Supporting Information Table A. Characteristics of the studies included in the systematic review and meta-analysis.

Authors	Type of publication and study	Country	Clinical Setting	Prior antibiotic use allowed	Test to diagnose SIBO	Criteria used to diagnose SIBO	Patients in the rifaximin arm	Dosage of rifaximin	Duration of therapy	Time of follow-up
Corazza et al.(1988)[29]	Full Paper Cohort Study	Italy	GI	nr	LHBT	Presence of a hydrogen peak > 10 ppm above the fasting level (basal value) and preceding the colonic excretion peak by at least 20 min	12	800 mg/die 1200 mg/die	5 days	1 day after EOT
Biancone et al.(2000)[30]	Full Paper RCT	Italy	GI	None within prior 1 month	GHBT	In at least one sample an H_2 level increase higher than 12 ppm when compared with minimum value before this increase	7	1200 mg/die	7 days	7 days after EOT
Di Stefano et al.(2000)[31]	Full Paper RCT	Italy	GI	None within prior 1 month	GHBT	an increase in breath H_2 excretion > 12 ppm over the baseline value within 2 hours of the ingestion of a glucose solution or an increase in breath H_2 excretion > 12 ppm in the fasting state	13	1200 mg/die	7 days	3 day after EOT
Cuoco et al. (2002)[32]	Full Paper Cohort Study	Italy	Extra GI (DM type I or II)	None within prior 3 months	LHBT	Early peak of H_2 represented by the findings of two consecutive values more than 10 ppm above the baseline values	21	1200 mg/die	10 days	1 month after EOT
Tursi et al. (2003)[33]	Full Paper Cohort Study	Italy	GI	nr	LHBT	Presence of a peak >20 ppm occurring >15 min before the colonic peak; also patients with an elevated fasting H_2 combined with an early increase in H_2 after lactulose ingestion were considered positive for bacterial overgrowth	10	800 mg/die	7 days	1 month after EOT
Lauritano et al. (2005)[34]	Full Paper RCT	Italy	GI	None within prior 1 month	GHBT	Increase in H_2 excretion >12 ppm over the baseline value within 2 hrs	90	600 mg/die 800 mg/die 1200 mg/die	7 days	1 month after EOT
Tursi et al. (2005)[35]	Full Paper Cohort Study	Italy	GI	nr	LHBT	Presence of a H_2 peak >20 ppm occurring >15 min before the colonic peak; also patients with an elevated fasting H_2 combined with an early increase in H_2 after lactulose ingestion were considered positive for bacterial overgrowth	53	800 mg/die	10 days	8 weeks after EOT
Cazzato et al. (2006)[36]	Cohort Study	Italy	GI	nr	GHBT	Increase in H_2 excretion >12 ppm over the baseline value	19	1200 mg/die	7 days	1 month after EOT
Cuoco et al. (2006)[37]	Full Paper Cohort Study	Italy	GI	nr	GHBT	At least one of the sample expired air the H_2 value was more than 10 ppm higher than baseline value	23	1200 mg/die	14 days	4-5 months after EOT
D'incà et al. (2007)[38]	Full Paper Cross-Over RCT	Italy	GI	None within prior 1 month	LHBT	Presence of an early increase (> 10 ppm above the baseline level) in H_2 after lactulose ingestion in at least two consecutive samples, or an increase in H_2 value (> 20 ppm above the baseline level) occurring ≥ 20 min after the early increase in H_2	21	1200 mg/die	14 days	within 3 day after EOT
Esposito et al. (2007)[39]	Full Paper Cohort Study	Italy	GI	No patients under antibiotic tx	LHBT	An elevated breath hydrogen concentration higher than 10 ppm over basal values	33	1200 mg/die	7 days	7 days after EOT

nr, not reported; RCT, randomized controlled trial; GI, gastrointestinal; LHBT, lactulose hydrogen breath test; GHBT, glucose hydrogen breath test; min, minutes; hrs, hours; ppm, part per million; EOT, end of treatment; DM, Diabetes mellitus.

Supporting Information Table A. Characteristics of the studies included in the systematic review and meta-analysis (continued).

Authors	Type of publication and study	Country	Clinical Setting	Prior antibiotic use allowed	Test to diagnose SIBO	Criteria used to diagnose SIBO	Patients in the rifaximin arm	Dosage of rifaximin	Duration of therapy	Time of follow-up
Lauritano et al. (2007)[40]	Full Paper Cohort Study	Italy	Extra GI (Hypothyroidism)	None within prior 3 months	GHBT	Increase over the baseline of H_2 levels > 12 ppm	27	1200 mg/die	7 days	1 month after EOT
Majewski et al. (2007)[41]	Full Paper Cohort Study	USA	GI	None within prior 1 month	GHBT	A hydrogen and/or methane peak >20 ppm when the baseline was <10 ppm or in cases where the patient started with baseline of >10 ppm a further increase of >12 ppm indicated a positive result	8	800 mg/die	28 days	within 7 days after EOT
Majewski et al. (2007)[42]	Full Paper Cohort Study	USA	GI	None within prior 6 weeks	GHBT	Hydrogen and methane peak was above 20 ppm when baseline was below 10 ppm or when the patient started with baseline above 10 ppm, a further increase of more than 12 ppm was indicative of positive result	20	800 mg/die	28 days	within 7 days after EOT
Resmini et al. (2007)[43]	Full Paper Cohort Study	Italy	Extra GI (Acromegaly)	nr	LHBT	Presence of two or more distinct peaks of H_2 excretion (10 ppm compared with the basal value)	18	1200 mg/die	10 days	1 month after EOT
Scarpellini et al. (2007)[44]	Full Paper RCT	Italy	GI	None within prior 3 months	GHBT	An increase of H_2 levels over the baseline value was >12 ppm and/or CH_4 levels increased >100% with respect to the basal value	80	1200 mg/die 1600 mg/die	7 days	1 month after EOT
Yang et al. (2008)[45]	Full Paper Cohort Study	USA	GI	nr	LHBT	Hydrogen or methane values rose to more than 20 ppm at or before 90 min. of ingestion of lactulose	50	1200 mg/die	10 days	within 1 week after EOT
Parodi et al. (2008)[46]	Full Paper Cohort Study	Italy	Extra GI (Scleroderma)	None within prior 2 weeks	LHBT	Presence of two or more distinct peaks ofH_2/CH_4 excretion (>10 ppm compared to the basal value)	30	1200 mg/die	10 days	1 month after EOT
Parodi et al. (2008)[47]	Full Paper RCT	Italy	Extra GI (Rosacea)	nr	LHBT- GHBT	GHBT: a single H_2/CH_4 peak higher than 10 ppm LHBT: presence of 2 distinct peaks of H_2/CH_4 excretion (>10 ppm compared with the basal value)	52	1200 mg/die	10 days	1 month after EOT
Lauritano et al. (2009)[48]	Full Paper RCT	Italy	GI	None within prior 3 months	GHBT	Increase over the baseline of H_2 levels >12 ppm	71	1200 mg/die	7 days	1 month after EOT
Parodi et al. (2009)[49]	Full Paper Cohort Study	Italy	GI	None within prior 2 weeks	GHBT	Single H_2 peak higher than 12 ppm	23	1200 mg/die	10 days	1 month after EOT

nr, not reported; RCT, randomized controlled trial; GI, gastrointestinal; LHBT, lactulose hydrogen breath test; GHBT, glucose hydrogen breath test; min, minutes; hrs, hours; ppm, part per million; EOT, end of treatment.

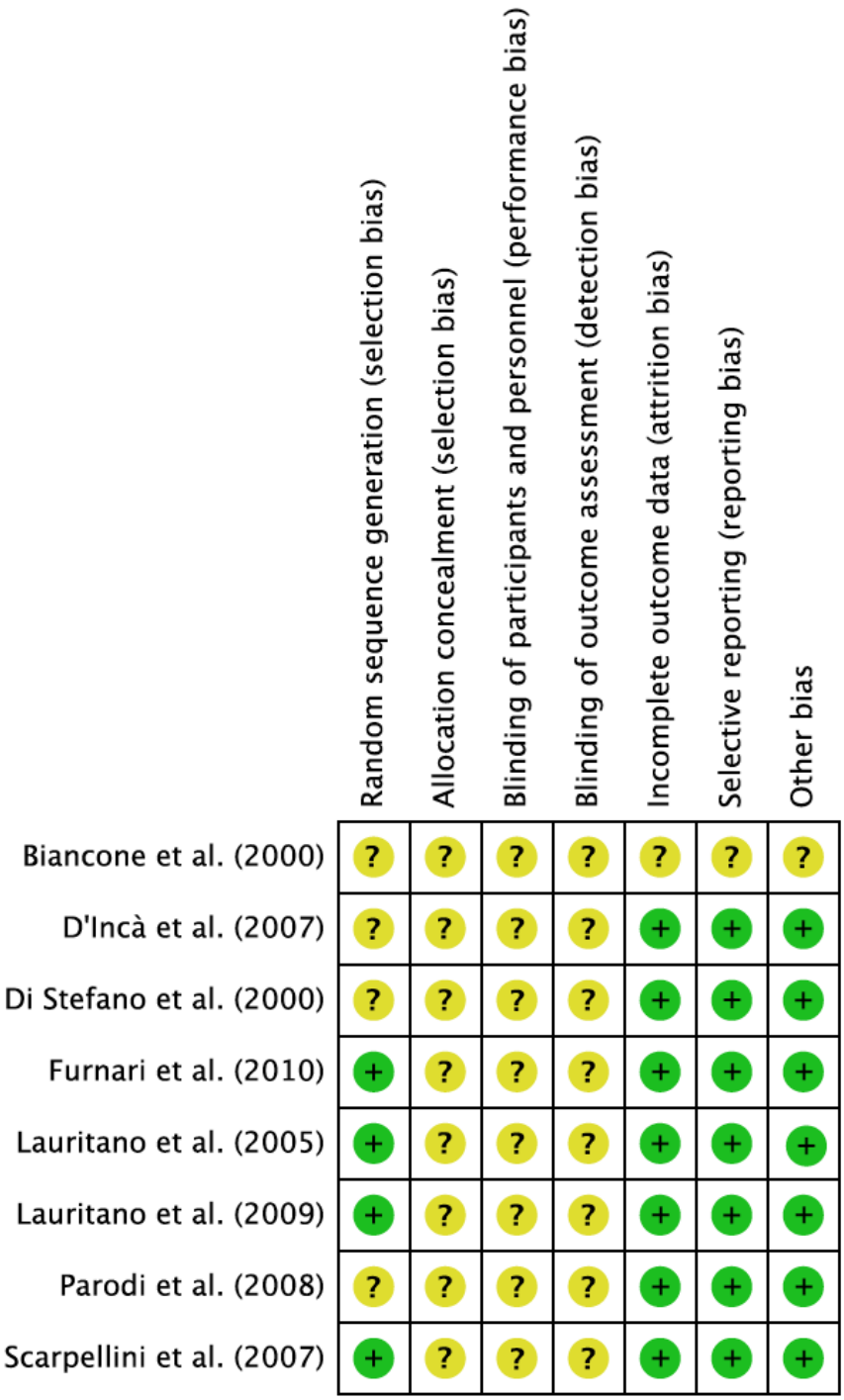
Supporting Information Table A. Characteristics of the studies included in the systematic review and meta-analysis (continued).

