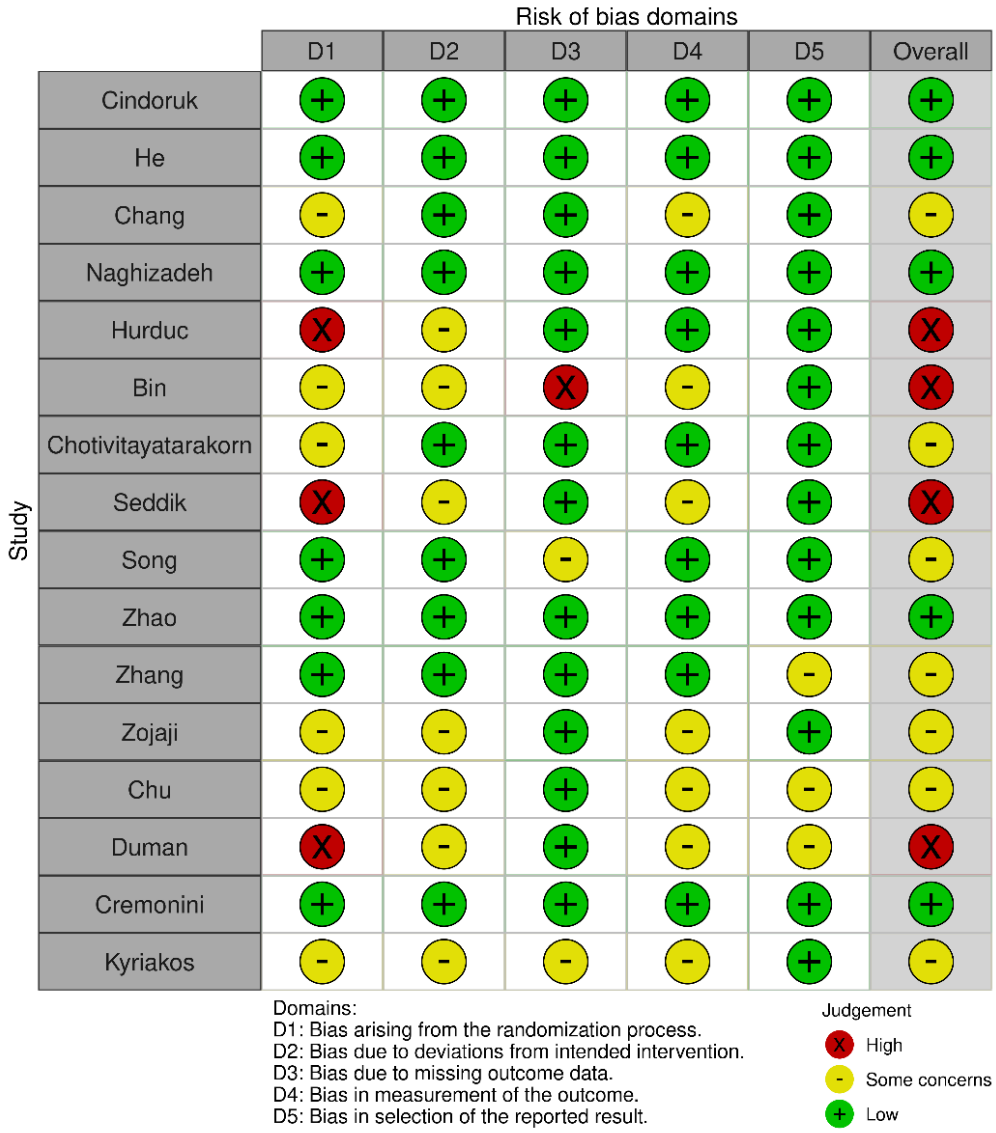
Supplementary materials

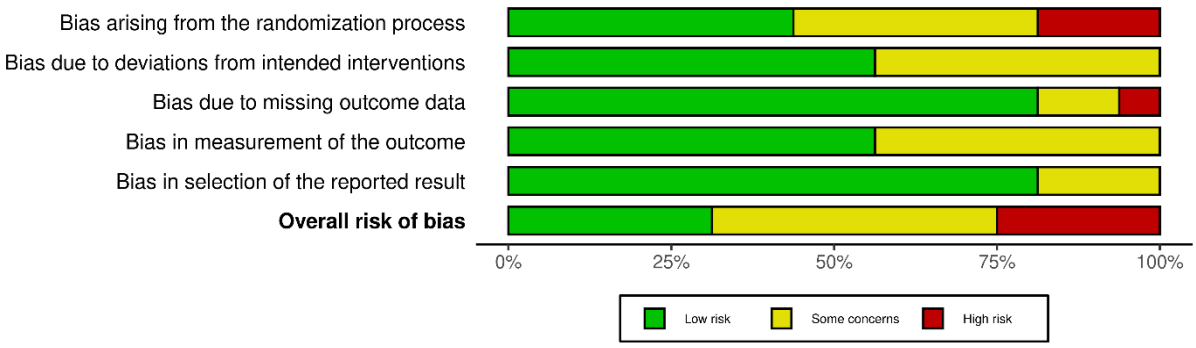
Article: *Saccharomyces boulardii* as a probiotic supplement in *Helicobacter pylori* eradication therapy: A Meta-Analysis

Supplementary Table I: Excluded studies during full-text-screening

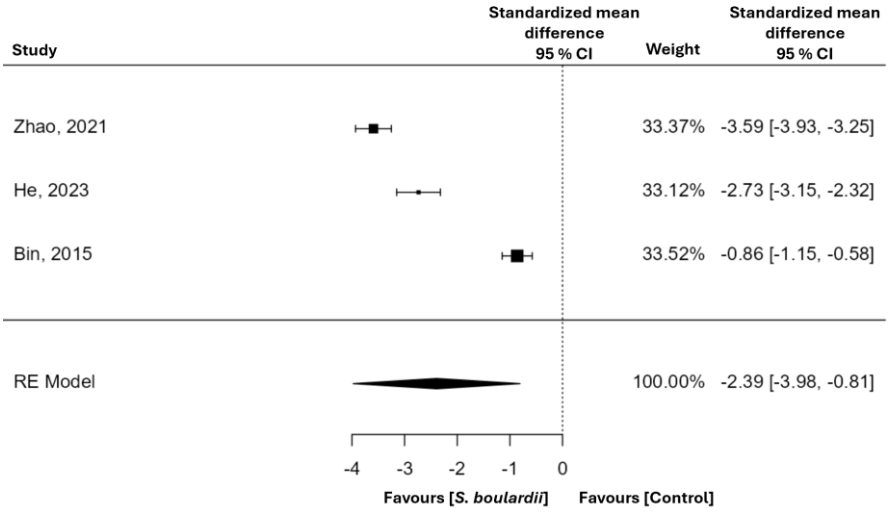
No.	Study	Reason for exclusion	Doi
1	Viazis, 2022 [1]	Intervention group received a combination of 4 probiotics (*L. acidophilus*, *L. plantarum*, *B. lactis*, *S. boulardii*)	10.3390/nu14030632
2	Qu, 2022 [2]	Control group received no eradication therapy during treatment phase of the intervention group (non-fitting study setting)	10.3389/fcimb.2022.903002
3	Yu, 2023 [3]	Single-arm pilot study with no control group	10.3748/wjg.v29.i20.3133
4	Namkin, 2016 [4]	Patients received *S. boulardii* as a single-treatment without antibiotics	10.5812/ijp.3768
5	Cárdenas, 2020 [5]	Patients were assessed for symptoms during and after treatment, but data was not shown completely	10.1007/s10096-020-03854-3
6	Gotteland, 2005 [6]	Patients received *S. boulardii* as a single-treatment without antibiotics	10.1111/j.1651-2227.2005.tb01848.x
7	Minoretti, 2024 [7]	Intervention group received a combination of 2 probiotics (*E. faecium* and *S. boulardii*)	10.7759/cureus.52502
8	Ozdil, 2011 [8]	The three treatment arms received different antibiotic treatment regimens (non fitting study setting)	10.5754/hge11075



