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Interventions for the management of malignant pleural effusions: a network meta-analysis (Review)

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[Intervention Review]

Interventions for the management of malignant pleural effusions: a network meta-analysis

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ABSTRACT

Background

Malignant pleural effusion (MPE) is a common problem for people with cancer and usually associated with considerable breathlessness. A number of treatment options are available to manage the uncontrolled accumulation of pleural fluid, including administration of a pleurodesis agent (via a chest tube or thoracoscopy) or placement of an indwelling pleural catheter (IPC). This is an update of a review published in Issue 5, 2016, which replaced the original, published in 2004.

Objectives

To ascertain the optimal management strategy for adults with malignant pleural effusion in terms of pleurodesis success and to quantify differences in patient-reported outcomes and adverse effects between interventions.

Search methods

We searched CENTRAL, MEDLINE (Ovid), Embase (Ovid) and three other databases to June 2019. We screened reference lists from other relevant publications and searched trial registries.

Selection criteria

We included randomised controlled trials of intrapleural interventions for adults with symptomatic MPE, comparing types of sclerosant, mode of administration and IPC use.

Data collection and analysis

Two review authors independently extracted data on study design, characteristics, outcome measures, potential effect modifiers and risk of bias.

The primary outcome was pleurodesis failure rate. Secondary outcomes were adverse events, patient-reported breathlessness control, quality of life, cost, mortality, survival, duration of inpatient stay and patient acceptability.

We performed network meta-analyses of primary outcome data and secondary outcomes with enough data. We also performed pair-wise meta-analyses of direct comparison data. If we deemed interventions not jointly randomisable, or we found insufficient available data, we reported results by narrative synthesis. For the primary outcome, we performed sensitivity analyses to explore potential causes of heterogeneity and to evaluate pleurodesis agents administered via a chest tube only.

We assessed the certainty of the evidence using GRADE.

Main results

We identified 80 randomised trials (18 new), including 5507 participants. We found all except three studies at high or unclear risk of bias for at least one domain. Due to the nature of the interventions, most studies were unblinded.

Pleurodesis failure rate

We included 55 studies of 21 interventions in the primary network meta-analysis. We estimated the rank of each intervention's effectiveness. Talc slurry (ranked 6, 95% credible interval (Cr-I) 3 to 10) is an effective pleurodesis agent (moderate certainty for comparison with placebo) and may result in fewer pleurodesis failures than bleomycin and doxycycline (bleomycin versus talc slurry: odds ratio (OR) 2.24, 95% Cr-I 1.10 to 4.68; low certainty; ranked 11, 95% Cr-I 7 to 15; doxycycline versus talc slurry: OR 2.51, 95% Cr-I 0.81 to 8.40; low certainty; ranked 12, 95% Cr-I 5 to 18).

There is little evidence of a difference between the pleurodesis failure rate of talc poudrage and talc slurry (OR 0.50, 95% Cr-I 0.21 to 1.02; moderate certainty). Evidence for any difference was further reduced when restricting analysis to studies at low risk of bias (defined as maximum one high risk domain in the risk of bias assessment) (pleurodesis failure talc poudrage versus talc slurry: OR 0.78, 95% Cr-I 0.16 to 2.08).

IPCs without daily drainage are probably less effective at obtaining a definitive pleurodesis (cessation of pleural fluid drainage facilitating IPC removal) than talc slurry (OR 7.60, 95% Cr-I 2.96 to 20.47; rank = 18/21, 95% Cr-I 13 to 21; moderate certainty). Daily IPC drainage or instillation of talc slurry via IPC are likely to reduce pleurodesis failure rates.

Adverse effects

Adverse effects were inconsistently reported. We performed network meta-analyses for the risk of procedure-related fever and pain.

The evidence for risk of developing fever was of low certainty, but suggested there may be little difference between interventions relative to talc slurry (talc poudrage: OR 0.89, 95% Cr-I 0.11 to 6.67; bleomycin: OR 2.33, 95% Cr-I 0.45 to 12.50; IPCs: OR 0.41, 95% Cr-I 0.00 to 50.00; doxycycline: OR 0.85, 95% Cr-I 0.05 to 14.29).

Evidence also suggested there may be little difference between interventions in the risk of developing procedure-related pain, relative to talc slurry (talc poudrage: OR 1.26, 95% Cr-I 0.45 to 6.04; very-low certainty; bleomycin: OR 2.85, 95% Cr-I 0.78 to 11.53; low certainty; IPCs: OR 1.30, 95% Cr-I 0.29 to 5.87; low certainty; doxycycline: OR 3.35, 95% Cr-I 0.64 to 19.72; low certainty).

Patient-reported control of breathlessness

Pair-wise meta-analysis suggests there is likely no difference in breathlessness control, relative to talc slurry, of talc poudrage ((mean difference (MD) 4.00 mm, 95% CI −6.26 to 14.26) on a 100 mm visual analogue scale for breathlessness; studies = 1; participants = 184; moderate certainty) and IPCs without daily drainage (MD −6.12 mm, 95% CI −16.32 to 4.08; studies = 2; participants = 160; low certainty).

Overall mortality

There may be little difference between interventions when compared to talc slurry (bleomycin and IPC without daily drainage; low certainty) but evidence is uncertain for talc poudrage and doxycycline.

Patient acceptability

Pair-wise meta-analysis demonstrated that IPCs probably result in a reduced risk of requiring a repeat invasive pleural intervention (OR 0.25, 95% Cr-I 0.13 to 0.48; moderate certainty) relative to talc slurry. There is likely little difference in the risk of repeat invasive pleural intervention with talc poudrage relative to talc slurry (OR 0.96, 95% CI 0.59 to 1.56; moderate certainty).

Authors' conclusions

Based on the available evidence, talc poudrage and talc slurry are effective methods for achieving a pleurodesis, with lower failure rates than a number of other commonly used interventions.

IPCs provide an alternative approach; whilst associated with inferior definitive pleurodesis rates, comparable control of breathlessness can probably be achieved, with a lower risk of requiring repeat invasive pleural intervention.

Local availability, global experience of agents and adverse events (which may not be identified in randomised trials) and patient preference must be considered when selecting an intervention.

Further research is required to delineate the roles of different treatments according to patient characteristics, such as presence of trapped lung. Greater attention to patient-centred outcomes, including breathlessness, quality of life and patient preference is essential to inform

clinical decision-making. Careful consideration to minimise the risk of bias and standardise outcome measures is essential for future trial design.

PLAIN LANGUAGE SUMMARY

Interventions for the management of fluid around the lungs (pleural fluid) caused by cancer

Review question

We reviewed the evidence on the effectiveness of different methods to manage a build-up of fluid around the lungs in people where this is caused by cancer.

Background

Malignant pleural effusion (MPE) is a condition that affects people with cancer of the lining of the lung. This can cause fluid to build up in the space between the outside of the lungs and rib cage (pleural cavity), often resulting in breathlessness. Treatment options focus on controlling symptoms. These include removal of the fluid using a temporary chest drain, a camera examination of the pleural cavity (thoracoscopy) or a semi-permanent chest drain tunnelled under the skin (an indwelling pleural catheter). Introducing a chemical into the pleural cavity can also be used to prevent the fluid coming back (pleurodesis). We wanted to find out which method was the most effective for preventing fluid re-accumulation (pleurodesis failure) and which was best in terms of side effects (including pain and fever) and other important outcomes such as breathlessness and quality of life.

Study characteristics

We collected and analysed relevant studies to answer this question. We were interested in high quality research, so only searched for randomised controlled trials (in which participants are randomly allocated to the treatments being tested). We analysed most data using 'network meta-analysis', which allows lots of different interventions to be compared in one analysis. This analysis ranks the interventions in order of their effectiveness.

Certainty of the evidence

We rated the certainty of the evidence from studies using four levels: very low, low, moderate or high. Very low-certainty evidence means that we are very uncertain about the results. High-certainty evidence means that we are very confident in the results. Many of the studies were of low quality and the individual studies were quite different to each other. This made it difficult to reach definite conclusions.

Key results

From our searches in June 2019, we found 80 studies (18 new) involving 5507 participants (2079 new).

In the network meta-analysis, we found that giving talc through a chest tube after draining the fluid (talc slurry) resulted in fewer pleurodesis failures than other commonly used methods, such as the medicines doxycycline or bleomycin through a chest tube (low certainty). Using a thoracoscopy procedure to remove the fluid and blow talc into the chest (talc poudrage) is likely to be as effective as talc slurry (moderate certainty).

We had a low level of certainty that the risk of having a fever is similar between treatments. There may be little difference between treatments in the chance of having pain (low certainty for bleomycin, IPCs and doxycycline; very-low certainty for talc poudrage).

Using an IPC, which allows intermittent drainage of fluid at home, may relieve breathlessness as much as a talc slurry procedure (low certainty).

There may be little difference in the risk of death between treatments when compared to talc slurry (low certainty for bleomycin and IPC without daily drainage; very low certainty for talc poudrage and doxycycline).

The chance of needing another invasive procedure to remove fluid was lower after having an IPC than after talc slurry pleurodesis (moderate certainty).

Conclusions

The available evidence shows that talc poudrage and talc slurry are effective ways of managing MPEs, with lower pleurodesis failure rates than a number of other commonly used methods. However, it is also important to consider global experience of these agents and knowledge of their safety and side effects when selecting the most appropriate pleurodesis method.

IPCs are less likely to prevent pleural fluid from re-accumulating than talc slurry, but may be as good at helping breathlessness. People who have an IPC are less likely to need another invasive procedure in the future to manage the pleural effusion.

Further research is required to look at particular patient groups and explore outcomes such as breathlessness and quality of life in more detail. Ideally a fuller understanding of the potential harms of the treatments from the patients' perspective would also be beneficial.

Summary of findings for the main comparison. Pleurodesis failure rate in adults with malignant pleural effusion

Patient or population: adults with malignant pleural effusion

Interventions: talc poudrage, bleomycin, IPC – not daily drainage, doxycycline, placebo

Comparator (reference): talc slurry

Outcome: pleurodesis failure rate

Setting: inpatient and outpatients

Data: based on network meta-analysis of eligible studies

Total studies: 55* **Total participants: 3758** **No. interventions in network: 21**	**Relative effect** **Odds ratio** **(95% Cr-I)** **Network estimate**	**Relative effect^^** **Odds ratio** **(95% Cr-I)** **Network estimate from studies at low risk of bias**	**Anticipated absolute effect (95% Cr-I)***** **With talc slurry^**	**With intervention**	**Difference**	**Certainty of evidence**	**Interpretation of findings**
Talc slurry (19 RCTs, 907 participants) Follow-up: up to 12 months	Reference comparator	Reference comparator	18 failures per 100 participants (11 to 24)	Not estimable	Not estimable	**Moderate**[a]	Reference comparator
Talc poudrage (9 RCTs, 530 participants) Follow-up: up to 24 months	0.50 (0.21 to 1.02)	0.78 (0.16 to 2.08)	18 failures per 100 participants (11 to 24)	10 failures per 100 participants (4 to 19)	–8 (–15 to 0) i.e. 8 fewer failures per 100 participants	**Moderate**[b]	Probably comparable
Bleomycin (21 RCTs, 528 participants)	2.24 (1.10 to 4.68)	3.93 (1.10 to 16.94)	18 failures per 100 participants (11 to 24)	32 failures per 100 participants (17 to 52)	15 (2 to 32) i.e. 15 more failures per 100 participants	**Low**[a,b]	May be inferior

Follow-up: up to 24 months							
IPC –not daily drainage (6 RCTs, 405 participants) Follow-up: up to 12 months	7.60 (2.96 to 20.47)	8.60 (2.26 to 30.15)	18 failures per 100 participants (11 to 24)	62 failures per 100 participants (36 to 82)	44 (20 to 63) i.e. 44 more failures per 100 participants	**Moderate**[c]	Probably inferior
Doxycycline (5 RCTs, 117 participants) Follow-up: up to 12 months	2.51 (0.81 to 8.40)	1.89 (0.32 to 8.84)	18 failures per 100 participants (11 to 24)	35 failures per 100 participants (13 to 65)	17 (–3 to 46) i.e. 17 more failures per 100 participants	**Low**[a,d]	May be inferior
Placebo (4 RCTs, 159 participants) Follow-up: up to 3 months	15.90 (3.76 to 79.90)	17.46 (3.33 to 97.26)	18 failures per 100 participants (11 to 24)	77 failures per 100 participants (42 to 95)	59 (26 to 77) i.e. 59 more failures per 100 participants	**Moderate**[d]	Probably inferior

Network meta-analysis summary of findings definitions:

*Information is reported from studies included in the network meta-analysis for pleurodesis failure.

**Network meta-analysis estimates are reported as ORs.

***Calculated using data from primary outcome network of pleurodesis failure.

Anticipated absolute effect: compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

'Absolute effect' and 'difference' estimates are posterior medians from a Bayesian statistical analysis. These may not sum exactly, due to skew in the posterior distributions.

^Reference comparator absolute event rate estimates are based on a random-effects meta-analysis of arm-level data from all trials including a talc slurry arm and reporting the relevant outcome. Cr-Is around 'differences' allow for sampling uncertainty in this baseline parameter, as well as uncertainty in the OR.

^^Network estimate from sensitivity analysis of studies at low risk of bias. These data are included within the summary of findings to reflect the ORs and Cr-Is from the network estimates in which we have the greatest level of certainty in the evidence.

Cr-I: credible interval; **IPC:** indwelling pleural catheter; **OR:** odds ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence (or certainty in the evidence):

High certainty: we are very confident that the true effect lies close to that of the estimate effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate in limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level: evidence of indirectness. Of the studies evaluating talc slurry, 13/19 excluded trapped lung and 12/19 used a clinical definition of pleurodesis success. Of the studies in the network evaluating bleomycin, 9/21 excluded trapped lung and 12/21 used a clinical definition of pleurodesis success and variability in the dose of bleomycin noted.
There was no direct evidence in the network comparing doxycycline and talc slurry and almost all indirect comparisons forming network loops were based on a single study.
[b]Downgraded one level for study limitations: overall high risk of bias for trials forming direct and indirect evidence loops for this agent.
[c]Downgraded one level: evidence of inconsistency: I^2 statistic between talc slurry and IPC (not daily drainage) comparison 61%.
[d]Downgraded one level: evidence of imprecision. Wide Cr-Is reduce the certainty in the estimate effect.

Summary of findings 2. Adverse effects: procedure-related fever in adults with malignant pleural effusion

Patient or population: adults with malignant pleural effusion

Interventions: talc poudrage, bleomycin, IPC – not daily drainage, doxycycline, placebo

Comparator (reference): talc slurry

Outcome: fever

Setting: inpatient and outpatients

Data: based on network meta-analysis of eligible studies

Total studies: 30 * **Total participants: 2004** **No. interventions in network: 14**	**Relative effect**** **OR** **(95% Cr-I)** **Network estimate**	**Anticipated absolute effect (95% Cr-I)*****			**Certainty of evidence**	**Interpretation of findings**
		With talc slurry^	**With intervention**	**Difference**		
Talc slurry (9 RCTs; 823 participants)	Reference comparator	21 cases in every 100 participants (11 to 33)	Not estimable	Not estimable	**Low**[a,b]	Reference comparator

Talc poudrage (4 RCTs; 553 participants)	0.89 (0.11 to 6.67)	21 cases in every 100 participants (11 to 33)	19 cases in every 100 participants (3 to 67)	2 (–21 to 43) i.e. 2 fewer cases per 100 participants	**Low**[a,b]	May be comparable
Bleomycin (14 RCTs; 774 participants)	2.33 (0.45 to 12.50)	21 cases in every 100 participants (11 to 33)	39 cases in every 100 participants (10 to 79)	17 (–10 to 55) i.e. 17 more cases per 100 participants	**Low**[a,b]	May be comparable
IPC – not daily drainage (1 RCT; 101 participants)	0.41 (0.00 to 50.00)	21 cases in every 100 participants (11 to 33)	10 cases in every 100 participants (0 to 93)	–10 (–28 to 70) i.e. 10 fewer cases per 100 participants	**Low**[a,b]	May be comparable
Doxycycline (4 RCTs; 308 participants)	0.85 (0.05 to 14.29)	21 cases in every 100 participants (11 to 33)	19 cases in every 100 participants (1 to 80)	–2 (–23 to 56) i.e. 2 fewer cases per 100 participants	**Low**[a,b]	May be comparable
Placebo (2 RCTs; 118 participants)	0.09 (0.00 to 5.00)	21 cases in every 100 participants (11 to 33)	2 cases in every 100 participants (0 to 59)	–17 (–30 to 36) i.e. 17 fewer cases per 100 participants	**Low**[a,b]	May be comparable

Network meta-analysis summary of findings definitions:

*Information is reported from studies included in the network meta-analysis for fever.

**Network meta-analysis estimates are reported as odds ratios.

***Anticipated absolute effect: compares two risks by calculating the difference between the risk of the intervention group with the risk of the control. group.

'Absolute effect' and 'difference' estimates are posterior medians from a Bayesian statistical analysis. These may not sum exactly, due to skew in the posterior distributions.

^Reference comparator absolute event rate estimates are based on a random-effects meta-analysis of arm-level data from all trials including a talc slurry arm and reporting the relevant outcome. Cr-Is around 'differences' allow for sampling uncertainty in this baseline parameter, as well as uncertainty in the OR.

Cr-I: credible interval; **IPC:** indwelling pleural catheter; **OR:** odds ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence (or certainty in the evidence):

High certainty: we are very confident that the true effect lies close to that of the estimate effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate in limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level for imprecision due to wide credible intervals of all network estimates.
[b]Downgraded one level for indirectness: due to the nature of outcome (presence/absence of procedure-related fever) this was commonly reported as an adverse event and so the time point at which measured is likely to differ between studies. Many studies did not define the definition of fever used, and where this was defined there was some variation between studies.

Summary of findings 3. Adverse effects: procedure-related pain in adults with malignant pleural effusion

Patient or population: adults with malignant pleural effusion

Interventions: talc poudrage, bleomycin IPC – not daily drainage, doxycycline, placebo

Comparator (reference): talc slurry

Outcome: procedure-related pain

Setting: inpatient and outpatient

Data: based on network meta-analysis of eligible studies

Total studies: 31* **Total participants: 2753** **No. interventions in network: 14**	**Relative effect**** **Odds ratio** **(95% Cr-I)** **Network estimate**	**Anticipated absolute effect (95% Cr-I)***** **With talc slurry^**	**With intervention**	**Difference**	**Certainty of evidence**	**Interpretation of findings**
Talc slurry (9 RCTs, 1320 participants)	Reference comparator	8 out of every 100 participants experiencing pain (1 to 35)	Not estimable	Not estimable	**Low**[a,b]	Reference comparator
Talc poudrage (4 RCTs, 886 participants)	1.26 (0.45 to 6.04)	8 out of every 100 participants experiencing pain (1 to 35)	10 out of every 100 participants experiencing pain (1 to 55)	2 additional participants experiencing pain per 100 participants (–6 to 30)	**Very low**[a,b,c]	May be comparable but evidence uncertain
Bleomycin (13 RCTs, 724 participants)	2.85 (0.78 to 11.53)	8 out of every 100 participants experiencing pain (1 to 35)	19 out of every 100 participants experiencing pain (1 to 71)	10 additional participants experiencing pain per 100 participants	**Low**[a,b]	May be comparable

				(–1 to 46)		
IPC – not daily drainage (6 RCTs, 738 participants)	1.30 (0.29 to 5.87)	8 out of every 100 participants experiencing pain (1 to 35)	10 out of every 100 participants experiencing pain (1 to 55)	1 additional participant experiencing pain per 100 participants (–9 to 30)	**Low**[a,b]	May be comparable
Doxycycline (4 RCTs, 308 participants)	3.35 (0.64 to 19.72)	8 out of every 100 participants experiencing pain (1 to 35)	22 out of every 100 participants experiencing pain (1 to 79)	13 additional participants experiencing pain per 100 participants (–3 to 56)	**Low**[a,b]	May be comparable
Placebo	3 studies reported data for procedure-related pain in participants receiving placebo but could not be included in the network as no events occurred in each study arm, causing computational problems. 1 study compared placebo with talc slurry and reported 0/17 participants receiving placebo and 0/14 receiving talc slurry required analgesia post procedure (Sorensen 1984).				—	—

Network meta-analysis summary of findings definitions:

*Information is reported from studies included in the network meta-analysis for pain.

**Network meta-analysis estimates are reported as odds ratios. Cr-I: credible interval.

***Anticipated absolute effect: compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

'Absolute effect' and 'difference' estimates are posterior medians from a Bayesian statistical analysis. These may not sum exactly, due to skew in the posterior distributions.

^Reference comparator absolute event rate estimates are based on a random-effects meta-analysis of arm-level data from all trials including a talc slurry arm and reporting the relevant outcome. Cr-Is around 'differences' allow for sampling uncertainty in this baseline parameter, as well as uncertainty in the OR.

Cr-I: credible interval; **IPC:** indwelling pleural catheter; **OR:** odds ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence (or certainty in the evidence):

High certainty: we are very confident that the true effect lies close to that of the estimate effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate in limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level for imprecision due to wide credible intervals of network estimates.

[b]Downgraded one level for indirectness. Due to the nature of outcome (presence/absence of procedure-related pain), this was commonly reported as an adverse event and so the time point at which measured, threshold for reporting and mode of assessment is often unstated and likely to differ between studies.
[c]Downgraded one level for inconsistency in the talc poudrage to talc slurry comparison (I^2 = 69%).

Summary of findings 4. Patient-reported control of breathlessness in adults with malignant pleural effusion

Patient or population: adults with malignant pleural effusion

Interventions: talc poudrage, bleomycin, IPC – not daily drainage, doxycycline, placebo

Comparator (reference): talc slurry

Outcome: postintervention patient-reported control of breathlessness?

Setting: inpatient and outpatient

Data: based on direct meta-analysis of 100-mm VAS breathless score

Intervention **Total studies: 4*** **Total participants: 379**	**Relative effect** **mean difference**** **(95% CI)*****	**Anticipated absolute effect****** **Change from baseline VAS score in mm** **(mean (95% CI))**		**Certainty of evidence**	**Interpretation of findings**
		With talc slurry	**With intervention**		
Talc slurry (2 RCTs, 248 participants)	Reference comparator	–26.29 (–35.26 to –17.34)	Not estimable	**Moderate**[a]	Reference comparator
Talc poudrage (1 RCT, 184 participants) 90-day VAS score	4.00 (–6.26 to 14.26)	–26.29 (–35.26 to –17.34)	–22.29 (–39.93 to –8.70)	**Moderate**[a]	Probably comparable
Bleomycin (1 RCT, 35 participants)	1 study assessed breathlessness by functional class score (numerical scale 1–4, where 1 = none and 4 = breathless at rest) and found no difference between talc slurry and bleomycin (Zimmer 1997).			**Very low**[c,d,e]	Uncertain
IPC –not daily drainage (2 RCTs, 160 participants) VAS scores at 42 days and 180 days	–6.12 (–16.32 to 4.08)	–26.29 (–35.26 to –17.34)	–32.41 (–45.98 to –18.86)	**Low**[a,b]	May be comparable

Doxycycline	There was no direct evidence comparing talc slurry and doxycycline	—	—
Placebo	There were no data reported on breathlessness improvement in people receiving placebo	—	—

Direct meta-analysis summary of findings definitions:

*Information is included from direct meta-analysis of studies using a 100-mm VAS breathlessness scale.

**The minimum clinically important difference for dyspnoea in malignant pleural effusion using the VAS breathlessness scale was 19 mm (95% CI 14 to 24) (Mishra 2015).

***Direct meta-analysis results are reported as standardised mean difference.

****Anticipated absolute effect: compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

'Absolute effect' and 'difference' estimates are posterior medians from a Bayesian statistical analysis. These may not sum exactly, due to skew in the posterior distributions.

^Reference comparator absolute event rate estimates are based on a random-effects meta-analysis of arm-level data from all trials including a talc slurry arm and reporting the relevant outcome.

CI: confidence interval; **IPC:** indwelling pleural catheter; **OR:** odds ratio; **RCT:** randomised controlled trial; **VAS:** visual analogue scale.

GRADE Working Group grades of evidence (or certainty in the evidence):

High certainty: we are very confident that the true effect lies close to that of the estimate effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate in limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level for study limitations: lack of blinding of participants and clinicians (due to nature of trial interventions) leading to increased risk of bias in VAS score reporting.
[b]Downgraded one level: evidence of indirectness: different time points at which the VAS dyspnoea scores were measured (Davies 2012: 42 days, Thomas 2017: 180 days).
[c]Downgraded one level for study limitations due to lack of blinding of participants and clinicians.
[d]Downgraded one level for indirectness: participants were assessed before and 'after treatment' with no longer-term breathlessness outcomes. A functional scale was used to assess breathlessness on a 1–4 scale, whereas other studies used a 100 mm VAS scale.
[e]Downgraded one level for imprecision due to low numbers of participants.

Summary of findings 5. Overall mortality in adults with malignant pleural effusion

Patient or population: adults with malignant pleural effusion

Interventions: talc poudrage, bleomycin IPC – not daily drainage, doxycycline, placebo

Comparator (reference): talc slurry

Outcome: mortality

Setting: inpatient and outpatient

Data: based on network meta-analysis of eligible studies

Total studies: 31* **Total participants: 2816** **No. interventions in network: 15**	**Relative effect**** **Odds ratio** **(95% Cr-I)** **Network estimate**	**Anticipated absolute effect (95% Cr-I)***** **With talc slurry^**	**With intervention**	**Difference**	**Certainty of evidence**	**Interpretation of findings**
Talc slurry (13 RCTs, 1574 participants) Follow-up: up to 12 months	Reference comparator	31 deaths out of every 100 participants (14 to 55)	Not estimable	Not estimable	**Low**[a,b]	Reference comparator
Talc poudrage (7 RCTs, 878 participants) Follow-up: up to 10 months	0.87 (0.53 to 1.43)	31 deaths out of every 100 participants (14 to 55)	28 deaths out of every 100 participants (11 to 55)	–3 (–12 to 8) i.e. 3 fewer deaths per 100 participants	**Very low**[a,b,c]	May be comparable but evidence uncertain
Bleomycin (9 RCTs, 664 participants) Follow-up: up to 9 months	1.03 (0.45 to 2.41)	31 deaths out of every 100 participants (14 to 55)	32 deaths out of every 100 participants (11 to 63)	1 (–15 to 21) i.e. 1 additional death per 100 participants	**Low**[a,b]	May be comparable
IPC – not daily drainage 6 RCTs, 587 participants Follow-up: up to 12 months	0.80 (0.47 to 1.40)	31 deaths out of every 100 participants (14 to 55)	26 deaths out of every 100 participants (10 to 53)	–4 (–14 to 7) i.e. 4 fewer deaths per 100 participants	**Low**[a,b]	May be comparable
Doxycycline (1 RCT, 80 participants) Follow-up 30 days	0.70 (0.16 to 3.00)	31 deaths out of every 100 participants (14 to 55)	24 deaths out of every 100 participants (5 to 64)	–6 (–28 to 25)	**Very low**[a,b,d]	May be comparable but evidence uncertain

		i.e. 6 fewer deaths per 100 participants	
Placebo	No studies reported mortality data for participants receiving placebo	—	—

Network meta-analysis summary of findings definitions:

*Information is reported from studies included in the network meta-analysis for mortality.

**Network meta-analysis estimates are reported as ORs.

***Anticipated absolute effect: compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

'Absolute effect' and 'difference' estimates are posterior medians from a Bayesian statistical analysis. These may not sum exactly, due to skew in the posterior distributions.

^Reference comparator absolute event rate estimates are based on a random-effects meta-analysis of arm-level data from all trials including a talc slurry arm and reporting the relevant outcome. Cr-Is around 'differences' allow for sampling uncertainty in this baseline parameter, as well as uncertainty in the OR

Cr-I: credible interval; **IPC:** indwelling pleural catheter; **OR:** odds ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence (or certainty in the evidence):

High certainty: we are very confident that the true effect lies close to that of the estimate effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate in limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level for imprecision due to wide credible intervals of all network estimates.
[b]Downgraded one level for indirectness due to different time points at which mortality was assessed (range 30 days to 12 months).
In the talc poudrage to talc slurry comparison 3/7 RCTs included only people with breast cancer.
[c]Downgraded one level for inconsistency in the talc poudrage to talc slurry comparison (I^2 = 40%).
[d]Downgraded one level for study limitations in the doxycycline to talc slurry comparison, where direct evidence is formed from one study at high risk of bias in three domains.

Summary of findings 6. Patient acceptability: need for repeat invasive pleural intervention in adults with malignant pleural effusion

Patient or population: adults with malignant pleural effusion

Interventions: talc poudrage, bleomycin, IPC – not daily drainage, doxycycline, placebo

Comparator (reference): talc slurry

Outcome: patient acceptability (need for repeat invasive pleural intervention)

Setting: inpatient and outpatient

Data: based on available direct evidence*

Intervention Total studies: 9 Total participants: 883	Relative effect** Odds ratio (95% CI)	Anticipated absolute effect (95% CI)***			Certainty of evidence	Interpretation of findings
		With talc slurry^	With intervention	Difference		
Talc slurry (8 RCTs, 850 participants) Follow-up: 12 months	Reference comparator	20 out of every 100 participants requiring repeat invasive interventions (16 to 24)	Not estimable	Not estimable	**Moderate**[a,b]	Reference comparator
Talc poudrage (2 RCTs, 380 participants) Follow-up: 6 months	0.96 (0.59 to 1.56)	20 out of every 100 participants requiring repeat invasive interventions (16 to 24)	19 out of every 100 participants (11 to 30)	–1 out of every 100 participants (–7 to +8) i.e. 1 less per 100 participants	**Moderate**[b,c]	Probably comparable
Bleomycin (1 RCT, 33 participants) Follow-up to 8 months	4.33 (0.16 to 114.58)	20 out of every 100 participants requiring repeat invasive interventions (16 to 24)	52 out of every 100 participants (4 to 97)	+32 out of every 100 participants (–16 to 77) i.e. 32 more repeat procedures required per 100 participants	**Very low**[d,e]	May be inferior but the evidence is uncertain
IPC –not daily drainage (3 RCTs, 343 participants) Follow-up: 12 months	0.25 (0.13 to 0.48)	20 out of every 100 participants requiring repeat invasive interventions (16 to 24)	6 out of every 100 participants (3 to 11)	–14 out of every 100 participants (–19 to –8) i.e. 14 less per 100 participants	**Moderate**[a,b]	Probably superior
Doxycycline	There were no direct data comparing doxycycline and talc slurry.				—	—
Placebo	There were no direct data comparing placebo and talc slurry.				—	—

Direct meta-analysis summary of findings definitions:

*Based on direct meta-analysis.

**Estimates are reported as ORs.

***Anticipated absolute effect: compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

'Absolute effect' and 'difference' estimates are posterior medians from a Bayesian statistical analysis. These may not sum exactly, due to skew in the posterior distributions.

^Reference comparator absolute event rate estimates are based on a random-effects meta-analysis of arm-level data from all trials including a talc slurry arm and reporting the relevant outcome.

CI: confidence interval; **IPC:** indwelling pleural catheter; **OR:** odds ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence (or certainty in the evidence):

High certainty: we are very confident that the true effect lies close to that of the estimate effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate in limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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[a]Downgraded one level: evidence of indirectness: people with trapped lung excluded by Thomas 2017, but not Boshuizen 2017 or Davies 2012.
[b]Study limitations noted as blinding of participants and clinicians was not possible due to nature of the interventions. Evidence was not downgraded, as requirement for repeat procedural intervention guided by symptoms and radiology. In one study, clinicians were required to discuss with a second, blinded clinician prior to repeat intervention in participants with less than one-third opacification of the hemithorax (Bhatnagar 2020).
[c]Downgraded one level: evidence of indirectness: one study gave 5 g 'non-calibrated' talc via 28-Fr drains in both study arms (Terra 2009), whereas in Bhatnagar 2020 4 g graded talc used and administered by 12- to 14-Fr drains in talc slurry arm (size 16- to 24-Fr drains placed in talc poudrage arm).
[d]Downgraded one level: study limitations: bleomycin data derived from one study, at high risk of bias in three domains and 'unclear' risk of bias for randomisation and sequence generation.
[e]Downgraded two levels: evidence of imprecision: low number of participants and very wide confidence interval.

BACKGROUND

Malignant pleural effusion (MPE) is a common clinical problem, with an estimated annual incidence of at least 150,000 in the USA (American Thoracic Society 2000). Fifteen percent of people diagnosed with cancer will develop pleural effusion during the course of their disease as a result of malignant infiltration of the pleura. It often confers a poor prognosis (Rodrîguez-Panadero 1989). Breathlessness results from compression of the underlying lung and impaired diaphragmatic and chest wall movement and is often relieved by pleural fluid aspiration.

This is the first update of the review published in Issue 5, 2016 (Clive 2016), which replaced the original review published in 2004 (Shaw 2004).

Description of the condition

MPE is a condition whereby excess fluid accumulates in the pleural cavity. It is thought to be caused by a combination of direct pleural tumour invasion, resulting in increased permeability of the pleural microvessels and obstruction of local lymph drainage channels causing reduced fluid re-absorption (Rodrîguez-Panadero 2008). The most common primary sites which metastasise to the pleura are lung cancer in men and breast cancer in women, but other primary sites include lymphoma, genitourinary and gastrointestinal malignancy (DiBonito 1992; Sears 1987). In addition, the pleura may be the primary site of the malignancy, as is the case in mesothelioma. In the majority of cases, the diagnosis of pleural malignancy is made by cytological analysis of the pleural fluid or pleural biopsy. Depending on the clinical situation, confirmation of malignancy elsewhere and an otherwise unexplained (usually exudative) effusion may also be attributed to malignancy. Survival of these patients varies widely (Bielsa 2008; Burrows 2000). Tools have been developed to aid estimation of an individual's prognosis, which may in turn help with selection of the most appropriate management strategy (Clive 2014; Psallidas 2018).

Description of the intervention

A number of different approaches may be used to manage MPE and the chosen method is likely to depend on clinical factors, patient preferences and local availability of the various techniques. Instillation of a sclerosant into the pleural cavity through an intercostal chest drain, after complete fluid drainage has been the mainstay of treatment for many years (known as 'bedside' or 'slurry' pleurodesis). This technique aims to fuse the pleural layers together by means of local inflammation induced by the pleurodesis agent, thereby preventing pleural fluid re-accumulation. The optimal management strategy to maximise pleurodesis success in terms of the size of chest drain, patient positioning, use of analgesia and type of sclerosant has historically been the subject of debate (Roberts 2010).

Thoracoscopy is a method which can be used to drain an effusion and, during the same procedure, deliver a sclerosant into the pleural cavity with a view to achieving pleurodesis (Rahman 2010). Thoracoscopy can either be performed under moderate sedation (medical thoracoscopy), or as a surgical procedure under general anaesthetic (video-assisted thoracoscopic surgery (VATS)). In both techniques, the pleural fluid is drained and the pleural cavity is visualised using a fibreoptic camera. Loculations can be broken down and biopsies may be taken to gain a histological diagnosis. At the end of the procedure, a temporary chest tube is left in place to allow the lung to re-expand.

An alternative approach in the management of MPE is the use of indwelling pleural catheters (IPCs). These are long-term chest tubes which are tunnelled under the skin and therefore allow regular, intermittent fluid drainage to be performed in the community, potentially minimising recurrent hospital attendances. They have an established role in the management of pleural effusions in people with trapped lung, but are increasingly being used for the primary management of malignant effusions as an alternative to chemical pleurodesis (Davies 2012; Demmy 2012; Thomas 2017). Spontaneous pleurodesis may occur, allowing the drain to be removed without recurrence of the effusion (Tremblay 2006).

In certain clinical scenarios, none of the above options may be suitable and simple pleural fluid aspiration or medical management of a patient's breathlessness (e.g., using opiates) may be deemed more appropriate. This may be the case for people in the terminal phase of their illness where invasive techniques may be considered to confer unnecessary discomfort.

How the intervention might work

Pleurodesis aims to induce inflammation between the pleural layers causing them to become adhered. This effectively obliterates the pleural space and by so doing, prevents fluid recurrence. For pleurodesis to be successful, the visceral and parietal pleural surfaces must be opposed, hence if lung expansion is incomplete, pleurodesis is more likely to fail.

Trapped lung (also known as 'entrapped' or 'non-expandable' lung) can occur when full lung expansion is limited by either a visceral pleural peel or endobronchial obstruction. In this situation, even once the fluid is drained, visceral and parietal pleural apposition does not readily occur, with attempts at inflating the lung potentially distressing for patients. This results in pleurodesis attempts being less effective and often limits the treatment options to either an IPC or surgery.

IPCs allow regular, intermittent pleural fluid drainage, which relieves the pressure on the diaphragm and chest wall, and promotes lung re-expansion. By so doing, breathlessness is improved and, in a small proportion of people, autopleurodesis may occur (Dipper 2019).

Why it is important to do this review

Due to wider availability of pleural interventions, such as thoracoscopy under sedation and IPCs, the management options available to people with MPE are expanding. This review will help to define the most effective pleurodesis approach, primarily addressing the type of agent used.

Given the availability of many pair-wise comparisons for the method of pleurodesis administration, type of pleurodesis agent and approaches to IPC use, this is a multiple interventions review. We performed network meta-analysis (NMA) to synthesise all the available evidence and determine a treatment hierarchy.

In 2019, the National Institute for Health and Care Excellence (NICE) in the UK commissioned the priority updating of this review

to inform the guideline *Lung cancer: diagnosis and management [NG122]* (NICE 2019).

OBJECTIVES

To ascertain the optimal management strategy for adults with malignant pleural effusion in terms of pleurodesis success and to quantify differences in patient-reported outcomes and adverse effects between interventions.

METHODS

Criteria for considering studies for this review

Types of studies

We included reports of randomised controlled trials (RCTs) in this review. This included randomised cross-over trials and cluster randomised trials, although we did not identify any studies of these types. We included both single- and multicentre studies. We excluded studies that were stated to be randomised, but were at high risk of bias for adequate sequence generation or allocation concealment.

Types of participants

Inclusion

- Adults over the age of 16 years.
- Symptomatic pleural effusion resulting from an underlying malignant process (of any type and stage).

Exclusion

- Studies recruiting both malignant and non-malignant participants with no clear distinction between the two groups in the results section.
- Studies evaluating the effect of a drug administered via any method other than the intrapleural route.
- Studies including participants with effusions within a variety of body cavities (e.g. pleural, peritoneal, pericardial), where the effect of the treatments in the subgroup of participants with pleural effusions could not be distinguished in the results section.

Types of interventions

We identified studies comparing the following.

- Type of sclerosant.
- Mode of administration of sclerosant (thoracoscopic pleurodesis and bedside pleurodesis).
- Bedside or thoracoscopic pleurodesis and IPC insertion.
- Techniques used to optimise pleurodesis success rate, namely:
  - chest drain size;
  - type of analgesia given;
  - duration of drainage after instillation of sclerosant;
  - patient positioning after pleurodesis (e.g. patient rotation);
  - use of intrapleural fibrinolytics;
  - methods to optimise IPC use including IPC drainage regimen and combined talc administration via IPC.

We generated a network of interventions, including comparisons between the types of sclerosant, mode of administration and IPC use. We assumed that any participant meeting the inclusion criteria could be, in principle, randomised to any of the eligible interventions. This is referred to as the interventions being 'jointly randomisable'. However, if we considered an intervention was not jointly randomisable, for example the treatment was specific to a certain tumour type, we reported the results separately from the network (Salanti 2012).

Interventions of direct interest

We included RCTs that evaluated one or more of the following intrapleural interventions: talc poudrage, talc slurry, bleomycin, tetracycline, doxycycline, iodine, *C parvum*, IPC (both daily drainage and without daily drainage), talc administered via IPC, mitoxantrone, mustine, mepacrine, interferon, triethylenethiophosphoramide and adriamycin compared with another intervention or placebo. If we identified other sclerosants that we were not aware of, we considered them as eligible and included them in the network after assessing their comparability with the prespecified set of competing interventions. We reported the findings for these interventions in the results and the conclusions of the review.

Types of outcome measures

Primary outcomes

Efficacy of pleurodesis was our primary outcome measure.

Definitions of pleurodesis failure varied between studies and although current practice would define this by a lack of recurrence of symptoms or need for a repeat pleural intervention to manage the effusion, some older studies used less clinically relevant definitions (e.g. re-accumulation of effusion on imaging). We still included these studies in the review, and documented the method used to define pleurodesis for all studies in the assessment of the risk of bias.

For the purposes of the primary outcome, we used the following hierarchy of preferences to judge pleurodesis failure (if a study reported more than one definition of pleurodesis failure, the highest of these according to this hierarchy was used):

- need for a repeat pleural procedure to manage recurrence of the effusion, or continued drainage of pleural fluid from an IPC (if applicable);
- evidence of significant pleural fluid re-accumulation on radiological imaging (e.g. chest X-ray or ultrasound);
- pleurodesis failure in the opinion of the trial investigators.

For studies evaluating IPCs, we judged that an effective pleurodesis was achieved when there was cessation of pleural fluid drainage or device removal due to cessation of drainage, or both.

Similarly, we selected the time point used to define pleurodesis efficacy using the following hierarchy of preferences:

- 2 - 4 months;
- more than 4 - 7 months;
- more than 7 - 11 months;
- more than 11-12 months;
- less than 2 months;
- more than 12 months.

For participants who died before the time point at which pleurodesis efficacy was assessed, we classified these according to their last known pleurodesis outcome prior to their death (i.e. their last observation carried forward). If these data were not provided, we used the available reported data.

Secondary outcomes

- Adverse effects and complications due to interventions, specifically the presence or absence of pain and fever after the intervention.
- Patient-reported control of breathlessness, as measured by a valid and reliable scale (e.g. visual analogue scale (VAS), numerical rating scale or dyspnoea/breathlessness-specific multidimensional scale).
- Participants' quality of life and symptom control (including pain), measured by a valid and reliable scale.
- Relative costs of the comparative techniques as reported by the individual trials. For ease of comparison, data reported in other currencies were converted to USD.
- Overall mortality (we used the data for the reported outcomes closest to three months).
- Median survival.
- Duration of inpatient stay in days (both total length of stay and from time of intervention until discharge).
- Patient acceptability of the interventions as judged by a valid scale (e.g. VAS or numerical rating scale). Within this, we included the need for repeat invasive pleural intervention.

Search methods for identification of studies

Trials that compared at least two of the interventions (including placebo) were eligible. We included all possible comparisons formed by the interventions of interest.

Electronic searches

To identify studies for inclusion in this review, we searched the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library) 2019, Issue 5;
- MEDLINE (Ovid) 1948 to 24 June 2019;
- Embase (Ovid) 1974 to week 25 2019;
- CINAHL (EBSCO) 1980 to June 2019;
- Web of Science Science Citation Index Expanded (SCI-EXPANDED) and Social Sciences Citation Index (SSCI) searched to 2015. (Due to a change in library provision we did not have access beyond 2015.)

The search strategies can be viewed in Appendix 1. There were no language restrictions. We included single and multicentre studies.

Searching other resources

We screened the reference lists from the included studies for additional publications. We searched the reference lists from relevant chapters in key resources, such as the British Thoracic Society Pleural Disease Guidelines (Roberts 2010). We searched clinicaltrials.gov (www.clinicaltrials.gov), and the World Health Organization International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) for ongoing trials.

Data collection and analysis

Selection of studies

One author screened all titles and abstracts retrieved by the search for relevance (AOC). For the 2020 update, this was performed by two authors (AOC and AD) using the Covidence platform. We identified potentially eligible studies and obtained the full papers. Two review authors (AOC and NAM or AD) independently assessed each full text for inclusion in the review and resolved any disagreement through discussion or by a third review author (NP).

Data extraction and management

Two review authors (two of AOC, RB, NP and NAM up to 2016; two of AOC, AD and RB; and NP and NAM from 2016 to 2020) extracted data from each included study.

We resolved disagreements through discussion and referral to one of the other review authors. If a review author was involved in one of the included studies, they did not perform the data extraction for that study. Data collected included the following.

- Publication details including:
  - title, author(s), date, country and other citation details;
  - study aim and design;
  - study funding sources and author declarations of conflicts of interest;
  - primary and secondary outcomes;
  - number of participants randomised.
- Details of the interventions and comparison group including type of intervention, duration, dose, mode of administration and number of doses.
- Primary and secondary outcomes (as detailed in Primary outcomes; Secondary outcomes), and data on adverse effects and complications.
- Assessment of the study's risk of bias.
- Data on potential effect modifiers including the following study and participant characteristics:
  - how pleurodesis was defined (radiology only or including clinical need as well as radiology);
  - whether people with trapped lung were included or not;
  - size of the chest tube through which bedside pleurodesis was administered (defined as small (less than 20-French (Fr)), large (20-Fr or greater) or unknown);
  - time point at which pleurodesis was defined;
  - tumour types included in the study.

We requested additional data from the study authors as required. One review author (AOC or AD) entered outcome data suitable for pooling into Cochrane's statistical software (RevMan Web). Where we performed a NMA, we transferred data to the WinBUGS software (Lunn 2000).

Assessment of risk of bias in included studies

We limited inclusion to studies that were randomised as a minimum. Two review authors (two of AOC, RB, NP and NAM up to 2016; two of AOC, AD, RB, NP and NAM from 2016 to 2020) independently assessed risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), with any disagreements resolved

by discussion. In our original protocol, we had planned to include sample size in our risk of bias assessment. However, in view of Cochrane guidance stating imprecision should not be considered a risk of bias, we did not perform this assessment (Higgins 2011a). We assessed the following for each study.

Random sequence generation (checking for possible selection bias)

We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g. random number table; computer random-number generator); unclear risk of bias (method used to generate sequence not clearly stated). We excluded studies using a non-random process, that is, at high risk of bias (e.g. odd or even date of birth; hospital or clinic record number).

Allocation concealment (checking for possible selection bias)

The method used to conceal allocation to interventions prior to assignment determines 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); unclear risk of bias (method not clearly stated). We excluded studies at high risk of bias that did not conceal allocation (e.g. open list).

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

We assessed the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study stated there was blinding of participants and key study personnel and unlikely blinding could be broken, or no blinding or incomplete blinding but the outcome not likely to be influenced by lack of blinding); unclear risk of bias (insufficient information to permit judgement of low or high risk of bias); high risk of bias (no blinding or incomplete blinding, which is likely to influence the trial outcome or blinding attempted but likely it could have been broken and the outcome is likely to be influenced by lack of blinding).

Blinding of outcome assessment (checking for possible detection bias)

We assessed the methods used to blind outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study stated that it was not blinded but the review authors judged that the outcome measurement was not likely to be influenced by lack of blinding or blinding of outcome assessment was ensured); unclear risk of bias (study provided an inadequate description to permit judgement of low risk or high risk); high risk of bias (no blinding of outcome assessment and outcome likely to be influenced by lack of blinding, or there was blinding of the outcome assessment but likely that the blinding could have been broken).

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

We assessed the methods used to deal with loss to follow-up (LTFU) for each of the given studies. Due to the challenges of inevitable missing outcome data given the predictable attrition of patients due to death in the palliative care population, we took into account whether missing data had been justified, whether the rate was similar in the different treatment arms, whether the treatment being evaluated was felt to have an impact on the degree of missing outcome data and whether an intention-to-treat (ITT) analysis had been attempted. We assessed the methods used to deal with incomplete data as: low risk (rate of missing data were balanced between the treatment arms, seemed reasonable and had been justified; data had been analysed according to the participants' randomised treatment allocation; a suitable imputation method may have been used to account for missing data); unclear risk of bias (insufficient information given to allocate trial to high- or low-risk group); high risk of bias (imbalanced missing outcome data between the treatment arms or missing outcome data felt to be related to the true outcome; reasons for LTFU poorly justified; no attempt at ITT analysis; inappropriate imputation used).

Selective outcome reporting

We assessed the studies for selective outcome reporting using the following criteria: low risk of bias (all outcomes predefined and reported, e.g. in a published protocol, or all clinically relevant and reasonably expected outcomes were reported); uncertain risk of bias (unclear whether all predefined and clinically relevant outcomes were reported); high risk of bias (one or more clinically relevant and reasonably expected outcome was not reported and data on these outcomes were likely to have been recorded).

Other sources of bias

This section was used to report other biases, which were detected but did not fit into the above categories (e.g. industry bias, academic bias or other methodological flaws that may have caused bias). We assessed the methods used to deal with other sources of bias as: low risk of bias (the trial appeared free from other potential biases); unclear risk of bias; high risk of bias (other source of bias was identified).

Measures of treatment effect

Relative treatment effects

For proportions (dichotomous outcomes), such as pleurodesis efficacy and mortality, we calculated the odds ratio (OR) with 95% confidence intervals (CIs). For continuous data (such as length of hospital stay and cost), we planned to use the mean difference (MD) with 95% CIs and the number needed to treat for an additional beneficial efficacy outcome (NNTB), and the number needed to treat for an additional harmful outcome (NNTH) for adverse effects.

We planned to treat ordinal outcome measures (e.g. breathlessness scales and quality of life data) as continuous so long as the scale was sufficiently long. If different scales were used by the included studies, we planned to use the standardised mean difference (SMD) in meta-analyses.

We presented results from both pair-wise standard meta-analysis (both random and fixed effect) and NMA (random effects only) as summary relative effect sizes (OR, MD or SMD with 95% CIs) for each possible pair of treatments (Deeks 2011).

Relative treatment ranking

Based on the results of the NMA, we estimated the rank of each competing intervention's effectiveness. We presented estimated

ranks (medians) with 95% credible intervals (Cr-Is) (representing uncertainty about the true rank) produced from the Bayesian analyses (Higgins 2011b).

Unit of analysis issues

If repeated observations on the same participants occurred during the trial (e.g. pleurodesis success rate at different time points), we analysed these separately. We used only one measure per participant for the primary endpoint (according to the hierarchy of preferences detailed above Primary outcomes).

For the purpose of meta-analysis, if a study had multiple doses for a certain substance, we combined and compared all relevant experimental intervention groups with the combination of all relevant control groups. We reported any evidence for effects of the different doses descriptively.

For cross-over trials, we planned to analyse data using pair-wise meta-analysis, taking into account the cross-over design. If meta-analysis had been performed containing cluster randomised trials and the presented results had not accounted for clustering, then we planned to make an appropriate adjustment, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

We treated multi-arm studies as multiple independent two-arm studies in the standard pair-wise meta-analysis. In the NMA, we accounted for the correlation between the effect sizes from multi-arm studies.

In meta-analysis of continuous outcomes, we pooled differences in change from baseline, rather than differences in final values (Higgins 2019).

Dealing with missing data

We attempted to contact the authors of included studies to clarify any missing data.

We imputed missing standard deviations (SD) based on the mean SDs from the other included studies if SDs for mean scores had not been reported and it had not been possible to obtain the information from the study authors. We only included data for those participants whose results were known if an ITT analysis was not reported by the study. However, we assessed the potential impact of these missing data in the 'Risk of bias' table.

For continuous outcomes, where baseline and final values were reported without a SD of change score or correlation coefficient, we imputed correlation coefficients based on other studies in order to estimate the SD of change.

Assessment of heterogeneity

Assessment of clinical and methodological heterogeneity within treatment comparisons

We extracted data from study reports regarding clinical heterogeneity such as details on the intervention and control treatments, participant characteristics and the outcomes evaluated.

We assessed the presence of clinical heterogeneity within each pair-wise comparison by comparing the study population characteristics across all eligible trials. We only performed meta-analysis when considered reasonable based on the degree of heterogeneity.

Assessment of transitivity across treatment comparisons

We assessed the assumption of transitivity by comparing the distribution of the potential effect modifiers across the different pair-wise comparisons (Jansen 2013).

Assessment of reporting biases

We performed searches in multiple databases to ensure all potentially eligible studies were identified (Electronic searches). The review authors were alert to duplicated publication of results when analysing the studies to ensure each participant was only included once in the analysis.

If unpublished studies were identified, we tried to obtain sufficient information in order for them to be included in the analysis. The same applied for data published in abstract format.

In studies published in a language other than English, we made every effort to obtain a translation of at least the abstract. If sufficient information was available, we included the study in the analysis.

Data synthesis

Methods for direct treatment comparisons

Since we expected some clinical heterogeneity between studies (e.g. due to different definitions of pleurodesis success, different time points and doses used), we believed that the assumption of a single fixed intervention effect across included studies was unlikely to be valid. Our primary analyses therefore employed random-effects models. Since pooled effect estimates from random-effects models give relatively more weight to smaller studies, which is often considered undesirable, we performed sensitivity analyses using fixed-effect meta-analysis models. We performed standard pair-wise meta-analysis using a random-effects model in Cochrane's statistical software, RevMan Web, for every treatment comparison with two or more studies.

For binary outcome data, we meta-analysed ORs. For continuous data, we planned to use the MD or SMD and perform a check to identify if continuous outcome data were skewed. If this was the case, we planned to analyse the data on a log scale. If we assessed studies as unsuitable for meta-analysis, or insufficient studies were identified for meta-analysis to be performed, we planned to present data by means of a narrative synthesis. If sufficient data were available, we used similar analysis methods to analyse the adverse effects data. Alternatively, we summarised this qualitatively.

Methods for indirect and mixed comparisons

Wherever possible, we performed a multiple-intervention, NMA of primary and (separately) of each secondary outcome measure. We used a Bayesian random-effects model, fitted using the WinBUGS software (Dias 2018; Lunn 2000). We assumed binomial likelihoods for count data, and modelled log ORs as random effects across studies. We assigned vague prior distributions with mean 0 and SD of 100 to all mean log ORs and to baseline event rates in each study on the logit scale. We assumed a common between-studies SD within a network, represented by the parameter Tau which was assigned a Uniform (0.2) prior distribution.

For each NMA, we used the Stata software to generate a network plot (using the networkplot command) and inconsistency plot (using the ifplot command) (Chaimani 2013).

Subgroup analysis and investigation of heterogeneity

Assessment of statistical heterogeneity

In pair-wise meta-analyses, we estimated the between-study SD (Tau^2) separately for each intervention comparison. We also reported the I^2 statistic for each pair-wise meta-analysis, which is an estimate of the proportion of variability in effect estimates that is due to heterogeneity (Higgins 2003).

The assessment of statistical heterogeneity in the NMA was based on the magnitude of and Cr-Is for the between-studies SD (Tau), which was assumed to be common across all comparisons within a network.

As described below, reasons for heterogeneity were investigated using subgroup or sensitivity analyses.

Assessment of statistical inconsistency

Inconsistency in the network refers to differences between the direct and indirect effect estimates for the same comparison (Donegan 2013). We used both a loop-specific approach and a global approach to evaluate these effects.

To evaluate the presence of inconsistency locally we used the loop-specific approach. This assesses the consistency assumption in each closed loop of the network separately. We identified all the triangular loops (comprising three direct treatment comparisons, all compared with each other) and all the quadratic loops (involving four comparisons) in the network. We compared the differences between the direct and indirect estimates for these loops to generate inconsistency factors, with 95% CIs, calculated and displayed graphically using the 'ifplot' command in Stata (Chaimani 2013; Chaimani 2015). We assumed the estimated between-study SD (Tau) from the Bayesian analysis of the full network for each loop. We used the magnitude of the inconsistency factors to infer the presence and degree of inconsistency in each loop.

In addition to this, we used a global approach, involving formally comparing the fit of the NMA model (which assumes consistency) with that of an 'inconsistency' model (in which all consistency constraints are removed). The inconsistency model used is equivalent to fitting a random-effects meta-analysis model for all pair-wise comparisons, with a shared between-studies variance parameter but no assumptions about direct and indirect evidence forming coherent 'loops'. We calculated the mean residual deviance and the deviance information criterion (DIC) for each model (mean residual difference +pD). If the DIC for the inconsistency model was more than five units higher than that of the consistency model, this was viewed as evidence of inconsistency (Dias 2013). We further examined differences in the estimated between-study SD parameter (Tau) across the two models: a reduced estimate of Tau in the inconsistency relative to the NMA model may also be indicative of inconsistency (Dias 2018).

Further, for the main analyses, we plotted the mean residual deviance contributions of each data point under the inconsistency versus NMA models. This allows identification of specific data points for which the inconsistency model has improved fit, that is, data points that are potentially inconsistent with the network (Dias 2018).

Assessment of statistical imprecision

We evaluated precision of results, and subsequent rankings, based on their 95% CIs (for pair-wise analysis) or Cr-Is (for Bayesian NMA).

Sensitivity analysis

Sensitivity analysis and investigation of heterogeneity and inconsistency

We conducted subgroup or sensitivity network meta-analyses by re-running the model on restricted numbers of studies according to the following potential effect modifiers, which we felt could be sources of inconsistency or heterogeneity, or both:

- analysis only including studies which used a clinico-radiological definition of pleurodesis failure;
- analysis only including studies which analysed pleurodesis efficacy at one month after the intervention;
- analysis only including studies which analysed pleurodesis efficacy at three months after the intervention;
- analysis only including studies which analysed pleurodesis efficacy at more than six months after the intervention;
- analysis only including studies which excluded participants with trapped lung;
- analysis only including studies which administered pleurodesis through a large-bore chest tube (greater than 20-Fr)
- analysis only including studies which administered pleurodesis through a chest tube (any size)
- analysis only including studies at a low risk of bias (maximum of one domain assessed as high risk of bias).

In the protocol, we planned to investigate different tumour types, age of participants and baseline performance status, although there were insufficient data on this in the included studies to perform these subgroup analyses.

We performed a post-hoc sensitivity NMA evaluating only pleurodesis agents delivered via a chest tube (as opposed to being given at thoracoscopy). We removed the trials evaluating talc poudrage and IPC use from the main network and repeated the analysis.

We performed sensitivity analyses of direct evidence on pleurodesis failure using fixed-effect meta-analysis models, since pooled effect estimates from random-effects models give relatively more weight to smaller studies, which is often considered undesirable.

We performed an additional post-hoc pair-wise meta-analysis comparing ipsilateral repeat invasive pleural intervention rates (where data were available).

Summary of findings and assessment of the certainty of the evidence

We created 'summary of findings' tables for the most clinically relevant outcomes: pleurodesis failure and breathlessness. We summarised adverse event data for procedure-related pain and fever. Data on mortality were also included. We included the need for an additional invasive pleural procedure, due to failure

of the initial intervention for pleural fluid control, as this is an important outcome of relevance to both patients and clinicians.

We used talc slurry as our reference comparator. We graded evidence relating to the most commonly compared interventions with the most widespread availability. We calculated anticipated absolute effect estimates using data from NMA for pleurodesis failure, pain, mortality and fever. We used pair-wise analysis results for breathlessness and repeat pleural intervention.

We followed the approach proposed by Yepes-Nunez and colleagues and the methods and recommendations described in Chapter 14 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2019; Yepes-Nunez 2019). Two review authors (AD and AOC) rated the quality of the direct and indirect evidence using GRADE methodology. We considered study limitations (overall risk of bias), assessments of inconsistency (heterogeneity), indirectness and intransitivity, imprecision and publication bias. We justified and documented judgements, which have been incorporated into the reporting of results for each outcome.

We reached an overall judgement on the certainty in the estimate of the effect across these considerations, classified as 'high', 'moderate', 'low' or 'very low'. Our 'interpretation of findings' reflects this certainty of evidence outcome and, where available, this was combined with the overall ranking of each intervention in our NMA.

RESULTS

Description of studies

Results of the search

We performed the literature search in June 2019, covering the period from April 2015 when searches for the previous edition of this review were conducted (Figure 1). We identified 1396 records from database searches before exclusion of three duplicates. We identified one additional record from references listed in a systematic review (Putnam 1999, referenced in Sivakumar 2019). From trials registry searches, we identified 21 records.

Figure 1. Study flow diagram.

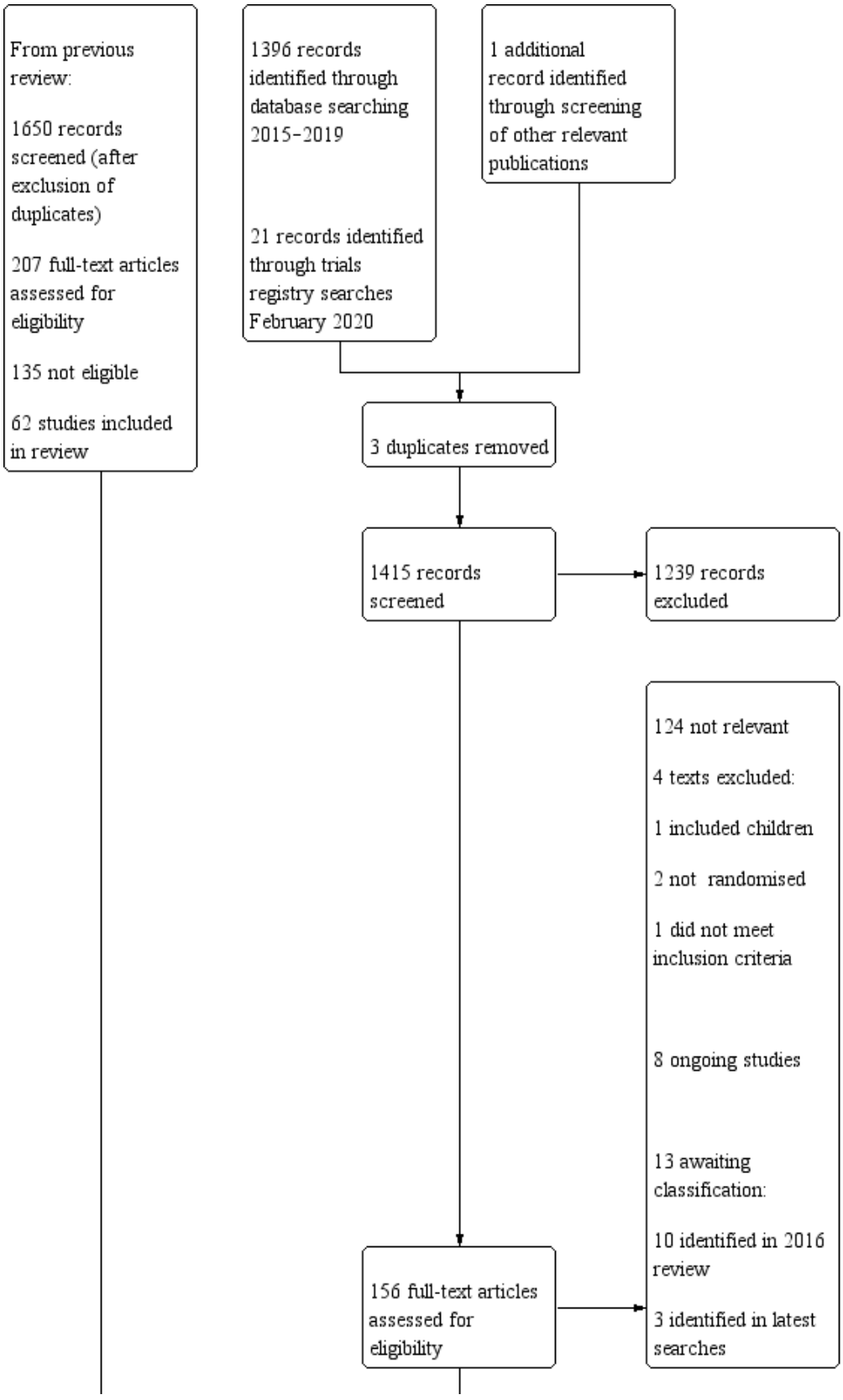
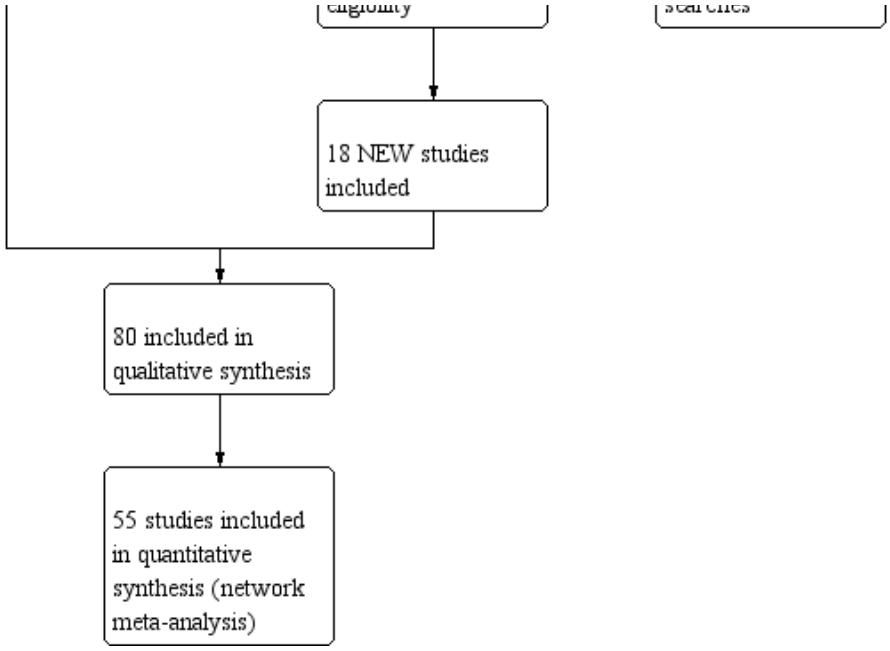


Figure 1. (Continued)



We screened 1415 abstracts, of which 156 full-text articles were retrieved and assessed for eligibility. A total of 18 studies met eligibility criteria (see Characteristics of included studies table).

The 18 studies identified in our updated literature search were combined with the 62 studies from the previous Cochrane Review (Clive 2016). From the combined total of 3065 records screened and 363 full-text reviews across the two searches, we included 80 studies (5507 participants randomised between 1977 and 2018) in this review.

We excluded 15 studies (four identified from the 2019 literature search), following an initial assessment that they were eligible for inclusion (see Characteristics of excluded studies table). Thirteen texts are awaiting classification (see Characteristics of studies awaiting classification table). Eight studies are ongoing (see Characteristics of ongoing studies table).

Included studies

Forty-six studies analysed the efficacy of a variety of pleurodesis agents. Twenty-seven trials evaluated talc, which was the most studied agent. Bleomycin and tetracycline were other commonly studied agents. Eight studies evaluated IPCs. Four studies compared IPCs with talc slurry (Boshuizen 2017; Davies 2012; Demmy 2012; Thomas 2017), and one with doxycycline pleurodesis (Putnam 1999). Techniques to optimise outcomes from IPCs were also considered; two examined IPC drainage regimens (daily drainage versus symptom-guided or alternate day regimens) (Muruganandan 2018; Wahidi 2017), and one randomised participants to talc slurry administered via IPC or IPC with saline placebo (Bhatnagar 2018).

Five studies evaluated the mode of administration of the pleurodesis agent; four compared talc poudrage with talc slurry (Bhatnagar 2020; Dresler 2005; Terra 2009; Yim 1996), and one compared instillation of tetracycline thoracoscopically or through an intercostal cannula (Evans 1993). Some studies evaluated alternative techniques to improve pleurodesis success rates; one study examined catheter size (Clementsen 1998); one examined a combination of chest drain size and analgesia (non-steroidal anti-inflammatory drugs (NSAIDs) versus opiates) (Rahman 2015); three evaluated the duration of drainage after pleurodesis (Goodman 2006; Villanueva 1994; Yildirim 2005); one evaluated the duration of drainage prior to instillation of the sclerosant (Ozkul 2014); one assessed whether participant rotation improved pleurodesis rate (Mager 2002); and one evaluated the effect of talc particle size (Maskell 2004). Three studies evaluated intrapleural fibrinolytics (Mishra 2018; Okur 2011; Saydam 2015). One RCT evaluated administration of three different doses of silver nitrate through a chest tube (Terra 2015), and one evaluated two different doses of iodine through a chest tube (Neto 2015).

Three studies compared surgical techniques to talc pleurodesis; one comparing talc pleurodesis with pleurectomy (Rintoul 2014), and two comparing talc slurry with thoracoscopic mechanical pleurodesis (TMP) (Crnjac 2004; Hojski 2015).

Additionally, we identified eight studies of agents specifically for the treatment of effusions due to lung cancer (Du 2013; Ishida 2006; Kasahara 2006; Luh 1992; Masuno 1991; Wang 2018; Yoshida 2007; Zhao 2009).

There were a number of methodological differences between the included studies. Fifty-nine of 80 studies included all tumour types. Two included all except mesothelioma; one included only mesothelioma; one included all except lymphoma and small cell lung cancer; two included only adenocarcinoma; eight included only breast cancer; and seven studies included only participants with lung cancer.

The time point at which pleurodesis was evaluated varied widely between studies, from one to 12 months. In addition, the methods used to define pleurodesis failure varied. Nineteen of the 80 studies used radiological criteria only to define a pleurodesis failure. The

remaining 61 studies incorporated symptomatic recurrence or need for a repeat pleural intervention into their definition. Six studies evaluating IPCs defined pleurodesis success by cessation of drainage from the catheter.

Pleurodesis techniques were not standardised. Studies used a variety of chest drain sizes and durations of drainage after sclerosant administration. Participants with trapped lung were excluded from 38/80 studies.

Excluded studies

We excluded 15 studies in total after initially being considered eligible for inclusion, but with reasons for exclusion identified later (Characteristics of excluded studies table). Three studies included data for participants with ascites, which could not be separated from participants with pleural effusions (Kwasniewska-Rokicinska 1979; Lissoni 1995; Nio 1999).

Ten studies were not randomised (high risk of bias for sequence generation) and therefore excluded as per protocol (Caglayan 2008; Dryzer 1993; Elayouty 2012; Engel 1981; Gust 1990; Kleontas 2019; Liu 2017; Maiche 1993; Manes 2000; Tattersall 1982). One study combined data for adults and children (Ogunrombi 2014). One study, initially included as an ongoing study, was published during the process of this review. On full-text review of the published paper, it did not meet criteria for inclusion, as the primary outcome was recruitment rate for a future multicenter phase 3 trial (Martin 2019).

Studies awaiting classification

Thirteen texts are awaiting classification (Characteristics of studies awaiting classification table).

Ongoing studies

Eight studies are ongoing (Characteristics of ongoing studies table).

Risk of bias in included studies

A summary assessment of the risk of bias is presented in the Characteristics of included studies table, Figure 2 and Figure 3. Three studies were at low risk of bias in all domains (Bhatnagar 2018; Keeratichananont 2018; Mishra 2018).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

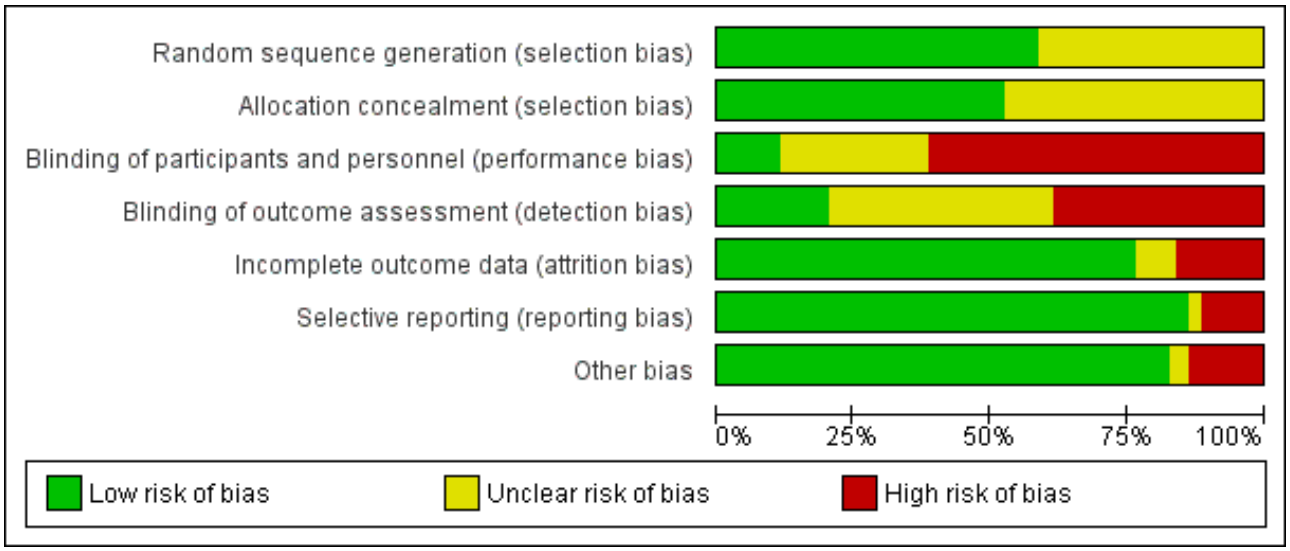


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

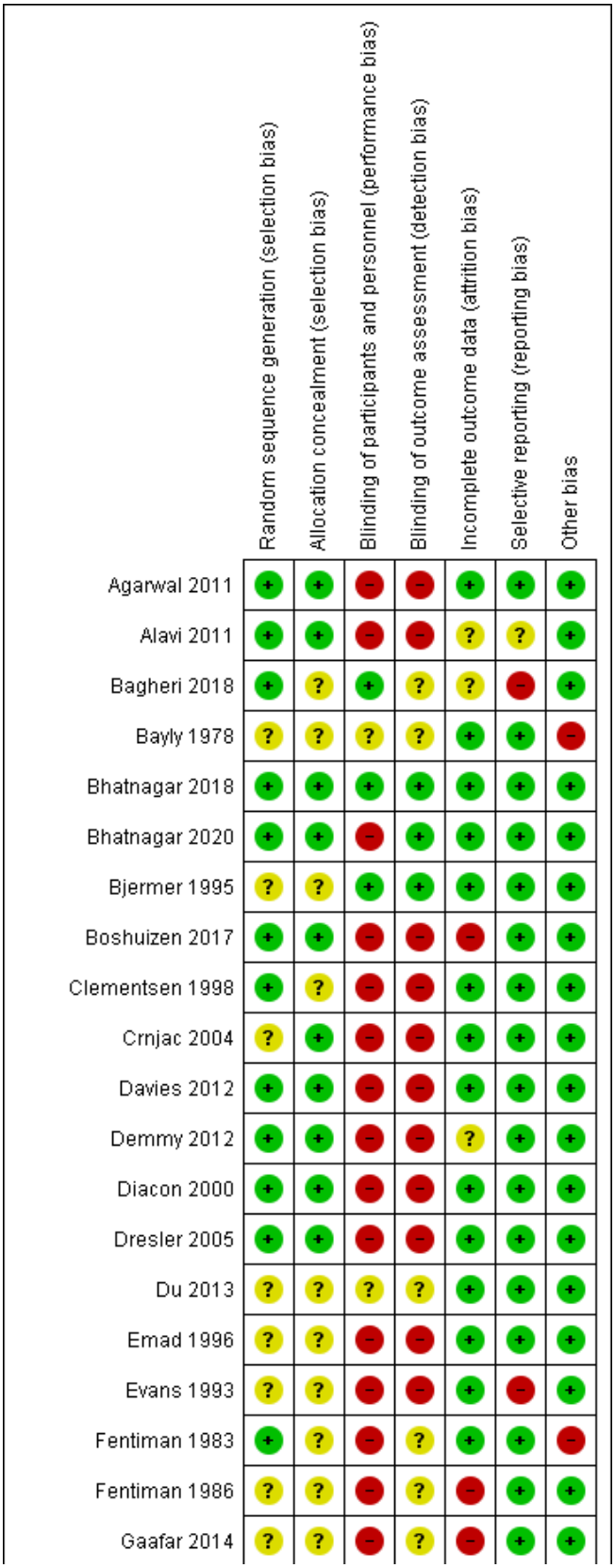
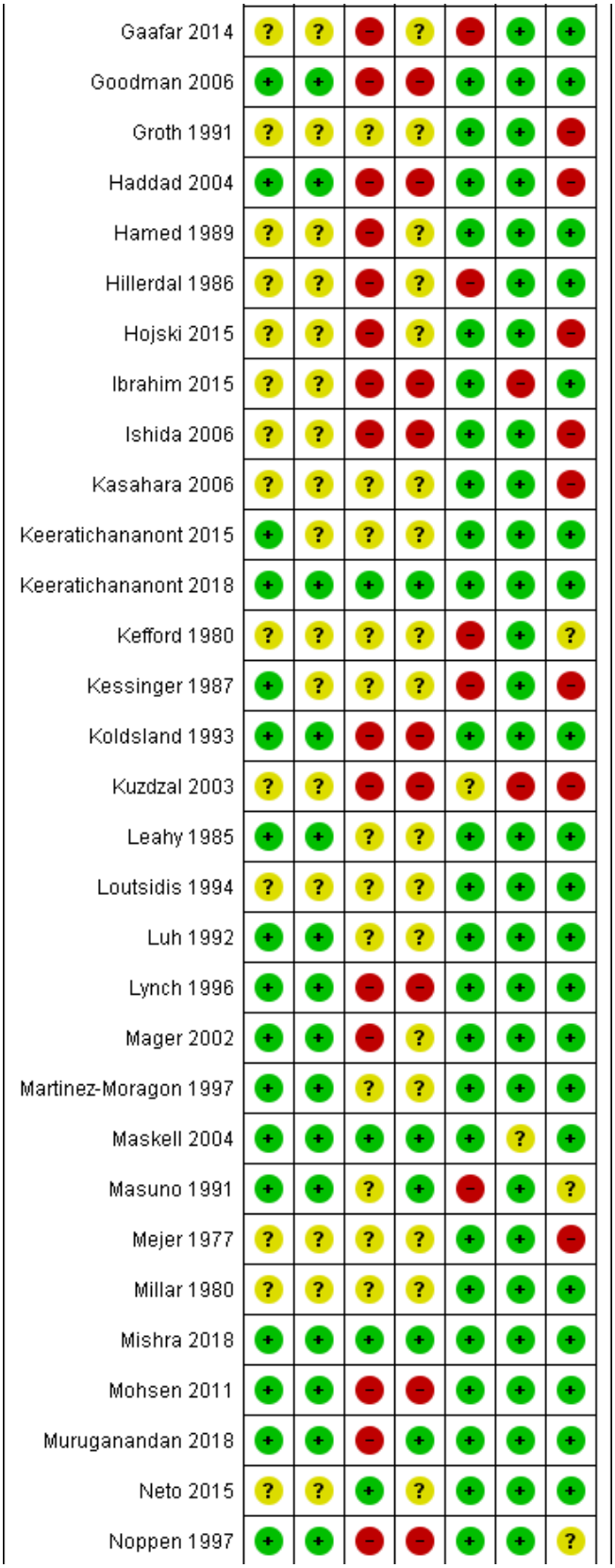


Figure 3. (Continued)



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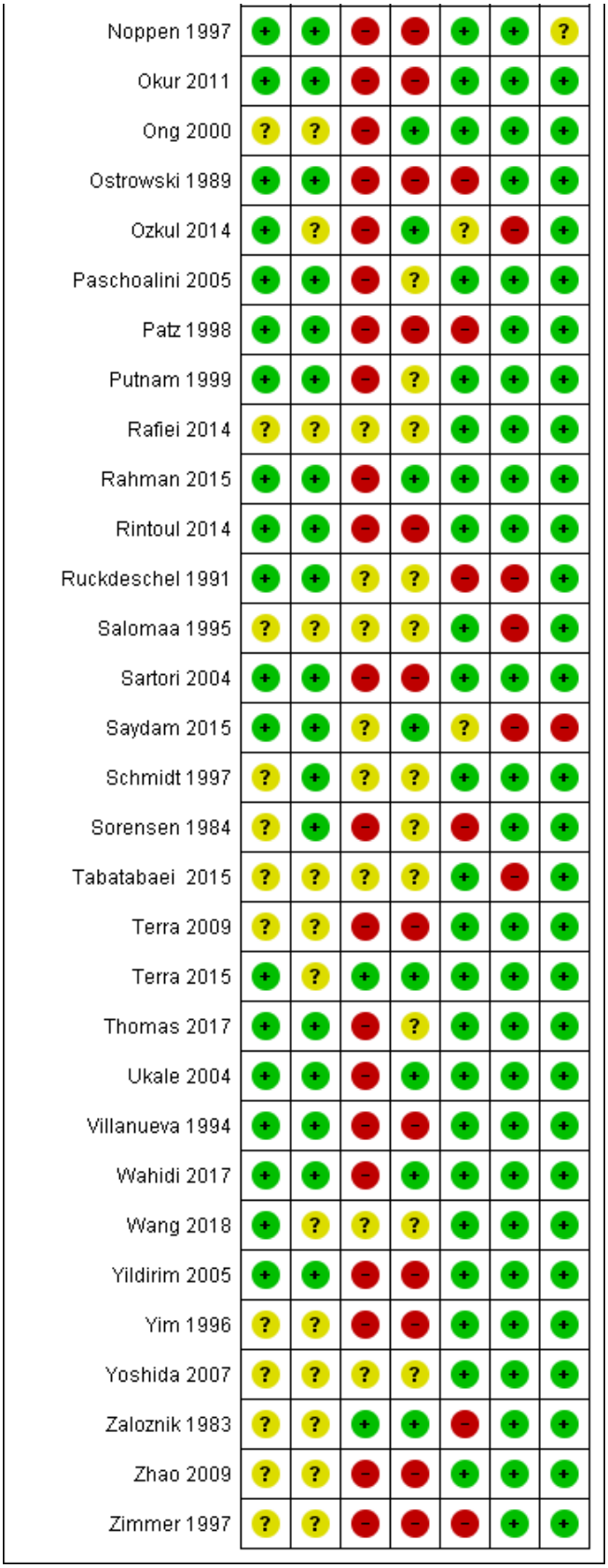


Allocation

All 80 studies were stated to have been randomised. Forty-seven of these documented adequate sequence generation. The most commonly used methods were computer or telephone randomisation services, block randomisation, stratification, opaque sealed envelopes or a random number generator. Since we excluded studies with inadequate methods of sequence generation as per the protocol, sequence generation was unclear in the remaining 33 studies.

Allocation concealment was at low risk of bias in 42 studies. Since we excluded studies with inadequate allocation concealment, as per the protocol, allocation concealment was unclear for the remaining 38 studies.

Blinding

Blinding of participants and personnel (performance bias)

Due to the nature of many of the interventions evaluated in this review, blinding of the participants and clinicians was often not possible. Thus, 49/80 studies were at high risk of bias for this domain. Many of the pleurodesis agents have differing visual appearances and those studies randomising participants to different modes of administration, an IPC or surgery could not feasibly be blinded.

We assessed nine studies as low risk of performance bias and 22 as unclear.

Blinding of outcome assessment (detection bias)

The assessment of pleurodesis success could often not be blinded, as it was reliant on symptom reporting from unblinded participants, in association with the radiological findings of effusion recurrence. Few studies reported whether the radiological assessments were performed using a blinded method. Thirty-one of 80 studies were at high risk of detection bias, and a further 33 of 80 studies had an unclear risk of bias for this domain. Sixteen studies were low risk of detection bias.

Incomplete outcome data

Most studies were at low risk of bias because although there was some inevitable attrition due to death, the rates were comparable for the treatment arms. We classified 13 studies at high risk of bias; nine due to very high attrition rates (Boshuizen 2017; Kefford 1980; Kessinger 1987; Masuno 1991; Ostrowski 1989; Patz 1998; Ruckdeschel 1991; Sorensen 1984; Zaloznik 1983); one due to very imbalanced LTFU between the treatment arms (Fentiman 1986); in one the number randomised was not stated (Zimmer 1997); for one the numbers provided did not add up (Hillerdal 1986); and one excluded participants from the analysis who discontinued treatment due to an allergic reaction (Gaafar 2014).

The risk of bias was unclear in six (Kuzdzal 2003: number of randomised participants not stated, only stated number of participants analysed; Alavi 2011: unable to access tables, and numbers only given as percentages, rather than absolute values; Demmy 2012: duration of trial follow-up unclear; Bagheri 2018 and Ozkul 2014: numbers of participants LTFU not stated; Saydam 2015: withdrawals not stated, and unclear how many participants included in final outcome analysis).

Selective reporting

Most studies were at low risk of bias for selective outcome reporting. We classified two studies as unclear; one as minimal raw data were presented in the text and the tables could not be accessed (Alavi 2011), and the other because pleurodesis success data were not collected in an RCT of talc and tetracycline pleurodesis (although the study was not designed to evaluate this) (Maskell 2004).

Nine studies were at high risk; four provided minimal or no data regarding adverse effects or survival, or both (Evans 1993; Kuzdzal 2003; Ozkul 2014; Salomaa 1995); one did not report data on 15/100 participants randomised (Ruckdeschel 1991); one did not report pleurodesis outcomes for 11/40 participants and did not give information on LTFU (Saydam 2015); one did not report how long participants were followed up for or state the time at which pleurodesis failure was assessed (Ibrahim 2015); and two did not report on a stated outcome (Bagheri 2018: time to pleural effusion relapse; Tabatabaei 2015: breathlessness).

Other potential sources of bias

We classified 11/80 studies at high risk of bias in the 'other' domain. The risk of bias was unclear in three studies. This was for a variety of reasons (see Characteristics of included studies table). The remaining studies had a low risk of bias for this domain.

Effects of interventions

See: **Summary of findings for the main comparison** Pleurodesis failure rate in adults with malignant pleural effusion; **Summary of findings 2** Adverse effects: procedure-related fever in adults with malignant pleural effusion; **Summary of findings 3** Adverse effects: procedure-related pain in adults with malignant pleural effusion; **Summary of findings 4** Patient-reported control of breathlessness in adults with malignant pleural effusion; **Summary of findings 5** Overall mortality in adults with malignant pleural effusion; **Summary of findings 6** Patient acceptability: need for repeat invasive pleural intervention in adults with malignant pleural effusion

Primary outcome: pleurodesis failure rate

Pair-wise (direct) meta-analysis

Results of the direct, pair-wise random-effects meta-analysis of the main pleurodesis techniques for the primary outcome of pleurodesis failure are presented in Table 1. Few studies made the same direct comparisons; meta-analysis was therefore only possible for 12 direct comparisons. Results are also displayed for an additional 30 direct comparisons that were each made in only one study (Table 1).

In most cases, there was no evidence against the null hypothesis of no true difference between interventions (Table 1). However, in 14/42 direct comparisons made, the OR and 95% CI lay away from the null value of 1, giving evidence against the null hypothesis of no difference.

A number of interventions had a higher pleurodesis failure rate than talc poudrage. This included tetracycline (pleurodesis failure of tetracycline versus talc poudrage: OR 12.10, 95% CI 1.32 to 111.30; studies = 1; participants = 33; Analysis 4.1; bleomycin: OR 9.70, 95% CI 2.10 to 44.78; studies = 2, participants = 57; Analysis

1.1; doxycycline: OR 42.69, 95% CI 2.13 to 856.61; studies = 1, participants = 31; Analysis 8.1; mustine: OR 8.00, 95% CI 1.40 to 45.76; studies = 1, participants = 37; Analysis 16.1).

The evidence suggests that participants treated with an IPC had more pleurodesis failures than those receiving talc slurry. Two studies compared talc slurry to IPCs without daily drainage (OR 0.18, 95% CI 0.07 to 0.45; studies = 2, participants = 249; Analysis 2.1; Davies 2012; Thomas 2017). One study compared talc slurry to daily IPC drainage (Demmy 2012: OR 0.30, 95% CI 0.08 to 1.14; participants = 55; Analysis 2.1). Two studies comparing IPCs without daily drainage to IPCs with daily drainage suggested a higher pleurodesis failure rate in those without daily drainage (OR 3.23, 95% CI 1.79 to 5.85; participants = 236; Analysis 6.1; Muruganandan 2018; Wahidi 2017). Results from one study suggest that talc administration via IPC may result in fewer pleurodesis failures than drainage alone (OR 0.36, 95% CI 0.18 to 0.73; participants = 139; Analysis 25.1; Bhatnagar 2018).

There was evidence that tetracycline, mitoxantrone and interferon were less effective (i.e. associated with a higher likelihood of pleurodesis failure) than bleomycin (tetracycline: OR 2.00, 95% CI 1.07 to 3.75; studies = 5, participants = 220; Analysis 4.1; mitoxantrone: OR 3.18, 95% CI 1.17 to 8.65; studies = 1, participants = 85; Analysis 17.1; interferon: OR 3.25, 95% CI 1.54 to 6.89; studies = 1, participants = 160; Analysis 12.1). Bleomycin and triethylenephosphoramide were less effective than mepacrine (bleomycin: OR 6.40, 95% CI 1.12 to 36.44; studies = 1, participants = 36; Analysis 1.1; triethylenephosphoramide: OR 4.95, 95% CI 1.02 to 24.10; studies = 1, participants = 29; Analysis 13.1).

There was generally little evidence of statistical heterogeneity between studies making direct comparisons. However, the comparison between *C parvum* and bleomycin estimated a very high level of heterogeneity (Tau^2 = 10.59, I^2 = 94%) because the two included studies had conflicting results (*C parvum* versus bleomycin: OR 0.05, 95% CI 0.01 to 0.29 in Hillerdal 1986; OR 5.69, 95% CI 1.38 to 23.48 in Ostrowski 1989; Analysis 5.1). The number of participants in the comparison was small (98 participants randomised across the two studies; 78 of whom had sufficient data to be included in the primary outcome analysis) and Hillerdal 1986 was at high risk of bias for two domains and unclear risk of bias for a further two. Hillerdal 1986 only included people with adenocarcinoma or bronchogenic carcinoma, whereas Ostrowski 1989 included all cell types. The evidence suggests that there may be some heterogeneity in the direct comparison of IPC without daily drainage and talc slurry (I^2 = 61%, Chi^2 = 2.58, P = 0.11; studies = 2; participants = 249; Analysis 6.1).

Appendix 2 demonstrates no obvious difference in the distribution of potential effect modifiers between direct comparisons.

Sensitivity analysis of the direct comparisons using the fixed-effect meta-analysis model did not reveal any clinically or statistically meaningful differences (see Appendix 3).

Network meta-analysis

Selection of trials for inclusion in the network meta-analysis

We evaluated and assessed all the interventions from the included studies for inclusion in the network. We considered a number of interventions were not jointly randomisable and hence we did not include them. These interventions included specific surgical techniques (Rintoul 2014), different talc particle sizes (Maskell 2004), interventions to improve the efficacy of pleurodesis (Clementsen 1998; Evans 1993; Goodman 2006; Mager 2002; Mishra 2018; Okur 2011; Ozkul 2014; Rahman 2015; Saydam 2015; Villanueva 1994; Yildirim 2005), tumour-specific intrapleural therapy (Du 2013; Ishida 2006; Kasahara 2006; Luh 1992; Masuno 1991; Wang 2018; Yoshida 2007; Zhao 2009), different doses of silver nitrate (Terra 2015), and different doses of iodine (Neto 2015).

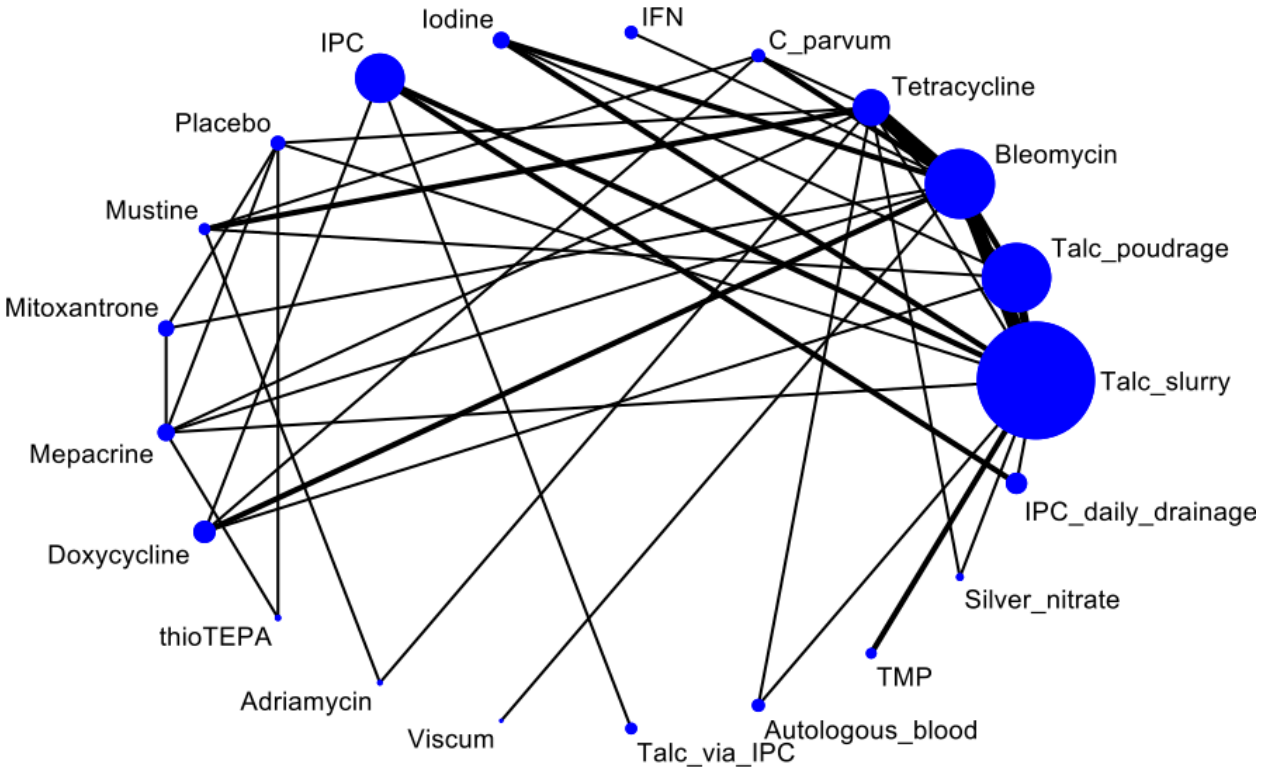
For computational reasons, we could not include one intervention (combined tetracycline and bleomycin) in the NMA: this combination was evaluated in only one trial, with no pleurodesis failures occurring in the relevant study arm. Inclusion of this trial led to convergence problems (Emad 1996). We did not include an additional study in the analysis as there were no pleurodesis failures in either study arm (Yim 1996). Such studies cannot statistically contribute to the estimate of relative intervention effects (Higgins 2011b).

We included 55 studies in the primary NMA. Most studies included all cell types. Twenty-six of 55 excluded participants with trapped lung. Pleurodesis was defined using symptom recurrence and radiology in 37/55 studies and usually defined within four months of the intervention.

It was difficult for us to assess whether the distribution of potential effect modifiers was comparable for all the direct treatment comparisons because there were few studies per direct comparison (at most five studies per comparison, seen in the bleomycin versus talc slurry and bleomycin versus tetracycline comparisons) (see Appendix 2).

The final network can be seen in Figure 4.

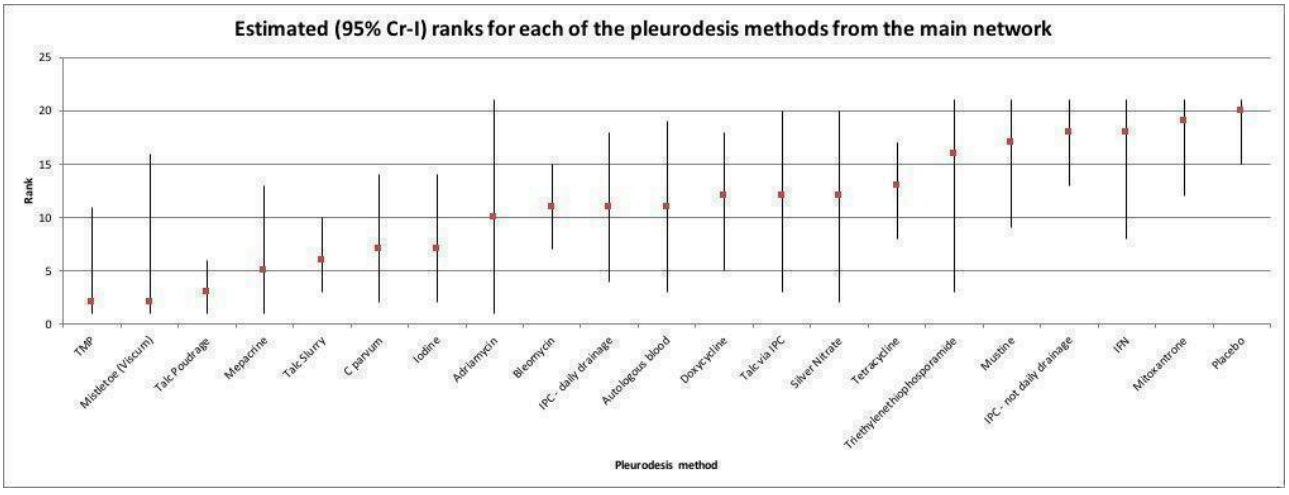
Figure 4. Network plot of the pleurodesis efficacy network. The nodes are weighted according to the number of participants randomised to the intervention. The edges (line thicknesses) are weighted according to the number of studies included in each comparison. IFN: interferon; IPC: indwelling pleural catheter without daily drainage; thioTEPA: triethylenephosphoramide; TMP: thoracoscopic mechanical pleurodesis.



Results from network meta-analysis

Estimated ORs for the pleurodesis failure outcome generated by the NMA, which comprised 55 studies of 21 agents and included 3758 participants, are shown in Table 2. The estimated ranks for each of the interventions in terms of pleurodesis success (i.e. lowest chance of failure) are shown in Figure 5. The summary of findings from the NMA of pleurodesis failure rate are shown in Summary of findings for the main comparison.

Figure 5. Estimated (95% credible interval (Cr-I)) ranks for each of the pleurodesis methods from the main network. IFN: interferon; IPC: indwelling pleural catheter without daily drainage; thioTEPA: triethylenephosphoramide; TMP: thoracoscopic mechanical pleurodesis.



Based on the NMA, there was evidence that talc poudrage results in fewer pleurodesis failures than bleomycin, tetracycline, mustine, interferon, IPC not daily drainage, mitoxantrone and placebo (Table 2). The estimated (posterior median) rank of talc poudrage was third of 21 interventions, but with a much tighter Cr-I than those interventions with median rank of 1 or 2 (estimated rank 3, 95% Cr-I 1 to 6).

We had a moderate level of certainty in the network estimate of the pleurodesis failure rate of talc poudrage compared to talc slurry. We downgraded evidence by one level for serious study limitations due to an overall high risk of bias for trials forming direct and indirect evidence loops in the talc poudrage to talc slurry comparison. There was little evidence of a difference between these two interventions in the primary NMA (talc poudrage versus talc slurry: OR 0.50, 95% Cr-I 0.21 to 1.02). Restricting analysis only to studies at low risk of bias provided greater certainty that these interventions have a comparable pleurodesis failure rate (OR 0.78, 95% Cr-I 0.16 to 2.08).

The OR and 95% Cr-I for IPC (without daily drainage) compared to talc slurry demonstrates that IPCs are likely to have a higher pleurodesis failure rate than talc slurry (OR 7.60, 95% Cr-I 2.96 to 20.47). Our level of certainty in this result is moderate. We downgraded one level for inconsistency, due to a high I^2 value (I^2 = 61%) in the IPC without daily drainage to talc slurry comparison.

Talc slurry was associated with fewer pleurodesis failures than mitoxantrone and placebo (talc slurry versus mitoxantrone: OR 0.10, 95% Cr-I 0.02 to 0.41; talc slurry versus placebo: OR 0.06, 95% Cr-I 0.01 to 0.27). We had a low level of certainty that talc slurry may result in fewer pleurodesis failures than bleomycin and doxycycline (bleomycin versus talc slurry: OR 2.24, 95% Cr-I 1.10 to 4.68; doxycycline versus talc slurry: OR 2.51, 95% Cr-I 0.81 to 8.40). We downgraded by one level in the bleomycin to talc slurry comparison for serious study limitations due to an overall high risk of bias for trials forming direct and indirect evidence loops, and by one level for evidence of indirectness (due to variation in the dose of bleomycin used and different approaches between studies to inclusion of patients with trapped lung and definition of pleurodesis failure). We downgraded evidence in the doxycycline to talc slurry comparison for imprecision (due to the wide Cr-I around the effect estimate) and indirectness (as there was no direct evidence comparing doxycycline and talc slurry, and evidence forming indirect evidence loops were based on few studies).

The NMA provides some evidence that mistletoe (viscum) may be associated with fewer pleurodesis failures than placebo, mitoxantrone and IPC without daily drainage, with ORs and 95% Cr-Is lying away from the null value of 1. However, these comparisons are based only on indirect data with small sample sizes. The only direct evidence on mistletoe (viscum) was from a comparison with bleomycin made in a single study (OR 0.19, 95% Cr-I 0.02 to 1.62; participants = 17). Mistletoe (viscum) was estimated to have a high rank (rank 2/21) but with a very wide Cr-I (1 to 16) reflecting uncertainty within the network as to its true rank.

The NMA also provides some evidence that TMP may be more effective (i.e. result in fewer pleurodesis failures) than interferon, IPC – not daily drainage, mitoxantrone and placebo. TMP similarly ranked highly on average, but with a wide Cr-I reflecting considerable uncertainty (ranked joint second with mistletoe (viscum), 95% Cr-I 1 to 11). The evidence for TMP is based on two studies, recruiting a combined total of 123 participants. We considered both studies at high risk of bias and therefore we did not include them in the sensitivity analysis of studies at low risk of bias.

The NMA results are consistent with the pair-wise meta-analysis results in providing some evidence that a daily IPC drainage regimen (ranked joint 11th of 21 interventions, 95% Cr-I 4 to 18) has increased chance of pleurodesis success compared with IPCs without daily drainage (ranked 18th, 95% Cr-I 13 to 21). Talc administration combined with IPC ranked joint 12th but the very wide Cr-I demonstrates uncertainty of its true rank (95% Cr-I 3 to 20).

Placebo administration was associated with the highest likelihood of pleurodesis failure, with an estimated rank lowest of 21 interventions (95% Cr-I 15 to 21). We had a moderate level of certainty that placebo is associated with more pleurodesis failures than talc slurry (OR 15.90, 95% Cr-I 3.76 to 79.90) with evidence downgraded one level for imprecision due to the wide Cr-I of this estimate. The ORs and 95% Cr-Is comparing placebo with TMP, talc poudrage, mepacrine, talc slurry, *C parvum* and iodine were all far away from 1, providing evidence that placebo is less effective at achieving a pleurodesis.

Other potentially efficacious agents were mepacrine, iodine and *C parvum*, with estimated ranks of 5th (95% Cr-I 1 to 13) for mepacrine and joint 7th (95% Cr-I 2 to 14) for iodine and *C parvum*.

Heterogeneity within the network meta-analysis

We estimated the between-study SD in treatment effect estimates (log ORs) across the whole network to be Tau = 0.70 (95% Cr-I 0.30 to 1.17), suggesting a high degree of heterogeneity, although the wide Cr-I indicates a substantial degree of uncertainty around this.

We performed several sensitivity analyses to explore potential reasons for this heterogeneity, based on predefined potential clinical effect modifiers (see Appendix 4). Due to the smaller number of studies in these analyses, many of them contained fewer interventions than the main network. The estimated rank orders were generally similar to those in the main network (Appendix 5; Appendix 6).

The estimated between-trial heterogeneity across the network remained high for most sensitivity analyses, but was reduced in the NMA restricted to trials at low risk of bias (Tau 0.37, 95% Cr-I 0.02 to 1.47) and the NMA restricted to trials excluding people with trapped lung (Tau 0.31, 95% Cr-I 0.01 to 1.19). We note however that the Cr-Is around these estimates of Tau are very wide, indicating considerable uncertainty about the extent of heterogeneity. More generally, estimates of Tau in all sensitivity analyses were very imprecise. The upper limit of the 95% Cr-Is for these values was often close to 2. Since we assumed a uniform (0.2) prior distribution for Tau in each analysis, it is likely that the upper limits would increase further still if we assumed a wider prior distribution (Appendix 4; Appendix 5; Appendix 7).

