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Interventions for treating tuberculous pericarditis (Review)

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Interventions for treating tuberculous pericarditis.
Cochrane Database of Systematic Reviews 2017, Issue 9. Art. No.: CD000526.
DOI: 10.1002/14651858.CD000526.pub2.

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[Intervention Review]

Interventions for treating tuberculous pericarditis

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Editorial group: Cochrane Infectious Diseases Group.
Publication status and date: Unchanged, published in Issue 9, 2017.

Citation: Wiysonge CS, Ntsekhe M, Thabane L, Volmink J, Majombozi D, Gumedze F, Pandie S, Mayosi BM. Interventions for treating tuberculous pericarditis. *Cochrane Database of Systematic Reviews* 2017, Issue 9. Art. No.: CD000526. DOI: 10.1002/14651858.CD000526.pub2.

ABSTRACT

Background

Tuberculous pericarditis can impair the heart's function and cause death; long term, it can cause the membrane to fibrose and constrict causing heart failure. In addition to antituberculous chemotherapy, treatments include corticosteroids, drainage, and surgery.

Objectives

To assess the effects of treatments for tuberculous pericarditis.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register (27 March 2017); the Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library (2017, Issue 2); MEDLINE (1966 to 27 March 2017); Embase (1974 to 27 March 2017); and LILACS (1982 to 27 March 2017). In addition we searched the metaRegister of Controlled Trials (mRCT) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal using 'tuberculosis' and 'pericard*' as search terms on 27 March 2017. We searched ClinicalTrials.gov and contacted researchers in the field of tuberculous pericarditis. This is a new version of the original 2002 review.

Selection criteria

We included randomized controlled trials (RCTs) and quasi-RCTs.

Data collection and analysis

Two review authors independently screened search outputs, evaluated study eligibility, assessed risk of bias, and extracted data; and we resolved any discrepancies by discussion and consensus. One trial assessed the effects of both corticosteroid and *Mycobacterium indicus pranii* treatment in a two-by-two factorial design; we excluded data from the group that received both interventions. We conducted fixed-effect meta-analysis and assessed the certainty of the evidence using the GRADE approach.

Main results

Seven trials met the inclusion criteria; all were from sub-Saharan Africa and included 1959 participants, with 1051/1959 (54%) HIV-positive. All trials evaluated corticosteroids and one each evaluated colchicine, *M. indicus pranii* immunotherapy, and open surgical drainage. Four trials (1841 participants) were at low risk of bias, and three trials (118 participants) were at high risk of bias.

In people who are not infected with HIV, corticosteroids may reduce deaths from all causes (risk ratio (RR) 0.80, 95% confidence interval (CI) 0.59 to 1.09; 660 participants, 4 trials, *low certainty evidence*) and the need for repeat pericardiocentesis (RR 0.85, 95% CI 0.70 to 1.04; 492 participants, 2 trials, *low certainty evidence*). Corticosteroids probably reduce deaths from pericarditis (RR 0.39, 95% CI 0.19 to 0.80; 660 participants, 4 trials, *moderate certainty evidence*). However, we do not know whether or not corticosteroids have an effect on constriction or cancer among HIV-negative people (*very low certainty evidence*).

In people living with HIV, only 19.9% (203/1959) were on antiretroviral drugs. Corticosteroids may reduce constriction (RR 0.55, 0.26 to 1.16; 575 participants, 3 trials, *low certainty evidence*). It is uncertain whether corticosteroids have an effect on all-cause death or cancer (*very low certainty evidence*); and may have little or no effect on repeat pericardiocentesis (RR 1.02, 0.89 to 1.18; 517 participants, 2 trials, *low certainty evidence*).

For colchicine among people living with HIV, we found one small trial (33 participants) which had insufficient data to make any conclusions about any effects on death or constrictive pericarditis.

Irrespective of HIV status, due to very low certainty evidence from one trial, it is uncertain whether adding *M. indicus pranii* immunotherapy to antituberculous drugs has an effect on any outcome.

Open surgical drainage for effusion may reduce repeat pericardiocentesis In HIV-negative people (RR 0.23, 95% CI 0.07 to 0.76; 122 participants, 1 trial, *low certainty evidence*) but may make little or no difference to other outcomes. We did not find an eligible trial that assessed the effects of open surgical drainage in people living with HIV.

The review authors found no eligible trials that examined the length of antituberculous treatment needed nor the effects of other adjunctive treatments for tuberculous pericarditis.

Authors' conclusions

For HIV-negative patients, corticosteroids may reduce death. For HIV-positive patients not on antiretroviral drugs, corticosteroids may reduce constriction. For HIV-positive patients with good antiretroviral drug viral suppression, clinicians may consider the results from HIV-negative patients more relevant.

Further research may help evaluate percutaneous drainage of the pericardium under local anaesthesia, the timing of pericardiectomy in tuberculous constrictive pericarditis, and new antibiotic regimens.

2 April 2019

Up to date

All studies incorporated from most recent search

All eligible published studies found in the last search (27 Mar, 2017) were included and one ongoing study was identified (see 'Characteristics of ongoing studies' section)

PLAIN LANGUAGE SUMMARY

Treatment for tuberculosis infection of the membrane around the heart

What is the issue?

Tuberculosis infection of the pericardium surrounding the heart is uncommon but life-threatening.

What is the aim of this review?

The aim of this Cochrane Review was to assess the effects of treatments for people with tuberculous pericarditis.

What is this important?

Doctors prescribe antituberculous drugs for six months, drain fluid from the pericardium if the patient has heart failure, and sometimes remove the pericardium if it is thick and making the patient ill and sometimes give corticosteroids to reduce the effects of the inflammation.

What are the main results of the review?

Cochrane researchers collected and examined all potentially relevant studies and found seven trials, all conducted in sub-Saharan Africa. Six trials evaluated corticosteroids. Other treatments evaluated included *Mycobacterium indicus pranii* immunotherapy, colchicine, and surgical removal of fluid under general anaesthesia. This review is a new edition of the 2002 review.

In people not infected with HIV, six trials found that additional steroids may reduce deaths overall (*low certainty evidence*) and probably reduce deaths caused by pericarditis (*moderate certainty evidence*). Steroids may prevent reaccumulation of fluid in the pericardial space (*low certainty evidence*). However, we do not know whether or not corticosteroids have an effect on constriction or cancer among HIV-negative people (*very low certainty evidence*).

In people living with HIV, most people evaluated in the included trials were not on antiretroviral drugs. For these patients, corticosteroids may reduce constrictive pericarditis (*low certainty evidence*), but we do not know if this translates into a reduction in the number of deaths or cancer (*very low certainty evidence*). Corticosteroids may have little or no effect on reaccumulation of fluid in the pericardial space (*low certainty evidence*).

Colchicine was evaluated in one trial of 33 people, with insufficient data to make any conclusions about an effect.

Based on one trial, it is uncertain whether adding *M. indicus pranii* immunotherapy to antituberculous drugs has an effect on any outcome in people with tuberculous pericarditis regardless of their HIV status (*very low certainty evidence*).

Open surgical drainage of the fluid accumulating between the heart and the membrane using general anaesthesia may be associated with less life-threatening reaccumulation of fluid in people who are not infected with HIV, but conclusions are not possible as the number of participants studied was too small. We did not find an eligible trial that assessed the effects of open surgical drainage in people living with HIV.

The review authors found no eligible trials that examined the length of antituberculous treatment needed nor the effects of other adjunctive treatments for tuberculous pericarditis.

How up-to-date is this review?

The review authors searched for trials published up to 27 March 2017.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Corticosteroids for tuberculous pericarditis in HIV-negative people

Population: HIV-negative people with tuberculous pericarditis
Settings: any setting
Intervention: corticosteroids

Comaprison: placebo

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Placebo	Steroids				
Death from all causes	22 per 100	18 per 100 (13 to 24)	RR 0.80 (0.59 to 1.09)	660 (4 trials)	⊕⊕⊖⊖ low[1,2]	Steroids may reduce the risk of deaths from all causes among HIV-negative people.
Death from pericarditis	8 per 100	3 per 100 (1 to 6)	RR 0.39 (0.19 to 0.80)	660 (4 trials)	⊕⊕⊕⊖ moderate[2]	Steroids probably reduce the risk of deaths from pericarditis among HIV-negative people.
Constrictive pericarditis	10 per 100	7 per 100 (3 to 15)	RR 0.72 (0.34 to 1.55)	281 (2 trials)	⊕⊖⊖⊖ very low[2,3,4]	It is uncertain whether steroids have an effect on the risk of constriction among HIV-negative people.
Repeat pericardiocentesis	40 per 100	34 per 100 (28 to 41)	RR 0.85 (0.70 to 1.04)	492 (2 trials)	⊕⊕⊖⊖ low[1,4]	Steroids may reduce the risk of repeat drainage of the pericardium among HIV-negative people.
Cancer	1 per 100	1 per 100 (0 to 12)	RR 0.85 (0.05 to 13.80)	256 (1 trial)	⊕⊖⊖⊖ very low[3,5]	It is uncertain whether steroids have an effect on the risk of cancer among HIV-negative people.

Abbreviations: CI: confidence interval; RR: risk ratio.

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

[1]We downgraded by 1 for imprecision: the CI ranges from a large clinical benefit to a small increase in harm.
[2]We downgraded by 1 for study limitations: one trial was at high risk of bias.
[3]We downgraded by 2 for imprecision: the CI ranges from clinically important benefits to a large increase in harm.
[4]We downgraded by 1 for selective reporting: data were only reported by 2 of the 4 trials that recruited HIV-negative people.
[5]We downgraded by 1 for selective reporting: data were only reported by 1 of the 4 trials that recruited HIV-negative people.

Summary of findings 2. Corticosteroids for tuberculous pericarditis in HIV-positive people

Population: HIV-positive people with tuberculous pericarditis. Most patients (80%) not on antiretroviral drugs
Settings: any setting
Intervention: corticosteroids

Comparison: placebo

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Placebo	Corticosteroids				
Death from all causes	17 per 100	15 per 100 (6 to 40)	RR 0.91 (0.34 to 2.42)	575 (3 trials)	⊕⊖⊖⊖ very low[1,2]	It is uncertain whether steroids have an effect on the risk of deaths from all causes among people living with HIV.
Death from pericarditis	4 per 100	4 per 100 (2 to 10)	RR 1.07 (0.46 to 2.54)	517 (2 trials)	⊕⊖⊖⊖ very low[1,3]	It is uncertain whether steroids have an effect on the risk of deaths from pericarditis among people living with HIV.
Constrictive pericarditis	6 per 100	4 per 100 (2 to 7)	RR 0.55 (0.26 to 1.16)	575 (3 trials)	⊕⊕⊖⊖ low[1]	Steroids may reduce the risk of developing constriction among people living with HIV.
Repeat pericardiocentesis	60 per 100	61 per 100 (53 to 71)	RR 1.02 (0.89 to 1.18)	517 (2 trials)	⊕⊕⊖⊖ low[3,5]	Steroids may have little or no effect on the risk of repeat pericardiocentesis among people living with HIV.
Cancer	1 per 100	1 per 100 (0 to 8)	RR 1.62 (0.27 to 9.77)	502 (1 trial)	⊕⊖⊖⊖ very low[1,3]	It is uncertain whether steroids have an effect on the risk of cancer among people living with HIV.

Abbreviations: CI: confidence interval; RR: risk ratio.

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

[1]We downgraded by 2 for imprecision: the CI ranges from substantial clinical benefits to substantial harm.
[2]We downgraded by 1 for unexplained heterogeneity ($Chi^2 = 3.82$, df = 1 (P = 0.05); I^2 statistic = 74%).
[3]We downgraded by 1 for selective reporting: only 2 of the 3 studies that recruited HIV-positive people reported data.

[4]We downgraded by 1 for study limitations: 1 study had a high risk of bias.
[5]We downgraded by 1 for imprecision: the CI ranges from a small beneficial effect to clinically important harms.

BACKGROUND

Description of the condition

Tuberculous pericarditis refers to an infection of the membrane that covers the heart (pericardium) by the bacterium *Mycobacterium tuberculosis*. Infection of the pericardium can result in fluid accumulation around the heart, which constrains the heart's pumping action (tamponade), and is life-threatening. Sometimes the infection causes a thickening of the pericardium without an effusion (constrictive pericarditis), and this can also constrain the pumping action (Mayosi 2005; Ntsekhe 2012). Tuberculous pericarditis manifests with fatigue, shortness of breath, swelling of the body, and can cause death.

Healthcare practitioners in low- and middle-income countries, where tuberculosis is common, are familiar with the condition (Gelfand 1957; Strang 1984). In high-income countries, the condition occurs in less than 5% of all people with tuberculosis (Lorell 1997; Imazio 2015). The human immunodeficiency virus (HIV) epidemic has resulted in more cases of tuberculosis in Africa and other resource-constrained regions, with a consequent rise in tuberculous pericarditis (Cegielski 1990; Mayosi 2006; Mayosi 2008). Post-mortem examinations conducted before the HIV era indicate that the pericardium is involved in 1% of people infected with tuberculosis (Fowler 1991). However, identical studies in people who died with advanced HIV reveal that extrapulmonary disease with multiple organ involvement is more frequent (Lucas 1993; Rana 1997). In people living with HIV who have pericardial effusion, tuberculosis is the cause in over four-fifths of cases (Ntsekhe 2005). In addition, the burden of tuberculous pericarditis experienced a rapid increase in regions of the world where tuberculosis-HIV co-infection is common (Ntsekhe 2013). This could be explained in part by the fact that the lifetime risk of tuberculosis in immune-competent people without HIV infection is 10% (Lawn 2011), which increases to a yearly risk of 10% early in HIV infection and up to a 30% yearly risk in people with advanced immunosuppression (Maartens 2007).

In the pre-antibiotic era, mortality of people with tuberculous pericarditis was 80% to 90% (Harvey 1937), but the advent of effective antituberculous chemotherapy in the 1940s resulted in a decrease in case fatality rate to about 35% by 1970 (Rooney 1970). However, even with antituberculous drug regimens that contain rifampicin and isoniazid, the mortality rate remains high and is estimated to be between 8% and 17% in people without HIV infection (Desai 1979; Bhan 1980). In addition, HIV infection has an adverse effect on mortality rate (Mayosi 2005; Ntsekhe 2008; Wiysonge 2008). In one study, 185 participants with tuberculous pericarditis were consecutively enrolled in 15 referral hospitals in three African countries (Cameroon, Nigeria, and South Africa) between March 2004 and October 2004; and followed up during the six-month course of antituberculous treatment (Mayosi 2006). The mortality rate in this study was 17% in people without clinical evidence of HIV infection and 40% in people with clinical features of HIV infection (Mayosi 2008). HIV-associated tuberculous pericarditis more often occurs as part of a disseminated process with a greater amount of heart muscle involvement, and patients have larger fluid accumulation in the pericardium (Ntsekhe 2013).

Description of the intervention

Doctors currently prescribe rifampicin, isoniazid, pyrazinamide, and ethambutol for six months; remove fluid from the pericardium if the patient is very sick; and remove the membrane if it is thick and making the patient ill (Mayosi 2002). However, the number of complications and deaths due to the disease remain high (Mayosi 2008; Ntsekhe 2013). It has been proposed that adding corticosteroids to antituberculous antibiotics would lead to further decreases in the aggressiveness of the disease and deaths. Some study authors recommend the routine use of corticosteroids in all cases of tuberculous pericarditis (Alzeer 1993; Senderovitz 1994; Strang 1997). In contrast, other experts advise that corticosteroids should be reserved for people who are critically ill with recurrent large effusion and who do not respond to pericardial drainage and antituberculous drugs alone (Lorell 1997).

In addition to the corticosteroid controversy, there is no consensus regarding the optimal use of other therapeutic interventions (Ntsekhe 2013). Removal of fluid can be percutaneous under local anaesthesia or surgical under general anaesthesia. Furthermore, doctors can differ in the way they manage this condition in terms of duration of antituberculous drugs and when to operate. Other potential treatments for tuberculous pericarditis may include intrapericardial fibrinolysis (Augustin 2011), cellular therapy, use of repurposed drugs, cytokine therapy (Zumla 2015), and surgical removal of the thickened membrane (that is pericardiectomy) (Schrire 1967; Quayle 1987).

How the intervention might work

Length of treatment

Various specialists recommend different antibiotic treatment regimens of different lengths, from six months to 12 months (Sagristà-Sauleda 1988; Fowler 1991; Koh 1994; Strang 2004a; Strang 2004b). It is uncertain whether longer treatment leads to better outcomes (Mayosi 2002).

Corticosteroids

The inflammatory response to tuberculous bacilli penetrating the pericardium is responsible for the morbidity and mortality associated with tuberculous pericarditis (Mayosi 2005). Corticosteroids are anti-inflammatory drugs that may attenuate the inflammatory response and improve outcomes by reducing the accumulation of fluid or development of adhesions in the pericardium (Wiysonge 2008). In people living with HIV, active tuberculosis increases immune activation and accelerates progression to the acquired immunodeficiency syndrome; which results in early death. Corticosteroids may improve survival in HIV-positive people that have tuberculous pericarditis by modulating this immunological response (Wiysonge 2008). However, there is concern that corticosteroids may increase the risk of opportunistic infections and cancer in people living with HIV (Mayosi 2014).

Immunomodulators

As a result of advancements in the understanding of the immunopathogenesis of tuberculosis, there has been an increasing interest in immunotherapies as adjunctive treatments to standard antituberculous drug regimens. *Mycobacterium indicus pranii* is a non-pathogenic, saprophytic, rapidly growing atypical *Mycobacterium* species that has immunomodulating properties (Saini 2009). When administered as an intradermal heat-killed

vaccine, *M. indicus pranii* stimulates a Th1 cellular immune response against shared epitopes for *M. tuberculosis*, which leads to an improved cell-mediated immune response, and therefore less severe disease (Ganju 1990; Singh 1992). A systematic review suggested that *M. indicus pranii* administration may reduce the time to cure of pulmonary tuberculosis, while acknowledging the need for further large trials (Pandie 2014).

Surgical options

Early drainage

Complete drainage of the pericardial fluid is sometimes performed as an open surgical procedure under general anaesthesia (Strang 2004b), or percutaneously under local anaesthesia with ultrasound or fluoroscopic guidance. The requirement and optimal method for drainage is not known (Strang 2004b).