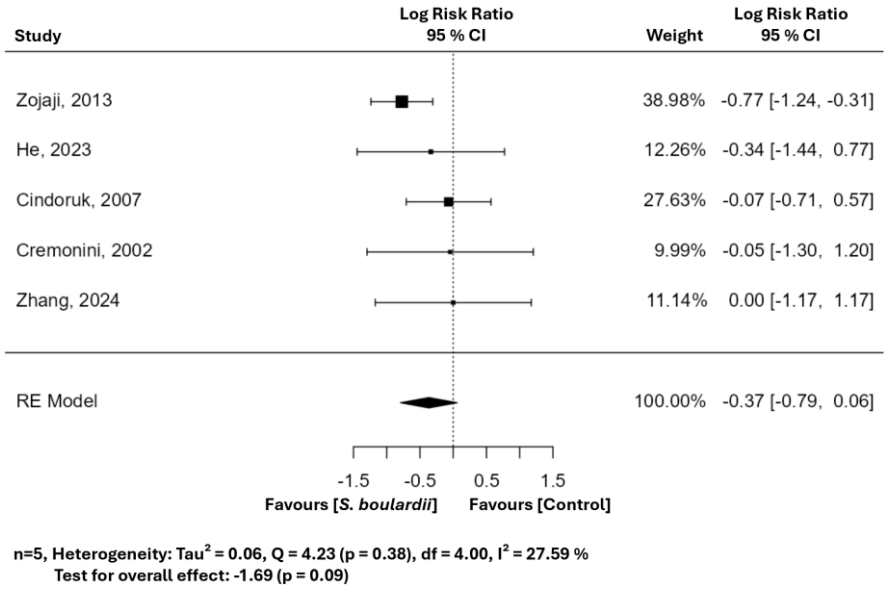
Supplementary Figure 1: Risk of bias of the included clinical studies, assessed through RoB 2.0



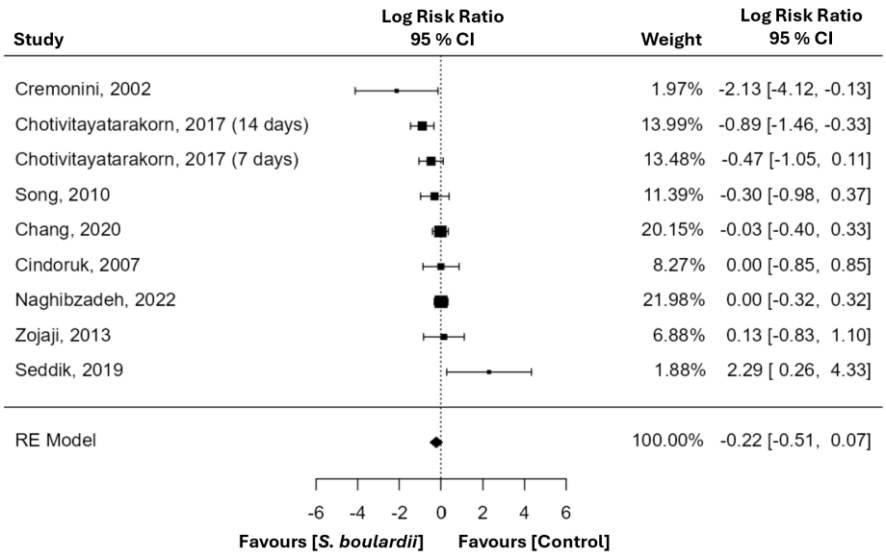
Supplementary Figure 2: Relative distribution of the five investigated bias domains of the risk of bias assessment of the included clinical studies (performed with RoB 2.0)



Supplementary Figure 3: Forest plot, with ITT data, displaying the effect of *S. boulardii* supplementation on decreasing diarrhea duration associated with *H. pylori* infection and eradication

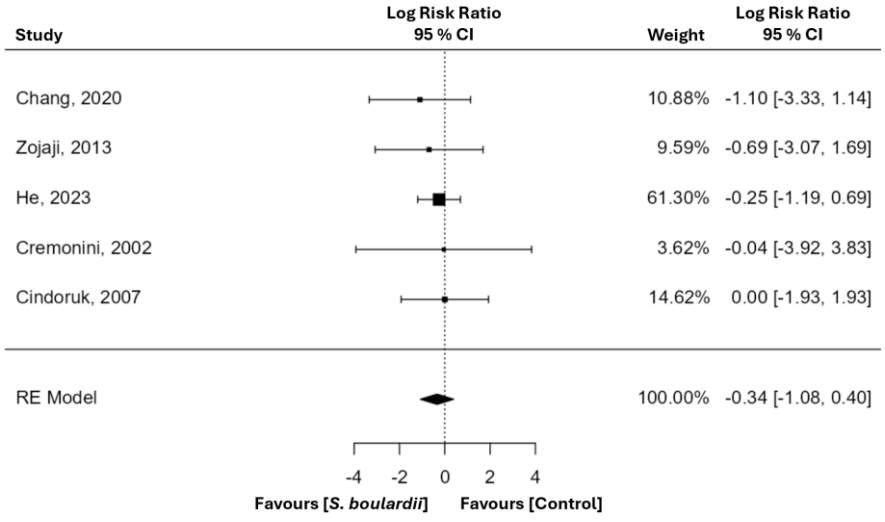


Supplementary Figure 4: Forest plot, with ITT data, displaying the effect of *S. boulardii* supplementation on decreasing meteorism rates associated with *H. pylori* infection and eradication