Authors	Type of publication and study	Country	Clinical Setting	Prior antibiotic use allowed	Test to diagnose SIBO	Criteria used to diagnose SIBO	Patients in the rifaximin arm	Dosage of rifaximin	Duration of therapy	Time of follow-up
Peralta et al. (2009)[50]	Full Paper Cohort Study	Italy	GI	No patients under antibiotic tx	LHBT	An early increase of H_2 concentration in the expired air higher than 20 ppm over basal values within 90 min of the oral administration of lactulose, followed by a second distinct peak after additional 15 min or more	54	1200 mg/die	7 days	3 weeks after EOT
Furnari et al. (2010)[51]	Full Paper RCT	Italy	GI	None within prior 10 days	GHBT	A single peak of H_2 excretion higher than 12 ppm was the cut-off value for test positivity	77	1200 mg/die	10 days	4 weeks after EOT
Lauritano et al. (2010)[52]	Full Paper Cohort Study	Italy	GI	nr	GHBT	Increase over baseline H_2 levels > 12 ppm	11	1200 mg/die	7 days	1 month after EOT
Lombardo et al. (2010)[53]	Full Paper Cohort Study	Italy	GI	None within prior 6 months	GHBT	Increase over the baseline H_2 level was >10 ppm	149	1200 mg/die	14 days	2 months after EOT
Cerda et al. (2012)[54]	Abstract Cohort Study	Mexico	GI	nr	GHBT	Increase over the baseline level H_2 was >10 ppm	50	1200 mg/die	10 days	EOT
Meyrat et al. (2012)[55]	Full Paper Cohort Study	Switzerland	GI	None within prior 4 weeks	LHBT	An increase in breath- H_2 concentration of at least 12 ppm above basal level was observed within 60 min of ingesting lactulose on the condition that this early rise in H_2 concentration preceded the second prolonged rise in H_2 concentration by at least 15 min	64	800 mg/die	14 days	2 weeks after EOT
Fasano et al. (2013)[56]	Full Paper Cohort Study	Italy	Extra GI (Parkinson's disease)	None within prior 1 month	LHBT & GHBT	GHBT: increase over the baseline of hydrogen levels > 12 ppm LHBT: Presence of an early increase (> 10 ppm above the baseline level within 30-60 min) in H_2 after lactulose ingestion in two consecutive samples, or an increase in H_2 value (> 20 ppm above the baseline level)	18	1200 mg/die	7 days	1 month after EOT
Boltin et al. (2014)[57]	Full Paper Cohort Study	Israel	GI	None within prior 6 months	LHBT	The test was considered positive for SIBO when an increase over the baseline level was >10 ppm	22	1200 mg/die	10 days	2 weeks after EOT
Chedid et al. (2014)[58]	Full Paper Cohort Study	USA	GI	None within prior 3 months	LHBT	A baseline breath concentration of >10 ppm for hydrogen or >7 ppm for methane only if patients were compliant with their preparation or an increase within 90 minutes (small intestine) that was followed by a larger peak (colonic), indicative of a positive study (with a decrease of at least 5 ppm following the first peak)	67	1200 mg/die	28 days	EOT
Moraru et al. (2014)[59]	Full Paper Cohort Study	Romania	GI	None within prior 4 weeks	GHBT	A clear H_2 peak, exceeding 20 ppm before the 120 minutes have passed	112	1200 mg/die	7 days	1 week after EOT
Gravina et al. (2015)[60]	Full Paper Cohort Study	Italy	Extra GI (Rosacea)	None within prior 2 months	GHBT	Increasing over the baseline of H_2 levels, was more than 12 ppm in a least two readings	16	1200 mg/die	10 days	1 & 2 month after EOT

nr, not reported; RCT, randomized controlled trial; GI, gastrointestinal; LHBT, lactulose hydrogen breath test; GHBT, glucose hydrogen breath test; min, minutes; hrs, hours; ppm, part per million; EOT, end of treatment; HGG, hydrolysed guar gum.

Supporting Information

Table B. Risk bias assessment of RCTs included into systematic review and meta-analysis**.**



Supporting Information

Table C. IHE's quality appraisal checklist for cohort studies [20].

	Studies				
	Corazza et al. (1988) [29]	Cuoco et al. (2002)[32]	Tursi et al. (2003)[33]	Tursi et al. (2005)[35]	Cazzato et al. (2006)[36]
Criterions					
Study objective					
1. Was the hypothesis/aim/objective of the study clearly stated?	Y	Y	Y	Y	Y
Study design					
2. Was the study conducted prospectively?	U	U	U	Y	Y
3. Were the cases collected in more than one center?	N	N	N	N	N
4. Were patients recruited consecutively?	U	U	Y	Y	Y
Study population					
5. Were the characteristics of the patients included in the study described?	Y	Y	Y	Y	Y
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	P	P	Y	Y	P
7. Did patients enter the study at a similar point in the disease?	U	U	Y	Y	U
Intervention and cointervention					
8. Was the intervention of interest clearly described?	Y	Y	Y	Y	Y
9. Were additional interventions (cointerventions) clearly described?	N	Y	N	Y	Y
Outcome measures					
10. Were relevant outcome measures established a priori?	Y	Y	Y	Y	Y
11. Were outcome assessors blinded to the intervention that patients received?	N	N	N	N	N
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Y	Y	Y	Y	Y
13. Were the relevant outcome measures made before and after the intervention?	Y	Y	Y	Y	Y
Statistical analysis					
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Y	Y	Y	Y	Y
Results and conclusions					
15. Was follow-up long enough for important events and outcomes to occur?	Y	Y	Y	Y	Y
16. Were losses to follow-up reported?	Y	Y	Y	Y	Y
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Y	Y	Y	Y	Y
18. Were the adverse events reported?	N	Y	N	N	N
19. Were the conclusions of the study supported by the results?	Y	Y	Y	Y	Y
Competing interests and sources of support					
20. Were both competing interests and sources of support for the study reported?	N	N	N	N	N

IHE, Institute of Health Economics; Y, Yes; N, No; P, Partial; U, Unclear.

Supporting Information

Table C. IHE's quality appraisal checklist for cohort studies [20].

	Studies				
	Cuoco et al. (2006)[37]	Esposito et al. (2007)[39]	Lauritano et al. (2007)[40]	Majewski et al. (2007)[41]	Majewski et al. (2007)[42]
Criterions					
Study objective					
1. Was the hypothesis/aim/objective of the study clearly stated?	Y	Y	Y	Y	Y
Study design					
2. Was the study conducted prospectively?	N	Y	Y	U	Y
3. Were the cases collected in more than one center?	N	N	N	N	N
4. Were patients recruited consecutively?	U	Y	Y	U	Y
Study population					
5. Were the characteristics of the patients included in the study described?	Y	Y	Y	Y	P
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Y	Y	Y	Y	Y
7. Did patients enter the study at a similar point in the disease?	U	U	N	U	U
Intervention and cointervention					
8. Was the intervention of interest clearly described?	Y	Y	Y	Y	Y
9. Were additional interventions (cointerventions) clearly described?	Y	N	Y	N	N
Outcome measures					
10. Were relevant outcome measures established a priori?	Y	Y	Y	Y	Y
11. Were outcome assessors blinded to the intervention that patients received?	N	N	N	N	N
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Y	Y	Y	Y	Y
13. Were the relevant outcome measures made before and after the intervention?	Y	Y	Y	Y	Y
Statistical analysis					
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Y	Y	Y	Y	Y
Results and conclusions					
15. Was follow-up long enough for important events and outcomes to occur?	Y	Y	Y	Y	Y
16. Were losses to follow-up reported?	Y	Y	Y	N	Y
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Y	Y	Y	Y	Y
18. Were the adverse events reported?	N	Y	Y	Y	Y
19. Were the conclusions of the study supported by the results?	Y	Y	Y	Y	Y
Competing interests and sources of support					
20. Were both competing interests and sources of support for the study reported?	N	N	Y	N	N

IHE, Institute of Health Economics; Y, Yes; N, No; P, Partial; U, Unclear.

Supporting Information

Table C. IHE's quality appraisal checklist for cohort studies [20].

	Studies				
	Resmini et al. (2007)[43]	Yang et al. (2008)[45]	Parodi et al. (2008)[46]	Parodi et al. (2009)[49]	Peralta et al. (2009)[50]
Criterions					
Study objective					
1. Was the hypothesis/aim/objective of the study clearly stated?	Y	Y	Y	Y	Y
Study design					
2. Was the study conducted prospectively?	Y	N	Y	Y	Y
3. Were the cases collected in more than one center?	N	N	N	N	N
4. Were patients recruited consecutively?	U	Y	Y	Y	U
Study population					
5. Were the characteristics of the patients included in the study described?	Y	N	Y	Y	Y
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Y	Y	Y	Y	Y
7. Did patients enter the study at a similar point in the disease?	N	U	N	U	U
Intervention and cointervention					
8. Was the intervention of interest clearly described?	Y	Y	Y	Y	Y
9. Were additional interventions (cointerventions) clearly described?	Y	N	Y	N	N
Outcome measures					
10. Were relevant outcome measures established a priori?	Y	Y	Y	Y	Y
11. Were outcome assessors blinded to the intervention that patients received?	N	N	N	N	N
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Y	Y	Y	Y	Y
13. Were the relevant outcome measures made before and after the intervention?	Y	Y	Y	Y	Y
Statistical analysis					
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Y	Y	Y	Y	Y
Results and conclusions					
15. Was follow-up long enough for important events and outcomes to occur?	Y	Y	Y	Y	Y
16. Were losses to follow-up reported?	Y	U	Y	Y	Y
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Y	Y	Y	Y	Y
18. Were the adverse events reported?	Y	N	Y	N	Y
19. Were the conclusions of the study supported by the results?	Y	Y	Y	Y	Y
Competing interests and sources of support					
20. Were both competing interests and sources of support for the study reported?	Y	Y	Y	Y	N

IHE, Institute of Health Economics; Y, Yes; N, No; P, Partial; U, Unclear.

Supporting Information

Table C. IHE's quality appraisal checklist for cohort studies [20].

	Studies				
	Lauritano et al. (2010)[52]	Lombardo et al. (2010)[53]	Cerda et al. (2012)[54]	Meyrat et al. (2012)[55]	Fasano et al. (2013)[56]
Criterions					
Study objective					
1. Was the hypothesis/aim/objective of the study clearly stated?	Y	Y	Y	Y	Y
Study design					
2. Was the study conducted prospectively?	U	Y	U	Y	Y
3. Were the cases collected in more than one center?	N	N	U	N	U
4. Were patients recruited consecutively?	U	Y	U	Y	Y
Study population					
5. Were the characteristics of the patients included in the study described?	P	Y	P	Y	Y
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	P	Y	P	Y	Y
7. Did patients enter the study at a similar point in the disease?	U	U	U	U	U
Intervention and cointervention					
8. Was the intervention of interest clearly described?	Y	Y	Y	Y	Y
9. Were additional interventions (cointerventions) clearly described?	N	N	N	N	Y
Outcome measures					
10. Were relevant outcome measures established a priori?	Y	Y	Y	Y	Y
11. Were outcome assessors blinded to the intervention that patients received?	N	N	N	N	N
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Y	Y	Y	Y	Y
13. Were the relevant outcome measures made before and after the intervention?	Y	Y	Y	Y	Y
Statistical analysis					
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Y	Y	Y	Y	Y
Results and conclusions					
15. Was follow-up long enough for important events and outcomes to occur?	Y	Y	Y	Y	Y
16. Were losses to follow-up reported?	U	Y	Y	U	Y
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Y	Y	Y	Y	Y
18. Were the adverse events reported?	N	Y	N	Y	Y
19. Were the conclusions of the study supported by the results?	Y	Y	Y	Y	Y
Competing interests and sources of support					
20. Were both competing interests and sources of support for the study reported?	Y	Y	Y	Y	Y

IHE, Institute of Health Economics; Y, Yes; N, No; P, Partial; U, Unclear.

Supporting Information

Table C. IHE's quality appraisal checklist for cohort studies [20].

	Studies			
	Boltin et al. (2014)[57]	Chedid et al. (2014)[58]	Moraru et al. (2014)[59]	Gravina et al. (2015)[60]
Criterions				
Study objective				
1. Was the hypothesis/aim/objective of the study clearly stated?	Y	Y	Y	Y
Study design				
2. Was the study conducted prospectively?	Y	N	Y	Y
3. Were the cases collected in more than one center?	N	N	Y	N
4. Were patients recruited consecutively?	Y	U	Y	Y
Study population				
5. Were the characteristics of the patients included in the study described?	Y	P	Y	Y
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Y	Y	Y	Y
7. Did patients enter the study at a similar point in the disease?	U	U	U	N
Intervention and cointervention				
8. Was the intervention of interest clearly described?	Y	Y	Y	Y
9. Were additional interventions (cointerventions) clearly described?	N	N	N	N
Outcome measures				
10. Were relevant outcome measures established a priori?	Y	Y	Y	Y
11. Were outcome assessors blinded to the intervention that patients received?	N	N	N	N
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Y	Y	Y	Y
13. Were the relevant outcome measures made before and after the intervention?	Y	Y	Y	Y
Statistical analysis				
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Y	Y	Y	Y
Results and conclusions				
15. Was follow-up long enough for important events and outcomes to occur?	Y	Y	Y	Y
16. Were losses to follow-up reported?	Y	Y	Y	Y
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Y	Y	Y	Y
18. Were the adverse events reported?	Y	Y	N	N
19. Were the conclusions of the study supported by the results?	Y	Y	Y	Y
Competing interests and sources of support				
20. Were both competing interests and sources of support for the study reported?	Y	Y	Y	Y

IHE, Institute of Health Economics; Y, Yes; N, No; P, Partial; U, Unclear.

Supporting Information

Table D. Meta-regression of eradication rate according to ITT analyses (studies included: 24*).

