1992	0/40	2/35		0.99%	0.18[0.01,3.54]
Yamada 1993	2/52	7/51		2.63%	0.28[0.06,1.29]
Talbot 1993	1/62	14/57		5.43%	0.07[0.01,0.48]
Maiche 1993	0/29	1/30		0.55%	0.34[0.01,8.13]
Patrick 1995	0/15	1/19		0.5%	0.42[0.02,9.55]
Moreau 1995	0/44	0/22			Not estimable
Thomas 2000	18/99	16/52		7.81%	0.59[0.33,1.06]
Lalami 2004	0/25	0/23			Not estimable
Bucaneve 2005	20/339	56/336		20.95%	0.35[0.22,0.58]
Cullen 2005	2/781	4/784		1.49%	0.5[0.09,2.73]
Rahman 2009	1/25	3/23		1.16%	0.31[0.03,2.74]
Papaiakovou 2010	0/89	8/68		3.58%	0.05[0,0.77]
Subtotal (95% CI)	**1663**	**1565**		**51.67%**	**0.33[0.24,0.45]**
Total events: 48 (Treatment), 129 (Control)					
Heterogeneity: Tau^2=0; Chi^2=9.13, df=12(P=0.69); I^2=0%					
Test for overall effect: Z=7.02(P<0.0001)					

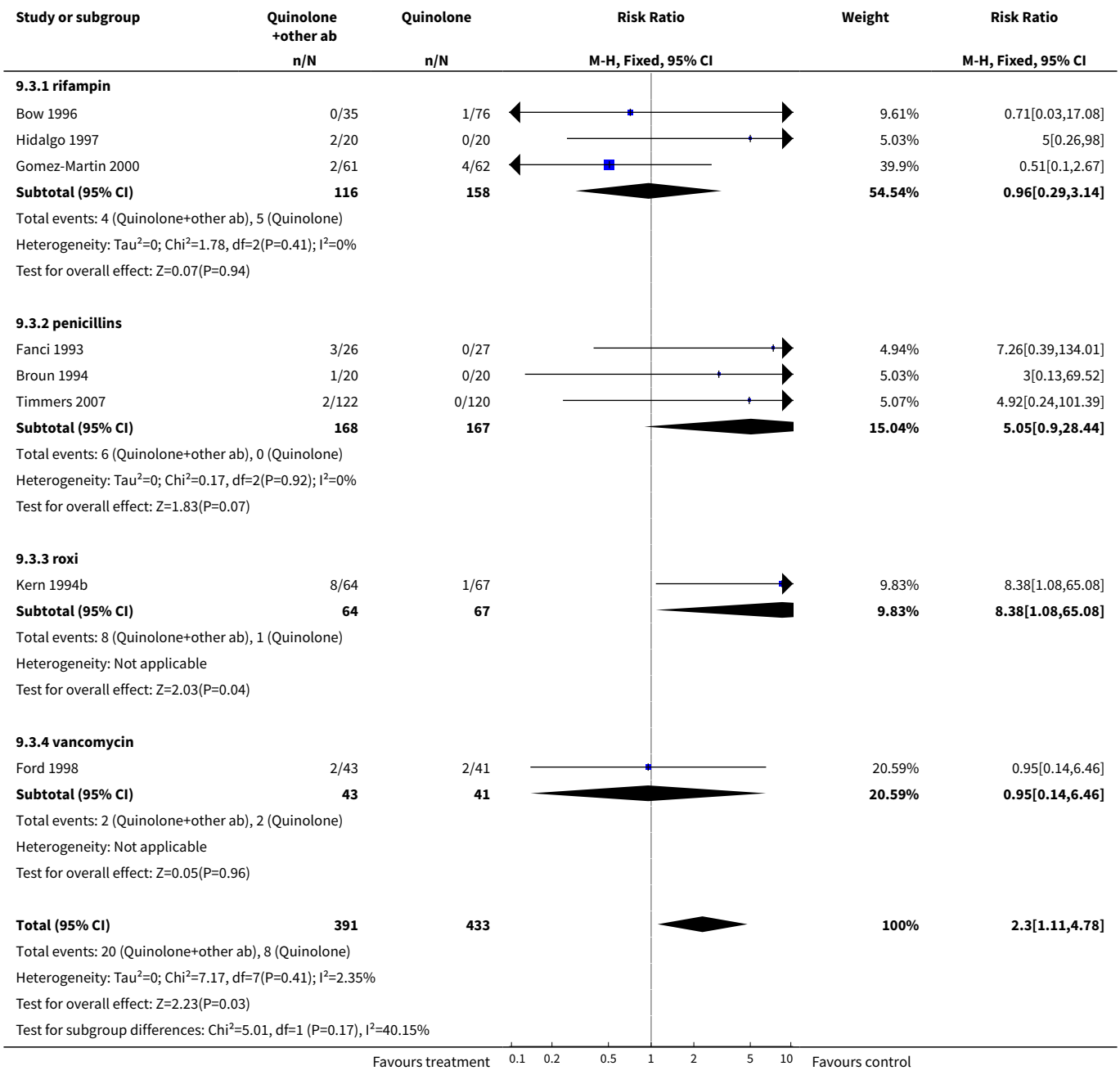




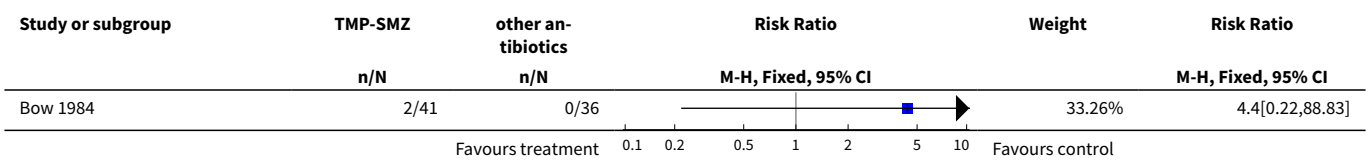
Analysis 9.2. Comparison 9 Gram-negative bacteraemia, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 2 quinolone vs. TMP-SMZ.

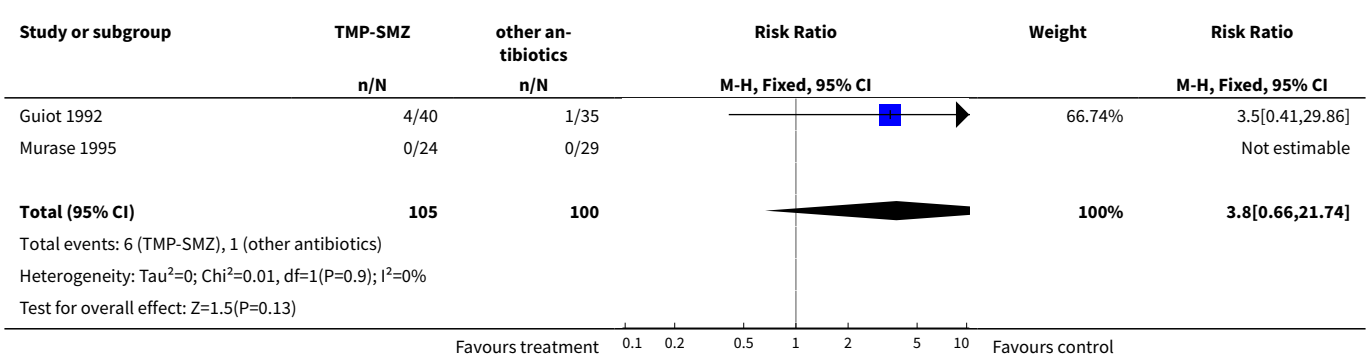


Analysis 9.3. Comparison 9 Gram-negative bacteraemia, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 3 quinolone+other vs. quinolone.

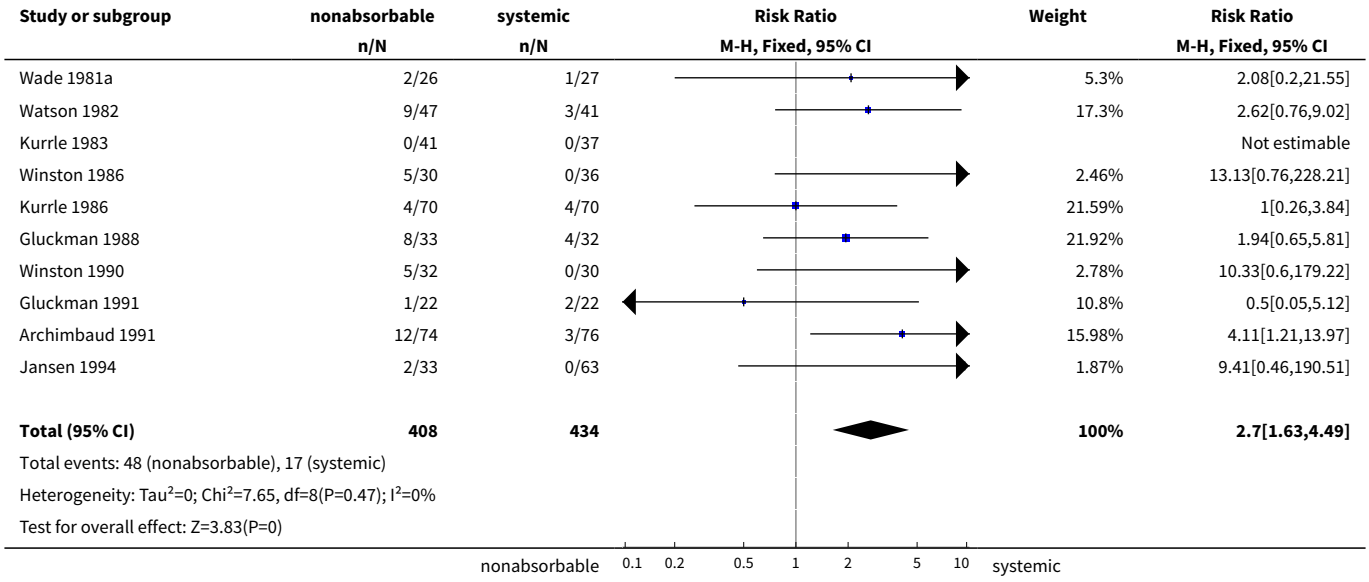


Analysis 9.4. Comparison 9 Gram-negative bacteraemia, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 4 TMP-SMZ vs. other.

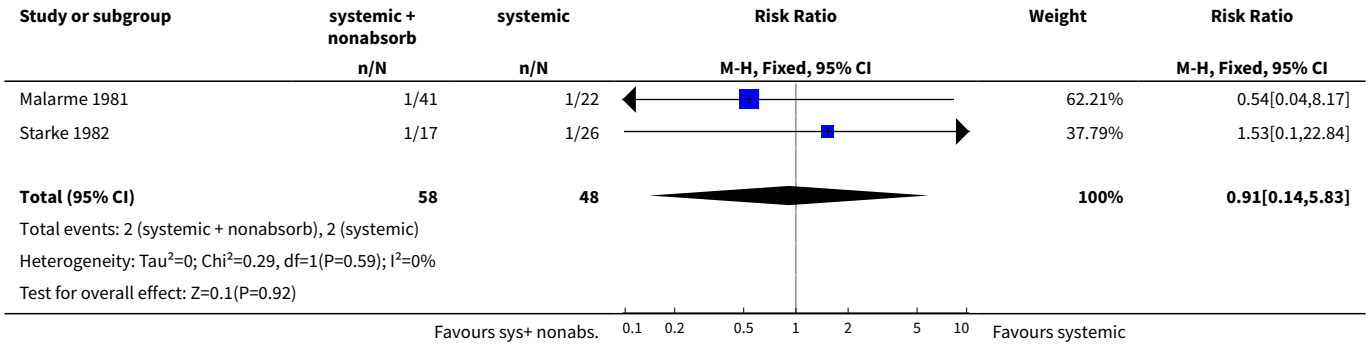




Analysis 9.5. Comparison 9 Gram-negative bacteraemia, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 5 nonabsorbable vs. systemic.



Analysis 9.6. Comparison 9 Gram-negative bacteraemia, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 6 systemic + nonabsorbable vs systemic.

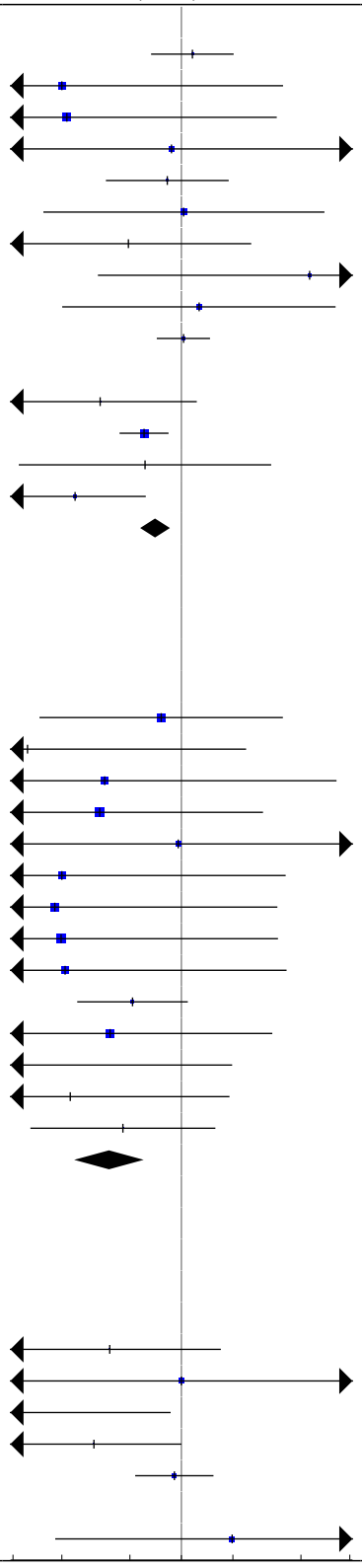


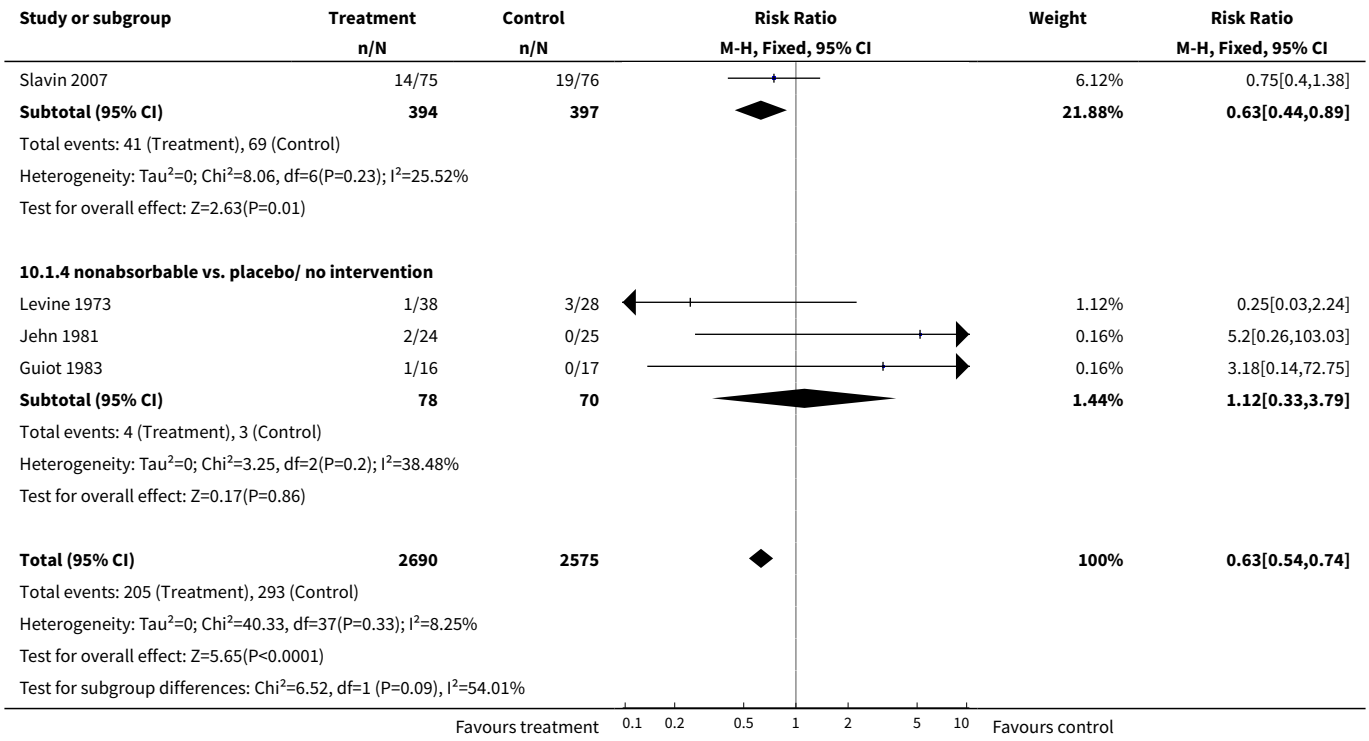
Comparison 10. Gram-positive bacteraemia, prophylaxis versus placebo or no intervention or other antibiotic

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 drug vs. placebo/ no intervention	39	5265	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.54, 0.74]
1.1 quinolone vs. placebo/ no intervention	15	3228	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.57, 0.86]
1.2 TMP-SMZ vs. placebo/ no intervention	14	1098	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.24, 0.60]
1.3 other systemic vs. placebo/ no intervention	8	791	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.44, 0.89]
1.4 nonabsorbable vs. placebo/ no intervention	3	148	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.33, 3.79]
2 quinolone vs. TMP-SMZ	10	931	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.71, 2.15]
2.1 ciprofloxacin vs. TMP-SMZ	3	431	Risk Ratio (M-H, Random, 95% CI)	1.48 [0.60, 3.65]
2.2 ofloxacin vs. TMP-SMZ	3	272	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.40, 0.99]
2.3 norfloxacin vs. TMP-SMZ	3	166	Risk Ratio (M-H, Random, 95% CI)	4.17 [1.46, 11.92]
2.4 Nalidixic acid vs. TMP-SMZ	1	62	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.28, 2.06]
3 quinolone+other vs. quinolone	8	824	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.44, 0.83]
3.1 rifampin	3	274	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.11, 0.72]
3.2 penicillins	3	335	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.49, 1.13]
3.3 roxi	1	131	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.31, 1.24]
3.4 vancomycin	1	84	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.28, 1.59]
4 TMP-SMZ vs. other	3	205	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.57, 2.24]
5 nonabsorbable vs. systemic	9	692	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.63, 2.03]
6 systemic + nonabsorbable vs systemic	2	106	Risk Ratio (M-H, Fixed, 95% CI)	2.57 [0.36, 18.46]

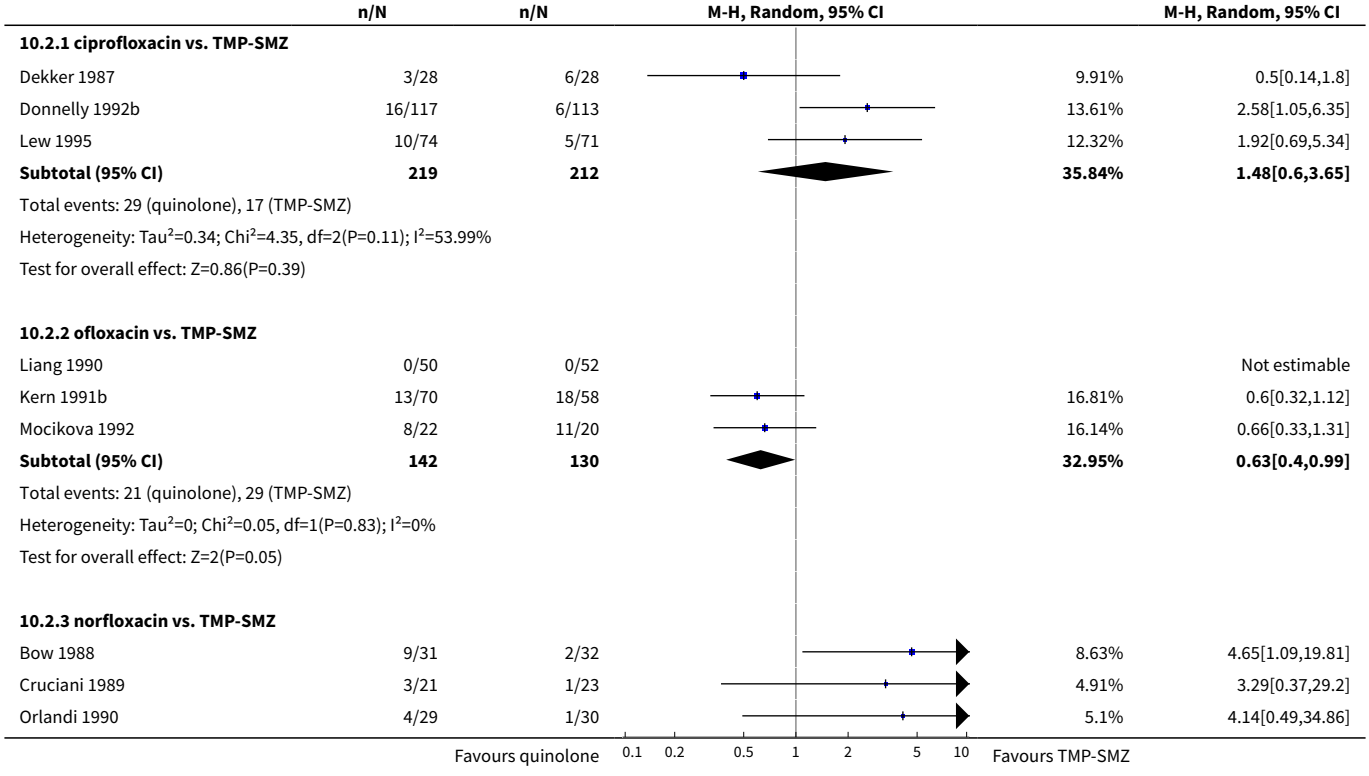
Analysis 10.1. Comparison 10 Gram-positive bacteraemia, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 1 drug vs. placebo/ no intervention.

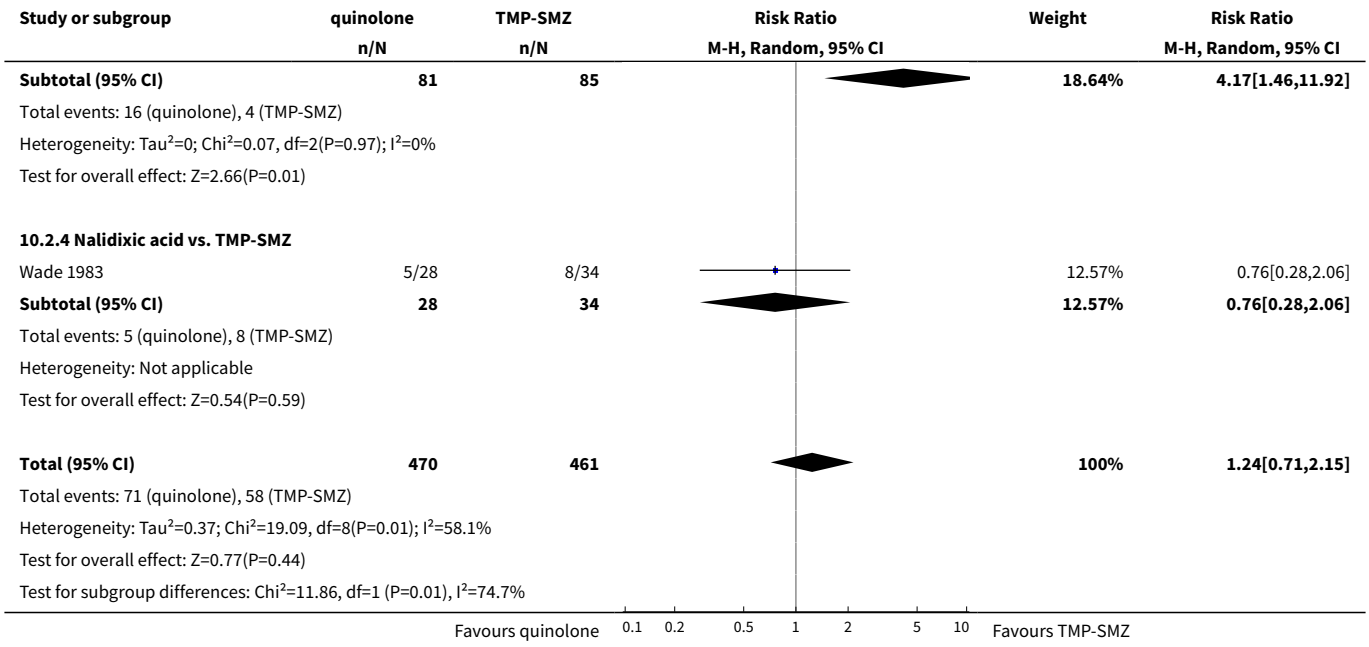
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
10.1.1 quinolone vs. placebo/ no intervention					
Karp 1987	16/35	13/33		4.34%	1.16[0.67,2.02]
Hartlapp 1987	0/21	2/21		0.81%	0.2[0.01,3.93]
Lew 1991	0/7	3/11		0.91%	0.21[0.01,3.61]
Schroeder 1992	1/40	1/35		0.35%	0.88[0.06,13.48]
Talbot 1993	9/62	10/57		3.38%	0.83[0.36,1.89]
Maiche 1993	2/29	2/30		0.64%	1.03[0.16,6.86]
Yamada 1993	2/52	4/51		1.31%	0.49[0.09,2.56]
Moreau 1995	5/44	0/22		0.21%	5.62[0.32,97.31]
Patrick 1995	2/15	2/19		0.57%	1.27[0.2,7.97]
Thomas 2000	47/99	24/52		10.2%	1.03[0.72,1.47]
Lalami 2004	0/25	0/23			Not estimable
Cullen 2005	3/781	9/784		2.91%	0.33[0.09,1.23]
Bucaneve 2005	47/339	77/336		25.07%	0.6[0.43,0.84]
Rahman 2009	2/25	3/23		1.01%	0.61[0.11,3.35]
Papaiakovou 2010	5/89	16/68		5.88%	0.24[0.09,0.62]
Subtotal (95% CI)	**1663**	**1565**		**57.59%**	**0.7[0.57,0.86]**
Total events: 141 (Treatment), 166 (Control)					
Heterogeneity: Tau^2=0; Chi^2=18.78, df=13(P=0.13); I^2=30.78%					
Test for overall effect: Z=3.48(P=0)					
10.1.2 TMP-SMZ vs. placebo/ no intervention					
Enno 1978	2/14	3/16		0.91%	0.76[0.15,3.92]
Gurwith 1979	0/59	3/52		1.2%	0.13[0.01,2.39]
Weiser 1981	0/14	1/15		0.47%	0.36[0.02,8.07]
Dekker 1981	1/26	3/26		0.97%	0.33[0.04,3]
Gualtieri 1983	1/24	1/23		0.33%	0.96[0.06,14.43]
Inoue 1983	0/51	2/51		0.81%	0.2[0.01,4.07]
de Jongh 1983	0/32	2/29		0.85%	0.18[0.01,3.64]
Lange 1984	0/25	3/35		0.95%	0.2[0.01,3.67]
Kramer 1984	0/22	2/23		0.79%	0.21[0.01,4.12]
EORTC 1984	10/177	18/165		6.04%	0.52[0.25,1.09]
Henry 1984b	1/20	3/23		0.9%	0.38[0.04,3.4]
Goorin 1985	0/30	4/30		1.46%	0.11[0.01,1.98]
Kovatch 1985	1/39	4/35		1.37%	0.22[0.03,1.91]
Ward 1993	3/22	6/20		2.04%	0.45[0.13,1.58]
Subtotal (95% CI)	**555**	**543**		**19.1%**	**0.38[0.24,0.6]**
Total events: 19 (Treatment), 55 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.15, df=13(P=0.99); I^2=0%					
Test for overall effect: Z=4.09(P<0.0001)					
10.1.3 other systemic vs. placebo/ no intervention					
Petersen 1986	2/40	8/61		2.05%	0.38[0.09,1.7]
Pignon 1990	1/22	1/22		0.32%	1[0.07,15]
Attal 1991	0/30	9/30		3.08%	0.05[0,0.87]
Lamy 1993	3/26	9/24		3.03%	0.31[0.09,1]
Teinturier 1995	19/75	22/79		6.95%	0.91[0.54,1.54]
Moreau 1995	0/42	0/22			Not estimable
Castagnola 2003	2/84	1/83		0.33%	1.98[0.18,21.38]



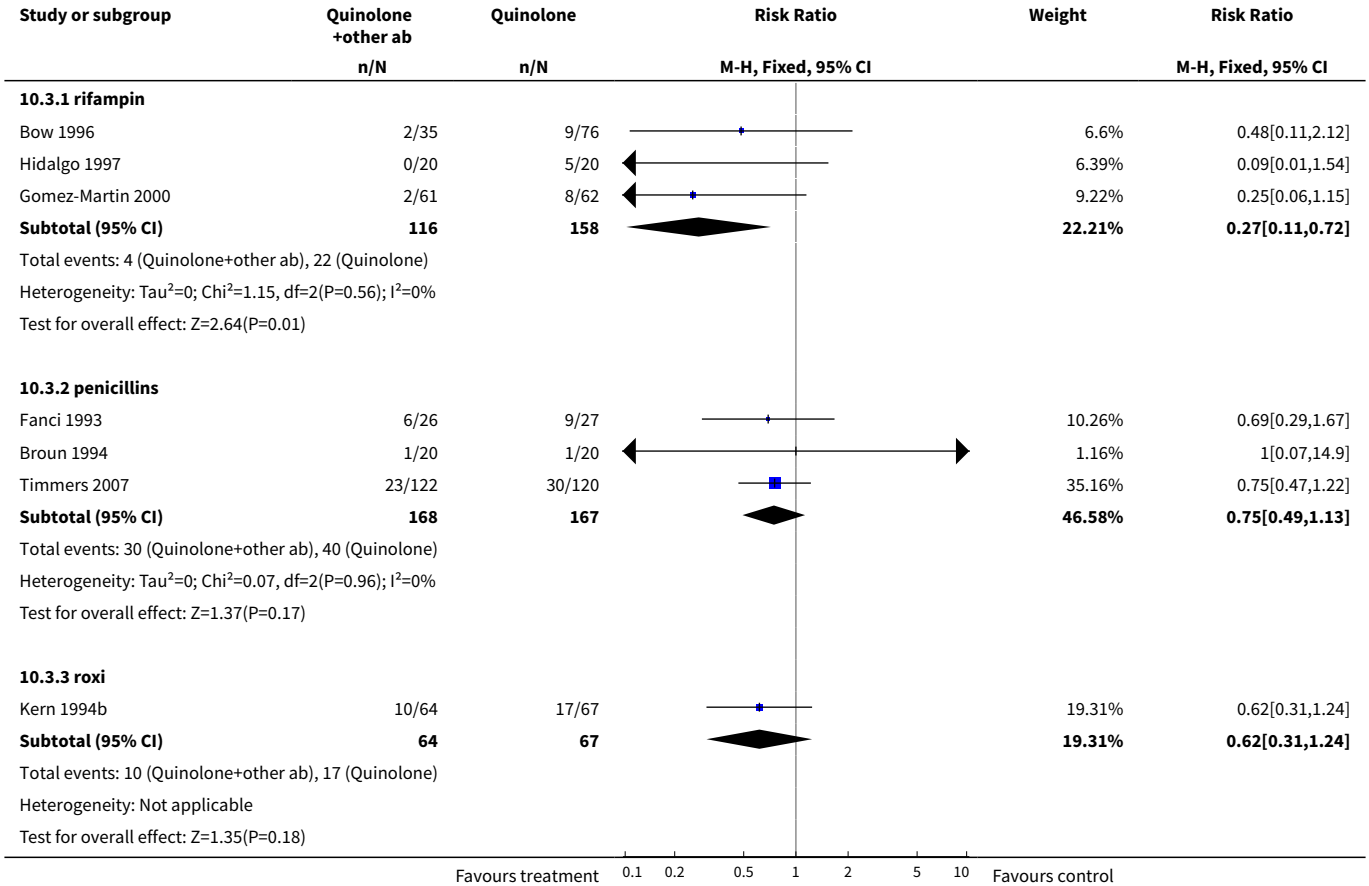


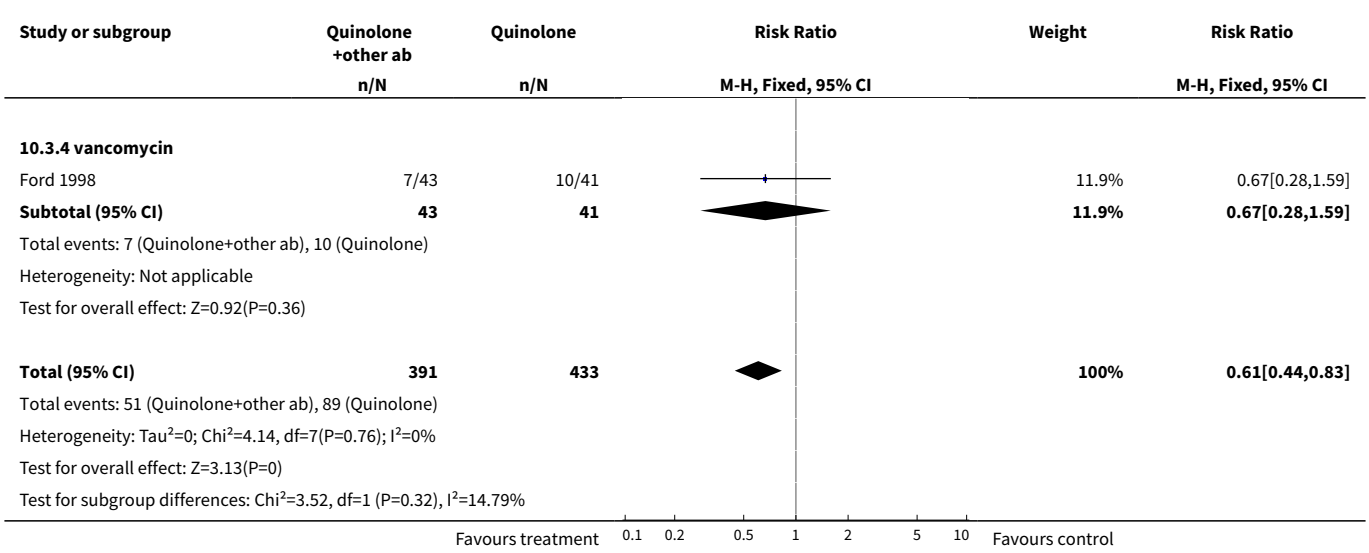
Analysis 10.2. Comparison 10 Gram-positive bacteraemia, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 2 quinolone vs. TMP-SMZ.



