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[Intervention Review]

Prophylaxis for Pneumocystis pneumonia (PCP) in non-HIV immunocompromised patients

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ABSTRACT

Background

Pneumocystis pneumonia (PCP) is a disease affecting immunocompromised patients. PCP among these patients is associated with significant morbidity and mortality.

Objectives

To assess the effectiveness of PCP prophylaxis among non-HIV immunocompromised patients; and to define the type of immunocompromised patient for whom evidence suggests a benefit for PCP prophylaxis.

Search methods

Electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2014, Issue 1), MEDLINE and EMBASE (to March 2014), LILACS (to March 2014), relevant conference proceedings; and references of identified trials.

Selection criteria

Randomised controlled trials (RCTs) or quasi-RCTs comparing prophylaxis with an antibiotic effective against PCP versus placebo, no intervention, or antibiotic(s) with no activity against PCP; and trials comparing different antibiotics effective against PCP among immunocompromised non-HIV patients. We only included trials in which Pneumocystis infections were available as an outcome.

Data collection and analysis

Two review authors independently assessed risk of bias in each trial and extracted data from the included trials. We contacted authors of the included trials to obtain missing data. The primary outcome was documented PCP infections. Risk ratios (RR) with 95% confidence intervals (CI) were estimated and pooled using the random-effects model.

Main results

Thirteen trials performed between the years 1974 and 2008 were included, involving 1412 patients. Four trials included 520 children with acute lymphoblastic leukemia and the remaining trials included adults with acute leukemia, solid organ transplantation or autologous bone marrow transplantation. Compared to no treatment or treatment with fluoroquinolones (inactive against Pneumocystis), there was an 85% reduction in the occurrence of PCP in patients receiving prophylaxis with trimethoprim/sulfamethoxazole, RR of 0.15 (95% CI 0.04 to 0.62; 10 trials, 1000 patients). The evidence was graded as moderate due to possible risk of bias. PCP-related mortality was also significantly reduced, RR of 0.17 (95% CI 0.03 to 0.94; nine trials, 886 patients) (low quality of evidence due to possible risk of bias and imprecision), but in trials comparing PCP prophylaxis against placebo or no treatment there was no significant effect on all-cause

mortality (low quality of evidence due to imprecision). Occurrence of leukopenia or neutropenia and their duration were not reported consistently. No significant differences in overall adverse events or events requiring discontinuation were seen comparing trimethoprim/sulfamethoxazole to no treatment or placebo (four trials, 470 patients, moderate quality evidence). No differences between once daily versus thrice weekly trimethoprim/sulfamethoxazole were seen (two trials, 207 patients).

Authors' conclusions

Given an event rate of 6.2% in the control groups of the included trials, prophylaxis for PCP using trimethoprim/sulfamethoxazole is highly effective among non-HIV immunocompromised patients, with a number needed to treat to prevent PCP of 19 patients (95% CI 17 to 42). Prophylaxis should be considered for patients with a similar baseline risk of PCP.

PLAIN LANGUAGE SUMMARY

Antibiotic treatment for the prevention of Pneumocystis pneumonia (PCP) in non-HIV immunocompromised patients

Pneumocystis jiroveci is a fungus causing pneumonia mainly among patients with an impaired immune system, such as those infected with the human immunodeficiency virus (HIV), cancer patients, following organ transplantation, and patients receiving immune suppressive medications. Previous evidence shows that preventive antibiotic treatment (before the onset of the disease) could reduce mortality and morbidity from PCP among patients with HIV. We assessed whether this is also true for immunocompromised non-HIV patients.

The patients included in the 13 trials we identified were adults with acute leukemia or solid organ transplantation and children with acute leukemia. This review of randomised controlled trials (RCTs) found that prophylaxis with trimethoprim/sulfamethoxazole, an antibiotic effective against PCP, significantly reduced the occurrence of PCP by 85%. We found no evidence for a reduction in all cause mortality. Confidence in the results for PCP was moderate to high, while for mortality it was low due to paucity of data. Preventive treatment was not associated with an increased rate of adverse events. Trimethoprim/sulfamethoxazole may be administered thrice weekly as effectively as once daily.

Based on our results, the number of people that need to be treated with trimethoprim/sulfamethoxazole for a prolonged period of time (ranging between several weeks to three years in the included trials) in order to prevent one episode of PCP infection was 19; when PCP infection occurs at a rate of about 6% without prophylaxis. Given the low rate of adverse events, prophylaxis should be considered for patients at similar risk of PCP.

Summary of findings for the main comparison. TMP/SMX versus placebo, no treatment or non-PCP drug for Pneumocystis pneumonia (PCP) in non-HIV immunocompromised patients

TMP/SMX versus placebo, no treatment or non-PCP drug for Pneumocystis pneumonia (PCP) in non-HIV immunocompromised patients

Patient or population: patients with Pneumocystis pneumonia (PCP) in non-HIV immunocompromised patients
Settings:
Intervention: TMP/SMX versus placebo, no treatment or non-PCP drug

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	TMP/SMX versus placebo, no treatment or non-PCP drug				
Documented PCP infections Clinical and microbiological criteria Follow-up: 1-36 months	**Study population**		See comment	1000 (10 studies)	⊕⊕⊕⊖ **moderate** [1,2]	Risks were calculated from pooled risk differences
	62 per 1000	**9 per 1000** (2 to 39)				
	Moderate					
	10 per 1000	**2 per 1000** (0 to 6)				
All cause mortality - TMP/SMX versus placebo or no treatment Follow-up: 2-36 months	**Study population**		**RR 0.58** (0.17 to 2)	461 (4 studies)	⊕⊕⊖⊖ **low** [3]	
	31 per 1000	**18 per 1000** (5 to 62)				
	Moderate					
	10 per 1000	**6 per 1000** (2 to 20)				
PCP-related mortality Clinical only	**18 per 1000**	**3 per 1000** (1 to 17)	**RR 0.17** (0.03 to 0.94)	886 (9 studies)	⊕⊕⊖⊖ **low** [1,4]	
Adverse events: severe adverse events requiring treatment discontinuation	**16 per 1000**	**4 per 1000** (1 to 27)	**RR 0.28** (0.05 to 1.7)	530 (5 studies)	⊕⊕⊕⊖ **moderate** [5]	

- TMP/SMX versus placebo or no treatment Clinical and laboratory criteria and treatment discontinuations				

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

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

[1] Randomisation methods were not described in most trials and only half were blinded.
[2] No serious inconsistency (I^2 = 0%).
[3] Small trials with few events (11 deaths in total), unpowered to examine the effects of prophylaxis on mortality. Pooled effect ranges from no benefit to benefit.
[4] Broad 95% CI for pooled effect (RR 0.03-0.94) but always below 1.
[5] Broad 95% CI ranging from less to more adverse events with prophylaxis.

BACKGROUND

Description of the condition

Pneumocystis jirovecii is a ubiquitous, species-specific fungus. Infection with *Pneumocystis jirovecii* is common and occurs at an early age. Serologic surveys have shown nearly universal seropositivity to Pneumocystis by two years of age (Vargas 2001). Primary infection is probably largely asymptomatic (Mandel 2010). Colonization with PCP is common, documented to occur in more than 50% of the general adult population, and is assumed to represent re-infections through person-to-person transmission or environmental re-exposures rather than re-activation (Gigliotti 2012; Ponce 2010). Symptomatic, tissue invasive disease is rare and limited to immunocompromised individuals, mainly patients with human immunodeficiency virus infection (HIV) before immune reconstitution. The most common manifestation is Pneumocystis pneumonia (PCP). Common symptoms of PCP include progressive shortness of breath, nonproductive cough, and low-grade fever. Physical examination often reveals tachypnea, tachycardia, and normal or near-normal findings on lung ausculation. Hypoxemia is found in most patients. In HIV patients the clinical presentation is usually subtle, despite high organism load, and the mortality rate is 10% to 20% (Mandel 2010; Morris 2012). In contrast, among non-HIV patients PCP typically presents with an abrupt onset of respiratory failure. The mortality rate among non-HIV patients is 30% to 60%, with a greater risk of death amongst cancer patients in part related to delays in diagnosis (Mandel 2010; Morris 2012). In a retrospective study of Pneumocystis infections at Beth Israel Deaconess Medical Center, admissions to the intensive care unit (ICU), mechanical ventilation and mortality rates were 10%, 7% and 10% among HIV patients versus 69%, 66% and 39% among non-HIV patients (Mansharamani 2000).

The incidence of PCP among HIV patients in developed countries has decreased with the advent of highly active antiretroviral therapy and prophylaxis, although it remains the most prevalent opportunistic infection in this population (Morris 2012). Conversely, the incidence of PCP in immunocompromised patients without HIV is increasing (Morris 2012). Patients at risk include cancer patients receiving chemotherapy, bone marrow and solid organ transplant recipients, and other patients treated with corticosteroids or other immune suppressive medications.

Description of the intervention

Pneumocystis jirovecii, despite its classification as a fungus, is susceptible to several antibacterial and antiparasitic drugs that can be used for prevention of infection among patients at high risk for PCP. The agent most commonly used for prophylaxis is trimethoprim/sulfamethoxazole (TMP/SMX). Other agents that have activity against *Pneumocystis jirovecii* include dapsone, pentamidine, atovaquone, pyrimethamine, sulfadoxine, and clindamycin and primaquine in combination. All these drugs can cause side effects that may counterbalance the benefits of PCP prevention. TMP/SMX can cause mild to severe skin rash (up to the life threatening reactions of Stevens-Johnson syndrome or toxic epidermal necrolysis). Leukopenia (a decrease in the white blood cell count) induced by TMP/SMX may adversely affect patients with hematological cancer. Liver and renal dysfunction may be detrimental to solid organ transplant recipients. The common side effects of dapsone are hemolysis and methemoglobinemia. Hypersensitivity can be life-threatening, as for TMP/SMX. Pentamidine must be administered through the aerosolized route and can cause acute reactions during inhalation both for the patient being treated and for bystanders (which include respiratory and cardiac manifestations).

While guidelines for PCP prophylaixs among HIV patients (Panel HIV 2013) are specific and universally accepted, there is a lack of consensus on prophylaxis in other immunocompromised people. Current guidelines for patients undergoing stem cell transplantation recommend that allogeneic recipients receive PCP prophylaxis from engraftment until at least six months after the transplantation (Tomblyn 2009). Some experts initiate PCP prophylaxis prior to transplantation, depending on the underlying disease and the pretransplant conditioning regimens or prior chemotherapy. Prophylaxis is recommended for longer than six months in patients who continue to receive immunosuppressive drugs (Tomblyn 2009). The rate of PCP in autologous stem cell transplant recipients is much lower than among allogeneic recipients and prophylaxis is recommended only for specific high-risk populations, such as patients with multiple myeloma, or following treatment with purine analogues or high-dose corticosteroids. The duration of PCP prophylaxis in this setting has not been evaluated, but common practice is to extend prophylaxis to three to six months post-transplantation (Tomblyn 2009). Among other hematologic and solid cancer patients an increased risk of PCP was found in patients with acute lymphoblastic leukemia (ALL), prolonged CD4 counts of less than 200/µL, or long term treatment with steroids. Prophylaxis is recommended for the duration of therapy or until the CD4 count is > 200/µL (Neumann 2013). The risk status is less conclusive in patients treated with standard or salvage regimens for lymphoma, and patients with prolonged neutropenia or acute myeloid leukemia. Some experts suggest prophylaxis for the duration of chemotherapy (Neumann 2013). Guidelines for solid organ transplant recipients recommend anti-Pneumocystis prophylaxis for all recipients for at least six to 12 months post-transplant, though longer durations can be considered (Martin 2013). For lung and small bowel transplant recipients, as well as any transplant patient with a history of prior PCP infection or chronic cytomegalovirus (CMV) disease, lifelong prophylaxis may be indicated (Martin 2013). In addition, PCP prophylaxis is recommended for kidney transplant recipients for at least six weeks during and after treatment for acute rejection (Kasiske 2010). It is suggested that patients with inflammatory bowel disease receive prophylaxis if treated with three immunomodulatory drugs including a calcineurin inhibitor or anti-TNF therapy (Rahier 2009). Other populations in whom experts suggest considering prophylaxis include (Mandel 2010):

1. primary immune deficiency diseases;
2. severe protein malnutrition;
3. persistent CD4 counts of less than 200/µL;
4. cytotoxic or immunosuppressive therapy for the treatment of collagen vascular diseases and other disorders;
5. patients given the equivalent of 20 mg of prednisone or more, for more than one month.

Why it is important to do this review

Since PCP is relatively rare and prevention entails the use of drugs with significant adverse effects, it is important to document the risk-benefit profile of PCP chemoprophylaxis. It is necessary to define the effects of PCP chemoprophylaxis for the different drugs

available and different patient populations at different risk levels for PCP. In the previous version of this review we showed that TMP/SMX results in a 91% reduction in the occurrence of PCP compared to no treatment (95% confidence interval 68% to 98%), with few adverse events reported in the included trials (Green 2007; Green 2007a). We have conducted an update of the aforementioned review.

OBJECTIVES

- To assess the effectiveness of PCP prophylaxis among non-HIV immunocompromised patients
- To define the type of immunocompromised patient for whom evidence suggests a benefit for PCP prophylaxis

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) or quasi-RCTs

Types of participants

- Cancer patients (hematological and solid organ malignancy)
- Bone marrow recipients
- Solid organ transplant patients
- Patients receiving corticosteroids
- Patients receiving other immunosuppressive medications (for connective tissue disease, chronic lung disease, inflammatory bowel disease)
- Severe malnutrition
- Primary immune-deficiency diseases

HIV positive patients were excluded.

Types of interventions

Any chemoprophylaxis administered for the prevention of Pneumocystis infections versus placebo, no intervention, or an antibiotic(s) with no activity against Pneumocystis pneumonia. We also included trials that compared different antibiotics for the prevention of Pneumocystis infections. Only trials in which an outcome of Pneumocystis infections was available (in the original report or through correspondence with the authors) were included. We searched specifically for the following antibiotics, which are effective against Pneumocystis in vitro, considered for prophylaxis:

- trimethoprim/sulfamethoxazole (TMP/SMX);
- pentamidine;
- atovaquone;
- dapsone;
- pyrimethamine;
- clindamycin.

Types of outcome measures

Primary outcomes

- Documented Pneumocystis infections, defined as documentation of Pneumocystis from a properly obtained specimen (bronchoalveolar lavage, induced sputum, or biopsy) in a patient with clinical manifestations compatible with PCP. Accepted methods for documentation included: staining techniques (methenamine silver, Wright-Giemase, or other), immunofluorescence on clinical specimens or immunohistochemistry on tissue sections and polymerase chain reaction (PCR) (Mandel 2010).

Secondary outcomes

- All cause mortality at end of study follow-up
- PCP-related mortality at end of study follow-up
- Infections other than Pneumocystis (bacterial infections specifically)

Adverse effects

- Any adverse event
- Adverse events requiring temporary or permanent treatment discontinuation
- Severe adverse events requiring treatment discontinuation: defined as leukopenia, thrombocytopenia or severe dermatological reaction
- Specific adverse events: any dermatological, any leukopenia
- Resistance of PCP to antibiotics
- Resistance of other bacteria to antibiotics

Search methods for identification of studies

Electronic searches

We identified studies by searching the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2014, Issue 1), MEDLINE and EMBASE (to March 2014), LILACS (to March 2014), and by handsearching the following conference proceedings: European Congress of Clinical Microbiology and Infectious Diseases (2001 to 2014) and Annual Meeting of the Infectious Diseases Society of America (IDSA) (2001 to 2014).

We searched the following trial databases for ongoing and unpublished trials: Current Controlled Trials in the meta-register of controlled clinical trials (http://www.controlled-trials.com/); and the National Institutes of Health database (http://clinicaltrials.gov/).

The search strategies are listed in Appendix 1, Appendix 2, Appendix 3.

Searching other resources

We inspected the references of all identified studies for more trials.

Data collection and analysis

Selection of studies

For the original 2007 review, HG performed the search and inspected the abstracts of each reference identified. AS performed the search and inspection of abstracts for the review update. Where relevant articles were identified, the full article was obtained and inspected independently by HG and MP (in the original review) and AS and MP in the updated review. We resolved disagreements by discussion.

Data extraction and management

Data from the included trials were independently extracted into a data extraction sheet by HG and MP in the original review

and by AS and MP in the updated review. Differences in the data extraction were resolved by discussion with a third review author (LV or LL). Any missing information was requested from the authors. Outcomes were extracted preferentially by intention to treat, including all the individuals randomised in the outcome assessments.