Covariate	Number of Studies	Coefficient	95% CI	p value
RCT	6	ref		
No RCT	18	*0.989*	*0.07 to 1.902*	*0.035*
Dosage of rifaximin	24	*0.002*	*0.0003 to 0.003*	*0.020*
Duration of treatment	24	-0.020	-0.084 to 0.043	0.512
GHBT	14	ref		
LHBT	10	-0.717	-1.535 to 0.099	0.081
Sample Size ≥ 50 patients	7	ref		
Sample Size < 50 patients	17	-0.093	-0.843 to 0.657	0.797
Studies performed in Italy	19	ref		
Studies not performed in Italy	5	-0.610	-1.808 to 0.587	0.299
Rifaximin as only treatment	21	ref		
Concomitant use of treatments affecting gut microbiota	3	*2.031*	*0.662 to 3.400*	*0.005*
Follow-up within 1 week after EOT	9	ref		
Follow-up between 2 and 4 weeks after EOT	13	-0.234	-1.064 to 0.596	0.562
Follow-up > 4 weeks after EOT	2	0.636	-0.856 to 2.130	0.383

*, being only two the studies where both breath tests were used [47, 56], these were not included in the regression analysis.
ref, reference; EOT, end of treatment.

Supporting Information

Table E. Sub-group analysis of eradication rate according to ITT analysis (studies included: 24*).

Variable	Number of Studies	Eradication Rate	95% CI
Randomization			
RCTs	6	65.8%	48.0 to 80.5
Not RCTs	18	71.4%	59.7 to 81.9
Daily dose of rifaximin and duration of treatment°			
600 mg/die for 7 days	1	16.7%	7.3 to 33.6
800 mg/die for 5 days	1	66.7%	30.0 to 90.3
800 mg/die for 7 days	2	68.5%	1.5 to 93.7
800 mg/die for 10 days	1	100%	93.2 to 100
800 mg/die for 28 days	1	50.0%	29.9 to 70.1
1200 mg/die for 5 days	1	66.7%	30.0 to 90.3
1200 mg/die for 7 days	10	62.9%	57.2 to 68.5
1200 mg/die for 10 days	9	72.9%	62.3 to 82.4
1200 mg/die for 14 days	1	87.9%	81.7 to 92.2
1200 mg/die for 28 days	1	34.3%	24.1 to 46.3
1600 mg/die for 7 days	1	80.0%	65.2 to 89.5
Type of H_2BT used			
GBT	14	70.8%	60.3 to 80.3
LHBT	10	68.8%	47.4 to 86.9
Number of patients enrolled in the study			
≥ 50 patients	7	73.4%	53.8 to 89.3
< 50 patients	17	67.7%	57.7 to 77.0
Country where the study was performed			
Italy	19	73.8%	63.0 to 83.3
Other Countries	5	55.8%	34.5 to 76.0
Concomitant use of treatments affecting gut microbiota			
Yes	3	95.1%	65.9 to 74.6
No	21	65.6%	56.1 to 74.6
Length of Follow-up			
Within 1 week	9	72.0%	51.1 to 89.1
Between 2 and 4 weeks	13	65.6%	55.1 to 75.3
> 4 weeks	2	88.2%	82.5 to 93.0

*, being only two the studies where both breath tests were used [47, 56], these were not included in the sub-group analysis.

°: number of studies is > 24 as several trials had ≥ 2 arms evaluating different doses and/or treatment durations.

Supporting Information

Table F. Synopsys of evaluation of symptoms in patients with SIBO after therapy in the studies included in the meta-analysis.

Authors	Clinical Setting	Diagnosis of IBS	Symptoms evaluated according to the Author definition	Symptom Response according to the Author definition
Corazza et al. (1988)[29]	GI	nr	Diarrhoea, bloating, weight loss, abdominal pain	Improvement of symptoms in 87.5% (95% CI: 52.9 to 97.8) of the eradicated patients Improvement of symptoms in 75.0% (95% CI: 30.1 to 95.4) of not eradicated patients
Biancone et al. (2000)[30]	GI (Patients with Crohn's Disease)	nr	CDAI	No change in CDAI
Di Stefano et al. (2000)[31]	GI	nr	GSS considering: abdominal pain, bloating, diarrhoea, borborygmi, lassitude, and anorexia evaluated and graded using a semi-quantitative scale (absent, mild, moderate, severe)	Only patients in the rifaximin group showed a significant reduction in symptom score for diarrhoea, borborygmi, and lassitude after therapy. In addition, the reduction in mean cumulative score of the patients treated with rifaximin was significantly higher ($p< 0.05$) than in those treated with chlortetracycline ($p=0.2$)
Cuoco et al. (2002)[32]	Extra GI (DM type I or II)	nr	GSS considering: bloating, diarrhoea, alternate alvine habits, using a four-point scale (absent, mild, moderate, severe)	Absence of symptoms in 72.2% (95% CI: 49.1 to 87.5) of the eradicated patients No change of symptoms in 66.7% (95% CI: 20.8 to 93.9) of not eradicated patients
Tursi et al. (2003)[33]	GI (Celiac Patients with persistence of gastrointestinal symptoms after gluten withdrawal)	nr	GSS considering: diarrhoea, slow gastric emptying, abdominal discomfort /abdominal pain with meteorism; symptoms were graded using the following scale: absence, slight symptoms, mild symptoms, severe symptoms	Absence of symptoms in 100% (95% CI: 72.2 to 100) of the eradicated patients
Lauritano et al. (2005)[34]	GI	nr	nr	nr
Tursi et al. (2005)[35]	GI (acute uncomplicated diverticulitis)	nr	Constipation, diarrhoea, abdominal pain, rectal bleeding, and mucus passage with the stools. Intensity of the symptoms quantified with a quantitative scale (0-10 according to increasing worsening of symptoms)	ne
Cazzato et al. (2006)[36]	GI (NERD)	nr	Heartburn relief	Absence of heartburn in 64.3% (95% CI: 38.8 to 83.7) of eradicated patients Absence of heartburn in 16.7% (95% CI: 31.0 to 56.4) of not eradicated patients
Cuoco et al. (2006)[37]	GI	Yes (diagnostic criteria not reported)	Abdominal discomfort, abdominal pain, meteorism, abdominal distension, irregular bowel movement or diarrhoea, evaluated using a four-level score scale (absence, mild to moderate, severe, very severe)	Statistically significant decrease of presence of symptoms ($p<0.05$) observed after treatment

GI, gastrointestinal; nr, not reported; IBS, irritable bowel syndrome; CDAI, Crohn's Disease Activity Index; GSS, global symptom score; NERD, non-erosive reflux disease; VAS, visual analogue scale; ne, not possible to extract data. °, not possible to calculate 95% CI.

Supporting Information

Table F. Synopsys of evaluation of symptoms in patients with SIBO after therapy in the studies included in the meta-analysis (continued).

Authors	Clinical Setting	Diagnosis of IBS	Symptoms evaluated according to the Author definition	Symptom Response according to the Author definition
D'Incà et al. (2007)[38]	GI (UDD)	nr	Upper or lower abdominal pain, bloating, tenesmus, straining, stool frequency and characteristics, tenderness, dyspepsia recorded and graded according to the four-level score scale (no symptoms, mild, moderate, and severe); a GSS was calculated; a VAS was used to evaluate the overall treatment efficacy	GSS significantly reduced in the rifaximin group, while it remained practically unchanged after placebo administration ($p<0.005$); a similar result was observed when symptoms were evaluated according to the VAS
Esposito et al. (2007)[39]	GI	Yes (diagnostic criteria not reported)	Chronic diarrhoea, upper abdominal pain, lower abdominal pain, tenesmus, pain to palpation, abdominal bloating, flatulence, reduced body weight, nausea, steatorrhea, megaloblastic anaemia, stipsis, fever, others; GSS by means of VAS	Significantly reduction of symptom score from baseline in eradicated patients ($p = 0.004$)
Lauritano et al. (2007)[40]	Extra GI (Hypothyroidism)	nr	Abdominal discomfort/pain, bloating, flatulence, constipation, and diarrhoea assessed by a four-point scale (absence, mild, moderate, and severe symptoms)	A significant improvement in abdominal discomfort ($p<0.01$), bloating ($p<0.01$), and flatulence ($p<0.01$) was observed in the eradicated patients
Majewski et al. (2007)[41]	GI	Yes (Rome II Criteria)	Symptom assessment, and an overall score obtained by analysing frequency of stools, abdominal pain, bloating and gas before and after therapy	Improvement in overall symptom score was observed in 87.5% (95% CI: 52.9 to 97.8)
Majewski et al. (2007)[42]	GI	Yes[§] (diagnostic criteria not reported)	Bloating, gas, abdominal pain, and bowel movements evaluated using a 4-point scale (non-disturbing or absent, mild, moderate; and severe)	After therapy, among patients with diarrhoea, 85.7% (95% CI: 60.1 to 96) of patients stated that they had improvement in their symptom score > 50%; among patients with either gas and bloating or constipation, 33% (95% CI: 9.7 to 70) had improvement between 50% and 75%, and 50% (95% CI: 18.8 to 81.2) an improvement between 25% and 50%. 16.7% (95% CI: 3.0 to 56.4) had no response to treatment
Resmini et al. (2007)[43]	Extra GI (Acromegaly)	nr	Chronic diarrhoea, abdominal pain either in the upper or lower part, meteorism, flatulence, nausea, tenesmus, weight loss, constipation, and fever	Disappearance of symptoms in 60%° of the treated patients
Scarpellini et al. (2007)[44]	GI	Yes[§] (Rome II Criteria)	nr	nr

GI, gastrointestinal; nr, not reported; IBS, irritable bowel syndrome; GSS, global symptom score; UDD, uncomplicated diverticular disease; VAS, visual analogue scale; ne, not possible to extract data.
[§], part of the patients enrolled in the study presented IBS.

Supporting Information

Table F. Synopsys of evaluation of symptoms in patients with SIBO after therapy in the studies included in the meta-analysis (continued).

Authors	Clinical Setting	Diagnosis of IBS	Symptoms evaluated according to the Author definition	Symptom Response according to the Author definition
Yang et al. (2008)[45]	GI	Yes (Rome I Criteria)	Percent improvement in IBS (number of participants with improvement of greater than 50%)	69% (95% CI: 58.5 to 77.9) of patients treated with rifaximin had a clinical response
Parodi et al. (2008)[46]	Extra GI (Scleroderma)	nr	Diarrhoea, upper and lower abdominal pain/discomfort, bloating, abdominal tenderness, nausea, emesis, dysuria, tenesmus, fever, general illness each carrying a score from 0 (no symptoms) to 3 (severe); a GSS was calculated	Eradicated patients had a significant decrease in the median GSS score ($p<0.05$)
Parodi et al. (2008)[47]	Extra GI (Rosacea)	nr	Diarrhoea, upper and lower abdominal pain/discomfort, bloating, abdominal tenderness, nausea, emesis, dysuria, tenesmus, fever, general illness assessed using a score from 0 (no symptoms) to 3 (severe); a GSS was calculated	Eradicated patients had a significant decrease in the median GSS score ($p=0.02$)
Lauritano et al. (2009)[48]	GI	Yes[§] (Rome II Criteria)	nr	nr
Parodi et al. (2009)[49]	GI	Yes[§] (Rome III Criteria)	Diarrhoea, upper and lower abdominal pain/discomfort, bloating, flatulence, abdominal tenderness, weight loss, nausea, constipation, and tenesmus assessed using a score from 0 (no symptoms) to 3 (severe); a GSS was calculated	The median symptom severity score significantly decreased (> 50%) in eradicated patients as compared with the not eradicated ones ($p<0.001$)

GI, gastrointestinal; nr, not reported; IBS, irritable bowel syndrome; GSS, global symptom score; VAS, visual analogue scale; ne, not possible to extract data; [§], part of the patients enrolled in the study presented IBS.

Supporting Information

Table F. Synopsys of evaluation of symptoms in patients with SIBO after therapy in the studies included in the meta-analysis (continued).

