



META-ANALYSIS: LONG-TERM THERAPY WITH RIFAXIMIN IN UNCOMPLICATED DIVERTICULAR DISEASE

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META-ANALYSIS: LONG-TERM THERAPY WITH RIFAXIMIN IN UNCOMPLICATED DIVERTICULAR DISEASE

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Key words: non absorbable-antibiotics, rifaximin, uncomplicated diverticular disease, diverticulitis, meta-analysis

SUMMARY

Background: Diverticular disease of the colon is a common gastrointestinal disease. Although most patients remain asymptomatic for their whole life, about 20-25% present symptoms related to “diverticular disease”. Several randomized trials verified efficacy of a poorly absorbed antibiotic, such as rifaximin- α (rifaximin), in soothing symptoms and preventing diverticulitis. **Aim** of this study is to evaluate the long-term efficacy administration of rifaximin plus fiber supplementation versus fiber supplementation alone, on symptoms and complications, in patient with symptomatic uncomplicated diverticular disease.

Methods: Pertinent studies were selected from the Medline, and the Cochrane Library Databases, references from published articles and reviews. Conventional meta-analysis according to DerSimonian and Laird method was used for the pooling of the results. The outcomes were 1- year complete symptom relief, and 1- year complication incidence. The Rate Difference (RD, with 95% CI) and the Number Needed to Treat (NNT) were used as measure of the therapeutic effect on each outcome.

Results: Four prospective randomized trials including 1660 patients were selected.

The pooled RD for symptom relief was 29.0% (rifaximin vs control ; 95% CI 24.5 to 33.6%; $P < 0.0001$; NNT= 3). The pooled RD for complication rate was -1.7% in favor of rifaximin (95% CI -3.2 to -0.1%; $P = 0.03$; NNT= 59). When considering only acute diverticulitis, the pooled RD in the treatment group was -2% (95% CI -3.4 to -0.6%; $P = 0.0057$; NNT= 50).

Conclusions: in symptomatic uncomplicated diverticular disease, treatment with rifaximin plus fiber supplementation is effective in obtaining symptom relief and preventing complications at 1 year.

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INTRODUCTION

Diverticular disease of the colon is one of the most common gastrointestinal disease, with a prevalence increasing with age, from 5% of people in the fifth decade of life, to almost 50% by the ninth decade (1-3). The epidemiological dimension of the disease is sharply changing the pattern. Overall annual age-adjusted admissions for acute diverticulitis are strikingly increasing. For example, in the United States population, a 26% increase between 1998 and 2005 has been recorded (4) . Rates of admission increased more rapidly within patients aged 18 to 44 years (+82%) and 45 to 74 years (+36%). Elective operations for diverticulitis rose from 16,100 to 22,500 per year during the same time period (+29%), also with a more rapid increase (73%) in rates of surgery for individuals aged 18 to 44 years. (4).

Although most patients remain asymptomatic for their whole life, about 20-25% present symptoms related to “diverticular disease” at some point (5-8).

Diverticular disease can be classified in symptomatic uncomplicated disease (diverticulosis), recurrent symptomatic disease or complicated disease (9-10).

Symptomatic uncomplicated disease is characterized by abdominal pain (principally colicky left iliac fossa pain), and altered bowel habits (9,11). ~~After a first symptomatic episode, 20% of the treated patients develop recurrent symptoms (10).~~

Among patients with diverticular disease, 25% develop complications, 1-2% require hospitalization and 0.5% surgery (4,11).

Acute diverticulitis is the most common complication of diverticular disease: it will develop in 10-25% of people with diverticula (3). Recurrent diverticulitis is observed in 7-42% of people with diverticular disease, and after recovery the calculated yearly risk of suffering another episode is 3% (12). Some 50% of recurrence occur within 1 year of the initial episode, and 90% occur within 5 years (13).

Haemorrhage occurs in 5-15% of patients (being severe in 3-5%) (7, 11-13). Surgery, when performed in urgency and in the septic forms like peritonitis, is loaded with a non-negligible high mortality rate, up to 26% (14-17).

Concerning medical therapy, current guidelines actually recommend only the use of high spectrum antibiotics in the initial treatment of acute diverticulitis (18). Clinical trials have provided evidence of the substantial benefit of rifaximin-alfa (rifaximin), a poor absorbable antibiotic, in diverticular disease. Indeed, available data show the efficacy of the drug in reducing symptoms in most patients with uncomplicated disease (19-23). However, its value in modifying the clinical course of the disease, and in primary prevention of diverticulitis needs to be fully quantified.

We therefore carried out a meta-analysis of randomized controlled trials (RCTs) with rifaximin plus fiber supplementation, to provide an evidence-based assessment of its potential efficacy.

The objective of this meta-analysis was to compare the efficacy of rifaximin plus fiber supplementation vs placebo on 1-year symptom disappearance and complication rate in patients with symptomatic uncomplicated diverticular disease.

METHODS

General recommendations from PRISMA revision (24) with regard to processing and reporting of results were taken into account conducting this meta-analysis (Appendix 1).

Trial Criteria

This meta-analysis includes RCTs of patients with symptomatic uncomplicated diverticular disease with the following design: rifaximin therapy, or placebo, followed by clinical re-evaluation (at least every 3 months) to assess symptom relief and complications . Cohort studies, case series, case reports were excluded .