We extracted data on trial characteristics, including time, location and methods of PCP diagnosis, risk of bias (as specified below), interventions, the duration of follow-up, and outcomes as specified above.

Assessment of risk of bias in included studies

Assessment of risk of bias in each study was performed independently by two authors (HG and MP in the original review and AS and MP in the update). An individual component approach to quality assessment was undertaken using the following variables: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data) and reporting bias (selective reporting). The grading of the specific risks of bias was expressed as 'Low risk', 'High risk' or 'Unclear risk' of bias using the criteria suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Cochrane Handbook and Table 1).

The quality of the evidence was graded in the Summary of Findings tables for the main outcomes.

Measures of treatment effect

We calculated risk ratios (RR) for dichotomous data with 95% confidence intervals (CI). The number needed to treat for an additional beneficial outcome was calculated as 1/(CER - RR*CER), where CER is the control event rate.

Unit of analysis issues

Whenever trials recruited patients more than once for different episodes of immune suppression (for example neutropenia), we attempted to include each patient only once, preferably in the first randomisation.

Dealing with missing data

We contacted the first or corresponding author of each included trial for information regarding unpublished trials or supplementary information on their own trial.

Assessment of heterogeneity

The percentage of variation between the results of trials which could not be ascribed to sampling variation was assessed using the I^2 statistic, and the statistical significance of the heterogeneity was assessed using a Chi^2 test of heterogeneity.

Assessment of reporting biases

Funnel plots for PCP infections (SE of log (RR) plotted against RR) were visually examined in order to estimate potential selection bias (publication or other).

Data synthesis

We pooled trials comparing:

- an antibiotic effective against Pneumocystis versus no treatment or placebo;
- an antibiotic effective against Pneumocystis versus antibiotic(s) with no activity against Pneumocystis;
- the same antibiotic effective against PCP given in a different daily or weekly schedule.

For PCP-related outcomes we also pooled the first two comparisons, thus assessing the overall efficacy of anti-Pneumocystis prophylaxis. Where possible, we abstracted data by intention-to-treat analysis for all randomised patients. We used the random-effects model throughout the review.

Subgroup analysis and investigation of heterogeneity

In this update we planned the following subgroup analyses for the primary outcome in order to explore heterogeneity.

- Underlying patient conditions: solid organ transplant recipients or other patients.
- Adults and children.

Too few trials were identified to permit other subgroup analyses that were planned in the original review (type of anti-Pneumocystis antibiotic and incidence of PCP infections in study).

Sensitivity analysis

To assess the effect of study quality on outcomes we planned sensitivity analyses for allocation concealment. This was based on previous evidence showing overestimation of effects with inadequate or unclear allocation concealment (Moher 1998; Schulz 1995). However, too few trials were included in the different comparisons to allow sensitivity analyses.

RESULTS

Description of studies

Results of the search

The search yielded over 1000 references, most of them not relevant for this review. Forty-seven studies were considered for the review, of which 13 were included: 11 were included in the original review and two were added in the current update (Vesole 2012; Ward 1993). One study found in the trial registry search is ongoing (Fengchun Zhang).

Included studies

A total of 1412 patients were randomised of which 520 were children, in five studies. Two trials (Arning 1990; Ward 1993) evaluated neutropenic episodes (allowing the recruitment of patients more than once), while all other trials included patients only once. The studies were performed between the years 1974 and 2008. One trial that did not specify recruitment dates was published in 1999 (Torre-Cisneros 1999). The trial characteristics are described in the Characteristics of included studies table.

Comparisons

The 13 trials included 14 comparisons. Seven trials compared oral (TMP/SMX) prophylaxis given daily versus placebo or no intervention (Fox 1990; Goorin 1985; Hughes 1977; Olsen 1993; Van Eys 1987; Vesole 2012; Ward 1993). Two of these included three arms: Olsen 1993 compared TMP/SMX given daily, TMP/SMX given

thrice weekly and no prophylaxis; and Vesole 2012 compared oral TMP/SMX given daily, quinolones and no prophylaxis. Three trials compared oral TMP/SMX given daily versus quinolones (that have no known anti-PCP activity) (Arning 1990; Hibberd 1992; Liang 1990).

Two trials compared TMP/SMX given daily versus TMP/SMX given thrice weekly, both orally (Arning 1990; Hughes 1987). One trial compared oral TMP/SMX given daily versus oral sulfadoxine/pyrimethamine given once a week (Torre-Cisneros 1999); and one trial compared oral TMP/SMX versus oral atovaquone, both drugs given daily for the first five days of the trial and thrice weekly thereafter (Colby 1999). In one trial another antibiotic (colistin) was administrated with TMP/SMX (Arning 1990).

Underlying immunosuppression

The four trials recruiting children included only children with ALL (Goorin 1985; Hughes 1977; Hughes 1987; Van Eys 1987). The trials in adults included mainly cancer patients: acute myelocytic leukemia (AML) or ALL (Arning 1990; Liang 1990; Ward 1993), multiple myeloma (Vesole 2012), and autologous stem cell transplantation for hematologic and solid cancer (Colby 1999). Four adult trials included solid organ transplant recipients: heart (Olsen 1993), renal (Fox 1990; Hibberd 1992), and liver transplantation (Torre-Cisneros 1999).

All patients were given chemotherapy or anti-rejection treatment, including corticosteroids in eight trials. None of the trials included patients treated with corticosteroids alone as the underlying risk factor for PCP.

Timing of PCP prophylaxis administration

Among hematological cancer patients, prophylaxis was initiated on the first day of induction chemotherapy in three trials (Arning 1990; Hughes 1987; Vesole 2012), immediately following diagnosis in one trial (Goorin 1985), with neutropenia onset in one trial (Liang 1990), and variously during anticancer treatment in three trials (Hughes 1977; Van Eys 1987; Ward 1993). Prophylaxis was continued until resolution of neutropenia, development of adverse effects, throughout chemotherapy, until relapse, or up to three years of follow-up (Van Eys 1987). In one trial including bone marrow transplant patients (Colby 1999) prophylaxis was administered between days -1 to -5 and from neutropenia resolution (> 100/mm^3) to day +100.

Among solid organ transplant recipients, prophylaxis was initiated in the first week after transplantation and continued for four months (Olsen 1993), six months (Hibberd 1992; Torre-Cisneros 1999), or up to one year or until graft failure was recorded (Fox 1990).

Outcomes assessed

All trials except one reported on PCP infections, and in one PCP information was completed by contacting the author (Vesole 2012). Three trials described the occurrence of PCP following prophylaxis discontinuation because of adverse events (Hibberd 1992; Torre-Cisneros 1999) or after the trial ended (Olsen 1993); these were not included in the overall outcome assessment. Seven trials reported overall mortality and 10 reported on PCP-related mortality. Thirteen trials reported any infection other than PCP, five of which reported on infection episodes. Neutropenia duration was reported in five trials and four reported bacterial resistance development (Fox 1990; Goorin 1985; Liang 1990; Ward 1993).

Methods for PCP surveillance and diagnosis

Active surveillance for PCP was conducted in two trials, using monoclonal antibodies in sputum (Torre-Cisneros 1999) or transthoracic percutaneous needle aspiration of lung parenchyma when diffuse alveolar disease was encountered on chest x-ray (Hughes 1977). Routine follow-up chest x-rays were performed in three trials (Hughes 1977; Liang 1990; Torre-Cisneros 1999).

In all trials PCP infections were defined as a clinical disease, not only by microbiological detection. Six trials defined diagnosis of PCP by staining or monoclonal antibodies from a tissue (bronchoalveolar lavage or autopsy). Seven studies did not describe the methods used for the diagnosis of PCP.

Excluded studies

Thirty-four studies were excluded (Characteristics of excluded studies). Seventeen were observational studies, four were reviews, and one study was a computer-based simulation (Chung 2000). We excluded five trials in HIV patients, a RCT that assessed treatment for PCP rather than prophylaxis (Young 1976), one trial that did not use bacteriologic methods to define PCP infection (Rossi 1987), and one trial was never published and data were lost (Pedagogos 1994). Finally, we excluded three RCTs that did not assess PCP as an outcome: Arico 1992 evaluated toxicity only, Oken 1996 evaluated bacterial infections with no specific data on PCP, and Stegeman 1996 evaluated the effect of TMP/SMX on relapses in Wegener's granulomatosis.

Risk of bias in included studies

The risk of bias in the included studies is summarized overall in Figure 1 and per study in Figure 2.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

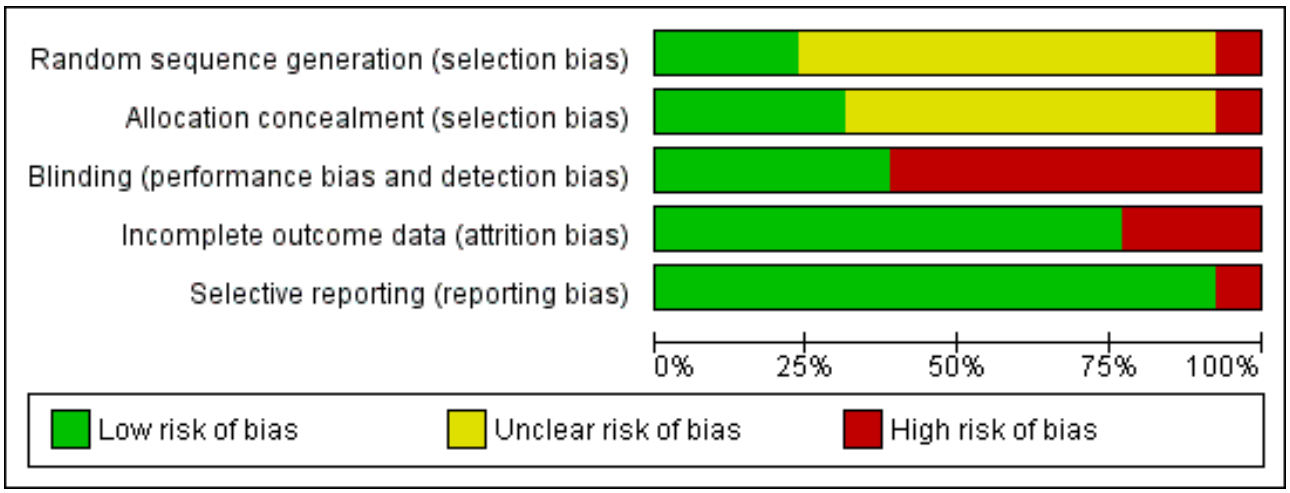
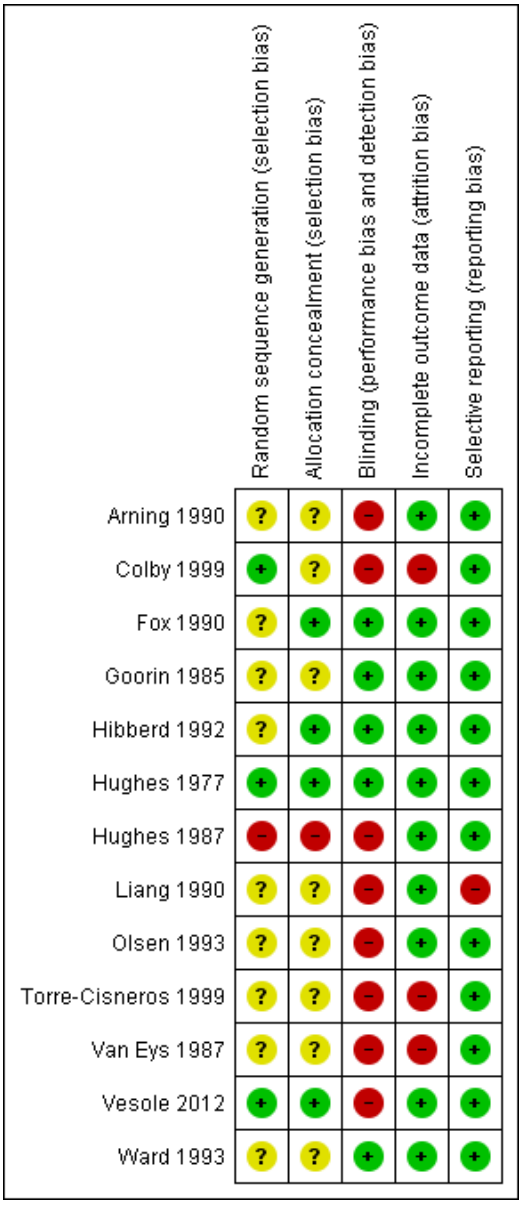


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random generation of recruitment sequence was described in three trials that were classified as having low risk of bias (Colby 1999; Hughes 1977; Vesole 2012). One trial that compared once versus thrice weekly TMP/SMX prophylaxis used birth dates for randomisation (Hughes 1987) and was classified at high risk of bias. All the other studies did not describe the methods used for generation of randomisation, and hence were classified as having an unclear risk.

Allocation concealment was classified as low risk in four trials (Fox 1990; Hibberd 1992; Hughes 1977; Vesole 2012), high risk in the trial using birth dates (Hughes 1987), and was not reported in all other trials.

Blinding

Five trials used double blinding (Fox 1990; Goorin 1985; Hibberd 1992; Hughes 1977; Ward 1993), while all others were open-label trials.

Incomplete outcome data

All randomised patients were included for assessment of the primary outcome in three trials that were classified as low-risk (Hibberd 1992; Hughes 1977; Hughes 1987). Seven trials described the reasons for dropouts and non-evaluability and were similarly considered at low risk for attrition bias. The remaining three trials were classified as high risk (Colby 1999; Torre-Cisneros 1999; Van Eys 1987).

Selective reporting

Based on the comparison between methods and results (lacking protocols, trial registry data for all trials), all but one study quantitatively reported the designated outcomes. In one study outcomes were not defined in the methods (Liang 1990).

Other potential sources of bias

All trials but three (Olsen 1993; Van Eys 1987; Vesole 2012) reported that informed consent was obtained from patients. Eight trials reported ethics committee approval.

Effects of interventions

See: **Summary of findings for the main comparison** TMP/SMX versus placebo, no treatment or non-PCP drug for Pneumocystis pneumonia (PCP) in non-HIV immunocompromised patients

Prophylaxis with TMP/SMX versus no intervention, placebo or a non-antiPCP antibiotic

Documented PCP infection

Ten trials, including 1000 patients, were included in this comparison. No events occurred in four trials. Only one case of PCP occurred in the prophylaxis arms. There was a significant reduction in the occurrence of PCP infections in the TMP/SMX prophylaxis group compared to the other groups, RR of 0.15 (95% CI 0.04 to 0.62) (Analysis 1.1). Minor heterogeneity was present within this comparison (I^2 = 27%, P = 0.23). The number of patients needed to treat to prevent one episode of PCP was 19 patients (95% CI 17 to 42) with a control event rate (CER) of 31/497 (6.2%). The funnel plot demonstrated a similar SE for trials with different effects, with no small study effect. The quality of the evidence for PCP prevention was graded as moderate, being downgraded only for possible risk of bias related to unknown randomisation methods for most trials and lack of blinding in half of the trials (Summary of findings for the main comparison). In four trials no events occurred, in both arms.

Seven trials, including 707 patients, compared daily administered TMP/SMX prophylaxis versus no intervention or placebo. Prophylaxis resulted in a decrease in the occurrence of PCP infections, RR of 0.17 (95% CI 0.03 to 1,0). Total events were 26 out of 335 in the no treatment or placebo group compared to 1 out of 372 in the TMP/SMX group. Four trials compared TMP/SMX prophylaxis versus a non-antiPCP antibiotic (quinolones). One of the trials (Vesole 2012) was a three armed trial and was already included in the TMX/SMX versus no intervention analysis, and was thus excluded from this category of the meta-analysis. In the three trials that were included in the analysis (total of 293 patients) prophylaxis with TMP/SMX reduced PCP but without statistical significance (RR 0.09, 95% CI 0.01 to 1.57). All events (5/162 in the quinolone group) occurred in a single trial involving renal transplant recipients (Hibberd 1992).