Results were fairly robust to exclusion of the higher risk of bias studies, although doxycycline and *C parvum* both ranked higher than in the main NMA, probably due to the removal of two particular studies (Kuzdzal 2003; Ostrowski 1989) (Appendix 5; Appendix 7). Talc poudrage and talc slurry were associated with the least pleurodesis failures and their Cr-Is were the same (talc poudrage: rank 2, 95% Cr-I 1 to 9; talc slurry: rank 4, 95% Cr-I 1 to 9) with

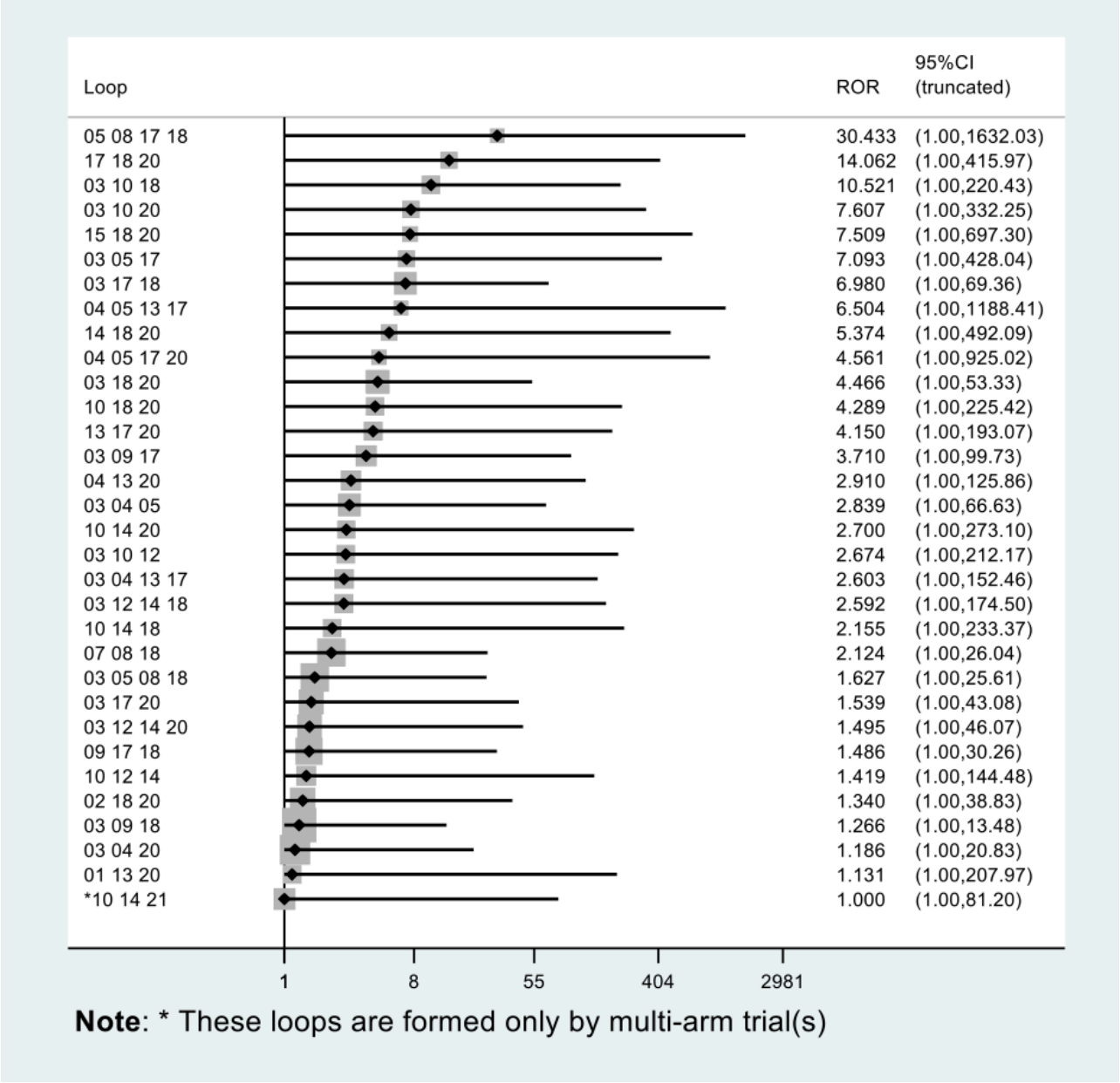
the OR and Cr-I of talc poudrage versus talc slurry suggesting little difference between the two agents (OR 0.78, 95% Cr-I 0.16 to 2.08).).

We observed a diverse range of doses used for many of the pleurodesis agents evaluated, which is a potential cause for the unexplained heterogeneity. Unfortunately, it was not feasible to examine the effect of dose on comparative estimates (ORs).

Inconsistency within the network meta-analysis

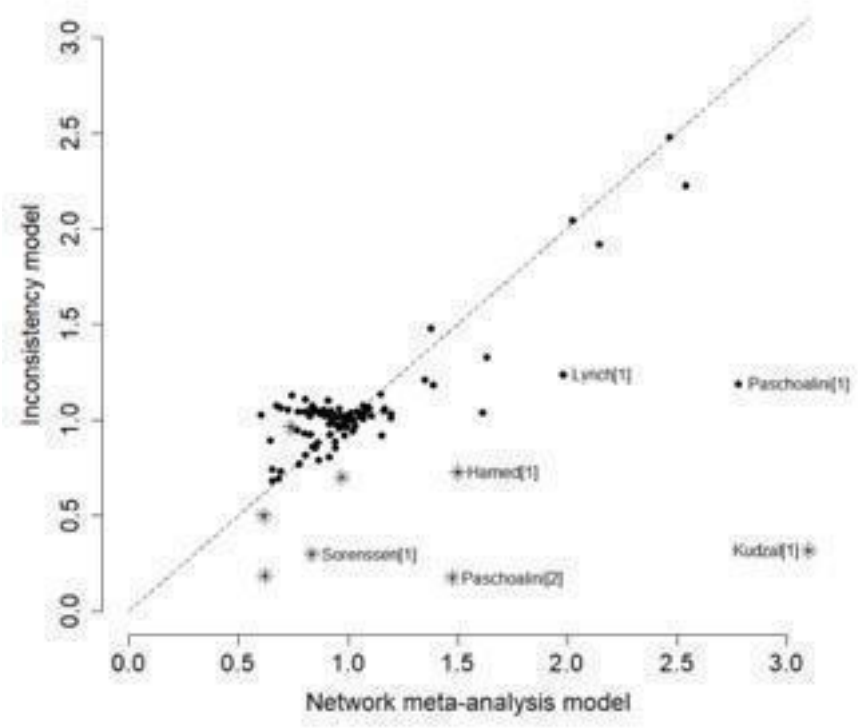
There was no statistical evidence for global inconsistency in the main network or in any of the subgroup or sensitivity NMAs (see Figure 6). For the primary outcome analysis of pleurodesis failure, the residual deviance was four points lower (indicating slightly better fit) for the 'inconsistency model' relative to the NMA. However, after penalising for the increased complexity of the inconsistency model (101 'effective parameters' required versus 91 for the NMA), the DIC indicated a preference for the NMA model (DIC of 209.3 relative to 214.9 for the inconsistency model).

Figure 6. Inconsistency plot for the main network. ***Treatment codes: 01: adriamycin; 02:autologous blood; 03:bleomycin; 04:C parvum; 05:doxycycline; 06:interferon; 07:indwelling pleural catheter (IPC) –daily drainage; 08:IPC –not daily drainage; 09:iodine; 10:mepacrine; 11:mistletoe (viscum); 12:mitoxantrone; 13:mustine; 14:placebo; 15:silver nitrate; 16:thoracoscopic mechanical pleurodesis (TMP); 17:talc poudrage; 18:talc slurry; 19:talc via IPC; 20:tetracycline; 21:triethylenethiophosphoramide. Abbreviations: ROR:ratio of odds ratios; 95% CI:95% confidence interval. Heterogeneity variance was set at 0.4929 (reflecting the estimation of Tau from the network).***



Similarly, there was no statistical evidence for loop-specific inconsistency within any of the networks. Inconsistency factors (ratio of odds ratios (RORs)) with 95% CIs for the main network can be found in Figure 6. Although none of these CIs exclude the null value of 1, we note that some of the RORs are large, with extremely wide CIs, due to the small volume of evidence per loop. The possibility of true inconsistencies cannot therefore be excluded. The largest ROR (30.4, truncated 95% CI 1 to 1632.0) related to the loop doxycycline – IPC not daily drainage – talc slurry – talc poudrage. We note that the only direct evidence on doxycycline versus talc poudrage was from a small trial of 31 participants, with zero pleurodesis failures in the talc poudrage arm (Kuzdzal 2003), which appears to be the driver of this large ROR. The residual deviance contribution plot (Figure 7) indicates that the data points that were fitted 'better' by the inconsistency model relative to the NMA tended to similarly be those with zero cells: in particular, the Kuzdzal 2003 trial is highlighted again as potentially inconsistent from other evidence using this approach. As the residual deviance is known to be numerically unstable in the presence of zero cells, this does not cause concern (Dias 2018).

Figure 7. Residual deviance contribution plot for the main network meta-analysis. * indicates 0 events.



Additional post-hoc sensitivity analysis

The post-hoc sensitivity analysis that only evaluated agents given through an intercostal chest tube included 37 studies of 16 agents (Appendix 7; Appendix 8). There was very little evidence of difference between the agents: Cr-Is were wide and the estimated rankings for the individual agents were also very imprecise. The estimated degree of heterogeneity was even higher than the main network (Tau 0.87, 95% Cr-I 0.37 to 1.52).

Primary outcomes for the methods not included in the network meta-analysis

Pleurodesis techniques

The results of the pair-wise comparisons of the interventions not included in the NMA are shown in Table 3.

We did not include one study in the NMA as it was a three-arm trial evaluating different doses of silver nitrate administered via a chest tube (Terra 2015). Only two of 60 participants had a failed pleurodesis, both in the group receiving the highest dose of silver nitrate.

We could not include eight studies in the NMA as they evaluated tumour-specific therapies for people with MPE due to non-small cell lung cancer (NSCLC) (Du 2013; Ishida 2006; Kasahara 2006; Luh 1992; Masuno 1991; Wang 2018; Yoshida 2007; Zhao 2009). The results could not be generalised to people with other tumour types and hence we did not consider these interventions to be jointly randomisable. All of these studies randomised only small numbers of participants. However, in five of the direct comparisons, the OR and 95% CI lay far away from the null value of 1, giving evidence against the null hypothesis of no difference (Table 3).

Du 2013 randomised people with NSCLC to receive three cycles of either cisplatin plus intrapleural bevacizumab (a humanised monoclonal antibody to vascular endothelial growth factor (VEGF)) or cisplatin alone. More participants in the cisplatin-alone group had pleurodesis failure than in the combination group (6/36 with cisplatin plus bevacizumab versus 17/34 with cisplatin alone; OR 5.00, 95% CI 1.66 to 15.09; studies = 1; participants = 70; Analysis 22.1).

Masuno 1991 randomised people with NSCLC with MPE to receive up to two doses of either intrapleural LC9018 (lyophilised *Lactobacillus casei*) plus adriamycin or adriamycin alone. There were more pleurodesis failures in the control group compared to those who received LC9018 (23/38 with adriamycin alone versus 10/38 with LC9018 plus adriamycin; OR 4.29, 95% CI 1.62 to 11.35; studies = 1, participants = 76; Analysis 14.1).

Ishida 2006 conducted a three-arm trial, comparing intrapleural OK-432, an inactivated product of *Streptococcus pyogenes* A3 with antitumour immune-modulatory effects in lung cancer, with cisplatin and combined therapy (both OK-432 and cisplatin). People treated with OK-432 alone had a higher pleurodesis failure rate than those receiving combination treatment (OR 12.44, 95% CI 1.32 to 117.03; studies = 1, participants = 32), but a lower failure rate than those receiving cisplatin alone (OR 0.48, 95% CI 0.12 to 1.92; studies = 1, participants = 34; Analysis 10.1).

Wang 2018 administered intrathoracic cisplatin in combination with intravenous pemetrexed as the control intervention for people with lung adenocarcinoma and compared this with the addition of intrathoracic Endostar. Participants in the intervention arm had a lower pleurodesis failure rate after three cycles of treatment (OR 0.43, 95% Cr-I 0.20 to 0.93; participants = 128; Analysis 29.1).

Other methods to optimise pleurodesis

We evaluated several other methods to optimise pleurodesis, but did not include them in the NMA because we did not consider them to be jointly randomisable (see Table 4). Most studies included small numbers of participants and none provided evidence of a difference in pleurodesis failure rates between the treatments being compared (see Table 4).

Three studies investigated the use of intrapleural fibrinolytics. Mishra 2018 recruited people with non-draining MPE to receive either intrapleural urokinase or placebo with coprimary outcome measures of dyspnoea change and time to pleurodesis failure. Seventy-one participants were randomised. The authors reported no significant difference between groups in time to pleurodesis failure over the 12-month study period (13/35 failures in participants receiving urokinase compared with 11/34 receiving placebo; OR 1.24, 95% CI 0.46 to 3.34; Analysis 27.1), and no difference between groups in the number of participants achieving a clinically significant decrease in VAS dyspnoea scores.

Saydam 2015 randomised 40 participants to receive either streptokinase or saline placebo in people with multiloculated MPE. Pleurodesis outcome data were not presented for 11 participants, but failure occurred in 2/18 participants receiving streptokinase and 5/11 receiving placebo control (P = 0.07). In Okur 2011, the total volume of pleural fluid drained was higher in the streptokinase group than control; however, there was no difference observed between groups in pleurodesis failure rates (streptokinase versus control: OR 0.46, 95% CI 0.11 to 1.90; Analysis 28.1).

Two studies compared small- and large-bore chest drains. Clementsen 1998 randomised 21 participants to receive tetracycline via 10-Fr and 24-Fr drains (administered at the end of medical thoracoscopy). They observed no difference in pleurodesis failures between groups (small-bore versus large-bore pleurodesis failure: OR 0.57, 95% CI 0.07 to 4.64; Analysis 18.1).

The TIME-1 2×2 factorial study (Rahman 2015), compared the effect of small- and large-bore drains and analgesia (NSAIDs versus opiates) on pain and pleurodesis outcomes in 320 people with MPE. Small chest tubes (12 Fr) failed to meet non-inferiority for pleurodesis efficacy at three months when compared with large (24 Fr) drains, with 15/50 pleurodesis failures in the 12-Fr group and 12/50 failures in the 24-Fr group (small versus large bore: OR 1.36, 95% CI 0.56 to 3.30; Analysis 18.1).

We did not identify any RCTs examining the role of pleuroperitoneal shunts.

Secondary outcomes

Due to the diversity of reporting techniques and outcome measures, it was not possible to perform a formal statistical analysis of many of the predefined secondary outcomes.

Adverse effects and complications

Most studies reported data on adverse effects of the interventions, however four studies did not (Evans 1993; Kuzdzal 2003; Saydam 2015; Villanueva 1994). Kefford 1980 reported adverse events but we could not differentiate the participants with pleural effusions from those with ascites or pericardial effusions. Two study authors provided data on adverse events by personal communications (Goodman 2006; Mager 2002). The methods used to describe the adverse effects observed varied widely between studies.

One study demonstrated that mixed particle talc is associated with more lung and systemic inflammation, hypoxaemia and acute respiratory distress syndrome (ARDS) than graded talc (with its smallest particles removed) and tetracycline (Maskell 2004).

Other notable complications included a possible increased risk of cellulitis and pleural infection associated with IPCs. One study comparing IPCs without daily drainage to talc slurry pleurodesis reported more cases of infection in the IPC arm (five cases of pleural infection requiring admission for intravenous antibiotics, plus 2/52 participants who were managed as outpatients with oral antibiotics in the IPC arm, compared to 1/54 participants requiring hospital admission for pleural infection in the talc slurry arm). However, no IPCs were removed as a consequence of infection (Davies 2012). In another study, 2/74 participants developed a pleural infection and 3/74 developed cellulitis in the IPC arm compared with 1/72 participants with pleural infection in the talc slurry arm (Thomas 2017). Boshuizen 2017, however, reported no difference in the rate of infection between participants receiving an IPC without daily drainage and those receiving a chest drain and talc slurry pleurodesis, with two infections occurring in each group. One study comparing daily IPC drainage to talc slurry pleurodesis reported only one wound infection in the IPC group (Demmy 2012).

One study comparing IPCs without daily drainage to doxycycline pleurodesis reported 6/99 participants receiving an IPC had a local cellulitis infection, which responded to oral antibiotics. No participants with an infection required IPC removal (Putnam 1999). Neither study comparing daily IPC drainage to IPCs without daily drainage observed a difference in the rate of pleural infection between study arms (Muruganandan 2018; Wahidi 2017).

We used NMA to compare rates of the most commonly reported adverse effects: fever and pain.

Presence of procedure-related fever

Pair-wise (direct) meta-analysis

The direct evidence regarding fever is shown in Appendix 9.

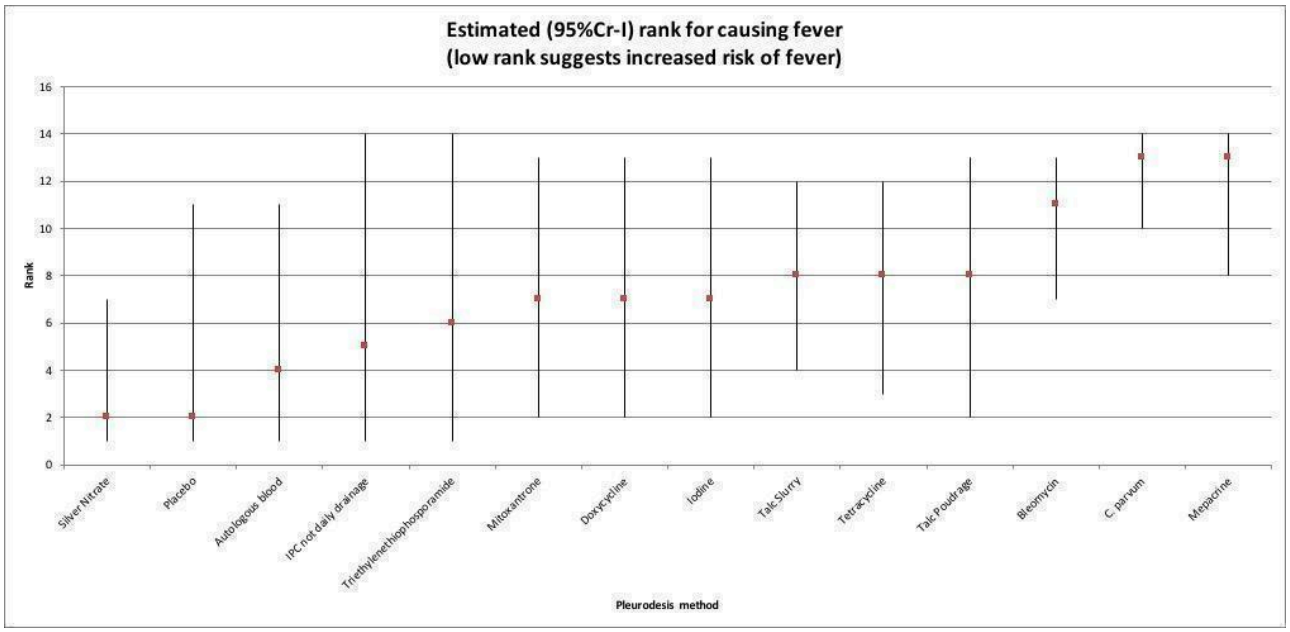
Twenty-six direct comparisons were each informed by between one and five studies.

There was evidence that talc slurry may be associated with more fever than autologous blood (OR 3.92, 95% CI 1.31 to 11.72; studies = 1; participants = 110; Analysis 2.2) and that placebo, tetracycline and triethylenethiophosphoramide were associated with less fever than mepacrine (placebo: OR 0.31, 95% CI 0.12 to 0.79; Analysis 15.2; tetracycline: OR 0.13, 95% CI 0.02 to 0.89; Analysis 4.2; triethylenethiophosphoramide: OR 0.04, 95% CI 0.01 to 0.30; Analysis 13.2).

Network meta-analysis

We performed NMA of fever data from 30 trials of 14 different treatments, including 2004 participants. ORs from the NMA are shown in Table 5 and estimated rankings of the interventions in Figure 8. The summary of findings from the NMA on risk of developing a fever can be seen in Summary of findings 2.

Figure 8. Estimated rank (95% credible interval (Cr-I)) for causing fever (a low rank suggests increased risk of fever).



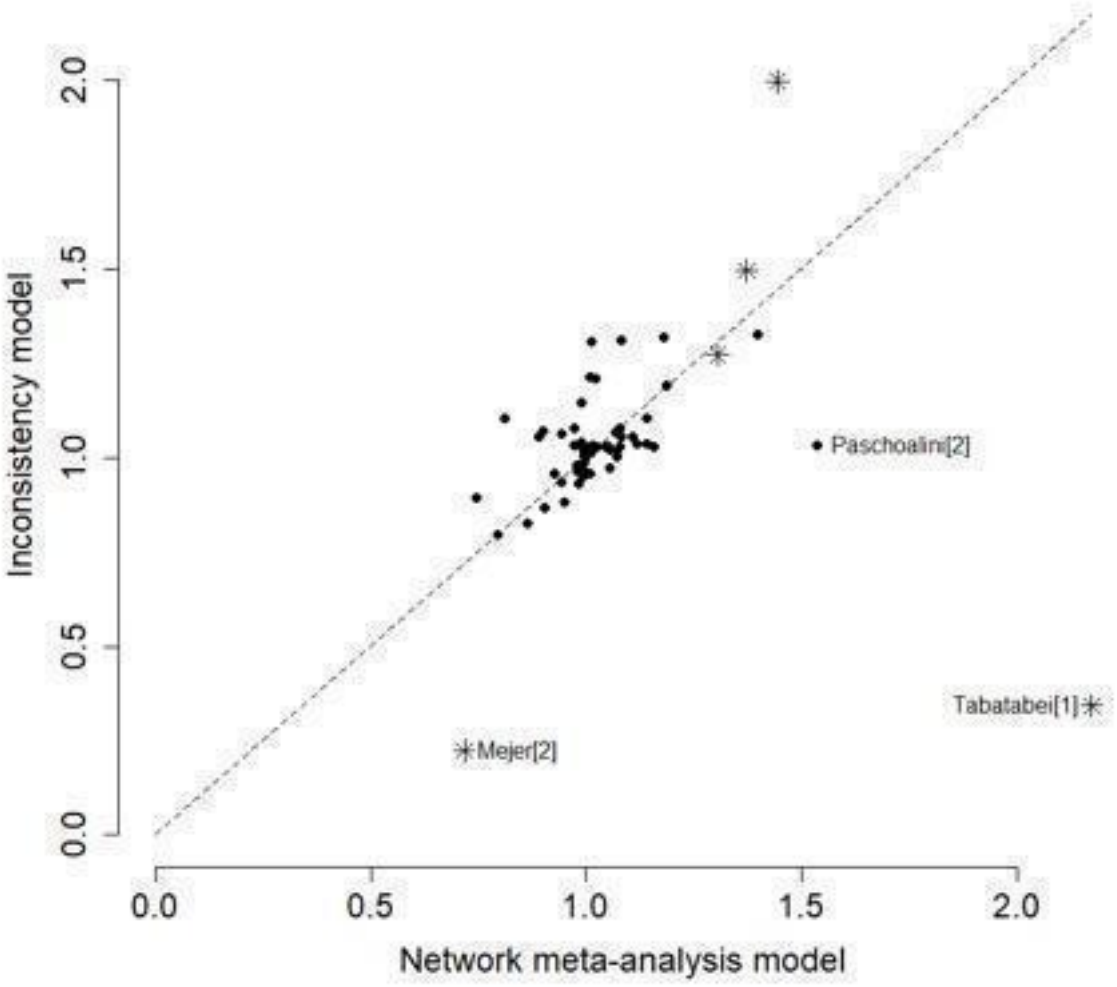
Most estimates had very wide Cr-Is, indicating a large degree of imprecision. Silver nitrate and placebo appeared to be associated with the least fever (estimated rank joint 2nd of 14 interventions (silver nitrate: 95% Cr-I 1 to 7; placebo: 95% Cr-I 1 to 11)) (talc slurry versus silver nitrate: OR 17.33, 95% CI 1.07 to 336.40; talc slurry versus placebo: OR 10.65, 95% CI 0.2 to 931). The interventions associated with the most fever appeared to be *C parvum* and mepacrine, with estimated ranks of joint 13th (*C parvum*: 95% Cr-I 10 to 14; mepacrine: 95% Cr-I 8 to 14) (talc slurry versus *C parvum*: OR 0.07, 95% CI 0.01 to 0.88; talc slurry versus mepacrine: OR 0.09, 95% CI 0.01 to 1.69).

There was no statistical evidence for a difference in the risk of fever, relative to talc slurry, of talc poudrage (OR 0.89, 95% Cr-I 0.11 to 6.67)), bleomycin (OR 2.33, 95% Cr-I 0.45 to 12.50)), IPC – not daily drainage (OR 0.41, 95% Cr-I 0.00 to 50.00) and doxycycline (OR 0.85, 95% Cr-I 0.05 to 14.29). We tentatively suggest that these interventions may be comparable to talc slurry, but we have a low level of certainty in this conclusion: we downgraded evidence for imprecision due to the wide Cr-Is of all network estimates. We also downgraded evidence for indirectness, due to differences in adverse event reporting of procedure-related fever, using different temperature thresholds and time frames for which a fever may be considered attributable to the intervention.

The between-study SD (Tau) for the fever NMA was 1.67 (95% Cr-I 1.08 to 1.98), indicating a very high degree of statistical heterogeneity. We note that the upper limit of the prior distribution was set to 2.

Comparison of DIC values for the NMA model versus the inconsistency model suggested comparable model fit after penalising for complexity (DIC 121.5 for the NMA model versus 121.2 for the inconsistency model). However, we noted a reduction in the SD when moving from the NMA to inconsistency model, which does indicate the possibility of inconsistency within the network. Comparison of residual deviance contributions of individual data points highlighted three studies as potentially inconsistent from the rest of the evidence, two of which included zero counts in the 2×2 outcome data (i.e. either all or no participants in one trial arm experienced fever, which leads to computational instability in residual deviance calculations) (Figure 9). The inconsistency factor method provided no evidence of loop inconsistency (Appendix 4).

Figure 9. Residual deviance contribution plot for the fever network meta-analysis. * indicates 0 events.



Other findings

For those studies that were not included in the NMA but provided data on fever, the majority revealed no difference between the interventions (Emad 1996; Kasahara 2006; Masuno 1991; Terra 2015). Two studies evaluating OK-432 revealed more fever in this group compared to the control groups (Ishida 2006; Luh 1992; Yoshida 2007) (Analysis 10.2). The mixed talc group had more fever than the graded talc group (OR 15.92, 95% CI 1.81 to 140.16; participants = 46; studies = 1; Analysis 20.2; Maskell 2004). The group who received cisplatin alone had less fever than those who also received rAd-p53 (OR 0.09, 95% CI 0.02 to 0.51; studies = 1, participants = 35; Analysis 22.2; Zhao 2009).

Presence of procedure-related pain

We only included studies reporting dichotomous outcomes (presence or absence of pain post procedure) in the pair-wise and NMA.

Pair-wise (direct) meta-analysis

The direct evidence regarding pain is shown in Appendix 10.

There was evidence that tetracycline pleurodesis may cause pain more frequently than autologous blood (OR 69.00, 95% CI 7.61 to 625; studies = 1), mustine (OR 33.87, 95% CI 1.80 to 636; studies = 1) and silver nitrate (OR 55.08, 95% CI 3.02 to 1003; studies = 1) (Analysis 4.3). One study provided evidence that talc slurry may cause pain more frequently than autologous blood (OR 3.57, 95% CI 1.19 to 10.74; participants = 110; Analysis 2.3).

Network meta-analysis

We included 31 studies and 14 treatments (including 2753 participants) in the NMA regarding pain (Appendix 11; Appendix 12). The summary of findings from the NMA of risk of developing procedure-related pain can be seen in Summary of findings 3.

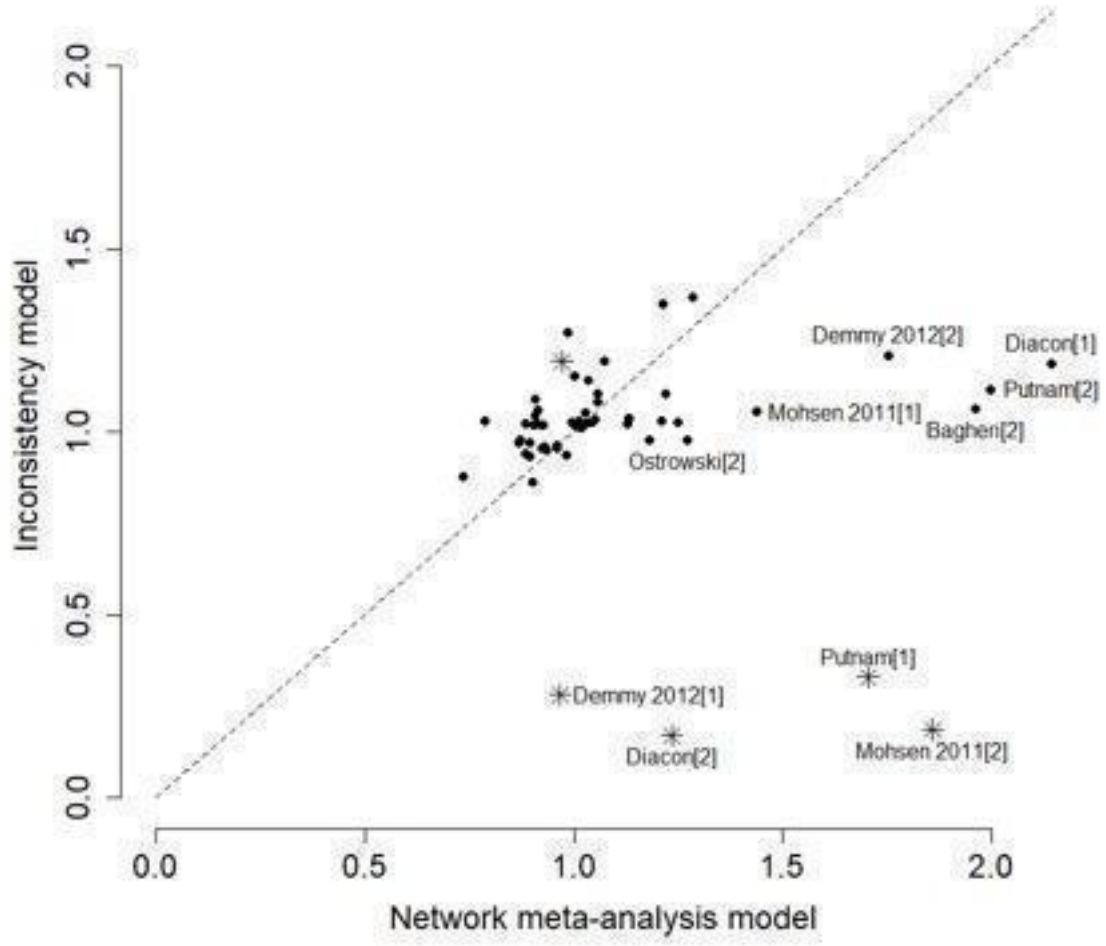
There was evidence to suggest that five agents, including bleomycin (OR 19.46, 95% Cr-I 3.47 to 138.70), doxycycline (OR

22.87, 95% Cr-I 2.99 to 223.60), talc poudrage (OR 8.64, 95% Cr-I 1.45 to 96.71) and talc slurry (OR 6.77, 95% Cr-I 1.40 to 39.01) may be associated with a higher number of participants having pain post procedure than autologous blood (estimated rank 1, 95% Cr-I 1 to 4).

There was no statistical evidence for a difference in risk of procedure-related pain, relative to talc slurry, of bleomycin (OR 2.85, 95% Cr-I 0.78 to 11.53), IPC – not daily drainage (OR 1.30, 95% Cr-I 0.29 to 5.87), doxycycline (OR 3.35, 95% Cr-I 0.64 to 19.72) or talc poudrage (OR 1.26, 95% Cr-I 0.45 to 6.04). We tentatively suggest that these interventions may have a comparable frequency of procedure-related pain to talc slurry, but we have a low level of certainty in this conclusion. Estimates had very wide CIs; therefore, we downgraded by one level in all comparisons for imprecision. We also downgraded evidence for indirectness for all comparisons. The time point at which pain was reported, threshold for reporting and mode of assessment was often unstated by studies (as occurrence of pain was reported as an adverse event) and therefore we felt this was likely to differ between studies. In addition, we downgraded evidence one level for inconsistency in the talc poudrage to talc slurry comparison (I^2 = 69%).

The between-study SD (Tau) for the network was 0.69 (95% Cr-I 0.11 to 1.51), indicating considerable heterogeneity. The DIC indicated comparable fit between the NMA and inconsistency models, with a difference in DIC of 4.8 points (marginally in favour of the inconsistency model, but not reaching the predefined cut-off of 5 points' difference for global inconsistency). There was a slight reduction in estimated Tau when moving to the inconsistency model, which is however suggestive of possible global inconsistency (Appendix 4). Inspection of the contributions of individual data points to the mean residual deviance showed that the slightly better fit of the inconsistency model was driven by trials in which either all or no participants in one trial arm experienced pain post procedure (i.e. presence of a zero count in the 2×2 outcome data) (Figure 10).

Figure 10. Residual deviance contribution plot for the pain network meta-analysis. * indicates 0 events.



Other findings

Seven studies reported results from pain scales rather than dichotomous outcome data and , therefore, we could not include these in the pair-wise analysis or NMA (Agarwal 2011; Alavi 2011; Bjermer 1995; Davies 2012; Hojski 2015; Paschoalini 2005; Zimmer 1997). Bjermer 1995 reported that "pain scores were significantly higher in the mepacrine group (p = < 0.001)" compared to the mitoxantrone group as measured by the WHO analgesic ladder (no raw figures provided) (WHO 2016). In Hojski 2015, VAS pain scores demonstrated that participants in the mechanical pleurodesis group had less pain than the talc slurry group at 12 hours' postpleurodesis; however, there was no difference between groups at 48 hours. The other six studies did not provide evidence of a difference in pain between the interventions studied.

Eight studies that we did not include in the network (as we did not consider interventions to be jointly randomisable) revealed no difference between interventions (Kasahara 2006; Luh 1992; Masuno 1991; Neto 2015; Okur 2011; Terra 2015; Yoshida 2007; Zhao 2009).

Two studies that evaluated interventions to optimise pleurodesis reported pain outcomes according to drain size. Clementsen 1998 reported fewer participants experienced pain at the time of drain insertion in those with small-bore drains (10 Fr) compared with large-bore drains (24 Fr) (OR 0.08, 95% CI 0.01 to 0.75; Analysis 18.2) and that smaller (10-Fr) drains were better tolerated. Placement of large-bore (24-Fr) chest tubes was associated with more pain in the TIME-1 study, but the study authors reported this was not clinically significant (Rahman 2015). There was no difference in pain scores between participants receiving NSAIDs and opiates, although participants in the NSAID group did require more rescue analgesia (Rahman 2015).

One study reported that more participants experienced pain in the OK-432 group than control (Analysis 10.3; Ishida 2006).

Patient-reported control of breathlessness

Twenty studies reported breathlessness outcomes, using a variety of scoring systems: Medical Research Council (MRC) Dyspnoea Scale (Mohsen 2011); VAS score (Bhatnagar 2018; Bhatnagar 2020; Bjermer 1995; Davies 2012; Diacon 2000; Mishra 2018; Muruganandan 2018; Terra 2015; Thomas 2017); 'dyspnoea index' (Demmy 2012); BORG score and Guyatt Chronic Respiratory Questionnaire (CRQ) (Putnam 1999); Modified Borg Score (Boshuizen 2017); EORTC Core Quality of Life Questionnaire (QLQ-C30)/Lung Cancer Module (EORTC QLQ-LC13) questionnaires (Hojski 2015; Rintoul 2014), functional class (Masuno 1991; Rafiei 2014; Zimmer 1997), scale 0 to 10 (Alavi 2011); and patient satisfaction questionnaire with breathlessness rating (Wahidi 2017).

Pair-wise (direct) meta-analysis

Results from meta-analysis of patient-reported control of breathlessness are presented in Summary of findings 4.

We performed direct meta-analysis of data from two studies which used a 100-mm VAS breathlessness scale in participants undergoing talc slurry pleurodesis and IPC insertion without daily drainage. Davies 2012 used a scale with no breathlessness at 0 mm and maximum possible breathlessness at 100 mm. We inverted the results reported by Thomas 2017, since they used a scale where 0 mm represented "worst imaginable breathlessness" and 100 mm no breathlessness. The minimum clinically important difference using a 100-mm VAS breathlessness scale in MPE was 19 mm (95% CI 14 to 24) (Mishra 2015). We had low certainty in the evidence from our results that IPC without daily drainage may offer comparable breathlessness improvement when compared to talc slurry (MD −6.12 mm, 95% CI −16.32 to 4.08) from a fixed-effect meta-analysis. We downgraded evidence for serious study limitations due to lack of blinding (which was not possible due to the nature of the interventions). We also downgraded for indirectness due to the different time points at which VAS data with total numbers of participants was reported by studies (Davies 2012: 42 days; Thomas 2017: 180 days).

One study used a 100-mm VAS breathlessness scale (0 mm representing absence of breathlessness and 100 mm most severe symptoms) to compare talc poudrage with talc slurry pleurodesis (Bhatnagar 2020). The authors reported no significant difference in VAS dyspnoea scores between intervention arms at all time points (absolute difference in mean VAS score from baseline of talc poudrage versus talc slurry: 0.8, 95% CI −4.6 to 6.2; P = 0.78). Data from this study demonstrated an MD of 4 mm (95% CI −6.26 to 14.26) between talc poudrage and talc slurry. We had a moderate level of certainty in the evidence and downgraded for serious study limitations only, due to lack of blinding of participants and clinicians (which was not possible due to the nature of the interventions).

Network meta-analysis

There were insufficient comparable data to perform an NMA.

Other findings

Two studies compared dyspnoea scores for participants with daily IPC drainage and IPCs without daily drainage. In the AMPLE-2 study, authors reported that there was no significant difference between VAS breathlessness scores over the first 60 days postintervention (ratio of geometric means 1.32, 95% CI 0.88 to 1.97; P = 0.18; Muruganandan 2018). In the ASAP study, the proportion of participants with relief of breathlessness at two weeks was 0.65 in the aggressive (daily) drainage arm and 0.40 in the standard (alternate day drainage), with between-group differences maintained at 12 weeks' postintervention (Wahidi 2017).

Putnam 1999 compared IPC without daily drainage and doxycycline pleurodesis, demonstrating an improvement in breathlessness in all groups and time points compared to baseline. The only between-group difference identified was change in Borg score on exertion at 30 days, which appeared to favour IPC (mean 2.2 (SD 2.4) in IPC group versus mean 1.0 (SD 2.4) in doxycycline group; P = 0.05).

One study comparing talc slurry pleurodesis with IPC – not daily drainage found that participants from both groups reported less breathlessness at six weeks and the improvement was similar in both treatment arms (mean Modified Borg Score improvement: 2.2 in talc slurry group versus 1.6 in IPC group; P = 0.44), although there was substantial data attrition due to 35/94 participants dying within six weeks (Boshuizen 2017).

Demmy 2012 demonstrated that participants with an IPC drained on a daily basis had significantly better dyspnoea scores at 30 days

than those in the talc slurry group (8.5 with IPC drained daily versus 6.1 with talc slurry; P = 0.047).

Participants receiving talc through their IPC had less breathlessness at day 56 than those with an IPC alone in the IPC Plus study (mean VAS score difference −7.9 points, 95% CI −15.5 to −0.3 in IPC plus talc group; P = 0.04). However, mean VAS dyspnoea scores over the 70-day trial period did not differ between the treatment arms (−3.6 points, 95% CI −8.5 to 1.3; P = 0.15) (Bhatnagar 2018).

Urokinase for multi-loculated malignant effusions had no significant impact on breathlessness when compared to placebo (adjusted MD from baseline between groups 23.8 mm, 95% CI 212 to 4.4; P = 0.36; Mishra 2018).

Rafiei 2014 found more participants receiving doxycycline had severe dyspnoea at two months compared to those receiving bleomycin (5/20 (24%) with doxycycline versus 1/21 (5%) with bleomycin; P = 0.01). Bjermer 1995 noted that participants receiving mitoxantrone had a larger reduction in breathlessness than the mepacrine-treated participants (absolute values not reported; P ≤ 0.001). Masuno 1991 did not provide the absolute figures but reported "statistically significant" improvements in dyspnoea one week after treatment at "the final judgement" in the LC9018 group. Alavi 2011 observed lower dyspnoea scores for participants receiving bleomycin than those receiving iodine at one-month postintervention, although no figures were included in the paper. Hojski 2015 observed improved QLQ-C30 dyspnoea scores in the TMP group compared to talc slurry.

In the remaining studies reporting dyspnoea, there were no differences between the study arms in terms of the degree of improvement of dyspnoea (Diacon 2000; Mohsen 2011; Rintoul 2014; Terra 2015; Zimmer 1997).

Participants' quality of life and symptom control

Twenty-four of 80 studies reported quality of life or assessed a symptom score other than dyspnoea. We did not perform pair-wise (direct) meta-analysis or NMA of quality of life scores as there was insufficient comparable data.

The methods used were Karnofsky Performance Score (KPS) (Demmy 2012; Du 2013; Groth 1991; Masuno 1991; Wahidi 2017; Zhao 2009), QLQ-C30 questionnaire (Bagheri 2018; Davies 2012; Dresler 2005; Hojski 2015; Rintoul 2014; Wang 2018), SF36 scale (Bhatnagar 2020; Terra 2009; Wahidi 2017), WHOQOL-BREF scale (Neto 2015; Terra 2015), EQ-5D (Bagheri 2018; Bhatnagar 2020; Muruganandan 2018; Rintoul 2014; Thomas 2017), VAS Score (Diacon 2000; Thomas 2017), Guyatt CRQ (Putnam 1999), a symptom questionnaire (Bjermer 1995), and numerical pain scale (Alavi 2011; Paschoalini 2005; Zimmer 1997).

Five studies evaluating IPCs reported quality of life data. One study found no difference in the number of participants experiencing 'general malaise' between those randomised to IPC without daily drainage and talc slurry pleurodesis (Boshuizen 2017). Neither study comparing IPC (without daily drainage) to talc slurry observed a difference in quality of life between treatment arms (Davies 2012; Thomas 2017). KPS (MD 8.5, 95% CI −6.2 to 23.3; P = 0.24) and 36-item Short Form (SF-36) (MD −12.6, 95% CI −29.3 to 4.1) scores were similar in participants with daily IPC drainage versus IPC without daily drainage at 12 weeks in the ASAP trial (Wahidi 2017). Participants were asked to complete a 'social functioning score' as a component of the SF-36 survey in Wahidi 2017. There were similar improvements across quality of life measures in participants with both daily and alternate day IPC drainage regimens. Participants in the daily IPC drainage group had a bigger improvement in EQ-5D-5L scores over the six-month AMPLE-2 study period, compared with those in the symptom-guided drainage group, representing a better quality of life (estimated difference in means 0.112, 95% CI 0.0198 to 0.204; P = 0.0174; Muruganandan 2018). However, the authors reported no between-group differences in the VAS quality of life scores (ratio of geometric means 1.220, 95% CI 0.871 to 1.709; P = 0.25; Muruganandan 2018). There was no difference in Guyatt CRQ scores between participants randomised to IPC (without daily drainage) and doxycycline pleurodesis (Putnam 1999).

Bhatnagar 2018 reported that participants who received talc via IPC had higher quality of life scores (with higher scores indicating a better quality of life) than those who received placebo at all time points. Differences in QLQ-C30 scores reached significance at day 28 (difference 9.2 points, 95% CI 1.1 to 17.4; P = 0.03) and EQ-5D-5L at day 42 (difference 0.12 points, 95% CI 0.01 to 0.22; P = 0.03) (Bhatnagar 2018).

Most studies reported no difference in quality of life measures between the treatment groups (Alavi 2011; Bhatnagar 2020; Davies 2012; Diacon 2000; Groth 1991; Paschoalini 2005; Terra 2009; Terra 2015; Zimmer 1997). Bjermer 1995 reported a "larger reduction" in tiredness in the mitoxantrone group compared to the mepacrine group (absolute figures not provided; P ≤ 0.001). Dresler 2005 noted less fatigue in the talc poudrage group than the talc slurry group (absolute figures not provided; P = 0.016). Those participants who received LC9018 "demonstrated a significant improvement of PS (performance status) at 1 week" than those who did not (absolute figures not provided; P ≤ 0.05) (Masuno 1991). Zhao 2009 found that more participants who received combination treatment with cisplatin plus Ad-p53 had a performance score "improvement rate that was significantly higher" at six weeks than those receiving cisplatin alone (11/17 (65%) with cisplatin plus Ad-p53 versus 6/18 (33%) with cisplatin alone; P = < 0.05). The participants who underwent a video-assisted thoracoscopic partial pleurectomy had "significantly better" EQ-5D scores at six months than the talc group in the MesoVATS study (MD 0.08, 95% CI 0.003 to 0.16); P = 0.042), but no difference in their QLQ-C30 scores (Rintoul 2014). Demmy 2012 did not provide data by treatment group. Du 2013 reported 30 participants (83%) receiving bevacizumab and cisplatin had an "improved quality of life" (measured by KPS) as opposed to 15 (50%) in the cisplatin group. Hojski 2015 observed an "improvement of quality of life" in both the TMP and talc slurry groups, but with pre- and post-treatment QLQ-C30 scores demonstrating higher global health scores and less fatigue in the TMP group compared to talc slurry.

No studies reported on the potential patient burden of community IPC drainages and impact this may have on quality of life.

Relative costs of the comparative techniques

Seven of 80 trials reported the relative costs of the interventions. Rapid pleurodesis was cheaper than standard care in Yildirim 2005 (USD 245 (SD 71.5) with rapid pleurodesis versus USD 860 (SD 496) with standard care). Talc slurry was cheaper than bleomycin in three studies: Ong 2000 evaluated the cost per dose (USD 1 per dose with talc slurry versus USD 309 per dose with bleomycin);

Haddad 2004 calculated the complete cost for the entire procedure (USD 488 (SD 212.5) with talc slurry versus USD 796 (SD 207.3) with bleomycin) and Zimmer 1997 calculated the cost of each treatment (USD 12.36 with talc slurry versus USD 955.83 with bleomycin). Talc poudrage was also cheaper than bleomycin in Diacon 2000 (CHF 3893 (Swiss Francs) (USD 4206) with talc poudrage versus CHF 4169 (USD 4504) with bleomycin). The total cost of VATS pleurectomy was more than talc pleurodesis (GBP 14,252 (USD 21,682) with VATS pleurectomy versus GBP 10,436 (USD 15,876) with talc pleurectomy) (Rintoul 2014). Dresler 2005 reported no difference between the cost of talc slurry and poudrage (no figures quoted).

A costing study performed alongside the TIME-2 study found IPCs to be a cost-effective choice when compared to talc slurry and most economical in participants with limited survival. "Substantial uncertainty" about the longer-term cost-effectiveness of IPCs was acknowledged due to limitations including sample size of the study population (which was not powered to detect cost-effectiveness differences) and variables such as nursing time required for IPC drainage and life-expectancy (Olfert 2017).

At 12 weeks' postintervention, nine (69%) participants undergoing daily IPC drainage and seven (58%) participants with alternate-day IPC drainage in the ASAP trial considered that catheter supplies posed no financial burden. Ten (77%) participants in the 'aggressive drainage' arm and six (50%) participants in the standard care arm had costs completely covered by insurance (Wahidi 2017).

Overall mortality

Forty-five studies provided participant mortality data (number of study participants who had died).

Pair-wise (direct) meta-analysis

The direct evidence regarding mortality is shown in Appendix 13. Only one direct comparison found evidence of a difference between treatment arms; in the comparison between interferon and bleomycin those receiving interferon had a higher rate of mortality (OR 2.16, 95% CI 1.15 to 4.07; participants = 160; Analysis 12.4).

Network meta-analysis

We incorporated 31 trials of 15 treatments, including 2816 participants, into an NMA analysing mortality (Appendix 14; Appendix 15). Results from the NMA are summarised in Summary of findings 5.

Rankings within the network were imprecise, with wide CIs; for this reason, we downgraded certainty in the evidence by one level in all comparisons. We also downgraded for indirectness, due to the different time points at which studies reported mortality data.

Tetracycline may be associated with higher mortality rates than six agents including bleomycin (OR 2.58, 95% Cr-I 1.09 to 6.76), talc poudrage (OR 3.06, 95% Cr-I 1.05 to 9.76) and talc via IPC (OR 7.74, 95% Cr-I 1.33 to 50.51). We tentatively suggest that bleomycin (OR 1.03, 95% Cr-I 0.43 to 2.50) and IPC – not daily drainage (OR 0.80, 95% Cr-I 0.42 to 1.61) may be comparable to talc slurry but have a low level of certainty in this conclusion.

We are uncertain whether talc poudrage may be comparable to talc slurry (OR 0.87, 95% Cr-I 0.51 to 1.49; very-low certainty). In addition to downgrading for imprecision and indirectness, we also downgraded the evidence for this comparison for inconsistency (I^2 = 40%). We are uncertain whether doxycycline may be comparable to talc slurry (OR 0.71, 95% Cr-I 0.15 to 3.23); very-low certainty) and downgraded evidence for serious study limitations in addition to imprecision and indirectness.

The degree of heterogeneity was low (Tau 0.22, 95% Cr-I 0.01 to 0.73).

There was no evidence of global inconsistency in this network: the DIC was 5 points lower (indicating better fit after penalising for complexity) for the NMA model than for the inconsistency model, and the estimate of between-study heterogeneity (Tau) was very similar under both models. The residual deviance under each of the two models was almost identical (53.8 NMA versus 54.1 inconsistency model): therefore, we did not present plots of residual deviance contributions for this outcome, as these are uninformative. Similarly, there was no evidence of loop inconsistency (Appendix 4).

Other findings

Most studies that were not included in the network showed no differences in mortality (Clementsen 1998; Crnjac 2004; Goodman 2006; Ishida 2006; Mager 2002; Maskell 2004; Rahman 2015; Rintoul 2014; Terra 2015; Villanueva 1994; Yildirim 2005; Yoshida 2007; Zhao 2009).

Median survival

Thirty studies reported median survival (days) for the treatment groups. Two studies found a survival difference between the treatment arms. Masuno 1991 found a median survival of 232 days with LC9018 versus 125 days with control (participants = 95; P = 0.008). Mishra 2018 observed an increase in time to death in the urokinase group (median survival: 69 days with urokinase versus 48 days with placebo; P = 0.026).

Kasahara 2006 reported a longer median survival in participants receiving high-dose OK-432 than low-dose OK-432, but did not report the spread or whether this difference was significant (33.6 days with high dose versus 22.6 days with low dose; participants = 38). Evans 1993 found survival was longer after thoracoscopic tetracycline pleurodesis than bedside administration (total participants = 34; P = 0.03; raw data only available as a survival curve).

Duration of inpatient stay

Twenty-eight of 80 studies reported data for duration of inpatient stay.

Total length of stay

Many studies reported no difference between interventions (Bayly 1978; Bhatnagar 2018; Bhatnagar 2020; Haddad 2004; Ibrahim 2015; Lynch 1996; Muruganandan 2018; Ong 2000; Paschoalini 2005; Rahman 2015; Schmidt 1997; Terra 2009; Yim 1996; Zimmer 1997).

Yildirim 2005 and Goodman 2006 reported a shorter length of stay when chest drains were removed earlier following sclerosant administration compared to standard care (Yildirim 2005: mean: 2.33 days (SD 0.62) with shorter versus 8.33 days (SD 4.85) with

standard; P ≤ 0.001; participants = 27; Goodman 2006: median: 4 days (interquartile range (IQR) 4 to 8) with shorter versus 8 (IQR 6 to 9) with standard; P ≤ 0.01; participants = 41). Ozkul 2014, which evaluated a rapid drainage strategy prior to sclerosant administration, also showed this group had a shorter length of stay than the standard care group (mean: 2.2 days with rapid versus 9.0 days with standard; P ≤ 0.001; participants = 79). The talc group had a shorter length of stay than the VATS partial pleurectomy group in the MesoVATS study (median: 3 days (IQR 2 to 5) with talc versus 7 days (IQR 5 to 11) with VATS; P ≤ 0.001; participants = 196) (Rintoul 2014). Participants undergoing TMP had a shorter hospital stay than those receiving talc slurry in Crnjac 2004 (mean: 5.5 days (SD 2.5) with TMP versus 7.5 (SD 3.3) with talc slurry; P = 0.001; participants = 87). Although the mean duration of thoracic drainage was shorter for participants undergoing TMP in Hojski 2015, there was no difference in the total length of hospital stay.

Thomas 2017 reported that participants receiving an IPC (without daily drainage) spent fewer days in hospital from procedure to death or 12 months compared to those receiving talc slurry (10 days (IQR 3 to 17) with IPC (without daily drainage) versus 12 days (IQR 7 to 21) with talc slurry; P = 0.03; participants = 146). Over the 12-month TIME-2 study, participants receiving an IPC (without daily drainage) spent a median of 1 day (IQR 0 to 3 days) in hospital for drainage or drainage-related complications compared to a median of 4.5 days (IQR 2.5 to 7.5) in the talc slurry pleurodesis group (P ≤ 0.001) (Davies 2012). Talc administration via IPC and daily IPC drainage did not result in a difference in the number of days spent in hospital when compared to IPC without daily drainage (Bhatnagar 2018; Muruganandan 2018).

Time from intervention to discharge

Putnam 1999 reported that participants randomised to receive an IPC had a reduced hospital admission time from randomisation to discharge compared to those receiving doxycycline pleurodesis (median: 1 day with IPC versus 6.5 with doxycycline; P ≤ 0.001; participants = 144). This was mirrored by Boshuizen 2017 who reported a median hospitalisation period of 4 days versus 0 days (P ≤ 0.0001) favouring participants in the IPC without daily drainage arm compared to those receiving talc slurry pleurodesis. Thomas 2017 reported a reduced length of initial hospital admission for IPC insertion (median stay: 1 day (IQR 1-2 days) with IPC insertion versus 3 days (IQR 3-4 days) with talc pleurodesis; P ≤ 0.001). In the TIME-2 study, time from randomisation to discharge was a median of 0 days (IQR 0 to 1) in the IPC (without daily drainage) group and 4 days (IQR 2 to 6) in the talc pleurodesis group (difference: 3.5 days fewer, 95% CI −4.8 to −1.5; P ≤ 0.01) (Davies 2012).

Participants receiving urokinase for non-draining MPE had a shorter length of hospital stay from randomisation to discharge compared to those receiving placebo (mean 6.2 days (SD 2.7) with urokinase versus 8.7 days (SD 6.5) with placebo; P = 0.049) (Mishra 2018).

Participants randomised to autologous blood pleurodesis had a shorter duration of postpleurodesis hospital stay than those receiving talc slurry (mean: 2.8 days (SD 0.9) with autologous blood pleurodesis versus 3.6 days (SD 1.8) with talc slurry; P = 0.04) (Keeratichananont 2018), and tetracycline (2.6 (SD 1.2) with autologous blood pleurodesis versus 4.3 days (SD 2.4) with tetracycline; P = 0.03) (Keeratichananont 2015).

Mohsen 2011 found participants receiving iodine had a shorter postprocedural length of stay than those undergoing talc poudrage (mean: 4.5 days (SD 1.1) with iodine versus 5.7 (SD 2) with talc poudrage; P = 0.02; participants = 42).

Patient acceptability

Three trials reported patient acceptability of the interventions (Demmy 2012; Dresler 2005; Wahidi 2017).

Participants recruited to the ASAP trial showed an overall high level of satisfaction with IPCs when asked to complete a patient satisfaction questionnaire. At 12 weeks' postintervention, 12 participants (92%) in the 'aggressive' daily drainage study arm and 11 participants (92%) in the standard (not daily drainage) arm felt they would choose an IPC again as a treatment for pleural effusion-related breathlessness. When asked at 12 weeks' postintervention, nine (69%) participants in the daily drainage group and five (42%) participants in the standard care group reported it was 'extremely easy' to drain the catheter at home (Wahidi 2017).

No studies reported on the potential patient burden of community IPC drainages and the impact this may have on quality of life.

Demmy 2012 did not provide raw data by treatment group. Dresler 2005 reported no difference between talc slurry and talc poudrage in terms of participants' perception of convenience (no raw data provided).

The only trial evaluating mistletoe (viscum) reported that 2/13 participants in the mistletoe arm withdrew their consent for ongoing study participation after experiencing allergic reactions to the first dose. The outcomes for these participants were not available and hence the trial deemed them non-evaluable (Gaafar 2014).

Need for repeat invasive pleural intervention

We considered that the risk of requiring a repeat invasive pleural procedure for symptomatic re-accumulation of pleural fluid is an important factor when selecting an initial management strategy for MPE. Pleural fluid re-accumulation, due to failure of the initial pleurodesis, is frequently associated with increasing breathlessness. Undergoing an additional procedure commonly incurs more time in hospital and re-exposure to the risk of procedure-related complications.

Direct (pair-wise) meta-analysis

We performed pair-wise meta-analyses comparing talc poudrage, bleomycin and IPCs without daily drainage to talc slurry, in terms of need for repeat invasive pleural intervention. Results are summarised in Summary of findings 6.

We had a moderate level of certainty that participants receiving talc poudrage probably have a comparable risk of requiring repeat invasive pleural intervention than those receiving talc slurry (OR 0.96, 95% Cr-I 0.59 to 1.56; studies = 2; participants = 380; Bhatnagar 2020; Terra 2009). We downgraded certainty in the evidence by one level for indirectness, due to differences between study protocols (Bhatnagar 2020 administered 4 g of graded talc by 12-Fr to 14-Fr drains in the talc slurry arm and by 16-Fr to 24-Fr drains in the talc poudrage arm, whereas Terra 2009 administered 5 g of 'non-calibrated' talc via 28-Fr drains).

Participants receiving an IPC (without daily drainage) are probably less likely to require repeat invasive pleural intervention than participants receiving talc slurry pleurodesis (OR 0.25, 95% Cr-I 0.13 to 0.48; studies = 3; participants = 343; moderate certainty; Boshuizen 2017; Davies 2012; Thomas 2017). We downgraded evidence by one level for indirectness, as participants with trapped lung were excluded by one study (Thomas 2017), but included by Boshuizen 2017 and Davies 2012.

We made note of study limitations due to lack of blinding (which was not possible due to the nature of the study interventions) in the talc poudrage to talc slurry and IPC without daily drainage to talc slurry comparisons, but did not downgrade evidence as requirement for repeat intervention was guided by symptoms and radiology, with involvement of a second blinded clinician in one study (Bhatnagar 2020) prior to repeat intervention in participants with less than one-third opacification of the hemithorax.

Data were also available from one study comparing bleomycin to talc slurry, but the result was very imprecise (OR for repeat procedure 4.33, 95% Cr-I 0.16 to 114.58; participants = 33; very-low certainty; Zimmer 1997). We downgraded evidence by one level for serious study limitations, as data comparing bleomycin to talc slurry were available from only one study, at high risk of bias in three domains. We downgraded evidence by two levels due to gross concerns of imprecision due to the small number of participants (33) and very wide CIs.

There was no direct evidence comparing doxycycline or placebo to talc slurry.

From these results, we estimated that 20/100 participants (95% CI 16 to 24) will require a repeat invasive procedure with talc slurry, 19/100 (95% CI 11 to 30) with talc poudrage, 6/100 (95% CI 3 to 11) with IPC without daily drainage and 52/100 (95% CI 4 to 97) with bleomycin.

Network meta-analysis

We performed a post-hoc NMA for requirement for ipsilateral repeat invasive pleural intervention. However, there were no meaningful results. There was only one evidence loop in the entire network and the indirect evidence was computationally unstable due to the presence of a zero cell count.

DISCUSSION

This is the first update of the review published in Issue 5, 2016 (Clive 2016), which replaced the original review published in 2004 (Shaw 2004).

Summary of main results

The management of MPE has long been subject to debate and research. This systematic review of the current literature attempts to combine all the available randomised evidence regarding the wide variety of interventions for the condition.

Since the last iteration of this review in 2016, a number of robust, large randomised trials have been published evaluating some key, clinically important questions in this area. These have provided us with a wealth of new data, including more important patient-reported outcomes and better insights into the role for IPCs in MPE management.

Our primary NMA evaluating pleurodesis failure indicated that talc poudrage may have fewer pleurodesis failures than talc slurry (OR 0.50, 95% Cr-I 0.21 to 1.02; moderate-certainty evidence). However, direct evidence from four statistically homogeneous trials (I^2 = 0%) estimated an OR closer to the null value of 1 (OR 0.81, 95% CI 0.61 to 1.08; Analysis 3.1), indicating that the two interventions may have comparable efficacy. A sensitivity NMA restricted to studies at low risk of bias provided a similar effect estimate, with a wide Cr-I (OR 0.78, 95% Cr-I 0.16 to 2.08). Estimated ranks of talc poudrage and talc slurry were third (95% Cr-I 1 to 6) and sixth (95% Cr-I 3 to 10) of 21 interventions from the primary NMA and second (95% Cr-I 1 to 9) and fourth (95% Cr-I 1 to 9) of 18 interventions from the sensitivity analysis restricted to trials at low risk of bias.

A large number of trials estimated pleurodesis failure rates with talc slurry (907 participants randomised to this intervention across 19 studies): talc slurry was therefore used as the comparator intervention in the 'Summary of findings' tables (Summary of findings for the main comparison;Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6). Although other interventions, such as mistletoe (viscum) and TMP, appeared to rank highly within the primary NMA, these interventions were only evaluated by very small studies (63 participants randomised to TMP and 10 to mistletoe (viscum) in total), all with an overall high risk of bias. Hence, estimates of the relative efficacy or rank of these interventions are very imprecise (wide Cr-Is) and we excluded both of these agents from the low risk of bias sensitivity analysis. Given the very small number of participants randomised to these interventions, it is not possible to draw conclusions about their use in routine clinical practice.

Our results indicate that IPCs without daily drainage (rank 18th, 95% Cr-I 13 to 21) of 21 interventions in the main network and rank 15th (95% Cr-I 9 to 18) of 18 interventions in the sensitivity analysis excluding studies at high risk of bias) are less likely to effect a definitive pleurodesis allowing IPC removal than several other interventions, including talc poudrage and talc slurry (moderate certainty). However, pleurodesis efficacy may be increased with daily IPC drainage or by administration of talc slurry via the IPC. Importantly, direct meta-analysis demonstrated that participants with an IPC (without daily drainage) were less likely to require repeat invasive pleural intervention than participants treated with talc slurry pleurodesis (OR 0.25, 95% CI 0.13 to 0.48; studies = 3, participants = 343; moderate-certainty evidence). This is a potentially important finding for patients, since requirement of a repeat invasive pleural intervention may be a more relevant and meaningful outcome than obtaining a definitive pleurodesis. We considered this an important factor with regard to patient acceptability of the available interventions.

The networks evaluating fever and pain found only uncertain evidence of minimal differences between agents, with no evidence for differences between the most commonly used interventions reported in the 'Summary of findings' tables.

Five studies provided data on infection rates in participants receiving IPCs compared to chemical pleurodesis (Boshuizen 2017; Davies 2012; Demmy 2012; Putnam 1999; Thomas 2017). Data from three studies suggest participants receiving an IPC may have a higher risk of developing cellulitis or pleural infection. Notably, no

IPCs were removed as a consequence of infection (Davies 2012; Putnam 1999; Thomas 2017).

There were insufficient comparable data to perform an NMA of breathlessness outcomes. However, the evidence suggests no difference in postintervention VAS breathlessness scores of participants receiving an IPC (without daily drainage) compared to talc slurry pleurodesis, based on a direct meta-analysis of data from two studies (MD in change in 0-mm to 100-mm VAS score –6.12 mm, 95% CI –16.32 to 4.08; low-certainty evidence) (minimum clinically important difference for dyspnoea in MPE using the VAS breathlessness scale 19 mm, 95% CI 14 to 24; Mishra 2015). Direct comparison from one study demonstrated likely comparable outcomes for breathlessness control between talc poudrage and talc slurry (MD 4.00 mm, 95% CI –6.26 to 14.26; moderate-certainty evidence; Bhatnagar 2020).

There was also insufficient comparable data to perform an NMA of quality of life outcomes. Most studies reported no difference between interventions on quality of life outcomes.

Only seven studies reported the relative costs of interventions. Three studies found talc slurry to be cheaper than bleomycin. A costing study performed alongside the TIME-2 trial found IPCs to be a cost-effective choice when compared to talc slurry and most economical in participants with limited survival, but noted further research is needed about the longer-term cost-effectiveness of IPCs (Olfert 2017).

The NMA evaluating mortality found only uncertain evidence of minimal differences between agents, with no evidence for differences between the most commonly used interventions reported in the 'Summary of findings' tables.

Twenty-eight of 30 studies reporting median survival (days) found no difference between interventions.

Participants receiving an IPC spent fewer days in hospital over the course of their remaining life, or until 12 months, in two studies (Davies 2012; Thomas 2017). Data also demonstrates that participants undergoing an IPC insertion had a faster time to hospital discharge than those admitted for a chemical pleurodesis (Boshuizen 2017; Davies 2012; Putnam 1999; Thomas 2017).

Overall completeness and applicability of evidence

This is the largest systematic review of the evidence surrounding interventions in MPE in the published literature. We used robust search strategies to identify all the available randomised evidence and diligently contacted the study authors regarding missing data where possible.

However, despite attempting to contact the study authors, we were unable to obtain additional information regarding 40 records during the full-text screening process (36/207 records identified from searches in 2016, included within the 135 listed as 'not eligible' and a further 4/156 records identified in 2019 updated searches, included within the 124 'not relevant' records) in order to confirm whether eligibility criteria for inclusion in the review were met. We only included RCTs within this review. As per the protocol, we excluded studies which were not randomised (at high risk of bias for sequence generation, allocation concealment, or both). It is possible that publication bias may therefore affect the validity of the results.

The small number of studies for each pair-wise comparison (maximum of five), meant funnel plots would not be informative (Sterne 2011). As the interventions could not be logically ordered, we also decided a comparison-adjusted funnel plot for the network was not valid (Salanti 2014).

Several studies included in this review had very small numbers of participants, which raises the possibility of small-study effects, which may have resulted in an overestimation of treatment efficacy. Only 13/80 included studies had outcome data for more than 100 participants (Bhatnagar 2018; Bhatnagar 2020; Davies 2012; Dresler 2005; Keeratichananont 2018; Putnam 1999; Rahman 2015; Rintoul 2014; Sartori 2004; Thomas 2017; Wahidi 2017; Wang 2018; Yoshida 2007). However, a comparison between pair-wise meta-analysis results from random-effects versus fixed-effect models (which gives relatively more weight to larger studies, hence reducing the impact of small studies) found no meaningful differences.

When evaluating different pleurodesis agents, we elected to combine different doses of each agent from the available studies for the purposes of comparison. This was necessary due to variation in the doses between studies, which would have made the network more sparse and unconnected. This is a limitation of our review, since differential treatment effects according to doses could have been missed. This is one possible explanation for the high levels of heterogeneity observed in our meta-analyses, which we were unable to investigate further due to the complexity of the data. One included study was designed to compare different doses of silver nitrate and this revealed no difference in terms of pleurodesis efficacy or adverse effects (Terra 2015).

Many of the included studies did not assess patient quality of life, symptom control, acceptability of the intervention to the patient, duration of inpatient stay and costs. Of those that did, we were limited by the diversity of outcome measurement systems used and inconsistent reporting of data and it was therefore not possible to perform an NMA for these outcomes. Although pair-wise and NMA of the risk of having procedure-related pain was possible using data from studies that reported the presence or absence of pain, we were unable to incorporate data from studies which used a scoring system to grade severity of pain (continuous outcome data), due to the range of different scales used. Although such outcomes were secondary objectives of our review, they are important factors when selecting a management strategy and hence the paucity of data on these important patient-reported outcome measures limits the applicability of the evidence from this review to everyday clinical practice.

It is also important to consider the global availability of some of these agents when considering the clinical applicability of our findings. Agents such as tetracycline and *C parvum* are not widely available, precluding their routine use. Other sclerosants included in this review are unlicensed for use as a pleurodesis agent.

Our data regarding the adverse effects of these treatments are limited. As we have selected only RCTs for inclusion in this review, there is the potential that rare but important adverse effects were missed using our methodology. There are reports of adverse effects of pleurodesis agents resulting from absorption of the agent into the systemic circulation. For example, systemic absorption of mixed particle size talc is thought to be linked to rare but occasionally life-threatening acute respiratory distress syndrome, a risk that is minimised by the use of graded (large-

particle) talc (Maskell 2004), now standard practice in Europe and increasingly available worldwide. Mepacrine gained popularity in Scandinavia as a pleurodesis agent, although rare psychotic episodes and seizures, thought to be related to systemic absorption if administered at high doses, limited its use (Bjorkman 1989).

We only managed to synthesise the data on the main adverse effects and so we cannot reliably infer the full adverse effect profiles of these treatments from this review. An appreciation of the adverse effect profile of these interventions is vital when weighing up the risks and benefits of the procedures, particularly as many of the patients in this population have a limited life-expectancy and hence minimising discomfort during their remaining time is imperative.

The definition of pleurodesis efficacy varied between studies, with many relying on radiology alone, which is increasingly considered inadequate without considering symptom recurrence. Achieving a pleurodesis may not represent the best strategy for all. Patients may have a personal preference regarding the best treatment strategy for themselves. Therefore, factors such as breathlessness control and risk of repeat invasive pleural intervention are also important to discuss when selecting the best treatment strategy. Many patients would rather avoid hospital admission and elect for an outpatient pathway, which may make the use of an IPC more appealing than a chemical pleurodesis.

Quality of the evidence

The overall certainty of the evidence ranged from moderate to very low (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6).

The risk of bias in several included studies is substantial and we downgraded evidence for study limitations in the pleurodesis failure rate network, patient-reported breathlessness control meta-analysis, mortality NMA and meta-analysis of risk of requiring a repeat invasive pleural intervention. The vast majority of studies were unblinded, which in part reflects the nature of the interventions but also the symptom-based nature of the endpoints measured, precluding blinding of the outcome reporting as well. Documentation of the methods used for sequence generation and allocation concealment were frequently omitted and it was often not possible to obtain this information retrospectively. However, in a sensitivity analysis including only studies at low risk of bias (defined as a maximum of one high-risk domain in the risk of bias assessment), the relative rankings of interventions were similar. The heterogeneity estimate (Tau) was substantially reduced in this sensitivity analysis (from 0.70 to 0.37), indicating that bias may have been a contributor to the high level of heterogeneity in the primary analysis.

Given the inevitable death of patients in this palliative population, true ITT analysis was often not performed, resulting in the potential for attrition bias. These missing data were handled differently by the various included studies. Some studies included participants on the basis of their 'last observation carried forward' (i.e. their last outcome prior to death) and others excluded these participants from the analysis completely. No studies used other imputation methods to account for these missing data.

We downgraded evidence for indirectness due to variation in definitions of pleurodesis failure, inconsistencies in the doses of sclerosant used and the different approaches towards inclusion or exclusion of participants with trapped lung. There was also variation in how participant attrition was handled and the time point at which pleurodesis failure was assessed. We did state how this would be handled a priori, using hierarchies of preferences; however, these factors may have impacted on the results of the final NMA.

Additionally, we downgraded evidence due to imprecision; many ranks and effect estimates had wide Cr-Is. This was particularly evident in the NMAs of risk of procedure-related fever and pain, and risk of mortality, where all relative effect estimates had wide Cr-Is. We had very high concerns of imprecision in the bleomycin to talc slurry comparison in the risk of repeat pleural intervention meta-analysis and evidence was downgraded by two levels.

We downgraded evidence by one level for inconsistency for the IPC without daily drainage to talc slurry comparison for pleurodesis failure rate (I^2 = 61%) and for the talc poudrage to talc slurry comparison within the pain (I^2 = 69%) and mortality (I^2 = 40%) outcomes.

There was a substantial degree of both statistical and clinical heterogeneity in each network of comparisons. Aside from the analyses restricted to studies at lower risk of bias and trials excluding trapped lung (which did appear to reduce the degree of heterogeneity) the other sensitivity analyses, selected on the basis of factors hypothesised to be clinical effect modifiers, did not appear to explain the high level of heterogeneity. This signifies the complexity of this condition and the treatments, which results in substantial clinical heterogeneity. Possible explanations include different effects of varying tumour subtypes, early lung entrapment which is not clinically detectable, varying drug doses and subtle technique-related procedural factors, such as adequacy of pleural fluid drainage prior to instillation of the sclerosant.

Potential biases in the review process

This review is based on the available published evidence and not on individual patient data, which would give a more accurate estimation of treatment effect and a clearer understanding of the heterogeneity (Deeks 2011). However, as we have included studies published as long ago as 1977, individual patient information was therefore not available and patient-level meta-analysis would not be possible without excluding the majority of the available evidence.

In order to allow inclusion of as many eligible studies as possible, we combined data obtained using different definitions of pleurodesis failure and timings in the same analysis. We predefined the methodology for this in the protocol using hierarchies of preferences. We performed sensitivity analyses to ensure the results were robust.

A potential source of bias in our primary outcome measure, pleurodesis failure, is the inevitable participant attrition due to mortality reported in many studies. If there had been real differences in mortality (and therefore dropout) across the interventions, this could bias the estimates of relative pleurodesis failure rates. However, analysis of the data on mortality and median survival times showed only a possible association between tetracycline and increased mortality rates and no differences in the vast majority of comparisons.

It should also be noted that the initial screening of titles and abstracts up to 2016 was performed by just one review author. From 2016 to 2020, this was done by two review authors.

Agreements and disagreements with other studies or reviews

Several other systematic reviews have been published in this area (Iyer 2019; Mummadi 2015; Shaw 2004; Sivakumar 2019; Tan 2006; Xia 2014). All have presented only direct comparisons, rather than also incorporating indirect comparisons of alternative agents using NMA methods. We consider that NMA is much more informative, as the diversity of the control groups used when comparing one agent with 'all others' means that important relative treatment effects may be either over- or underestimated.

We used robust inclusion and exclusion criteria to identify eligible studies, which resulted in some studies included in other systematic reviews in this field being excluded from this one. These studies have been recorded in the Excluded studies section of this review, with justifications given for their exclusion. The main reasons were failure to use a truly random process to assign treatment groups and the inclusion of ascites or pericardial fluid accumulation, which could not be differentiated in the results section.

Previously published meta-analyses have suggested that talc is the most effective agent (associated with the fewest pleurodesis failures) and is best delivered thoracoscopically, however, Mummadi 2015 found both talc poudrage and talc slurry offered similar rates of pleurodesis efficacy, in keeping with our results.

In a systematic review of quality of life following intervention for MPE, Sivakumar 2019 also acknowledged limitations due to heterogeneity in study design and varied measurement tools. While thoracoscopic talc poudrage, talc slurry and IPCs improved short-term health-related quality of life, no consensus was formed on the overall best treatment approach, with particular respect to long-term outcomes.

Our review has demonstrated that IPCs are associated with reduced rates of invasive ipsilateral re-intervention and reduced procedure-related length of hospital stay, mirrored by Iyer 2019.

AUTHORS' CONCLUSIONS

Implications for practice

For clinicians and for people with malignant pleural effusions

This systematic review suggests that of the commonly available pleurodesis techniques, talc poudrage and talc slurry both rank highly and are more effective at achieving a pleurodesis than sclerosants such as bleomycin (rank 11th, 95% credible interval (Cr-I) 7 to 15) and doxycycline (rank 12th, 95% Cr-I 5 to 18).

Although indwelling pleural catheters (IPCs) are probably associated with higher pleurodesis failure rates than many of the other interventions described, this is likely to be improved by daily catheter drainage or instillation of talc slurry via the IPC. Moreover, pair-wise meta-analysis suggests that the use of IPCs results in less need for further invasive pleural interventions than talc slurry, which may be an important advantage for some patients. Talc poudrage was associated with a similar risk of requiring further invasive pleural procedures when compared to talc slurry (odds ratio (OR) 0.96, 95% Cr-I 0.59 to 1.56).

Where breathlessness outcomes were reported, symptom relief for participants with IPCs may be comparable to talc slurry. For those undergoing talc poudrage pleurodesis, breathlessness relief was probably comparable to talc slurry pleurodesis. In four studies, IPCs were associated with a reduced length of hospital stay (Boshuizen 2017; Davies 2012; Putnam 1999; Thomas 2017), a clinically relevant outcome for a patient group where anticipated survival is often short. Where pleurodesis success is not the primary outcome of interest, such as for those with trapped lung or previous pleurodesis failure, or for patients who wish to minimise repeated invasive procedures or avoid a hospital admission, IPCs may be a favourable choice.

We have noted comparable improvements in postintervention quality of life outcomes in participants with IPCs (with or without daily drainage), talc slurry, talc poudrage and doxycycline pleurodesis (Bhatnagar 2020; Davies 2012; Muruganandan 2018; Putnam 1999; Thomas 2017; Wahidi 2017). The OPTIMUM study, which is currently recruiting in the UK, with health-related quality of life as its primary outcome in participants undergoing IPC with talc via IPC and talc slurry pleurodesis, will further inform practice.

This review was not designed to evaluate rarer but potentially clinically important adverse effects. However, graded (large particle talc) has less systemic absorption than mixed particle size talc and should therefore be used to reduce the rare but important risk of acute respiratory distress syndrome (Maskell 2004). Concerns regarding the dose-dependent systemic absorption of intrapleural mepacrine, and the subsequent risk of transient psychotic episodes and seizures, have not been identified in the randomised trials of these agents, but are likely to limit its routine use (Bjorkman 1989). Non-steroidal anti-inflammatory drug (NSAID) use has not been shown to adversely affect pleurodesis outcomes (Rahman 2015). Data from three studies suggest participants receiving an IPC may have a higher risk of cellulitis and pleural infection (Davies 2012; Putnam 1999; Thomas 2017). Therefore, appropriate information regarding IPC care and symptoms of infection should be given.

Worldwide, talc is reported to be the most commonly used pleurodesis agent (Lee 2003; Roberts 2010; Zarogoulidis 2013), and consequently it is likely to have the best appreciated adverse effect profile. Therefore, if graded talc is available, this would appear to be an effective choice for bedside pleurodesis, supported by the largest body of evidence.

For policy makers

We have identified that many of the available treatment options have their own advantages and disadvantages, in terms of their effectiveness at inducing a pleurodesis, their adverse event profile and the chance a patient will need a subsequent invasive pleural intervention. Therefore, it is important that a range of treatment strategies are accessible and available to patients depending on their clinical situation and their personal preference. For example, there should be adequate provision of both IPC and an inpatient pleurodesis to allow patients and clinicians to decide on an optimal treatment pathway for that individual.

For funders of the intervention

There are insufficient data regarding the relative costs of many of the interventions described in this review to provide robust conclusions regarding this. In the short term, IPCs have been found to be a cost-effective choice but the longer-term cost implications have not been formally established.

Implications for research

General implications

There is a paucity of data regarding patient preference. Although people with an IPC are likely to spend less time in hospital, we found no data relating to considerations such as lifestyle restrictions imposed by drainage regimens, limitation on social and functional activities, and consequent impact on wellbeing. An improved understanding of the key outcomes which are important to people with malignant pleural effusion (MPE) would be beneficial. Carer burden is another significant consideration, particularly in regions where community healthcare services do not provide IPC drainage.

The health economic implications of the available interventions are additional important factors that warrant further research. Limited data suggest that IPCs are a cost-effective choice in people with limited survival (Olfert 2017), but substantial uncertainty around this estimate remains, particularly in respect to long-term outcomes. The cost of community nursing and environmental implications associated with single-use drainage equipment may make IPCs a less favourable choice in some settings.

There is a lack of robust randomised evidence for surgical interventions in the MPE population. Our review has highlighted that pleurodesis success from thoracoscopic mechanical pleurodesis may yield results similar to talc poudrage, but further high-quality evidence is required to delineate the role of this. The AMPLE 3 study, comparing talc slurry via IPC with video-assisted thoracoscopic surgery (VATS) mechanical abrasion or talc poudrage may provide further clarity.

There is limited evidence regarding the most effective management of people with trapped lung. Case series suggest trapped lung affects 10% to 20% of people with MPE and the rapid recurrence of fluid after pleural interventions and the loss of elasticity of the visceral pleura often results in severe symptoms of recurrent breathlessness and pain during fluid aspirations (Brims 2012; Lan 1997; Warren 2008). Often these patients are excluded from MPE trials given the lack of efficacy of pleurodesis in this subgroup and hence there is a dearth of evidence on how best to manage them. Future randomised controlled trials (RCTs) to delineate the optimal management strategy specific to this population would be beneficial. Further understanding of how the disease course of mesothelioma may differ from metastatic pleural disease may influence future treatment choices when considering the management of MPE. The MesoTRAP pilot study, which is currently recruiting in the UK, may lead to a phase III study comparing the efficacy of IPC versus VATS partial pleurectomy/decortication for participants with malignant pleural mesothelioma with pleural effusion and trapped lung.

As our understanding of the pathology of MPE develops and our knowledge of the available management options expands, a universal approach to all patients with malignant effusions is likely to underestimate the complexity of this condition and a hunt for the 'best' pleurodesis technique to over-simplify its challenges. Different strategies are already known to have unique advantages and disadvantages and may therefore be suited to different cohorts of patients. We have demonstrated the heterogeneity of this patient population. It is only by gaining an understanding of the priorities of patients themselves and the real-life implications of the various treatment options that we will be able to select the most appropriate management strategy for an individual. Further patient-centred qualitative research, as well as study of the methods to optimise current strategies (SIMPLE trial) and combine techniques to amalgamate the benefits of the varying modalities, are exciting potential areas of ongoing and future research.

Design

Understanding the factors contributing to the high risk of bias in a large number of the previous studies in this field is crucial when designing future clinical trials in MPE. Attempting to minimise these risks by careful trial design has the potential to improve our evidence base and ensure robust, valid conclusions are drawn from the available evidence.

Measurement (endpoints)

An important limitation of this review is the heterogeneous reporting of patient-centred outcome measures across trials, which precluded network meta-analyses of these clinically important outcomes. This has important implications for future research. Selection of appropriate, clinically relevant, standardised outcome measures is essential to aid robust, unbiased analysis of trial data and facilitate future systematic reviews (Williamson 2012). Specific to this review, an international agreement on the definition of pleurodesis success, the timing at which it should be assessed and development of MPE-specific, validated patient-reported outcome measurement tools would be hugely beneficial when combining data from future RCTs, along with a consensus about how to handle the inevitable patient attrition due to death.

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Clive 2016

Clive A, Jones H, Bhatnagar R, Preston N, Maskell N. Interventions for the management of malignant pleural effusions: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2016, Issue 5. [DOI: 10.1002/14651858.CD010529.pub2]

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CHARACTERISTICS OF STUDIES

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

Agarwal 2011

Methods	Single-centre RCT comparing the efficacy of cosmetic talc with iodopovidone for pleurodesis (India).
Participants	Inclusion criteria: recurrent symptomatic pleural effusion with improvement of breathlessness with thoracentesis; or primary or secondary pneumothorax. Exclusion criteria: allergy to iodine; thyroid disorder; trapped lung; air leak; advanced malignancy with expected survival < 30 days. 36 participants randomised.
Interventions	28-Fr intercostal drain to completely drain effusion or treat pneumothorax. Pleurodesis agent given when < 150 mL/day drainage and complete lung re-expansion on CXR. All participants received intrapleural lignocaine 2 mg/kg and IV tramadol prior to pleurodesis. Iodopovidone: 20 mL 10% iodopovidone in 80 mL saline. Cosmetic talc: 5 g sterilised 'baby powder.' After agent administered, chest tube clamped for 4 hours. Repeat administration of agent if > 250 mL/day drainage. Drain removed when < 100 mL/day output. Follow-up at 1 week, 1 month, 3 months and 6 months, and then every 3 months thereafter.

Agarwal 2011 *(Continued)*

Outcomes	Pleurodesis success according to need for thoracentesis (CR: relief of symptoms related to the effusion and no re-accumulation on CXR at 30 days; PR: reduced dyspnoea related to effusion with only partial re-accumulation of fluid on CXR and no requirement for therapeutic thoracentesis; failure: lack of success as defined above) Chest pain (measured by VAS) Complications Time to pleurodesis
Notes	People with trapped lung excluded. Unpublished data obtained from authors relating to subgroup of participants in the study with MPE – only these data were included for the purposes of this review. Included in network meta-analysis for pleurodesis failure and fever. Study funding source: not stated. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence.
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Blinding of the allocation to treatments was not possible." Comment: agents had different appearances.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Symptom recurrence, VAS scores and complications would all be biased by lack of participant blinding. Mortality would not be affected by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No LTFU. ITT analysis performed.
Selective reporting (reporting bias)	Low risk	All reported.
Other bias	Low risk	Cosmetic talc used rather than medicinal talc, but sterilised and comparable particle size by electron microscopy. No external funding for study.

Alavi 2011

Methods	Single-centre RCT of povidone-iodine and bleomycin pleurodesis for MPE (Iran).
Participants	Inclusion criteria: biopsy or cytologically confirmed MPE (all tumour types); recurrent and symptomatic effusion; CXR confirming lung expansion of 90% after thoracentesis; KPS > 70.

Alavi 2011 *(Continued)*

	Exclusion criteria: comorbidities that precluded GA; bleeding disorders; massive thoracic skin infiltration; active infectious disease. 39 participants randomised.
Interventions	All participants underwent a 28-Fr intercostal drain under local anaesthetic (± IV opiates if required). Study agent administered intrapleurally the next day with 5 mL 2% lidocaine. Bleomycin group: bleomycin 1 mg/kg in 60 mL saline. 1 dose. Povidone-iodine group: 5% (volume unclear). 1 dose. After administration of study agent, drain was clamped for 1 hour and removed when < 200 mL fluid output/day. If fluid output remained high after 10 days, they were discharged home with a Heimlich valve in place.
Outcomes	Effusion recurrence on CXR at 30 days Pain (measured by numerical scale) at discharge and day 30 Dyspnoea (measured by numerical scale) at discharge and day 30
Notes	Minimal raw data in results section – tables quoted in text but not available online. Attempted to contact study authors by emails – no response. People with trapped lung excluded from trial entry. Pleurodesis success measured only using CXR criteria. Included in network meta-analysis for pleurodesis failure. Study funding source: not stated. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation.
Allocation concealment (selection bias)	Low risk	Block randomisation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Differing appearances of bleomycin and iodine make blinding not possible (although not stated explicitly in paper).
Blinding of outcome assessment (detection bias) All outcomes	High risk	Pain and dyspnoea may be biased by lack of blinding. Not stated whether CXRs were evaluated by a blinded clinician. No response from study authors regarding this.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to obtain the tables. Response rates only given as % (no actual numbers), so unclear whether there was LTFU.
Selective reporting (reporting bias)	Unclear risk	Raw data not provided for many of the outcomes. Tables missing.

Alavi 2011 *(Continued)*

Other bias	Low risk	No other biases identified.

Bagheri 2018

Methods	Single-centre RCT comparing efficacy and safety of iodopovidone and bleomycin for pleurodesis in MPE (Iran).
Participants	Inclusion criteria: MPE with positive cytology who were candidates for pleurodesis. Exclusion criteria: none stated. 60 participants randomised.
Interventions	All participants underwent chest tube insertion and entered the study once drain output < 100 mL and CXR confirmed complete lung expansion. Bleomycin group: 15 mg in 100 mL normal saline via chest tube, clamped for 6 hours. Iodopovidone group: 20 mL 10% iodopovidone in 80 mL normal saline via chest tube, clamped for 6 hours. CXRs obtained 24 hours postprocedure and at 2 weeks, 1 month and 6 months after discharge.
Outcomes	Response to treatment, defined as no fluid accumulation on CXR obtained 6 months after pleurodesis and relapse time Fever Chest pain Hypotension
Notes	Attempted to contact study authors by email for further information – no response. Trapped lung excluded. Included in network meta-analysis for pleurodesis failure, pain and fever. Study funding source: no financial support received for the research, authorship, publication, or a combination of these. Study author conflicts of interest statements: none.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation and random numbers table.
Allocation concealment (selection bias)	Unclear risk	No information given on who determined treatment allocation or how this was communicated. Authors contacted by email for further information – no reply.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Investigators and participants were unaware of the treatment allocation; however, no description of practical aspects and methods to maintain blinding were given.

Bagheri 2018 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No comment made on outcome assessment. Authors contacted by email for further information – no reply.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No comment on whether there was a target for recruitment. No information regarding data completeness or withdrawals. Mortality rate not stated, although results given for all participants randomised. Authors contacted by email to clarify – no reply.
Selective reporting (reporting bias)	High risk	Limited outcome data given. No data presented on time to relapse.
Other bias	Low risk	None identified.

Bayly 1978

Methods	2-centre RCT of intrapleural quinacrine (mepacrine) vs tetracycline via tube thoracostomy for MPE (USA).
Participants	Inclusion criteria: documented cancer with pleural effusion; pleural fluid cytology or pleural biopsy confirming malignancy or exudate effusion presumed to be malignant; symptomatic from the effusion or rapidly re-accumulating effusion > 500 mL. All cell types. Exclusion criteria: none. 20 participants randomised.
Interventions	Both groups had a closed tube thoracostomy, drained overnight prior to installation. Quinacrine group: intrapleural quinacrine 100 mg in 30 mL normal saline once daily for 4 days. Tetracycline group: 1 dose of intrapleural tetracycline 500 mg in 30 mL normal saline. Drains clamped for 6 hours postinstallation with patient rotation. Drain removed when < 60 mL/24-hour drainage.
Outcomes	Pleurodesis success (defined on CXR criteria only at 30 days as CR: complete lack of re-accumulation of pleural fluid; PR: re-accumulation of pleural fluid < 50% of the volume present before the sclerosis; failure: re-accumulation of fluid to > 50% of the volume present before the attempted sclerosis) Adverse effects of treatment (pain, fever)
Notes	People with trapped lung not excluded. CR and PR counted as a pleurodesis success for purposes of analysis. 1 participant allocated to quinacrine arm having had treatment failure with tetracycline not included in analysis. Included in network meta-analysis for pleurodesis failure, fever and pain. Study funding source: not stated. Study author conflicts of interest statements: not declared.

Risk of bias

Bayly 1978 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified and unable to contact study authors.
Allocation concealment (selection bias)	Unclear risk	Not specified and unable to contact study authors.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No comment on whether study was blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated whether CXR evaluation was blinded. Pain and fever outcomes may have been affected if participants were unblinded to treatment allocation; however, not stated in paper whether this was the case.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/14 randomised to tetracycline excluded from analysis (1 died and 1 LTFU). No LTFU in mepacrine arm (overall LTFU 13%).
Selective reporting (reporting bias)	Low risk	All specified endpoints reported.
Other bias	High risk	8/22 participants included in the study did not have confirmed pleural malignancy.

Bhatnagar 2018

Methods	Multicentre RCT comparing talc slurry pleurodesis via IPC with saline placebo (UK) – IPC Plus.
Participants	Inclusion criteria: symptomatic MPE, IPC chosen for treatment, expected survival > 2 months, ECOG performance status ≤ 2 after fluid removal. Exclusion criteria: aged < 18 years, extensive lung entrapment or fluid loculation, ipsilateral attempt at pleurodesis within the previous 8 weeks, any contraindication to trial procedures. 154 participants randomised.
Interventions	Insertion of IPC under local anaesthetic with maximal fluid drainage at time of catheter placement. Discharged home same day, with minimum of 3 further IPC drainages. Review at day 10 and randomisation if > 75% pleural apposition on CXR or < 1/3 opacification due to fluid on USS. Talc group: 4 g sterile, graded talc slurry with 50 mL 0.9% saline. Placebo group: 50 mL intrapleural 0.9% saline. Participants discharged after 2-hour observation period with next IPC drainage 12–36 hours after administration of talc or placebo. Subsequent drainage frequency determined by local team, but minimum twice per week for duration of trial. Follow-up until 70 days postrandomisation or death, with trial consultations every 14 days.
Outcomes	Primary: pleurodesis success at day 35 (< 50 mL fluid drained on 3 consecutive occasions through the IPC and CXR taken after these drainages showing < 25% opacification). Secondary: QoL, breathlessness, chest pain, total volume drained from IPC, number of inpatient hospital days, all-cause mortality, degree of fluid complexity (septation or loculation), successful pleurodesis

Bhatnagar 2018 *(Continued)*

	at day 70, successful pleurodesis at both day 35 and day 70, number of therapeutic pleural procedures, adverse events and deaths.
Notes	People with some lung entrapment on CXR at day 10 were eligible for randomisation, but this was included as a variable in the minimisation criteria. Severe lung entrapment was an exclusion criteria. Included in network meta-analysis for pleurodesis failure, pain and mortality. Study funding source: unrestricted grant from Becton Dickinson. Study author conflicts of interest statements: Dr Bishop received educational fees and donated medical equipment from Rocket Medical UK and educational fees and equipment from Becton Dickinson; Dr Ahmed received grant support from Becton Dickinson and GE Medical; Dr Psallidas employed by AstraZeneca in addition to his affiliation with the University of Oxford; Dr Lee received grant support and medical supplies from Rocket Medical UK and fees for serving on an advisory board from Becton Dickinson; Dr Rahman received consulting fees from Rocket Medical UK; Dr Miller received lecture fees and travel support from Gilead Sciences and lecture fees from Janssen, Merck and ViiV Health-care; and Dr Maskell received grant support and consulting fees from Becton Dickinson and grant support from Rocket Medical UK. No other potential conflict of interest relevant to this article was reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised computer-based randomisation with minimisation variables.
Allocation concealment (selection bias)	Low risk	Centralised computer-based randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants blinded. Talc and placebo administered with opaque syringes. Community nurses who recorded the drainage volumes were also blinded. Trial group assignments were known only to the local clinical team.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	CXR used to judge pleurodesis success were interpreted by 2 independent-blinded physicians.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	Commercially funded but no involvement in study design, implementation or analysis.

Bhatnagar 2020

Methods	Multicentre (17 sites) RCT comparing talc poudrage with talc slurry pleurodesis (UK) – TAPPS.
Participants	Inclusion criteria: MPE (histocytologically confirmed or unexplained effusion and cancer or pleural changes on cross-sectional imaging consistent with malignancy), able to tolerate local anaesthetic thoracoscopy under moderate sedation and estimated survival > 3 months.

Bhatnagar 2020 *(Continued)*

	Exclusion criteria: aged < 18 years, requiring diagnostic thoracoscopy, pregnant or lactating, contraindication to pleurodesis (e.g. trapped lung or loculation), insufficient pleural fluid to perform local anaesthetic thoracoscopy without an induced pneumothorax, contraindication to any study intervention. 330 participants randomised.
Interventions	Local anaesthetic thoracoscopy arm: 4 g sterile graded talc insufflated following complete drainage and inspection of pleural cavity. Placement of a 16- to 24-Fr drain. Talc slurry group: 12- to 14-Fr seldinger drain placed under USS guidance. 4 g sterile talc slurry 18–24 hours later if no evidence of non-expanded lung or significant residual pleural opacification on CXR. Unless clinically indicated, chest tubes were not removed within 24 hours of talc administration or if fluid output remained > 250 mL/24 hours.
Outcomes	Primary outcome: pleurodesis failure at 90 days. Defined as requirement for therapeutic thoracentesis of > 100 mL, chest tube insertion for fluid management, insertion of an IPC or thoracoscopy of any type on the same side during the trial follow-up period. Secondary outcomes: pleurodesis failure at day 30 and day 180, time to pleurodesis failure, number of nights in hospital, thoracic pain (VAS score), breathlessness (VAS score), QoL (EQ-5D-5L), mortality, % radiographic opacification at time of drain removal.
Notes	Included in network meta-analysis for pleurodesis failure, pain and mortality. Study funding source: University of Bristol, to which Dr Bhatnagar, Dr Walker, Dr Clive, Ms Zahan-Evans and Dr Maskell were affiliated, and to the University of Oxford, to which Ms Laskawiec-Szkonter, Ms Piotrowska, Dr Little, Ms Mei, Dr Luengo-Fernandez, Mr Quaddy and Dr Rahman were affiliated. The study was funded by the UK National Institute for Health Research and sponsored by North Bristol National Health Service (NHS) Trust. Study author conflicts of interest statements: Dr Maskell reported receiving grants and personal fees from Beckton Dickinson (BD), grants from Rocket Medical and personal fees from Cook Medical outside the submitted work. Dr Ahmed received grants from BD and Rostrees Charity Trust outside the submitted work. Dr Blyth received grants from Rocket Medical UK Ltd outside the submitted work. Dr Miller received personal fees from Gilead outside the submitted work. Dr Psallidas served as a medical science director for Astra Zeneca in a field unrelated to pleural diseases. No other disclosures reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised web-based computer system.
Allocation concealment (selection bias)	Low risk	Centralised web-based computer system.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and clinicians aware of treatment allocation – blinding not possible due to practical differences between interventions.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Although data collectors unblinded to treatment allocation, if fluid recurrence postintervention was limited to within 1/3 of the hemithorax, a second blinded clinician advised on need for repeat pleural intervention. Adverse events categorised by a blinded independent pulmonologist. Authors confirmed that statisticians were blinded to treatment allocation.

Bhatnagar 2020 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis. LTFU well matched between study arms.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	None identified.

Bjermer 1995

Methods	RCT of mitoxantrone vs mepacrine via an intercostal drain (Sweden – number of centres not specified).
Participants	Cytologically confirmed, symptomatic MPE with an expected survival > 3 months (KPS > 60). Excluded if cytotoxic chemotherapy in the preceding month. All cell types included. 30 participants randomised.
Interventions	Both groups had a 12- to 14-Fr chest tube inserted and effusion drained. Pleurodesis agent was given through the chest tube and participant's position changed for 2 hours after administration. Group 1: 1 dose of intrapleural mitoxantrone 30 mg in 50 mL normal saline; drain closed for 48 hours and removed after the 'pleural cavity was emptied.' Group 2: 2 doses of intrapleural mepacrine chloride 200 mg in 20 mL normal saline given on consecutive days and drain removed when < 150 mL fluid production/day.
Outcomes	Pleural fluid re-accumulation at 4 weeks and 12 weeks (defined as CR; PR: if recurrence of pleural fluid but thoracentesis not considered to be indicated; or progressive disease. Adverse effects/toxicity (VAS pain and fever scores) Symptom questionnaires (participant grades symptom on a numerical scale for 4 key symptoms – pain, shortness of breath, nausea and tiredness) Pharmacokinetics of mitoxantrone
Notes	People with trapped lung not excluded from study. CR and PR counted as pleurodesis success for analysis. Included in network meta-analysis for pleurodesis failure and mortality. Study funding source: grants from Swedish Society Against Cancer and the Lions Foundation. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified and unable to find contact details for study authors.
Allocation concealment (selection bias)	Unclear risk	Not specified and unable to find contact details for study authors.

Bjermer 1995 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study personnel not blinded as drugs were different colours. However, participants were blinded to treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants blind to treatment allocation, therefore, fever, pain and symptom scores unbiased. Quote: "Radiological evaluation was made by an independent radiologist."
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant in each study arm did not receive treatment due to "unexpected medical emergencies," therefore deemed non-evaluable. Follow-up data clearly documented for the remaining participants.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported.
Other bias	Low risk	Drain suction use was imbalanced between the treatment arms (10/14 received suction in mepacrine group vs 1/14 in mitoxantrone group).

Boshuizen 2017

Methods	RCT comparing talc slurry pleurodesis with IPC and symptom-guided drainage.
Participants	Inclusion criteria: histocytologically confirmed MPE or progressive malignancy with pleural effusion after exclusion of an alternative cause. Exclusion criteria: previous ipsilateral talc pleurodesis, previous ipsilateral IPC, impaired immunity, platelets < 50×10^9/L. 94 participants randomised.
Interventions	Talc slurry group: 3–5 g talc, as per Dutch guidelines via 15- to 20-Fr drain. IPC group: IPC insertion with symptom-guided drainage.
Outcomes	Primary outcome: improvement in MBS score at rest and on exercise 6 weeks' postrandomisation. Secondary outcomes: daily MBS score at rest and on exercise for 2 weeks' postrandomisation, number of hospital visits, pleural re-intervention, hospital stay, time to pleurodesis failure, adverse events.
Notes	Treatment failure defined as fluid re-accumulation leading to ipsilateral repeat intervention, when no talc was instilled despite drain placement and when participants survived < 6 weeks. No data presented for number of participants with an IPC in whom the device could be removed due to pleurodesis success. Contacted authors for additional information. Included in network meta-analysis for mortality and pain.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised randomisation with stratification.

Boshuizen 2017 *(Continued)*

Allocation concealment (selection bias)	Low risk	Computerised randomisation with stratification.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Interventions unblinded to participants and clinicians.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Study authors contacted and confirmed that outcome assessors were unblinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Due to high attrition rate only 40/94 participants could be included in primary ITT analysis.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	None identified.

Clementsen 1998

Methods	Single-centre RCT of tetracycline pleurodesis using a small percutaneous catheter (CH10), compared to a large-bore chest tube (CH24) inserted after thoracoscopy (Denmark).
Participants	Symptomatic, recurrent MPE, confirmed on pleural fluid cytology. Expected survival of > 3 months (all tumour types included). 21 participants randomised.
Interventions	Group 1: small percutaneous catheter (CH10 65 cm) inserted under local anaesthesia. Group 2: medical thoracoscopy, followed by insertion of a large-bore chest tube (CH24). Both groups received pleurodesis with tetracycline 500 mg and bupivacaine 100 mg intrapleurally. The drain was clamped for 6 hours after instillation after which suction was applied. Drain removed when fluid output < 200 mL in 24 hours.
Outcomes	Treatment response at 3 weeks, 6 weeks and 9 weeks defined by roentgenographic response (CR: no recurrence of pleural fluid; PR: slight re-accumulation with blunted costophrenic angle; no response: complete recurrence of pleural fluid) and clinical response (by the need for new thoracentesis). Questionnaire evaluating discomfort in connection with the tube and the pleurodesis.
Notes	Trapped lung not accounted for in inclusion/exclusion criteria, but 1 participant excluded as they had hydropneumothorax at time of instillation. CR and PR included as pleurodesis successes for analysis. Not included in network meta-analysis. Study funding source: not stated. Study author conflicts of interest statements: not declared.
Risk of bias	

Clementsen 1998 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Allocation by lot."
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind, as different drain sizes used (although not stated explicitly in paper).
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "All data were evaluated by the same physician, who was without knowledge of the result of the randomisation." Comment: however, symptom-based adverse events and symptomatic need for repeat pleural intervention may be biased by lack of participant blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported and justified. Missing outcome data balanced between the 2 treatment arms (2 excluded from group 1 (1 died of cancer soon after drain insertion and 1 developed hydropneumothorax necessitating large-bore drain), 1 excluded from group 2 (participant withdrew consent for study participation).
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	No other biases identified.

Crnjac 2004

Methods	Single-centre RCT comparing TMP with talc slurry (Slovenia).
Participants	Inclusion criteria: breast carcinoma and a resulting morphologically confirmed MPE. Exclusion criteria: unfit for GA. 87 participants randomised.
Interventions	TMP: thoracoscopy (under GA) with adhesiolysis, pleural biopsy and scarification of the visceral and parietal pleura to induce bleeding. Chest tube inserted at the end of procedure. Talc slurry: chest tube inserted under local anaesthetic. 5 g talc in 100 mL saline insufflated through chest tube. Participants in both arms had the drain removed when < 100 mL/24-hour drainage.
Outcomes	Recurrence of effusion on CXR at 1 day, 1 week, 1 month, 3 months and 6 months Duration of chest tube drainage Duration of hospitalisation Complications Mortality (30 days and 6 months)

Crnjac 2004 *(Continued)*

Notes	People with trapped lung not excluded. Pleurodesis success defined using CXR criteria alone. Included in network meta-analysis for pleurodesis failure. Study funding source: not stated. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Low risk	Sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind the study as comparing talc slurry with TMP.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not stated whether radiological assessments were done using a blinded method. Complication reporting, time of tube drainage may be affected by lack of participant and personnel blinding. Mortality outcome not effected by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Minimal missing data. 6/45 participants died within 6 months in TMP group vs 8/42 in talc slurry arm.
Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	Low risk	No documentation of participant experience (e.g. QoL or degree of discomfort), relative costs or need for repeat pleural intervention. Pleurodesis success defined using radiology only. Participants who did not have evidence of recurrence at death were classified as pleurodesis successes.

Davies 2012

Methods	Unblinded, multicentre RCT comparing IPC with talc slurry pleurodesis (UK) – TIME-2 trial.
Participants	Inclusion criteria: clinically confident diagnosis of MPE requiring pleurodesis. Exclusion criteria: aged < 18 years, expected survival < 3 months, chylothorax, previous ipsilateral lobectomy or pneumonectomy, previous attempted pleurodesis, pleural infection, WCC < 1000/µL, hypercapnic ventilatory failure, pregnancy, lactating mothers, irreversible bleeding diathesis, irreversible visual impairment. 106 participants randomised.
Interventions	Group 1: IPC inserted with drainage 3 times a week (or as required to relieve dyspnoea).

Davies 2012 *(Continued)*

	Group 2: 12-F Seldinger chest tube and 4 g talc slurry as an inpatient. All participants had standard oncological management for the primary tumour.
Outcomes	Primary outcome: mean daily dyspnoea VAS over the first 42 days Secondary outcomes: proportion achieving clinically significant decrease in mean VAS dyspnoea; mean VAS dyspnoea at 6 weeks, 3 months and 6 months; mean daily chest pain VAS over the first 42 days; mean VAS chest pain at 6 weeks, 3 months and 6 months; nights spent in hospital; self-reported QoL; frequency of adverse events
Notes	Participants with trapped lung in group 2 did not receive talc pleurodesis, but remained in trial follow-up. Pleurodesis in the IPC group defined as removal of IPC following spontaneous cessation of drainage with no significant fluid recurrence on CXR or USS and no further ipsilateral pleural intervention. In the talc group, pleurodesis failure defined as the need for further ipsilateral pleural intervention. If participants died during follow-up, included as a pleurodesis success if no intervention prior to death. Included in network meta-analysis for pleurodesis failure and mortality. Study funding source: unrestricted education grant from the British Lung Foundation and the Robert Luff Foundation, London, UK. Sponsored by University of Oxford. The IPCs and drainage bottles were provided by Rocket Medical, Washington, UK. Study author conflicts of interest statements: all authors completed and submitted the ICMJE Form for Disclosure and Potential Conflicts of Interest. Dr Wrightson received honoraria, grant support to attend a conference from Boehringer Ingelheim. Dr Guhan received support from Medico for expert testimony; having served on the speakers' bureau for Astra Zeneca, Glaxo Smith Kline, and Chiesi; and received support for conference attendance from Chiesi and Glaxo Smith Kline. Dr C Davies served on the speakers' bureau for AstraZeneca. Dr Lee received honoraria from Care Fusion and Sequana Medical as an advisory board member. Dr Miller received support for lectures on HIV infection from Merck and Gilead. Dr Rahman acted as a consultant to Rocket Medical for device development. No other conflicts of interest reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central telephone randomisation.
Allocation concealment (selection bias)	Low risk	Central telephone randomisation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants or personnel due to nature of interventions (IPC vs talc slurry).
Blinding of outcome assessment (detection bias) All outcomes	High risk	VAS scores, QoL and symptom recurrence (which informs assessment of pleurodesis efficacy) could be biased by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	LTFU clearly documented with reasons given.