Removal of the pericardium

In tuberculous constrictive pericarditis, some specialists advise an early conservative approach with surgery applied to patients who do not respond after an initial period of antituberculous medication (Schrire 1967). Others advise early surgery in all affected cases (Quayle 1987).

Why it is important to do this review

This is an update of a Cochrane Review first published in 2000 (Mayosi 2000), and previously updated in 2002 (Mayosi 2002). The previous version included four trials of corticosteroids (Schrire 1959; Hakim 2000; Strang 2004a; Strang 2004b). Early publications of small trials conducted in the pre-HIV era reported fewer deaths with corticosteroids compared to placebo, but the confidence interval (CI) ranged from a substantial reduction to a clinically important increase in deaths (risk ratio 0.65, 95% CI 0.36 to 1.16; 350 participants, 2 trials) (Strang 2004a; Strang 2004b). Similar results were obtained among people living with HIV (risk ratio 0.50, 95% CI 0.19 to 1.28; 58 participants, 1 trial) (Hakim 2000). One trial showed that complete drainage of the pericardial fluid may relieve cardiac tamponade (Strang 2004b). However, two previously included trials have reported additional data (Strang 2004a; Strang 2004b), and various potentially eligible trials have been published since 2002 (Strang 2004a; Strang 2004b; Cui 2005; Reuter 2006; Mayosi 2014; Liebenberg 2016).

OBJECTIVES

To assess the effects of treatments for tuberculous pericarditis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) and quasi-RCTs.

Types of participants

People of all ages that required treatment for clinically diagnosed tuberculous pericarditis (effusive, constrictive, or effusive-constrictive), whether HIV-negative or HIV-positive.

Types of interventions

- Long versus shorter durations of antituberculous chemotherapy.
- Corticosteroids versus no corticosteroids.
- Immunomodulators versus no immunomodulators.
- Surgical procedures versus conservative management.
- Other treatments for tuberculous pericarditis.

Types of outcome measures

Primary outcomes

- Deaths from all causes.

Secondary outcomes

- Death from pericarditis.
- Constrictive pericarditis.
- Repeat pericardiocentesis.
- Cancer.
- Hospitalization.
- Pericardiectomy.
- Opportunistic infections.

Search methods for identification of studies

Electronic searches

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

We searched the following databases using the strategy described in Appendix 1: the Cochrane Infectious Diseases Group Specialized Register (27 March 2017); the Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library (2017, Issue 2); MEDLINE (1966 to 27 March 2017); Embase (1974 to 27 March 2017); and LILACS (1982 to 27 March 2017).

Searching other resources

We searched the metaRegister of Controlled Trials (mRCT) and the WHO International Clinical Trials Registry Platform (ICTRP) search portal using 'tuberculosis' and 'pericard*' as search terms on 27 March 2017.

We also searched ClinicalTrials.gov and contacted researchers in the field of tuberculous pericarditis in March 2017.

In addition, we examined existing reviews of tuberculous pericarditis for relevant citations (Schrire 1967; Bhan 1980; Fowler 1991; Fowler 1992; Alzeer 1993; Senderovitz 1994; Fowler 1995; Cisneros 1996; Dooley 1997; Strang 1997; Mayosi 2002; Ntsekhe 2003; Mayosi 2005; Syed 2007; Imazio 2015; Zumla 2015).

Data collection and analysis

We conducted screening of search outputs, assessment of potentially eligible studies, assessment of risk of bias, and data extraction for this review in line with the Cochrane policy on trial authors who are also review authors (Kliner 2014). In addition, two Cochrane Infectious Disease Group (CIDG) Editors (Paul Garner and David Sinclair) provided oversight for data collection and analysis.

Selection of studies

Three review authors, Charles Wiysonge (CSW), Dumo Majombozi (DM), and Bongani M Mayosi (BMM), independently screened abstracts identified by the search strategy for potentially eligible studies. The three review authors obtained the full-text articles of any potentially relevant articles and then assessed these studies using the prespecified trial inclusion criteria, respecting the Cochrane policy on trial authors who are also review authors (Kliner 2014). We resolved any disagreements by discussion and consensus.

Six review authors, Mpiko Ntsekhe (MN), Lehana Thabane (LT), Jimmy Volmink (JV), Freedom Gumedze (FG), Shaheen Pandie (SP), and BMM, were involved in one trial that met the inclusion criteria of this review (Mayosi 2014). Two review authors who were not involved with this trial, namely CSW and DM, independently performed the application of the inclusion criteria, 'Risk of bias' assessments, and data extraction for this trial. We excluded one potentially eligible study that did not meet the inclusion criteria and documented the reason for exclusion in the 'Characteristics of excluded studies' table. Four review authors, CSW, MN, FG, JV, and BMM, are the authors of an excluded study (Wiysonge 2008). In order to conform to existing Cochrane policies (Higgins 2011; Kliner 2014), a review author who was not involved in this study (DM) made the initial assessment of the eligibility of this study. We have included a study that is awaiting assessment in the 'Characteristics of studies awaiting classification' table (Cui 2005).

Data extraction and management

Two review authors (either CSW and BMM, or CSW and DM) independently extracted information from the included trials on methods used, participant characteristics, interventions, and outcomes. For all outcomes, we extracted the number of participants randomized and the number of participants analysed. The trials identified and included in this review all randomized individual participants and reported dichotomous outcomes. For each trial, we extracted the number of participants randomized to each intervention, as well as the number of participants with an outcome of interest and the number included in the analysis by the trial authors.

The published article from the Mayosi 2014 trial did not provide data by HIV status, but we requested and obtained these data from the study statistician (FG). CSW entered the data into Review Manager (RevMan) (RevMan 2014), and the study statistician FG verified the entered data for accuracy.

Multiple publications from the same data constituted one included trial, and we marked the publication that provided the most data to the analyses as the primary reference (Hakim 2000; Strang 2004a; Strang 2004b; Mayosi 2014). If data were available on prespecified outcomes at two or more periods, we took the more complete or later one into account (Strang 2004a; Strang 2004b).

Assessment of risk of bias in included studies

One review author (CSW) assessed the risk of bias in each included trial using Cochrane's 'Risk of bias' assessment tool for assessing the risk of bias in intervention studies (Higgins 2011), and two review authors (BMM and DM) verified this assessment; in line with the Cochrane policy on trial authors who are also review authors (Kliner 2014). We assessed whether adequate steps were taken to reduce the risk of bias across seven specific domains, namely, random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; completeness of outcome data; selective outcome reporting; and other issues. For each included trial, we described what the trial authors reported that they did for each domain and decided the risk of bias for that domain by assigning a judgement of 'low', 'high', or 'unclear risk' of bias.

We categorized each included study into one of two levels of bias: low or high risk of bias. Studies with a high risk of selection bias (from inadequate random sequence generation and/or allocation concealment), detection bias (from lack of blinding of outcome assessment), or attrition bias (from incomplete outcome data) were categorized as having high risk of bias. We considered all other included trials to have a low risk of bias. We compared the results of independent 'Risk of bias' assessments and resolved disagreements by consensus.

Measures of treatment effect

All of the included trials reported dichotomous data, so we expressed the results as risk ratios (RR) with 95% CIs for each outcome.

Unit of analysis issues

We did not encounter any unit of analysis issues in this review, as all included trials were individually RCTs.

Dealing with missing data

We stratified analyses by HIV status. However, data on HIV status were unavailable in three trials that were conducted (or started recruitment) in South Africa before the onset of the HIV epidemic in the country. We have assumed that the participants in these studies did not have HIV infection (Schrire 1959; Strang 2004a; Strang 2004b). One trial only enrolled HIV-positive people (Hakim 2000), and two recruited both HIV-positive and HIV-negative people (Reuter 2006; Mayosi 2014). The published paper from one of the two trials did not disaggregate results by HIV status (Mayosi 2014). We requested and obtained the disaggregated outcome data from the trial statistician (FG).

Assessment of heterogeneity

We assessed whether there was heterogeneity of study participants, interventions, and outcomes in order to make a qualitative assessment of the extent to which the included studies were similar to each other. We then included clinically homogeneous studies in meta-analyses and assessed heterogeneity of study results by visually inspecting the forest plots to check for overlapping CIs. In addition, we assessed heterogeneity of effects using the Chi^2 test of homogeneity; with statistical significance defined at the 10% alpha level (that is, P = 0.10). We also used the I^2 statistic to quantify the proportion of observed variation of effects across studies, which reflected variation in true effect sizes rather than sampling error (Higgins 2011).

Assessment of reporting biases

There were too few included studies to examine publication bias using a funnel plot (Higgins 2011).

Data synthesis

Using both unpublished (Mayosi 2014), and published data (Schrire 1959; Hakim 2000; Strang 2004a; Strang 2004b; Reuter 2006; Mayosi 2014), we analysed trial participants in groups to which they were randomized; regardless of how much of the intended intervention they actually received. One included study used a 2 x 2 factorial design, in which participants received prednisolone plus *M. indicus pranii*, prednisolone plus placebo, *M. indicus pranii* plus placebo, or double placebo. There was a suggestion of clinical interaction between prednisolone and *M. indicus pranii* on cancer incidence (Mayosi 2014). Ten of the 14 cases of cancer (71.4%) occurred in the group that took prednisolone plus *M. indicus pranii.* Therefore, in the analysis of intervention effects, we considered data from the group that took only one active intervention (that is, prednisolone or *M. indicus pranii*, as the case may be); and excluded data from the group that received both interventions.

We used meta-analysis with a fixed-effect model to calculate the summary statistics. We stratified analyses according to HIV status and the type of treatment and control intervention, for example, adjunctive corticosteroids versus placebo or no treatment in HIV-negative people, adjunctive corticosteroids versus placebo or no treatment in people living with HIV.

In addition, we used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to assess the certainty of the evidence for each outcome (Guyatt 2008). We have summarized the certainty of the evidence for corticosteroids in the 'Summary of findings' tables (Summary of findings for the main comparison; Summary of findings 2), which we constructed using GRADEpro Guideline Development Tool software (GRADEpro GDT 2014).

Subgroup analysis and investigation of heterogeneity

We only conducted meta-analyses for studies with homogeneous participants, interventions, and outcomes. If we had at least 10 studies in any meta-analysis that showed significant statistical heterogeneity (that is, $P < 0.10$), we would have explored possible sources of heterogeneity by performing subgroup analyses; with subgroups defined by clinical syndromes of tuberculous pericarditis (that is, pericardial effusion versus constriction) and risk of bias (that is, low versus high).

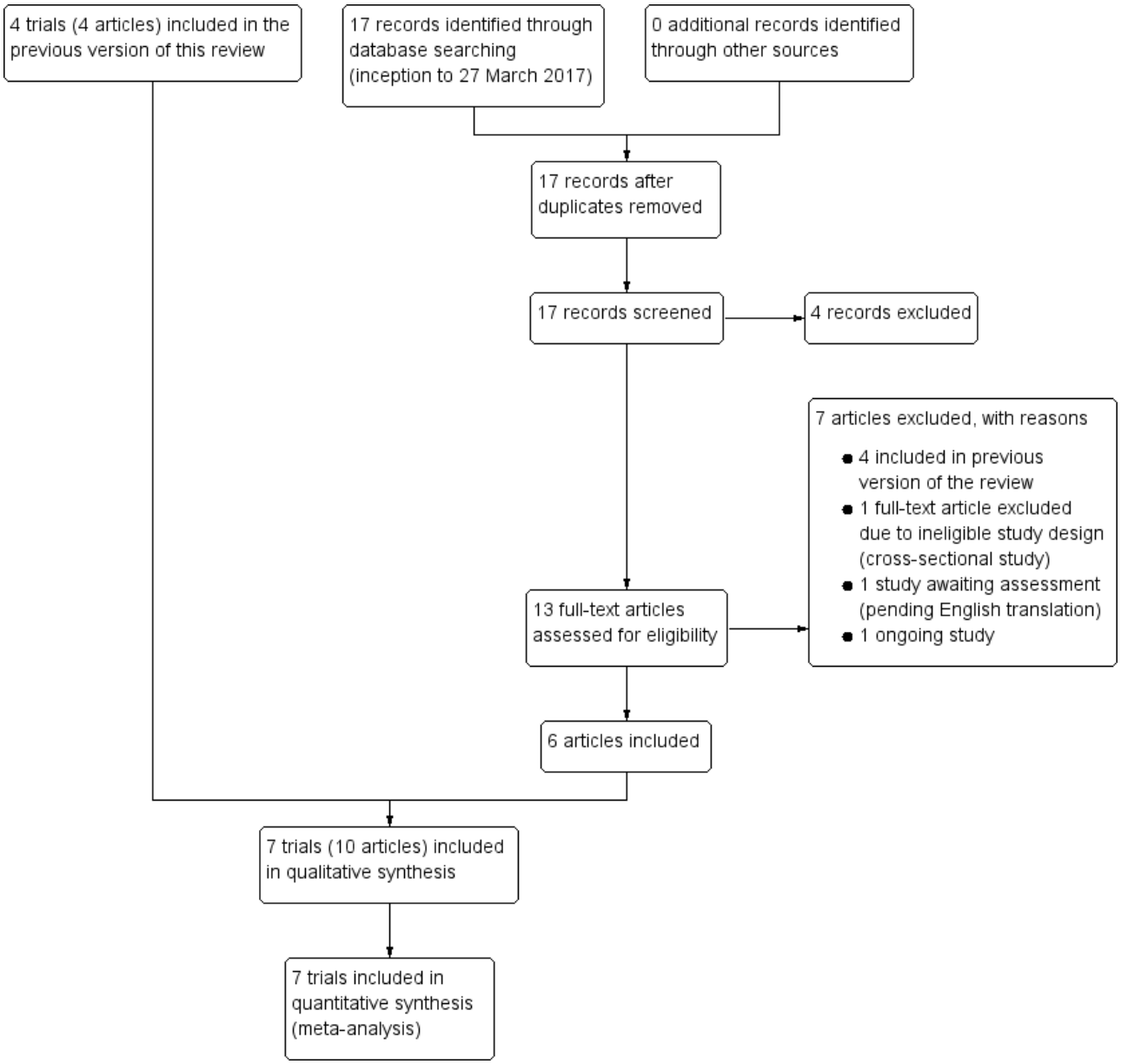
RESULTS

Description of studies

Results of the search

We have presented a PRISMA diagram that illustrates the study selection process in Figure 1.

Figure 1. Study flow diagram



For this Cochrane Review update, we performed a literature search up to 27 March 2017 covering all years; including the years covered by the previous version of the review (Mayosi 2002). This literature search yielded 17 publications. We judged four of the publications to be clearly irrelevant to the review and excluded them. We obtained the full-text articles of the 13 potentially eligible publications and assessed them for eligibility. Four articles, which contain data from four distinct studies (Schrire 1959; Hakim 2000; Strang 2004a; Strang 2004b), were already included in the previous published version of the review (Mayosi 2002). We excluded one article due to ineligible study design (Wiysonge 2008), and another one is awaiting assessment (Cui 2005). One study has not yet published outcome data and we classified it as ongoing (NCT02673879). The remaining six publications, which contain data from six distinct studies, met our inclusion criteria (Hakim 2000; Strang 2004a; Strang 2004b; Reuter 2006; Mayosi 2014; Liebenberg 2016). The most recent follow-up data for two included trials were published as one article (Strang 2004a; Strang 2004b).

Included studies

The seven eligible trials consisted of six single-country studies conducted in South Africa (Schrire 1959; Strang 2004a; Strang 2004b; Reuter 2006; Liebenberg 2016) and Zimbabwe (Hakim 2000), as well as a multicountry study conducted in Kenya, Malawi, Mozambique, Nigeria, Sierra Leone, South Africa, Uganda, and Zimbabwe (Mayosi 2014). The interventions evaluated were as follows.

- Corticosteroids (Schrire 1959; Hakim 2000; Strang 2004a; Strang 2004b; Reuter 2006; Mayosi 2014).
- Colchicine (Liebenberg 2016).
- *M. indicus pranii* immunotherapy (Mayosi 2014).

- Open surgical drainage on admission in participants with tuberculous pericardial effusion (Strang 2004b).

We have provided details of the included studies in the 'Characteristics of included studies' tables.

Optimum duration of treatment

We did not find any eligible studies that assessed different durations of antituberculosis drug regimens .

Corticosteroids

We have provided key characteristics of the six included corticosteroid trials in Table 1.

The six trials enrolled a total of 1926 participants. Over half of the participants (1018/1926; 52.9%) were confirmed HIV-positive. Only one study gave antiretroviral drugs to participants, with 203 (22%) of these HIV-positive participants on antiretroviral drugs, and thus overall only 19.9% of participants in the meta-analysis on antiretroviral therapy at enrolment. Five trials enrolled people with pericardial effusion (Schrire 1959; Hakim 2000; Strang 2004b; Reuter 2006; Mayosi 2014), and one enrolled those with pericardial constriction (Strang 2004a).

The corticosteroids assessed were cortisone (Schrire 1959), prednisone and triamcinolone hexacetonide (Reuter 2006), and prednisolone (Schrire 1959; Hakim 2000; Strang 2004a; Strang 2004b; Mayosi 2014). Schrire 1959 did not specify the length of follow-up and Reuter 2006 reported it as one year; Hakim 2000 as 18 months; Mayosi 2014 as two years; and Strang 2004a and Strang 2004b as 10 years.

Colchicine

One trial tested the effects of colchicine among 33 people with a definite or probable diagnosis of tuberculous pericarditis in Kimberley, South Africa (Liebenberg 2016). All 33 participants were HIV-positive and had pericardial effusion at enrolment. Participants in the intervention arm received colchicine 1.0 mg per day for six weeks. The control arm received identical placebo for six weeks as well. The length of follow-up was 16 weeks (Liebenberg 2016).

M. indicus pranii immunotherapy

One trial evaluated the effects of an immunomodulator, *M. indicus pranii,* among 1250 people aged 18 years or older in sub-Saharan Africa (Mayosi 2014). Two thirds (840/1250; 67.2%) of the participants were confirmed to be HIV-positive; with 172 (20.5%) on antiretroviral therapy at enrolment. All participants had pericardial effusion at enrolment. The *M. indicus pranii* preparation was given in five doses; at the time of enrolment and at 2 weeks, 4 weeks, 6 weeks, and 3 months. The control arm received identical placebo following the same schedule, and the length of follow-up was two years. This trial also assessed the effects of corticosteroids (Mayosi 2014).