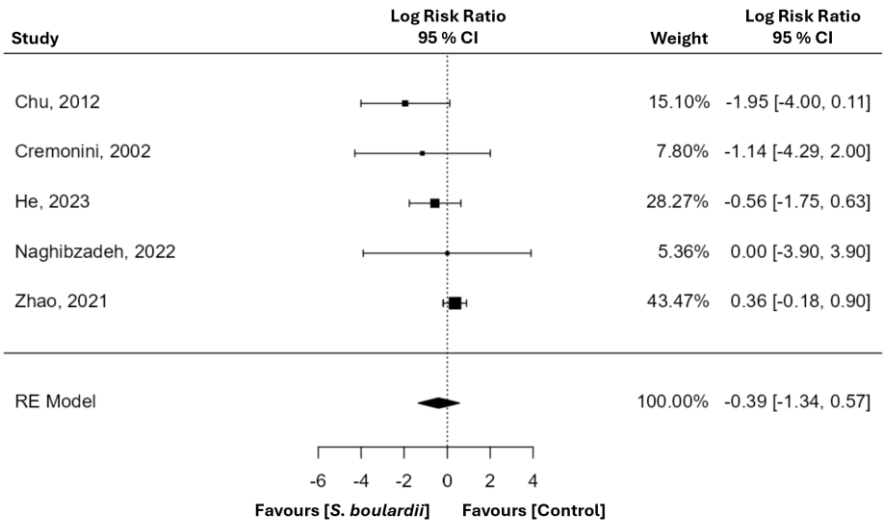
n=9, Heterogeneity: Tau^2 = 0.07, Q = 19.01 (p = 0.01), df = 8.00, I^2 = 43.83 %
Test for overall effect: -1.49 (p = 0.14)

Supplementary Figure 5: Forest plot, with ITT data, displaying the effect of *S. boulardii* supplementation on decreasing taste disturbance rates associated with *H. pylori* infection and eradication



n=5, Heterogeneity: Tau^2 = 0.00, Q = 0.70 (p = 0.95), df = 4.00, I^2 = 0 %
Test for overall effect: -0.91 (p = 0.36)

Supplementary Figure 6: Forest plot, with ITT data, displaying the effect of *S. boulardii* supplementation on decreasing urticaria/rash rates associated with *H. pylori* infection and eradication



n=5, Heterogeneity: Tau^2 = 0.47, Q = 6.42 (p = 0.17), df = 4.00, I^2 = 45.18 %
Test for overall effect: -0.79 (p = 0.43)

Supplementary Figure 7: Forest plot, with ITT data, displaying the effect of *S. boulardii* supplementation on decreasing vomiting rates associated with *H. pylori* infection and eradication

Supplementary Table II: Summarized data of the included studies for participating patients, number of observed eradication, diarrhea and epigastric pain events. Symptoms were not homogenously named in all studies. Due to high similarity, 'Epigastric pain'-data and 'Abdominal discomfort'-data were combined. Only Naghibzadeh *et al*. assessed both symptoms separately. In that case the data of epigastric pain was used. As Bin *et al*. used different numbers of patients for eradication and symptoms (diarrhea, etc.), different 'total' numbers of patients were used for the various endpoints. (s) refers to the 'total' number of patients used to assess the symptoms, (e) refers to the 'total' number of patients used to assess the eradication effects

