



**HAL**  
open science

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

Marco Bianchi, Virginia Festa, Alessandra Moretti, Antonio Ciaco, Manuela Mangone, Valentina Tornatore, Angelo Dezi, Roberto Luchetti, Barbara de Pascalis, Claudio Papi, et al.

► **To cite this version:**

Marco Bianchi, Virginia Festa, Alessandra Moretti, Antonio Ciaco, Manuela Mangone, et al.. META-ANALYSIS: LONG-TERM THERAPY WITH RIFAXIMIN IN UNCOMPLICATED DIVERTICULAR DISEASE. *Alimentary Pharmacology and Therapeutics*, 2011, 33 (8), pp.902. 10.1111/j.1365-2036.2011.04606.x . hal-00618501

**HAL Id: hal-00618501**

**<https://hal.science/hal-00618501v1>**

Submitted on 2 Sep 2011

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

Journal:	<i>Alimentary Pharmacology &amp; Therapeutics</i>
Manuscript ID:	APT-0066-2011.R2
Wiley - Manuscript type:	SuperFast
Date Submitted by the Author:	02-Feb-2011
Complete List of Authors:	Bianchi, Marco; ACO S.Filippo Neri, gastroenterology and Hepatology Festa, Virginia; ACO S.Filippo Neri, Gastroenterology and Hepatology Moretti, Alessandra; ACO S.Filippo Neri, Gastroenterology and Hepatology Ciaco, Antonio; ACO S.Filippo Neri, Gastroenterology and Hepatology Mangone, Manuela; ACO S.Filippo Neri, Gastroenterology and Hepatology Tornatore, Valentina; ACO S.Filippo Neri, Gastroenterology and Hepatology Dezi, Angelo; ACO S.Filippo Neri, Gastroenterology and Hepatology Luchetti, Roberto; ACO S.Filippo Neri, Gastroenterology and Hepatology De Pascalis, Barbara; ACO S.Filippo Neri, Gastroenterology and Hepatology Papi, Claudio; ACO S.Filippo Neri, Gastroenterology and Hepatology Koch, Maurizio; ACO S.Filippo Neri, Gastroenterology and Hepatology
Keywords:	Diverticular disease < Disease-based, Large intestine < Organ-based, Meta-analyses < Topics, X keyword = no topic

1  
2  
3  
4 **META-ANALYSIS: LONG-TERM THERAPY WITH RIFAXIMIN IN**  
5  
6 **UNCOMPLICATED DIVERTICULAR DISEASE**  
7  
8

9 **Authors:** Marco Bianchi, MD, Virginia Festa, MD, Alessandra Moretti, MD, Antonio Ciaco, MD,  
10  
11 Manuela Mangone, MD, Valentina Tornatore, MD, Angelo Dezi, MD, Roberto Luchetti, MD,  
12  
13 Barbara De Pascalis, MD, Claudio Papi, MD, Maurizio Koch, MD.  
14  
15

16  
17 **Affiliations:**  
18

19  
20 Gastroenterology and Liver Unit  
21

22  
23 Azienda Ospedaliera San Filippo Neri  
24

25  
26 Via Martinotti 20, 00135 Rome – Italy  
27  
28  
29

30 **Corresponding author:**  
31

32  
33 Virginia Festa, MD  
34

35  
36 Gastroenterology and Liver Unit  
37

38  
39 Azienda Ospedaliera San Filippo Neri  
40

41  
42 Via Martinotti 20, 00135 Rome – Italy  
43  
44

45  
46 Phone: +390633062444 Fax: +390633062641  
47

48  
49 e-mail: [v.festa@sanfilipponeri.roma.it](mailto:v.festa@sanfilipponeri.roma.it)  
50  
51

52  
53 These data were presented as oral communication at FISMAD, “Italian National Congress of  
54  
55 Digestive Diseases”, March 9, 2010, Verona, Italy, and as a poster presentation at DDW 2010, May  
56  
57 3, 2010, New Orleans, USA  
58  
59

60 **WORD COUNT: 2978**

1  
2  
3 Short title : Rifaximin therapy in uncomplicated diverticular disease  
4  
5

6 Key words: non absorbable-antibiotics, rifaximin, uncomplicated diverticular disease, diverticulitis,  
7  
8 meta-analysis  
9

## 10 11 SUMMARY

12 Background: Diverticular disease of the colon is a common gastrointestinal disease. Although  
13  
14 most patients remain asymptomatic for their whole life, about 20-25% present symptoms related to  
15  
16 “diverticular disease”. Several randomized trials verified efficacy of a poorly absorbed antibiotic,  
17  
18 such as rifaximin- $\alpha$  (rifaximin), in soothing symptoms and preventing diverticulitis. Aim of this  
19  
20 study is to evaluate the long-term efficacy administration of rifaximin plus fiber supplementation  
21  
22 versus fiber supplementation alone, on symptoms and complications, in patient with symptomatic  
23  
24 uncomplicated diverticular disease.  
25  
26  
27  
28  
29