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Literature Search

RCTs were identified by searching MEDLINE, and the Cochrane Central Register of Controlled Trials from 1966 to September 2010. A computer-assisted search was conducted using the following combination of medical subject heading terms (MESH and not MESH terms): “diverticular disease” AND “antibiotics” AND “clinical trial”. The search strategy for PubMed used the strings: (("diverticulum"[MeSH Terms] OR "diverticulum"[All Fields] OR ("diverticular"[All Fields] AND "disease"[All Fields]) OR "diverticular disease"[All Fields]) AND ("anti-bacterial agents"[MeSH Terms] OR ("anti-bacterial"[All Fields] AND "agents"[All Fields]) OR "anti-bacterial agents"[All Fields] OR "antibiotics"[All Fields] OR "anti-bacterial agents"[Pharmacological Action]) AND (("colon"[MeSH Terms] OR "colon"[All Fields] OR "colonic"[All Fields]) OR ("colon"[MeSH Terms] OR "colon"[All Fields])))) NOT ("review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "review"[All Fields]). No language limits were imposed. We supplemented the electronic search by scanning the reference lists of relevant publications, including review articles and guidelines (8-10,14,25-27). When published data were insufficient for our analyses, additional details were sought from the investigators of the corresponding clinical trials.

Study Selection

Our predefined inclusion criteria were: (1) prospective RCTs of treatment with poorly absorbed antibiotics versus no treatment in symptomatic colonic diverticular disease; (2) well defined outcomes including at least one of the following: (a) pain (b) complications (local and/or systemic). The outcomes considered were the number of patients symptom free at the end of follow-up (1 year), and complications within 12 months from the first examination. So we performed a dichotomous analysis on the presence or absence of: (a) symptoms (primary outcome), (b) complications (secondary outcome). Diverticulitis was predefined as abdominal pain attributed to diverticular disease and 1 of the following criteria: (1) treated with antibiotics, hospitalization, or

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3 surgery; or (2) described as severe or acute or presenting with fever, requiring medication, or
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5 evaluated with computed tomography. Only results fully reported in journal articles were
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7 considered. All articles passed through a multilevel, systematic review by a team of four physicians
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9 (MB, VF, AC, RL): methodological criteria and the results of each study were recorded. Studies
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11 that fulfilled the inclusion criteria were reviewed blindly and independently by the same four
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13 authors (MB, VF, AC, RL) to tabulate subject demographics, study design, definition of primary
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15 and secondary outcomes, and frequencies of each end-point, using a standardized data abstract
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17 form. Disagreement was resolved by consensus.
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22 23 **Assessment of risk of bias**

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27 We aimed to reduce the possibility of publication bias through searches of conference abstracts and
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29 contacting authors for any additional unreported data. An estimate of the publication bias was
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31 calculated according to Rosenthal (28).
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37 **Validity Assessment**

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41 Methodological quality was assessed independently by 2 reviewers (M.B. and V.F.) using the
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43 Cochrane risk of bias tool, an established tool based on assessing sequence generation for the
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45 randomization of subjects, allocation concealment of treatment, blinding, reporting of data, and
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47 other sources of bias (29). The methodological quality of each study was also evaluated by the same
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49 authors, using the system described by Jadad et al (30). Each study was evaluated using a 5-point
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51 scale, with 1 point being awarded for each of the following criteria: randomized controlled trial,
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53 details of randomization methods provided, double-blind study, details of blinding method
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55 provided, and information on study withdrawals provided. Discrepancies in ratings were resolved by
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57 discussion between the 2 of us. When discrepancies arose, a third party (M.K.) was consulted.
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Statistical analysis

Results were analyzed by the DerSimonian–Laird method (31) for comparing and summarizing outcomes of individual RCTs. We pre-decided to use the random effect model, since it is more conservative. The term rate difference (RD), i.e. the difference in event rates between the treatment and control groups, was used as a measure of the therapeutic effect. Confidence intervals (CI) were always calculated at 95%. Number needed to treat (NNT), that is the number of patients who must be treated in order to obtain one more therapeutic effect in comparison to control group, was also calculated (32): mathematically, NNT is equivalent to the reciprocal of RD and the 95% confidence intervals for the NNT are the reciprocal of the 95% confidence intervals for RD. The alpha level was set at 0.05, for a two-tailed test. A statistical program published by T. Chalmers and us was used for this purpose (33). Results were also checked using Epistat (copyright © Epistat Services, 1991), StatsDirect statistical tools (Copyright © 1990–2001) and an appropriate meta-analysis software (34). Intertrial heterogeneity in treatment effect was evaluated using the Q statistic of DerSimonian–Laird (31), and the quantity of heterogeneity was measured using the I^2 (35). To compensate somewhat for the lack of the power of the test, we decided not to accept evidence of a therapeutic effect, even if statistically significant, in the event of a P value < 0.10 for heterogeneity. Furthermore, to detect heterogeneity, a visual display was obtained, representing the results on a L’Abbé plot (36).

RESULTS

Search Findings

The initial combined search identified 108 reports, and we excluded 80 because of the title or abstract. Of the remaining 28 articles, 24 were excluded. Nineteen had a non-randomized design. Five trials, published between 1992 and 2007, met the inclusion criteria (19-23). One of these was excluded because study design was a randomized cross-over trial (23). This review is therefore

based upon the results from four studies (19-22) ; for the Colecchia's study (22) dichotomous data were obtained directly by the investigator . Upon initial analysis, concordance implied 95% agreement between the authors.

A total of 1660 patients had been enrolled: 970 were randomized to treatment with a poorly absorbed antibiotic, and 690 were randomized to no treatment. The characteristics of studies are shown in Table 1. In all studies the antibiotic used was rifaximin 400 mg bid for 7 days every month; all patients in both the treated group and control group, received a standard supplement of dietary fibers (Table 1). In only one study, control group received placebo (20).