Surgical drainage

One trial assessed the effects of routine open surgical drainage on admission compared to no open surgical drainage in 122 participants with tuberculous pericardial effusion in Umtata, South Africa (Strang 2004b). This trial was conducted before the onset of the HIV epidemic in the country. This study reported data at two years and at 10 years of follow-up. This trial also assessed the effects of corticosteroids (Strang 2004b).

Intrapericardial fibrinolysis

We found an ongoing trial that is assessing the effects of complete percutaneous pericardial drainage using intrapericardial alteplase compared to conventional pericardiocentesis in Cape Town, South Africa. The study started in 2016 and plans to recruit 2176 people with large pericardial effusion due to tuberculous and non-tuberculous pericarditis. The trial started with a pilot phase involving 218 people. This will confirm the feasibility of conducting a large-scale multicentre clinical trial of intrapericardial fibrinolysis in people with large pericardial effusions (NCT02673879).

Other treatments

We did not find eligible studies that assessed other potential treatments for tuberculous pericarditis such as pericardiectomy, percutaneous drainage of the pericardium under local anaesthesia, cellular therapy, use of repurposed drugs, or cytokine therapy.

Excluded studies

The excluded study is a cross-sectional analysis of the contemporary use of adjunctive corticosteroids in the management of patients with tuberculous pericarditis in Africa (Wiysonge 2008). Despite being observational in nature, this study is indexed in electronic databases as a controlled trial. We have provided furthermore details on this study in the 'Characteristics of excluded studies' table.

Studies awaiting assessment

One study is awaiting assessment, because the full-text article is in Chinese and we do not yet have an English translation (Cui 2005). In the study, consecutively recruited participants were "randomly" assigned to intervention or control arms, but the study authors did not provide any details about random sequence generation and allocation concealment in the study abstract. We have provided available details on this study in the 'Characteristics of studies awaiting classification' table.

Risk of bias in included studies

We have summarized our 'Risk of bias' judgements for each included trial in Figure 2 and Figure 3.

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

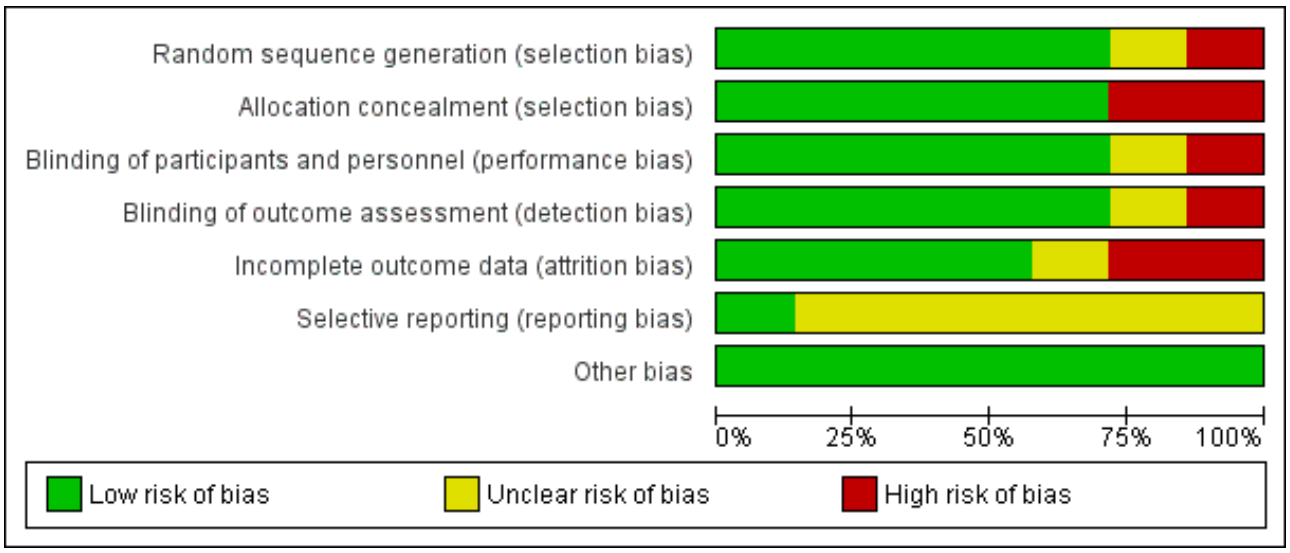
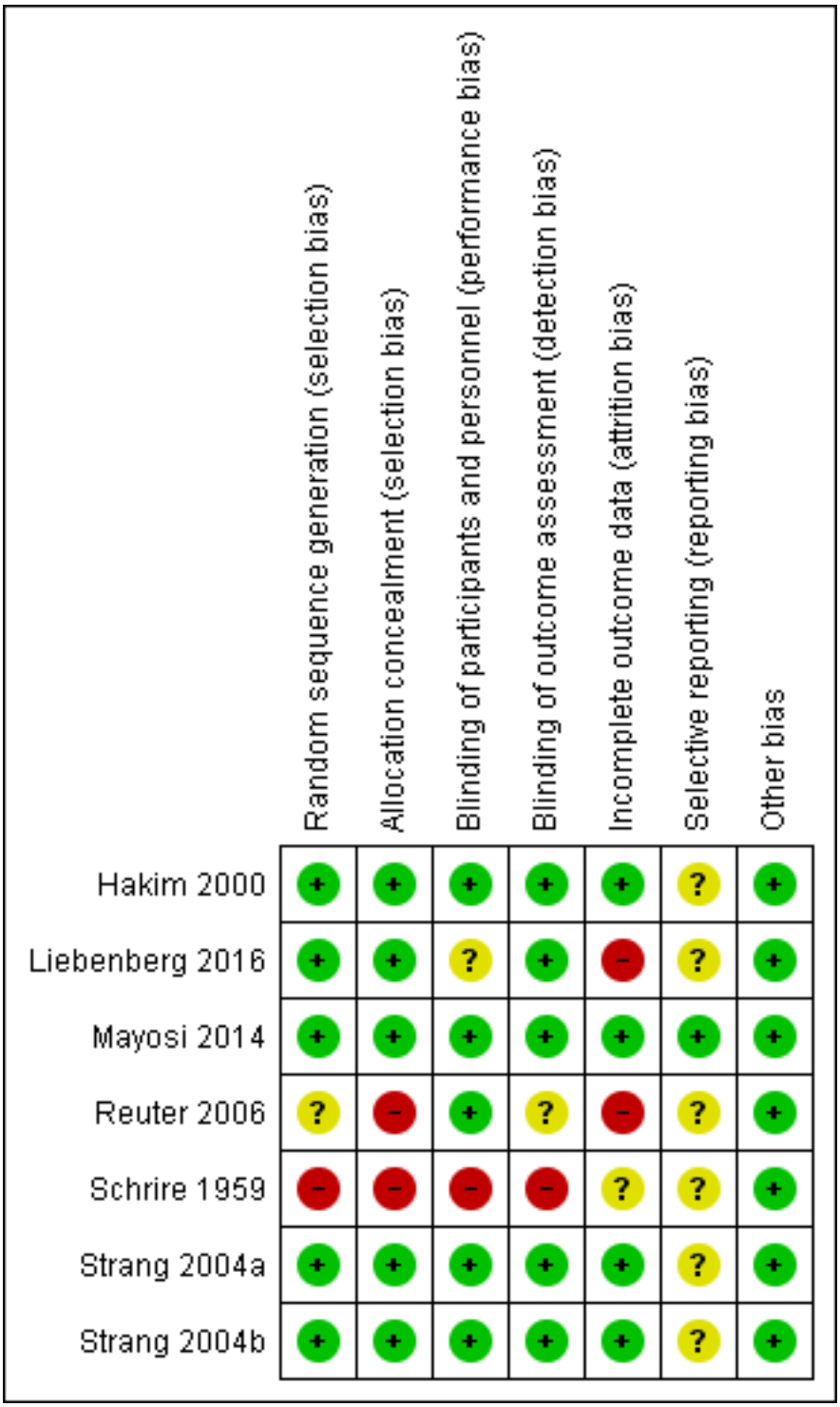


Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study



Allocation

Five trials adequately generated the randomization sequence by either a computer (Hakim 2000; Mayosi 2014; Liebenberg 2016), or a random number list (Strang 2004a; Strang 2004b). The adequacy of the generation of the randomization sequence was unclear in one trial (Reuter 2006), and inadequate in the other trial (Schrire 1959). The concealment of allocation to treatment arms was adequate in five trials (Hakim 2000; Strang 2004a; Strang 2004b; Mayosi 2014; Liebenberg 2016), and inadequate in two trials (Schrire 1959; Reuter 2006).

Blinding

Participants, care providers, and outcome assessors were blinded to treatment allocation in four trials (Hakim 2000; Strang 2004a;

Strang 2004b; Mayosi 2014). One study did not use blinding (Schrire 1959). One study reported that "upon completion of the research period, the blinding was unveiled", but does not provide details on how the blinding was done (Liebenberg 2016). In the sixth study there was blinding of participants and care providers, but it is unclear if outcome assessors were blind to treatment allocation (Reuter 2006).

Incomplete outcome data

Loss to follow-up was minimal (0% to 5%) and non-differential in four included trials (Hakim 2000; Strang 2004a; Strang 2004b; Mayosi 2014). One trial did not adequately report losses to follow-up (Schrire 1959), but losses to follow-up were high (15% to 16%) in two trials (Reuter 2006; Liebenberg 2016).

Selective reporting

One trial was free of reporting bias as the planned outcomes (as indicated in the prospective trial registration [ClinicalTrials.gov registration; NCT100810849] and published protocol) were reported in the trial report (Mayosi 2014). It was unclear to us if the remaining six studies (Schrire 1959; Hakim 2000; Strang 2004a; Strang 2004b; Reuter 2006; Liebenberg 2016) were free from reporting bias; since none of the study protocols were available and none of the trials were prospectively registered.

Other potential sources of bias

There is no evidence that the included studies had a high risk of other sources of bias; apart from those described above.

Overall 'Risk of bias' assessment

Based on the results of the 'Risk of bias' assessments for the seven domains above, we classified each included trial as either at low risk of bias or high risk of bias. Four trials had a low risk of bias (Hakim 2000; Strang 2004a; Strang 2004b; Mayosi 2014). The other three included trials were each at high risk of bias (Schrire 1959; Reuter 2006; Liebenberg 2016).

Effects of interventions

See: **Summary of findings for the main comparison** Corticosteroids for tuberculous pericarditis in HIV-negative people; **Summary of findings 2** Corticosteroids for tuberculous pericarditis in HIV-positive people

1. Corticosteroids versus no corticosteroids in HIV-negative people

1.1. Deaths from all causes

Four trials showed that corticosteroids may reduce deaths from all causes in HIV-negative people (Strang 2004a; Strang 2004b; Reuter 2006; Mayosi 2014), but the 95% CI includes the possibility of both a large beneficial effect and a small increase in harm: risk ratio (RR) 0.80, 95% CI 0.59 to 1.09; 660 participants, 4 trials; Analysis 1.1). We rated the certainty of the evidence as low (Summary of findings for the main comparison).

1.2. Deaths from pericarditis

Four trials provided data on deaths from pericarditis in people without HIV infection (Strang 2004a; Strang 2004b; Reuter 2006; Mayosi 2014). Pooling these data shows that corticosteroids probably reduce deaths from pericarditis: RR 0.39, 95% CI 0.19 to 0.80; 660 participants, 4 trials; Analysis 1.2. We rated the certainty of the evidence as moderate (Summary of findings for the main comparison).

1.3. Constrictive pericarditis

Based on two included trials, Reuter 2006 and Mayosi 2014, we are uncertain whether corticosteroids reduce the risk of constrictive pericarditis in people without HIV infection: RR 0.72, 95% CI 0.34 to 1.55; 281 participants, 2 trials; Analysis 1.3). This evidence is of very low certainty (Summary of findings for the main comparison).

1.4. Repeat pericardiocentesis

Based on two included trials, Strang 2004b and Mayosi 2014, corticosteroids may reduce the reaccumulation of fluid requiring repeat drainage of the pericardium among HIV-negative people, but the CIs include the possibility of both large beneficial effects and a small increase in harm: RR 0.85, 95% CI 0.70 to 1.04; 492 participants, 2 trials; Analysis 1.4. We rated the certainty of the evidence as low (Summary of findings for the main comparison).

1.5. Cancer

From the limited data on cancer reported by one trial (Mayosi 2014), we are uncertain about the effect of corticosteroids on the risk of cancer (RR 0.85, 95% CI 0.05 to 13.80; 256 participants (Analysis 1.5) in HIV-negative people, as the evidence is of very low certainty (Summary of findings for the main comparison).

1.6. Hospitalization

Only one trial reported on this outcome (Mayosi 2014). We are uncertain whether corticosteroids reduce the risk of hospitalization in HIV-negative people (RR 0.98, 95% CI 0.57 to 1.70; 256 participants, 1 trial; Analysis 1.6), as the currently available evidence is of very low certainty. We downgraded the evidence by two for imprecision, as the CI ranges from clinically important benefits to a large increase in harm. In addition, we downgraded by one for selective reporting, given that data were only reported by one of four trials that recruited HIV-negative people.

1.7. Pericardiectomy

Based on data from four trials (Schrire 1959; Strang 2004a; Strang 2004b; Reuter 2006), we are uncertain about the effects of corticosteroids on the risk of pericardiectomy in HIV-negative people: RR 0.91, 95% CI 0.58 to 1.41; 432 participants, 4 trials; Analysis 1.7). We rated the evidence to be of very low certainty. We downgraded the evidence by two for imprecision, as the CI ranges from large benefits to clinically important harms. We further downgraded by one for study limitations, given that two of the four trials were at high risk of bias.

1.8. Opportunistic infections

We do not know whether corticosteroids have an effect on opportunistic infections as the certainty of the evidence was assessed as very low (RR 1.71, 95% CI 0.44 to 6.69; 256 participants, 1 trial; Analysis 1.8). We downgraded the evidence by two for imprecision, as the CI ranges from clinically important benefits to a large increase in harm. In addition, we downgraded by one for selective reporting, given that data were only reported by one of four trials that recruited HIV-negative people.

2. Corticosteroids versus no corticosteroids in people living with HIV infection

2.1. Deaths from all causes

Three included trials reported on this outcome (Hakim 2000; Reuter 2006; Mayosi 2014). It is uncertain whether corticosteroids have an effect on the risk of deaths from any cause among people living with HIV (RR 0.91, 95% CI 0.34 to 2.42; 575 participants, 3 trials; Analysis 2.1). This evidence is of very low certainty (Summary of findings 2).

2.2. Deaths from pericarditis

Two trials provided data on the effects of corticosteroids on deaths from pericarditis among 517 people living with HIV (Reuter 2006; Mayosi 2014). From these data, we are uncertain whether corticosteroids have an effect on the risk of deaths from pericarditis in HIV-positive people (RR 1.07, 95% CI 0.46 to 2.54; 517 participants, 2 trials; Analysis 2.2; *very low certainty evidence*; Summary of findings 2).

2.3. Constrictive pericarditis

Currently available data from three included trials (Hakim 2000; Reuter 2006; Mayosi 2014), show that corticosteroids may reduce the risk of constrictive pericarditis among people living with HIV, but the CIs include the possibility of both large beneficial effects and a small increase in harm (RR 0.55, 0.26 to 1.16; 575 participants, 3 trials; Analysis 2.3; *low certainty evidence*; Summary of findings 2).

2.4. Repeat pericardiocentesis

Two trials reported data on the risk of reaccumulation of fluids requiring repeat drainage of the pericardium in HIV-positive people (Reuter 2006; Mayosi 2014). The combined data show that corticosteroids may have little or no effect on this outcome (RR 1.02, 95% CI 0.89 to 1.18; 517 participants, 2 trials; Analysis 2.4; *low certainty evidence*; Summary of findings 2).

2.5. Cancer

Based on currently available data from one included trial, Mayosi 2014, we are uncertain about the effects of corticosteroids on the risk of cancer in people living with HIV (RR 1.62, 95% CI 0.27 to 9.77; 502 participants, 1 trial; Analysis 2.5; *very low certainty evidence*; Summary of findings 2).

2.6. Hospitalization

Based on one included trial, Mayosi 2014, corticosteroids may reduce the risk of hospitalization in people living with HIV, but the CIs include the possibility of both large beneficial effects and a small increase in harm (RR 0.80, 95% CI 0.59 to 1.09; 502 participants, 1 trial; Analysis 2.6). This evidence is of low certainty. We downgraded the evidence by one for imprecision, as the CI ranges from clinically important benefits to little or no effect. In addition, we downgraded by one for selective reporting, given that data were only reported by one of three trials that recruited HIV-negative people.

2.7. Pericardiectomy

There is insufficient evidence from one included trial, Reuter 2006, to determine whether corticosteroids have an effect on the risk of pericardiectomy in people living with HIV (RR 2.10, 95% CI 0.10 to 44.40; 15 participants, 1 trial; Analysis 2.7; *very low certainty evidence*). We downgraded the evidence by two for imprecision, as the CI ranges from substantial benefits to clinically important harms. We further downgraded by one for selective reporting, given that data were only reported by one of three trials that recruited HIV-negative people.

2.8. Opportunistic infections

Based on data from two included trials, Reuter 2006 and Mayosi 2014, it is uncertain whether corticosteroids have an effect on the risk of opportunistic infections in HIV-positive people (RR 0.95, 95% CI 0.61 to 1.48; 517 participants, 2 trials; Analysis 2.8). We assessed the certainty of this evidence as very low. We downgraded the evidence by two for imprecision, as the CI ranges from substantial benefits to clinically important harms. We further downgraded by one for study limitations, given that one of the two trials has a high risk of bias.