Authors	Clinical Setting	Diagnosis of IBS	Symptoms evaluated according to the Author definition	Symptom Response according to the Author definition
Peralta et al. (2009)[50]	GI	Yes (Rome II Criteria)	According to their intestinal habits, patients were divided into a constipation-variant, diarrhoea-variant or alternated alveus-variant; the severity of the alveus disturbances was scored according to a 5-point semi-quantitative scale (0 = none; 1 = minimum; 2 = mild; 3 = moderate; 4 = severe)	In eradicated patients, a statistically significant reduction of the symptomatological score was achieved (p = 0.003); on the contrary, in non-eradicated patients no change in the symptomatological score was observed (p = not significant)
Furnari et al. (2010)[51]	GI	nr	Diarrhoea, upper and lower abdominal pain / discomfort, bloating, flatulence, abdominal tenderness, weight loss, nausea, constipation and tenesmus assessed using a score from 0 (no symptoms) to 3 (severe); a GSS was calculated	Clinical improvement (> 50% GSS) was observed in 86.9% (95% CI: 67.9 to 95.5) and 91.1% (95% CI: 77.0 to 97.0) of eradicated cases in rifaximin and rifaximin-plus-partially hydrolysed guar gum group, respectively (p = 0.677); among patients who did not obtain eradication, clinical improvement was observed in 7.1% (95% CI: 1.3 to 31.5) and 16.6% (95% CI: 3 to 56.46) respectively (P = 0.521)
Lauritano et al. (2010)[52]	GI	nr	nr	nr
Lombardo et al. (2010)[53]	GI	Yes[§] (Rome III Criteria)	Pain severity, pain duration, pain frequency, bloating, and constipation/diarrhoea assessed using a 4-point scale (absence, mild, moderate, and severe)	In eradicated patients, bloating was improved or absent in 90%°, diarrhoea in 94%°, and abdominal pain in 92%° of the cases; in non-eradicated patients, bloating was improved or absent in 30%°, diarrhoea in 35%°, and abdominal pain in 20%° of the cases
Cerda et al. (2012)[54]	GI	Yes (Rome III Criteria)	ne	ne
Meyrat et al. (2012)[55]	GI	Yes (Rome III Criteria)	Bloating, diarrhoea, flatulence, abdominal pain and overall well-being. The symptom severity as well as changes in overall well-being assessed on a 11-point Likert scale, where 0 corresponded to absence of symptoms or no reduction in overall well-being and 10 corresponded to most severe symptoms or severe reduction in overall well-being	2 and 12 weeks after completion of therapy a significant reduction in all the assessed items was observed (p ≤ 0.015)
Fasano et al. (2013)[56]	Extra GI (Parkinson's disease)	ns	ne	ne

GI, gastrointestinal; nr, not reported; IBS, irritable bowel syndrome; GSS, global symptom score; VAS, visual analogue scale; ne, not possible to extract data.

[§], part of the patients enrolled in the study presented IBS.

Supporting Information

Table F. Synopsys of evaluation of symptoms in patients with SIBO after therapy in the studies included in the meta-analysis (continued).

Authors	Clinical Setting	Diagnosis of IBS	Symptoms evaluated according to the Author definition	Symptom Response according to the Author definition
Boltin et al. (2014)[57]	GI	Excluded IBS patients according to Rome III criteria	Bloating, flatulence	No patients reported any degree of resolution for either bloating or flatulence
Chedid et al. (2014)[58]	GI	Yes[§] (Rome III Criteria)	nr	nr
Moraru et al. (2014)[59]	GI	Yes[§] (Rome III Criteria)	Severity (using a Likert scale) and type of IBS symptoms	Among IBS patients treated with rifaximin 46.7% (95% CI. 37.4 to 56.2) had a complete response, 31.4% (95% CI. 23.3 to 40.8) had a partial response, and 21.9% (95% CI. 15.1 to 30.7) had no response
Gravina et al. (2015)[60]	Extra GI (Rosacea)	ns	Upper GI symptoms using SF-LDQ + bloating, flatulence, abdominal pain, diarrhoea and constipation using a questionnaire assessing frequency and severity of each symptom during the last two months	nr

GI, gastrointestinal; nr, not reported; IBS, irritable bowel syndrome; GSS, global symptom score; VAS, visual analogue scale; ne, not possible to extract data; SF-LDQ, Short-Form Leeds Dyspepsia Questionnaire.
[§], part of the patients enrolled in the study presented IBS.

Supporting Information

Table G. Meta-regression of adverse events rates*.

Covariate	Number of Studies	Coefficient	95% CI	p value
RCT	4	ref		
No RCT	13	*-1.577*	*-2.484 to -0.670*	*0.002*
Dosage of rifaximin	17	0.0005	-0.0009 to 0.0018	0.446
Duration of treatment	17	0.026	-0.059 to 0.112	0.520
Sample Size ≥ 50 patients	5	ref		
Sample Size < 50 patients	12	0.514	-0.268 to 1.296	0.180
Studies performed in Italy	12	ref		
Studies not performed in Italy	5	0.771	-0.700 to 2.243	0.279

*: concomitant use of fibre, mesalazine, pre or probiotics was not evaluated as all the studies included in the model used only rifaximin.
ref, reference.

Supporting Information

Table H. Sub-group analysis of adverse event rate*.

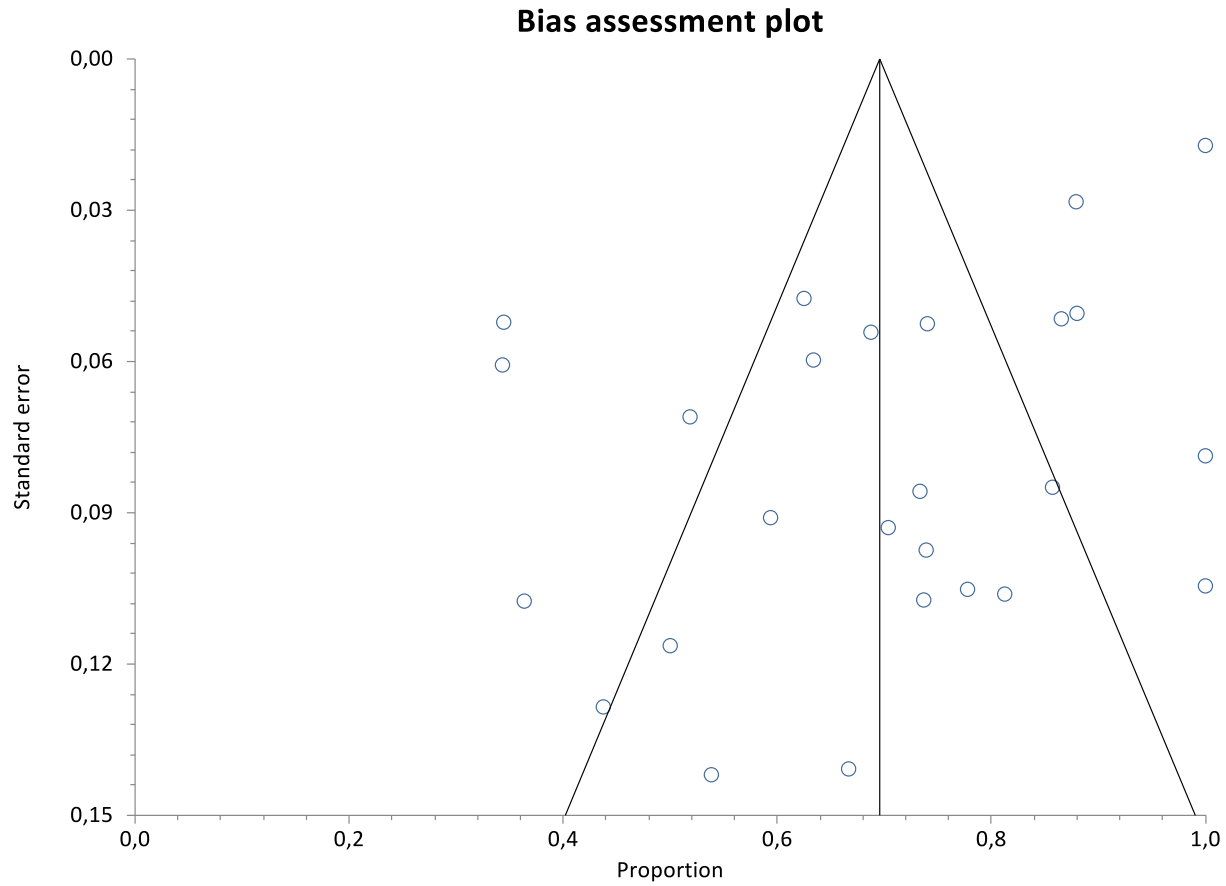
Variable	Number of Studies	Adverse Event Rate	95% CI
Randomization			
RCTs	4	13.1%	9.4 to 18.1
Not RCTs	13	4.6%	3.0 to 6.9
Daily dose of rifaximin and duration of treatment°			
600 mg/die for 7 days	1	10%	3.3 to 26.8
800 mg/die for 7 days	1	13.3%	5.1 to 30.6
800 mg/die for 14 days	1	4.7%	1.5 to 10.7
800 mg/die for 28 days	2	3.6%	0.5 to 21.7
1200 mg/die for 7 days	8	8.8%	4.8 to 15.6
1200 mg/die for 10 days	4	3.5%	1.0 to 11.4
1200 mg/die for 14 days	1	2.0%	0.7 to 6.1
1200 mg/die for 28 days	1	9.0%	4.1 to 18.5
1600 mg/die for 7 days	1	15.0%	6.9 to 29.6
Number of patients enrolled in the study			
≥ 50 patients	5	5.1%	2.7 to 9.5
< 50 patients	12	10.9%	7.7 to 15.3
Country where the study was performed			
Italy	12	8.0%	5.1 to 12.3
Other Countries	5	6.1%	3.5 to 10.3

*: concomitant use of fibre, mesalazine, pre or probiotics was not evaluated as all the studies included in the model used only rifaximin.

°: number of studies is > 17 as several trials had ≥ 2 arms evaluating different doses and/or treatment durations.

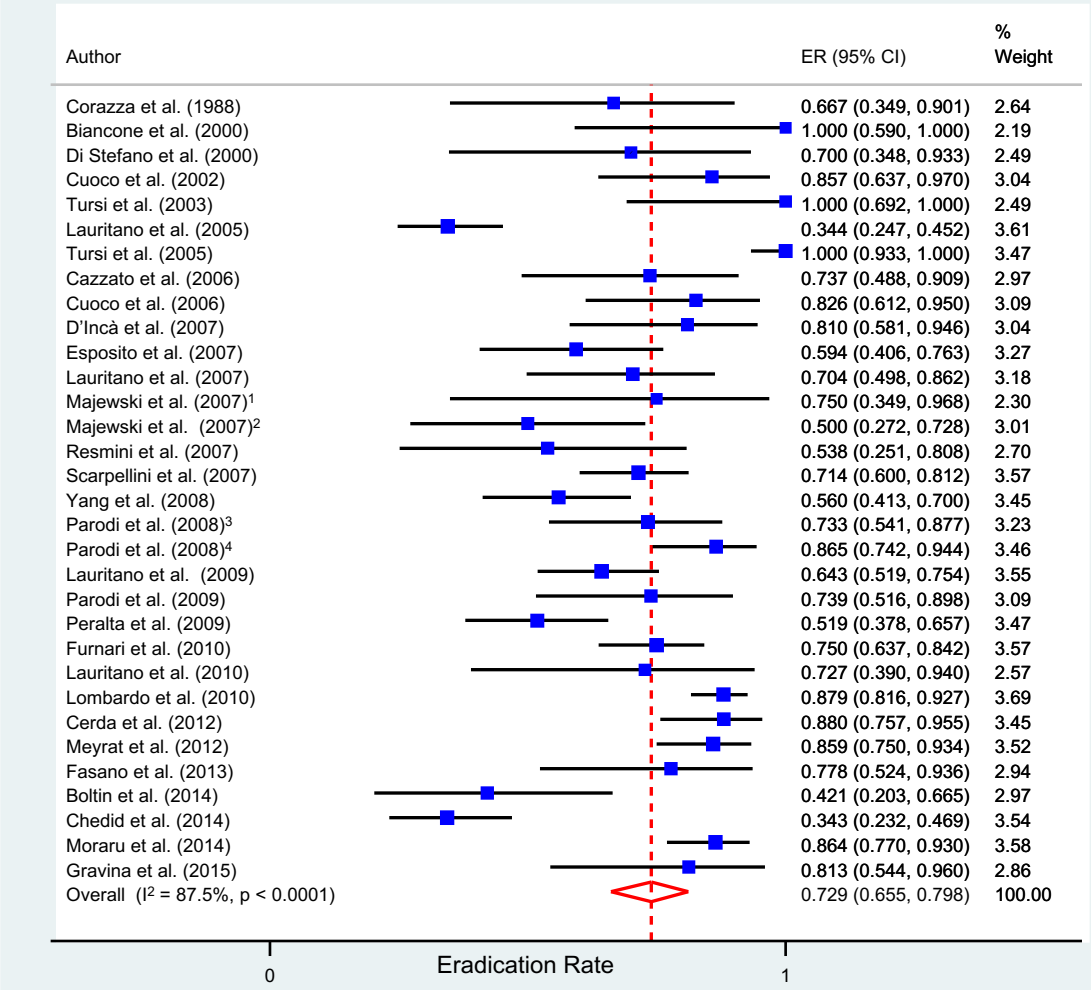
Supporting Information

Figure A. Funnel plot of SIBO eradication rate according to ITT analysis.