Davies 2012 *(Continued)*

Selective reporting (reporting bias)	Low risk	All predefined endpoints reported.
Other bias	Low risk	No other biases identified.

Demmy 2012

Methods	Multicentre RCT comparing bedside talc pleurodesis and daily tunnelled catheter drainage for management of MPE (USA).
Participants	Inclusion criteria: symptomatic people with histo/cytologically confirmed malignancy and a previously untreated, unilateral pleural effusion requiring management; ECOG Performance Score 0–2. Exclusion criteria: active pleural infection; talc allergy; contraindications to talc use; trapped lung; survival < 60 days; severe comorbid medical conditions. 68 participants randomised.
Interventions	Talc pleurodesis group: 4–5 g sterile talc slurry in 100 mL saline infused into pleural space via > 24-Fr chest drain. Tube clamped for 2 hours. Drain removed when < 150 mL drainage/24 hours. IPC group: PleurX catheter inserted and drained daily (output volumes recorded). Removed when < 30 mL output on 3 consecutive days.
Outcomes	Primary: compare the proportion of maintained successful treatments 30 days after the intervention (success defined as being alive, no effusion recurrence, > 90% lung re-expansion after complete drainage and completion of the intervention by 2 weeks, i.e. drain removed or IPC functioning normally) Secondary: QoL; dyspnoea; patient satisfaction and acceptability; lung expansion; pleurodesis success; fluid drainage volume; days device in place; removal of device before death; survival
Notes	Pleurodesis success measured at 30 days according to CXR and need for repeat pleural intervention. People with known trapped lung excluded from trial entry. Included in network meta-analysis for pleurodesis failure, mortality and pain. Study funding source: supported, in part, by grants from the NCI (CA31946) to CALGB and to the CALGB Statistical Centre (CA33601). Study author conflicts of interest statements: individual authors disclosed they had no financial relationships.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Permuted block randomisation via a web-based randomisation service.
Allocation concealment (selection bias)	Low risk	Permuted block randomisation via a web-based randomisation service.
Blinding of participants and personnel (performance bias)	High risk	Due to nature of interventions, not possible to blind participants or personnel (IPC vs talc slurry).

Demmy 2012 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (personal communication): "Pleurodesis success was classified by an unblinded local investigator." Comment: QoL, symptom recurrence and patient satisfaction questionnaires may have been biased by lack of participant blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5 excluded from analysis in each arm, but justifications given. Some aspects unclear, e.g. trial follow-up period 60 days but range of days drainage device in place for IPC group was up to 286 days suggesting longer follow-up.
Selective reporting (reporting bias)	Low risk	All reported.
Other bias	Low risk	Target recruitment numbers not reached.

Diacon 2000

Methods	Prospective, single-centre RCT of thoracoscopic talc poudrage vs bedside bleomycin pleurodesis via a small-bore chest tube (Switzerland).
Participants	Inclusion criteria: documented MPE (all cell types); complete lung expansion on postdrainage CXR; improvement in symptoms after drainage; expected survival > 1 month; capable of undergoing medical thoracoscopy. Exclusion criteria: loculated effusion; previous drainage or previous pleurodesis; adverse reaction to the study medication; severe coagulation disorder. 36 participants randomised.
Interventions	Group 1: bedside pleurodesis via small-bore chest tube (outside diameter 2.7 mm) of bleomycin 60 IU. Tube unclamped after 2 hours and left on suction until removal ≥ 48 hours later. Group 2: thoracoscopy with induced pneumothorax under sedation. 5 g talc sprayed into pleural cavity under direct vision after drainage of effusion and disruption of adhesions. Drain kept under suction for ≥ 48 hours.
Outcomes	Recurrence of effusion (defined as a newly detected effusion needing drainage or occupying > 33% of the pleural space on CXR as compared with the first CXR after drain removal, or death from any cause) at 30 days, 90 days and 180 days Medication use Volume of fluid drained Duration of hospital stay Cost Symptom VAS scores (pain, shortness of breath, cough and general well-being)
Notes	People with trapped lung excluded from study enrolment. Included in network meta-analysis for pleurodesis failure, mortality, fever and pain. Study funding source: not stated. Study author conflicts of interest statements: not declared.

Diacon 2000 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence.
Allocation concealment (selection bias)	Low risk	Sequential sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants or personnel due to nature of interventions (talc poudrage vs bleomycin via chest tube).
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not stated if radiology was interpreted by a blinded physician. However, length of stay, VAS scores and symptom recurrence may be biased by lack of participant blinding. Mortality would not be affected by unblinded nature of the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 withdrawals in total, but a similar number in each group.
Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	Low risk	No external funding source.

Dresler 2005

Methods	Multicentre RCT comparing talc poudrage with talc slurry pleurodesis in MPE. Both groups received 4–5 g sterile talc intrapleurally (USA).
Participants	Inclusion criteria: history of malignancy (all tumour types), pleural effusion requiring sclerosis, ECOG performance status 0–2, life-expectancy > 2 months, ability to undergo GA. Exclusion criteria: pregnancy, previous intrapleural therapy or radiotherapy encompassing the entire hemithorax, changes in systemic therapy within 2 weeks, chylous or bilateral effusions requiring therapy. 501 participants randomised.
Interventions	Talc slurry group: talc administered as a slurry in 100 mL saline through a chest tube at bedside. Talc insufflation group: talc insufflated during thoracoscopy in operating theatre.
Outcomes	Primary outcome: percentage of participants whose lung initially re-expanded > 90% and who had a successful pleurodesis at 30 days after treatment (defined according to CXR criteria) Secondary outcomes: time to recurrence of effusion; frequency of complications and toxicities; ability to re-expand the lung as assessed by CXR; pain; patient satisfaction; QoL
Notes	People with trapped lung excluded from analysis. Included in network meta-analysis for pleurodesis failure, mortality, pain and fever.

Dresler 2005 *(Continued)*

Study funding source: not stated.

Study author conflicts of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation lists.
Allocation concealment (selection bias)	Low risk	Computer-generated randomisation lists.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind the study due to the nature of the interventions (talc poudrage vs talc slurry).
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not stated if radiological assessment was blinded. QoL and complications may be affected by lack of participant and personnel blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data accounted for and balanced between the treatment arms (10 in slurry group vs 9 in thoracoscopy group excluded as ineligible or participant withdrew consent; 33/163 slurry participants vs 25/177 thoracoscopy participants died within 30 days of randomisation).
Selective reporting (reporting bias)	Low risk	All outcomes reported on.
Other bias	Low risk	Trapped lung defined by different means in the 2 treatment arms, which may have affected their primary endpoint. However, this does not have an impact on the pleurodesis success rates.

Du 2013

Methods	Single-centre RCT of intrapleural cisplatin ± bevacizumab in MPE due to NSCLC (China).
Participants	Inclusion criteria: advanced NSCLC; large uni- or bilateral pleural effusion; positive pleural fluid cytology; no intrapleural therapy in previous month; KPS > 60; aged > 18 years; predicted survival > 3 months; no major organ dysfunction; no previous chemotherapy in previous 6 weeks. Exclusion criteria: squamous cell carcinoma; allergy to biological agents; no detectable lesions; uncontrolled central nervous system metastasis; pregnancy or breastfeeding; infected wound; refractory psychiatric illness. 72 participants randomised.
Interventions	Participants underwent pleural fluid drainage by thoracentesis. Treatment given intrapleurally. Rest for 2 hours. Then rotate every 15 minutes. Given every 2 weeks for 3 cycles. Cisplatin: cisplatin 30 mg intrapleurally. Cisplatin + bevacizumab: cisplatin 30 mg + bevacizumab 300 mg intrapleurally.
Outcomes	Treatment response (CR: accumulated fluid disappeared and stable for at least 4 weeks; PR: ≥ 50% of the accumulated fluid had disappeared, symptoms had improved and the remaining fluid had not in-

Du 2013 *(Continued)*

	creased for ≥ 4 weeks; remission not obvious: ≤ 50% of the accumulated fluid had disappeared; progression: accumulated fluid had increased). Treatment success defined as CR + PR. Progression-free survival Overall survival Adverse reactions QoL Pleural fluid VEGF levels
Notes	People with trapped lung eligible for trial involvement. Pleurodesis defined clinically and using radiology. Not included in network meta-analysis. Study funding source: supported by grants from the National Health Research Foundation (no. W2010BX055), the National Natural Science Foundation of China (no. 81000994), the Chinese Wu Jieping Medical Foundation (no. 320.6750.1083), the Beijing Municipal Science and Technology Commission (no. Z121107001012080) and the National Natural Science Outstanding Youth Foundation of China (no. 39825111). Study author conflicts of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods not stated and no response from study authors to clarify.
Allocation concealment (selection bias)	Unclear risk	Methods not stated and no response from study authors to clarify.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated if blinded and no response from study authors to clarify.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if anyone was blinded. If not blinded, QoL, performance status, adverse effects and symptom recurrence could be biased by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data accounted for. ITT analysis.
Selective reporting (reporting bias)	Low risk	All outcomes reported on.
Other bias	Low risk	No other biases identified.

Emad 1996

Methods	3-arm, single-centre RCT comparing intrapleural bleomycin, tetracycline and combination treatment for pleurodesis of MPE (Iran).
Participants	Inclusion criteria: histologically or cytologically confirmed, symptomatic MPE (all cell types). Exclusion criteria: none. 60 participants randomised.
Interventions	All participants had 28-Fr intercostal drain inserted into 6th intercostal space. Complete drainage of the effusion was confirmed on CXR. All participants given 10–15 mL 1% lignocaine intrapleurally. Tetracycline arm: tetracycline 20 mg/kg (maximum 2 g) in 50 mL saline given intrapleurally. 1 dose. Bleomycin arm: bleomycin 1 U/kg (maximum 60 units) in 50 mL saline given intrapleurally. 1 dose. Combination arm: tetracycline 20 mg/kg in 40 mL saline + bleomycin 1 U/kg in 50 mL saline, given intrapleurally, 1 after the other (tube clamped for 5 minutes between instillations). Drain clamped for 2 hours postinstillation with participant rotation. Suction connected after 24 hours. Drain removed when < 50 mL/8 hours drainage and complete lung expansion on CXR.
Outcomes	Pleurodesis success (defined as CR: no accumulation of effusion on CXR; PR: effusion recurred but did not require aspiration; or failure: participant required repeat thoracentesis for re-accumulation of the effusion) at 30 days (also at 60 days, 90 days and 6 months) Adverse effects
Notes	All participants in the study were receiving chemotherapy or tamoxifen, or both. People with trapped lung not excluded from participation in study. Participants who died prior to the analysed time point were excluded from analysis. Combination of clinical need for repeat intervention and radiological re-accumulation of effusion used to define pleurodesis failure. Included in network meta-analysis for pleurodesis failure, mortality and fever. Study funding source: not stated. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "…simple randomised manner." Comment: no further details given.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not stated explicitly and unable to contact authors. However, different volumes and regimens were used for the 3 groups.
Blinding of outcome assessment (detection bias)	High risk	Not stated if radiology reported blindly. Complication-reporting may have been affected by lack of participant blinding.

Emad 1996 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal data on baseline participant characteristics, but all outcome data reported and withdrawals justified. 6 participants died within 6 months of randomisation (2 in tetracycline arm, 1 in bleomycin arm and 3 in combination arm).
Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	Low risk	No other biases identified.

Evans 1993

Methods	Single-centre RCT of medical vs surgical pleurodesis with tetracycline (UK).
Participants	Inclusion criteria: cytology-confirmed MPE and histological or cytological evidence of metastatic breast cancer. Exclusion criteria: unsuitable for GA; aged > 75 years; severe non-metastatic lung disease; evidence of life-threatening metastatic disease at other sites. 34 participants randomised.
Interventions	Medical group: intercostal cannula inserted into mid-axillary line 7th/8th intercostal space and fluid aspirated. When drainage complete, tetracycline 500 mg in 100 mL normal saline inserted intrapleurally. Drain removed after 24 hours. Surgical group: under GA, bronchoscopy then thoracoscopy performed. 500 mL tetracycline in 100 mL saline inserted after fluid removed. Drain removed at 24 hours.
Outcomes	Fluid re-accumulation on CXR Need for repeat pleural aspirations Mortality
Notes	Pleurodesis failure defined as need for repeat aspiration. Trapped lung not accounted for. Not included in network meta-analysis. Study funding source: not stated. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given regarding randomisation.
Allocation concealment (selection bias)	Unclear risk	No details given regarding randomisation.
Blinding of participants and personnel (performance bias)	High risk	Unable to blind due to nature of the interventions (surgery vs chest tube).

Evans 1993 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	High risk	Need for repeat aspirations and other treatments given for cancer after pleurodesis may have been biased by lack of blinding of personnel and participants. Not stated if CXRs were reported by a blinded person.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons given for withdrawals (5/34 excluded (15%) – 3 never received the treatment, 1 was randomised in error, 1 participant's records were lost).
Selective reporting (reporting bias)	High risk	No data on safety or adverse effects.
Other bias	Low risk	No other biases identified.

Fentiman 1983

Methods	Single-centre RCT of talc poudrage and mustine (via chest tube) in people with breast cancer. All participants underwent VATS procedure under GA (UK).
Participants	Inclusion criteria: histologically confirmed breast cancer and radiologically verified pleural effusion. Exclusion criteria: no previous local treatment; non-malignant cause for the effusion. 46 participants randomised.
Interventions	Talc group: talc poudrage performed during VATS (dose of talc not stated), 2 chest drains in place for 5 days (with or without suction). Mustine group: after VATS and once lung fully re-expanded on CXR, mustine 15 mg solution instilled via intercostal drain. Clamped for 2 hours. Drain removed when drainage stopped.
Outcomes	Success of pleurodesis (defined by lack of re-accumulation of effusion on CXR) at 1 month Complications
Notes	If died prior to 1-month follow-up, excluded from analysis of pleurodesis success. Participants with trapped lung eligible for enrolment. Included in network meta-analysis for pleurodesis failure and mortality. Study funding source: not stated. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified for metastatic disease requiring treatment. Quote: "balanced randomisation."
Allocation concealment (selection bias)	Unclear risk	Not stated.

Fentiman 1983 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants or personnel due to nature of procedures.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated whether radiographic interpretation of CXRs were performed by a blinded person. Reporting of complications could be biased by lack of participant and personnel blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/23 non-evaluable in talc group; 6/23 non-evaluable in mustine group. All non-evaluable participants died prior to 1-month follow-up.
Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	High risk	Different number of intercostal drains in the 2 groups. Different duration of drainage for 2 groups.

Fentiman 1986

Methods	Single-centre RCT of intrapleural talc and tetracycline in MPE secondary to breast cancer (UK).
Participants	Inclusion criteria: histologically confirmed breast cancer and a symptomatic pleural effusion on radiology. Exclusion criteria: previous treatment for effusion, other than simple needle aspiration; non-malignant cause for effusion; unsuitable for GA; history of sensitivity to tetracycline. 41 participants randomised.
Interventions	Talc group: thoracoscopy, talc insufflated (dose not stated). Intercostal drain remained in situ for 5 days. Tetracycline group: thoracoscopy. Tetracycline 500 mg in 40 mL normal saline inserted 16–24 hours later via chest tube. Intercostal drain left in place for 3–5 days.
Outcomes	Pleurodesis success (defined by lack of re-accumulation on CXR) Complications Mortality
Notes	Pleurodesis success defined according to CXR only. Participants with trapped lung eligible for trial entry. Included in network meta-analysis of pleurodesis failure and mortality. Study funding source: not stated. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement

Fentiman 1986 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "randomised with stratification for metastatic disease."
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants or personnel due to the nature of the procedures.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated whether radiographic interpretation of CXRs were performed by a blinded person. Reporting of complications could be biased by lack of participant and personnel blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	Participants were excluded from the primary analysis if they died within first month. Higher proportion of deaths in the talc group (6/18 = 33%) compared to the tetracycline group (2/23 = 9%).
Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	Low risk	No other biases identified.

Gaafar 2014

Methods	Single-centre, prospective RCT comparing intrapleural administration of mistletoe preparation (viscum fraxini-2) with bleomycin in people with MPE (Egypt).
Participants	Inclusion criteria: histologically confirmed, recurrent, symptomatic MPE (all cell types); aged > 18 years; ECOG Performance Score ≤ 2; adequate bone marrow, liver and kidney function; written consent; ability to comply with the follow-up. Exclusion criteria: chronic air leak; known hypersensitivity to mistletoe (viscum); uncorrectable bleeding tendency; encysted pleural effusion; pregnancy/breastfeeding; currently active second malignancy; co-enrolment in another clinical trial; previous unsuccessful pleurodesis; pleural infection. 23 participants randomised.
Interventions	Participants underwent effusion drainage using a chest tube or needle drainage (depending on effusion size). Agent injected through the needle or chest tube. Mistletoe (viscum) group: 5 ampoules in 10 mL 5% glucose instilled intrapleurally. Bleomycin group: 60 units delivered intrapleurally.
Outcomes	Pleurodesis efficacy (assessed at 6 weeks) Toxicity (measured using NCI common terminology for adverse events)
Notes	People with trapped lung not excluded from participation. Pleurodesis defined using radiology and symptomatic effusion recurrence. Included in network meta-analysis for pleurodesis failure. Study funding source: not stated

Gaafar 2014 *(Continued)*

Study author conflicts of interest statements: no conflicts of interest to declare.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised." Comment: no other details given and no response from study authors.
Allocation concealment (selection bias)	Unclear risk	Quote: "randomised." Comment: no other details given and no response from study authors.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not stated explicitly but drugs were of different formulations.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if outcome assessment was blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	2 participants in mistletoe (viscum) arm excluded from analysis as treatment was discontinued due to an allergic reaction.
Selective reporting (reporting bias)	Low risk	Data available although minimal data on adverse effects.
Other bias	Low risk	No other risks of bias identified.

Goodman 2006

Methods	Single-centre RCT evaluating duration of chest tube drainage after talc slurry pleurodesis (UK).
Participants	Inclusion criteria: confirmed MPE requiring palliation of breathlessness due to the effusion (all cell types). Exclusion criteria: expected survival < 3 months; KPS < 40; previous unsuccessful pleurodesis; ipsilateral endobronchial obstruction; evidence of trapped lung. 41 participants randomised.
Interventions	All participants had 8- to 14-Fr intercostal drain inserted under USS guidance. 4 g talc slurry when effusion fully drained and trapped lung excluded on CXR. Group 1: drain removed after 24 hours. Group 2: drain removed at 72 hours. Drains removed regardless of fluid drainage.
Outcomes	Pleurodesis failure at 1 month (defined according to fluid recurrence requiring repeat aspiration) Length of hospital stay Mortality

Goodman 2006 *(Continued)*

Notes	People with trapped lung excluded from the study. Study did not complete recruitment numbers required by the power calculation. Participants who died in first month after randomisation excluded from the analysis. Not included in network meta-analysis. Study funding source: not stated. Study author conflicts of interest statements: no conflicts of interest for either author relating to this study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sealed envelopes in random blocks of 10.
Allocation concealment (selection bias)	Low risk	Sealed envelopes in random blocks of 10.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind due to nature of interventions (drain removal after 24 or 48 hours).
Blinding of outcome assessment (detection bias) All outcomes	High risk	Need for repeat pleural interventions, length of stay may be biased by lack of blinding. Mortality data not biased.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Deaths within the first month well matched between the 2 arms (3 participants in each arm). No other LTFU.
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported. Unpublished data on complications provided by the authors.
Other bias	Low risk	No other biases identified.

Groth 1991

Methods	RCT comparing intrapleural mitoxantrone with normal saline after thoracoscopy in people with MPE (Germany).
Participants	Inclusion criteria: complete resolution of the effusion after thoracoscopy; malignancy on pleural biopsy. Exclusion criteria: no chemotherapy within 4 weeks of pleurodesis. 103 participants randomised.
Interventions	All participants underwent thoracoscopy. After 24 hours, participants were randomised. Mitoxantrone arm: mitoxantrone 30 mg given intrapleurally. Control arm: isotonic saline instilled intrapleurally.

Groth 1991 *(Continued)*

	Drain clamped for 48 hours and if > 300 mL effusion after 48 hours, a second dose was given; if not, the drain was removed. If a second dose was given, the drain was removed 48 hours later.
Outcomes	Pleural fluid re-accumulation at 2 months (defined as a CR: complete disappearance of all pleural effusion; PR: half of the effusion or doubling of the time for thoracentesis; no change: the same volume of effusion; or progressive disease: uncontrollable effusion) Toxicity Remission duration Survival
Notes	Treatment response definitions unclear. People with trapped lung eligible for trial involvement. Included in network meta-analysis for pleurodesis failure and fever. Study funding source: not stated. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified.
Allocation concealment (selection bias)	Unclear risk	Not specified.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No mention of blinding or whether drugs were of similar appearances or volumes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated whether CXR interpretation was blinded to treatment allocation. Adverse effects and performance status reporting could be biased if participants and personnel were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	8/103 participants excluded from the analysis (7 died within 4 weeks of randomisation due to tumour progression; 1 LTFU).
Selective reporting (reporting bias)	Low risk	All reported.
Other bias	High risk	Ambiguous definitions of pleurodesis success.

Haddad 2004

Methods	Single-centre RCT comparing talc slurry and bleomycin pleurodesis (Brazil).
Participants	Inclusion criteria: documented recurrent symptomatic MPE (with positive cytology or confirmed metastatic disease elsewhere with no other cause found for the effusion); symptomatic relief by therapeutic aspiration; complete lung re-expansion after therapeutic aspiration.

Haddad 2004 *(Continued)*

	Exclusion criteria: previous unsuccessful pleurodesis; pleural infection; chronic air leak; KPS < 30%. 71 participants randomised.
Interventions	28- to 36-Fr chest tube inserted under local anaesthetic. Lung re-expansion confirmed prior to randomisation. Talc group: 4 g talc in 100 mL saline intrapleurally. Bleomycin group: bleomycin 60 units in 100 mL saline intrapleurally. After instillation, drain clamped for 4 hours, then put on suction for 24 hours. Drain removed when < 200 mL/24 hours drained.
Outcomes	Pleurodesis success (defined as no recurrence of effusion on clinical and radiological follow-up or patient symptom-free with small residual effusion not requiring thoracentesis) at 1 month, 3 months and 6 months Length of hospital stay Cost analysis Complications
Notes	People with trapped lung excluded from trial entry. Included in network meta-analysis for pleurodesis failure and mortality. Study funding source: not stated. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence.
Allocation concealment (selection bias)	Low risk	Computer randomisation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (personal communication with authors): "study not blinded."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (personal communication with authors): "study not blinded." Comment: not stated if radiology reported blindly but pleurodesis efficacy also based on symptom recurrence, so could be biased by lack of participant blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All reported.
Selective reporting (reporting bias)	Low risk	All outcomes reported and further clarification received from authors regarding complications and mortality.

Haddad 2004 *(Continued)*

Other bias	High risk	High levels of steroid use in participants, which may have affected pleurodesis success rates. Steroid use not well balanced between the treatment arms (4/37 in talc group, 8/34 in bleomycin group).

Hamed 1989

Methods	Prospective, single-centre RCT of bleomycin and talc in MPE secondary to breast cancer (UK).
Participants	Inclusion criteria: breast carcinoma with radiographically confirmed pleural effusion. Exclusion criteria: previous local treatment (apart from simple aspiration); evidence of a non-malignant cause for the effusion. 29 participants randomised.
Interventions	All participants had effusion drained to dryness under GA. Talc group: talc pleurodesis (dose and mode of administration not specified, but assumed to be poudrage from text). Bleomycin group: chest tube inserted. Bleomycin 1 mg/kg in 50 mL normal saline instilled after a CXR confirming lung re-expansion.
Outcomes	Success of pleurodesis (defined as continued absence of re-accumulation of pleural fluid on all follow-up radiographs)
Notes	Different modes of administration of talc and bleomycin. Contacted study authors for more information, but no reply. People with trapped lung eligible for study entry. Included in network meta-analysis for pleurodesis failure. Study funding source: not stated. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind due to the nature of the interventions (talc poudrage vs bleomycin).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated whether radiology reporting was blinded.

Hamed 1989 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	A number of participants not included in the primary analysis, but balanced numbers between the 2 treatment arms (4/13 in talc group vs 3/16 in bleomycin group).
Selective reporting (reporting bias)	Low risk	All reported.
Other bias	Low risk	No other biases identified.

Hillerdal 1986

Methods	Multicentre RCT of pleurodesis using *Corynebacterium parvum* vs bleomycin (Sweden).
Participants	Inclusion criteria: pleural effusion due to metastases from cytologically or histologically confirmed bronchogenic carcinoma or adenocarcinoma; ≥ 2 previous aspirations of effusion. 40 participants randomised.
Interventions	*C parvum* group: *C parvum* 7 mg in 10–20 mL saline intrapleurally. Bleomycin group: bleomycin 60 mg in 100 mL saline intrapleurally. A second dose of the allocated agent was given if the first was ineffective. No details given about method of drainage prior to instillation of pleurodesis agent or how long the drain remained in place.
Outcomes	Pleurodesis success (success: no recurrence of fluid within 6 weeks; partial success: 2 instillations required within 6 weeks, with no recurring effusion within 6 weeks of the second instillation)
Notes	People with trapped lung eligible for trial entry. For the purposes of this review, if participants required > 1 treatment due to effusion recurrence within 6 weeks, they were counted as a failure. Included in network meta-analysis for pleurodesis failure, fever and pain. Study funding source: not stated. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No specific mention of blinding but drugs reconstituted in different volumes.

Hillerdal 1986 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Definition of pleurodesis efficacy quite vague and not stated if blinded. Adverse effect reporting may have been influenced by lack of blinding of participants and personnel.
Incomplete outcome data (attrition bias) All outcomes	High risk	No data on mortality. Numbers did not add up for adverse effects data.
Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	Low risk	No other biases identified.

Hojski 2015

Methods	Single-centre RCT analysing release of growth factors in pleural fluid and blood following talc slurry and mechanical pleurodesis (Slovenia).
Participants	Inclusion criteria: breast carcinoma and cytologically confirmed MPE, lung re-expanded after thoracic drainage, eligible for surgery, ECOG Performance Score 0–2. Exclusion criteria: unfit for surgery under GA, trapped lung. 36 participants randomised.
Interventions	Chemical pleurodesis group: 40 mL 1% lidocaine 20–30 minutes prior to 5 g talc and 100 mL 0.9% saline slurry via chest drain. Drain clamped for 2 hours then placed on suction. Mechanical pleurodesis group: 2-port VATS with mechanical abrasion of parietal pleura. All participants received suction at –15 cmH_2O applied for 24 hours. Drains removed once < 200 mL/24 hour output and CXR favourable. Pleural fluid and blood samples were taken at baseline, 3 hours, 12 hours, 24 hours, 36 hours and 48 hours. Participants followed up for 12 months.
Outcomes	Primary outcome: analysis of growth factor release for 48 hours postpleurodesis Secondary outcomes: pleurodesis effectiveness, symptoms (VAS pain score at 0 hours, 12 hours, 24 hours and 48 hours), QoL (EORTC QLQ-C30) at 1 week pre-, 1 week and 1 month postpleurodesis
Notes	Trapped lung excluded. Pleurodesis success determined by CXR and pleural USS and by requirement for additional thoracentesis. Raw data only provided for number of participants requiring additional thoracentesis, which was used for network meta-analysis of pleurodesis success. Contacted authors by email for further information but no reply received. Included in network meta-analysis for pleurodesis failure. Study funding source: University Medical Centre Maribor, Ljubljanska 5, 2000 Maribor, Slovenia for full amount. Study author conflicts of interest statements: no conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement

Hojski 2015 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "Random numbers were assigned." Comment: method unclear.
Allocation concealment (selection bias)	Unclear risk	No information given.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded due to nature of interventions.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No comment on whether outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No comment on withdrawals or LTFU over trial period. 5 participants survived for ≥ 1, but mortality data for each trial arm not given. Results presented for all participants randomised.
Selective reporting (reporting bias)	Low risk	All outcome measures reported.
Other bias	High risk	Pleurodesis success and participant-reported outcomes measured as secondary endpoints, with small numbers of participants randomised to each arm. Radiological criteria for pleural effusion re-accumulation not given. Time point at which pleurodesis success measured not given.

Ibrahim 2015

Methods	Single-centre RCT comparing talc slurry pleurodesis and iodine for treatment of recurrent MPE (Egypt).
Participants	Inclusion criteria: clinical and histopathologically diagnosed recurrent MPE. Exclusion criteria: allergy to iodine, incompletely inflated lung on radiograph. 39 participants randomised.
Interventions	Therapeutic thoracentesis performed for all participants. After randomisation, all participants received a wide-bore chest drain 28- to 36-Fr, under local anaesthetic with free drainage of pleural fluid over 6–12 hours. Group 1: 5 g sterile talc in 50 mL 0.9% saline. Group 2: 20 mL 10% povidone-iodine mixed with 10 mL 1% lidocaine and 30 mL 0.9% saline. Drain clamped for 6 hours in both groups. Chest drains removed once < 100 mL fluid drained in 24 hours, with no air leak, and a CXR showed satisfactory lung expansion. Outpatient follow-up at 2 weeks, 2 months and 6 months.
Outcomes	Primary outcome: pleurodesis success, defined on CXR as CR: absence of pleural fluid re-accumulation; PR: residual pleural fluid or re-accumulation which did not require further drainage or remained asymptomatic; and failed: additional pleural procedures necessary Secondary outcomes: pain (assessed with a comparative pain scale into minor, moderate and severe), complications (fever, allergy and empyema)

Ibrahim 2015 *(Continued)*

Notes	Trapped lung excluded. Attempt to contact authors by email for further information – no reply received. Included in network meta-analysis for pleurodesis failure, chest pain, fever and mortality. For chest pain analyses, participants who experienced minor and moderate pain were included in the total (no participants from either arm experienced severe pain). Study funding source: not stated. Study author conflicts of interest statements: declared they have no competing interests.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "simple randomisation with allocation concealment." Comment: no clear description of method used for randomisation.
Allocation concealment (selection bias)	Unclear risk	Quote: "simple randomisation with allocation concealment." Comment: no further information given regarding measures taken.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded trial.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded trial. Outcome assessment could be affected by knowledge of intervention.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Mortality and withdrawals not commented upon, but results reported for all participants randomised.
Selective reporting (reporting bias)	High risk	Participants were followed up at 2 weeks, 2 months and 6 months, but the time point at which data for pleurodesis success were measured was unclear. Unclear if all participants were followed to 6 months.
Other bias	Low risk	Participants receiving talc pleurodesis did not receive lidocaine, which may affect chest pain scores. The time point at which participants were asked to rate their pain was unclear.

Ishida 2006

Methods	Single-centre RCT of intrapleural cisplatin vs OK-432 vs combination (Japan).
Participants	Inclusion criteria: symptomatic, histocytologically confirmed pleural malignancy secondary to NSCLC, ECOG Performance Score 0–3, adequate renal, haematological and cardiac function. Exclusion criteria: previous intrapleural therapy, trapped lung or atelectasis after chest tube inserted. 49 participants randomised.

Ishida 2006 *(Continued)*

Interventions	All participants underwent pleural fluid drainage via a 20-Fr chest tube. After administration of the allocated treatment, chest drain was clamped for 6 hours and then connected to 20 cmH_2O suction. Drain removed when < 100 mL/day. Cisplatin group: cisplatin 50 mg via chest tube on day 1 and 4. OK-432 group: 1 dose of OK-432 5 KE via chest tube. Combination group: 50 mg cisplatin on day 1 and 4, followed by OK-432 5 KE on day 7.
Outcomes	Effusion recurrence (as defined by a newly detected effusion needing drainage or occupying > 33% of pleural space on CXR); mortality; adverse events
Notes	People with trapped lung excluded from study. Study authors contacted for further information, but no response. Not included in network meta-analysis. Study funding source: not stated. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No mention of blinding but participants received different dosing regimens depending on study arm.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Adverse event reporting could be affected by knowledge of treatment allocation. Not stated whether CXR interpretation was performed using a blinded method for definition of pleurodesis efficacy.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of deaths clearly stated. If participants died, still included in analysis for pleurodesis success prior to death.
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.
Other bias	High risk	Drain left in for different durations in the 3 groups. Steroids were given to participants who received cisplatin.

Kasahara 2006

Methods	Multicentre phase II trial of OK-432, evaluating 2 different doses of intrapleural OK-432 (Japan).

Kasahara 2006 *(Continued)*

Participants	Inclusion criteria: histological or cytological proof of MPE with NSCLC; no previous therapy for MPE; aged > 20 years; ECOG Performance Score 0–3; life-expectancy > 12 weeks; adequate organ and bone marrow function; daily chest tube drainage < 200 mL. Exclusion criteria: previous tuberculosis pleuritis; unstable heart disease or diabetes; active double cancer; pregnancy; lactation; allergy to OK-432 or benzylpenicillin. 38 participants randomised.
Interventions	All participants underwent chest tube drainage. 2 doses of OK-432 given (on days 1 and 3). Group A: intrapleural OK-432 at dose of 10 KE in 100 mL saline. Group B: intrapleural OK-432 at dose of 1 KE in 100 mL saline.
Outcomes	MPE control on day 28 (defined as a CR: effusion disappeared completely and no further treatment required; PR: effusion persisted but local treatment not needed; or no change: further local treatment needed or the residual effusion volume > 100 mL) MPE control rate Duration of drainage Fluid volume drained Time to progression Drug adverse events Overall survival
Notes	People with trapped lung included in study. For purposes of this review, CR and PR were counted as pleurodesis successes. Not included in network meta-analysis. Study funding source: not stated. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated whether blinded. Drugs diluted in same volume in both study groups.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Need for repeat intervention and adverse effects could be biased if participants and personnel unblinded, but not stated if this was the case.
Incomplete outcome data (attrition bias)	Low risk	No LTFU.

Kasahara 2006 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	High risk	In group B, if low dose ineffective, participants given a high dose of OK-432 anyway (prior to measurement of primary outcome). Paper did not state whether participants were symptomatic from MPE at enrolment.

Keeratichananont 2015

Methods	Single-centre RCT to determine efficacy and safety of autologous blood pleurodesis compared with tetracycline for MPE (Thailand).
Participants	Inclusion criteria: aged > 18 years, symptomatic MPE (histocytologically confirmed), life-expectancy > 3 months, agreement to receive chemical pleurodesis. Exclusion criteria: active pleural or systemic infection, haemodynamic instability, haemothorax, serum haematocrit < 25%, chylothorax, combined causes of pleural effusion, history of tetracycline or lidocaine allergy, CXR showing trapped lung after chest tube drainage, pregnancy. 48 participants randomised.
Interventions	Participants received either 8- to 10-Fr small-bore drain or 20- to 32-Fr large-bore drain. Pleural fluid drained until < 100 mL/24 hour and CXR showed full lung expansion. The autologous blood group received 100 mL autologous venous blood instilled via the chest drain without intrapleural lidocaine, followed by 50 mL 0.9% saline. The tetracycline group received 20 mL 1% lidocaine, made up to 50 mL with 0.9% saline, instilled via the chest drain, followed by tetracycline 1 g diluted in 100 mL 0.9% saline. The chest drain was clamped for 2 hours, then placed on –20 cmH_2O pressure suction. Chest drains removed once draining < 150 mL/24 hours with full lung re-expansion on. CXR. Non-response to autologous blood pleurodesis were treated with tetracycline pleurodesis. Non-response to tetracycline was treated with other sclerosants such as iodine or talc.
Outcomes	Primary outcome: pleurodesis efficacy at 30 days assessed as CR: no pleural effusion; PR: minimal pleural fluid without need for repeat thoracentesis or drainage; no response: massive effusion or need for repeat thoracentesis or pleurodesis). CR and PR defined as success Secondary outcomes: length of stay, complications, pleurodesis-related pain (numerical rating scale 0–10)
Notes	Trapped lung excluded. Of 4 participants who had 'no response' to autologous blood pleurodesis, 2 underwent repeat pleurodesis with tetracycline, with success in 1 participant. Included in network meta-analysis for pleurodesis failure, fever and chest pain (those who required additional IV analgesia). Unable to include in network for mortality as 0 events in both study arms which caused computational problems. Authors contacted by email for further information, no reply received. Study funding source: Thoracic Society of Thailand for Clinical Fellowship Research Award 2013. Study author conflicts of interest statements: no conflicts of interest to declare.

Risk of bias

Keeratichananont 2015 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation.
Allocation concealment (selection bias)	Unclear risk	No information given. The authors were contacted by email to seek further information but no reply was received.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information regarding blinding of participants or clinicians was given. Contacted authors for further information but no reply received.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given. Contacted authors for further information but no reply received.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No data given on withdrawals, LTFU or mortality, but results reported for all participants randomised.
Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	Low risk	Treatment groups were broadly similar; however, 17 of the tetracycline group received chemotherapy within 2 weeks of pleurodesis compared with 9 in the autologous blood group.

Keeratichananont 2018

Methods	Single-centre RCT comparing the efficacy of autologous blood and talc for pleurodesis (Thailand).
Participants	Inclusion criteria: aged > 18 years, recurrent symptomatic MPE (cytologically or histologically confirmed), predicted life-expectancy > 1 month (ECOG Performance Score 0–2 and without severe comorbidity), who agreed to receive chemical pleurodesis. Exclusion criteria: active pleural or systemic infection, serum haematocrit < 25% or haemodynamic instability, haemothorax, chylothorax or pleural effusion or multiple aetiology, history of previous chemical pleurodesis, allergy to talc or lidocaine, CXR after chest tube drainage showing a trapped lung on the affected side, pregnancy. 123 participants randomised.
Interventions	A small-bore 8- to 10-Fr or wide-bore 20- to 32-Fr drain was inserted. Drainage until < 150 mL/day and CXR. Autologous blood pleurodesis group: 100 mL autologous peripheral venous blood instilled via drain, without intrapleural lidocaine, followed by 50 mL 0.9% saline. Drain clamped for 2 hours. Talc slurry group: 20 mL 1% lidocaine made up to 50 mL with 0.9% saline, followed by 4 g sterile graded talc in 100 mL 0.9% saline instilled over 5–10 minutes. Drain clamped for 2 hours. All participants then had –20 cmH_2O suction applied. When drainage < 150 mL within 8 hours of thoracic suction CXR was repeated and drain removed after full lung re-expansion.

Keeratichananont 2018 *(Continued)*

	In cases of non-response to autologous blood pleurodesis, repeat pleurodesis with talc was administered. For non-response to talc pleurodesis, another sclerosing agent (except autologous blood) was offered.
Outcomes	Primary outcome: pleurodesis effectiveness at 30 days, defined as CR: no re-accumulation on CXR; PR: recurrence of small volume effusion, not requiring repeat drainage; and no response: recurrence of effusion requiring repeat drainage). CR and PR were considered successful. Secondary outcomes: length of stay, postpleurodesis hospital stay, pleurodesis-related complications, cardiopulmonary adverse events, fever, pleurodesis-related pain (measured on a 0–10 scale).
Notes	Trapped lung excluded. Included in network meta-analysis for pleurodesis failure, mortality, fever and pain. Participants included in the chest pain analysis were those requiring additional IV opioid analgesia. Study funding source: no specific grants or funding received. Study author conflicts of interest statements: no conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Web-based central randomisation system.
Allocation concealment (selection bias)	Low risk	Web-based central randomisation system.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and clinicians unblinded to treatment allocation. However, pleurodesis success assessed against objective criteria by blinded chest physicians, therefore lack of blinding not likely to influence primary outcome.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded assessment of pleurodesis effectiveness by chest physician.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 LTFU from each study arm – reasons stated for all (all due to chemotherapy-related adverse events). 3 deaths from the blood pleurodesis arm and 4 from the talc pleurodesis arm. LTFU and death not included in primary analysis.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	None identified.

Kefford 1980

Methods	Single-centre RCT of intrapleural adriamycin, nitrogen mustard and rolitetracycline (Australia).
Participants	Histocytologically confirmed malignant effusions (pleural or pericardial or peritoneal); no previous intracavitary chemotherapy; no concurrent radiotherapy or systemic treatment.

Kefford 1980 *(Continued)*

	38 participants reported as being randomised in total (26 of whom had MPE). However, the discussion referred to 90 participants being randomised originally.
Interventions	All participants had a needle thoracentesis to dryness. The drug was diluted in 20 mL saline and injected through needle as a bolus. Adriamycin group: adriamycin 30 mg intrapleurally. Nitrogen mustard group: nitrogen mustard 20 mg intrapleurally. Rolitetracycline group: rolitetracycline 500 mg intrapleurally.
Outcomes	Pleurodesis success at 8 weeks (defined as CR: absence of significant effusion on CXR; PR: reduction in frequency of aspiration with improvement in exercise tolerance and CXR; or no response) Complications
Notes	People with trapped lung eligible for the trial. For the purposes of this review, only data on participants with pleural effusions included in our analysis and only CR counted as a pleurodesis success. Included in network meta-analysis for pleurodesis failure. Study funding source: not stated. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No mention of whether anyone was blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if CXR interpretation was done blind to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "More than half of the original 90 patients randomised were ineligible for assessment because of subsequent systemic therapy … or … early death." Comment: although in the results, it stated 38 participants were randomised.
Selective reporting (reporting bias)	Low risk	Only a brief report and adverse effects data for the pleural and peritoneal effusions combined. However, generally all predefined outcomes reported.
Other bias	Unclear risk	6 participants received > 1 of the treatments, but not clear whether rerandomised separately each time.

Kessinger 1987

Methods	Single-centre RCT comparing intrapleural bleomycin and tetracycline in MPE (USA).
Participants	Inclusion criteria: histologically confirmed malignancy; symptomatic pleural effusion with either > 3 g/dL protein or malignant cells on cytology. Exclusion criteria: allergy to either study drug. 42 procedures randomised in 34 participants.
Interventions	All participants underwent chest tube drainage. Tetracycline group: tetracycline 500 mg in 50 mL saline intrapleurally. 1 dose. Bleomycin group: bleomycin 89 units in 50 mL saline intrapleurally. 1 dose. For both arms, drain clamped for 8 hours after instillation and participant moved positions. Thereafter, tube opened and suction applied. Drain removed when < 40 mL/24 hours drained (or on day 7 if ongoing high output).
Outcomes	Treatment response at 1 month (CR: no re-accumulation of the effusion; PR: asymptomatic re-accumulation of the effusion developed that was < 50% of its original volume; and no response) Adverse effects Length of time chest tube in place following pleurodesis
Notes	Bilateral disease included. Some participants randomised to the trial more than once. People with trapped lung eligible for trial entry. Included in network meta-analysis for pleurodesis failure, fever and pain. Study funding source: not stated. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "toss of coin."
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No mention of blinding. Both drugs administered in 50 mL saline.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated. No mention of whether CXR interpretation was performed by a blinded individual.
Incomplete outcome data (attrition bias) All outcomes	High risk	11/34 (32%) participants non-evaluable for pleurodesis outcome (3 in bleomycin group and 8 in tetracycline group).

Kessinger 1987 *(Continued)*

Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	High risk	Unclear whether participants who were given both agents because the first agent failed were included in the analysis.

Koldsland 1993

Methods	Single-centre, prospective RCT of mepacrine vs bleomycin as pleurodesis agent in MPE (Norway).
Participants	Inclusion criteria: MPE; previous treatment with a therapeutic tap; life-expectancy > 1 month. Exclusion criteria: previous pleurodesis; renal failure; participant requiring continuous oxygen. 40 participants randomised.
Interventions	28-Fr or 32-Fr chest tube inserted under local anaesthetic. Suction applied until fluid production about 100 mL/day and no effusion on CXR. Tube clamped and sclerosing agent injected. Participant rotation for 2 hours after instillation. Drain removed when < 100 mL/day output. Mepacrine group: mepacrine 800 mg in 20 mL saline. Bleomycin group: bleomycin 60 mg in 100 mL saline.
Outcomes	Pleurodesis success (classified as no re-accumulation, small amounts of fluid re-accumulation with no or mild symptoms, re-accumulation of fluid with severe dyspnoea needing thoracentesis) Median survival Adverse effects
Notes	People with trapped lung not excluded from trial entry. For purposes of this review, participants with no re-accumulation or small amount of re-accumulation with no or mild symptoms were counted as pleurodesis successes. Included in network meta-analysis for pleurodesis failure, fever and pain. Study funding source: not stated. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised using sealed envelopes.
Allocation concealment (selection bias)	Low risk	Sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not stated specifically but drugs reconstituted in different volumes.

Koldsland 1993 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Participant reporting of symptoms may be affected by lack of blinding. Not stated whether CXR interpretation was blind to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	High mortality in first 3 months, therefore data only analysed at month 1.
Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	Low risk	No other biases identified.

Kuzdzal 2003

Methods	Single-centre, prospective RCT of talc vs doxycycline in the control of MPE (Poland).
Participants	Inclusion criteria: pleural effusion with clinical suspicion of malignant origin. Exclusion criteria: failure to confirm malignancy by pleural biopsy; mesothelioma; failure to achieve full re-expansion of the lungs. 33 participants randomised.
Interventions	All participants all VATS under GA and pleural biopsy. First dose of sclerosant given at end of procedure. Tube removed when full re-expansion, no air leak and < 150 mL/day drainage. Rotation after procedure. Talc: single 10 g dose intrapleurally by insufflation. Doxycycline: 500 mg in 25 mL solution given intrapleurally. Up to 3 doses (if daily drainage > 150 mL/day).
Outcomes	'Long-term' and 'short-term' pleurodesis outcome (defined by need for repeat thoracentesis as excellent: no fluid re-accumulation; good: limited residual fluid, not increasing, no indications for thoracentesis; or poor: fluid re-accumulation requiring thoracentesis Complications
Notes	For purposes of this review, 'Excellent' and 'Good' pleurodesis outcomes included as pleurodesis successes for analysis. Study authors emailed for further information, but no response. Included in network meta-analysis for pleurodesis failure. Study funding source: not stated. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.

Kuzdzal 2003 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unable to blind due to the nature of the interventions, although not stated explicitly.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Pleurodesis efficacy defined by symptom recurrence and hence could be biased by lack of blinding. Not stated whether assessment of fluid re-accumulation was performed by a blinded individual.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of participants randomised not clear from paper.
Selective reporting (reporting bias)	High risk	Treatment complications and survival not reported.
Other bias	High risk	Number of doses for the 2 arms, therefore potential for confounding.

Leahy 1985

Methods	RCT (2 recruiting centres) of intrapleural *Corynebacterium parvum* and tetracycline for pleurodesis of MPE (UK).
Participants	Inclusion criteria: histologically or cytologically confirmed MPE. Exclusion criteria: participants on chemotherapy; participants receiving treatment with steroids. 36 participants randomised.
Interventions	Effusion aspirated to dryness prior to administering study agent. After agent instilled, the participants moved from side to side for 6 hours. If the participant had symptomatic recurrence of the effusion within 1 month, the allocated treatment was repeated. Tetracycline group: tetracycline 500 mg in 20 mL saline given intrapleurally via an intercostal tube at 1 centre and with needle drainage at the other centre. *C parvum* group: *C parvum* 7 mg in 20 mL saline intrapleurally through a needle, after the effusion was drained to dryness.
Outcomes	Symptomatic recurrence of pleural effusion 1 month after the last dose Adverse effects (pain, fever, nausea and vomiting, and rash)
Notes	People with trapped lung eligible for trial entry. Adverse effects were reported per procedure rather than per participant. For this review, if participants had a successful pleurodesis after the second dose of study agent, these were included in the analysis as a success. For the tetracycline group, the results from the 2 administration methods were combined for the purposes of analysis. Included in network meta-analysis for pleurodesis failure, fever, pain and mortality. Study funding source: not stated.

Leahy 1985 *(Continued)*

Study author conflicts of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer randomisation.
Allocation concealment (selection bias)	Low risk	Computer randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not mentioned in the paper. Both drugs reconstituted in 20 mL saline.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	If study was unblinded, reporting of adverse effects, symptomatic pleural fluid re-accumulation could be biased.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants excluded from analysis if died prior to 1 month, but the numbers were small and fairly well balanced between the groups (1/17 in *C parvum* group vs 3/19 in tetracycline group, i.e. 11% LTFU in total).
Selective reporting (reporting bias)	Low risk	Thorough reporting of toxicity.
Other bias	Low risk	No other biases identified.

Loutsidis 1994

Methods	Single-centre RCT of tetracycline and mechlorethamine (mustine) for pleurodesis of MPEs (Greece).
Participants	Inclusion criteria: documented MPE (all tumour types); respiratory distress was the main problem of participants. Exclusion criteria: other therapy given simultaneously (chemotherapy or radiotherapy). 40 participants randomised.
Interventions	All participants had a 32-Fr intercostal drain inserted with local anaesthetic and effusion drained overnight. Complete drainage confirmed on CXR. After pleurodesis, drain flushed with 20 mL saline. Participants rotated and drain unclamped after 2 hours and put onto –20 cmH_2O suction. Drain removed when < 50 mL/day drainage. Tetracycline group: tetracycline 500 mg in 20 mL 2% lignocaine intrapleurally. 1 dose. Mechlorethamine group: mechlorethamine 0.2 mg/kg in 20 mL saline intrapleurally. 1 dose.
Outcomes	Response to therapy at 60 days (CR: complete lack of re-accumulation of pleural fluid for ≥ 60 days; PR: small pleural effusion, asymptomatic, not requiring further treatment; failure: all other cases) Adverse effects
Notes	Minimal data provided on baseline participant characteristics of the 2 groups.

Loutsidis 1994 *(Continued)*

	Pleurodesis defined according to symptomatic effusion recurrence. For the purposes of this review, CR and PR included as a successful pleurodesis. People with trapped lung included in the study. Included in network meta-analysis for pleurodesis failure. Study funding source: not stated. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No mention of blinding in the paper. Drugs given in the same volume but not stated whether their appearances were similar.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if CXR interpretation was blinded for assessment of pleurodesis efficacy.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants followed up until the primary endpoint at 60 days.
Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	Low risk	No other biases identified.

Luh 1992

Methods	Single-centre RCT of OK-432 and mitomycin C pleurodesis in people with lung cancer with MPE (Taiwan).
Participants	Inclusion criteria: histology/cytology confirmed MPE due to lung cancer; effusion requiring repeated thoracentesis; ECOG performance score 0–3. Exclusion criteria: previous anticancer chemotherapy within 4 weeks; previous radiotherapy to the ipsilateral chest within 4 weeks; concomitant systemic chemo or radiotherapy; history or evidence of penicillin allergy. 55 participants randomised.
Interventions	All participants hospitalised and a chest drain or pigtail catheter inserted into effusion. Drainage until < 200 mL/day. Tube clamped for 1 hour after drug administration. Drug administration repeated weekly for 4 weeks or until effusion resolved.

Luh 1992 *(Continued)*

	OK-432 group: OK-432 1 KE intrapleurally. Mitomycin C: mitomycin C 8 mg in 30 mL water intrapleurally.
Outcomes	Pleurodesis success at 4 weeks (defined as CR: no fluid accumulation and participants free of symptoms; PR: recurrence of effusion < 50% of original effusion volume, not symptomatic and no need for thoracentesis for symptom relief; or failure: recurrence of effusion > 50% of the original volume, symptomatic and need for thoracentesis to relieve symptoms) Survival Effusion-free period
Notes	People with trapped lung included in the study. For this review, PR and CR counted as pleurodesis successes. Not included in network meta-analysis. Study funding source: not stated. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sealed envelopes.
Allocation concealment (selection bias)	Low risk	Sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No mention of whether the study was blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants excluded due to early death, both in OK-432 group.
Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	Low risk	No other biases identified.

Lynch 1996

Methods	RCT of bleomycin, tetracycline and talc for pleurodesis of MPE.
Participants	Inclusion criteria: MPE (either cytology positive or an exudative effusion attributed to a histologically confirmed malignancy elsewhere) (all cell types); life-expectancy > 2 months.

Lynch 1996 *(Continued)*

	Exclusion criteria: contraindication to placement of a chest tube; allergy to bleomycin, talc or tetracycline. 50 participants randomised.
Interventions	Chest tube placed using blunt dissection and allowed to drain for ≥ 24 hours until < 150 mL/day output. Sclerosing agent instilled intrapleurally. Participants repositioned every 7 minutes after agent instilled. Then, tube unclamped and suction applied, until < 150 mL/24 hours drainage when the drain was removed. If the drainage remained high, a second instillation was attempted. Bleomycin group: bleomycin 60 units in 50 mL 5% dextrose. Tetracycline group: tetracycline 750 mg in 100 mL saline, with lidocaine 100 mg. Talc group: 5 g talc in 250 mL saline, with lidocaine 100 mg.
Outcomes	Success of sclerosis at 30 days (defined as a lack of significant re-accumulation on CXR with control of symptoms due to the effusion) Survival Median length of hospitalisation from date of sclerosis to discharge Adverse effects
Notes	Participants who died within 30 days of the sclerosis were included as treatment failures in the study. Small difference in median age and cell types between the treatment arms. Trapped lung not accounted for. Included in network meta-analysis for pleurodesis failure, fever and pain. Study funding source: partially supported by grants CA-06516 and CA-19589 awarded by the NCI, NIH and DHHS. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number generator.
Allocation concealment (selection bias)	Low risk	Random number generator.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not stated explicitly if the study was blinded, but the different drugs were given as different volumes.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Symptom and adverse effect reporting would be affected by lack of blinding. Not stated if CXR interpretation was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/50 (8%) LTFU for primary outcome but balanced between the treatment arms.

Lynch 1996 *(Continued)*

Selective reporting (reporting bias)	Low risk	All reported.
Other bias	Low risk	No other biases identified.

Mager 2002

Methods	Single-centre RCT evaluating the distribution of talc during a talc slurry pleurodesis – comparing rotation with non-rotation of participants after instillation of talc slurry (the Netherlands).
Participants	Inclusion criteria: symptomatic MPE confirmed by cytology or histology (all cell types). Exclusion criteria: haemorrhagic disease; trapped lung; previous pleurodesis on ipsilateral side; other disease which would interfere with the study; participants on systemic treatment or expected to be within 4 weeks of pleurodesis; expected survival < 1 month. 20 participants randomised.
Interventions	Chest drain inserted and pleurodesis performed when drainage < 150 mL/24 hours and lung fully re-expanded. Talc suspension was radiolabelled. Dynamic scintigraphy performed during, immediately after and 1 hour after instillation. Rotation arm: sequence of 4 positions changing every 10 minutes after instillation of talc for 1 hour. Non-rotation arm: strict bed rest in supine position after instillation. Tube removed when < 100 mL/24 hour fluid drained.
Outcomes	Distribution of talc in the thoracic cavity, measured on scintigram immediately after instillation of talc and after 1 hour Success rate of pleurodesis (defined on CXR) at 4 weeks
Notes	People with trapped lung excluded. Not included in network meta-analysis. Study funding source: not stated. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sealed envelopes (10 allocating participant to rotation and 10 to non-rotation).
Allocation concealment (selection bias)	Low risk	Sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unable to blind due to the nature of the interventions.
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated if CXR reporting was performed by a blinded individual.

Mager 2002 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Small numbers but no LTFU. Minimal data on baseline participant characteristics.
Selective reporting (reporting bias)	Low risk	No serious adverse effects. Some discomfort in rotation group (not quantified). All study participants alive at 1 months' follow-up (personal communication).
Other bias	Low risk	CXR only used to define pleurodesis. Small numbers in study.

Martinez-Moragon 1997

Methods	Single-centre RCT of tetracycline vs bleomycin pleurodesis in MPE (Spain).
Participants	Inclusion criteria: MPE (all cell types) causing respiratory symptoms, confirmed by cytological examination or pleural biopsy and an expected survival ≥ 1 month, with a KPS ≥ 50. Exclusion criteria: prior intrapleural instillation therapy; CXR during the preceding 2 weeks; previously received systemic bleomycin; trapped lung; allergy to study drugs. 70 participants randomised.
Interventions	All participants underwent tube thoracostomy with suction drainage until < 100 mL/day output. Tetracycline group: tetracycline 1.5 g in 100 mL saline intrapleurally, with 9 mL 5% lignocaine. Bleomycin group: bleomycin 60 mg in 100 mL saline intrapleurally. Tube clamped for 4 hours after instillation, then suction drainage. Drain removed when < 100–150 mL/day output.
Outcomes	Response to pleurodesis (defined as CR: no clinical or radiological recurrence of effusion; PR: small amount of fluid re-accumulation on CXR but no symptoms; failure: re-accumulation of fluid causing symptoms or needing thoracentesis) Adverse effects of procedure
Notes	People with trapped lung excluded from trial entry. For this review, CR and PR included as pleurodesis successes. Included in network meta-analysis for pleurodesis failure, fever and pain. Study funding source: not stated. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer randomisation.
Allocation concealment (selection bias)	Low risk	Computer randomisation.

Martinez-Moragon 1997 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No mention of blinding in the paper. Agents given in the same volume but no comment on whether appearances were similar.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if CXR interpretation was blinded. Other symptom and adverse effect outcomes could be biased if participants and personnel not blind to treatment allocation, but not stated if this was the case.
Incomplete outcome data (attrition bias) All outcomes	Low risk	8/70 (11%) participants excluded from analysis due to death (5) or LTFU (3).
Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	Low risk	No other biases identified.

Maskell 2004

Methods	Single-centre RCT comparing pleurodesis using mixed particle Talc (> 50% of particles are < 20 µm) vs graded talc (< 50% of particles are < 20 µm) (UK).
Participants	Inclusion criteria: symptomatic pleural effusion, confirmed to be malignant by cytology or pleural biopsy (all cell types). Exclusion criteria: expected survival < 6 weeks; bleeding diathesis contraindicating intercostal drain insertion; extensive trapped lung; previous ipsilateral pleurodesis; aged < 18 years; inability to give informed consent. 48 participants randomised.
Interventions	12-Fr intercostal drain inserted. Drainage until < 150 mL/day output. Agent instilled and left in for 2 hours, before suction being applied. Drain removed after 48 hours. Mixed particle talc group: > 50% of talc particles are < 20 µm. Single 4 g intrapleural dose. Graded talc group: < 50% of talc particles are < 20 µm. Single 4 g intrapleural dose.
Outcomes	Change in alveolar–arterial gradient 48 hours postpleurodesis breathing air Change in partial pressure of oxygen at 48 hours postpleurodesis Clinical efficacy of pleurodesis at 3 months Presence/absence of fever at 48 hours Change in C-reactive protein Change in interleukin-8
Notes	People with trapped lung excluded. Pleurodesis success defined as no re-accumulation of pleural fluid sufficient to require drainage. Paper presented 2 trials and only trial 2 was relevant to this review (trial 1 was RCT of mixed talc vs tetracycline, but pleurodesis success data were not collected). Not included in network meta-analysis.

Maskell 2004 *(Continued)*

Study funding source: supported partly by a Medical Research Council grant (G9721289) covering NAMs salary and partly through internal funds.

Study author conflicts of interest statements: no authors have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Presealed numbered, opaque, sealed envelopes with stratification.
Allocation concealment (selection bias)	Low risk	Presealed numbered, opaque, sealed envelopes with stratification.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (personal communication with authors): "investigators and patients blind to treatment allocation."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (personal communication with authors): "investigators and patients blind to treatment allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data justified and balanced between the 2 groups (3 participants LTFU).
Selective reporting (reporting bias)	Unclear risk	Study comprised 2 sections and pleurodesis success only reported for the particle size section. The RCT of talc/tetracycline did not report pleurodesis success, but this was not 1 of the predefined outcome measures.
Other bias	Low risk	No other biases identified.

Masuno 1991

Methods	Multicentre RCT of LC9018 + doxorubicin vs doxorubicin alone in MPE secondary to lung cancer (Japan). LC9018 is a biological response modifier prepared from heat-killed, freeze-dried *Lactobacillus casei* YIT 9018.
Participants	Inclusion criteria: positive histology for primary lung cancer; unilateral pleural effusion; expected survival > 8 weeks; no treatment within 4 weeks; performance score 0–3; no concurrent cancer; no severe hepatic/renal/bone marrow failure; aged ≤ 75 years. Exclusion criteria: previous intrapleural treatment with a biological response modifier; pregnant women and women of child-bearing potential; history of allergy. 95 participants randomised.
Interventions	Effusion completely drained. Both treatment arms received ≤ 2 intrapleural doses, 1 week apart. Control group: doxorubicin 40 mg in 20–50 mL saline. LC9018 group: as control group, then LC9018 0.2 mg in 20–50 mL saline.

Masuno 1991 *(Continued)*

Outcomes	Efficacy of effusion control at 4 weeks (defined as CR: negative cytological findings with no re-accumulation of fluid; PR: negative cytological findings with asymptomatic minimal fluid accumulation, not requiring additional aspiration; or failure: detectable intrapleural fluid even after tube drainage with no improvement or exacerbation on radiology compared with before treatment, or failure to confirm conversion to negative cytology) Adverse effects Change in performance status
Notes	People with trapped lung excluded postrandomisation. For this review, CR and PR counted as pleurodesis success. Not included in network meta-analysis. Note: doxorubicin is the generic name for adriamycin. Study funding source: not stated. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central telephone randomisation system.
Allocation concealment (selection bias)	Low risk	Central telephone randomisation system.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not clear.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Blinded committee assessed data regarding safety and efficacy."
Incomplete outcome data (attrition bias) All outcomes	High risk	19/95 participants excluded from final analysis, for a variety of reasons, including 5 participants with protocol violations.
Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	Unclear risk	Primary outcome measure included CXR resolution and conversion to cytology negative effusion. Not clear from methodology whether some participants who were asymptomatic had effusion drained to evaluate cytology status and were then classified as 'failures.'

Mejer 1977

Methods	Single-centre RCT of mepacrine hydrochloride, triethylenethiophosphoramide and pleurocentesis alone in the treatment of MPE (Denmark).

Mejer 1977 *(Continued)*

Participants	Inclusion criteria: unilateral MPE (positive cytology > 200 IU/L lactate dehydrogenase and > 30 g/L protein) (all cell types); 1 previous pleurocentesis of > 500 mL. Exclusion criteria: participant receiving chemotherapy or radiotherapy. 41 participants randomised.
Interventions	Pleurocentesis with intrapleural instillation of the study agent, 3 times a week for 1 week. Mepacrine group: mepacrine 100 mg for first dose, 200 mg for second dose, 200 mg for third dose (i.e. 500 mg in total). Triethylenethiophosphoromide group: triethylenethiophosphoromide 20 mg at each instillation (i.e. 60 mg total). Pleurocentesis group: 10 mL saline at each instillation. All participants were followed up at 3 weeks, 6 weeks, 2 months and 3 months, when a pleurocentesis was performed.
Outcomes	Treatment effect (a beneficial effect was defined as < 500 mL fluid aspirated at each pleurocentesis performed up to 3 months) Adverse effects
Notes	People with trapped lung not excluded from trial entry. Minimal data presented on whether the treatment groups were well balanced at baseline. Included in network meta-analysis for pleurodesis failure, pain and fever. Study funding source: mepacrine hydrochloride (Atabrine) supplied by Winthrop Medicinal Company A/S, Copenhagen. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given.
Allocation concealment (selection bias)	Unclear risk	No details given.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No mention of blinding in the paper.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention of blinding in the paper.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal early deaths (3/25) and numbers well matched between the groups.
Selective reporting (reporting bias)	Low risk	All stated outcomes reported.

Mejer 1977 *(Continued)*

Other bias	High risk	Unsure if groups well balanced at baseline. Pleurodesis success defined by aspirating fluid on all participants and not by clinical need for pleural intervention.

Millar 1980

Methods	RCT of intrapleural *Corynebacterium parvum* vs mustine in recurrent MPE (UK).
Participants	Recurrent effusion associated with histologically confirmed malignant disease (all cell types); ≥ 2 previous pleural aspirations; symptoms of dyspnoea, cough or local pain. 21 participants randomised.
Interventions	Effusion completely aspirated using an Abrams pleural biopsy needle. Group A: intrapleural mustine 20 mg (maximum 2 doses). Group B: intrapleural *C parvum* 7 mg (maximum 2 doses).
Outcomes	Response to pleurodesis (defined by fluid re-accumulation on CXR and need for repeat aspiration – success/partial success/failure) at 4 weeks Symptoms (nausea, vomiting, pain)
Notes	Trapped lung not accounted for. Only 'success' counted as a pleurodesis success for analysis (not partial successes as these participants required a further aspiration of effusion). Included in network meta-analysis for pleurodesis failure and mortality. Study funding source: *C parvum* supplied by Dr Priestman of the Wellcome Research Laboratories. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No mention of blinding in the paper.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention of blinding in the paper. If unblinded, symptom and adverse effect reporting could have been biased.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 participants excluded from analysis as died before primary outcome measure.

Millar 1980 *(Continued)*

Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	Low risk	Unclear who provided *C parvum* and their study involvement.

Mishra 2018

Methods	Multicentre RCT comparing the effect of intrapleural urokinase on dyspnoea and pleurodesis success in people with non-draining MPE – TIME 3 (UK).
Participants	Inclusion criteria: adults with MPE (histocytological diagnosis or a recurrent large pleural effusion in the context of histologically confirmed cancer outside the pleural space), with a patent and correctly sited chest tube inserted for dyspnoea relief and significant residual pleural fluid (> 25% opacification of the hemithorax on CXR). A trial modification was made from March 2011 in response to increasing use of USS in the UK to include people with > 15% opacification on CXR or > 2 cm of loculated pleural fluid on USS. Exclusion criteria: aged < 18 years, expected survival < 28 days, trapped lung of sufficient severity that pleurodesis would be futile, previous lobectomy or pneumonectomy on the side of the effusion, pleural infection, previous intrapleural fibrinolytic use, urokinase allergy, coincidental stroke, major haemorrhage or major trauma, major surgery in the previous 5 days, chylothorax, pregnancy, lactation, irreversible bleeding diathesis, platelet count < 100×10^9/L, irreversible visual impairment, inability to consent or comply with protocol. 71 participants randomised.
Interventions	Urokinase group: 3 doses of urokinase 100,000 units in 20 mL 0.9% saline intrapleurally at 12-hour intervals via chest tube. Placebo: 3 doses of exactly matched placebo vials in 20 mL 0.9% saline intrapleurally at 12-hour intervals via chest tube. CXR obtained in all participants 24 hours after last dose and talc slurry pleurodesis performed with 4 g sterile graded talc. Pleurodesis was performed regardless of ongoing fluid drainage volume and CXR appearance. Chest drain removed once draining < 150 mL/24 hours.
Outcomes	Primary outcomes: mean daily dyspnoea score over first 28 days after enrolment by VAS and time to pleurodesis failure (defined as symptomatic ipsilateral pleural fluid recurrence). Secondary outcomes: radiographic change on day 2 postrandomisation, total volume pleural fluid drained, all-cause mortality to 12 months, length of stay postrandomisation, frequency of serious and non-serious adverse events, blood parameters including biomedical and full blood count.
Notes	Trapped lung excluded. Initially participants with highly chemosensitive tumours such as small cell lung cancer were excluded unless the participant had already undergone chemotherapy, but this exclusion was removed in March 2011. Not included in network meta-analysis. Study funding source: urokinase and placebo supplied by Syner-Med Ltd, who had no role in design and conduct of the study, data or manuscript. Study author conflicts of interest statements: Dr Mishra reported grants from National Cancer Research Institute, during the conduct of the study; Dr Rahman reported grants from Synermed UK, during the conduct of the study; and received consultancy fees from Rocket Medical UK; Dr Rehal reported grants from Oxford Respiratory Trials Unit, during the conduct of the study; Dr Corcoran reported grants from National Cancer Research Institute, non-financial support from Syner-Med Ltd, during the conduct of

Mishra 2018 *(Continued)*

	the study; Dr Lee reported grants and non-financial support from Rocket Medical Ltd, outside the submitted work; and he was an advisor to Lung Therapeutic Ltd which is conducting a phase I study of a fibrinolytic drug for intrapleural use in pleural infection. The other authors had no disclosures.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Telephone randomisation with minimisation criteria.
Allocation concealment (selection bias)	Low risk	Centralised allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treating physicians and participants were blinded to treatment allocation throughout.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis. Significant mortality rate (31/36 in urokinase group vs 35/35 in placebo group) over 12-month trial period; however, deaths occurring after day 3 postrandomisation included as pleurodesis success. VAS scores missing for 8 participants.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	None identified.

Mohsen 2011

Methods	Single-centre RCT of thoracoscopic talc poudrage vs povidone-iodine pleurodesis through an intercostal drain (Egypt).
Participants	Inclusion criteria: MPE as a complication of breast carcinoma. Exclusion criteria: performance status > 3; allergy to iodine; trapped lung; no change in MRC Dyspnoea Scale after thoracentesis; pleural fluid pH < 7.2; pleural fluid glucose < 60 mg/dL; extrathoracic metastasis. 42 participants randomised.
Interventions	All participants underwent a VATS drainage and adhesiolysis. Talc poudrage group: 4 g talc insufflation under thoracoscopic guidance at the end of the VATS procedure. Iodine group: recovered from VATS. Then later that day, 20 mL 10% povidone-iodine in 30 mL saline injected through the chest drain at the bedside. Drain clamped for 4 hours after instillation.
Outcomes	Efficacy of pleurodesis at 2 months (response defined as CR: absence of fluid re-accumulation; PR: residual pleural fluid or re-accumulation, which did not require further thoracentesis or remained asymptomatic; or failure: additional pleural procedures were necessary

Mohsen 2011 *(Continued)*

	Complications
	Length of hospital stay (in days)
	Survival
	Change in MRC Dyspnoea Score
Notes	People with trapped lung excluded from trial entry.
	CR and PR counted as pleurodesis success for analysis.
	Included in network meta-analysis for pleurodesis failure, mortality and fever.
	Study funding source: not stated.
	Study author conflicts of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer randomisation software used.
Allocation concealment (selection bias)	Low risk	Computer randomisation software used.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not able to blind given the nature of the interventions.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Symptom and adverse effect reporting would be affected by lack of blinding. Not stated if radiology was interpreted blindly. Mortality would not be biased by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal missing data (primary outcome data available for all participants at 2 months).
Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	Low risk	No other biases identified.

Muruganandan 2018

Methods	Multicentre RCT comparing daily vs symptom-guided IPC drainage and breathlessness scores in people with symptomatic MPE (11 centres in Australia, New Zealand, Hong Kong and Malaysia).
Participants	Inclusion criteria: adults requiring IPC for management of MPE, malignant cells in pleural fluid or pleural biopsy or large exudative effusion without other cause in people with known disseminated extrapleural malignancy.
	Exclusion criteria: aged < 18 years, expected survival < 3 months, pleural infection, chylothorax, pregnancy, lactation, uncorrectable bleeding diathesis, previous ipsilateral lobectomy or pneumonecto-

Muruganandan 2018 *(Continued)*

	my, significant loculation likely to preclude effective drainage, significant visual impairment, inability to consent or comply with study protocol. 87 participants randomised.
Interventions	All participants received an IPC and were randomised within 72 hours of insertion and after maximum pleural fluid drainage. 'Aggressive' daily drainage group: participants (or their carers or community nurses) were asked to drain the IPC daily for the first 60 days unless clinically contraindicated or spontaneous pleurodesis had occurred. Symptom-guided group: IPC drainage when they had effusion-related symptoms, with minimum drainage once every 2 weeks.
Outcomes	Primary outcome: mean daily breathlessness score in first 60 days postrandomisation (VAS score). Secondary outcomes: rate of spontaneous pleurodesis, QoL (EQ-5D-5L and VAS at randomisation, 2 weeks, 4 weeks and then monthly to 6 months), number of episodes and duration of hospital stay for any cause (excluding elective admissions for chemotherapy), adverse and serious adverse events.
Notes	Pleurodesis defined as < 50 mL of fluid removed on 3 consecutive drainages in the aggressive group and at 2 attempts 2 weeks apart in the symptom-guided group, in the absence of substantial residual pleural fluid collection on imaging. Included in network meta-analysis for pleurodesis failure, mortality and pain (defined as those who required narcotics). Contacted authors for further information by email but no reply received. Study funding source: Cancer Council of Western Australia and the Sir Charles Gairdner Research Advisory Group. Study author conflicts of interest statements: YCGL, DF-K and NAM served on the advisory board of CareFusion/BD Ltd. NAM received an unrestricted educational grant from Rocket Medical plc (UK) and CareFusion/BD. YCGL received an unrestricted educational grant from Rocket Medical plc (UK). All other authors declared no competing interests.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Automated telephone-based randomisation service with minimisation for cancer type, performance status, trapped lung and prior pleurodesis.
Allocation concealment (selection bias)	Low risk	Central allocation system. Imbalance window within which treatments were completely random.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not possible due to nature of interventions. Primary outcome was VAS breathlessness score, which may be influenced by knowledge of the treatment arm.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	VAS scores measured by 2 independent assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis.

Muruganandan 2018 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	None identified.

Neto 2015

Methods	RCT comparing pleurodesis with 1% and 2% iodopovidone for MPE (Brazil).
Participants	Inclusion criteria: recurrent symptomatic MPE, > 70% lung re-expansion on CX.R after drainage, Karnofsky Performance Status > 40. Exclusion criteria: < 70% lung re-expansion after drainage, haemorrhagic diathesis (prothrombin time < 50%, platelets < 80 × 10^9/L), active pleural or systemic infection, neoplastic infiltration of the skin at the site of pleural catheter insertion, aged < 18 years, previous ipsilateral pleural intervention (exception of thoracentesis and pleural needle biopsies), inability to understand QoL questionnaires, contralateral pleurodesis < 30 days prior to enrolment, iodine allergy, thyroid disease. 60 participants randomised.
Interventions	All participants had a 28-Fr drain inserted with a CXR 24 hours after insertion to evaluate lung re-expansion. Pleurodesis performed 48 hours after chest drain insertion with either 100 mL 1% iodopovidone or 100 mL 2% iodopovidone. 2 mg/kg lidocaine was added to each solution.
Outcomes	Primary objective: identification of adverse events and evaluation of the influence of iodopovidone dose on incidence of adverse events. Secondary: pleurodesis efficacy, QoL (WHOQOL-BREF questionnaire at baseline and 4 weeks postpleurodesis), chest pain (VAS score at baseline, day 2, day 4, day 10 and day 30), dyspnoea (MRC Dyspnoea Score at day 2, day 4, day 10, day 30), observations (oxygen saturation, blood pressure, heart rate, temperature), visual acuity, electrocardiogram, blood tests.
Notes	Trapped lung excluded. Pleurodesis efficacy based on need for further pleural procedures or recurrence of pleural fluid associated with worsening symptoms within 30 days of pleurodesis. Not included in network meta-analysis. Contacted authors via email for further information but no reply received. Study funding source: not stated. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Block randomisation.
Allocation concealment (selection bias)	Unclear risk	No comment on measures taken.
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Investigators and patients were blinded to group allocation."

Neto 2015 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No comment on blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Slightly higher number of deaths in group receiving 2% iodine (5 with 2% vs 2 with 1%) suggested by consort diagram, but due to discrepancy in total number of deaths in the 2% arm we did not include mortality in our direct analysis. ITT analysis.
Selective reporting (reporting bias)	Low risk	No data given regarding MRC Dyspnoea Scores. All other outcomes reported.
Other bias	Low risk	None identified.

Noppen 1997

Methods	Single-centre RCT of talc vs bleomycin in MPE (Belgium).
Participants	Inclusion criteria: hist/cytologically confirmed, symptomatic MPE; KPS ≥ 50; expected survival ≤ 1 year. Exclusion criteria: previous pleurodesis attempt. 26 participants randomised.
Interventions	14-Fr chest drain with suction drainage until completely drained. Intrapleural lignocaine and subcutaneous morphine given prior to instillation of study drug. After instillation of drug, drain clamped for 30 minutes and then left on suction drainage until output < 150 mL/24 hours. Bleomycin group: bleomycin 1 mg/kg in 50 mL saline intrapleurally. 1 dose. Talc group: 5 g talc in 50 mL saline intrapleurally. 1 dose.
Outcomes	Response to therapy (defined by re-accumulation on CXR and need for repeat procedure). Time point unclear Adverse effects Survival
Notes	People with trapped lung were included in the study. Included in network meta-analysis for pleurodesis failure and fever. Study funding source: not stated. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated numerical table.
Allocation concealment (selection bias)	Low risk	Computer-generated numerical table.

Noppen 1997 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not stated explicitly but drugs had different appearances.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Symptom recurrence and adverse effects could be biased by lack of blinding. Not stated if CXR interpretation was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No LTFU. Outcome data provided on all participants.
Selective reporting (reporting bias)	Low risk	Time point used to define pleurodesis not specified.
Other bias	Unclear risk	No fixed endpoint for follow-up.

Okur 2011

Methods	Single-centre RCT of intrapleural streptokinase in MPE undergoing chest drainage (Turkey).
Participants	Inclusion criteria: definitive diagnosis of MPE with dyspnoea. Exclusion criteria: mesothelioma; endobronchial tumour causing obstruction; anticoagulant medication. 48 participants randomised between January 2007 and December 2008.
Interventions	All participants had 10-Fr pleural catheter inserted under local anaesthetic. Pleurodesis (5 g talc in 50 mL saline) given only in those participants with complete lung re-expansion and < 250 mL drain output per day. Drain removed when output < 150 mL/day or after 3 days. Those randomised to streptokinase received 3 doses of 250,000 IU in 100 mL normal saline at 12-hourly intervals intrapleurally prior to pleurodesis.
Outcomes	Primary: lung expansion on CXR Secondary: success of pleurodesis at 1 month; volume of 24-hour pleural drainage before and after fibrinolytic
Notes	Pleurodesis defined as "no accumulation of moderate to massive pleural fluid or any accumulation which causes dyspnoea." Did not pleurodese people with trapped lung. Degree of loculation or septation on imaging at baseline not recorded. Not included in network meta-analysis. Study funding source: no specific grant from any funding agency received. Study author conflict of interest statements: no conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement

Okur 2011 *(Continued)*

Random sequence generation (selection bias)	Low risk	Web-based random-number generator.
Allocation concealment (selection bias)	Low risk	Web-based random-number generator.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Nature of interventions precluded blinding (1 group received 3 doses of drug and other group received nothing).
Blinding of outcome assessment (detection bias) All outcomes	High risk	No mention of blinding and adverse effects and symptom reporting could be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	LTFU for pleurodesis success (1/17 in control group; 4/23 in streptokinase group – 1 died; 1 in intensive care; 3 LTFU). Only those with full lung re-expansion were given pleurodesis and this could have been affected by giving streptokinase, which might affect pleurodesis success rate, although this was not the study's primary outcome measure.
Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	Low risk	No other biases identified.

Ong 2000

Methods	Single-centre RCT of talc vs bleomycin in MPE (Singapore).
Participants	Inclusion criteria: symptomatic, unilateral MPE confirmed by cytology or pleural biopsy (all cell types). Exclusion criteria: trapped lung or loculated effusion; incomplete drainage (e.g. > 100 mL/day for 10 days); previously treated effusions; life-expectancy < 1 month. 50 participants randomised.
Interventions	20- to 24-Fr tube thoracostomy until complete lung re-expansion on CXR and < 100 mL/day for 2 days. Both drugs diluted in 50 mL saline and 10 mL 1% lignocaine. After study drug inserted, drain clamped for 6 hours with patient rotation. Then suction applied. Drain removed when < 200 mL/day drainage. Talc group: 5 g talc intrapleurally. 1 dose. Bleomycin group: bleomycin 1 unit/kg intrapleurally. 1 dose.
Outcomes	Treatment response at 1 month (according to recurrence of effusion on CXR. Scoring system 0–3 used for size of effusion) Hospital stay (days) Adverse effects within 48 hours of pleurodesis
Notes	People with trapped lung excluded from trial entry. Pleurodesis success based only on radiology. Included in network meta-analysis for pleurodesis failure, pain, fever and mortality.

Ong 2000 *(Continued)*

	Study funding source: not stated. Study author conflict of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not stated explicitly, however, drugs had differing appearances.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "A single investigator who was blinded to treatment allocation scored all the follow up chest x rays."
Incomplete outcome data (attrition bias) All outcomes	Low risk	12/50 participants excluded due to death or LTFU in first month, but balanced between treatment arms.
Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	Low risk	No other biases identified.

Ostrowski 1989

Methods	Multicentre RCT bleomycin vs *C parvum* in MPE (UK).
Participants	Inclusion criteria: histocytologically confirmed malignancy with effusion (all cell types); life-expectancy > 30 days. Exclusion criteria: previous intrapleural drug administration; change in cancer treatment in previous 30 days. 58 participants randomised.
Interventions	Aspiration of effusion with a cannula. Study drug instilled through cannula. After cannula removed, participant repositioned every 5 minutes. Bleomycin group: bleomycin 60 mg in 100 mL saline. Single dose intrapleurally. *C parvum* group: 7 mg in 20 mL saline. Single dose intrapleurally.
Outcomes	Efficacy of pleurodesis agent at 30 days (defined as: CR: no re-accumulation of fluid confirmed by CXR; PR: minimal fluid re-accumulation not sufficient to produce symptoms or need for a further aspiration (or both); or failure) Duration of treatment response Toxicity

Ostrowski 1989 *(Continued)*

	Efficacy of pleurodesis at 2 months, 3 months, 6 months, 9 months and 12 months
Notes	People with trapped lung included in study. For this review, CR and PR counted as pleurodesis success. Included in network meta-analysis for pleurodesis failure, mortality, fever and pain. Study funding source: not stated. Study author conflict of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequentially labelled sealed envelopes.
Allocation concealment (selection bias)	Low risk	Sequentially labelled sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not stated explicitly, but agents given as different volumes.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Symptom recurrence and adverse effect reporting would be influenced by lack of blinding. Not stated if CXR assessment was blinded. Mortality data would not be biased by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	14/58 (24%) participants excluded from primary analysis due to death or not receiving drug. But, balanced numbers between groups.
Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	Low risk	No other biases identified.

Ozkul 2014

Methods	Single-centre, prospective RCT comparing rapid and standard drainage prior to talc slurry pleurodesis (Turkey).
Participants	Inclusion criteria: potentially recurrent histologically or cytologically confirmed MPE, or both (all cell types). Exclusion criteria: participants whose lung did not expand; endobronchial lesion; suitable for curative therapy. 79 participants randomised.
Interventions	All participants underwent insertion of 12-Fr chest drain in the posterior axillary lune with local anaesthetic (bupivacaine) and intramuscular ketorolac. Rapid group: 1 L drained every 8 hours until complete drainage. Then talc slurry administered once CXR showed complete fluid evacuation and no trapped lung.

Ozkul 2014 *(Continued)*

	Standard group: drainage of a maximum of 1.5 L/day. Talc slurry administered once CXR showed complete fluid evaluation and no trapped lung and pleural fluid drainage < 300 mL/day.
Outcomes	Primary outcome: efficacy of pleurodesis assessed at 1 month, 2 months, 3 months and 6 months Secondary outcome: hospital length of stay
Notes	People with trapped lung excluded from study entry. Pleurodesis efficacy defined using a combination of radiology and symptomatic effusion re-accumulation. Not included in network meta-analysis. Study funding source: not stated. Study author conflict of interest statements: authors declared no conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Internet-based random-number generator.
Allocation concealment (selection bias)	Unclear risk	Not stated and no response from study authors.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind given nature of 2 treatment groups with such different drainage regimens.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The assessment of success was performed by an investigator blinded to allocation."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if any LTFU – not stated in paper and no response from study authors.
Selective reporting (reporting bias)	High risk	Minimal data provided on adverse effect and mortality data. Not all time points reported as stated in methods.
Other bias	Low risk	No other sources of bias identified.

Paschoalini 2005

Methods	2-centre, prospective RCT of silver nitrate vs talc slurry in MPE (Brazil).
Participants	Inclusion criteria: documented MPE (positive pleural biopsy or cytology – all cell types); KPS > 60; life-expectancy > 1 month. Exclusion criteria: loculated or trapped lungs after drainage. 60 participants randomised.

Paschoalini 2005 *(Continued)*

Interventions	26/28-Fr chest tube. After study drug instilled, clamped for 1 hour with patient rotation. Then suction applied. Drain removed when < 100 mL drained. Talc group: 5 g talc in 50 mL saline. 1 dose intrapleurally. Silver nitrate group: 20 mL of 0.5 mL silver nitrate. 1 dose intrapleurally.
Outcomes	Radiological resolution of effusion on CXR (monthly for 4 months) Pain before and after treatment (measured on a 0–10 linear scale)
Notes	People with trapped lung excluded from study entry. Included in network meta-analysis for pleurodesis failure and fever. Study funding source: not stated. Study author conflict of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Picking paper from a box.
Allocation concealment (selection bias)	Low risk	Picking paper from a box.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not stated if blinded but agents had different appearances.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if CXR interpretation was blinded. Pain scores may be biased if participants not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	High rate of LTFU (11/60 (18%)) but reasons explored in the discussion.
Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	Low risk	No other biases identified.

Patz 1998

Methods	Prospective RCT of bleomycin vs doxycycline in MPE (USA).
Participants	Inclusion criteria: symptomatic effusion; confirmed or strongly suspected that malignancy is the cause for the effusion. Exclusion criteria: previous pleurodesis; allergy to bleomycin or doxycycline; chemotherapy in the previous 30 days.

Patz 1998 *(Continued)*

	106 participants randomised.
Interventions	All participants underwent 14-Fr chest drain insertion. When drainage < 200 mL/day and lung fully re-expanded on CXR, participant randomised. Bleomycin group: bleomycin 60 units in 50 mL saline intrapleurally. Doxycycline group: doxycycline 500 mg in 50 mL saline + 10 mL lignocaine. After 18–24 hours, if drainage < 200 mL, drain removed. If > 200 mL, second dose of the same agent given and drain then removed.
Outcomes	Radiographic response at 30 days (classified as: CR, PR, progressive disease, expired with no re-accumulation, expired with re-accumulation, LTFU) Mortality Adverse effects
Notes	Trapped lung not accounted for. If participants died prior to day 30, included in analysis according to their outcome at the time of their death. For this review, CR, PR and expired with no re-accumulation counted as pleurodesis success. Included in network meta-analysis for pleurodesis failure, mortality, fever and pain. Study funding source: not stated. Study author conflict of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation.
Allocation concealment (selection bias)	Low risk	Computer-generated randomisation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (personal communication with study authors): "Study investigators and participants not blinded to treatment allocation."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (personal communication with study authors): "Study investigators and participants not blinded to treatment allocation."
Incomplete outcome data (attrition bias) All outcomes	High risk	Significant LTFU rate (26/106 (25%)).
Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	Low risk	Radiological outcome on CXR used to define pleurodesis success.

Putnam 1999

Methods	RCT comparing IPCs and doxycycline pleurodesis for MPE.
Participants	Inclusion criteria: malignancy with moderate pleural effusion and breathlessness relived after thoracentesis. Exclusion criteria: chylothorax, previous ipsilateral lobectomy or pneumonectomy, previous attempted pleurodesis, autoimmune deficiency syndrome, KPS < 50, bilateral moderate/large effusion, multiple loculations, mediastinal shift towards side of effusion, pleural infection, abnormal coagulation. 144 participants randomised.
Interventions	IPC group: IPC insertion and drainage up to 1.5 L. A further 1 L was drained every 8 hours until drainage complete. Participants were instructed to drain the IPC on alternate days. If no pleural fluid drained on 3 consecutive drainages and pleurodesis had occurred, the IPC was removed. Doxycycline group: chest drain insertion (any size) and effusion drainage. If lung failed to re-expand by 72 hours, the participant was assumed to have trapped lung and pleurodesis not attempted. If lung expanded and drainage < 150 mL/24 hours doxycycline 500 mg administered via chest tube. Doxycycline was re-administered if the 24-hourh drainage volume failed to fall below 100 mL/24 hours by day 4.
Outcomes	Length of hospital stay QoL (Guyatt Chronic Respiratory Questionnaire) Dyspnoea (Borg scale) Pleurodesis Adverse events
Notes	Included in network meta-analysis for pleurodesis failure, pain and fever. Study funding source: supported by Denver Biomaterials, CO. Study author conflict of interest statements: Dr Light, Dr Rodriguez and Dr Putnam owned shares of stock in Surgimedics, which is a parent company of Denver Biomaterials.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table.
Allocation concealment (selection bias)	Low risk	Allocation concealed with envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to different types of intervention.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	Low risk	Participants with protocol violations excluded from analysis; however, withdrawals well matched between interventions.

Putnam 1999 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	None identified.

Rafiei 2014

Methods	Single-centre RCT comparing the pleurodesis success of doxycycline and bleomycin in MPE (Iran).
Participants	Inclusion criteria: symptomatic, cytologically confirmed MPE. Exclusion criteria: allergy to doxycycline or bleomycin; history of sclerotherapy; systemic chemotherapy immediately prior to or in the next 2 months after sclerotherapy. 42 participants randomised.
Interventions	All participants underwent 'fluid evacuation'. Agent then instilled through the tube, which was clamped for 1 hour. Then suction applied and drain removed when < 100 mL/24-hour drainage. Bleomycin group: bleomycin 45 mg intrapleurally. Doxycycline group: doxycycline 600 mg in 50 mL saline and 10 mL 1% lignocaine intrapleurally.
Outcomes	CXR appearances of the effusion size at 2 months (mild, moderate or severe) Need for repeat pleural fluid drainage Dyspnoea (mild, moderate or severe) Complications
Notes	People with trapped lung not excluded. Pleurodesis success primarily defined radiologically, but data presented at 3 months for need for repeat pleural intervention. For this review, need for repeat pleural drainage was used as measure of pleurodesis success. Included in network meta-analysis for pleurodesis failure, fever and pain. Study funding source: financial support from Islamic Azad University Najafabad. Study author conflict of interest statements: authors declared no conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated and no response from study authors to clarify.
Allocation concealment (selection bias)	Unclear risk	Not stated and no response from study authors to clarify.
Blinding of participants and personnel (performance bias)	Unclear risk	Not stated if anyone was blinded. No response from study authors.

Rafiei 2014 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if anyone was blinded. No response from study authors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No LTFU.
Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	Low risk	No other biases identified.

Rahman 2015

Methods	2×2 factorial design multicentre RCT assessing the effect of chest tube size and analgesia on pain and clinical efficacy related to pleurodesis in people with MPE – TIME 1 (UK, USA, Canada).
Participants	Inclusion criteria: aged > 18 years, symptomatic MPE clinically determined to require pleurodesis (histocytologically confirmed pleural malignancy or typical features of pleural malignancy visualised during thoracoscopy or pleural effusion in the context of histologically confirmed cancer elsewhere). Exclusion criteria: primary lymphoma or small cell lung cancer, pregnant or lactating, history of gastrointestinal bleed or peptic ulceration, sensitivity to NSAIDs or opiates, hypercapnic respiratory failure, current IV drug misuse, severe renal or liver disease, known bleeding diathesis, current warfarin therapy, expected survival < 1 month. 320 participants randomised.
Interventions	Participants undergoing thoracoscopy received a 24Fr drain and were randomised to either NSAID or opioid analgesic treatment and were not included in primary analysis of chest tube size outcome. Participants not undergoing thoracoscopy were randomised to one of four groups (24Fr drain and opioid analgesia; 24Fr drain and NSAID analgesia; 12Fr drain and opioid analgesia; 12Fr drain and NSIAD analgesia). All received regular background analgesia (paracetamol 1 g 4 times a day). Participants allocated to NSAID treatment received Ibuprofen 800 mg 3 times a day and those to opiate received oral morphine 10 mg 4 times a day, escalating to 20 mg 4 times a day if needed for the duration that the drain was in situ. Breakthrough analgesia with IV morphine was permitted in both groups. Pleurodesis performed using 4 g sterile graded talc according to written standard operating procedures.
Outcomes	Primary outcomes: superiority comparison of pain scores (mean VAS measured 4 times a day and prior to any rescue analgesia over duration of chest drain treatment) and a non-inferiority comparison of the occurrence of pleurodesis failure at 3 months. Secondary outcomes: change in pain over time, time to pleurodesis failure 6 months postrandomisation, pain scores at 4 weeks and 12 weeks postrandomisation, volume of pleural fluid drained, number of times rescue medication taken, all-cause mortality up to 12 months, complications during chest drain insertion, safety outcomes, serious and non-serious adverse events.
Notes	Pleurodesis failure judged as requirement for further ipsilateral pleural intervention as per trial protocol (breathlessness and > 50% opacification of the hemithorax on CXR. If < 50% opacification, the case was referred to a second blinded clinician).

Rahman 2015 *(Continued)*

	Trapped lung not excluded. Participants who died but did not require further drainage were classified as pleurodesis success. Not included in network meta-analysis. Study funding source: Grant G0600475 from UK Medical Research Council. Dr Rahman funded by UK Medical Research Council and UK National Institute for Health Research Oxford Biomedical Research Center Programme. Study author conflicts of interest statements: Dr Miles reported receipt of fees for educational meetings sponsored by GlaxoSmithKline, AstraZeneca, Meda, Pfizer and Chiesi. Dr Lee reported advisory board membership for CareFusion and Sequana Medical and receipt of equipment from Rocket Ltd for a clinical trial. No other disclosures were reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central telephone randomisation service. Minimisation (histological tissue type, procedure and centre of recruitment) with a random component.
Allocation concealment (selection bias)	Low risk	Central telephone randomisation service.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants aware of treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded to primary outcome of mean pain score and pleurodesis failure.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis. Mortality and withdrawals similar across intervention groups.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	None identified.

Rintoul 2014

Methods	Open-label, multicentre, parallel group RCT of VATS pleurectomy and talc pleurodesis (either slurry or poudrage) in mesothelioma (UK).
Participants	Inclusion criteria: aged > 18 years; confirmed or suspected MPM with pleural effusion; fit enough for VATS pleurectomy. Exclusion criteria: previous pleurodesis; previous primary treatment for MPM; history of previous malignancy and suspected MPM. People with suspected MPM who were found to have a different cause after randomisation were excluded from analysis. 196 participants randomised.

Rintoul 2014 *(Continued)*

Interventions	VATS pleurectomy group: thoracoscopic debulking pleurectomy-decortication under GA, according to agreed protocol. Pleurodesis group: 4 g talc pleurodesis (either slurry or poudrage).
Outcomes	Primary outcome: survival at 1 year postrandomisation Secondary outcomes: presence or absence of effusion on CXR, QoL (EQ-5D and QLQ-LC13, QLQ-C30), lung function and exercise tolerance, complications, healthcare utilisation costs
Notes	People with trapped lung included. No data available on whether participants in the pleurodesis arm who had poudrage may have had trapped lung released at the same time. Pleurodesis success defined according to CXR (as assessed by reporting radiologist, unblinded to treatment allocation). Not included in network meta-analysis. Study funding source: BUPA Foundation. Study author conflicts of interest statements: RCR was a member of an advisory board for Lilly UK. JGE received honoraria from Lilly UK. All other authors declared no competing interests.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised random-number generator in blocks of 10. 1:1. stratified by EORTC score (low or high).
Allocation concealment (selection bias)	Low risk	Telephone randomisation line operated by staff independent to study.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind due to nature of interventions.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Participants and investigators not blinded, leading to potential bias in reporting of QoL, exercise tolerance and complications. CXRs not interpreted blindly (personal communication with authors).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants excluded after randomisation if MPM not confirmed, but this was stated a priori. Missing data well balanced between the treatment arms.
Selective reporting (reporting bias)	Low risk	Very thorough reporting of all stated outcomes.
Other bias	Low risk	No other biases identified.

Ruckdeschel 1991

Methods	Multicentre RCT of intrapleural bleomycin and tetracycline in MPE (USA).
Participants	Inclusion criteria: exudative MPE (confirmed by cytology or pleural biopsy); ECOG Performance Score 0–2.

Ruckdeschel 1991 *(Continued)*

	Exclusion criteria: previous intrapleural therapy; prior systemic therapy with bleomycin; severe congestive heart failure; radiotherapy to the chest in the previous 2 weeks. 115 participants randomised.
Interventions	All participants had a chest tube placed and evidence of lung re-expansion on CXR. After the study drug was inserted the tube was clamped and the participant's position rotated. After several hours the chest tube was removed. Group 1: tetracycline 1 g intrapleurally in 100 mL saline. Group 2: bleomycin 120 units intrapleurally in 100 mL saline (due to slow accrual, this group was dropped after accruing 15 participants). Group 3: bleomycin 60 units intrapleurally in 100 mL saline.
Outcomes	Recurrence of effusion at 30 days and 90 days (defined according to CXR). Time to effusion recurrence within 90 days. Time to maximum change in ECOG Performance Score. Change from initial Performance Score to the best Performance Score (worsened/no change/improved). Adverse events.
Notes	People with trapped lung excluded. Group 2 dropped due to slow accrual and data on the 15 participants assigned to this group not provided. Included in network meta-analysis for pleurodesis failure, mortality, pain and fever. Study funding source: supported by Bristol Myers US Pharmaceutical Group. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation, with stratification.
Allocation concealment (selection bias)	Low risk	Computer randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated if anyone was blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if anyone was blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	41/115 "non-evaluable" participants excluded from analysis. Reasons given.

Ruckdeschel 1991 *(Continued)*

Selective reporting (reporting bias)	High risk	Data on 15 participants randomised to high-dose bleomycin group not reported.
Other bias	Low risk	No other biases identified.

Salomaa 1995

Methods	Single-centre RCT of pleurodesis with doxycycline and *C parvum* in MPE (Finland).
Participants	Inclusion criteria: pleural effusion refractory to repeat aspirations; pleural malignancy – all cell types (histocytologically confirmed or confirmed malignancy elsewhere). Exclusion criteria: none. 41 participants randomised.
Interventions	16-Fr Argyll drain inserted under local anaesthetic and drained with suction until output < 100 mL/day. CXR to confirm lung re-expansion prior to pleurodesis. D100 group: doxycycline 100 mg intrapleurally. 1 dose. D600 group: doxycycline 600 mg intrapleurally. 1 dose. C1 group: *C parvum* 1 mg intrapleurally. 1 dose. C7 group: *C parvum* 7 mg intrapleurally. 1 dose. All drugs diluted in 20 mL saline with 50-mL flush administered after dose. Chest tube removed immediately after sclerosant given.
Outcomes	Pleurodesis success (defined using CXR and need for repeat thoracentesis at 30 days) Mortality Adverse effects Blood/pleural fluid interleukin-6 Daily C-reactive protein for 7 days
Notes	For the purposes of our analysis, we decided to combine the 2 doses of each agent to allow comparison between the agents themselves. People with trapped lung excluded from study. Included in network meta-analysis for pleurodesis failure, fever and pain. Study funding source: Finnish Antituberculous Association and the Vaino and Laina Kivi Foundation. Study author conflicts of interest statements: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.

Salomaa 1995 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated if anyone was blinded. Unable to contact study authors.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if anyone was blinded. Unable to contact study authors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	6/41 (15%) participants LTFU.
Selective reporting (reporting bias)	High risk	Minimal data provided on survival or biochemical markers. Minimal data on baseline participant characteristics and whether treatment groups were well matched.
Other bias	Low risk	Underpowered.

Sartori 2004

Methods	Single-centre RCT evaluating intrapleural bleomycin vs interferon alfa-2b in the palliative treatment of malignant effusion (Italy).
Participants	Inclusion criteria: cytologically confirmed MPE requiring ≥ 2 thoracenteses in preceding 4 weeks; ≥ 3 L drained in the preceding 4 weeks; adequate pulmonary re-expansion on CXR after thoracentesis; last systemic treatment administered ≥ 6 weeks prior to enrolment; no further chemotherapy options; KPS > 40. Exclusion criteria: none. 160 participants randomised.
Interventions	All participants underwent a 9-Fr intercostal drain insertion under USS guidance. Fluid drained via a 3-way-tap until USS revealed no residual effusion. Study drug administered intrapleurally via the chest tube. Tube was then clamped for 2 hours and participants changed position every 15 minutes. Tube removed 24–48 hours after last dose. Bleomycin group: bleomycin 0.75 mg/kg in 50 mL saline. A repeated dose was given if > 100 mL/day output 3 days after the first dose. Interferon alpha-2b group: interferon alpha-2b 1 million units/10 kg in 200 mL saline. 6 doses given every 4 days.
Outcomes	Treatment response at 30 days (CR: no fluid re-accumulation; PR: asymptomatic fluid recurrence < 50% of the original effusion, not requiring thoracentesis; no response: fluid recurrence > 50% of the original effusion, requiring thoracentesis) Time to progression Number of thoracenteses until death
Notes	Deaths included in the analysis as failures (as presented in the paper as ITT analysis). People with trapped lung excluded from trial entry.

Sartori 2004 *(Continued)*

Not included in network meta-analysis.

Study funding source: not stated.

Study author conflicts of interest statements: the authors indicated no potential conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation.
Allocation concealment (selection bias)	Low risk	Computer-generated randomisation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not stated explicitly but 2 drugs were given as different volumes.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Symptom recurrence and adverse event reporting may be biased by lack of blinding. Mortality not biased by lack of blinding. Not stated if CXR interpretation was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	No other biases identified.

Saydam 2015

Methods	RCT comparing the effect of streptokinase on pleurodesis therapy in multiloculated MPE (Turkey).
Participants	Inclusion criteria: multiloculated MPE. Exclusion criteria: lung carcinoma with endobronchial obstruction, bleeding diathesis, anticoagulation. 40 participants randomised.
Interventions	CT performed on all participants prior to drain insertion. 20-Fr drain inserted into largest locule and maintained on continuous suction at –20 cmH_2O. Fibrinolytic group: streptokinase 250,000 units in 50 mL saline delivered via chest drain 24 hours, 36 hours, 48 hours and 60 hours after drain insertion. After each instillation, the drain was clamped for 2 hours and on unclamping attached to suction. Control group: 50 mL saline placebo used at same time intervals with the same trial procedures. Pleurodesis with 4 g sterile talc performed 4 days following chest drain insertion and drains removed on day 5 unless participants were oxygen dependent.
Outcomes	Drainage volume at 48 hours and 72 hours postdrain insertion

Saydam 2015 *(Continued)*

	CT images pre- and post-therapy (repeated on day 3) Dyspnoea after treatment (oxygen-dependence) Pleural effusion recurrence
Notes	Excluded from network meta-analysis. Contacted authors for further information but no reply received. No comment regarding inclusion/exclusion of people with trapped lung. Study funding source: not stated. Study author conflicts of interest statement: authors declared no conflict of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated permuted blocks.
Allocation concealment (selection bias)	Low risk	Computer generated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants and physicians not stated.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "CT scans reviewed by one radiologist who was blinded to clinical and laboratory information."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals/LTFU and mortality unreported. Unclear how many participants were followed to 30 days.
Selective reporting (reporting bias)	High risk	Limited results presented – pleurodesis outcomes given for 29/40 participants, outcomes for remaining 11 participants unclear with no explanation regarding LTFU or withdrawals. Number of participants followed to 30 days unstated. Data presented on number of participants with 'dyspnoea' but unclear at which time point and how this was measured as definition uncertain (the text suggests this is the number of participants dependent on oxygen rather than symptom based). Limited information about baseline characteristics of the 2 groups was given.
Other bias	High risk	Primary outcome of study was unclear. The method used and time point for diagnosis of pleural effusion recurrence not stated.

Schmidt 1997

Methods	Multicentre RCT comparing pleurodesis using bleomycin with mitoxantrone (Germany). Paper in German.
Participants	Inclusion criteria: symptomatic, cytologically confirmed MPE; life-expectancy > 3 months; WHO Performance Score 0–2

Schmidt 1997 *(Continued)*

	Exclusion criteria: prior chemotherapy or pleurodesis in previous 4 weeks; contraindication to bleomycin or mitoxantrone; persistent pneumothorax; leukopenia; thrombocytopenia; incomplete pleural fluid drainage. 102 participants randomised.
Interventions	All participants had 24-Fr chest drain inserted and left in situ for 48 hours. Bleomycin group: bleomycin 60 mg in 100 mL saline intrapleurally. 1 dose. Mitoxantrone group: mitoxantrone 30 mg in 100 mL saline intrapleurally. 1 dose. Drains clamped for 6 hours after instillation and left in place for 24–48 hours with or without suction.
Outcomes	Pleurodesis success rate at 4 weeks (defined by recurrence of effusion requiring repeat pleural procedure) Toxicity/adverse events Length of hospital stay Time to repeat pleural intervention
Notes	Translated from German. People with trapped lung excluded from participation. Included in network meta-analysis for pleurodesis failure, mortality, fever and pain. Study funding source: not stated. Study author conflicts of interest statement: not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Low risk	Telephone randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated if anyone was blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if anyone was blinded. If unblinded, symptom recurrence, adverse event reporting and length of stay could have been biased.
Incomplete outcome data (attrition bias) All outcomes	Low risk	6 participants excluded from analysis, but reasons given and balanced numbers in the 2 treatment arms.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	No other biases identified.

Sorensen 1984

Methods	Single-centre RCT comparing talc instillation with pleural drainage only in the treatment of MPE (Denmark).
Participants	Inclusion criteria: histologically confirmed MPE (all cell types) causing respiratory distress, which is progressive and resistant to conventional therapy. Exclusion criteria: failure of the underlying lung to totally re-expand within 72 hours of the thoracoscopy. 31 participants randomised.
Interventions	All participants underwent thoracoscopy, during which multiple biopsies were taken and a drain inserted. Suction applied until complete lung re-expansion. Drainage alone group: constant suction for 72 hours after complete lung re-expansion. Then, drain removed. Talc and drainage group: 10 g sterile talc in 250 mL saline instilled through chest tube and clamped for 2 hours. Then suction applied for 72 hours and the drain was removed.
Outcomes	Fluid re-accumulation on CXR every month for 3 months
Notes	People with trapped lung excluded from trial entry. No data provided on whether treatment arms well matched at baseline. Power calculation performed. Unclear if adverse events reported for all participants or only those who completed the follow-up. Pleurodesis defined using radiology only. Included in network meta-analysis for pleurodesis failure. Study funding source: not stated. Study author conflicts of interest statement: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Low risk	Quote: "Closed envelope system."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unable to blind due to nature of the interventions (pleural drainage alone, or with talc administration).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Adverse event reporting could be biased by lack of blinding. Not stated if CXR interpretation was blinded.
Incomplete outcome data (attrition bias)	High risk	10/31 (32%) participants excluded from primary analysis (but well balanced between the 2 treatment arms).