For the planned subgroup of solid organ transplant recipients (only adults included) the RR was 0.09 (95% CI 0.02 to 0.48) (Analysis 1.2), while among hematological cancer adults and children the RR was 0.28 (95% CI 0.02 to 4.57) (Analysis 1.3). Too few studies were available to perform subgroup analysis according to different rates of PCP infection in the studies, and no trials assessed antibiotics other than TMP/SMX. The effects among adults (RR 0.20, 95% CI 0.03 to 1.37, CER 4.0%) and children with ALL (RR 0.09, 95% CI 0.01 to 1.15, CER 10.6%) were similar, not reaching statistical significance in either subgroup (Analysis 1.4).

All cause mortality

Six trials, including 652 patients, reported this outcome (Analysis 1.5). Four trials compared TMP/SMX to placebo, RR of 0.58 (95% CI 0.17 to 2). This result was graded as low quality due to high imprecision. Two trials compared TMP/SMX versus quinolones (RR 0.49, 95% CI 0.02 to 10.73) and the pooled RR for all trials examining anti-PCP prophylaxis was 0.71 (95% CI 0.28 to 1.80), without heterogeneity.

PCP-related mortality

Nine trials, including 886 patients, reported on PCP-related mortality. Overall, TMP/SMX prophylaxis reduced PCP-related mortality, RR of 0.17 (95% CI 0.03 to 0.94) (Analysis 1.6). The quality of the evidence was graded as low due to possible risk of bias, as above, and imprecision.

Six trials, including 593 patients, compared TMP/SMX versus no intervention or placebo and three studies, including 293 patients, compared TMP/SMX versus quinolones. In both comparisons the PCP rates were lower with TMP/SMX but without statistical significance due to small sample sizes and low event rates.

Any infection other than PCP

Three studies, including 299 patients, comparing TMP/SMX prophylaxis versus no intervention or placebo reported this outcome (Analysis 1.8). There was no statistically significant difference between the groups, RR of 0.90 (95% CI 0.74 to 1.1). Four studies that compared TMP/SMX prophylaxis versus quinolones, including 431 patients, reported this outcome. Significantly more infections other than PCP occurred in the TMP/SMX arm compared to the quinolones arm, RR of 1.49 (95% CI 1.14 to 1.96).

Bacterial infections

Four studies (399 patients) comparing TMP/SMX versus no treatment reported on the incidence of bacterial infections (Analysis 1.7). There was a significant decrease in the rate of bacterial infections in the prophylaxis group, RR.of 0.44 (95% CI 0.21 to 0.9).

Four studies (431 patients) comparing TMP/SMX versus quinolones reported this outcome. There were more bacterial infections in the TMP/SMX group, RR of 2.04 (95% CI 0.8 to 5.23).

Resistance development

Three studies comparing TMP/SMX versus no treatment reported on resistance to TMP/SMX for bacterial infections developing during the trial. Resistance rates were 62% versus 18% of isolates in one trial (Fox 1990) and 26% versus 0 patients in the other (Goorin 1985). The third trial reported that all patients in both groups acquired one or more trimetoprim-resistant organisms throughout the study period (Ward 1993).

One trial comparing TMP/SMX to ofloxacin (Liang 1990) reported that colonisation with isolates resistant to TMP/SMX increased from 24% of isolates to 66% during treatment, whereas resistance to ofloxacin remained null throughout the trial.

Adverse events

Four trials comparing TMP/SMX prophylaxis versus no intervention or placebo reported on the occurrence of any type of adverse effects (Analysis 1.9). These studies included 470 patients. There was no significant difference in the adverse effects rate between the two groups, RR of 1.01 (95% CI 0.82 to 1.24). Three trials reported adverse events that required discontinuation of the treatment (Analysis 1.10) and five trials reported on severe adverse events requiring permanent discontinuation, as defined in our protocol (Analysis 1.11). No severe adverse events or adverse events requiring treatment discontinuation were reported with TMP/SMX, while several events were reported with placebo or no treatment. It should be noted that adverse events were caused by underlying conditions or chemotherapy as well as by TMP/SMX. The quality of the evidence for this outcome was rated as moderate due to imprecision.

Two trials comparing TMP/SMX prophylaxis versus quinolones reported on any adverse effects (Analysis 1.9). These trials included 191 patients. There were significantly more adverse effects in the TMP/SMX group, RR of 4.66 (95% CI 2.55 to 8.53). Adverse events requiring temporary treatment discontinuation (Analysis 1.10) and severe adverse events requiring permanent discontinuation (Analysis 1.11) were also more common with TMP/SMX. Severe adverse events, which included leukopenia and thrombocytopenia, resolved following treatment withdrawal.

When looking for the more common adverse events associated with TMP/SMX, rash was reported in four trials comparing TMP/SMX prophylaxis versus no intervention or placebo (392 patients) and in two trials comparing TMP/SMX versus quinolones (191 patients). The RRs were 0.38 (95% CI 0.09 to 1.52) and 3.94 (95% CI 1.35 to 11.46), respectively (Analysis 1.12). Three studies that compared TMP/SMX prophylaxis versus no intervention or placebo reported the rates of leukopenia. Only one study comparing TMP/SMX versus quinolones reported this outcome. The RRs were 1.45 (95% CI 0.84 to 2.5) and 1.96 (95% CI 0.18 to 20.97), respectively (Analysis 1.13). Trials reporting on neutropenia duration could not be combined. The mean number of days with neutropenia were reported in one trial involving adults with acute myeloid leukemia (AML) or ALL (Liang 1990): 15.8 ± 1.1 days for TMP/SMX versus 14.9 ± 1.1 days for ofloxacin. The median number of days with neutropenia was reported in two trials. Ward 1993 (AML and ALL adults) reported medians of 26 days with TMP/SMX versus 30 days with the placebo groups; Arning 1990 (AML and ALL adults) reported 20 days in the TMP/SMX group versus 10 days in the ciprofloxacin group versus 16 days in the ofloxacin group. The total number of days with neutropenia were reported in one trial in renal transplantation patients (Fox 1990): 35 days for the TMP/SMX group and 23 days for the placebo group. Goorin 1985 (ALL children) reported on the mean nadir of the neutrophil count, which was 172 (113 to 262) in the TMP/SMX group versus 172 (240 to 343) in the placebo group.

Daily versus thrice weekly TMP/SMX prophylaxis

Documented PCP infections and PCP-related mortality

Two studies, including 205 patients, were included in this comparison (Analysis 2.1). No events occurred in either study arm. The trials included patients with acute leukemia (Hughes 1987) and cardiac transplantation (Olsen 1993).

Any infection other than PCP

This outcome was reported in one study (Analysis 2.8) including 167 patients. There was no difference between daily administered TMP/SMX versus thrice weekly TMP/SMX (RR 1.06, 95% CI 0.58 to 1.93).

Bacterial infections

One study, including 167 patients, reported this outcome (Analysis 2.9). There was no significant difference in the occurrence of bacterial infections (RR 1.35, 95% CI 0.66 to 2.78).

All cause mortality, resistance development, and adverse effects requiring discontinuation were not reported in this subgroup of studies.

Adverse events

The two trials, including 207 patients, reported on adverse events. There were no significant differences in rates of any adverse event or adverse events requiring discontinuation, and no severe adverse events were reported (Analysis 2.3, Analysis 2.4, Analysis 2.5). Rash occurred less frequently with daily TMP/SMX administration but this was not significant (RR 0.51, 95% CI 0.23 to 1.16) (Analysis 2.6). Leukopenia was reported in only one study (Analysis 2.7), including 167 patients, and occurred more frequently with daily TMP/SMX but the difference was not statistically significant (RR 2.78, 95% CI 0.60 to 13.01).

Other comparisons

Two trials fulfilling the inclusion criteria were not included in the previous comparisons. One trial compared daily TMP/SMX versus sulfadoxine/pyrimethamine given once a week (Torre-Cisneros 1999), including 125 patients following liver transplantation. There were two documented PCP infections out of 60 patients in the TMP/SMX group, versus no infections in the sulfadoxine/pyrimethamine group. Both cases of PCP occurred after TMP/SMX prophylaxis was discontinued because of adverse effects. All cause mortality rates were 13/60 and 12/60 respectively. None of the deaths were due to PCP infection. Infections other than PCP were detected among 35/60 patients in the TMP/SMX group and among 39/60 in the sulfadoxine/pyrimethamine group. Any adverse event occurred in 11/60 versus 10/60, respectively; three required discontinuation in the TMP/SMX group and four in the sulfadoxine/pyrimethamine group. Leukopenia developed in six patients in the TMP/SMX group versus four patients in the sulfadoxine/pyrimethamine group.

One trial including 39 patients after autologous peripheral blood stem cell (PBSC) transplantation for hematologic and solid malignancies compared TMP/SMX versus atovaquone (Colby 1999). Both drugs were given daily for five days before transplantation (until day -1) and then thrice weekly. No cases of PCP were recorded in either group. All cause mortality was not reported and no infection other than PCP developed. There were eight adverse events recorded in the TMP/SMX group (8/18, two cases of leukopenia, all requiring discontinuation of treatment) versus none in the atovaquone group.

DISCUSSION

Summary of main results

TMP/SMX was the antibiotic most commonly assessed for prevention of PCP infections, thus the review addressed mainly

the efficacy of TMP/SMX. Overall, TMP/SMX was highly effective in preventing PCP infections, showing a 85% reduction in the incidence of PCP infections (RR 0.15, 95% CI 0.04 to 0.62) without significant heterogeneity. All cause mortality was not significantly reduced with prophylaxis (RR 0.71, 95% CI 0.28 to 1.8) but since there were fewer PCP infections, PCP-related mortality was reduced by 83% (RR 0.17, 95% CI 0.03 to 0.94).

There was an advantage for TMP/SMX prophylaxis over no treatment in preventing bacterial infections (RR 0.44, 95% CI 0.21 to 0.90) in the populations assessed in the included trials. Quinolone treatment was significantly better than TMP/SMX in preventing any infection other than PCP (RR 1.90, 95% CI 1.14 to 1.96) but not specifically bacterial infections (RR 2.04, 95% CI 0.80 to 5.23).

No difference was encountered between once versus thrice weekly prophylaxis with TMP/SMX for all outcomes described above, but few trials were included in this comparison. According to these results, there is no superiority for daily prophylaxis over thrice weekly prophylaxis with TMP/SMX.

For adverse effects, a meta-analysis of four trials showed no difference between TMP/SMX and no prophylaxis (RR 1.01, 95% CI 0.82 to 1.24), while two trials comparing TMP/SMX to quinolone prophylaxis showed more adverse effects with TMP/SMX (RR 4.66, 95% CI 2.55 to 8.53). Among trials comparing TMP/SMX to placebo or no treatment, no severe adverse events were observed with TMP/SMX. Overall, combining all TMP/SMX treatment arms included in this systematic review, severe adverse events requiring permanent discontinuation, including leukopenia, thrombocytopenia or severe dermatological reactions, occurred in 3.1% of adults (six trials) and 0% among children (five trials). The adverse effect most important to the patient population assessed in these trials (hematological cancer patients and organ transplant recipients) is leukopenia. There was a greater risk of leukopenia in the TMP/SMX group when compared to placebo or no intervention (RR 1.45, 95% CI 0.84 to 2.50) and when comparing with quinolones (RR 1.96, 95% CI 0.18 to 20.97). However, only four trials were included in these comparisons. Longer duration of neutropenia was reported with TMP/SMX treatment compared to quinolone treatment but, again, only the minority of trials reported this outcome and the data could not be combined.

Overall completeness and applicability of evidence

The trials included in this review assessed patients with hematological malignancies, bone marrow transplant patients (five trials with children, three trials with adults) or solid organ transplant recipients (four trials). The overall rate of PCP infections in these studies was 6.2%, and for this control event rate the number needed to treat in order to prevent one PCP infection is 19 patients (95% CI 17 to 42). Our results apply to populations with a similar risk of PCP infections.

Among most cancer patients rates are usually below 1% (Roux 2014; Sepkowitz 2002). Higher rates are observed among patients after allogeneic bone marrow transplantation. Reported rates were 5% to 16% before the use of PCP prophylaxis, declining to 1.5% to 2.5% with the widespread use of TMP/SMX prophylaxis in this population (De Castro 2005; Roblot 2002). The risk of PCP in patients with autologous stem cell transplantation is unknown. In a study from France, the incidence of PCP in patients with autologous hematopoietic stem cell transplantation (HSCT) was 0.54% (Roblot 2002). In solid organ transplant patients, without prophylaxis the rate of PCP ranges from 5% to 15%. Among lung and heart-lung transplant recipients the rates are high, ranging from 10% to 40% without prophylaxis (Martin 2013; Sepkowitz 2002). PCP occurs in 1% to 2% of all patients with rheumatologic disorders, most often, but not always, among those receiving immunosuppressive therapy (Singer 1999). Patients with Wegener's granulomatosis, polyarteritis nodosa, and to a lesser degree polymyositis or dermatomyositis are at higher risk, with incidence rates of 8% to 12%, 6.5% and 2.7%, respectively (Roux 2014). While the risk among patients with inflammatory bowel disease is higher than the general population, it is low in absolute terms (about 1/1000), and most patients who are affected receive steroids combined with other immunosuppressive medications (Long 2013; Sepkowitz 2002). PCP has been described among other patients who have been administered chronic steroid treatment for autoimmune disease, dermatological diseases, chronic pulmonary disease and hematological malignancy (Raychaudhuri 1999; Worth 2005). In a retrospective analysis from the Mayo Clinic, the median steroid dose was equivalent to 30 mg of prednisone and the median duration of treatment before the development of PCP was 12 weeks (Yale 1996). Recently, reports of PCP among patients with rheumatoid arthritis and Crohn's disease who are receiving anti-TNFalfa antibodies have been described, but the incidence rates are lower than 0.5% (Ellerin 2003; FDA 2001; Roux 2014). Outbreaks with suspected airborne person-to-person transmission have been documented in high-risk units, increasing the risk for individuals exposed above their baseline risk (Chapman 2013; Nankivell 2013; Rostved 2013; Yazaki 2009).

Our original intention was to search for evidence on PCP prophylaxis for non-HIV patients chronically treated with steroids for collagen vascular diseases, chronic lung disease, inflammatory bowel disease, etc. We did not find published studies addressing this patient population.

Quality of the evidence

Most of the studies used for this review are old (eight out of 13 were published from 1977 to 1990) and included a small number of patients. One trial (Arning 1990) included patients more than once in the trial, for different neutropenic episodes, and we did not have the data to adjust for clustering. The 95% CI for this trial might be artificially narrow and the weight assigned to it in the meta-analysis artificially high. The confidence in the main results was low to moderate (Summary of findings for the main comparison) due to unclear risk of bias in most trials and imprecision of results, mainly for all cause mortality, which was reported in a selection of the trials only.

These trials could not assess the effect of TMP/SMX prophylaxis on development of *Pneumocystis jirovecii* resistance to TMP/SMX or clinical failure with TMP/SMX treatment following TMP/SMX prophylaxis since only one infection occurred in the prophylaxis group. Among HIV patients, a previous systematic review showed that TMP/SMX prophylaxis was significantly associated with mutations in the dihydropteroate synthase (DHPS) enzyme of *Pneumocystis spp*. (Stein 2004). Clinically, the relationship between DHPS mutations and failure of TMP/SMX treatment is unclear; studies show results that are highly heterogeneous, which precludes an appraisal of the effect of TMP/SMX prophylaxis on clinical resistance to treatment of subsequent PCP with TMP/SMX (Huang 2004; Stein 2004). In one study that evaluated 152 episodes

of PCP in 144 HIV patients, DHPS mutations were found to be an independent predictor associated with increased death rates. Whether this increased death rate was due to failure of TMP/SMX for PCP treatment is unclear (Helweg-Larsen 1999). In a different study, among 97 patients with AIDS and PCP the presence of DHPS mutations was associated with an increased risk for PCP treatment failure (RR 2.1, P = 0.01) (Kazanjian 2000). In contrast, other studies found no association between the presence of DHPS mutations and mortality or PCP treatment failure (Navin 2001; Rabodonirina 2013).

Potential biases in the review process

Data from this review are insufficient to address the overall gain versus detrimental effects associated with TMP/SMX prophylaxis since we limited inclusion to trials that assessed PCP infections. Thus, our comparisons for all cause mortality, infections other than PCP, bacterial infections and adverse events are incomplete.

Publication bias is of concern since almost all trials showed absolute PCP protection with TMP/SMX. However, TMP/SMX, available in the US since 1973 and in the UK since 1969, was no longer a patented drug at the time most of these trials were conducted. Most commonly PCP was not the primary outcome, thus intentional bias is unlikely. For these reasons we do not believe that our results are due to publication bias, though some effect cannot be ruled out.