30  
31 Methods: Pertinent studies were selected from the Medline, and the Cochrane Library Databases,  
32  
33 references from published articles and reviews. Conventional meta-analysis according to  
34  
35 DerSimonian and Laird method was used for the pooling of the results. The outcomes were 1- year  
36  
37 complete symptom relief, and 1- year complication incidence. The Rate Difference (RD, with 95%  
38  
39 CI) and the Number Needed to Treat (NNT) were used as measure of the therapeutic effect on each  
40  
41 outcome.  
42  
43  
44

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

46  
47 The pooled RD for symptom relief was 29.0% (rifaximin vs control ; 95% CI 24.5 to 33.6%;  
48  
49  $P < 0.0001$ ; NNT= 3). The pooled RD for complication rate was -1.7% in favor of rifaximin (95% CI  
50  
51 -3.2 to -0.1%;  $P = 0.03$ ; NNT= 59). When considering only acute diverticulitis, the pooled RD in  
52  
53 the treatment group was -2% (95% CI -3.4 to -0.6%;  $P = 0.0057$ ; NNT= 50).  
54  
55  
56

57 Conclusions: in symptomatic uncomplicated diverticular disease, treatment with rifaximin plus fiber  
58  
59 supplementation is effective in obtaining symptom relief and preventing complications at 1 year.  
60

## 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).

1  
2  
3 Haemorrhage occurs in 5-15% of patients (being severe in 3-5%) (7, 11-13). Surgery, when  
4 performed in urgency and in the septic forms like peritonitis, is loaded with a non-negligible high  
5 mortality rate, up to 26% (14-17).  
6  
7

8  
9  
10 Concerning medical therapy, current guidelines actually recommend only the use of high spectrum  
11 antibiotics in the initial treatment of acute diverticulitis (18). Clinical trials have provided evidence  
12 of the substantial benefit of rifaximin-alfa (rifaximin), a poor absorbable antibiotic, in diverticular  
13 disease. Indeed, available data show the efficacy of the drug in reducing symptoms in most  
14 patients with uncomplicated disease (19-23). However, its value in modifying the clinical course  
15 of the disease, and in primary prevention of diverticulitis needs to be fully quantified.  
16  
17

18  
19 We therefore carried out a meta-analysis of randomized controlled trials (RCTs) with rifaximin  
20 plus fiber supplementation, to provide an evidence-based assessment of its potential efficacy.  
21  
22

23  
24 The objective of this meta-analysis was to compare the efficacy of rifaximin plus fiber  
25 supplementation vs placebo on 1-year symptom disappearance and complication rate in patients  
26 with symptomatic uncomplicated diverticular disease.  
27  
28

## 29 30 31 32 33 34 35 36 37 38 39 **METHODS**

40  
41  
42 General recommendations from PRISMA revision (24) with regard to processing and reporting of  
43 results were taken into account conducting this meta-analysis ( Appendix 1).  
44  
45

### 46 47 48 **Trial Criteria**

49  
50 This meta-analysis includes RCTs of patients with symptomatic uncomplicated diverticular disease  
51 with the following design: rifaximin therapy, or placebo, followed by clinical re-evaluation (at least  
52 every 3 months) to assess symptom relief and complications . Cohort studies, case series, case  
53 reports were excluded .  
54  
55  
56  
57  
58  
59  
60

## 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

1  
2  
3 surgery; or (2) described as severe or acute or presenting with fever, requiring medication, or  
4  
5 evaluated with computed tomography. Only results fully reported in journal articles were  
6  
7 considered. All articles passed through a multilevel, systematic review by a team of four physicians  
8  
9 (MB, VF, AC, RL): methodological criteria and the results of each study were recorded. Studies  
10  
11 that fulfilled the inclusion criteria were reviewed blindly and independently by the same four  
12  
13 authors (MB, VF, AC, RL) to tabulate subject demographics, study design, definition of primary  
14  
15 and secondary outcomes, and frequencies of each end-point, using a standardized data abstract  
16  
17 form. Disagreement was resolved by consensus.  
18  
19  
20  
21

### 22 23 **Assessment of risk of bias**

24  
25  
26  
27 We aimed to reduce the possibility of publication bias through searches of conference abstracts and  
28  
29 contacting authors for any additional unreported data. An estimate of the publication bias was  
30  
31 calculated according to Rosenthal (28).  
32  
33

### 34 35 36 37 **Validity Assessment**

38  
39  
40  
41 Methodological quality was assessed independently by 2 reviewers (M.B. and V.F.) using the  
42  
43 Cochrane risk of bias tool, an established tool based on assessing sequence generation for the  
44  
45 randomization of subjects, allocation concealment of treatment, blinding, reporting of data, and  
46  
47 other sources of bias (29). The methodological quality of each study was also evaluated by the same  
48  
49 authors, using the system described by Jadad et al (30). Each study was evaluated using a 5-point  
50  
51 scale, with 1 point being awarded for each of the following criteria: randomized controlled trial,  
52  
53 details of randomization methods provided, double-blind study, details of blinding method  
54  
55 provided, and information on study withdrawals provided. Discrepancies in ratings were resolved by  
56  
57 discussion between the 2 of us. When discrepancies arose, a third party (M.K.) was consulted.  
58  
59  
60



## 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

1  
2  
3 based upon the results from four studies (19-22) ; for the Colecchia's study (22) dichotomous data  
4  
5 were obtained directly by the investigator . Upon initial analysis, concordance implied 95%  
6  
7 agreement between the authors.  
8  
9