Sorensen 1984 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	No comment on mortality or survival, but an old study and not stated as an outcome measure in the paper.
Other bias	Low risk	No other biases identified.

Tabatabaei 2015

Methods	RCT investigating the effectiveness of silver nitrate vs tetracycline for pleurodesis in MPE (Iran).
Participants	Inclusion criteria: cytologically or histologically confirmed MPE, anticipated survival > 1 month, dyspnoea secondary to the effusion. Exclusion criteria: 'inappropriate expansion of lungs during drainage of the effusion', 'pulmonary involvement with tumoral mass', air leak, previous pleurodesis, history of ipsilateral intrapleural therapy or radiotherapy. 50 participants randomised.
Interventions	All participants received a 26-Fr or 28-Fr drain under local anaesthetic and drainage of effusion. Silver nitrate group: 20 mL 0.5% silver nitrate in 30 mL 0.9% saline and 0.1% lidocaine via chest drain. Tetracycline group: tetracycline 2.5 g in 30 mL 0.9% saline and 0.1% lidocaine via chest drain. Drains were clamped for 1 hour after pleurodesis and participants were asked to rotate from right to left decubitus, prone and supine positions for 10–15 minutes. Drains removed once volume drained < 100 mL.
Outcomes	Pleurodesis success (radiological criteria) at 24 hours and 30 days Chest pain (scale of mild/moderate/severe) Fever (> 38 °C) Dyspnoea score
Notes	Trapped lung excluded. Contacted authors via email for further information but no reply received. Included in the network meta-analysis for pleurodesis failure. Unable to include mortality network as zero events per arm and unable to include in pain network as 100% event rate in 1 arm and only trial included in that network for silver nitrate. Study funding source: none. Study author conflicts of interest statement: none declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used for randomisation not stated.
Allocation concealment (selection bias)	Unclear risk	Methods used not stated.

Tabatabaei 2015 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data, all participants included in analyses.
Selective reporting (reporting bias)	High risk	Limited reporting of results. Dyspnoea scores unreported. Time point for evaluation of fever, chest pain and dyspnoea unclear.
Other bias	Low risk	Pleurodesis success based on CXR recurrence of pleural effusion.

Terra 2009

Methods	Single-centre RCT evaluating VATS talc poudrage and talc slurry in MPE (Brazil).
Participants	Inclusion criteria: biopsy or cytology confirmed MPE (all cell types); recurrent and symptomatic effusion; CXR confirming lung expansion of > 90% after thoracentesis; KPS ≥ 70. Exclusion criteria: comorbidities that precluded GA; bleeding disorders; massive thoracic skin infiltration; active infection; refusal to sign informed consent. 60 participants randomised.
Interventions	1 dose of 5 g non-calibrated talc given intrapleurally to both trial groups. Postprocedure care and analgesia the same for the 2 groups. No suction used in either group. Drain removed when < 200 mL/24-hour drainage, or after 10 days if drain volume too high, participants were discharged with the drain in situ and a Heimlich valve. VATS group: VATS performed under GA, followed by talc poudrage. 28-Fr chest drain inserted at end of procedure. Talc slurry group: 28-Fr chest drain inserted under local anaesthetic. Following day, talc suspended in 60 mL saline with 5 mL 2% lignocaine and instilled through chest drain. Clamped for 1 hour postprocedure.
Outcomes	Lung expansion on CT measured on a 3-point scale at baseline, 1 month, 3 months and 6 months Clinical efficacy (success defined as no need for a new pleural procedure due to symptoms and radiological effusion recurrence) QoL Safety Survival Chest drain duration Length of hospital stay Perioperative complications

Terra 2009 *(Continued)*

Notes	Raw data for survival, pleurodesis rates at certain time points, intervention rates at certain time points and QoL data not presented. People with trapped lung excluded from trial entry. Pleurodesis success rate defined using symptoms and radiology. Contacted study authors for further information, but no reply. Included in network meta-analysis for pleurodesis failure and fever. Study funding source: not stated. Study author conflicts of interest statement: no significant conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unable to blind due to nature of the interventions (talc poudrage vs talc slurry).
Blinding of outcome assessment (detection bias) All outcomes	High risk	Symptom recurrence, QoL, inpatient stay and adverse event reporting could be biased by lack of blinding. Interpretation of CTs was done by 2 blinded observers; however, pleurodesis efficacy was defined by need for repeat intervention.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No LTFU.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	No other biases identified.

Terra 2015

Methods	Single-centre RCT evaluating 3 different doses of silver nitrate for pleurodesis in MPE (Brazil).
Participants	Inclusion criteria: recurrent and symptomatic MPE (with pleural histological or cytological confirmation); previous CXR showing full lung expansion (> 90%) after chest drainage; KPS > 40; written consent. Exclusion criteria: trapped lung after pleural catheter insertion; haemorrhagic diathesis (prothrombin < 50% or platelets < 80×10^9/L); active pleural or systemic infection; neoplastic infiltration of the skin at the site of pleural catheter insertion; inability to understand QoL questionnaires; contralateral pleurodesis < 30 days before study entry. 60 participants randomised.

Terra 2015 *(Continued)*

Interventions	All participants were admitted for 5 days and had baseline assessment. All had a 14-Fr chest drain inserted under USS guidance prior to randomisation. The randomised interventions were given via the chest tube, which was then clamped for 1 hour. Drain removed on day 5. The silver nitrate was dissolved in 100 mL distilled water, which was passed through a 0.22 µm filter to ensure sterility within 6 hours of instillation. Group 1: 30 mL of 0.3% silver nitrate 90 mg intrapleurally. 1 dose. Group 2: 30 mL of 0.5% silver nitrate 150 mg intrapleurally. 1 dose. Group 3: 60 mL of 0.3% silver nitrate 180 mg intrapleurally. 1 dose.
Outcomes	Primary outcome: occurrence of serious or severe adverse event during follow-up Secondary outcomes: systemic inflammation (measured using C-reactive protein); chest pain (measured using VAS score); effusion recurrence (defined as need for additional pleural procedures during trial follow-up); residual pleural cavity volume (calculated using difference between day 5 and day 30 on CT)
Notes	People with trapped lung excluded from study entry. Pleurodesis failure defined as need for additional pleural procedure during follow-up. Not included in network meta-analysis. Study funding source: not stated. Study author conflicts of interest statement: Renato T Bellato received an institutional (Heart Institute, University of Sao Paulo Medical School) fellowship grant for participating in this work.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Pharmacy employees and clinicians who instilled the sclerosant were aware of treatment allocation, but these clinicians were not involved in patient follow-up. Participants, investigators that followed participants up and rated their complications were blinded to group allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Pharmacy employees and clinicians who instilled the sclerosant were aware of treatment allocation, but these clinicians were not involved in patient follow-up. Participants, investigators that followed participants up and rated their complications were blinded to group allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	LTFU well balanced and justified.
Selective reporting (reporting bias)	Low risk	No data provided for MRC dyspnoea score. Otherwise all predefined outcome measures reported.
Other bias	Low risk	No other biases identified.

Thomas 2017

Methods	Multicentre RCT comparing IPCs with talc slurry pleurodesis for MPE (Australia, New Zealand, Singapore, Hong Kong).
Participants	Inclusion criteria: histocytologically confirmed pleural malignancy or recurrent exudative pleural effusion with no alternative cause in the setting of histocytologically confirmed extrapleural cancer. Exclusion criteria: aged < 18 years, effusion < 2 cm maximum depth on imaging, expected survival < 3 months, chylothorax, previous lobectomy or pneumonectomy on side of effusion, previous attempted pleurodesis, pleural infection, hypercapnic ventilatory failure, blood leukocyte count < 1 x 10^9/L, pregnancy, lactating, irreversible bleeding diathesis, visual impairment. 146 participants randomised.
Interventions	Participants randomised to the IPC group had fluid removed at the time of catheter insertion, followed by ambulatory drainage as guided by symptoms. IPCs were removed when clinically indicated. Participants randomised to receive talc pleurodesis underwent 12- to 18-Fr intercostal drain insertion, followed by instillation of talc slurry as per routine practice of the recruiting hospital. All participants received usual standard care including chemotherapy, radiotherapy and palliative care.
Outcomes	Primary outcome: total number of days spent in hospital from trial intervention to death or follow-up at 12 months. Any hospital (or hospice) admission for ≥ 1 days was included. Secondary outcomes: total number of days and episodes of hospitalisation from pleural effusion-related causes, need for further pleural drainage procedures, breathlessness (VAS score), QoL (EQ-5D questionnaire and VAS scale), survival, adverse and serious adverse events.
Notes	Trapped lung included, which was balanced for in minimisation criteria. Included in network meta-analysis for pleurodesis failure, mortality and pain (participants with procedure-related pain). Study funding source: trial received funding support from the Sir Charles Gairdner Research Advisory Committee, Cancer Council of Western Australia, and the Dust Disease Board of New South Wales, Australia. Investigators had research fellowship funding support from the National Health and Medical Research Council (Drs YCG Lee, Thomas, and Fysh) and the WA Cancer and Palliative Care Network (Dr Thomas). Dr Smith received grants from Health Research Council New Zealand, the New Zealand Cancer Society and the New Zealand Lotteries Commission. Study author conflicts of interest statements: Dr YCG Lee reported receiving grants, non-financial support, personal fees, other funding (or a combination of these) from the Cancer Council of Western Australia, Dust Diseases Board of New South Wales, Sir Charles Gairdner Research Advisory Committee, National Health & Medical Research Council Australia, Rocket Ltd (unrestricted educational grant), CareFusion/BD (advisory board) and Sequana Medical (advisory board). Dr Kosky reported serving on the advisory board of Teva Pharmaceutical Australia and receiving travel grants and speakers' fees from UCBUK. Drs Thomas, Kwan, Yap, Lam, Garske, Shrestha, and YCG Lee are investigators of the AMPLE-2 trial for which Rocket Ltd provided the drainage supplies without charge. No other disclosures were reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based randomisation.

Thomas 2017 *(Continued)*

Allocation concealment (selection bias)	Low risk	Real-time randomisation using computer-based system.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and trial personnel unblinded to trial intervention – due to nature of the interventions blinding was not possible.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	All admissions were reviewed by an independent physician to ensure need for admission and duration were within common clinical practice. Blinding of statisticians not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis.
Selective reporting (reporting bias)	Low risk	Full healthcare economic analysis not calculated, which may bias in favour of IPCs; however, all stated outcomes reported.
Other bias	Low risk	No other biases identified.

Ukale 2004

Methods	Single-centre RCT comparing intrapleural talc and mepacrine given via a chest tube after thoracoscopy (Sweden).
Participants	Inclusion criteria: recurrent, symptomatic pleural effusions, known or suspected to be due to malignancy; eligible for thoracoscopy and pleurodesis. Exclusion criteria: incomplete lung re-expansion after thoracoscopy. 89 participants with confirmed MPEs were randomised (110 participants randomised in total, but some had benign causes).
Interventions	All participants underwent a local anaesthetic thoracoscopy, with biopsies and a 20-Fr drain was inserted at end of procedure. CXR performed to ensure lung re-expansion before randomisation. Mepacrine group: mepacrine 500 mg in 200 mL saline intrapleurally. Talc group: 5 g talc in 200 mL saline intrapleurally. In both groups, second dose given if > 50 mL/day drainage on day 3. Drains removed when < 50 mL/24-hour drainage.
Outcomes	Primary: pleurodesis success (using clinical and radiological definition). Reported at day 6, 2 weeks, 2 months, 4 months and 6 months Secondary: analgesia use; adverse effects; mortality
Notes	People with trapped lung excluded. Note that 2 doses may have been given. Included in network meta-analysis for pleurodesis failure and mortality. Study funding source: grants from King Oscar II Jubilee Foundation and the Stockholm City Council. Study author conflicts of interest statements: not stated.

Risk of bias

Ukale 2004 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation.
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unable to blind as drugs had different appearances.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Radiologists reporting CXRs were blind to treatment allocation. Symptom recurrence and adverse event reporting may be biased by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for LTFU and exclusions reported and well matched between groups.
Selective reporting (reporting bias)	Low risk	Data for those with confirmed MPE obtained from authors.
Other bias	Low risk	No other biases identified.

Villanueva 1994

Methods	Single-centre RCT of short-term vs long-term drainage before tetracycline pleurodesis of MPE (USA).
Participants	Inclusion criteria: moderate-to-large MPE, confirmed by cytology or pleural biopsy, causing respiratory symptoms; expected survival > 1 month; KPS > 40%. Exclusion criteria: previous chemical pleurodesis on the ipsilateral side; ipsilateral atelectasis due to complete airway obstruction by tumour. 25 participants randomised.
Interventions	28-Fr chest drain inserted. Tetracycline 1.5 g in 100–150 mL pleurodesis. Standard care (long-term drainage): tube suction drainage until lung re-expansion and < 150 mL/day drainage, then tetracycline pleurodesis and drain removed the following day. Short-term drainage: tube suction drainage until lung re-expansion, then tetracycline pleurodesis and drain removed the following day.
Outcomes	Pleurodesis success at 1 month (defined using CXR and need for repeat procedure) Duration of tube drainage Patient outcome (dead/alive – time point unclear)
Notes	Lung re-expansion confirmed on CXR prior to instillation of tetracycline. Not included in network meta-analysis. Study funding source: not stated.

Villanueva 1994 *(Continued)*

Study author conflicts of interest statements: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer randomisation.
Allocation concealment (selection bias)	Low risk	Computer randomisation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unable to blind as different timings of interventions.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Symptom recurrence could be biased by lack of blinding. Not stated if radiology was reported blindly.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1/25 participants LTFU.
Selective reporting (reporting bias)	Low risk	All stated outcomes reported; minimal information on safety/complications.
Other bias	Low risk	None.

Wahidi 2017

Methods	Multicentre RCT comparing daily IPC drainage with alternate day drainage in achieving autopleurodesis for people with MPE (USA).
Participants	Inclusion criteria: aged > 18 years, recurrent symptomatic pleural effusion in the setting of known malignancy with positive fluid cytology or pleural biopsy or recurrent effusion with no other identifiable cause, symptomatic improvement after therapeutic thoracentesis, recurrent symptoms with recurrence of pleural effusion. Exclusion criteria: life-expectancy < 30 days, trapped lung on CXR, loculated pleural effusion, ipsilateral previous surgery or attempted pleurodesis, chylothorax, pleural infection, inability to adequately perform pleural drainage at home, uncorrectable bleeding disorder, skin infection at site of intended IPC insertion, pregnancy. 149 participants randomised.
Interventions	IPC drainage performed at home by a visiting nurse or family member. Standard care: maximum 1 L drained alternate days. 'Aggressive' arm: maximum 1 L drained daily. In either group, drainage was stopped if cessation of pleural fluid flow occurred or participant developed persistent cough, breathlessness, chest tightness or pain.
Outcomes	Primary endpoint: incidence of autopleurodesis following placement of an IPC.

Wahidi 2017 *(Continued)*

	Secondary endpoints: time to autopleurodesis, KPS, QoL (SF-36 questionnaire), satisfaction of participants and carers (questionnaire) and adverse event rate.
Notes	Trapped lung excluded. Autopleurodesis defined as CR (≤ 50 mL drained on 3 consecutive drainages, radiographic score 0–1 and lack of symptoms) or PR (as per CR but radiographic scores of 2–5). Included in network meta-analysis for pleurodesis failure, mortality and pain (agreed between data extractors as those experiencing pain with IPC drainages). Study funding source: supported by an unrestricted grant from CareFusion, Inc. Study author conflicts of interest statements: Dr Feller-Kopman reported personal fees from CareFusion, Inc, during the conduct of the study; Dr Lamb reported other from Boston Scientific, outside the submitted work; Dr Light reported non-financial support from Care Fusion, outside the submitted work; in addition, Dr Light has a patent transforming growth factor-beta pleurodesis issued; Dr Reddy reported personal fees and non-financial support from Carefusion, Inc., outside the submitted work; Dr Wahidi reported consulting fees from Carefusion, outside the submitted work. The remaining authors had nothing to disclose.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based block design.
Allocation concealment (selection bias)	Low risk	Centralised randomisation by telephone call to co-ordinating centre.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participant and treating physicians not blinded to treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	CXR interpretation and management decisions were made by the treating physician (unblinded); however, assessment of primary outcome based on objective criteria and an independent blinded pulmonologist provided additional review of CXRs.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis. Significant withdrawal rate from standard arm before 12 weeks (22/76 participants) compared with daily drainage arm (9/73 participants). Authors commented that "the rate of death and inability to complete the study were anticipated because of the known medical complexity and short survival" of participants with MPE. Their data were included in the analysis up to the point they left the study.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	None identified.

Wang 2018

Methods	RCT evaluating the effects of intrathoracic perfusion of Endostar with chemotherapy in the management of MPE (China).

Wang 2018 *(Continued)*

Participants	Inclusion criteria: pathological or cytologically confirmed diagnosis of lung adenocarcinoma, KPS 1–2, estimated survival > 3 months, measurable primary and metastatic disease allowing for an objective judgement of any therapeutic effect, medium-to-large MPE confirmed by USS or CT and who had not received intrathoracic chemotherapy within the last month, no chemotherapy contraindications, normal liver/kidney/heart function, normal routine blood tests. 128 participants randomised.
Interventions	All participants received an USS-guided central venous catheter inserted into the thoracic cavity with intrathoracic chemotherapy once the effusion was drained. The drain was clamped for 24 hours and removed when the volume of drained was < 50 mL. Prior to treatment all participants received dexamethasone, folic acid and vitamin B_{12}. Endostar group: IV pemetrexed 500 mg/m^2 on day 1; intrathoracic cisplatin 75 mg/m^2 day 2, day 5 and day 8; intrathoracic Endostar 45 mg day 1, day 4 and day 7 in a 21-day cycle. Control group: IV pemetrexed 500 mg/m^2 on day 1; intrathoracic cisplatin 75 mg/m^2 day 2, day 5 and day 8. Evaluation of therapeutic effect assessed after 3 cycles.
Outcomes	Outcomes: effective treatment rate defined as CR or PR (CR: pleural effusion disappeared for > 4 weeks; PR: pleural effusion reduced by > 50% for > 4 weeks; stable disease: pleural effusion reduced < 50% or increased < 25%; progressive disease: pleural effusion increased by > 25% with other signs of progressive disease). Pleural effusion control rate was the proportion of participants who did not require repeat thoracentesis. QoL (EORTC QLQ C30 questionnaire at baseline and after 3 cycles of treatment). Toxicity and adverse effects.
Notes	Not included in network meta-analysis. Included people with lung adenocarcinoma only. No comment on exclusion criteria. Attempted to contact authors by email for further information. Study funding source: not stated. Study author conflicts of interest statements: authors declared no conflicts of interests.

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 information regarding measures taken.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated.
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated.

Wang 2018 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Duration of follow-up unclear ("all patients followed up for 6 months to 1 year"); however, not thought to influence outcome.
Selective reporting (reporting bias)	Low risk	Definition of pleurodesis success was unclear, as 2 different definitions were stated by the paper (quote: "the proportion of patients who did not need thoracentesis again" and "CR+PR+SD [stable disease]"). Limited reporting of QoL outcome data.
Other bias	Low risk	None identified.

Yildirim 2005

Methods	Single-centre RCT of rapid vs standard pleurodesis with oxytetracycline (Turkey).
Participants	Symptomatic MPE, confirmed on cytology or pleural biopsy. 27 participants randomised.
Interventions	12-Fr drain inserted. Pleurodesis agent: oxytetracycline 35 mg/kg. Standard protocol: drainage until lung re-expansion and fluid drainage < 150 mL/day. Then pleurodesis as a single dose. Drain clamped for 6 hours and removed when < 150 mL/day drainage. Rapid protocol: pleurodesis given as 4 divided doses, every 6 hours after aspiration through the drain.
Outcomes	Response to pleurodesis (CR/PR/failure) as defined by radiological recurrence and need for thoracentesis
Notes	People with trapped lung not excluded. Not included in network meta-analysis. Study funding source: not stated. Study author conflicts of interest statements: not stated.

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	Random number table.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unable to blind as different durations of drainage and aspiration schedules.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Symptom recurrence and duration of hospital stay may be biased by lack of blinding. Mortality not biased by lack of blinding.

Yildirim 2005 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data well balanced between the groups. At 1 month, 2/27 participants had died and were therefore non-evaluable.
Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	Low risk	No other biases identified.

Yim 1996

Methods	Single-centre RCT of talc insufflation vs talc slurry for symptomatic MPE (Hong Kong).
Participants	Inclusion criteria: established, symptomatic MPE (all cell types); dyspnoea improved after tube thoracostomy or large volume thoracentesis. Exclusion criteria: KPS < 30%; FEV_1 < 0.5 L; trapped lung; chemotherapy or radiotherapy within 6 months. 57 participants randomised.
Interventions	Talc insufflation group: all participants underwent a GA with 1 lung ventilation in the lateral decubitus position. 10 mm port inserted. Adhesions and loculations broken down. 5 g talc insufflated into the chest. 28-Fr tube at end of procedure, connected to suction. Drain removed when < 50 mL/24 hours drainage. Talc slurry group: chest tube. 5 g talc in 50 mL saline and 10 mL 2% lidocaine instilled through the drain. Drain clamped for 2 hours and participant turned Drain reconnected to suction and removed when output < 50 mL/24hours.
Outcomes	Radiological recurrence of effusion Complications of the procedure Postprocedure chest drain duration Length of hospital stay Parenteral meperidine use
Notes	People with trapped lung excluded from trial entry. Included in network meta-analysis for mortality. Excluded from main network meta-analysis as no pleurodesis failures in either study arm. Study funding source: this study was supported by University Funds (A/C 1635-23). Study author conflicts of interest statements: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.

Yim 1996 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Unable to blind due to nature of interventions.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Adverse event reporting and length of stay may be biased by lack of blinding. Not stated whether radiology was reported blindly.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported. Survival data not entirely clear.
Selective reporting (reporting bias)	Low risk	All outcomes reported on.
Other bias	Low risk	Unclear how many participants in the poudrage arm had a drain in situ at the time of trial entry. Pleurodesis success only defined using radiology.

Yoshida 2007

Methods	Multicentre RCT of bleomycin, OK-432 and cisplatin plus etoposide pleurodesis in MPE (Japan).
Participants	Inclusion criteria: cytology or histology confirmed MPE associated with newly diagnosed NSCLC; aged ≤ 75 years; ECOG Performance Score 0–2; full lung re-expansion after chest drainage; adequate bone marrow reserve, liver and renal functions. Exclusion criteria: prior chemotherapy, thoracic radiotherapy or thoracic surgery; bilateral pleural effusion or pericardial effusion; symptomatic brain metastases; active synchronous cancer; interstitial pneumonitis; pulmonary fibrosis; uncontrolled angina/myocardial infarction in preceding 3 months; uncontrolled diabetes or hypertension; pregnancy or breastfeeding; penicillin allergy. 102 participants randomised.
Interventions	Large- or small-bore chest tube inserted. After instillation of the study agent, participant rotated position for 3 hours. Bleomycin group: bleomycin 1 mg/kg (maximum 60 mg) intrapleurally in 100 mL saline. 1 dose. OK-432 group: OK-432 0.2 KE units/kg (maximum 10 KE) intrapleurally in 100 mL saline. 1 dose. Cisplatin + etoposide group: cisplatin 80 mg/m^2 1 dose + etoposide 80 mg/m^2 intrapleurally in 100 mL saline.
Outcomes	Pleural progression-free survival at 4 weeks, 8 weeks, 12 weeks and 24 weeks (defined on CXR and need for local treatment) Overall survival Toxicity
Notes	People with trapped lung not eligible for inclusion. Study authors emailed for more information, but no response. Not included in network meta-analysis. Study funding source: supported in part by Grants-in-Aid for cancer research from the Ministry of Health and Welfare of Japan.

Yoshida 2007 *(Continued)*

Study author conflicts of interest statement: authors had none to declare.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated if anyone was blinded. Same volume of instillate in both arms.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if anyone was blinded. If unblinded, reporting of symptom recurrence and toxicity could have been biased. Not stated if radiology was reported blindly but the definition of pleurodesis also incorporated symptom recurrence.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No LTFU.
Selective reporting (reporting bias)	Low risk	All stated outcomes reported.
Other bias	Low risk	Radiology may be difficult to assess as population has underlying lung cancer.

Zaloznik 1983

Methods	RCT of tetracycline pleurodesis vs placebo of the same pH as tetracycline (USA).
Participants	Inclusion criteria: biopsy confirmed malignancy; recurrent pleural effusion; expected survival > 1 month; KPS ≥ 40%. 30 participants randomised.
Interventions	Chest tube inserted and in place for ≥ 24 hours. After pleurodesis agent instilled, tube clamped for 2 hours and participant's position changed. Then left in place for 12–24 hours until minimal drainage. Tetracycline group: tetracycline 500 mg in 50 mL saline intrapleurally. 1 dose. Control group: 0.6 mL multivitamins, 5 mL of 0.1 normal hydrochloric acid and 50 mL saline intrapleurally. 1 dose.
Outcomes	Re-accumulation of effusion on CXR at 1 month and 3 months (CR/PR/stabilisation/progression) Adverse effects
Notes	CR, PR and stable disease counted as pleurodesis success for purposes of analysis. Some participants with bilateral effusions entered into the study, but not clear whether both sides were randomised. Therefore, for purposes of analysis, only the first side has been included. Included in network meta-analysis for pleurodesis failure.

Zaloznik 1983 *(Continued)*

Study funding source: not stated.

Study author conflicts of interest statement: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind" (no further details given).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind" (no further details given).
Incomplete outcome data (attrition bias) All outcomes	High risk	Time point at which primary outcome measured not clear. Minimal data on baseline participant characteristics. Participants who died within 1 month excluded from analysis (11/30 not evaluable).
Selective reporting (reporting bias)	Low risk	All outcomes reported on.
Other bias	Low risk	No other biases identified.

Zhao 2009

Methods	Single-centre RCT of intrapleural Ad-p53 and cisplatin, compared with cisplatin alone in MPE due to lung cancer (China).
Participants	Inclusion criteria: MPE due to lung cancer confirmed by CT, thoracic ultrasound and cytohistological examination; expected survival > 3 months; KPS > 60. Exclusion criteria: abnormal ECG, liver function, kidney function and routine blood examination; previous chemotherapy, radiotherapy or biological therapy. 35 participants randomised.
Interventions	All participants had chest drain inserted and effusion drained completely. All received systemic vinorelbine. All received dexamethasone 10 mg intrapleurally after instillation of trial drugs. Drug administration was repeated weekly for 4 weeks or until pleural effusion resolved. Combination group: Ad-p53 (1×10^{12} viral particles) in 100 mL saline intrapleurally. Then cisplatin 40 mg/m^2 in 100 mL saline intrapleurally. Single agent group: cisplatin 40 mg/m^2 in 100 mL saline intrapleurally.
Outcomes	Therapeutic efficacy (CR/PR/stable disease/progressive disease) – as defined by extent of effusion and radiology and symptoms, at 4 weeks Change in KPS from baseline to 4 weeks

Zhao 2009 *(Continued)*

	Adverse events
Notes	People with trapped lung not excluded from the study. CR and PR counted as a successful pleurodesis for the purposes of analysis. Study authors emailed for further information, but no response. Not included in network meta-analysis. Study funding source: not stated. Study author conflicts of interest statements: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not stated explicitly but combination group received 2 intrapleural treatments, while other arm only received 1.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Symptoms, QoL and adverse events could be biased by lack of blinding. Not stated if radiology was reported blindly.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No LTFU.
Selective reporting (reporting bias)	Low risk	All outcomes reported on.
Other bias	Low risk	No other biases identified.

Zimmer 1997

Methods	Prospective RCT of talc vs bleomycin pleurodesis for symptomatic MPE (USA).
Participants	Inclusion criteria: MPE (all cell types); life-expectancy > 1 month. Exclusion criteria: significant loculated effusions; trapped lung. 40 procedures randomised in 35 participants.
Interventions	All participants underwent tube thoracostomy (either at the end of a limited thoracotomy (2 participants) or inserted at bedside (33 participants)). Tube remained on suction. After sclerosant injected intrapleurally, tube clamped for 2 hours and participant rotated. Talc group: 5 g talc in 50 mL saline, with 20 mL 1% lignocaine. 1 dose.

Zimmer 1997 *(Continued)*

	Bleomycin group: bleomycin 60 U in 50 mL saline, with 20 mL 1% lignocaine. 1 dose.
Outcomes	Effusion control on CXR (at a minimum of 2 weeks) Dyspnoea (according to functional class 1–4) Pain (according to scale 0–10) Cost Length of hospital stay
Notes	People with trapped lung excluded. Participants only included in primary analysis if out of hospital and able to attend follow-up at 2 weeks. Study authors emailed for more information, but no response. Included in network meta-analysis for pleurodesis failure. Study funding source: not stated. Study author conflicts of interest statement: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not explicitly stated but drugs had different appearances.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Symptom recurrence, pain, breathlessness, duration of stay and adverse events could all be biased by lack of blinding. Not stated if radiology reported blindly.
Incomplete outcome data (attrition bias) All outcomes	High risk	No clear time point when follow-up performed. Only those available for follow-up included in the analysis. Unclear how many randomised to each arm (only data on numbers analysed by treatment arm).
Selective reporting (reporting bias)	Low risk	All outcomes reported on.
Other bias	Low risk	No other biases identified.

CALGB: Cancer and Leukemia Group B; CR: complete response; CT: computer tomography; CXR: chest x-ray; DHHS: Department of Health and Human Services; ECOG: Eastern Cooperative Oncology Group; EQ-5D-5L: 5-level EQ-5D; FEV_1: forced expiratory volume in one second; Fr: French; GA: general anaesthetic; IPC: indwelling pleural catheter; ITT: intention to treat; IV: intravenous; KE: klinische Einheit (clinical unit); KPS: Karnofsky Performance Score; LTFU: loss to follow-up; MBS: Modified Borg Scale; MPE: malignant pleural effusion; MPM: malignant pleural mesothelioma; NCI: National Cancer Institute; NSAID: non-steroidal anti-inflammatory drug; NSCLC: non-small cell lung cancer; PR: partial response; QoL: quality of life; RCT: randomised controlled trial; SF-36: 36-item Short Form; TMP: thoracoscopic mechanical pleurodesis; USS: ultrasound scan; VAS: visual analogue scale; VATS: video-assisted thoracoscopic surgery; VEGF: vascular

endothelial growth factor; WCC: white cell count; WHO: World Health Organization; WHOQOL-BREF: World Health Organization Quality of Life: Brief Version.

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

Study	Reason for exclusion
Caglayan 2008	Study not truly randomised (high risk of bias for sequence generation). Participants allocated to treatment groups using alternation.
Dryzer 1993	Unable to differentiate between participants with benign and malignant disease in the results section. Also, not truly randomised (high risk of bias from randomisation method as allocated to treatment groups based on the last digit of their hospital number).
Elayouty 2012	Unclear from text if truly randomised – participants given number on entering study – allocated to bleomycin if number was odd and allocated to povidone group if number was even. Study authors emailed for clarification but no response.
Engel 1981	Study not truly randomised. Participants allocated to treatment groups based on the day of the calendar month. High risk of bias for sequence generation.
Gust 1990	Pilot data (not randomised) and randomised data presented grouped together. Unable to differentiate out the non-randomised data. No contact details available for study authors.
Kleontas 2019	Not truly randomised (high risk of bias for sequence generation and allocation concealment. Additional information obtained from author who explained participants allocated to each arm consecutively).
Kwasniewska-Rokicinska 1979	Participants with pleural effusions and ascites included, but unable to differentiate between them in the results section.
Lissoni 1995	Unable to differentiate between pleural, pericardial and peritoneal effusions in the results. No response from study authors.
Liu 2017	High risk of bias for sequence generation and allocation concealment (not randomised). We were unable to contact the authors for further clarification.
Maiche 1993	Study not randomised (high risk of bias for sequence generation). Participants allocated to bleomycin group if met a list of criteria, otherwise given mitoxantrone.
Manes 2000	Study not truly randomised (high risk of bias for sequence generation). Participants allocated to treatment groups based on the month of their diagnosis with MPE.
Martin 2019	Feasibility study to determine whether sufficient numbers could be recruited for a future multicentre RCT to test the impact of pleural elastance directed indwelling pleural catheter or talc slurry pleurodesis management. Excluded from review as does not meet inclusion criteria (study does not give outcome data from comparison of different methods of managing malignant pleural effusion).
Nio 1999	Participants with pleural and peritoneal effusions included in the study and unable to differentiate them in the results.
Ogunrombi 2014	Excluded due to inclusion of a child in study. An attempt was made to contact the authors by email to obtain data for adults only but no reply was received.
Tattersall 1982	Not randomised (high risk of bias for sequence generation and allocation concealment), therefore excluded.

MPE: malignant pleural effusion.

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

Amjadi – OPUS Trial

Methods	RCT comparing the time to pleurodesis in people with MPE receiving doxycycline + IPC vs IPC alone (OPUS).
Participants	MPE
Interventions	IPC + doxycycline: doxycycline 500 mg in 50 mL saline via IPC. Placebo: 50 mL normal saline via IPC.
Outcomes	Primary outcome: time to pleurodesis Secondary outcomes: pleurodesis rate at 90 days postinsertion of IPC, adverse events, effects on pulmonary function
Notes	Study identified from clinical trials registry during literature search and listed as currently recruiting. Authors contacted for further information but no reply received. Recruitment started 2009.

Bo 1998

Methods	Randomised study comparing highly agglutinative staphylococcin plus cisplatin with cisplatin alone.
Participants	74 participants with MPE and ascites.
Interventions	Unclear from abstract how agents were delivered.
Outcomes	Reduction in effusion/ascites volume KPS
Notes	Full text only available in Chinese and unable to translate. Need to confirm if pleural and ascites data were presented separately and how the agents were delivered.

Chen 2015

Methods	Randomised study comparing the therapeutic effect and safety of bevacizumab combined with cisplatin on MPE of people with NSCLC.
Participants	54 people with NSCLC and MPE.
Interventions	Control group: intrathoracic injection of cisplatin 75 mg/m^2 twice, each cycle 21 days. Combined treatment group: intrathoracic bevacizumab 5 mg/kg twice, plus cisplatin as per control group regimen.
Outcomes	Pleural effusion control rate, adverse reactions, level of pleural fluid vascular endothelial growth factor before each cycle.
Notes	Full text only available in Chinese alphabet and unable to translate.

Cong 2010

Methods	RCT of pleural perfusion of nedaplatin and cisplatin in MPE due to NSCLC.
Participants	68 participants with lung cancer associated with MPE.
Interventions	Participants randomised into 2 groups. Group 1: nedaplatin 40 mg/m^2 and dexamethasone 10 mg given intrapleurally. Group 2: cisplatin 40 mg/m^2 and dexamethasone 10 mg in 40 mL saline given intrapleurally. Agents given weekly for 2–4 weeks.
Outcomes	Treatment response, adverse effects, KPS, survival.
Notes	Full text only available in Chinese and unable to translate.

Fukuoka 1984

Methods	RCT of intrapleural adriamycin and *Nocardia rubra* cell wall skeleton compared with adriamycin alone.
Participants	55 participants with MPE due to lung cancer.
Interventions	Agents given via tube thoracostomy. No other details available.
Outcomes	Treatment response.
Notes	In Japanese. Unable to translate.

Miyanaga 2011

Methods	Trial comparing bleomycin, OK-432 and cisplatin + etoposide in MPE due to NSCLC.
Participants	MPE due to previously untreated NSCLC.
Interventions	Intrapleural bleomycin, OK-432 and cisplatin + etoposide.
Outcomes	Progression-free survival.
Notes	In Japanese. Unable to translate. No details in abstract as to whether it is randomised or the number of participants in the study.

Mohamed 2013

Methods	Randomised study evaluating the efficacy and safety of tranexamic and bleomycin for pleurodesis in MPE.
Participants	63 people with MPE.

Mohamed 2013 *(Continued)*

Interventions	Randomised to receive tranexamic acid, bleomycin or tranexamic acid + bleomycin via chest drain.
Outcomes	Pleurodesis success, complications.
Notes	Abstract. Contacted authors for further information, which is pending at the time of review completion.

Song 2013

Methods	RCT comparing intrapleural *Pseudomonas aeruginosa*, with cisplatin and interleukin-2.
Participants	90 participants with MPE.
Interventions	Agents administered through intrathoracic infusion. No other information available.
Outcomes	Clinical efficacy and adverse reactions.
Notes	Written in Chinese and unable to obtain a translation. Only abstract available in English.

Sun 2002

Methods	RCT of intrapleural Ya-Dan-Zhi's grease (YDZ) and cisplatin in MPE.
Participants	72 participants with MPE.
Interventions	Randomly divided between 3 groups: Group 1: YDZ 80 mL and cisplatin 60 mg intrapleurally once per week; Group 2: YDZ 80 mL intrapleurally once per week; Group 3: cisplatin 60 mg intrapleurally once per week.
Outcomes	Treatment effect, adverse effects.
Notes	In Chinese and unable to obtain a translation. Unclear from abstract if study would be eligible for inclusion in the review.

Won 1997

Methods	RCT comparing intrapleural doxycycline and bleomycin.
Participants	34 participants with MPE requiring repeated thoracentesis.
Interventions	Participants received either intrapleural doxycycline or bleomycin.
Outcomes	Fluid volume, adverse effects, response to treatment (on CXR and clinical examination), survival.
Notes	In Korean. Only abstract available in English. Unable to obtain a translation.

Xu 2010

Methods	RCT evaluating the effect of intrapleural highly agglutinative staphylococcin combined with nedaplatin, compared to nedaplatin alone.
Participants	58 participants with MPE.
Interventions	Participants randomised to 2 groups. Group 1: intrapleural highly agglutinative staphylococcin with nedaplatin. Group 2: nedaplatin alone.
Outcomes	Treatment response, adverse effects, quality of life.
Notes	In Chinese. Only abstract available in English and unclear from it whether the study is eligible. Unable to obtain translation of the full text.

Yu 2003

Methods	RCT comparing cisplatin and lentinan in MPE.
Participants	64 participants with MPE.
Interventions	Randomised into 2 groups: Group 1: intrathoracic cisplatin and lentinan; Group 2: intrathoracic cisplatin only.
Outcomes	Response rates.
Notes	In Chinese. Only abstract available in English and unclear from it whether the study is eligible. Unable to obtain translation of the full text.

Zhuang 2012

Methods	RCT comparing matrine injection (yanshu) combined with intrapleural cisplatin for treatment of haematological malignancies complicated by pleural effusion.
Participants	46 participants with haematological malignancy complicated by pleural effusion.
Interventions	Participants randomly divided into 2 groups. Group 1: intrapleural cisplatin 20 mg/m^2 and yanshu 10 mL/m^2 and dexamethasone 5 mg/m^2. Group 2: intrapleural cisplatin 20 mg/m^2 and dexamethasone 5 mg/m^2.
Outcomes	Efficacy, adverse effects.
Notes	In Chinese. Only abstract available in English and unclear from it whether the study is eligible. Unable to obtain translation of the full text.

CXR: chest x-ray; IPC: indwelling pleural catheter; KPS: Karnofsky Performance Score; MPE: malignant pleural effusion; NSCLC: non-small cell lung cancer; RCT: randomised controlled trial.

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

AMPLE 3

Trial name or title	The Australasian Malignant Pleural Effusion (AMPLE) Trial 3: a randomised study of the relative benefits of combined indwelling pleural catheter (IPC) and talc pleurodesis therapy or video-assisted thoracoscopic surgery (VATS) in the management of participants with malignant pleural effusion.
Methods	Multicentre, international RCT comparing IPC and talc pleurodesis to VATS for the management of MPE.
Participants	Inclusion criteria: people with symptomatic MPE, predicted survival > 6 months, ECOG score 0–1. Exclusion criteria: aged < 18 years, unable to undergo surgical procedure, pleural infection, chylothorax, pregnancy or lactation, uncorrectable bleeding diathesis, previous ipsilateral lobectomy/pneumonectomy, unable to consent or comply with protocol.
Interventions	IPC arm: after complete evacuation of the pleural space and if lung fully expanded with no contraindication 4–5 g talc administered by IPC with daily drainage for 14 days. VATS arm: VATS pleurodesis by talc poudrage or thoracoscopic mechanical pleural abrasion.
Outcomes	Primary outcome: proportion of participants requiring a repeat ipsilateral pleural procedure for symptomatic effusion re-accumulation. Secondary outcomes: time to effusion recurrence, all-cause hospital days, breathlessness (VAS), pain (VAS), QoL (EQ-5D-5L), physical activity patterns (measured by actigraphy), adverse event reporting, pleural-related hospital days.
Starting date	2019
Contact information	deirdre.fitzgerald@health.wa.gov.au
Notes	

MesoTRAP

Trial name or title	MesoTRAP
Methods	Feasibility study that includes a pilot multicentre, RCT comparing VAT partial pleurectomy/decortication with IPC in people with trapped lung and pleural effusion due to MPM.
Participants	Inclusion criteria: trapped lung requiring intervention in people with MPM with pleural effusion, aged > 18 years, expected survival > 4 months, suitable and willing to undergo VAT partial pleurectomy/decortication or IPC insertion. Exclusion criteria: full lung re-expansion following pleural drainage and evidence of active pleural infection.
Interventions	VAT-PD: VAT partial pleurectomy/decortication under general anaesthetic. IPC: IPC insertion under local anaesthetic.
Outcomes	Primary outcome: VAS Dyspnoea Score.

MesoTRAP *(Continued)*

	Secondary outcomes: VAS chest pain score, EQ-5D-5L and EORTC QLQ-C30 scores, 30-day and 12-month survival, serious adverse events, prevalence of trapped lung in mesothelioma.
Starting date	2017
Contact information	carolfreeman@nhs.net
Notes	

NCT02583282

Trial name or title	A study to compare the efficacy and safety of intrapleural doxycycline vs iodopovidone for performing pleurodesis in malignant pleural effusion.
Methods	RCT comparing doxycycline and iodine pleurodesis.
Participants	Inclusion criteria: recurrent, symptomatic MPE with dyspnoea improvement follow thoracentesis.
Interventions	Participants randomised to receive doxycycline 500 mg slurry via chest drain or 20 mL 10% betadine via chest drain.
Outcomes	Pleurodesis success, defined as absence of effusion re-accumulation on CXR at 30 days and relief of symptoms.
Starting date	2015
Contact information	riteshpgi@gmail.com
Notes	Study details as listed on clinical trials registry. Confirmation received from author that study is continuing to recruit.

OPTIMUM

Trial name or title	OPTIMUM
Methods	Multicentre RCT comparing whether outpatient management of MPE with an IPC and pleurodesis improves QoL compared with inpatient care with a chest drain and talc pleurodesis.
Participants	Inclusion criteria: MPE, WHO Performance Score 0–2, expected survival > 3 months. Exclusion criteria: aged < 18 years, pregnant or lactating, allergy to talc or lignocaine, lack of symptomatic relief from effusion drainage, district nurse/carer/hospital unable to carry out at least twice weekly IPC drainage, lymphoma or small cell carcinoma except if failure of chemotherapy or for palliative management, non-malignant effusion, loculated effusion that would prevent successful drain insertion or symptomatic benefit, unable to provide written consent.
Interventions	IPC group: talc pleurodesis via IPC day 4 postprocedure if output < 150 mL/day and satisfactory lung expansion. Usual care: ultrasound-guided chest drain and talc pleurodesis.
Outcomes	Primary outcome: health-related QoL at 30 days measured using the EORTC QLQ-C30.

OPTIMUM *(Continued)*

	Secondary: QoL at 60 days and 90 days, pleurodesis failure rate, pain and breathlessness, complications.
Starting date	2015
Contact information	joanna.peel@gstt.nhs.uk
Notes	

SIMPLE

Trial name or title	Efficacy of sonographic and biological pleurodesis indicators of malignant pleural effusion (SIMPLE).
Methods	Multicentre RCT designed to evaluate whether use of thoracic ultrasound in hospitalised people with MPE before and during the first 24–72 hours post-talc administration, accurately identifies pleural adherence early in treatment, permitting shorter hospital stay without adversely affecting pleurodesis success.
Participants	Inclusion criteria: confirmed MPE requiring pleurodesis. Exclusion criteria: aged < 18 years, poor prognosis (patient in whom pleurodesis would not be offered in normal practice), irreversible contraindication to chest drain insertion.
Interventions	Control: chest drain removed postpleurodesis once pleural fluid output < 250 mL/24 hours, there is satisfactory evacuation of the fluid on CXR and the lung remains fully expanded. Thoracic ultrasound group: talc pleurodesis once there is ultrasound evidence of effusion resolution. Drain removed postpleurodesis on the basis of ultrasound appearances.
Outcomes	Primary outcome: number of days in hospital during the initial hospitalisation. Secondary outcomes: pleurodesis success at 1 month' and 3 months' postrandomisation, number of days postrandomisation with chest drain in situ, breathlessness (VAS) and thoracic pain (VAS), QoL (EQ-5D-5L), cost-effectiveness, 12-month mortality.
Starting date	2015
Contact information	ioannis.psallidas@ndm.ox.ac.uk
Notes	

Sterile-graded talc versus OK-432

Trial name or title	A randomised comparative phase 3 trial of pleurodesis in malignant pleural effusions: sterile graded talc vs. OK-432 (WJOG8415L).
Methods	RCT to compare efficacy and safety of graded talc and OK-432 in pleurodesis for MPE.
Participants	Inclusion criteria: histocytologically confirmed symptomatic MPE, previous chest tube drainage, life-expectancy > 30 days, aged > 20 years. Exclusion criteria: hypersensitivity to talc or OK-432, hypersensitivity to penicillin, severe infection, severe pulmonary fibrosis or emphysema, myocardial infarction within 30 days, severe coagulopathy, indication for bilateral pleurodesis, major surgical intervention of the affected hemithorax,

Sterile-graded talc versus OK-432 *(Continued)*

	previous ipsilateral pleurodesis, concurrent massive ascites, glucocorticoid treatment, pregnancy or lactation, unable to co-operate with study.
Interventions	Instillation of OK-432 distilled in 50 mL of saline into thoracic cavity. Talc group: 4 g graded talc distilled in 50 mL of saline.
Outcomes	Primary outcome: pleural effusion recurrence-free rate at 30 days after primary pleurodesis. Secondary outcomes: pleural effusion recurrence free survival time, pleural effusion recurrence free rate at 3 months, QoL (FACT-L measurement).
Starting date	2016
Contact information	saka@med.nagoya-u.ac.jp
Notes	

SWIFT

Trial name or title	Pivotal multi center, randomized, controlled, single-blinded study comparing the silver nitrate coated indwelling pleural catheter to the uncoated PleurX catheter for the management of symptomatic, recurrent, malignant pleural effusions.
Methods	RCT to determine whether a silver nitrate-coated IPC is safe and effective in treating MPEs compared to approved catheters.
Participants	Inclusion criteria: symptomatic MPE requiring intervention, aged > 18 years, ≥ 1 ipsilateral pleural effusion causing dyspnoea that responded to thoracentesis where the lung expanded and the dyspnoea was improved, sufficient pleural fluid to allow safe insertion of an IPC, negative pregnancy test if appropriate, participant or carer is able to perform home drainage of the pleural effusion (UK participants will have drainage managed by home-care nurses). Exclusion criteria: significant trapped lung, or a proximal bronchial obstruction which is likely to lead to trapped lung, KPS < 50 or ECOG > 3, pregnant or lactating, empyema, chylothorax, uncorrectable coagulopathy, hypersensitivity to new or existing pleural catheter, systemic or pleural infection, ipsilateral lobectomy or pneumonectomy, previous attempt at ipsilateral pleurodesis which has failed, immunodeficiency, bilateral pleural effusions, fluid loculation such that attempts at pleurodesis are likely to be futile, mediastinal shift of ≥ 2 cm toward the side of the effusion, receiving concurrent intrapleural chemotherapy or radiotherapy to the ipsilateral chest, no access to a telephone.
Interventions	Silver nitrate-coated IPC vs standard IPC.
Outcomes	Primary outcome: proportion of participants achieving pleurodesis without recurrence. Secondary outcomes: time to pleurodesis; time to recurrence; proportion of surviving participants without a trapped lung diagnosis following IPC placement who have confirmed pleurodesis without recurrence at 14 days, 30 days, 60 days and 90 days; proportion of participants with confirmed pleurodesis and without recurrence 30 days after IPC placement by cancer type (lung, breast and others); incidence of IPC occlusion; incidence of empyema and cellulitis; pain (VAS).
Starting date	April 2018
Contact information	Joseph B Shrager, Stanford University
Notes	

TILT

Trial name or title	A Trial of Intra-pleuraL bacterial immuno-Therapy in mesothelioma (TILT): a feasibility study using the 'trial within a cohort' methodology.
Methods	RCT investigating intrapleural bacterial immunotherapy in MPM using the 'Trial within a Cohort' (TwiC) methodology. Participants are recruited from an existing observational cohort (the ASSESS-meso study).
Participants	24 eligible participants are identified from the cohort, of whom 16 participants are randomly selected to be offered either OK432 or BCG. Inclusion criteria: histocytological diagnosis of MPM, enrolled in ASSESS-meso cohort study and given consent to undergo randomisation for future trials, IPC in situ that has drained > 50 mL of fluid on previous 3 drainages or willing to have an IPC and has a pleural effusion suitable for IPC insertion, no chemotherapy in preceding 4 weeks and none planned in subsequent 4 weeks, Performance Status ≤ 2, Performance Status 3 and felt clinically suitable for trial, predicted survival ≥ 12 weeks, to consent. Exclusion criteria: no IPC in situ and has contraindication to IPC insertion; clinico-radiological diagnosis of mesothelioma; trapped lung with < 50% pleural apposition on x-ray; moderately heavy or heavily loculated pleural effusion; known immunodeficiency or immunosuppressive medication; intercurrent infection (pleural or elsewhere) or clinical signs of sepsis; known sensitivity or allergy to OK432 or penicillin; previous treatment with immunotherapy; currently enrolled in any other interventional clinical trial; brain metastases or central nervous system involvement of mesothelioma; pregnancy or lactation; aged < 18 years; any other factor that, in the opinion of the chief investigator, would mean participation in the study would be contraindicated.
Interventions	Either OK432 or BCG delivered intrapleurally as a single dose via IPC. Participants are followed up at 4 trial visits over 12 weeks. On completion of the trial, they return to standard follow-up in the ASSESS-meso cohort study. Outcome data compared with 8 control participants from ASSESS-meso. Qualitative interviews are undertaken at the end of trial to assess acceptability of the methodology to participants.
Outcomes	Feasibility assessed by: recruitment rates to time and target > 66%, attrition rate < 20%, data completeness rates > 90%. Secondary outcomes: acceptability of the TwiC methodology; acceptability of the intervention; safety of intrapleural OK432 or BCG; tumour response rates measured on CT chest at baseline and week 12 using modified RECIST criteria; progression-free survival rates at week 12; patient-reported chest pain and breathlessness (VAS); patient-reported QoL (EQ-5D-5L); pleurodesis rates; biomarker response, assessed using serum mesothelin blood tests at baseline, week 3, week 6 and week 12; immunological response (BCG arm only) assessed using Mantoux skin testing at baseline and week 6.
Starting date	2018
Contact information	Dr A Bibby
Notes	

BCG: Bacillus Calmette-Guérin; CT: computer tomography; CXR: chest x-ray; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L: 5-level EQ-5D; FACT-L: Functional Assessment of Cancer Therapy – Lung; IPC: indwelling pleural catheter; KPS: Karnofsky Performance Score; MPE: malignant pleural effusion; MPM: malignant pleural mesothelioma; QoL: quality of life; RCT: randomised controlled trial; RECIST: Response Evaluation Criteria in Solid Tumors; VAS: visual analogue scale; VAT-PD: video-assisted thoracoscopic partial pleurectomy/decortication; VATS: video-assisted thoracoscopic surgery; WHO: World Health Organization.

DATA AND ANALYSES

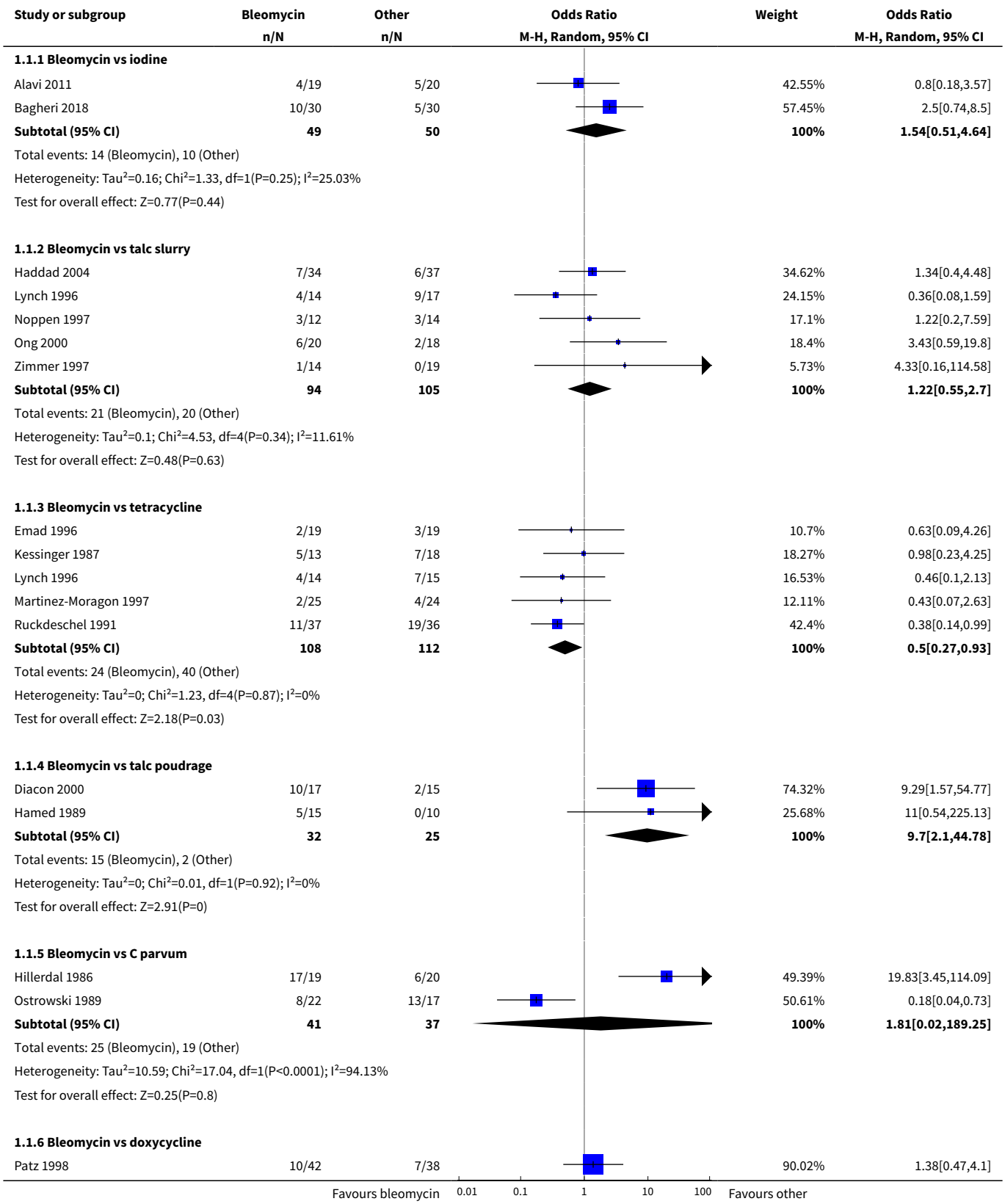
Comparison 1. Bleomycin

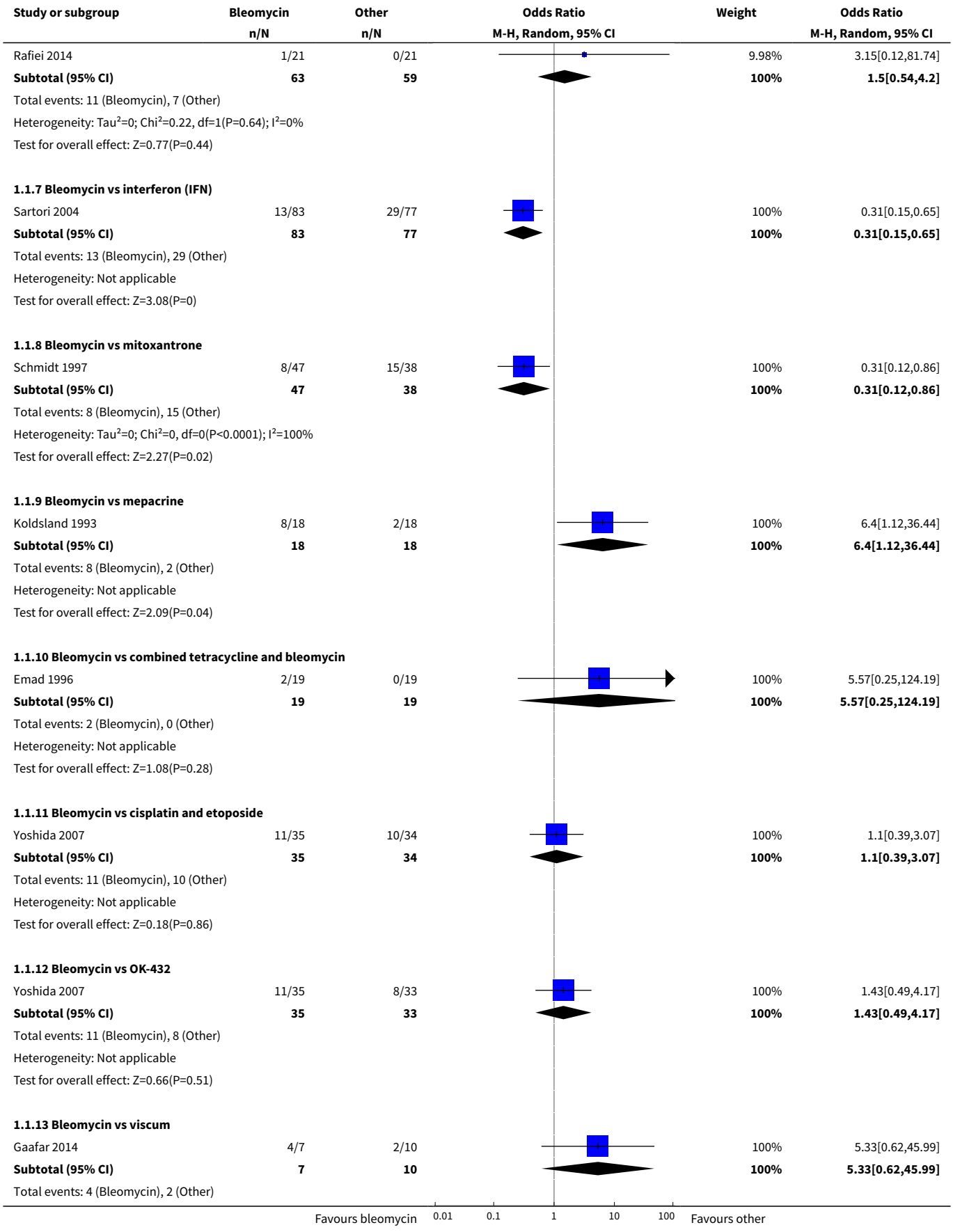
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Pleurodesis failure rate	22		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Bleomycin vs iodine	2	99	Odds Ratio (M-H, Random, 95% CI)	1.54 [0.51, 4.64]
1.2 Bleomycin vs talc slurry	5	199	Odds Ratio (M-H, Random, 95% CI)	1.22 [0.55, 2.70]
1.3 Bleomycin vs tetracycline	5	220	Odds Ratio (M-H, Random, 95% CI)	0.50 [0.27, 0.93]
1.4 Bleomycin vs talc poudrage	2	57	Odds Ratio (M-H, Random, 95% CI)	9.70 [2.10, 44.78]
1.5 Bleomycin vs *C parvum*	2	78	Odds Ratio (M-H, Random, 95% CI)	1.81 [0.02, 189.25]
1.6 Bleomycin vs doxycycline	2	122	Odds Ratio (M-H, Random, 95% CI)	1.50 [0.54, 4.20]
1.7 Bleomycin vs interferon (IFN)	1	160	Odds Ratio (M-H, Random, 95% CI)	0.31 [0.15, 0.65]
1.8 Bleomycin vs mitoxantrone	1	85	Odds Ratio (M-H, Random, 95% CI)	0.31 [0.12, 0.86]
1.9 Bleomycin vs mepacrine	1	36	Odds Ratio (M-H, Random, 95% CI)	6.40 [1.12, 36.44]
1.10 Bleomycin vs combined tetracycline and bleomycin	1	38	Odds Ratio (M-H, Random, 95% CI)	5.57 [0.25, 124.19]
1.11 Bleomycin vs cisplatin and etoposide	1	69	Odds Ratio (M-H, Random, 95% CI)	1.1 [0.39, 3.07]
1.12 Bleomycin vs OK-432	1	68	Odds Ratio (M-H, Random, 95% CI)	1.43 [0.49, 4.17]
1.13 Bleomycin vs viscum	1	17	Odds Ratio (M-H, Random, 95% CI)	5.33 [0.62, 45.99]
2 Fever	17		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Bleomycin vs talc slurry	3	99	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.31, 2.56]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.2 Bleomycin vs talc poudrage	1	32	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.11, 7.05]
2.3 Bleomycin vs tetracycline	5	250	Odds Ratio (M-H, Random, 95% CI)	2.05 [0.67, 6.34]
2.4 Tetracycline vs *C parvum*	2	80	Odds Ratio (M-H, Random, 95% CI)	0.43 [0.17, 1.12]
2.5 Bleomycin vs IFN	1	160	Odds Ratio (M-H, Random, 95% CI)	151.35 [9.08, 2522.62]
2.6 Bleomycin vs mitoxantrone	1	96	Odds Ratio (M-H, Random, 95% CI)	1.11 [0.37, 3.36]
2.7 Bleomycin vs mepacrine	1	40	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.14, 1.92]
2.8 Bleomycin vs doxycycline	2	148	Odds Ratio (M-H, Random, 95% CI)	2.69 [0.08, 89.51]
2.9 Bleomycin vs combined tetracycline and bleomycin	1	40	Odds Ratio (M-H, Random, 95% CI)	0.47 [0.04, 5.69]
2.10 Bleomycin vs OK432	1	67	Odds Ratio (M-H, Random, 95% CI)	0.7 [0.23, 2.13]
2.11 Bleomycin vs cisplatin and etoposide	1	69	Odds Ratio (M-H, Random, 95% CI)	2.22 [0.82, 6.01]
2.12 Bleomycin vs iodine	1	60	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.13, 7.60]
3 Pain	15		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Bleomycin vs talc slurry	2	73	Odds Ratio (M-H, Random, 95% CI)	1.66 [0.41, 6.80]
3.2 Bleomycin vs tetracycline	4	220	Odds Ratio (M-H, Random, 95% CI)	0.61 [0.29, 1.27]
3.3 Bleomycin vs talc poudrage	1	32	Odds Ratio (M-H, Random, 95% CI)	0.28 [0.01, 7.31]
3.4 Bleomycin vs *C parvum*	2	71	Odds Ratio (M-H, Random, 95% CI)	0.70 [0.27, 1.85]
3.5 Bleomycin vs IFN	1	160	Odds Ratio (M-H, Random, 95% CI)	32.34 [1.89, 552.23]
3.6 Bleomycin vs mitoxantrone	1	96	Odds Ratio (M-H, Random, 95% CI)	0.48 [0.15, 1.56]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.7 Bleomycin vs mepacrine	1	40	Odds Ratio (M-H, Random, 95% CI)	0.46 [0.11, 1.94]
3.8 Bleomycin vs doxycycline	2	148	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.26, 2.70]
3.9 Bleomycin vs OK-432	1	67	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.14, 1.12]
3.10 Bleomycin vs cisplatin and etoposide	1	69	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.32, 2.16]
3.11 Bleomycin vs iodine	1	60	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.13, 7.60]
4 Mortality	11		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Bleomycin vs combined tetracycline and bleomycin	1	40	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.06, 17.18]
4.2 Bleomycin vs talc slurry	2	116	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.29, 2.75]
4.3 Bleomycin vs tetracycline	2	125	Odds Ratio (M-H, Random, 95% CI)	0.63 [0.27, 1.44]
4.4 Bleomycin vs talc poudrage	1	32	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.20, 3.43]
4.5 Bleomycin vs *C parvum*	1	55	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.19, 1.94]
4.6 Bleomycin vs IFN	1	160	Odds Ratio (M-H, Random, 95% CI)	0.46 [0.25, 0.87]
4.7 Bleomycin vs mitoxantrone	1	96	Odds Ratio (M-H, Random, 95% CI)	2.15 [0.95, 4.86]
4.8 Bleomycin vs OK-432	1	68	Odds Ratio (M-H, Random, 95% CI)	2.66 [0.98, 7.23]
4.9 Bleomycin vs doxycycline	2	122	Odds Ratio (M-H, Random, 95% CI)	1.44 [0.53, 3.90]
4.10 Bleomycin vs cisplatin and etoposide	1	69	Odds Ratio (M-H, Random, 95% CI)	2.22 [0.82, 6.01]
5 Repeat pleural intervention	1	33	Odds Ratio (M-H, Fixed, 95% CI)	4.33 [0.16, 114.58]
5.1 Bleomycin vs talc slurry	1	33	Odds Ratio (M-H, Fixed, 95% CI)	4.33 [0.16, 114.58]

Analysis 1.1. Comparison 1 Bleomycin, Outcome 1 Pleurodesis failure rate.

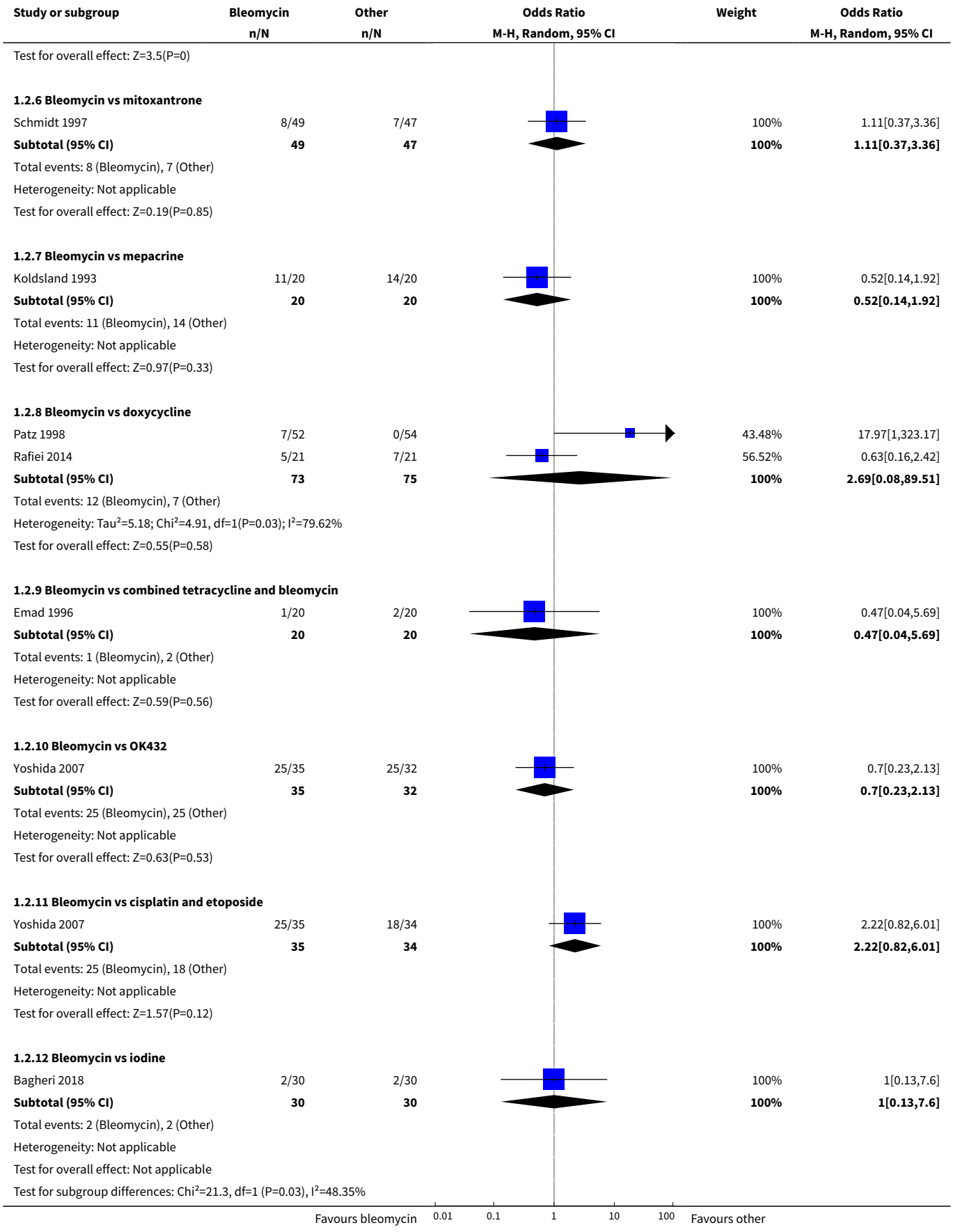




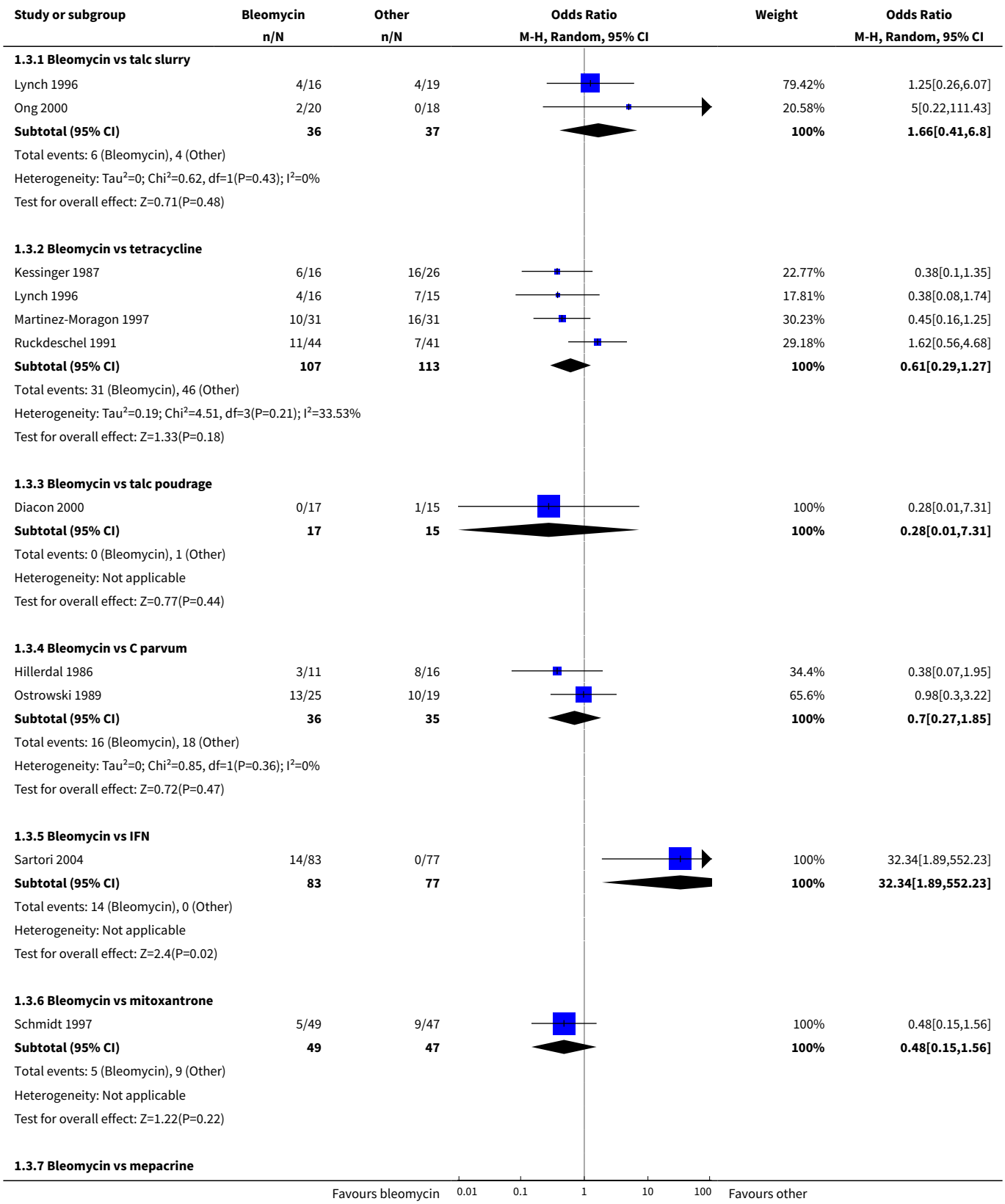
Study or subgroup	Bleomycin n/N	Other n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Heterogeneity: Not applicable					
Test for overall effect: Z=1.52(P=0.13)					
Test for subgroup differences: Chi²=36.99, df=1 (P=0), I²=67.56%					

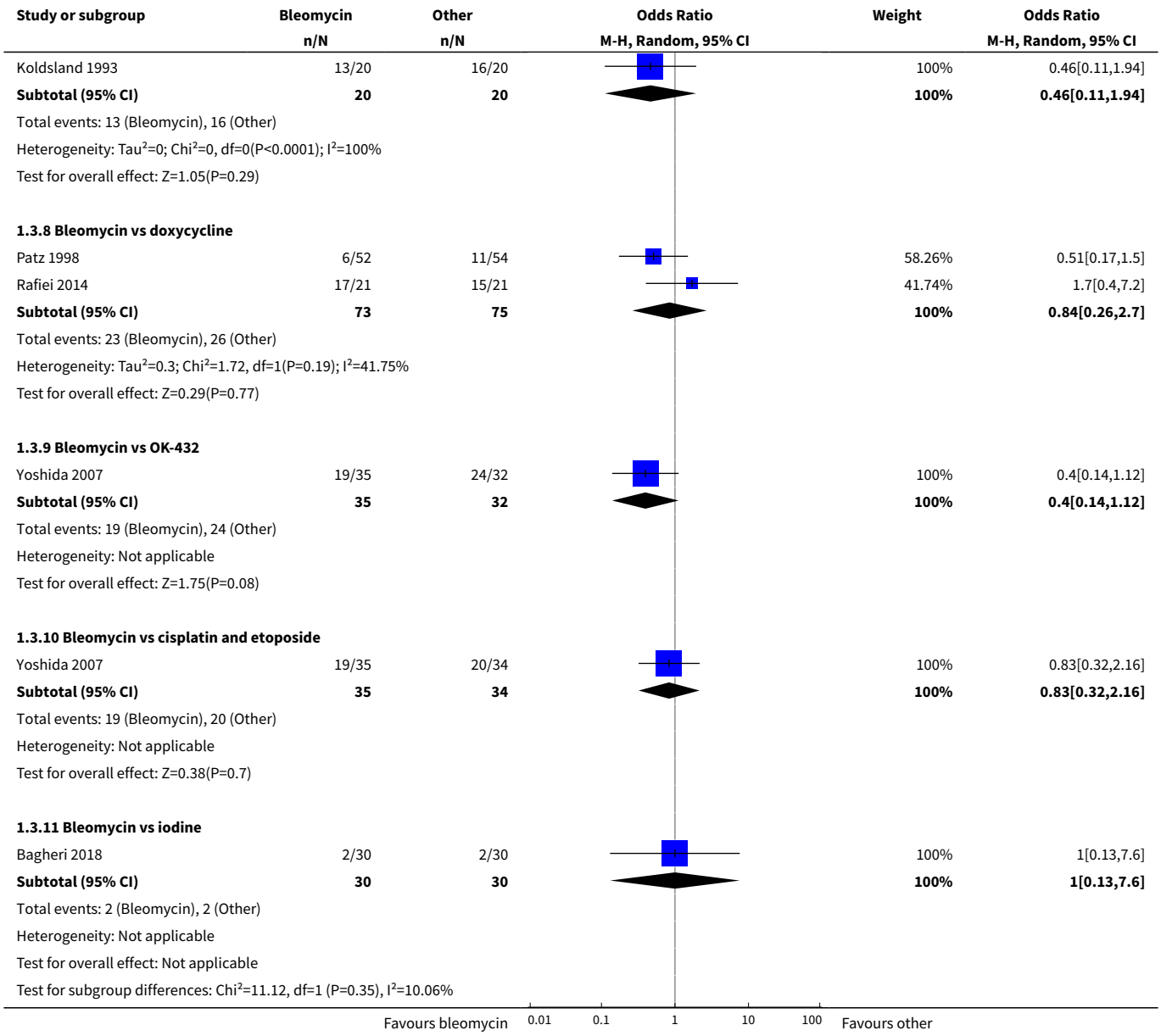
Analysis 1.2. Comparison 1 Bleomycin, Outcome 2 Fever.

Study or subgroup	Bleomycin n/N	Other n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.2.1 Bleomycin vs talc slurry					
Lynch 1996	5/16	8/19		47.08%	0.63[0.15,2.52]
Noppen 1997	3/12	5/14		33.44%	0.6[0.11,3.3]
Ong 2000	4/20	1/18		19.48%	4.25[0.43,42.19]
Subtotal (95% CI)	**48**	**51**		**100%**	**0.9[0.31,2.56]**
Total events: 12 (Bleomycin), 14 (Other)					
Heterogeneity: Tau²=0.1; Chi²=2.26, df=2(P=0.32); I²=11.4%					
Test for overall effect: Z=0.21(P=0.84)					
1.2.2 Bleomycin vs talc poudrage					
Diacon 2000	2/17	2/15		100%	0.87[0.11,7.05]
Subtotal (95% CI)	**17**	**15**		**100%**	**0.87[0.11,7.05]**
Total events: 2 (Bleomycin), 2 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.13(P=0.89)					
1.2.3 Bleomycin vs tetracycline					
Emad 1996	1/20	1/20		12.08%	1[0.06,17.18]
Kessinger 1987	8/16	2/16		22.74%	7[1.18,41.36]
Lynch 1996	5/16	6/15		27.52%	0.68[0.16,2.99]
Martinez-Moragon 1997	6/31	0/31		11.57%	16.06[0.86,298.78]
Ruckdeschel 1991	4/44	3/41		26.09%	1.27[0.27,6.04]
Subtotal (95% CI)	**127**	**123**		**100%**	**2.05[0.67,6.34]**
Total events: 24 (Bleomycin), 12 (Other)					
Heterogeneity: Tau²=0.63; Chi²=6.6, df=4(P=0.16); I²=39.43%					
Test for overall effect: Z=1.25(P=0.21)					
1.2.4 Tetracycline vs C parvum					
Hillerdal 1986	10/16	14/20		46.02%	0.71[0.18,2.87]
Ostrowski 1989	6/25	10/19		53.98%	0.28[0.08,1.03]
Subtotal (95% CI)	**41**	**39**		**100%**	**0.43[0.17,1.12]**
Total events: 16 (Bleomycin), 24 (Other)					
Heterogeneity: Tau²=0; Chi²=0.91, df=1(P=0.34); I²=0%					
Test for overall effect: Z=1.73(P=0.08)					
1.2.5 Bleomycin vs IFN					
Sartori 2004	41/83	0/77		100%	151.35[9.08,2522.62]
Subtotal (95% CI)	**83**	**77**		**100%**	**151.35[9.08,2522.62]**
Total events: 41 (Bleomycin), 0 (Other)					
Heterogeneity: Not applicable					

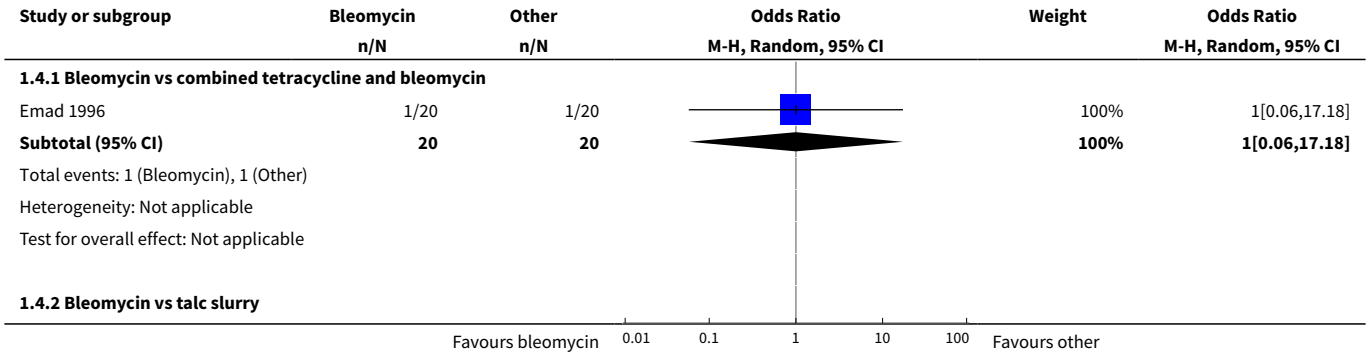


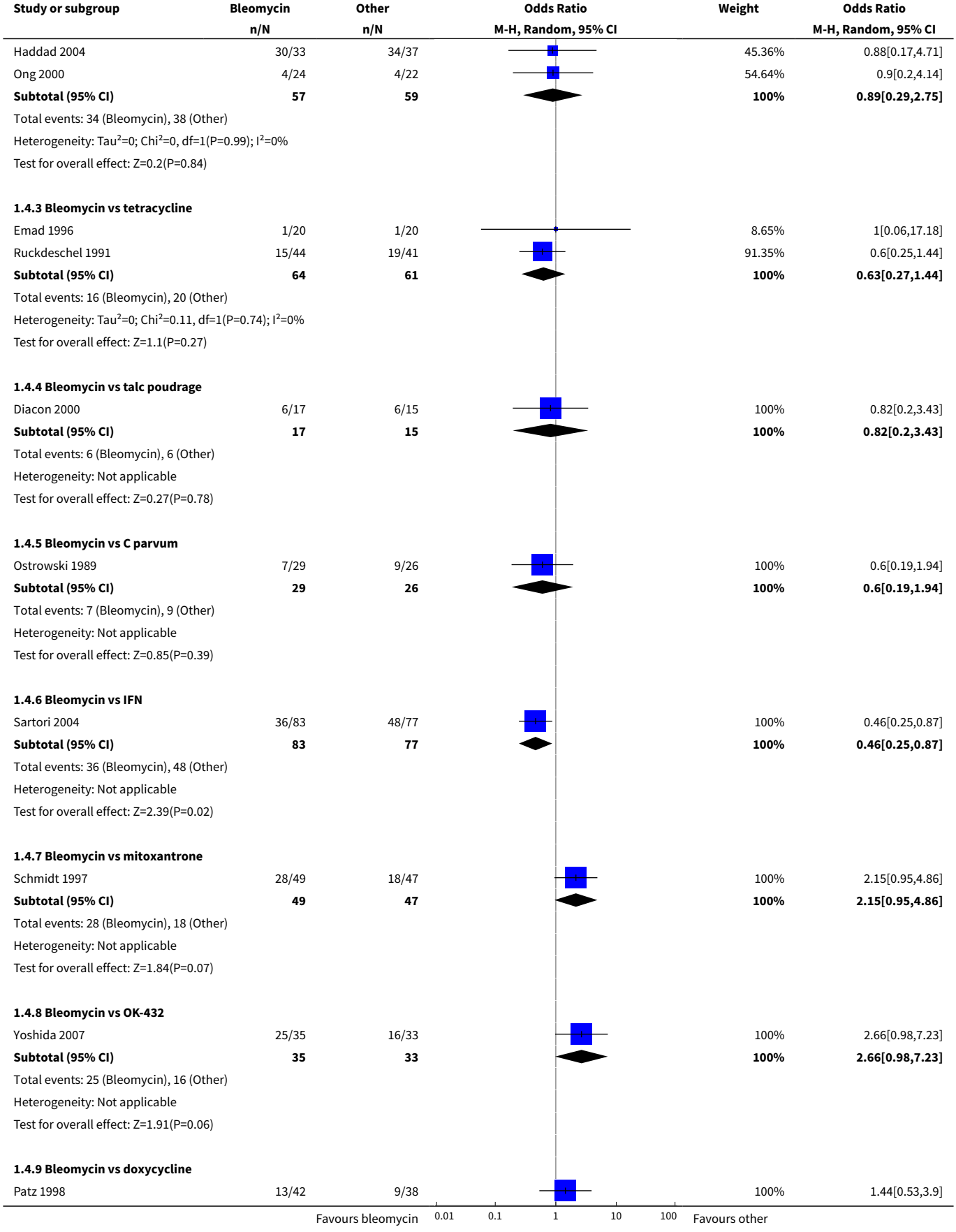
Analysis 1.3. Comparison 1 Bleomycin, Outcome 3 Pain.



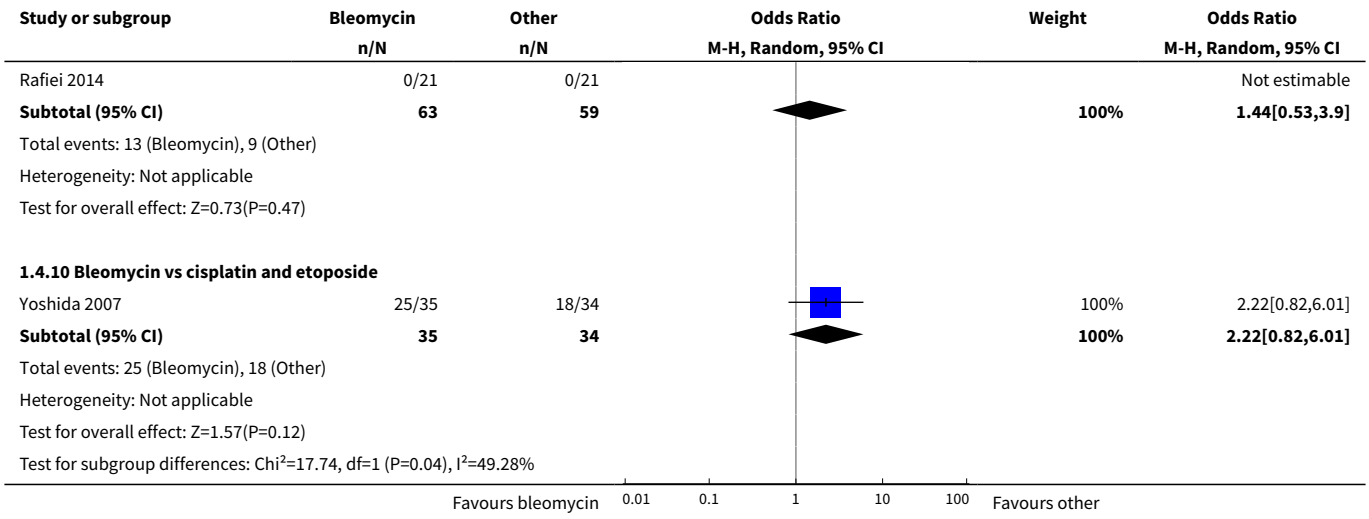


Analysis 1.4. Comparison 1 Bleomycin, Outcome 4 Mortality.

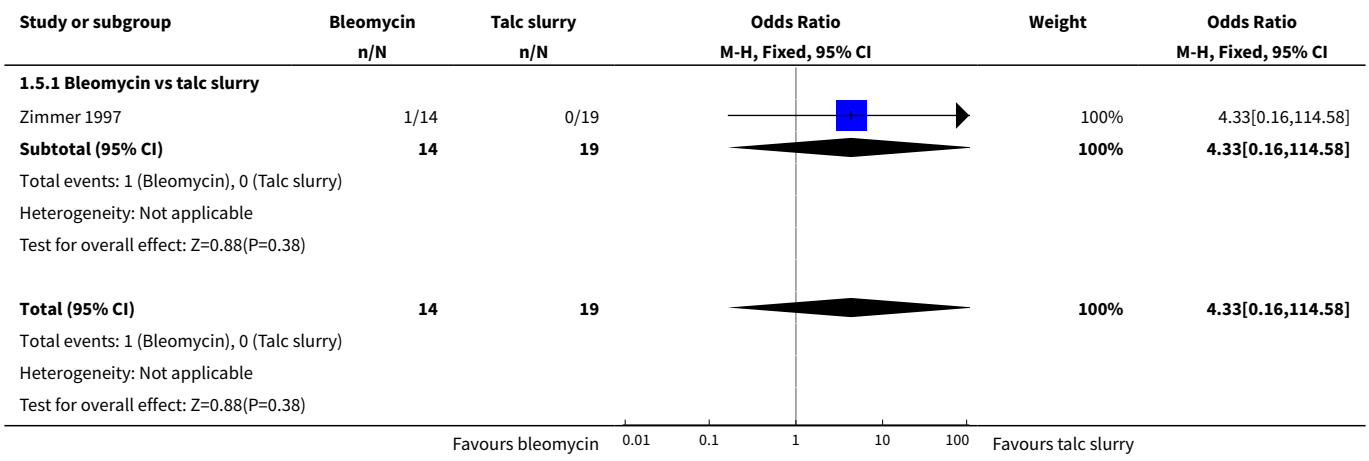




Study or subgroup	Bleomycin n/N	Other n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Haddad 2004	30/33	34/37		45.36%	0.88[0.17,4.71]
Ong 2000	4/24	4/22		54.64%	0.9[0.2,4.14]
Subtotal (95% CI)	**57**	**59**		**100%**	**0.89[0.29,2.75]**
Total events: 34 (Bleomycin), 38 (Other)					
Heterogeneity: Tau²=0; Chi²=0, df=1(P=0.99); I²=0%					
Test for overall effect: Z=0.2(P=0.84)					
1.4.3 Bleomycin vs tetracycline					
Emad 1996	1/20	1/20		8.65%	1[0.06,17.18]
Ruckdeschel 1991	15/44	19/41		91.35%	0.6[0.25,1.44]
Subtotal (95% CI)	**64**	**61**		**100%**	**0.63[0.27,1.44]**
Total events: 16 (Bleomycin), 20 (Other)					
Heterogeneity: Tau²=0; Chi²=0.11, df=1(P=0.74); I²=0%					
Test for overall effect: Z=1.1(P=0.27)					
1.4.4 Bleomycin vs talc poudrage					
Diacon 2000	6/17	6/15		100%	0.82[0.2,3.43]
Subtotal (95% CI)	**17**	**15**		**100%**	**0.82[0.2,3.43]**
Total events: 6 (Bleomycin), 6 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.27(P=0.78)					
1.4.5 Bleomycin vs C parvum					
Ostrowski 1989	7/29	9/26		100%	0.6[0.19,1.94]
Subtotal (95% CI)	**29**	**26**		**100%**	**0.6[0.19,1.94]**
Total events: 7 (Bleomycin), 9 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.85(P=0.39)					
1.4.6 Bleomycin vs IFN					
Sartori 2004	36/83	48/77		100%	0.46[0.25,0.87]
Subtotal (95% CI)	**83**	**77**		**100%**	**0.46[0.25,0.87]**
Total events: 36 (Bleomycin), 48 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.39(P=0.02)					
1.4.7 Bleomycin vs mitoxantrone					
Schmidt 1997	28/49	18/47		100%	2.15[0.95,4.86]
Subtotal (95% CI)	**49**	**47**		**100%**	**2.15[0.95,4.86]**
Total events: 28 (Bleomycin), 18 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.84(P=0.07)					
1.4.8 Bleomycin vs OK-432					
Yoshida 2007	25/35	16/33		100%	2.66[0.98,7.23]
Subtotal (95% CI)	**35**	**33**		**100%**	**2.66[0.98,7.23]**
Total events: 25 (Bleomycin), 16 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.91(P=0.06)					
1.4.9 Bleomycin vs doxycycline					
Patz 1998	13/42	9/38		100%	1.44[0.53,3.9]



Analysis 1.5. Comparison 1 Bleomycin, Outcome 5 Repeat pleural intervention.



Comparison 2. Talc slurry

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pleurodesis failure rate	20		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Talc slurry vs talc poudrage	4	919	Odds Ratio (M-H, Random, 95% CI)	1.24 [0.92, 1.65]
1.2 Talc slurry vs bleomycin	5	199	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.37, 1.82]
1.3 Talc slurry vs indwelling pleural catheter (IPC) – not daily drainage	2	249	Odds Ratio (M-H, Random, 95% CI)	0.18 [0.07, 0.45]

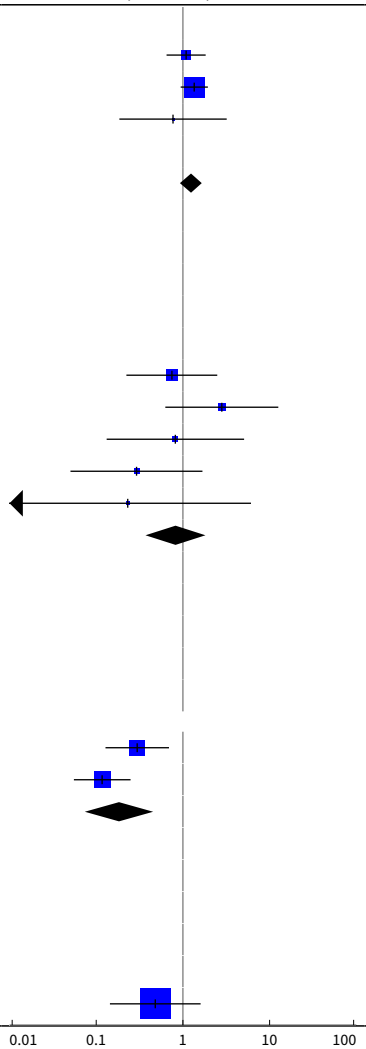
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.4 Talc slurry vs mepacrine	1	89	Odds Ratio (M-H, Random, 95% CI)	0.48 [0.14, 1.60]
1.5 Talc slurry vs placebo	1	21	Odds Ratio (M-H, Random, 95% CI)	0.07 [0.00, 1.51]
1.6 Talc slurry vs iodine	2	75	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.24, 3.08]
1.7 Talc slurry vs tetracycline	1	32	Odds Ratio (M-H, Random, 95% CI)	1.29 [0.32, 5.17]
1.8 Talc slurry vs silver nitrate	1	25	Odds Ratio (M-H, Random, 95% CI)	5.82 [0.21, 158.82]
1.9 Talc slurry vs thoracoscopic mechanical pleurodesis (TMP)	2	123	Odds Ratio (M-H, Random, 95% CI)	2.28 [0.83, 6.23]
1.10 Talc slurry vs autologous blood	1	110	Odds Ratio (M-H, Random, 95% CI)	0.69 [0.24, 1.95]
1.11 Talc slurry vs IPC – daily drainage	1	55	Odds Ratio (M-H, Random, 95% CI)	0.30 [0.08, 1.14]
2 Fever	9		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Talc slurry vs talc poudrage	2	479	Odds Ratio (M-H, Random, 95% CI)	1.65 [0.42, 6.48]
2.2 Talc slurry vs bleomycin	3	98	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.36, 2.51]
2.3 Talc slurry vs tetracycline	1	34	Odds Ratio (M-H, Random, 95% CI)	1.09 [0.28, 4.32]
2.4 Talc slurry vs iodine	2	75	Odds Ratio (M-H, Random, 95% CI)	1.07 [0.32, 3.59]
2.5 Talc slurry vs silver nitrate	1	60	Odds Ratio (M-H, Random, 95% CI)	0.7 [0.15, 3.24]
2.6 Talc slurry vs autologous blood	1	110	Odds Ratio (M-H, Random, 95% CI)	3.92 [1.31, 11.72]
3 Pain	12		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Talc slurry vs bleomycin	3	99	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.15, 2.46]
3.2 Talc slurry vs talc poudrage	2	812	Odds Ratio (M-H, Random, 95% CI)	1.27 [0.41, 3.96]

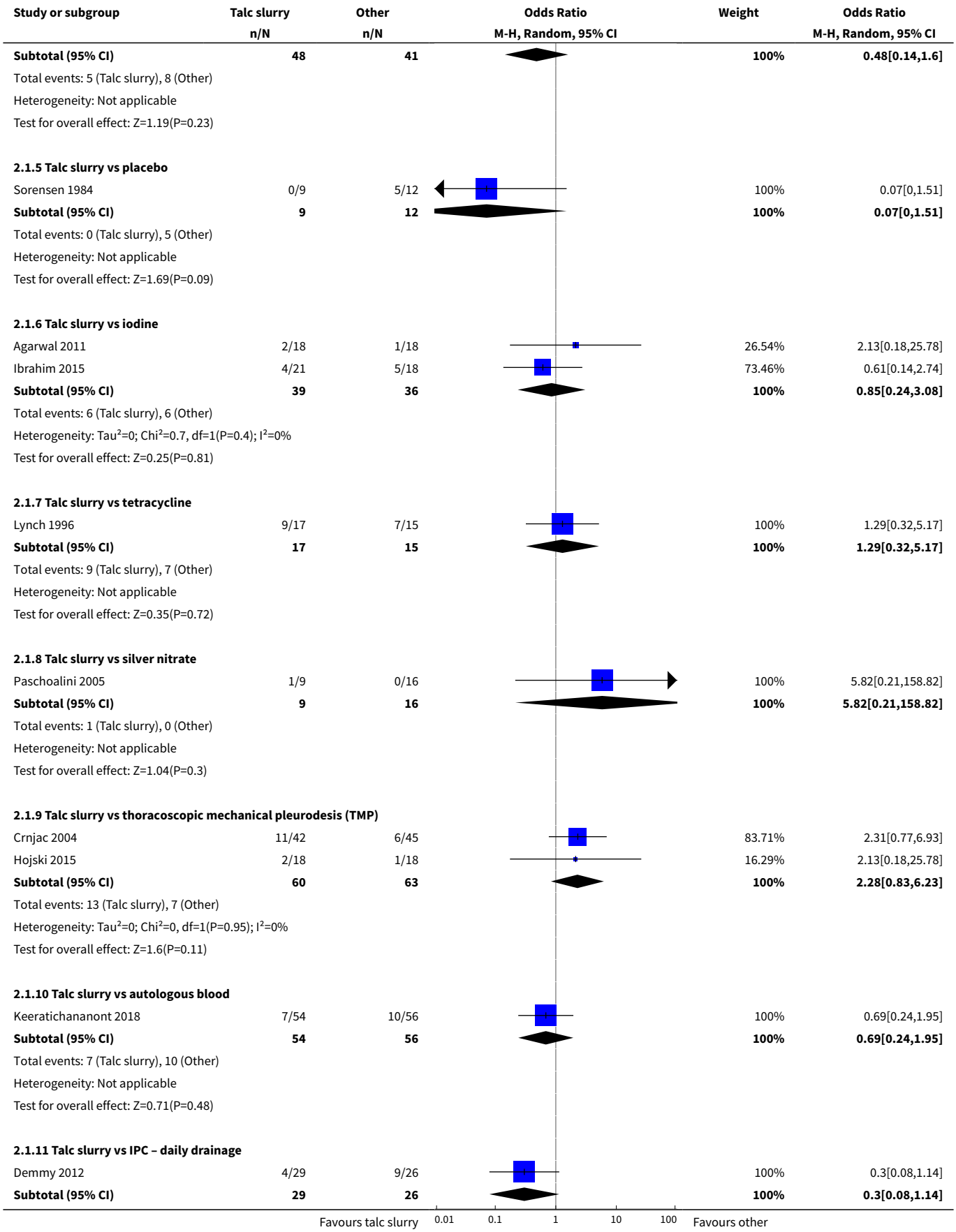
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.3 Talc slurry vs tetracycline	1	34	Odds Ratio (M-H, Random, 95% CI)	0.30 [0.07, 1.36]
3.4 Talc slurry vs iodine	2	75	Odds Ratio (M-H, Random, 95% CI)	2.0 [0.55, 7.30]
3.5 Talc slurry vs IPC – not daily drainage	2	232	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.19, 1.95]
3.6 Talc slurry vs placebo	1	31	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.7 Talc slurry vs autologous blood	1	110	Odds Ratio (M-H, Random, 95% CI)	3.57 [1.19, 10.74]
3.8 Talc slurry vs IPC – daily drainage	1	57	Odds Ratio (M-H, Random, 95% CI)	0.31 [0.01, 7.95]
4 Breathlessness	3	344	Mean Difference (IV, Fixed, 95% CI)	1.09 [-6.14, 8.32]
4.1 Talc slurry vs IPC (not daily drainage)	2	160	Mean Difference (IV, Fixed, 95% CI)	6.12 [-4.08, 16.32]
4.2 Talc slurry vs talc poudrage	1	184	Mean Difference (IV, Fixed, 95% CI)	-4.0 [-14.26, 6.26]
5 Mortality	14		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Talc slurry vs talc poudrage	3	725	Odds Ratio (M-H, Random, 95% CI)	1.10 [0.69, 1.75]
5.2 Talc slurry vs bleomycin	2	116	Odds Ratio (M-H, Random, 95% CI)	1.12 [0.36, 3.46]
5.3 Talc slurry vs iodine	2	75	Odds Ratio (M-H, Random, 95% CI)	2.71 [0.10, 70.65]
5.4 Talc slurry vs IPC – not daily drainage	3	344	Odds Ratio (M-H, Random, 95% CI)	1.43 [0.91, 2.23]
5.5 Talc slurry vs mepacrine	1	89	Odds Ratio (M-H, Random, 95% CI)	1.88 [0.70, 5.02]
5.6 Talc slurry vs TMP	1	87	Odds Ratio (M-H, Random, 95% CI)	10.64 [0.55, 203.85]
5.7 Talc slurry vs autologous blood	1	117	Odds Ratio (M-H, Random, 95% CI)	1.38 [0.30, 6.47]
5.8 Talc slurry vs IPC – daily drainage	1	57	Odds Ratio (M-H, Random, 95% CI)	0.59 [0.19, 1.79]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
6 Repeat pleural intervention	6	756	Odds Ratio (M-H, Random, 95% CI)	1.95 [0.90, 4.20]
6.1 Talc slurry vs IPC – not daily drainage	3	343	Odds Ratio (M-H, Random, 95% CI)	3.91 [1.98, 7.72]
6.2 Talc slurry vs talc poudrage	2	380	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.64, 1.71]
6.3 Talc slurry vs bleomycin	1	33	Odds Ratio (M-H, Random, 95% CI)	0.23 [0.01, 6.10]

Analysis 2.1. Comparison 2 Talc slurry, Outcome 1 Pleurodesis failure rate.

Study or subgroup	Talc slurry n/N	Other n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
2.1.1 Talc slurry vs talc poudrage					
Bhatnagar 2020	38/159	36/161		31.17%	1.09[0.65,1.83]
Dresler 2005	114/240	97/242		64.67%	1.35[0.94,1.94]
Terra 2009	4/30	5/30		4.15%	0.77[0.19,3.2]
Yim 1996	0/29	0/28			Not estimable
Subtotal (95% CI)	**458**	**461**		**100%**	**1.24[0.92,1.65]**
Total events: 156 (Talc slurry), 138 (Other)					
Heterogeneity: Tau^2=0; Chi^2=0.89, df=2(P=0.64); I^2=0%					
Test for overall effect: Z=1.43(P=0.15)					
2.1.2 Talc slurry vs bleomycin					
Haddad 2004	6/37	7/34		34.62%	0.75[0.22,2.49]
Lynch 1996	9/17	4/14		24.15%	2.81[0.63,12.61]
Noppen 1997	3/14	3/12		17.1%	0.82[0.13,5.08]
Ong 2000	2/18	6/20		18.4%	0.29[0.05,1.68]
Zimmer 1997	0/19	1/14		5.73%	0.23[0.01,6.1]
Subtotal (95% CI)	**105**	**94**		**100%**	**0.82[0.37,1.82]**
Total events: 20 (Talc slurry), 21 (Other)					
Heterogeneity: Tau^2=0.1; Chi^2=4.53, df=4(P=0.34); I^2=11.61%					
Test for overall effect: Z=0.48(P=0.63)					
2.1.3 Talc slurry vs indwelling pleural catheter (IPC) – not daily drainage					
Davies 2012	12/54	25/51		47.79%	0.3[0.13,0.69]
Thomas 2017	16/71	52/73		52.21%	0.12[0.06,0.25]
Subtotal (95% CI)	**125**	**124**		**100%**	**0.18[0.07,0.45]**
Total events: 28 (Talc slurry), 77 (Other)					
Heterogeneity: Tau^2=0.26; Chi^2=2.58, df=1(P=0.11); I^2=61.31%					
Test for overall effect: Z=3.66(P=0)					
2.1.4 Talc slurry vs mepacrine					
Ukale 2004	5/48	8/41		100%	0.48[0.14,1.6]





Study or subgroup	Talc slurry n/N	Other n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Total events: 4 (Talc slurry), 9 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.76(P=0.08)					
Test for subgroup differences: Chi^2=27.35, df=1 (P=0), I^2=63.43%					

Favours talc slurry 0.01 0.1 1 10 100 Favours other

Analysis 2.2. Comparison 2 Talc slurry, Outcome 2 Fever.