A clinical question that is raised when considering TMP/SMX prophylaxis, mainly among cancer patients, is the adjunctive administration of leucovorin (folinic acid) to prevent myelosuppression. It is unclear whether leucovorin can prevent TMP/SMX-induced neutropenia, and whether it interferes with the efficacy of TMP/SMX. No studies examining this question in non-HIV patients were found. A randomised controlled trial compared tolerance to prophylaxis with TMP-SMX versus TMP-SMX with leucovorin in patients with advanced HIV. There was a non-significantly lower rate of leucopenia in recipients of leucovorin compared to patients who did not receive leucovorin (rate ratio 0.2, 95% CI 0.0 to 1.7) but there was no difference in discontinuation of the prophylaxis. Clinical efficacy was not addressed in this study (Bozzette 1995). In a randomised trial evaluating the ability of leucovorin to reduce TMP/SMX-induced toxicity in the treatment of acute PCP in 92 AIDS patients, a significant reduction in neutropenia was noted in patients receiving leucovorin (23% versus 47%, P = 0.03) (Safrin 1994). However, leucovorin also resulted in a reduction in treatment efficacy (15% versus 0% failures, P = 0.005; 11% versus 0% deaths, P = 0.02 for leucovorin versus placebo). Thus, the overall benefit-risk of administering leucovorin concomitantly with TMP/SMX for prophylaxis is unclear for HIV patients and there are no data for non-HIV patients.

Agreements and disagreements with other studies or reviews

A Cochrane systematic review assessed TMP/SMX prophylaxis among adults with HIV (Grimwade 2005). In three randomised controlled trials comparing TMP/SMX versus placebo or no treatment, no PCP events occurred and mortality was significantly reduced with prophylaxis. In a single trial comparing TMP/SMX with leucovorin versus no treatment among patients with HIV who were not on antiretroviral therapy and were receiving chemotherapy for Kaposi sarcoma, PCP infections were significantly reduced with a RR of 0.31 (95% CI 0.13 to 0.74). In two trials of cotrimoxazole prophylaxis for children with HIV, mortality was significantly reduced with prophylaxis in both trials; in one trial PCP was not reported (Mermin 2004) and in the other a single case of PCP occurred in the placebo group (Chintu 2004). Thus, among HIV patients TMP/SMX prophylaxis significantly reduces mortality, and PCP infections were not always examined. In our review, TMP/SMX prophylaxis prevented PCP infections and PCP-related mortality.

AUTHORS' CONCLUSIONS

Implications for practice

Our review shows that TMP/SMX prophylaxis is highly effective for prevention of PCP in patients with hematological malignancies, bone marrow transplantation and solid organ transplantation, both for children and adults. The overall prevalence of severe adverse events with TMP/SMX was low and did not result in treatment discontinuations. Given the observed efficacy of TMP/SMX with regard to PCP prevention, prophylactic TMP/SMX should be considered when the risk of PCP is above the rate we observed (6.2% overall). Clinical conditions in which the rates of PCP for patients not receiving prophylaxis might be above 6.2% include the following (Rodriguez 2004).

- Allogeneic bone marrow transplantation, during the six months post-transplantation and afterwards with continued immunosuppression.
- Solid organ transplantation, in the first six months after transplantation.
- Acute lymphoblastic leukemia.

The PCP incidence is probably lower for most patients with solid malignancies. Patients receiving corticosteroids for primary or metastatic brain tumours may be at a higher risk warranting prophylaxis (Sepkowitz 1993). Among patients with collagen vascular diseases, only Wegener's granulomatosis has been associated with PCP rates above 2.5%. Quantitative incidence or relative risk data are lacking for patients treated with corticosteroids for chronic lung disease, inflammatory bowel disease, dermatological conditions or other conditions. Similarly, incidence data are lacking for acute myeloid leukemia, treatment with anti-TNF agents, and newer biological treatments for hematological malignancies. During outbreaks of PCP among immunocompromised patients the incidence of PCP might be high enough to justify prophylaxis.

Using the data from our review and data available from studies conducted among HIV-positive patients, TMP/SMX may be administered thrice weekly as the efficacy is similar to once daily administration. The adult dose of TMP/SMX most commonly administered in our review was 160/800 mg.

Implications for research

Treatment with steroids for more than a month, in a dose equivalent to 20 mg of prednisone or more, may be a risk factor for the development of PCP (Yale 1996). Patients with collagen vascular diseases or inflammatory bowel disease receiving other immunosuppressive medication (including anti-TNFalfa antibodies) are also at risk. Trials are needed for this large population of patients. Documentation of the actual adverse event rate associated with prophylaxis in clinical practice, especially leukopenia, will assist future decisions regarding prophylaxis

in immunocompromised patients. The effect of prophylaxis on Pneumocystis resistance should be assessed in longitudinal studies or when TMP/SMX prophylaxis is used in practice.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Arning 1990

Methods	Allocation generation: not mentioned Allocation concealment: not mentioned Blinding: no ITT: no Number of dropouts: 6/65
Participants	Patients and ages: 59 patients (88 episodes of neutropenia), median age 47 years Underlying immune suppression: ALL (acute lymphocytic leukaemia) , ANLL (acute non-lymphocytic leukaemia) and neutrophils count < 500 Chemotherapy: ANLL: thioguanine + cytarabine + daunorubicin or high dose cytarabine + mitoxantrone. ALL: according to the German protocol ANLL: thioguanine + cytarabine + daunorubicin or high dose cytarabine + mitoxantrone. ALL: according to the German protocol Steroid use: no Duration of follow-up: median days of neutropenia: 20 (1 to 58); 16 (4 to 44); 10 (1 to 52)
Interventions	PO: co-trimoxazole (in combination with colistin IV 2 million IU once daily) 160 mg/800 mg twice daily versus ofloxacin 200 mg twice daily versus ciprofloxacin 500 mg twice daily. Starting at the initiation of cytotoxic therapy until neutrophils count > 500
Outcomes	Outcomes reported in the trial: mortality from any cause, documented PCP infections, PCP-related mortality, any infections other then PCP, number of bacterial infections, adverse events
Notes	Trial location: Dusseldorf Study years: not mentioned performance of surveillance cultures: yes- Urine + stool for bacterial + mycological culture once weekly Method for PCP surveillance: not mentioned Method to confirm PCP when infection suspected: not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not mentioned
Allocation concealment (selection bias)	Unclear risk	not mentioned
Blinding (performance bias and detection bias) All outcomes	High risk	no blinding
Incomplete outcome data (attrition bias) Documented PCP infections	Low risk	59/65 evaluated - reasons for non-evaluability are detailed (2 deaths shortly after admission, 6 protocol violations)

Arning 1990 *(Continued)*

Selective reporting (reporting bias)	Low risk	no selective outcome reporting

Colby 1999

Methods	Allocation generation: random number table Allocation concealment: not mentioned Blinding: no ITT: no Number of dropouts: 5/39
Participants	Patients and ages: 34 patients, median age 44 to 47 years Underlying immune suppression: patients that underwent autologous peripheral blood stem cell (PBSC) transplantation, with the following underlying diseases: breast cancer, ovarian cancer, Ewings sarcoma, non-Hodgkin's lymphoma, Hodgkin's disease and multiple myeloma Steroid use: no
Interventions	PO: atovaquone 1500 mg once daily versus trimethoprim/sulphamethoxazole 160 mg/800 mg once daily, every day for five days (D-5 before PBSC transplantation until D-1 before transplantation) and after neutrophils count > 500 then thrice weekly for 100 days
Outcomes	Outcomes reported in the trial: documented PCP infections, PCP-related mortality, any infection other than PCP, adverse reactions
Notes	Trial location: USA Study years: 1/1997 to 12/1997 performance of surveillance cultures: no Method for PCP surveillance: not mentioned Method to confirm PCP when infection suspected: not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	random number table
Allocation concealment (selection bias)	Unclear risk	not mentioned
Blinding (performance bias and detection bias) All outcomes	High risk	no blinding
Incomplete outcome data (attrition bias) Documented PCP infections	High risk	34/39 evaluated. patients not evaluated: 3 because of not being transplanted (1TMP-SMX and 2 atovaquone) and 2 atovaquone patients because of protocol violation
Selective reporting (reporting bias)	Low risk	no selective outcome reporting

Fox 1990

Methods	Allocation generation: not specified Allocation concealment: in pharmacy Blinding: double blind ITT: no Number of dropouts: 3/135
Participants	Patients and ages: 132 patients, mean age 36 to 38 years Underlying immune suppression: renal transplantation Steroid use: yes Duration of follow-up: average of 8.5 months
Interventions	PO: trimethoprim/sulphamethoxazole 160mg/800 mg versus placebo. Tailored according to GFR; for normal GFR the dose was given once daily, for reduced GFR the dose was reduced to half. Starting when patients were able to take oral medicine (usually day + 2), for the whole study period (at least 3 weeks) -unless graft failure, in that case until no more immunosuppression. Average 8.5 months
Outcomes	Outcomes reported in the trial: documented PCP infections, PCP-related mortality, any infections other then PCP, number of bacterial infections, developing of resistance to the drug, adverse events (in related article)
Notes	Trial location: USA Study years: 9/1984 to 9/1985 performance of surveillance cultures: yes -Urine culture 1 day after removal of catheter and weekly thereafter. Surveillance culture using selective media for MRSA, TMP/SMX resistant gram negative bacilli, fungi - on admission, prior to discharge and at least once more in outpatient setting. specimens from nares, pharynx, axilla, anterior abdomen, rectum and urine Method for PCP surveillance: not mentioned Method to confirm PCP when infection suspected: microbiological or histopathological confirmation of infection with clinical manifestations in BAL (bronchoalveolar lavage) or bronchoscopy with lung biopsy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not specified (preselected randomisation schedule)
Allocation concealment (selection bias)	Low risk	allocation conducted in pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	double blinding with placebo
Incomplete outcome data (attrition bias) Documented PCP infections	Low risk	all patients randomised were evaluated
Selective reporting (reporting bias)	Low risk	no selective outcome reporting (A/E outcomes reported in a different publication)

Goorin 1985

Methods	Allocation generation: not specified

Goorin 1985 *(Continued)*

	Allocation concealment: not specified Blinding: double blind ITT: no Number of dropouts: 1/61
Participants	Patients and ages: 60 patients, all children, median age 4.5 to 5 years Underlying immune suppression: ALL (acute lymphocytic leukemia) Chemotherapy: anthracycline, 6MP, MTX (methotrexate) Steroid use: no
Interventions	PO: trimethoprim/sulfamethoxazole (160 mg/m^2 + 800 mg /m^2) divided in two doses versus placebo. Starting immediately after diagnosis of ALL, for 40 weeks
Outcomes	Outcomes reported in trial: mortality from any cause, documented PCP infections, PCP-related mortality, any infections other then PCP, number of bacterial infections, developing of resistance to the drug, adverse events
Notes	Trial location: USA Study years: 5/1979 to 1/1982 performance of surveillance cultures: yes - stool cultures at time of enrolment and at 2 months intervals (Y stool cultures for 37/61 patients at 2 months intervals for 1 year monitoring for SA, enteric gram negative bacilli, yeasts and resistance to TMP/SMX) Method for PCP surveillance: as in Hughes 1977? Method to confirm PCP when infection suspected: as in Hughes 1977?

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not specified
Allocation concealment (selection bias)	Unclear risk	not specified
Blinding (performance bias and detection bias) All outcomes	Low risk	double blinding
Incomplete outcome data (attrition bias) Documented PCP infections	Low risk	1 of 61 randomised patients not evaluated, reasons not specified
Selective reporting (reporting bias)	Low risk	no selective outcome reporting

Hibberd 1992

Methods	Allocation generation: not specified Allocation concealment: in pharmacy Blinding: double blind ITT: yes Number of dropouts: none
Participants	Patients and ages: 103 patients, mean age 39.5 to 44.5 years Underlying immune suppression: renal transplantation

Hibberd 1992 *(Continued)*

	Steroid use: yes Duration of follow-up: 6 months
Interventions	PO: trimethoprim/sulfamethoxazole 80 mg/ 400 mg once daily versus ciprofloxacin 250 mg once daily. Started at day of bladder catheter removal (D + 1 or D + 5), for 6 months
Outcomes	Outcomes reported in trial: mortality from any cause, documented PCP infections, PCP-related mortality, any infections other then PCP, number of bacterial infections, adverse events
Notes	Trial location: USA Study years: 6/1988 to 8/1990 performance of surveillance cultures: yes - Urine cultures: 48 hours prior to prophylaxis, weekly / bi-weekly for the first 3 months, every month during the last 3 months Method for PCP surveillance: not mentioned Method to confirm PCP when infection suspected: when dyspnea + fever + interstitial disease on chest X-ray, direct demonstration of the organism in induced sputum/ BAL (bronchoalveolar lavage) by monoclonal Antibodies detected by fluorescence microscopy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not specified
Allocation concealment (selection bias)	Low risk	allocation performed in pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	double blinding
Incomplete outcome data (attrition bias) Documented PCP infections	Low risk	all patients randomised were evaluated
Selective reporting (reporting bias)	Low risk	no selective outcome reporting

Hughes 1977

Methods	Allocation generation: computer randomised code Allocation concealment: in pharmacy (central) Blinding: double blind (carer + patient) ITT: Yes Number of dropouts: none
Participants	Patients and age: 160 patients, nearly all children, median age 6 to 6.5 years Underlying immune suppression: malignancies at high risk for PCP - ALL (acute lymphocytic leukemia) treated with vincristine, MTX (methotrexate), cyclophosphamide and cytarabine; or ALL + 3 of these chemotherapeutic drugs + mediastinal irradiation; non-responsive; or Rhabdomyosarcoma + chemotherapy Steroid use: no Duration of follow-up: 2 years

Hughes 1977 *(Continued)*

Interventions	PO: trimethoprim/sulfamethoxazole (150 mg/m^2 + 750 mg/m^2) in two divided doses (maximum 320 mg /1600 mg per day) versus placebo. Started at various times from onset of anticancer therapy, until completion of total anticancer therapy or 2 years
Outcomes	Outcomes reported in trial: mortality from any cause, documented PCP infections, PCP-related mortality, any infections other then PCP, number of bacterial infections, developing of resistance to the drug, adverse events
Notes	Trial location: USA Study years: 10/1974 to 10/1976 Performance of surveillance cultures: yes, Culture of pharynx + rectum before entry into the study and at least every 3 months. Collected with sterile cotton-tip swab on standard medium. Chest x-ray before entry and at 3 month intervals Method for PCP surveillance: patients with diffuse alveolar disease on chest x-ray underwent transthoracic percutaneous needle aspiration of lung parenchyma Chest x-ray every 3 months and for every febrile illness Method to confirm PCP when infection suspected: Identification of *P. carinii* organism in fluid obtained by needle aspiration of lung or autopsy (lung section stained with H&E and Gomori). Cultures + stains: Gomori's methamine silver nitrate; toluidine blue O; polychrome methylene blue

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computer randomised code
Allocation concealment (selection bias)	Low risk	allocation by pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	double blinding
Incomplete outcome data (attrition bias) Documented PCP infections	Low risk	all patients randomised were evaluated
Selective reporting (reporting bias)	Low risk	no selective outcome reporting

Hughes 1987

Methods	Allocation generation: birth dates Allocation concealment: birth dates Blinding: no ITT: yes Number of dropouts: none
Participants	Patients and age: 167 patients, all children. Underlying immune suppression: ALL (acute lymphocytic leukemia) Chemotherapy: prednisone, vincristine, asparginase, daunorubicin, teniposide, cytarabine, MTX.intrathecal Steroid use: yes Duration of follow-up: 2 years

Hughes 1987 *(Continued)*

	Steroid use: yes
Interventions	PO: trimethoprim / sulfamethoxazole, (150 mg/m^2 + 750 mg/m^2) in two divided doses, every day versus thrice weekly. Starting at induction therapy, throughout the period of antileukemic therapy - until the end of maintenance phase (120 weeks at least)
Outcomes	Outcomes reported in trial: documented PCP infections, PCP-related mortality, any infections other then PCP, number of bacterial infections, adverse events
Notes	Trial location: USA Study years: 2/1984 to 2/1986 Performance of surveillance cultures: yes - on admission: culture for bacteria + fungi of throat, anterior nares, stool, urine, CSF, blood, bone marrow. Throughout the period: routine culture of all bone marrow for bacteria + fungi Method for PCP surveillance: not mentioned Method to confirm PCP when infection suspected: radiographic evidence of pneumonitis + identification of *P. carinii* in lung tissue obtained in invasive diagnostic procedure or autopsy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	assignment according to birth dates
Allocation concealment (selection bias)	High risk	birth dates
Blinding (performance bias and detection bias) All outcomes	High risk	no blinding
Incomplete outcome data (attrition bias) Documented PCP infections	Low risk	all randomised evaluated, one patient added to the daily prophylaxis arm non-randomly, excluded from most outcomes
Selective reporting (reporting bias)	Low risk	no selective outcome reporting