10 A total of 1660 patients had been enrolled: 970 were randomized to treatment with a poorly  
11  
12 absorbed antibiotic, and 690 were randomized to no treatment. The characteristics of studies are  
13  
14 shown in Table 1. In all studies the antibiotic used was rifaximin 400 mg bid for 7 days every  
15  
16 month; all patients in both the treated group and control group, received a standard supplement of  
17  
18 dietary fibers (Table 1). In only one study, control group received placebo (20).  
19  
20  
21

22 In all studies the diagnosis of symptomatic uncomplicated diverticular disease was made by double  
23  
24 contrast barium enema and/or colonoscopy. Clinical evaluation was performed on admission and at  
25  
26 2-4 months interval, for the following 12 months in 4 studies (19-21), and for 24 months in one  
27  
28 study (22). Side effects were recorded and reported in table 2 .All studies used different symptom  
29  
30 score system based on several clinical variables. However, this review focus only the dichotomous  
31  
32 analysis (presence/absence of any symptom).  
33  
34  
35

36 At baseline, the specific symptoms rate were similar in both treated and control groups among all  
37  
38 studies. The most frequent symptom was "lower abdominal pain" (range from 87.5% to 97.3% in  
39  
40 treatment groups, and from 90.2% to 94.7% in control groups) (see Table 3).  
41  
42

43 At 1 year, the rate of patients without any symptom, as registered in the previous 6 months, ranged  
44  
45 from 23.6% to 59.3% in control groups, and from 56.5% to 89.7% in treatment groups (Table 4).  
46  
47

48 Complication rate ranged from 2.3% to 7.3% in control group, and from 0.9% to 2.3% in treatment  
49  
50 group (Table 4).  
51  
52

### 53 **Quantitative data synthesis**

54  
55 In all studies, the primary outcome was considered symptoms relief; complication rate was  
56  
57 considered as a secondary outcome (15-18). Results of outcomes measures through the four studies  
58  
59 are reported in Table 4.  
60

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.

1  
2  
3 The Jadad score is reported in Table 1. Three out of 4 trials had a score equal or higher than 3. A  
4  
5 sufficient methodological quality was so guaranteed.  
6  
7  
8  
9

## 10 11 **DISCUSSION**

12  
13  
14 Most patients with colonic uncomplicated diverticular disease do not report any gastrointestinal  
15  
16 symptoms during their lifespan; only a minority of individuals, about 20%, complain of symptoms  
17  
18 (37). Most of the patients treated for the first episode of diverticulitis will recover and have no  
19  
20 further clinical problems, while only 20% of these patients will develop recurrent symptoms.  
21  
22  
23 Consistent evidence indicates that dietary fibre, especially the insoluble fibre found mostly in fruits  
24  
25 and vegetables rather than cereals, **decreases risk of diverticula development** (38,39).  
26  
27  
28

29  
30 The protective action of dietary fibre would make the stools bulkier, thereby increasing the colon  
31  
32 size and decreasing intraluminal pressures, and reducing colonic transit time (40, 41).  
33  
34

35  
36 The administration of the non-absorbable antibiotic **rifaximin** is able to reduce most of the clinical  
37  
38 manifestations of diverticular disease, when compared with fiber supplementation alone. This  
39  
40 effect is reached mainly through the reduction of the intestinal bacterial overgrowth (42).  
41

42  
43 The interaction between dietary fiber and locally acting antibiotics, such as **rifaximin**, represents an  
44  
45 intriguing aspect of the treatment of diverticular disease, as **rifaximin** has been reported to improve  
46  
47 the clinical benefits of dietary fibers in uncomplicated diverticular disease (19-22). It has been  
48  
49 suggested that the synergistic effect of **rifaximin** on a high-fiber diet may be due to a reduced  
50  
51 proliferation of gut microflora, with a consequent decrease in bacterial hydrogen (H<sub>2</sub>) and methane  
52  
53 (CH<sub>4</sub>) production, and/or to an expansion in fecal mass, due to a decrease in bacterial degradation of  
54  
55 fiber, thus reducing pain (43). Furthermore, it has been suggested that these effects could induce an  
56  
57 acceleration in intestinal transit time, thus reducing constipation, which is frequently present in  
58  
59 patients with diverticular disease (41). **Rifaximin** administration was shown to be effective in  
60

1  
2  
3 normalizing breath H<sub>2</sub> profile in patients with intestinal bacterial overgrowth (41,43). Rifaximin  
4  
5 absorption from the bowel is considered to be less than 1%, even in presence of colitis (44, 45).

6  
7  
8 The purpose of our meta-analysis was to evaluate the long-term efficacy administration of rifaximin  
9  
10 plus fiber supplementation versus fiber supplementation alone, on symptoms and complications in  
11  
12 patient with symptomatic uncomplicated diverticular disease.