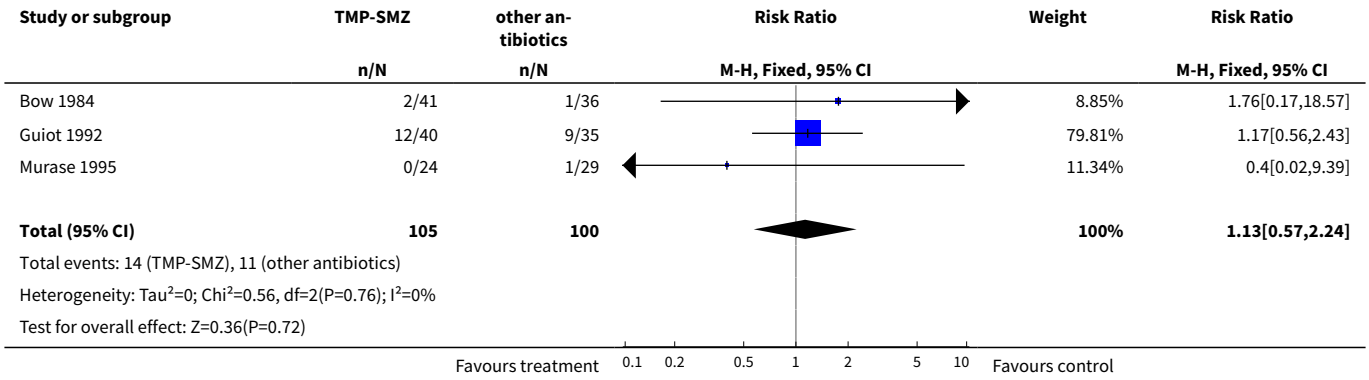


Analysis 10.3. Comparison 10 Gram-positive bacteraemia, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 3 quinolone+other vs. quinolone.

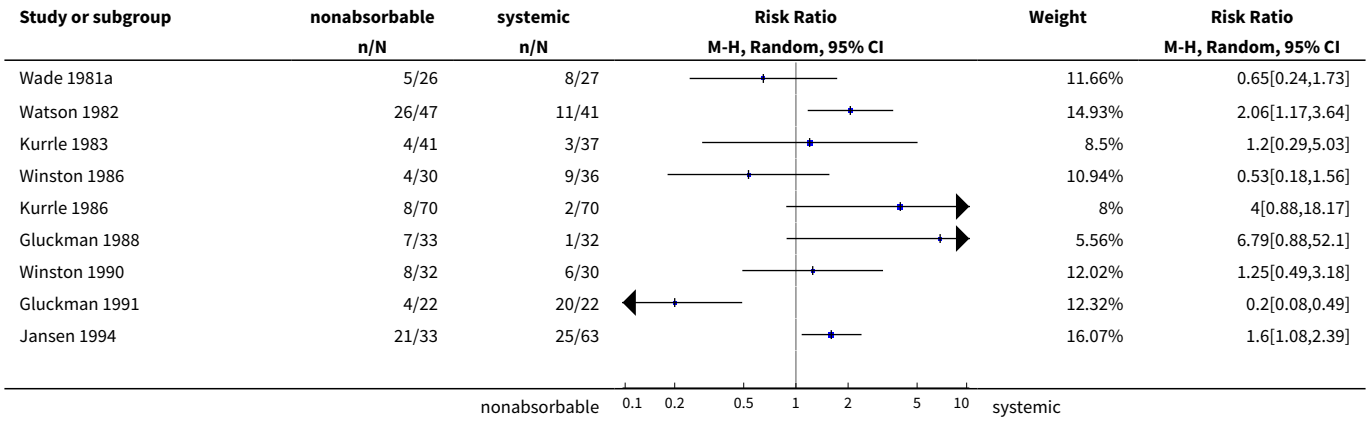


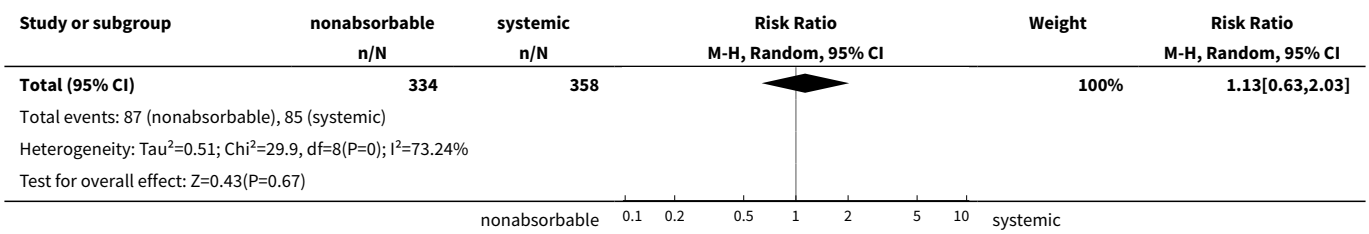


Analysis 10.4. Comparison 10 Gram-positive bacteraemia, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 4 TMP-SMZ vs. other.

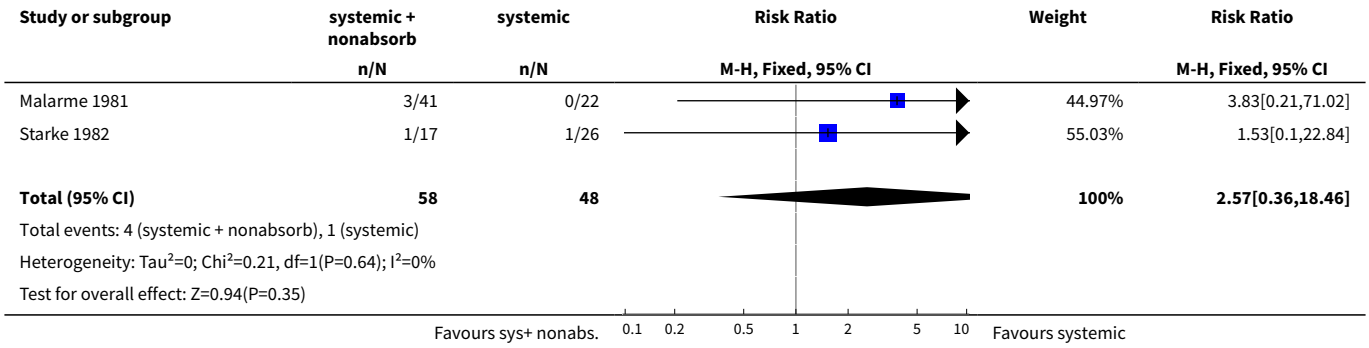


Analysis 10.5. Comparison 10 Gram-positive bacteraemia, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 5 nonabsorbable vs. systemic.





Analysis 10.6. Comparison 10 Gram-positive bacteraemia, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 6 systemic + nonabsorbable vs systemic.



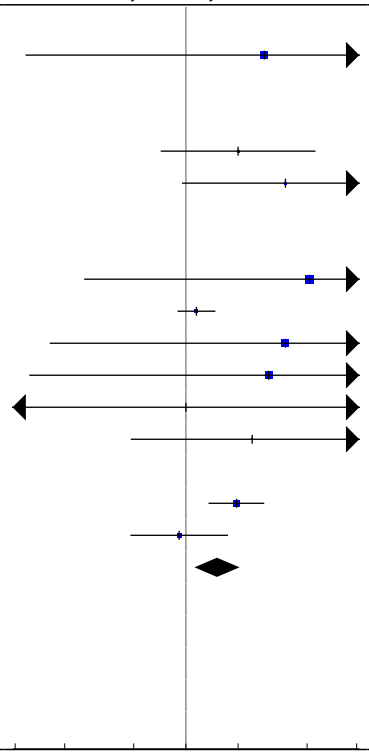
Comparison 11. Side effects, prophylaxis versus placebo or no intervention or other antibiotic

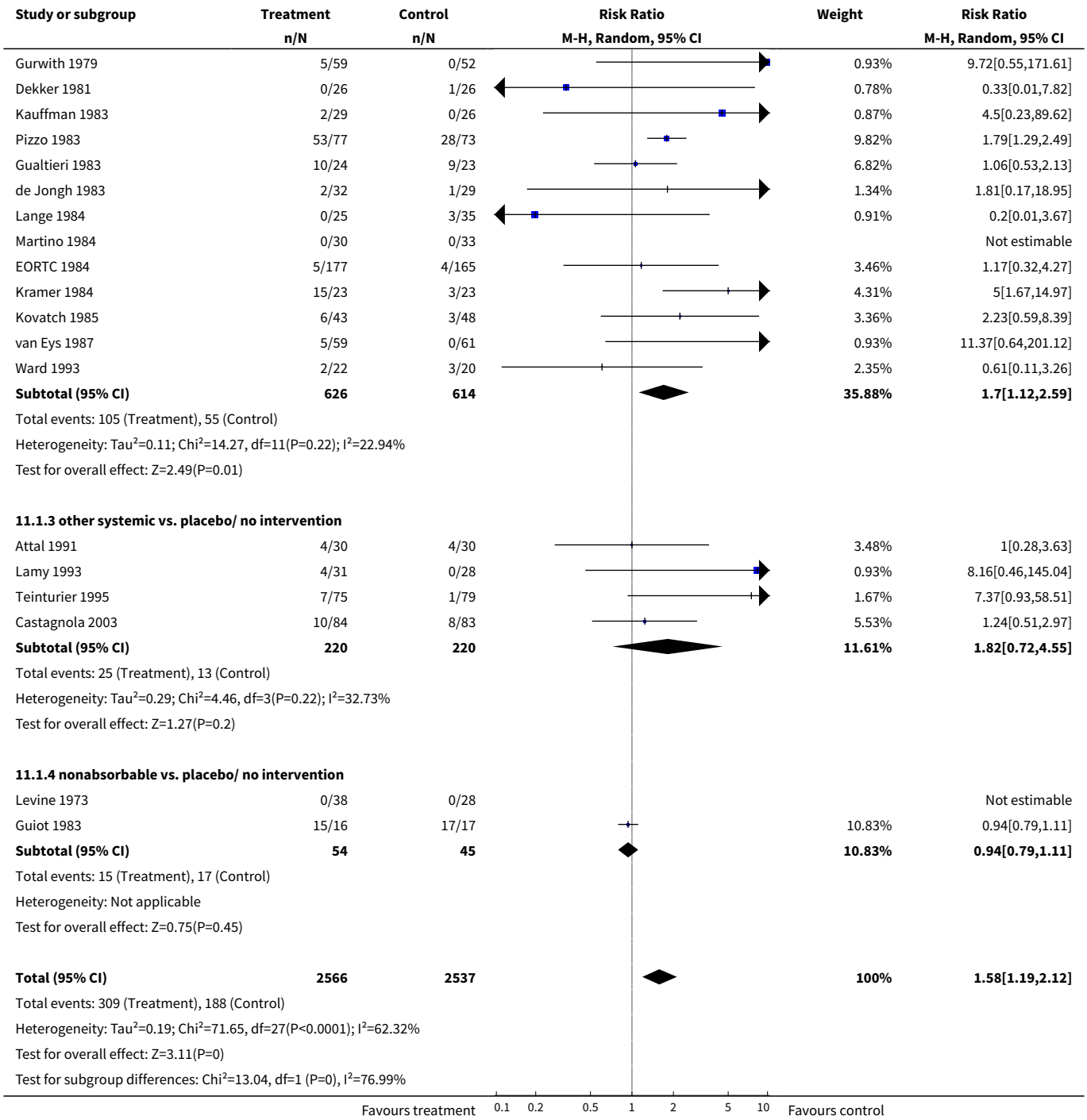
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 drug vs. placebo/ no intervention	35	5103	Risk Ratio (M-H, Random, 95% CI)	1.58 [1.19, 2.12]
1.1 quinolone vs. placebo/ no intervention	16	3324	Risk Ratio (M-H, Random, 95% CI)	1.51 [1.12, 2.04]
1.2 TMP-SMZ vs. placebo/ no intervention	13	1240	Risk Ratio (M-H, Random, 95% CI)	1.70 [1.12, 2.59]
1.3 other systemic vs. placebo/ no intervention	4	440	Risk Ratio (M-H, Random, 95% CI)	1.82 [0.72, 4.55]
1.4 nonabsorbable vs. placebo/ no intervention	2	99	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.79, 1.11]
2 quinolone vs. TMP-SMZ	10	1027	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.43, 0.90]
2.1 ciprofloxacin vs. TMP-SMZ	4	537	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.46, 1.13]
2.2 ofloxacin vs. TMP-SMZ	2	262	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.24, 0.69]
2.3 norfloxacin vs. TMP-SMZ	3	166	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.27, 1.43]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.4 Nalidixic acid vs. TMP-SMZ	1	62	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.15, 4.51]
3 quinolone+other vs. quinolone	6	516	Risk Ratio (M-H, Random, 95% CI)	2.69 [0.78, 9.27]
3.1 rifampin	3	243	Risk Ratio (M-H, Random, 95% CI)	5.49 [0.30, 100.07]
3.2 penicillins	1	58	Risk Ratio (M-H, Random, 95% CI)	1.4 [0.25, 7.77]
3.3 roxi	1	131	Risk Ratio (M-H, Random, 95% CI)	9.42 [0.52, 171.44]
3.4 vancomycin	1	84	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.14, 6.46]
4 TMP-SMZ vs. other	2	128	Risk Ratio (M-H, Fixed, 95% CI)	3.06 [0.68, 13.79]
5 nonabsorbable vs. systemic	10	934	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.65, 1.96]
6 systemic + nonabsorbable vs systemic	3	146	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [1.02, 3.00]

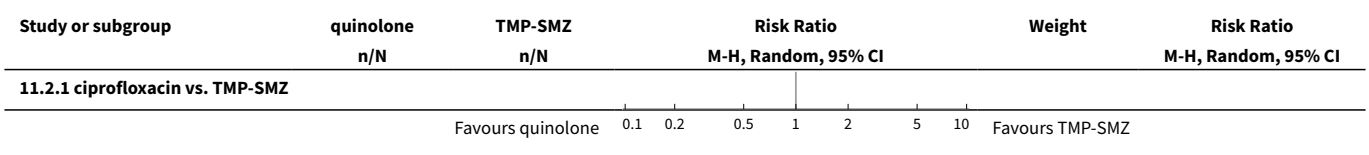
Analysis 11.1. Comparison 11 Side effects, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 1 drug vs. placebo/ no intervention.

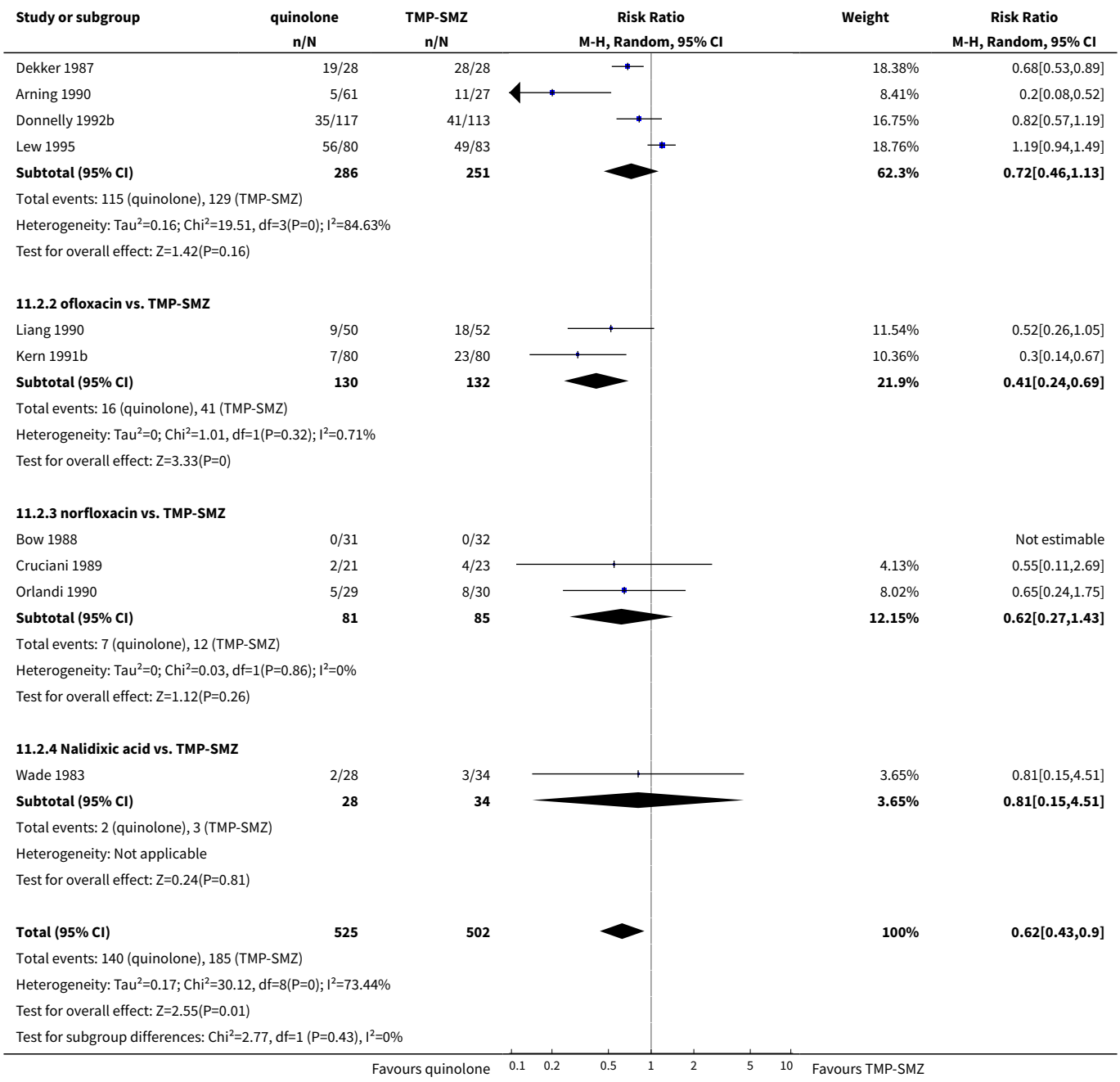
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
11.1.1 quinolone vs. placebo/ no intervention					
Karp 1987	1/35	0/33		0.78%	2.83[0.12,67.19]
Hartlapp 1987	0/21	0/21			Not estimable
Casali 1988	0/30	0/35			Not estimable
Rafecas 1989	8/20	4/20		4.66%	2[0.72,5.59]
Lew 1991	5/8	2/12		3.19%	3.75[0.95,14.82]
Schroeder 1992	0/40	0/35			Not estimable
Yamada 1993	0/52	0/51			Not estimable
Maiche 1993	2/29	0/30		0.86%	5.17[0.26,103.21]
Talbot 1993	45/62	36/57		10.36%	1.15[0.89,1.48]
Patrick 1995	1/15	0/19		0.8%	3.75[0.16,85.98]
Carlson 1997	1/45	0/45		0.78%	3[0.13,71.74]
Ruiz 2001	1/25	1/25		1.03%	1[0.07,15.12]
Tjan Heijnen 2001	5/82	2/79		2.51%	2.41[0.48,12.05]
Lee 2002	0/46	0/49			Not estimable
Cullen 2005	78/781	40/784		9.51%	1.96[1.35,2.83]
Bucaneve 2005	17/375	18/363		7.2%	0.91[0.48,1.75]
Subtotal (95% CI)	**1666**	**1658**		**41.68%**	**1.51[1.12,2.04]**
Total events: 164 (Treatment), 103 (Control)					
Heterogeneity: Tau^2=0.05; Chi^2=13.07, df=10(P=0.22); I^2=23.48%					
Test for overall effect: Z=2.69(P=0.01)					
11.1.2 TMP-SMZ vs. placebo/ no intervention					



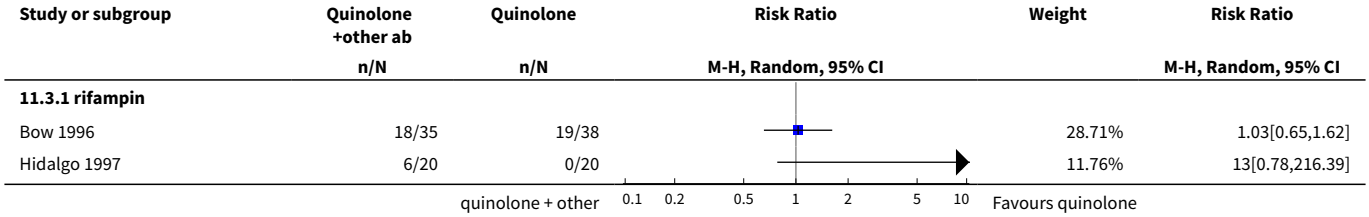


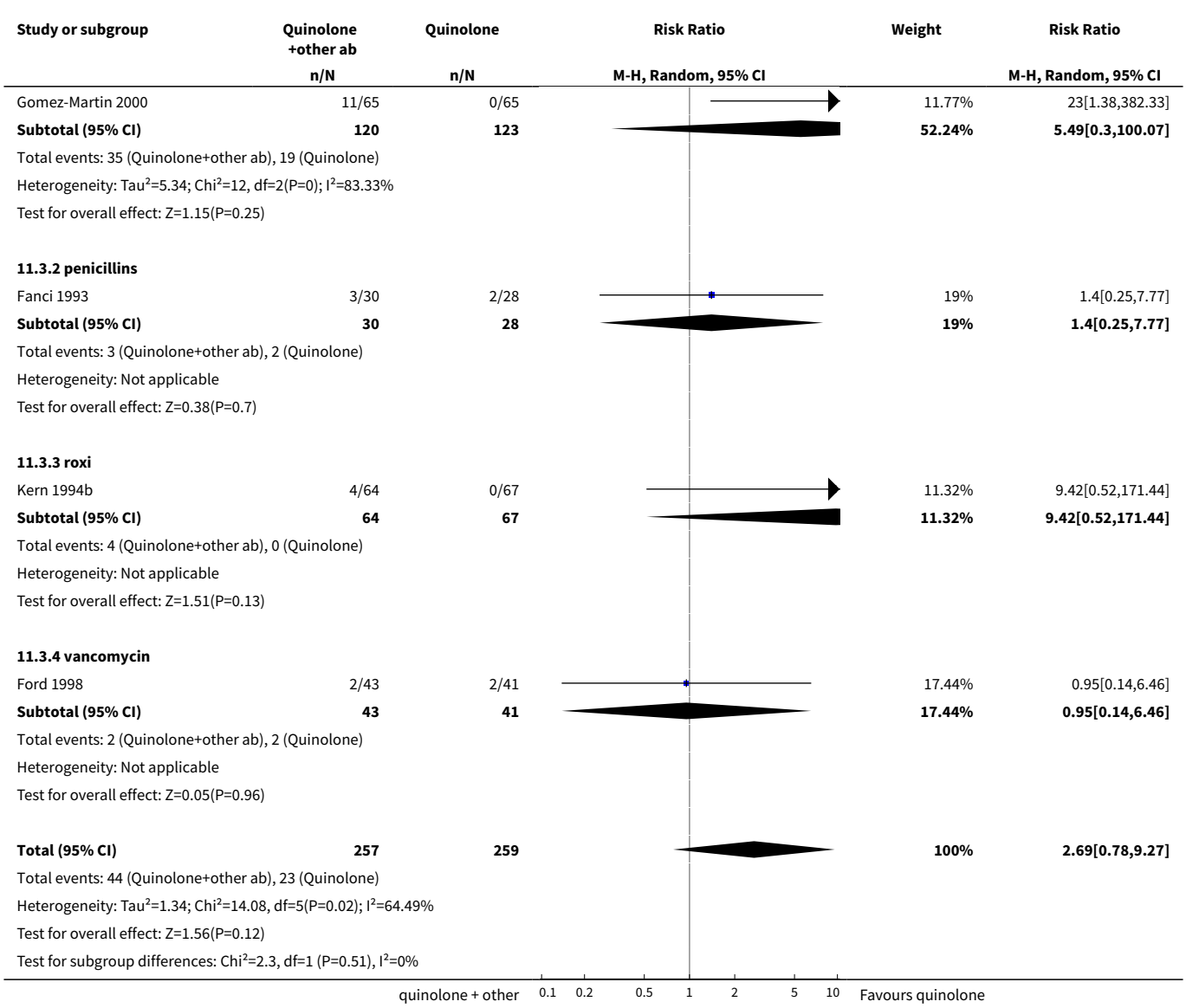
Analysis 11.2. Comparison 11 Side effects, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 2 quinolone vs. TMP-SMZ.



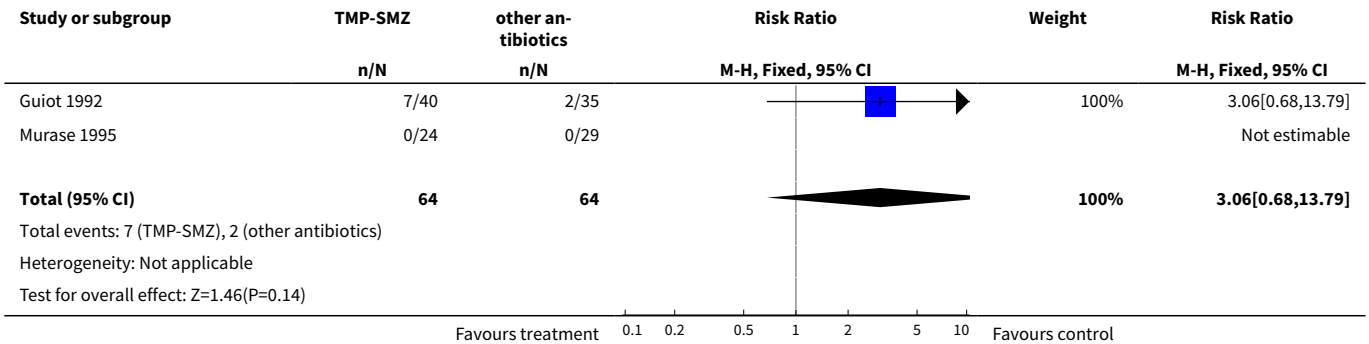


Analysis 11.3. Comparison 11 Side effects, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 3 quinolone+other vs. quinolone.



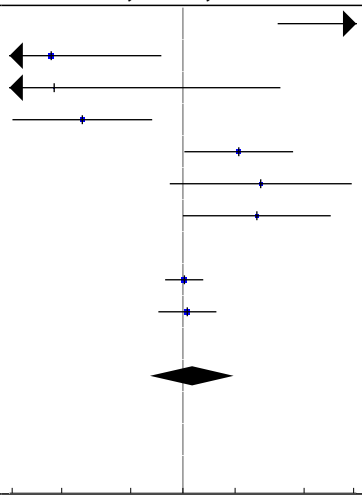


Analysis 11.4. Comparison 11 Side effects, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 4 TMP-SMZ vs. other.



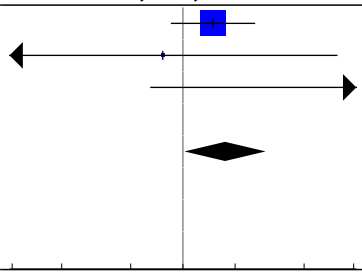
Analysis 11.5. Comparison 11 Side effects, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 5 nonabsorbable vs. systemic.

Study or subgroup	nonabsorbable n/N	systemic n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Wade 1981a	26/26	0/27		3.36%	54.96[3.52,857.56]
Watson 1982	2/47	10/41		8.26%	0.17[0.04,0.75]
Kurrle 1983	0/41	2/37		2.9%	0.18[0.01,3.65]
Kurrle 1986	5/70	19/70		12.54%	0.26[0.1,0.67]
Winston 1986	14/30	8/36		14.56%	2.1[1.02,4.32]
Winston 1990	9/32	3/30		10.08%	2.81[0.84,9.41]
Archimbaud 1991	13/74	5/76		12.04%	2.67[1,7.12]
Gluckman 1991	0/22	0/22			Not estimable
Jansen 1994	26/36	49/69		18.58%	1.02[0.79,1.31]
Prentice 2001	31/73	30/75		17.68%	1.06[0.72,1.56]
Total (95% CI)	**451**	**483**		**100%**	**1.13[0.65,1.96]**
Total events: 126 (nonabsorbable), 126 (systemic)					
Heterogeneity: Tau^2=0.41; Chi^2=35.5, df=8(P<0.0001); I^2=77.46%					
Test for overall effect: Z=0.42(P=0.68)					



Analysis 11.6. Comparison 11 Side effects, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 6 systemic + nonabsorbable vs systemic.