In all studies the diagnosis of symptomatic uncomplicated diverticular disease was made by double contrast barium enema and/or colonoscopy. Clinical evaluation was performed on admission and at 2-4 months interval, for the following 12 months in 4 studies (19-21), and for 24 months in one study (22). Side effects were recorded and reported in table 2 .All studies used different symptom score system based on several clinical variables. However, this review focus only the dichotomous analysis (presence/absence of any symptom).

At baseline, the specific symptoms rate were similar in both treated and control groups among all studies. The most frequent symptom was "lower abdominal pain" (range from 87.5% to 97.3% in treatment groups, and from 90.2% to 94.7% in control groups) (see Table 3).

At 1 year, the rate of patients without any symptom, as registered in the previous 6 months, ranged from 23.6% to 59.3% in control groups, and from 56.5% to 89.7% in treatment groups (Table 4).

Complication rate ranged from 2.3% to 7.3% in control group, and from 0.9% to 2.3% in treatment group (Table 4).

Quantitative data synthesis

In all studies, the primary outcome was considered symptoms relief; complication rate was considered as a secondary outcome (15-18). Results of outcomes measures through the four studies are reported in Table 4.

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Two hundred forty-one out of 690 patients in control group (pooled rate 34.9%) were symptom-free at end the follow-up, compared to 621 out of 970 patients in the treatment group (pooled rate 64.0%). The pooled RD for complete symptom relief in favor of rifaximin group was 29.0% (95% CI 24.5% to 33.6%; $P < 0.0001$; NNT= 3). No heterogeneity was found ($Q = 1.12$, d.f. = 3, $P = 0.77$; $I^2 = 0\%$) (Figure 2).

Twenty-two out of 690 patients in control group (pooled rate 3.2%) suffered at least one complication, during 1-year follow up, compared to 15 out of 970 patients in the treatment group (pooled rate 1.5%).

A “bowel infection” occurred in 4 more patients in the control group reported in one trial (22), but they were excluded from the cumulative analysis, because possibly not related to the diverticular disease.

The pooled RD for complication rate in favor of rifaximin was -1.7% (95% CI -3.2% to -0.15%; $P=0.03$; NNT= 59). No heterogeneity was found ($Q = 0.57$, d.f. = 3, $P = 0.9$; ; $I^2 = 0\%$) (Figure 3).

Considering only acute diverticulitis, 20 out of 690 patients in control group (2.8%) suffered of this complication compared to 10 out of 970 patients in the treatment group (1.0%). The pooled RD for diverticulitis rate in the treatment group was -1.9% (95% CI -3.4% to -0.57%; $P=0.0057$; NNT= 50) (Figure 4).

Three out of 4 trials reported side effect data (19-21). No significant difference was found between control group and treatment group.

Bias assessment

We did not find any evidence of publication bias. The risk of publication bias across 4 trials was investigated: the number of null studies needed to lead our meta-analysis result to a level of statistical non-significance is 148, considering the primary end-point complete symptom relief, and 4, for the secondary end-point occurrence rate of major complications (35).

The Cochrane Collaboration’s tool for assessing risk of bias is shown in Table 5.

The knowledge of the allocated intervention was not adequately prevented in 3 studies.

The Jadad score is reported in Table 1. Three out of 4 trials had a score equal or higher than 3. A sufficient methodological quality was so guaranteed.

DISCUSSION

Most patients with colonic uncomplicated diverticular disease do not report any gastrointestinal symptoms during their lifespan; only a minority of individuals, about 20%, complain of symptoms (37). Most of the patients treated for the first episode of diverticulitis will recover and have no further clinical problems, while only 20% of these patients will develop recurrent symptoms. Consistent evidence indicates that dietary fibre, especially the insoluble fibre found mostly in fruits and vegetables rather than cereals, **decreases risk of diverticula development** (38,39).

The protective action of dietary fibre would make the stools bulkier, thereby increasing the colon size and decreasing intraluminal pressures, and reducing colonic transit time (40, 41).

The administration of the non-absorbable antibiotic **rifaximin** is able to reduce most of the clinical manifestations of diverticular disease, when compared with fiber supplementation alone. This effect is reached mainly through the reduction of the intestinal bacterial overgrowth (42).

The interaction between dietary fiber and locally acting antibiotics, such as **rifaximin**, represents an intriguing aspect of the treatment of diverticular disease, as **rifaximin** has been reported to improve the clinical benefits of dietary fibers in uncomplicated diverticular disease (19-22). It has been suggested that the synergistic effect of **rifaximin** on a high-fiber diet may be due to a reduced proliferation of gut microflora, with a consequent decrease in bacterial hydrogen (H₂) and methane (CH₄) production, and/or to an expansion in fecal mass, due to a decrease in bacterial degradation of fiber, thus reducing pain (43). Furthermore, it has been suggested that these effects could induce an acceleration in intestinal transit time, thus reducing constipation, which is frequently present in patients with diverticular disease (41). **Rifaximin** administration was shown to be effective in

normalizing breath H₂ profile in patients with intestinal bacterial overgrowth (41,43). Rifaximin absorption from the bowel is considered to be less than 1%, even in presence of colitis (44, 45).

The purpose of our meta-analysis was to evaluate the long-term efficacy administration of rifaximin plus fiber supplementation versus fiber supplementation alone, on symptoms and complications in patient with symptomatic uncomplicated diverticular disease.