13  
14  
15 The results of our study confirm previous observations, that cyclic administration of rifaximin , a  
16  
17 poorly absorbable antibiotic, achieves symptomatic relief in a large proportions of patients with  
18  
19 uncomplicated diverticular disease, in comparison to control. After 12 months of follow up, 64.0%  
20  
21 (pooled rate: CI 95% 31.4 – 38.6) of patients treated with rifaximin plus standard supplement of  
22  
23 dietary fibers were symptom-free, in comparison to 34.9% (CI 95% 60.9 – 67.0) of patients treated  
24  
25 with fibers supplement. The 1-year gain in total symptom relief resulted statistically significant, and  
26  
27 clinically relevant (+ 29%, NNT 3).

28  
29  
30 Although a meta-analysis does not replace a large-scale, well-designed, randomized controlled trial,  
31  
32 individual studies may be limited by small sample sizes, especially for end points with relatively  
33  
34 low incidences. By pooling all available data, meta-analysis allows for a more precise estimate, than  
35  
36 that which can be obtained from the results of any individual study.

37  
38  
39  
40  
41 This meta-analysis has some limitations. The study overall is limited by the quality of the trials that  
42  
43 are included. This could lead to an overestimation of the treatment effect of rifaximin. Blinding and  
44  
45 a placebo-controlled group was guaranteed only in one study (20). Lack of heterogeneity between  
46  
47 studies is not surprising, due to the reduced number of admitted trials. Publication bias should also be  
48  
49 hypothesized, due to the lack of power: the number of null studies needed to lead our meta-analysis  
50  
51 result to a level of statistical non-significance is 148, considering complete symptom relief, but is  
52  
53 only 4, for the incidence of major complications..

54  
55  
56  
57 This study suggests that rifaximin treatment significantly could be of value in reducing  
58  
59 complication development: at 1 year, 1.5% of patients treated with rifaximin plus standard  
60

1  
2  
3 supplement of dietary fibers developed complications, versus 3.2% of patients treatment with  
4  
5 supplement of dietary fibers.  
6

7  
8 However, the 1-year gain in primary prevention of complications was statistically, but not clinically  
9  
10 relevant (-1.7%; NNT 59).  
11

12 Further studies would be appropriate to check if rifaximin could have a role in modifying the  
13  
14 clinical course of the disease, i.e. in reducing complication rate in a population with a higher  
15  
16 probability of the event, like patients with a previous episode of diverticulitis. In fact, one-third of  
17  
18 patients will proceed to a second attack of diverticulitis (46-48). Moreover, it is generally believed  
19  
20 that the prognosis is worse with a second attack, since some studies have reported that the rate of  
21  
22 complicated diverticulitis in such patients approaches 60 percent and the mortality rate is doubled  
23  
24 (47,49-50). Recurrent diverticulitis ranges from 7 to 42% of patients (11). Some 50% of  
25  
26 recurrence occur within 1 year of the initial episode (12).  
27  
28  
29  
30

31 Assuming the observed OR for 1-year complication rate from this meta-analysis (0.37, 95% CL  
32  
33 0.17-0.79), the 1-year NNT to prevent a second episode of diverticulitis could be expected to range  
34  
35 from 44 for a 1-year risk of 3.5% (50% of 7%, the minimum range we found in the literature) to 8  
36  
37 for a 1-year risk of 21% (50% of 42%, the maximum range).  
38  
39  
40  
41  
42

43 In conclusion, the present meta-analysis confirms that the cyclic treatment with rifaximin plus fiber  
44  
45 supplementation is more effective in obtaining symptom relief and could prevent more  
46  
47 complications, in comparison to fiber supplementation, in symptomatic uncomplicated diverticular  
48  
49 disease. ~~We conclude that the evidence that cyclic rifaximin may further reduce symptoms at 12~~  
50  
51 ~~months, in comparison to fiber supplementation, should move from level 2 (mid-level), as indicated~~  
52  
53 ~~in reference 51, to level 1 (meta-analysis of multiple well designed, controlled studies), according~~  
54  
55 ~~to the Standards Committee of American Society of Colon and Rectal Surgeons (5).~~  
56  
57  
58  
59

60 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 20<sup>th</sup> 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/cweb>, accessed on 2010 Dec 1.