Study or subgroup	systemic + nonabsorb n/N	systemic n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Malarme 1981	25/41	9/22		84.91%	1.49[0.85,2.61]
Starke 1982	1/17	2/26		11.46%	0.76[0.08,7.79]
Nemet 1989	5/20	0/20		3.62%	11[0.65,186.62]
Total (95% CI)	**78**	**68**		**100%**	**1.75[1.02,3]**
Total events: 31 (systemic + nonabsorb), 11 (systemic)					
Heterogeneity: Tau^2=0; Chi^2=2.43, df=2(P=0.3); I^2=17.66%					
Test for overall effect: Z=2.05(P=0.04)					



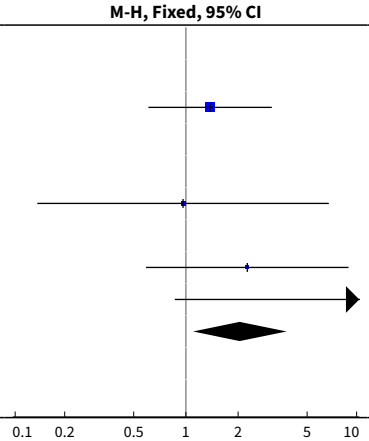
Comparison 12. Side effects requiring discontinuation, prophylaxis versus placebo or no intervention or other antibiotic

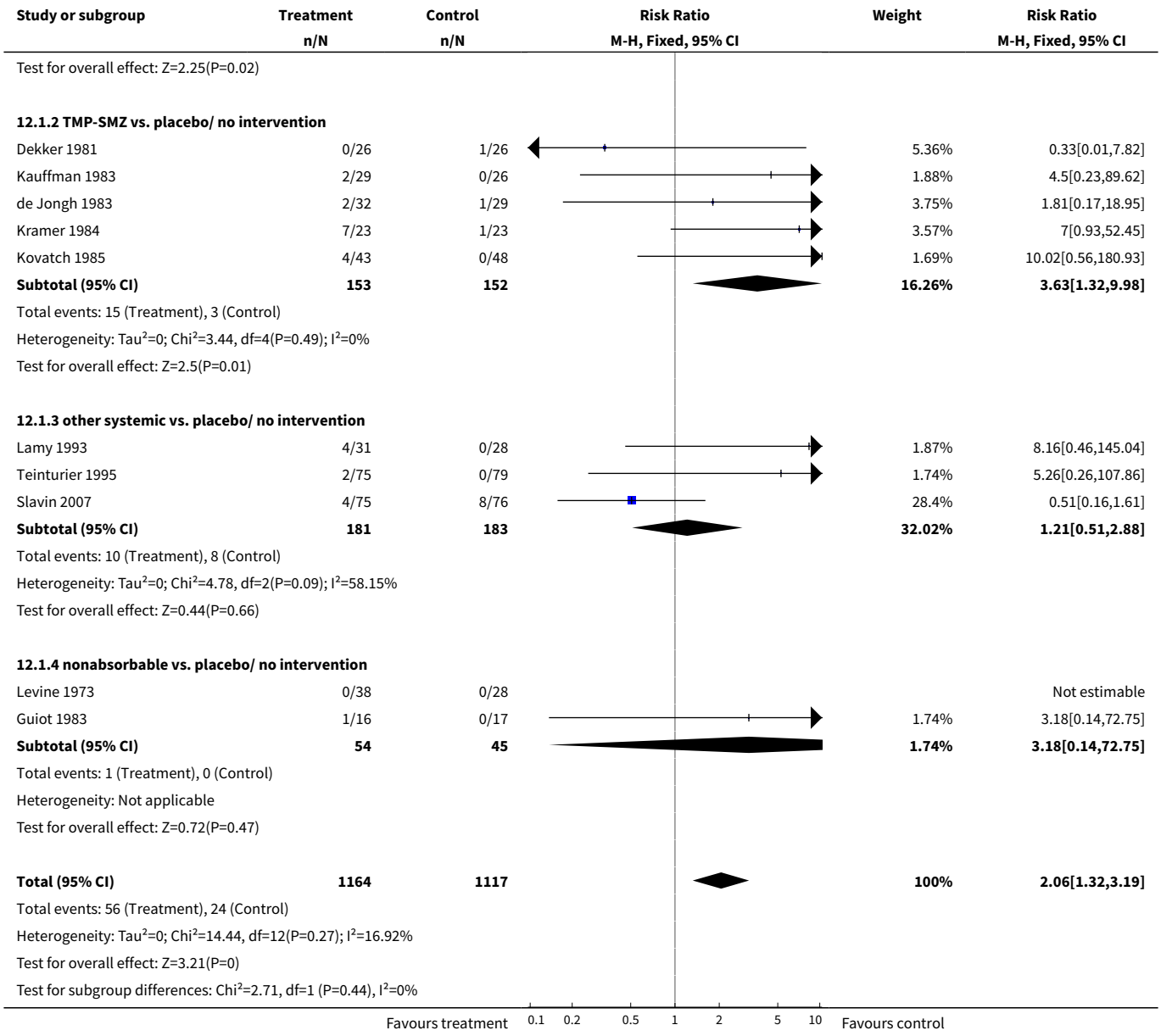
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 drug vs. placebo/no intervention	18	2281	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [1.32, 3.19]
1.1 quinolone vs. placebo/ no intervention	8	1513	Risk Ratio (M-H, Fixed, 95% CI)	2.04 [1.10, 3.81]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 TMP-SMZ vs. placebo/ no intervention	5	305	Risk Ratio (M-H, Fixed, 95% CI)	3.63 [1.32, 9.98]
1.3 other systemic vs. placebo/ no intervention	3	364	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.51, 2.88]
1.4 nonabsorbable vs. placebo/ no intervention	2	99	Risk Ratio (M-H, Fixed, 95% CI)	3.18 [0.14, 72.75]
2 quinolone vs. TMP-SMZ	7	850	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.16, 0.87]
2.1 ciprofloxacin vs. TMP-SMZ	3	481	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.12, 1.68]
2.2 ofloxacin vs. TMP-SMZ	2	262	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.10, 0.53]
2.3 norfloxacin vs. TMP-SMZ	2	107	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.11, 2.69]
3 quinolone+other vs. quinolone	5	432	Risk Ratio (M-H, Fixed, 95% CI)	4.92 [1.61, 15.01]
3.1 rifampin	3	243	Risk Ratio (M-H, Fixed, 95% CI)	10.0 [1.32, 75.73]
3.2 penicillins	1	58	Risk Ratio (M-H, Fixed, 95% CI)	1.4 [0.25, 7.77]
3.3 roxi	1	131	Risk Ratio (M-H, Fixed, 95% CI)	9.42 [0.52, 171.44]
4 TMP-SMZ vs. other	1	53	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 nonabsorbable vs. systemic	2	132	Risk Ratio (M-H, Fixed, 95% CI)	0.04 [0.00, 0.69]
6 systemic + nonabsorbable vs systemic	1	63	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.56, 2.80]

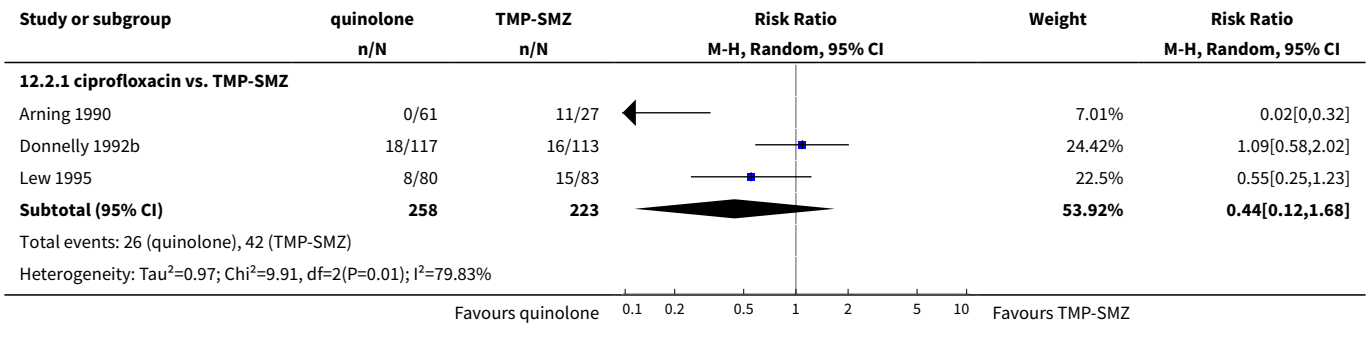
Analysis 12.1. Comparison 12 Side effects requiring discontinuation, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 1 drug vs. placebo/no intervention.

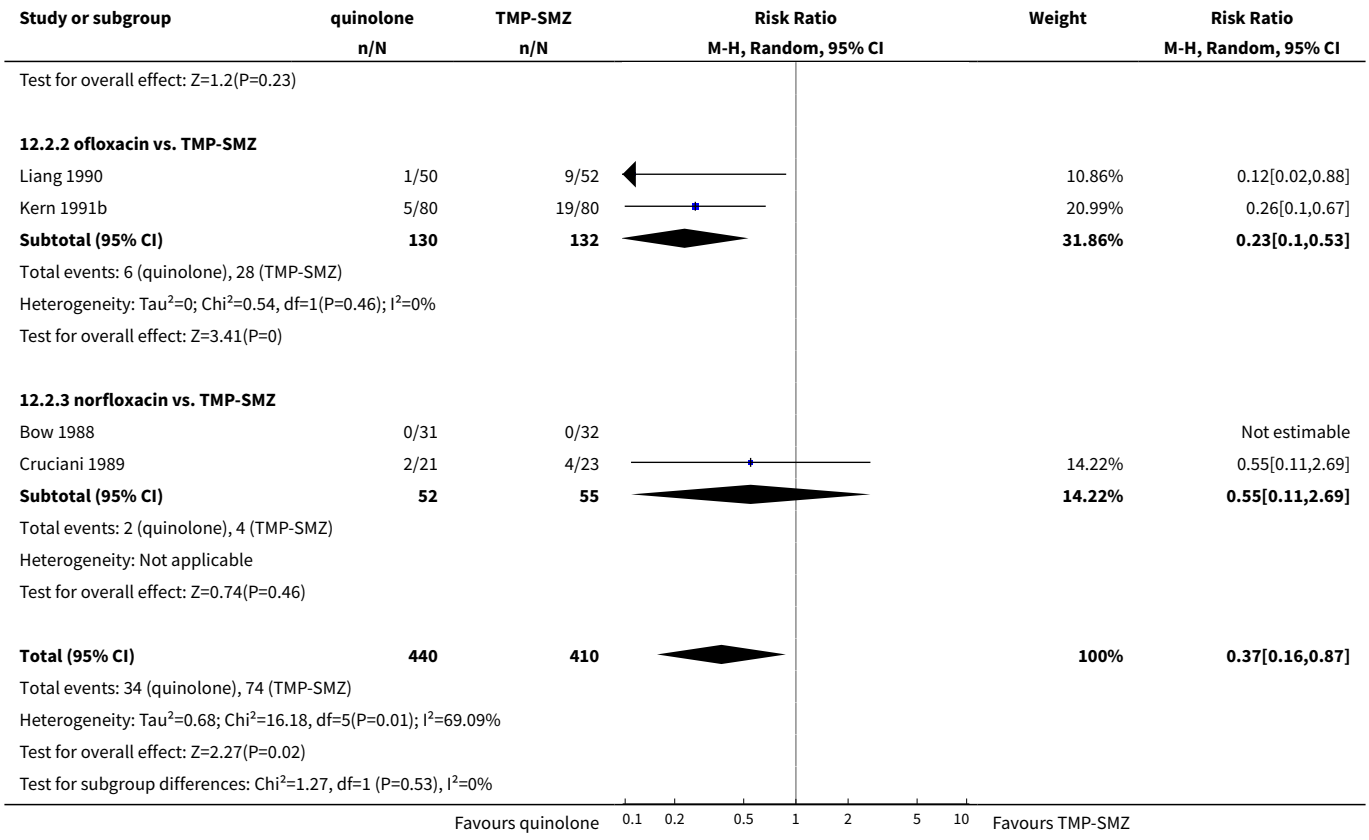
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
12.1.1 quinolone vs. placebo/ no intervention					
Yamada 1993	0/52	0/51			Not estimable
Talbot 1993	12/62	8/57		29.79%	1.38[0.61,3.13]
Carlson 1997	0/45	0/45			Not estimable
Ruiz 2001	0/25	0/25			Not estimable
Tjan Heijnen 2001	2/82	2/79		7.28%	0.96[0.14,6.67]
Lee 2002	0/46	0/49			Not estimable
Bucaneve 2005	7/375	3/363		10.9%	2.26[0.59,8.67]
Papaiakovou 2010	9/89	0/68		2.02%	14.57[0.86,245.97]
Subtotal (95% CI)	**776**	**737**		**49.99%**	**2.04[1.1,3.81]**
Total events: 30 (Treatment), 13 (Control)					
Heterogeneity: $Tau^2=0$; $Chi^2=3.34$, df=3(P=0.34); $I^2=10.24\%$					



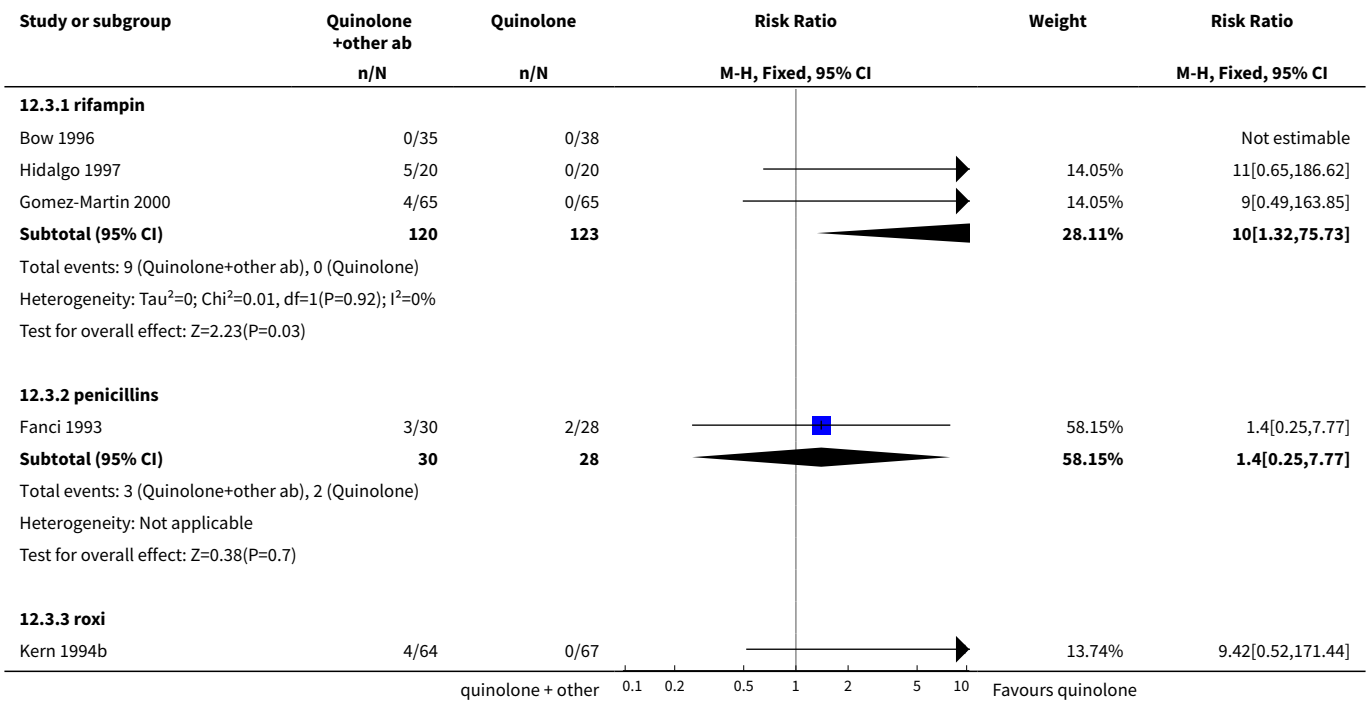


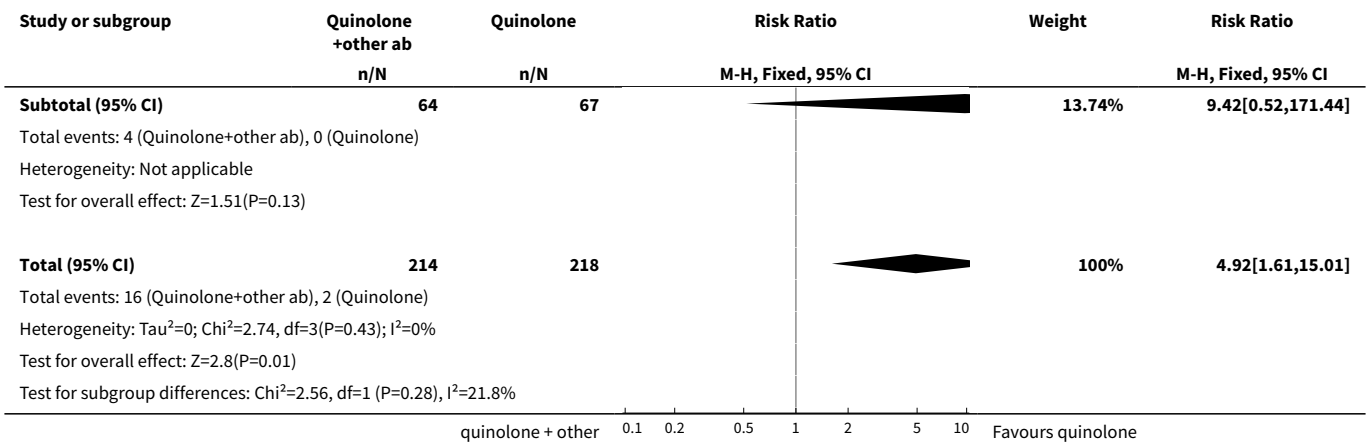
Analysis 12.2. Comparison 12 Side effects requiring discontinuation, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 2 quinolone vs. TMP-SMZ.



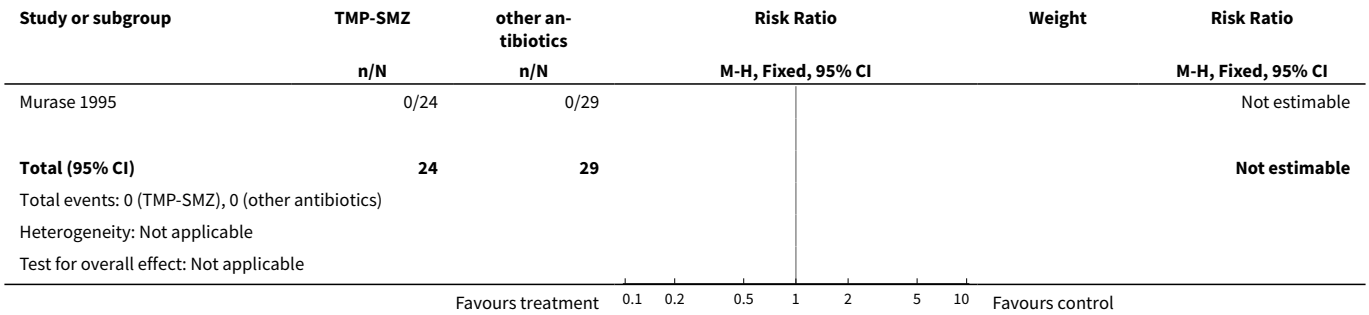


Analysis 12.3. Comparison 12 Side effects requiring discontinuation, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 3 quinolone+other vs. quinolone.

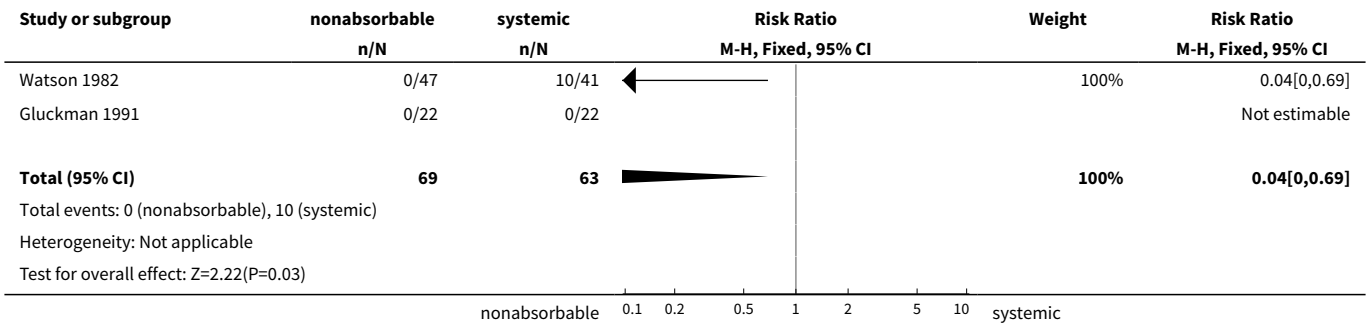




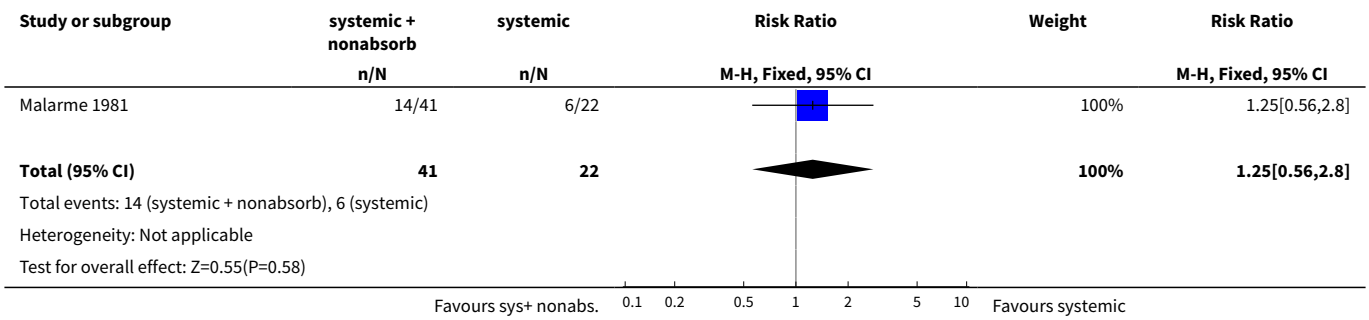
Analysis 12.4. Comparison 12 Side effects requiring discontinuation, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 4 TMP-SMZ vs. other.



Analysis 12.5. Comparison 12 Side effects requiring discontinuation, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 5 nonabsorbable vs. systemic.



Analysis 12.6. Comparison 12 Side effects requiring discontinuation, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 6 systemic + nonabsorbable vs systemic.



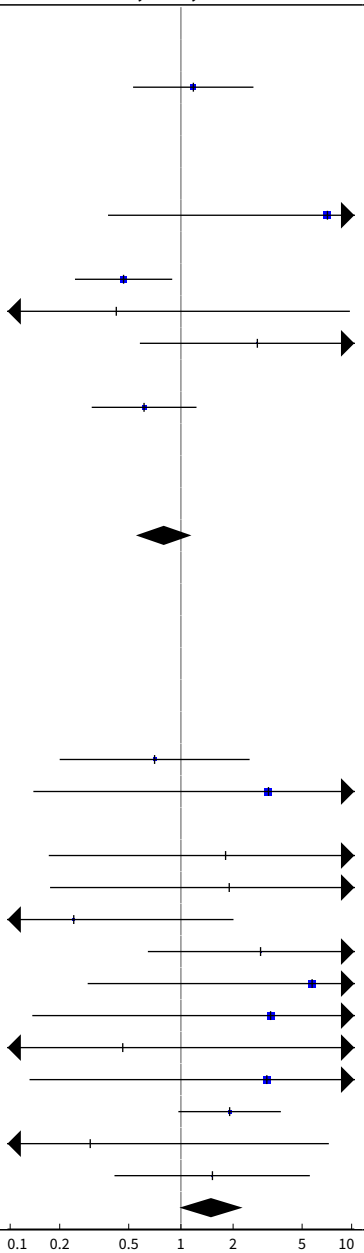
Comparison 13. Fungal infection, prophylaxis versus placebo or no intervention or other antibiotic

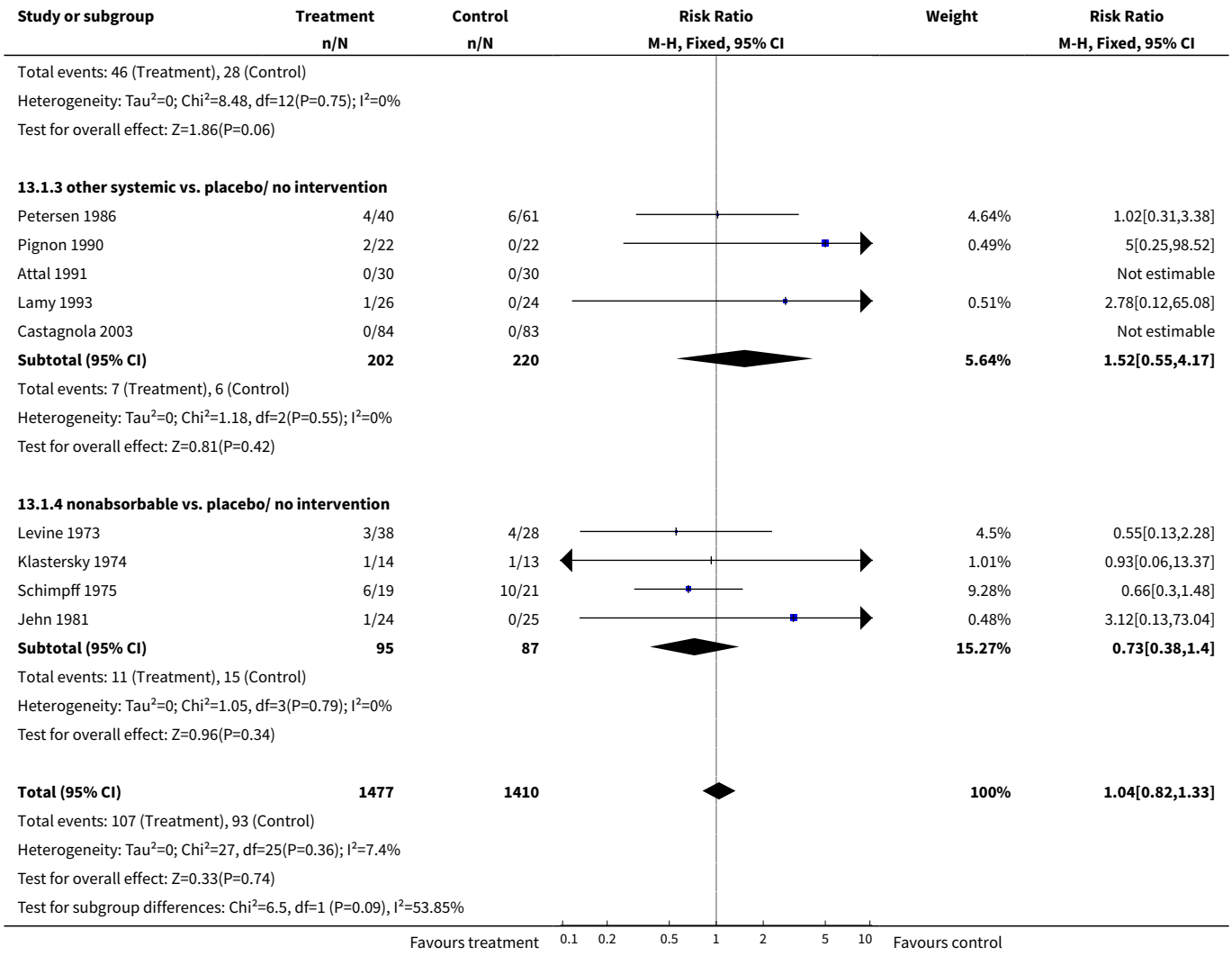
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 drug vs. placebo/ no intervention	39	2887	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.82, 1.33]
1.1 quinolone vs. placebo/ no intervention	15	1276	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.55, 1.15]
1.2 TMP-SMZ vs. placebo/ no intervention	15	1007	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.98, 2.27]
1.3 other systemic vs. placebo/ no intervention	5	422	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.55, 4.17]
1.4 nonabsorbable vs. placebo/ no intervention	4	182	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.38, 1.40]
2 quinolone vs. TMP-SMZ	10	789	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.36, 1.16]
2.1 ciprofloxacin vs. TMP-SMZ	3	289	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.39, 3.92]
2.2 ofloxacin vs. TMP-SMZ	3	272	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.25, 1.37]
2.3 norfloxacin vs. TMP-SMZ	3	166	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.12, 1.68]
2.4 Nalidixic acid vs. TMP-SMZ	1	62	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.01, 4.83]
3 quinolone+other vs. quinolone	5	489	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.37, 3.47]
3.1 rifampin	3	274	Risk Ratio (M-H, Fixed, 95% CI)	6.42 [0.27, 153.69]
3.2 roxi	1	131	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.12, 4.04]
3.3 vancomycin	1	84	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.14, 6.46]
4 TMP-SMZ vs. other	2	152	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.20, 10.81]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 nonabsorbable vs. systemic	10	800	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.64, 2.17]
6 systemic + nonabsorbable vs systemic	2	103	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.22, 3.02]

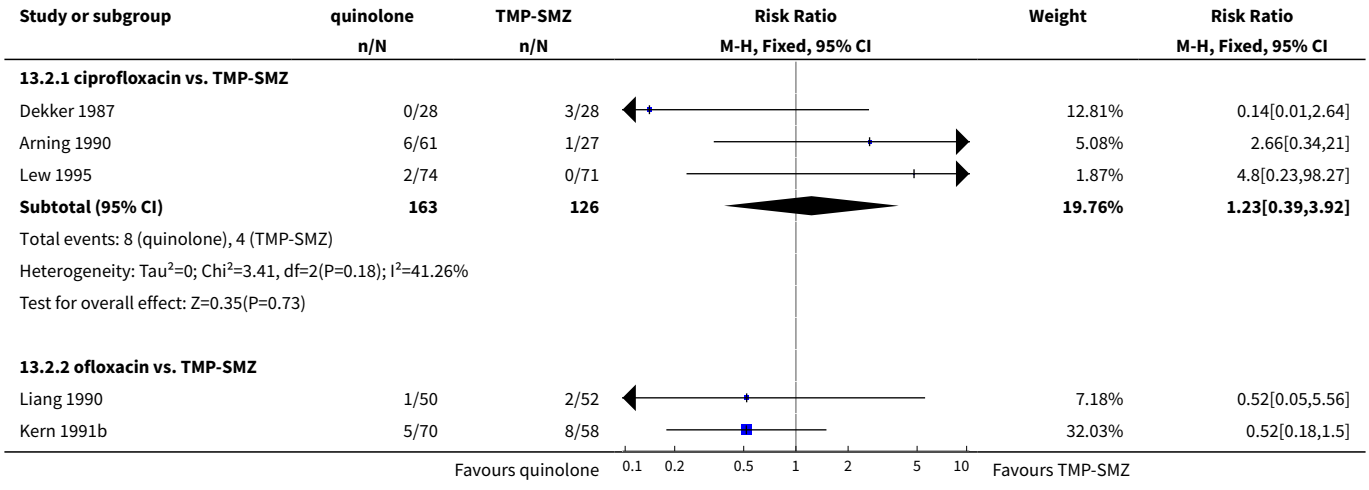
Analysis 13.1. Comparison 13 Fungal infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 1 drug vs. placebo/ no intervention.