3. Colchicine versus placebo

From the results of one trial among 33 HIV-positive people (Liebenberg 2016), it is uncertain whether colchicine has an effect on the risk of deaths from all causes (RR 0.74, 95% CI 0.17 to 3.12; Analysis 3.1) or constrictive pericarditis (RR 1.11, 95% CI 0.21 to 5.76; Analysis 3.2). We assessed the certainty of the evidence for each outcome as very low. We downgraded the evidence by two for imprecision, as the CI ranges from substantial benefits to clinically important harms. We further downgraded by one for study limitations, given that the included trial has a high risk of bias.

4. *M. indicus pranii* versus placebo

One trial evaluated the effects of *M. indicus pranii* immunotherapy in a two-by-two factorial design among 1250 people aged 18 years or older in Zimbabwe, South Africa, Sierra Leone, Uganda, Nigeria, Mozambique, Malawi, and Kenya (Mayosi 2014).

The trial reveals uncertainty about the effects of *M. indicus pranii* on deaths from all causes (RR 1.07, 95% CI 0.56 to 2.03; Analysis 4.1), deaths from pericarditis (RR 1.50, 95% CI 0.44 to 5.15; Analysis 4.2), constrictive pericarditis (RR 1.56, 95% CI 0.71 to 3.42; Analysis 4.3), repeat pericardiocenthesis (RR 1.21, 95% CI 0.96 to 1.52; Analysis 4.4), cancer (RR 3.03, 95% CI 0.12 to 75.37; Analysis 4.5), hospitalization (RR 1.22, 95% CI 0.70 to 2.13; Analysis 4.6), and opportunistic infections (RR 0.67, 95% CI from 0.11 to 3.90; Analysis 4.7) in HIV-negative people. The certainty of the evidence was very low for all the outcomes. We downgraded the evidence by two for imprecision, as the CIs for all outcomes range from substantial benefits to clinically important harms. We further downgraded by one for possibility of publication bias, as only one trial has so far reported data on this intervention.

Similar to HIV-negative people, among people living with HIV, we are also uncertain whether *M. indicus pranii* has an effect on the risk of deaths from all causes (Analysis 5.1), deaths from pericarditis (Analysis 5.2), constrictive pericarditis (Analysis 5.3), repeat pericardiocenthesis (Analysis 5.4), cancer (Analysis 5.5), hospitalization (Analysis 5.6), or opportunistic infections (Analysis 5.7) as the current evidence is of very low certainty. There were too few HIV-positive patients on antiretroviral treatment to assess the effects of *M. indicus pranii* in this group of participants. We downgraded the evidence by two for imprecision, as the CIs for all outcomes range from clinically important benefits to substantial increases in harms. We further downgraded by one for possibility of

publication bias, as only one trial has so far reported data on this intervention.

5. Open surgical drainage for effusion versus no drainage

One trial, conducted in South Africa, assessed the effects of routine open surgical drainage on admission to hospital compared to no intervention among 122 participants with tuberculous pericardial effusion (Strang 2004b). This trial started before the onset of the HIV epidemic in South Africa and, although no HIV testing was done, we have assumed the participants to be HIV-negative.

The results of the trial show that open surgical drainage may reduce the risk of reaccumulation of fluid requiring repeat pericardiocentesis in people without HIV infection (RR 0.23, 95% CI 0.07 to 0.76; Analysis 6.3). However, the intervention may make little or no difference to any other outcome measured in the study; including deaths from all causes (Analysis 6.1), deaths from pericarditis (Analysis 6.2), and pericardiectomy (Analysis 6.4). We rated the certainty of the evidence for each of these outcomes as low. We downgraded the evidence by one for imprecision, as the CIs for most outcomes range from clinically important benefits to little or no effect. We further downgraded by one for possibility of publication bias, as only one trial has so far reported data on this intervention.

DISCUSSION

Summary of main results

This is an update of a Cochrane Review published in 2002 (Mayosi 2002). Seven randomized controlled trials (RCTs) met the inclusion criteria of this review, and all were conducted in sub-Saharan Africa. The 2002 review included four trials (Schrire 1959; Strang 2004a; Strang 2004b; Hakim 2000). In addition to updated outcome data from two previously included trials (Strang 2004a; Strang 2004b), we have included three new trials in this update (Reuter 2006; Mayosi 2014; Liebenberg 2016). Four studies are at low risk of bias (Hakim 2000; Strang 2004a; Strang 2004b; Mayosi 2014), and three are at high risk of bias (Schrire 1959; Reuter 2006; Liebenberg 2016). The included trials enrolled 1959 participants (54% of them HIV-positive). Six trials evaluated corticosteroids (Schrire 1959; Hakim 2000; Strang 2004a; Strang 2004b; Reuter 2006; Mayosi 2014), and one each evaluated colchicine (Liebenberg 2016), *M. indicus pranii* immunotherapy (Mayosi 2014), and open surgical drainage of pericardial effusion (Strang 2004b).

The key findings from these studies are as follows.

- In people without HIV infection, corticosteroids probably reduce deaths from pericarditis (*moderate certainty evidence*) and may reduce deaths from all causes and the need for repeat pericardiocentesis (*low certainty evidence*). However, it is uncertain whether corticosteroids have an effect on any other outcome among HIV-negative people (*very low certainty evidence*) (Summary of findings for the main comparison).
- In people living with HIV and not on antiretroviral drugs, corticosteroids may reduce constrictive pericarditis and hospitalization (*low certainty evidence*). However, corticosteroids may make little or no difference to the need for repeat pericardiocentesis (*low certainty evidence*) and it is uncertain whether the intervention has an effect on deaths or any other outcome in HIV-positive people (*very low certainty evidence*) (Summary of findings 2).
- It is uncertain whether colchicine has an effect on any outcome among HIV-positive people (*very low certainty evidence*). All participants were on antiretroviral treatment.
- It is uncertain whether *M. indicus pranii* has an effect on the risk of deaths or any other outcome, regardless of HIV status (*very low certainty evidence*).
- In people without HIV infection, routine open surgical drainage for effusion may reduce the need for repeat pericardiocentesis, but may make little or no difference to any other outcome (*low certainty evidence*).

Overall completeness and applicability of evidence

We found that adjunctive corticosteroids may lead to a modest relative reduction of about 20% on the risk of all-cause mortality among HIV-negative people. Before the biggest trial on the subject was published (Mayosi 2014), two small trials, Strang 2004a and Strang 2004b, had previously suggested that adjunctive corticosteroids may reduce mortality by 35% among HIV-negative patients (Ntsekhe 2003). Regarding people living with HIV, currently available data suggest a relative reduction of 9% in mortality, but the CI ranges very widely from a 66% relative reduction to a massive 142% relative increase in mortality. Before the publication of the big trial, Mayosi 2014, data from one small trial suggested that the use of adjunctive corticosteroids among HIV-positive people with tuberculous pericarditis would result in a 50% relative reduction in mortality (Hakim 2000).

Evidence from small early trials on health interventions is often untrustworthy (Wiysonge 2014). An examination of more than 85,000 binary-outcome forest plots from more than 3000 Cochrane Reviews found that most large treatment effects emerged from small trials and when additional larger trials were performed, the effect sizes typically became much smaller (Pereira 2012).

Apart from corticosteroids, we found only one trial each that assessed the effects of colchicine (Liebenberg 2016), *M. indicus pranii* immunotherapy (Mayosi 2014), and open surgical drainage (Strang 2004b).

There is unclear evidence regarding the relationship between corticosteroids, *M. indicus pranii*, and increased rates of cancer. This merits further study. One trial found an association between increased rates of cancer among people randomized to receive both*M. indicus pranii* and corticosteroids (Mayosi 2014). However, this trial was inadequately powered to determine whether this effect was due to corticosteroids alone, *M. indicus pranii* alone, or a synergistic action between the two interventions.

We aimed to identify the optimal drug combination and treatment duration, but found no eligible trials. This is an important question in the light of the recent demonstration that the concentrations of rifampicin, ethambutol, and pyrazinamide in pericardial fluid based on current treatment regimens were dramatically low and below the minimum inhibitory concentrations of *M. tuberculosis* (Shenje 2015). Furthermore, patients with culture-confirmed tuberculous pericarditis have a high bacillary burden, and this bacterial burden drives mortality (Pasipanodya 2015). Therefore the design of a highly bactericidal regimen for this condition is needed, and testing of its effectiveness in RCTs.

Currently there are no RCTs studying the issue of timing of pericardiectomy in people with a diagnosis of tuberculous

constrictive pericarditis. The current recommendation of pericardiectomy for persistent signs of constriction after at least six weeks of antituberculous chemotherapy is based on expert opinion (Commerford 1991; Mutyaba 2014).

In addition, we found no eligible completed trials that assessed the effects of percutaneous drainage of the pericardium under local anaesthesia, intrapericardial fibrinolysis (Augustin 2011), nor novel therapies such as cellular therapy, use of repurposed drugs, and cytokine therapy (Zumla 2015).

Quality of the evidence

We included seven RCTs in this review. In the GRADE system, RCTs without important limitations constitute high certainty evidence. However, the system considers five factors that can lower the certainty of the evidence: study limitations, heterogeneity, indirectness, imprecision, and publication bias (Balshem 2011). Four included studies were well-conducted RCTs (Hakim 2000; Strang 2004a; Strang 2004b; Mayosi 2014), at a low overall risk of bias (Figure 2; Figure 3). Each of the remaining three trials had a high overall risk of bias (Schrire 1959; Reuter 2006; Liebenberg 2016). These study limitations, as well as the imprecision of most effects, had an important impact on our rating of the certainty of the evidence (see the 'Summary of findings' tables: Summary of findings for the main comparison; Summary of findings 2).

Potential biases in the review process

We minimized potential biases in the review process by adhering to the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We conducted comprehensive searches of both peer-reviewed and grey literature, without limiting the searches to a specific language. Two review authors independently assessed study eligibility, extracted data, and assessed the risk of bias in each included trial. When a potentially eligible study was conducted by review co-authors, we requested independent researchers (who were not involved in the article under consideration) to assess eligibility and (if eligible for inclusion) extract data (Kliner 2014).

Agreements and disagreements with other studies or reviews

The previously published version of this Cochrane Review, Mayosi 2002, found that corticosteroids could have important clinical benefits in both HIV-negative and HIV-positive people. However, the three included trials were too small to demonstrate a significant effect (Hakim 2000; Strang 2004a; Strang 2004b). The review authors also included one trial that examined open surgical drainage compared with conservative management, and showed that surgery relieved cardiac tamponade (Strang 2004b). A year later, Ntsekhe and colleagues published a systematic review of the effectiveness of adjunctive corticosteroids in tuberculous pericarditis, in which they concluded that corticosteroids could have large beneficial effects on mortality and morbidity in tuberculous pericarditis but published trials were too small to be conclusive (Ntsekhe 2003). No other systematic review of treatments for tuberculous pericarditis has been published since then.

Imazio 2015 published a systematic review on the causes, diagnosis, therapy, prevention, and prognosis of pericarditis. However, the authors focused the treatment component of the review on interventions for idiopathic and viral pericarditis in North America and Europe.

This Cochrane Review is therefore the most comprehensive review to date on interventions for treating tuberculous pericarditis.The review's findings are slightly different to the largest trial ever completed, authored by some of the authors of this review, which showed no significant difference for corticosteroids on a composite outcome reflecting benefit, and a slight increase in HIV-associated cancer . The finessing of the results and the interpretation is probably due to multiple factors, including combining with other studies; and re-analysing the the original trial data stratified by HIV status.

AUTHORS' CONCLUSIONS

Implications for practice

Our review shows that corticosteroids and open surgical drainage have evidence of benefit in people with tuberculous pericarditis.

In HIV-negative people, corticosteroids probably reduce deaths from pericarditis (*moderate certainty evidence*) and may reduce deaths from all causes (*low certainty evidence*) and the need for repeat pericardiocentesis (*low certainty evidence*); while open surgical drainage may reduce the subsequent need for pericardiocentesis (*low certainty evidence*).

In the treatment of people living with HIV not on antiretroviral drugs, corticosteroids may reduce constrictive pericarditis (*low certainty evidence*) and hospitalizations (*low certainty evidence*); with little or no effect on deaths (*low certainty evidence*).

Implications for research

The relationship between corticosteroids, immunomodulators, and increased rates of cancer needs to be investigated further. In addition, high-quality randomized trials are needed on percutaneous drainage of the pericardium under local anaesthesia, the timing of pericardiectomy in tuberculous constrictive pericarditis, new antibiotic regimens, cellular therapy, use of repurposed drugs, and cytokine therapy.

We will update this Cochrane Review when the ongoing trial of intrapericardial fibrinolysis is published (NCT02673879).

ACKNOWLEDGEMENTS

We thank Paul Garner and David Sinclair for guidance in the preparation of this Cochrane Review.

We are also grateful to Patrick Commerford, for contributing to earlier versions of this review.

Charles S Wiysonge's work is supported by the South African Medical Research Council, the National Research Foundation of South Africa (Grant Numbers: 106035 and 108571), and by the Effective Health Care Research Consortium. This Consortium and the CIDG editorial base are funded by UK aid from the UK Government for the benefit of developing countries (Grant: 5242). The views expressed in this publication do not necessarily reflect UK government policy.

The work of BM Mayosi is funded by the South African Medical Research Council, the National Research Foundation of South

Africa, the Wellcome Trust, and the Lily and Ernst Hausmann Research Trust.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Hakim 2000

Methods	Computer-generated randomization list Double blind placebo controlled trial
Participants	58 HIV-positive participants who were on antituberculous chemotherapy for suspected tuberculous pericarditis. Inclusion criteria: (a) age 18 to 55 years; (b) residence in Harare city to ensure good follow up; (c) HIV seropositive; (d) no diagnosis of tuberculosis within the past two years; (e) large pericardial effusion on echocardiography (> 1 cm anteriorly and > 1 cm posteriorly; and (f) pericardial aspirate with > 50% lymphocytes and protein content > 30 g/L. Exclusion criteria: (a) antituberculous treatment started more than 48 hours before recruitment; (b) corticosteroid treatment within previous one month; (c) presence of Kaposi's sarcoma or any other malignancy; (d) coexisting life threatening disease; (e) bacterial pneumonia; (f) pregnancy; (g) cavitating pulmonary tuberculosis; and (h) other causes of pericardial effusion. "All patients received a standard short course anti tuberculous regimen in accordance with national guidelines. This included rifampicin, isoniazid, pyrazinamide, and ethambutol for two months, followed by rifampicin and isoniazid for a further four months in standard doses."
Interventions	**Intervention** • Prednisolone for the first 6 weeks of antituberculous chemotherapy. • Dose for adults: 60 mg for the first week, and tapering by 10 mg every week. **Control** • Placebo.
Outcomes	**Primary outcomes** • Death. • Resolution of pericardial effusion. **Secondary outcomes** • Resolution of pretreatment symptoms and signs, and ECG changes. • Corticosteroid-related adverse effects.
Notes	Study location: Harare, Zimbabwe
Risk of bias	

Hakim 2000 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was achieved by the use of a computer generated randomisation list".
Allocation concealment (selection bias)	Low risk	"Prednisolone/placebo packages were prepared according to the randomisation list, but labelled with the study number only. A package consisted of six well labelled bottles each containing the number of tablets required in each of the six weeks of the intervention. Eligible patients were given a drug package consecutively working down the randomisation list."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Clinicians and patients were blinded to the identity of the tablets. A randomisation code list was kept sealed and was released at the end of the study".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Two cardiologists with extensive experience of echocardiography in this setting performed all examinations. "Clinicians and patients were blinded to the identity of the tablets. A randomisation code list was kept sealed and was released at the end of the study".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up data was available on all 58 enrolled participants.
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available and there is no earlier methods paper listing the prespecified outcomes.
Other bias	Low risk	There is no evidence that the study had any additional biases to the ones mentioned above.

Liebenberg 2016

Methods	Participants "were randomised to an intervention and control group using a web-based computer system that ensured assignment concealment". "Upon completion of the research period, the blinding was unveiled and data were presented for statistical analysis".
Participants	33 HIV-positive people with definite or probable tuberculous pericarditis at a secondary level hospital in the Northern Cape of South Africa. All participants received standard treatment according to the South African National Tuberculosis Management Guidelines, that is weight-adjusted antituberculosis drugs and oral corticosteroids for 4 weeks. Participants also had pericardial "aspiration until dryness", and antiretroviral therapy.
Interventions	**Intervention** • Colchicine 1.0 mg per day for 6 weeks. **Comparison** • Placebo for 6 weeks. Participants were followed up with serial echocardiography for 16 weeks.
Outcomes	**Primary outcome**

Liebenberg 2016 *(Continued)*

- Constrictive pericarditis.

Notes	Study location: Kimberley, South Africa.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The mention of an internet-based computer system implies use of a computer-generated randomization sequence.
Allocation concealment (selection bias)	Low risk	Participants "were randomised to an intervention and control group using a web-based computer system that ensured assignment concealment".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study authors reported that "Upon completion of the research period, the blinding was unveiled and data were presented for statistical analysis", but did not provide further details of blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study reported that blinding was unveiled only after completion of the follow-up period, when presenting data to the statistician.
Incomplete outcome data (attrition bias) All outcomes	High risk	In this study, 5/33 (15.15%) participants were lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	We do not have access to the study protocol and are unable to comment on whether there was selective reporting of outcomes in this study.
Other bias	Low risk	There was no evidence of other sources of bias in the study.

Mayosi 2014

Methods	Computer-generated randomization list Double-blind placebo-controlled 2 × 2 factorial study
Participants	1400 participants (two-thirds HIV-positive) 18 years of age or older, with a pericardial effusion confirmed by echocardiography, evidence of definite or probable tuberculous pericarditis, and had begun antituberculous treatment less than 1 week before enrolment. “Trial participants received antimicrobial treatment for tuberculosis and antiretroviral treatment for HIV according to World Health Organization (WHO) guidelines; management during the course of the trial was revised as recommended treatment practices evolved”.
Interventions	**Intervention 1** • Prednisolone for 6 weeks at a dose of 120 mg per day in the first week, 90 mg per day in the second week, 60 mg per day in the 3rd week, 30 mg per day in the 4th week, 15 mg per day in the 5th week, and 5 mg per day in the 6th week. **Control 1** • Identical placebo for 6 weeks at a dose of 120 mg per day in the 1st week, 90 mg per day in the 2nd week, 60 mg per day in the 3rd week, 30 mg per day in the 4th week, 15 mg per day in the 5th week, and 5 mg per day in the 6th week.