The results of our study confirm previous observations, that cyclic administration of rifaximin, a poorly absorbable antibiotic, achieves symptomatic relief in a large proportions of patients with uncomplicated diverticular disease, in comparison to control. After 12 months of follow up, 64.0% (pooled rate: CI 95% 31.4 – 38.6) of patients treated with rifaximin plus standard supplement of dietary fibers were symptom-free, in comparison to 34.9% (CI 95% 60.9 – 67.0) of patients treated with fibers supplement. The 1-year gain in total symptom relief resulted statistically significant, and clinically relevant (+ 29%, NNT 3).

Although a meta-analysis does not replace a large-scale, well-designed, randomized controlled trial, individual studies may be limited by small sample sizes, especially for end points with relatively low incidences. By pooling all available data, meta-analysis allows for a more precise estimate, than that which can be obtained from the results of any individual study.

This meta-analysis has some limitations. The study overall is limited by the quality of the trials that are included. This could lead to an overestimation of the treatment effect of rifaximin. Blinding and a placebo-controlled group was guaranteed only in one study (20). Lack of heterogeneity between studies is not surprising, due to the reduced number of admitted trials. Publication bias should also be hypothesized, due to the lack of power: the number of null studies needed to lead our meta-analysis result to a level of statistical non-significance is 148, considering complete symptom relief, but is only 4, for the incidence of major complications..

This study suggests that rifaximin treatment significantly could be of value in reducing complication development: at 1 year, 1.5% of patients treated with rifaximin plus standard

supplement of dietary fibers developed complications, versus 3.2% of patients treatment with supplement of dietary fibers.

However, the 1-year gain in primary prevention of complications was statistically, but not clinically relevant (-1.7%; NNT 59).

Further studies would be appropriate to check if rifaximin could have a role in modifying the clinical course of the disease, i.e. in reducing complication rate in a population with a higher probability of the event, like patients with a previous episode of diverticulitis. In fact, one-third of patients will proceed to a second attack of diverticulitis (46-48). Moreover, it is generally believed that the prognosis is worse with a second attack, since some studies have reported that the rate of complicated diverticulitis in such patients approaches 60 percent and the mortality rate is doubled (47,49-50). Recurrent diverticulitis ranges from 7 to 42% of patients (11). Some 50% of recurrence occur within 1 year of the initial episode (12).

Assuming the observed OR for 1-year complication rate from this meta-analysis (0.37, 95% CL 0.17-0.79), the 1-year NNT to prevent a second episode of diverticulitis could be expected to range from 44 for a 1-year risk of 3.5% (50% of 7%, the minimum range we found in the literature) to 8 for a 1-year risk of 21% (50% of 42%, the maximum range).

In conclusion, the present meta-analysis confirms that the cyclic treatment with rifaximin plus fiber supplementation is more effective in obtaining symptom relief and could prevent more complications, in comparison to fiber supplementation, in symptomatic uncomplicated diverticular disease. ~~We conclude that the evidence that cyclic rifaximin may further reduce symptoms at 12 months, in comparison to fiber supplementation, should move from level 2 (mid-level), as indicated in reference 51, to level 1 (meta-analysis of multiple well designed, controlled studies), according to the Standards Committee of American Society of Colon and Rectal Surgeons (5).~~

However, at the moment the evidence of an effect of rifaximin over fiber supplementation on the clinical course of diverticular disease is poor.

References

1. Painter NS, Burkitt DP. Diverticular disease of the colon, a 20th century problem. Clin Gastroenterol 1975; 4: 3-22.
2. Schoetz DJ. Diverticular disease of the colon: a century-old problem. Dis Colon Rectum 1999; 42: 703–709.
3. Parks TG. Natural history of diverticular disease of the colon. Clin Gastroenterol 1975; 4: 53–69.
4. Etzioni DA, Mack TM, Beart RW Jr, et al. Diverticulitis in the United States:1998–2005: changing patterns of disease and treatment. Ann Surg. 2009;249: 210–217.
5. Rafferty J, Shellito P, Hyman NH, Buie WD. Standards Committee of American Society of Colon and Rectal Surgeons. Practice parameters for sigmoid diverticulitis. Dis Colon Rectum 2006; 49: 939-944
6. Bogardus ST Jr. What do we know about diverticular disease? A brief overview. J Clin Gastroenterol 2006; 40: S108-111
7. Simpson J, Neal KR, Scholefield JH, Spiller RC. Patterns of pain in diverticular disease and the influence of acute diverticulitis. Eur J Gastroenterol Hepatol 2003;15:1005–1010
8. Tursi A, Papagrigoriadis S. Review article: the current and evolving treatment of colonic diverticular disease. Aliment Pharmacol Ther 2009; 30: 532-546
9. Petruzzello L, Iacopini F, Bulajic M, et al. Review article: uncomplicated diverticular disease of the colon. Aliment Pharmacol Ther 2006; 23: 1379-1391.
10. Humes D., Simpson J. and Spiller R. . Colonic diverticular disease : in <http://clinicalevidence.bmj.com/ceweb>, accessed on 2010 Dec 1.