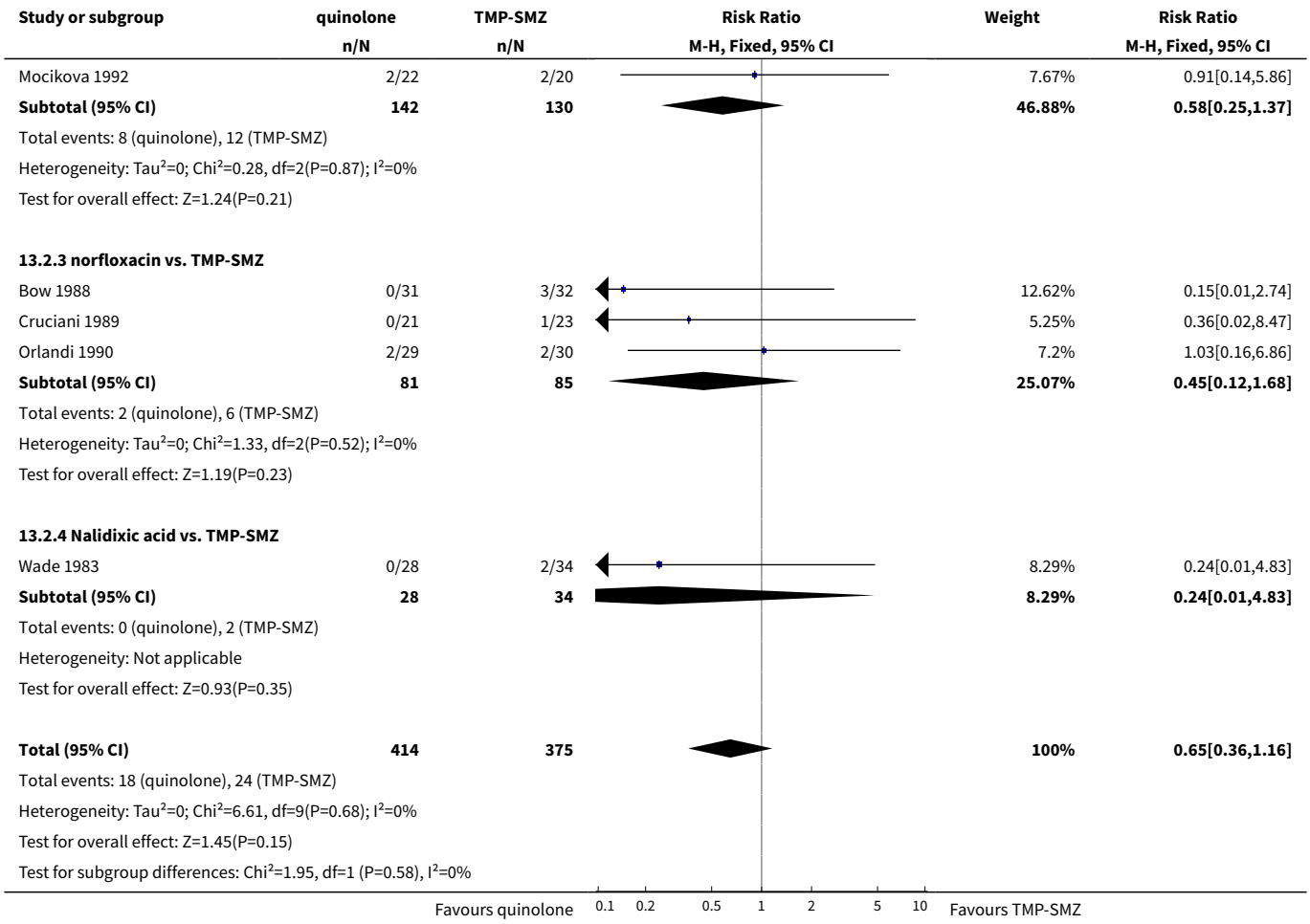
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
13.1.1 quinolone vs. placebo/ no intervention					
Hartlapp 1987	0/21	0/21			Not estimable
Karp 1987	10/35	8/33		8.04%	1.18[0.53,2.62]
Casali 1988	0/30	0/35			Not estimable
Lew 1991	0/7	0/11			Not estimable
Schroeder 1992	0/40	0/35			Not estimable
Tsutani 1992	3/25	0/25		0.49%	7[0.38,128.87]
Maiche 1993	0/29	0/30			Not estimable
Yamada 1993	10/52	21/51		20.71%	0.47[0.24,0.89]
Brodsky 1993	0/10	1/13		1.29%	0.42[0.02,9.43]
Talbot 1993	6/62	2/57		2.04%	2.76[0.58,13.12]
Carlson 1997	0/45	0/45			Not estimable
Thomas 2000	14/99	12/52		15.37%	0.61[0.31,1.23]
Tjan Heijnen 2001	0/82	0/79			Not estimable
Lee 2002	0/46	0/49			Not estimable
Papaiakovou 2010	0/89	0/68			Not estimable
Subtotal (95% CI)	**672**	**604**		**47.94%**	**0.8[0.55,1.15]**
Total events: 43 (Treatment), 44 (Control)					
Heterogeneity: Tau^2=0; Chi^2=8.82, df=5(P=0.12); I^2=43.33%					
Test for overall effect: Z=1.21(P=0.23)					
13.1.2 TMP-SMZ vs. placebo/ no intervention					
Enno 1978	0/14	0/16			Not estimable
Gurwith 1979	4/59	5/52		5.19%	0.71[0.2,2.49]
Weiser 1981	1/14	0/15		0.47%	3.2[0.14,72.62]
Dekker 1981	0/26	0/26			Not estimable
de Jongh 1983	2/32	1/29		1.02%	1.81[0.17,18.95]
Pizzo 1983	2/77	1/73		1%	1.9[0.18,20.47]
Kauffman 1983	1/27	4/26		3.98%	0.24[0.03,2.01]
Gualtieri 1983	6/24	2/23		2%	2.88[0.64,12.82]
Henry 1984b	2/20	0/23		0.46%	5.71[0.29,112.43]
Martino 1984	1/30	0/33		0.47%	3.29[0.14,77.82]
Lange 1984	0/25	1/35		1.23%	0.46[0.02,10.89]
Kramer 1984	1/22	0/23		0.48%	3.13[0.13,72.99]
Estey 1984	21/77	10/70		10.23%	1.91[0.97,3.77]
Kovatch 1985	0/39	1/35		1.54%	0.3[0.01,7.13]
Ward 1993	5/22	3/20		3.07%	1.52[0.41,5.54]
Subtotal (95% CI)	**508**	**499**		**31.15%**	**1.49[0.98,2.27]**



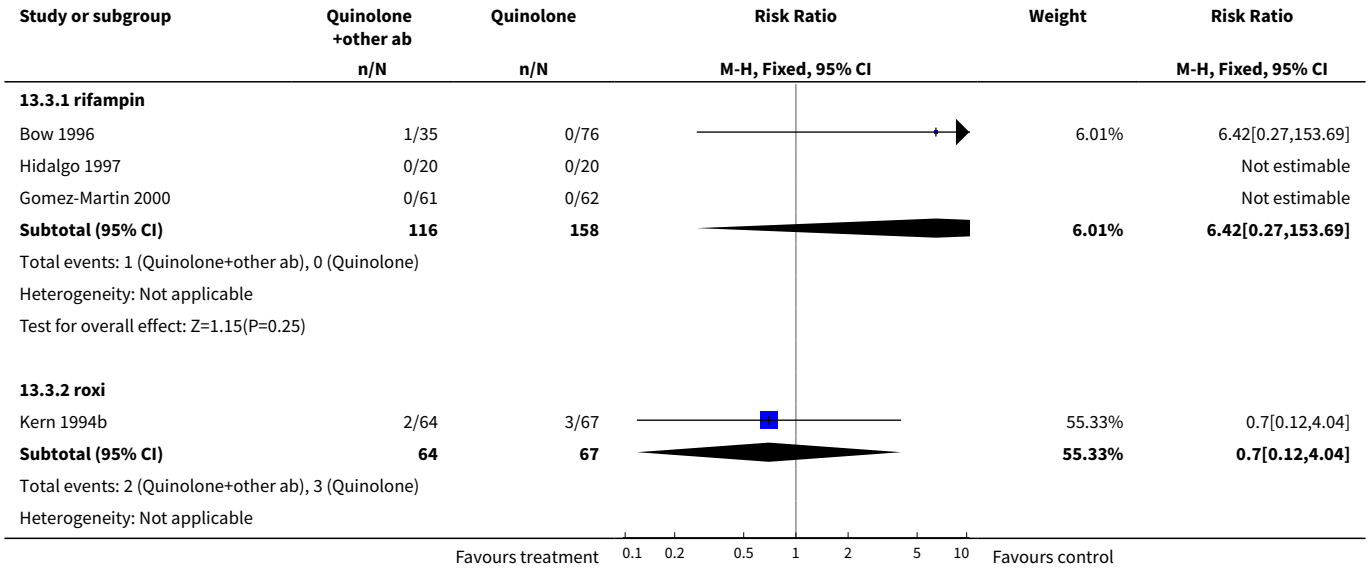


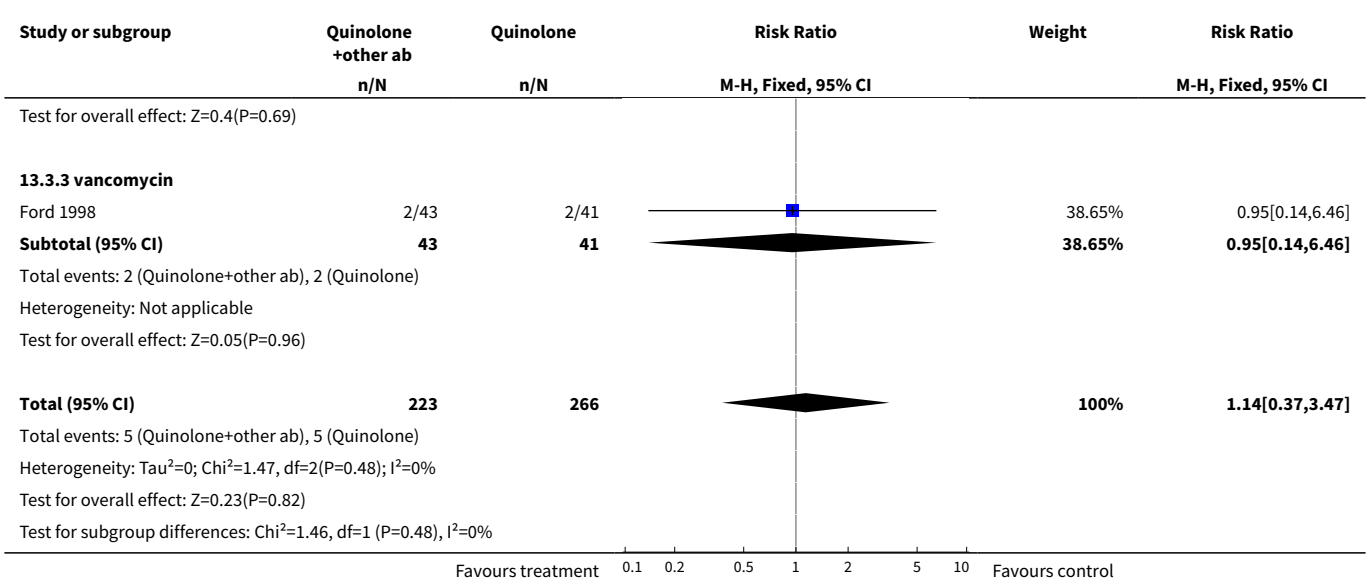
Analysis 13.2. Comparison 13 Fungal infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 2 quinolone vs. TMP-SMZ.



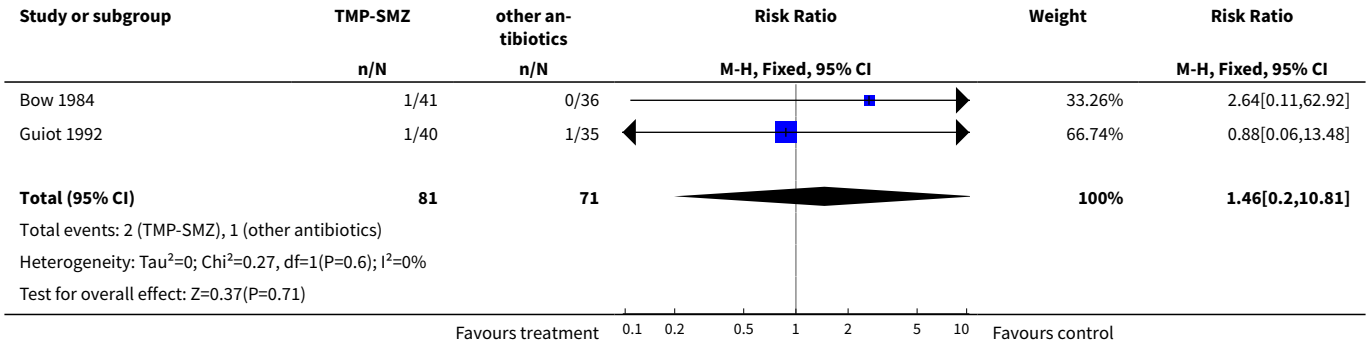


Analysis 13.3. Comparison 13 Fungal infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 3 quinolone+other vs. quinolone.

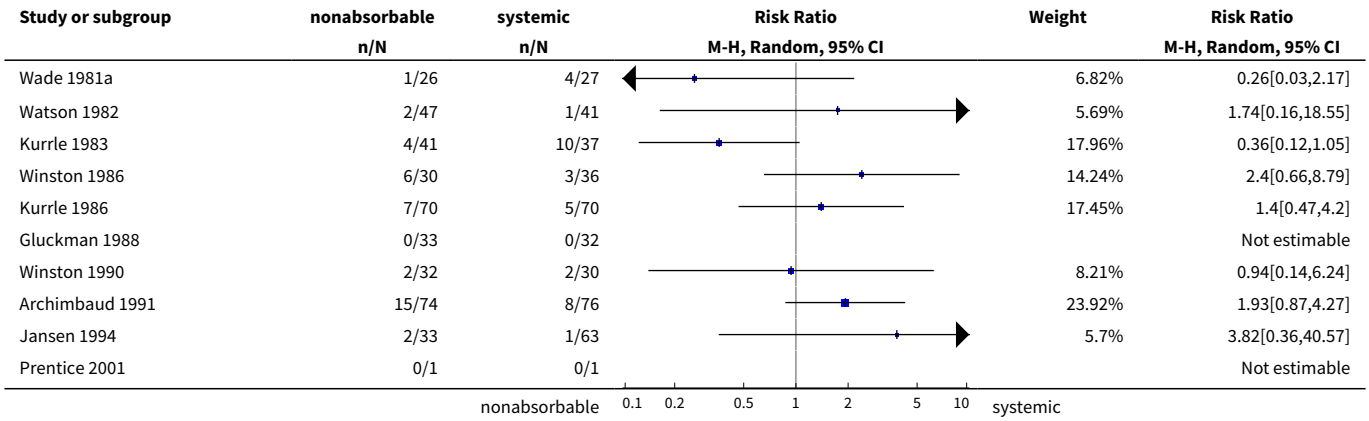


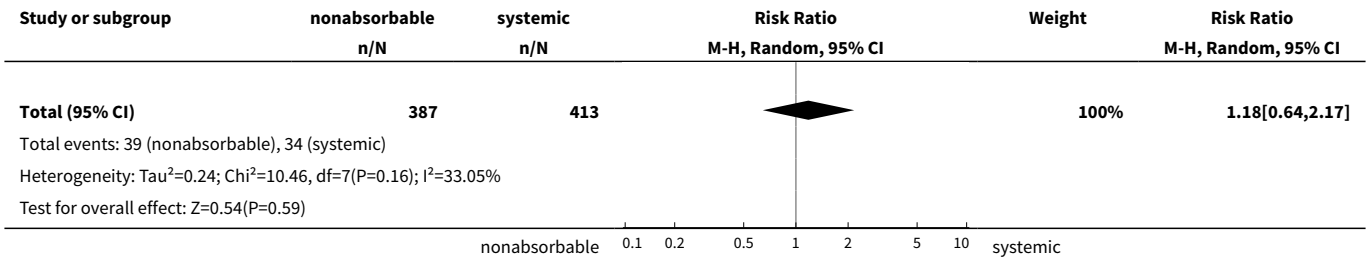


Analysis 13.4. Comparison 13 Fungal infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 4 TMP-SMZ vs. other.

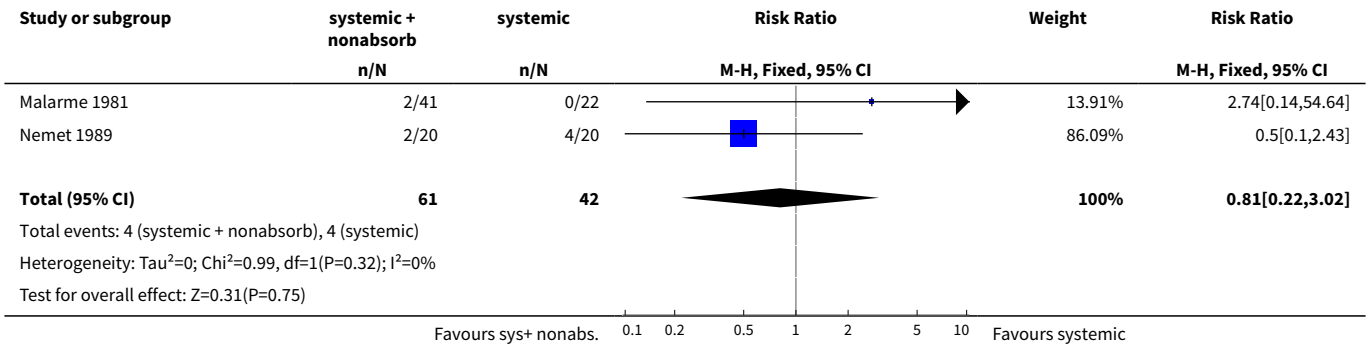


Analysis 13.5. Comparison 13 Fungal infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 5 nonabsorbable vs. systemic.





Analysis 13.6. Comparison 13 Fungal infection, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 6 systemic + nonabsorbable vs systemic.



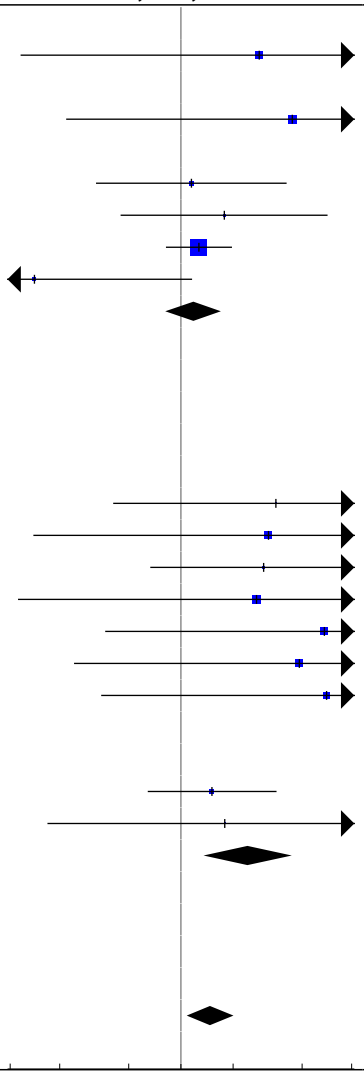
Comparison 14. Infection resistant to drug taken, prophylaxis versus placebo or no intervention or other antibiotic

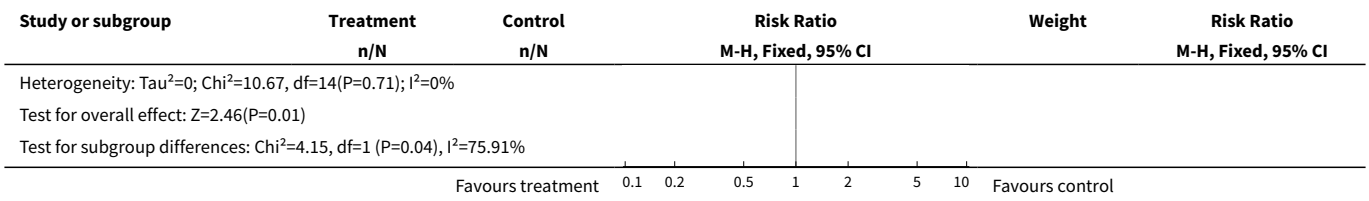
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 drug vs. placebo/ no intervention	19	3629	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [1.08, 2.01]
1.1 quinolone vs. placebo/ no intervention	8	2712	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.81, 1.70]
1.2 TMP-SMZ vs. placebo/ no intervention	11	917	Risk Ratio (M-H, Fixed, 95% CI)	2.42 [1.35, 4.36]
2 quinolone vs. TMP-SMZ	6	366	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.27, 0.74]
2.1 ciprofloxacin vs. TMP-SMZ	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.64]
2.2 ofloxacin vs. TMP-SMZ	2	144	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.07, 0.76]
2.3 norfloxacin vs. TMP-SMZ	3	166	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.35, 1.06]
3 ciprofloxacin vs. norfloxacin	1	619	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.16, 0.87]
4 norfloxacin vs. pefloxacin	1	136	Risk Ratio (M-H, Fixed, 95% CI)	2.15 [1.18, 3.91]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 quinolone+other vs. quinolone	4	463	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.06, 5.69]
5.1 rifampin	2	163	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 1.94]
5.2 penicillin	2	300	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.79, 2.04]
6 nonabsorbable vs. systemic	4	343	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.63, 1.12]
7 TMP-SMZ vs. other	2	152	Risk Ratio (M-H, Fixed, 95% CI)	4.74 [1.27, 17.65]

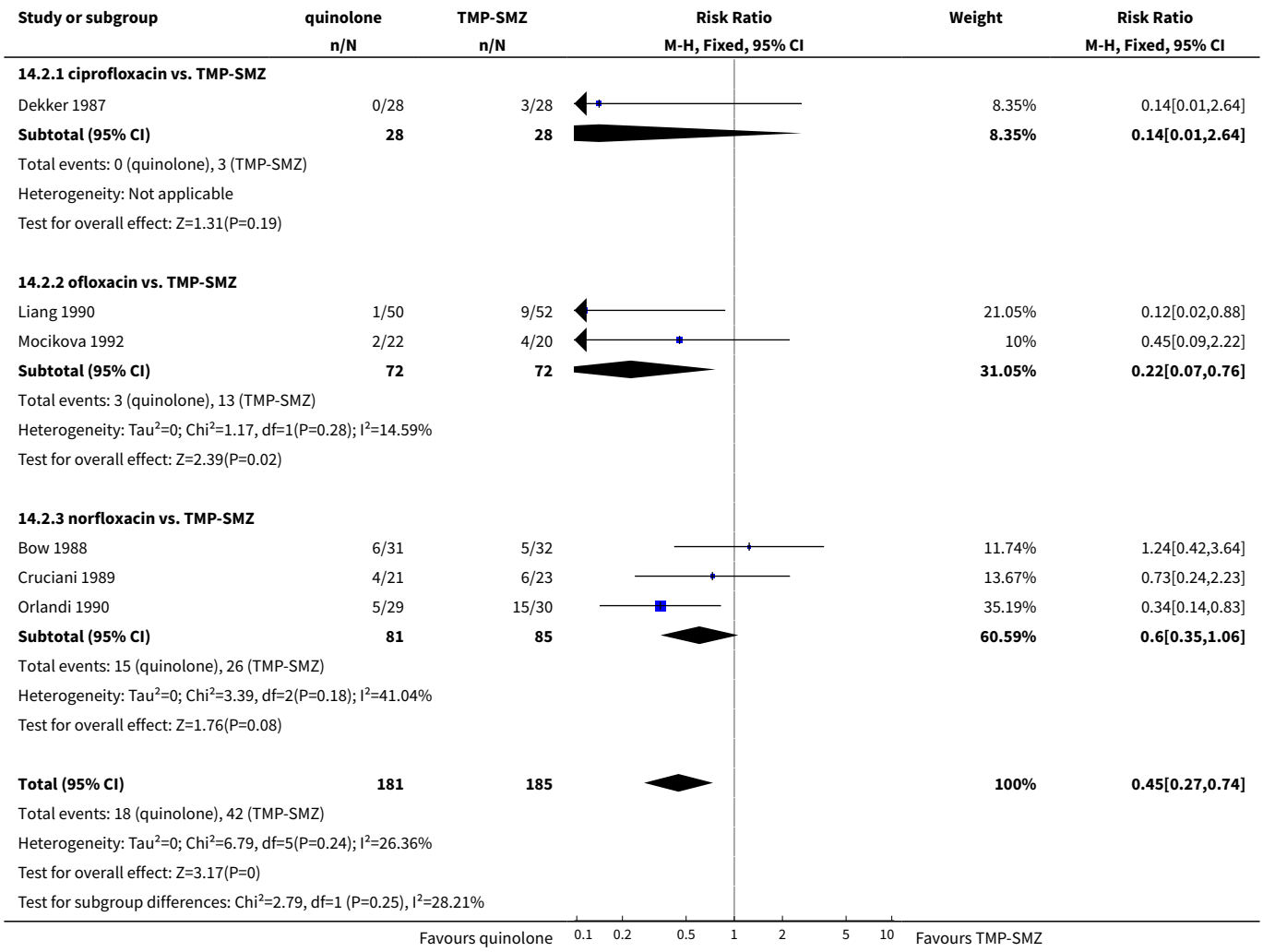
Analysis 14.1. Comparison 14 Infection resistant to drug taken, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 1 drug vs. placebo/ no intervention.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
14.1.1 quinolone vs. placebo/ no intervention					
Karp 1987	1/35	0/33		0.83%	2.83[0.12,67.19]
Casali 1988	0/30	0/35			Not estimable
Schroeder 1992	2/40	0/35		0.86%	4.39[0.22,88.46]
Tsutani 1992	0/25	0/25			Not estimable
Talbot 1993	5/62	4/57		6.71%	1.15[0.32,4.07]
Lee 2002	5/46	3/49		4.68%	1.78[0.45,7.01]
Bucaneve 2005	41/339	32/336		51.76%	1.27[0.82,1.97]
Cullen 2005	1/781	7/784		11.25%	0.14[0.02,1.16]
Subtotal (95% CI)	**1358**	**1354**		**76.09%**	**1.18[0.81,1.7]**
Total events: 55 (Treatment), 46 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.38, df=5(P=0.37); I^2=7.13%					
Test for overall effect: Z=0.86(P=0.39)					
14.1.2 TMP-SMZ vs. placebo/ no intervention					
Gurwith 1979	4/59	1/52		1.71%	3.53[0.41,30.55]
Weiser 1981	1/14	0/15		0.78%	3.2[0.14,72.62]
Dekker 1981	6/26	2/26		3.22%	3[0.67,13.51]
de Jongh 1983	1/32	0/29		0.84%	2.73[0.12,64.42]
Gualtieri 1983	3/24	0/23		0.82%	6.72[0.37,123.33]
Kauffman 1983	2/27	0/26		0.82%	4.82[0.24,95.88]
Lange 1984	2/25	0/35		0.68%	6.92[0.35,138.25]
Henry 1984b	0/20	0/23			Not estimable
Kramer 1984	0/22	0/23			Not estimable
EORTC 1984	13/177	8/165		13.34%	1.51[0.64,3.56]
Kovatch 1985	2/39	1/35		1.7%	1.79[0.17,18.95]
Subtotal (95% CI)	**465**	**452**		**23.91%**	**2.42[1.35,4.36]**
Total events: 34 (Treatment), 12 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.6, df=8(P=0.96); I^2=0%					
Test for overall effect: Z=2.95(P=0)					
Total (95% CI)	**1823**	**1806**		**100%**	**1.47[1.08,2.01]**
Total events: 89 (Treatment), 58 (Control)					

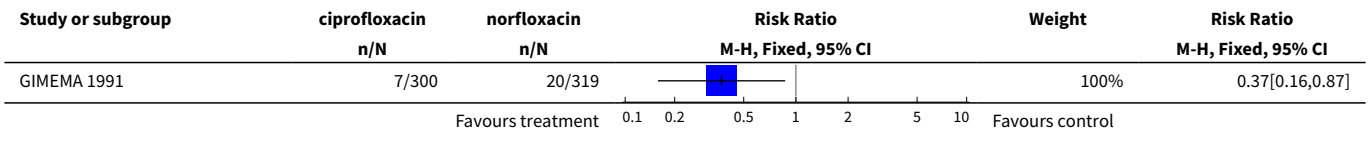


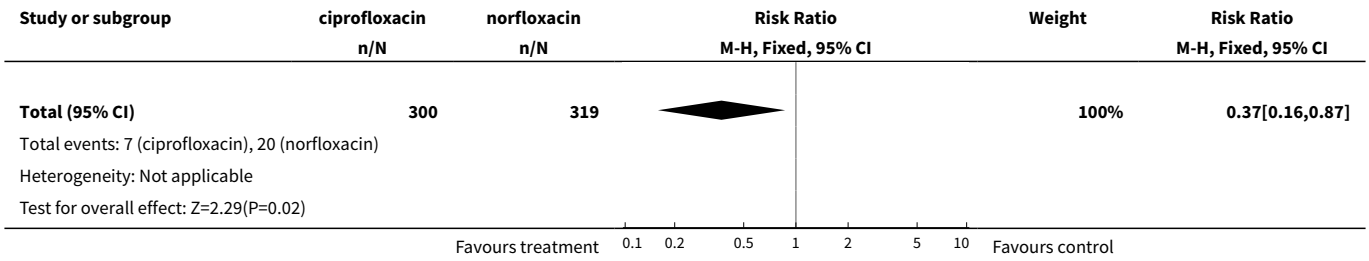


Analysis 14.2. Comparison 14 Infection resistant to drug taken, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 2 quinolone vs. TMP-SMZ.

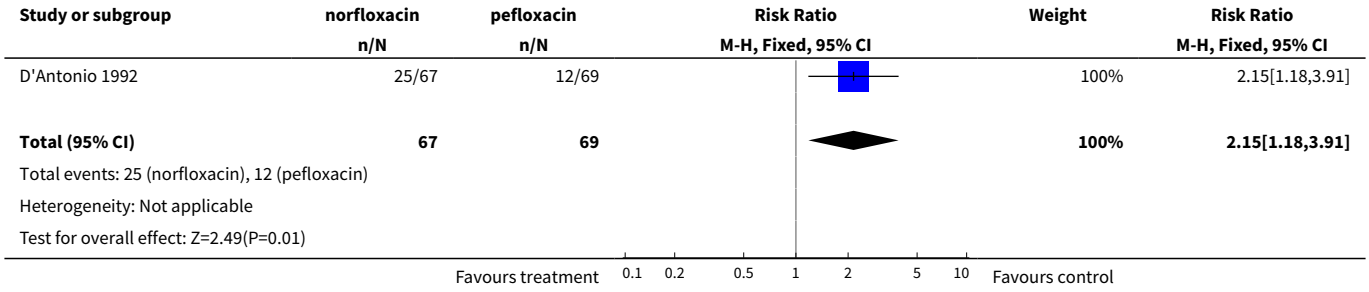


Analysis 14.3. Comparison 14 Infection resistant to drug taken, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 3 ciprofloxacin vs. norfloxacin.

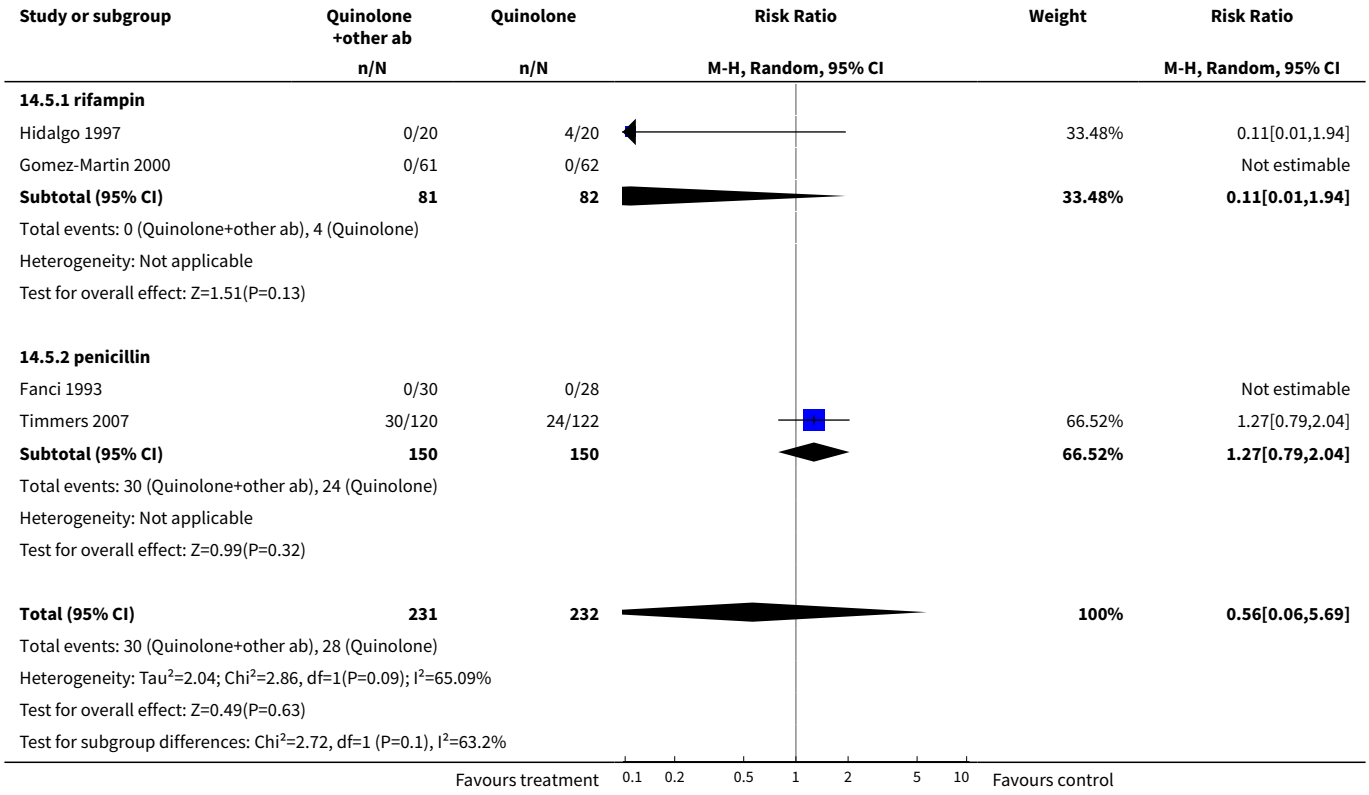




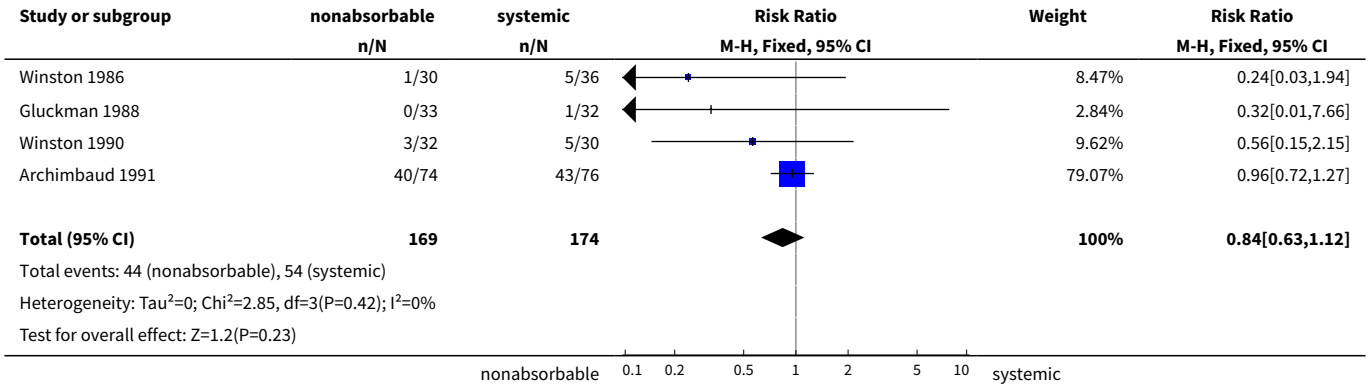
Analysis 14.4. Comparison 14 Infection resistant to drug taken, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 4 norfloxacin vs. pefloxacin.



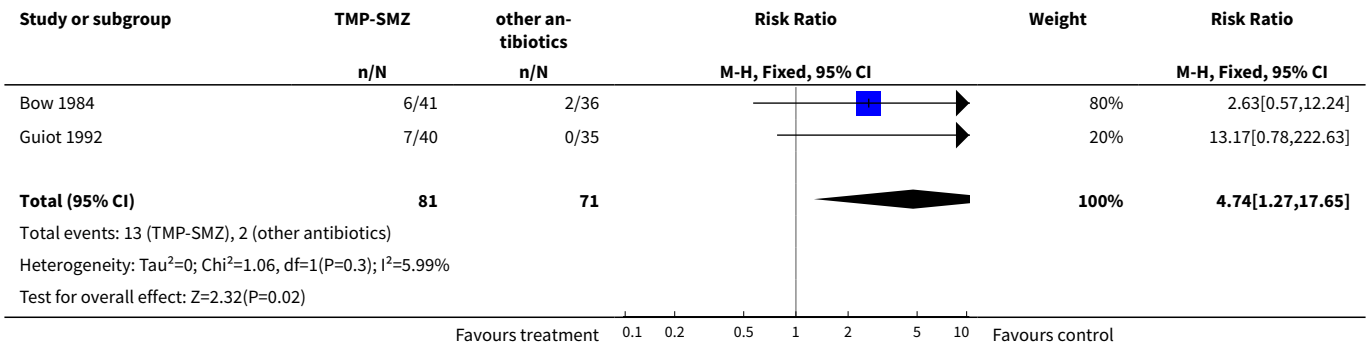
Analysis 14.5. Comparison 14 Infection resistant to drug taken, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 5 quinolone+other vs. quinolone.