Liang 1990

Methods	Allocation generation: not specified Allocation concealment: not specified Blinding: no ITT: no Number of dropouts: 8 /110
Participants	Patients and age: 102 patients, median age 36 to 39 years Underlying immune suppression: hematological malignancies {AML (acute myeloid leukemia) , ALL (acute lymphocytic leukemia), Lymphoma} with neutropenia (e.g. neutrophil count < 500) Steroid use: yes Duration of follow-up: not mentioned

Liang 1990 *(Continued)*

Interventions	PO: trimethoprim/sulfamethoxazole 80 mg/400 mg twice daily, versus ofloxacin 300 mg twice daily, started at neutrophil count < 500 after chemotherapy, continued until fever developed or neutrophil count > 500 or adverse event
Outcomes	Outcomes reported in the trial: documented PCP infections, PCP-related mortality, any infection other then PCP, number of bacterial infections, developing of resistance to the drug, adverse events
Notes	Trial location: Hong Kong Study years: 9/1986 to 4/1988 Performance of surveillance cultures: yes -rectal swabs on admission and then once weekly, chest x-ray at least once a week Method for PCP surveillance: not mentioned Method to confirm PCP when infection suspected: not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not specified
Allocation concealment (selection bias)	Unclear risk	not specified
Blinding (performance bias and detection bias) All outcomes	High risk	no blinding
Incomplete outcome data (attrition bias) Documented PCP infections	Low risk	102/110 evaluated; patients not evaluated: 2 patients because of history of allergy to co-trimoxazole, 2 patients because of poor compliance (both received ofloxacin), and 4 patients because of G6PD deficiency
Selective reporting (reporting bias)	High risk	no pre-specified outcomes

Olsen 1993

Methods	Allocation generation: not specified Allocation concealment: not specified Blinding: no ITT: no Number of dropouts: 2/58
Participants	Patients and age: 56 patients, median age 48.3 to 52.3 years Underlying immune suppression: cardiac transplantation Steroid use: yes Duration of follow-up: 4 months
Interventions	PO: trimethoprim /sulfamethoxazole, 160 mg/800 mg twice daily, every day versus thrice weekly versus no prophylaxis. Starting on D + 14 after transplantation for 4 consecutive months
Outcomes	Outcomes reported in trial: documented PCP infections, PCP-related mortality, adverse events
Notes	Trial location: USA Study years: 12/1988 to 9/1989

Olsen 1993 *(Continued)*

	performance of surveillance cultures: no Method for PCP surveillance: not mentioned Method to confirm PCP when infection suspected: if any two of the following: fever > 38, chest x-ray lobar consolidation or interstitial changes, hypoxemia -10% reduction in premorbid arterial room pO2, then BAL + silver stain on the acquired specimen

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not specified
Allocation concealment (selection bias)	Unclear risk	not specified
Blinding (performance bias and detection bias) All outcomes	High risk	no blinding
Incomplete outcome data (attrition bias) Documented PCP infections	Low risk	56/58 evaluated; patients not evaluated:1 in control group and 1 in intermittent therapy group because of protocol violation
Selective reporting (reporting bias)	Low risk	no selective outcome reporting

Torre-Cisneros 1999

Methods	Allocation generation: not specified Allocation concealment: not specified Blinding: no ITT: no Number of dropouts: 5/125
Participants	Patients and age: 120 patients, mean age 45 to 47 years Underlying immune suppression: liver transplantation Steroid use: no Duration of follow-up: 1 year
Interventions	PO: Sulfadoxine/pyrimethamine 500 mg/25 mg once weekly versus trimethoprim /sulfamethoxazole 480 mg once daily every day. Starting maximum D + 7 after transplantation
Outcomes	Outcomes reported in trial: mortality from any cause, documented PCP infections, PCP-related mortality, any infections other then PCP, number of bacterial infections, adverse events
Notes	Trial location: Spain Study years: not mentioned performance of surveillance cultures: yes - Induced sputum Method for PCP surveillance: Monoclonal Ab in sputum Method to confirm PCP when infection suspected: detection of organism (?) in BAL (bronchoalveolar lavage) or induced sputum

Risk of bias

Torre-Cisneros 1999 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	block randomisation for every 10 patients, otherwise not specified
Allocation concealment (selection bias)	Unclear risk	not specified
Blinding (performance bias and detection bias) All outcomes	High risk	no blinding
Incomplete outcome data (attrition bias) Documented PCP infections	High risk	120/125 evaluated. patients not evaluated because of early death or noncompliance
Selective reporting (reporting bias)	Low risk	no selective outcome reporting

Van Eys 1987

Methods	Allocation generation: not specified Allocation concealment: not specified Blinding: no ITT: no Number of dropouts: 5/126
Participants	Patients and age: 121 patients, less then 21 years old Underlying immune suppression: ALL (acute lymphocytic leukemia) Chemotherapy: vincristine, prednisone. Consolidation: cyclophosphamide, asparginase. CNS: MTX (methotrexate), cytosine arabinose, hydrocort + IV MTX Steroid use: yes Duration of follow-up: 3 years
Interventions	PO: trimethoprim /sulfamethoxazole 4/mg/kg/day once daily versus no prophylaxis. Starting at week 5 of induction, for 3 years or relapse.
Outcomes	Outcomes reported in trial: mortality from any cause, documented PCP infections, PCP-related mortality, any infections other then PCP, adverse events
Notes	Trial location: multi-center - USA Study years: not mentioned performance of surveillance cultures: not mentioned Method for PCP surveillance: not mentioned Method to confirm PCP when infection suspected: not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not specified (randomisation balanced within risk groups?)

Van Eys 1987 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	not specified
Blinding (performance bias and detection bias) All outcomes	High risk	no blinding
Incomplete outcome data (attrition bias) Documented PCP infections	High risk	120/126 evaluated. not evaluated:TMP-SMX group: 1 early death; 1 lost to follow-up; 1 major protocol violation; and 1 other; no TMP-SMX group: 1 inadequate data; 1 other
Selective reporting (reporting bias)	Low risk	no selective outcome reporting

Vesole 2012

Methods	Randomised open label
Participants	Patients and age: 212 patients, median age 63.8 (32-89) Underlying immune suppression: newly diagnosed multiple myeloma starting chemotherapy or high-dose steroids Chemotherapy: myelosuppressive/immunosuppressive Cxt or high dose dexamethazone Steroid use: yes (all patients) Duration of follow-up: 2 months
Interventions	PO cipro/ofloxacin 500/400 mg X2/D versus trimethoprim/sulfamethoxazole 160mg/800 mg starting at initiation of cytotoxic therapy for 2 months versus no treatment (our review included only the trimethoprim /sulfamethoxazole versus no treatment)
Outcomes	Outcomes reported in trial: PCP, the incidence of serious infections, the incidence of nonbacterial infections, the incidence of serious infection during the third month OFF of antibiotic prophylaxis, response rate and overall survival
Notes	Trial location: USA Study years: July 1998- Jan 2008 Performance of surveillance cultures: not mentioned Method for PCP surveillance: not mentioned Method to confirm PCP when infection suspected: not mentioned

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	computer randomisation
Allocation concealment (selection bias)	Low risk	kept in pharmacy
Blinding (performance bias and detection bias) All outcomes	High risk	patients and caregivers not blinded, no placebo used
Incomplete outcome data (attrition bias)	Low risk	201/212 evaluated for PCP infections - reasons for non-evaluability are detailed (death, protocol violations)

Vesole 2012 *(Continued)*

Documented PCP infections		
Selective reporting (reporting bias)	Low risk	no selective outcome reporting

Ward 1993

Methods	Randomised double blind
Participants	Patients and age: 51 patients, median age 55.4 Underlying immune suppression: patients with AML, relapsed ALL or CML in blast crisis Chemotherapy: yes, type not mentioned Steroid use: not mentioned Duration of follow-up: median of 30 days
Interventions	PO: trimethoprim/sulfamethoxazole, 160 mg/800 mg twice daily, every day versus placebo. Starting 1-3 days before induction therapy until granulocyte count >1000
Outcomes	Outcomes reported in trial: PCP, number of febrile episodes, number of documented infections, mortality from any cause, adverse effects, duration of neutropenia and response to chemotherapy
Notes	Trial location: multi-center USA Study years: Jan 1984 - April 1986 Performance of surveillance cultures: anterior nares, throat, rectal swabs at enrolment and every week Method for PCP surveillance: Cxr when febrile Method to confirm PCP when infection suspected: not mentioned

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	not specified
Allocation concealment (selection bias)	Unclear risk	not specified
Blinding (performance bias and detection bias) All outcomes	Low risk	double blinding with placebo
Incomplete outcome data (attrition bias) Documented PCP infections	Low risk	42/51 evaluated; patients not evaluated: 1 who died early and 8 who did not have neutropenia
Selective reporting (reporting bias)	Low risk	no selective outcome reporting

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

Study	Reason for exclusion
Arend 1996	non-randomised
Arico 1992	randomised controlled trial that compared of two regimens of TMP/SMX assessing only toxicity
Carlin 1993	study of HIV patients
Chung 2000	computer-based simulation
Coker 1992	study of HIV patients
De jongh	randomised controlled trial of TMP/SMX versus placebo for patients with small cell lung carcinoma that did not assess PCP infections among its outcomes
Elinder 1992	retrospective study
Golden 1993	study of HIV patients
Groll 2001	review
Holt 2000	non-randomised
Janner 1996	retrospective study
Kramer 1984	retrospective study
Kramer 1992	retrospective study
Mallolas 1991	study of HIV patients
Maschmeyer 1990	review
Mehta 1997	non-randomised
Meyers 2001	non-randomised
Moriuchi 1990	retrospective study
Mustafa 1994	non-randomised
Nucci 2003	retrospective study
Okada 1999	non-randomised
Oken 1996	randomised controlled trial of TMP/SMX versus placebo for patients with multiple myeloma that did not assess PCP infections among its outcomes
Pedagogos 1994	article never published, data lost (personal communication)
Rossi 1987	diagnostic criteria for PCP, did not fulfil inclusion criteria for our review
Singer 1999	review
Slavin 1992	study of HIV patients
Souza 1999	cohort

Study	Reason for exclusion
Stegeman 1996	randomised controlled trial of TMP/SMX versus placebo for patients with Wegener's granulomatosis that did not assess PCP infections among its outcomes
Torre-Cisneros 1996	non-randomised
Vasconcelles 2000	retrospective study
Weinthal 1994	non-randomised
Worth 2005	retrospective study
Young 1976	assessed treatment for PCP not prophylaxis
Young 1987	review

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

Fengchun Zhang

Trial name or title	The Safety and Effectiveness of Trimethoprim/Sulfamethoxazole as Pneumocystis Carinii Pneumonia (PCP) Prophylaxis in Patients With Connective Tissue Diseases
Methods	Randomised open label
Participants	Patients and age: 80 patients, age 18-65 years Underlying immune suppression: Patients with connective tissue diseases (CTD) treated with high-dose glucocorticoids and immunosuppressive agents Chemotherapy: no Steroid use: yes Duration of follow-up: 12 weeks
Interventions	PO: trimethoprim/sulfamethoxazole 80 mg/400 mg versus placebo
Outcomes	Documented PCP infection, PCP-related mortality, all cause mortality, other infections, PCP-related hospitalizations
Starting date	August 2012
Contact information	Fengchun Zhang, MD +86-10-69158794 ZhangFCcra@yahoo.com.cn
Notes	ClinicalTrials.gov Identifier: NCT01747278

DATA AND ANALYSES

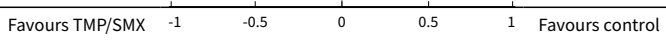
Comparison 1. TMP/SMX versus placebo, no treatment or non-PCP drug

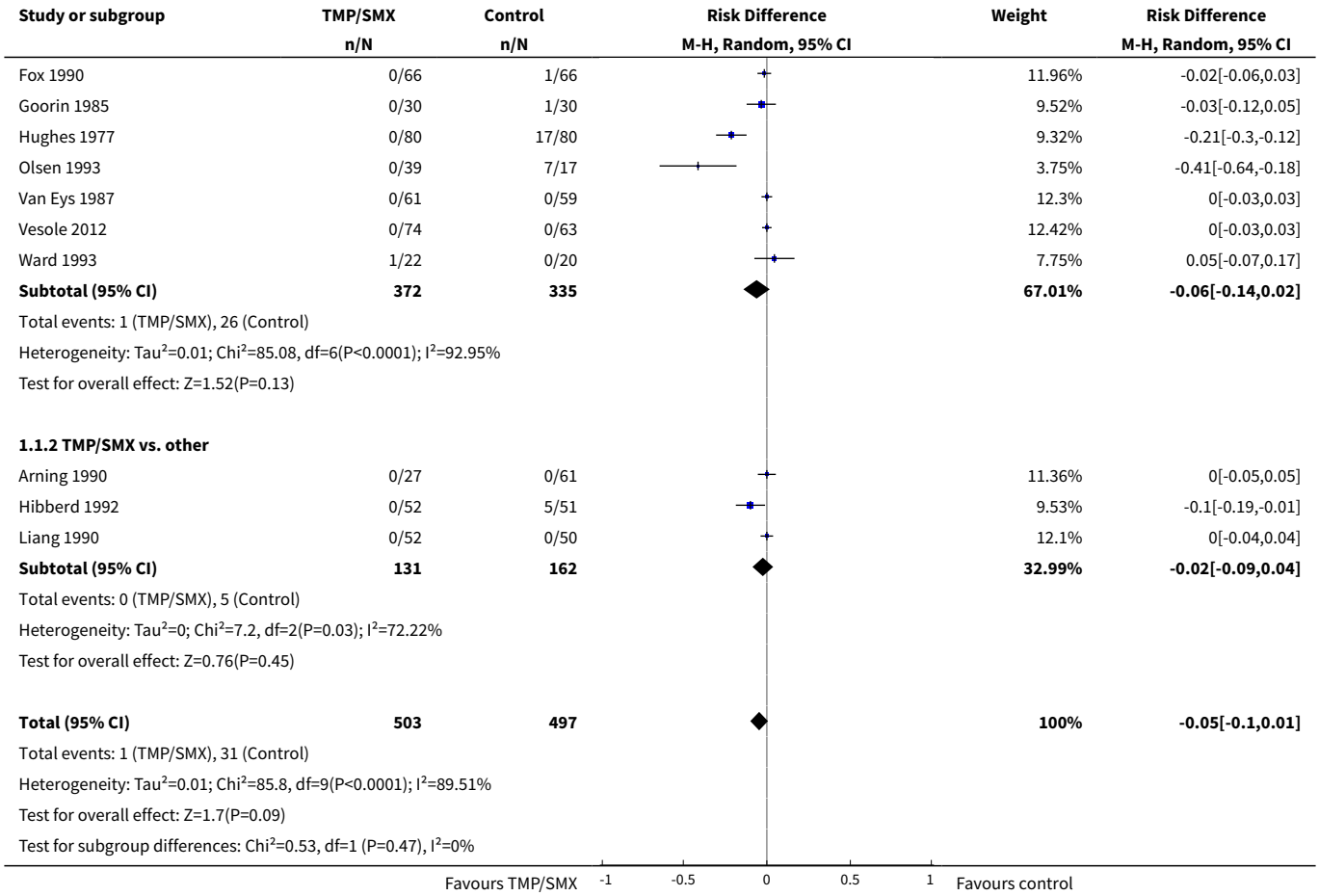
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Documented PCP infections	10	1000	Risk Difference (M-H, Random, 95% CI)	-0.05 [-0.10, 0.01]
1.1 TMP/SMX vs. placebo or no treatment	7	707	Risk Difference (M-H, Random, 95% CI)	-0.06 [-0.14, 0.02]
1.2 TMP/SMX vs. other	3	293	Risk Difference (M-H, Random, 95% CI)	-0.02 [-0.09, 0.04]
2 Documented PCP infections - solid organ transplant subgroup	3	291	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.02, 0.48]
2.1 TMP/SMX vs. placebo or no treatment	2	188	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.01, 0.97]
2.2 TMP/SMX vs. other	1	103	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.01, 1.57]
3 Documented PCP infections - hematological cancer subgroup	7	847	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.02, 4.57]
3.1 TMP/SMX vs. placebo or no treatment	5	519	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.02, 4.57]
3.2 TMP/SMX vs. other	3	328	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Documented PCP infections - adults vs. children	10	1000	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.04, 0.62]
4.1 Adults	7	660	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.03, 1.37]
4.2 Children	3	340	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.01, 1.15]
5 All cause mortality	6	652	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.28, 1.80]
5.1 TMP/SMX vs. placebo or no treatment	4	461	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.17, 2.00]
5.2 TMP/SMX vs. other	2	191	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.02, 10.73]
6 PCP-related mortality	9	886	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.03, 0.94]
6.1 TMP/SMX vs. placebo or no treatment	6	593	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.02, 1.56]
6.2 TMP/SMX vs. other	3	293	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.65]
7 Bacterial infections	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 TMP/SMX vs. placebo or no treatment	4	399	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.21, 0.90]
7.2 TMP/SMX vs. other	4	431	Risk Ratio (M-H, Random, 95% CI)	2.04 [0.80, 5.23]
8 Any infections other than PCP	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 TMP/SMX vs. placebo or no treatment	3	299	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.74, 1.10]
8.2 TMP/SMX vs. other	4	431	Risk Ratio (M-H, Random, 95% CI)	1.49 [1.14, 1.96]
9 Adverse events: any	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 TMP/SMX vs. placebo or no treatment	4	470	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.82, 1.24]
9.2 TMP/SMX vs. other	2	191	Risk Ratio (M-H, Random, 95% CI)	4.66 [2.55, 8.53]
10 Adverse events: requiring temporary or permanent treatment discontinuation	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 TMP/SMX vs. placebo or no treatment	3	350	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.36, 1.87]
10.2 TMP/SMX vs. other	4	344	Risk Ratio (M-H, Random, 95% CI)	3.80 [1.11, 13.05]
11 Adverse events: severe adverse events requiring treatment discontinuation	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 TMP/SMX vs. placebo or no treatment	5	530	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.05, 1.70]
11.2 TMP/SMX vs. other	3	256	Risk Ratio (M-H, Random, 95% CI)	4.59 [0.80, 26.28]
12 Adverse events: rash	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 TMP/SMX vs. placebo or no treatment	4	392	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.09, 1.52]
12.2 TMP/SMX vs. other	2	191	Risk Ratio (M-H, Random, 95% CI)	3.94 [1.35, 11.46]
13 Adverse events: leukopenia	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 TMP/SMX vs. placebo or no treatment	3	412	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.84, 2.50]
13.2 TMP/SMX vs. other	1	103	Risk Ratio (M-H, Random, 95% CI)	1.96 [0.18, 20.97]