11. Haglund U, Hellberg R, Johnsen C, et al. Complicated diverticular disease of the sigmoid colon. An analysis of short and long term outcome in 392 patients. *Ann Chir Gynaecol* 1979;68:41–46.
12. Parks TG, Connell AM. The outcome in 455 patients admitted for treatment of diverticular disease of the colon. *Br J Surg* 1970;57:775–778.
13. Boles RS, Jordon SM. The clinical significance of diverticulosis. *Gastroenterology* 1958;35:579–581.
14. Folch MH, White JA. Management of diverticular disease is changing. *World J Gastroenterol* 2006; 12: 3225-3228.
15. Wong SK, Ho YH, Leong AP, et al. Clinical behavior of complicated right-sided and left-sided diverticulosis. *Dis Colon Rectum* 1997; 40: 344–348.
16. Kronborg O. Treatment of perforated sigmoid diverticulitis: A prospective randomised trial. *Br J Surg* 1993; 80: 505-507.
17. Zeitoun G, Laurent A, Rouffet F. Multicentre, randomized, clinical trial of primary versus secondary sigmoid resection in generalized peritonitis complicating sigmoid diverticulitis. *Br J Surg* 2000; 87:1366-1374
18. World Gastroenterology Organisation. Practice Guidelines: Diverticular Disease, 2007
19. Papi C, Ciaco A, Koch M, et al. Efficacy of rifaximin on symptoms of uncomplicated diverticular disease of the colon. A pilot multicentre open trial. Diverticular Disease Study Group. *Ital J Gastroenterol* 1992; 24: 452–456.
20. Papi C, Ciaco A, Koch M, et al. Efficacy of rifaximin in the treatment of symptomatic diverticular disease of the colon. A multicenter double-blind placebo-controlled trial. *Aliment Pharmacol Ther* 1995; 9: 33-39
21. Latella G, Pimpo MT, Sottili S, et al. rifaximin improves symptoms of acquired uncomplicated diverticular disease of the colon. *Int J Colorectal Dis* 2003; 18: 55-62

22. Colecchia A, Vestito A, Pasqui F, et al. Efficacy of long term administration of the poorly absorbed antibiotic rifaximin in symptomatic, uncomplicated colonic diverticular disease. *World J Gastroenterol* 2007; 13: 264-269
23. D'Incà R, Pomerri F, Vettorato GM. Interaction between rifaximin and dietary fibre in patients with diverticular disease. *Aliment Pharmacol Ther* 2007;25: 771-779
24. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009 Jul 21;6(7):e1000097.
25. Stollman NH, Raskin JB. Diagnosis and management of diverticular disease of the colon in adults. Ad Hoc Practice Parameters Committee of the American College of Gastroenterology. *Am J Gastroenterol* 1999; 94: 3110-3121
26. Kohler L, Sauerland S, Neugebauer E. For the scientific committee of the european association for endoscopic surgery (EAES). Diagnosis and treatment of diverticular disease. Results of a consensus development conference. *Surg Endosc* 1999; 13:430-436
27. Colecchia A, Sandri L, Capodicasa S, et al. Diverticular disease of the colon: new perspectives in symptom development and treatment. *World J Gastroenterol* 2003; 9: 1385–1389
28. Rosenthal R. The 'File Drawer Problem' and tolerance for null results. *Psycho Bull* 1979;86: 638–641.
29. Julian PT Higgins and Sally Green Editors. *Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series* .© 2008 The Cochrane Collaboration. Published Online, 2008 Sept 22 .
30. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1–12
31. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clin Trials* 1986;7:177–188.

32. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. *N Engl J Med* 1988;318:1728–1733.
33. Chalmers TC, Blum A, Buyse M, Hewitt P, Koch M, editors. *Data analysis for clinical medicine. The quantitative approach to patient care in gastroenterology.* Rome, Manchester, New York, Hong Kong: International University Press; 1988.
34. Messori A, Rampazzo R. Meta-analysis of clinical trials based on censored end-points: simplified theory and implementation of the statistical algorithms on a microcomputer. *Comput Methods Programs Biomed* 1993;40:261-267
35. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat med* 2002; 21: 1539-1558
36. L'Abbé KA, Detsky AS, O' Rourke K. Meta-analysis in clinical research. *Ann Intern Med* 1987;107:224–233.
37. Stollman N, Raskin JB. Diverticular disease of the colon. *Lancet* 2004; 363:631–639.
38. Aldoori W, Ryan-Harshman M. Preventing diverticular disease. Review of recent evidence on high-fibre diets. *Can Fam Physician.* 2002 48:1632-1637;
39. Painter NS. The cause of diverticular disease of the colon, its symptoms and its complications. Review and hypothesis. *J R Coll Surg Edinb.* 1985;30:118-122.
40. Lupton JR, Turner ND. Potential protective mechanisms of wheat bran fiber. *Am J Med.* 1999;106:24-27
41. Ventrucchi M, Ferrieri A, Bergami R, et al. Evaluation of the effect of rifaximin in colon diverticular disease by means of lactulose hydrogen breath test. *Curr Med Res Opin* 1994; 13: 202-206
42. Corazza GR, Ventrucchi M, Strocchi A, et al. Treatment of small intestine bacterial overgrowth with rifaximin a non-absorbable rifamycin. *J Internat Med Res* 1988; 16: 312-316.

43. Di Stefano M, Malservisi S, Veneto G, et al. Rifaximin versus chlortetracycline in the short-term treatment of small intestine bacterial overgrowth. *Aliment Phar Ther* 2000; 14: 551-556.
44. Descombe JJ, Dubourg D, Picard M, et al. Pharmacokinetic study of rifaximin after oral administration in healthy volunteers. *Int J Clin Pharmacol Res* 1994; 14: 51-56
45. Rizzello F, Gionchetti P, Venturi A. Rifaximin systemic absorption in patients with ulcerative colitis. *Eur J Clin Pharmacol* 1998; 54: 91-93
46. Larson DM; Masters SS; Spiro HM. Medical and surgical therapy in diverticular disease: a comparative study. *Gastroenterol* 1976; 71: 734-737.
47. Parks, TG. Natural history of diverticular disease of the colon. *Clin Gastroenterol* 1975; 4:53.
48. Rege RV; Nahrwold DL. Diverticular disease. *Curr Probl Surg* 1989; 26: 133-189.
49. Rodkey GV; Welch CE. Changing patterns in the surgical treatment of diverticular disease. *Ann Surg* 1984; 200: 466-478.
50. Sarin S, Boulos PB Long-term outcome of patients presenting with acute complications of diverticular disease. *Ann R Coll Surg Engl* 1994; 76: 117-120.
51. Diverticulitis. In DynaMed, <http://dynaweb.ebscohost.com>. Updated 2010, Dec 13. Accessed on 2010, Dec 30..