Mayosi 2014 *(Continued)*

	Intervention 2 • *M. indicus pranii* preparation (CADI-Mw injection, Cadila Pharmaceuticals) in 5 doses: at the time of enrolment and at 2 weeks, 4 weeks, 6 weeks, and 3 months. The 1st dose was given as 2 injections of 0.1 mL (containing 0.5×10^9 organisms) in each deltoid region of the upper arm; the 4 subsequent doses were given as a single injection of 0.1 mL. **Control 2** • Identical placebo in 5 doses: at the time of enrolment and at 2 weeks, 4 weeks, 6 weeks, and 3 months. The 1st dose was given as 2 injections of 0.1 mL in each deltoid region of the upper arm; the 4 subsequent doses were given as a single injection of 0.1 mL.
Outcomes	**Primary outcome** • Composite of death or 1st occurrence of cardiac tamponade requiring pericardiocentesis or constrictive pericarditis. **Secondary outcomes** • Individual components of the primary outcome. • Hospitalization. **Safety outcomes** • Opportunistic infections. • Cancer. • CD4+ T-lymphocyte cell count (measure of immunosuppression) and immune reconstitution inflammatory syndrome (in HIV-positive).
Notes	Study location: multiple sites in South Africa, Mozambique, Malawi, Uganda, Sierra Leone, Zimbabwe, Kenya, and Nigeria

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization list.
Allocation concealment (selection bias)	Low risk	Central allocation, stratified by centre, with random block sizes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both prednisolone and *M. indicus pranii* preparation had identical placebos.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	A committee of clinicians blinded to treatment allocation (the Outcomes Adjudication Committee) adjudicated all primary and secondary outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants were analysed in groups to which they were randomized, regardless of how much of the intended intervention they actually received. Primary outcome data were known for 1371 of 1400 (97.9%) participants in the prednisolone-placebo comparison; with no significant differences between prednisolone (688/706;. 97.5%) and placebo (683/694; 98.4%) arms. For the *M. indicus pranii* - placebo comparison, primary outcome data were available for 1223 of 1250 participants (97.8%); with no significant differences between *M. indicus pranii* (611/625; 97.8%) and placebo (612/625; 97.9%).

Mayosi 2014 *(Continued)*

Selective reporting (reporting bias)	Low risk	The study authors reported the outcomes planned for in the prospective trial registration (ClinicalTrials.gov registration number NCT100810849) and published protocol in the trial report.
Other bias	Low risk	There was no evidence of other biases in the study.

Reuter 2006

Methods	Computer-generated randomization list Double-blind placebo-controlled study
Participants	57 participants, aged 17 to 66 years, with large pericardial effusions on echocardiography, pericardial aspirate with protein content > 30 g/L, and pericardial fluid adenosine deaminase (ADA) activity > 35 U/L; 23 females and 34 males; 40 had microbiological or histological evidence of TB or both, and 17 patients were diagnosed by clinical and supportive laboratory data. 21 (37.0%) were HIV-positive. "A standard short-course anti-tuberculous regimen was initiated according to national guidelines, namely a combination of rifampicin, isoniazid, pyrazinamide and ethambutol for two months, followed by rifampicin and isoniazid for a further four months...Patients were discharged on anti-tuberculous therapy and pyridoxine, with or without adjunctive prednisone. HIV-positive patients also received daily oral cotrimoxazole; due to the prevailing national policy at the time of this study, none of these patients received antiretroviral therapy".
Interventions	**Intervention 1** • 200 mg (5 mL) intrapericardial triamcinolone hexacetonide. Triamcinolone was injected directly into the pericardium just prior to the removal of the indwelling catheter. Due to limited resources, an oral placebo was not used in conjunction with the intrapericardial triamcinolone. 17 participants were in this arm, 6 (35%) were HIV-positive. **Intervention 2** • Oral prednisone plus intrapericardial placebo (5 mL 0.9% saline solution). Oral prednisone was started at 60 mg/day for 4 weeks, followed by 30 mg/day for 4 weeks, 15 mg/day for 2 weeks and 5 mg/day for 1 week. There were 16 participants in this arm, 9 (56%) were HIV-positive. **Control** • Placebo (5 mL intrapericardial 0.9% saline). 24 participants were included in this arm, and 6 (25%) were HIV-positive.
Outcomes	**Primary outcome** • All-cause mortality. **Secondary outcomes** • Death attributed to pericarditis. • Disability related to pericardial disease at 1 year (defined as a history of restricted physical activity using New York Heart Association functional classification. • Effusive constriction. • Fibrous constrictive pericarditis requiring pericardiectomy.
Notes	Study location: Cape Town, South Africa. We excluded data from the intrapericardial triamcinolone arm from this review.

Reuter 2006 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were "randomly assigned as per a predetermined randomisation schedule for 100 patients on a 3:3:4 basis. Numbers were drawn from a hat, stored on a list on a computer and provided to the treating physician with the assigned treatment by a non-clinical administrator."
Allocation concealment (selection bias)	High risk	An unblinded, independent physician administered one of the three randomly assigned treatment options.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The randomisation code remained concealed and was not revealed to the investigators or the study subjects until completion of the study."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study states that outcomes were assessed using a combination of clinical and echocardiographic features, but there is no mention of blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	High risk	Nine (16.0%) participants were lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	We do not have access to the study protocol and are unable to comment on whether there was selective reporting of outcomes in this study.
Other bias	Low risk	No evidence of other biases

Schrire 1959

Methods	Alternate allocation of 28 participants to adjuvant steroids or no steroids
Participants	28 participants who were on antituberculous chemotherapy for suspected tuberculous pericarditis. The trial authors did not provide the characteristics of the included participants, and did not specify the antituberculous drugs used.
Interventions	**Intervention** • Cortisone with a loading dose of 300 mg and maintenance dose of 100 mg daily for several weeks was prescribed for 14 participants. At a later date, prednisolone 60 mg/day with a maintenance dose of 20 mg was substituted. **Control** • No corticosteroids. The trial authors did not specify the length of follow-up.
Outcomes	Constriction requiring pericardiectomy
Notes	Study location: Cape Town, South Africa

Risk of bias

Schrire 1959 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	The trial authors performed randomization by alternation.
Allocation concealment (selection bias)	High risk	There was no allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The trial did not perform any blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	There was no evidence of blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The trial authors did not adequately report losses to follow-up.
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available.
Other bias	Low risk	There was no evidence of other sources of bias.

Strang 2004a

Methods	Central randomization Double blind placebo-controlled study
Participants	143 participants with suspected tuberculous constrictive pericarditis aged 5 years and older. The participants in the treatment and control groups were well-matched in terms of clinical characteristics and completion of antituberculous chemotherapy. "Those consenting to take part were all prescribed the same 6-month standard antituberculosis regimen of streptomycin, isoniazid, rifampicin, and pyrazinamide daily for 14 weeks as an in-patient, followed by isoniazid and rifampicin daily up to 6 months."
Interventions	**Intervention** • Prednisolone for the first 11 weeks of antituberculous chemotherapy. The dose for children aged 5 to 9 years was 30 mg daily for weeks 1 to 4; 15 mg daily for weeks 5 to 8; 7.5 mg daily for weeks 9 to 10; and 2.5 mg daily for week 11. Regarding children aged 10 to 14 years, the dose was 45 mg for weeks 1 to 4; 22.5 mg for weeks 5 to 8; 7.5 mg for weeks 9 to 10; and 2.5 mg for week 11. The dose for adults was 60 mg for the first 4 weeks; 30 mg for weeks 5 to 8; 15 mg for weeks 9 to 10; and 5 mg for week 1. **Control** • Matching placebo.
Outcomes	• Death. • Death from pericarditis. • Favourable clinical status at 24 months. • Pericardiectomy.

Strang 2004a *(Continued)*

Notes	Study location: Umtata, South Africa

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The trial authors used a random number list.
Allocation concealment (selection bias)	Low risk	The trial authors used central randomization.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Particianpts and care providers were blinded to treatment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators, including outcome assessors, were blinded to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	During 10 years of follow-up, 1 participant (1.4%) was lost to follow-up in the prednisolone group and 2 participants (2.7%) in the placebo group.
Selective reporting (reporting bias)	Unclear risk	There was no study protocol available.
Other bias	Low risk	There was no evidence of other sources of bias.

Strang 2004b

Methods	Central randomization Double blind placebo-controlled study Factorial design
Participants	240 participants aged 5 years or more diagnosed as having active tuberculous pericardial effusion. The participants in the treatment and control groups were well-matched in terms of their clinical characteristics and completion of antituberculous chemotherapy. "Those consenting to take part were all prescribed the same 6-month standard antituberculosis regimen of streptomycin, isoniazid, rifampicin, and pyrazinamide daily for 14 weeks as an in-patient, followed by isoniazid and rifampicin daily up to 6 months."
Interventions	**Intervention 1** • Complete open surgical drainage on admission. **Control 1** • No open drainage. **Intervention 2** • Prednisolone for the first 11 weeks of antituberculous chemotherapy. The dose for children aged 5 to 9 years was 30 mg daily for weeks 1 to 4; 15 mg daily for weeks 5 to 8; 7.5 mg daily for weeks 9 to 10;

Strang 2004b *(Continued)*

	and 2.5 mg daily for week 11. Regarding children aged 10 to 14 years, the dose was 45 mg for weeks 1 to 4; 22.5 mg for weeks 5 to 8; 7.5 mg for weeks 9 to 10; and 2.5 mg for week 11. The dose for adults was 60 mg for the first 4 weeks; 30 mg for weeks 5 to 8; 15 mg for weeks 9 to 10; and 5 mg for week 1. **Control 2** • Matching placebo.
Outcomes	• Death. • Death from pericarditis. • Favourable clinical status at 24 months. • Tamponade requiring pericardiocentesis. • Constriction. • Pericardiectomy.
Notes	Study location: Umtata, South Africa

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The trial used a random number list to perform random sequence generation.
Allocation concealment (selection bias)	Low risk	The trial authors performed central randomization.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participants and investigators were blinded to the steroid component, but not to the surgical drainage component.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"For patients who died, information was obtained on cause of death from hospital records, relatives, or other contacts. All the deaths were reviewed by an independent assessor without knowledge of the treatment group, and where possible, he classified the cause."
Incomplete outcome data (attrition bias) All outcomes	Low risk	5/117 (4.3%) participants were lost to follow-up in the prednisolone group compared to 7/119 (5.9%) in the placebo group. 2/64 (3.1%) participants were lost to follow-up in the drainage group compared to 3/58 (5.2%) in the no drainage group.
Selective reporting (reporting bias)	Unclear risk	There was no study protocol available.
Other bias	Low risk	There was no evidence of other sources of bias.

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

Study	Reason for exclusion
Wiysonge 2008	Although this study is indexed in electronic databases as a controlled trial, it is actually a cross-sectional study of the contemporary use of adjunctive steroids by physicians treating patients with tuberculous pericarditis. We thus excluded it from this review due to ineligible study design.

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

Cui 2005

Methods	Consecutively recruited participants were "randomly" assigned to intervention or control arms, but no further details about random sequence generation and allocation concealment are not provided in the abstract. The length of following-up varied from 8 to 120 months (mean 56.8 ± 29.0 months).
Participants	Ninety-four participants with infectious exudative pericarditis (34 with purulent pericarditis and 60 with tuberculous pericarditis); disease course less than 1 month; 44 males and 50 females; age 9 to 66 years (mean 45.4 ± 14.7 years); consecutively enrolled between 1993 to 2002 in China. The hospital and city are not specified.
Interventions	Intervention arm: intrapericardial urokinase along with conventional treatment in intervention arm, or conventional treatment alone (including pericardiocentesis and drainage) in the control arm. The dosage of urokinase ranged from 200,000 to 600,000 U (mean 320,000 ± 70,000 U).
Outcomes	Pericardial constriction, as detected by pericardiography with sterilized air and diatrizoate meglumine as contrast media (in the short-tem) and telephonic survey and echocardiographic examination (in the long-term).
Notes	Study published in Chinese. Only the abstract is currently available in English.

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

NCT02673879

Trial name or title	The Second Investigation of the Management of Pericarditis (IMPI-2) Trial
Methods	**Study design**: randomized trial **Intervention model**: parallel assignment **Blinding**: single blind (outcomes assessor)
Participants	The study plans to enrol 2176 participants. **Inclusion criteria** • Age ≥ 18 years of age. • Confirmed large pericardial effusion on echocardiography (that is, echo free space ≥ 1 cm anterior to the right ventricle of the heart in diastole). • Willingness to participate for the full duration of the trial (that is, 12 months). • Provision of written informed consent. **Exclusion criteria** • Age < 18 years. • Uraemic pericarditis (that is, urea > 21.4 mmol/L). • Thrombocytopenia (that is, < 100,000 platelets/μL). • Presence of a contraindication to the administration of a fibrinolytic agent (major haemorrhage or major trauma; coincidental stroke; major surgery in the previous 5 days; blood pressure > 200/100 mmHg).
Interventions	**Intervention**: complete percutaneous pericardial drainage facilitated by intrapericardial alteplase (recombinant human tissue-type plasminogen activator).

NCT02673879 *(Continued)*	**Comparison**: conventional pericardiocentesis.
Outcomes	**Primary outcomes** • Composite outcome of cardiac tamponade requiring pericardiocentesis or constrictive pericarditis. **Secondary outcomes** • Major bleeding. • Clinically relevant non-major bleeding. • Any bleeding. • Any other form of bleeding that is not covered by safety outcomes 1-3. • Other adverse events. • Any other adverse events. • Persistent pericardial effusion without cardiac tamponade. • Recurrent pericardial effusion without cardiac tamponade. • Hospitalization for any cause; and death from any cause. • Cardiac tamponade requiring pericardiocentesis. • Constrictive pericarditis. • Death from any cause. • Proportion with proven tuberculosis. • Time to diagnosis of proven tuberculosis. • Proportion with proven tuberculosis on novel tests who are not put on treatment. • Diagnostic accuracy of novel tests of tuberculosis. • Drug-resistant tuberculosis. • Specific diagnosis of tuberculous pericarditis. • Time to diagnosis of specific pericardial disease.
Starting date	The study started in February 2016, with the planned completion date as January 2019.
Contact information	**Principal investigator**: Professor Bongani M, Mayosi, University of Cape Town, Cape Town, South Africa. **Contacts:** • Shaheen Pandie: Phone +27823199030; Email: s.pandie@uct.ac.za • Veronica Francis: Phone +27832449895; Email: veronica.francis@uct.ac.za
Notes	**Sponsor:** University of Cape Town, South Africa. **Collaborators:** Walter Sisulu University, South Africa; Population Health Research Institute, Canada

DATA AND ANALYSES

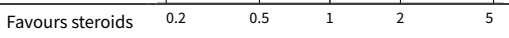
Comparison 1. Steroids versus placebo in HIV-negative people

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Deaths from all causes	4	660	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.59, 1.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Deaths from pericarditis	4	660	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.19, 0.80]
3 Constrictive pericarditis	2	281	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.34, 1.55]
4 Repeat pericardiocentesis	2	492	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.70, 1.04]
5 Cancer	1	256	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.05, 13.80]
6 Hospitalization	1	256	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.57, 1.70]
7 Pericardiectomy	4	432	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.58, 1.41]
8 Opportunistic infections	1	256	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [0.44, 6.69]

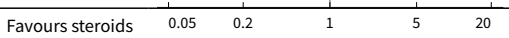
Analysis 1.1. Comparison 1 Steroids versus placebo in HIV-negative people, Outcome 1 Deaths from all causes.

Study or subgroup	Steroids n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Strang 2004a	16/70	21/73		28.29%	0.79[0.45,1.39]
Strang 2004b	26/117	33/119		45.02%	0.8[0.51,1.25]
Reuter 2006	0/7	0/18			Not estimable
Mayosi 2014	17/138	18/118		26.7%	0.81[0.44,1.49]
Total (95% CI)	**332**	**328**		**100%**	**0.8[0.59,1.09]**
Total events: 59 (Steroids), 72 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=2(P=1); I^2=0%					
Test for overall effect: Z=1.43(P=0.15)					

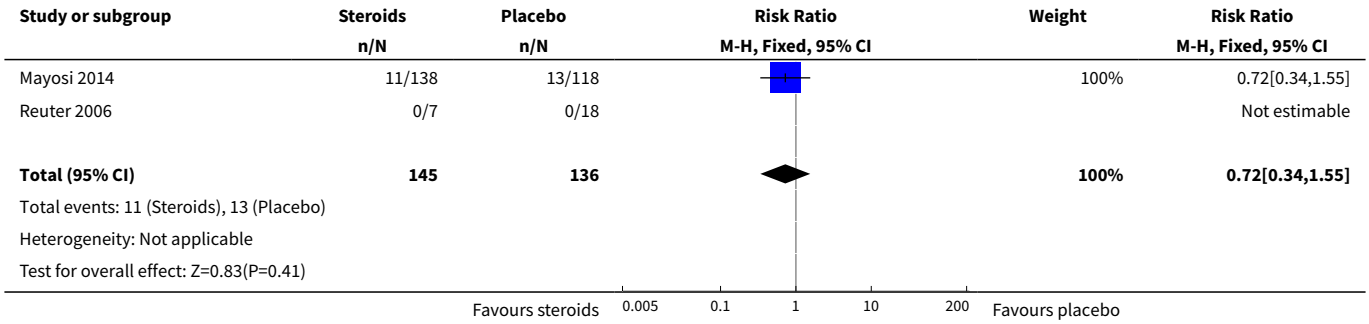


Analysis 1.2. Comparison 1 Steroids versus placebo in HIV-negative people, Outcome 2 Deaths from pericarditis.