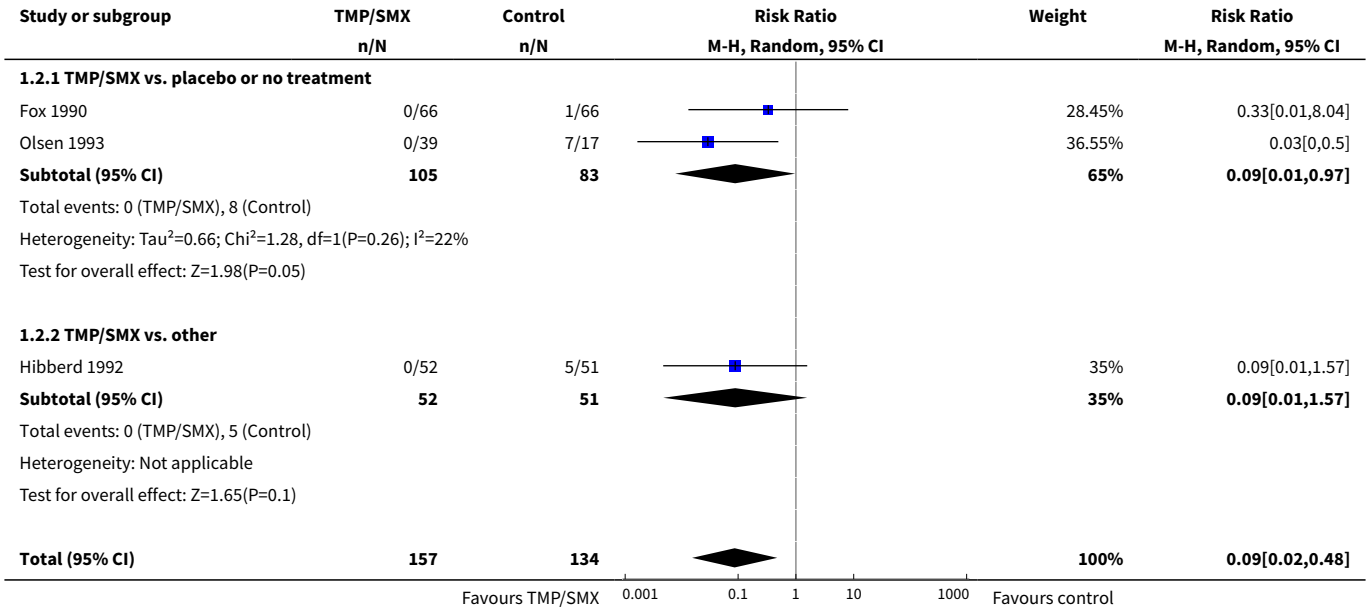
Analysis 1.1. Comparison 1 TMP/SMX versus placebo, no treatment or non-PCP drug, Outcome 1 Documented PCP infections.

Study or subgroup	TMP/SMX n/N	Control n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
1.1.1 TMP/SMX vs. placebo or no treatment					

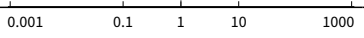




Analysis 1.2. Comparison 1 TMP/SMX versus placebo, no treatment or non-PCP drug, Outcome 2 Documented PCP infections - solid organ transplant subgroup.

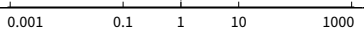


Study or subgroup	TMP/SMX n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 0 (TMP/SMX), 13 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.27, df=2(P=0.53); I^2=0%					
Test for overall effect: Z=2.82(P=0)					
Test for subgroup differences: Chi^2=0, df=1 (P=1), I^2=0%					



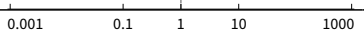
Analysis 1.3. Comparison 1 TMP/SMX versus placebo, no treatment or non-PCP drug, Outcome 3 Documented PCP infections - hematological cancer subgroup.

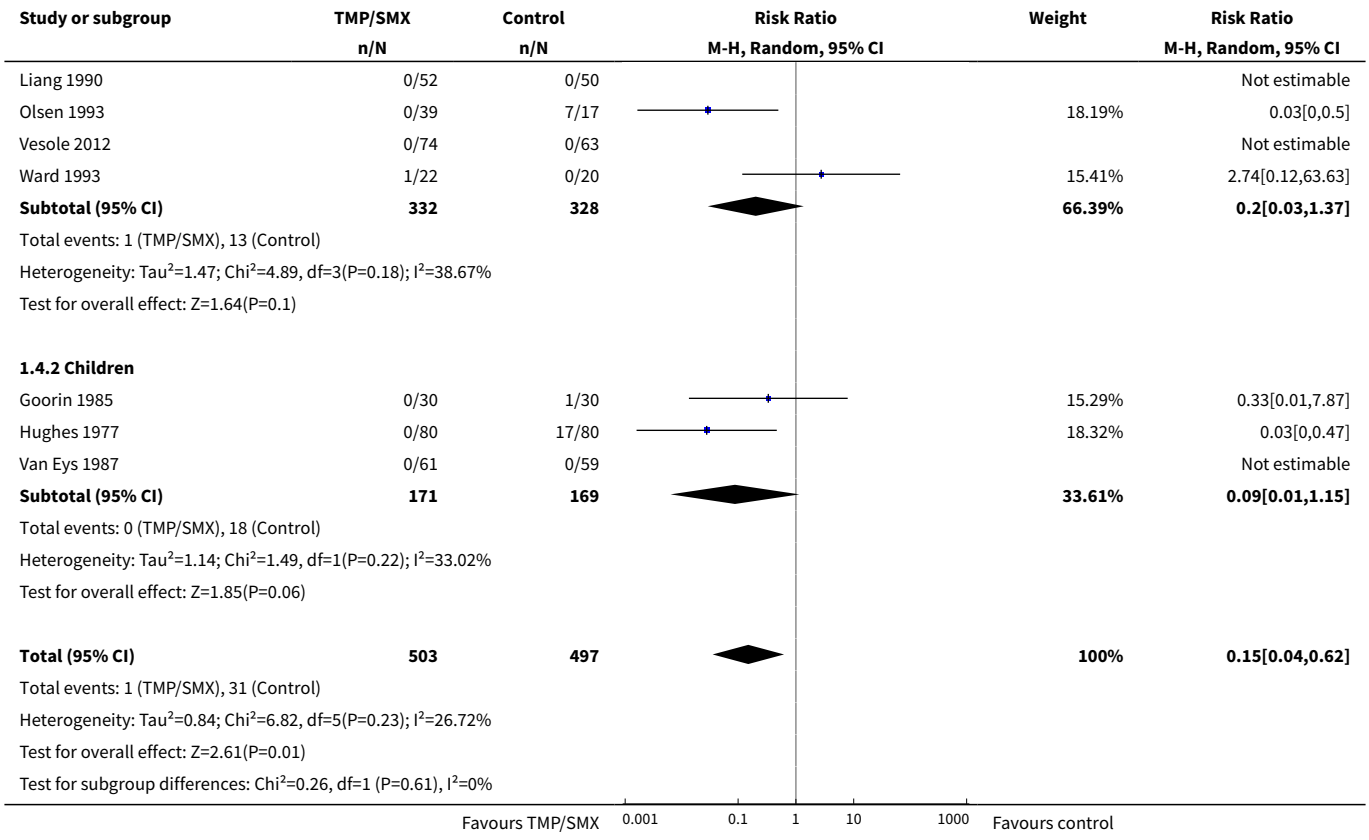
Study or subgroup	TMP/SMX n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 TMP/SMX vs. placebo or no treatment					
Goorin 1985	0/30	1/30		32.23%	0.33[0.01,7.87]
Hughes 1977	0/80	17/80		35.4%	0.03[0,0.47]
Van Eys 1987	0/61	0/59			Not estimable
Vesole 2012	0/74	0/63			Not estimable
Ward 1993	1/22	0/20		32.37%	2.74[0.12,63.63]
Subtotal (95% CI)	**267**	**252**		**100%**	**0.28[0.02,4.57]**
Total events: 1 (TMP/SMX), 18 (Control)					
Heterogeneity: Tau^2=3.76; Chi^2=5.15, df=2(P=0.08); I^2=61.15%					
Test for overall effect: Z=0.9(P=0.37)					
1.3.2 TMP/SMX vs. other					
Arning 1990	0/27	0/61			Not estimable
Liang 1990	0/52	0/50			Not estimable
Vesole 2012	0/74	0/64			Not estimable
Subtotal (95% CI)	**153**	**175**			**Not estimable**
Total events: 0 (TMP/SMX), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**420**	**427**		**100%**	**0.28[0.02,4.57]**
Total events: 1 (TMP/SMX), 18 (Control)					
Heterogeneity: Tau^2=3.76; Chi^2=5.15, df=2(P=0.08); I^2=61.15%					
Test for overall effect: Z=0.9(P=0.37)					
Test for subgroup differences: Not applicable					



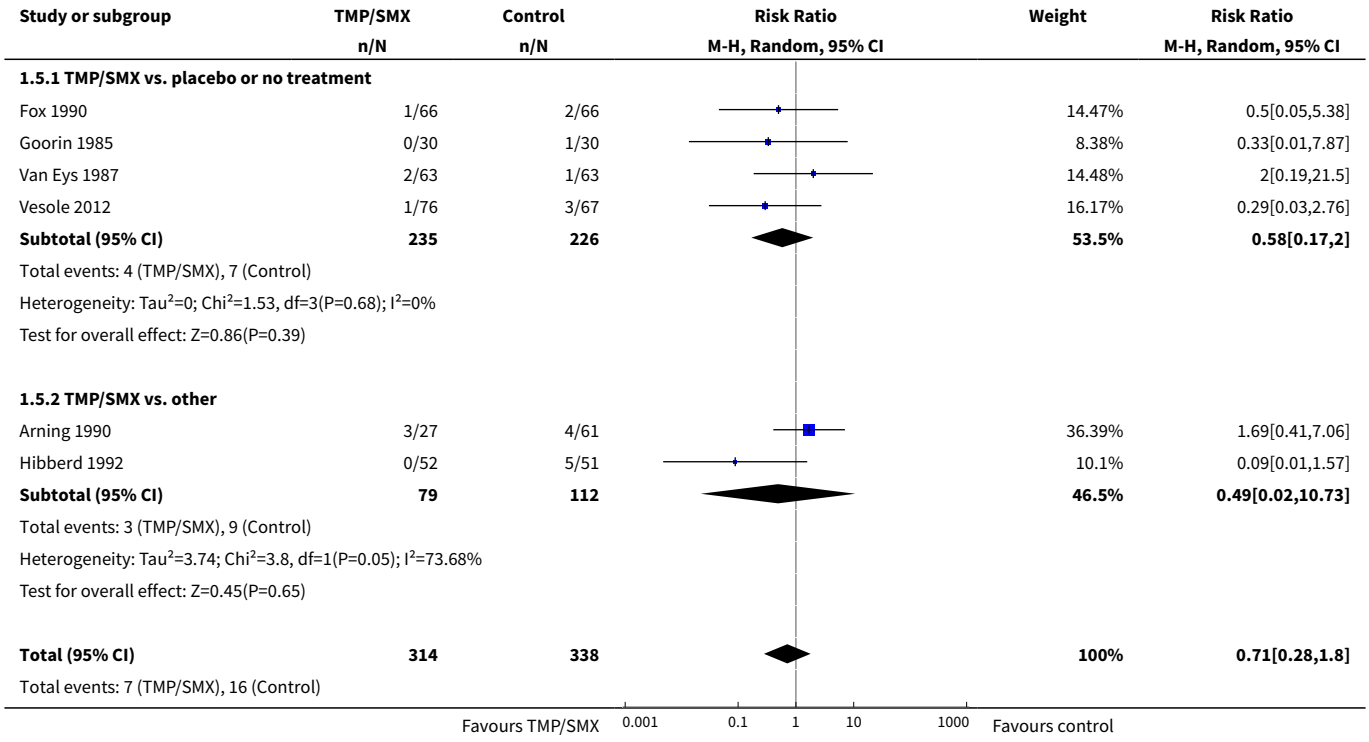
Analysis 1.4. Comparison 1 TMP/SMX versus placebo, no treatment or non-PCP drug, Outcome 4 Documented PCP infections - adults vs. children.

Study or subgroup	TMP/SMX n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Adults					
Arning 1990	0/27	0/61			Not estimable
Fox 1990	0/66	1/66		15.14%	0.33[0.01,8.04]
Hibberd 1992	0/52	5/51		17.64%	0.09[0.01,1.57]





Analysis 1.5. Comparison 1 TMP/SMX versus placebo, no treatment or non-PCP drug, Outcome 5 All cause mortality.



Study or subgroup	TMP/SMX n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0.09; Chi²=5.34, df=5(P=0.38); I²=6.33%					
Test for overall effect: Z=0.72(P=0.47)					
Test for subgroup differences: Chi²=0.01, df=1 (P=0.92), I²=0%					

Favours TMP/SMX 0.001 0.1 1 10 1000 Favours control

Analysis 1.6. Comparison 1 TMP/SMX versus placebo, no treatment or non-PCP drug, Outcome 6 PCP-related mortality.