- 1  
2  
3 11. Haglund U, Hellberg R, Johnsen C, et al. Complicated diverticular disease of the sigmoid  
4 colon. An analysis of short and long term outcome in 392 patients. *Ann Chir Gynaecol*  
5 1979;68:41–46.  
6  
7
- 8  
9  
10 12. Parks TG, Connell AM. The outcome in 455 patients admitted for treatment of diverticular  
11 disease of the colon. *Br J Surg* 1970;57:775–778.  
12  
13
- 14  
15 13. Boles RS, Jordon SM. The clinical significance of diverticulosis. *Gastroenterology*  
16 1958;35:579–581.  
17  
18
- 19  
20 14. Folch MH, White JA. Management of diverticular disease is changing. *World J*  
21 *Gastroenterol* 2006; 12: 3225-3228.  
22  
23
- 24  
25 15. Wong SK, Ho YH, Leong AP, et al. Clinical behavior of complicated right-sided and left-  
26 sided diverticulosis. *Dis Colon Rectum* 1997; 40: 344–348.  
27  
28
- 29  
30 16. Kronborg O. Treatment of perforated sigmoid diverticulitis: A prospective randomised  
31 trial. *Br J Surg* 1993; 80: 505-507.  
32  
33
- 34  
35 17. Zeitoun G, Laurent A, Rouffet F. Multicentre, randomized, clinical trial of primary versus  
36 secondary sigmoid resection in generalized peritonitis complicating sigmoid diverticulitis.  
37 *Br J Surg* 2000; 87:1366-1374  
38  
39
- 40  
41 18. World Gastroenterology Organisation. Practice Guidelines: Diverticular Disease, 2007  
42  
43
- 44  
45 19. Papi C, Ciaco A, Koch M, et al. Efficacy of rifaximin on symptoms of uncomplicated  
46 diverticular disease of the colon. A pilot multicentre open trial. Diverticular Disease Study  
47 Group. *Ital J Gastroenterol* 1992; 24: 452–456.  
48  
49
- 50  
51 20. Papi C, Ciaco A, Koch M, et al. Efficacy of rifaximin in the treatment of symptomatic  
52 diverticular disease of the colon. A multicenter double-blind placebo-controlled trial.  
53 *Aliment Pharmacol Ther* 1995; 9: 33-39  
54  
55
- 56  
57 21. Latella G, Pimpo MT, Sottili S, et al. rifaximin improves symptoms of acquired  
58 uncomplicated diverticular disease of the colon. *Int J Colorectal Dis* 2003; 18: 55-62  
59  
60



- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
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.

- 1  
2  
3 32. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the  
4 consequences of treatment. *N Engl J Med* 1988;318:1728–1733.  
5  
6  
7  
8 33. Chalmers TC, Blum A, Buyse M, Hewitt P, Koch M, editors. *Data analysis for clinical*  
9 *medicine. The quantitative approach to patient care in gastroenterology.* Rome,  
10 *Manchester, New York, Hong Kong: International University Press; 1988.*  
11  
12  
13 34. Messori A, Rampazzo R. Meta-analysis of clinical trials based on censored end-points:  
14 simplified theory and implementation of the statistical algorithms on a microcomputer.  
15 *Comput Methods Programs Biomed* 1993;40:261-267  
16  
17  
18 35. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat med* 2002;  
19 21: 1539-1558  
20  
21  
22 36. L'Abbé KA, Detsky AS, O' Rourke K. Meta-analysis in clinical research. *Ann Intern Med*  
23 1987;107:224–233.  
24  
25  
26 37. Stollman N, Raskin JB. Diverticular disease of the colon. *Lancet* 2004; 363:631–639.  
27  
28  
29 38. Aldoori W, Ryan-Harshman M. Preventing diverticular disease. Review of recent evidence  
30 on high-fibre diets. *Can Fam Physician.* 2002 48:1632-1637;  
31  
32  
33 39. Painter NS. The cause of diverticular disease of the colon, its symptoms and its  
34 complications. Review and hypothesis. *J R Coll Surg Edinb.* 1985;30:118-122.  
35  
36  
37 40. Lupton JR, Turner ND. Potential protective mechanisms of wheat bran fiber. *Am J Med.*  
38 1999;106:24-27  
39  
40  
41 41. Ventrucchi M, Ferrieri A, Bergami R, et al. Evaluation of the effect of rifaximin in colon  
42 diverticular disease by means of lactulose hydrogen breath test. *Curr Med Res Opin* 1994;  
43 13: 202-206  
44  
45  
46 42. Corazza GR, Ventrucchi M, Strocchi A, et al. Treatment of small intestine bacterial  
47 overgrowth with rifaximin a non-absorbable rifamycin. *J Internat Med Res* 1988; 16: 312-  
48 316.  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 43. Di Stefano M, Malservisi S, Veneto G, et al. Rifaximin versus chlortetracycline in the  
4  
5 short-term treatment of small intestine bacterial overgrowth. *Aliment Phar Ther* 2000; 14:  
6  
7 551-556.  
8  
9
- 10 44. Descombe JJ, Dubourg D, Picard M, et al. Pharmacokinetic study of rifaximin after oral  
11  
12 administration in healthy volunteers. *Int J Clin Pharmacol Res* 1994; 14: 51-56  
13  
14
- 15 45. Rizzello F, Gionchetti P, Venturi A. Rifaximin systemic absorption in patients with  
16  
17 ulcerative colitis. *Eur J Clin Pharmacol* 1998; 54: 91-93  
18  
19
- 20 46. Larson DM; Masters SS; Spiro HM. Medical and surgical therapy in diverticular disease: a  
21  
22 comparative study. *Gastroenterol* 1976; 71: 734-737.  
23  
24
- 25 47. Parks, TG. Natural history of diverticular disease of the colon. *Clin Gastroenterol* 1975;  
26  
27 4:53.  
28
- 29 48. Rege RV; Nahrwold DL. Diverticular disease. *Curr Probl Surg* 1989; 26: 133-189.  
30
- 31 49. Rodkey GV; Welch CE. Changing patterns in the surgical treatment of diverticular disease.  
32  
33 *Ann Surg* 1984; 200: 466-478.  
34  
35
- 36 50. Sarin S, Boulos PB Long-term outcome of patients presenting with acute complications of  
37  
38 diverticular disease. *Ann R Coll Surg Engl* 1994; 76: 117-120.  
39  
40
- 41 51. Diverticulitis. In DynaMed, <http://dynaweb.ebscohost.com>. Updated 2010, Dec 13.  
42  
43 Accessed on 2010, Dec 30.  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10 **Figure legends:**  
11