Figure legends:

Figure 1: PRISMA 2009 Flow Diagram

Figure 2 : Rate differences (RD) (95% CI) for complete symptom relief at the end the follow-up in prospective randomized trials addressing Rifaximin group vs control group. Random effect model.

Figure 3: Rate differences (RD) (95% CI) for complication rate in prospective randomized trials addressing Rifaximin group vs control group. Random effect model.

Figure 4: Rate differences (RD) (95% CI) for complication rate (acute diverticulitis alone) in prospective randomized trials addressing Rifaximin group vs control group. Random effect model.

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Drafting the manuscript: M. Bianchi, V.Festa, A. Moretti, C. Papi, B. De Pascalis

The final draft submitted has been approved by all authors.

Figure1

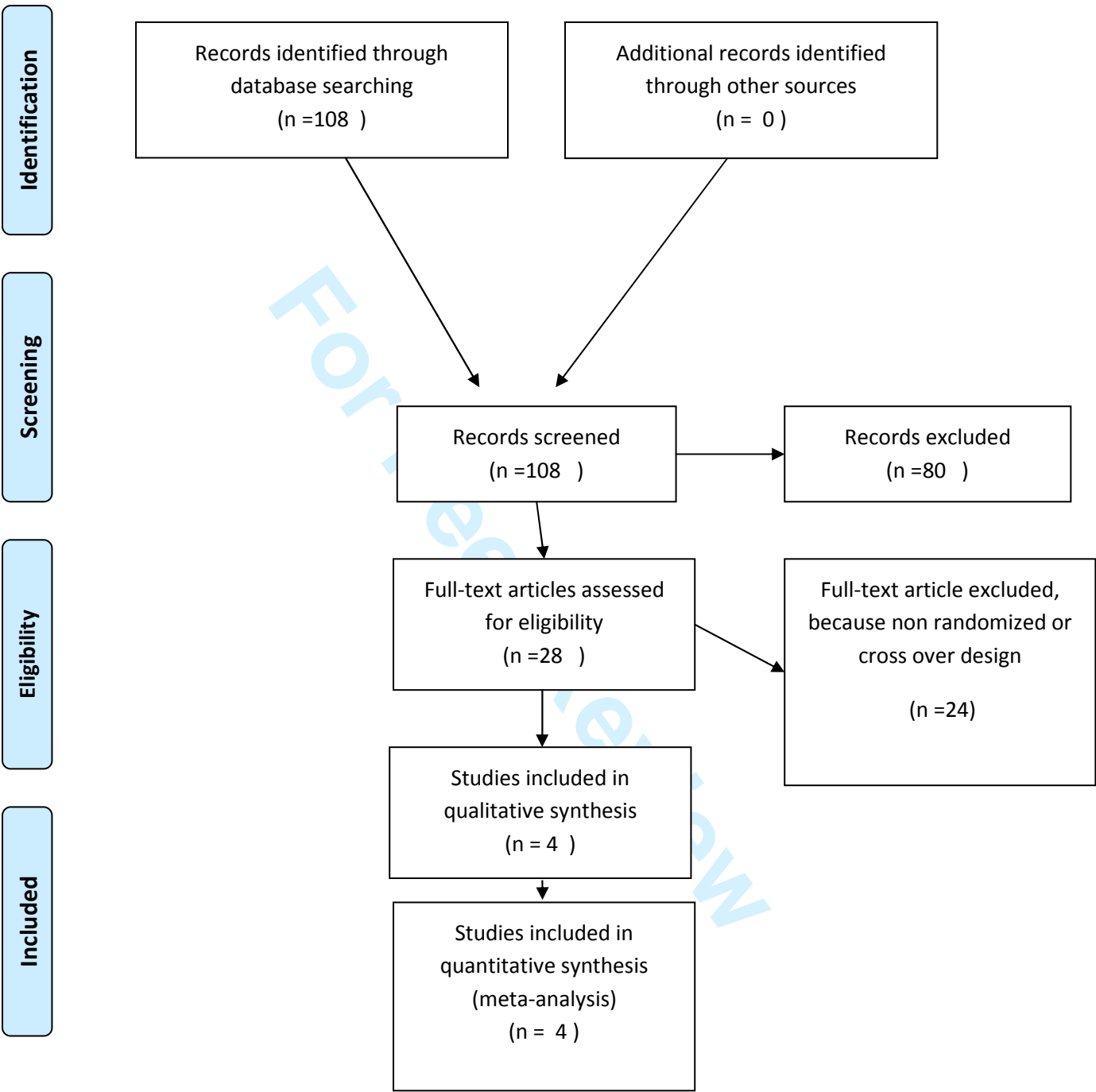
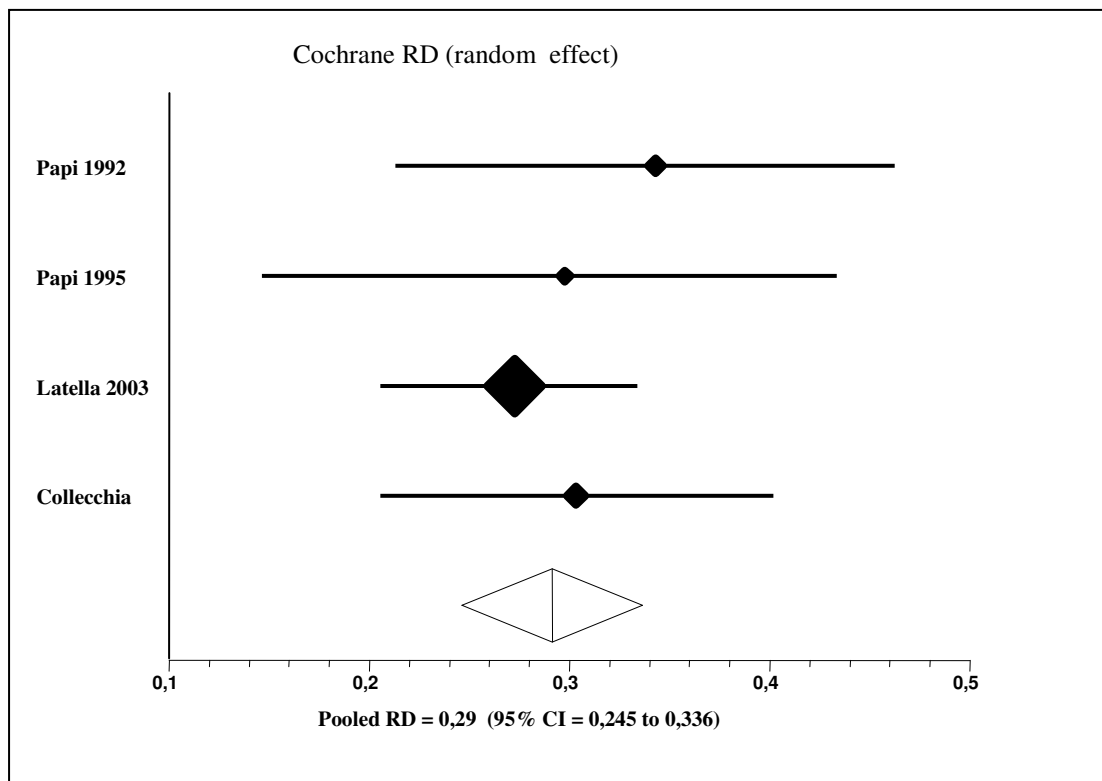
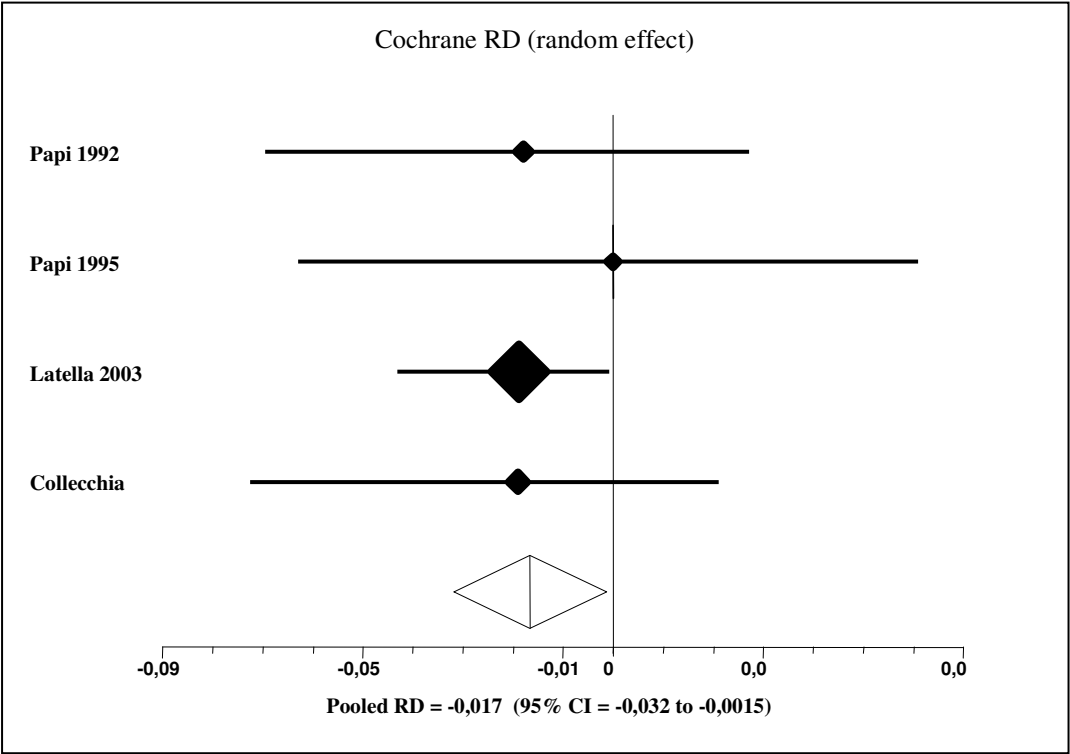