Supporting Information

Figure B. Forest plot of SIBO eradication rate according to PP analysis.

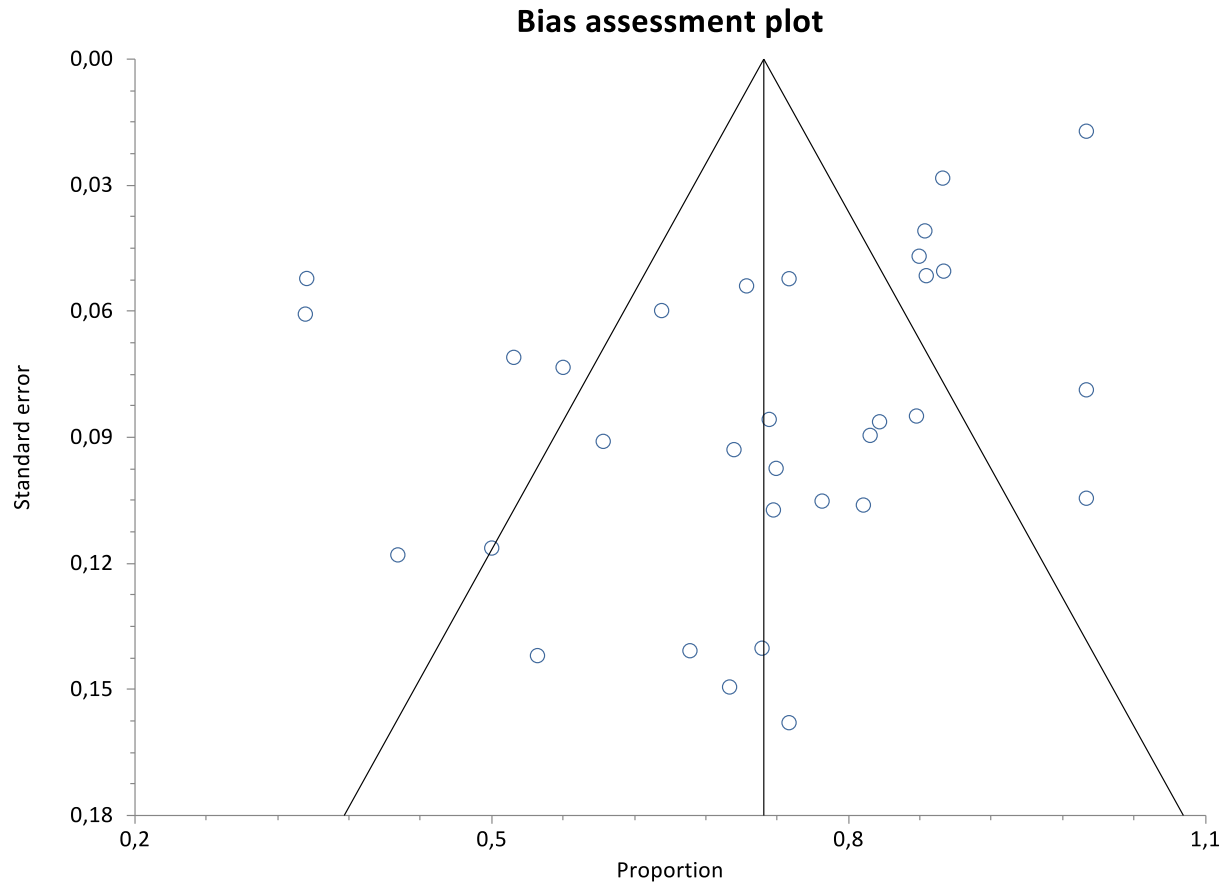


ER, eradication rate.

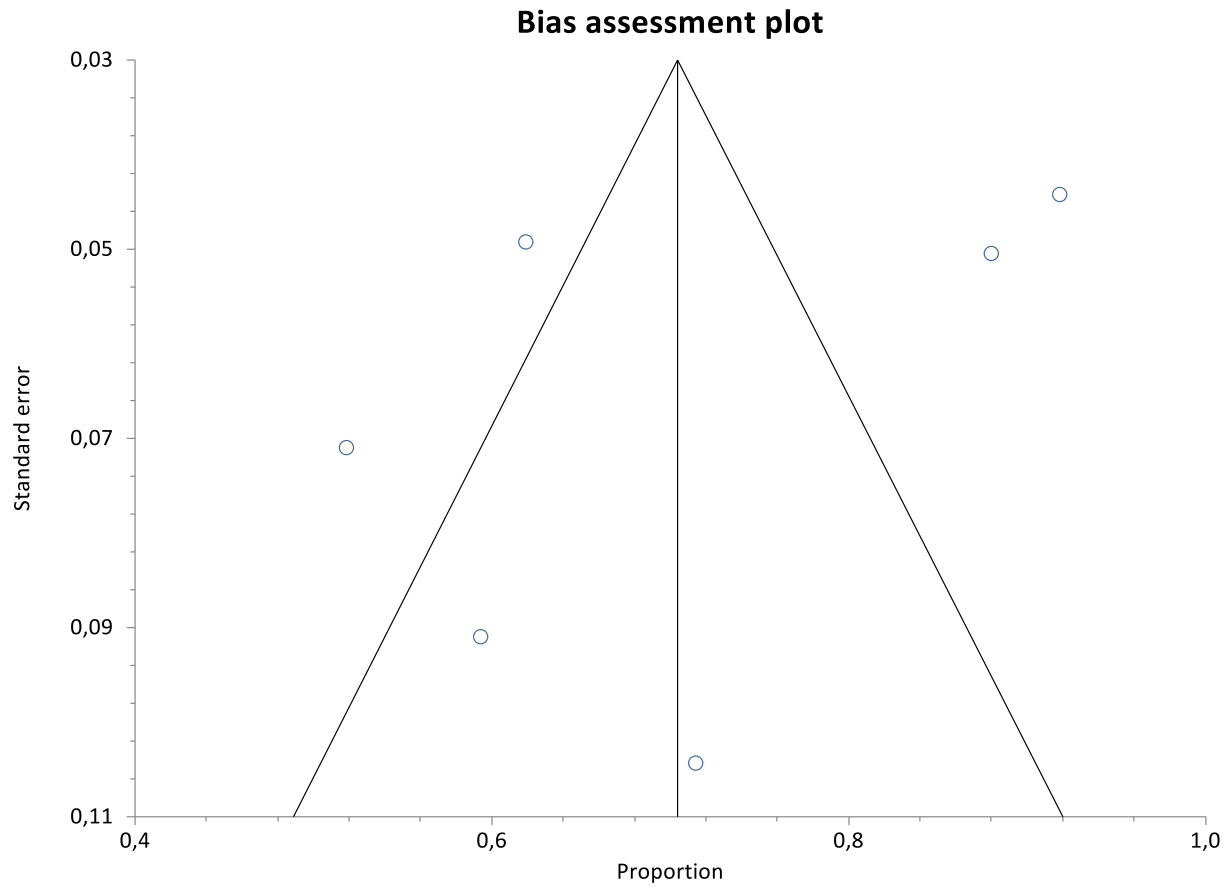
1, ref; 41; 2, ref. 42; 3 , ref; 46; 4 , ref. 47.

Supporting Information

Figure C. Funnel plot of SIBO eradication rate according to PP analysis.

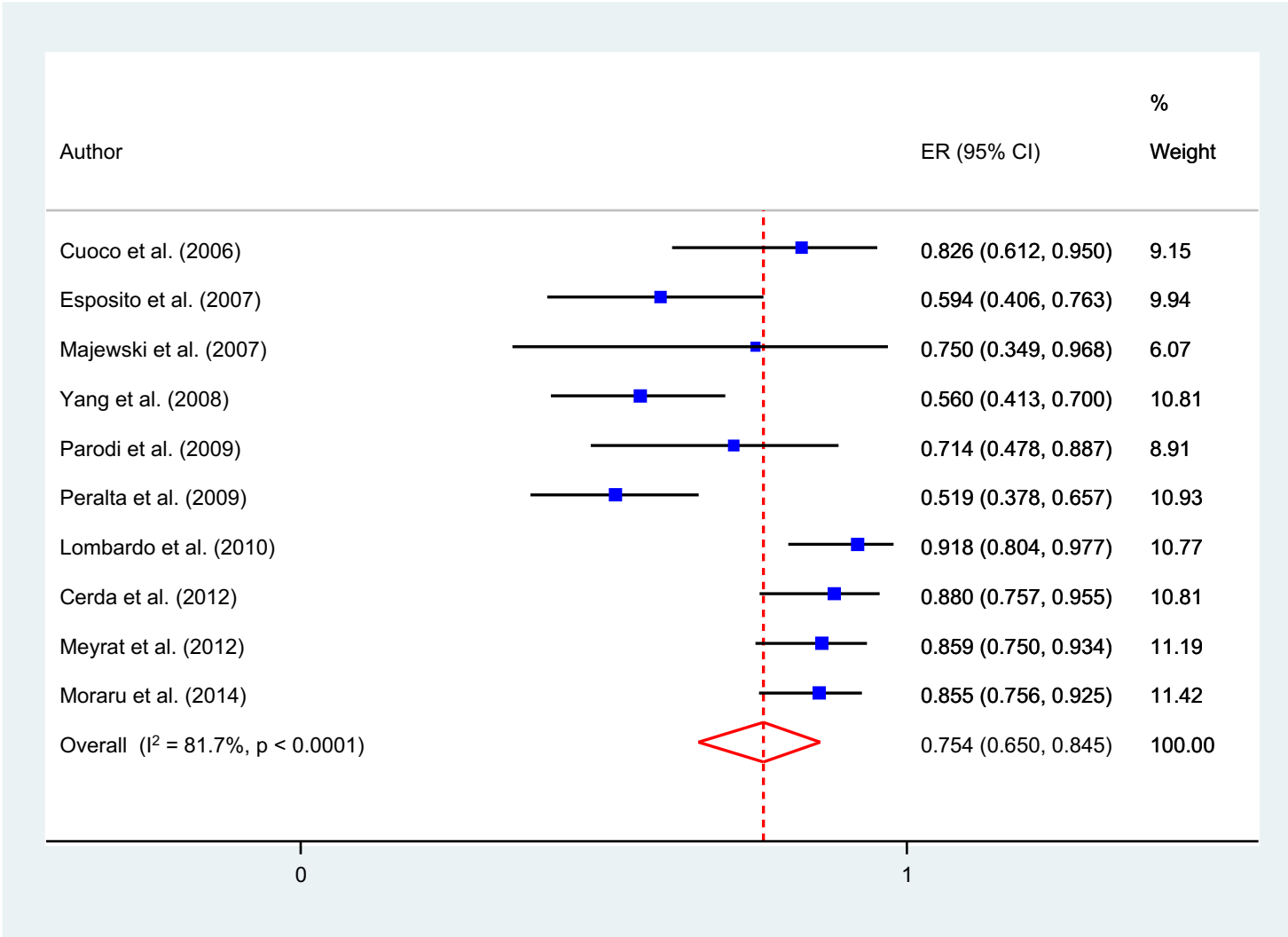


Supporting Information
Figure D. Funnel plot of SIBO eradication rate in IBS according to ITT analysis.