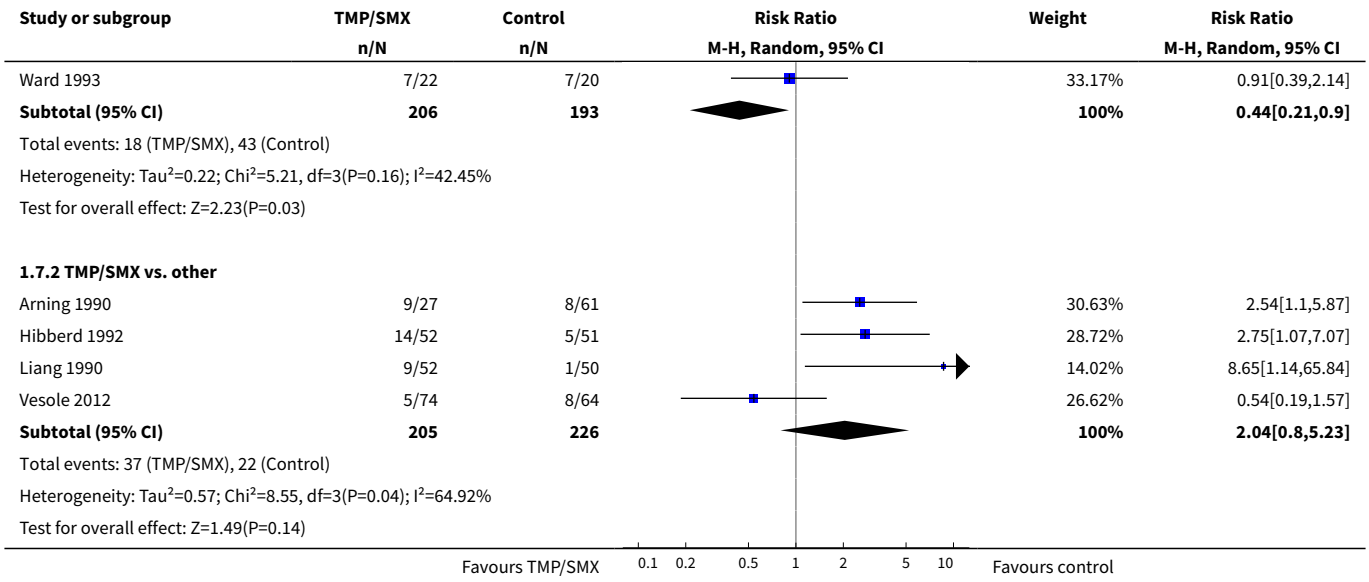
Study or subgroup	TMP/SMX n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 TMP/SMX vs. placebo or no treatment					
Fox 1990	0/66	0/66			Not estimable
Goorin 1985	0/30	1/30		29.92%	0.33[0.01,7.87]
Hughes 1977	0/80	4/80		35.43%	0.11[0.01,2.03]
Olsen 1993	0/39	0/17			Not estimable
Vesole 2012	0/76	0/67			Not estimable
Ward 1993	0/22	0/20			Not estimable
Subtotal (95% CI)	**313**	**280**		**65.36%**	**0.18[0.02,1.56]**
Total events: 0 (TMP/SMX), 5 (Control)					
Heterogeneity: Tau²=0; Chi²=0.26, df=1(P=0.61); I²=0%					
Test for overall effect: Z=1.55(P=0.12)					
1.6.2 TMP/SMX vs. other					
Arning 1990	0/27	0/61			Not estimable
Hibberd 1992	0/52	3/51		34.64%	0.14[0.01,2.65]
Liang 1990	0/52	0/50			Not estimable
Subtotal (95% CI)	**131**	**162**		**34.64%**	**0.14[0.01,2.65]**
Total events: 0 (TMP/SMX), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.31(P=0.19)					
Total (95% CI)	**444**	**442**		**100%**	**0.17[0.03,0.94]**
Total events: 0 (TMP/SMX), 8 (Control)					
Heterogeneity: Tau²=0; Chi²=0.28, df=2(P=0.87); I²=0%					
Test for overall effect: Z=2.03(P=0.04)					
Test for subgroup differences: Chi²=0.02, df=1 (P=0.88), I²=0%					

Favours TMP/SMX 0.001 0.1 1 10 1000 Favours control

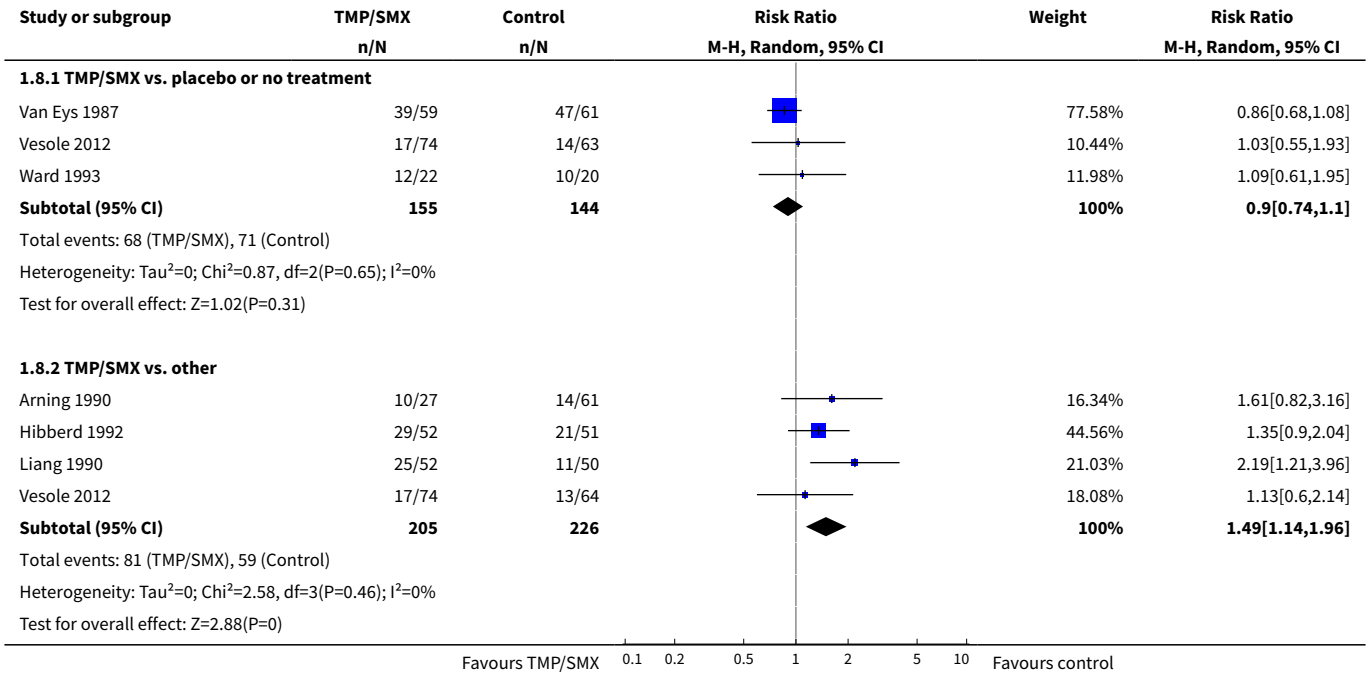
Analysis 1.7. Comparison 1 TMP/SMX versus placebo, no treatment or non-PCP drug, Outcome 7 Bacterial infections.

Study or subgroup	TMP/SMX n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 TMP/SMX vs. placebo or no treatment					
Goorin 1985	0/30	5/30		5.84%	0.09[0.01,1.57]
Hughes 1977	6/80	21/80		33.24%	0.29[0.12,0.67]
Vesole 2012	5/74	10/63		27.75%	0.43[0.15,1.18]

Favours TMP/SMX 0.1 0.2 0.5 1 2 5 10 Favours control

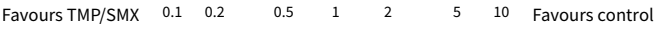


Analysis 1.8. Comparison 1 TMP/SMX versus placebo, no treatment or non-PCP drug, Outcome 8 Any infections other than PCP.



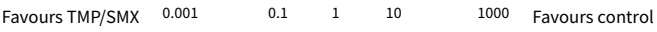
Analysis 1.9. Comparison 1 TMP/SMX versus placebo, no treatment or non-PCP drug, Outcome 9 Adverse events: any.

Study or subgroup	TMP/SMX n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 TMP/SMX vs. placebo or no treatment					
Fox 1990	8/66	9/66		5.26%	0.89[0.37,2.16]
Hughes 1977	18/80	11/80		8.92%	1.64[0.83,3.24]
Olsen 1993	2/40	0/18		0.47%	2.32[0.12,45.95]
Van Eys 1987	42/59	45/61		85.35%	0.96[0.77,1.2]
Subtotal (95% CI)	**245**	**225**		**100%**	**1.01[0.82,1.24]**
Total events: 70 (TMP/SMX), 65 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.88, df=3(P=0.41); I^2=0%					
Test for overall effect: Z=0.11(P=0.91)					
1.9.2 TMP/SMX vs. other					
Arning 1990	19/27	8/61		76.56%	5.37[2.69,10.71]
Hibberd 1992	9/52	3/51		23.44%	2.94[0.84,10.25]
Subtotal (95% CI)	**79**	**112**		**100%**	**4.66[2.55,8.53]**
Total events: 28 (TMP/SMX), 11 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.71, df=1(P=0.4); I^2=0%					
Test for overall effect: Z=4.99(P<0.0001)					



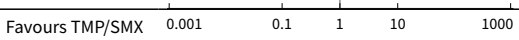
Analysis 1.10. Comparison 1 TMP/SMX versus placebo, no treatment or non-PCP drug, Outcome 10 Adverse events: requiring temporary or permanent treatment discontinuation.

Study or subgroup	TMP/SMX n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.10.1 TMP/SMX vs. placebo or no treatment					
Fox 1990	8/66	9/66		85.75%	0.89[0.37,2.16]
Hughes 1977	0/80	2/80		7.43%	0.2[0.01,4.1]
Olsen 1993	1/40	0/18		6.82%	1.39[0.06,32.57]
Subtotal (95% CI)	**186**	**164**		**100%**	**0.82[0.36,1.87]**
Total events: 9 (TMP/SMX), 11 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1, df=2(P=0.61); I^2=0%					
Test for overall effect: Z=0.47(P=0.64)					
1.10.2 TMP/SMX vs. other					
Arning 1990	11/27	5/61		36.81%	4.97[1.91,12.92]
Colby 1999	8/18	0/16		13.93%	15.21[0.95,244.22]
Liang 1990	9/52	1/50		20.74%	8.65[1.14,65.84]
Torre-Cisneros 1999	3/60	4/60		28.53%	0.75[0.18,3.21]
Subtotal (95% CI)	**157**	**187**		**100%**	**3.8[1.11,13.05]**
Total events: 31 (TMP/SMX), 10 (Control)					
Heterogeneity: Tau^2=0.84; Chi^2=6.77, df=3(P=0.08); I^2=55.68%					
Test for overall effect: Z=2.12(P=0.03)					



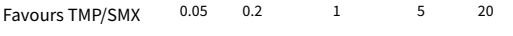
Analysis 1.11. Comparison 1 TMP/SMX versus placebo, no treatment or non-PCP drug, Outcome 11 Adverse events: severe adverse events requiring treatment discontinuation.

Study or subgroup	TMP/SMX n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.11.1 TMP/SMX vs. placebo or no treatment					
Fox 1990	0/66	2/66		35.75%	0.2[0.01,4.09]
Goorin 1985	0/30	0/30			Not estimable
Hughes 1977	0/80	1/80		32.07%	0.33[0.01,8.06]
Olsen 1993	0/40	0/18			Not estimable
Van Eys 1987	0/59	1/61		32.17%	0.34[0.01,8.29]
Subtotal (95% CI)	**275**	**255**		**100%**	**0.28[0.05,1.7]**
Total events: 0 (TMP/SMX), 4 (Control)					
Heterogeneity: Tau²=0; Chi²=0.08, df=2(P=0.96); I²=0%					
Test for overall effect: Z=1.38(P=0.17)					
1.11.2 TMP/SMX vs. other					
Colby 1999	2/18	0/16		34.64%	4.47[0.23,86.77]
Liang 1990	1/52	0/50		30.17%	2.89[0.12,69.24]
Torre-Cisneros 1999	3/60	0/60		35.19%	7[0.37,132.66]
Subtotal (95% CI)	**130**	**126**		**100%**	**4.59[0.8,26.28]**
Total events: 6 (TMP/SMX), 0 (Control)					
Heterogeneity: Tau²=0; Chi²=0.16, df=2(P=0.92); I²=0%					
Test for overall effect: Z=1.71(P=0.09)					

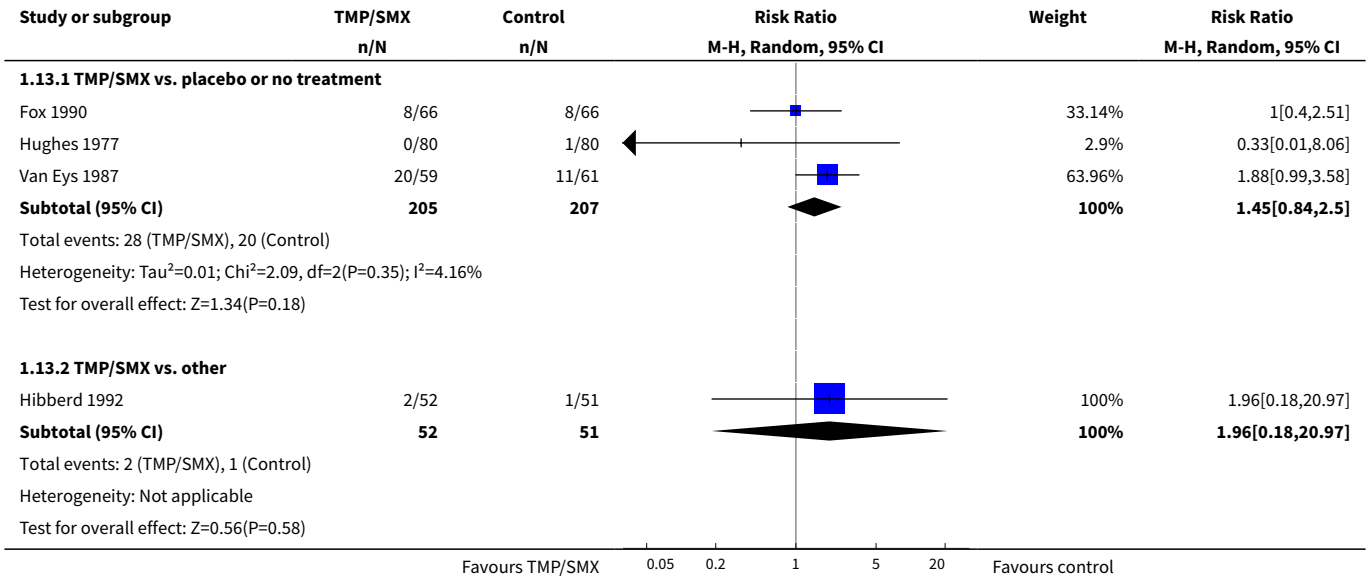


Analysis 1.12. Comparison 1 TMP/SMX versus placebo, no treatment or non-PCP drug, Outcome 12 Adverse events: rash.

Study or subgroup	TMP/SMX n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 TMP/SMX vs. placebo or no treatment					
Fox 1990	0/66	2/66		21.15%	0.2[0.01,4.09]
Hughes 1977	0/80	1/80		18.98%	0.33[0.01,8.06]
Olsen 1993	1/40	0/18		19.36%	1.39[0.06,32.57]
Ward 1993	1/22	3/20		40.5%	0.3[0.03,2.68]
Subtotal (95% CI)	**208**	**184**		**100%**	**0.38[0.09,1.52]**
Total events: 2 (TMP/SMX), 6 (Control)					
Heterogeneity: Tau²=0; Chi²=0.87, df=3(P=0.83); I²=0%					
Test for overall effect: Z=1.37(P=0.17)					
1.12.2 TMP/SMX vs. other					
Arning 1990	8/27	3/61		62.13%	6.02[1.73,20.97]
Hibberd 1992	4/52	2/51		37.87%	1.96[0.38,10.24]
Subtotal (95% CI)	**79**	**112**		**100%**	**3.94[1.35,11.46]**
Total events: 12 (TMP/SMX), 5 (Control)					
Heterogeneity: Tau²=0.07; Chi²=1.13, df=1(P=0.29); I²=11.6%					
Test for overall effect: Z=2.52(P=0.01)					



Analysis 1.13. Comparison 1 TMP/SMX versus placebo, no treatment or non-PCP drug, Outcome 13 Adverse events: leukopenia.