Figure 2



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Figure 3



Review

Figure 4

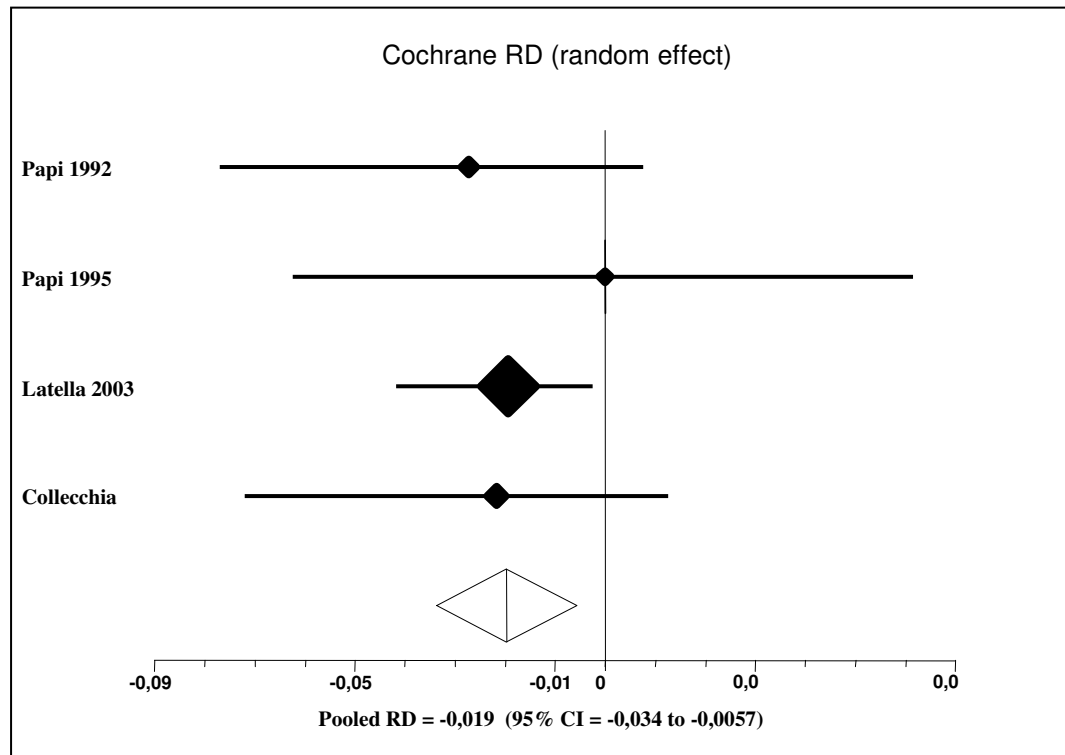


Table 1. Studies addressing Rifaximin in the treatment of symptomatic diverticular disease

Author	pts n.	Study design	Jadad scale	Treatment	Study period (months)
Papi 1992	217	open	2	Glucomannan 2 g Glucomannan 2 g + Rifaximin*	12
Latella 2003	968	open	3	Glucomannan 4 g Glucomannan 4 g + Rifaximin*	12
Papi 1995	168	RCT	4	Glucomannan 2 g + Placebo Glucomannan 2 g + Rifaximin*	12
Colecchia 2007	307	open	3	Dietary fiber Supp§ Dietary fiber Supp§+ Rifaximin*	24

* Rifaximin 400 mg b.i.d. for 7 days each month for 12 months

§ Dietary fiber Supplementation (20gr/die)

Table 2. Side effects recorded in patients enrolled in randomized controlled trials

Author	pts		Side Effects Patients n° (%)
Papi 1992	217	Controll group=110 Treatment group=107	NR* NR*
Latella 2003	968	Controll group= 373 Treatment group=595	5 (1.3) 10 (1.7)
Papi 1995	168	Controll group= 84 Treatment group=84	0 0
Colecchia 2007	307	Controll group= 123 Treatment group=184	3 (2.4) 4 (2.2)

*NR= Not reported

Table 3. Baseline symptoms in patients enrolled in randomized controlled trials

Author	pts	Randomization	Lower AP* patients (%)	Abdominal tenderness patients (%)	Bloating patients (%)
Papi 1992	217	Controll group=110 Treatment group=107	91.8 91.4	74.7 82.0	85.6 79.0
Latella 2003	968	Controll group= 373 Treatment group=595	90.4 90.1	70.8 70.4	83.9 86.1
Papi 1995	168	Controll group= 84 Treatment group=84	94.7 97.3	64.5 65.3	84.0 88.0
Colecchia 2007	307	Controll group= 123 Treatment group=184	90.2 87.5	69.1 71.2	85.9 78.0

*AP Abdominal Pain

Table 4. Primary end points in randomized controlled trials

Author	pts	Randomization	Asymptomatic Patients n° (%)	Patients with complications n° (%)	Type of Complications
Papi 1992	217	Control group=110 Treatment group=107	26 (23.6) 62 (57.9)	3 (2.7) 1 (0.9)	3 diverticulitis 1 recto-vaginal fistula
Latella 2003	968	Control group= 373 Treatment group=595	109 (29.2) 336 (56.5)	12 (3.2) 8 (1.3)	11 diverticulitis 1 rectal bleeding 6 diverticulitis 2 rectal bleeding
Papi 1995	168	Control group= 84 Treatment group=84	33 (39.3) 58 (69.0)	2 (2.3) 2 (2.3)	2 diverticulitis 2 diverticulitis
Colecchia 2007	307	Control group= 123 Treatment group=184	73 (59.3) 165 (89.7)	9 (7.3) 4 (2.1)	4 diverticulitis 1 rectal bleeding 4 intestinal infections* 2 diverticulitis 2 rectal bleeding

*Not considered in pooling analysis

Table.5 Risk of bias assessed by The Cochrane Collaboration's tool

Author	Papi	Papi	Latella	Colecchia
Year	1992	1995	2003	2007
Adequate sequence generation	no	yes	yes	yes
Allocation concealment?	yes	yes	yes	yes
Blinding?	no	yes	no	no
Incomplete outcome data addressed?	yes	yes	yes	yes
Free of selective reporting	yes	yes	yes	yes
Free of other bias ?	yes	yes	yes	yes

Appendix 1: Prisma 2009 check-list

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18