Studies	***S. boulardii* group size (ITT/PP)**	**Control group size (ITT/PP)**	**Eradication *S. boulardii* groups**	**Eradication Control groups**	**Diarrhea *S. boulardii* groups**	**Diarrhea Control groups**	**Epigastric pain *S. boulardii* groups**	**Epigastric pain Control groups**
Cindoruk	62/62	62/62	44	37	9	19	9	27
He	86/83	86/82	80	78	6	12	4	5
Chang	61/59	61/59	52	50	5	9	3	4
Naghibzadeh	52/52	52/52	49	45	0	7	3	8
Hurduc	48/48	42/42	45	34				
Bin	105/102 for symptoms (21 for eradication)	100/92 for symptoms (21 for eradication)	15	13	12	26		
Chotivitayatarakorn (7 days)	27/27	27/27	27	24	0	1	0	1
Chotivitayatarakorn (14 days)	27/27	27/27	25	26	0	4	0	7
Seddik	100/92	99/95	86	74	2	45	2	4
Song	339/309	331/296	264	237	11	20	11	11
Zhao	169/154	179/165	145	148	19	38		
Zhang TT	48/48	48/46	36	30	1	6	0	3
Zojaji	80/80	80/80	75	65	10	21	18	36
Chu	50/50	50/50	42	32	3	8		
Duman	204/196	185/172			14	28		
Cremonini	22/21	21/20	17	16	1	6	3	3

Kyriakos	36/33	34/27	30	20				
Total	**ITT: 1432 (e) PP: 1362 (e) ITT: 1516 (s) PP: 1443 (s)**	**ITT: 1405 (e) PP: 1323 (e) ITT:1484 (s) PP: 1394 (s)**	**1032**	**929**	**93**	**250**	**53**	**109**
Number needed to treat based on ITT data			**17**		**10**		**26**	

Supplementary Table III: Summarized data of the included studies for participating patients, number of observed nausea, vomiting and taste disturbance events. Symptoms were not homogenously named in all studies. Taste disturbance summarizes all taste related irritations reported by patients, also including 'Metallic taste sensation' (Naghibzadeh *et al*., Zojaji *et al*.) or 'bitter taste sensation' (Chotivitayatarakorn *et al*.). As Bin *et al*. used different numbers of patients for eradication and symptoms (diarrhea, etc.), different 'total' numbers of patients were used for the various endpoints. (s) refers to the 'total' number of patients used to assess the symptoms, (e) refers to the 'total' number of patients used to assess the eradication effects

Studies	***S. boulardii* group size (ITT/PP)**	**Control group size (ITT/PP)**	**Nausea *S. boulardii* groups**	**Nausea Control groups**	**Vomiting *S. boulardii* groups**	**Vomiting Control groups**	**Taste disturbance *S. boulardii* groups**	**Taste disturbance Control groups**
Cindoruk	62/62	62/62	7	13			9	9
He	86/83	86/82			4	7		
Chang	61/59	61/59	2	3			29	30
Naghibzadeh	52/52	52/52	11	20	0	0	31	31
Hurduc	48/48	42/42						
Bin	105/102 for symptoms (21 for eradication)	100/92 for symptoms (21 for eradication)						

Chotivitayatarakorn (7 days)	27/27	27/27	1	3			10	16
Chotivitayatarakorn (14 days)	27/27	27/27	3	9			9	22
Seddik	100/92	99/95	2	2			10	1
Song	339/309	331/296	5	7			14	19
Zhao	169/154	179/165			27	20		
Zhang	48/48	48/46	3	2				
Zojaji	80/80	80/80	14	29			8	7
Chu	50/50	50/50	2	5	1	7		
Duman	204/196	185/172						
Cremonini	22/21	21/20	1	4	0	1	1	8
Kyriakos	36/33	34/27						
Total	**ITT: 1432 (e) PP: 1362 (e) ITT: 1516 (s) PP: 1443 (s)**	**ITT: 1405 (e) PP: 1323 (e) ITT:1484 (s) PP: 1394 (s)**	**50**	**97**	**32**	**35**	**121**	**143**
Number needed to treat based on ITT data			**31**		**400**		**61**	

Supplementary Table IV: Summarized data of the included studies for participating patients, number of observed meteorism and urticaria/rash events. Diarrhea duration in days is provided with the mean difference and standard deviation. As Bin *et al*. used different numbers of patients for eradication and symptoms (diarrhea, etc.), different 'total' numbers of patients were used for the various endpoints. (s) refers to the 'total' number of patients used to assess the symptoms, (e) refers to the 'total' number of patients used to assess the eradication effects

Studies	***S. boulardii* group size (ITT/PP)**	**Control group size (ITT/PP)**	**Meteorism *S. boulardii* groups**	**Meteorism Control groups**	**Urticaria/**	**Urticaria/**	**Diarrhea duration**	**Diarrhea duration**