Supporting Information

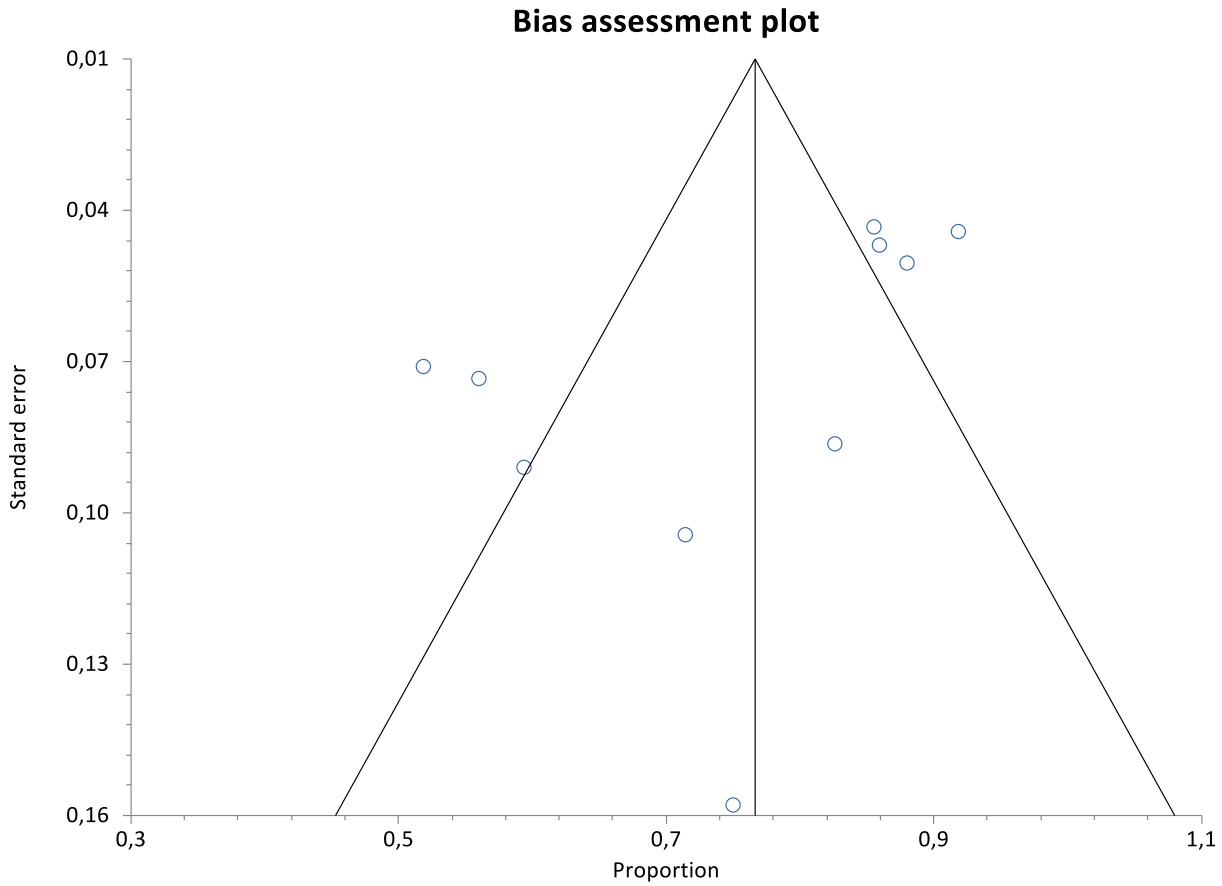
Figure E. Forest plot of SIBO eradication rate in IBS according to PP analysis.



ER, eradication rate.

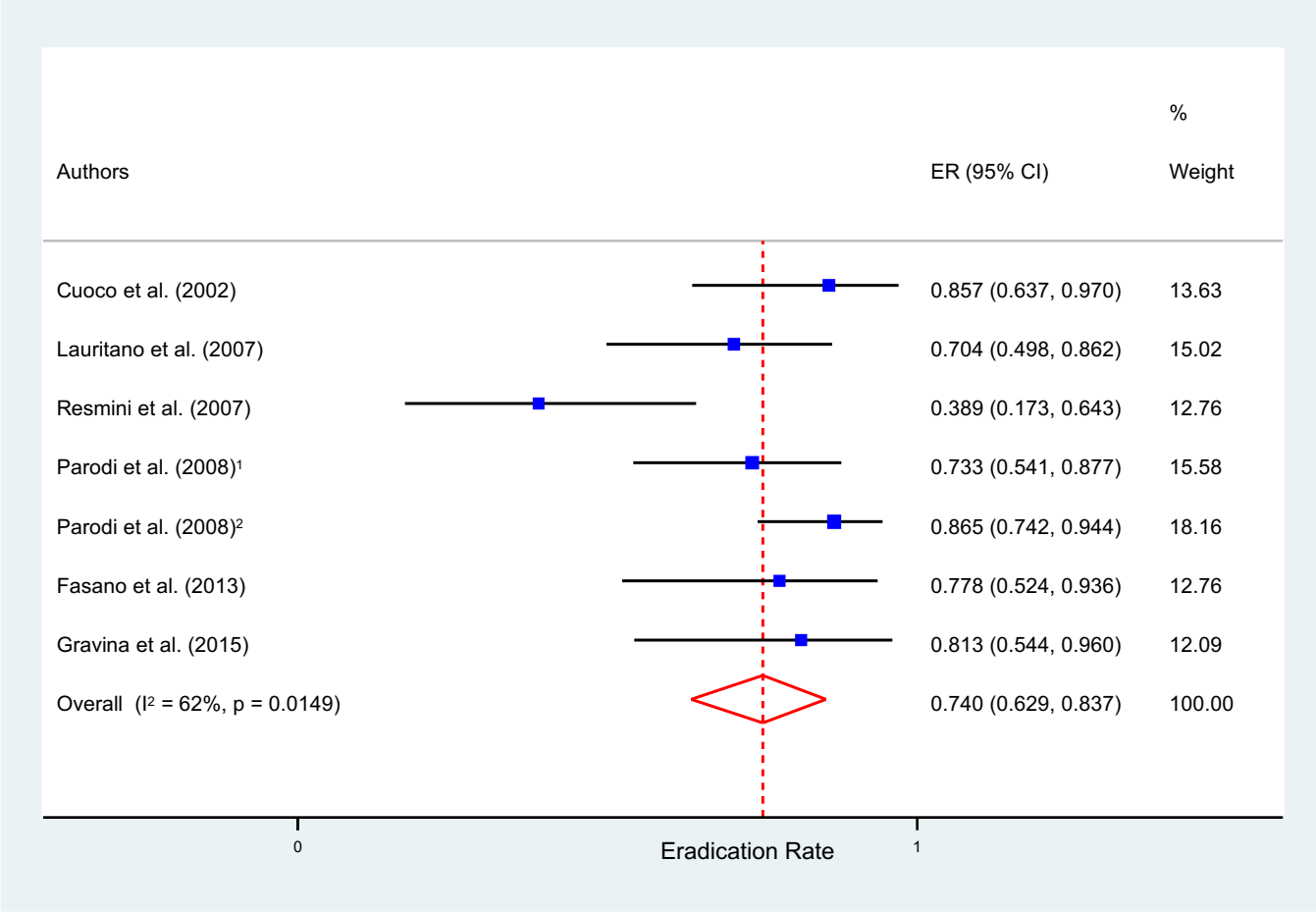
Supporting Information

Figure F. Funnel plot of SIBO eradication rate in IBS according to PP analysis.



Supporting Information

Figure G. Forest plot of SIBO eradication rate in Extra GI settings according to ITT analysis.

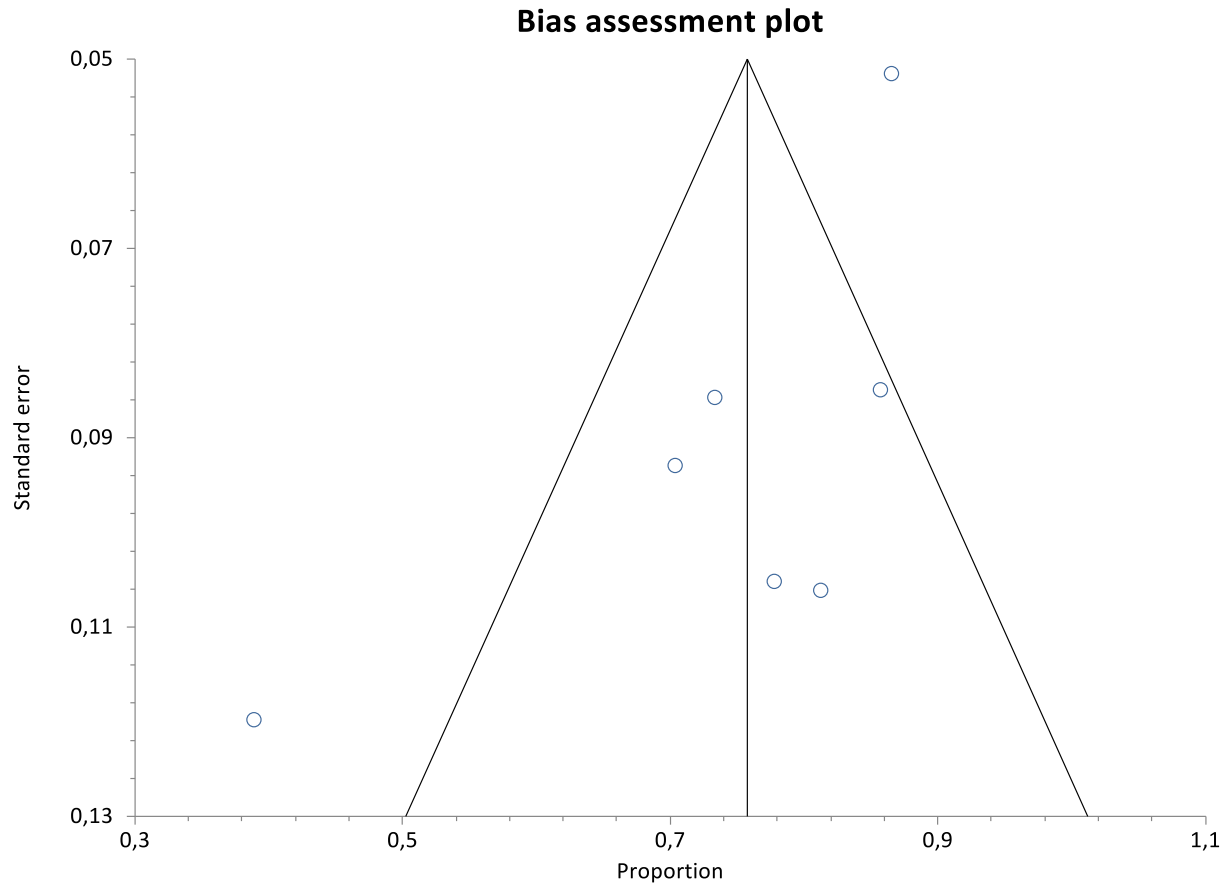


ER, eradication rate.

1, ref; 46; 2, ref. 47.

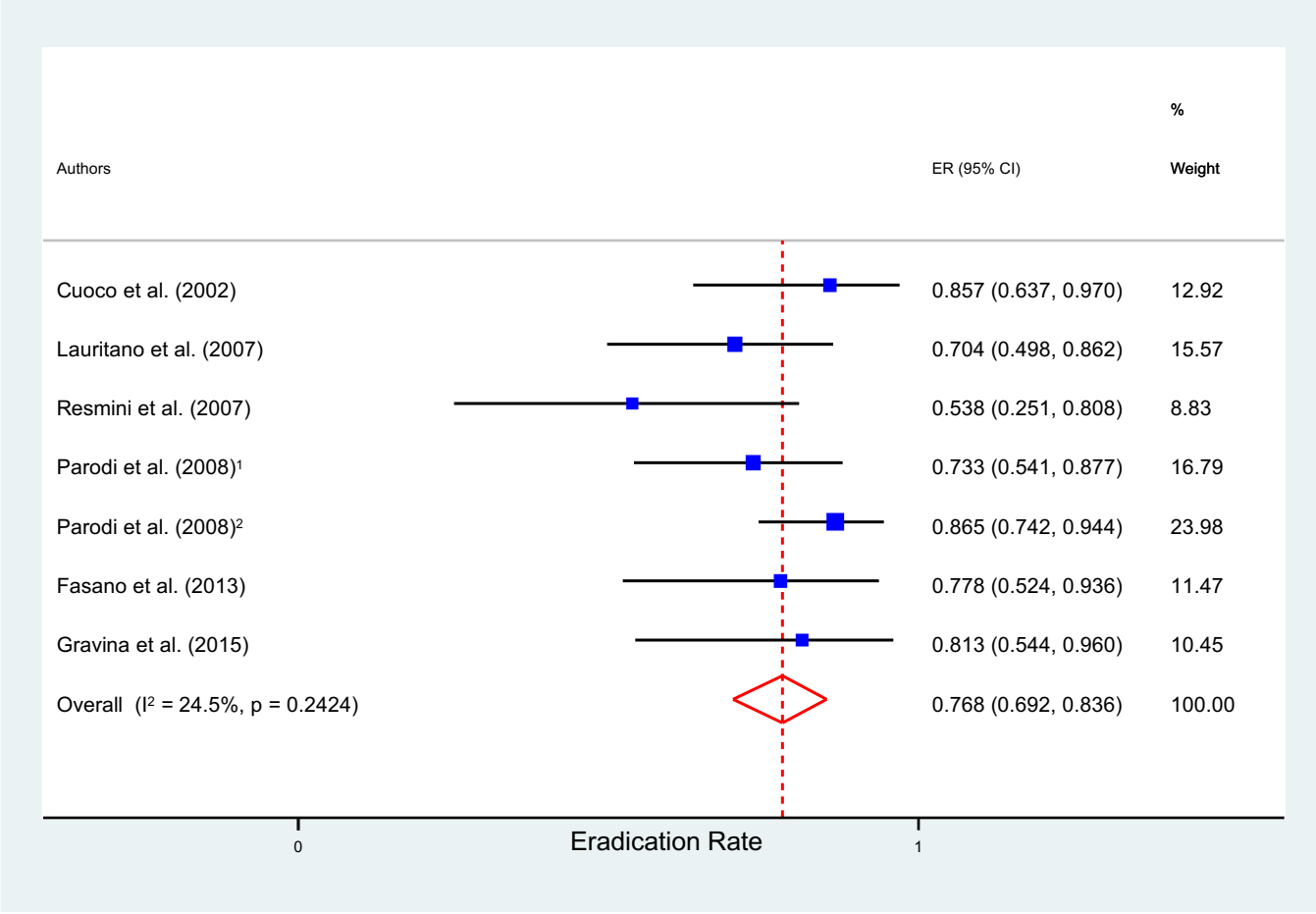
Supporting Information

Figure H. Funnel plot of SIBO eradication rate in Extra GI settings according to ITT analysis.