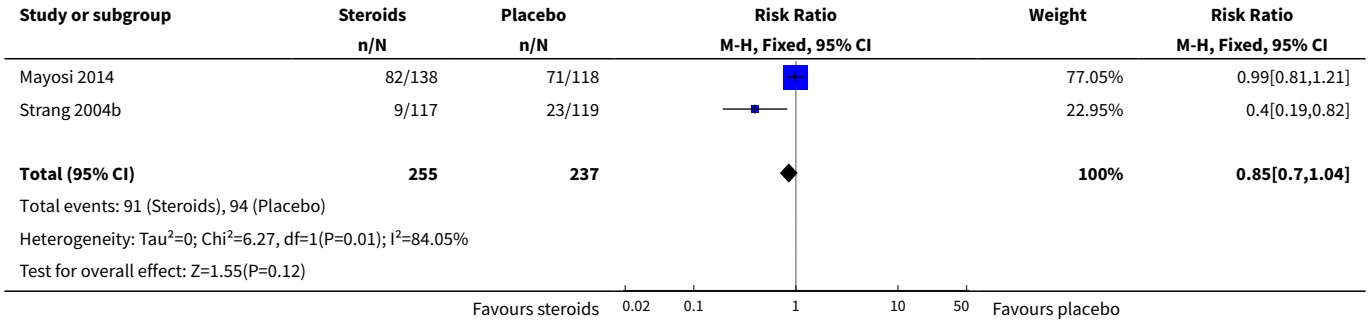
Study or subgroup	Steroids n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Mayosi 2014	3/138	6/118		25.66%	0.43[0.11,1.67]
Reuter 2006	0/7	0/18			Not estimable
Strang 2004a	2/70	8/73		31.07%	0.26[0.06,1.19]
Strang 2004b	5/117	11/119		43.27%	0.46[0.17,1.29]
Total (95% CI)	**332**	**328**		**100%**	**0.39[0.19,0.8]**
Total events: 10 (Steroids), 25 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.39, df=2(P=0.82); I^2=0%					
Test for overall effect: Z=2.57(P=0.01)					



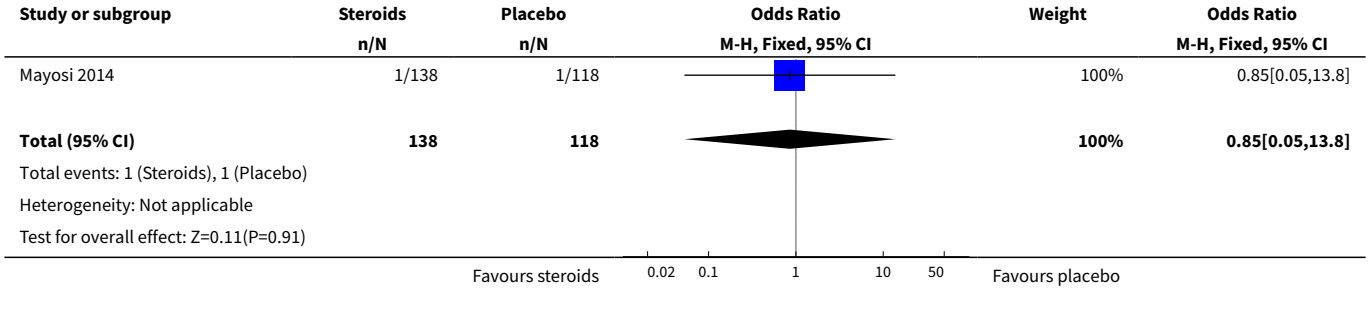
Analysis 1.3. Comparison 1 Steroids versus placebo in HIV-negative people, Outcome 3 Constrictive pericarditis.



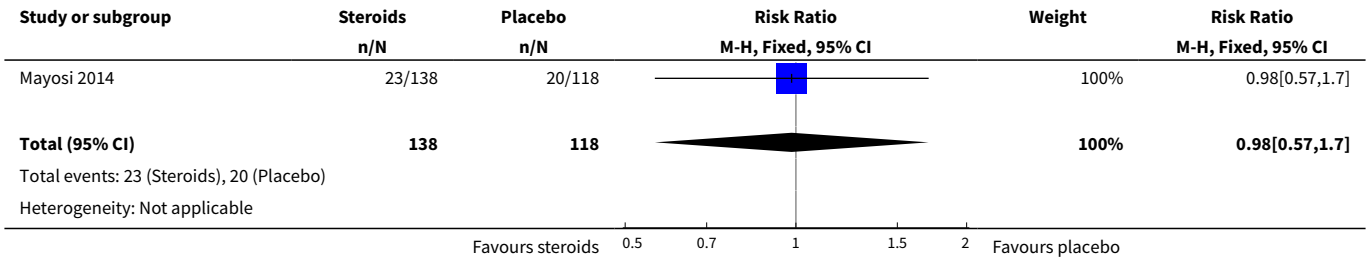
Analysis 1.4. Comparison 1 Steroids versus placebo in HIV-negative people, Outcome 4 Repeat pericardiocentesis.

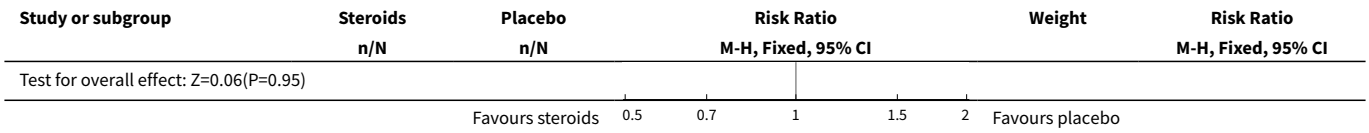


Analysis 1.5. Comparison 1 Steroids versus placebo in HIV-negative people, Outcome 5 Cancer.

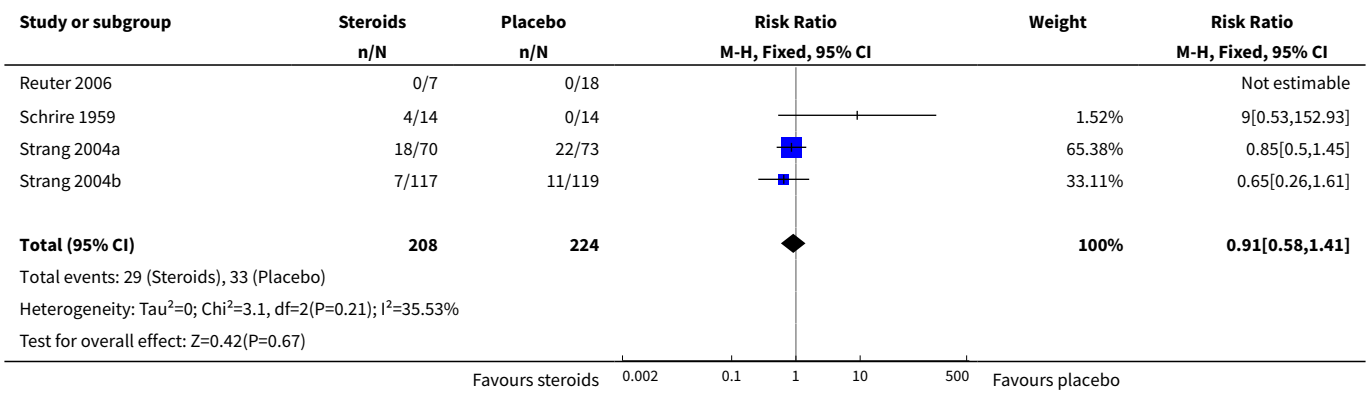


Analysis 1.6. Comparison 1 Steroids versus placebo in HIV-negative people, Outcome 6 Hospitalization.

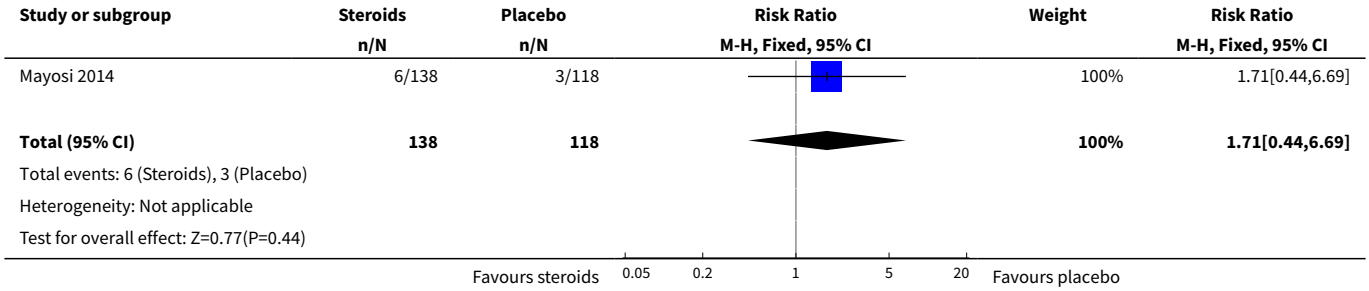




Analysis 1.7. Comparison 1 Steroids versus placebo in HIV-negative people, Outcome 7 Pericardiectomy.



Analysis 1.8. Comparison 1 Steroids versus placebo in HIV-negative people, Outcome 8 Opportunistic infections.

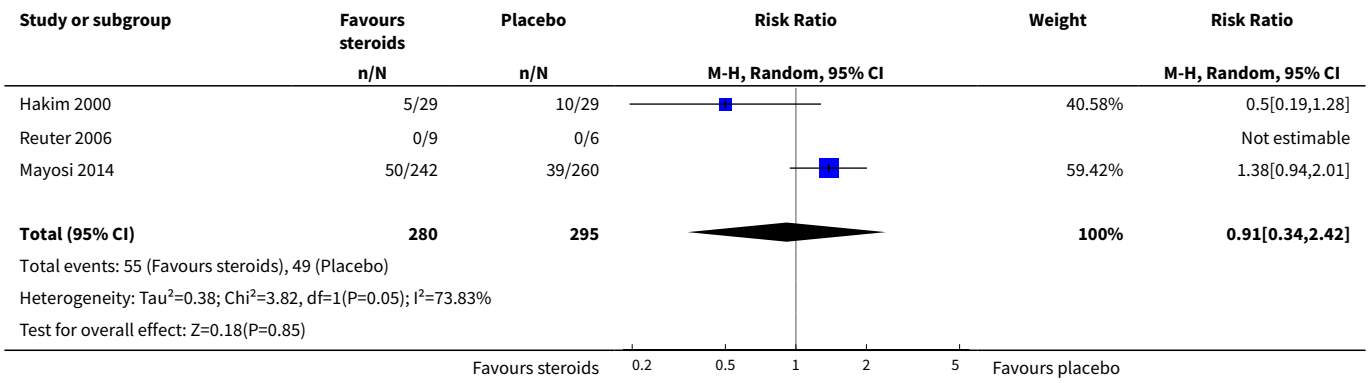


Comparison 2. Steroids versus placebo in HIV-positive people

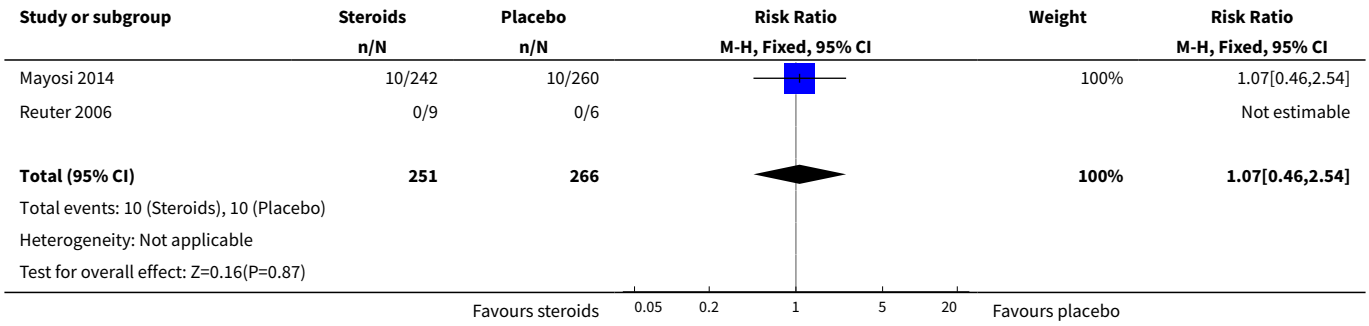
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Deaths from all causes	3	575	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.34, 2.42]
2 Deaths from pericarditis	2	517	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.46, 2.54]
3 Constrictive pericarditis	3	575	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.26, 1.16]
4 Repeat pericardiocentesis	2	517	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.89, 1.18]
5 Cancer	1	502	Odds Ratio (M-H, Fixed, 95% CI)	1.62 [0.27, 9.77]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Hospitalization	1	502	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.59, 1.09]
7 Pericardiectomy	1	15	Risk Ratio (M-H, Fixed, 95% CI)	2.1 [0.10, 44.40]
8 Opportunistic infections	2	517	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.61, 1.48]

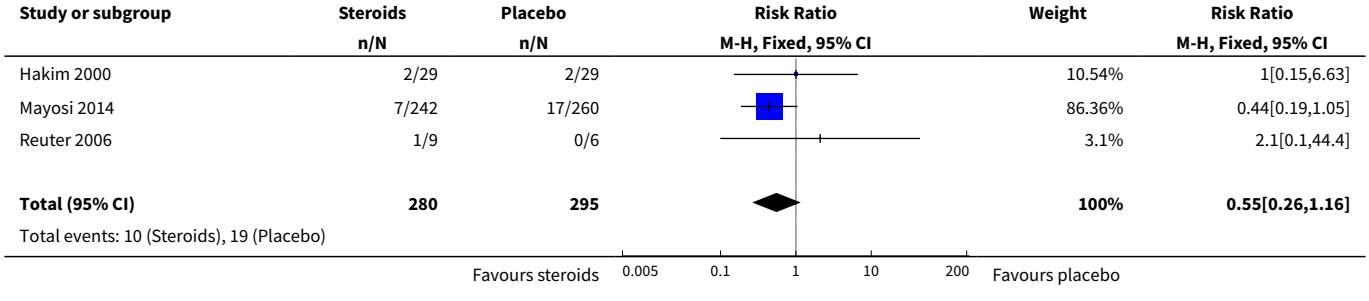
Analysis 2.1. Comparison 2 Steroids versus placebo in HIV-positive people, Outcome 1 Deaths from all causes.

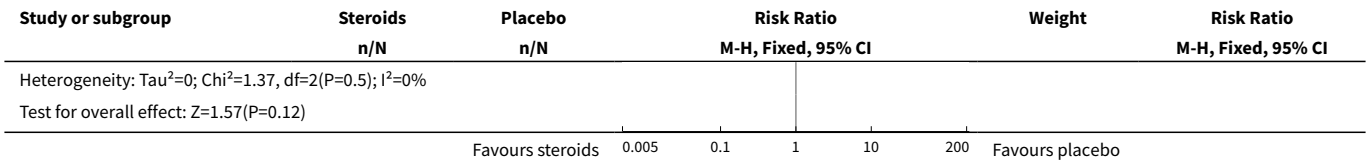


Analysis 2.2. Comparison 2 Steroids versus placebo in HIV-positive people, Outcome 2 Deaths from pericarditis.

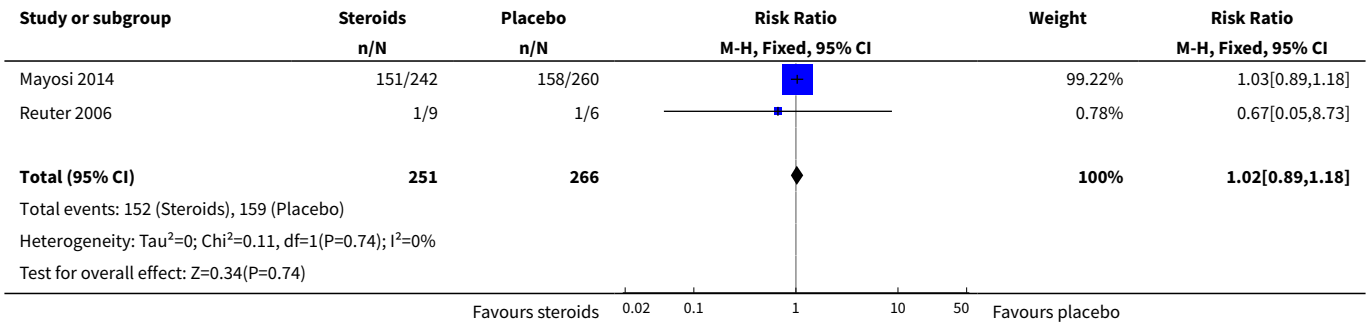


Analysis 2.3. Comparison 2 Steroids versus placebo in HIV-positive people, Outcome 3 Constrictive pericarditis.

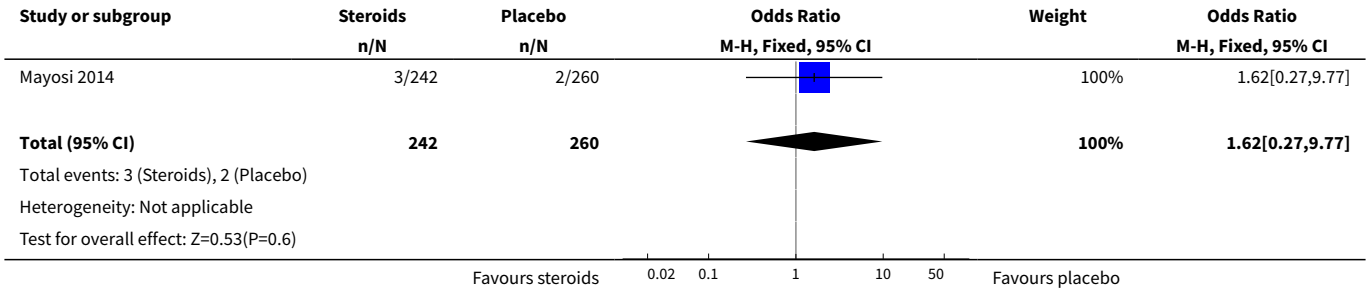




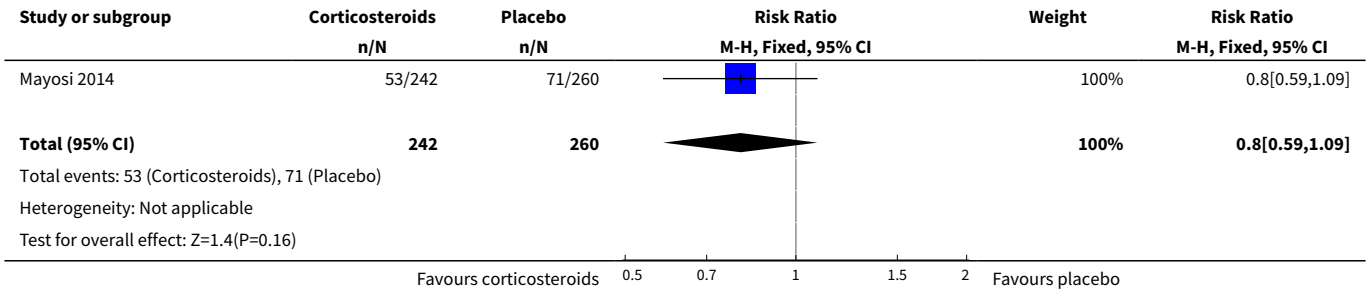
Analysis 2.4. Comparison 2 Steroids versus placebo in HIV-positive people, Outcome 4 Repeat pericardiocentesis.