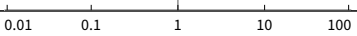
Study or subgroup	Talc slurry n/N	Other n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
2.2.1 Talc slurry vs talc poudrage					
Dresler 2005	68/196	68/223		83.22%	1.21[0.8,1.82]
Terra 2009	3/30	0/30		16.78%	7.76[0.38,157.14]
Subtotal (95% CI)	**226**	**253**		**100%**	**1.65[0.42,6.48]**
Total events: 71 (Talc slurry), 68 (Other)					
Heterogeneity: Tau^2=0.54; Chi^2=1.45, df=1(P=0.23); I^2=31.05%					
Test for overall effect: Z=0.72(P=0.47)					
2.2.2 Talc slurry vs bleomycin					
Lynch 1996	8/19	6/15		49.67%	1.09[0.28,4.32]
Noppen 1997	5/14	3/12		32.45%	1.67[0.3,9.16]
Ong 2000	1/18	4/20		17.88%	0.24[0.02,2.34]
Subtotal (95% CI)	**51**	**47**		**100%**	**0.95[0.36,2.51]**
Total events: 14 (Talc slurry), 13 (Other)					
Heterogeneity: Tau^2=0; Chi^2=1.89, df=2(P=0.39); I^2=0%					
Test for overall effect: Z=0.1(P=0.92)					
2.2.3 Talc slurry vs tetracycline					
Lynch 1996	8/19	6/15		100%	1.09[0.28,4.32]
Subtotal (95% CI)	**19**	**15**		**100%**	**1.09[0.28,4.32]**
Total events: 8 (Talc slurry), 6 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.12(P=0.9)					
2.2.4 Talc slurry vs iodine					
Agarwal 2011	3/18	2/18		39.57%	1.6[0.23,10.94]
Ibrahim 2015	4/21	4/18		60.43%	0.82[0.17,3.9]
Subtotal (95% CI)	**39**	**36**		**100%**	**1.07[0.32,3.59]**
Total events: 7 (Talc slurry), 6 (Other)					
Heterogeneity: Tau^2=0; Chi^2=0.28, df=1(P=0.6); I^2=0%					
Test for overall effect: Z=0.11(P=0.91)					
2.2.5 Talc slurry vs silver nitrate					
Paschoalini 2005	3/27	5/33		100%	0.7[0.15,3.24]
Subtotal (95% CI)	**27**	**33**		**100%**	**0.7[0.15,3.24]**
Total events: 3 (Talc slurry), 5 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.46(P=0.65)					

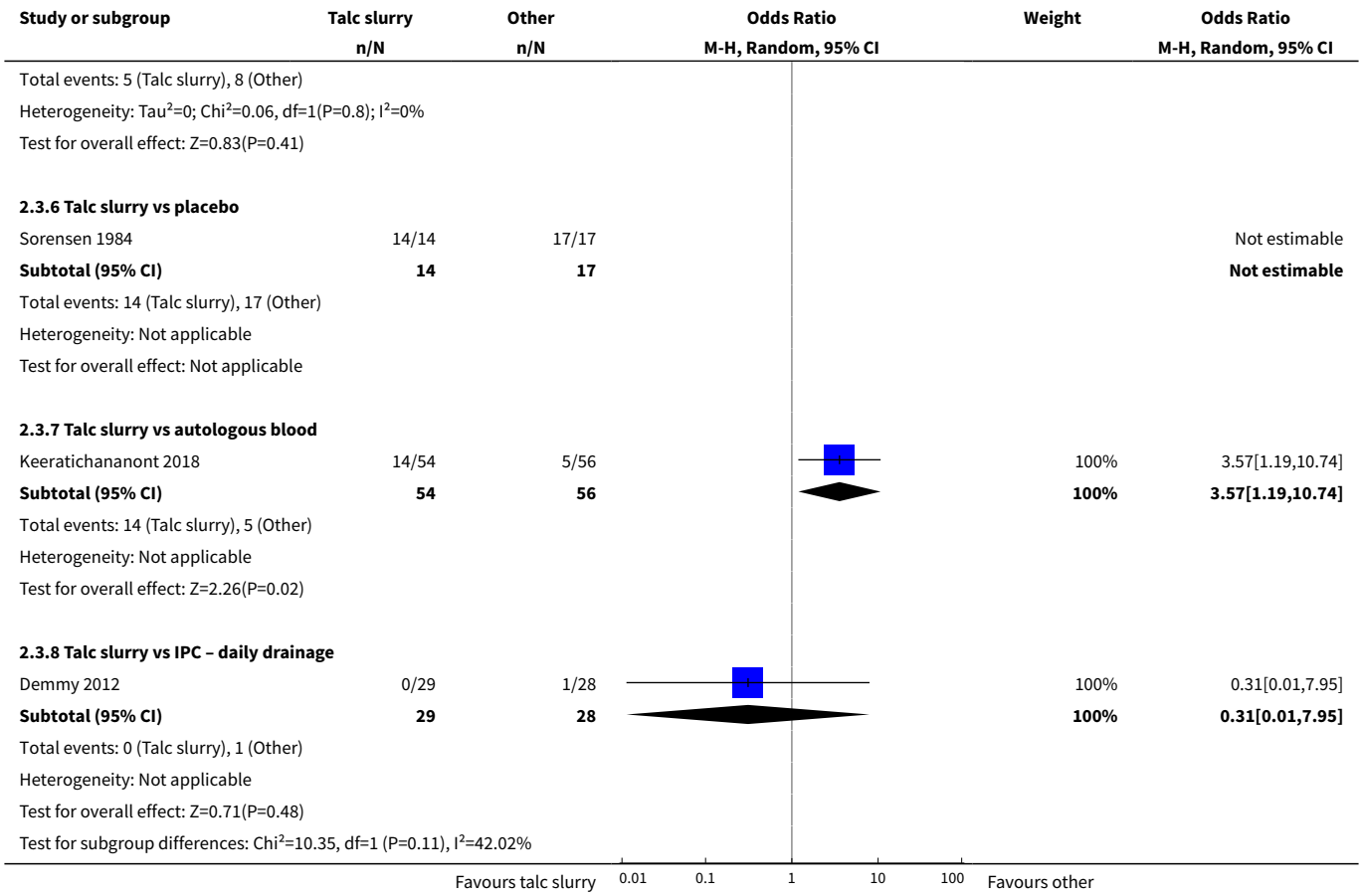
Favours talc slurry 0.01 0.1 1 10 100 Favours other

Study or subgroup	Talc slurry n/N	Other n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
2.2.6 Talc slurry vs autologous blood					
Keeratichananont 2018	15/54	5/56		100%	3.92[1.31,11.72]
Subtotal (95% CI)	**54**	**56**		**100%**	**3.92[1.31,11.72]**
Total events: 15 (Talc slurry), 5 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.45(P=0.01)					
Test for subgroup differences: Chi²=5.17, df=1 (P=0.4), I²=3.21%					

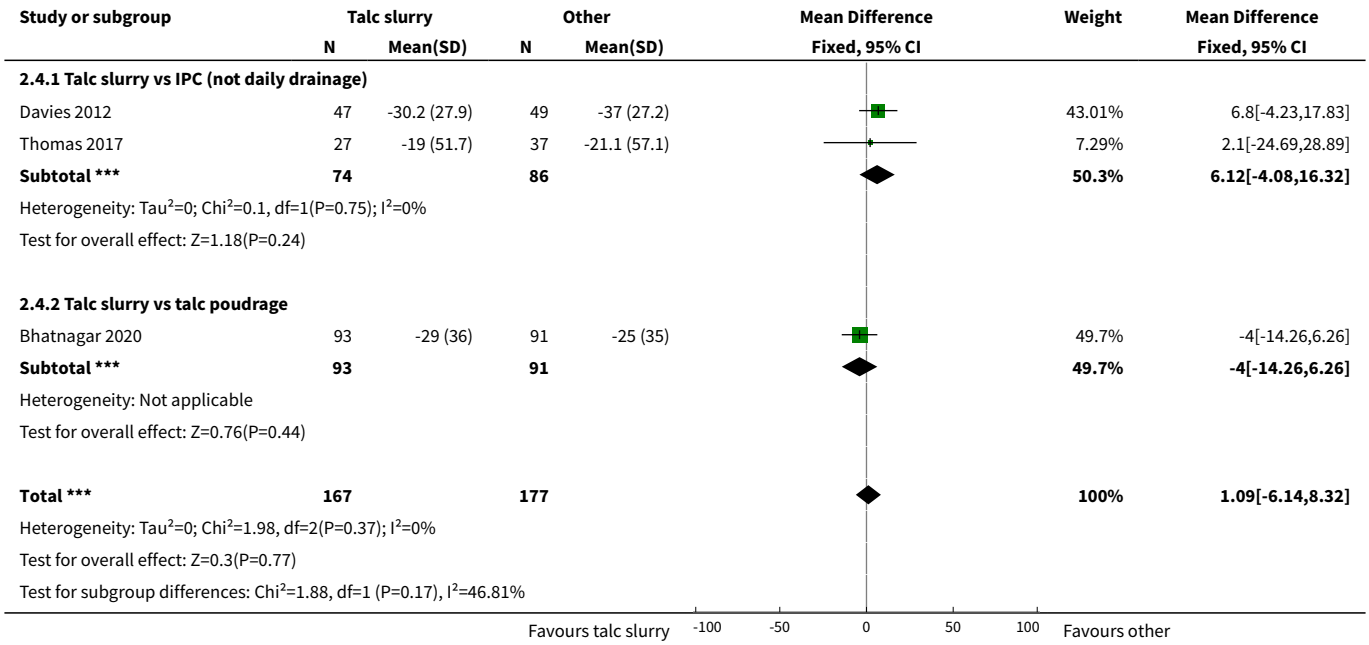
Analysis 2.3. Comparison 2 Talc slurry, Outcome 3 Pain.

Study or subgroup	Talc slurry n/N	Other n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
2.3.1 Talc slurry vs bleomycin					
Lynch 1996	4/19	4/16		79.42%	0.8[0.16,3.88]
Noppen 1997	0/14	0/12			Not estimable
Ong 2000	0/18	2/20		20.58%	0.2[0.01,4.46]
Subtotal (95% CI)	**51**	**48**		**100%**	**0.6[0.15,2.46]**
Total events: 4 (Talc slurry), 6 (Other)					
Heterogeneity: Tau²=0; Chi²=0.62, df=1(P=0.43); I²=0%					
Test for overall effect: Z=0.71(P=0.48)					
2.3.2 Talc slurry vs talc poudrage					
Bhatnagar 2020	6/164	9/166		44.26%	0.66[0.23,1.91]
Dresler 2005	24/240	12/242		55.74%	2.13[1.04,4.36]
Subtotal (95% CI)	**404**	**408**		**100%**	**1.27[0.41,3.96]**
Total events: 30 (Talc slurry), 21 (Other)					
Heterogeneity: Tau²=0.47; Chi²=3.21, df=1(P=0.07); I²=68.87%					
Test for overall effect: Z=0.41(P=0.68)					
2.3.3 Talc slurry vs tetracycline					
Lynch 1996	4/19	7/15		100%	0.3[0.07,1.36]
Subtotal (95% CI)	**19**	**15**		**100%**	**0.3[0.07,1.36]**
Total events: 4 (Talc slurry), 7 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.55(P=0.12)					
2.3.4 Talc slurry vs iodine					
Agarwal 2011	18/18	18/18			Not estimable
Ibrahim 2015	14/21	9/18		100%	2[0.55,7.3]
Subtotal (95% CI)	**39**	**36**		**100%**	**2[0.55,7.3]**
Total events: 32 (Talc slurry), 27 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.05(P=0.29)					
2.3.5 Talc slurry vs IPC – not daily drainage					
Boshuizen 2017	1/45	2/43		22.4%	0.47[0.04,5.33]
Thomas 2017	4/71	6/73		77.6%	0.67[0.18,2.47]
Subtotal (95% CI)	**116**	**116**		**100%**	**0.62[0.19,1.95]**



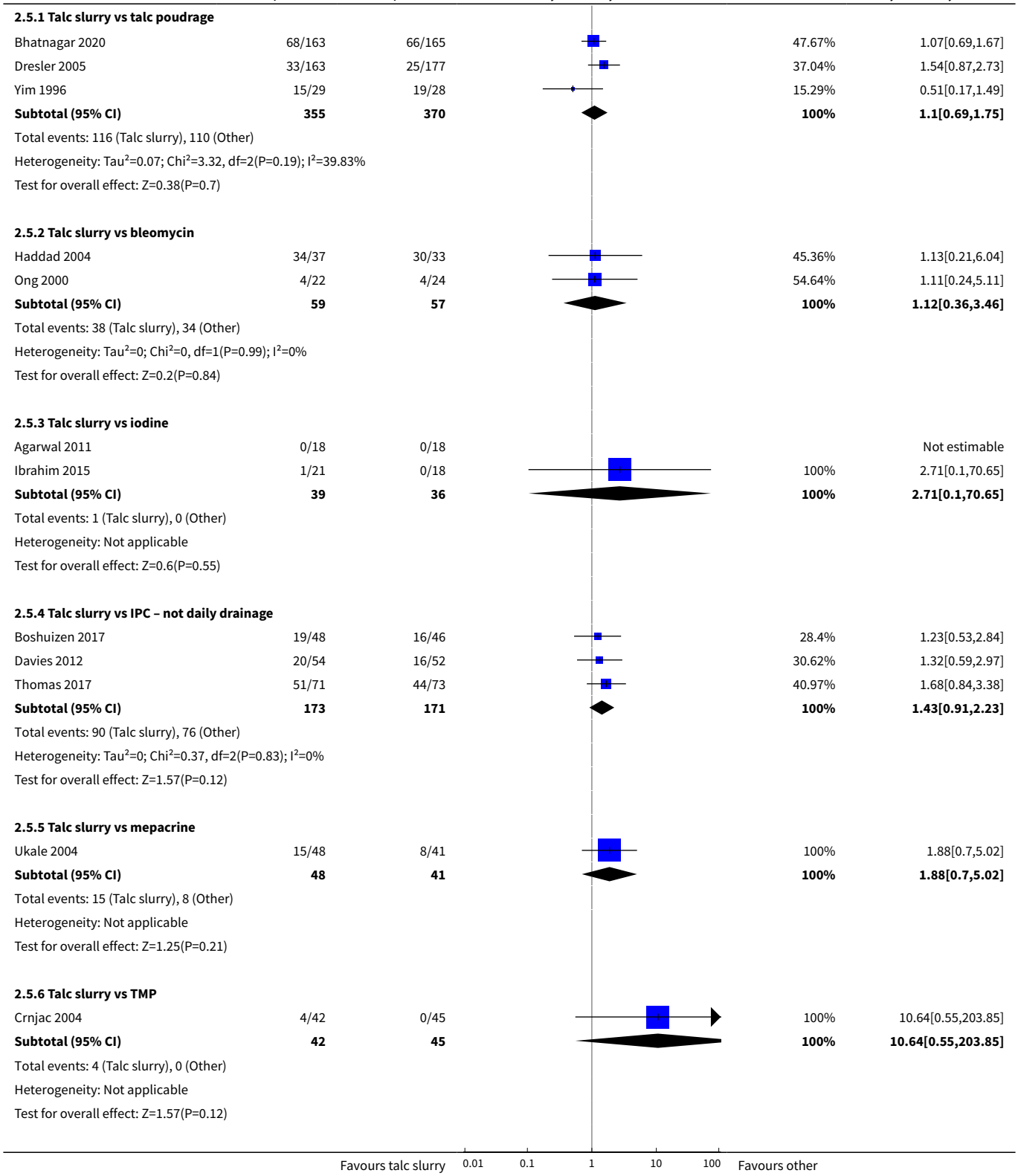


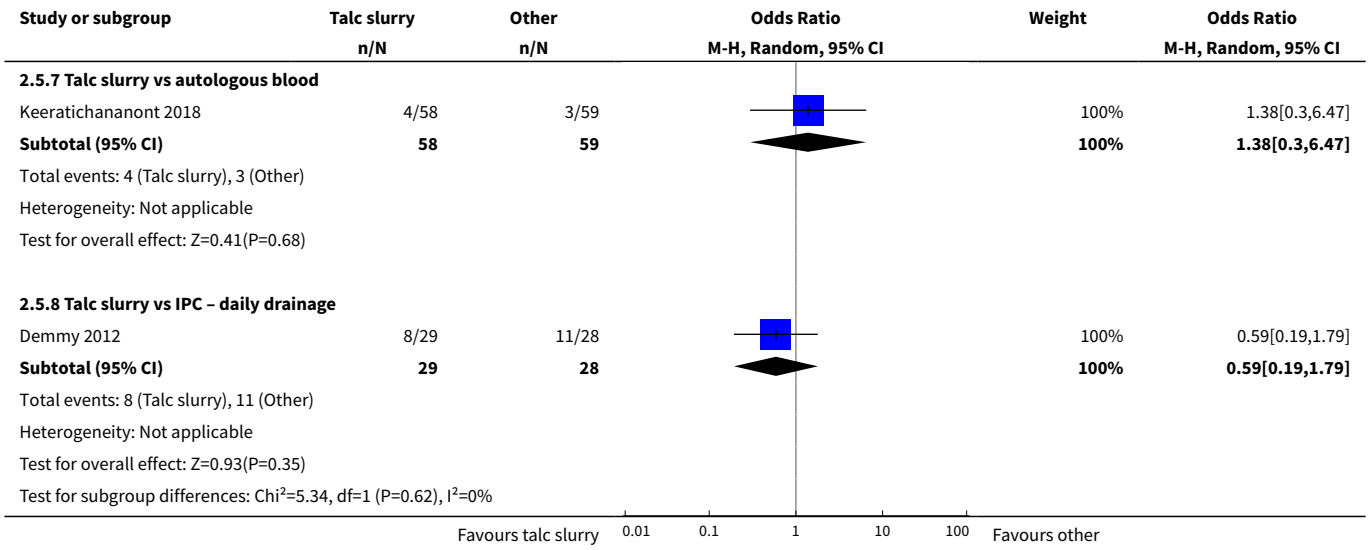
Analysis 2.4. Comparison 2 Talc slurry, Outcome 4 Breathlessness.



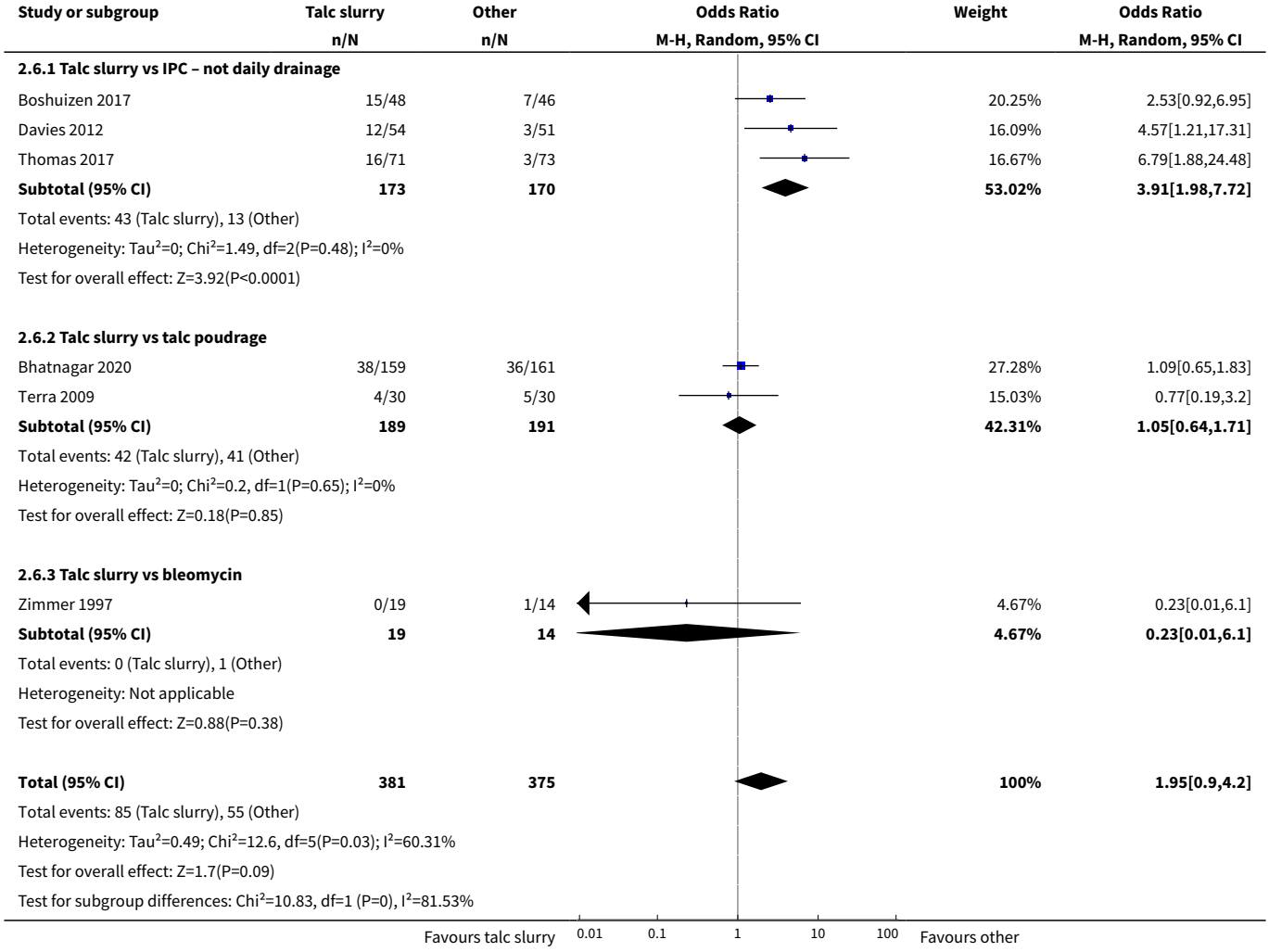
Analysis 2.5. Comparison 2 Talc slurry, Outcome 5 Mortality.

Study or subgroup	Talc slurry n/N	Other n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
2.5.1 Talc slurry vs talc poudrage					
Bhatnagar 2020	68/163	66/165		47.67%	1.07[0.69,1.67]
Dresler 2005	33/163	25/177		37.04%	1.54[0.87,2.73]
Yim 1996	15/29	19/28		15.29%	0.51[0.17,1.49]
Subtotal (95% CI)	**355**	**370**		**100%**	**1.1[0.69,1.75]**
Total events: 116 (Talc slurry), 110 (Other)					
Heterogeneity: Tau^2=0.07; Chi^2=3.32, df=2(P=0.19); I^2=39.83%					
Test for overall effect: Z=0.38(P=0.7)					
2.5.2 Talc slurry vs bleomycin					
Haddad 2004	34/37	30/33		45.36%	1.13[0.21,6.04]
Ong 2000	4/22	4/24		54.64%	1.11[0.24,5.11]
Subtotal (95% CI)	**59**	**57**		**100%**	**1.12[0.36,3.46]**
Total events: 38 (Talc slurry), 34 (Other)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.99); I^2=0%					
Test for overall effect: Z=0.2(P=0.84)					
2.5.3 Talc slurry vs iodine					
Agarwal 2011	0/18	0/18			Not estimable
Ibrahim 2015	1/21	0/18		100%	2.71[0.1,70.65]
Subtotal (95% CI)	**39**	**36**		**100%**	**2.71[0.1,70.65]**
Total events: 1 (Talc slurry), 0 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.6(P=0.55)					
2.5.4 Talc slurry vs IPC – not daily drainage					
Boshuizen 2017	19/48	16/46		28.4%	1.23[0.53,2.84]
Davies 2012	20/54	16/52		30.62%	1.32[0.59,2.97]
Thomas 2017	51/71	44/73		40.97%	1.68[0.84,3.38]
Subtotal (95% CI)	**173**	**171**		**100%**	**1.43[0.91,2.23]**
Total events: 90 (Talc slurry), 76 (Other)					
Heterogeneity: Tau^2=0; Chi^2=0.37, df=2(P=0.83); I^2=0%					
Test for overall effect: Z=1.57(P=0.12)					
2.5.5 Talc slurry vs mepacrine					
Ukale 2004	15/48	8/41		100%	1.88[0.7,5.02]
Subtotal (95% CI)	**48**	**41**		**100%**	**1.88[0.7,5.02]**
Total events: 15 (Talc slurry), 8 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.25(P=0.21)					
2.5.6 Talc slurry vs TMP					
Crnjac 2004	4/42	0/45		100%	10.64[0.55,203.85]
Subtotal (95% CI)	**42**	**45**		**100%**	**10.64[0.55,203.85]**
Total events: 4 (Talc slurry), 0 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.57(P=0.12)					





Analysis 2.6. Comparison 2 Talc slurry, Outcome 6 Repeat pleural intervention.



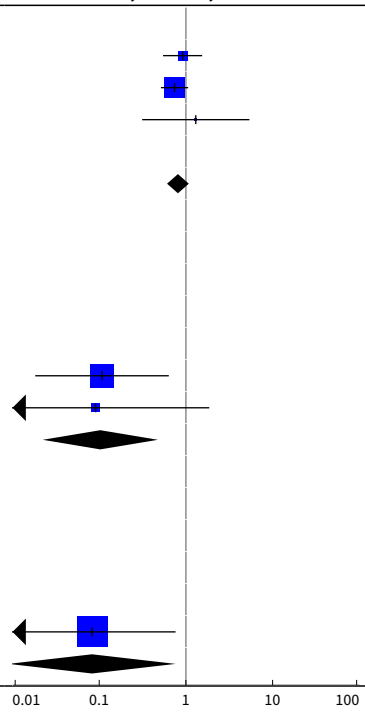
Comparison 3. Talc poudrage

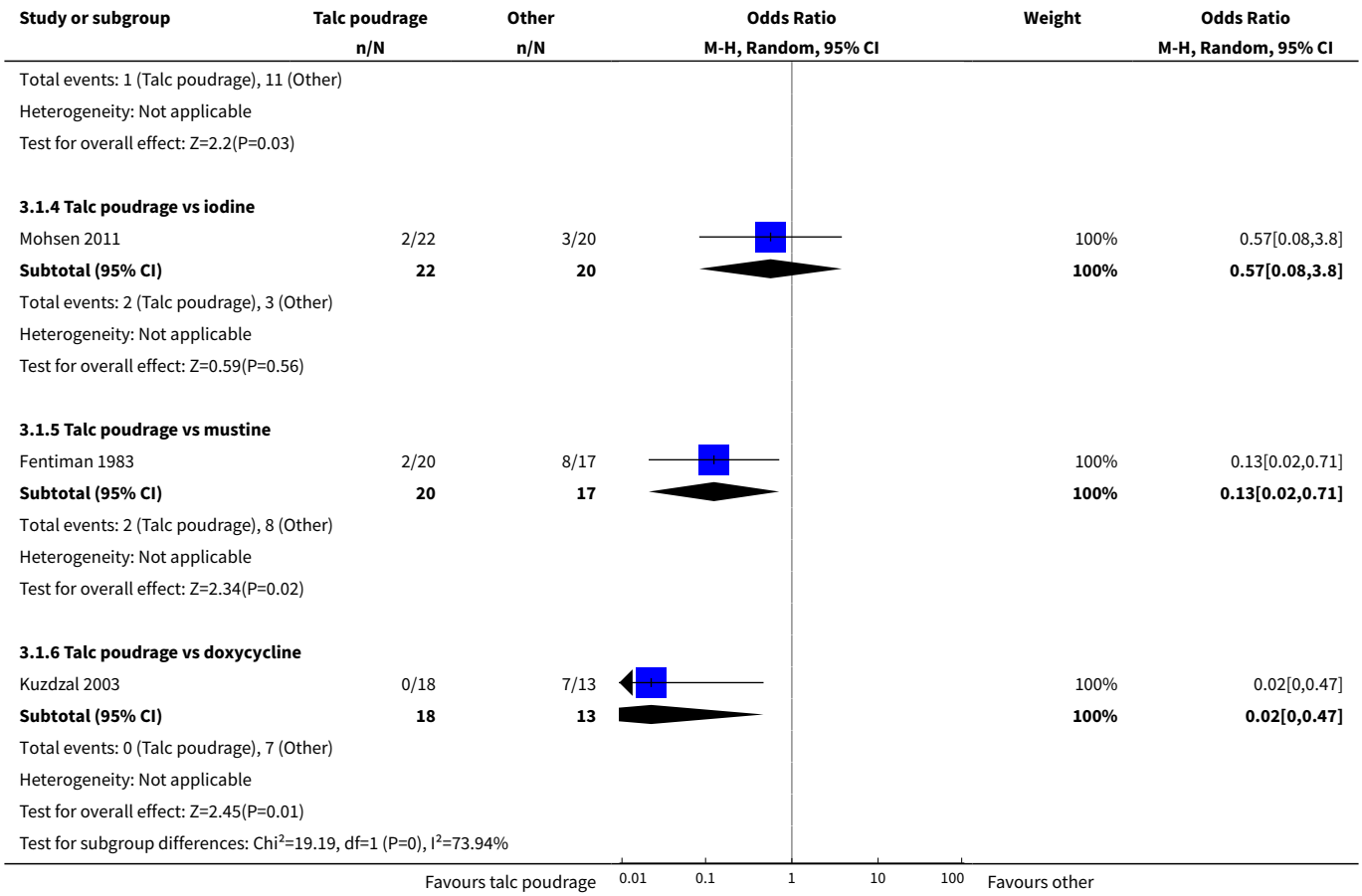
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Pleurodesis failure rate	10		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Talc poudrage vs talc slurry	4	919	Odds Ratio (M-H, Random, 95% CI)	0.81 [0.61, 1.08]
1.2 Talc poudrage vs bleomycin	2	57	Odds Ratio (M-H, Random, 95% CI)	0.10 [0.02, 0.48]
1.3 Talc poudrage vs tetracycline	1	33	Odds Ratio (M-H, Random, 95% CI)	0.08 [0.01, 0.76]
1.4 Talc poudrage vs iodine	1	42	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.08, 3.80]
1.5 Talc poudrage vs mustine	1	37	Odds Ratio (M-H, Random, 95% CI)	0.13 [0.02, 0.71]
1.6 Talc poudrage vs doxycycline	1	31	Odds Ratio (M-H, Random, 95% CI)	0.02 [0.00, 0.47]
2 Fever	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Talc poudrage vs talc slurry	2	479	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.15, 2.37]
2.2 Talc poudrage vs bleomycin	1	32	Odds Ratio (M-H, Random, 95% CI)	1.15 [0.14, 9.38]
2.3 Talc poudrage vs iodine	1	42	Odds Ratio (M-H, Random, 95% CI)	4.22 [0.43, 41.45]
3 Pain	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Talc poudrage vs talc slurry	2	812	Odds Ratio (M-H, Random, 95% CI)	0.79 [0.25, 2.45]
3.2 Talc poudrage vs bleomycin	1	32	Odds Ratio (M-H, Random, 95% CI)	3.62 [0.14, 95.78]
3.3 Talc poudrage vs iodine	1	42	Odds Ratio (M-H, Random, 95% CI)	9.97 [0.50, 198.04]
4 Breathlessness	1	184	Mean Difference (IV, Random, 95% CI)	4.0 [-6.26, 14.26]
4.1 Talc poudrage vs talc slurry	1	184	Mean Difference (IV, Random, 95% CI)	4.0 [-6.26, 14.26]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
5 Mortality	7		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Talc poudrage vs talc slurry	3	725	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.57, 1.46]
5.2 Talc poudrage vs bleomycin	1	32	Odds Ratio (M-H, Random, 95% CI)	1.22 [0.29, 5.13]
5.3 Talc poudrage vs tetracycline	1	41	Odds Ratio (M-H, Random, 95% CI)	5.25 [0.91, 30.22]
5.4 Talc poudrage vs iodine	1	42	Odds Ratio (M-H, Random, 95% CI)	2.64 [0.58, 12.09]
5.5 Talc poudrage vs mustine	1	46	Odds Ratio (M-H, Random, 95% CI)	0.43 [0.09, 1.96]
6 Repeat pleural intervention	2	380	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.59, 1.56]
6.1 Talc poudrage vs talc slurry	2	380	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.59, 1.56]

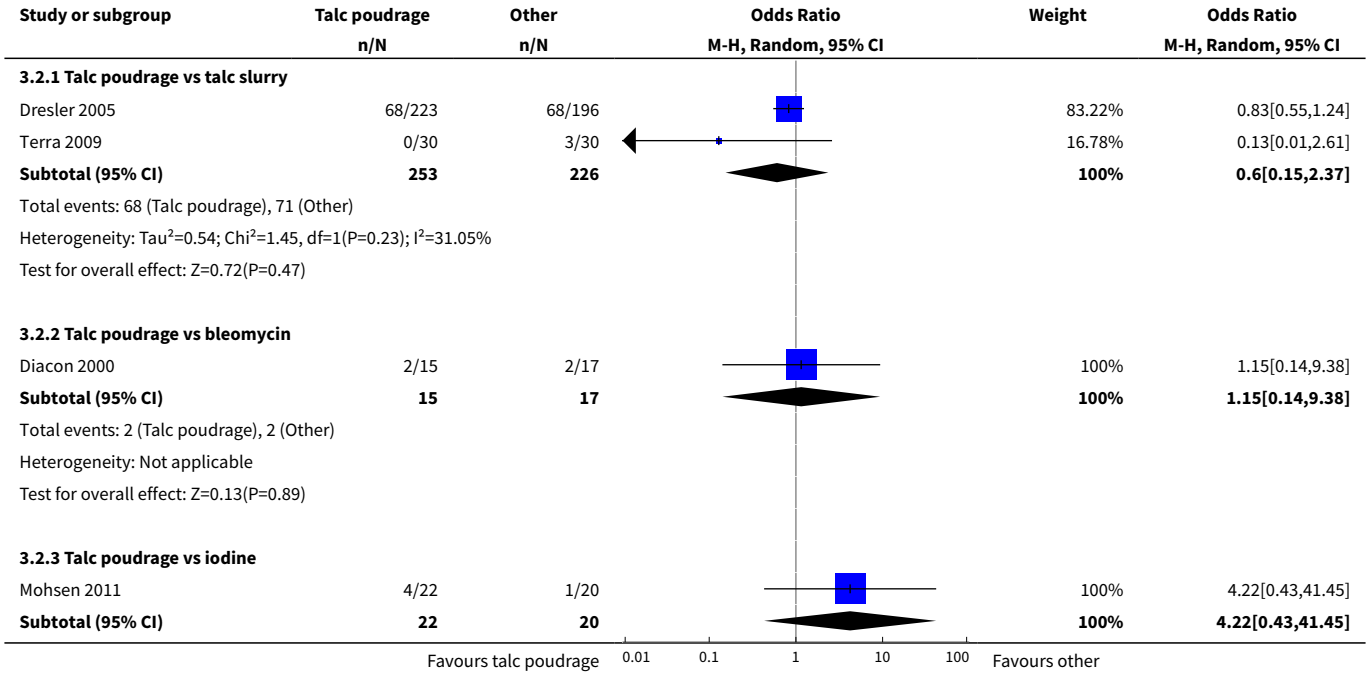
Analysis 3.1. Comparison 3 Talc poudrage, Outcome 1 Pleurodesis failure rate.

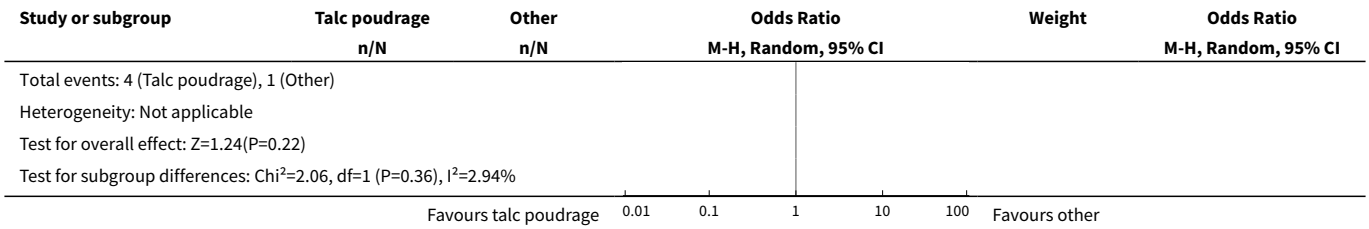
Study or subgroup	Talc poudrage n/N	Other n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
3.1.1 Talc poudrage vs talc slurry					
Bhatnagar 2020	36/161	38/159		31.17%	0.92[0.55,1.54]
Dresler 2005	97/242	114/240		64.67%	0.74[0.52,1.06]
Terra 2009	5/30	4/30		4.15%	1.3[0.31,5.4]
Yim 1996	0/28	0/29			Not estimable
Subtotal (95% CI)	**461**	**458**		**100%**	**0.81[0.61,1.08]**
Total events: 138 (Talc poudrage), 156 (Other)					
Heterogeneity: Tau^2=0; Chi^2=0.89, df=2(P=0.64); I^2=0%					
Test for overall effect: Z=1.43(P=0.15)					
3.1.2 Talc poudrage vs bleomycin					
Diacon 2000	2/15	10/17		74.32%	0.11[0.02,0.64]
Hamed 1989	0/10	5/15		25.68%	0.09[0,1.86]
Subtotal (95% CI)	**25**	**32**		**100%**	**0.1[0.02,0.48]**
Total events: 2 (Talc poudrage), 15 (Other)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.92); I^2=0%					
Test for overall effect: Z=2.91(P=0)					
3.1.3 Talc poudrage vs tetracycline					
Fentiman 1986	1/12	11/21		100%	0.08[0.01,0.76]
Subtotal (95% CI)	**12**	**21**		**100%**	**0.08[0.01,0.76]**



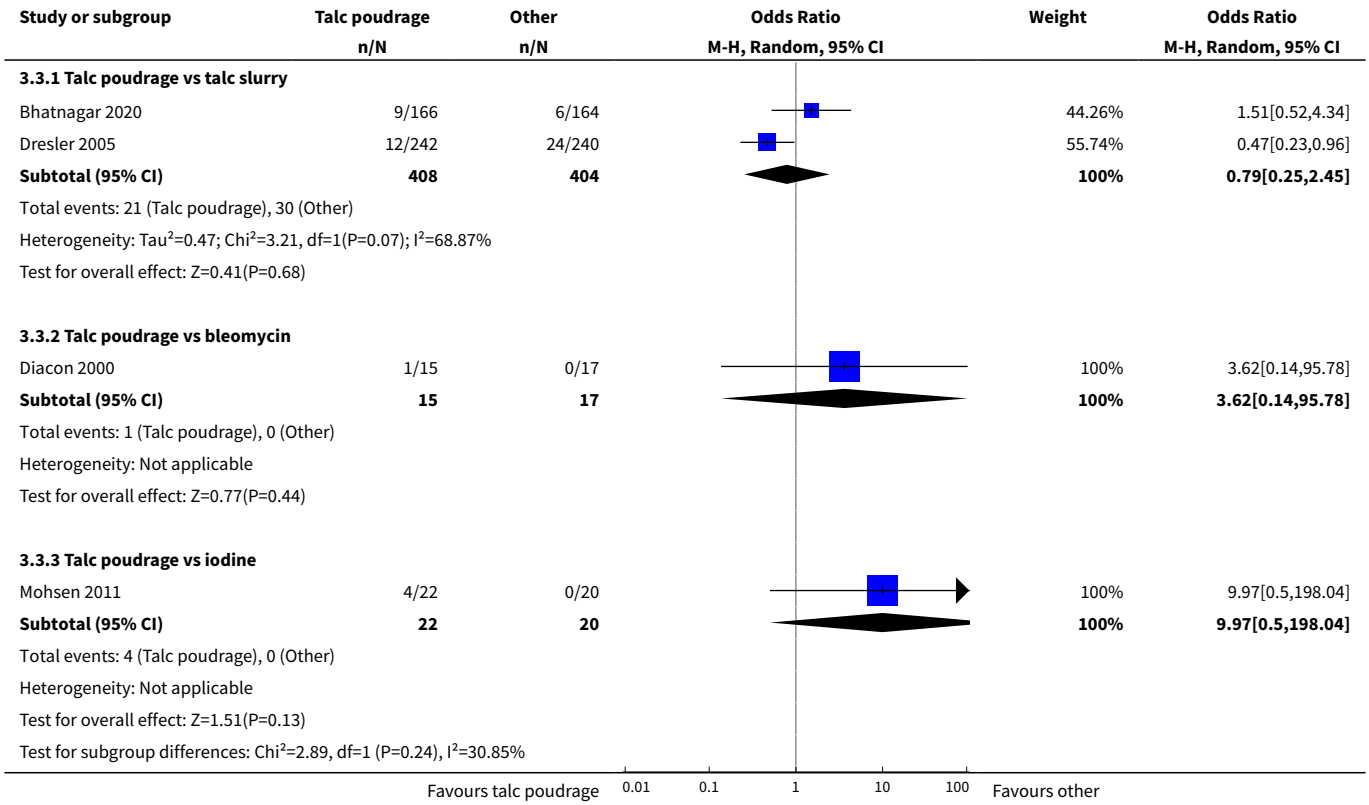


Analysis 3.2. Comparison 3 Talc poudrage, Outcome 2 Fever.

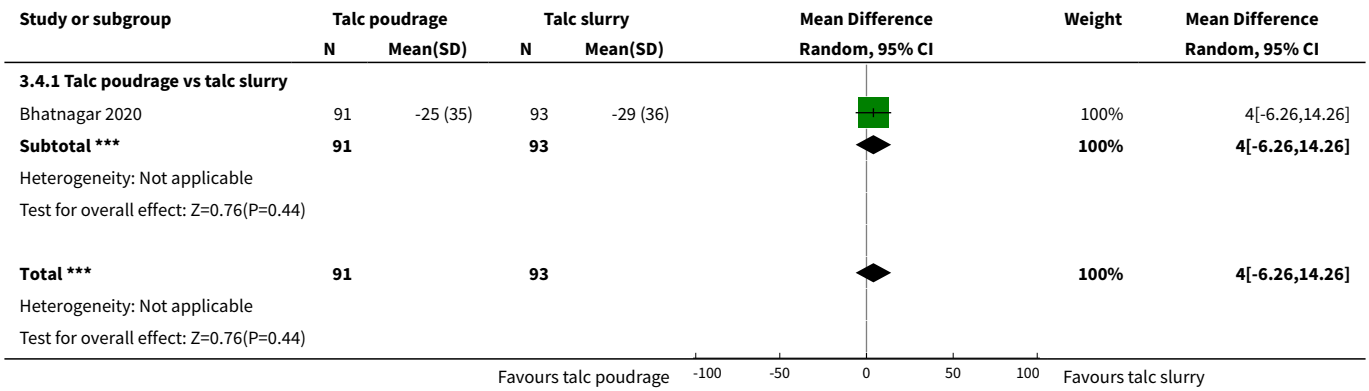




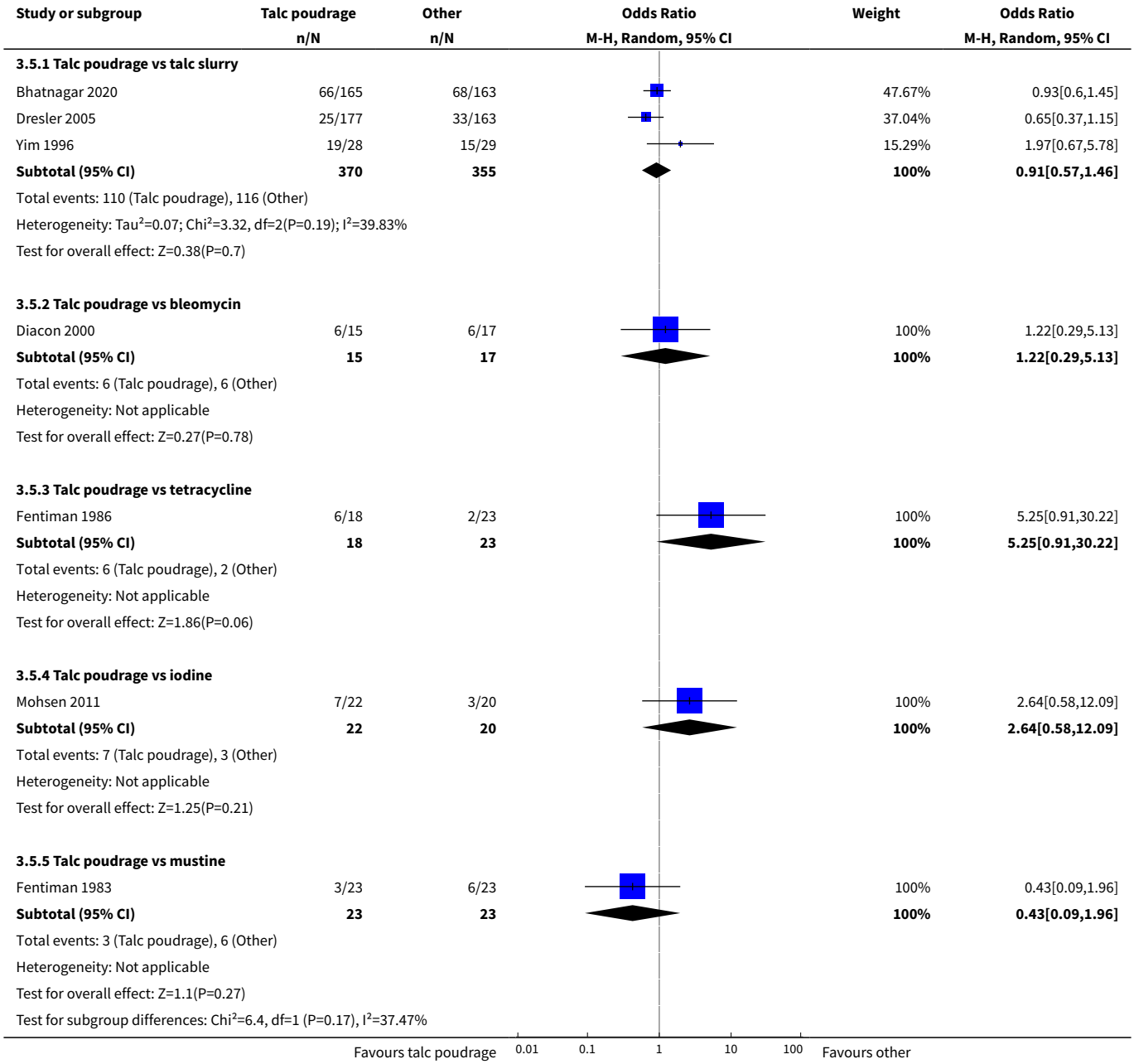
Analysis 3.3. Comparison 3 Talc poudrage, Outcome 3 Pain.



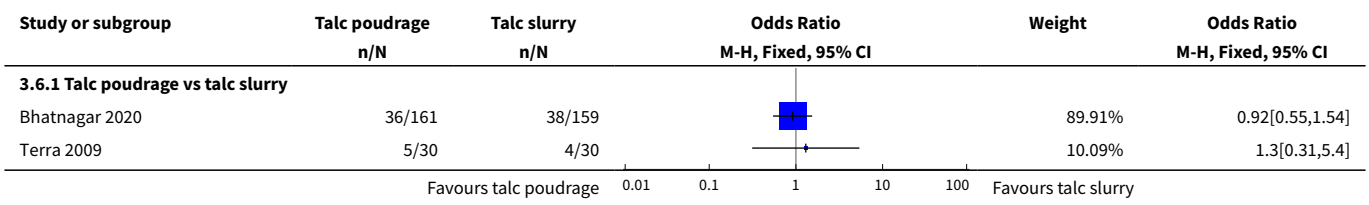
Analysis 3.4. Comparison 3 Talc poudrage, Outcome 4 Breathlessness.

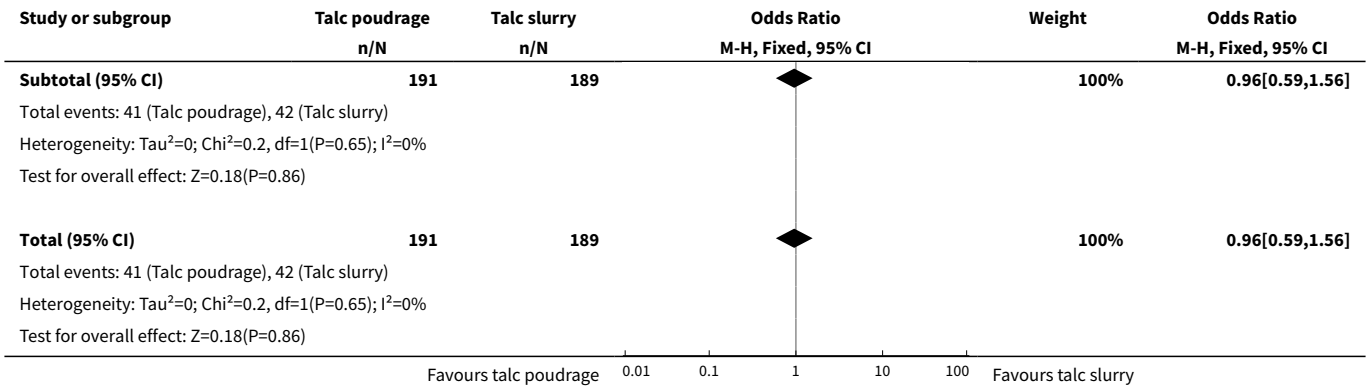


Analysis 3.5. Comparison 3 Talc poudrage, Outcome 5 Mortality.



Analysis 3.6. Comparison 3 Talc poudrage, Outcome 6 Repeat pleural intervention.





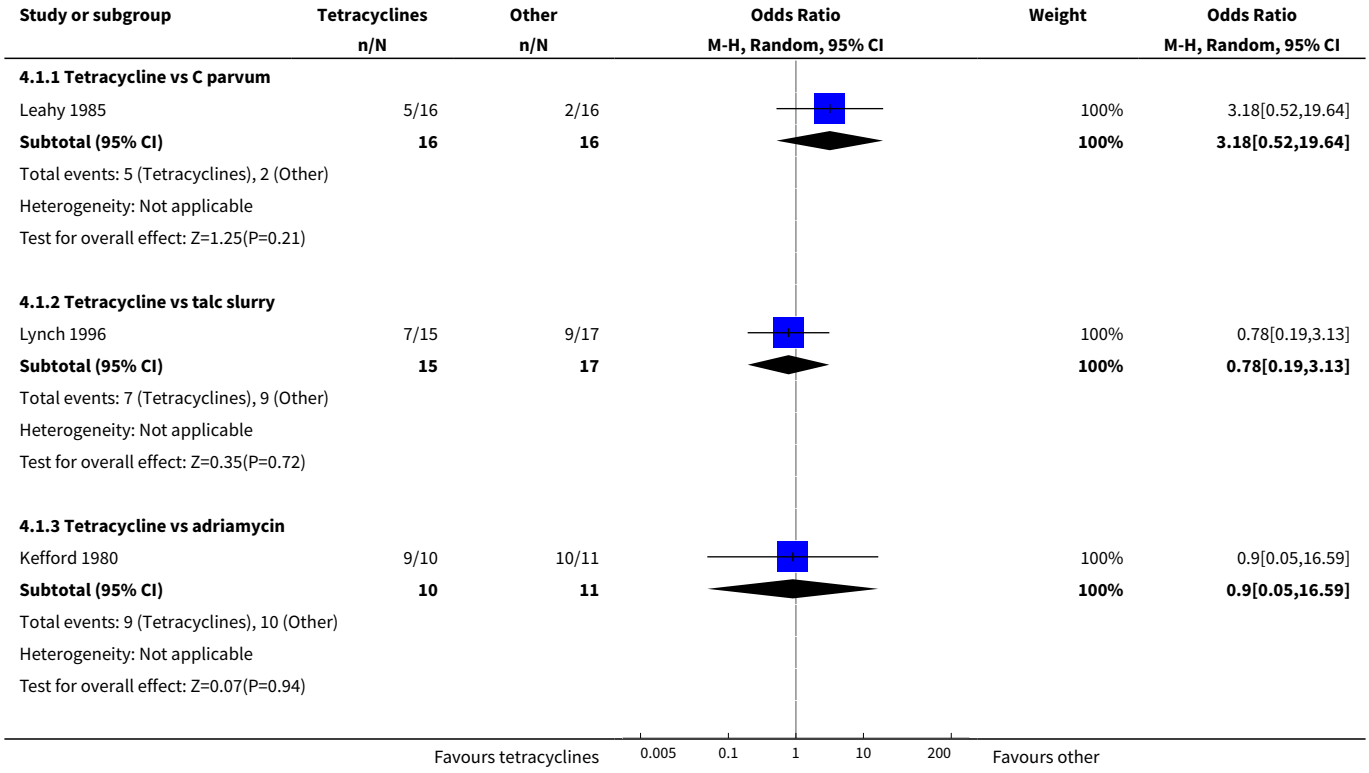
Comparison 4. Tetracycline

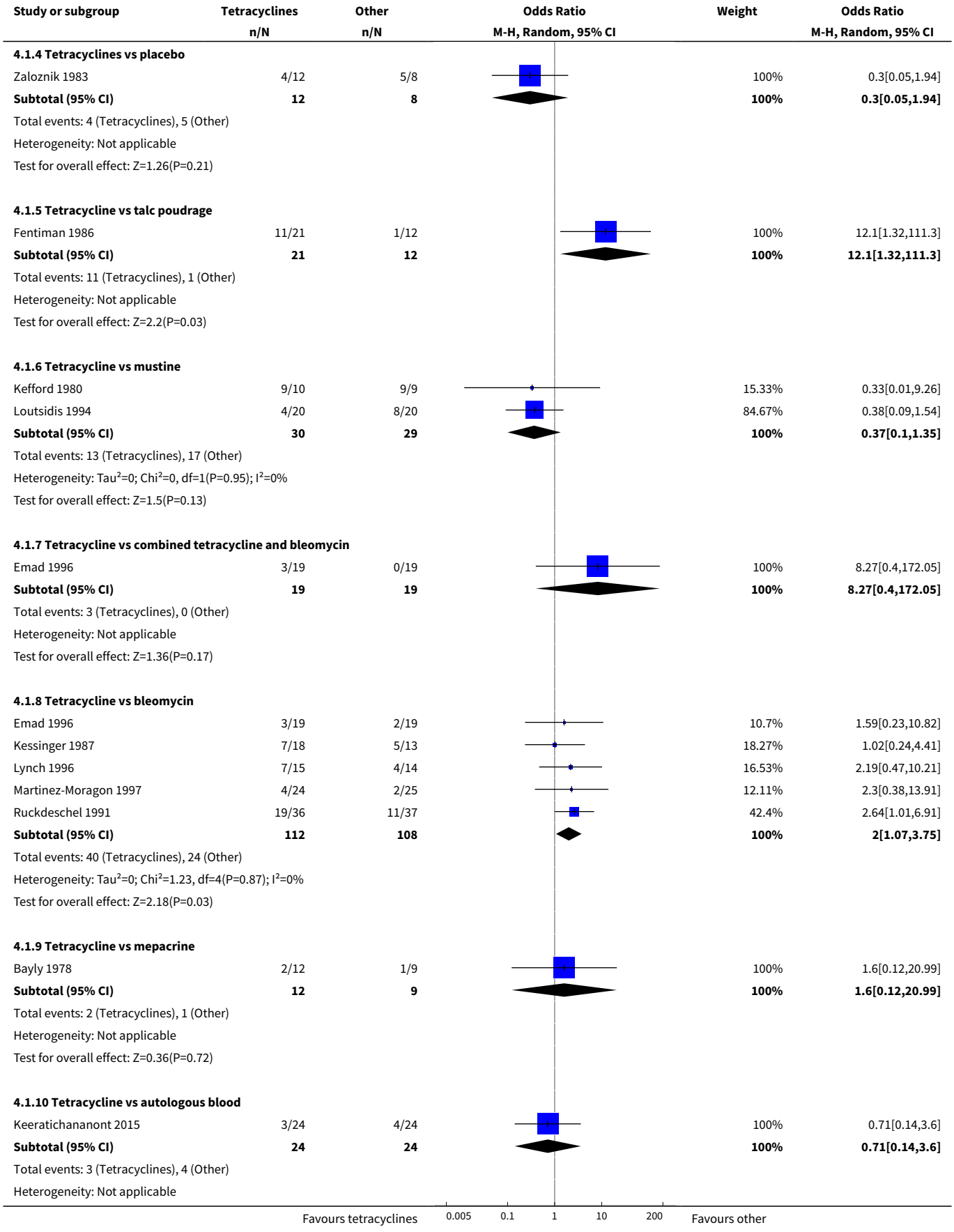
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Pleurodesis failure rate	14		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Tetracycline vs *C parvum*	1	32	Odds Ratio (M-H, Random, 95% CI)	3.18 [0.52, 19.64]
1.2 Tetracycline vs talc slurry	1	32	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.19, 3.13]
1.3 Tetracycline vs adriamycin	1	21	Odds Ratio (M-H, Random, 95% CI)	0.9 [0.05, 16.59]
1.4 Tetracyclines vs placebo	1	20	Odds Ratio (M-H, Random, 95% CI)	0.3 [0.05, 1.94]
1.5 Tetracycline vs talc poudrage	1	33	Odds Ratio (M-H, Random, 95% CI)	12.1 [1.32, 111.30]
1.6 Tetracycline vs mustine	2	59	Odds Ratio (M-H, Random, 95% CI)	0.37 [0.10, 1.35]
1.7 Tetracycline vs combined tetracycline and bleomycin	1	38	Odds Ratio (M-H, Random, 95% CI)	8.27 [0.40, 172.05]
1.8 Tetracycline vs bleomycin	5	220	Odds Ratio (M-H, Random, 95% CI)	2.00 [1.07, 3.75]
1.9 Tetracycline vs mepacrine	1	21	Odds Ratio (M-H, Random, 95% CI)	1.6 [0.12, 20.99]
1.10 Tetracycline vs autologous blood	1	48	Odds Ratio (M-H, Random, 95% CI)	0.71 [0.14, 3.60]
1.11 Tetracycline vs silver nitrate	1	50	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.15, 2.47]

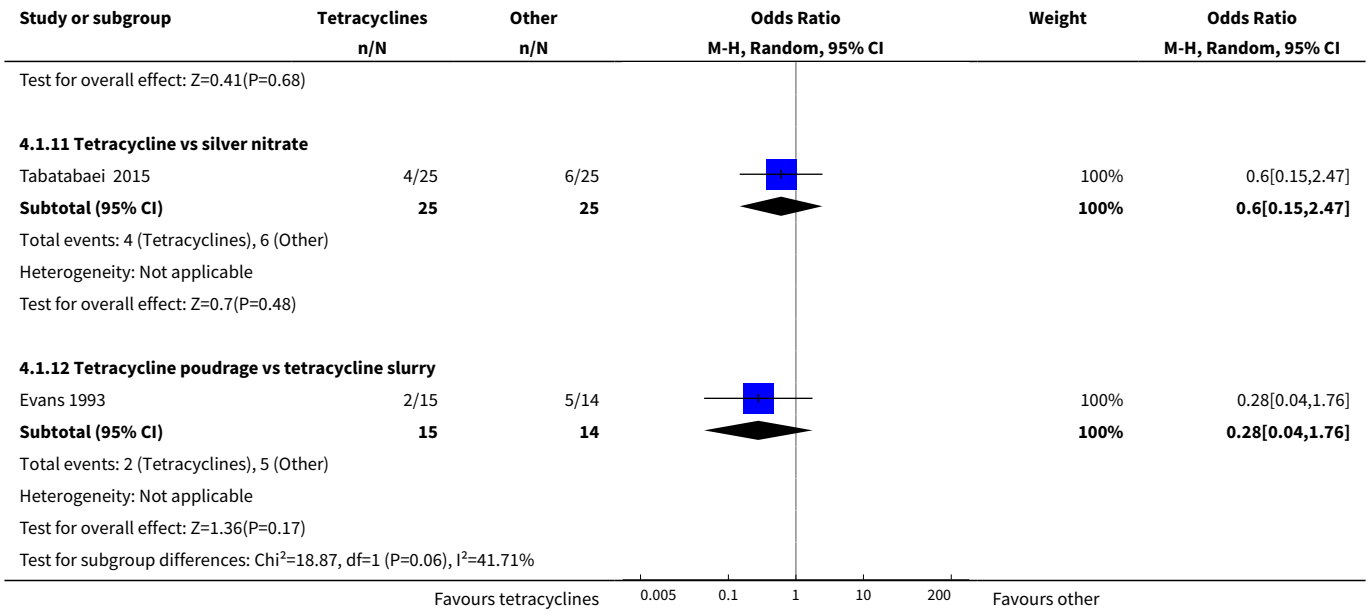
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.12 Tetracycline poudrage vs tetracycline slurry	1	29	Odds Ratio (M-H, Random, 95% CI)	0.28 [0.04, 1.76]
2 Fever	11		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Tetracycline vs talc slurry	1	34	Odds Ratio (M-H, Random, 95% CI)	0.92 [0.23, 3.63]
2.2 Tetracycline vs bleomycin	5	250	Odds Ratio (M-H, Random, 95% CI)	0.49 [0.16, 1.50]
2.3 Tetracycline vs *C parvum*	1	36	Odds Ratio (M-H, Random, 95% CI)	0.00 [0.00, 0.06]
2.4 Tetracycline vs mepacrine	1	22	Odds Ratio (M-H, Random, 95% CI)	0.13 [0.02, 0.89]
2.5 Tetracycline vs combination tetracycline and bleomycin	1	40	Odds Ratio (M-H, Random, 95% CI)	0.47 [0.04, 5.69]
2.6 Tetracycline vs placebo	1	22	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.7 Tetracycline vs mustine	1	40	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.8 Tetracycline vs autologous blood	1	48	Odds Ratio (M-H, Random, 95% CI)	4.53 [0.83, 24.65]
2.9 Tetracycline vs silver nitrate	1	50	Odds Ratio (M-H, Random, 95% CI)	327.86 [16.05, 6697.61]
3 Pain	10		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Tetracycline vs talc slurry	1	34	Odds Ratio (M-H, Random, 95% CI)	3.28 [0.73, 14.68]
3.2 Tetracycline vs bleomycin	4	220	Odds Ratio (M-H, Random, 95% CI)	1.65 [0.79, 3.43]
3.3 Tetracycline vs *C parvum*	1	41	Odds Ratio (M-H, Random, 95% CI)	0.41 [0.12, 1.45]
3.4 Tetracycline vs mustine	1	40	Odds Ratio (M-H, Random, 95% CI)	33.87 [1.80, 636.88]
3.5 Tetracycline vs mepacrine	1	22	Odds Ratio (M-H, Random, 95% CI)	0.18 [0.03, 1.23]
3.6 Tetracycline vs placebo	1	22	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.7 Tetracycline vs autologous blood	1	48	Odds Ratio (M-H, Random, 95% CI)	69.00 [7.61, 625.86]
3.8 Tetracycline vs silver nitrate	1	50	Odds Ratio (M-H, Random, 95% CI)	55.08 [3.02, 1003.70]
4 Mortality	6	300	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.30, 3.26]
4.1 Tetracycline vs talc poudrage	1	41	Odds Ratio (M-H, Random, 95% CI)	0.19 [0.03, 1.10]
4.2 Tetracycline vs bleomycin	2	125	Odds Ratio (M-H, Random, 95% CI)	1.60 [0.69, 3.69]
4.3 Tetracycline vs *C parvum*	1	36	Odds Ratio (M-H, Random, 95% CI)	3.00 [0.28, 31.99]
4.4 Tetracycline vs silver nitrate	1	50	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.5 Tetracycline vs autologous blood	1	48	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

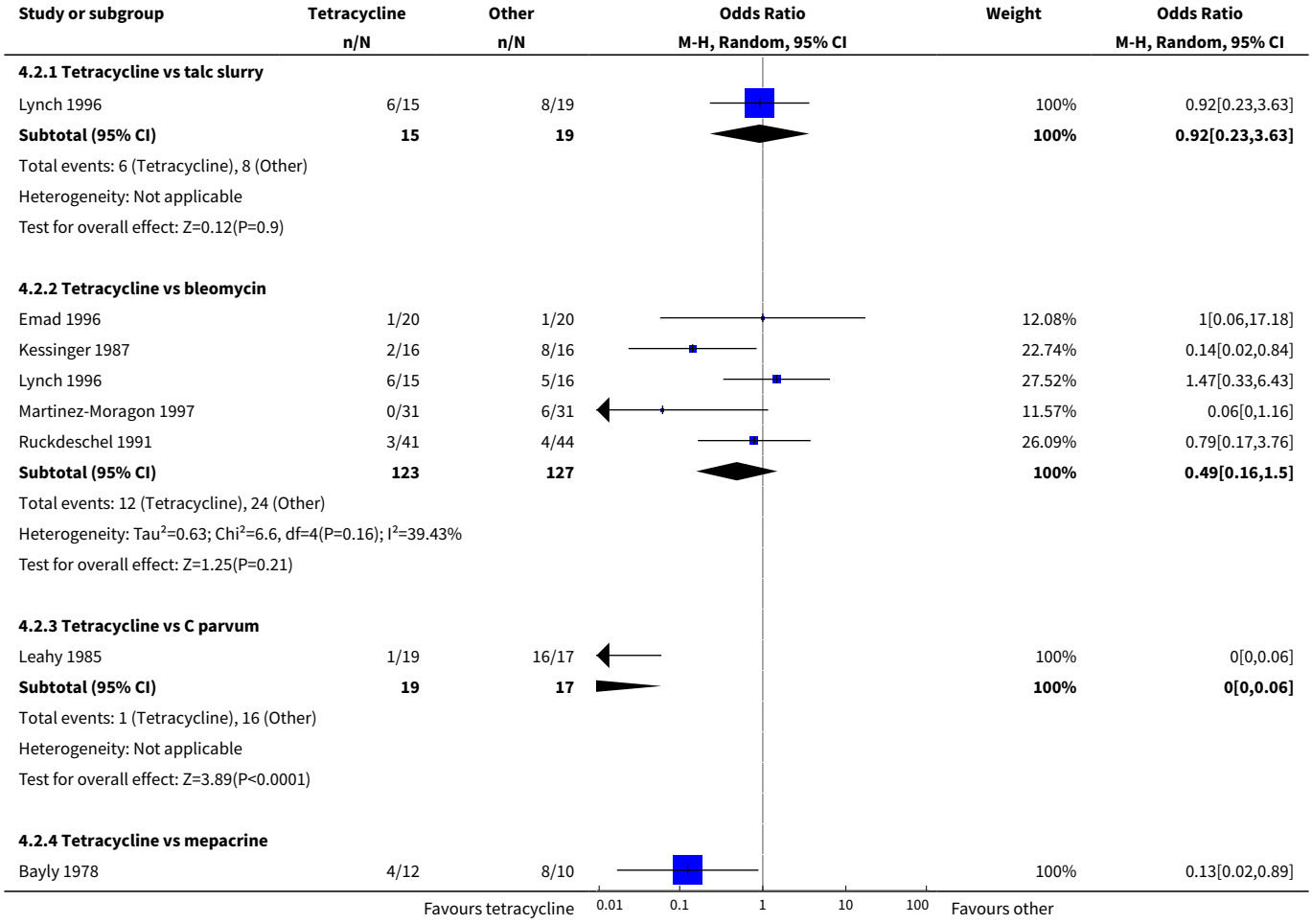
Analysis 4.1. Comparison 4 Tetracycline, Outcome 1 Pleurodesis failure rate.

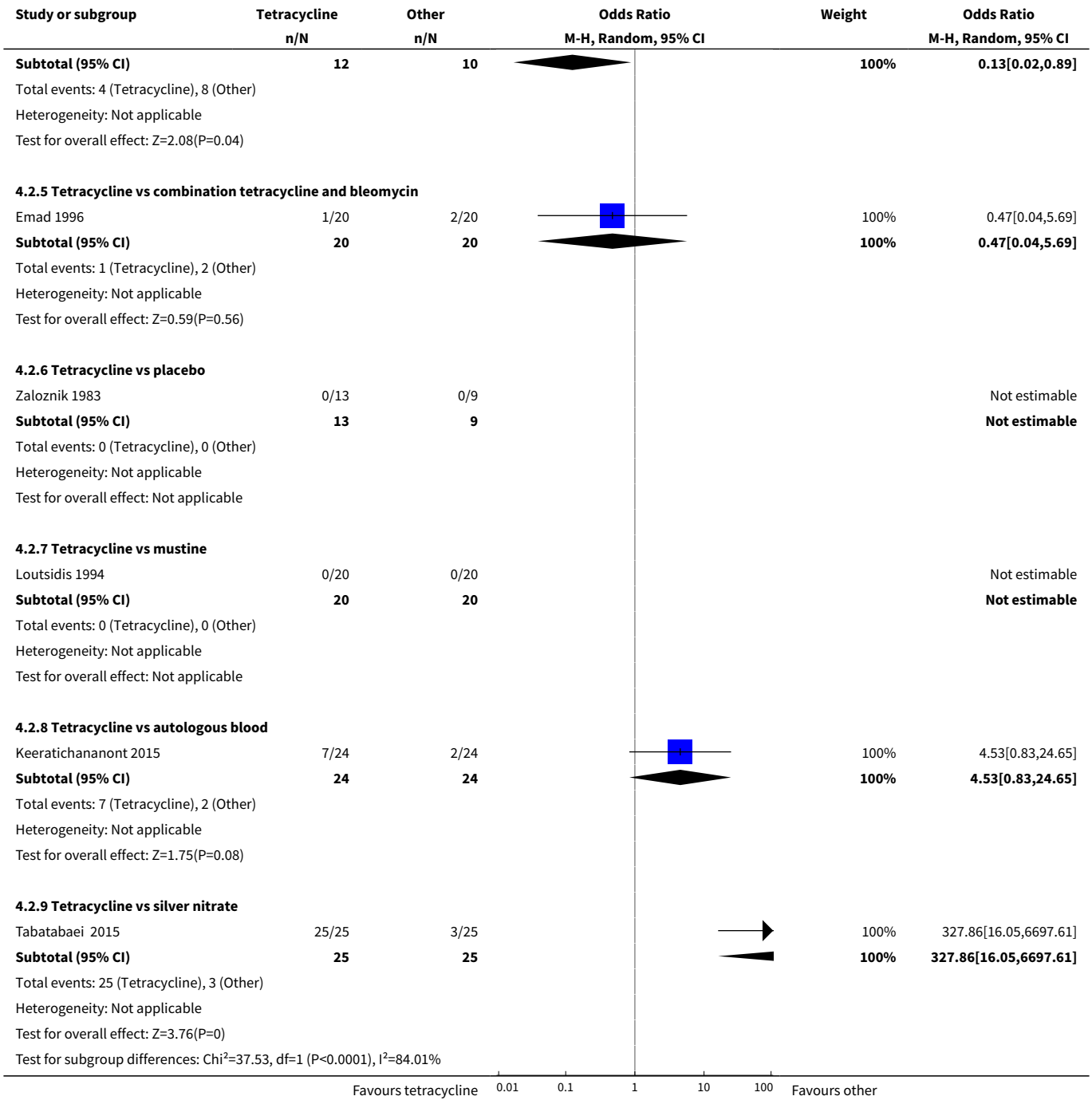




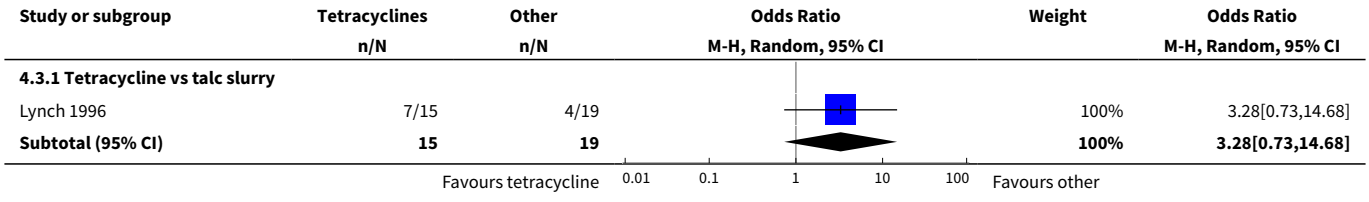


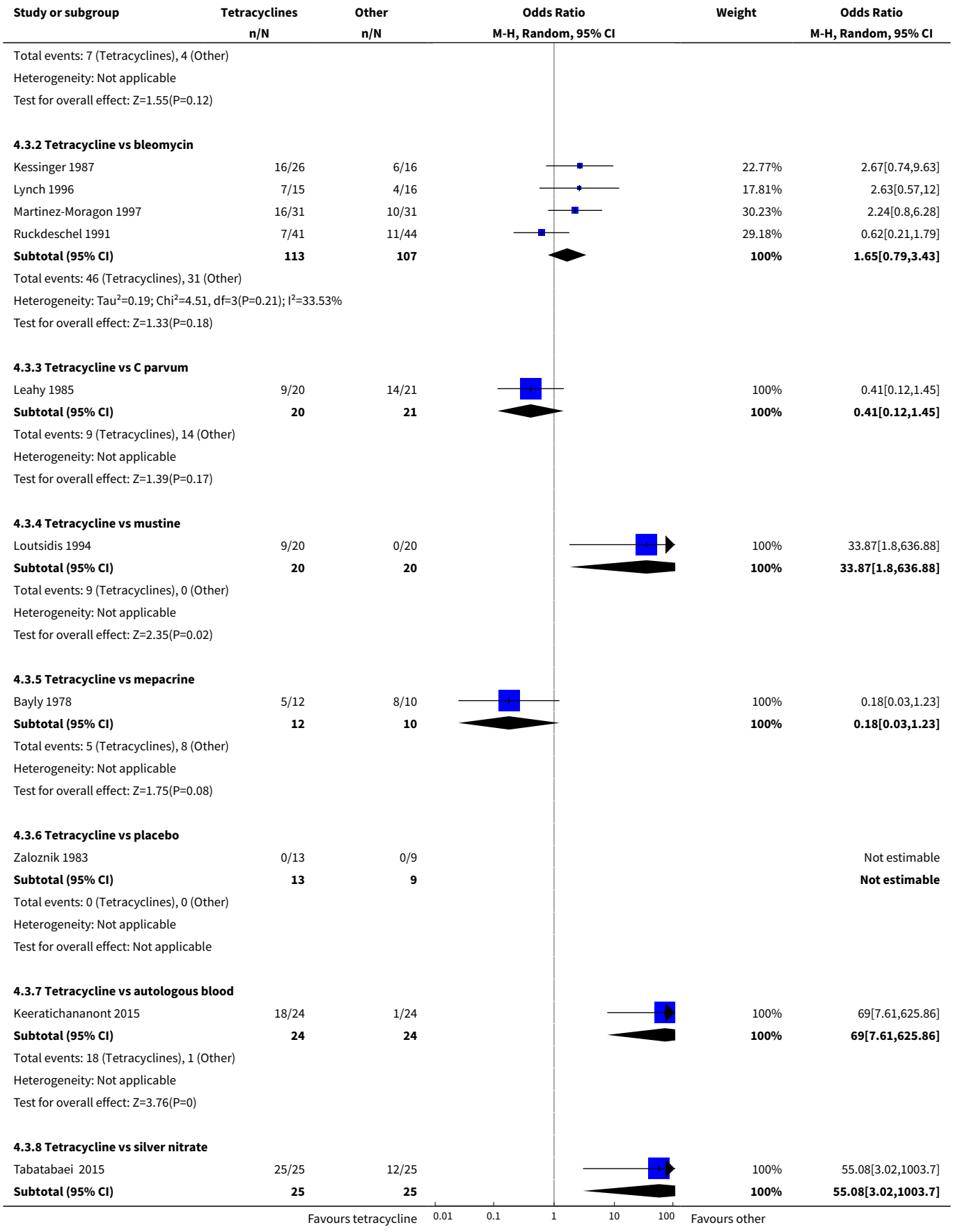
Analysis 4.2. Comparison 4 Tetracycline, Outcome 2 Fever.



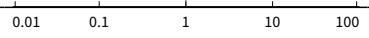


Analysis 4.3. Comparison 4 Tetracycline, Outcome 3 Pain.





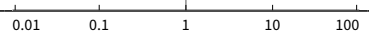
Study or subgroup	Tetracyclines n/N	Other n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Total events: 25 (Tetracyclines), 12 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.71(P=0.01)					
Test for subgroup differences: Chi²=31.14, df=1 (P<0.0001), I²=80.73%					



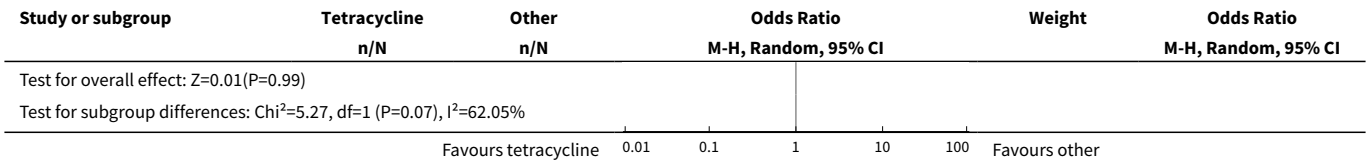
Favours tetracycline Favours other

Analysis 4.4. Comparison 4 Tetracycline, Outcome 4 Mortality.

Study or subgroup	Tetracycline n/N	Other n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
4.4.1 Tetracycline vs talc poudrage					
Fentiman 1986	2/23	6/18		25.51%	0.19[0.03,1.1]
Subtotal (95% CI)	**23**	**18**		**25.51%**	**0.19[0.03,1.1]**
Total events: 2 (Tetracycline), 6 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.86(P=0.06)					
4.4.2 Tetracycline vs bleomycin					
Emad 1996	1/20	1/20		13.37%	1[0.06,17.18]
Ruckdeschel 1991	19/41	15/44		43.64%	1.67[0.7,4]
Subtotal (95% CI)	**61**	**64**		**57.01%**	**1.6[0.69,3.69]**
Total events: 20 (Tetracycline), 16 (Other)					
Heterogeneity: Tau²=0; Chi²=0.11, df=1(P=0.74); I²=0%					
Test for overall effect: Z=1.1(P=0.27)					
4.4.3 Tetracycline vs C parvum					
Leahy 1985	3/19	1/17		17.48%	3[0.28,31.99]
Subtotal (95% CI)	**19**	**17**		**17.48%**	**3[0.28,31.99]**
Total events: 3 (Tetracycline), 1 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.91(P=0.36)					
4.4.4 Tetracycline vs silver nitrate					
Tabatabaei 2015	0/25	0/25			Not estimable
Subtotal (95% CI)	**25**	**25**			**Not estimable**
Total events: 0 (Tetracycline), 0 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
4.4.5 Tetracycline vs autologous blood					
Keeratichananont 2015	0/24	0/24			Not estimable
Subtotal (95% CI)	**24**	**24**			**Not estimable**
Total events: 0 (Tetracycline), 0 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**152**	**148**		**100%**	**0.99[0.3,3.26]**
Total events: 25 (Tetracycline), 23 (Other)					
Heterogeneity: Tau²=0.64; Chi²=5.4, df=3(P=0.14); I²=44.46%					



Favours tetracycline Favours other



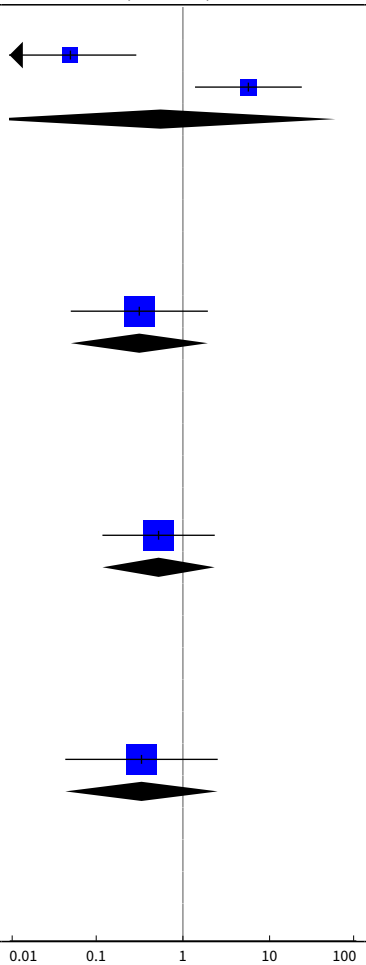
Comparison 5. *C parvum*

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pleurodesis failure rate	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 *C parvum* vs bleomycin	2	78	Odds Ratio (M-H, Random, 95% CI)	0.55 [0.01, 57.48]
1.2 *C parvum* vs tetracycline	1	32	Odds Ratio (M-H, Random, 95% CI)	0.31 [0.05, 1.94]
1.3 *C parvum* vs doxycycline	1	35	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.12, 2.33]
1.4 *C parvum* vs mustine	1	18	Odds Ratio (M-H, Random, 95% CI)	0.33 [0.04, 2.52]
2 Fever	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 *C parvum* vs bleomycin	2	80	Odds Ratio (M-H, Random, 95% CI)	2.30 [0.90, 5.92]
2.2 *C parvum* vs tetracycline	1	36	Odds Ratio (M-H, Random, 95% CI)	288.00 [16.62, 4991.05]
2.3 *C parvum* vs mustine	1	21	Odds Ratio (M-H, Random, 95% CI)	4.41 [0.16, 121.68]
2.4 *C parvum* vs doxycycline	1	41	Odds Ratio (M-H, Random, 95% CI)	7.37 [1.84, 29.55]
3 Pain	4	153	Odds Ratio (M-H, Random, 95% CI)	2.51 [1.10, 5.75]
3.1 *C parvum* vs bleomycin	2	71	Odds Ratio (M-H, Random, 95% CI)	1.42 [0.54, 3.75]
3.2 *C parvum* vs tetracycline	1	41	Odds Ratio (M-H, Random, 95% CI)	2.44 [0.69, 8.66]
3.3 *C parvum* vs doxycycline	1	41	Odds Ratio (M-H, Random, 95% CI)	7.37 [1.84, 29.55]

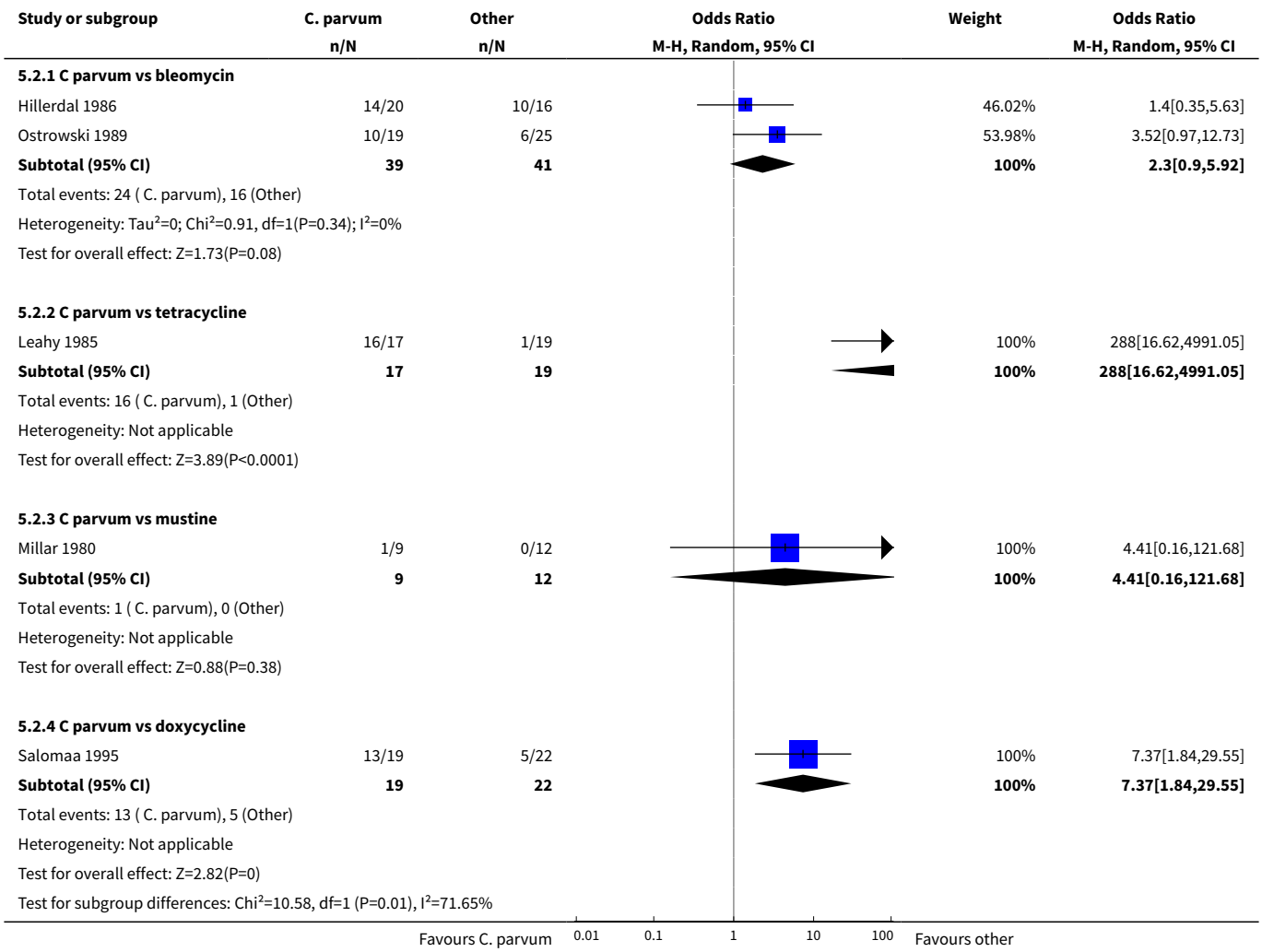
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4 Mortality	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 *C parvum* vs bleomycin	1	55	Odds Ratio (M-H, Random, 95% CI)	1.66 [0.51, 5.38]
4.2 *C parvum* vs tetracycline	1	36	Odds Ratio (M-H, Random, 95% CI)	0.33 [0.03, 3.55]
4.3 *C parvum* vs mustine	1	21	Odds Ratio (M-H, Random, 95% CI)	0.42 [0.07, 2.66]

Analysis 5.1. Comparison 5 *C parvum*, Outcome 1 Pleurodesis failure rate.

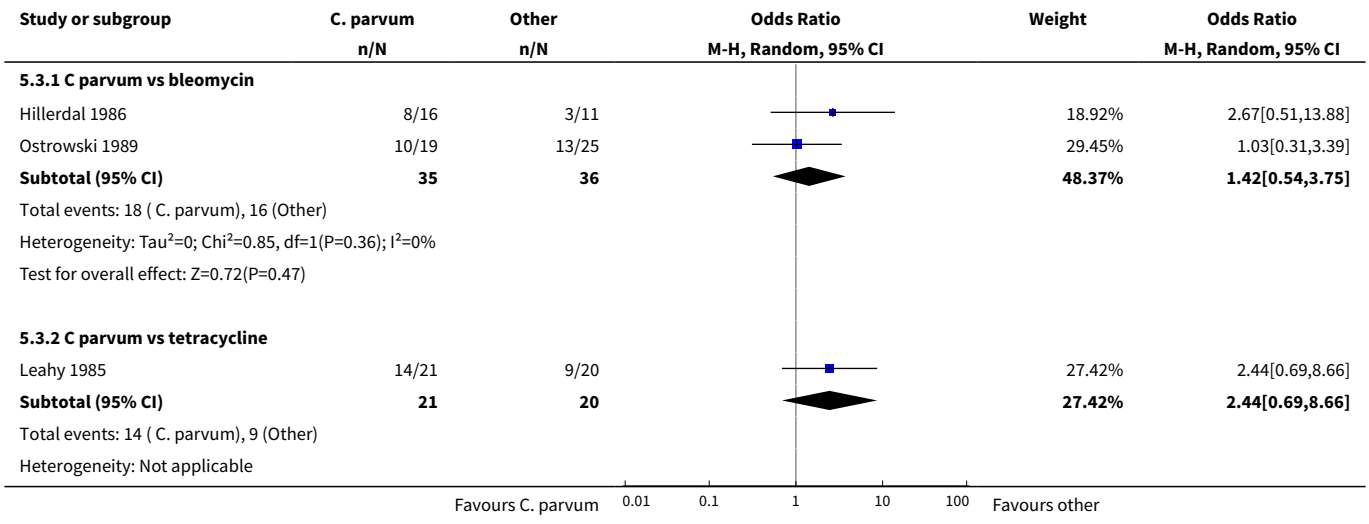
Study or subgroup	C parvum n/N	Other n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
5.1.1 C parvum vs bleomycin					
Hillerdal 1986	6/20	17/19		49.39%	0.05[0.01,0.29]
Ostrowski 1989	13/17	8/22		50.61%	5.69[1.38,23.48]
Subtotal (95% CI)	**37**	**41**		**100%**	**0.55[0.01,57.48]**
Total events: 19 (C parvum), 25 (Other)					
Heterogeneity: Tau²=10.59; Chi²=17.04, df=1(P<0.0001); I²=94.13%					
Test for overall effect: Z=0.25(P=0.8)					
5.1.2 C parvum vs tetracycline					
Leahy 1985	2/16	5/16		100%	0.31[0.05,1.94]
Subtotal (95% CI)	**16**	**16**		**100%**	**0.31[0.05,1.94]**
Total events: 2 (C parvum), 5 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.25(P=0.21)					
5.1.3 C parvum vs doxycycline					
Salomaa 1995	4/18	6/17		100%	0.52[0.12,2.33]
Subtotal (95% CI)	**18**	**17**		**100%**	**0.52[0.12,2.33]**
Total events: 4 (C parvum), 6 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.85(P=0.4)					
5.1.4 C parvum vs mustine					
Millar 1980	2/7	6/11		100%	0.33[0.04,2.52]
Subtotal (95% CI)	**7**	**11**		**100%**	**0.33[0.04,2.52]**
Total events: 2 (C parvum), 6 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.06(P=0.29)					
Test for subgroup differences: Chi²=0.24, df=1 (P=0.97), I²=0%					

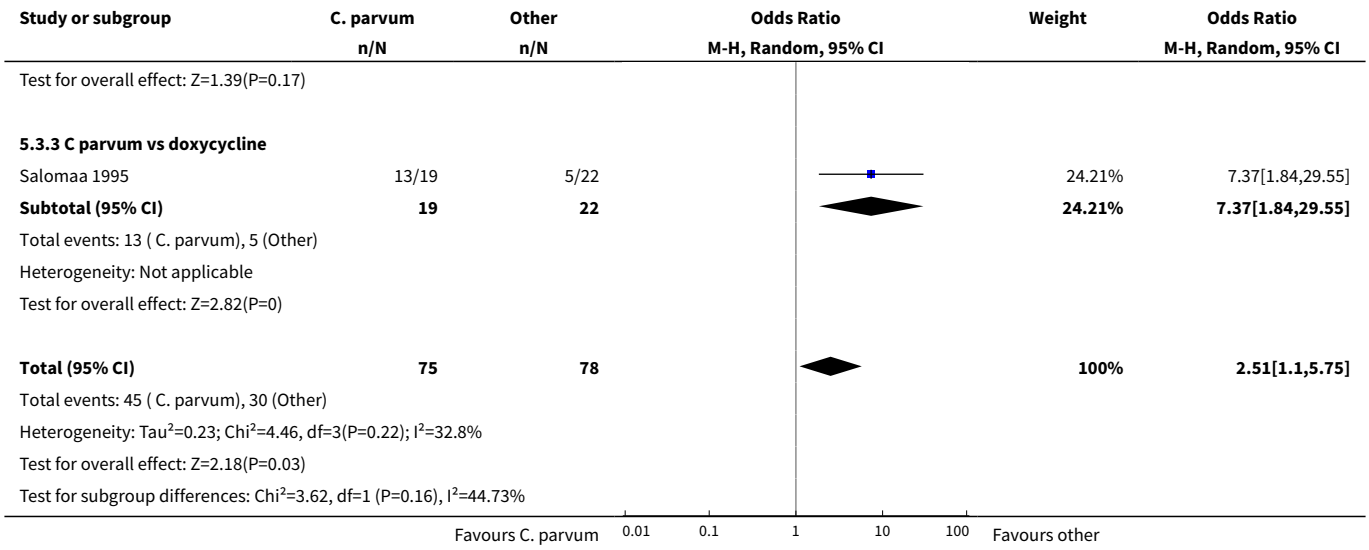


Analysis 5.2. Comparison 5 *C parvum*, Outcome 2 Fever.

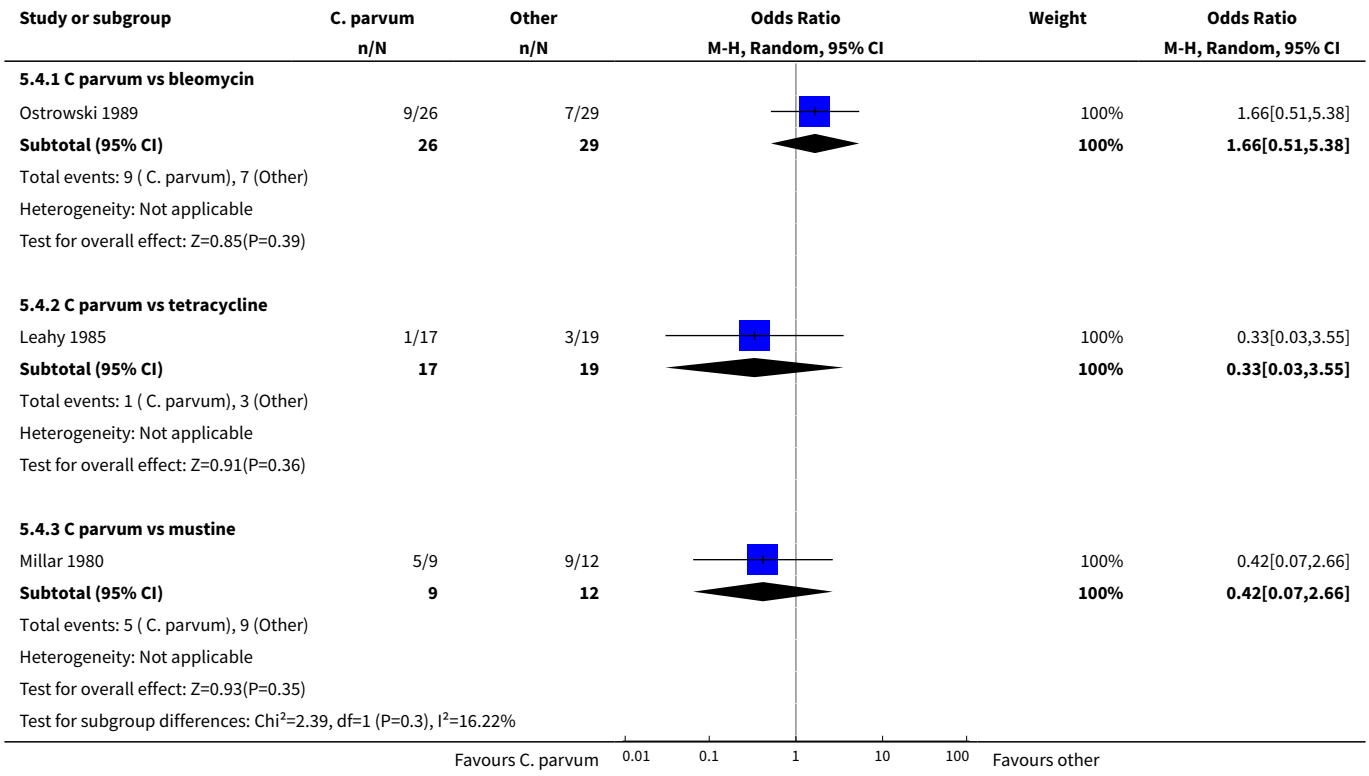


Analysis 5.3. Comparison 5 *C parvum*, Outcome 3 Pain.





Analysis 5.4. Comparison 5 *C parvum*, Outcome 4 Mortality.

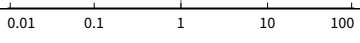


Comparison 6. Indwelling pleural catheter (IPC) – not daily drainage

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pleurodesis failure rate	6		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 IPC – not daily drainage vs talc slurry	2	249	Odds Ratio (M-H, Random, 95% CI)	5.46 [2.20, 13.55]
1.2 IPC – not daily drainage vs talc via IPC	1	139	Odds Ratio (M-H, Random, 95% CI)	2.76 [1.36, 5.60]
1.3 IPC – not daily drainage vs IPC – daily drainage	2	236	Odds Ratio (M-H, Random, 95% CI)	3.23 [1.79, 5.85]
1.4 IPC – not daily drainage vs doxycycline	1	119	Odds Ratio (M-H, Random, 95% CI)	4.28 [1.59, 11.54]
2 Fever	1	119	Odds Ratio (M-H, Fixed, 95% CI)	0.44 [0.07, 2.80]
3 Pain	6		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 IPC – not daily drainage vs talc slurry	2	232	Odds Ratio (M-H, Random, 95% CI)	1.63 [0.51, 5.15]
3.2 IPC – not daily drainage vs talc via IPC	1	154	Odds Ratio (M-H, Random, 95% CI)	1.41 [0.47, 4.28]
3.3 IPC – not daily drainage vs IPC – daily drainage	2	236	Odds Ratio (M-H, Random, 95% CI)	1.36 [0.78, 2.37]
3.4 IPC – not daily drainage vs doxycycline	1	119	Odds Ratio (M-H, Random, 95% CI)	0.06 [0.00, 1.24]
4 Breathlessness	2	160	Mean Difference (IV, Fixed, 95% CI)	-6.12 [-16.32, 4.08]
4.1 IPC – not daily drainage vs talc slurry	2	160	Mean Difference (IV, Fixed, 95% CI)	-6.12 [-16.32, 4.08]
5 Mortality	6	734	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.66, 1.49]
5.1 IPC – not daily drainage vs talc slurry	3	344	Odds Ratio (M-H, Random, 95% CI)	0.70 [0.45, 1.09]
5.2 IPC – not daily drainage vs talc via IPC	1	154	Odds Ratio (M-H, Random, 95% CI)	2.29 [0.87, 6.04]
5.3 IPC – not daily drainage vs IPC – daily drainage	2	236	Odds Ratio (M-H, Random, 95% CI)	1.29 [0.72, 2.32]
6 Repeat pleural procedure	3	343	Odds Ratio (M-H, Fixed, 95% CI)	0.25 [0.13, 0.48]

Analysis 6.1. Comparison 6 Indwelling pleural catheter (IPC) – not daily drainage, Outcome 1 Pleurodesis failure rate.

Study or subgroup	IPC – not daily drainage n/N	Other n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
6.1.1 IPC – not daily drainage vs talc slurry					
Davies 2012	25/51	12/54		47.79%	3.37[1.45,7.83]
Thomas 2017	52/73	16/71		52.21%	8.51[4.01,18.07]
Subtotal (95% CI)	**124**	**125**		**100%**	**5.46[2.2,13.55]**
Total events: 77 (IPC – not daily drainage), 28 (Other)					
Heterogeneity: Tau^2=0.26; Chi^2=2.58, df=1(P=0.11); I^2=61.31%					
Test for overall effect: Z=3.66(P=0)					
6.1.2 IPC – not daily drainage vs talc via IPC					
Bhatnagar 2018	51/70	34/69		100%	2.76[1.36,5.6]
Subtotal (95% CI)	**70**	**69**		**100%**	**2.76[1.36,5.6]**
Total events: 51 (IPC – not daily drainage), 34 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.82(P=0)					
6.1.3 IPC – not daily drainage vs IPC – daily drainage					
Muruganandan 2018	39/44	27/43		28.22%	4.62[1.51,14.13]
Wahidi 2017	58/76	39/73		71.78%	2.81[1.39,5.66]
Subtotal (95% CI)	**120**	**116**		**100%**	**3.23[1.79,5.85]**
Total events: 97 (IPC – not daily drainage), 66 (Other)					
Heterogeneity: Tau^2=0; Chi^2=0.55, df=1(P=0.46); I^2=0%					
Test for overall effect: Z=3.87(P=0)					
6.1.4 IPC – not daily drainage vs doxycycline					
Putnam 1999	49/91	6/28		100%	4.28[1.59,11.54]
Subtotal (95% CI)	**91**	**28**		**100%**	**4.28[1.59,11.54]**
Total events: 49 (IPC – not daily drainage), 6 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.87(P=0)					
Test for subgroup differences: Chi^2=1.58, df=1 (P=0.66), I^2=0%					



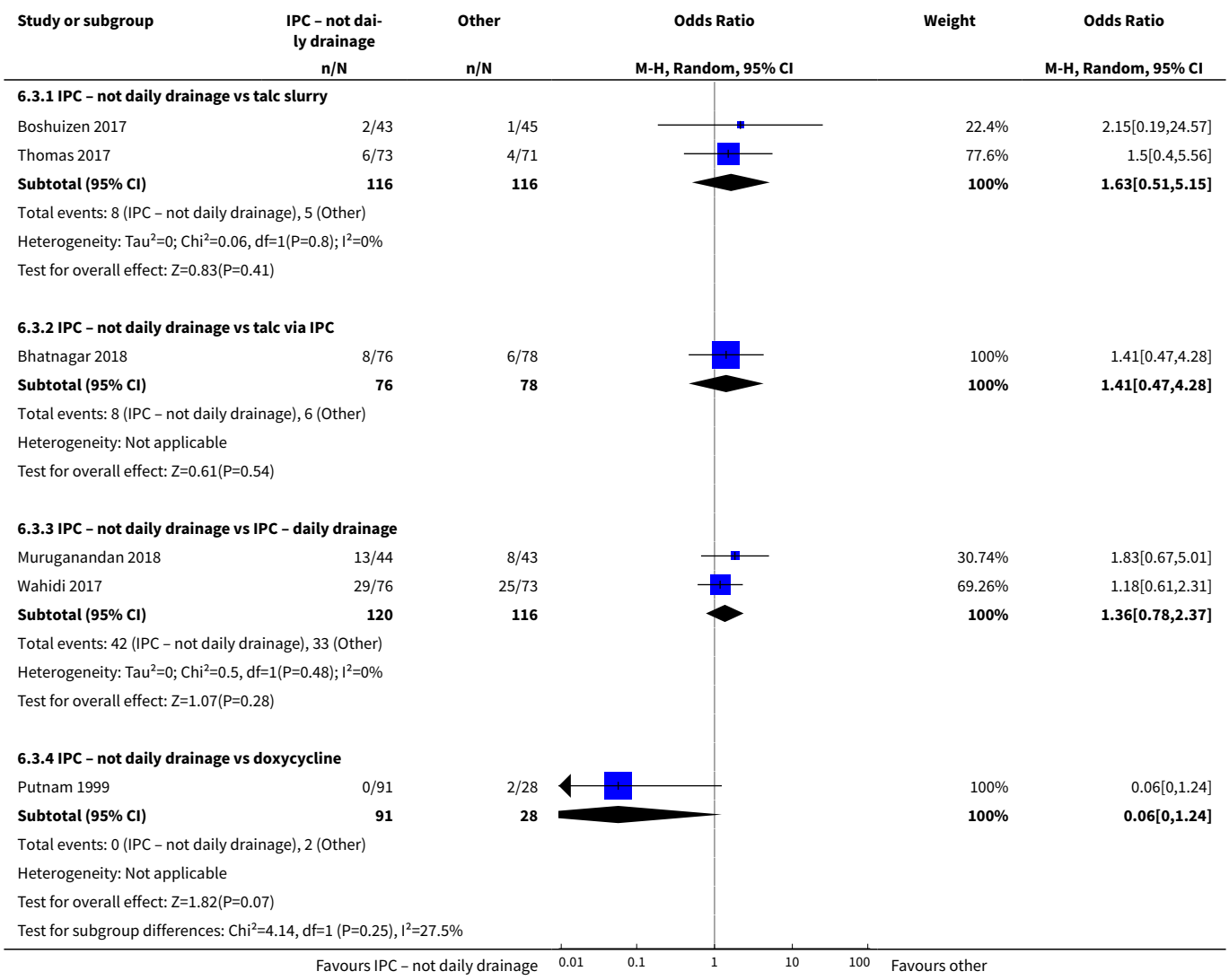
Favours IPC -– not daily drainage — Favours other

Analysis 6.2. Comparison 6 Indwelling pleural catheter (IPC) – not daily drainage, Outcome 2 Fever.

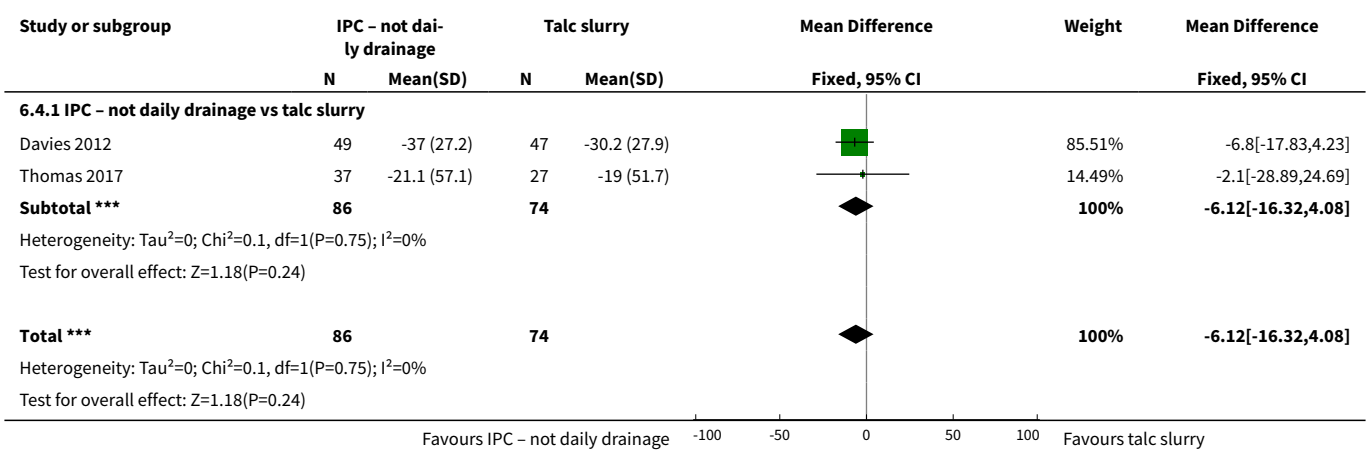
Study or subgroup	IPC – not daily drainage n/N	Doxycycline n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Putnam 1999	3/91	2/28		100%	0.44[0.07,2.8]
Total (95% CI)	**91**	**28**		**100%**	**0.44[0.07,2.8]**
Total events: 3 (IPC – not daily drainage), 2 (Doxycycline)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.87(P=0.39)					

Favours IPC – not daily drainage — Favours doxycycline

Analysis 6.3. Comparison 6 Indwelling pleural catheter (IPC) – not daily drainage, Outcome 3 Pain.