Supporting Information

Figure I. Forest plot of SIBO eradication rate in Extra GI settings according to PP analysis.

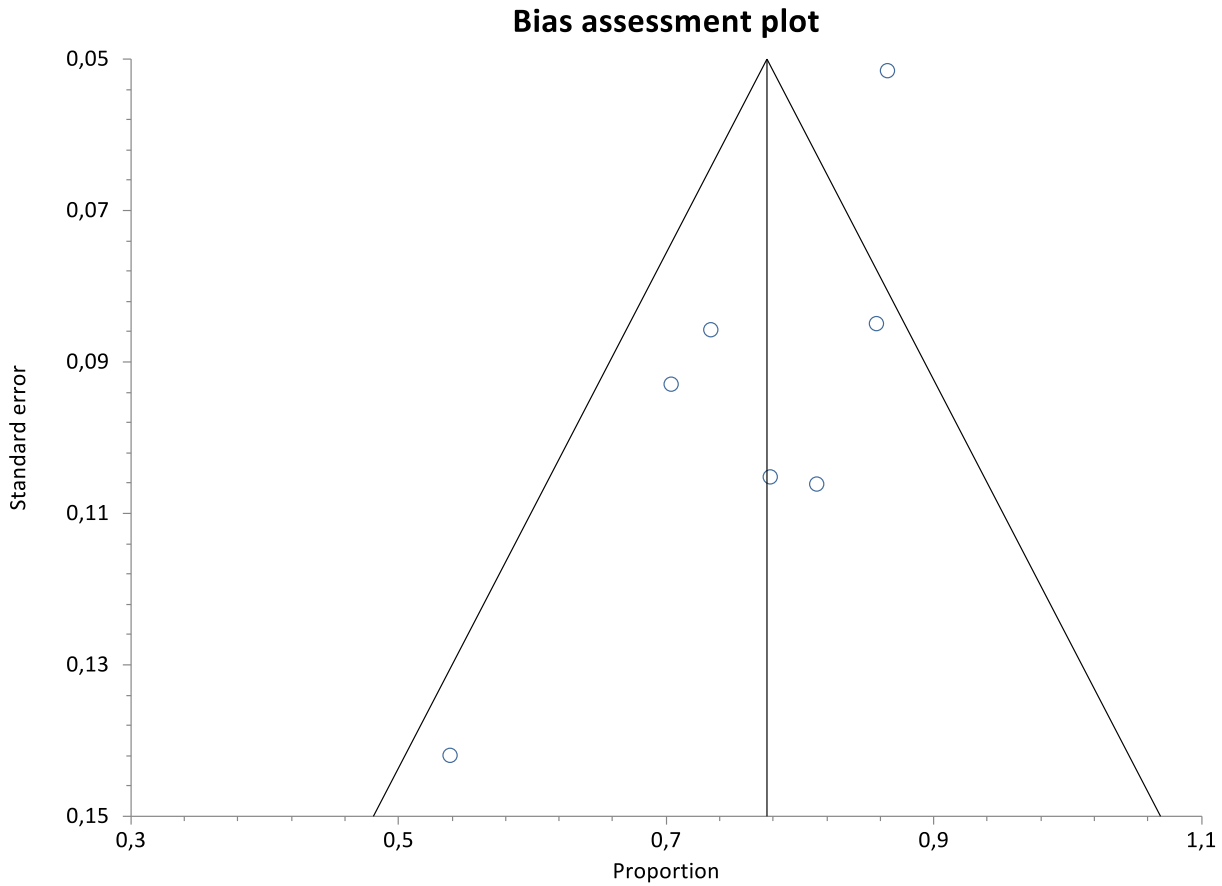


ER, eradication rate.

1, ref; 46; 2, ref. 47.

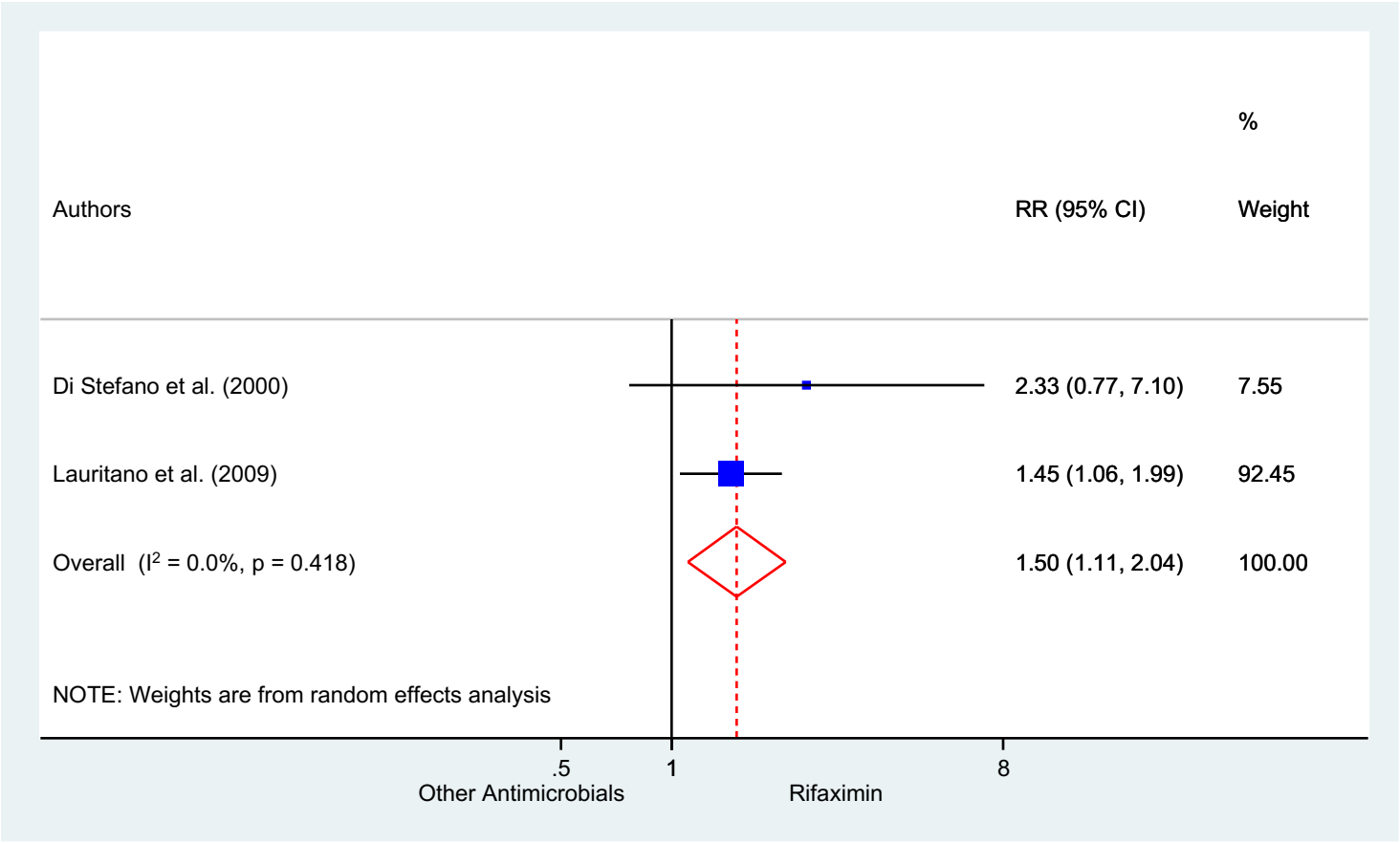
Supporting Information

Figure J. Funnel plot of SIBO eradication rate in Extra GI settings according to PP analysis.



Supporting Information

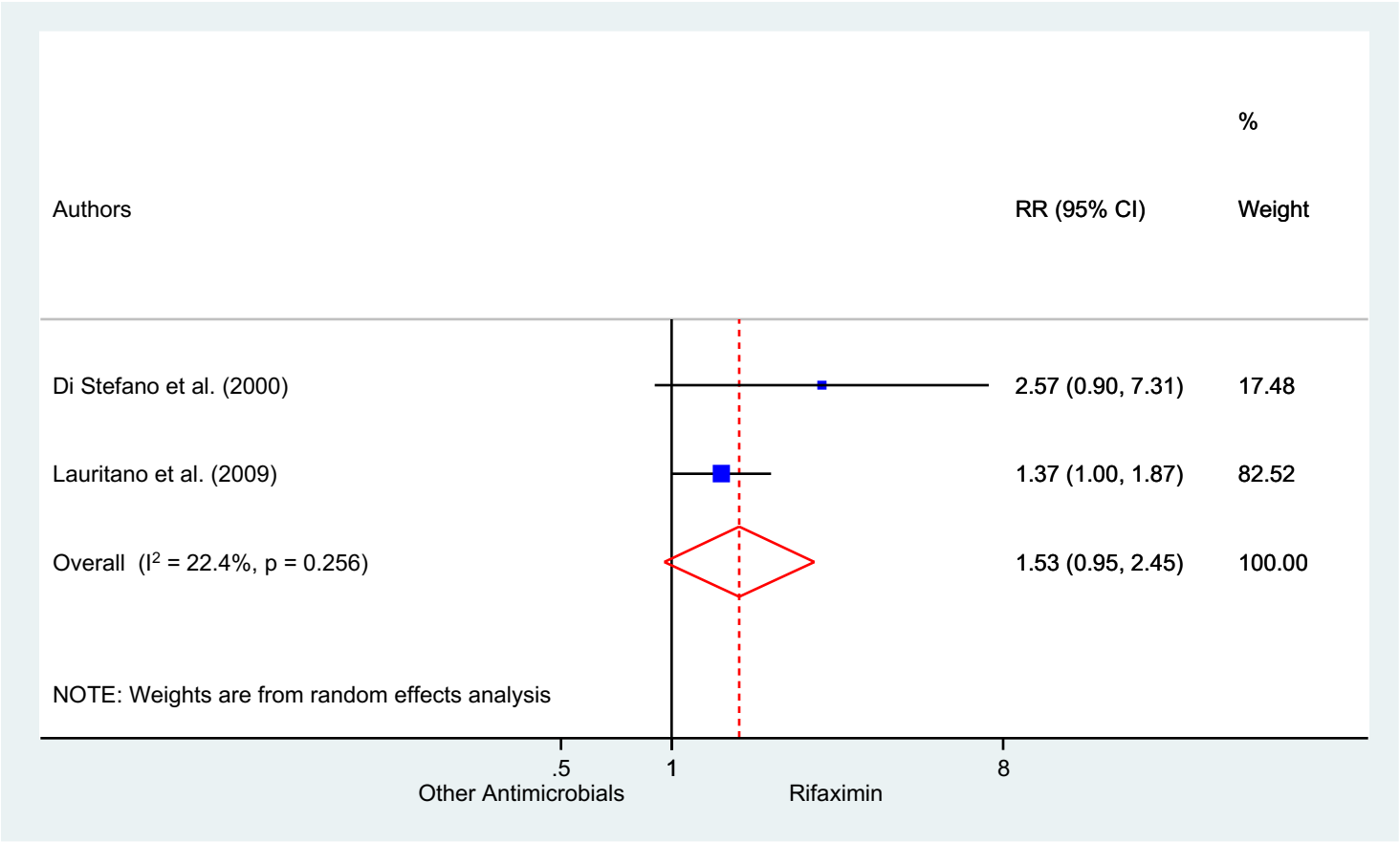
Figure K. Forest Plot: rifaximin vs. other antimicrobials in RCTs according to ITT analysis.