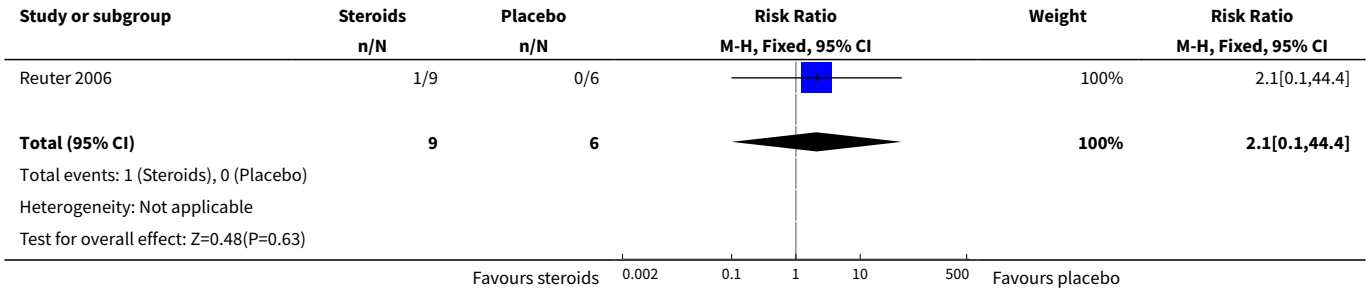
Analysis 2.5. Comparison 2 Steroids versus placebo in HIV-positive people, Outcome 5 Cancer.



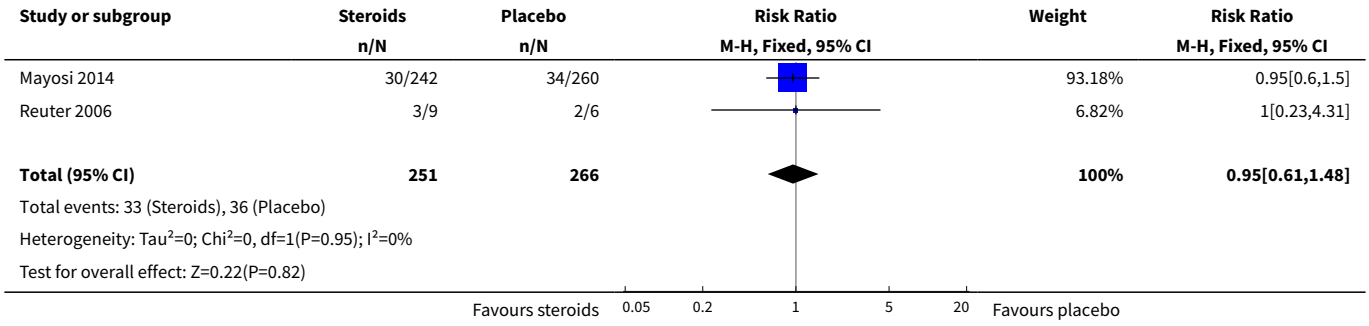
Analysis 2.6. Comparison 2 Steroids versus placebo in HIV-positive people, Outcome 6 Hospitalization.



Analysis 2.7. Comparison 2 Steroids versus placebo in HIV-positive people, Outcome 7 Pericardiectomy.



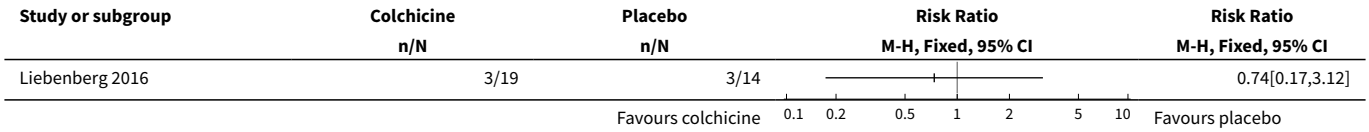
Analysis 2.8. Comparison 2 Steroids versus placebo in HIV-positive people, Outcome 8 Opportunistic infections.



Comparison 3. Colchicine versus placebo in HIV-positive people

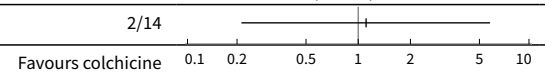
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death from all causes	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Constrictive pericarditis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3 Colchicine versus placebo in HIV-positive people, Outcome 1 Death from all causes.



Analysis 3.2. Comparison 3 Colchicine versus placebo in HIV-positive people, Outcome 2 Constrictive pericarditis.

Study or subgroup	Colchicine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Liebenberg 2016	3/19	2/14		1.11[0.21,5.76]

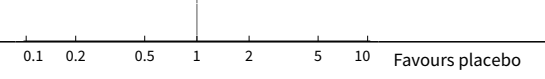


Comparison 4. *M. indicus pranii* versus placebo in HIV-negative people

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Deaths from all causes	1	190	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.56, 2.03]
2 Deaths from pericarditis	1	190	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.44, 5.15]
3 Constrictive pericarditis	1	190	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.71, 3.42]
4 Repeat pericardiocentesis	1	190	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.96, 1.52]
5 Cancer	1	190	Odds Ratio (M-H, Fixed, 95% CI)	3.03 [0.12, 75.37]
6 Hospitalization	1	190	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.70, 2.13]
7 Opportunistic infections	1	190	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.11, 3.90]

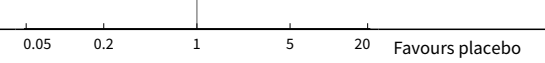
Analysis 4.1. Comparison 4 *M. indicus pranii* versus placebo in HIV-negative people, Outcome 1 Deaths from all causes.

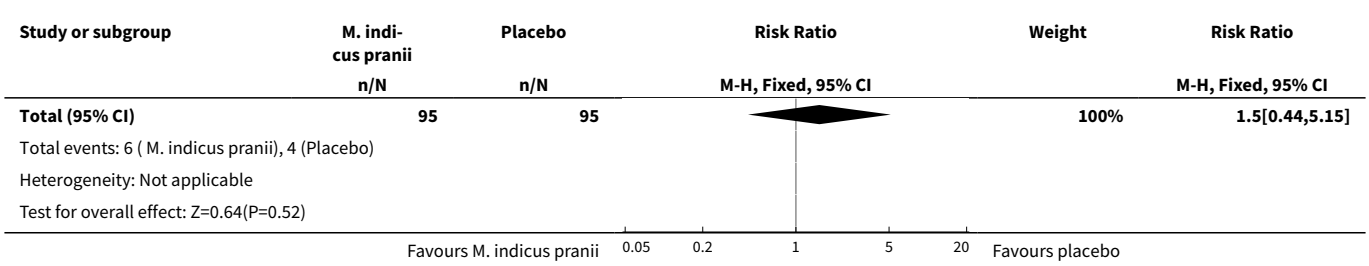
Study or subgroup	M. indicus pranii n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Mayosi 2014	16/95	15/95		100%	1.07[0.56,2.03]
Total (95% CI)	**95**	**95**		**100%**	**1.07[0.56,2.03]**
Total events: 16 (M. indicus pranii), 15 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.2(P=0.84)					



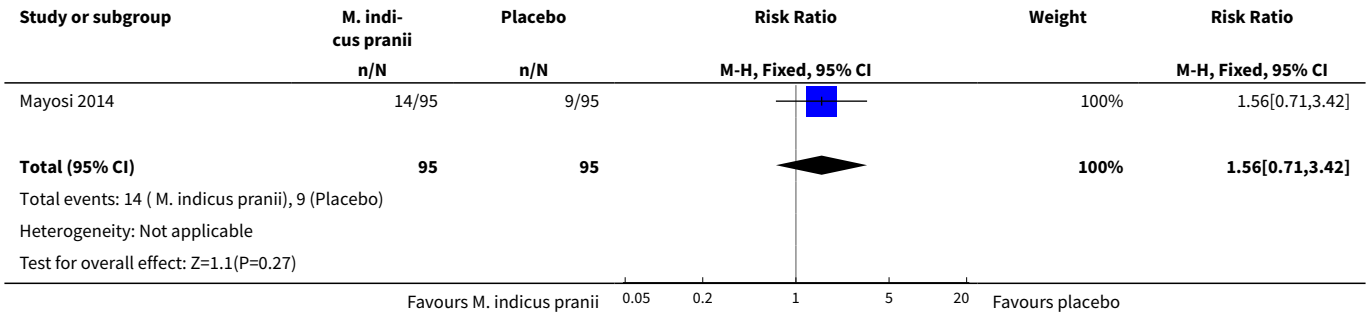
Analysis 4.2. Comparison 4 *M. indicus pranii* versus placebo in HIV-negative people, Outcome 2 Deaths from pericarditis.

Study or subgroup	M. indicus pranii n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Mayosi 2014	6/95	4/95		100%	1.5[0.44,5.15]

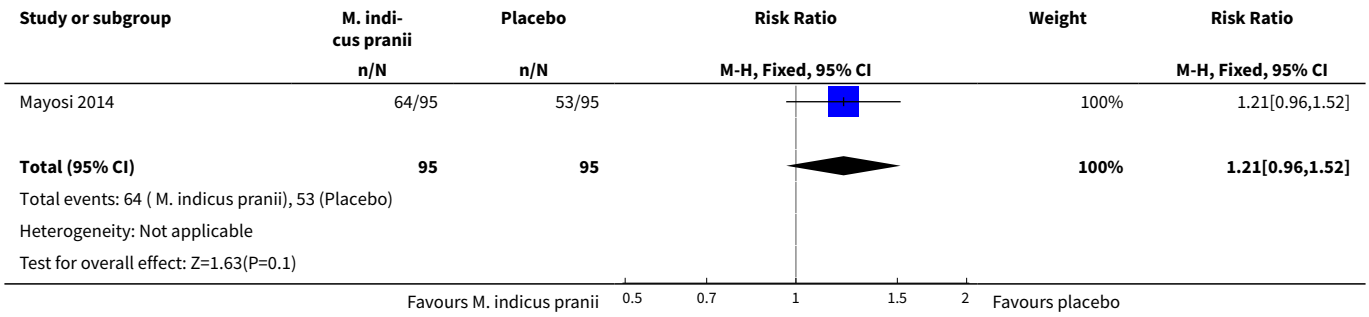




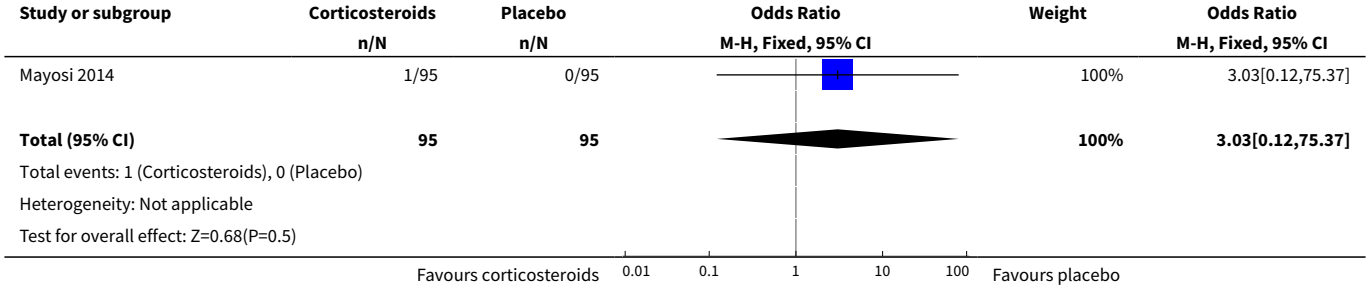
Analysis 4.3. Comparison 4 *M. indicus pranii* versus placebo in HIV-negative people, Outcome 3 Constrictive pericarditis.



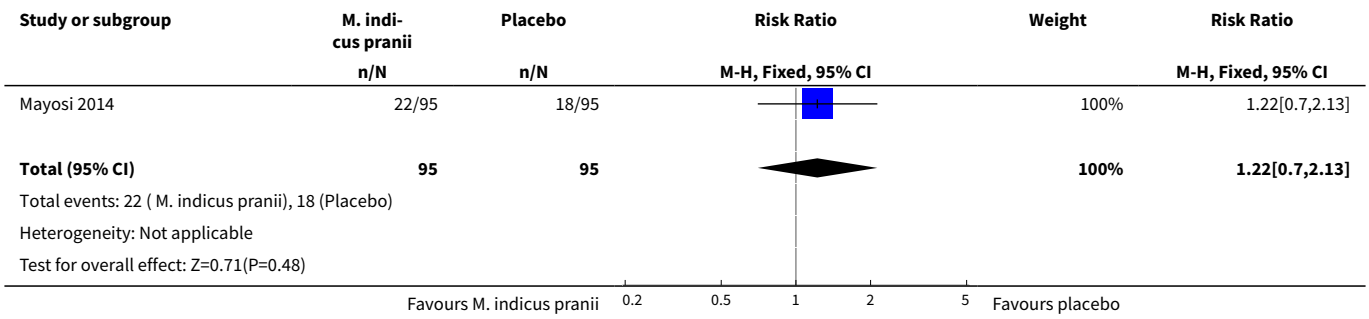
Analysis 4.4. Comparison 4 *M. indicus pranii* versus placebo in HIV-negative people, Outcome 4 Repeat pericardiocentesis.



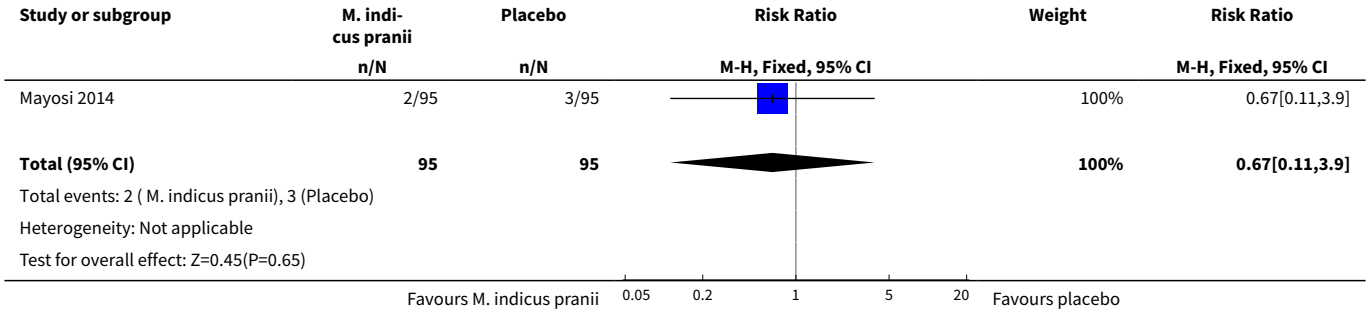
Analysis 4.5. Comparison 4 *M. indicus pranii* versus placebo in HIV-negative people, Outcome 5 Cancer.



Analysis 4.6. Comparison 4 *M. indicus pranii* versus placebo in HIV-negative people, Outcome 6 Hospitalization.



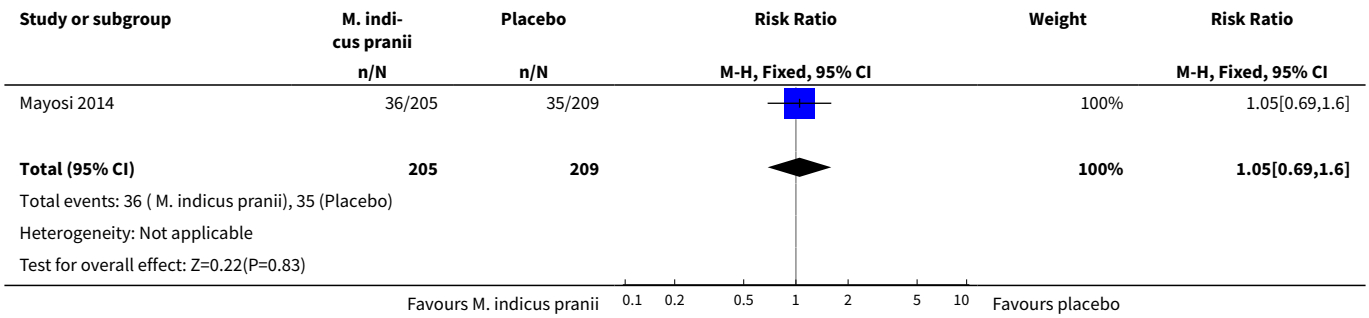
Analysis 4.7. Comparison 4 *M. indicus pranii* versus placebo in HIV-negative people, Outcome 7 Opportunistic infections.