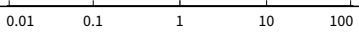


Analysis 6.4. Comparison 6 Indwelling pleural catheter (IPC) – not daily drainage, Outcome 4 Breathlessness.



Analysis 6.5. Comparison 6 Indwelling pleural catheter (IPC) – not daily drainage, Outcome 5 Mortality.

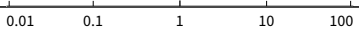
Study or subgroup	IPC – not daily drainage n/N	Other n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
6.5.1 IPC – not daily drainage vs talc slurry					
Boshuizen 2017	16/46	19/48		16.33%	0.81[0.35,1.88]
Davies 2012	16/52	20/54		17.19%	0.76[0.34,1.69]
Thomas 2017	44/73	51/71		20.72%	0.59[0.3,1.2]
Subtotal (95% CI)	**171**	**173**		**54.24%**	**0.7[0.45,1.09]**
Total events: 76 (IPC – not daily drainage), 90 (Other)					
Heterogeneity: Tau^2=0; Chi^2=0.37, df=2(P=0.83); I^2=0%					
Test for overall effect: Z=1.57(P=0.12)					
6.5.2 IPC – not daily drainage vs talc via IPC					
Bhatnagar 2018	14/76	7/78		13.26%	2.29[0.87,6.04]
Subtotal (95% CI)	**76**	**78**		**13.26%**	**2.29[0.87,6.04]**
Total events: 14 (IPC – not daily drainage), 7 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.68(P=0.09)					
6.5.3 IPC – not daily drainage vs IPC – daily drainage					
Muruganandan 2018	9/44	10/43		12.3%	0.85[0.31,2.35]
Wahidi 2017	26/76	18/73		20.2%	1.59[0.78,3.24]
Subtotal (95% CI)	**120**	**116**		**32.5%**	**1.29[0.72,2.32]**
Total events: 35 (IPC – not daily drainage), 28 (Other)					
Heterogeneity: Tau^2=0; Chi^2=0.98, df=1(P=0.32); I^2=0%					
Test for overall effect: Z=0.86(P=0.39)					
Total (95% CI)	**367**	**367**		**100%**	**0.99[0.66,1.49]**
Total events: 125 (IPC – not daily drainage), 125 (Other)					
Heterogeneity: Tau^2=0.08; Chi^2=7.34, df=5(P=0.2); I^2=31.9%					
Test for overall effect: Z=0.03(P=0.98)					
Test for subgroup differences: Chi^2=6, df=1 (P=0.05), I^2=66.64%					



Favours IPC – not daily drainage — Favours other

Analysis 6.6. Comparison 6 Indwelling pleural catheter (IPC) – not daily drainage, Outcome 6 Repeat pleural procedure.

Study or subgroup	IPC – not daily drainage n/N	Talc slurry n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Boshuizen 2017	7/46	15/48		31.94%	0.39[0.14,1.08]
Davies 2012	3/51	12/54		28.15%	0.22[0.06,0.83]
Thomas 2017	3/73	16/71		39.91%	0.15[0.04,0.53]
Total (95% CI)	**170**	**173**		**100%**	**0.25[0.13,0.48]**
Total events: 13 (IPC – not daily drainage), 43 (Talc slurry)					
Heterogeneity: Tau^2=0; Chi^2=1.49, df=2(P=0.48); I^2=0%					
Test for overall effect: Z=4.09(P<0.0001)					

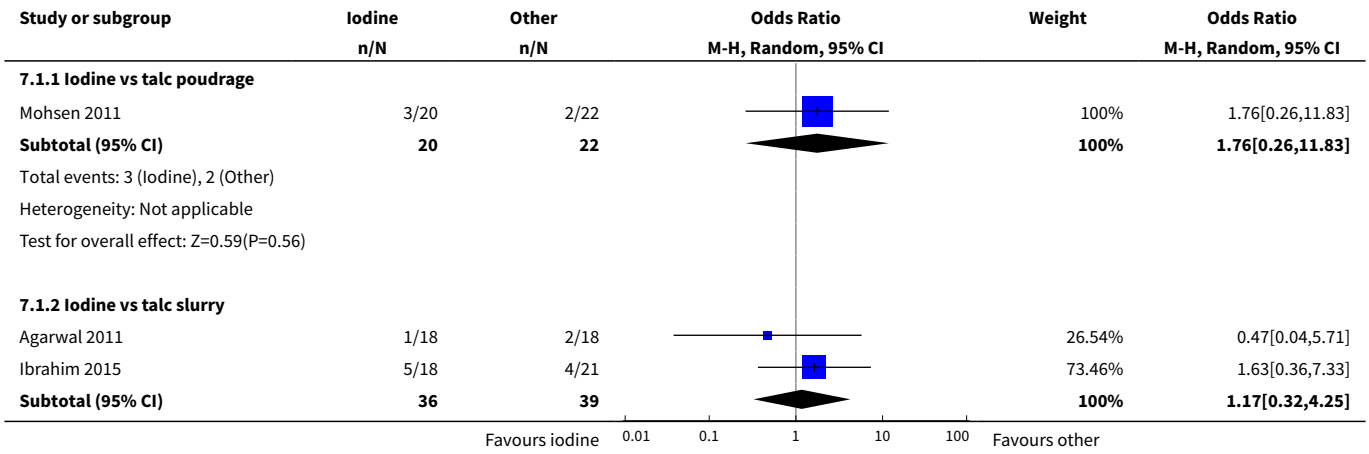


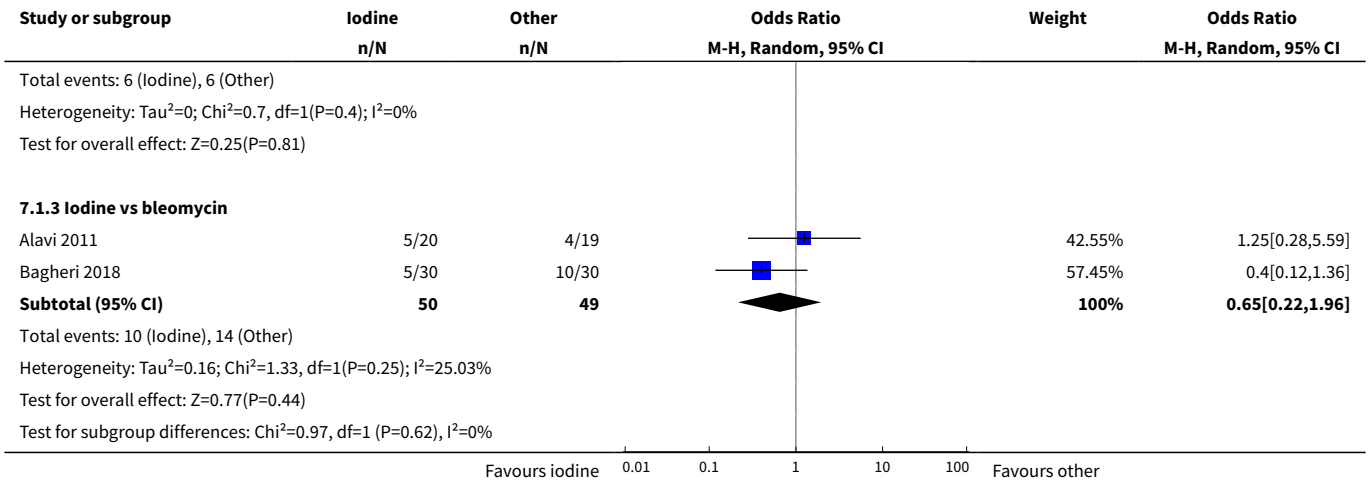
Favours IPC – not daily drainage — Favours talc slurry

Comparison 7. Iodine

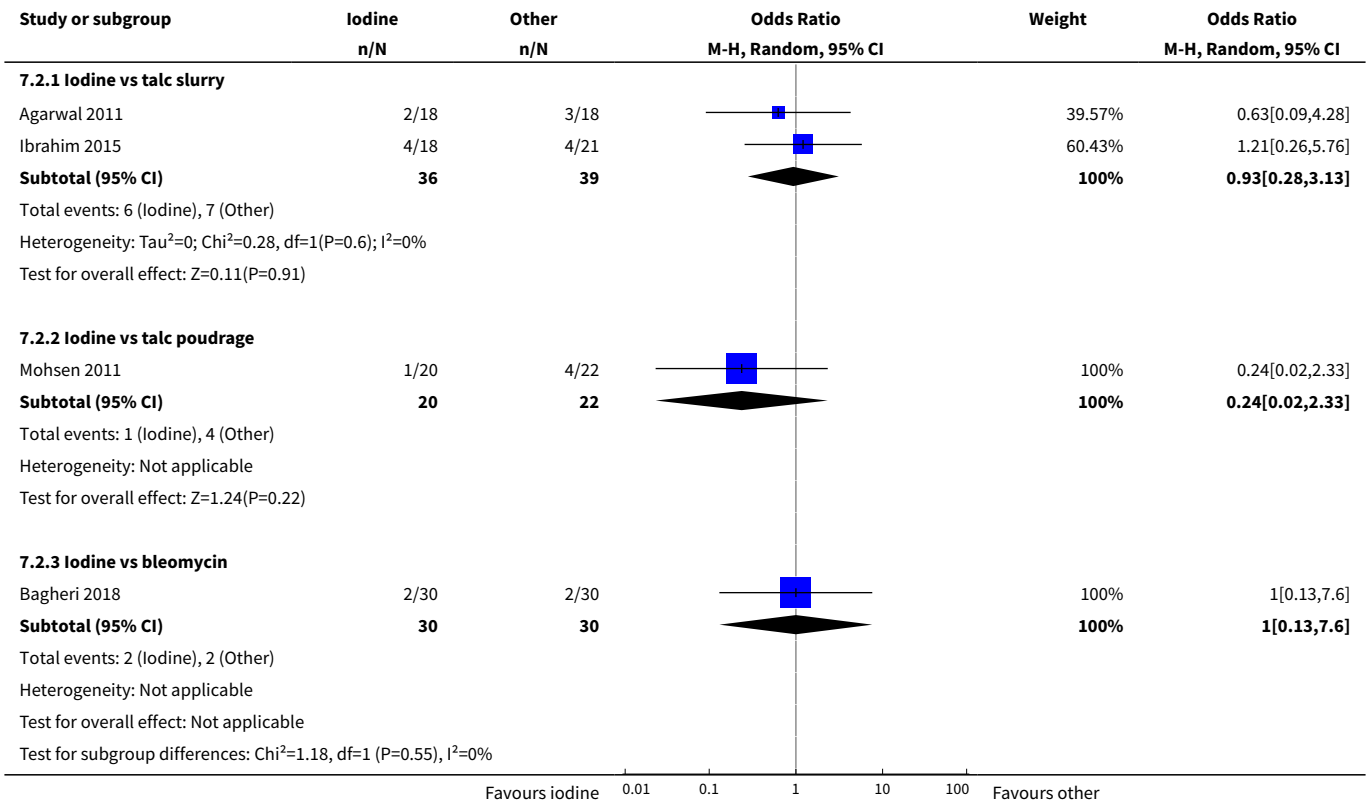
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pleurodesis failure rate	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Iodine vs talc poudrage	1	42	Odds Ratio (M-H, Random, 95% CI)	1.76 [0.26, 11.83]
1.2 Iodine vs talc slurry	2	75	Odds Ratio (M-H, Random, 95% CI)	1.17 [0.32, 4.25]
1.3 Iodine vs bleomycin	2	99	Odds Ratio (M-H, Random, 95% CI)	0.65 [0.22, 1.96]
2 Fever	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Iodine vs talc slurry	2	75	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.28, 3.13]
2.2 Iodine vs talc poudrage	1	42	Odds Ratio (M-H, Random, 95% CI)	0.24 [0.02, 2.33]
2.3 Iodine vs bleomycin	1	60	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.13, 7.60]
3 Pain	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Iodine vs talc slurry	2	75	Odds Ratio (M-H, Random, 95% CI)	0.5 [0.14, 1.83]
3.2 Iodine vs talc poudrage	1	42	Odds Ratio (M-H, Random, 95% CI)	0.10 [0.01, 1.99]
3.3 Iodine vs bleomycin	1	60	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.13, 7.60]
4 Mortality	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Iodine vs talc poudrage	1	42	Odds Ratio (M-H, Random, 95% CI)	0.38 [0.08, 1.73]
4.2 Iodine vs talc slurry	1	39	Odds Ratio (M-H, Random, 95% CI)	0.37 [0.01, 9.64]

Analysis 7.1. Comparison 7 Iodine, Outcome 1 Pleurodesis failure rate.

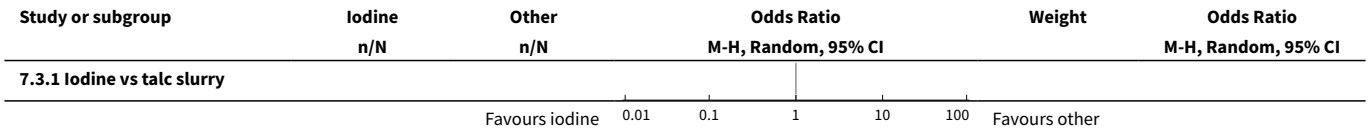


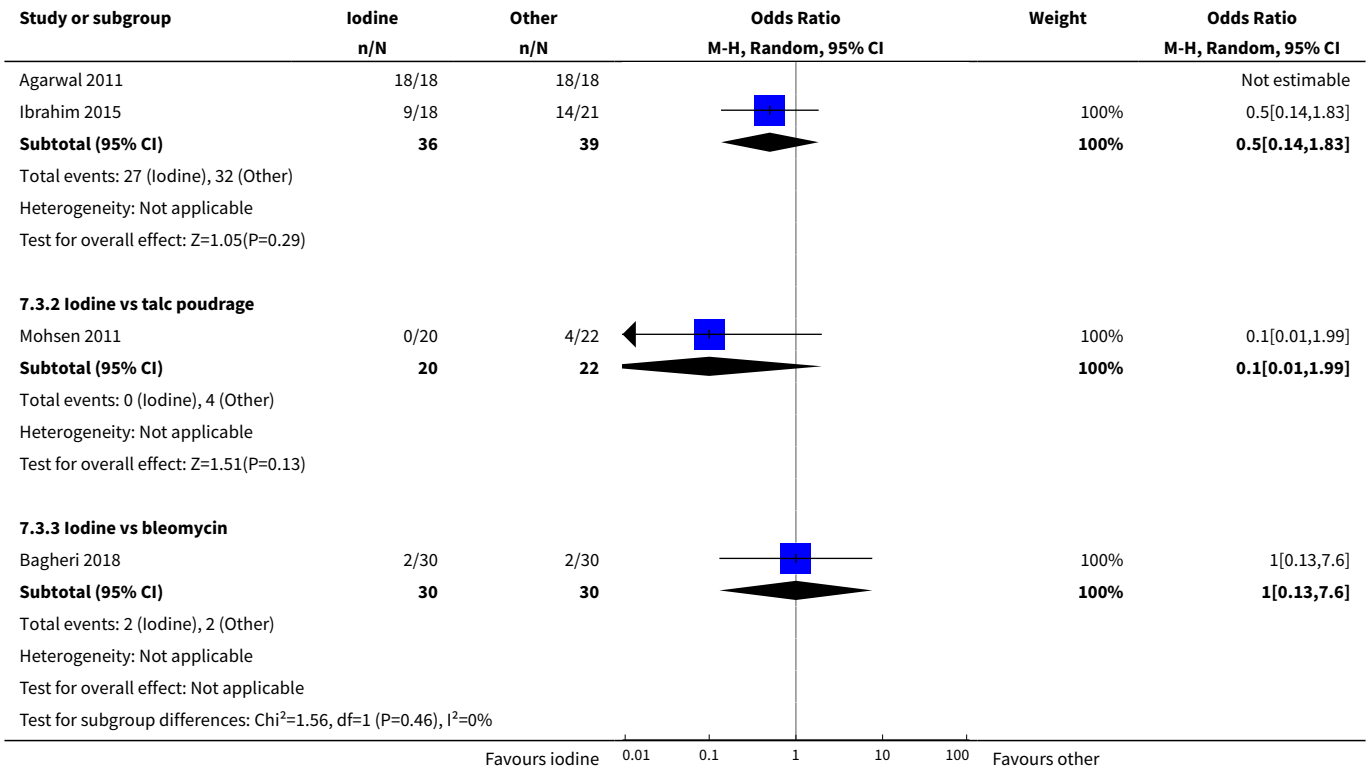


Analysis 7.2. Comparison 7 Iodine, Outcome 2 Fever.

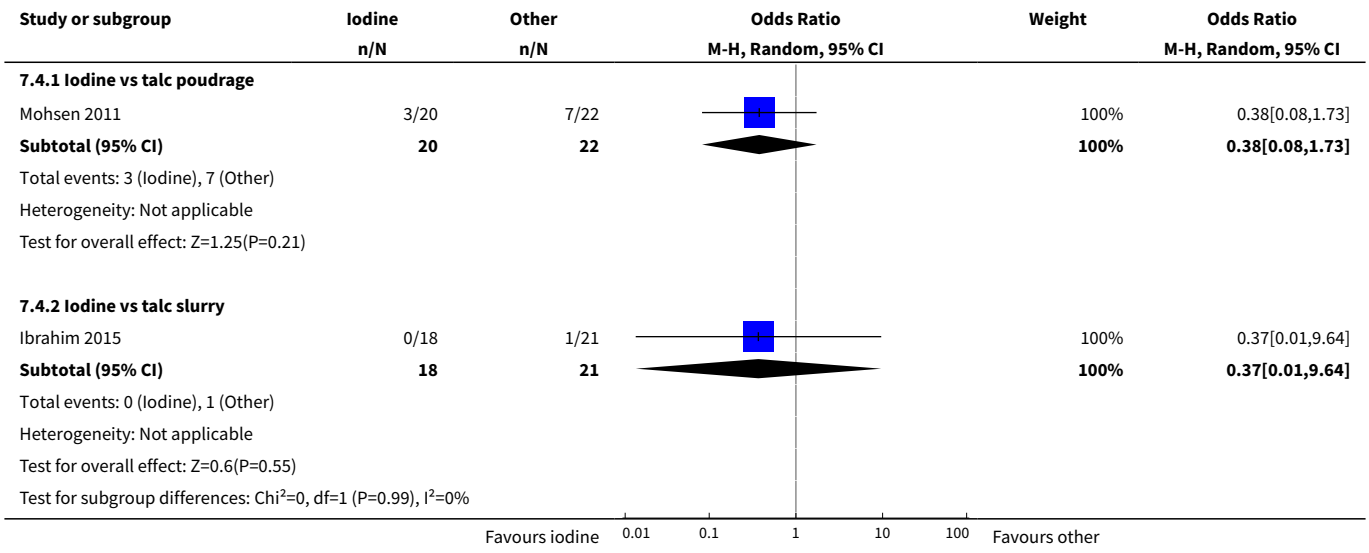


Analysis 7.3. Comparison 7 Iodine, Outcome 3 Pain.





Analysis 7.4. Comparison 7 Iodine, Outcome 4 Mortality.

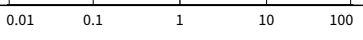


Comparison 8. Doxycycline

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Pleurodesis failure rate	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Doxycycline vs talc poudrage	1	31	Odds Ratio (M-H, Random, 95% CI)	42.69 [2.13, 856.61]
1.2 Doxycycline vs bleomycin	2	122	Odds Ratio (M-H, Random, 95% CI)	0.67 [0.24, 1.86]
1.3 Doxycycline vs *C parvum*	1	35	Odds Ratio (M-H, Random, 95% CI)	1.91 [0.43, 8.48]
1.4 Doxycycline vs IPC – not daily drainage	1	119	Odds Ratio (M-H, Random, 95% CI)	0.23 [0.09, 0.63]
2 Fever	4	308	Odds Ratio (M-H, Random, 95% CI)	0.48 [0.09, 2.59]
2.1 Doxycycline vs bleomycin	2	148	Odds Ratio (M-H, Random, 95% CI)	0.37 [0.01, 12.35]
2.2 Doxycycline vs *C parvum*	1	41	Odds Ratio (M-H, Random, 95% CI)	0.14 [0.03, 0.54]
2.3 Doxycycline vs IPC – not daily drainage	1	119	Odds Ratio (M-H, Random, 95% CI)	2.26 [0.36, 14.23]
3 Pain	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Doxycycline vs bleomycin	2	148	Odds Ratio (M-H, Random, 95% CI)	1.19 [0.37, 3.80]
3.2 Doxycycline vs *C parvum*	1	41	Odds Ratio (M-H, Random, 95% CI)	0.10 [0.01, 0.96]
3.3 Doxycycline vs IPC – not daily drainage	1	119	Odds Ratio (M-H, Random, 95% CI)	17.26 [0.80, 370.79]
4 Mortality	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Doxycycline vs bleomycin	1	80	Odds Ratio (M-H, Random, 95% CI)	0.69 [0.26, 1.87]

Analysis 8.1. Comparison 8 Doxycycline, Outcome 1 Pleurodesis failure rate.

Study or subgroup	Doxycyline n/N	Other n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
8.1.1 Doxycycline vs talc poudrage					
Kuzdzal 2003	7/13	0/18		100%	42.69[2.13,856.61]
Subtotal (95% CI)	**13**	**18**		**100%**	**42.69[2.13,856.61]**
Total events: 7 (Doxycyline), 0 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.45(P=0.01)					
8.1.2 Doxycycline vs bleomycin					
Patz 1998	7/38	10/42		90.02%	0.72[0.24,2.14]
Rafiei 2014	0/21	1/21		9.98%	0.32[0.01,8.26]
Subtotal (95% CI)	**59**	**63**		**100%**	**0.67[0.24,1.86]**
Total events: 7 (Doxycyline), 11 (Other)					
Heterogeneity: Tau^2=0; Chi^2=0.22, df=1(P=0.64); I^2=0%					
Test for overall effect: Z=0.77(P=0.44)					
8.1.3 Doxycycline vs C parvum					
Salomaa 1995	6/17	4/18		100%	1.91[0.43,8.48]
Subtotal (95% CI)	**17**	**18**		**100%**	**1.91[0.43,8.48]**
Total events: 6 (Doxycyline), 4 (Other)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.85(P=0.4)					
8.1.4 Doxycycline vs IPC – not daily drainage					
Putnam 1999	6/28	49/91		100%	0.23[0.09,0.63]
Subtotal (95% CI)	**28**	**91**		**100%**	**0.23[0.09,0.63]**
Total events: 6 (Doxycyline), 49 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.87(P=0)					
Test for subgroup differences: Chi^2=13.56, df=1 (P=0), I^2=77.88%					

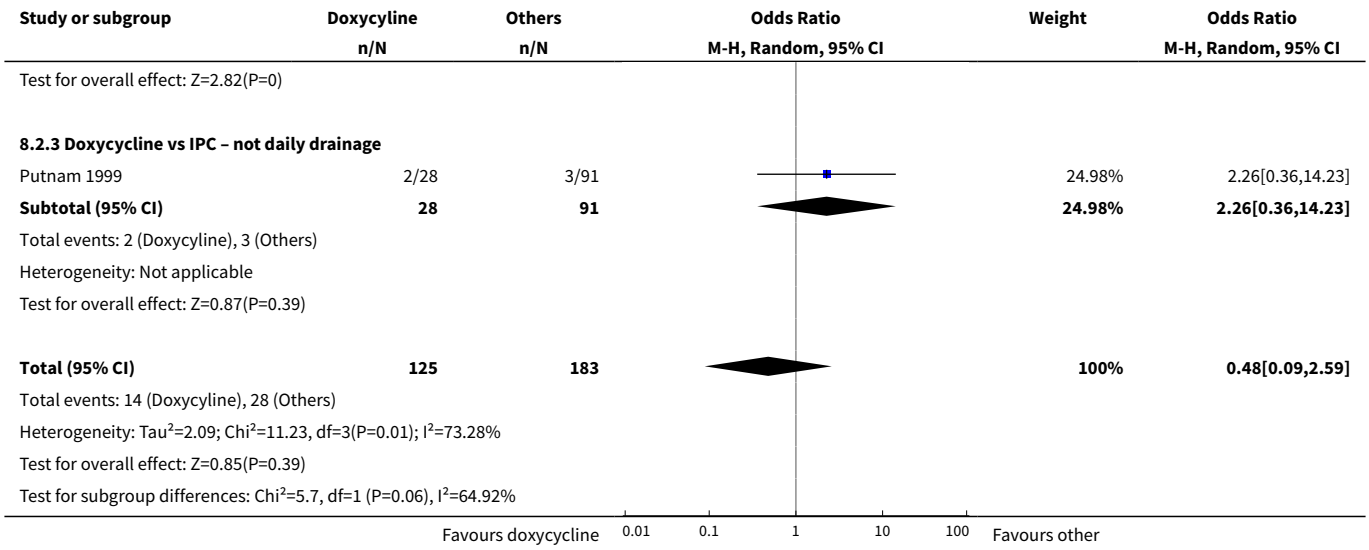


Favours doxycycline — Favours other

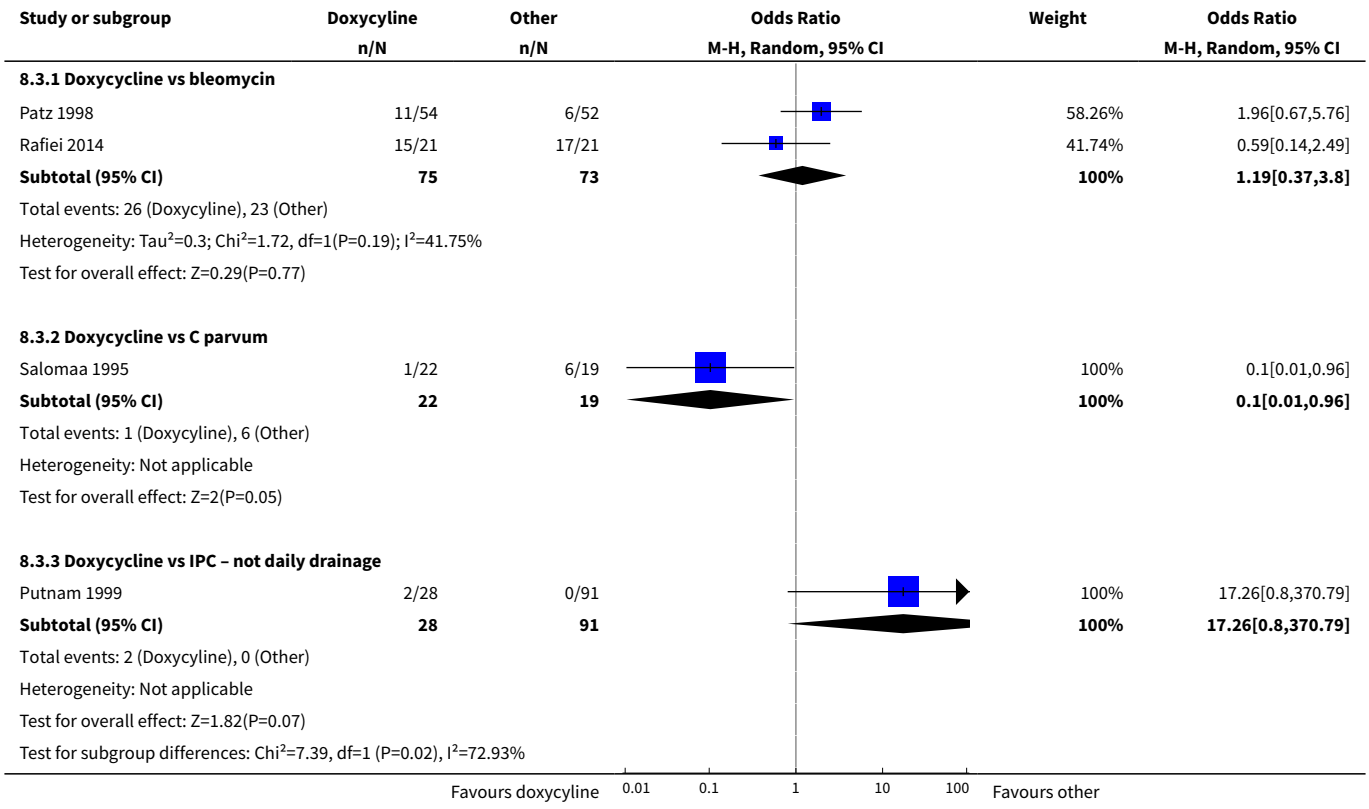
Analysis 8.2. Comparison 8 Doxycycline, Outcome 2 Fever.

Study or subgroup	Doxycyline n/N	Others n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
8.2.1 Doxycycline vs bleomycin					
Patz 1998	0/54	7/52		17.41%	0.06[0,1]
Rafiei 2014	7/21	5/21		28.95%	1.6[0.41,6.19]
Subtotal (95% CI)	**75**	**73**		**46.36%**	**0.37[0.01,12.35]**
Total events: 7 (Doxycyline), 12 (Others)					
Heterogeneity: Tau^2=5.18; Chi^2=4.91, df=1(P=0.03); I^2=79.62%					
Test for overall effect: Z=0.55(P=0.58)					
8.2.2 Doxycycline vs C parvum					
Salomaa 1995	5/22	13/19		28.66%	0.14[0.03,0.54]
Subtotal (95% CI)	**22**	**19**		**28.66%**	**0.14[0.03,0.54]**
Total events: 5 (Doxycyline), 13 (Others)					
Heterogeneity: Not applicable					

Favours doxycycline — Favours other

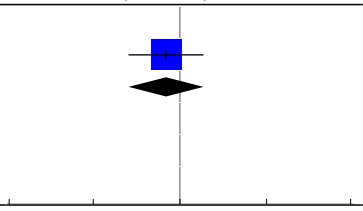


Analysis 8.3. Comparison 8 Doxycycline, Outcome 3 Pain.



Analysis 8.4. Comparison 8 Doxycycline, Outcome 4 Mortality.

Study or subgroup	Doxycyline n/N	Others n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
8.4.1 Doxycycline vs bleomycin					
Patz 1998	9/38	13/42		100%	0.69[0.26,1.87]
Subtotal (95% CI)	**38**	**42**		**100%**	**0.69[0.26,1.87]**
Total events: 9 (Doxycyline), 13 (Others)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.73(P=0.47)					



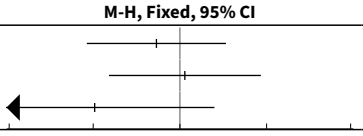
Favours doxycycline — Favours other

Comparison 9. Duration of drainage after pleurodesis administration

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pleurodesis failure rate	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Mortality	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 9.1. Comparison 9 Duration of drainage after pleurodesis administration, Outcome 1 Pleurodesis failure rate.

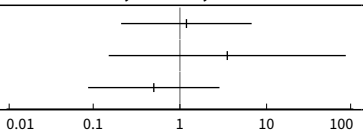
Study or subgroup	Rapid n/N	Standard n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Goodman 2006	2/16	4/19		0%	0.54[0.08,3.4]
Villanueva 1994	2/9	3/15		0%	1.14[0.15,8.59]
Yildirim 2005	0/12	2/8		0%	0.1[0,2.5]



Favours rapid pleurodesis — Favours standard

Analysis 9.2. Comparison 9 Duration of drainage after pleurodesis administration, Outcome 2 Mortality.

Study or subgroup	Rapid n/N	Standard n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Goodman 2006	3/19	3/22		0%	1.19[0.21,6.72]
Villanueva 1994	9/9	13/15		0%	3.52[0.15,81.92]
Yildirim 2005	3/15	4/12		0%	0.5[0.09,2.86]



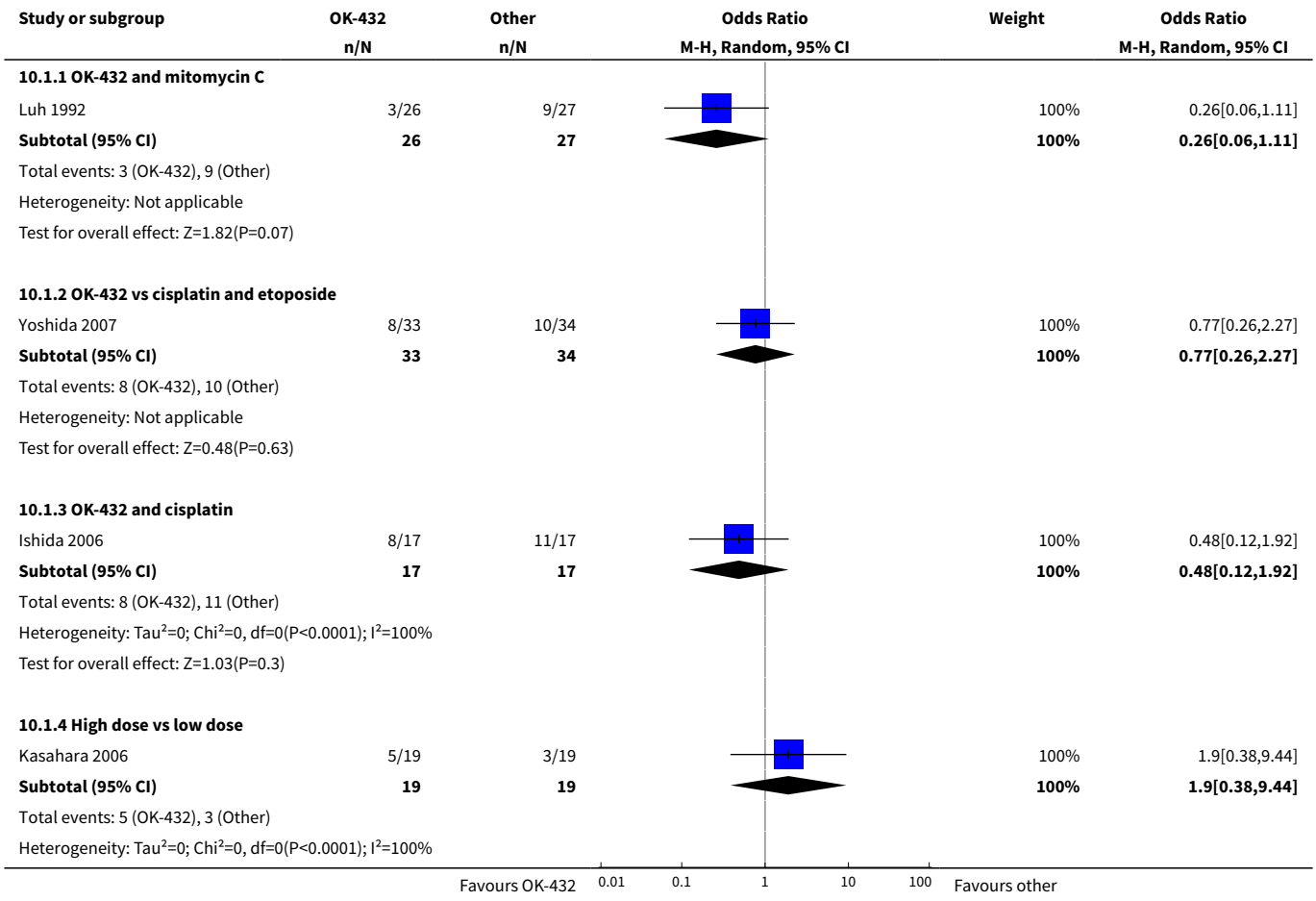
Favours rapid pleurodesis — Favours standard

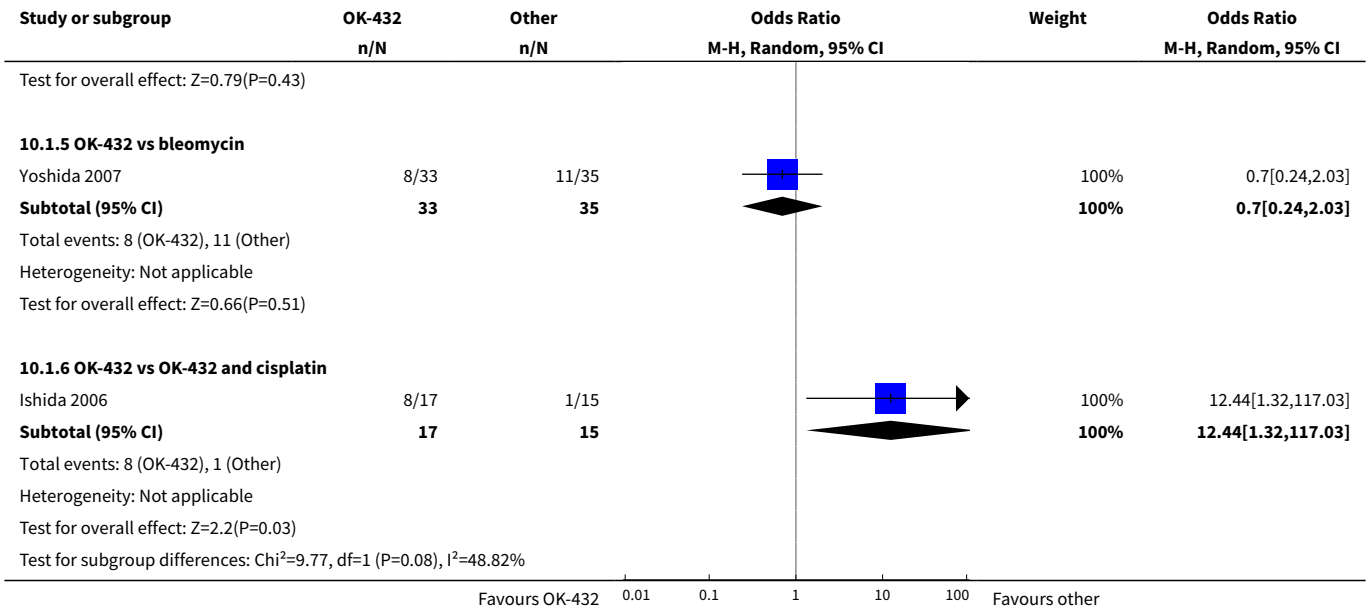
Comparison 10. OK-432

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Pleurodesis failure rate	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 OK-432 and mitomycin C	1	53	Odds Ratio (M-H, Random, 95% CI)	0.26 [0.06, 1.11]
1.2 OK-432 vs cisplatin and etoposide	1	67	Odds Ratio (M-H, Random, 95% CI)	0.77 [0.26, 2.27]
1.3 OK-432 and cisplatin	1	34	Odds Ratio (M-H, Random, 95% CI)	0.48 [0.12, 1.92]
1.4 High dose vs low dose	1	38	Odds Ratio (M-H, Random, 95% CI)	1.90 [0.38, 9.44]
1.5 OK-432 vs bleomycin	1	68	Odds Ratio (M-H, Random, 95% CI)	0.70 [0.24, 2.03]
1.6 OK-432 vs OK-432 and cisplatin	1	32	Odds Ratio (M-H, Random, 95% CI)	12.44 [1.32, 117.03]
2 Fever	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 OK-432 vs cisplatin	1	34	Odds Ratio (M-H, Random, 95% CI)	256.00 [14.70, 4457.27]
2.2 OK-432 vs OK-432 and cisplatin	1	32	Odds Ratio (M-H, Random, 95% CI)	14.00 [1.46, 134.25]
2.3 OK-432 vs mitomycin C	1	53	Odds Ratio (M-H, Random, 95% CI)	26.67 [5.91, 120.42]
2.4 OK-432 vs bleomycin	1	67	Odds Ratio (M-H, Random, 95% CI)	1.43 [0.47, 4.35]
2.5 OK-432 vs cisplatin and etoposide	1	66	Odds Ratio (M-H, Random, 95% CI)	3.17 [1.08, 9.30]
3 Pain	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 OK-432 vs cisplatin	1	34	Odds Ratio (M-H, Random, 95% CI)	6.67 [1.15, 38.60]
3.2 OK-432 vs OK-432 and cisplatin	1	32	Odds Ratio (M-H, Random, 95% CI)	1.33 [0.33, 5.43]
3.3 OK-432 vs mitomycin C	1	53	Odds Ratio (M-H, Random, 95% CI)	1.04 [0.14, 8.00]
3.4 OK-432 vs bleomycin	1	67	Odds Ratio (M-H, Random, 95% CI)	2.53 [0.89, 7.15]

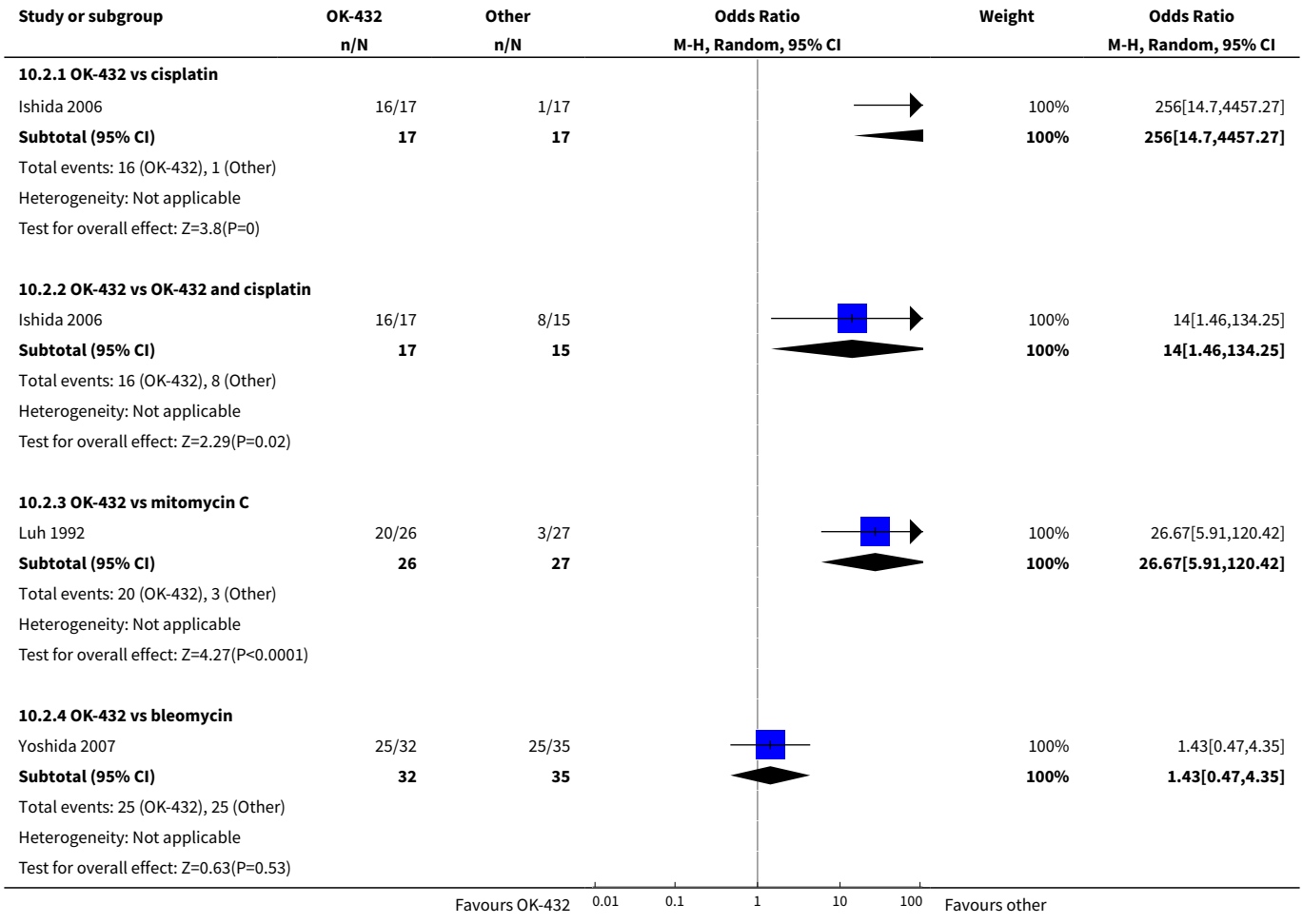
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.5 OK-432 vs cisplatin and etoposide	1	66	Odds Ratio (M-H, Random, 95% CI)	2.1 [0.73, 6.01]
4 Mortality	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 OK-432 vs cisplatin	1	34	Odds Ratio (M-H, Random, 95% CI)	1.31 [0.31, 5.53]
4.2 OK-432 vs combined OK-432 and cis-platin	1	32	Odds Ratio (M-H, Random, 95% CI)	2.18 [0.44, 10.91]
4.3 OK-432 vs bleomycin	1	68	Odds Ratio (M-H, Random, 95% CI)	0.38 [0.14, 1.03]
4.4 OK-432 vs cisplatin and etoposide	1	67	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.32, 2.18]

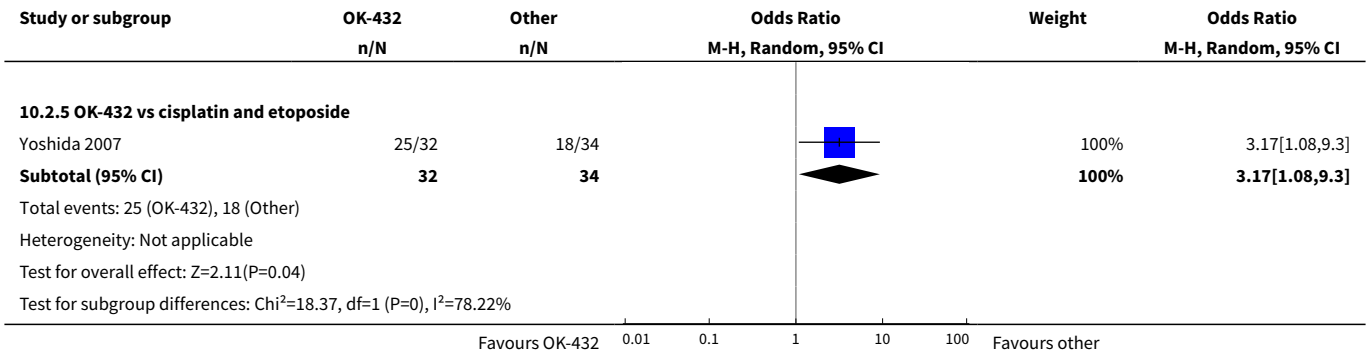
Analysis 10.1. Comparison 10 OK-432, Outcome 1 Pleurodesis failure rate.



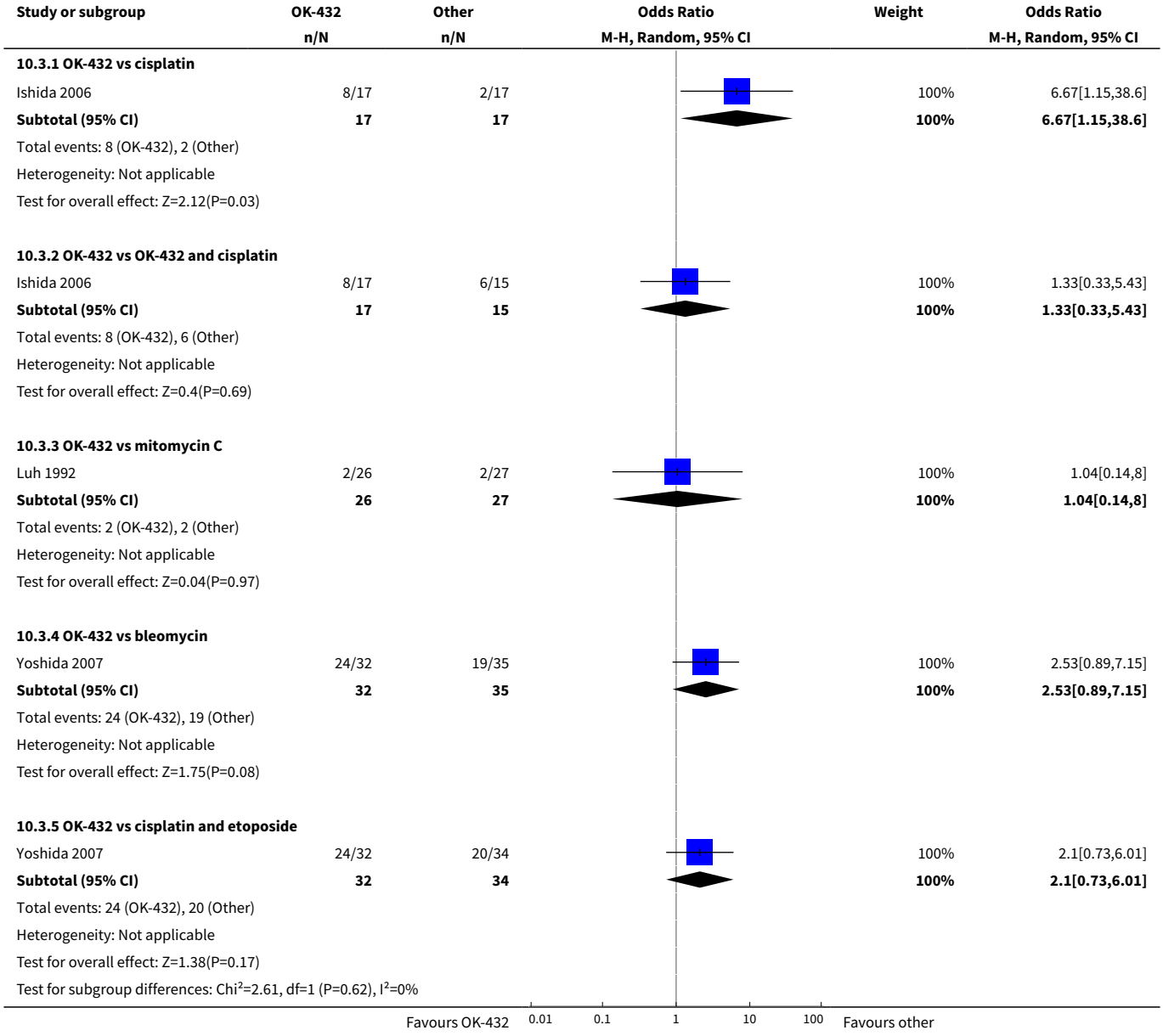


Analysis 10.2. Comparison 10 OK-432, Outcome 2 Fever.

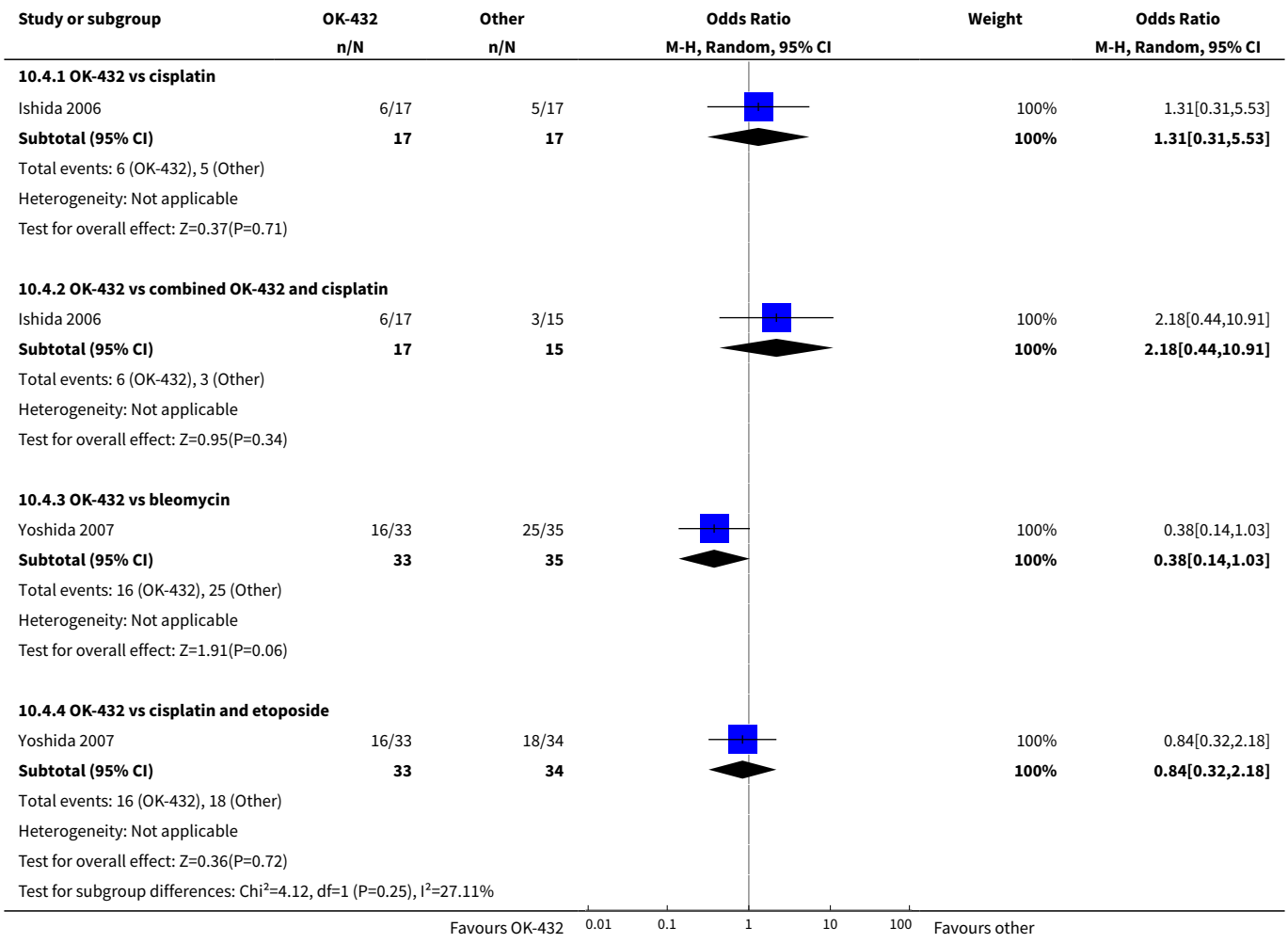




Analysis 10.3. Comparison 10 OK-432, Outcome 3 Pain.



Analysis 10.4. Comparison 10 OK-432, Outcome 4 Mortality.

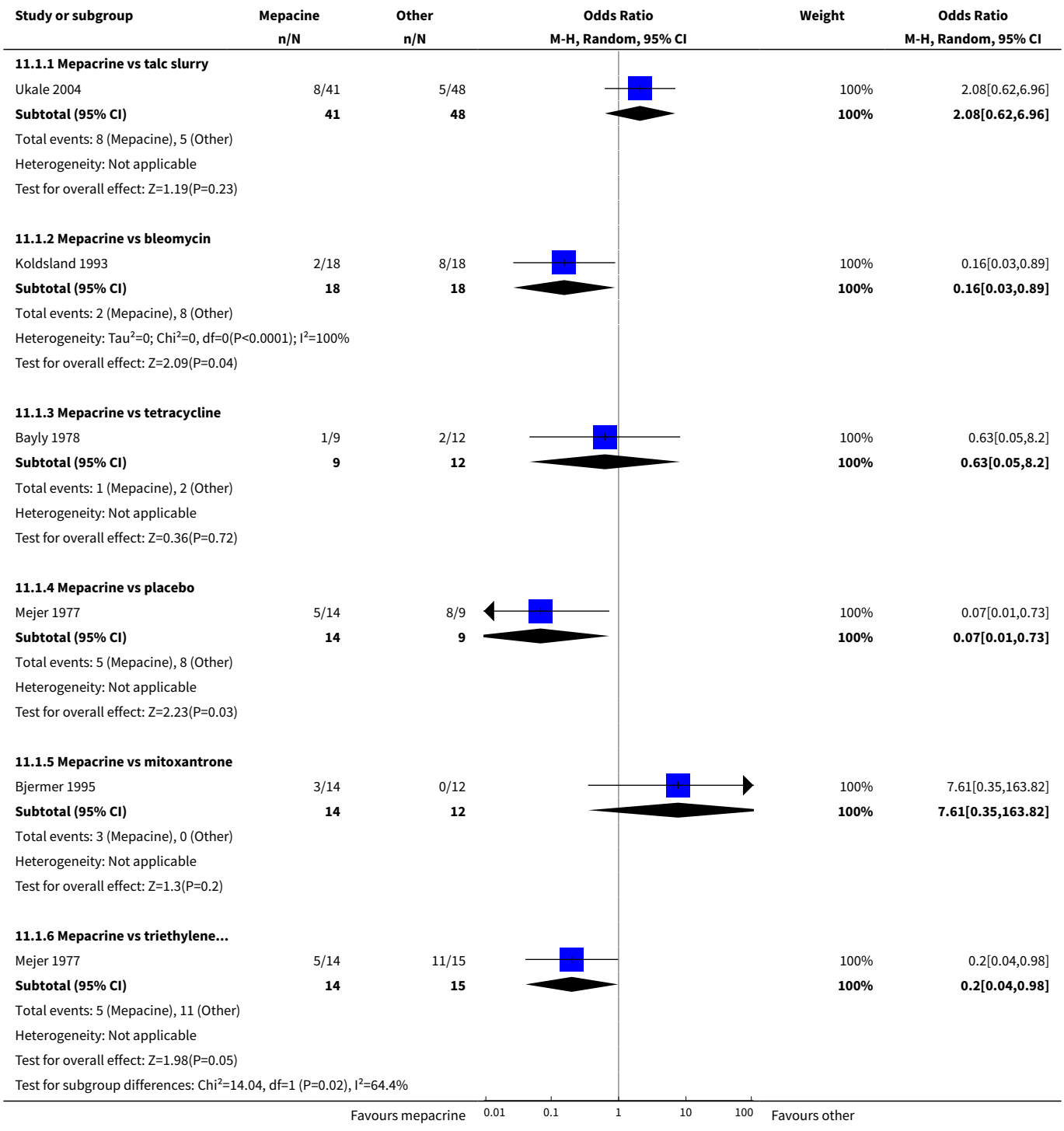


Comparison 11. Mepacrine

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Pleurodesis failure rate	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Mepacrine vs talc slurry	1	89	Odds Ratio (M-H, Random, 95% CI)	2.08 [0.62, 6.96]
1.2 Mepacrine vs bleomycin	1	36	Odds Ratio (M-H, Random, 95% CI)	0.16 [0.03, 0.89]
1.3 Mepacrine vs tetracycline	1	21	Odds Ratio (M-H, Random, 95% CI)	0.63 [0.05, 8.20]

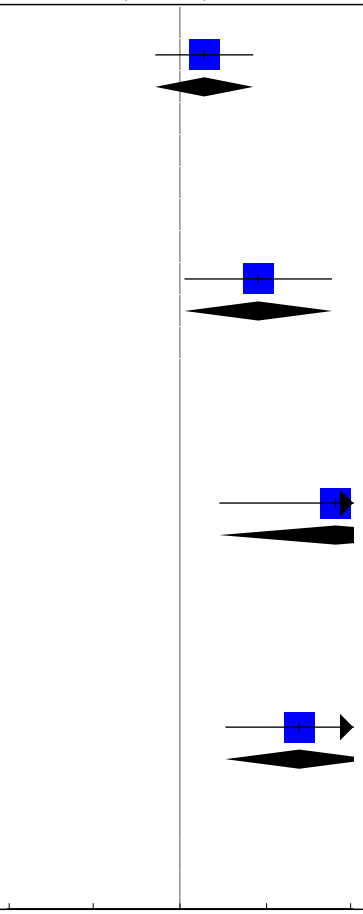
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 Mepacrine vs placebo	1	23	Odds Ratio (M-H, Random, 95% CI)	0.07 [0.01, 0.73]
1.5 Mepacrine vs mitoxantrone	1	26	Odds Ratio (M-H, Random, 95% CI)	7.61 [0.35, 163.82]
1.6 Mepacrine vs triethylene...	1	29	Odds Ratio (M-H, Random, 95% CI)	0.20 [0.04, 0.98]
2 Fever	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Mepacrine vs bleomycin	1	40	Odds Ratio (M-H, Random, 95% CI)	1.91 [0.52, 7.01]
2.2 Mepacrine vs tetracycline	1	22	Odds Ratio (M-H, Random, 95% CI)	8.00 [1.13, 56.79]
2.3 Mepacrine vs placebo	1	23	Odds Ratio (M-H, Random, 95% CI)	62.43 [2.85, 1365.52]
2.4 Mepacrine vs triethylene...	1	29	Odds Ratio (M-H, Random, 95% CI)	23.83 [3.35, 169.39]
3 Pain	3	114	Odds Ratio (M-H, Random, 95% CI)	4.56 [1.66, 12.52]
3.1 Mepacrine vs bleomycin	1	40	Odds Ratio (M-H, Random, 95% CI)	2.15 [0.52, 9.00]
3.2 Mepacrine vs tetracycline	1	22	Odds Ratio (M-H, Random, 95% CI)	5.6 [0.81, 38.51]
3.3 Mepacrine vs placebo	1	23	Odds Ratio (M-H, Random, 95% CI)	14.53 [0.71, 298.21]
3.4 Mepacrine vs triethylenethiophospho-ramide	1	29	Odds Ratio (M-H, Random, 95% CI)	23.71 [1.19, 474.06]
4 Mortality	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Mepacrine vs talc slurry	1	89	Odds Ratio (M-H, Random, 95% CI)	0.53 [0.20, 1.43]
4.2 Mepacrine vs mitoxantrone	1	28	Odds Ratio (M-H, Random, 95% CI)	1.64 [0.23, 11.70]

Analysis 11.1. Comparison 11 Mepacrine, Outcome 1 Pleurodesis failure rate.



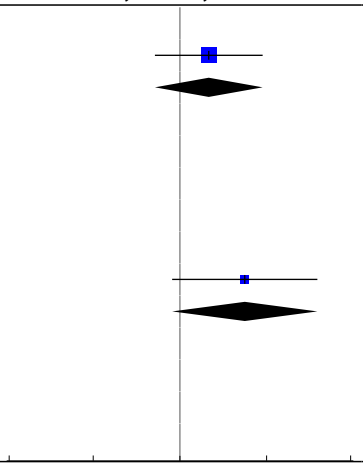
Analysis 11.2. Comparison 11 Mepacrine, Outcome 2 Fever.

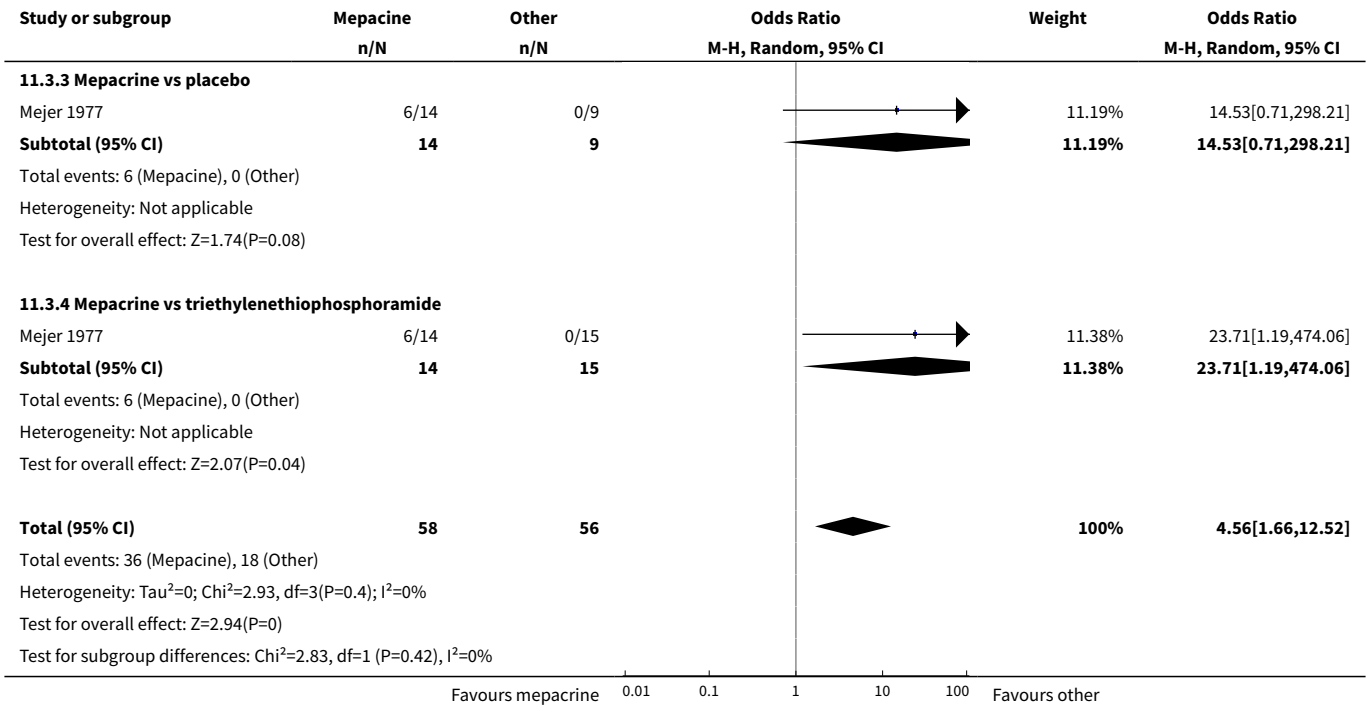
Study or subgroup	Mepacine n/N	Other n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
11.2.1 Mepacrine vs bleomycin					
Koldsland 1993	14/20	11/20		100%	1.91[0.52,7.01]
Subtotal (95% CI)	**20**	**20**		**100%**	**1.91[0.52,7.01]**
Total events: 14 (Mepacine), 11 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.97(P=0.33)					
11.2.2 Mepacrine vs tetracycline					
Bayly 1978	8/10	4/12		100%	8[1.13,56.79]
Subtotal (95% CI)	**10**	**12**		**100%**	**8[1.13,56.79]**
Total events: 8 (Mepacine), 4 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.08(P=0.04)					
11.2.3 Mepacrine vs placebo					
Mejer 1977	11/14	0/9		100%	62.43[2.85,1365.52]
Subtotal (95% CI)	**14**	**9**		**100%**	**62.43[2.85,1365.52]**
Total events: 11 (Mepacine), 0 (Other)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=2.63(P=0.01)					
11.2.4 Mepacrine vs triethylene...					
Mejer 1977	11/14	2/15		100%	23.83[3.35,169.39]
Subtotal (95% CI)	**14**	**15**		**100%**	**23.83[3.35,169.39]**
Total events: 11 (Mepacine), 2 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.17(P=0)					
Test for subgroup differences: Chi^2=7.18, df=1 (P=0.07), I^2=58.2%					



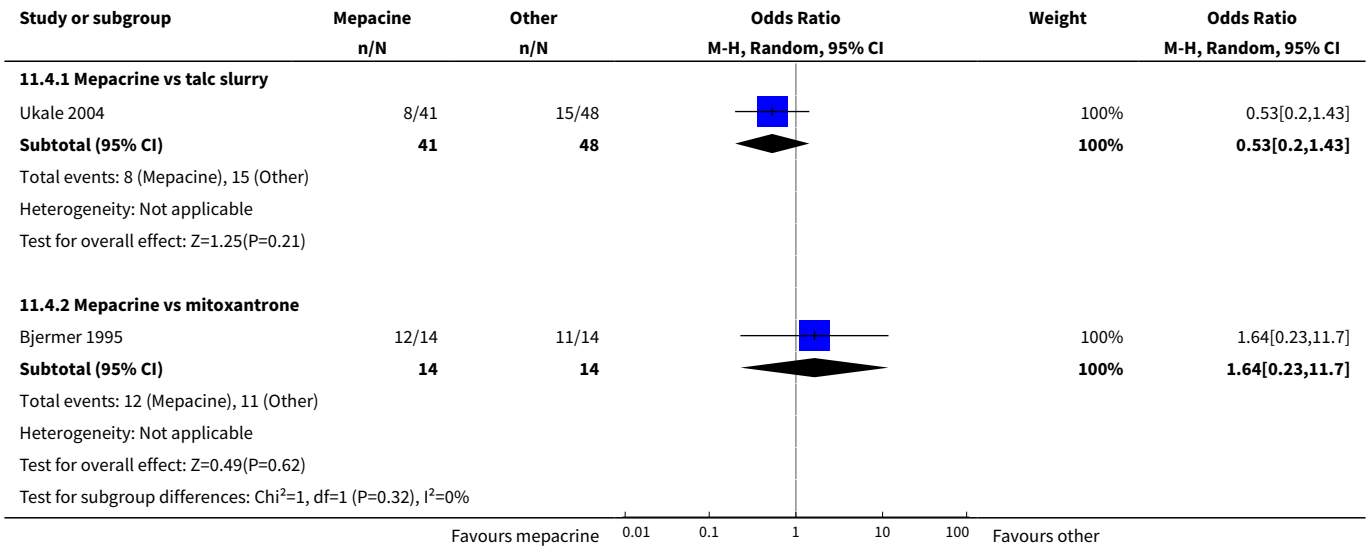
Analysis 11.3. Comparison 11 Mepacrine, Outcome 3 Pain.

Study or subgroup	Mepacine n/N	Other n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
11.3.1 Mepacrine vs bleomycin					
Koldsland 1993	16/20	13/20		49.96%	2.15[0.52,9]
Subtotal (95% CI)	**20**	**20**		**49.96%**	**2.15[0.52,9]**
Total events: 16 (Mepacine), 13 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.05(P=0.29)					
11.3.2 Mepacrine vs tetracycline					
Bayly 1978	8/10	5/12		27.47%	5.6[0.81,38.51]
Subtotal (95% CI)	**10**	**12**		**27.47%**	**5.6[0.81,38.51]**
Total events: 8 (Mepacine), 5 (Other)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=1.75(P=0.08)					





Analysis 11.4. Comparison 11 Mepacrine, Outcome 4 Mortality.



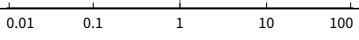
Comparison 12. Interferon (IFN)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pleurodesis failure rate	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 IFN vs bleomycin	1	160	Odds Ratio (M-H, Random, 95% CI)	3.25 [1.54, 6.89]
2 Fever	1	160	Odds Ratio (M-H, Random, 95% CI)	0.01 [0.00, 0.11]
3 Pain	1	160	Odds Ratio (M-H, Random, 95% CI)	0.03 [0.00, 0.53]
3.1 IFN vs bleomycin	1	160	Odds Ratio (M-H, Random, 95% CI)	0.03 [0.00, 0.53]
4 Mortality	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 IFN vs bleomycin	1	160	Odds Ratio (M-H, Random, 95% CI)	2.16 [1.15, 4.07]

Analysis 12.1. Comparison 12 Interferon (IFN), Outcome 1 Pleurodesis failure rate.

Study or subgroup	IFN n/N	Other n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
12.1.1 IFN vs bleomycin					
Sartori 2004	29/77	13/83		100%	3.25[1.54,6.89]
Subtotal (95% CI)	**77**	**83**		**100%**	**3.25[1.54,6.89]**
Total events: 29 (IFN), 13 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.08(P=0)					

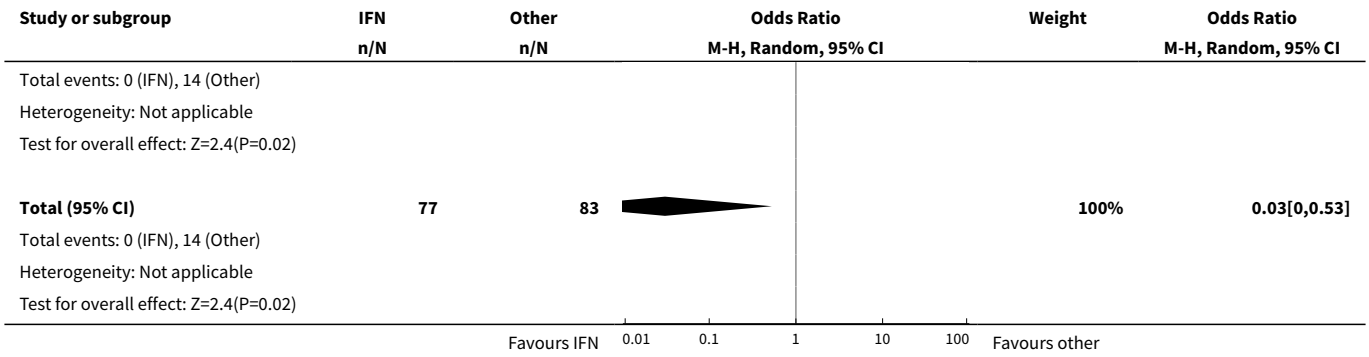


Analysis 12.2. Comparison 12 Interferon (IFN), Outcome 2 Fever.

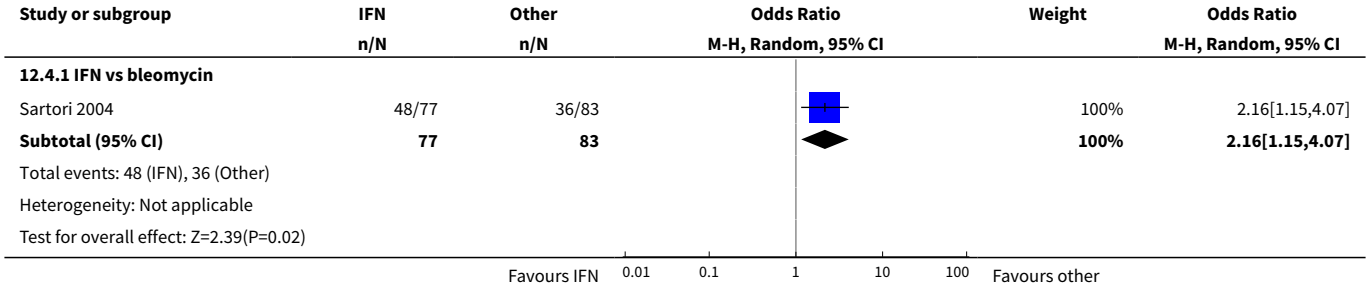
Study or subgroup	IFN n/N	Bleomycin n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Sartori 2004	0/77	41/83		100%	0.01[0,0.11]
Total (95% CI)	**77**	**83**		**100%**	**0.01[0,0.11]**
Total events: 0 (IFN), 41 (Bleomycin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.5(P=0)					

Analysis 12.3. Comparison 12 Interferon (IFN), Outcome 3 Pain.

Study or subgroup	IFN n/N	Other n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
12.3.1 IFN vs bleomycin					
Sartori 2004	0/77	14/83		100%	0.03[0,0.53]
Subtotal (95% CI)	**77**	**83**		**100%**	**0.03[0,0.53]**



Analysis 12.4. Comparison 12 Interferon (IFN), Outcome 4 Mortality.

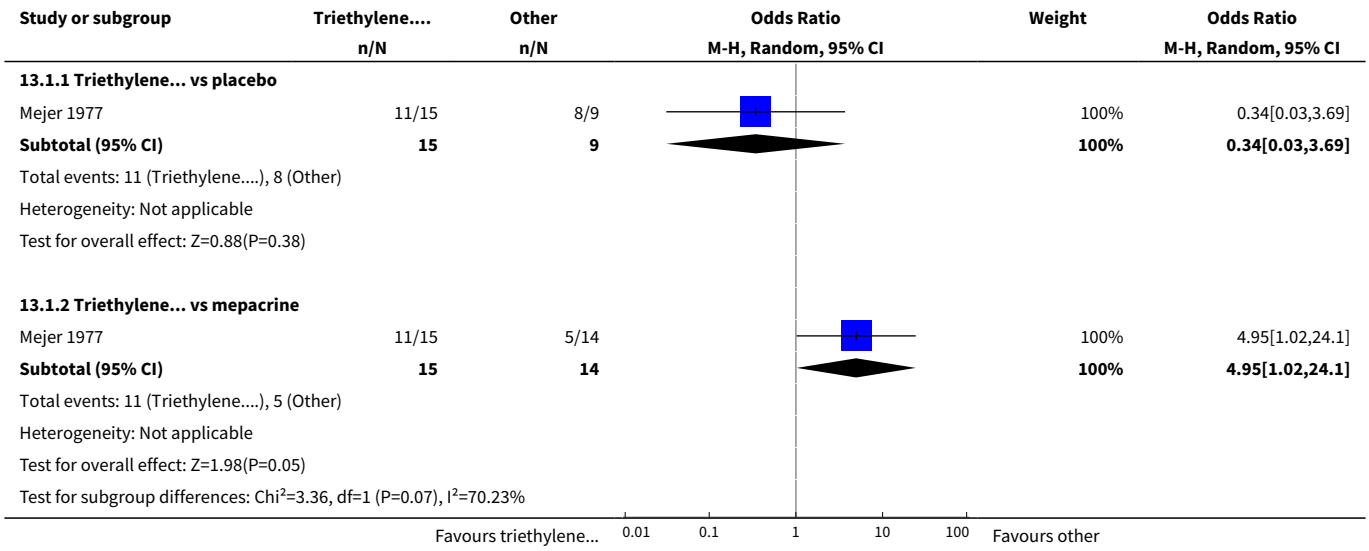


Comparison 13. Triethylenethiophosphoramide

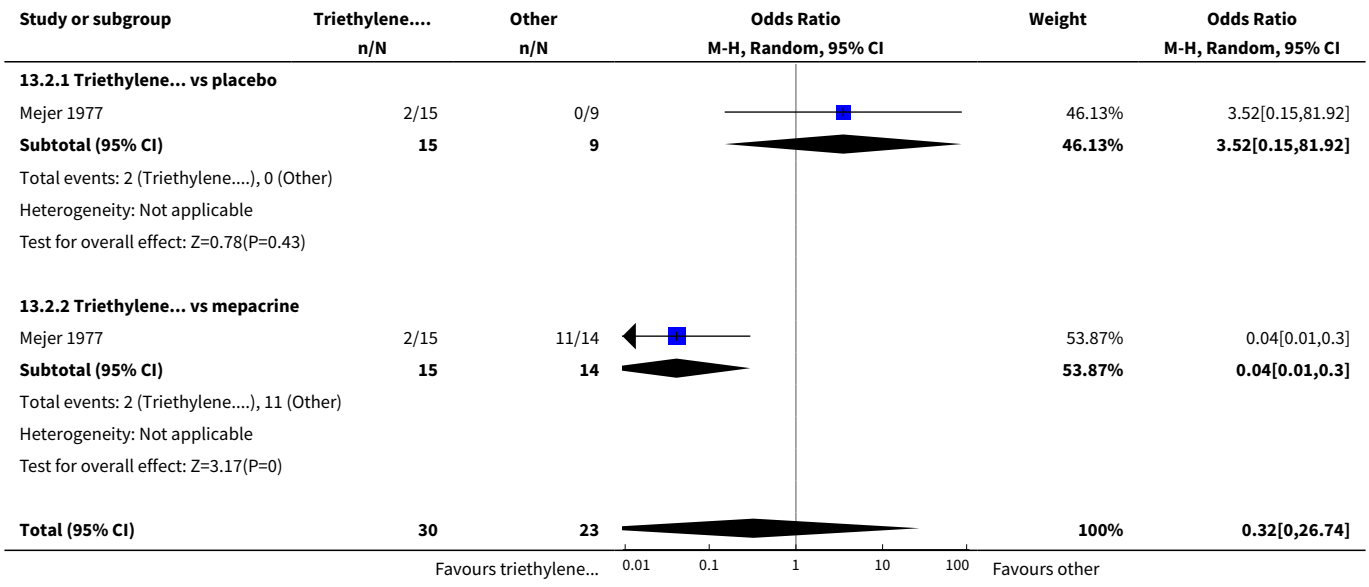
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pleurodesis failure rate	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Triethylene... vs placebo	1	24	Odds Ratio (M-H, Random, 95% CI)	0.34 [0.03, 3.69]
1.2 Triethylene... vs mepacrine	1	29	Odds Ratio (M-H, Random, 95% CI)	4.95 [1.02, 24.10]
2 Fever	1	53	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.00, 26.74]
2.1 Triethylene... vs placebo	1	24	Odds Ratio (M-H, Random, 95% CI)	3.52 [0.15, 81.92]
2.2 Triethylene... vs mepacrine	1	29	Odds Ratio (M-H, Random, 95% CI)	0.04 [0.01, 0.30]
3 Pain	1	53	Odds Ratio (M-H, Random, 95% CI)	1.39 [0.10, 20.15]

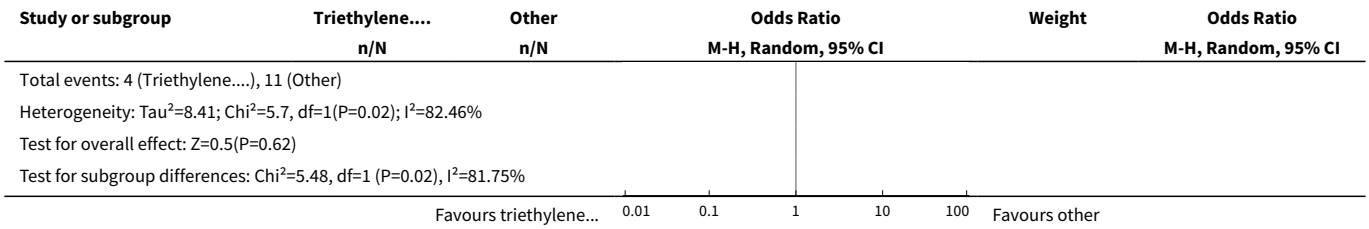
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.1 Triethylene... vs mepacrine	1	29	Odds Ratio (M-H, Random, 95% CI)	0.48 [0.10, 2.30]
3.2 Triethylene... vs placebo	1	24	Odds Ratio (M-H, Random, 95% CI)	7.43 [0.35, 156.28]

Analysis 13.1. Comparison 13 Triethylenethiophosphoramide, Outcome 1 Pleurodesis failure rate.

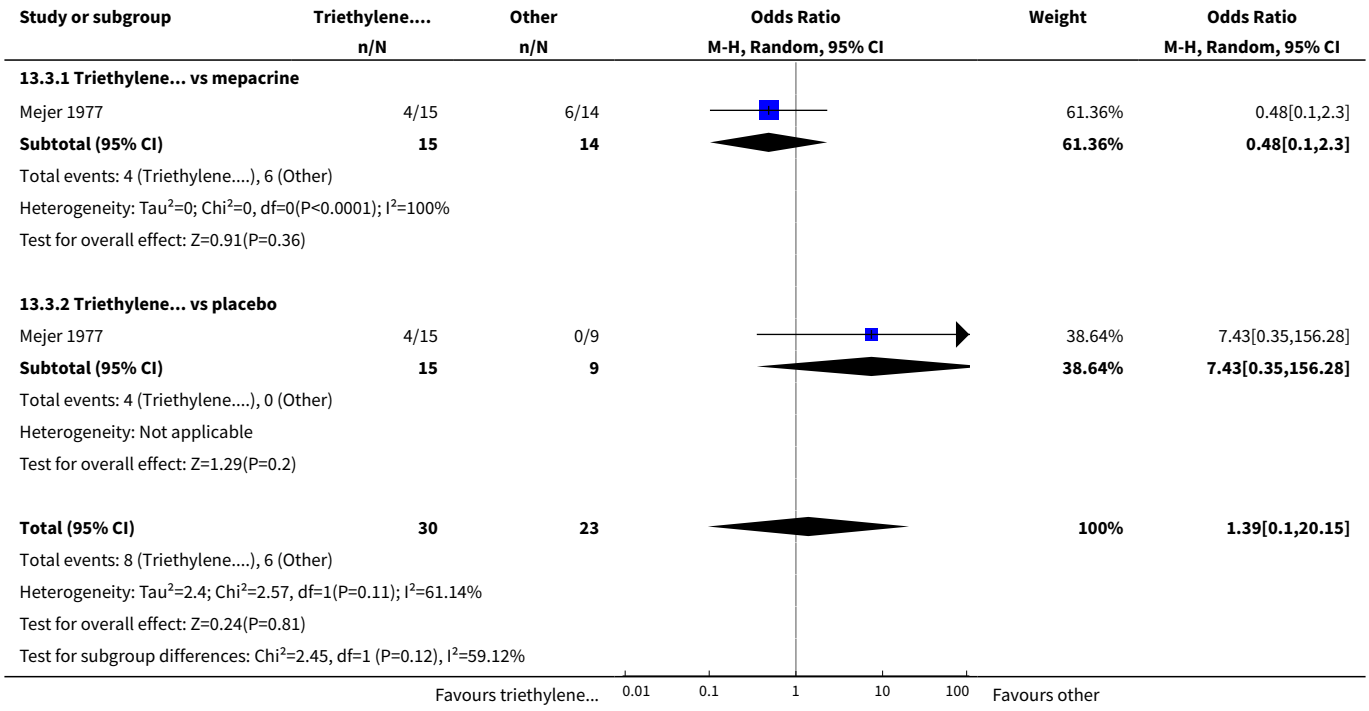


Analysis 13.2. Comparison 13 Triethylenethiophosphoramide, Outcome 2 Fever.





Analysis 13.3. Comparison 13 Triethylenethiophosphoramide, Outcome 3 Pain.



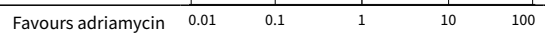
Comparison 14. Adriamycin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pleurodesis failure rate	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Adriamycin vs mustine	1	20	Odds Ratio (M-H, Random, 95% CI)	0.37 [0.01, 10.18]
1.2 Adriamycin vs tetracycline	1	21	Odds Ratio (M-H, Random, 95% CI)	1.11 [0.06, 20.49]
1.3 Adriamycin vs LC9018 and adriamycin	1	76	Odds Ratio (M-H, Random, 95% CI)	4.29 [1.62, 11.35]
2 Fever	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Pain	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only

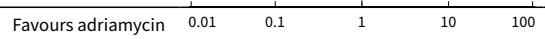
Analysis 14.1. Comparison 14 Adriamycin, Outcome 1 Pleurodesis failure rate.

Study or subgroup	Adriamycin n/N	Other n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
14.1.1 Adriamycin vs mustine					
Kefford 1980	10/11	9/9		100%	0.37[0.01,10.18]
Subtotal (95% CI)	**11**	**9**		**100%**	**0.37[0.01,10.18]**
Total events: 10 (Adriamycin), 9 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.59(P=0.56)					
14.1.2 Adriamycin vs tetracycline					
Kefford 1980	10/11	9/10		100%	1.11[0.06,20.49]
Subtotal (95% CI)	**11**	**10**		**100%**	**1.11[0.06,20.49]**
Total events: 10 (Adriamycin), 9 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.07(P=0.94)					
14.1.3 Adriamycin vs LC9018 and adriamycin					
Masuno 1991	23/38	10/38		100%	4.29[1.62,11.35]
Subtotal (95% CI)	**38**	**38**		**100%**	**4.29[1.62,11.35]**
Total events: 23 (Adriamycin), 10 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.94(P=0)					
Test for subgroup differences: Chi^2=2.49, df=1 (P=0.29), I^2=19.58%					



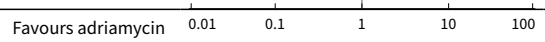
Analysis 14.2. Comparison 14 Adriamycin, Outcome 2 Fever.

Study or subgroup	Adriamycin n/N	Other n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Masuno 1991	13/45	11/41		0%	1.11[0.43,2.85]



Analysis 14.3. Comparison 14 Adriamycin, Outcome 3 Pain.

Study or subgroup	Adriamycin n/N	Other n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Masuno 1991	13/45	6/41		0%	2.37[0.81,6.98]

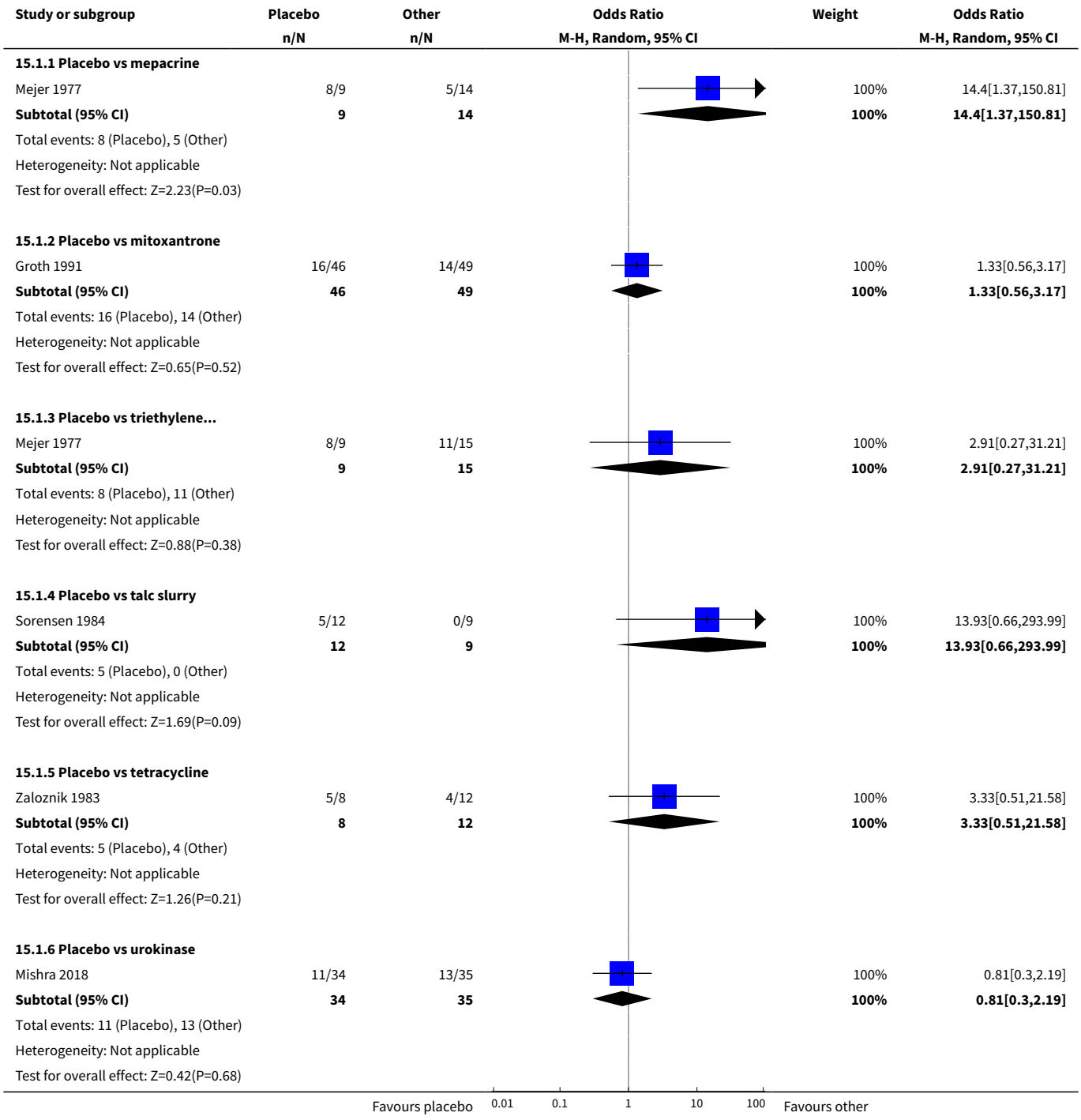


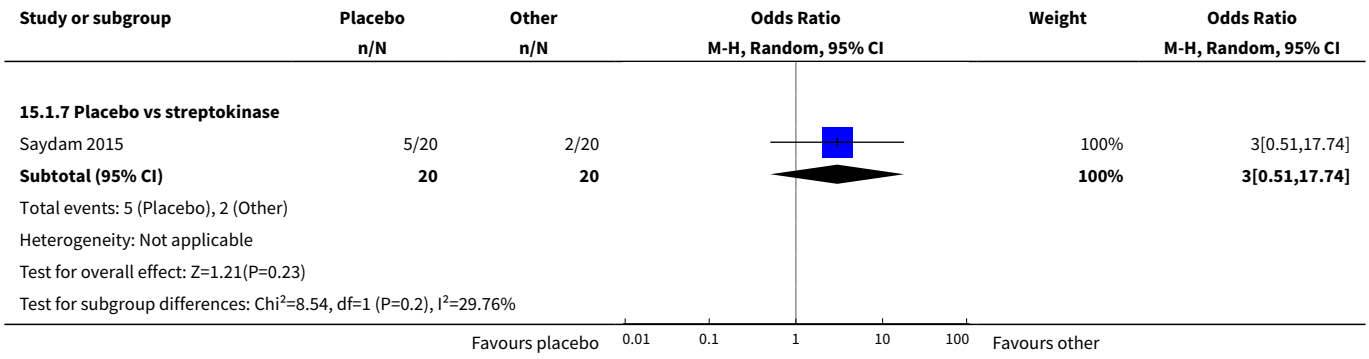
Comparison 15. Placebo

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Pleurodesis failure rate	6		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Placebo vs mepacrine	1	23	Odds Ratio (M-H, Random, 95% CI)	14.40 [1.37, 150.81]
1.2 Placebo vs mitoxantrone	1	95	Odds Ratio (M-H, Random, 95% CI)	1.33 [0.56, 3.17]
1.3 Placebo vs triethylene...	1	24	Odds Ratio (M-H, Random, 95% CI)	2.91 [0.27, 31.21]
1.4 Placebo vs talc slurry	1	21	Odds Ratio (M-H, Random, 95% CI)	13.93 [0.66, 293.99]
1.5 Placebo vs tetracycline	1	20	Odds Ratio (M-H, Random, 95% CI)	3.33 [0.51, 21.58]
1.6 Placebo vs urokinase	1	69	Odds Ratio (M-H, Random, 95% CI)	0.81 [0.30, 2.19]
1.7 Placebo vs streptokinase	1	40	Odds Ratio (M-H, Random, 95% CI)	3.00 [0.51, 17.74]
2 Fever	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Placebo vs mepacrine	1	95	Odds Ratio (M-H, Random, 95% CI)	0.31 [0.12, 0.79]
2.2 Placebo vs mitoxantrone	1	23	Odds Ratio (M-H, Random, 95% CI)	0.02 [0.00, 0.35]
2.3 Placebo vs triethylene...	1	24	Odds Ratio (M-H, Random, 95% CI)	0.28 [0.01, 6.62]
3 Pain	3	100	Odds Ratio (M-H, Random, 95% CI)	0.10 [0.01, 0.82]
3.1 Placebo vs talc slurry	1	31	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Placebo vs tetracycline	1	22	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Placebo vs mepacrine	1	23	Odds Ratio (M-H, Random, 95% CI)	0.07 [0.00, 1.41]
3.4 Placebo vs triethylene...	1	24	Odds Ratio (M-H, Random, 95% CI)	0.13 [0.01, 2.83]

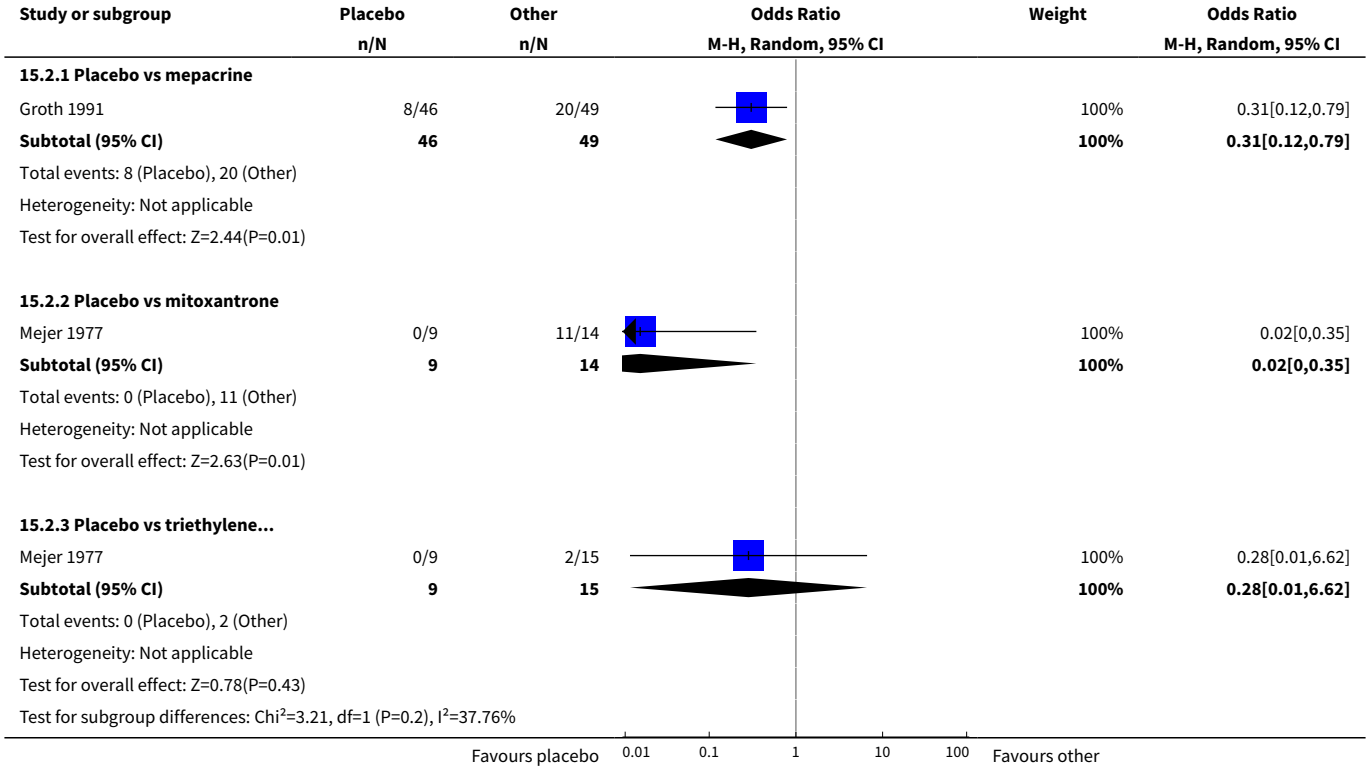
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4 Mortality	1	71	Odds Ratio (M-H, Fixed, 95% CI)	12.40 [0.66, 233.22]

Analysis 15.1. Comparison 15 Placebo, Outcome 1 Pleurodesis failure rate.

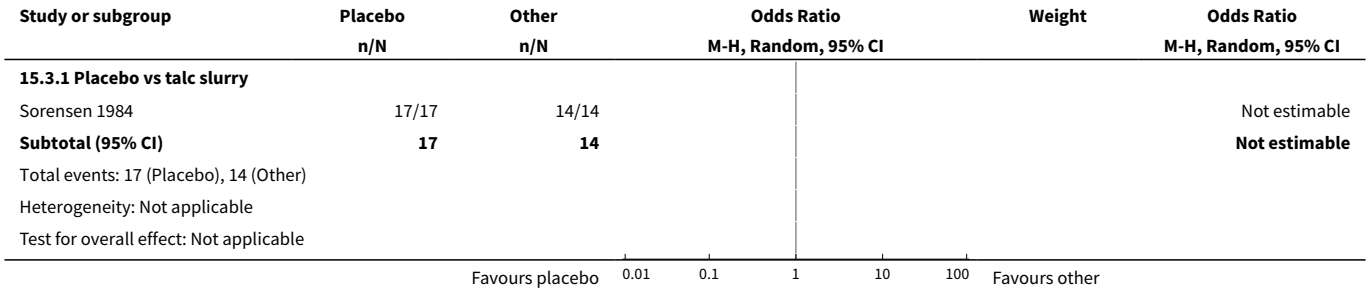


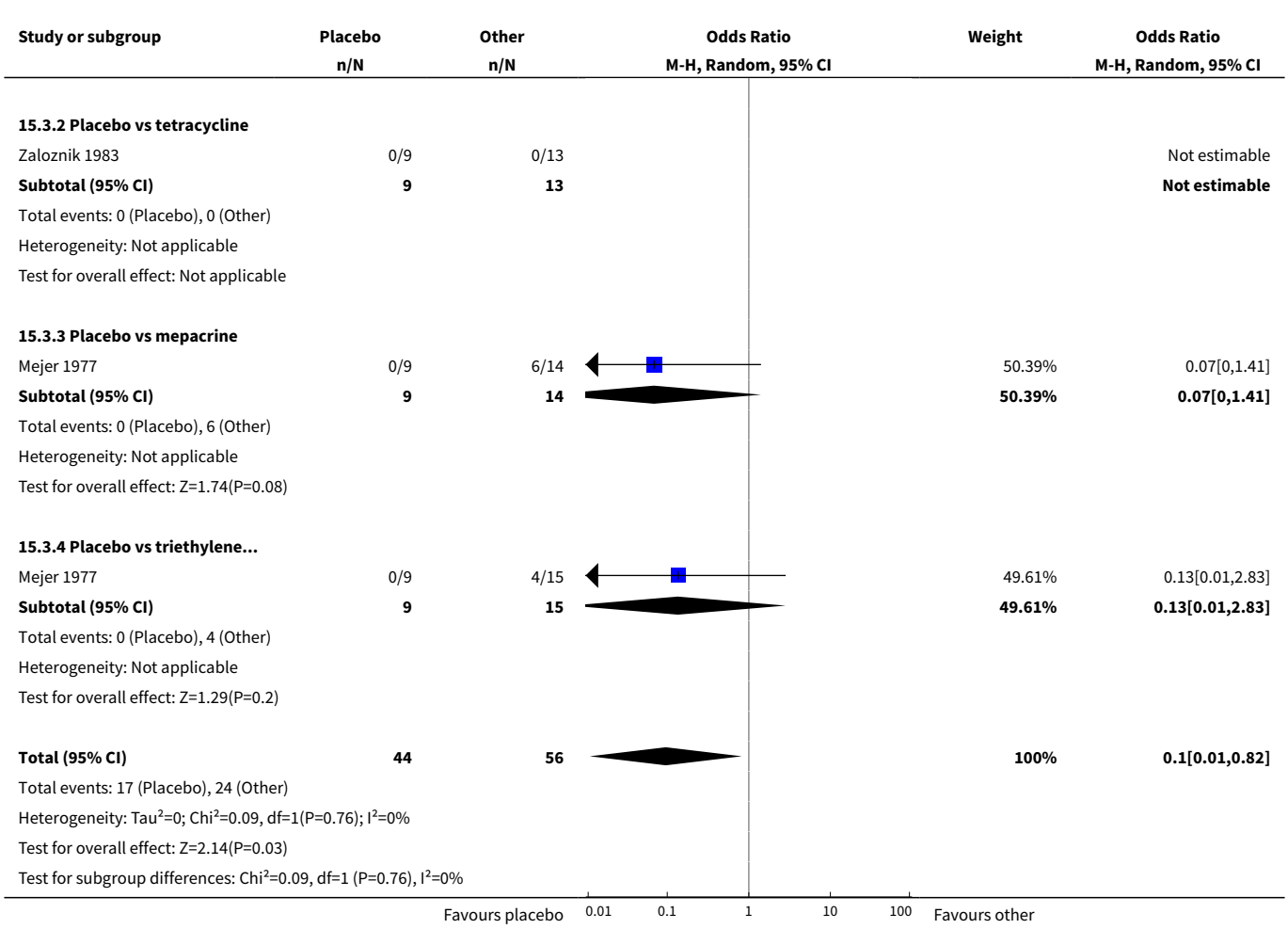


Analysis 15.2. Comparison 15 Placebo, Outcome 2 Fever.

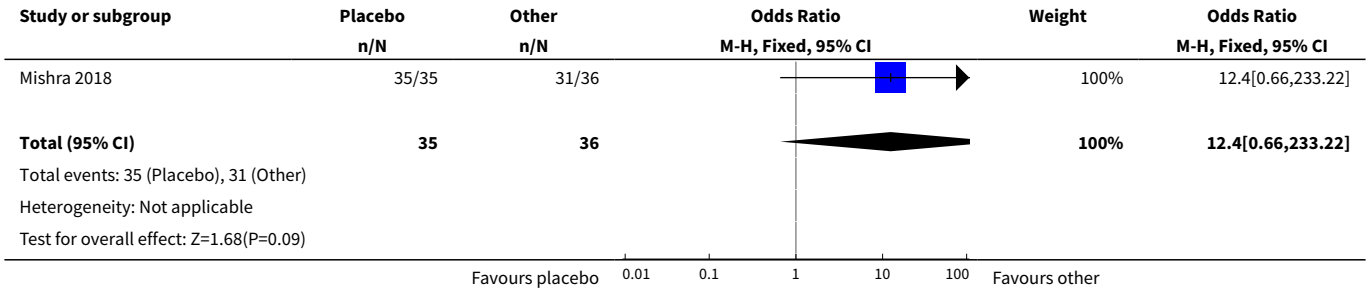


Analysis 15.3. Comparison 15 Placebo, Outcome 3 Pain.





Analysis 15.4. Comparison 15 Placebo, Outcome 4 Mortality.