12  
13  
14  
15 Figure 1: PRISMA 2009 Flow Diagram  
16

17  
18 Figure 2 : Rate differences (RD) (95% CI) for complete symptom relief at the end the follow-up in  
19  
20 prospective randomized trials addressing Rifaximin group vs control group. Random effect model.  
21

22  
23 Figure 3: Rate differences (RD) (95% CI) for complication rate in prospective randomized trials  
24  
25 addressing Rifaximin group vs control group. Random effect model.  
26

27  
28 Figure 4: Rate differences (RD) (95% CI) for complication rate (acute diverticulitis alone) in  
29  
30 prospective randomized trials addressing Rifaximin group vs control group. Random effect model.  
31  
32  
33  
34  
35  
36  
37

38 ***Conflict of interest statement: None declared.***  
39

40 ***Financial support: None declared.***  
41

42 Guarantor of the article: M. Koch  
43

44 Specific author contributions:  
45

46 Research design: M. Koch, M.Bianchi  
47

48 Acquisition , analysis and interpretation of data: M.Koch, M. Bianchi, A. Ciaco, A. Dezi, V. Festa,  
49

50 R. Luchetti, M. Mangone, V. Tornatore,  
51

52 Drafting the manuscript: M. Bianchi, V.Festa, A. Moretti, C. Papi, B. De Pascalis  
53

54 The final draft submitted has been approved by all authors.  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Figure1

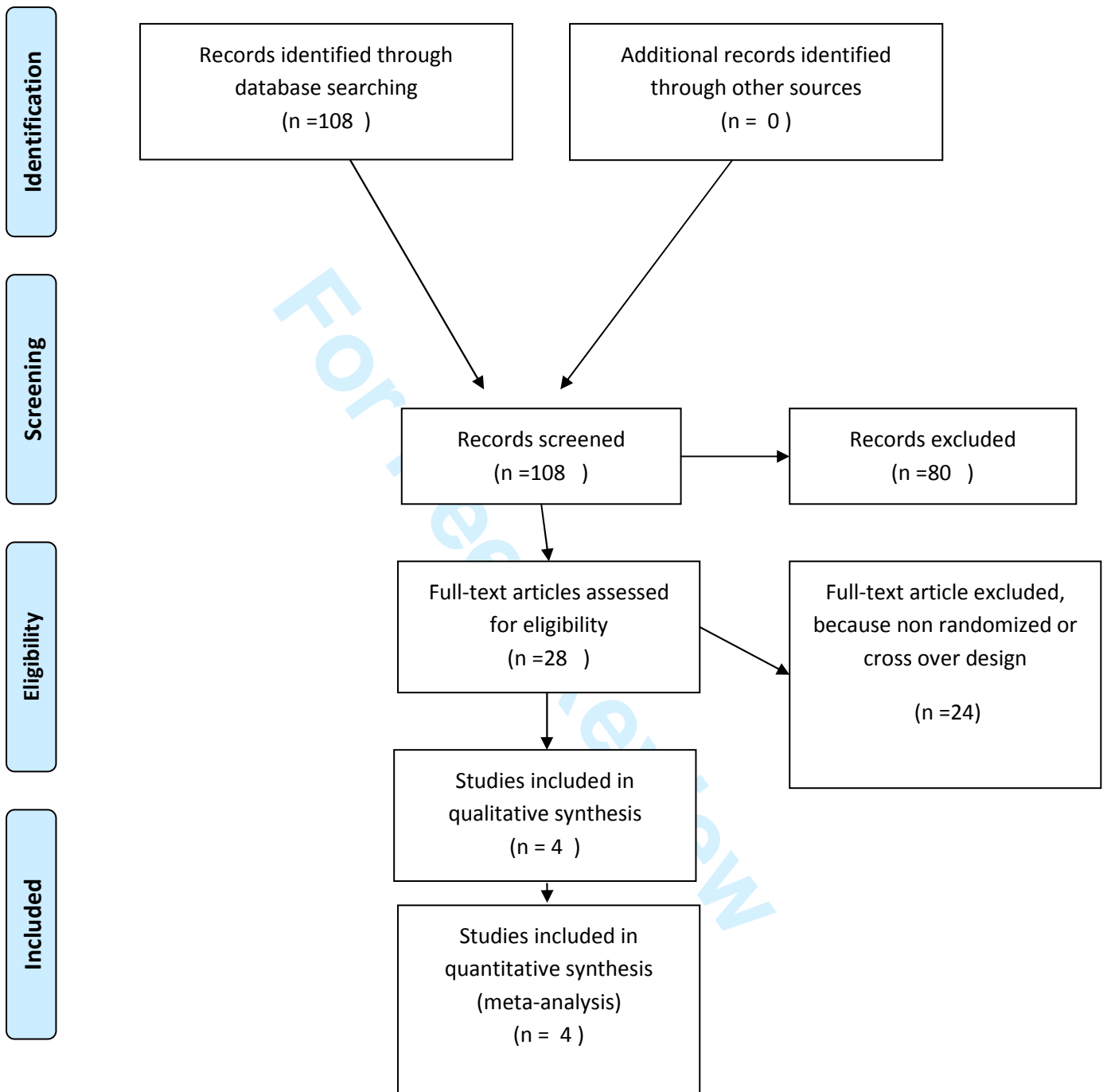
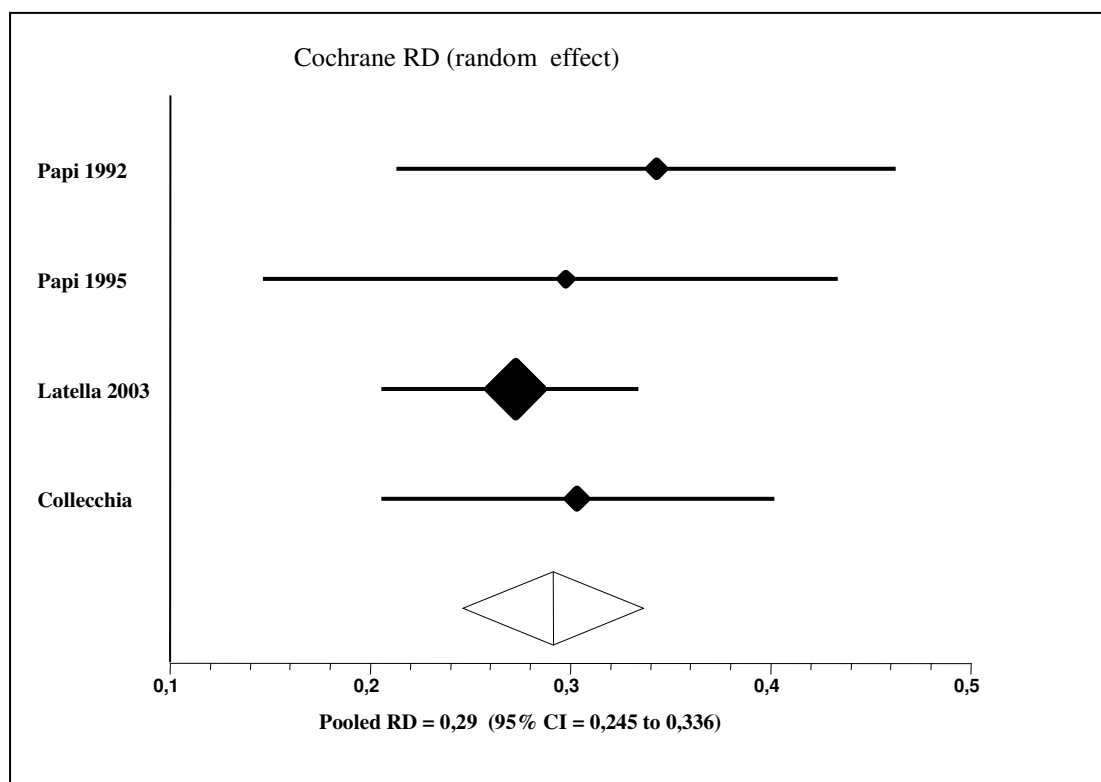