Analysis 14.6. Comparison 14 Infection resistant to drug taken, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 6 nonabsorbable vs. systemic.



Analysis 14.7. Comparison 14 Infection resistant to drug taken, prophylaxis versus placebo or no intervention or other antibiotic, Outcome 7 TMP-SMZ vs. other.



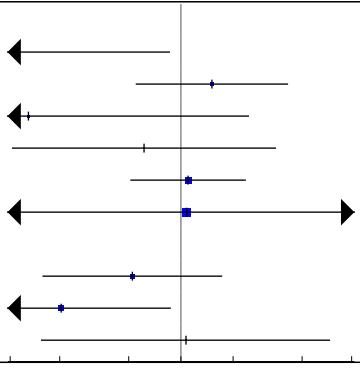
Comparison 15. All-cause mortality, quinolone versus placebo or no intervention, according to different characteristics

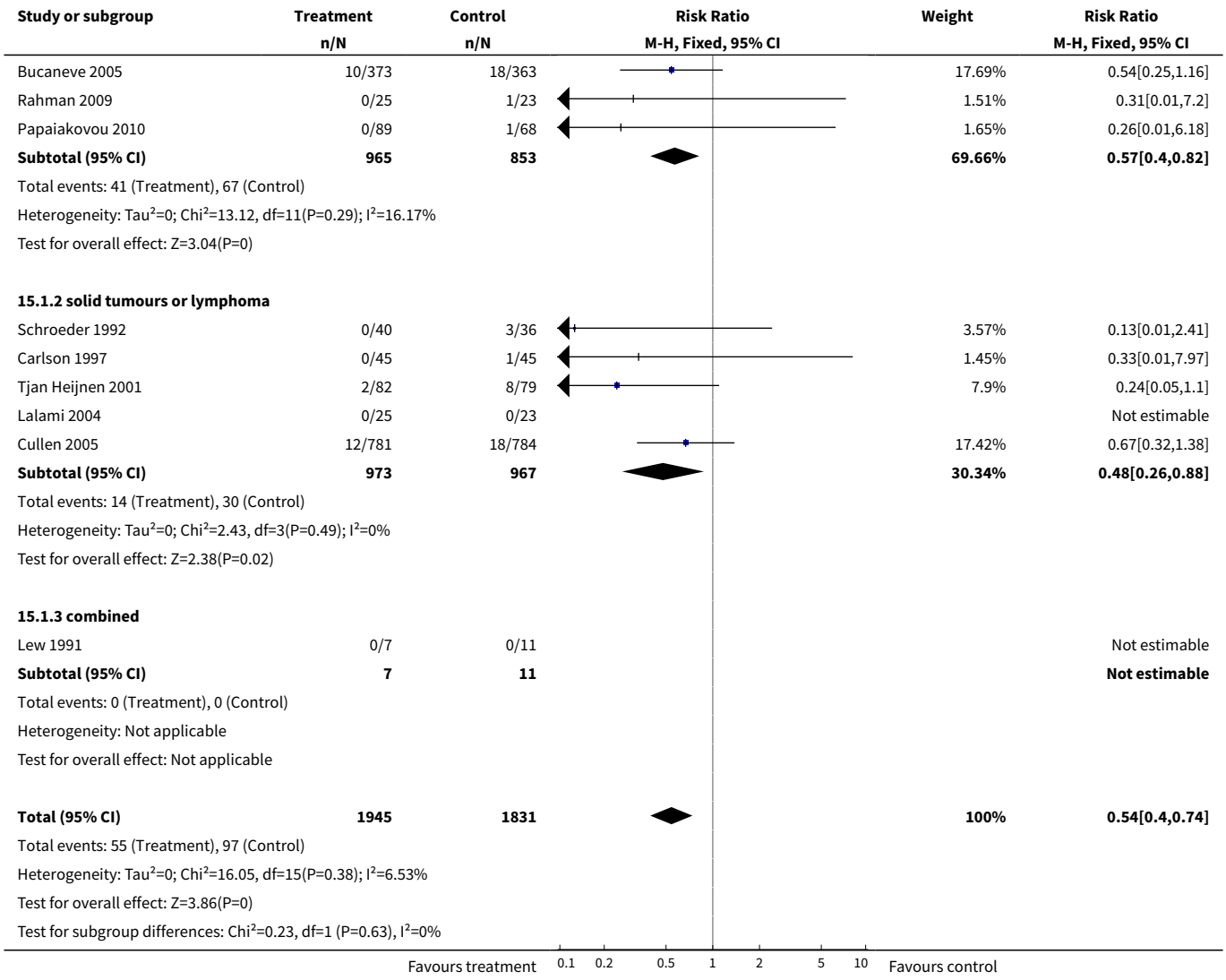
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 quinolone vs. placebo/no intervention according to disease status	19	3776	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.40, 0.74]
1.1 acute leukaemia or allogeneic hematopoietic cell transplant	13	1818	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.40, 0.82]
1.2 solid tumours or lymphoma	5	1940	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.26, 0.88]
1.3 combined	1	18	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 quinolone vs. placebo/no intervention according to type of quinolone	19	3776	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.40, 0.74]
2.1 levofloxacin	3	2349	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.35, 0.99]
2.2 ciprofloxacin	8	704	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.13, 0.69]
2.3 norfloxacin	4	272	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.58, 1.81]
2.4 other (ofloxacin/pefloxacin/enoxacin)	4	451	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.12, 0.64]
3 quinolone vs. placebo/no intervention according to timing of chemotherapy initiation	19	3776	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.40, 0.74]
3.1 with initiation of chemotherapy	15	1947	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.44, 0.92]
3.2 with appearance of neutropenia	4	1829	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.22, 0.70]
4 quinolone vs. placebo/no intervention according to year of publication	19	3776	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.40, 0.74]
4.1 studies published after 2000	8	2879	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.32, 0.75]
4.2 studies published before and until 2000	11	897	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.39, 0.96]

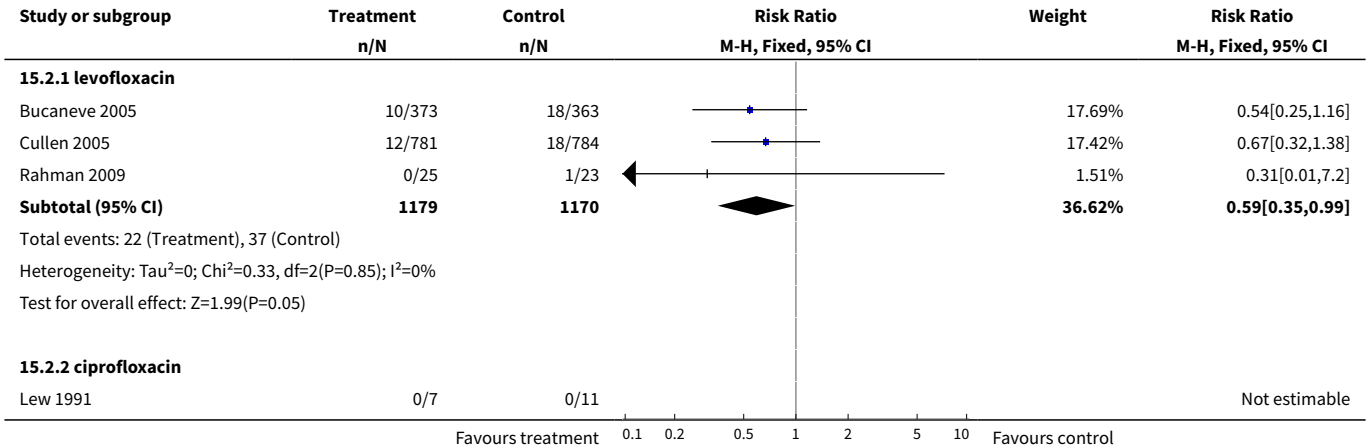
Analysis 15.1. Comparison 15 All-cause mortality, quinolone versus placebo or no intervention, according to different characteristics, Outcome 1 quinolone vs. placebo/no intervention according to disease status.

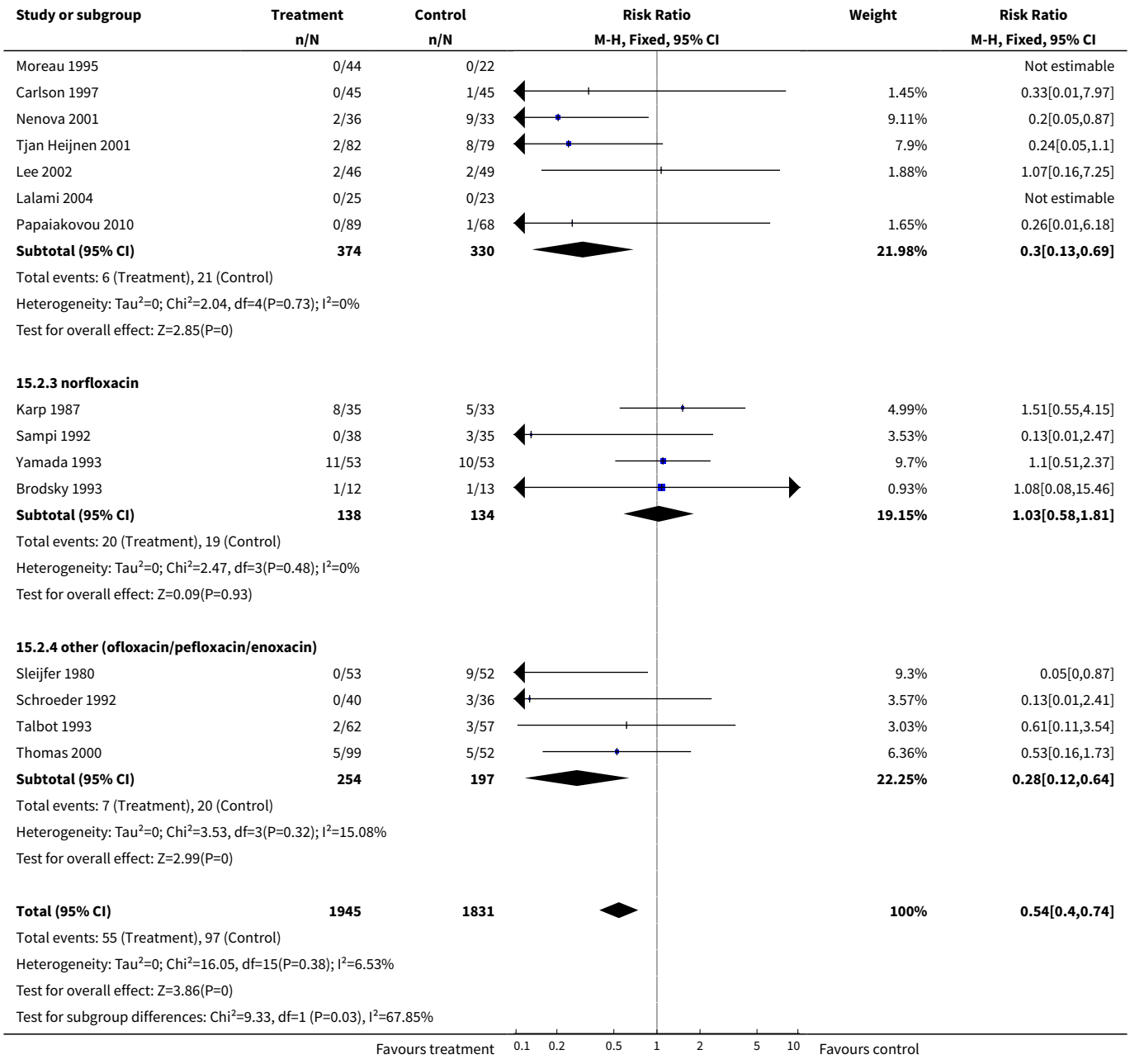
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
15.1.1 acute leukaemia or allogeneic hematopoietic cell transplant					
Sleijfer 1980	0/53	9/52		9.3%	0.05[0,0.87]
Karp 1987	8/35	5/33		4.99%	1.51[0.55,4.15]
Sampi 1992	0/38	3/35		3.53%	0.13[0.01,2.47]
Talbot 1993	2/62	3/57		3.03%	0.61[0.11,3.54]
Yamada 1993	11/53	10/53		9.7%	1.1[0.51,2.37]
Brodsky 1993	1/12	1/13		0.93%	1.08[0.08,15.46]
Moreau 1995	0/44	0/22			Not estimable
Thomas 2000	5/99	5/52		6.36%	0.53[0.16,1.73]
Nenova 2001	2/36	9/33		9.11%	0.2[0.05,0.87]
Lee 2002	2/46	2/49		1.88%	1.07[0.16,7.25]



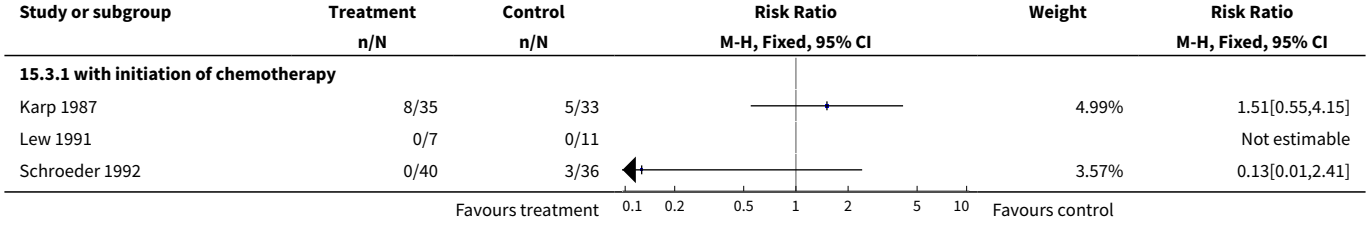


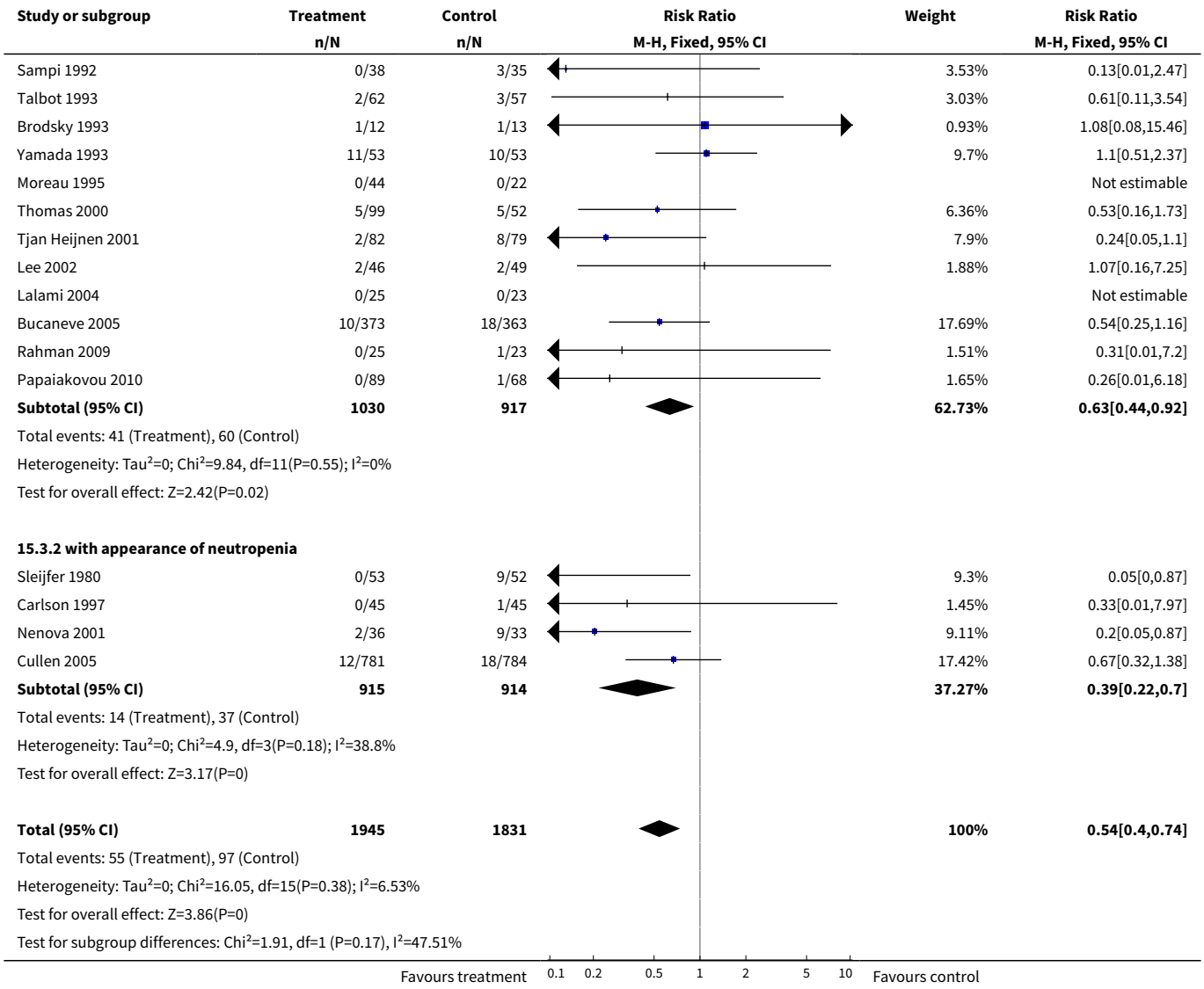
Analysis 15.2. Comparison 15 All-cause mortality, quinolone versus placebo or no intervention, according to different characteristics, Outcome 2 quinolone vs. placebo/no intervention according to type of quinolone.



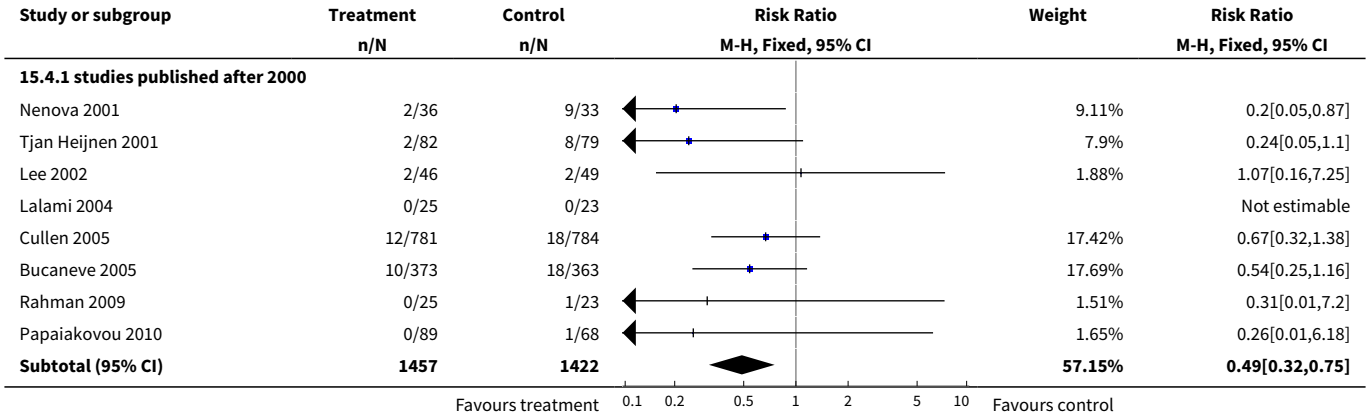


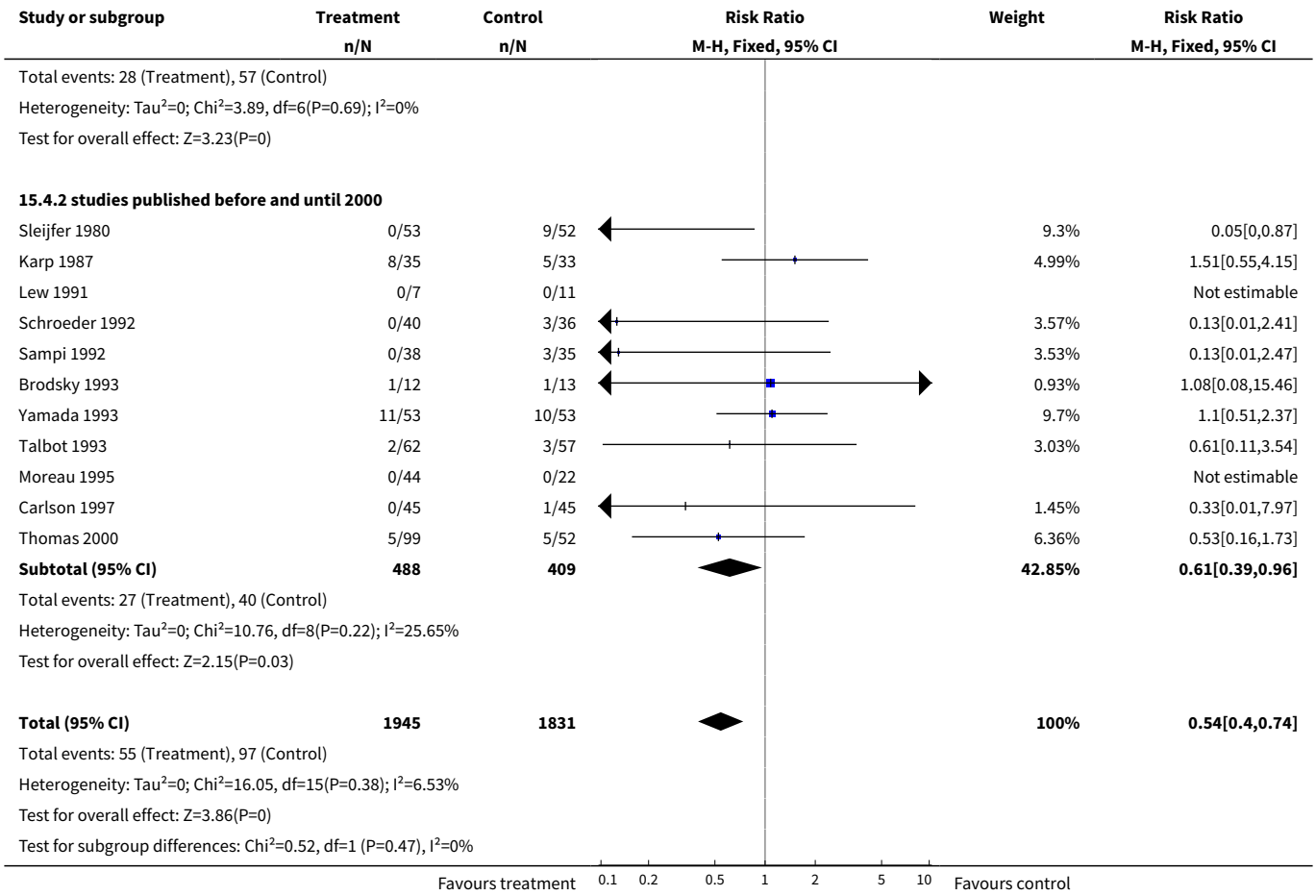
Analysis 15.3. Comparison 15 All-cause mortality, quinolone versus placebo or no intervention, according to different characteristics, Outcome 3 quinolone vs. placebo/no intervention according to timing of chemotherapy initiation.





Analysis 15.4. Comparison 15 All-cause mortality, quinolone versus placebo or no intervention, according to different characteristics, Outcome 4 quinolone vs. placebo/no intervention according to year of publication.





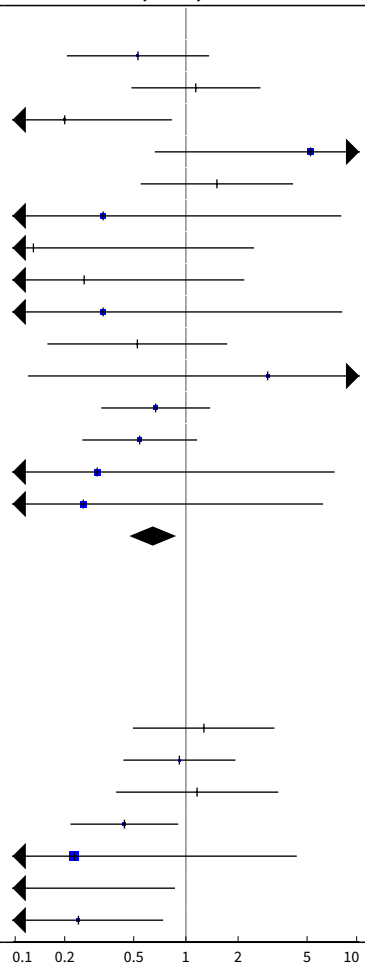
Comparison 16. Sensitivity analyses by randomisation generation, drug versus placebo or no intervention

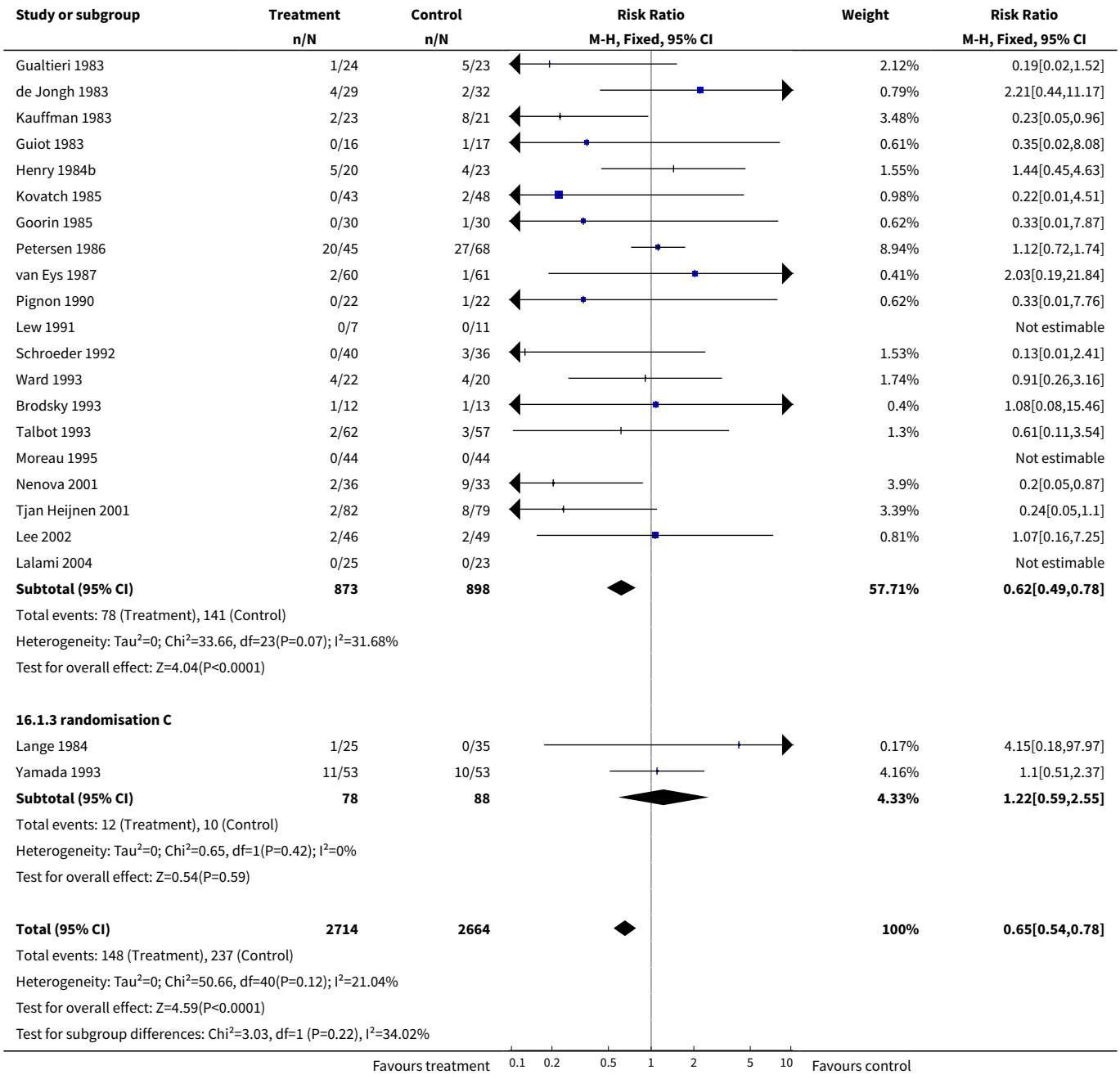
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	44	5378	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.54, 0.78]
1.1 randomisation A	15	3441	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.47, 0.88]
1.2 randomisation B	27	1771	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.49, 0.78]
1.3 randomisation C	2	166	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.59, 2.55]
2 Febrile patients	50	6267	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.74, 0.87]
2.1 randomisation A	15	3555	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.69, 0.93]
2.2 randomisation B	33	2549	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.71, 0.89]
2.3 randomisation C	2	163	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.38, 1.32]
3 Clinically documented infection	47	5660	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.57, 0.77]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 randomisation A	12	3112	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.61, 0.86]
3.2 randomisation B	33	2385	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.50, 0.75]
3.3 randomisation C	2	163	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.71, 1.42]
4 Microbiologically documented infection	51	6100	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.43, 0.62]
4.1 randomisation A	16	3599	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.38, 0.71]
4.2 randomisation B	33	2338	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.39, 0.65]
4.3 randomisation C	2	163	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.39, 0.73]

Analysis 16.1. Comparison 16 Sensitivity analyses by randomisation generation, drug versus placebo or no intervention, Outcome 1 Mortality.