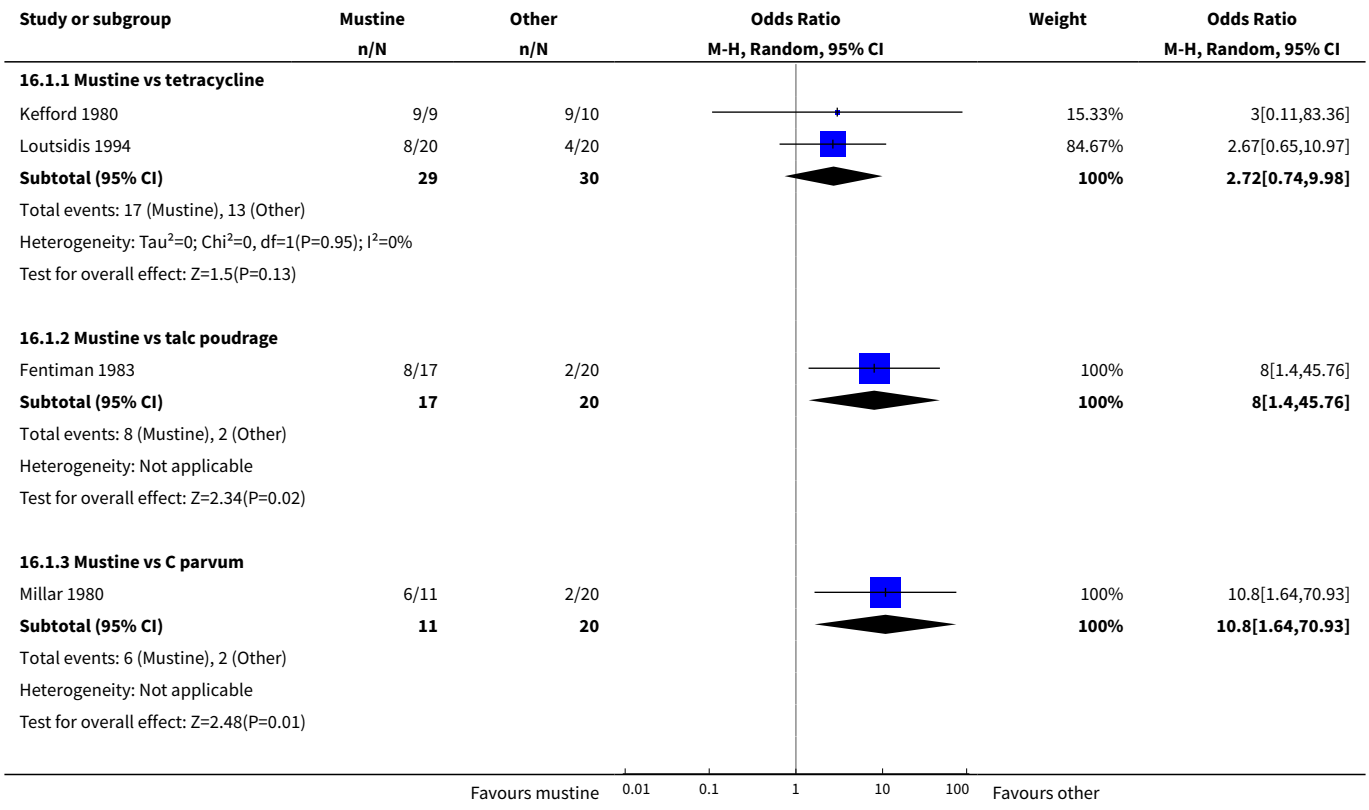


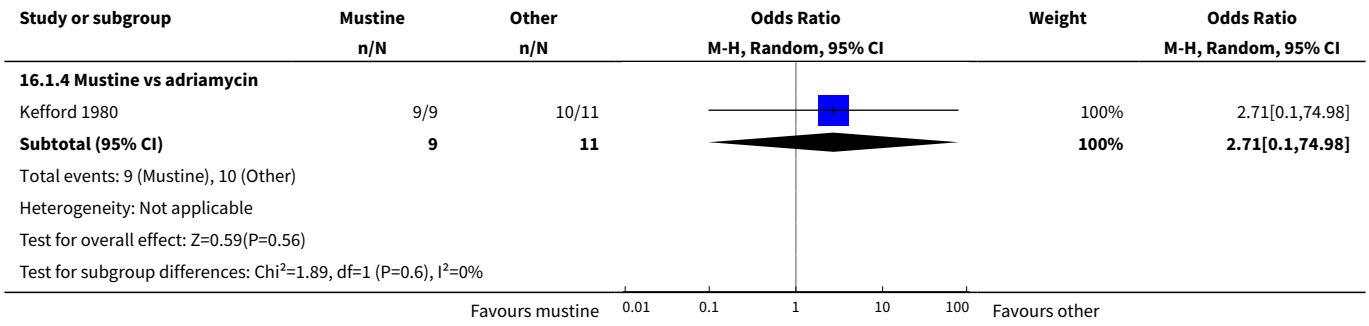
Comparison 16. Mustine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pleurodesis failure rate	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only

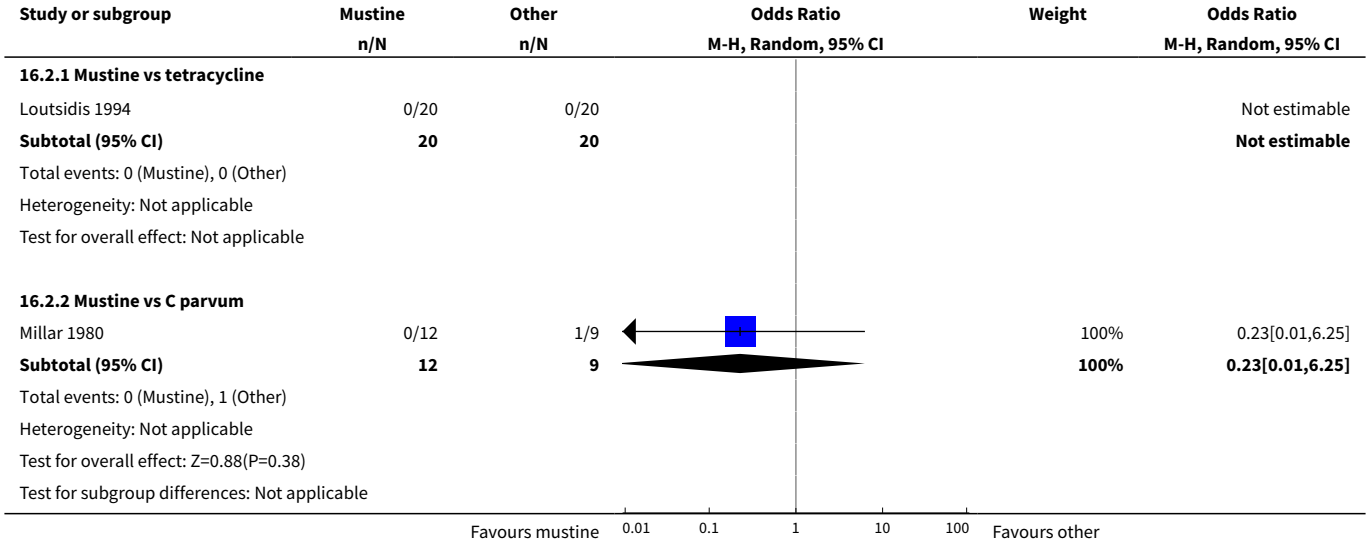
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.1 Mustine vs tetracycline	2	59	Odds Ratio (M-H, Random, 95% CI)	2.72 [0.74, 9.98]
1.2 Mustine vs talc poudrage	1	37	Odds Ratio (M-H, Random, 95% CI)	8.00 [1.40, 45.76]
1.3 Mustine vs *C parvum*	1	31	Odds Ratio (M-H, Random, 95% CI)	10.8 [1.64, 70.93]
1.4 Mustine vs adriamycin	1	20	Odds Ratio (M-H, Random, 95% CI)	2.71 [0.10, 74.98]
2 Fever	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Mustine vs tetracycline	1	40	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Mustine vs *C parvum*	1	21	Odds Ratio (M-H, Random, 95% CI)	0.23 [0.01, 6.25]
3 Pain	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4 Mortality	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Mustine vs talc poudrage	1	46	Odds Ratio (M-H, Random, 95% CI)	2.35 [0.51, 10.86]
4.2 Mustine vs *C parvum*	1	21	Odds Ratio (M-H, Random, 95% CI)	2.4 [0.38, 15.32]

Analysis 16.1. Comparison 16 Mustine, Outcome 1 Pleurodesis failure rate.

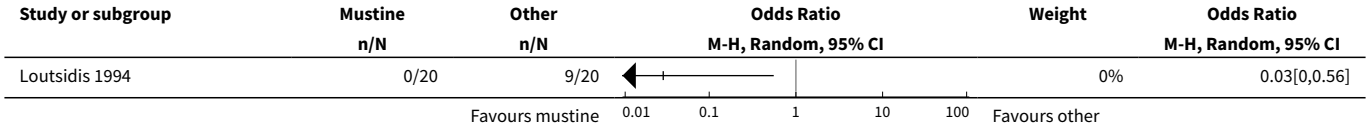




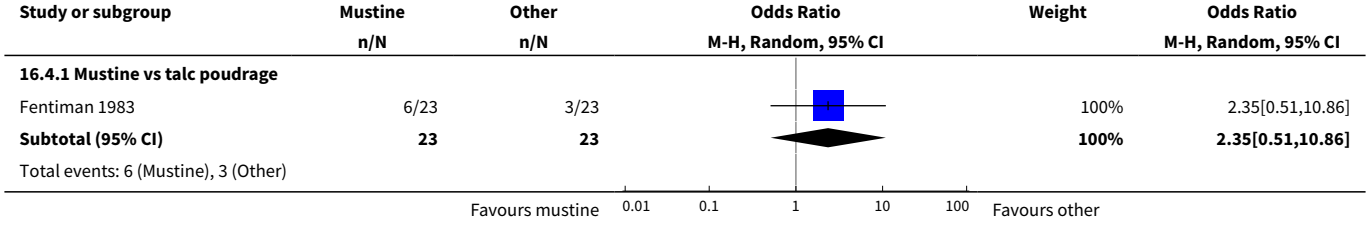
Analysis 16.2. Comparison 16 Mustine, Outcome 2 Fever.

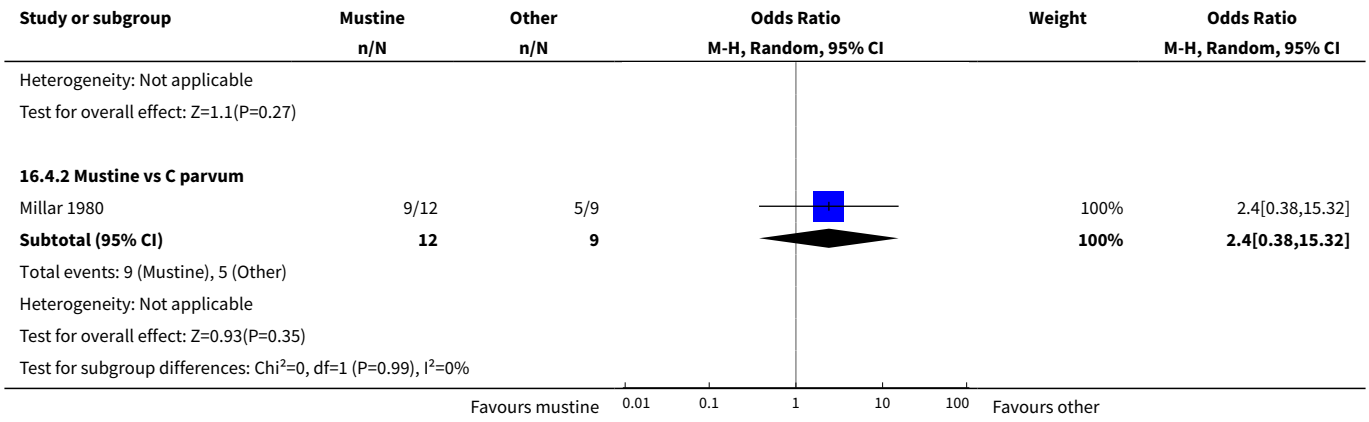


Analysis 16.3. Comparison 16 Mustine, Outcome 3 Pain.



Analysis 16.4. Comparison 16 Mustine, Outcome 4 Mortality.

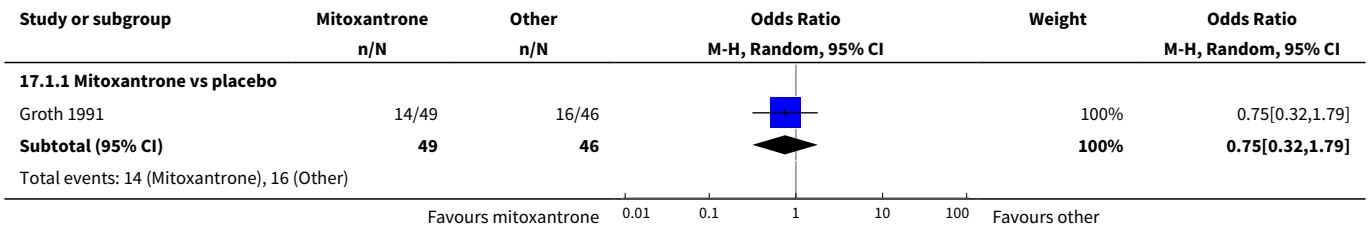


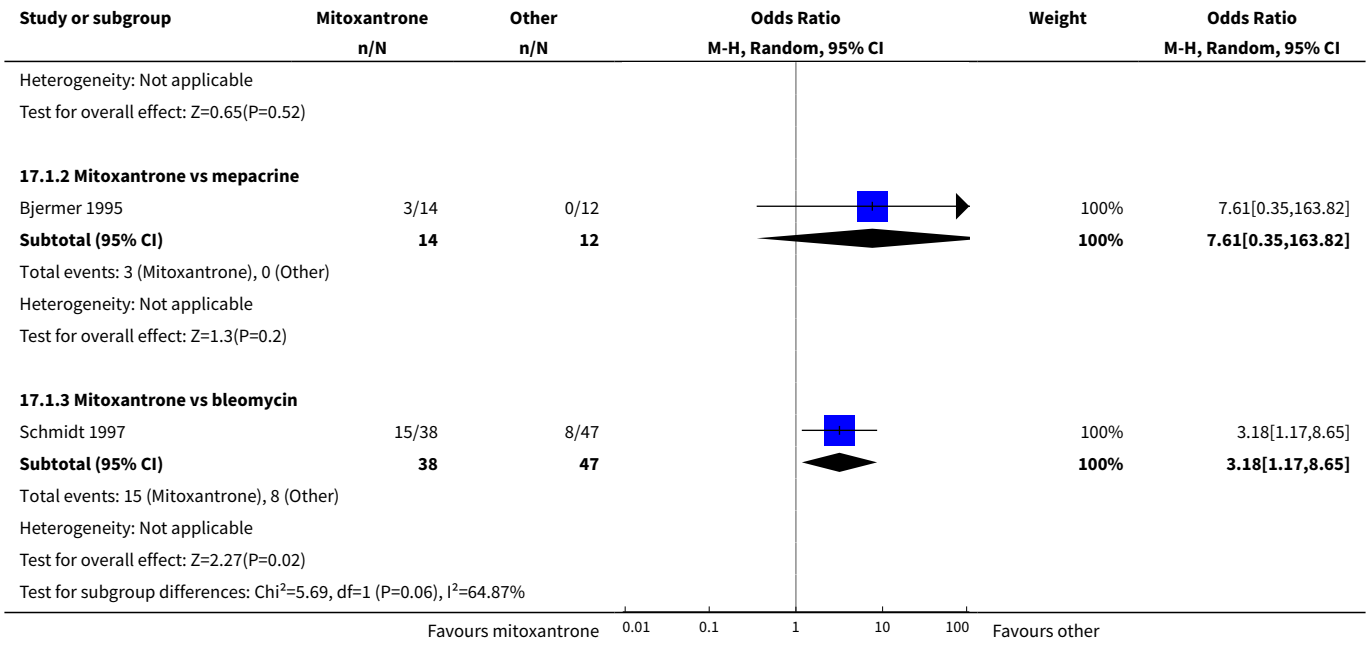


Comparison 17. Mitoxantrone

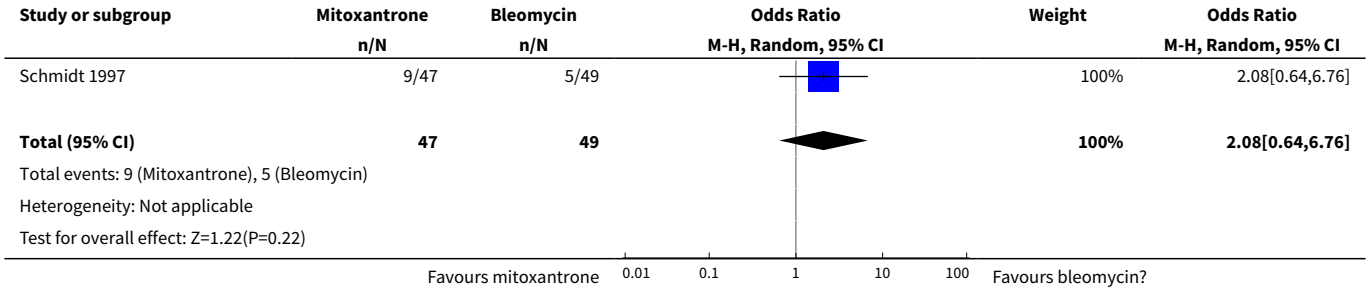
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pleurodesis failure rate	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Mitoxantrone vs placebo	1	95	Odds Ratio (M-H, Random, 95% CI)	0.75 [0.32, 1.79]
1.2 Mitoxantrone vs mepacrine	1	26	Odds Ratio (M-H, Random, 95% CI)	7.61 [0.35, 163.82]
1.3 Mitoxantrone vs bleomycin	1	85	Odds Ratio (M-H, Random, 95% CI)	3.18 [1.17, 8.65]
2 Pain	1	96	Odds Ratio (M-H, Random, 95% CI)	2.08 [0.64, 6.76]
3 Fever	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Mitoxantrone vs bleomycin	1	96	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.30, 2.71]
3.2 Mitoxantrone vs placebo	1	95	Odds Ratio (M-H, Random, 95% CI)	3.28 [1.26, 8.49]
4 Mortality	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Mitoxantrone vs bleomycin	1	96	Odds Ratio (M-H, Random, 95% CI)	0.47 [0.21, 1.05]
4.2 Mitoxantrone vs mepacrine	1	28	Odds Ratio (M-H, Random, 95% CI)	0.61 [0.09, 4.37]

Analysis 17.1. Comparison 17 Mitoxantrone, Outcome 1 Pleurodesis failure rate.

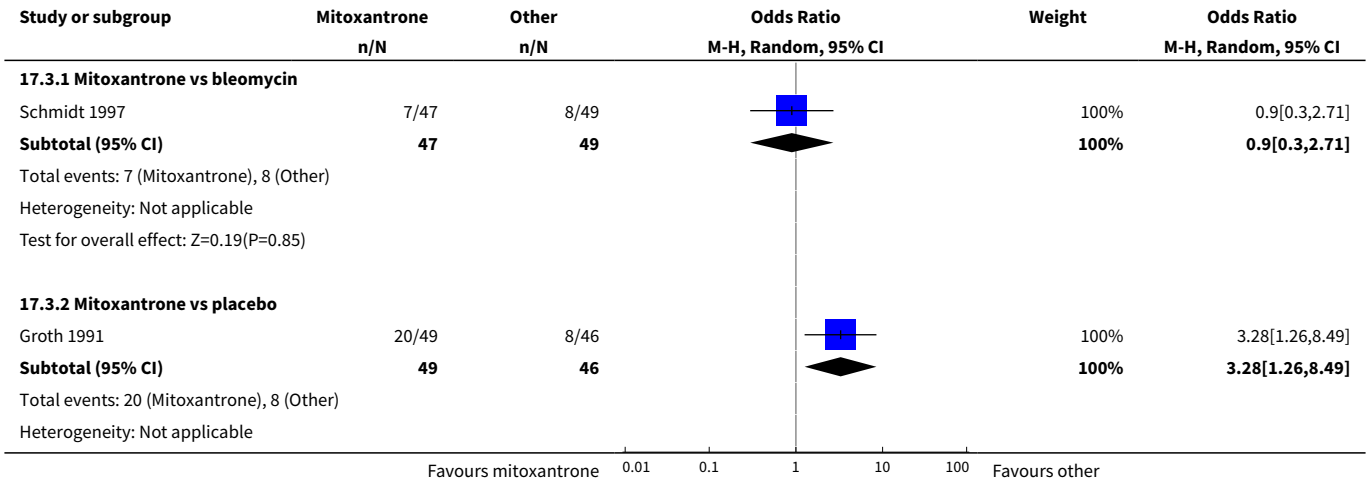


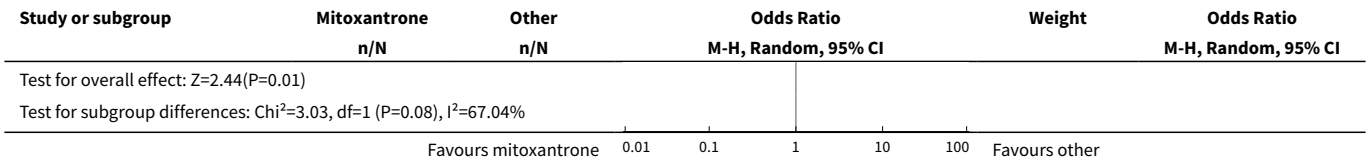


Analysis 17.2. Comparison 17 Mitoxantrone, Outcome 2 Pain.

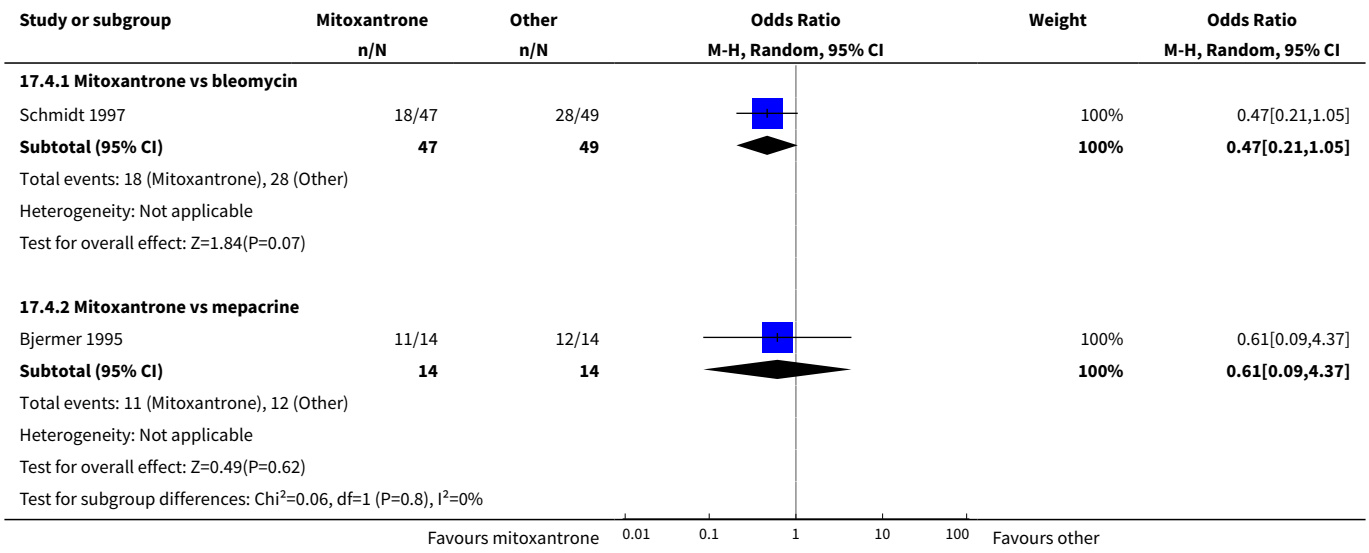


Analysis 17.3. Comparison 17 Mitoxantrone, Outcome 3 Fever.





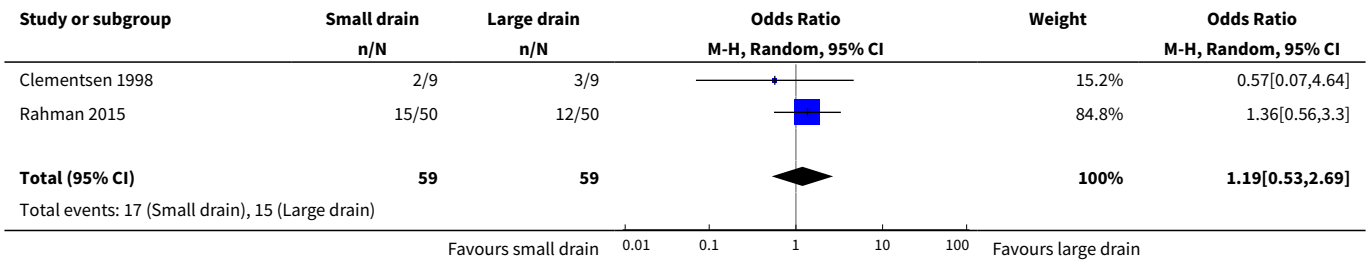
Analysis 17.4. Comparison 17 Mitoxantrone, Outcome 4 Mortality.

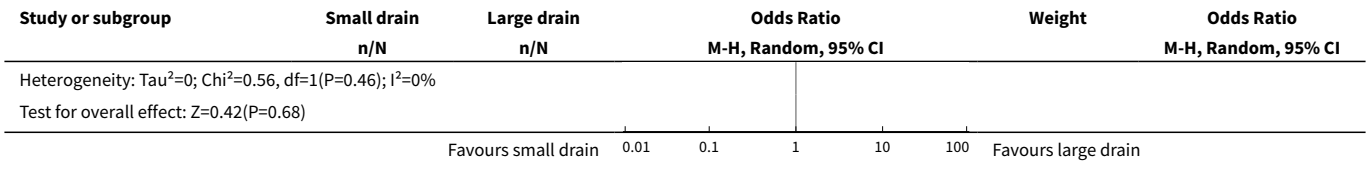


Comparison 18. Drain size

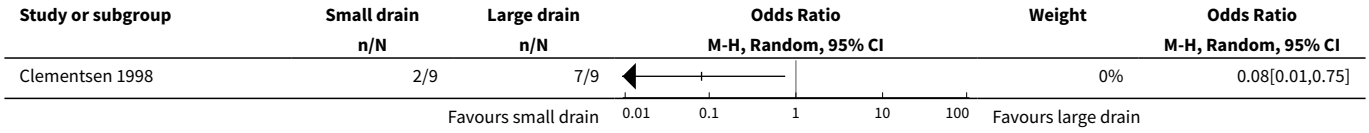
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pleurodesis failure rate	2	118	Odds Ratio (M-H, Random, 95% CI)	1.19 [0.53, 2.69]
2 Pain	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3 Mortality	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 18.1. Comparison 18 Drain size, Outcome 1 Pleurodesis failure rate.

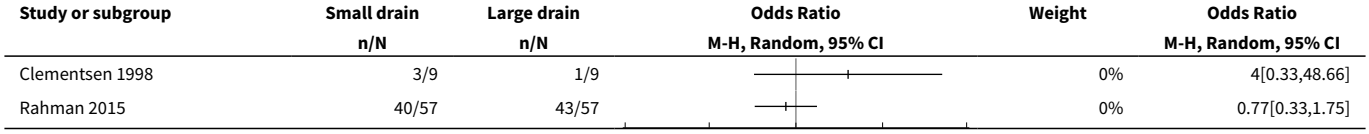




Analysis 18.2. Comparison 18 Drain size, Outcome 2 Pain.



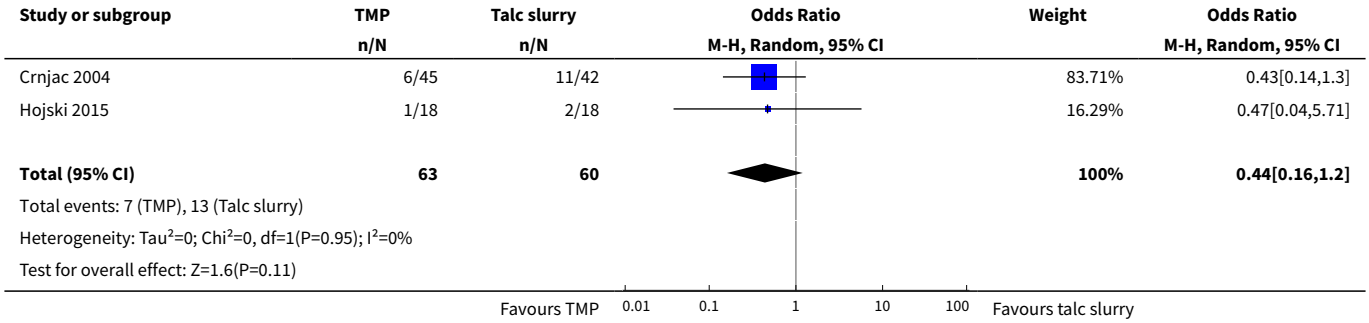
Analysis 18.3. Comparison 18 Drain size, Outcome 3 Mortality.



Comparison 19. Thoracoscopic mechanical pleurodesis (TMP)

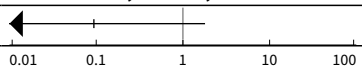
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Pleurodesis failure rate	2	123	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.16, 1.20]
2 Mortality	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 19.1. Comparison 19 Thoracoscopic mechanical pleurodesis (TMP), Outcome 1 Pleurodesis failure rate.



Analysis 19.2. Comparison 19 Thoracoscopic mechanical pleurodesis (TMP), Outcome 2 Mortality.

Study or subgroup	TMP n/N	Talc slurry n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Crnjac 2004	0/45	4/42		0%	0.09[0,1.8]



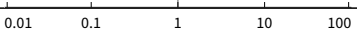
Favours TMP — Favours talc slurry

Comparison 20. Other

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pleurodesis failure rate	4	464	Odds Ratio (M-H, Random, 95% CI)	1.16 [0.76, 1.78]
1.1 Rotation vs no rotation	1	20	Odds Ratio (M-H, Random, 95% CI)	2.25 [0.17, 29.77]
1.2 Mixed particle talc vs graded talc	1	28	Odds Ratio (M-H, Random, 95% CI)	1.64 [0.23, 11.70]
1.3 Talc pleurodesis vs video-assisted thoracoscopic surgery (VATS) parietal pleurectomy	1	122	Odds Ratio (M-H, Random, 95% CI)	1.01 [0.49, 2.09]
1.4 Non-steroidal anti-inflammatory drugs (NSAIDs) vs opiates for analgesia	1	294	Odds Ratio (M-H, Random, 95% CI)	1.19 [0.68, 2.08]
2 Fever	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Mixed particle talc vs graded talc	1	46	Odds Ratio (M-H, Random, 95% CI)	15.92 [1.81, 140.16]
3 Pain	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Streptokinase vs control	1	47	Odds Ratio (M-H, Random, 95% CI)	3.00 [0.12, 77.47]
3.2 NSAID vs opiate (in requiring rescue analgesia)	1	320	Odds Ratio (M-H, Random, 95% CI)	1.73 [1.08, 2.78]
4 Mortality	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Mixed particle talc vs graded talc	1	43	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.25, 3.07]
4.2 Talc pleurodesis vs VATS partial pleurectomy	1	175	Odds Ratio (M-H, Random, 95% CI)	0.92 [0.45, 1.90]
4.3 NSAIDs vs opiates for analgesia	1	320	Odds Ratio (M-H, Random, 95% CI)	1.36 [0.87, 2.12]

Analysis 20.1. Comparison 20 Other, Outcome 1 Pleurodesis failure rate.

Study or subgroup	Treatment 1 n/N	Treatment 2 n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
20.1.1 Rotation vs no rotation					
Mager 2002	2/10	1/10		2.71%	2.25[0.17,29.77]
Subtotal (95% CI)	**10**	**10**		**2.71%**	**2.25[0.17,29.77]**
Total events: 2 (Treatment 1), 1 (Treatment 2)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.62(P=0.54)					
20.1.2 Mixed particle talc vs graded talc					
Maskell 2004	3/14	2/14		4.67%	1.64[0.23,11.7]
Subtotal (95% CI)	**14**	**14**		**4.67%**	**1.64[0.23,11.7]**
Total events: 3 (Treatment 1), 2 (Treatment 2)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.49(P=0.62)					
20.1.3 Talc pleurodesis vs video-assisted thoracoscopic surgery (VATS) parietal pleurectomy					
Rintoul 2014	25/62	24/60		34.49%	1.01[0.49,2.09]
Subtotal (95% CI)	**62**	**60**		**34.49%**	**1.01[0.49,2.09]**
Total events: 25 (Treatment 1), 24 (Treatment 2)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.04(P=0.97)					
20.1.4 Non-steroidal anti-inflammatory drugs (NSAIDs) vs opiates for analgesia					
Rahman 2015	33/144	30/150		58.13%	1.19[0.68,2.08]
Subtotal (95% CI)	**144**	**150**		**58.13%**	**1.19[0.68,2.08]**
Total events: 33 (Treatment 1), 30 (Treatment 2)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.61(P=0.54)					
Total (95% CI)	**230**	**234**		**100%**	**1.16[0.76,1.78]**
Total events: 63 (Treatment 1), 57 (Treatment 2)					
Heterogeneity: Tau^2=0; Chi^2=0.51, df=3(P=0.92); I^2=0%					
Test for overall effect: Z=0.69(P=0.49)					
Test for subgroup differences: Chi^2=0.51, df=1 (P=0.92), I^2=0%					



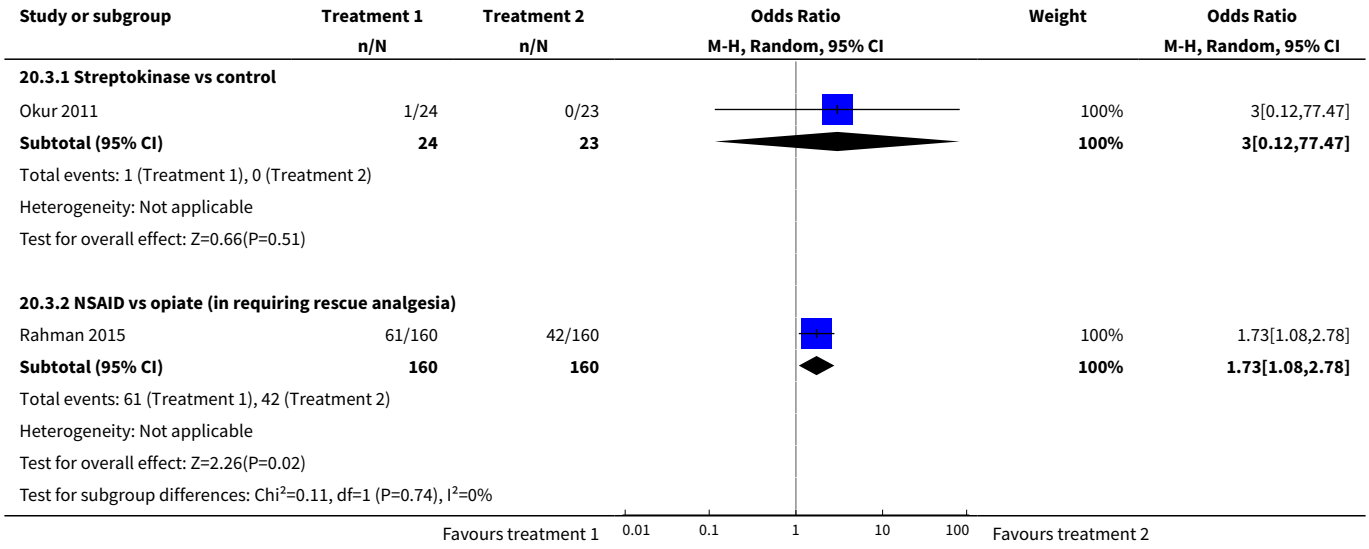
Favours treatment 1 — Favours treatment 2

Analysis 20.2. Comparison 20 Other, Outcome 2 Fever.

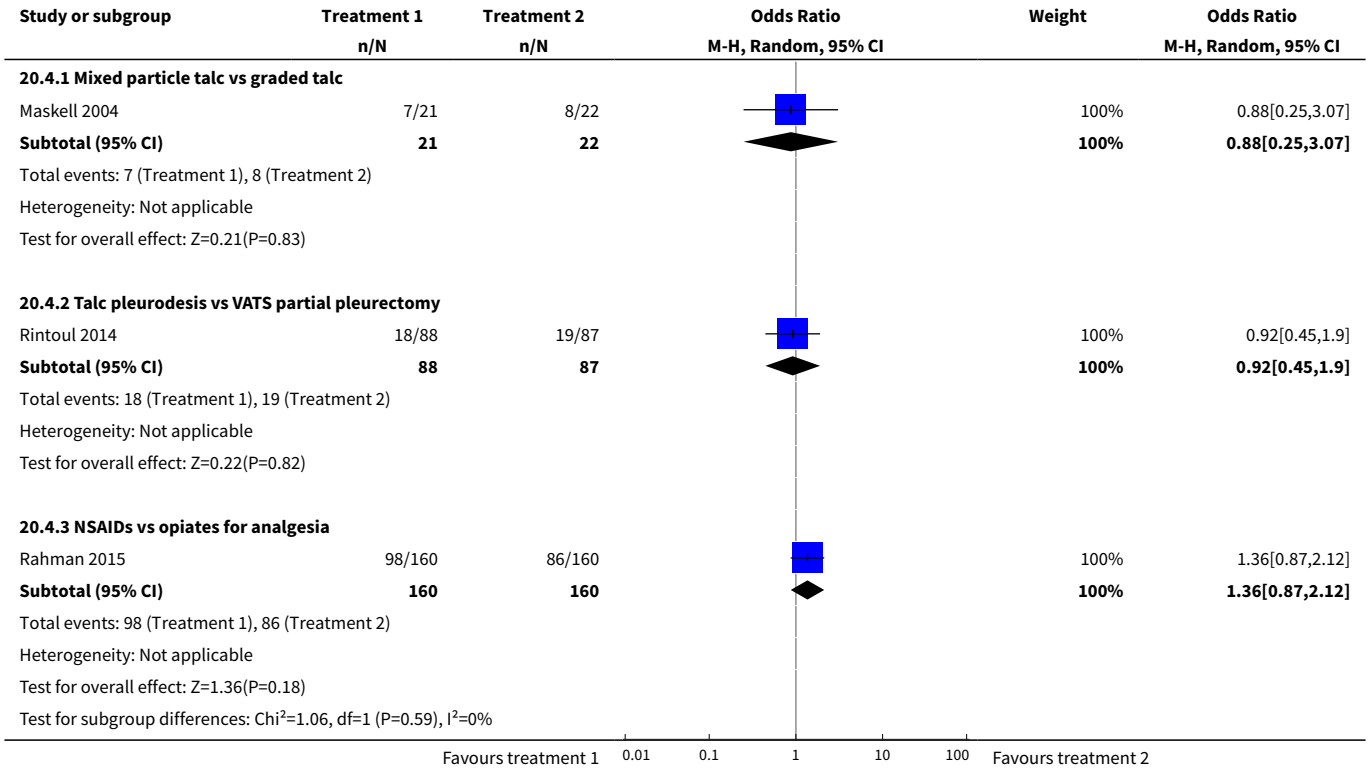
Study or subgroup	Treatment 1 n/N	Treatment 2 n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
20.2.1 Mixed particle talc vs graded talc					
Maskell 2004	9/22	1/24		100%	15.92[1.81,140.16]
Subtotal (95% CI)	**22**	**24**		**100%**	**15.92[1.81,140.16]**
Total events: 9 (Treatment 1), 1 (Treatment 2)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.49(P=0.01)					

Favours treatment 1 — Favours treatment 2

Analysis 20.3. Comparison 20 Other, Outcome 3 Pain.



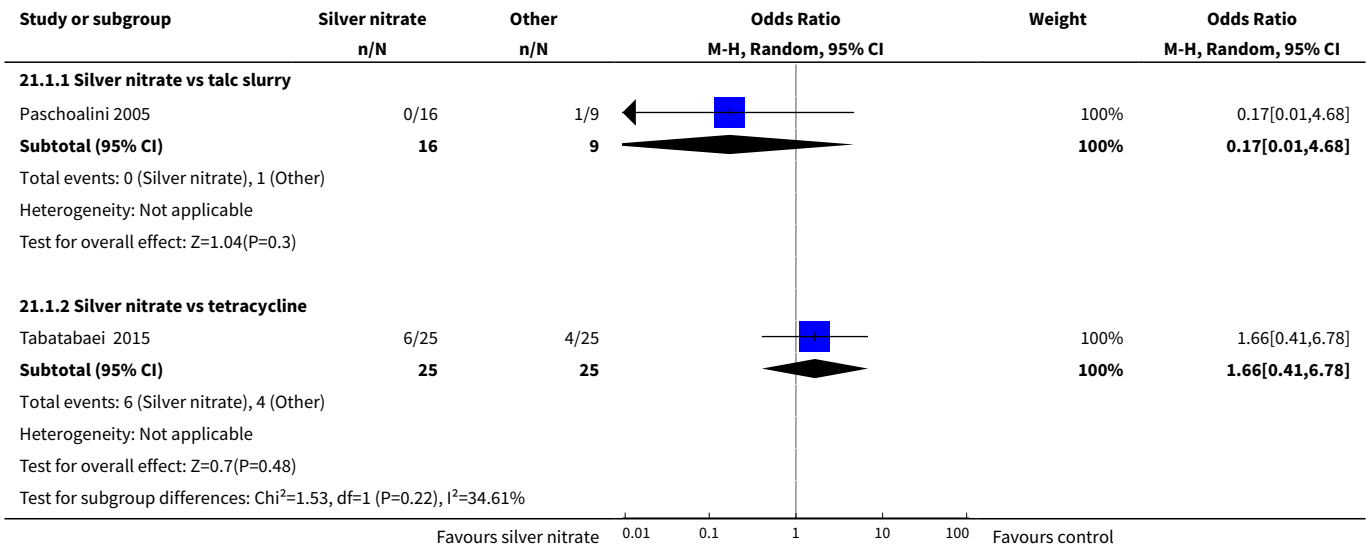
Analysis 20.4. Comparison 20 Other, Outcome 4 Mortality.



Comparison 21. Silver nitrate

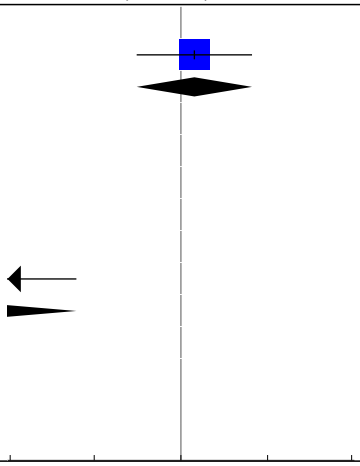
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Pleurodesis failure rate	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Silver nitrate vs talc slurry	1	25	Odds Ratio (M-H, Random, 95% CI)	0.17 [0.01, 4.68]
1.2 Silver nitrate vs tetracycline	1	50	Odds Ratio (M-H, Random, 95% CI)	1.66 [0.41, 6.78]
2 Fever	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Silver nitrate vs talc slurry	1	60	Odds Ratio (M-H, Random, 95% CI)	1.43 [0.31, 6.61]
2.2 Silver nitrate vs tetracycline	1	50	Odds Ratio (M-H, Random, 95% CI)	0.00 [0.00, 0.06]
3 Pain	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.02 [0.00, 0.33]
3.1 Silver nitrate vs tetracycline	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.02 [0.00, 0.33]
4 Mortality	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 21.1. Comparison 21 Silver nitrate, Outcome 1 Pleurodesis failure rate.



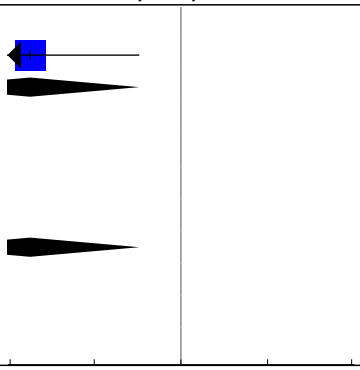
Analysis 21.2. Comparison 21 Silver nitrate, Outcome 2 Fever.

Study or subgroup	Silver nitrate n/N	Other n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
21.2.1 Silver nitrate vs talc slurry					
Paschoalini 2005	5/33	3/27		100%	1.43[0.31,6.61]
Subtotal (95% CI)	**33**	**27**		**100%**	**1.43[0.31,6.61]**
Total events: 5 (Silver nitrate), 3 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.46(P=0.65)					
21.2.2 Silver nitrate vs tetracycline					
Tabatabaei 2015	3/25	25/25		100%	0[0,0.06]
Subtotal (95% CI)	**25**	**25**		**100%**	**0[0,0.06]**
Total events: 3 (Silver nitrate), 25 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.76(P=0)					
Test for subgroup differences: Chi^2=12.69, df=1 (P=0), I^2=92.12%					



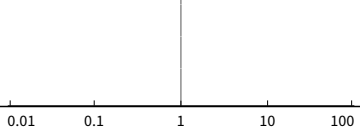
Analysis 21.3. Comparison 21 Silver nitrate, Outcome 3 Pain.

Study or subgroup	Silver nitrate n/N	Other n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
21.3.1 Silver nitrate vs tetracycline					
Tabatabaei 2015	12/25	25/25		100%	0.02[0,0.33]
Subtotal (95% CI)	**25**	**25**		**100%**	**0.02[0,0.33]**
Total events: 12 (Silver nitrate), 25 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.71(P=0.01)					
Total (95% CI)	**25**	**25**		**100%**	**0.02[0,0.33]**
Total events: 12 (Silver nitrate), 25 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.71(P=0.01)					



Analysis 21.4. Comparison 21 Silver nitrate, Outcome 4 Mortality.

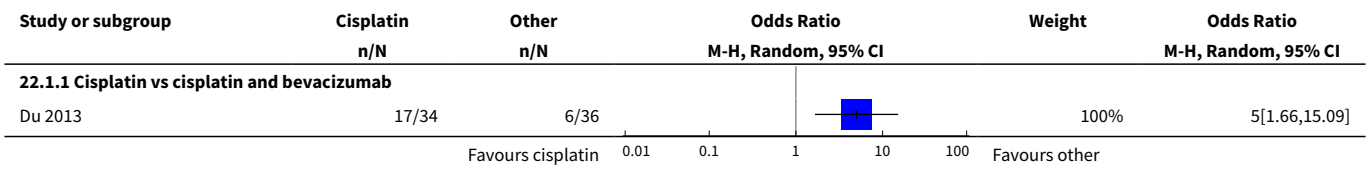
Study or subgroup	Silver nitrate n/N	Other n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Tabatabaei 2015	0/25	0/25			Not estimable
Total (95% CI)	**25**	**25**			**Not estimable**
Total events: 0 (Silver nitrate), 0 (Other)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

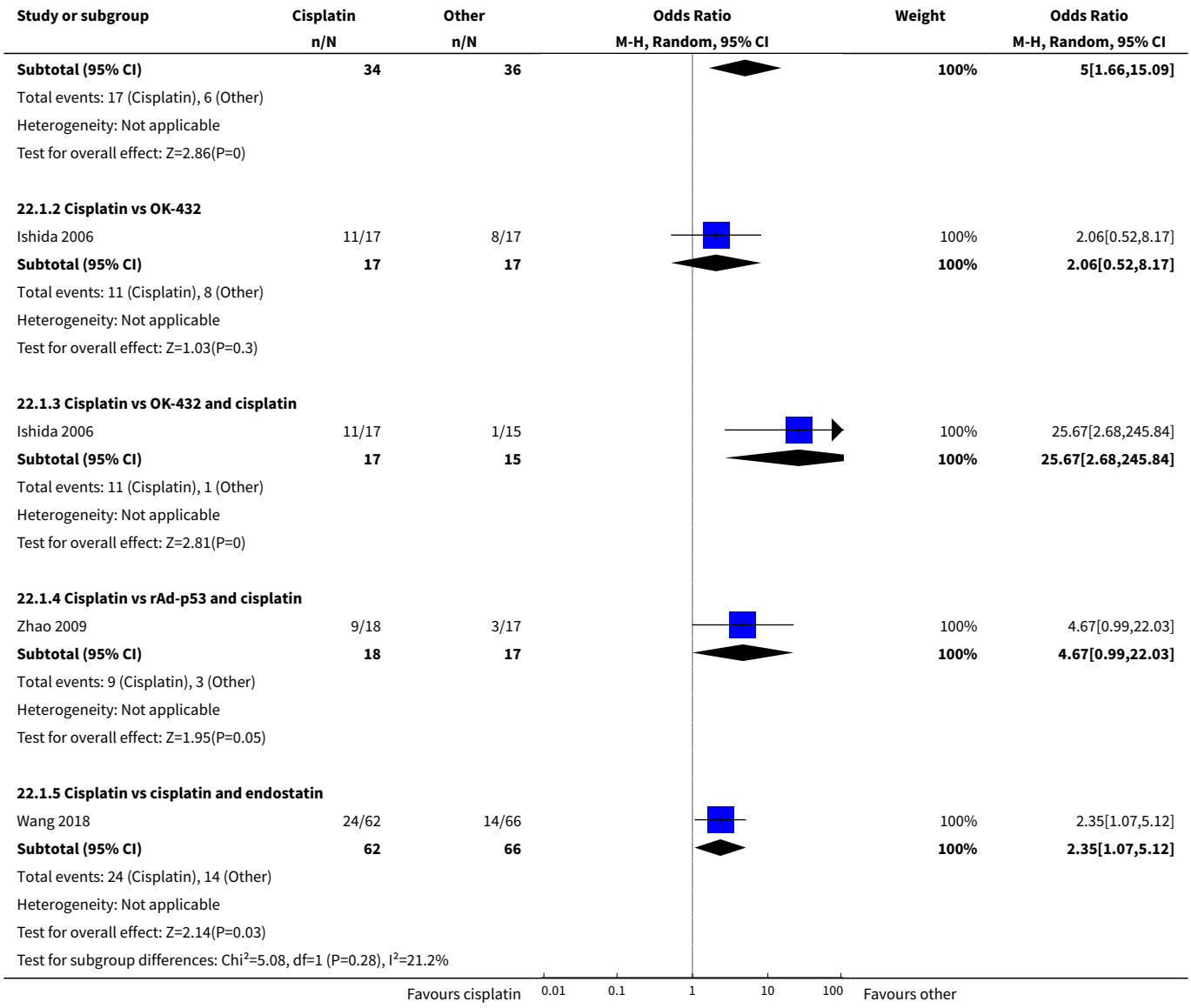


Comparison 22. Cisplatin

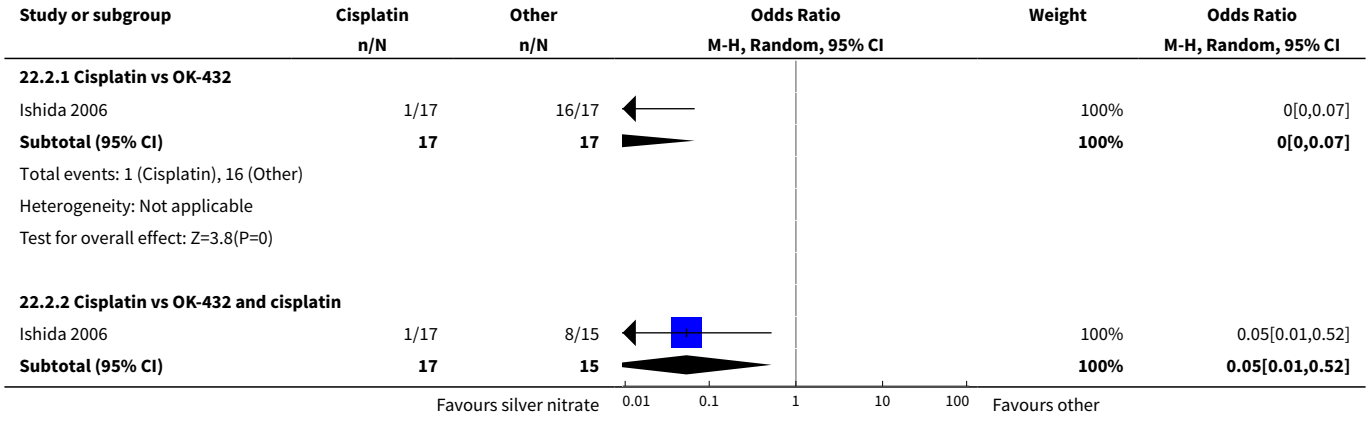
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pleurodesis failure rate	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Cisplatin vs cisplatin and bevacizumab	1	70	Odds Ratio (M-H, Random, 95% CI)	5.00 [1.66, 15.09]
1.2 Cisplatin vs OK-432	1	34	Odds Ratio (M-H, Random, 95% CI)	2.06 [0.52, 8.17]
1.3 Cisplatin vs OK-432 and cisplatin	1	32	Odds Ratio (M-H, Random, 95% CI)	25.67 [2.68, 245.84]
1.4 Cisplatin vs rAd-p53 and cisplatin	1	35	Odds Ratio (M-H, Random, 95% CI)	4.67 [0.99, 22.03]
1.5 Cisplatin vs cisplatin and endostatin	1	128	Odds Ratio (M-H, Random, 95% CI)	2.35 [1.07, 5.12]
2 Fever	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Cisplatin vs OK-432	1	34	Odds Ratio (M-H, Random, 95% CI)	0.00 [0.00, 0.07]
2.2 Cisplatin vs OK-432 and cisplatin	1	32	Odds Ratio (M-H, Random, 95% CI)	0.05 [0.01, 0.52]
2.3 Cisplatin vs rAd-p53 and cisplatin	1	35	Odds Ratio (M-H, Random, 95% CI)	0.09 [0.02, 0.51]
3 Pain	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Cisplatin vs OK-432	1	34	Odds Ratio (M-H, Random, 95% CI)	0.15 [0.03, 0.87]
3.2 Cisplatin vs OK-432 and cisplatin	1	32	Odds Ratio (M-H, Random, 95% CI)	0.2 [0.03, 1.21]
4 Mortality	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Cisplatin vs OK-432	1	34	Odds Ratio (M-H, Random, 95% CI)	0.76 [0.18, 3.23]
4.2 Cisplatin vs combination OK-432 and cisplatin	1	32	Odds Ratio (M-H, Random, 95% CI)	1.67 [0.32, 8.59]
4.3 Cisplatin vs combination rAd-p53 and cisplatin	1	35	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.4 Cisplatin vs combination cisplatin and endostatin	1	128	Odds Ratio (M-H, Random, 95% CI)	1.29 [0.57, 2.93]

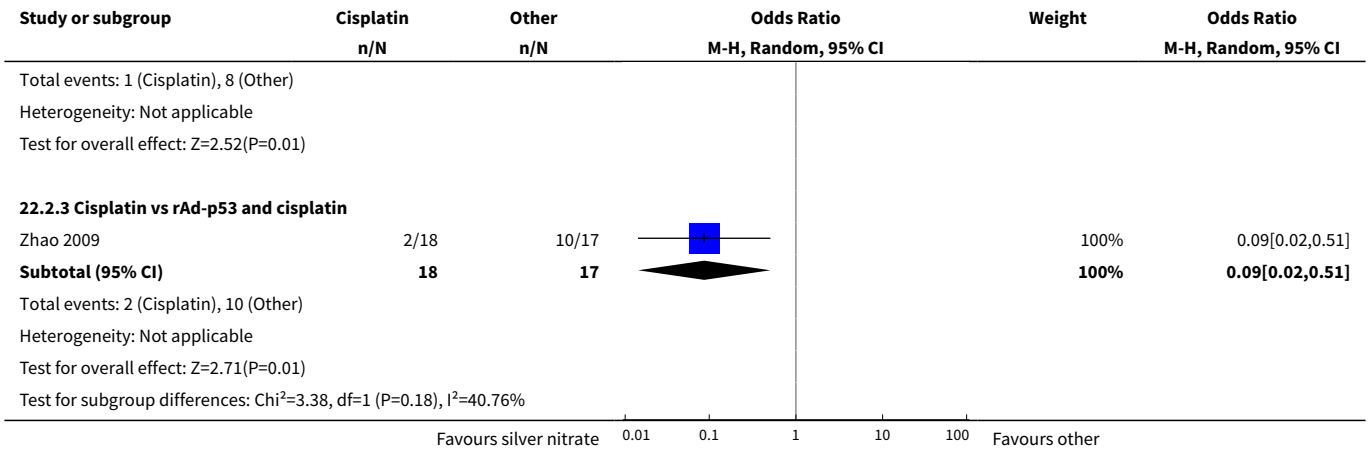
Analysis 22.1. Comparison 22 Cisplatin, Outcome 1 Pleurodesis failure rate.



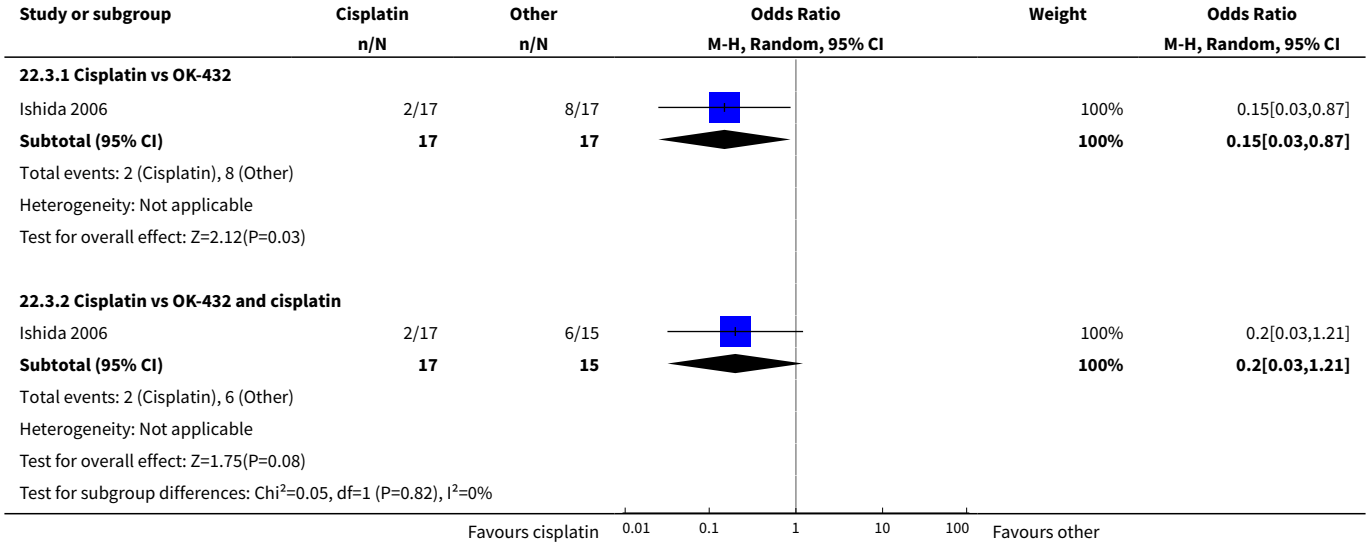


Analysis 22.2. Comparison 22 Cisplatin, Outcome 2 Fever.

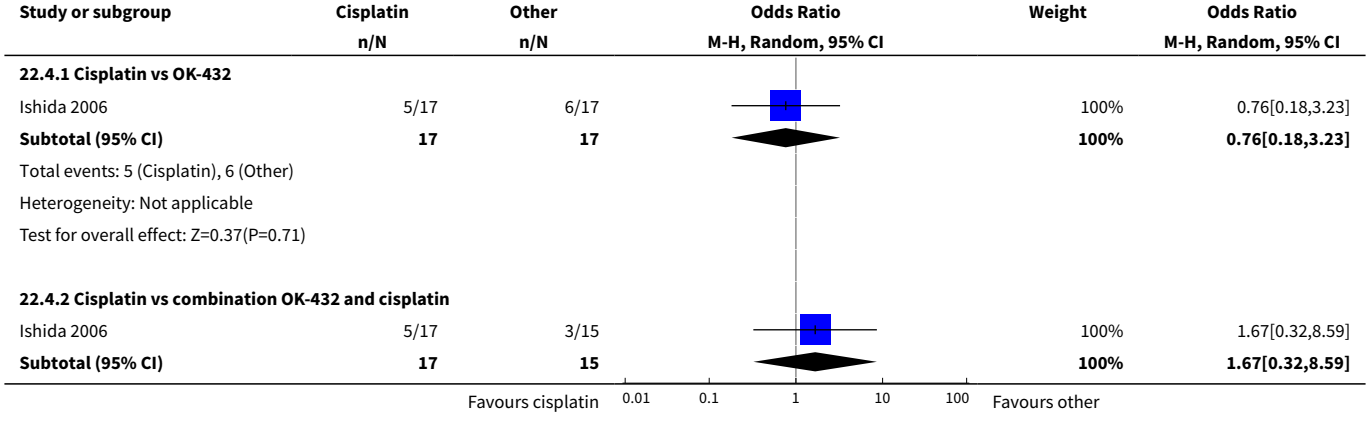


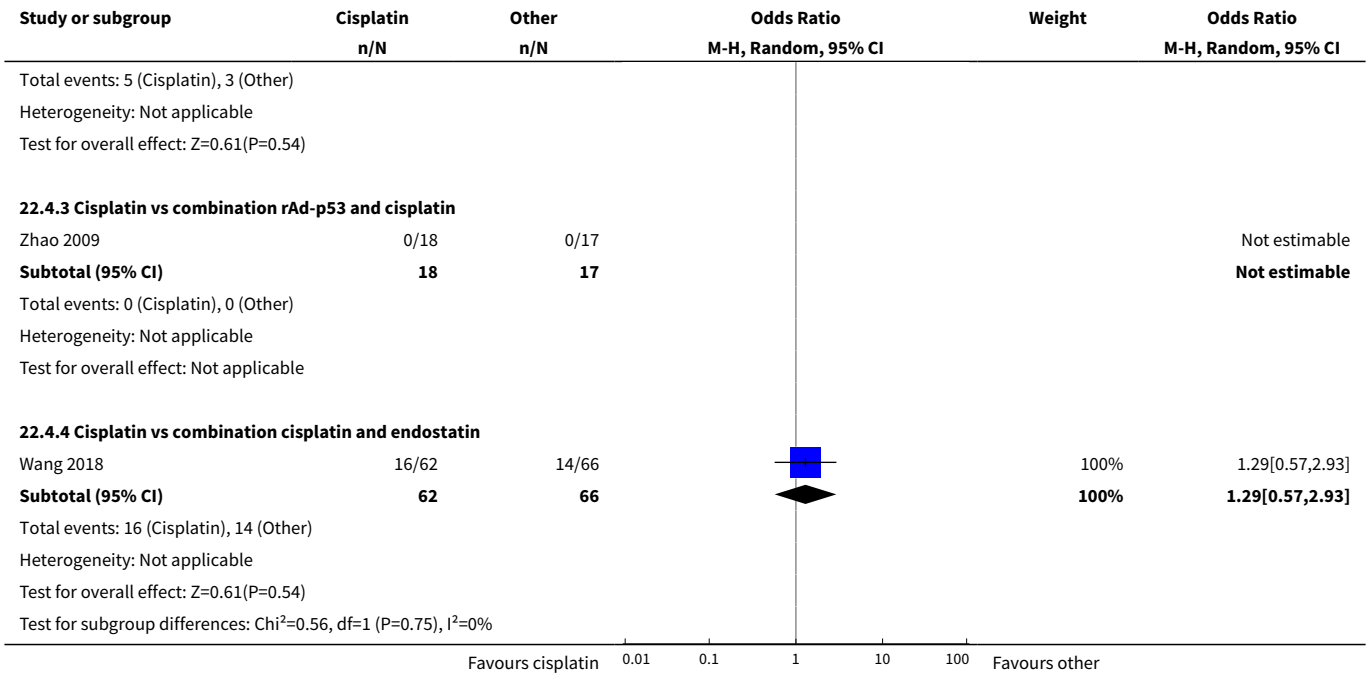


Analysis 22.3. Comparison 22 Cisplatin, Outcome 3 Pain.



Analysis 22.4. Comparison 22 Cisplatin, Outcome 4 Mortality.

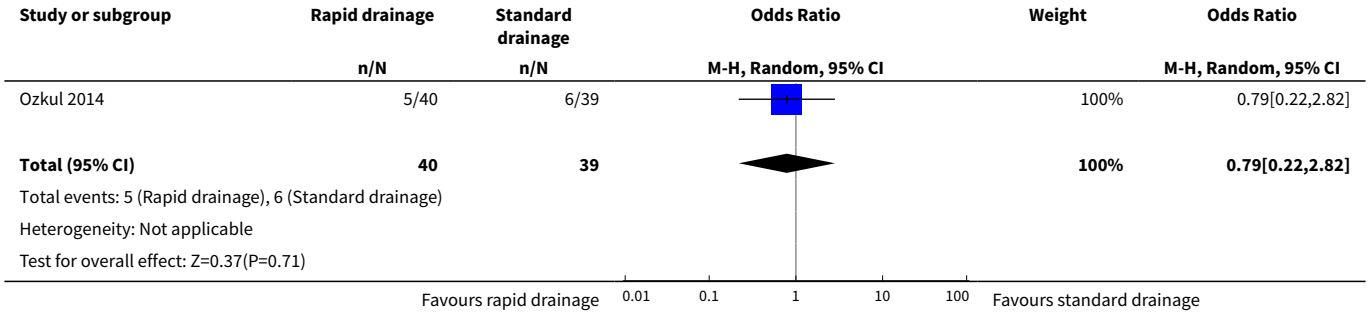




Comparison 23. Duration of drainage prior to administration of sclerosant

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pleurodesis failure rate	1	79	Odds Ratio (M-H, Random, 95% CI)	0.79 [0.22, 2.82]

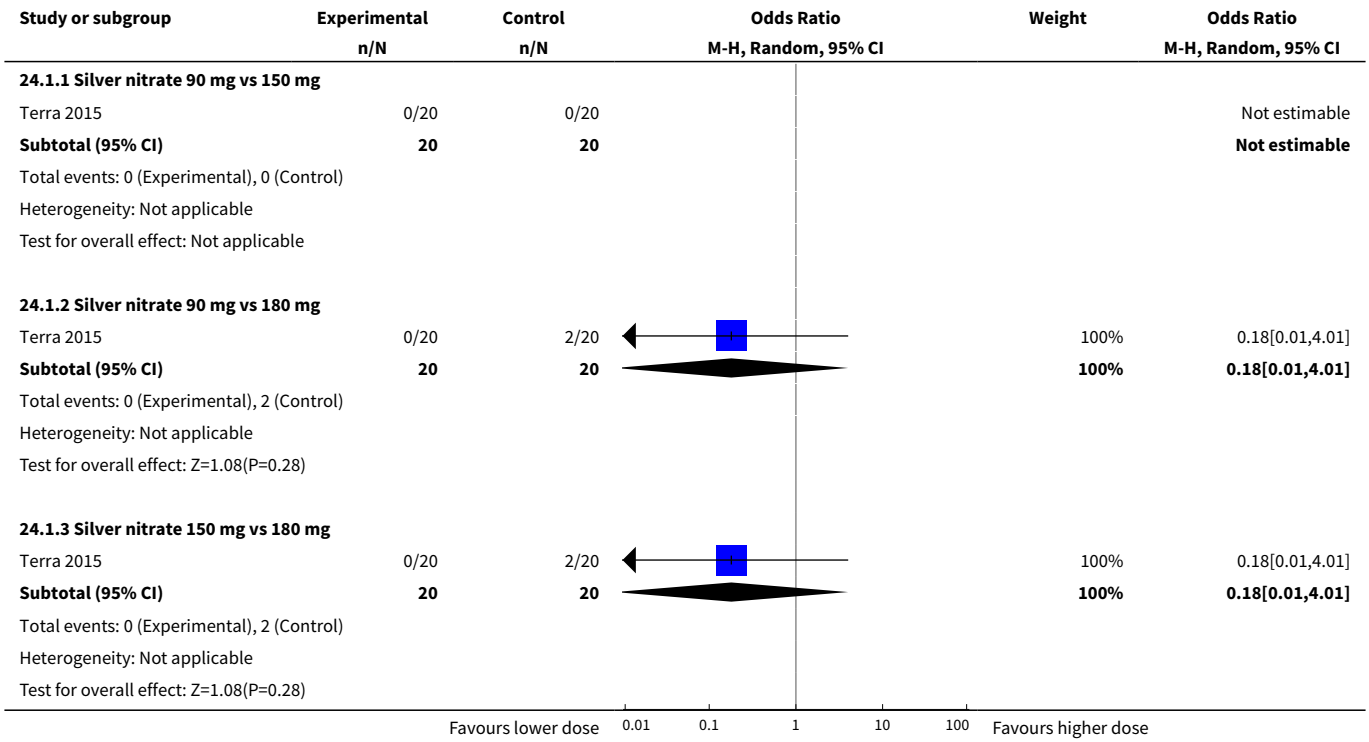
Analysis 23.1. Comparison 23 Duration of drainage prior to administration of sclerosant, Outcome 1 Pleurodesis failure rate.



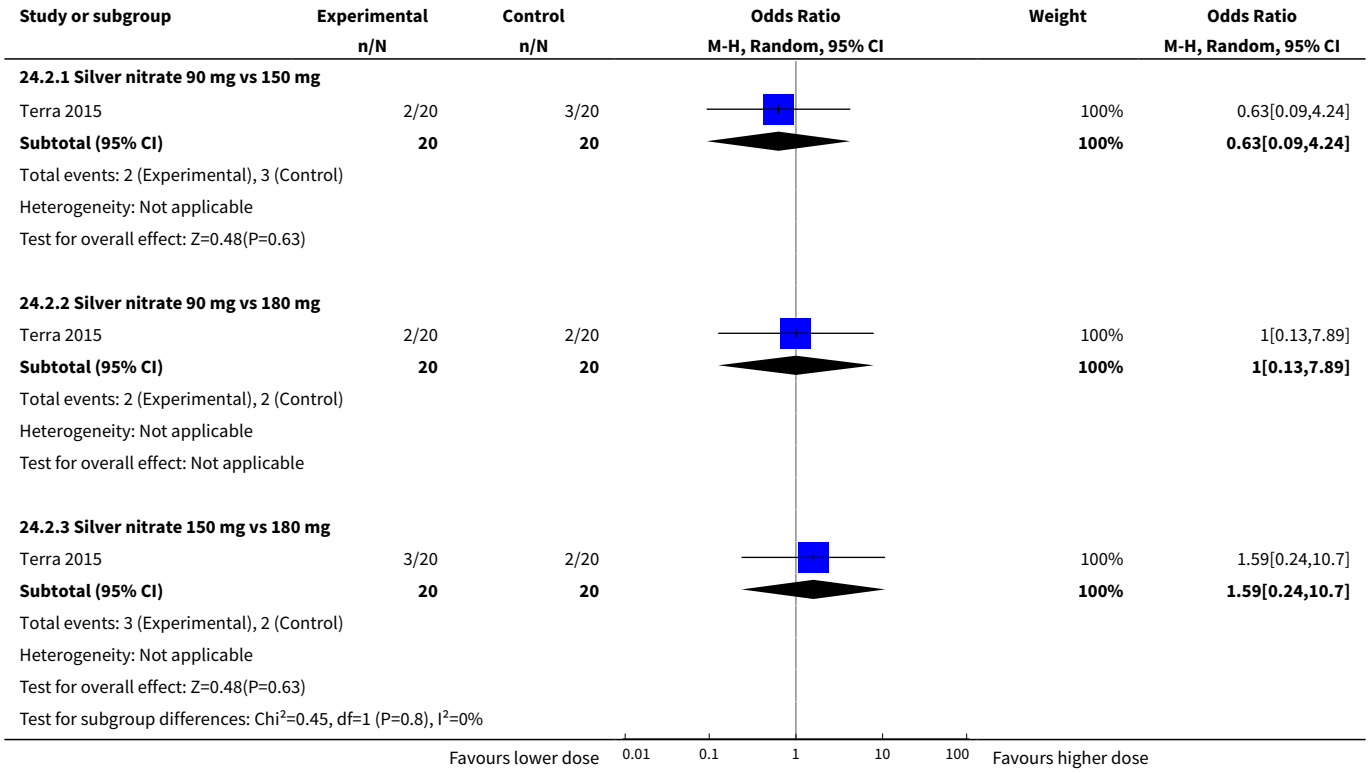
Comparison 24. Dose of silver nitrate

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Pleurodesis failure rate	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Silver nitrate 90 mg vs 150 mg	1	40	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Silver nitrate 90 mg vs 180 mg	1	40	Odds Ratio (M-H, Random, 95% CI)	0.18 [0.01, 4.01]
1.3 Silver nitrate 150 mg vs 180 mg	1	40	Odds Ratio (M-H, Random, 95% CI)	0.18 [0.01, 4.01]
2 Fever	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Silver nitrate 90 mg vs 150 mg	1	40	Odds Ratio (M-H, Random, 95% CI)	0.63 [0.09, 4.24]
2.2 Silver nitrate 90 mg vs 180 mg	1	40	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.13, 7.89]
2.3 Silver nitrate 150 mg vs 180 mg	1	40	Odds Ratio (M-H, Random, 95% CI)	1.59 [0.24, 10.70]
3 Pain	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Silver nitrate 90 mg vs 150 mg	1	40	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.13, 7.89]
3.2 Silver nitrate 90 mg vs 180 mg	1	40	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.13, 7.89]
3.3 Silver nitrate 150 mg vs 180 mg	1	40	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.13, 7.89]
4 Mortality	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Silver nitrate 90 mg vs 150 mg	1	39	Odds Ratio (M-H, Random, 95% CI)	3.18 [0.30, 33.58]
4.2 Silver nitrate 90 mg vs 180 mg	1	39	Odds Ratio (M-H, Random, 95% CI)	7.80 [0.38, 161.87]
4.3 Silver nitrate 150 mg vs 180 mg	1	38	Odds Ratio (M-H, Random, 95% CI)	3.16 [0.12, 82.64]

Analysis 24.1. Comparison 24 Dose of silver nitrate, Outcome 1 Pleurodesis failure rate.



Analysis 24.2. Comparison 24 Dose of silver nitrate, Outcome 2 Fever.

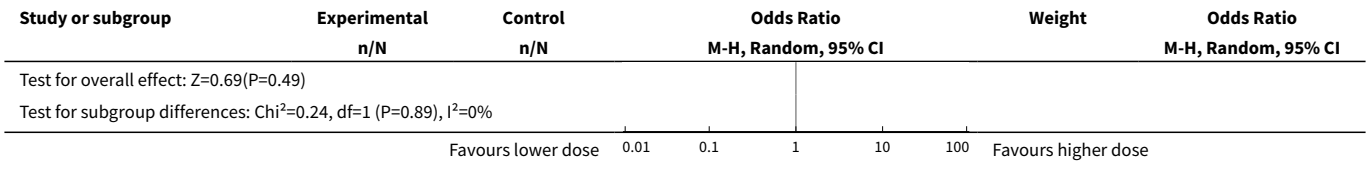


Analysis 24.3. Comparison 24 Dose of silver nitrate, Outcome 3 Pain.

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
24.3.1 Silver nitrate 90 mg vs 150 mg					
Terra 2015	2/20	2/20		100%	1[0.13,7.89]
Subtotal (95% CI)	**20**	**20**		**100%**	**1[0.13,7.89]**
Total events: 2 (Experimental), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
24.3.2 Silver nitrate 90 mg vs 180 mg					
Terra 2015	2/20	2/20		100%	1[0.13,7.89]
Subtotal (95% CI)	**20**	**20**		**100%**	**1[0.13,7.89]**
Total events: 2 (Experimental), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
24.3.3 Silver nitrate 150 mg vs 180 mg					
Terra 2015	2/20	2/20		100%	1[0.13,7.89]
Subtotal (95% CI)	**20**	**20**		**100%**	**1[0.13,7.89]**
Total events: 2 (Experimental), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Not applicable					

Analysis 24.4. Comparison 24 Dose of silver nitrate, Outcome 4 Mortality.

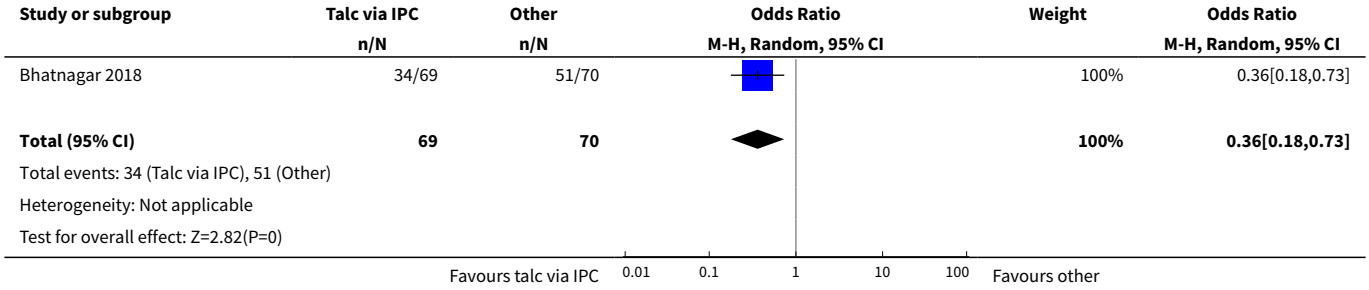
Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
24.4.1 Silver nitrate 90 mg vs 150 mg					
Terra 2015	3/20	1/19		100%	3.18[0.3,33.58]
Subtotal (95% CI)	**20**	**19**		**100%**	**3.18[0.3,33.58]**
Total events: 3 (Experimental), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.96(P=0.34)					
24.4.2 Silver nitrate 90 mg vs 180 mg					
Terra 2015	3/20	0/19		100%	7.8[0.38,161.87]
Subtotal (95% CI)	**20**	**19**		**100%**	**7.8[0.38,161.87]**
Total events: 3 (Experimental), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.33(P=0.18)					
24.4.3 Silver nitrate 150 mg vs 180 mg					
Terra 2015	1/19	0/19		100%	3.16[0.12,82.64]
Subtotal (95% CI)	**19**	**19**		**100%**	**3.16[0.12,82.64]**
Total events: 1 (Experimental), 0 (Control)					
Heterogeneity: Not applicable					



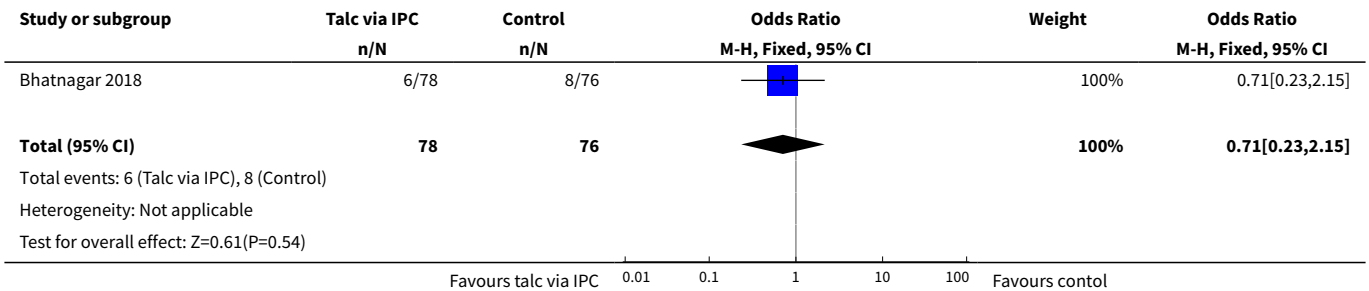
Comparison 25. Talc via indwelling pleural catheter (IPC)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pleurodesis failure rate	1	139	Odds Ratio (M-H, Random, 95% CI)	0.36 [0.18, 0.73]
2 Pain	1	154	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.23, 2.15]
3 Mortality	1	154	Odds Ratio (M-H, Fixed, 95% CI)	0.44 [0.17, 1.15]
3.1 Talc via IPC vs IPC – not daily drainage	1	154	Odds Ratio (M-H, Fixed, 95% CI)	0.44 [0.17, 1.15]

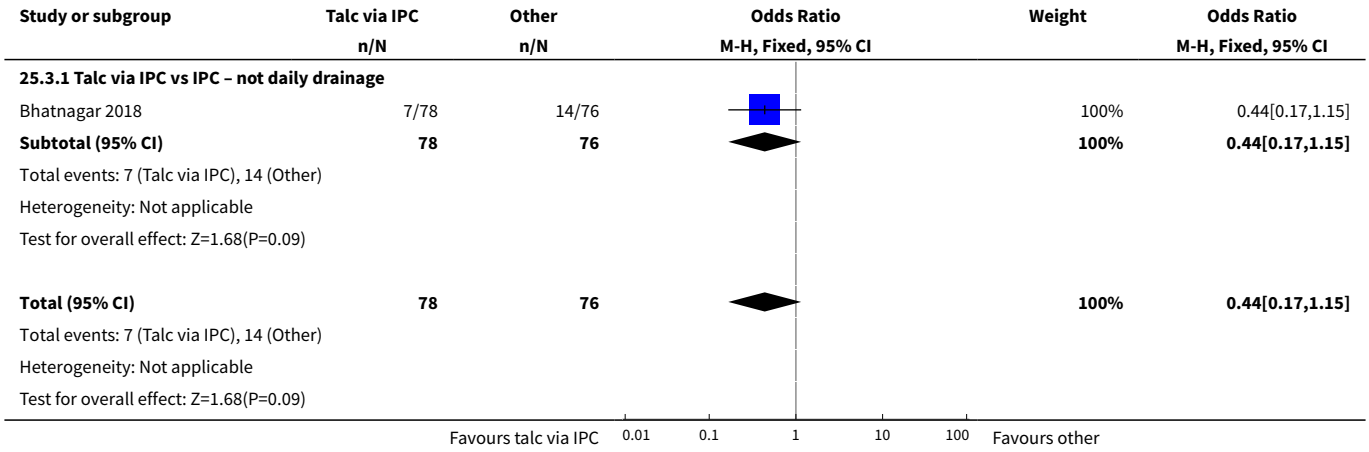
Analysis 25.1. Comparison 25 Talc via indwelling pleural catheter (IPC), Outcome 1 Pleurodesis failure rate.



Analysis 25.2. Comparison 25 Talc via indwelling pleural catheter (IPC), Outcome 2 Pain.



Analysis 25.3. Comparison 25 Talc via indwelling pleural catheter (IPC), Outcome 3 Mortality.

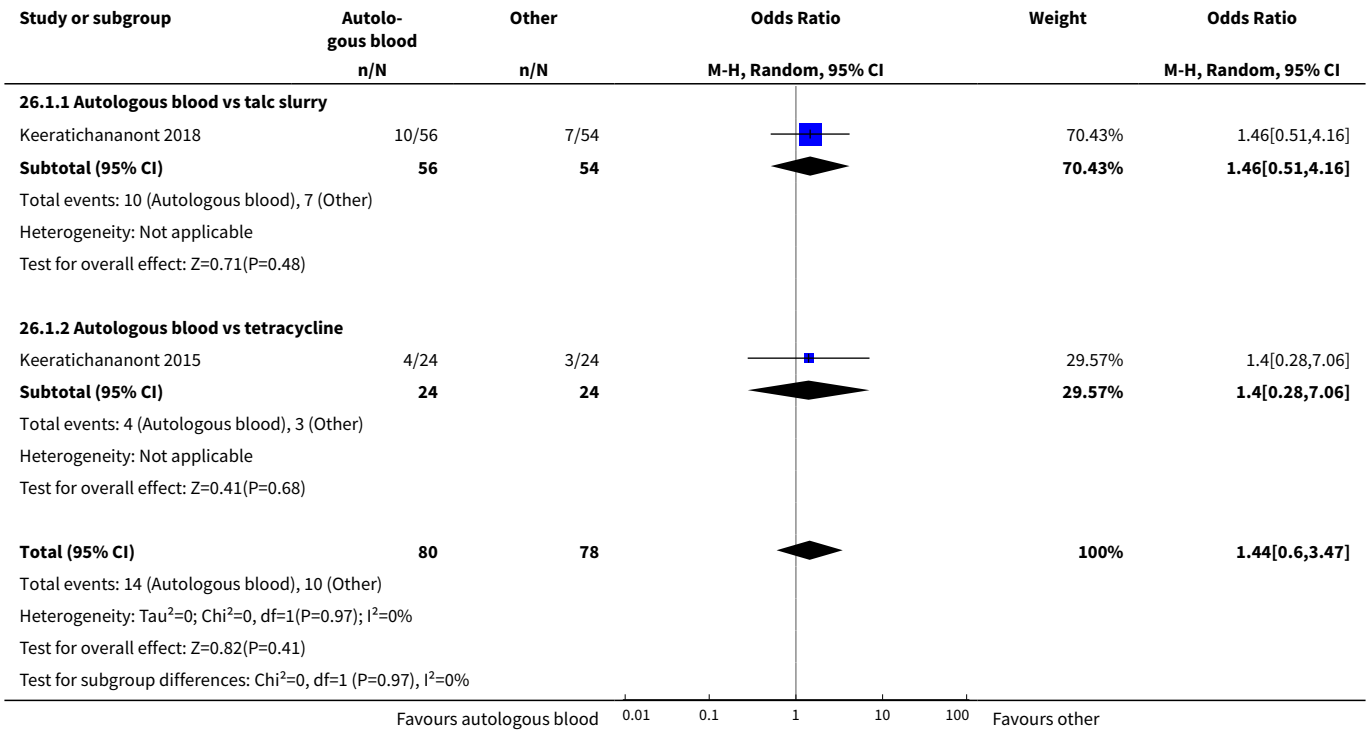


Comparison 26. Autologous blood

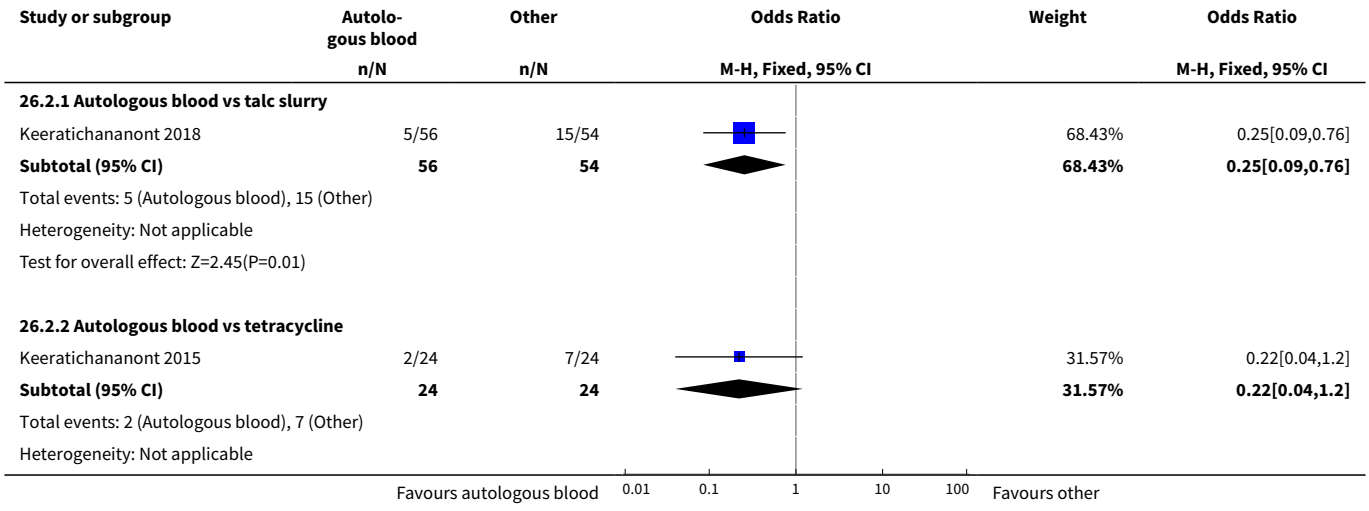
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pleurodesis failure rate	2	158	Odds Ratio (M-H, Random, 95% CI)	1.44 [0.60, 3.47]
1.1 Autologous blood vs talc slurry	1	110	Odds Ratio (M-H, Random, 95% CI)	1.46 [0.51, 4.16]
1.2 Autologous blood vs tetracycline	1	48	Odds Ratio (M-H, Random, 95% CI)	1.4 [0.28, 7.06]
2 Fever	2	158	Odds Ratio (M-H, Fixed, 95% CI)	0.24 [0.10, 0.61]
2.1 Autologous blood vs talc slurry	1	110	Odds Ratio (M-H, Fixed, 95% CI)	0.25 [0.09, 0.76]
2.2 Autologous blood vs tetracycline	1	48	Odds Ratio (M-H, Fixed, 95% CI)	0.22 [0.04, 1.20]
3 Pain	2	158	Odds Ratio (M-H, Fixed, 95% CI)	0.13 [0.05, 0.32]
3.1 Autologous blood vs talc slurry	1	110	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.09, 0.84]
3.2 Autologous blood vs tetracycline	1	48	Odds Ratio (M-H, Fixed, 95% CI)	0.01 [0.00, 0.13]
4 Mortality	2	165	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.15, 3.38]
4.1 Autologous blood vs talc slurry	1	117	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.15, 3.38]

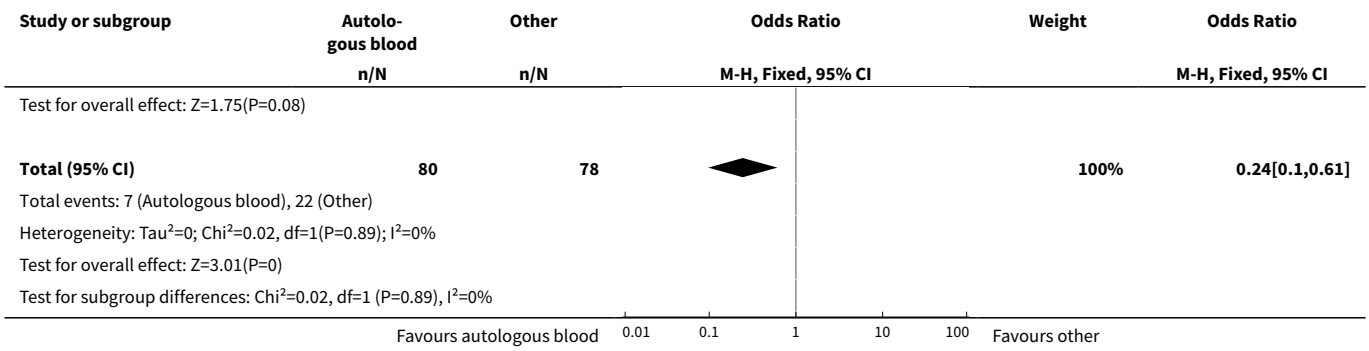
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.2 Autologous blood vs tetracycline	1	48	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 26.1. Comparison 26 Autologous blood, Outcome 1 Pleurodesis failure rate.

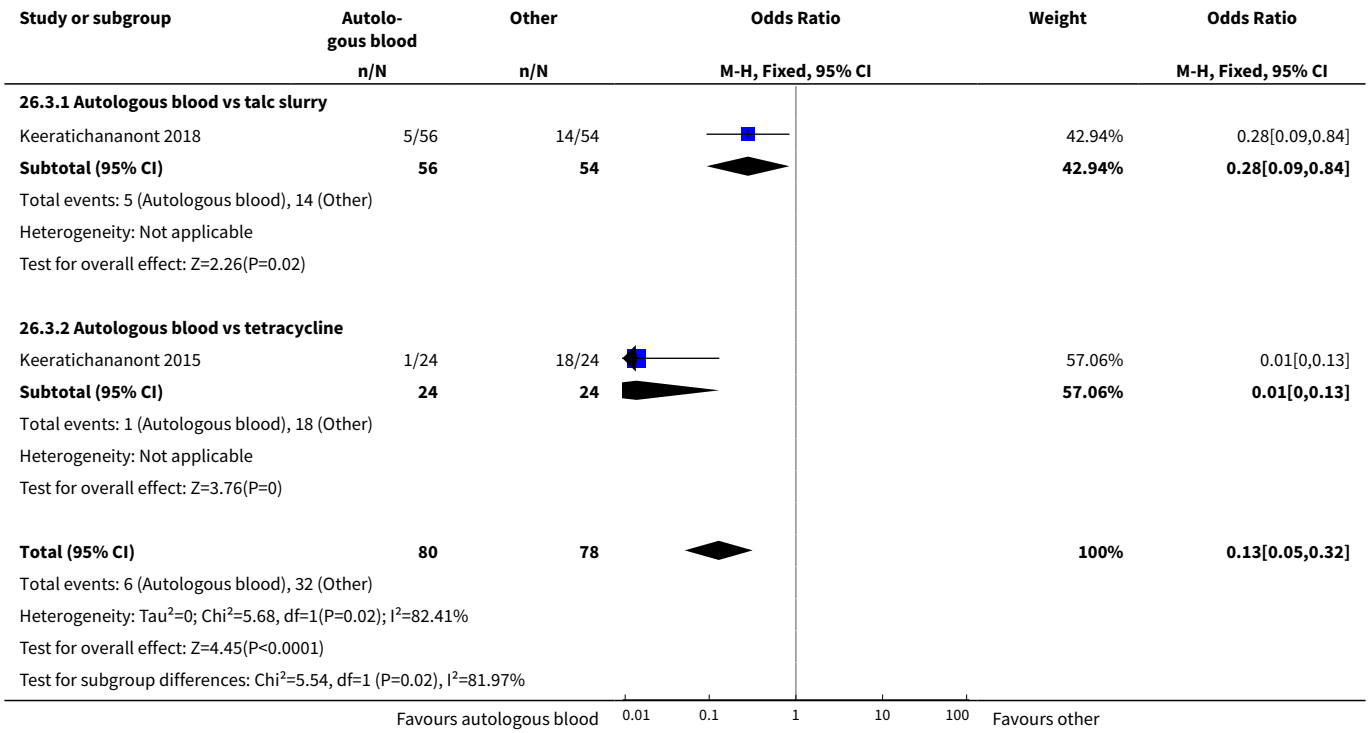


Analysis 26.2. Comparison 26 Autologous blood, Outcome 2 Fever.

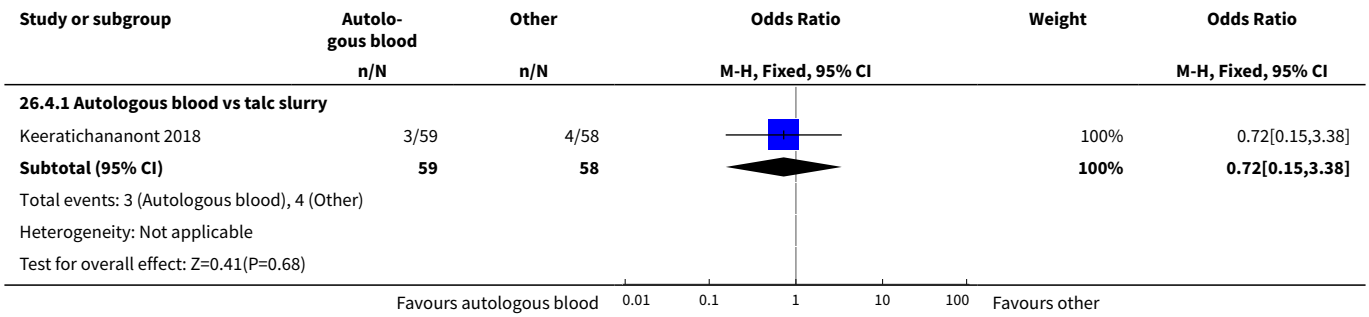


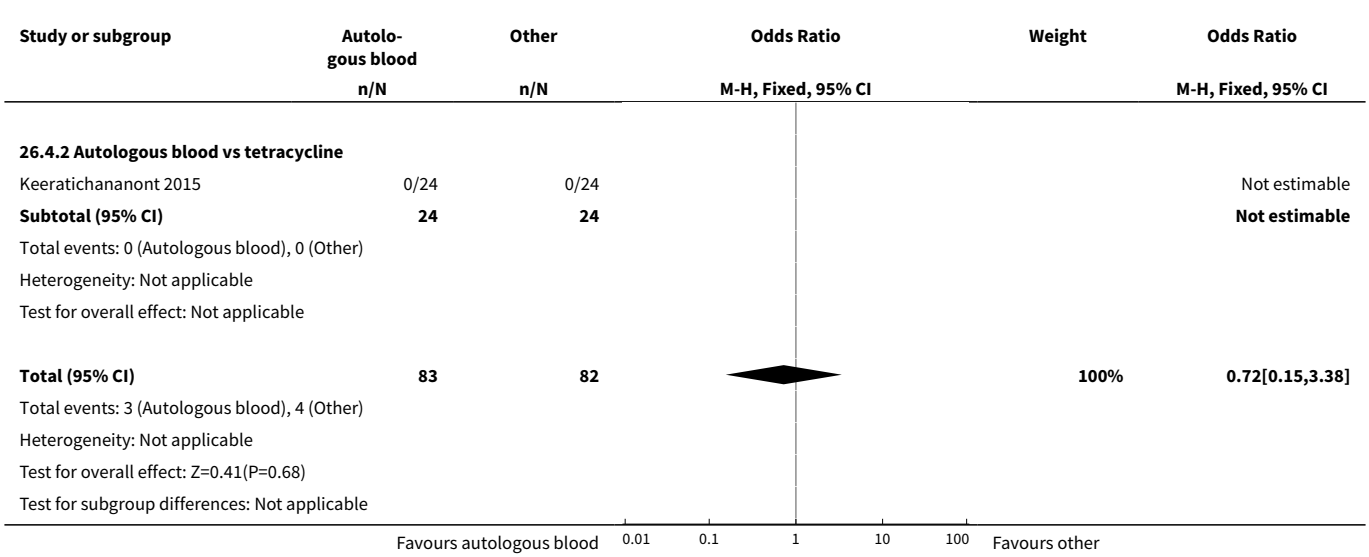


Analysis 26.3. Comparison 26 Autologous blood, Outcome 3 Pain.



Analysis 26.4. Comparison 26 Autologous blood, Outcome 4 Mortality.

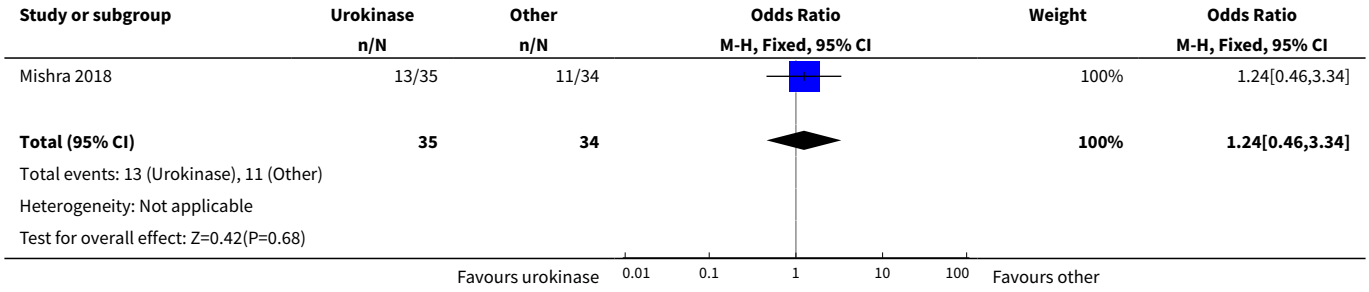




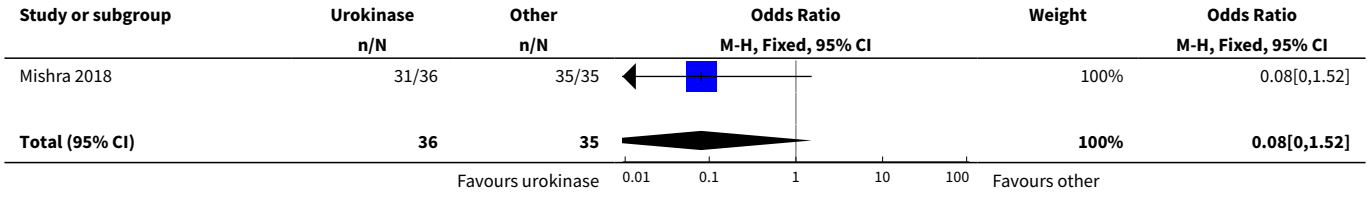
Comparison 27. Urokinase

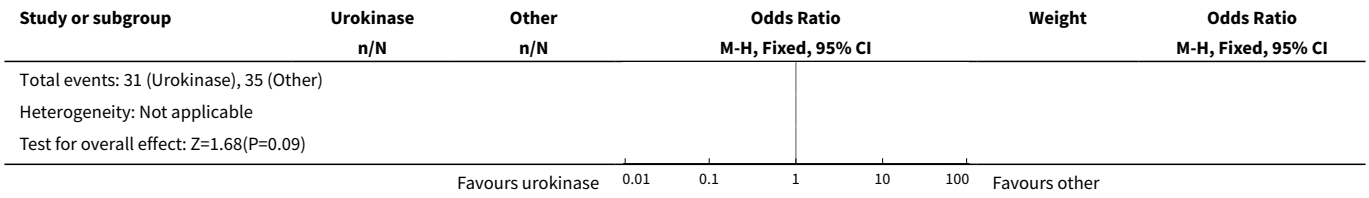
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pleurodesis failure rate	1	69	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [0.46, 3.34]
2 Mortality	1	71	Odds Ratio (M-H, Fixed, 95% CI)	0.08 [0.00, 1.52]

Analysis 27.1. Comparison 27 Urokinase, Outcome 1 Pleurodesis failure rate.



Analysis 27.2. Comparison 27 Urokinase, Outcome 2 Mortality.

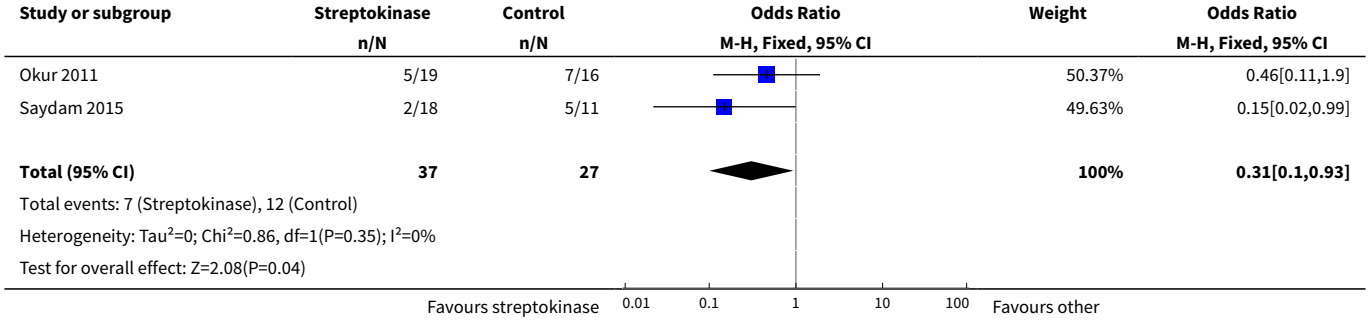




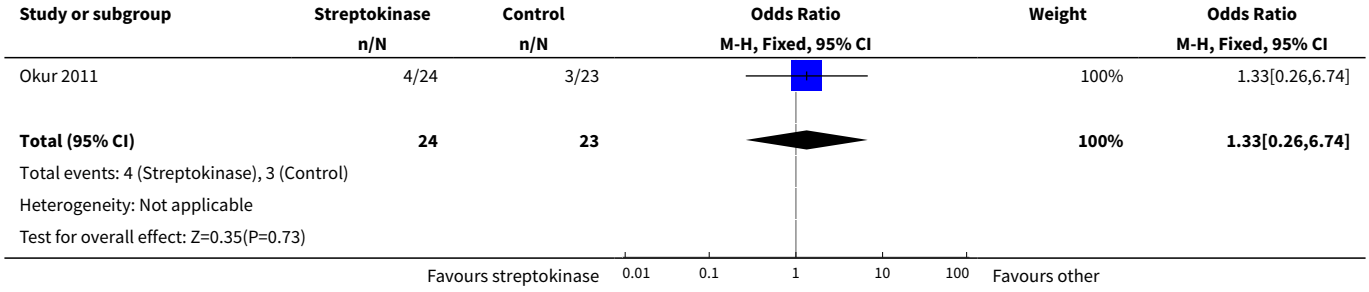
Comparison 28. Streptokinase

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pleurodesis failure rate	2	64	Odds Ratio (M-H, Fixed, 95% CI)	0.31 [0.10, 0.93]
2 Pain	1	47	Odds Ratio (M-H, Fixed, 95% CI)	1.33 [0.26, 6.74]

Analysis 28.1. Comparison 28 Streptokinase, Outcome 1 Pleurodesis failure rate.



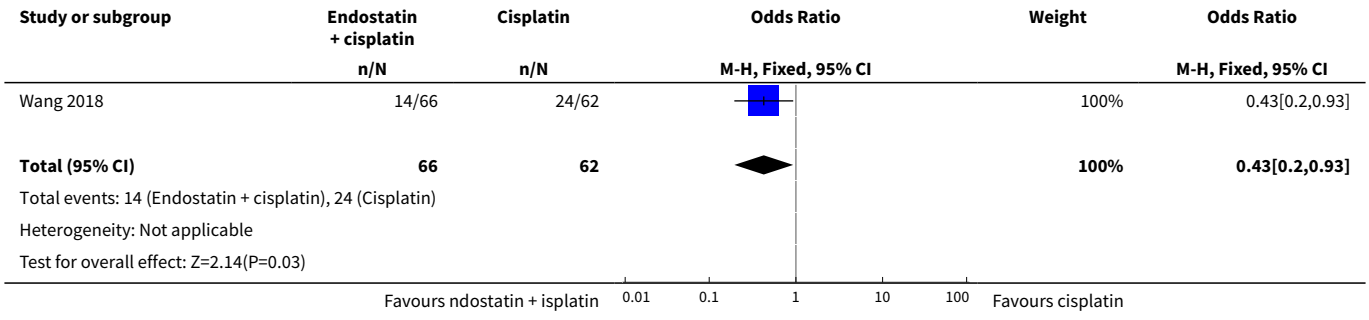
Analysis 28.2. Comparison 28 Streptokinase, Outcome 2 Pain.