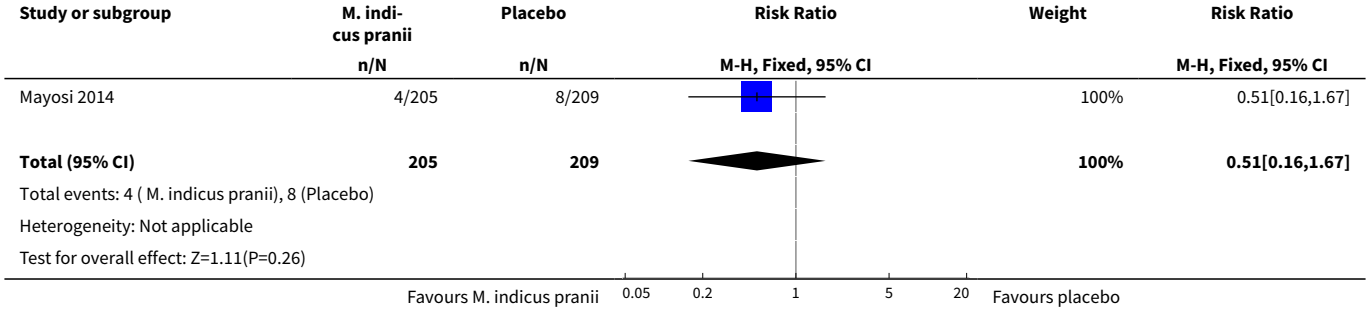
Comparison 5. *M. indicus pranii* versus placebo in HIV-positive people

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Deaths from all causes	1	414	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.69, 1.60]
2 Deaths from pericarditis	1	414	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.16, 1.67]
3 Constrictive pericarditis	1	414	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.33, 1.60]
4 Repeat pericardiocentesis	1	414	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.80, 1.10]
5 Cancer	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Hospitalization	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Opportunistic infections	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

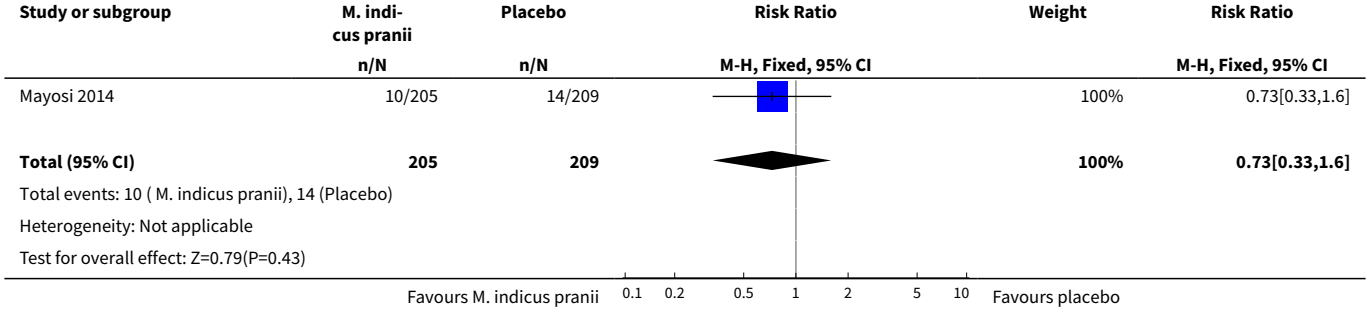
Analysis 5.1. Comparison 5 *M. indicus pranii* versus placebo in HIV-positive people, Outcome 1 Deaths from all causes.



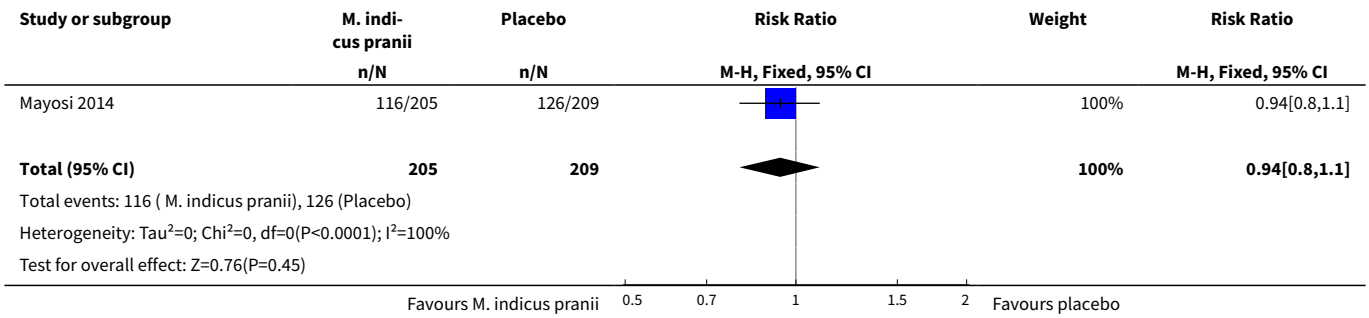
Analysis 5.2. Comparison 5 *M. indicus pranii* versus placebo in HIV-positive people, Outcome 2 Deaths from pericarditis.



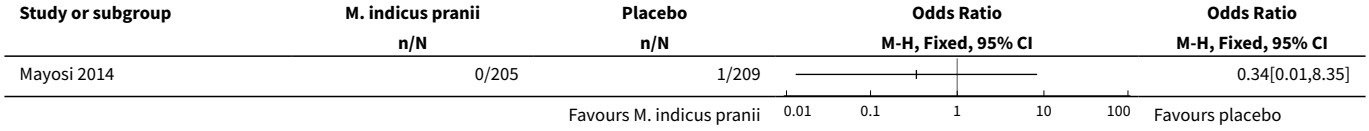
Analysis 5.3. Comparison 5 *M. indicus pranii* versus placebo in HIV-positive people, Outcome 3 Constrictive pericarditis.



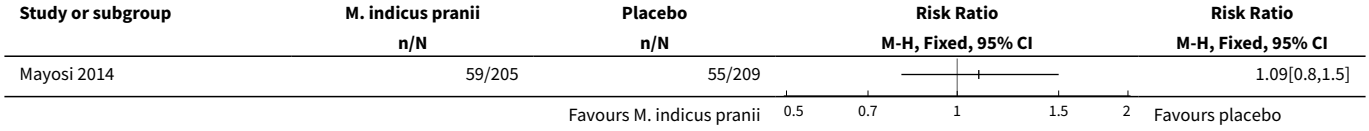
Analysis 5.4. Comparison 5 *M. indicus pranii* versus placebo in HIV-positive people, Outcome 4 Repeat pericardiocentesis.



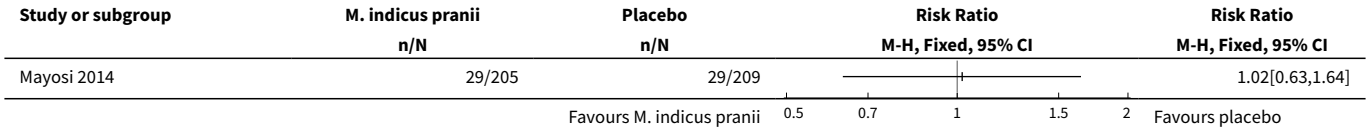
Analysis 5.5. Comparison 5 *M. indicus pranii* versus placebo in HIV-positive people, Outcome 5 Cancer.



Analysis 5.6. Comparison 5 *M. indicus pranii* versus placebo in HIV-positive people, Outcome 6 Hospitalization.



Analysis 5.7. Comparison 5 *M. indicus pranii* versus placebo in HIV-positive people, Outcome 7 Opportunistic infections.



Comparison 6. Surgical drainage versus no intervention in HIV-negative people

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death from all causes	1	122	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.52, 2.20]
2 Death from pericarditis	1	122	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.16, 2.91]
3 Repeat pericardiocentesis	1	122	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.07, 0.76]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Pericardiectomy	1	122	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.14, 2.18]

Analysis 6.1. Comparison 6 Surgical drainage versus no intervention in HIV-negative people, Outcome 1 Death from all causes.

Study or subgroup	Open drainage n/N	No open drainage n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Strang 2004b	13/64	11/58		100%	1.07[0.52,2.2]
Total (95% CI)	**64**	**58**		**100%**	**1.07[0.52,2.2]**
Total events: 13 (Open drainage), 11 (No open drainage)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.19(P=0.85)					

Favours open drainage — Favours no open drainage

Analysis 6.2. Comparison 6 Surgical drainage versus no intervention in HIV-negative people, Outcome 2 Death from pericarditis.

Study or subgroup	Open drainage n/N	No open drainage n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Strang 2004b	3/64	4/58		100%	0.68[0.16,2.91]
Total (95% CI)	**64**	**58**		**100%**	**0.68[0.16,2.91]**
Total events: 3 (Open drainage), 4 (No open drainage)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.52(P=0.6)					

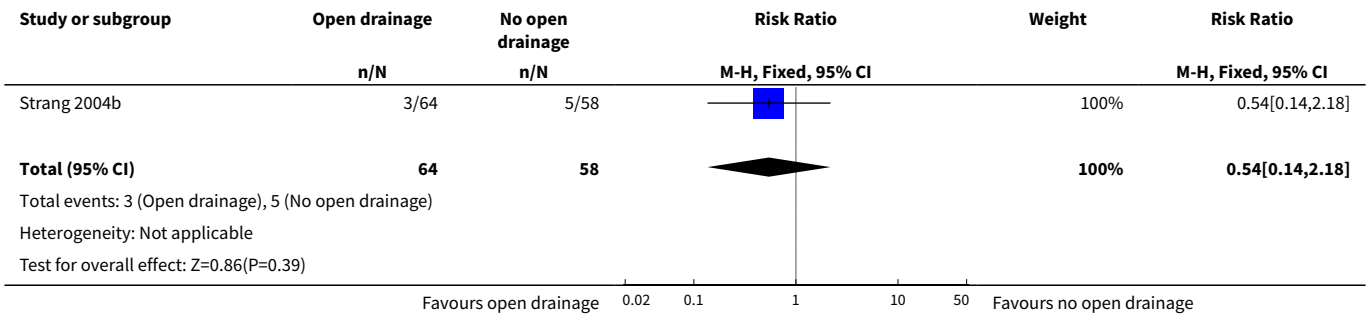
Favours open drainage — Favours no open drainage

Analysis 6.3. Comparison 6 Surgical drainage versus no intervention in HIV-negative people, Outcome 3 Repeat pericardiocentesis.

Study or subgroup	Open drainage n/N	No open drainage n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Strang 2004b	3/64	12/58		100%	0.23[0.07,0.76]
Total (95% CI)	**64**	**58**		**100%**	**0.23[0.07,0.76]**
Total events: 3 (Open drainage), 12 (No open drainage)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.4(P=0.02)					

Favours open drainage — Favours no open drainage

Analysis 6.4. Comparison 6 Surgical drainage versus no intervention in HIV-negative people, Outcome 4 Pericardiectomy.



ADDITIONAL TABLES

Table 1. Key characteristics of the corticosteroid trials

Trial	Location	Participants					Intervention	Outcomes
		Sample size	Age (years)	HIV-positive	ART	Definite TB		
Schrire 1959	South Africa	28 people with pericardial effusion	Adults	None	N/A	Not reported	Cortisone (or prednisolone) for several weeks versus no corticosteroids[1]	Pericardiectomy
Hakim 2000	Zimbabwe	58 people with pericardial effusion	18 to 55	100%	0%	38%	Prednisolone for 6 weeks versus placebo[3]	All-cause deaths; constrictive pericarditis.
Strang 2004a	South Africa	143 with constrictive pericarditis	≥ 5	Assume none	N/A	10%	Prednisolone first 11 weeks versus placebo[2]	All-cause deaths; deaths from pericarditis; pericardiectomy.
Strang 2004b	South Africa	240 people with pericardial effusion	≥ 5	Assume none	N/A	60%	(1) Prednisolone for 11 weeks versus placebo (2) Open surgical drainage versus no drainage	All-cause deaths; deaths from pericarditis; repeat pericardiocentesis; pericardiectomy.
Reuter 2006	South Africa	40 people with pericardial effusion	17 to 66	38%	0%	Not reported	Prednisone versus no prednisone (5 mL intrapericardial 0.9% saline)[4]	Repeat pericardiocentesis; pericardiectomy; constrictive pericarditis; infection.
Mayosi 2014	Kenya, Malawi, Mozambique, Nigeria, Uganda, Sierra Leone, South Africa, and Zimbabwe	1440 with pericardial effusion (83%) or constriction (17%)	≥ 18	67%	22%	17%	Prednisolone for 6 weeks with or without *M. indicus pranii* versus placebo[5]	All-cause deaths; deaths from pericarditis; constrictive pericarditis; hospitalization; infection; cancer.

Abbreviations: ART: proportion of participants on antiretroviral therapy; HIV: human immunodeficiency virus; TB: tuberculosis.

[1]In the Schrire 1959 study, corticosteroid dose was given at a loading dose of 300 mg daily followed by a maintenance dose of 100 mg daily. At a later date, cortisone was substituted by prednisolone with a loading dose of 60 mg daily and a maintenance dose of 20 mg daily.

[2]In the Strang 2004a and Strang 2004b , the trial authors stratified prednisolone dosing by age: The dose for children aged 5 to 9 years was 30 mg daily for weeks 1 to 4; 15 mg daily for weeks 5 to 8; 7.5 mg daily for weeks 9 to 10; and 2.5 mg daily for week 11. For children 10 to 14 years, the dose was 45 mg for weeks 1 to 4; 22.5 mg for weeks 5 to 8; 7.5 mg for weeks 9 to 10; and 2.5 mg for week 11. The dose for adults was 60 mg for the first 4 weeks; 30 mg for weeks 5 to 8; 15 mg for weeks 9 to 10; and 5 mg for week 11.

[3]In the Hakim 2000 study, the dose of prednisolone was 60 mg daily for the first week and was tapered thereafter by 10 mg every week.

[4]In the Reuter 2006 study, the corticosteroid arm received oral prednisone plus intrapericardial placebo (5 mL 0.9% saline solution). Oral prednisone was started at 60 mg per day for 4 weeks, followed by 30 mg per day for 4 weeks, 15 mg per day for 2 weeks, and 5 mg per day for 1 week. This study had 3 arms. We did not include the third trial arm, which received intrapericardial triamcinolone, in this current review.

[5] Mayosi 2014 used prednisolone for six weeks at a dose of 120 mg per day in the first week, 90 mg per day in the second week, 60 mg per day in the third week, 30 mg per day in the fourth week, 15 mg per day in the fifth week, and 5 mg per day in the sixth week.

APPENDICES

Appendix 1. Detailed search strategy

Search set	CIDG SR[1]	CENTRAL	MEDLINE[2]	Embase[2]	LILACS[2]
1	tuberculosis	Tuberculosis [MeSH]	Tuberculosis [MeSH]	Tuberculosis [MeSH]	tuberculosis
2	Pericard*	Tuberculosis ti, ab	Tuberculosis ti, ab	Tuberculosis ti, ab	Pericard*
3	heart	1 or 2	1 or 2	1 or 2	heart
4	2 or 3	heart or cardi* or pericard* ti, ab	heart or cardi* or pericard* ti, ab	heart or cardi* or pericard* ti, ab	2 or 3
5	1 and 4	3 and 4	3 and 4	3 and 4	1 and 4
6	—	"Pericarditis, Tuberculous"[Mesh]	"Pericarditis, Tuberculous"[Mesh]	tuberculous pericarditis [Emtree]	—
7	—	5 or 6	5 or 6	5 or 6	—

[1]Cochrane Infectious Diseases Group Specialized Register.
[2]Search terms used in combination with the search strategy for retrieving trials developed by the Cochrane Collaboration (Lefebvre 2011).

WHAT'S NEW

Date	Event	Description
12 September 2017	New citation required and conclusions have changed	We updated this review, added new authors, and included new trials. The conclusion of this review changed compared to the previous published version.
12 September 2017	New search has been performed	The author team updated this review.

HISTORY

Protocol first published: Issue 4, 1997
Review first published: Issue 3, 1998

Date	Event	Description
10 November 2008	Amended	Converted to new review format with minor editing.
12 January 2005	Amended	New studies found but not yet included or excluded.
18 May 2003	Amended	Minor update
17 June 2002	New citation required and conclusions have changed	Substantive amendment. Issue 4, 2002: Hakim 2000 added.

Date	Event	Description
		New studies found and included or excluded

CONTRIBUTIONS OF AUTHORS

Charles S Wiysonge and Bongani M Mayosi led the preparation of the current version of the review, with important intellectual inputs from all co-authors.
Charles S Wiysonge and Bongani M Mayosi were involved in all stages of the review.
Dumisani Majombozi was involved in screening of searches, study selection, data extraction, and verification of data analysis.
Freedom Gumedze provided the data on the Mayosi 2014 trial and verified the data analysis.
Mpiko Ntsekhe, Lehana Thabane, Jimmy Volmink, and Shaheen Pandie read and provided important input into successive drafts of the review.
All review authors read and approved the final version of the review.

DECLARATIONS OF INTEREST

Mpiko Ntsekhe, Lehana Thabane, Freedom Gumedze, Shaheen Pandie, and Bongani M Mayosi were investigators in an included study (Mayosi 2014). Jimmy Volmink was a member of the Data Safety and Monitoring Committee for the same study. However, two review authors (CSW and DM) who were not involved in this trial independently extracted the data for this study, which were verified by Paul Garner, David Sinclair, Hannah Ryan, and Maya Tickell-Painter.

Charles S Wiysonge, Mpiko Ntsekhe, Jimmy Volmink, and Bongani M Mayosi were co-authors of a study assessed and excluded from the review (Wiysonge 2008). A review author (DM) who was not involved in this study initially assessed the eligibility of this study.

SOURCES OF SUPPORT

Internal sources

- Cardiac Clinic Research Fund, University of Cape Town, South Africa.
- Stellenbosch University, South Africa.
- South African Medical Research Council, South Africa.
- Liverpool School of Tropical Medicine, UK.

External sources

- Department for International Development, UK.

  Grant: 5242

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are differences between the authors of the protocol and the current version of the review. The protocol had three authors (Bongani Mayosi, Jimmy Volmink, and Patrick Commerford), while this review update has eight review authors.

The protocol set out to assess the effects of only four interventions (six-month antituberculous drug regimens compared with regimens of nine months or more, corticosteroids, pericardial drainage, and pericardiectomy). However, in this review we have assessed the effects of any intervention used to treat tuberculous pericarditis.

The protocol did not report cancer as a potential outcome, but we have reported outcome data on cancer in this version of the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [therapeutic use]; Antitubercular Agents [therapeutic use]; Cause of Death; Colchicine [therapeutic use]; Drainage; HIV Seronegativity; HIV Seropositivity [drug therapy]; Immunotherapy; Pericardiectomy; Pericarditis, Tuberculous [complications] [*drug therapy] [mortality] [*surgery]; Pericardium [surgery]; Randomized Controlled Trials as Topic

MeSH check words

Humans