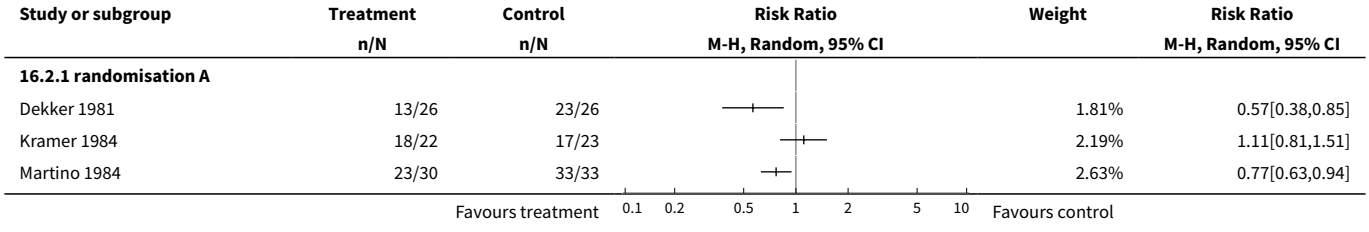
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
16.1.1 randomisation A					
Gurwith 1979	6/59	10/52		4.42%	0.53[0.21,1.36]
Dekker 1981	8/26	7/26		2.91%	1.14[0.49,2.69]
Martino 1984	2/30	11/33		4.35%	0.2[0.05,0.83]
Kramer 1984	5/22	1/23		0.41%	5.23[0.66,41.26]
Karp 1987	8/35	5/33		2.14%	1.51[0.55,4.15]
Attal 1991	0/30	1/30		0.62%	0.33[0.01,7.87]
Sampi 1992	0/38	3/35		1.51%	0.13[0.01,2.47]
Lamy 1993	1/27	4/28		1.63%	0.26[0.03,2.17]
Carlson 1997	0/45	1/45		0.62%	0.33[0.01,7.97]
Thomas 2000	5/99	5/52		2.73%	0.53[0.16,1.73]
Castagnola 2003	1/84	0/83		0.21%	2.96[0.12,71.75]
Cullen 2005	12/781	18/784		7.47%	0.67[0.32,1.38]
Bucaneve 2005	10/373	18/363		7.58%	0.54[0.25,1.16]
Rahman 2009	0/25	1/23		0.65%	0.31[0.01,7.2]
Papaiakovou 2010	0/89	1/68		0.71%	0.26[0.01,6.18]
Subtotal (95% CI)	**1763**	**1678**		**37.96%**	**0.64[0.47,0.88]**
Total events: 58 (Treatment), 86 (Control)					
Heterogeneity: Tau^2=0; Chi^2=15.06, df=14(P=0.37); I^2=7.03%					
Test for overall effect: Z=2.77(P=0.01)					
16.1.2 randomisation B					
Yates 1973	6/21	7/31		2.35%	1.27[0.49,3.24]
Levine 1973	11/40	9/30		4.28%	0.92[0.44,1.93]
Klastersky 1974	5/14	4/13		1.72%	1.16[0.4,3.41]
Schimpff 1975	6/19	15/21		5.92%	0.44[0.22,0.9]
Enno 1978	0/14	2/16		0.97%	0.23[0.01,4.36]
Sleijfer 1980	0/53	9/52		3.99%	0.05[0,0.87]
Jehn 1981	3/24	13/25		5.29%	0.24[0.08,0.74]



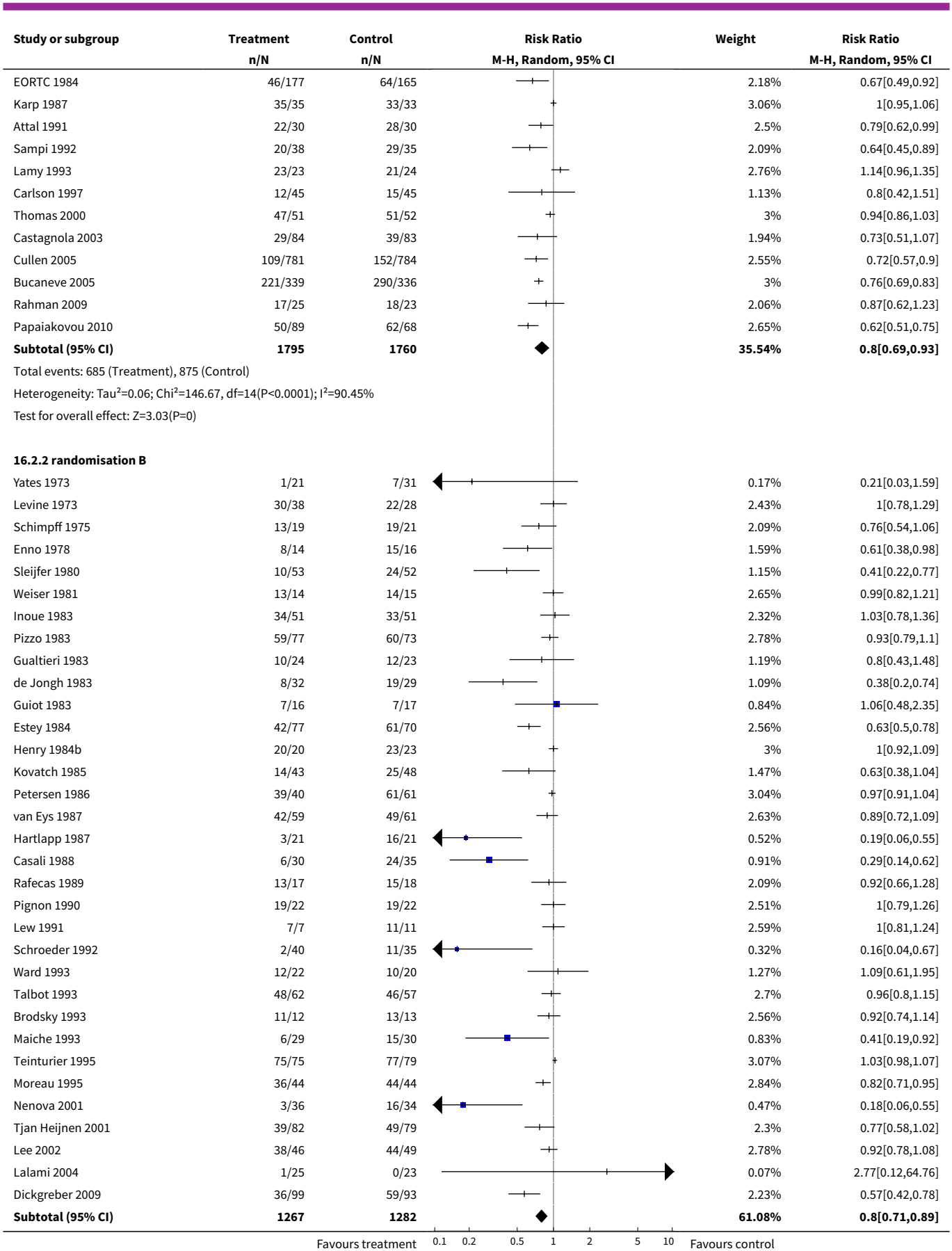


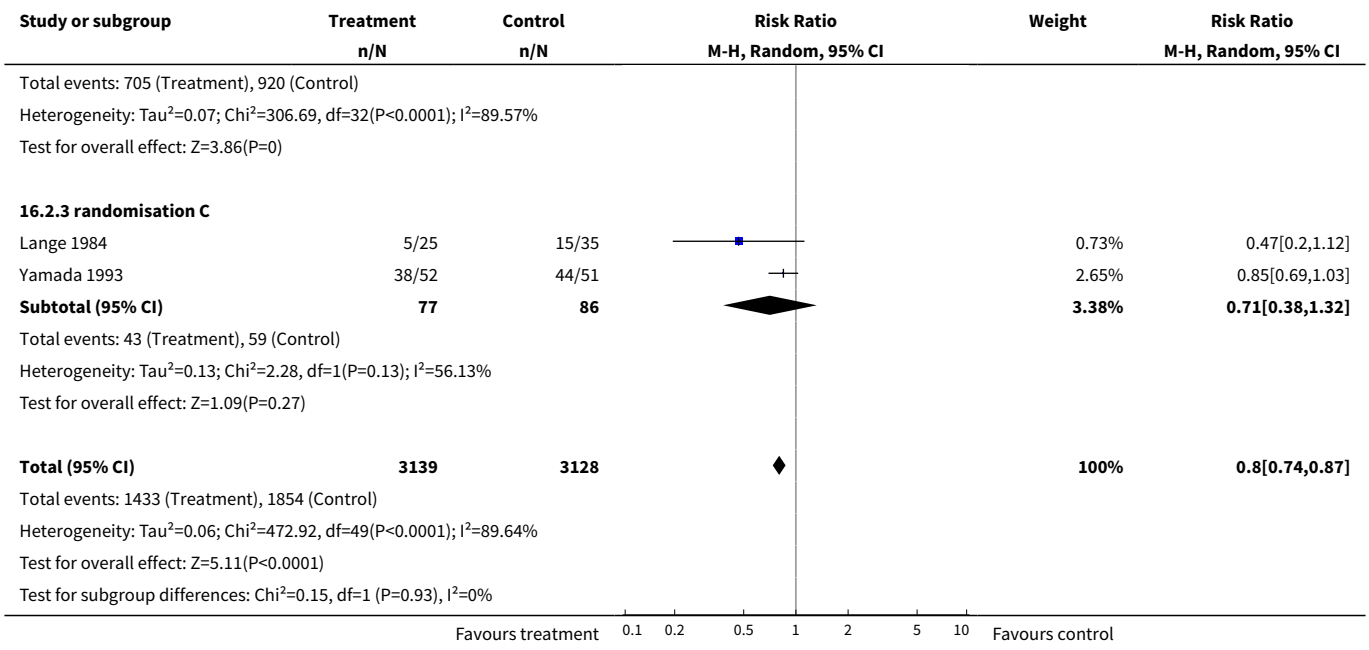
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Gualtieri 1983	1/24	5/23		2.12%	0.19[0.02,1.52]
de Jongh 1983	4/29	2/32		0.79%	2.21[0.44,11.17]
Kauffman 1983	2/23	8/21		3.48%	0.23[0.05,0.96]
Guiot 1983	0/16	1/17		0.61%	0.35[0.02,8.08]
Henry 1984b	5/20	4/23		1.55%	1.44[0.45,4.63]
Kovatch 1985	0/43	2/48		0.98%	0.22[0.01,4.51]
Goorin 1985	0/30	1/30		0.62%	0.33[0.01,7.87]
Petersen 1986	20/45	27/68		8.94%	1.12[0.72,1.74]
van Eys 1987	2/60	1/61		0.41%	2.03[0.19,21.84]
Pignon 1990	0/22	1/22		0.62%	0.33[0.01,7.76]
Lew 1991	0/7	0/11			Not estimable
Schroeder 1992	0/40	3/36		1.53%	0.13[0.01,2.41]
Ward 1993	4/22	4/20		1.74%	0.91[0.26,3.16]
Brodsky 1993	1/12	1/13		0.4%	1.08[0.08,15.46]
Talbot 1993	2/62	3/57		1.3%	0.61[0.11,3.54]
Moreau 1995	0/44	0/44			Not estimable
Nenova 2001	2/36	9/33		3.9%	0.2[0.05,0.87]
Tjan Heijnen 2001	2/82	8/79		3.39%	0.24[0.05,1.1]
Lee 2002	2/46	2/49		0.81%	1.07[0.16,7.25]
Lalami 2004	0/25	0/23			Not estimable
Subtotal (95% CI)	**873**	**898**		**57.71%**	**0.62[0.49,0.78]**
Total events: 78 (Treatment), 141 (Control)					
Heterogeneity: Tau^2=0; Chi^2=33.66, df=23(P=0.07); I^2=31.68%					
Test for overall effect: Z=4.04(P<0.0001)					
16.1.3 randomisation C					
Lange 1984	1/25	0/35		0.17%	4.15[0.18,97.97]
Yamada 1993	11/53	10/53		4.16%	1.1[0.51,2.37]
Subtotal (95% CI)	**78**	**88**		**4.33%**	**1.22[0.59,2.55]**
Total events: 12 (Treatment), 10 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.65, df=1(P=0.42); I^2=0%					
Test for overall effect: Z=0.54(P=0.59)					
Total (95% CI)	**2714**	**2664**		**100%**	**0.65[0.54,0.78]**
Total events: 148 (Treatment), 237 (Control)					
Heterogeneity: Tau^2=0; Chi^2=50.66, df=40(P=0.12); I^2=21.04%					
Test for overall effect: Z=4.59(P<0.0001)					
Test for subgroup differences: Chi^2=3.03, df=1 (P=0.22), I^2=34.02%					

Analysis 16.2. Comparison 16 Sensitivity analyses by randomisation generation, drug versus placebo or no intervention, Outcome 2 Febrile patients.

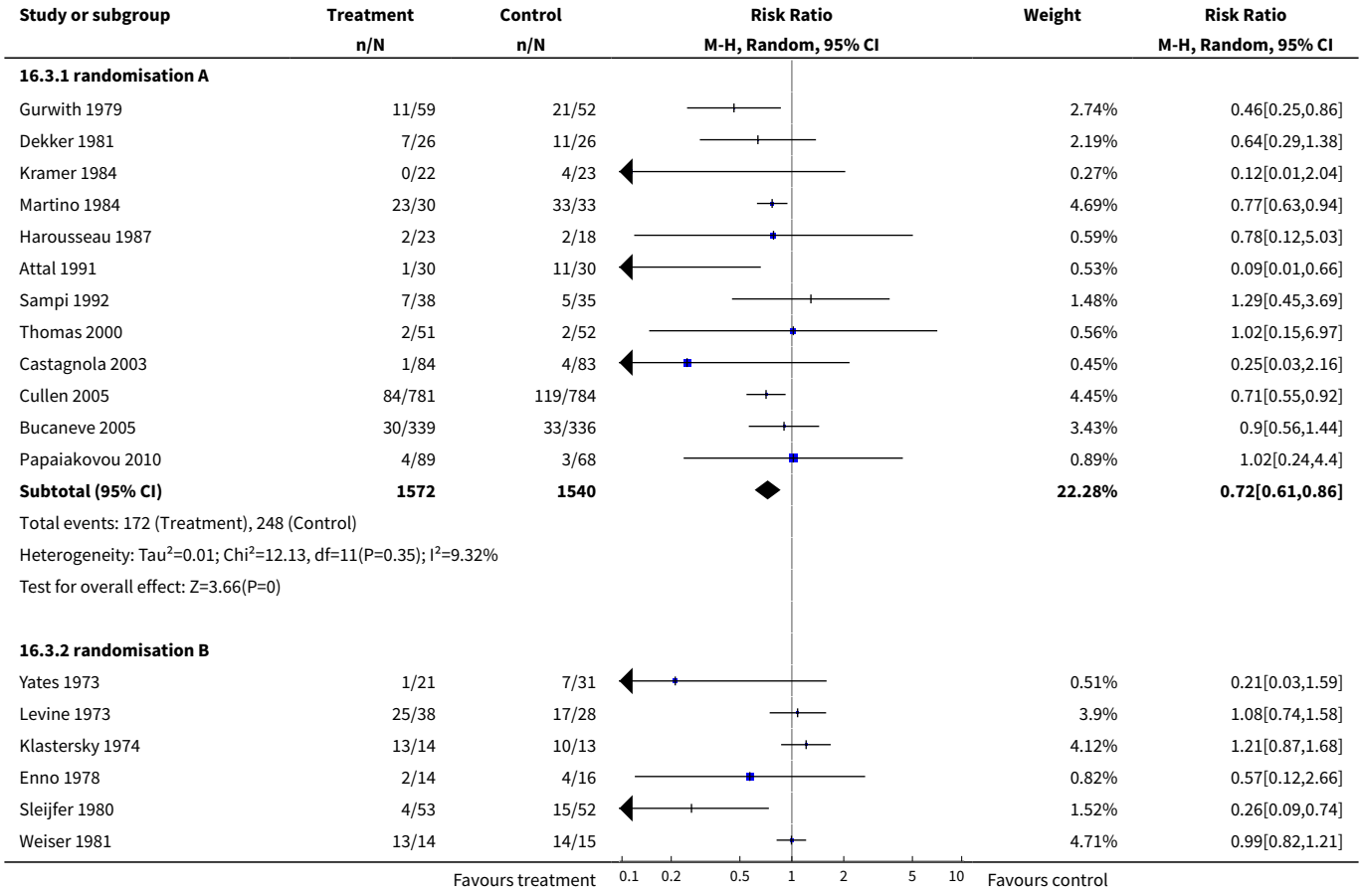


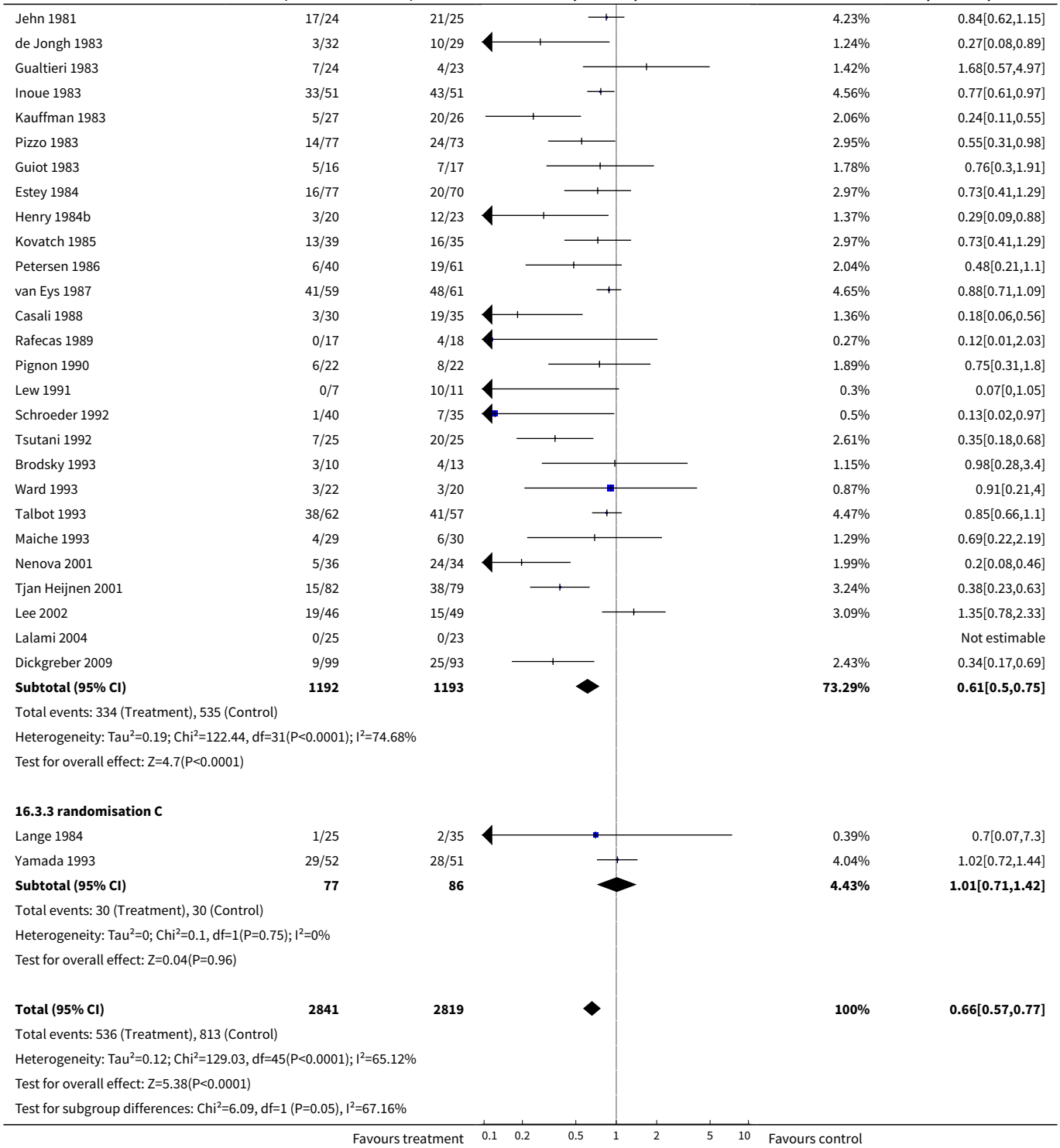
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
16.2.1 randomisation A					
Dekker 1981	13/26	23/26		1.81%	0.57[0.38,0.85]
Kramer 1984	18/22	17/23		2.19%	1.11[0.81,1.51]
Martino 1984	23/30	33/33		2.63%	0.77[0.63,0.94]





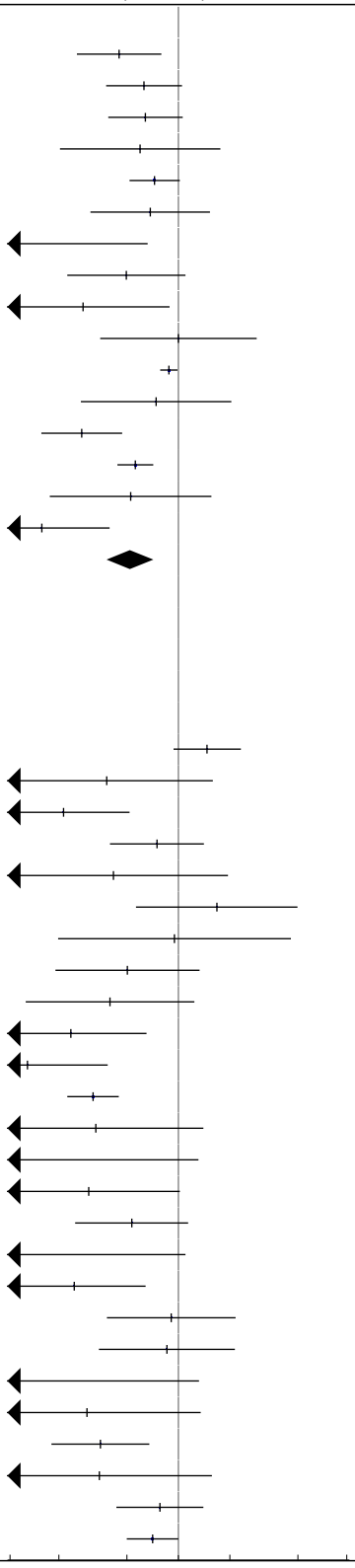
Analysis 16.3. Comparison 16 Sensitivity analyses by randomisation generation, drug versus placebo or no intervention, Outcome 3 Clinically documented infection.

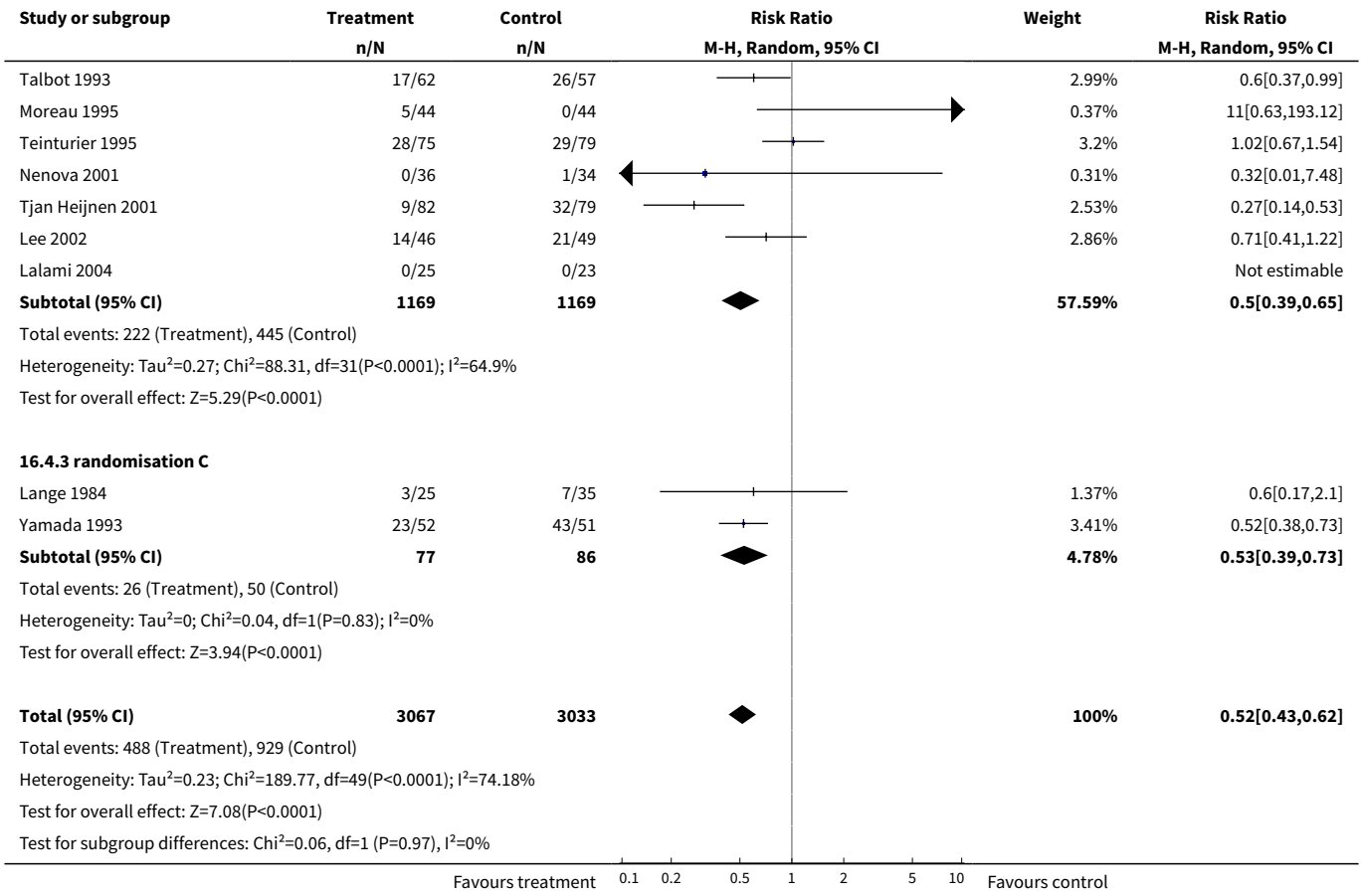




Analysis 16.4. Comparison 16 Sensitivity analyses by randomisation generation, drug versus placebo or no intervention, Outcome 4 Microbiologically documented infection.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
16.4.1 randomisation A					
Dekker 1981	9/26	20/26		2.79%	0.45[0.25,0.79]
Martino 1984	12/30	21/33		2.95%	0.63[0.38,1.05]
EORTC 1984	22/177	32/165		2.98%	0.64[0.39,1.06]
Kramer 1984	4/22	7/23		1.64%	0.6[0.2,1.76]
Karp 1987	20/35	26/33		3.39%	0.73[0.52,1.02]
Harousseau 1987	7/23	8/18		2.2%	0.68[0.31,1.53]
Attal 1991	1/30	11/30		0.7%	0.09[0.01,0.66]
Sampi 1992	7/38	13/35		2.22%	0.5[0.22,1.1]
Lamy 1993	3/26	10/24		1.5%	0.28[0.09,0.89]
Carlson 1997	6/45	6/45		1.69%	1[0.35,2.87]
Thomas 2000	44/51	51/52		3.77%	0.88[0.78,0.99]
Castagnola 2003	6/84	8/83		1.76%	0.74[0.27,2.04]
Cullen 2005	16/781	59/784		2.86%	0.27[0.16,0.47]
Bucaneve 2005	74/339	131/336		3.59%	0.56[0.44,0.71]
Rahman 2009	4/25	7/23		1.62%	0.53[0.18,1.56]
Papaiakovou 2010	5/89	24/68		1.97%	0.16[0.06,0.4]
Subtotal (95% CI)	**1821**	**1778**		**37.62%**	**0.52[0.38,0.71]**
Total events: 240 (Treatment), 434 (Control)					
Heterogeneity: Tau^2=0.27; Chi^2=92.27, df=15(P<0.0001); I^2=83.74%					
Test for overall effect: Z=4.06(P<0.0001)					
16.4.2 randomisation B					
Levine 1973	26/38	13/28		3.1%	1.47[0.94,2.32]
Enno 1978	2/14	6/16		1.15%	0.38[0.09,1.59]
Sleijfer 1980	5/53	23/52		2.01%	0.21[0.09,0.52]
Weiser 1981	7/14	10/15		2.62%	0.75[0.4,1.41]
Jehn 1981	2/24	5/25		1.03%	0.42[0.09,1.95]
Gualtieri 1983	7/24	4/23		1.63%	1.68[0.57,4.97]
Pizzo 1983	3/77	3/73		1.01%	0.95[0.2,4.55]
de Jongh 1983	5/32	9/29		1.84%	0.5[0.19,1.33]
Guiot 1983	3/16	8/17		1.54%	0.4[0.13,1.24]
Inoue 1983	4/51	17/51		1.75%	0.24[0.09,0.65]
Kauffman 1983	3/27	22/26		1.64%	0.13[0.04,0.39]
Estey 1984	23/77	66/70		3.36%	0.32[0.22,0.45]
Henry 1984b	2/20	7/23		1.12%	0.33[0.08,1.4]
Goorin 1985	0/30	6/30		0.38%	0.08[0,1.31]
Kovatch 1985	3/39	9/35		1.41%	0.3[0.09,1.02]
Petersen 1986	7/40	20/61		2.3%	0.53[0.25,1.14]
Hartlapp 1987	0/21	7/21		0.38%	0.07[0,1.1]
Casali 1988	4/30	19/35		1.86%	0.25[0.09,0.64]
Rafecas 1989	6/17	7/18		2.06%	0.91[0.38,2.16]
Pignon 1990	6/22	7/22		1.95%	0.86[0.34,2.14]
Lew 1991	0/7	8/11		0.41%	0.09[0.01,1.32]
Schroeder 1992	2/40	6/35		1.04%	0.29[0.06,1.35]
Tsutani 1992	7/25	20/25		2.56%	0.35[0.18,0.68]
Maiche 1993	2/29	6/30		1.06%	0.34[0.08,1.57]
Brodsky 1993	6/10	10/13		2.75%	0.78[0.43,1.4]
Ward 1993	14/22	18/20		3.36%	0.71[0.5,1]





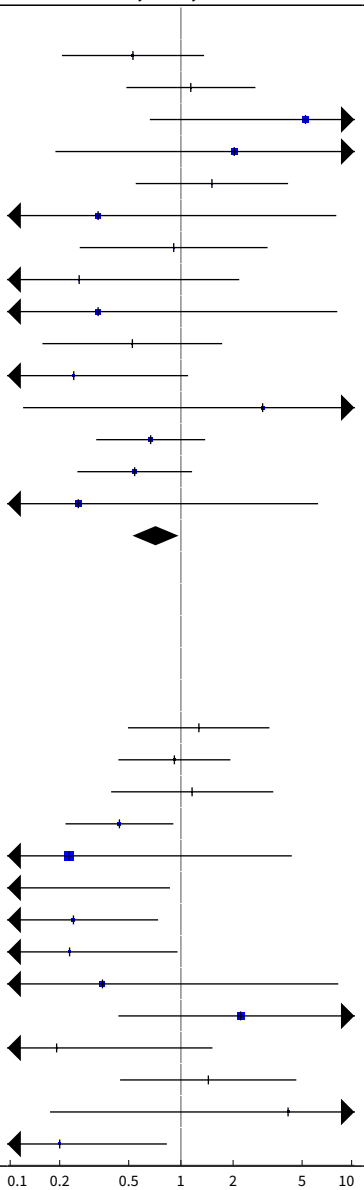
Comparison 17. Sensitivity analyses by allocation concealment, drug versus placebo or no intervention

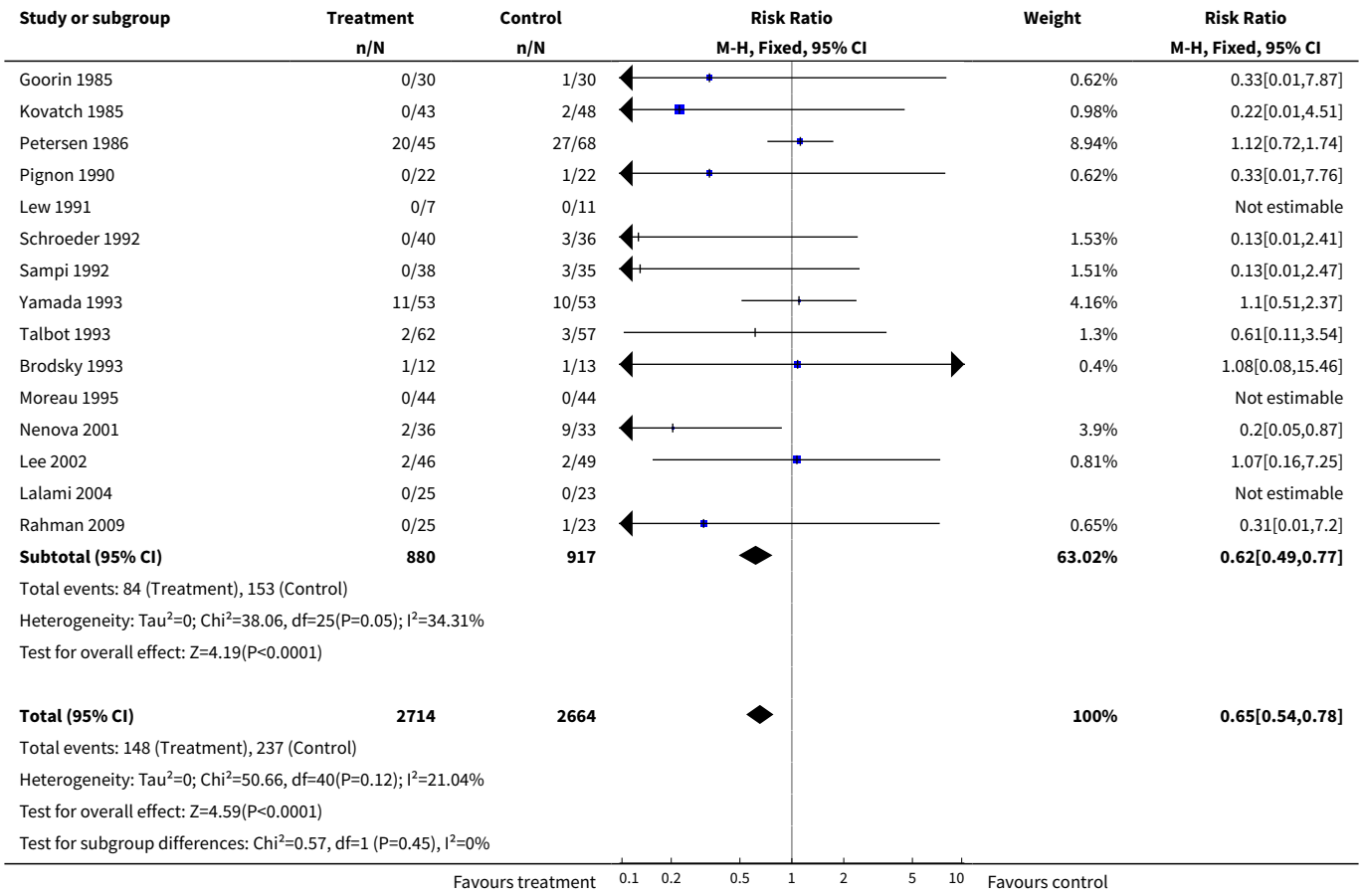
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	44	5378	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.54, 0.78]
1.1 allocation A	15	3581	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.53, 0.97]
1.2 allocation B	29	1797	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.49, 0.77]
2 Febrile patients	51	6317	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.73, 0.86]
2.1 allocation A	16	3844	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.73, 0.95]
2.2 allocation B	35	2473	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.66, 0.85]
3 Clinically documented infection	47	5660	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.57, 0.77]
3.1 allocation A	13	3408	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.50, 0.82]
3.2 allocation B	34	2252	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.55, 0.80]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Microbiologically documented infection	51	6100	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.43, 0.62]
4.1 allocation A	15	3727	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.36, 0.71]
4.2 allocation B	36	2373	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.42, 0.65]

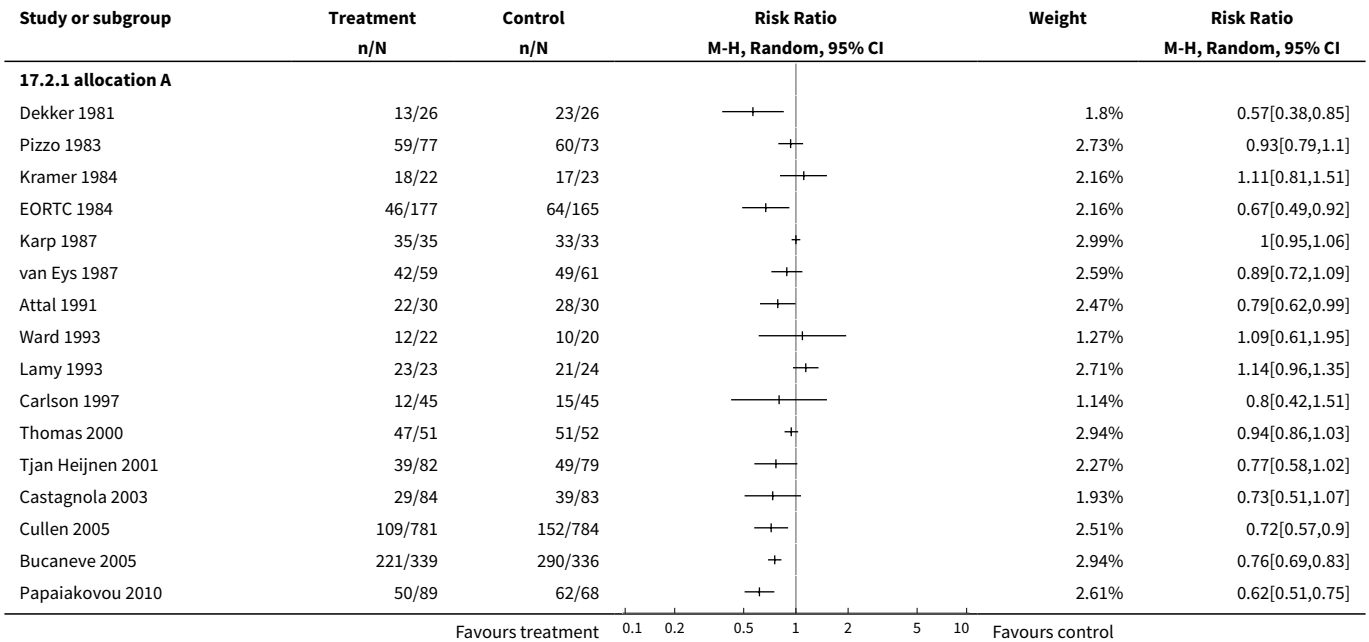
Analysis 17.1. Comparison 17 Sensitivity analyses by allocation concealment, drug versus placebo or no intervention, Outcome 1 Mortality.