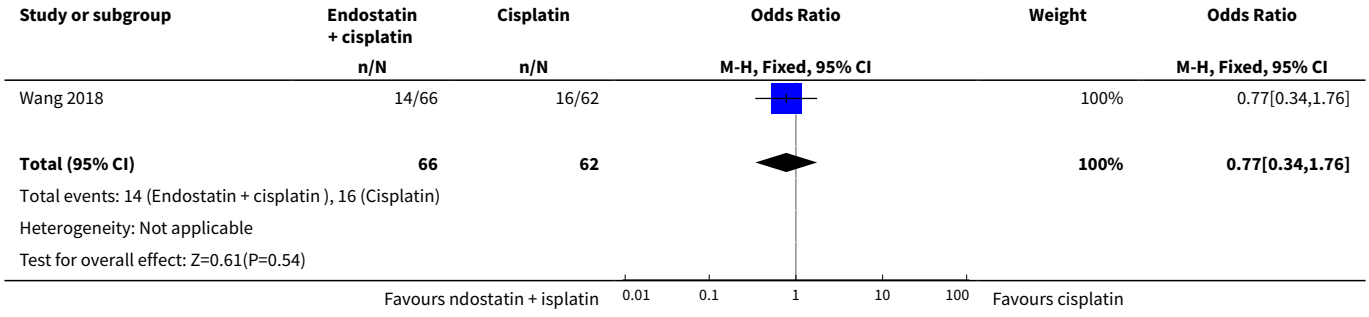
Comparison 29. Endostatin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pleurodesis failure rate	1	128	Odds Ratio (M-H, Fixed, 95% CI)	0.43 [0.20, 0.93]
2 Mortality	1	128	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.34, 1.76]

Analysis 29.1. Comparison 29 Endostatin, Outcome 1 Pleurodesis failure rate.



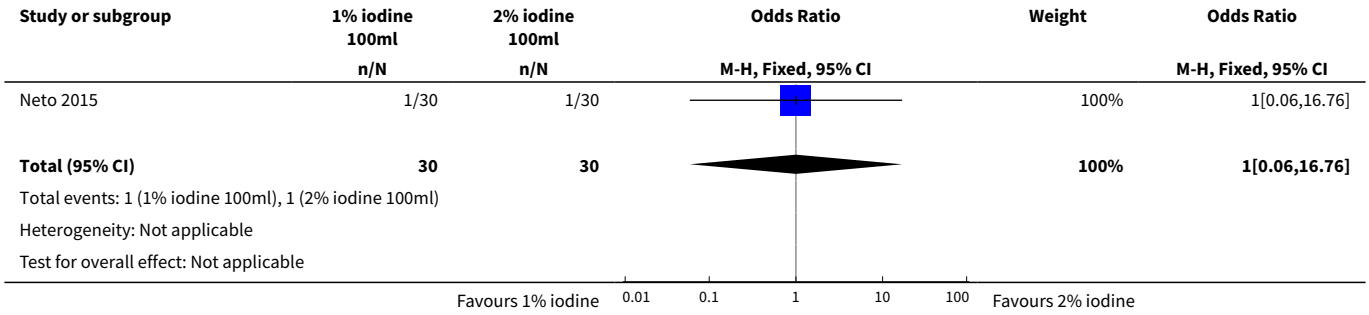
Analysis 29.2. Comparison 29 Endostatin, Outcome 2 Mortality.



Comparison 30. Dose of iodine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pleurodesis failure rate	1	60	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 16.76]

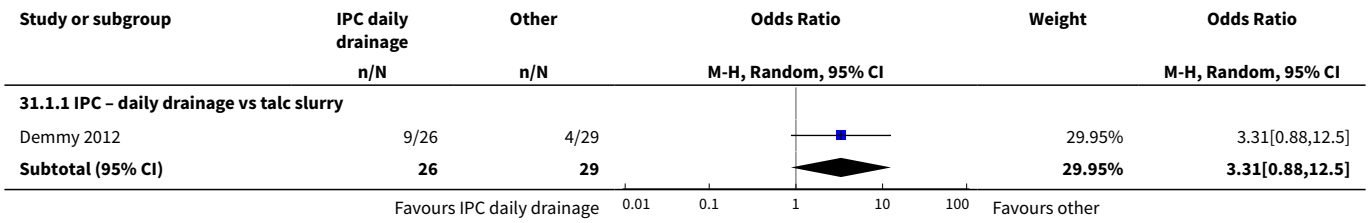
Analysis 30.1. Comparison 30 Dose of iodine, Outcome 1 Pleurodesis failure rate.

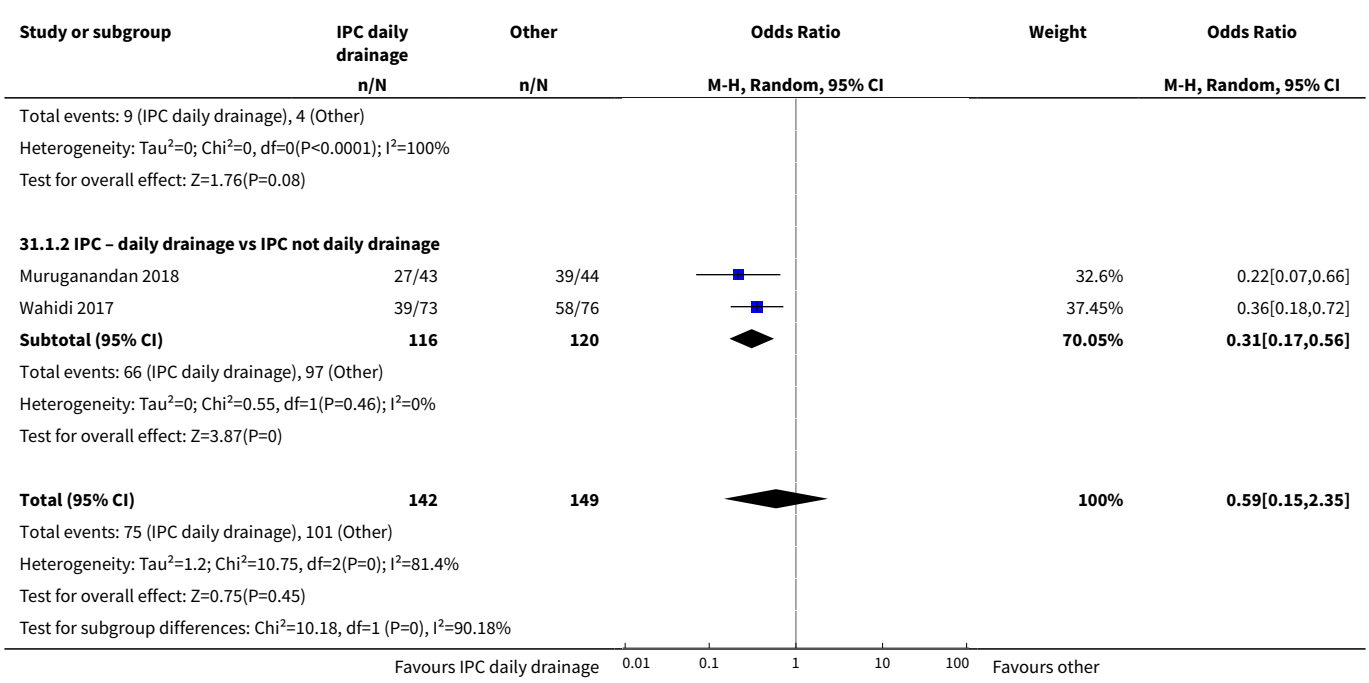


Comparison 31. Indwelling pleural catheter (IPC) – daily drainage

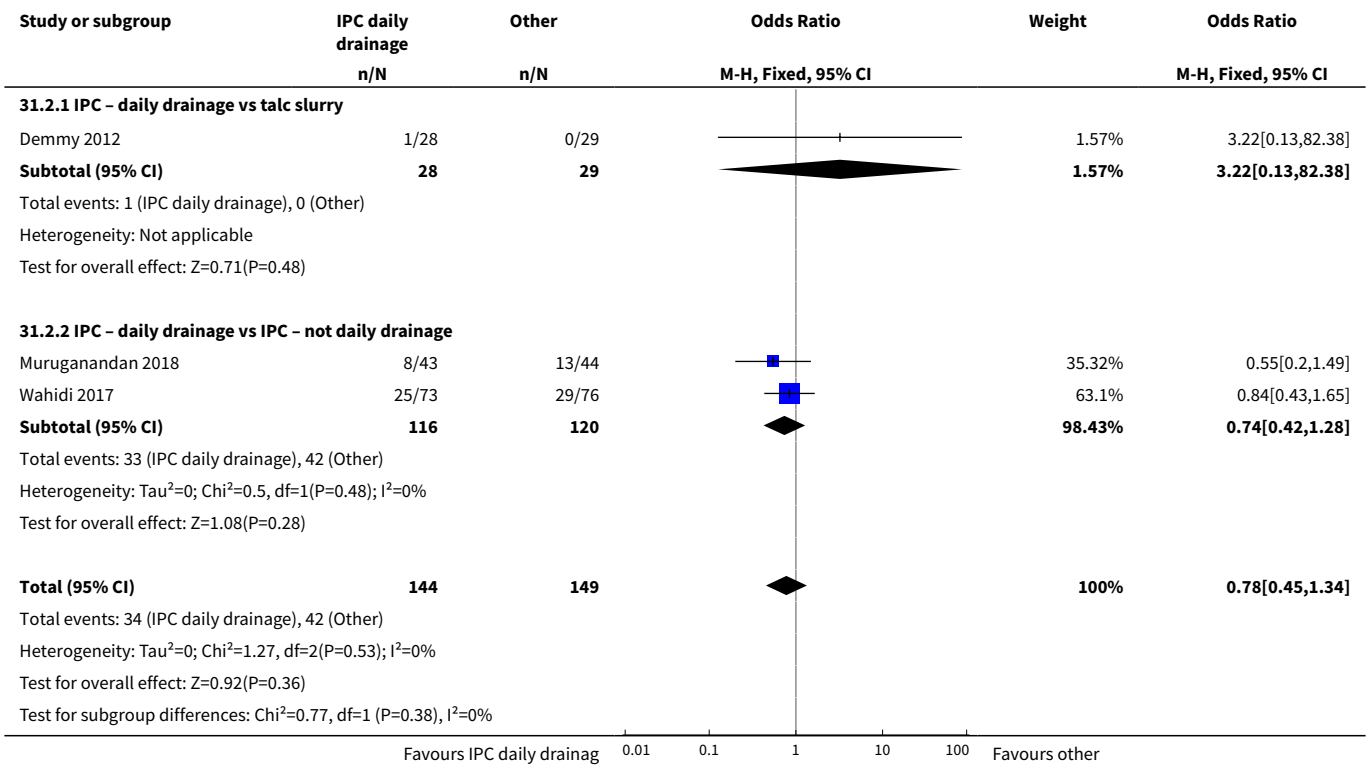
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Pleurodesis failure rate	3	291	Odds Ratio (M-H, Random, 95% CI)	0.59 [0.15, 2.35]
1.1 IPC – daily drainage vs talc slurry	1	55	Odds Ratio (M-H, Random, 95% CI)	3.31 [0.88, 12.50]
1.2 IPC – daily drainage vs IPC not daily drainage	2	236	Odds Ratio (M-H, Random, 95% CI)	0.31 [0.17, 0.56]
2 Pain	3	293	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.45, 1.34]
2.1 IPC – daily drainage vs talc slurry	1	57	Odds Ratio (M-H, Fixed, 95% CI)	3.22 [0.13, 82.38]
2.2 IPC – daily drainage vs IPC – not daily drainage	2	236	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.42, 1.28]
3 Mortality	3	293	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.55, 1.53]
3.1 IPC – daily drainage vs talc slurry	1	57	Odds Ratio (M-H, Fixed, 95% CI)	1.70 [0.56, 5.17]
3.2 IPC – daily drainage vs IPC – not daily drainage	2	236	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.43, 1.38]

Analysis 31.1. Comparison 31 Indwelling pleural catheter (IPC) – daily drainage, Outcome 1 Pleurodesis failure rate.

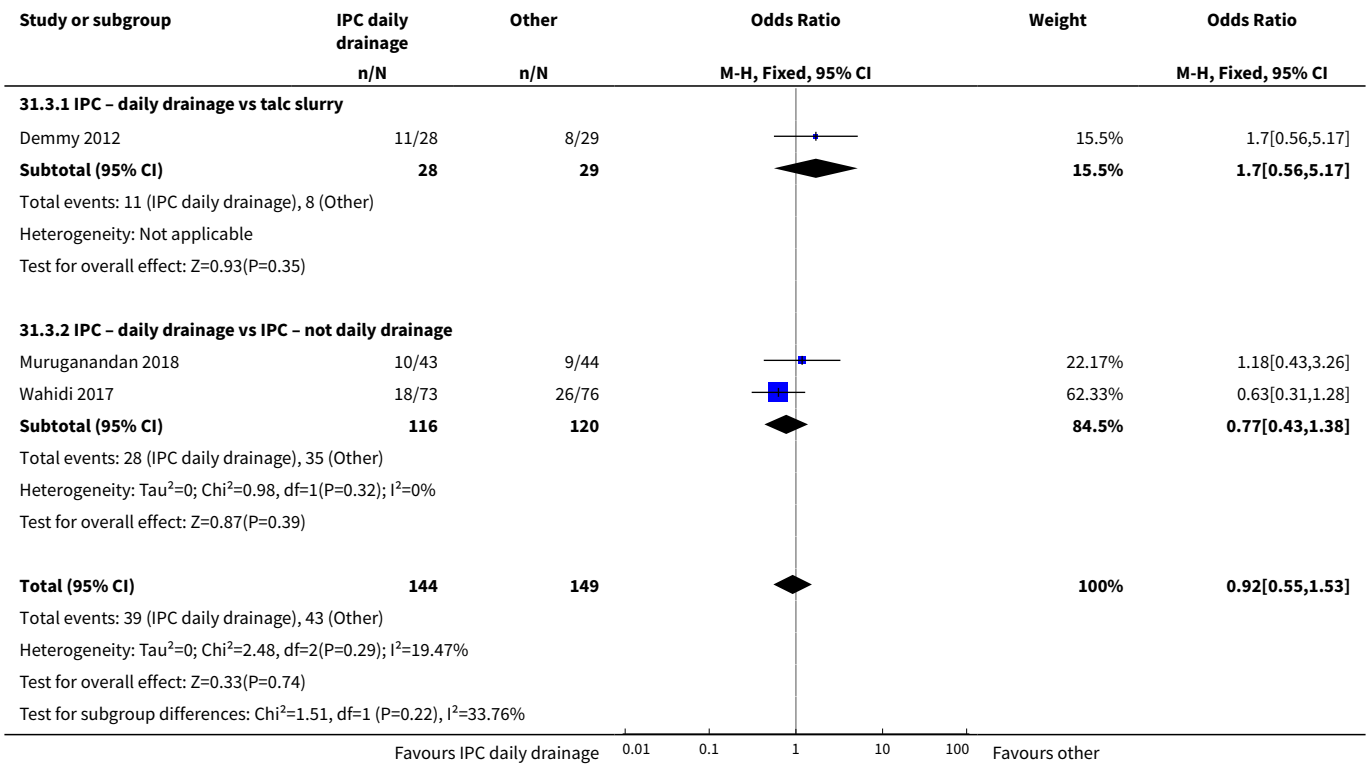




Analysis 31.2. Comparison 31 Indwelling pleural catheter (IPC) – daily drainage, Outcome 2 Pain.



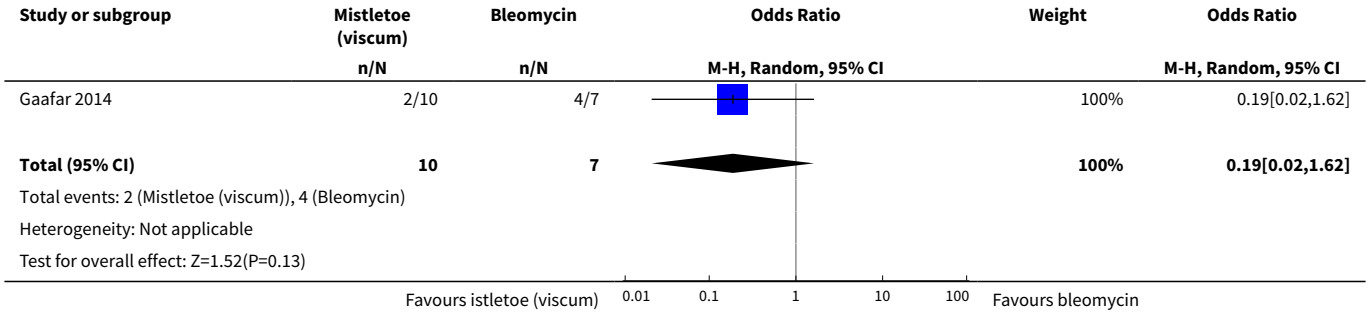
Analysis 31.3. Comparison 31 Indwelling pleural catheter (IPC) – daily drainage, Outcome 3 Mortality.



Comparison 32. Mistletoe (viscum)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pleurodesis failure rate	1	17	Odds Ratio (M-H, Random, 95% CI)	0.19 [0.02, 1.62]

Analysis 32.1. Comparison 32 Mistletoe (viscum), Outcome 1 Pleurodesis failure rate.



ADDITIONAL TABLES

Table 1. Direct meta-analysis of pleurodesis failure using the random-effects model showing the odds ratios (95% CI) of the rows compared to the columns

	Adriamycin	Autologous blood	Bleomycin	*C parvum*	Doxycycline	IFN	IPC – daily drainage	IPC – not daily drainage	Iodine	Mepacrine	Mitoxantrone	Mustine	Placebo	Silver nitrate	TMP	Talc poudrage	Talc slurry	Talc via IPC	Tetracycline
Autologous blood	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	/	NA	/
Bleomycin	NA	NA	NA	/	/	/	NA	NA	/	/	/	NA	NA	NA	NA	/	/	NA	/
C parvum	NA	NA	0.55 (0.01 to 57.48); n = 2; Tau^2 = 10.59; I^2 = 94%	NA	/	NA	NA	NA	NA	NA	NA	/	NA	NA	NA	NA	NA	NA	/
Doxycycline	NA	NA	0.67 (0.24 to 1.86); n = 2; Tau^2 = 0; I^2 = 0%	1.91 (0.43 to 8.48); n = 1	NA	NA	NA	/	NA	NA	NA	NA	NA	NA	NA	/	NA	NA	NA
IFN	NA	NA	**3.25 (1.54 to 6.89); n = 1**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
IPC – daily drainage	NA	NA	NA	NA	NA	NA	NA	/	NA	NA	NA	NA	NA	NA	NA	NA	/	NA	NA
IPC – not daily drainage	NA	NA	NA	NA	**4.28 (1.59 to 11.54); n = 1**	NA	**3.23 (1.79 to 5.85); n = 2; Tau^2 = 0; I^2 = 0%**	NA	NA	NA	NA	NA	NA	NA	NA	NA	/	/	NA
Iodine	NA	NA	0.65 (0.22 to 1.96); n = 2; Tau^2 = 0.16; I^2 = 25%	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	/	/	NA
Mepacrine	NA	NA	**0.16 (0.03 to 0.89); n = 1**	NA	NA	NA	NA	NA	NA	NA	/	NA	/	NA	NA	NA	/	NA	/

Table 1. Direct meta-analysis of pleurodesis failure using the random-effects model showing the odds ratios (95% CI) of the rows compared to the columns *(Continued)*

Mistletoe (viscum)	NA	NA	0.19 (0.02 to 1.62); n = 1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA NA
Mitoxantrone	NA	NA	**3.18 (1.17 to 8.65); n = 1**	NA	NA	NA	NA	NA	NA	7.61 (0.35to 163.82); n = 1	NA	NA	/	NA	NA	NA	NA	NA NA
Mustine	2.71 (0.1 to 74.98); n = 1	NA	NA	**10.80 (1.64 to 70.93); n = 1**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	/	NA	NA /
Placebo	NA	NA	NA	NA	NA	NA	NA	NA	NA	**14.4 (1.37 to 150.81); n = 1**	1.33 (0.56 to 3.17); n = 1	NA	NA	NA	NA	NA	/	NA /
Silver nitrate	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	/	NA /
TMP	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	/	NA NA
Talc poudrage	NA	NA	**0.1 (0.02 to 0.48); n = 2; Tau^2 = 0; I^2 = 0**	NA	**0.02 (0.00 to 0.47); n = 1**	NA	NA	NA	0.57 (0.08 to 3.80); n = 1	NA	NA	**0.13 (0.02 to 0.71); n = 1**	NA	NA	NA	NA	/	NA /
Talc slurry	NA	0.69 (0.24 to 1.95); n = 1	0.82 (0.37 to 1.82); n = 5; Tau^2 = 0.1; I^2 = 12%	NA	NA	NA	0.30 (0.08 to 1.14); n = 1	**0.18 (0.07 to 0.45); n = 2; Tau^2 = 0.26; I^2 = 61%**	0.85 (0.24 to 3.08); n = 2; Tau^2 = 0; I^2 = 0%	0.48 (0.14 to 1.60); n = 1	NA	NA	0.07 (0.00 to 1.51); n = 1	5.82 (0.21 to 158.82); n = 1	2.28 (0.83 to 6.23); n = 2; Tau^2 = 0;	1.24 (0.92 to 1.65); n = 4; Tau = 0; $I^2$2 = 0%	NA	NA /

Table 1. Direct meta-analysis of pleurodesis failure using the random-effects model showing the odds ratios (95% CI) of the rows compared to the columns *(Continued)*

														I^2 = 0%					
Talc via IPC	NA	NA	NA	NA	NA	NA	NA	**0.36 (0.18 to 0.73); n = 1**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Tetracycline	0.90 (0.05 to 16.59); n = 1	0.71 (0.14 to 3.60); n = 1	**2.00 (1.07 to 3.75); n = 5; Tau^2 = 0; I^2 = 0%**	3.18 (0.52 to 19.64); n = 1	NA	NA	NA	NA	NA	1.60 (0.12 to 20.99); n = 1	NA	0.37 (0.10 to 1.35); n = 2; Tau^2 = 0; I^2 = 0%	0.30 (0.05 to 1.94); n = 1	0.60 (0.15 to 2.47); n = 1	NA	**12.10 (1.32 to 111.30); n = 1**	0.78 (0.19 to 3.13); n = 1	NA	NA
Triethyl-enethiophos-phoramide	NA	NA	NA	NA	NA	NA	NA	NA	NA	**4.95 (1.02 to 24.10); n = 1**	NA	NA	0.34 (0.03 to 3.69); n = 1	NA	NA	NA	NA	NA	NA

* Indicates that the comparison included a three-arm study.

Results that are significant at the conventional level of P ≤ 0.05 are in bold.

/ indicates the odds ratio is already expressed elsewhere in the table comparing the interventions the other way around.

IFN: interferon; IPC: indwelling pleural catheter; n: number of studies included in the pair-wise comparison; NA: no direct pair-wise comparison available; TMP: thoracoscopic mechanical pleurodesis.

Table 2. Results of network meta-analysis for pleurodesis failure showing the odds ratios (95% Cr-I) of the agents in the rows compared to the agents in the columns

	Adri-amycin	Autol-ogous blood	Bleomycin	*C parvum*	Doxycy-cline	IFN	IPC – daily drainage	IPC – not daily drainage	Io-dine	Mepacrine	Mistle-toe (vis-cum)	Mi-tox-antrone	Mus-tine	Place-bo	Sil-ver ni-trate	TMP	Talc pou	Talc slurr-y	Talc via IPC	Tetra cy-cline

Table 2. Results of network meta-analysis for pleurodesis failure showing the odds ratios (95% Cr-I) of the agents in the rows compared to the agents in the columns *(Continued)*

Autologous blood	1.16 (0.02 to 101.8)	NA	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
Bleomycin	1.17 (0.02 to 83.72)	1.02 (0.22 to 4.72)	NA	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
C parvum	0.65 (0.01 to 49.54)	0.56 (0.09 to 3.38)	0.56 (0.18 to 1.60)	NA	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
Doxycycline	1.32 (0.02 to 107.3)	1.14 (0.19 to 7.07)	1.12 (0.37 to 3.51)	2.02 (0.53 to 8.43)	NA	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
IFN	3.93 (0.05 to 379)	3.39 (0.35 to 33.19)	3.34 (0.63 to 18.08)	6 (0.85 to 45.87)	2.98 (0.39 to 22.38)	NA	/	/	/	/	/	/	/	/	/	/	/	/	/	/
IPC – daily drainage	1.25 (0.02 to 111.4)	1.10 (0.16 to 7.49)	1.08 (0.26 to 4.46)	1.94 (0.36 to 11.11)	0.96 (0.20 to 4.53)	0.32 (0.04 to 2.90)	NA	/	/	/	/	/	/	/	/	/	/	/	/	/
IPC – not daily drainage	3.93 (0.06 to 325.5)	3.43 (0.60 to 19.68)	3.39 (1.10 to 10.68)	**6.09 (1.44 to 27.74)**	3.02 (0.85 to 10.54)	1.01 (0.13 to 7.78)	**3.14 (1.07 to 9.35)**	NA	/	/	/	/	/	/	/	/	/	/	/	/
Iodine	0.63 (0.01 to 49.04)	0.55 (0.09 to 3.16)	0.54 (0.18 to 1.54)	0.98 (0.22 to 4.29)	0.48 (0.11 to 2.05)	0.16 (0.02 to 1.15)	0.50 (0.09 to 2.53)	**0.16 (0.04 to 0.65)**	NA	/	/	/	/	/	/	/	/	/	/	/
Mepacrine	0.48 (0.01 to 38.24)	0.41 (0.06 to 2.59)	0.41 (0.11 to 1.37)	0.73 (0.14 to 3.64)	0.36 (0.07 to 1.74)	0.12 (0.01 to 0.94)	0.38 (0.06 to 2.13)	**0.12 (0.02 to 0.55)**	0.75 (0.15 to 3.54)	NA	/	/	/	/	/	/	/	/	/	/
Mistletoe	0.18 (0.001 to 26.42)	0.15 (0.006 to 3.25)	0.15 (0.008 to 2.15)	0.27 (0.01 to 4.85)	0.14 (0.006 to 2.39)	0.05 (0.002	0.14 (0.005	**0.05 (0.002 to 0.8)**	0.28 (0.01	0.38 (0.02	NA	/	/	/	/	/	/	/	/	/

Table 2. Results of network meta-analysis for pleurodesis failure showing the odds ratios (95% Cr-I) of the agents in the rows compared to the agents in the columns *(Continued)*

(viscum)						to 1.03)	to 2.82)		to 4.96)	to 7.19)									
Mitoxantrone	5.62 (0.08 to 485.4)	4.77 (0.65 to 38.43)	4.7 (1.21 to 20.78)	**8.5 (1.58 to 53.76)**	4.22 (0.73 to 25.95)	1.4 (0.17 to 13.52)	4.38 (0.64 to 32.63)	1.39 (0.25 to 8.62)	**8.71 (1.62 to 54.36)**	**11.54 (2.37 to 70.61)**	**31.44 (1.59 to 841.9)**	NA	/	/	/	/	/	/	/
Mustine	3.41 (0.06 to 246.5)	2.96 (0.40 to 21.37)	2.92 (0.70 to 12.46)	**5.26 (1.14 to 25.88)**	2.6 (0.46 to 14.5)	0.88 (0.09 to 7.84)	2.72 (0.39 to 18.45)	0.86 (0.15 to 4.86)	5.41 (0.98 to 30.75)	**7.2 (1.2 to 46.5)**	19.36 (0.93 to 502.7)	0.62 (0.08 to 4.26)	NA	/	/	/	/	/	/
Placebo	8.53 (0.13 to 713.2)	7.21 (0.99 to 57.97)	7.09 (1.74 to 33.09)	**12.82 (2.33 to 82.88)**	**6.33 (1.09 to 40.23)**	2.12 (0.24 to 21)	6.58 (0.98 to 49.75)	2.09 (0.38 to 13.13)	**13.15 (2.39 to 83.82)**	**17.44 (3.70 to 101.1)**	**47.4 (2.32 to 1298)**	1.51 (0.37 to 6.14)	2.43 (0.35 to 18.64)	NA	/	/	/	/	/
Silver nitrate	1.28 (0.02 to 123.1)	1.10 (0.09 to 11.67)	1.08 (0.13 to 8.03)	1.96 (0.20 to 17.79)	0.96 (0.09 to 9.07)	0.33 (0.02 to 4.24)	1.0 (0.08 to 10.47)	0.32 (0.03 to 2.9)	1.999 (0.2 to 18.56)	2.67 (0.26 to 26.41)	7.21 (0.24 to 243.8)	0.23 (0.02 to 2.44)	0.37 (0.03 to 3.75)	0.15 (0.01 to 1.59)	NA	/	/	/	/
TMP	0.22 (0.003 to 21.16)	0.19 (0.02 to 1.61)	0.19 (0.03 to 1.04)	0.34 (0.05 to 2.47)	0.17 (0.02 to 1.15)	**0.06 (0.005 to 0.61)**	0.17 (0.02 to 1.26)	**0.06 (0.008 to 0.34)**	0.35 (0.05 to 2.34)	0.46 (0.06 to 3.52)	1.23 (0.05 to 36.67)	**0.04 (0.004 to 0.33)**	**0.06 (0.007 to 0.55)**	**0.03 (0.003 to 0.22)**	0.17 (0.01 to 2.46)	NA	/	/	/
Talc poudrage	0.26 (0.004 to 18.64)	0.23 (0.04 to 1.05)	**0.22 (0.08 to 0.50)**	0.4 (0.10 to 1.41)	**0.2 (0.05 to 0.64)**	**0.07 (0.009 to 0.40)**	**0.21 (0.04 to 0.82)**	**0.07 (0.02 to 0.20)**	0.41 (0.12 to 1.29)	0.55 (0.13 to 2.18)	1.45 (0.09 to 30.25)	**0.05 (0.008 to 0.21)**	**0.08 (0.02 to 0.31)**	**0.03 (0.01 to 0.14)**	0.2 (0.03 to 1.7)	1.19 (0.19 to 6.77)	NA	/	/
Talc slurry	0.52 (0.01 to 38.37)	0.45 (0.10 to 1.93)	**0.45 (0.21 to 0.91)**	0.8 (0.24 to 2.76)	0.4 (0.12 to 1.24)	**0.13 (0.02 to 0.81)**	0.41 (0.12 to 1.43)	**0.13 (0.05 to 0.34)**	0.82 (0.28 to 2.47)	1.1 (0.32 to 4.02)	2.93 (0.19 to 60)	**0.10 (0.02 to 0.41)**	**0.15 (0.03 to 0.66)**	**0.06 (0.01 to 0.27)**	0.41 (0.05 to 3.43)	2.38 (0.5 to 11.99)	2.00 (0.98 to 4.79)	NA	/
Talc via IPC	1.41 (0.02 to 153.1)	1.22 (0.11 to 13.48)	1.2 (0.16 to 9.03)	2.17 (0.25 to 20.7)	1.08 (0.13 to 8.46)	0.36 (0.03 to 4.94)	1.12 (0.16 to 8.14)	0.36 (0.07 to 1.85)	2.22 (0.26 to 20.4)	2.96 (0.32 to 30.36)	7.996 (0.29 to 276.8)	0.26 (0.02 to 2.74)	0.41 (0.04 to 4.61)	0.17 (0.01 to 1.81)	1.1 (0.07 to 20.18)	6.47 (0.56 to 79.51)	5.39 (0.77 to 46.83)	2.7 (0.41 to 18.65)	NA

Table 2. Results of network meta-analysis for pleurodesis failure showing the odds ratios (95% Cr-I) of the agents in the rows compared to the agents in the columns *(Continued)*

Tetracycline	1.52 (0.03 to 100.3)	1.32 (0.28 to 5.82)	1.3 (0.60 to 2.73)	2.34 (0.72 to 7.62)	1.16 (0.31 to 4.01)	0.39 (0.06 to 2.36)	1.20 (0.26 to 5.33)	0.38 (0.1 to 1.31)	2.4 (0.7 to 8.26)	3.19 (0.86 to 12.47)	8.54 (0.54 to 176.8)	0.28 (0.06 to 1.18)	0.45 (0.11 to 1.73)	**0.18 (0.04 to 0.76)**	1.2 (0.18 to 8.71)	**6.95 (1.15 to 43.49)**	**5.85 (2.2 to 16.87)**	**2.91 (1.2 to 7.01)**	1.08 (0.13 to 8.3)	NA
Triethylenethiophosphoramide	2.63 (0.03 to 310.8)	2.23 (0.15 to 34.02)	2.21 (0.22 to 23.08)	3.98 (0.32 to 52.04)	1.96 (0.15 to 25.22)	0.66 (0.04 to 11.71)	2.05 (0.15 to 28.96)	0.65 (0.05 to 8.08)	4.08 (0.34 to 52.3)	5.41 (0.69 to 47.85)	14.73 (0.42 to 634.9)	0.47 (0.04 to 5.52)	0.75 (0.05 to 11.16)	0.31 (0.03 to 3.16)	2.04 (0.1 to 45.98)	11.87 (0.71 to 208.7)	9.95 (0.95 to 121.5)	4.95 (0.49 to 52.66)	1.83 (0.09 to 38.16)	1.7 (0.16 to 18.73)

Results that are significant at the conventional level of P < 0.05 are in bold.

/ indicates the odds ratio is already expressed elsewhere in the table comparing the interventions the other way around.

IFN: interferon; IPC: indwelling pleural catheter; NA: not applicable; TMP: thoracoscopic mechanical pleurodesis.

Table 3. Results for pleurodesis failure of the studies evaluating pleurodesis methods which were not included in the network meta-analysis

Study	Reason study excluded from network	Intrapleural agent or intervention 1	Pleurodesis failure rate for agent 1	Intrapleural agent or intervention 2	Pleurodesis failure rate for agent 2	OR (95% CI) of agent 1 compared with agent 2***
Du 2013	Lung cancer-specific therapy	Cisplatin and bevacizumab	6/36	Cisplatin	17/34	**0.20 (0.07 to 0.60)**
Emad 1996*	No pleurodesis failures in the combined group	Tetracycline**	3/19	Combined tetracycline and bleomycin	0/19	8.27 (0.40 to 172.05)
		Bleomycin**	2/19	Combined tetracycline and bleomycin	0/19	5.57 (0.25 to 124.19)
Ishida 2006*	Lung cancer-specific therapy	OK-432	8/17	Cisplatin	11/17	0.48 (0.12 to 1.92)
		OK-432	8/17	OK-432 and cisplatin	1/15	**12.44 (1.32 to 117.03)**
		Cisplatin	11/17	OK-432 and cisplatin	1/15	**25.67 (2.68 to 245.84)**
Kasahara 2006	Lung cancer-specific therapy	High-dose OK-432	5/19	Low-dose OK-432	3/19	1.90 (0.38 to 9.44)
Luh 1992	Lung cancer-specific therapy	OK-432	3/26	Mitomycin C	9/27	0.26 (0.06 to 1.11)
Maskell 2004	Two talc slurry preparations	Mixed-particle talc	3/14	Graded talc (particles > 20 µm)	2/14	1.64 (0.23 to 11.70)
Masuno 1991	Lung cancer-specific therapy	LC9018 and adriamycin	10/38	Adriamycin	23/38	**0.23 (0.09 to 0.62)**
Neto 2015	Comparison of different doses of iodine	1% iodine	1/30	2% iodine	1/30	1.00 (0.06 to 16.76)
Rintoul 2014	MPM specific surgical technique	Talc pleurodesis (slurry or poudrage)	25/62	VATS pleurectomy	24/60	0.88 (0.43 to 1.82)
Terra 2015*	Comparison of different doses of silver nitrate	90 mg silver nitrate	0/20	150 mg silver nitrate	0/20	Not estimable
		90 mg silver nitrate	0/20	180 mg silver nitrate	2/20	0.18 (0.01 to 4.01)
		150 mg silver nitrate	0/20	180 mg silver nitrate	2/20	0.19 (0.01 to 4.01)
Wang 2018	Lung cancer-specific therapy	Cisplatin + 45 mg endostatin	14/66	Cisplatin	24/62	**0.43 (0.2 to 0.93)**

Table 3. Results for pleurodesis failure of the studies evaluating pleurodesis methods which were not included in the network meta-analysis *(Continued)*

Yoshida 2007*	Lung cancer-specific therapy	OK-432	8/33	Bleomycin	11/35	0.70 (0.24 to 2.03)
		OK-432	8/33	Cisplatin and etoposide	10/34	0.77 (0.26 to 2.27)
		Bleomycin	11/35	Cisplatin and etoposide	10/34	1.10 (0.39 to 3.07)
Zhao 2009	Lung cancer specific therapy	rAd-p53 and cisplatin	3/17	Cisplatin	9/18	0.21 (0.05 to 1.01)

*Three-arm study.

**The results for the pair-wise comparison between tetracycline and bleomycin are included in the network meta-analysis.

***Results that are significant at the conventional level of P ≤ 0.05 are in bold.

CI: confidence interval; IPC: indwelling pleural catheter; MPM: malignant pleural mesothelioma; OR: odds ratio; VATS: video-assisted thoracoscopic surgery.

Table 4. Results for pleurodesis failure of the studies evaluating interventions to optimise pleurodesis which were not included in the network meta-analysis

Type of method to optimise pleurodesis	Study	Intervention 1	Pleurodesis failure rate for intervention 1	Intervention 2	Pleurodesis failure rate for intervention 2	OR (95% CI) of intervention 1 compared with intervention 2*
Mode of administration	Evans 1993	Tetracycline pleurodesis at the end of thoracoscopy	2/15	Tetracycline pleurodesis through an intercostal cannula	5/14	0.28 (0.04 to 1.76)
Chest tube size	Clementsen 1998	Small-bore chest drain	2/9	Large-bore chest drain	3/9	0.57 (0.07 to 4.64)
	Rahman 2015**	Small-bore chest drain	15/50	Large-bore chest drain	12/50	1.36 (0.56 to 3.30)
Type of analgesic agent	Rahman 2015**	NSAID	33/144	Opiate	30/150	1.19 (0.68 to 2.08)
Patient rotation	Mager 2002	Rotation after instillation of talc	2/10	No rotation after instillation of talc	1/10	2.25 (0.17 to 29.77)
Duration of drainage after administration of the sclerosant	Goodman 2006	Drain removed 24 hours after pleurodesis	2/16	Drain removed 72 hours after pleurodesis	4/19	0.54 (0.08 to 3.40)
	Villanueva 1994	Drain removal the day after pleurodesis	2/9	Drain removal when < 150 mL/day output	3/15	1.14 (0.15 to 8.59)

Table 4. Results for pleurodesis failure of the studies evaluating interventions to optimise pleurodesis which were not included in the network meta-analysis *(Continued)*

	Yildirim 2005	Fractionated dose oxytetracycline (4 divided doses at 6-hourly intervals)	0/12	Single bedside instillation of oxytetracycline	2/8	0.10 (0.00 to 2.50)
Duration of drainage prior to administration of the sclerosant	Ozkul 2014	Early instillation of talc slurry after drain insertion	5/40	Instillation of talc slurry when daily drainage from chest tube < 300 mL/day	6/39	0.79 (0.22 to 2.82)
Intrapleural fibrinolytics	Okur 2011	Intrapleural streptokinase	5/19	No intrapleural streptokinase	7/16	0.46 (0.11 to 1.90)
	Saydam 2015	Intrapleural streptokinase	2/18	50 mL saline placebo	5/11	0.15 (0.02 to 0.99)
	Mishra 2018	Intrapleural urokinase	13/35	Placebo	11/34	1.24 (0.46 to 3.34)

*Results that are significant at the conventional level of P ≤ 0.05 are in bold.

**Studies with more than 2 comparison arms.

CI: confidence interval; NSAID: non-steroidal anti-inflammatory drug; OR: odds ratio.

Table 5. Results of network meta-analysis for causing fever showing odds ratios (95% CI) of the agents in rows compared to the agents in columns

	Autologous blood	Bleomycin	*C parvum*	Doxycycline	IPC – not daily drainage	Iodine	Mepacrine	Mitoxantrone	Placebo	Silver nitrate	Talc poudrage	Talc slurry	Tetracycline
Bleomycin	11.53 (0.70 to 205.20)	NA	/	/	/	/	/	/	/	/	/	/	/
C parvum	**67.29 (2.44 to 2021)**	5.82 (0.82 to 41.96)	NA	/	/	/	/	/	/	/	/	/	/
Doxycycline	4.21 (0.11 to 157)	0.37 (0.03 to 3.49)	**0.063 (0.005 to 0.73)**	NA	/	/	/	/	/	/	/	/	/
IPC – not daily drainage	2.01 (0.01 to 401.30)	0.17 (0.002 to 15.18)	0.03 (0.00 to 2.93)	0.48 (0.01 to 23.3)	NA	/	/	/	/	/	/	/	/
Iodine	3.67 (0.14 to 101.60)	0.32 (0.03 to 3.09)	0.05 (0.003 to 1.05)	0.87 (0.03 to 22.91)	1.82 (0.01 to 281.7)	NA	/	/	/	/	/	/	/
Mepacrine	**53.76 (1.45 to 2277)**	4.65 (0.38 to 62.22)	0.80 (0.04 to 19.28)	12.72 (0.45 to 422.1)	26.79 (0.16 to 4813)	14.68 (0.52 to 452.2)	NA	/	/	/	/	/	/
Mitoxantrone	3.90 (0.05 to 251.30)	0.34 (0.01 to 7.14)	0.06 (0.001 to 2.12)	0.92 (0.02 to 43.82)	1.91 (0.01 to 434.1)	1.06 (0.02 to 47.81)	0.07 (0.002 to 2.53)	NA	/	/	/	/	/
Placebo	0.46 (0.003 to 46.52)	0.04 (0.00 to 1.55)	**0.01 (0.00 to 0.42)**	0.12 (0.001 to 8.56)	0.23 (0.001 to 73.08)	0.13 (0.001 to 9.2)	**0.01 (0.00 to 0.34)**	0.12 (0.01 to 2.35)	NA	/	/	/	/
Silver nitrate	0.28 (0.006 to 11.75)	**0.02 (0.001 to 0.47)**	**0.00 (0.00 to 0.13)**	0.07 (0.002 to 2.85)	0.14 (0.001 to 28.98)	0.08 (0.002 to 2.27)	**0.01 (0.00 to 0.22)**	0.07 (0.00 to 5.58)	0.62 (0.01 to 93.78)	NA	/	/	/
Talc poudrage	4.41 (0.16 to 120.20)	0.38 (0.04 to 3.72)	0.07 (0.003 to 1.25)	1.04 (0.04 to 27.59)	2.18 (0.01 to 330.6)	1.19 (0.10 to 14.14)	0.08 (0.003 to 2.28)	1.13 (0.02 to 58.56)	9.57 (0.13 to 1083)	15.42 (0.52 to 519.40)	NA	/	/

Table 5. Results of network meta-analysis for causing fever showing odds ratios (95% CI) of the agents in rows compared to the agents in columns *(Continued)*

Talc slurry	4.93 (0.34 to 74.37)	0.43 (0.08 to 2.22)	**0.07 (0.01 to 0.88)**	1.17 (0.07 to 20.57)	2.45 (0.02 to 289)	1.35 (0.17 to 10.59)	0.09 (0.005 to 1.69)	1.26 (0.04 to 47.32)	10.65 (0.20 to 931)	**17.33 (1.07 to 336.40)**	1.12 (0.15 to 9.12)	NA /
Tetracycline	4.37 (0.29 to 69.73)	0.38 (0.09 to 1.62)	**0.07 (0.01 to 0.60)**	1.04 (0.08 to 15.55)	2.16 (0.02 to 234.9)	1.19 (0.10 to 15.28)	0.08 (0.01 to 1.08)	1.12 (0.04 to 37.43)	9.45 (0.20 to 734.3)	15.26 (0.88 to 331.70)	0.1 (0.08 to 13.05)	0.89 (0.13 to 5.81)	NA
Triethylenethiophosphoramide	2.88 (0.02 to 523.50)	0.25 (0.003 to 20.37)	0.04 (0.00 to 5.12)	0.69 (0.01 to 102.5)	1.42 (0.003 to 786.5)	0.78 (0.006 to 110.5)	0.05 (0.001 to 2.24)	0.72 (0.01 to 118.3)	5.84 (0.07 to 1361)	10.11 (0.06 to 2164)	0.65 (0.005 to 94.31)	0.58 (0.01 to 61.79)	0.66 (0.01 to 58.19)

Results that are significant at the conventional level of P ≤ 0.05 are in bold.

/ indicates the odds ratio is already expressed elsewhere in the table comparing the interventions the other way round.

CI: confidence interval; IPC: indwelling pleural catheter; NA: not applicable.

APPENDICES

Appendix 1. Search strategies

CENTRAL (the Cochrane library)

#1 MeSH descriptor: [Pleural Effusion] explode all trees

#2 (pleura* near/5 (effusion* or fluid*)):ti,ab,kw (Word variations have been searched)

#3 #1 or #2

#4 MeSH descriptor: [Neoplasms] explode all trees

#5 (cancer* or tumor* or tumour* or neoplas* or carcinom* or malignan*):ti,ab,kw (Word variations have been searched)

#6 #4 or #5

#7 #3 and #6

MEDLINE (Ovid)

1 exp Pleural Effusion/

2 (pleura* adj5 (effusion* or fluid*)).mp.

3 or/1-2

4 exp Neoplasms/

5 (cancer* or tumor* or tumour* or neoplas* or carcinom* or malignan*).mp.

6 or/4-5

7 randomized controlled trial.pt.

8 controlled clinical trial.pt.

9 randomized.ab.

10 placebo.ab.

11 clinical trials as topic.sh.

12 randomly.ab.

13 trial.ti.

14 7 or 8 or 9 or 10 or 11 or 12 or 13

15 3 and 6 and 14

Embase (Ovid)

1 exp Pleural Effusion/

2 (pleura* adj5 (effusion* or fluid*)).mp.

3 or/1-2

4 exp neoplasm/

5 (cancer* or tumor* or tumour* or neoplas* or carcinom* or malignan*).mp.

6 or/4-5

7 random$.tw.

8 factorial$.tw.

9 crossover$.tw.

10 cross over$.tw.

11 cross-over$.tw.

12 placebo$.tw.

13 (doubl$ adj blind$).tw.

14 (singl$ adj blind$).tw.

15 assign$.tw.

16 allocat$.tw.

17 volunteer$.tw.

18 Crossover Procedure/

19 double-blind procedure.tw.

20 Randomized Controlled Trial/

21 Single Blind Procedure/

22 or/7-21

23 (animal/ or nonhuman/) not human/

24 22 not 23

25 3 and 6 and 24

Web of Science (ISI) SSCI & SCI

#11 #10 AND #2

#10 #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3

#9 Topic=((((("random* allocat*") or ("random* assign*"))))

#8 Topic=(((crossover)))

#7 Topic=((((("tripl* blind*") or ("tripl* mask*"))))

#6 Topic=((((("trebl* blind*") or ("trebl* mask*"))))

#5 Topic=((((("doubl* blind*") or ("doubl* mask*"))))

#4 Topic=((((("singl* blind*") or ("singl* mask*"))))

#3 Topic=((((("clin* trial*"))))

#2 Topic=((pleura* near/5 (effusion* or fluid*))) AND Topic=((cancer* or tumor* or tumour* or neoplas* or carcinom* or malignan*))

#1 Topic=((pleura* near/5 (effusion* or fluid*)))

CINAHL (EBSCO)

S25 S18 AND S21 AND S24

S24 S22 OR S23

S23 (cancer* or tumor* or tumour* or neoplas* or carcinom* or malignan*)

S22 (MH "Neoplasms+")

S21 S19 OR S20

S20 (pleura* N5 (effusion* or fluid*))

S19 (MH "Pleural Effusion+")

S18 S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17

S17 (allocat* random*)

S16 (MH "Quantitative Studies")

S15 (MH "Placebos")

S14 placebo*

S13 (random* allocat*)

S12 (MH "Random Assignment")

S11 (Randomi?ed control* trial*)

S10 (singl* blind*) or (doubl* blind*) or (tripl* blind*) or (trebl* blind*) or (trebl* mask*) or (tripl* mask*) or (doubl* mask*) or (singl* mask*)

S9 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8

S8 (allocat* random*)

S7 (MH "Quantitative Studies")

S6 (MH "Placebos")

S5 placebo*

S4 (random* allocat*)

S3 (MH "Random Assignment")

S2 (Randomi?ed control* trial*)

S1 (singl* blind*) or (doubl* blind*) or (tripl* blind*) or (trebl* blind*) or (trebl* mask*) or (tripl* mask*) or (doubl* mask*) or (singl* mask*)

Appendix 2. Distribution of study population characteristics across all the included studies and within each pair-wise comparison

Potential effect modifiers		Total n (%)	Bleomycin vs *C parvum* n (%)	Bleomycin vs doxycycline n (%)	Bleomycin vs iodine n (%)	Bleomycin vs talc poudrage n (%)	Bleomycin vs talc slurry n (%)	Bleomycin vs tetracycline n (%)	IPC daily drainage vs IPC –not daily drainage n (%)	IPC – not daily drainage vs talc slurry n (%)	Mustine vs tetracycline n (%)	Talc poudrage vs talc slurry n (%)	Talc slurry vs iodine n (%)	Talc slurry vs TMP n (%)
Number of studies	—	79	2	2	2	2	5	5	2	2	2	4	2	2
Cell types included	**All**	58 (73)	1 (50)	2 (100)	2 (100)	1 (50)	5 (100)	5 (100)	2 (100)	2 (100)	2 (100)	4 (100)	2 (100)	0
	Only breast	8 (10)	0	0	0	1 (50)	0	0	0	0	0	0	0	2 (100)
	Only lung	8 (10)	0	0	0	0	0	0	0	0	0	0	0	0
	Other	5 (6)	1 (50)	0	0	0	0	0	0	0	0	0	0	0
Trapped lung	**Excluded**	37 (47)	0	0	2 (100)	1 (50)	3 (60)	1 (20)	1 (50)	1 (50)	0	3 (75)	2 (100)	1 (50)
	Included	42 (53)	2 (100)	2 (100)	0	1 (50)	2 (40)	4 (80)	1 (50)	1 (50)	2 (100)	1 (25)	0	1 (50)
Drain size	**Unknown**	31 (39)	1 (50)	1 (50)	1 (50)	1 (50)	1 (20)	4 (80)	NA	NA	0	2 (50)	0	2 (100)
	Small (< 20-Fr)	14 (18)	1 (50)	1 (50)	0	1 (50)	1 (20)	0	NA	NA	1 (50)	0	0	0
	Large (≥ 20-Fr)	21 (27)	0	0	1 (50)	0	3 (60)	1 (20)	NA	NA	1 (50)	2 (50)	2 (100)	0
	Study comparing large with small drains	4 (5)	0	0	0	0	0	0	NA	NA	0	0	0	0
How was pleurodesis defined	**Clinicoradiological definition**	58 (73)	2 (100)	1 (50)	0	1 (50)	4 (80)	4 (80)	2 (100)	2 (100)	2 (100)	2 (50)	2 (100)	1 (50)

(Continued)

	Radiological recurrence only	22 (28)	0	1 (50)	2 (100)	1 (50)	1 (20)	1 (20)	0	0	0	2 (50)	0	1 (50)
Time point pleurodesis defined	**2–4 months**	31 (39)	1 (50)	1 (50)	0	1 (50)	1 (20)	2 (40)	2 (100)	0	2 (100)	2 (50)	0	1 (50)
	> 4–7 months	3 (4)	0	0	1 (50)	0	0	0	0	0	0	1 (25)	1 (50)	0
	> 11–12 months	4 (5)	0	0	0	0	0	0	0	2 (100)	0	0	0	1 (50)
	< 2 months	34 (42)	1 (50)	1 (50)	1 (50)	0	2 (40)	3 (60)	0	0	0	1 (25)	1 (50)	0
	Not stated	7 (9)	0	0	0	1 (50)	2 (40)	0	0	0	0	0	0	0

*If the study reported multiple time points, the one referred to here was that used in our primary analysis (according to our hierarchy of preferences (see Primary outcomes))

IPC: indwelling pleural catheter; n: number of participants; NA: not applicable; TMP: thoracoscopic mechanical pleurodesis

Appendix 3. Sensitivity analysis of the direct meta-analysis results for pleurodesis failure using the fixed-effect model showing odds ratios (95% CI) of the rows compared to the columns

	Adriamycin	Autologous blood	Bleomycin	*C parvum*	Doxycycline	IFN	IPC – daily drainage	IPC – not daily drainage	Iodine	Mepacrine	Mitoxantrone	Mustine	Placebo	Silver nitrate	TMP	Talc poudrage	Talc slurry	Talc via IPC	Tetracycline
Autologous blood	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	/	NA	/
Bleomycin	NA	NA	NA	/	/	/	NA	NA	/	/	/	NA	NA	NA	NA	/	/	NA	/
C parvum	NA	NA	0.72 (0.32 to 1.61); n = 2; Chi^2 = 17; I^2 = 94%	NA	/	NA	NA	NA	NA	NA	NA	/	NA	NA	NA	NA	NA	NA	/
Doxycycline	NA	NA	0.66 (0.24 to 1.83); Chi^2 = 0.22; I^2 = 0%	1.91 (0.43 to 8.48); n = 1	NA	NA	NA	/	NA	NA	NA	NA	NA	NA	NA	/	NA	NA	NA
IFN	NA	NA	**3.25 (1.54 to 6.89); n = 1**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
IPC –daily drainage	NA	NA	NA	NA	NA	NA	NA	/	NA	NA	NA	NA	NA	NA	NA	NA	/	NA	NA
IPC –not daily drainage	NA	NA	NA	NA	**4.28 (1.59 to 11.54); n = 1**	NA	**3.26 (1.80 to 5.88); n = 2; Chi^2 = 0.55; I^2 = 0%**	NA	NA	NA	NA	NA	NA	NA	NA	NA	/	/	NA
Iodine	NA	NA	0.63 (0.25 to 1.59); n = 2; Chi^2 = 1.33; I^2 = 25%	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	/	NA	NA
Mepacrine	NA	NA	**0.16 (0.03 to 0.89); n = 1**	NA	NA	NA	NA	NA	NA	NA	/	NA	/	NA	NA	NA	/	NA	/

(Continued)

Mistletoe (viscum)	NA	NA	0.19 (0.02 to 1.62); n = 1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Mitoxantrone	NA	NA	**3.18 (1.17 to 8.65); n = 1**	NA	NA	NA	NA	NA	NA	7.61 (0.35 to 163.82); n = 1	NA	NA	/	NA	NA	NA	NA	NA	NA
Mustine	2.71 (0.1 to 74.98); n = 1	NA	NA	**10.80 (1.64 to 70.93); n = 1**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	/	NA	NA	/
Placebo	NA	NA	NA	NA	NA	NA	NA	NA	NA	**14.4 (1.37 to 150.81); n = 1**	1.33 (0.56 to 3.17); n = 1	NA	NA	NA	NA	NA	/	NA	/
Silver nitrate	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	/	NA	/
TMP	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	/	NA	NA
Talc poudrage	NA	NA	**0.1 (0.02 to 0.48); n = 2; Chi^2 = 0.01; I^2 = 0%**	NA	**0.02 (0.00 to 0.47); n = 1**	NA	NA	NA	0.57 (0.08 to 3.80); n = 1	NA	NA	**0.13 (0.02 to 0.71); n = 1**	NA	NA	NA	NA	/	NA	/
Talc slurry	NA	0.69 (0.24 to 1.95); n = 1	0.82 (0.41 to 1.65); n = 5; Chi^2 = 4.53; I^2 = 12%	NA	NA	NA	0.30 (0.08 to 1.14); n = 1	**0.18 (0.10 to 0.31); n = 2; Chi^2 = 2.58; I^2 = 61%**	0.87 (0.25 to 3.04); n = 2; Chi^2 = 0.70; I^2 = 0%	0.48 (0.14 to 1.60); n = 1	NA	NA	0.07 (0.00 to 1.51); n = 1	5.82 (0.21 to 158.82); n = 1	2.28 (0.83 to 6.23); n = 2; Chi^2 = 0; I^2 = 0%	1.24 (0.92 to 1.65); n = 4; Chi^2 = 0.89; I^2 = 0%	NA	NA	/

(Continued)

Talc via IPC	NA	NA	NA	NA	NA	NA	NA	**0.36 (0.18 to 0.73); n = 1**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Tetracycline	0.90 (0.05 to 16.59); n = 1	0.71 (0.14 to 3.60); n = 1	**2.00 (1.07 to 3.73); n = 5; Chi^2 = 1.23; I^2 = 0%**	3.18 (0.52 to 19.64); n = 1	NA	NA	NA	NA	NA	1.60 (0.12 to 20.99); n = 1	NA	0.37 (0.10 to 1.35); n = 2; Chi^2 = 0; I^2 = 0%	0.30 (0.05 to 1.94); n = 1	0.60 (0.15 to 2.47); n = 1	NA	**12.10 (1.32 to 111.30); n = 1**	0.78 (0.19 to 3.13); n = 1	NA	NA
Triethyl-enethiophos-phoramide	NA	NA	NA	NA	NA	NA	NA	NA	NA	**4.95 (1.02 to 24.10); n = 1**	NA	NA	0.34 (0.03 to 3.69); n = 1	NA	NA	NA	NA	NA	NA

IFN: interferon; IPC: indwelling pleural catheter; n: the number of studies included in the pair-wise comparison; NA: no direct pair-wise comparison available; TMP: thoracoscopic mechanical pleurodesis

* indicates that the comparison included a three-arm study

/ indicates the odds ratio is already expressed elsewhere in the table comparing the interventions the other way around

Results that are significant at the conventional level of P ≤ 0.05 are in bold

Appendix 4. Overview of the network meta-analysis results for pleurodesis failure in the secondary endpoints and sensitivity analyses

	Number of pleurodesis methods evaluated	Number of trials included in network	Tau (95% CI)	Global inconsistency								Loop-specific inconsistency identified?
				Consistency model				Inconsistency model				
				Mean Res Dev	pD	DIC	SD	Mean Res Dev	pD	DIC	SD	
Whole network	21	55	0.70 (0.30 to 1.17)	118	91.3	209.3	0.7	113.9	101	214.9	0.8	No
Fever	14	30	1.67 (1.08 to 1.98)	65.2	56.2	121.5	1.67	64.5	56.7	121.2	1.24	No
Mortality	15	31	0.22 (0.01 to 0.73)	53.8	45.0	98.8	0.22	54.2	49.9	104.0	0.25	No
Pain	14	31	0.69 (0.11 to 1.51)	67.2	51.0	118.2	0.69	60.0	53.4	113.4	0.53	No
Only data collected at 1 month	16	30	0.71 (0.07 to 1.51)	63.7	53	116.8	0.71	63.2	56.9	120.1	0.4	No
Only data collected at 3 months	9	10	0.54 (0.03 to 1.83)	19.9	19	38.8	0.54	19.7	19.2	38.8	0.55	No
Only data collected at 6 months	7	9	0.44 (0.02 to 1.75)	16.9	16.2	33.1	0.44	17.3	16.9	34.2	0.53	No
Trials excluding people with trapped lung	13	23	0.31 (0.01 to 1.19)	47.3	37.2	84.5	0.31	45.5	41.4	86.9	0.45	No
Trials using a clinicoradiological definition of pleurodesis	19	37	0.89 (0.42 to 1.54)	78.5	66.8	145.3	0.89	78	71.3	149.4	1.09	No
Trials using large-bore chest tubes	12	19	0.73 (0.04 to 1.84)	42.4	33.5	75.9	0.73	39.3	35.1	74.4	0.83	No
Trials with a lower risk of bias (scoring 'high' risk of bias in maximum 1 domain)	18	27	0.37 (0.02 to 1.47)	56.9	46.2	103.2	0.37	54.1	51.2	105.3	0.59	No
Trials delivering agents by chest tube	16	37	0.87 (0.37 to 1.52)	78.7	63.6	142	0.87	76.6	69.5	146	1.19	No

CI: confidence interval; DIC: deviance information criterion; Mean Res Dev: mean residual deviance; pD: probability of direction; SD: standard deviation

Appendix 5. Estimated rank (95% Cr-I) for pleurodesis efficacy in the sensitivity analysis only evaluating those trials with a lower risk of bias (lower rank confers higher risk of pleurodesis failure)

Pleurodesis method	Estimated rank (95% Cr-I)
Talc poudrage	2 (1 to 9)
Talc slurry	4 (1 to 9)
C parvum	4 (1 to 12)
Mepacrine	6 (1 to 13)
Iodine	6 (1 to 16)
Doxycycline	7 (1 to 14)
Adriamycin	7 (1 to 18)
Autologous blood	8 (2 to 15)
Tetracycline	9 (4 to 14)
IPC – daily drainage	9 (2 to 15)
Silver nitrate	9 (1 to 17)
Talc via IPC	10 (2 to 17)
Bleomycin	12 (6 to 16)
Mustine	14 (6 to 18)
Triethylenethiophosphoramide	14 (4 to 18)
IPC – not daily drainage	15 (9 to 18)
Mitoxantrone	17 (12 to 18)
Placebo	17 (12 to 18)

Cr-I: credible interval; IPC: indwelling pleural catheter

Appendix 6. Estimated rank (95% Cr-I) for the subgroup analysis evaluating the network of agents given via a chest tube (IPC and talc poudrage studies excluded)

Pleurodesis agent	Estimated rank (95% Cr-I)
Mistletoe	1 (1 to 12)
C parvum	4 (1 to 11)

(Continued)

Mepacrine	4 (1 to 11)
Talc slurry	5 (2 to 10)
Iodine	6 (1 to 12)
Doxycycline	6 (1 to 13)
Adriamycin	7 (1 to 16)
Bleomycin	8 (5 to 12)
Silver nitrate	8 (1 to 15)
Autologous blood	9 (2 to 15)
Tetracycline	10 (5 to 13)
Triethylenethiophosphoramide	12 (2 to 16)
IFN	13 (4 to 16)
Mustine	13 (5 to 16)
Mitoxantrone	14 (9 to 16)
Placebo	15 (11 to 16)

Cr-I: credible interval; IFN: interferon

Appendix 7. Results of the sensitivity analysis only evaluating those studies with a lower risk of bias. Table of odds ratios (95% Cr-I) from network meta-analysis (agents in the rows compared to those in the columns)

	Adriamycin	Autologous blood	Bleomycin	*C parvum*	Doxycycline	IPC – daily drainage	IPC – not daily drainage	Iodine	Mepacrine	Mitoxantrone	Mustine	Placebo	Silver nitrate	Talc poudrage	Talc slurry	Talc via IPC	Tetracycline
Autologous blood	1.19 (0.02 to 93.9)	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
Bleomycin	2.22 (0.05 to 182.3)	1.92 (0.35 to 11.75)	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
C parvum	0.53 (0.01 to 40.43)	0.45 (0.05 to 3.39)	0.24 (0.03 to 1.6)	/	/	/	/	/	/	/	/	/	/	/	/	/	/
Doxycycline	1.03 (0.02 to 88.63)	0.89 (0.1 to 6.19)	0.46 (0.05 to 2.79)	1.93 (0.32 to 11.97)	/	/	/	/	/	/	/	/	/	/	/	/	/
IPC –daily drainage	1.39 (0.02 to 130.3)	1.21 (0.13 to 8.99)	0.63 (0.07 to 4.23)	2.61 (0.28 to 23.54)	1.35 (0.23 to 8.18)	/	/	/	/	/	/	/	/	/	/	/	/
IPC –not daily drainage	4.8 (0.09 to 396.5)	4.17 (0.6 to 24.27)	2.17 (0.32 to 11.31)	9.03 (1.32 to 65.19)	**4.64 (1.21 to 20.97)**	**3.44 (1.24 to 10.76)**	/	/	/	/	/	/	/	/	/	/	/
Iodine	0.86 (0.01 to 102)	0.74 (0.06 to 9.08)	0.39 (0.06 to 2.12)	1.62 (0.12 to 25.95)	0.83 (0.07 to 13.69)	0.6 (0.05 to 10.89)	0.18 (0.02 to 2.41)	/	/	/	/	/	/	/	/	/	/
Mepacrine	0.84 (0.02 to 65.69)	0.73 (0.1 to 3.93)	0.38 (0.06 to 1.71)	1.57 (0.19 to 12.5)	0.82 (0.1 to 6.23)	0.6 (0.07 to 4.91)	0.17 (0.03 to 1.02)	0.99 (0.07 to 9.67)	/	/	/	/	/	/	/	/	/
Mitoxantrone	7.95 (0.17 to 771.1)	**6.92 (1.03 to 55.22)**	3.59 (0.98 to 14.58)	**15.23 (1.95 to 158.8)**	**7.8 (1.05 to 86.25)**	5.68 (0.71 to 74.35)	1.66 (0.26 to 15.45)	9.33 (1.10 to 92.31)	**9.49 (2.06 to 71.96)**	/	/	/	/	/	/	/	/

(Continued)

Mustine	3.67 (0.09 to 242.7)	3.18 (0.37 to 26.7)	1.66 (0.2 to 12.24)	**6.94 (1.22 to 47.12)**	3.6 (0.42 to 35.78)	2.67 (0.25 to 33.31)	0.77 (0.09 to 7.21)	4.32 (0.27 to 62.01)	4.44 (0.54 to 42.76)	0.46 (0.05 to 3.92)	/	/	/	/	/	/	/
Placebo	9.9 (0.2 to 846.1)	**8.57 (1.2 to 61.69)**	4.47 (0.87 to 20.47)	**18.8 (2.39 to 170.9)**	**9.63 (1.21 to 96.37)**	7.0 (0.8 to 81.68)	2.04 (0.29 to 17.39)	**11.55 (1.07 to 118.7)**	**11.63 (2.55 to 74.49)**	1.24 (0.31 to 4.15)	2.67 (0.32 to 24.4)	/	/	/	/	/	/
Silver nitrate	1.44 (0.02 to 112.5)	1.23 (0.1 to 10.64)	0.64 (0.05 to 5.17)	2.71 (0.21 to 26.91)	1.42 (0.1 to 15.34)	1.0 (0.07 to 12.43)	0.3 (0.02 to 2.84)	1.68 (0.07 to 23.96)	1.73 (0.16 to 16.04)	0.18 (0.01 to 1.65)	0.39 (0.03 to 3.6)	0.15 (0.01 to 1.28)	/	/	/	/	/
Talc poudrage	0.43 (0.01 to 32.56)	0.37 (0.04 to 1.81)	**0.19 (0.02 to 0.82)**	0.8 (0.08 to 6.18)	0.42 (0.04 to 2.89)	0.31 (0.03 to 2.12)	**0.09 (0.01 to 0.44)**	0.5 (0.03 to 4.58)	0.51 (0.07 to 2.79)	**0.05 (0.005 to 0.29)**	**0.11 (0.009 to 0.95)**	**0.04 (0.004 to 0.26)**	0.3 (0.03 to 3.21)	/	/	/	/
Talc slurry	0.58 (0.01 to 43.55)	0.49 (0.12 to 1.85)	**0.26 (0.06 to 0.93)**	1.07 (0.17 to 7.11)	0.55 (0.11 to 3.31)	0.4 (0.08 to 2.43)	**0.12 (0.03 to 0.46)**	0.66 (0.07 to 5.83)	0.68 (0.18 to 3.01)	**0.07 (0.01 to 0.34)**	0.15 (0.02 to 1.11)	**0.06 (0.01 to 0.3)**	0.4 (0.05 to 3.98)	1.29 (0.47 to 6.64)	/	/	/
Talc via IPC	1.73 (0.02 to 184.8)	1.5 (0.13 to 14.11)	0.78 (0.07 to 6.62)	3.23 (0.3 to 36.3)	1.66 (0.24 to 13.33)	1.23 (0.22 to 7.85)	0.36 (0.08 to 1.51)	2.03 (0.1 to 32.3)	2.06 (0.22 to 23.2)	0.22 (0.02 to 2.18)	0.47 (0.03 to 6.06)	0.18 (0.01 to 1.92)	1.19 (0.09 to 23.75)	3.96 (0.49 to 52.51)	3.05 (0.41 to 20.77)	/	/
Tetracycline	1.49 (0.04 to 90.75)	1.28 (0.26 to 5.7)	0.67 (0.14 to 2.54)	2.8 (0.58 to 14.46)	1.44 (0.24 to 9.61)	1.06 (0.15 to 8.71)	0.31 (0.06 to 1.78)	1.75 (0.17 to 15.38)	1.78 (0.39 to 9.31)	**0.19 (0.03 to 0.86)**	0.4 (0.08 to 1.81)	**0.15 (0.03 to 0.68)**	1.04 (0.19 to 7.42)	3.46 (0.71 to 26.49)	2.61 (0.66 to 10.57)	0.86 (0.09 to 7.34)	/
Triethylenethiophosphoramide	4.1 (0.05 to 451.1)	3.58 (0.26 to 41.75)	1.86 (0.15 to 17.95)	7.76 (0.51 to 118.6)	4.02 (0.27 to 61.94)	2.94 (0.19 to 48.22)	0.85 (0.07 to 10.85)	4.85 (0.22 to 83.07)	4.9 (0.74 to 36.17)	0.52 (0.04 to 4.67)	1.12 (0.07 to 17.03)	0.43 (0.04 to 3.46)	2.89 (0.18 to 57.68)	9.77 (0.88 to 144.5)	7.28 (0.77 to 68.84)	2.4 (0.13 to 43.45)	2.78 (0.25 to 57.95)

Results that are significant at the conventional level of P < 0.05 are in bold

(Continued)

/ indicates the odds ratio is already expressed elsewhere in the table comparing the interventions the other way around

Cr-I: credible interval; IPC: indwelling pleural catheter; NA: not applicable

Appendix 8. Results of the sensitivity analysis only evaluating agents given via chest tube. Table of odds ratios (95% Cr-I) from network meta-analysis (the agents in the rows compared to the agents in the columns) for pleurodesis success

	Adriamycin	Autologous blood	Bleomycin	*C parvum*	Doxycycline	IFN	Iodine	Mepacrine	Mistletoe (viscum)	Mitoxantrone	Mustine	Placebo	Silver nitrate	Talc slurry	Tetracycline
Autologous blood	1.52 (0.02 to 136.90)	NA	/	/	/	/	/	/	/	/	/	/	/	/	/
Bleomycin	1.22 (0.02 to 82.63)	0.80 (0.13 to 4.81)	NA	/	/	/	/	/	/	/	/	/	/	/	/
C parvum	0.62 (0.01 to 46.29)	0.41 (0.05 to 3.31)	0.52 (0.14 to 1.75)	NA	/	/	/	/	/	/	/	/	/	/	/
Doxycycline	0.86 (0.01 to 76.37)	0.57 (0.05 to 6.10)	0.72 (0.13 to 3.56)	1.38 (0.23 to 8.17)	NA	/	/	/	/	/	/	/	/	/	/
IFN	4.03 (0.04 to 443.40)	2.65 (0.18 to 40.87)	3.33 (0.43 to 25.84)	6.45 (0.61 to 74.77)	4.66 (0.36 to 68.95)	NA	/	/	/	/	/	/	/	/	/
Iodine	0.80 (0.01 to 64.26)	0.53 (0.06 to 4.28)	0.66 (0.17 to 2.42)	1.28 (0.22 to 7.88)	0.92 (0.12 to 7.88)	0.20 (0.02 to 2.18)	NA	/	/	/	/	/	/	/	/
Mepacrine	0.55 (0.01 to 43.69)	0.37 (0.04 to 2.96)	0.46 (0.10 to 1.80)	0.89 (0.14 to 5.54)	0.64 (0.07 to 5.65)	0.14 (0.01 to 1.55)	0.70 (0.10 to 4.28)	NA	/	/	/	/	/	/	/
Mistletoe (viscum)	0.18 (0.00 to 30.85)	0.12 (0.00 to 3.75)	0.15 (0.01 to 2.73)	0.29 (0.01 to 7.09)	0.21 (0.01 to 6.20)	0.05 (0.00 to 1.55)	0.23 (0.01 to 5.58)	0.33 (0.01 to 8.72)	NA	/	/	/	/	/	/
Mitoxantrone	6.52 (0.08 to 615.00)	4.25 (0.43 to 49.93)	**5.30 (1.11 to 30.71)**	**10.33 (1.49 to 91.82)**	7.44 (0.82 to 91.14)	1.58 (0.13 to 24.39)	**8.06 (1.11 to 72.15)**	**11.54 (1.94 to 95.99)**	**35.67 (1.34 to 1301)**	NA	/	/	/	/	/
Mustine	4.18 (0.06 to 324.30)	2.76 (0.23 to 34.54)	3.45 (0.52 to 24.35)	**6.72 (1.01 to 50.82)**	4.85 (0.45 to 60.37)	1.04 (0.06 to 17.35)	5.26 (0.55 to 54.66)	7.57 (0.80	23.10 (0.71	0.65 (0.05	NA	/	/	/	/

(Continued)

								to 82.36)	to 929.90)	to 7.32)							
Placebo	10.25 (0.13 to 943.80)	6.64 (0.72 to 74.51)	**8.32 (1.72 to 48.89)**	**16.22 (2.35 to 140.30)**	**11.68 (1.27 to 139.60)**	2.49 (0.20 to 38.28)	**12.63 (1.76 to 111.10)**	**18.15 (3.28 to 135.80)**	**56.06 (2.05 to 2060)**	1.57 (0.30 to 8.24)	2.40 (0.22 to 29.19)	NA	/	/	/		
Silver nitrate	1.21 (0.01 to 122.10)	0.81 (0.05 to 11.30)	1.01 (0.09 to 9.14)	1.97 (0.14 to 22.51)	1.42 (0.08 to 21.46)	0.31 (0.01 to 5.68)	1.54 (0.10 to 18.64)	2.22 (0.15 to 27.79)	6.76 (0.14 to 300.90)	0.19 (0.01 to 2.57)	0.29 (0.01 to 4.31)	0.12 (0.01 to 1.58)	NA	/	/		
Talc slurry	0.77 (0.01 to 54.75)	0.51 (0.09 to 2.78)	0.64 (0.25 to 1.60)	1.24 (0.28 to 5.79)	0.90 (0.14 to 6.14)	0.19 (0.02 to 1.77)	0.97 (0.25 to 3.78)	1.39 (0.34 to 6.26)	4.25 (0.20 to 110.90)	**0.12 (0.02 to 0.66)**	0.19 (0.02 to 1.39)	**0.08 (0.01 to 0.40)**	0.64 (0.07 to 7.41)	NA	/		
Tetracycline	1.58 (0.03 to 98.83)	1.04 (0.17 to 5.93)	1.30 (0.52 to 3.12)	2.52 (0.66 to 9.98)	1.82 (0.30 to 11.75)	0.39 (0.04 to 3.49)	1.97 (0.42 to 9.10)	2.83 (0.65 to 13.53)	8.64 (0.40 to 223.90)	0.24 (0.04 to 1.30)	0.38 (0.06 to 2.16)	**0.16 (0.03 to 0.78)**	1.28 (0.16 to 12.58)	2.03 (0.66 to 6.22)	NA		
Triethylenethiophosphoramide	2.99 (0.02 to 418.10)	1.97 (0.09 to 42.32)	2.47 (0.18 to 33.93)	4.81 (0.28 to 86.73)	3.47 (0.16 to 79.33)	0.74 (0.03 to 20.29)	3.75 (0.21 to 67.61)	5.38 (0.53 to 61.45)	16.58 (0.33 to 967.70)	0.47 (0.02 to 7.31)	0.71 (0.03 to 16.62)	0.30 (0.02 to 3.74)	2.45 (0.09 to 83.81)	3.86 (0.28 to 55.32)	1.91 (0.14 to 27.69)		

Results that are significant at the conventional level of P < 0.05 are in bold

/ indicates the odds ratio is already expressed elsewhere in the table comparing the interventions the other way around

Cr-I: credible interval; IFN: interferon; NA: not applicable

Appendix 9. Direct pair-wise evidence for fever, expressed as odds ratios (95% CI) for the rows compared to the columns, using random-effects meta-analysis

	Autologous blood	Bleomycin	*C parvum*	Doxycycline	IPC – not daily drainage	Iodine	Mepacrine	Mitoxantrone	Mustine	Placebo	Silver Nitrate	Talc poudrage	Talc slurry	Tetracycline
Bleomycin	NA	NA	/	/	NA	/	/	/	NA	NA	NA	/	/	/
C parvum	NA	2.30 (0.9 to 5.92); n = 2; Tau^2 = 0; I^2 = 0%	NA	/	NA	NA	NA	NA	/	NA	NA	NA	NA	/
Doxycycline	NA	0.37 (0.01 to 12.35); n = 2;Tau^2 = 5.18; I^2 = 80%	**0.14 (0.03 to 0.54); n = 1**	NA	/	NA	NA	NA	NA	NA	NA	NA	NA	NA
Interferon	NA	**0.00 (0.00 to 0.11); n = 1**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
IPC –not daily drainage	NA	NA	NA	0.44 (0.07 to 2.8); n = 1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Iodine	NA	1.00 (0.13 to 7.6); n = 1	NA	NA	NA	NA	NA	NA	NA	NA	NA	/	/	NA
Mepacrine	NA	1.91 (0.52 to 7.01); n = 1	NA	NA	NA	NA	NA	NA	NA	/	NA	NA	NA	/
Mitoxantrone	NA	0.90 (0.30 to 2.71); n = 1	NA	NA	NA	NA	NA	NA	NA	/	NA	NA	NA	NA
Mustine	NA	NA	0.23 (0.01 to 6.25); n = 1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Placebo	NA	NA	NA	NA	NA	NA	**0.31 (0.12 to 0.79); n = 1**	**0.02 (0.0 to 0.35); n = 1**	NA	NA	NA	NA	NA	NA

(Continued)

Silver nitrate	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	/	/
Talc poudrage	NA	1.15 (0.14 to 9.38); n = 1	NA	NA	NA	4.22 (0.43 to 41.45); n = 1	NA	NA	NA	NA	NA	NA	/	NA
Talc slurry	**3.92 (1.31 to 11.72); n = 1**	0.95 (0.36 to 2.51); n = 3: Tau^2 = 0; I^2 = 0%	NA	NA	NA	1.07 (0.32 to 3.59); n = 2; Tau^2 = 0; I^2 = 0%	NA	NA	NA	0.70 (0.15 to 3.24); n = 1	1.65 (0.42 to 6.48); n = 2; Tau^2 = 0.54; I^2 = 31%	NA	/
Tetracycline	4.53 (0.83 to 24.65); n = 1	0.49 (0.16 to 1.5); n = 5; Tau^2 = 0.63; I^2 = 39%	**0.00 (0.00 to 0.06); n = 1**	NA	NA	NA	**0.13 (0.02 to 0.89); n = 1**	NA	NA	**327.86 (16.05 to 6697.61); n = 1**	NA	0.92 (0.23 to 3.63); n = 1	NA
Triethylenethio-phosphoramide	NA	NA	NA	NA	NA	NA	**0.04 (0.01 to 0.30); n = 1**	NA	NA	3.52 (0.15 to 81.92); n = 1	NA	NA	NA	NA

* indicates that the comparison included a three-arm study

Results that are significant at the conventional level of P ≤ 0.05 are in bold

/ indicates the odds ratio is already expressed elsewhere in the table comparing the interventions the other way around

CI: confidence interval; IPC: indwelling pleural catheter; n: number of studies included in the pair-wise comparison; NA: no direct pair-wise comparison available

Appendix 10. Table of the relative chance of pain from direct pair-wise evidence using random-effects model (odds ratios (95% Cr-I) (rows compared to columns)

	Autologous blood	Bleomycin	*C parvum*	Doxycycline	IPC – daily drainage	IPC – not daily drainage	Iodine	Mepacrine	Mitoxantrone	Mustine	Placebo	Silver nitrate	Talc poudrage	Talc slurry	Tetracycline
Bleomycin	NA	NA	/	/	NA	NA	/	/	/	NA	NA	NA	/	/	/
C parvum	NA	1.42 (0.54 to 3.75); n = 2; Tau^2 = 0; I^2 = 0%	NA	/	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	/
Doxycycline	NA	1.19 (0.37 to 3.80); n = 2; Tau^2 = 0.3; I^2 = 42%	**0.10 (0.01 to 0.96); n = 1**	NA	NA	/	NA	NA	NA	NA	NA	NA	NA	NA	NA
IFN	NA	**0.03 (0.00 to 0.53); n = 1**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
IPC –daily drainage	NA	NA	NA	NA	NA	/	NA	NA	NA	NA	NA	NA	NA	/	NA
IPC –not daily drainage	NA	NA	NA	0.06 (0.00 to 1.24); n = 1	1.36 (0.78 to 2.37); n = 2; Tau^2 = 0; I^2 = 0%	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Iodine	NA	1.00 (0.13 to 7.60); n = 1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	/	/	NA
Mepacrine	NA	2.15 (0.52 to 9.00); n = 1	NA	NA	NA	NA	NA	NA	NA	NA	14.53 (0.71 to 298); n = 1	NA	NA	NA	/
Mitoxantrone	NA	2.08 (0.64 to 6.76); n = 1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Talc poudrage	NA	3.62 (0.14 to 95.78); n = 1	NA	NA	NA	NA	9.97 (0.50 to 198); n = 1	NA	NA	NA	NA	NA	NA	/	NA

(Continued)

Talc slurry	**3.57 (1.19 to 10.74); n = 1**	0.60 (0.15 to 2.46); n = 3; Tau^2 = 0; I^2 = 0%	NA	NA	0.31 (0.01 to 7.95); n = 1	0.62 (0.19 to 1.95); n = 2; Tau^2 = 0%; I^2 = 0%	2.00 (0.55 to 7.30); n = 1	NA	NA	NA	NA	NA	NA	NA	/
Talc via IPC	NA	NA	NA	NA	NA	0.71 (0.23 to 2.15); n = 1	NA	NA	NA	NA	NA	NA	NA	NA	NA
Tetracycline	**69.00 (7.61 to 625); n = 1**	1.65 (0.79 to3.43); n = 4; Tau^2 = 0.19; I^2 = 34%	0.41 (0.12 to 1.45); n = 1	NA	NA	NA	NA	0.18 (0.03 to 1.23); n = 1	NA	**33.87 (1.80 to 636); n = 1**	NA	**55.08 (3.02 to 1003); n = 1**	NA	3.28 (0.73 to 14.68); n = 1	NA
Triethylenethio-phosphoramide	NA	NA	NA	NA	NA	NA	NA	0.48 (0.10 to 2.30); n = 1	NA	NA	7.43 (0.35 to 156); n = 1	NA	NA	NA	NA

* indicates that the comparison included a three-arm study

Results that are significant at the conventional level of P ≤ 0.05 are in bold

/ indicates the odds ratio is already expressed elsewhere in the table comparing the interventions the other way around

Cr-I: credible interval; IFN: interferon; IPC: indwelling pleural catheter; n: the number of studies included in the pair-wise comparison; NA: no direct pair-wise comparison available

Appendix 11. Table of the relative chances of pain from network meta-analysis (expressed as odds ratios (95% Cr-I) (rows compared to the columns)

	Autologous blood	Bleomycin	*C parvum*	Doxycycline	IPC – daily drainage	IPC – not daily drainage	Iodine	Mepacrine	Mitoxantrone	Talc poudrage	Talc slurry	Talc via IPC	Tetracycline
Bleomycin	**19.46 (3.47 to 138.70)**	NA	/	/	/	/	/	/	/	/	/	/	/
C parvum	**57.61 (8.11 to 559.60)**	2.94 (0.97 to 10.09)	NA	/	/	/	/	/	/	/	/	/	/
Doxycycline	**22.87 (2.99 to 223.60)**	1.17 (0.35 to 4.12)	0.40 (0.09 to 1.71)	NA	/	/	/	/	/	/	/	/	/
IPC – daily drainage	7.17 (0.70 to 95.49)	0.37 (0.04 to 3.29)	0.13 (0.01 to 1.33)	0.32 (0.03 to 3.21)	NA	/	/	/	/	/	/	/	/
IPC – not daily drainage	**8.93 (1.08 to 86.34)**	0.46 (0.07 to 2.84)	0.15 (0.02 to 1.20)	0.39 (0.05 to 2.84)	1.25 (0.32 to 4.08)	NA	/	/	/	/	/	/	/
Iodine	3.39 (0.40 to 33.84)	**0.18 (0.03 to 0.99)**	**0.06 (0.01 to 0.44)**	0.15 (0.02 to 1.16)	0.47 (0.04 to 4.96)	0.38 (0.05 to 3.21)	NA	/	/	/	/	/	/
Mepacrine	**82.89 (8.40 to 1105.00)**	4.21 (0.81 to 24.85)	1.43 (0.19 to 10.81)	3.63 (0.46 to 30.27)	11.55 (0.77 to 181.00)	9.35 (0.83 to 121.60)	**24.32 (2.29 to 303.60)**	NA	/	/	/	/	/
Mitoxantrone	**42.78 (3.08 to 742.30)**	2.18 (0.29 to 17.20)	0.74 (0.07 to 7.51)	1.87 (0.17 to 20.19)	5.97 (0.30 to 116.70)	4.82 (0.32 to 81.23)	12.62 (0.87 to 194.60)	0.52 (0.04 to 7.07)	NA	/	/	/	/
Talc poudrage	**8.64 (1.45 to 96.71)**	0.45 (0.09 to 3.00)	0.15 (0.02 to 1.29)	0.38 (0.06 to 3.41)	1.21 (0.16 to 13.50)	0.98 (0.17 to 8.81)	2.55 (0.52 to 20.24)	0.11 (0.01 to 1.29)	0.20 (0.02 to 3.57)	NA	/	/	/
Talc slurry	**6.77 (1.40 to 39.01)**	0.35 (0.09 to 1.28)	**0.12 (0.02 to 0.60)**	0.30 (0.05 to 1.56)	0.95 (0.14 to 5.77)	0.77 (0.17 to 3.39)	2.00 (0.42 to 9.70)	0.08 (0.01 to 0.63)	0.16 (0.01 to 1.73)	0.80 (0.17 to 2.20)	NA	/	/

(Continued)

Talc via IPC	6.16 (0.34 to 126.00)	0.32 (0.02 to 4.60)	0.11 (0.01 to 1.80)	0.27 (0.01 to 4.32)	0.86 (0.07 to 8.49)	0.69 (0.09 to 5.02)	1.82 (0.10 to 32.86)	0.07 (0.00 to 1.66)	0.14 (0.00 to 4.11)	0.71 (0.03 to 9.01)	0.91 (0.07 to 10.82)	NA	/
Tetracycline	**29.74 (5.70 to 207.90)**	1.54 (0.65 to 3.75)	0.52 (0.14 to 1.81)	1.31 (0.30 to 5.61)	4.17 (0.45 to 38.50)	3.37 (0.51 to 24.51)	**8.81 (1.42 to 61.82)**	0.36 (0.06 to 1.97)	0.70 (0.08 to 6.40)	3.44 (0.48 to 17.66)	**4.39 (1.14 to 19.03)**	4.86 (0.32 to 82.62)	NA
Triethylenethiophosphoramide	**38.85 (1.53 to 1235.00)**	1.97 (0.12 to 35.27)	0.67 (0.03 to 13.86)	1.69 (0.08 to 38.16)	5.37 (0.15 to 192.70)	4.35 (0.16 to 136.80)	11.37 (0.41 to 336.60)	0.47 (0.05 to 4.47)	0.90 (0.03 to 30.84)	4.39 (0.14 to 104.20)	5.66 (0.27 to 135.60)	6.28 (0.13 to 340.62)	1.29 (0.07 to 22.94)

Results that are significant at the conventional level of P ≤ 0.05 are in bold

/ indicates the odds ratio is already expressed elsewhere in the table comparing the interventions the other way around

Cr-I: credible interval; IPC: indwelling pleural catheter; NA: not applicable

Appendix 12. Estimated rank (95% Cr-I) for causing pain (a low rank suggesting more pain)

Pleurodesis agent	Estimated rank (95% Cr-I)
Autologous blood	1 (1 to 4)
Iodine	2 (1 to 8)
Talc via IPC	4 (1 to 13)
Talc slurry	5 (2 to 8)
IPC –daily drainage	5 (2 to 12)
IPC –not daily drainage	6 (2 to 12)
Talc poudrage	6 (2 to 12)
Bleomycin	8 (4 to 11)
Doxycycline	9 (4 to 13)
Tetracycline	10 (6 to 13)
Mitoxantrone	11 (3 to 14)
Triethylenethiophosphoramide	11 (2 to 14)
C parvum	12 (8 to 14)
Mepacrine	13 (8 to 14)

Cr-I: credible interval; IPC: indwelling pleural catheter

Appendix 13. Table of the relative chance of mortality from direct evidence using random-effects model (odds ratios (95% Cr-I) (rows compared to columns)

	Autologous blood	Bleomycin	*C parvum*	Doxycycline	IFN	IPC – daily drainage	IPC – not daily drainage	Iodine	Mepacrine	Mitoxantrone	Mustine	Talc poudrage	Talc slurry
Bleomycin	NA	NA	/	/	/	NA	NA	NA	NA	/	NA	/	/
C parvum	NA	1.66 (0.51 to 5.38); n = 1	NA	NA	NA	NA	NA	NA	NA	NA	/	NA	NA
Doxycycline	NA	0.69 (0.26 to 1.87); n = 1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
IFN	NA	**2.16 (1.15 to 4.07); n = 1**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
IPC –daily drainage	NA	NA	NA	NA	NA	NA	/	NA	NA	NA	NA	NA	/
IPC –not daily drainage	NA	NA	NA	NA	NA	1.29 (0.72 to 2.32); n = 2; $Tau^2 = 0$; $I^2 = 0\%$	NA	NA	NA	NA	NA	NA	/
Iodine	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	/	/
Mepacrine	NA	NA	NA	NA	NA	NA	NA	NA	NA	/	NA	NA	/
Mitoxantrone	NA	0.47 (0.21 to 1.05); n = 1	NA	NA	NA	NA	NA	NA	0.61 (0.09 to 4.37); n = 1	NA	NA	NA	NA
Mustine	NA	NA	2.40 (0.38 to 15.32); n = 1	NA	NA	NA	NA	NA	NA	NA	NA	/	NA
Talc poudrage	NA	1.22 (0.29 to 5.13); n = 1	NA	NA	NA	NA	NA	2.64 (0.58 to 12.09); n = 1	NA	NA	0.42 (0.09 to 1.96); n = 1	NA	/
Talc slurry	1.38 (0.30 to	1.12 (0.36 to 3.46); n = 2; $Tau^2 = 0$; $I^2 = 0\%$	NA	NA	NA	0.59 (0.19 to 1.79); n = 1	1.43 (0.91 to 2.23); n = 3;	2.71 (0.10 to 70.65); n = 1	1.88 (0.70 to 5.02); n = 1	NA	NA	1.10 (0.69 to 1.75); n = 3;	NA

(Continued)

	6.47); n = 1					Tau^2 = 0, I^2 = 0%					Tau^2 = 0.07, I^2 = 40%	
Talc via IPC	NA	NA	NA	NA	NA NA	0.44 (0.17 to 1.15); n = 1	NA	NA	NA	NA	NA	NA
Tetracycline	Not estimable	1.60 (0.69 to 3.69); n = 2; Tau^2 = 0%; I^2 = 0%	3.00 (0.28 to 31.99); n = 1	NA	NA NA	NA	NA	NA	NA	NA	0.19 (0.03 to 1.10); n = 1	NA

* indicates that the comparison included a three-arm study

Results that are significant at the conventional level of P ≤ 0.05 are shaded in grey

/ indicates the odds ratio is already expressed elsewhere in the table comparing the interventions the other way around

Cr-I: credible interval; IFN: interferon; IPC: indwelling pleural catheter; n: the number of studies included in the pair-wise comparison; NA: no direct pair-wise comparison available

Appendix 14. Table of the relative chances of mortality from network meta-analysis (expressed as odds ratios (95% Cr-I) (rows compared to columns)

	Autologous blood	Bleomycin	*C parvum*	Doxycycline	IFN	IPC – daily drainage	IPC – not daily drainage	Iodine	Mepacrine	Mitoxantrone	Mustine	Talc poudrage	Talc slurry	Talc via IPC
Bleomycin	1.51 (0.22 to 10.61)	NA	/	/	/	/	/	/	/	/	/	/	/	/
C parvum	1.98 (0.22 to 17.35)	1.3 (0.43 to 3.93)	NA	/	/	/	/	/	/	/	/	/	/	/
Doxycycline	1.03 (0.11 to 10.15)	0.68 (0.2 to 2.24)	0.52 (0.1 to 2.67)	NA	/	/	/	/	/	/	/	/	/	/
IFN	3.33 (0.4 to 28.88)	2.19 (0.88 to 5.44)	1.69 (0.41 to 7.1)	3.22 (0.72 to 14.52)	NA	/	/	/	/	/	/	/	/	/
IPC –daily drainage	1.2 (0.18 to 8.49)	0.79 (0.26 to 2.5)	0.61 (0.14 to 2.79)	1.15 (0.23 to 6.06)	0.36 (0.09 to 1.57)	NA	/	/	/	/	/	/	/	/
IPC –not daily drainage	1.2 (0.19 to 7.52)	0.78 (0.29 to 2.14)	0.6 (0.15 to 2.49)	1.15 (0.25 to 5.42)	0.36 (0.09 to 1.39)	0.995 (0.5 to 1.89)	NA	/	/	/	/	/	/	/
Iodine	0.37 (0.03 to 4.09)	0.24 (0.03 to 1.49)	0.19 (0.02 to 1.49)	0.36 (0.03 to 3.12)	**0.11 (0.01 to 0.83)**	0.31 (0.04 to 1.89)	0.31 (0.04 to 1.78)	NA	/	/	/	/	/	/
Mepacrine	0.84 (0.1 to 6.32)	0.55 (0.15 to 1.88)	0.42 (0.08 to 2.14)	0.81 (0.15 to 4.48)	0.25 (0.05 to 1.16)	0.7 (0.18 to 2.54)	0.7 (0.21 to 2.31)	2.25 (0.31 to 20.13)	NA	/	/	/	/	/
Mitoxantrone	0.65 (0.08 to 5.48)	0.43 (0.16 to 1.11)	0.33 (0.08 to 1.42)	0.63 (0.14 to 2.9)	**0.2 (0.05 to 0.73)**	0.55 (0.13 to 2.17)	0.55 (0.14 to 2.01)	1.77 (0.24 to 15.85)	0.78 (0.19 to 3.08)	NA	/	/	/	/
Mustine	3.83 (0.4 to 40.42)	2.55 (0.56 to 11.86)	1.96 (0.43 to 9.31)	3.74 (0.55 to 26.46)	1.17 (0.2 to 6.99)	3.25 (0.59 to 17.76)	3.26 (0.67 to 16.69)	**10.59 (1.24**	4.64 (0.79	**5.97 (1.02**	NA	/	/	/

(Continued)

								to 110.3)	to 29.42)	**to 34.98)**				
Talc poudrage	1.28 (0.21 to 7.98)	0.84 (0.36 to 1.95)	0.65 (0.18 to 2.35)	1.25 (0.29 to 5.33)	0.38 (0.11 to 1.33)	1.07 (0.42 to 2.61)	1.08 (0.51 to 2.23)	3.41 (0.7 to 21.88)	1.52 (0.49 to 4.997)	1.95 (0.59 to 6.87)	0.33 (0.07 to 1.37)	NA	/	/
Talc slurry	1.47 (0.25 to 8.55)	0.97 (0.41 to 2.22)	0.75 (0.21 to 2.74)	1.43 (0.33 to 6.04)	0.44 (0.13 to 1.51)	1.24 (0.55 to 2.6)	1.24 (0.71 to 2.12)	3.95 (0.76 to 26.47)	1.76 (0.61 to 5.24)	2.25 (0.69 to 7.66)	0.38 (0.08 to 1.67)	1.15 (0.70 to 1.87)	NA	/
Talc via IPC	0.5 (0.06 to 4.42)	0.33 (0.07 to 1.52)	0.25 (0.04 to 1.61)	0.49 (0.07 to 3.38)	**0.15 (0.02 to 0.89)**	0.42 (0.1 to 1.58)	0.42 (0.12 to 1.35)	1.35 (0.16 to 13.23)	0.6 (0.11 to 3.29)	0.77 (0.13 to 4.49)	**0.13 (0.02 to 0.92)**	0.39 (0.10 to 1.57)	0.34 (0.09 to 1.24)	NA
Tetra-cy-cline	3.87 (0.5 to 31.42)	**2.50 (1.08 to 6.42)**	1.94 (0.56 to 7.23)	3.7 (0.86 to 17.07)	1.14 (0.34 to 4.31)	3.22 (0.83 to 12.47)	3.21 (0.96 to 11.53)	**10.45 (1.50 to 89.12)**	**4.58 (1.12 to 21.00)**	**5.86 (1.65 to 22.83)**	0.99 (0.19 to 5.22)	**2.99 (1.07 to 9.3)**	2.59 (0.90 to 8.32)	**7.64 (1.46 to 43.73)**

Results that are significant at the conventional level of P ≤ 0.05 are in bold

/ indicates the odds ratio is already expressed elsewhere in the table comparing the interventions the other way around

Cr-I: credible interval; IFN: interferon; IPC: indwelling pleural catheter; NA: not applicable

Appendix 15. Estimated rank (95% Cr-I) for mortality (low rank suggesting higher mortality)

Pleurodesis agent	Estimated rank (95% Cr-I)
Talc via IPC	2 (1 to 11)
Iodine	2 (1 to 11)
Mitoxantrone	3 (1 to 10)
Mepacrine	5 (1 to 12)
Doxycycline	6 (1 to 14)
Autologous blood	6 (1 to 15)
IPC –not daily drainage	7 (3 to 12)
IPC –daily drainage	7 (3 to 13)
Talc Poudrage	8 (4 to 12)
Talc Slurry	9 (6 to 13)
Bleomycin	10 (4 to 13)
C parvum	11 (3 to 15)
IFN	13 (7 to 15)
Tetracycline	14 (10 to 15)
Mustine	14 (6 to 15)

Cr-I: credible interval; IFN: interferon; IPC: indwelling pleural catheter

WHAT'S NEW

Date	Event	Description
10 February 2020	New search has been performed	This review has been updated with the results of a new search in June 2019.
10 February 2020	New citation required and conclusions have changed	The conclusions have changed due to the inclusion of 18 new studies (2079 participants). We have more data to be more certain of the effects of talc slurry, talc poudrage and indwelling pleural catheters.

HISTORY

Protocol first published: Issue 5, 2013
Review first published: Issue 5, 2016

Date	Event	Description
9 April 2019	Amended	Comma deleted in ongoing study reference (OPUS Trial).
2 April 2019	Amended	Published Notes text amended.
11 January 2018	Review declared as stable	See Published notes.
21 August 2014	Amended	Updated the authors' Declaration of Interest statements.

CONTRIBUTIONS OF AUTHORS

The protocol was written collaboratively by AOC, HEJ, RB, NP, NAM.

AD and AOC screened the titles and abstracts and obtained the full-text papers for the 2020 update. Screening of titles and abstracts up to 2016 was by AOC only.

AD, AOC, NAM assessed the full-text articles for inclusion.

AD, AOC, NP, RB and NAM performed the data extractions.

AD and AOC entered the data into Review Manager (and RevMan Web for 2020 update) and undertook the direct pair-wise comparisons.

HJ performed the network meta-analysis and provided statistical support.

AD and AOC drafted the final report, which was reviewed and amended by all the authors.

AOC and NAM are responsible for future updates.

DECLARATIONS OF INTEREST

AD: none known.

HJ: none known.

RB was the trial co-ordinator for the TAPPS and IPC-Plus studies (Bhatnagar 2018; Bhatnagar 2020), but did not perform the data extractions, or any assessments of risk of bias or GRADE, for these studies for the purposes of this review.

NJP: none known.

NM was a member of the trial steering committee for TIME-1 and TIME-3 trials (Mishra 2018; Rahman 2015). NM is a co-author for one of the included studies (Maskell 2004). However, he did not perform the data extractions, nor any assessments of risk of bias or GRADE, for these studies for the purposes of this review. North Bristol NHS Trust received unrestricted research funding from CareFusion, to run the IPC-Plus trial (Bhatnagar 2018) (2012 to 2016) for which NM was the chief investigator. NM also received honoraria from CareFusion for medical advisory board meetings (2015 to 2019).

AOC was involved in co-ordinating and recruiting to the TIME-3 trial (Mishra 2018). She also recruited to the TAPPS trial (Bhatnagar 2020), and assisted with the data analysis. She did not perform the data extraction, nor any assessments of risk of bias or GRADE, for these studies for the purpose of this review.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health and Care Excellence (NICE), UK.

  NIHR Project Reference: NIHR 129794. Cochrane priority reviews for NICE: update commissioned by NICE for completion by March 2020; relevant guideline: Lung cancer: diagnosis and management, NICE guideline [NG122].

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2016 review

The wording of the background and methods sections have been improved to make them more concise, minimise repetition and to reflect the recently published literature.

In the original protocol, we stated we would use risk ratios for dichotomous outcomes; however, we elected to use odds ratios instead, since network meta-analysis models are more readily available for these.

The protocol stated that the size of the study would be assessed to look for bias associated with small-study effects. This was not performed, as size in itself should not affect the study results and inclusion of sample size in 'Risk of bias' tables would be against the advice in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), and training provided by the Cochrane Bias Methods Group.

The protocol combined blinding of participants and personnel and outcome assessment into a single domain. However, in light of new guidance from Cochrane, this was separated into 'blinding of participants and personnel' and 'blinding of outcome assessment', as per the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

The protocol stated we would evaluate mortality in the short, medium and long term. However, due to a paucity of evidence at all these different time points, an overall assessment was done using the available study data closest to three months after the intervention.

The wording of the planned sensitivity analyses has been amended for clarity.

For clarity, we added 'a network meta-analysis' to the title.

Post-hoc, we chose to perform a sensitivity analysis of the main network excluding talc poudrage and IPCs in order to remove the effect of mode of administration to identify which agent may be best delivered via a standard chest tube.

2020 update

We further updated the wording of the background sections to reflect recent literature. We performed a search for ongoing studies on clinical trial registries, and extracted information on study funding sources and study author conflicts of interest statements, in line with current Cochrane standards.

We added "methods to optimise IPC use including IPC drainage regimen and combined talc administration via IPC" to the list of types of interventions because data from newer studies, which have investigated whether daily IPC drainage or talc slurry via IPC may result in fewer pleurodesis failures in comparison to standard IPC use (with drainage based on symptoms), is included in this review.

We expanded the interventions of direct interest to include 'IPC (both daily drainage and without daily drainage) and talc administered via IPC' to reflect the different ways in which IPCs are studied in more recent literature.

We included that 'for studies evaluating IPCs, we judged that an effective pleurodesis was achieved when there was cessation of pleural fluid drainage or device removal due to cessation of drainage, or both' to reflect a more specific and clinically relevant definition of pleurodesis failure relating to IPC use. This was used in preference to the other definitions of pleurodesis failure, listed in the hierarchy of preferences, in participants receiving an IPC.

In the 'Methods', for unit of analysis issues we added that 'in meta-analysis of continuous outcomes, we pooled differences in change from baseline, rather than differences in final values (Higgins 2019)' in keeping with *Cochrane Handbook for Systematic Reviews of Interventions* guidance.

In the 'Methods', we added that 'for continuous outcomes, where baseline and final values were reported without a standard deviation of change score or correlation coefficient, we imputed correlation coefficients based on other studies in order to estimate the standard deviation of change' in keeping with *Cochrane Handbook for Systematic Reviews of Interventions* guidance.

Although the use of network meta-analysis was mentioned in the published protocol, further details have been included to clarify the methodology. This includes details on prior distributions and methodology used to quantify heterogeneity and check for inconsistency. Further, for the main analyses, we plotted the mean residual deviance contributions of each data point under the inconsistency versus network meta-analysis models. This allows identification of specific data points for which the inconsistency model has improved fit, that is, data points that are potentially inconsistent with the network (Dias 2018). These changes are based on the protocol template from the Comparing Multiple Interventions Methods Group, which was not available when we wrote our original protocol.

In 'Sensitivity analyses', we added 'analysis only including studies which administered pleurodesis through a chest tube (any size)', and slightly amended our criteria for low-risk studies to 'analysis only including studies at a low risk of bias (*maximum of one domain assessed as high risk of bias*)' to ensure the sensitivity analysis for studies at low risk of bias included only the most robust data, to give a greater level of certainty in the estimate of the effect.

We added that 'we performed a post-hoc sensitivity network meta-analysis evaluating only pleurodesis agents delivered via a chest tube (as opposed to being given at thoracoscopy). We removed the trials evaluating talc poudrage and IPC use from the main network and repeated the analysis. We performed an additional post-hoc pair-wise meta-analysis comparing ipsilateral repeat invasive pleural intervention rates (where data were available).'

We performed sensitivity analyses of direct evidence on pleurodesis failure using fixed-effect meta-analysis models, since pooled effect estimates from random-effects models give relatively more weight to smaller studies, which is often considered undesirable.

Within the patient acceptability secondary outcome, we considered that the risk of requiring a repeat invasive pleural procedure for symptomatic re-accumulation of pleural fluid is an important factor when selecting an initial management strategy for MPE. Therefore, we performed a post-hoc direct meta-analysis of requirement for a repeat ipsilateral invasive pleural intervention.

We added an assessment of the certainty of the body of evidence and include 'Summary of findings' tables, which present outcomes from the main network meta-analysis for pleurodesis failure, adverse events (fever and pain) and mortality. Where sufficient data enabled direct meta-analysis of breathlessness improvement and repeat invasive pleural intervention for the most commonly used interventions, we also included this information in the summary tables.

INDEX TERMS

Medical Subject Headings (MeSH)

Bleomycin [therapeutic use]; Doxycycline [therapeutic use]; Fever [etiology]; Iodine [therapeutic use]; Pleural Effusion, Malignant [etiology] [*therapy]; Pleurodesis [*methods]; Quinacrine [therapeutic use]; Randomized Controlled Trials as Topic; Talc [therapeutic use]; Treatment Failure

MeSH check words

Adult; Humans