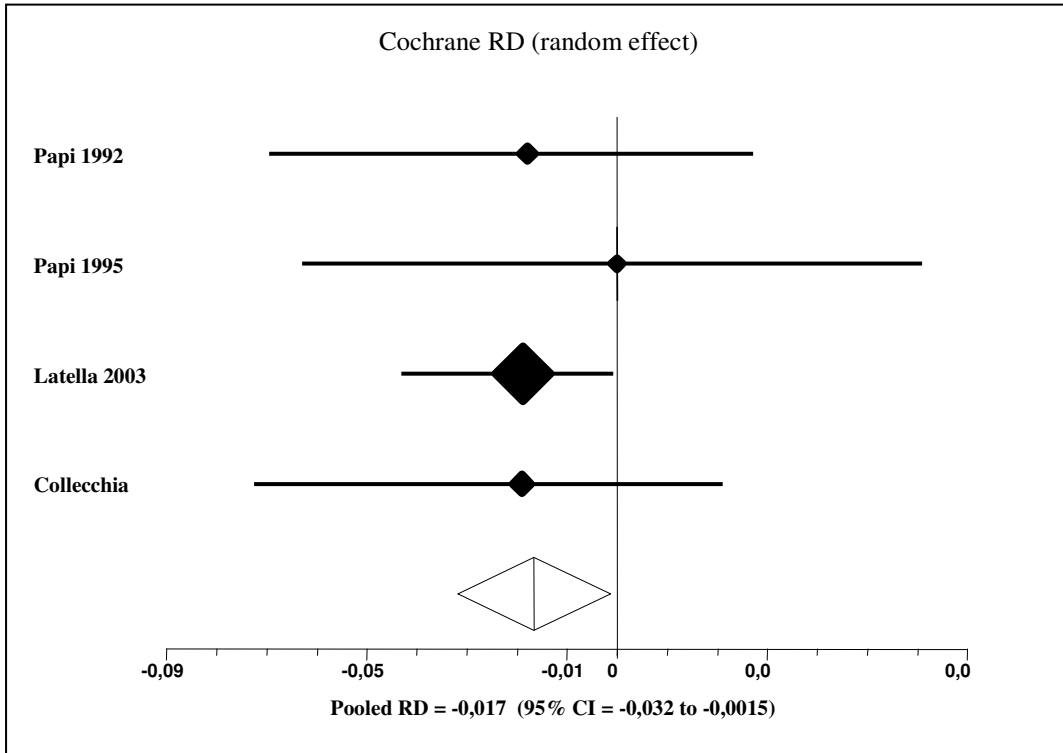
Figure 2



Review

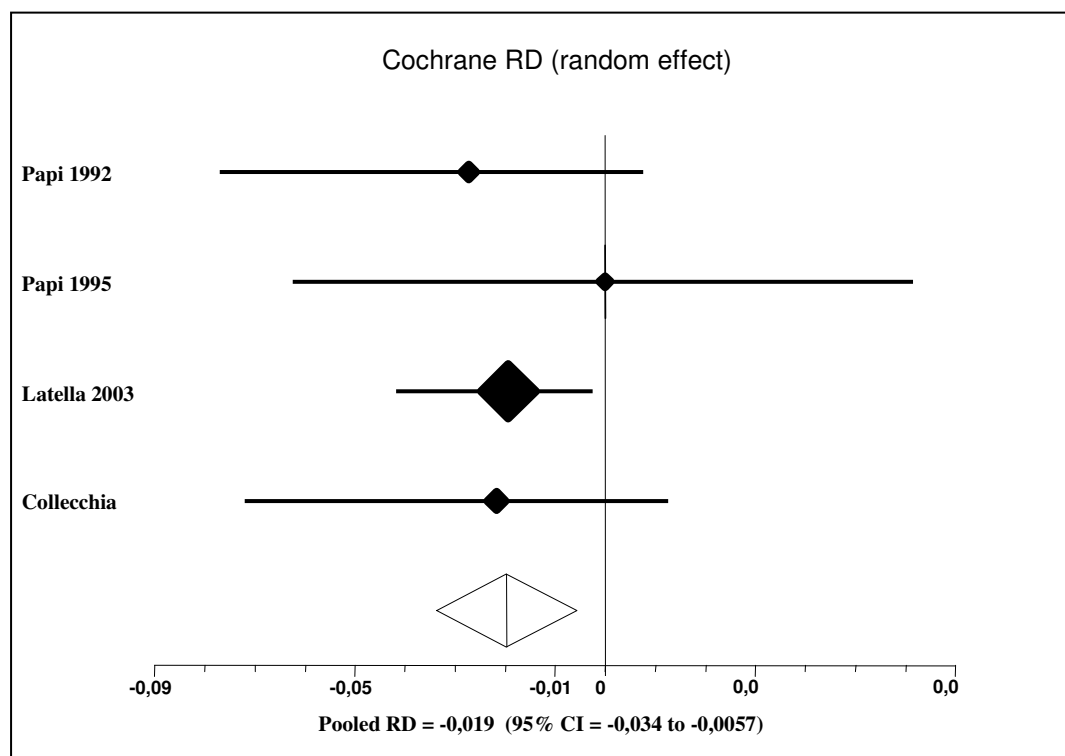
1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Figure 3



Review

Figure 4



review



**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	Glucosaminan 2 g Glucosaminan 2 g + Rifaximin*	12
Latella 2003	968	open	3	Glucosaminan 4 g Glucosaminan 4 g + Rifaximin*	12
Papi 1995	168	RCT	4	Glucosaminan 2 g + Placebo Glucosaminan 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	91.8	74.7	85.6
		Treatment group=107	91.4	82.0	79.0
Latella 2003	968	Controll group= 373	90.4	70.8	83.9
		Treatment group=595	90.1	70.4	86.1
Papi 1995	168	Controll group= 84	94.7	64.5	84.0
		Treatment group=84	97.3	65.3	88.0
Colecchia 2007	307	Controll group= 123	90.2	69.1	85.9
		Treatment group=184	87.5	71.2	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	26 (23.6)	3 (2.7)	3 diverticulitis
		Treatment group=107	62 (57.9)	1 (0.9)	1 recto-vaginal fistula
Latella 2003	968	Control group= 373	109 (29.2)	12 (3.2)	11 diverticulitis 1 rectal bleeding
		Treatment group=595	336 (56.5)	8 (1.3)	6 diverticulitis 2 rectal bleeding
Papi 1995	168	Control group= 84	33 (39.3)	2 (2.3)	2 diverticulitis
		Treatment group=84	58 (69.0)	2 (2.3)	2 diverticulitis
Colecchia 2007	307	Control group= 123	73 (59.3)	9 (7.3)	4 diverticulitis 1 rectal bleeding
		Treatment group=184	165 (89.7)	4 (2.1)	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**

<b>Author</b>	<b>Papi</b>	<b>Papi</b>	<b>Latella</b>	<b>Colecchia</b>
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

Peer Review

## Appendix 1: Prisma 2009 check-list

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
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
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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

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.	-
<b>RESULTS</b>			
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]).	-
<b>DISCUSSION</b>			
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
<b>FUNDING</b>			
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