RR, relative risk.

Supporting Information

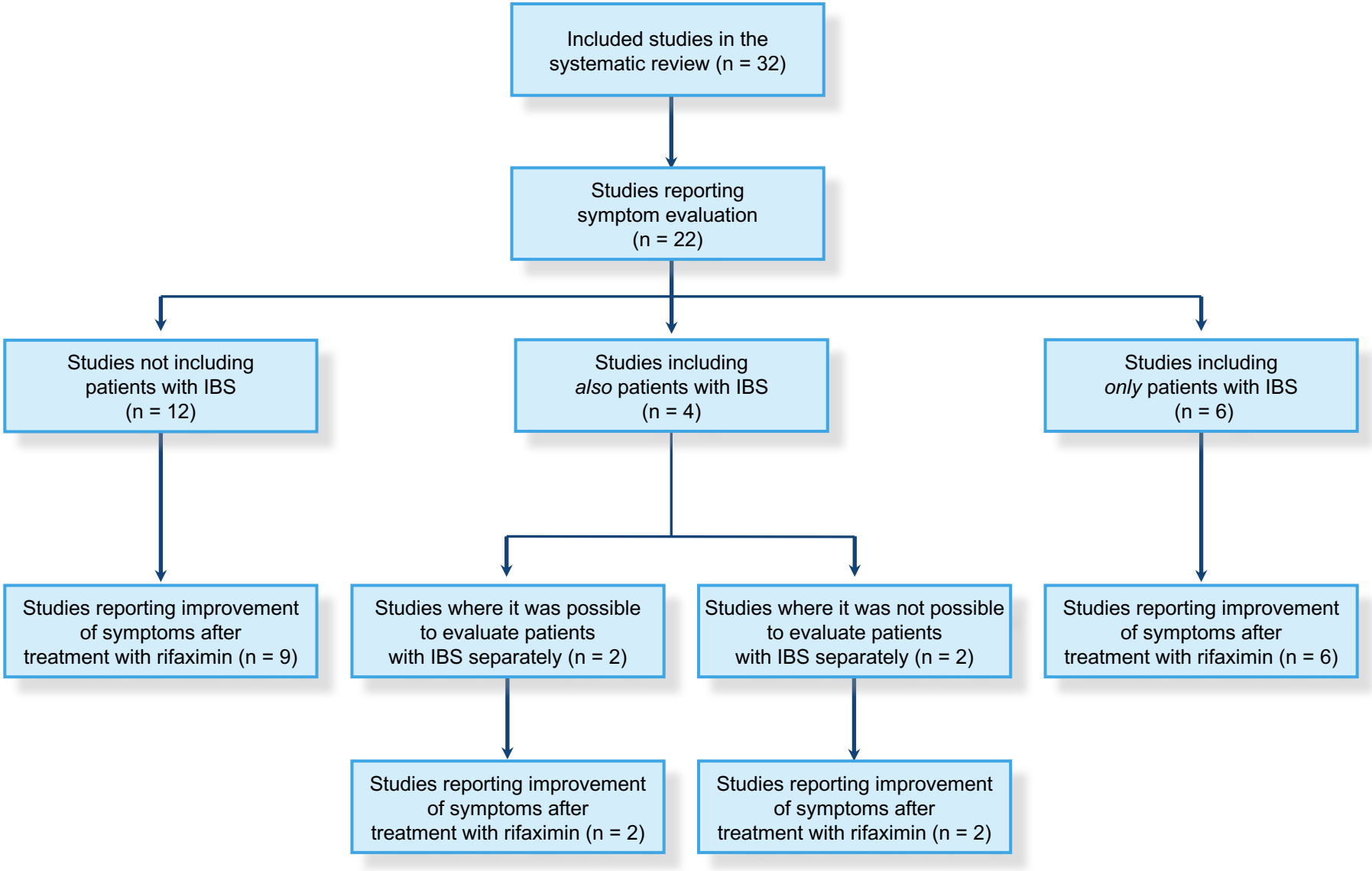
Figure L. Forest plot: rifaximin vs. other antimicrobials in RCTs according to PP analysis.



RR, relative risk.

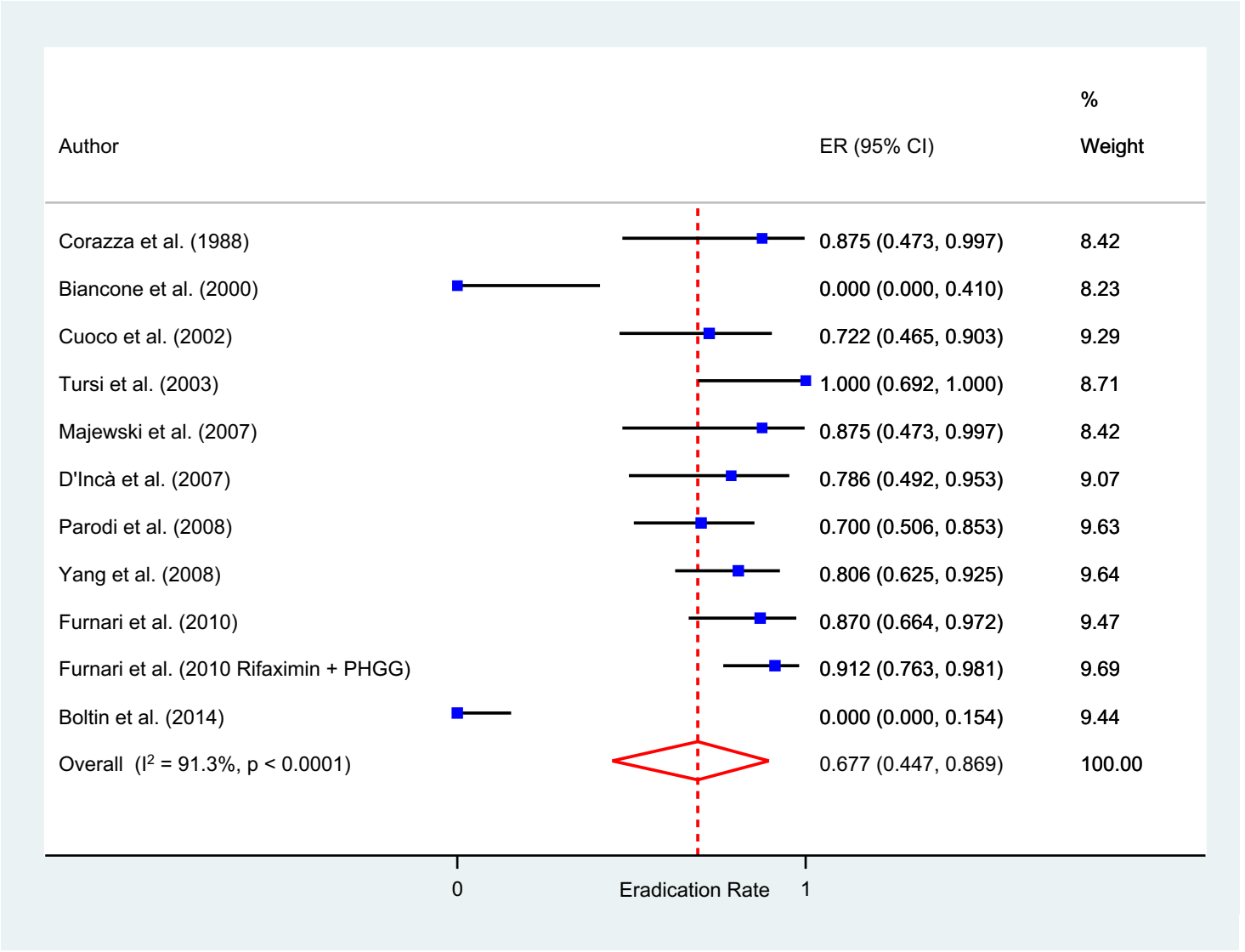
Supporting Information

Figure M. Symptom evaluation before and after treatment with rifaximin.



Supporting Information

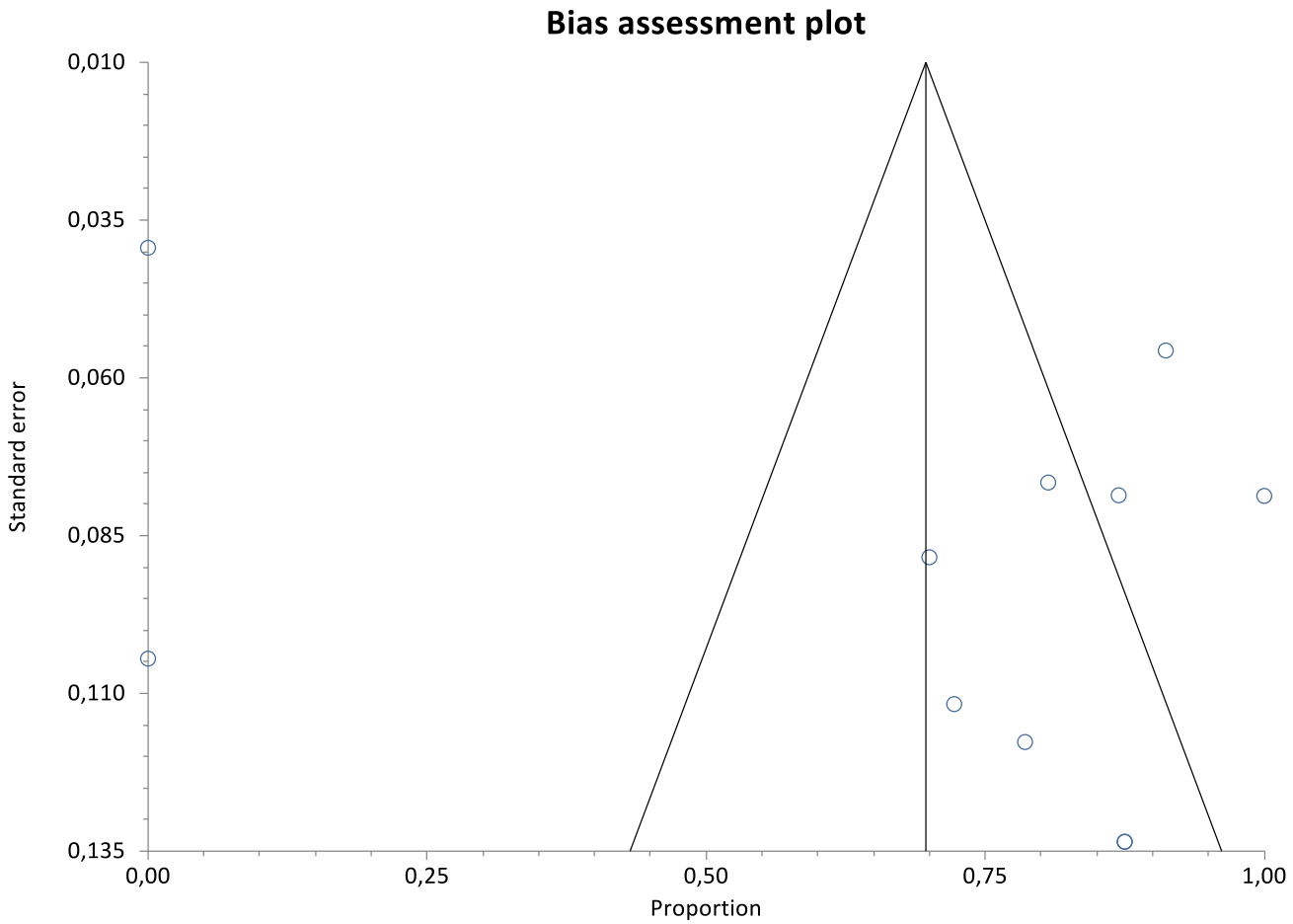
Figure N. Forest plot of improvement/resolution of symptom in patients eradicated from SIBO.



ER, eradication rate.

Supporting Information

Figure O. Funnel plot of improvement/resolution of symptom in patients eradicated from SIBO.



Supporting Information

Figure P. Funnel plot of adverse events in patients taking rifaximin alone for SIBO eradication.