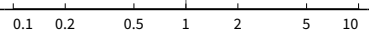


Comparison 2. Continuous daily versus thrice weekly TMP-SMX

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Documented PCP infections	2	205	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 PCP-related mortality	2	205	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Adverse events: any	2	207	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.43, 1.48]
4 Adverse events: requiring temporary or permanent treatment discontinuation	2	207	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.44, 1.52]
5 Adverse events: severe adverse events requiring treatment discontinuation	2	207	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Adverse events: rash	2	207	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.23, 1.16]
7 Adverse events: leukopenia	1	167	Risk Ratio (M-H, Random, 95% CI)	2.78 [0.60, 13.01]
8 Any infections other than PCP	1	167	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.58, 1.93]
9 Bacterial infections	1	167	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.66, 2.78]

Analysis 2.1. Comparison 2 Continuous daily versus thrice weekly TMP-SMX, Outcome 1 Documented PCP infections.

Study or subgroup	TMP/SMX daily n/N	TMP/SMX X3 week n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Hughes 1987	0/92	0/74			Not estimable
Olsen 1993	0/20	0/19			Not estimable
Total (95% CI)	**112**	**93**			**Not estimable**
Total events: 0 (TMP/SMX daily), 0 (TMP/SMX X3 week)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



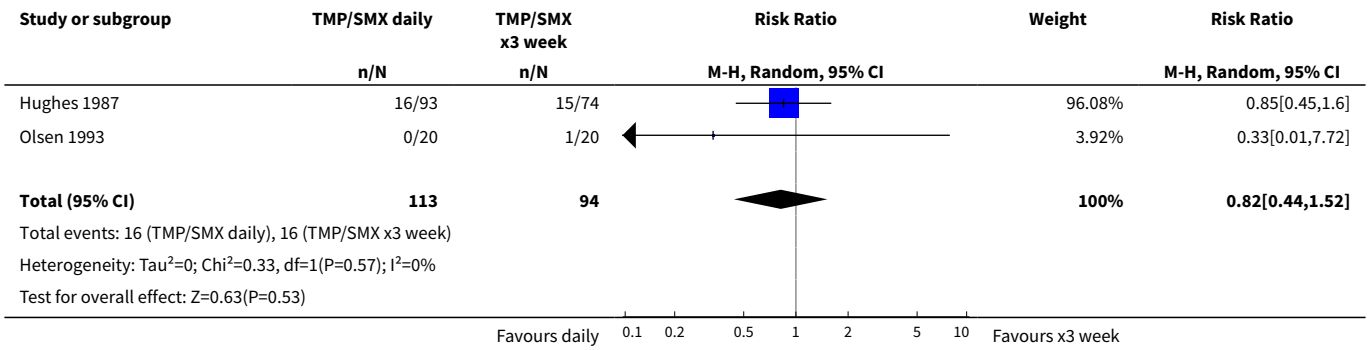
Analysis 2.2. Comparison 2 Continuous daily versus thrice weekly TMP-SMX, Outcome 2 PCP-related mortality.

Study or subgroup	TMP/SMX daily n/N	TMP/SMX x3 week n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Hughes 1987	0/92	0/74			Not estimable
Olsen 1993	0/20	0/19			Not estimable
Total (95% CI)	**112**	**93**			**Not estimable**
Total events: 0 (TMP/SMX daily), 0 (TMP/SMX x3 week)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

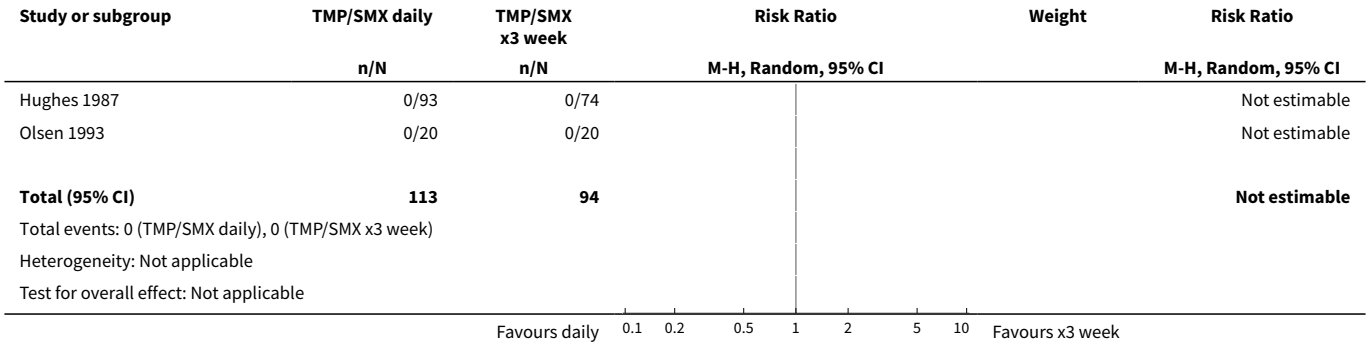
Analysis 2.3. Comparison 2 Continuous daily versus thrice weekly TMP-SMX, Outcome 3 Adverse events: any.

Study or subgroup	TMP/SMX daily n/N	TMP/SMX x3 week n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Hughes 1987	16/93	15/74		95.65%	0.85[0.45,1.6]
Olsen 1993	0/20	2/20		4.35%	0.2[0.01,3.92]
Total (95% CI)	**113**	**94**		**100%**	**0.8[0.43,1.48]**
Total events: 16 (TMP/SMX daily), 17 (TMP/SMX x3 week)					
Heterogeneity: Tau^2=0; Chi^2=0.88, df=1(P=0.35); I^2=0%					
Test for overall effect: Z=0.72(P=0.47)					

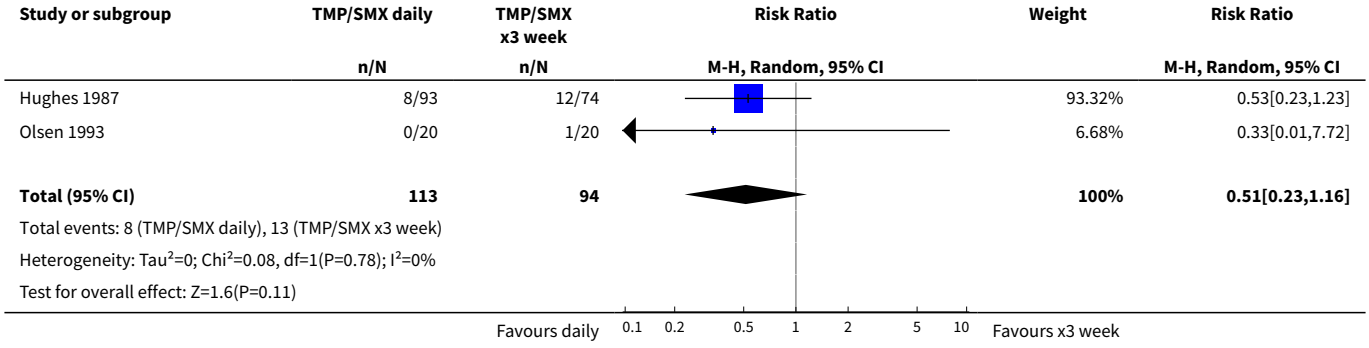
Analysis 2.4. Comparison 2 Continuous daily versus thrice weekly TMP-SMX, Outcome 4 Adverse events: requiring temporary or permanent treatment discontinuation.



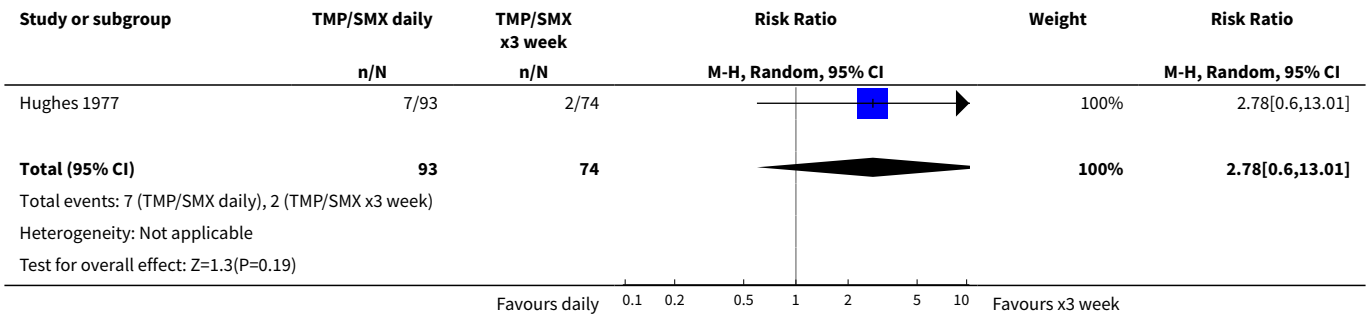
Analysis 2.5. Comparison 2 Continuous daily versus thrice weekly TMP-SMX, Outcome 5 Adverse events: severe adverse events requiring treatment discontinuation.



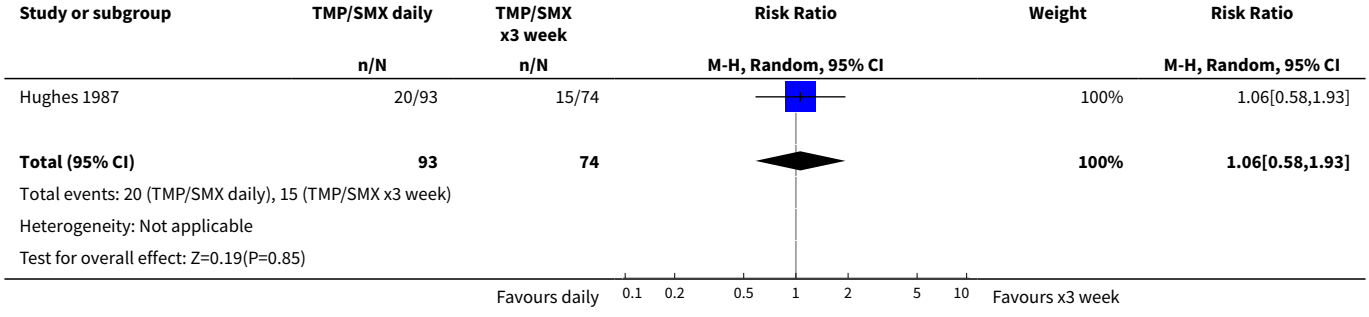
Analysis 2.6. Comparison 2 Continuous daily versus thrice weekly TMP-SMX, Outcome 6 Adverse events: rash.



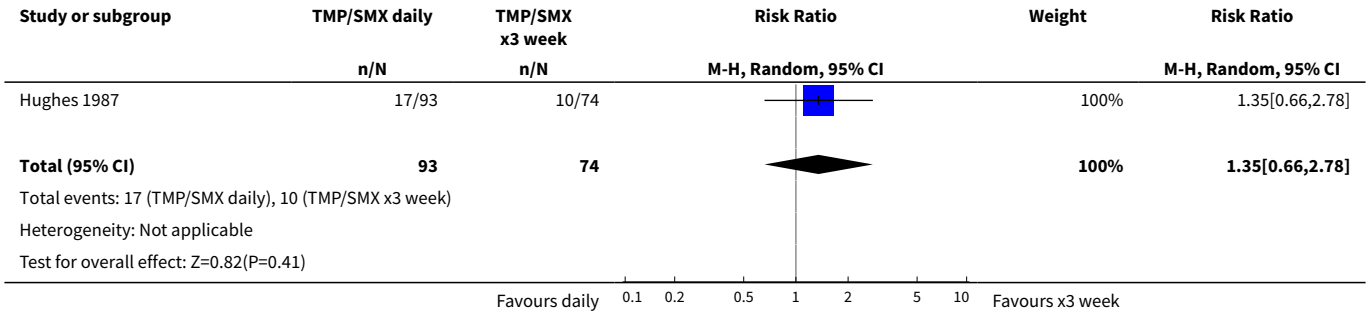
Analysis 2.7. Comparison 2 Continuous daily versus thrice weekly TMP-SMX, Outcome 7 Adverse events: leukopenia.



Analysis 2.8. Comparison 2 Continuous daily versus thrice weekly TMP-SMX, Outcome 8 Any infections other than PCP.



Analysis 2.9. Comparison 2 Continuous daily versus thrice weekly TMP-SMX, Outcome 9 Bacterial infections.



ADDITIONAL TABLES

Table 1. Study quality assessment criteria

Concealment A	Conceal-ment B	Concealment C	Generation A	Generation B	Generation C

Table 1. Study quality assessment criteria *(Continued)*

Central randomisation in a multi-center trial or randomisation in pharmacy in a single centre trial	No description of methods used for allocation concealment	Alternation	Any method resulting in a truly random sequence (computer-generated list, coin tossing, other)	No description of methods used for allocation generation	Use of case record numbers, patient identification or admission numbers
Pre-numbered or coded identical containers administered serially to patients	Not allocation concealment A or C	Use of case record numbers, patient identification or admission numbers		Not allocation generation A or C	Randomisation based on patient's room number
Sequentially numbered, sealed, opaque envelopes		Open randomisation lists			
Computer file accessed only after patient's recruitment		Use of birth date or admission day			

APPENDICES

Appendix 1. MEDLINE search strategy

1 exp Pneumocystis Infections/
2 exp Pneumocystis/
3 (pcp or pneumocystis).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
4 1 or 2 or 3
5 prevention & control.fs.
6 exp Chemoprevention/
7 (prophylaxis or chemoprophylaxis).mp.
8 5 or 6 or 7
9 4 and 8
10 randomized controlled trial.pt.
11 controlled clinical trial.pt.
12 randomized.ab.
13 placebo.ab.
14 drug therapy.fs.
15 randomly.ab.
16 trial.ab.
17 groups.ab.
18 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19 9 and 18

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

Appendix 2. EMBASE search strategy

1 exp pneumocystosis/
2 (pcp or pneumocystis).mp.
3 1 or 2
4 pc.fs.
5 chemoprophylaxis/

6 antibiotic prophylaxis/
7 (prophylaxis or chemoprophylaxis).mp.
8 4 or 5 or 6 or 7
9 3 and 8
10 crossover procedure/
11 double blind procedure/
12 randomized controlled trial/
13 single blind procedure/
14 random*.mp.
15 factorial*.mp.
16 crossover*.mp.
17 cross over*.mp.
18 cross-over*.mp.
19 placebo*.mp.
20 (double* adj blind*).mp.
21 (singl* adj blind*).mp.
22 assign*.mp.
23 allocat*.mp.
24 volunteer*.mp.
25 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26 9 and 25

key; mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, fs=floating subheading

Appendix 3. CENTRAL search strategy

#1 MeSH descriptor Pneumocystis Infections explode all trees
#2 MeSH descriptor Pneumocystis explode all trees
#3 pcp or pneumocystis
#4 (#1 OR #2 OR #3)
#5 Any MeSH descriptor with qualifier: PC
#6 MeSH descriptor Chemoprevention explode all trees
#7 prophylaxis or chemoprophylaxis
#8 (#5 OR #6 OR #7)
#9 (#4 AND #8)

WHAT'S NEW

Date	Event	Description
21 September 2016	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 1, 2006
Review first published: Issue 3, 2007

Date	Event	Description
11 February 2015	Amended	Contact details updated.
22 September 2014	Amended	Minor typographical error
15 September 2014	New citation required but conclusions have not changed	New studies added

Date	Event	Description
24 March 2014	New search has been performed	Searches re-run on 24 March 2014. Two studies with 263 patients added to data analyses. Conclusions not changed.
4 May 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Heftsiba Green, Anat Stern and Mical Paul performed the search, extracted the data, and compared results. Heftsiba Green and Anat Stern corresponded with the authors and analysed the data. All authors assisted in data analysis and interpretation. Anat Stern and Mical Paul wrote the updated review. All authors read and approved the review.

DECLARATIONS OF INTEREST

None declared

SOURCES OF SUPPORT

Internal sources

- New Source of support, Other.

External sources

- None, Other.

INDEX TERMS

Medical Subject Headings (MeSH)

*Immunocompromised Host; Anti-Infective Agents [adverse effects] [*therapeutic use]; HIV Seronegativity; Pneumonia, Pneumocystis [*prevention & control]; Randomized Controlled Trials as Topic; Trimethoprim, Sulfamethoxazole Drug Combination [adverse effects] [*therapeutic use]

MeSH check words

Adult; Child; Humans