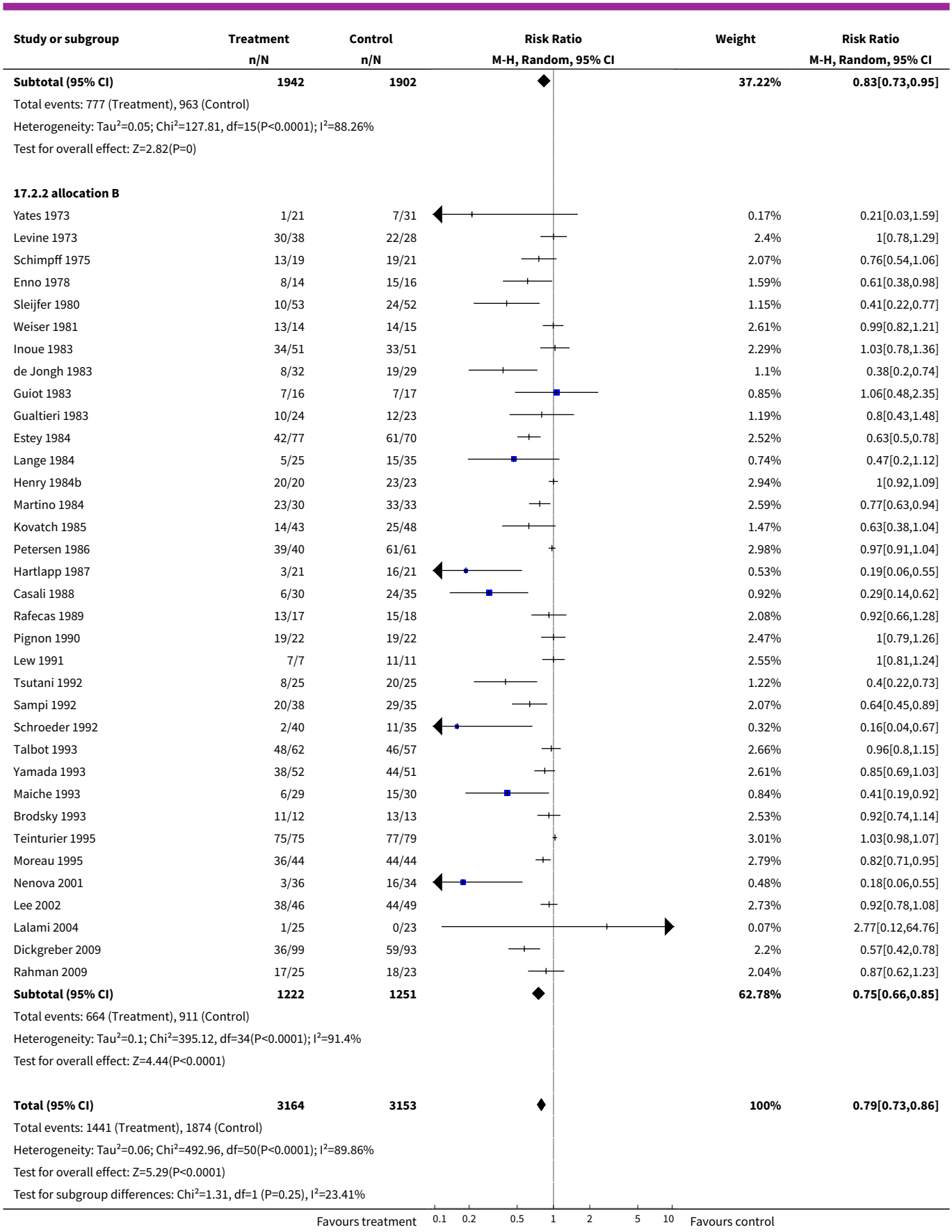
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
17.1.1 allocation A					
Gurwith 1979	6/59	10/52		4.42%	0.53[0.21,1.36]
Dekker 1981	8/26	7/26		2.91%	1.14[0.49,2.69]
Kramer 1984	5/22	1/23		0.41%	5.23[0.66,41.26]
van Eys 1987	2/60	1/61		0.41%	2.03[0.19,21.84]
Karp 1987	8/35	5/33		2.14%	1.51[0.55,4.15]
Attal 1991	0/30	1/30		0.62%	0.33[0.01,7.87]
Ward 1993	4/22	4/20		1.74%	0.91[0.26,3.16]
Lamy 1993	1/27	4/28		1.63%	0.26[0.03,2.17]
Carlson 1997	0/45	1/45		0.62%	0.33[0.01,7.97]
Thomas 2000	5/99	5/52		2.73%	0.53[0.16,1.73]
Tjan Heijnen 2001	2/82	8/79		3.39%	0.24[0.05,1.1]
Castagnola 2003	1/84	0/83		0.21%	2.96[0.12,71.75]
Cullen 2005	12/781	18/784		7.47%	0.67[0.32,1.38]
Bucaneve 2005	10/373	18/363		7.58%	0.54[0.25,1.16]
Papaiakovou 2010	0/89	1/68		0.71%	0.26[0.01,6.18]
Subtotal (95% CI)	**1834**	**1747**		**36.98%**	**0.71[0.53,0.97]**
Total events: 64 (Treatment), 84 (Control)					
Heterogeneity: Tau²=0; Chi²=13.36, df=14(P=0.5); I²=0%					
Test for overall effect: Z=2.16(P=0.03)					
17.1.2 allocation B					
Yates 1973	6/21	7/31		2.35%	1.27[0.49,3.24]
Levine 1973	11/40	9/30		4.28%	0.92[0.44,1.93]
Klastersky 1974	5/14	4/13		1.72%	1.16[0.4,3.41]
Schimpff 1975	6/19	15/21		5.92%	0.44[0.22,0.9]
Enno 1978	0/14	2/16		0.97%	0.23[0.01,4.36]
Sleijfer 1980	0/53	9/52		3.99%	0.05[0,0.87]
Jehn 1981	3/24	13/25		5.29%	0.24[0.08,0.74]
Kauffman 1983	2/23	8/21		3.48%	0.23[0.05,0.96]
Guiot 1983	0/16	1/17		0.61%	0.35[0.02,8.08]
de Jongh 1983	4/29	2/32		0.79%	2.21[0.44,11.17]
Gualtieri 1983	1/24	5/23		2.12%	0.19[0.02,1.52]
Henry 1984b	5/20	4/23		1.55%	1.44[0.45,4.63]
Lange 1984	1/25	0/35		0.17%	4.15[0.18,97.97]
Martino 1984	2/30	11/33		4.35%	0.2[0.05,0.83]





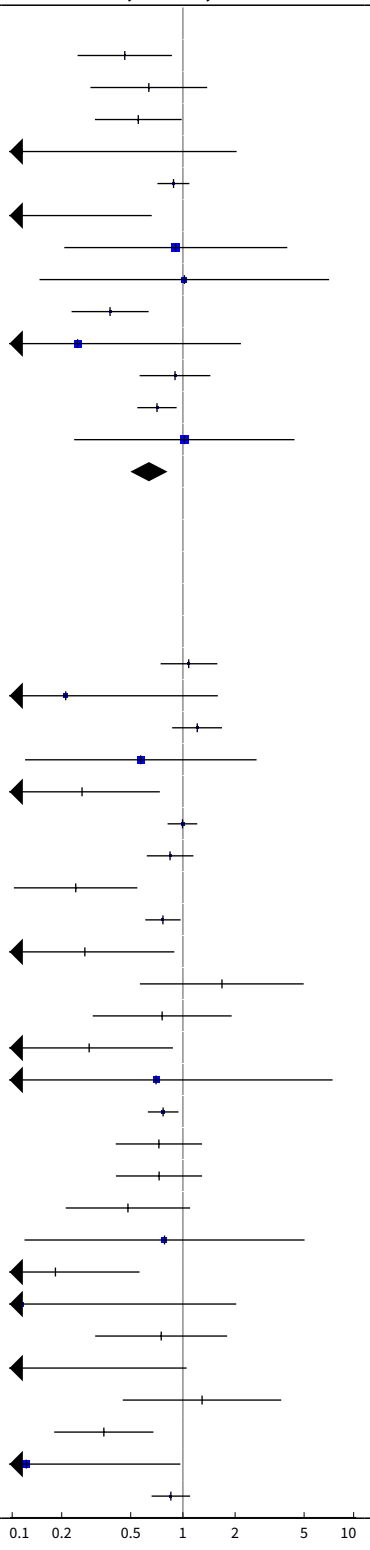
Analysis 17.2. Comparison 17 Sensitivity analyses by allocation concealment, drug versus placebo or no intervention, Outcome 2 Febrile patients.

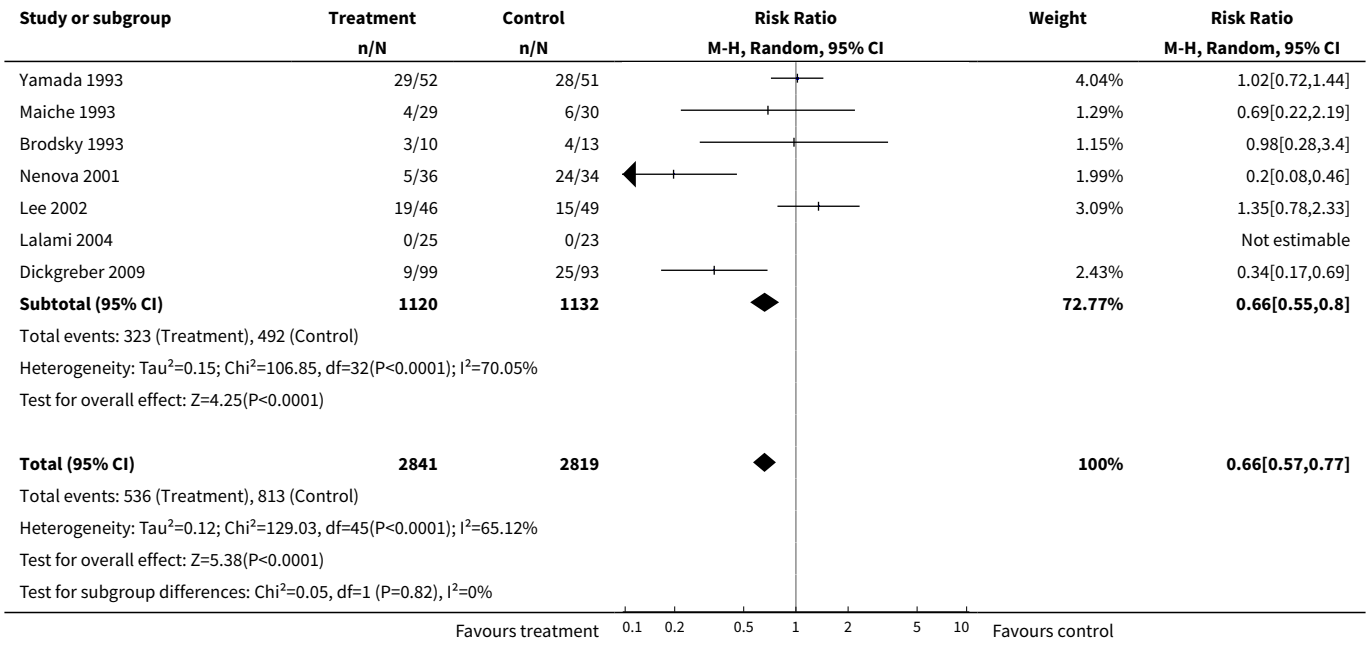




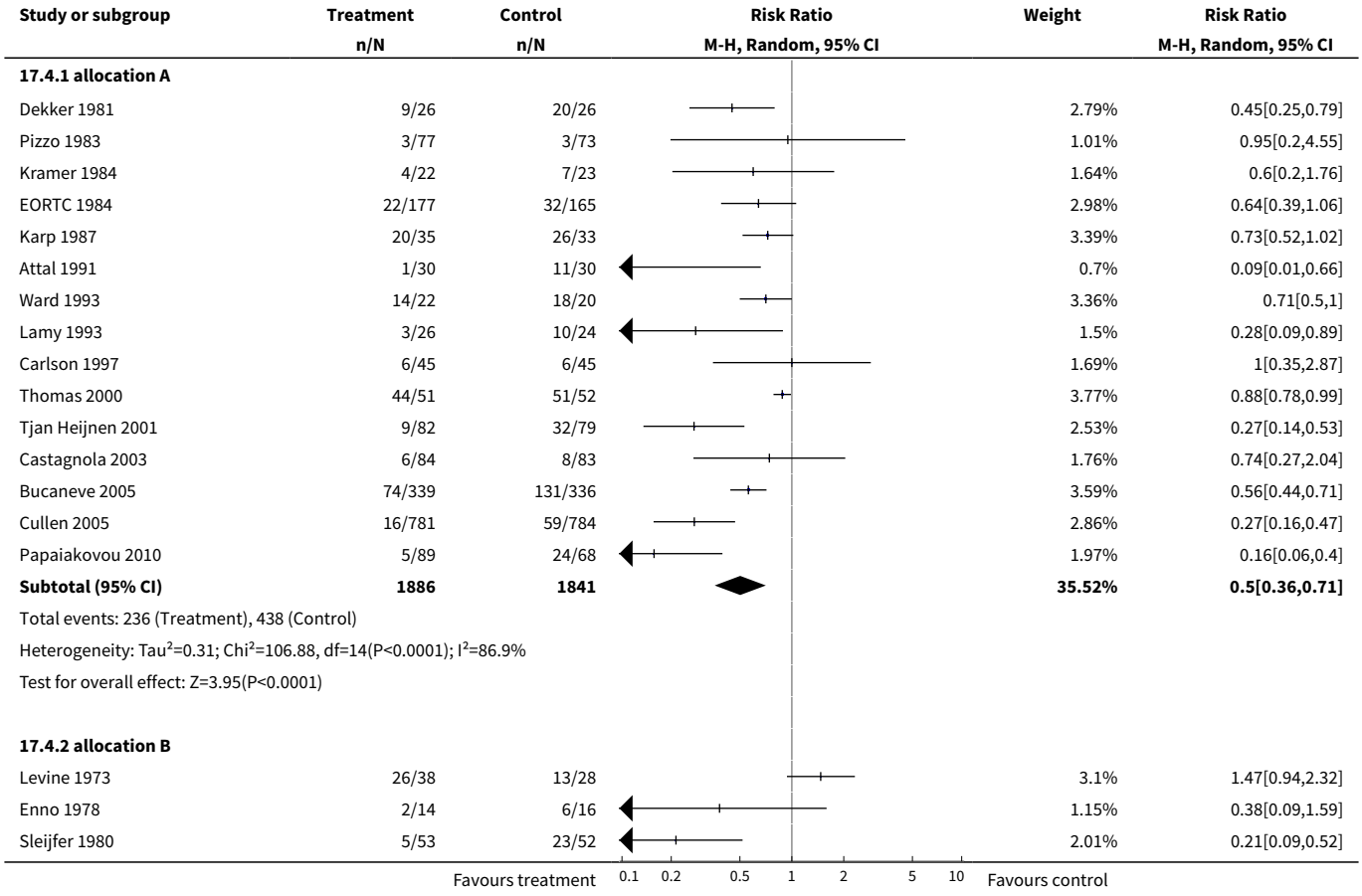
Analysis 17.3. Comparison 17 Sensitivity analyses by allocation concealment, drug versus placebo or no intervention, Outcome 3 Clinically documented infection.

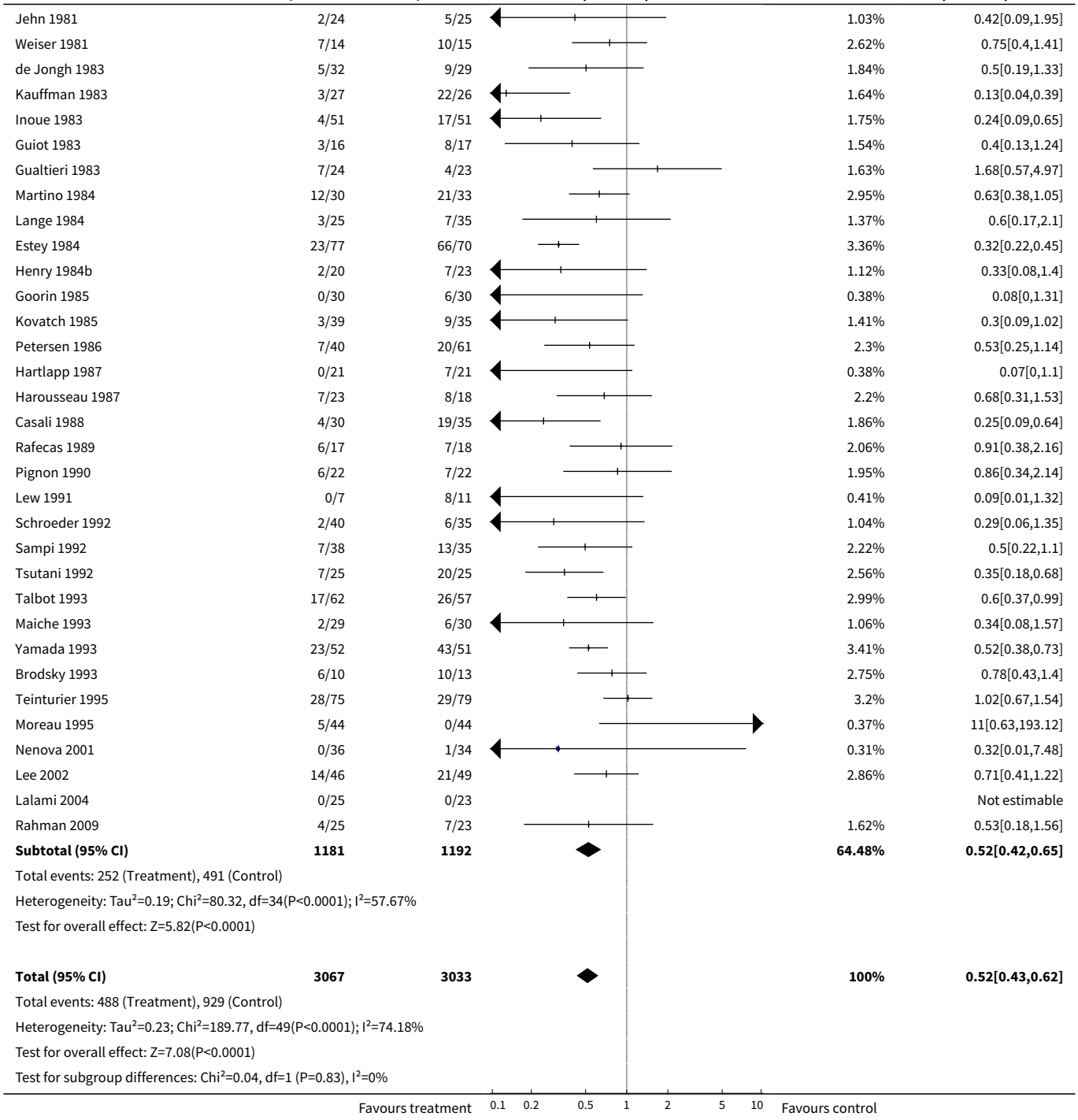
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
17.3.1 allocation A					
Gurwith 1979	11/59	21/52		2.74%	0.46[0.25,0.86]
Dekker 1981	7/26	11/26		2.19%	0.64[0.29,1.38]
Pizzo 1983	14/77	24/73		2.95%	0.55[0.31,0.98]
Kramer 1984	0/22	4/23		0.27%	0.12[0.01,2.04]
van Eys 1987	41/59	48/61		4.65%	0.88[0.71,1.09]
Attal 1991	1/30	11/30		0.53%	0.09[0.01,0.66]
Ward 1993	3/22	3/20		0.87%	0.91[0.21,4]
Thomas 2000	2/51	2/52		0.56%	1.02[0.15,6.97]
Tjan Heijnen 2001	15/82	38/79		3.24%	0.38[0.23,0.63]
Castagnola 2003	1/84	4/83		0.45%	0.25[0.03,2.16]
Bucaneve 2005	30/339	33/336		3.43%	0.9[0.56,1.44]
Cullen 2005	84/781	119/784		4.45%	0.71[0.55,0.92]
Papaiakovou 2010	4/89	3/68		0.89%	1.02[0.24,4.4]
Subtotal (95% CI)	**1721**	**1687**		**27.23%**	**0.64[0.5,0.82]**
Total events: 213 (Treatment), 321 (Control)					
Heterogeneity: Tau^2=0.07; Chi^2=22.2, df=12(P=0.04); I^2=45.94%					
Test for overall effect: Z=3.59(P=0)					
17.3.2 allocation B					
Levine 1973	25/38	17/28		3.9%	1.08[0.74,1.58]
Yates 1973	1/21	7/31		0.51%	0.21[0.03,1.59]
Klastersky 1974	13/14	10/13		4.12%	1.21[0.87,1.68]
Enno 1978	2/14	4/16		0.82%	0.57[0.12,2.66]
Sleijfer 1980	4/53	15/52		1.52%	0.26[0.09,0.74]
Weiser 1981	13/14	14/15		4.71%	0.99[0.82,1.21]
Jehn 1981	17/24	21/25		4.23%	0.84[0.62,1.15]
Kauffman 1983	5/27	20/26		2.06%	0.24[0.11,0.55]
Inoue 1983	33/51	43/51		4.56%	0.77[0.61,0.97]
de Jongh 1983	3/32	10/29		1.24%	0.27[0.08,0.89]
Gualtieri 1983	7/24	4/23		1.42%	1.68[0.57,4.97]
Guiot 1983	5/16	7/17		1.78%	0.76[0.3,1.91]
Henry 1984b	3/20	12/23		1.37%	0.29[0.09,0.88]
Lange 1984	1/25	2/35		0.39%	0.7[0.07,7.3]
Martino 1984	23/30	33/33		4.69%	0.77[0.63,0.94]
Estey 1984	16/77	20/70		2.97%	0.73[0.41,1.29]
Kovatch 1985	13/39	16/35		2.97%	0.73[0.41,1.29]
Petersen 1986	6/40	19/61		2.04%	0.48[0.21,1.1]
Harousseau 1987	2/23	2/18		0.59%	0.78[0.12,5.03]
Casali 1988	3/30	19/35		1.36%	0.18[0.06,0.56]
Rafecas 1989	0/17	4/18		0.27%	0.12[0.01,2.03]
Pignon 1990	6/22	8/22		1.89%	0.75[0.31,1.8]
Lew 1991	0/7	10/11		0.3%	0.07[0,1.05]
Sampi 1992	7/38	5/35		1.48%	1.29[0.45,3.69]
Tsutani 1992	7/25	20/25		2.61%	0.35[0.18,0.68]
Schroeder 1992	1/40	7/35		0.5%	0.13[0.02,0.97]
Talbot 1993	38/62	41/57		4.47%	0.85[0.66,1.1]





Analysis 17.4. Comparison 17 Sensitivity analyses by allocation concealment, drug versus placebo or no intervention, Outcome 4 Microbiologically documented infection.



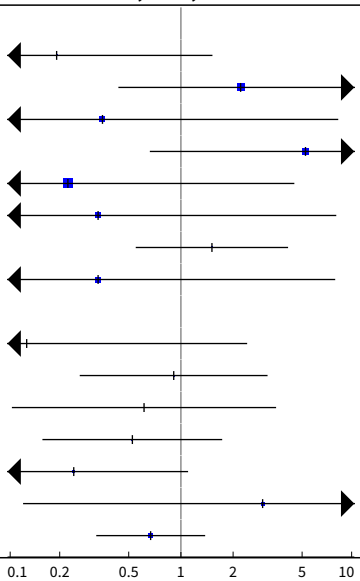


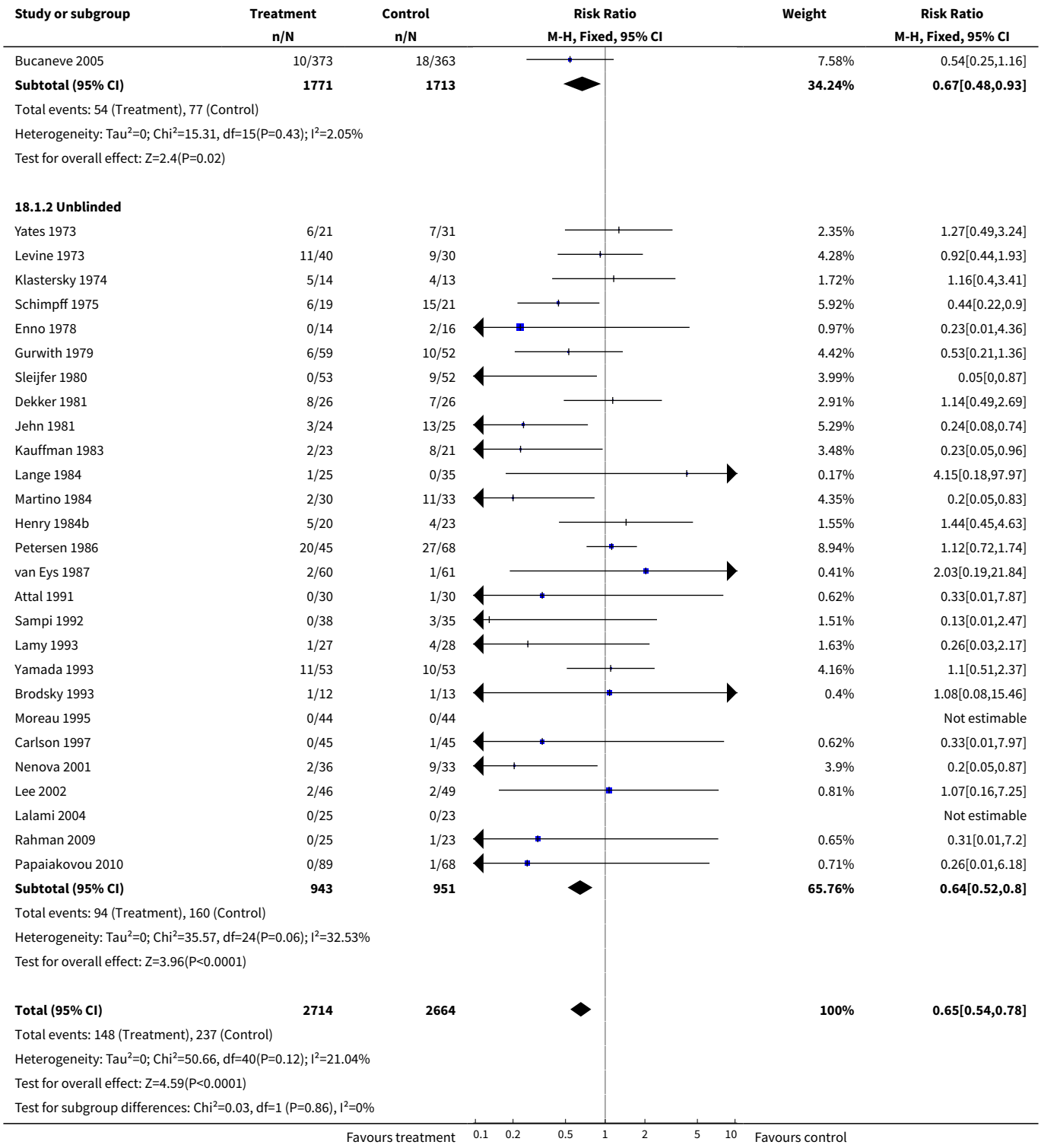
Comparison 18. Sensitivity analyses by blinding, drug versus placebo or no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	44	5378	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.54, 0.78]
1.1 Double Blind	17	3484	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.48, 0.93]
1.2 Unblinded	27	1894	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.52, 0.80]
2 Febrile patients	51	6317	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.73, 0.86]
2.1 Double Blind	22	4255	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.75, 0.94]
2.2 Unblinded	29	2062	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.64, 0.84]
3 Clinically documented infection	47	5660	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.57, 0.77]
3.1 Double Blind	20	3738	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.53, 0.79]
3.2 Unblinded	27	1922	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.54, 0.82]
4 Microbiologically documented infection	51	6144	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.44, 0.62]
4.1 Double Blind	20	3912	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.43, 0.75]
4.2 Unblinded	32	2232	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.39, 0.62]

Analysis 18.1. Comparison 18 Sensitivity analyses by blinding, drug versus placebo or no intervention, Outcome 1 Mortality.

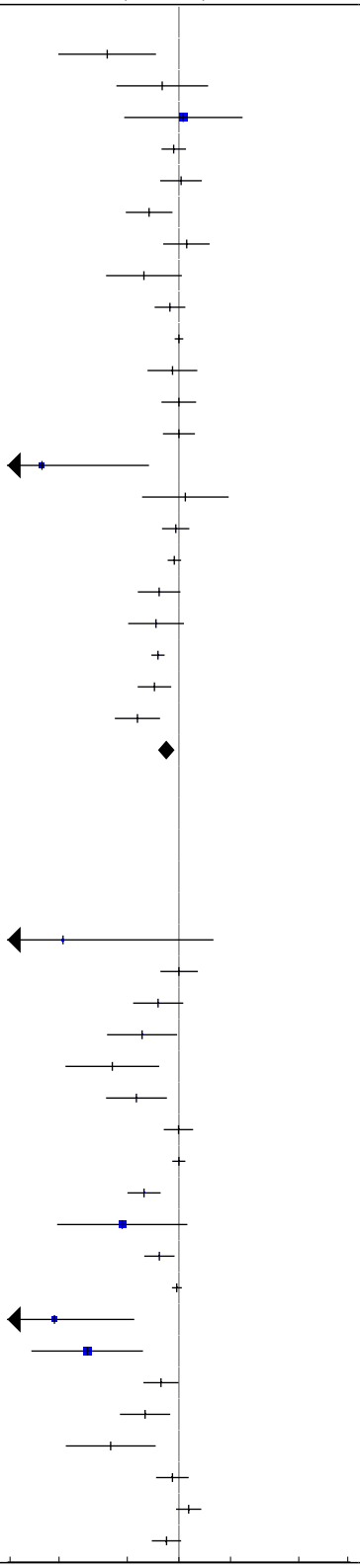
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
18.1.1 Double Blind					
Gualtieri 1983	1/24	5/23		2.12%	0.19[0.02,1.52]
de Jongh 1983	4/29	2/32		0.79%	2.21[0.44,11.17]
Guiot 1983	0/16	1/17		0.61%	0.35[0.02,8.08]
Kramer 1984	5/22	1/23		0.41%	5.23[0.66,41.26]
Kovatch 1985	0/43	2/48		0.98%	0.22[0.01,4.51]
Goorin 1985	0/30	1/30		0.62%	0.33[0.01,7.87]
Karp 1987	8/35	5/33		2.14%	1.51[0.55,4.15]
Pignon 1990	0/22	1/22		0.62%	0.33[0.01,7.76]
Lew 1991	0/7	0/11			Not estimable
Schroeder 1992	0/40	3/36		1.53%	0.13[0.01,2.41]
Ward 1993	4/22	4/20		1.74%	0.91[0.26,3.16]
Talbot 1993	2/62	3/57		1.3%	0.61[0.11,3.54]
Thomas 2000	5/99	5/52		2.73%	0.53[0.16,1.73]
Tjan Heijnen 2001	2/82	8/79		3.39%	0.24[0.05,1.1]
Castagnola 2003	1/84	0/83		0.21%	2.96[0.12,71.75]
Cullen 2005	12/781	18/784		7.47%	0.67[0.32,1.38]





Analysis 18.2. Comparison 18 Sensitivity analyses by blinding, drug versus placebo or no intervention, Outcome 2 Febrile patients.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
18.2.1 Double Blind					
de Jongh 1983	8/32	19/29		1.1%	0.38[0.2,0.74]
Gualtieri 1983	10/24	12/23		1.19%	0.8[0.43,1.48]
Guiot 1983	7/16	7/17		0.85%	1.06[0.48,2.35]
Pizzo 1983	59/77	60/73		2.73%	0.93[0.79,1.1]
Inoue 1983	34/51	33/51		2.29%	1.03[0.78,1.36]
EORTC 1984	46/177	64/165		2.16%	0.67[0.49,0.92]
Kramer 1984	18/22	17/23		2.16%	1.11[0.81,1.51]
Kovatch 1985	14/43	25/48		1.47%	0.63[0.38,1.04]
van Eys 1987	42/59	49/61		2.59%	0.89[0.72,1.09]
Karp 1987	35/35	33/33		2.99%	1[0.95,1.06]
Rafecas 1989	13/17	15/18		2.08%	0.92[0.66,1.28]
Pignon 1990	19/22	19/22		2.47%	1[0.79,1.26]
Lew 1991	7/7	11/11		2.55%	1[0.81,1.24]
Schroeder 1992	2/40	11/35		0.32%	0.16[0.04,0.67]
Ward 1993	12/22	10/20		1.27%	1.09[0.61,1.95]
Talbot 1993	48/62	46/57		2.66%	0.96[0.8,1.15]
Thomas 2000	47/51	51/52		2.94%	0.94[0.86,1.03]
Tjan Heijnen 2001	39/82	49/79		2.27%	0.77[0.58,1.02]
Castagnola 2003	29/84	39/83		1.93%	0.73[0.51,1.07]
Bucaneve 2005	221/339	290/336		2.94%	0.76[0.69,0.83]
Cullen 2005	109/781	152/784		2.51%	0.72[0.57,0.9]
Dickgreber 2009	36/99	59/93		2.2%	0.57[0.42,0.78]
Subtotal (95% CI)	**2142**	**2113**		**45.67%**	**0.84[0.75,0.94]**
Total events: 855 (Treatment), 1071 (Control)					
Heterogeneity: Tau^2=0.04; Chi^2=129.79, df=21(P<0.0001); I^2=83.82%					
Test for overall effect: Z=2.98(P=0)					
18.2.2 Unblinded					
Yates 1973	1/21	7/31		0.17%	0.21[0.03,1.59]
Levine 1973	30/38	22/28		2.4%	1[0.78,1.29]
Schimpff 1975	13/19	19/21		2.07%	0.76[0.54,1.06]
Enno 1978	8/14	15/16		1.59%	0.61[0.38,0.98]
Sleijfer 1980	10/53	24/52		1.15%	0.41[0.22,0.77]
Dekker 1981	13/26	23/26		1.8%	0.57[0.38,0.85]
Weiser 1981	13/14	14/15		2.61%	0.99[0.82,1.21]
Henry 1984b	20/20	23/23		2.94%	1[0.92,1.09]
Estey 1984	42/77	61/70		2.52%	0.63[0.5,0.78]
Lange 1984	5/25	15/35		0.74%	0.47[0.2,1.12]
Martino 1984	23/30	33/33		2.59%	0.77[0.63,0.94]
Petersen 1986	39/40	61/61		2.98%	0.97[0.91,1.04]
Hartlapp 1987	3/21	16/21		0.53%	0.19[0.06,0.55]
Casali 1988	6/30	24/35		0.92%	0.29[0.14,0.62]
Attal 1991	22/30	28/30		2.47%	0.79[0.62,0.99]
Sampi 1992	20/38	29/35		2.07%	0.64[0.45,0.89]
Tsutani 1992	8/25	20/25		1.22%	0.4[0.22,0.73]
Brodsky 1993	11/12	13/13		2.53%	0.92[0.74,1.14]
Lamy 1993	23/23	21/24		2.71%	1.14[0.96,1.35]
Yamada 1993	38/52	44/51		2.61%	0.85[0.69,1.03]



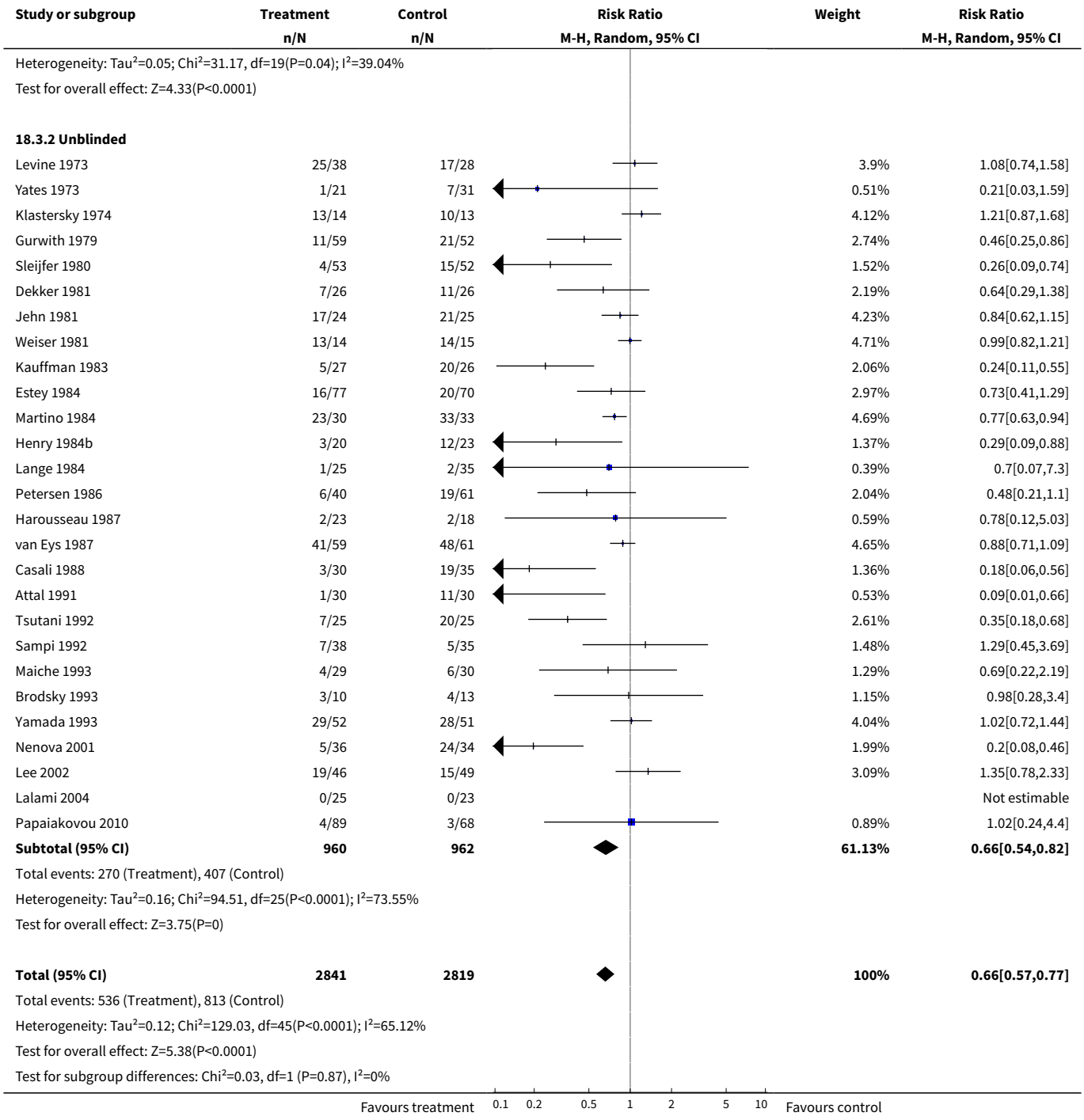
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Maiche 1993	6/29	15/30		0.84%	0.41[0.19,0.92]
Moreau 1995	36/44	44/44		2.79%	0.82[0.71,0.95]
Teinturier 1995	75/75	77/79		3.01%	1.03[0.98,1.07]
Carlson 1997	12/45	15/45		1.14%	0.8[0.42,1.51]
Nenova 2001	3/36	16/34		0.48%	0.18[0.06,0.55]
Lee 2002	38/46	44/49		2.73%	0.92[0.78,1.08]
Lalami 2004	1/25	0/23		0.07%	2.77[0.12,64.76]
Rahman 2009	17/25	18/23		2.04%	0.87[0.62,1.23]
Papaiakovou 2010	50/89	62/68		2.61%	0.62[0.51,0.75]
Subtotal (95% CI)	**1022**	**1040**		**54.33%**	**0.73[0.64,0.84]**
Total events: 586 (Treatment), 803 (Control)					
Heterogeneity: Tau^2=0.1; Chi^2=412.63, df=28(P<0.0001); I^2=93.21%					
Test for overall effect: Z=4.29(P<0.0001)					
Total (95% CI)	**3164**	**3153**		**100%**	**0.79[0.73,0.86]**
Total events: 1441 (Treatment), 1874 (Control)					
Heterogeneity: Tau^2=0.06; Chi^2=492.96, df=50(P<0.0001); I^2=89.86%					
Test for overall effect: Z=5.29(P<0.0001)					
Test for subgroup differences: Chi^2=2.34, df=1 (P=0.13), I^2=57.23%					

Favours treatment — Favours control

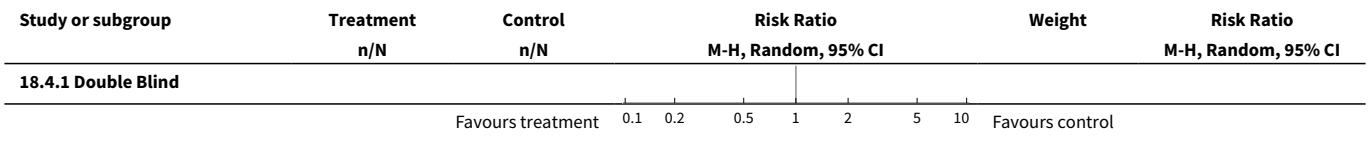
Analysis 18.3. Comparison 18 Sensitivity analyses by blinding, drug versus placebo or no intervention, Outcome 3 Clinically documented infection.

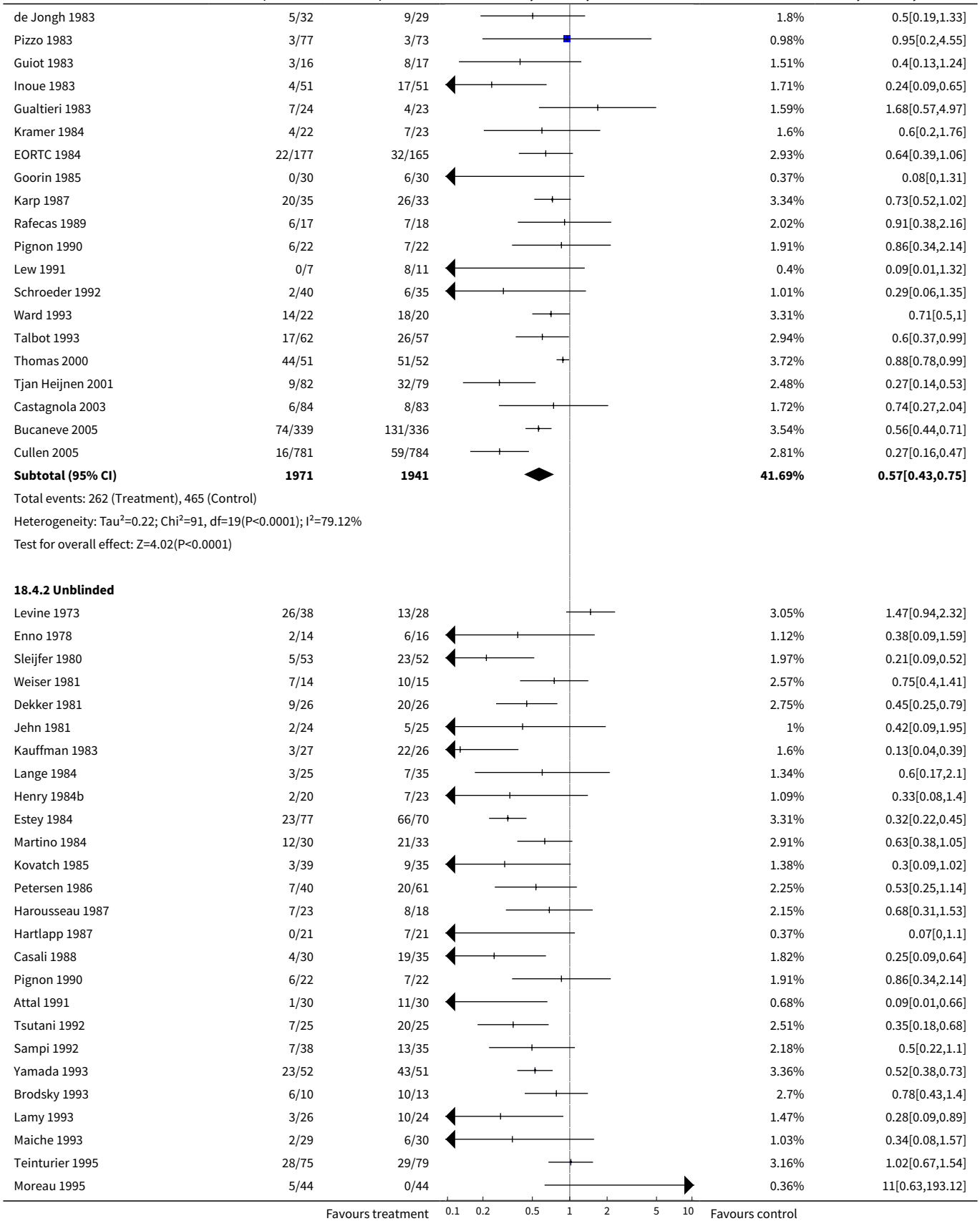
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
18.3.1 Double Blind					
Enno 1978	2/14	4/16		0.82%	0.57[0.12,2.66]
Gualtieri 1983	7/24	4/23		1.42%	1.68[0.57,4.97]
Pizzo 1983	14/77	24/73		2.95%	0.55[0.31,0.98]
de Jongh 1983	3/32	10/29		1.24%	0.27[0.08,0.89]
Inoue 1983	33/51	43/51		4.56%	0.77[0.61,0.97]
Guiot 1983	5/16	7/17		1.78%	0.76[0.3,1.91]
Kramer 1984	0/22	4/23		0.27%	0.12[0.01,2.04]
Kovatch 1985	13/39	16/35		2.97%	0.73[0.41,1.29]
Rafecas 1989	0/17	4/18		0.27%	0.12[0.01,2.03]
Pignon 1990	6/22	8/22		1.89%	0.75[0.31,1.8]
Lew 1991	0/7	10/11		0.3%	0.07[0,1.05]
Schroeder 1992	1/40	7/35		0.5%	0.13[0.02,0.97]
Ward 1993	3/22	3/20		0.87%	0.91[0.21,4]
Talbot 1993	38/62	41/57		4.47%	0.85[0.66,1.1]
Thomas 2000	2/51	2/52		0.56%	1.02[0.15,6.97]
Tjan Heijnen 2001	15/82	38/79		3.24%	0.38[0.23,0.63]
Castagnola 2003	1/84	4/83		0.45%	0.25[0.03,2.16]
Bucaneve 2005	30/339	33/336		3.43%	0.9[0.56,1.44]
Cullen 2005	84/781	119/784		4.45%	0.71[0.55,0.92]
Dickgreber 2009	9/99	25/93		2.43%	0.34[0.17,0.69]
Subtotal (95% CI)	**1881**	**1857**		**38.87%**	**0.65[0.53,0.79]**
Total events: 266 (Treatment), 406 (Control)					

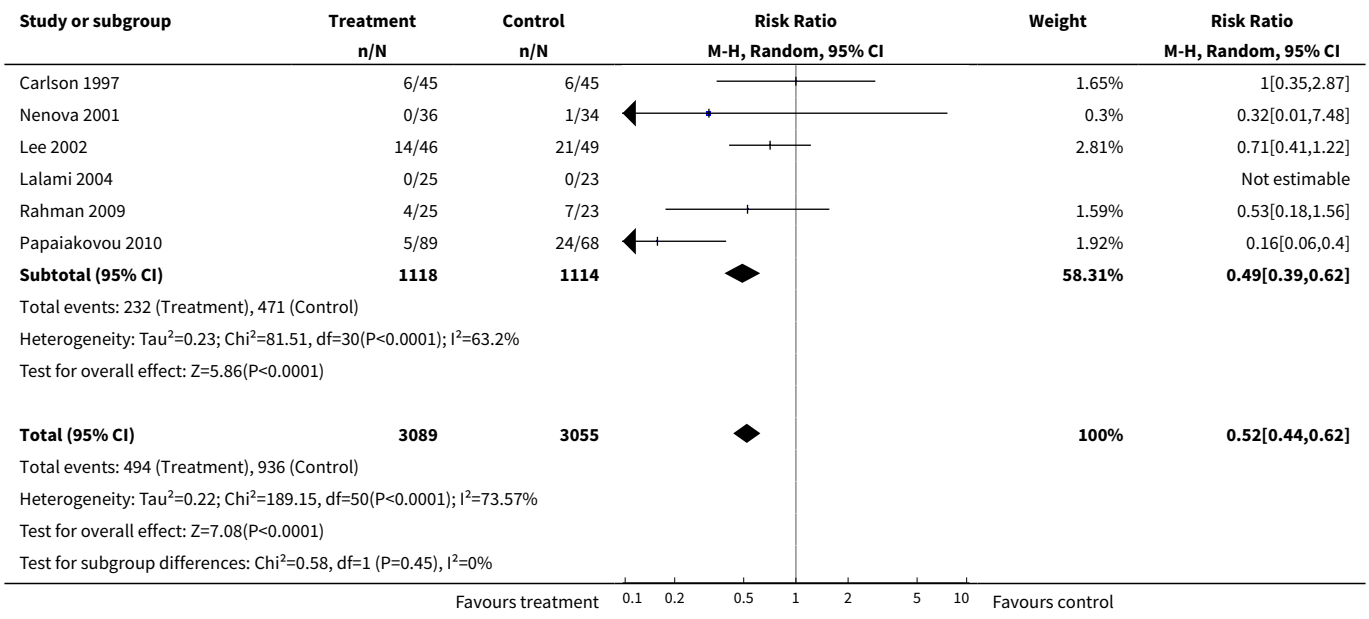
Favours treatment — Favours control



Analysis 18.4. Comparison 18 Sensitivity analyses by blinding, drug versus placebo or no intervention, Outcome 4 Microbiologically documented infection.







ADDITIONAL TABLES

Table 1. Other studies

Study ID	Intervention 1	Intervention 2	Overall mortality	Inf-related mortality	febrile patients	clin.doc.inf	micro.doc.inf	gram neg. inf	gram pos. inf
D'Antonio 1994	ciprofloxacin	ofloxacin	0.77(0.18-3.33)	0.77(0.18-3.33)		1.41(0.60-3.32)	0.9(0.47-1.71)	0.68(0.12-3.98)	0.95(0.46-1.94)
GIMEMA 1991	ciprofloxacin	norfloxacin	0.97(0.64-1.47)	1.11(0.72-1.72)	0.89(0.81-0.99)	0.92(0.62-1.37)	0.71(0.52-0.98)	0.46(0.24-0.88)	0.92(0.59-1.44)
Maschmeyer 1988	ciprofloxacin	norfloxacin	1.43(0.22-9.44)	0.46(0.04-4.74)	0.92(0.64-1.32)	1.84(0.52-6.52)	0.51(0.20-1.30)	0.18(0.01-3.65)	0.66(0.24-1.78)
D'Antonio 1991	norfloxacin	ofloxacin	3.08(0.13-73.23)	3.08(0.13-73.23)		9.25(0.52-165.69)	9.25(0.52-165.69)	11.31(0.65-197.11)	1.54(0.61-3.88)
D'Antonio 1992	norfloxacin	pefloxacin	1.03(0.22-4.92)	1.03(0.07-16.13)	1.3(1-1.69)	2.83(0.95-8.46)	2.06(1.06-4.00)	7.21(0.91-57.02)	1.69(0.86-3.30)
Bender 1979	gentamycin+vancomycin	gentamycin	3.15(0.14-72.88)		0.95(0.62-1.47)	0.48(0.14-1.57)	2.06(1.06-4.00)	4.44(1.08-18.25)	0.44(0.1-2.01)

Table 2. Other studies - continued

Study ID	Intervention 1	Intervention 2	Bacteremia	Gram neg bacteraemia	Gram pos bacteraemia	Side effects	S/E requiring D/C	fungal infection	Inf.res. to quinolon
D'Antonio 1994	ciprofloxacin	ofloxacin	1.03(0.35-3.04)	0.15(0.01-2.79)	2.05(0.53-7.92)	1.32(0.52-3.37)			0.96(0.50-1.85)
GIMEMA 1991	ciprofloxacin	norfloxacin	0.77(0.53-1.13)	0.57(0.23-1.42)	0.84(0.52-1.36)	1.58(0.75-3.33)	1.7(0.75-3.84)	1.06(0.22-5.23)	0.37(0.16-0.87)
Maschmeyer 1988	ciprofloxacin	norfloxacin	0.92(0.21-4.11)		0.92(0.21-4.11)	0.46(0.04-4.74)	0.18(0.01-3.65)	0.31(0.01-7.2)	
D'Antonio 1991	norfloxacin	ofloxacin	6.17(0.78-48.68)	5.14(0.26-103.37)	4.11(0.48-35.02)	2.06(0.2-21.68)		3.08(0.13-73.22)	2.4(1.04-5.53)

Table 2. Other studies - continued *(Continued)*

D'Antonio 1992	norfloxacin	pefloxacin	2.47(0.92-6.64)	4.12(0.47-35.91)	2.27(0.83-6.17)	0.69(0.2-2.32)	2.06(0.19-22.18)	2.15(1.18-3.91)
Bender 1979	gentamycin+vancomycin	gentamycin	1.11(0.48-2.55)	1.48(0.38-5.74)	0.56(0.05-5.62)			

APPENDICES

Appendix 1. Methodology of the original 2005 review

Searches

Relevant RCTs were identified by searching The Cochrane Cancer Network Register of Trials (Oct 2005), Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 4, 2005), MEDLINE (January 1966 to Oct 2005), EMBASE (January 1980 to Oct 2005), and the following conference proceedings: Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) (1995 to 2004), Annual Meetings of the Infectious Diseases Society of America (IDSA) (2001 to 2004) and European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) (2001 to 2004).

MEDLINE was searched using the following search phrase, which was adapted for searching the other databases:
(((neutropenia*:ME or agranulocytosis*:ME or neutropenia* or neutropeni* or neutropaeni* or agranulocyt*) and (quinolone:ME or trimethoprim-sulfamethoxazole:ME or vancomycin:ME or quinolone* or trimethoprim-sulfamethoxazole* or vancomycin* or antibiotic* or antimicrobial* or anti-microbial* or antibacterial* or anti-bacterial*) and (antibiotic prophylaxis*:ME or prophyla* or preventi*)))

The references of all identified studies were inspected for more trials. Additionally, the first or corresponding author of each included trial and the researchers active in the field were contacted for information regarding unpublished trials or complementary information on their own trial.

Risk of bias assessment

Trials fulfilling the review inclusion criteria were assessed for methodological quality by two authors (AGG and AF) independently. Trials which exceeded a threshold of 30% dropouts were excluded. We extracted information about randomisation and allocation concealment, blinding, sample size, exclusions after randomisation, and different lengths of follow-up. This was done using the criteria described in the Cochrane Reviewer's handbook (Higgins 2005), which were based on the empirical evidence of a strong association between poor allocation concealment and overestimation of effect (Schulz 1995). This is defined as below:

A. Low risk of bias (adequate allocation concealment)
B. Unclear risk of bias (unclear allocation concealment)
C. High risk of bias (inadequate allocation concealment, i.e. quasi-randomised studies)

In addition, sensitivity analyses was performed in order to assess the robustness of the findings to different aspects of the trials' methodology: randomisation generation, allocation concealment (adequate or unclear), blinding. Sensitivity analysis was conducted for the comparison of antibiotic versus placebo or no intervention. No data were found for conducting sensitivity analysis according to length of follow up (up to one month or one to 12 months).

Appendix 2. MEDLINE search strategy

1 Neutropenia/
2 (neutropaeni* or neutropeni*).mp.
3 1 or 2
4 exp Antibiotic Prophylaxis/
5 (antibiotic* or antimicrobial* or anti-microbial* or antibacterial* or anti-bacterial*).mp.
6 exp Quinolones/
7 quinolone*.mp.
8 ciprofloxacin.mp.
9 ofloxacin.mp.
10 norfloxacin.mp.
11 pefloxacin.mp.
12 exp Trimethoprim-Sulfamethoxazole Combination/
13 trimethoprim-sulfamethoxazole.mp.
14 TMP-SMZ.mp.
15 exp Aminoglycosides/
16 aminoglycoside*.mp.
17 gentamicin.mp.
18 neomycin.mp.
19 tobramycin.mp.
20 exp Colistin/
21 colistin.mp.
22 exp Polymyxins/
23 polymyxin*.mp.
24 exp Rifampin/

25 rifampin.mp.
26 exp Cephalosporins/
27 cephalosporin*.mp.
28 ceftriaxone.mp.
29 exp Vancomycin/
30 vancomycin.mp.
31 or/5-30
32 (prophyla* or prevent*).mp.
33 31 and 32
34 4 or 33
35 3 and 34
36 randomized controlled trial.pt.
37 controlled clinical trial.pt.
38 randomized.ab.
39 placebo.ab.
40 drug therapy.fs.
41 randomly.ab.
42 trial.ab.
43 groups.ab.
44 or/36-43
45 35 and 44
46 (animals not (humans and animals)).sh.
47 45 not 46

key:
mp=title, original title, abstract, name of substance word, subject heading word
ab=abstract
pt=publication type
fs=floating subheading
sh=subject heading

Appendix 3. CENTRAL search strategy

Issue 2 2009

#1 MeSH descriptor Neutropenia explode all trees
#2 neutropaeni* or neutropeni*
#3 (#1 OR #2)
#4 MeSH descriptor Antibiotic Prophylaxis explode all trees
#5 antibiotic* or antimicrobial* or anti-microbial* or antibacterial* or anti-bacterial*
#6 MeSH descriptor Quinolones explode all trees
#7 quinolone*
#8 ciprofloxacin
#9 ofloxacin
#10 norfloxacin
#11 pefloxacin
#12 MeSH descriptor Trimethoprim-Sulfamethoxazole Combination explode all trees
#13 trimethoprim-sulfamethoxazole
#14 TMP-SMZ
#15 MeSH descriptor Aminoglycosides explode all trees
#16 aminoglycoside*
#17 gentamicin
#18 neomycin
#19 tobramycin
#20 MeSH descriptor Colistin explode all trees
#21 colistin
#22 MeSH descriptor Polymyxins explode all trees
#23 polymyxin*
#24 MeSH descriptor Rifampin explode all trees
#25 rifampin
#26 MeSH descriptor Cephalosporins explode all trees
#27 cephalosporin*
#28 ceftriaxone

#29 MeSH descriptor Vancomycin explode all trees
#30 vancomycin
#31 (#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #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 OR #29 OR #30)
#32 prophyla* or prevent*
#33 (#31 AND #32)
#34 (#4 OR #33)
#35 (#3 AND #34)

Appendix 4. EMBASE search strategy

1 exp neutropenia/
2 (neutropaeni* or neutropeni*).mp.
3 1 or 2
4 exp antibiotic prophylaxis/
5 (antibiotic* or antimicrobial* or anti-microbial* or antibacterial* or anti-bacterial*).mp.
6 exp quinolone derivative/
7 quinolone*.mp.
8 ciprofloxacin.mp.
9 ofloxacin.mp.
10 norfloxacin.mp.
11 pefloxacin.mp.
12 trimethoprim-sulfamethoxazole.mp.
13 TMP-SMZ.mp.
14 exp aminoglycoside/
15 aminoglycoside*.mp.
16 gentamicin.mp.
17 neomycin.mp.
18 tobramycin.mp.
19 exp colistin/
20 colistin.mp.
21 exp polymyxin/
22 polymyxin*.mp.
23 exp rifampicin/
24 rifampin.mp.
25 cephalosporin derivative/
26 cephalosporin*.mp.
27 ceftriaxone.mp.
28 exp vancomycin/
29 vancomycin.mp.
30 or/5-29
31 (prophyla* or prevent*).mp.
32 30 and 31
33 4 or 32
34 3 and 33
35 exp controlled clinical trial/
36 randomized.ab.
37 placebo.ab.
38 dt.fs.
39 randomly.ab.
40 trial.ab.
41 groups.ab.
42 or/35-41
43 34 and 42
44 exp animal/
45 human/
46 44 not (44 and 45)
47 43 not 46

key:
mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name
ab=abstract

fs=floating subheading

Appendix 5. Assessment of risk of bias for the 2011 updated review

For each included study we assessed the following:

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator),
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number) or,
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes and assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel;

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes. We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we re-included missing data in the analyses which we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups; missing outcome data of < 20%);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);

- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not prespecified; outcomes of interest were reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias

Note: The risk of bias assessment performed for the original review only included points 1) to 3) above, therefore the updated 'risk of bias tables' for the original included trials in Characteristics of included studies were updated with details for points 4) to 5).

We explored the impact of the level of bias through undertaking sensitivity analyses - see 'Sensitivity analysis'.

Appendix 6. Results and conclusions of the original 2005 review

2005 Results

One-hundred and one trials (12,599 patients) conducted between the years 1973 to 2005 met the inclusion criteria. Antibiotic prophylaxis significantly decreased the risk for death when compared with placebo or no intervention (RR 0.66 [95% CI 0.55 to 0.79]). The authors estimated the number needed to treat (NNT) in order to prevent one death from all causes as 50 (95% CI 34 to 268).

Prophylaxis resulted in a significant decrease in the risk of infection-related death, RR 0.59 (95% CI 0.47 to 0.75) and in the occurrence of fever, RR 0.77 (95% CI 0.74 to 0.81). A reduction in mortality was also evident when the more recently conducted quinolone trials were analysed separately. Quinolone prophylaxis reduced the risk for all-cause mortality, RR 0.52 (95% CI, 0.37 to 0.74).

2005 Conclusions

Our review demonstrated that prophylaxis significantly reduced all-cause mortality. The most significant reduction in mortality was observed in trials assessing prophylaxis with quinolones. The benefit demonstrated in our review outweighs harm, such as adverse effects and development of resistance, since all-cause mortality is reduced. Since most trials in our review were of patients with haematologic cancer, prophylaxis, preferably with a quinolone, should be considered for these patients.

WHAT'S NEW

Date	Event	Description
17 July 2018	Amended	Next stage expected date amended
28 June 2018	Review declared as stable	Conclusions unlikely to change with the addition of new studies.

HISTORY

Protocol first published: Issue 3, 2003
Review first published: Issue 4, 2005

Date	Event	Description
12 October 2011	New citation required but conclusions have not changed	Eight new trials included:Garcia Saenz 2002, Lalami 2004, Rafecas 1989, Slavin 2007, Timmers 2007, Rahman 2009, Dickgreber 2009, Papaiakovou 2010. Ten newly identified trials excluded. New authors (LV and TL) added.
1 March 2011	New search has been performed	Search updated
30 July 2009	Amended	Tables linked to text
19 August 2008	Amended	Converted to new review format.
29 July 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Anat Gafter-Gvili - coordinating the review, data collection and management, analysis, interpretation of results and writing of the review, securing funding for the review.
Abigail Fraser - data collection and management, analysis, interpretation of results and writing of the review.
Mical Paul - data collection, interpretation of results and writing the review.
Liat Vidal - extraction of data from trials for the update.
Tess Lawrie - updated methodological and statistical aspects of the review.
Marianne van de Wetering - article retrieval.
Leontien Kremer - article retrieval.
Leonard Leibovici - conceiving and designing the review, analysis of data, interpretation of data and writing of the review, securing funding for the review.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- A grant from Rabin Medical Center, Israel.

External sources

- European Commission (TREAT Project, Contract 1999-11459), Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Since the original publication of this review, it has become clear that the main determinant of clinical practice in this area is all-cause mortality. Therefore, for the 2011 update, we retained all-cause mortality as the primary outcome, and considered infection-related mortality and febrile neutropenia as secondary outcomes.

INDEX TERMS

Medical Subject Headings (MeSH)

*Antibiotic Prophylaxis [adverse effects]; Anti-Bacterial Agents [adverse effects] [*therapeutic use]; Bacteremia [prevention & control]; Bacterial Infections [mortality] [*prevention & control]; Cause of Death; Drug Resistance, Bacterial; Fever [prevention & control]; Gram-Negative Bacterial Infections [prevention & control]; Gram-Positive Bacterial Infections [prevention & control]; Neoplasms [drug therapy]; Neutropenia [chemically induced] [*complications]; Quinolones [adverse effects] [therapeutic use]; Randomized Controlled Trials as Topic; Trimethoprim, Sulfamethoxazole Drug Combination [adverse effects] [therapeutic use]

MeSH check words

Humans