					Rash *S. boulardii* groups	**Rash Control groups**	***S. boulardii* groups**	**Control groups**
Cindoruk	62/62	62/62	14	15	2	2		
He	86/83	86/82	5	7	7	9	3.83+-1.47	9.33+-2.42
Chang	61/59	61/59			1	3		
Naghibzadeh	52/52	52/52						
Hurduc	48/48	42/42						
Bin	105/102 for symptoms (21 for eradication)	100/92 for symptoms (21 for eradication)					3.17+-1.08	4.02+-0.87
Chotivitayatarakorn (7 days)	27/27	27/27						
Chotivitayatarakorn (14 days)	27/27	27/27						
Seddik	100/92	99/95						
Song	339/309	331/296						
Zhao	169/154	179/165					5.0+-0.8	7.7+-0.7
Zhang	48/48	48/46	5	5				
Zojaji	80/80	80/80	18	39	1	2		
Chu	50/50	50/50						
Duman	204/196	185/172						
Cremonini	22/21	21/20	4	4	0	0		
Kyriakos	36/33	34/27						
Total	**ITT: 1432 (e) PP: 1362 (e) ITT: 1516 (s) PP: 1443 (s)**	**ITT: 1405 (e) PP: 1323 (e) ITT:1484 (s) PP: 1394 (s)**	**46**	**70**	**11**	**16**	**/**	**/**

Number needed to treat based on ITT data			**60**		**286**		**/**	

Supplementary Table V: Subgroup analysis: Effects of *S. boulardii* supplementation to triple therapy and quadruple therapy. With n = number of studies, assessing eradication/adverse events. LogRR = Log Risk Ratio (with confidence interval in square brackets). Heterogeneity analysis was performed, using Q-test, I^2 and Tau^2. Significant p-values are shown in bold. Data from Seddik *et al*. was not included in the subgroup analysis since the treatment regimen did not meet the inclusion criteria.

	n	**LogRR**	**p-value**	**Q-test**	**I^2**	**Tau^2**
Triple therapy	**12**					
Eradication	**12**	0.11 [0.06; 0.16]	**<0.001**	11.1 (p = 0.44)	6.7 %	0.0005
Diarrhea	**11**	-0.80 [-1.07; -0.53]	**<0.001**	3.4 (p = 0.97)	0 %	0.0000
Nausea	**9**	-0.67 [-1.03; -0.31]	**<0.001**	2.9 (p = 0.94)	0 %	0.0000
Epigastric pain	**8**	-0.66 [-1.06; -0.26]	**0.001**	7.9 (p = 0.34)	15.7 %	0.0519
Taste disturbance	**7**	-0.34 [-0.67; -0.02]	**0.04**	11.1 (p = 0.09)	38.2%	0.0691
Meteorism	**4**	-0.35 [-0.84; -0.14]	0.16	4.2 (p = 0.24)	37.7 %	0.0927
Urticaria	**4**	-0.48 [-1.67; 0.70]	0.42	0.6 (p = 0.89)	0 %	0.0000
Vomiting	**2**	/	/	/	/	/
Quadruple therapy	**3**					
Eradication	**3**	0.04 [-0.01; 0.10]	0.15	0.59 (p = 0.74)	0 %	0.0000
Diarrhea	**3**	-0.70 [-1.14; -0.26]	**0.002**	1.99 (p = 0.37)	0 %	0.0000
Nausea	**1**	/	/	/	/	/
Epigastric	**2**	/	/	/	/	/

pain						
Taste Disturbance	**1**	/	/	/	/	/
Meteorism	**1**	/	/	/	/	/
Urticaria	**1**	/	/	/	/	/
Vomiting	**3**	0.08 [-0.68; 0.84]	0.84	1.90 (p = 0.39)	26.9 %	0.1495

Supplementary table VI: Subgroup analysis: Effects of different *S. boulardii* dosages (1000mg/d vs. 500 mg/d), when supplemented to *H. pylori* eradication therapy. With n = number of studies, assessing eradication/adverse events. LogRR = Log Risk Ratio (with confidence interval in square brackets). Heterogeneity analysis was performed, using Q-test, I^2 and Tau^2. Significant p-values are shown in bold

	n	**LogRR**	**p-value**	**Q-test**	**I^2**	**Tau^2**
1000 mg/day	**5**					
Eradication	**4**	0.05 [-0.01; 0.11]	0.13	2.13 (p = 0.55)	0 %	0.0000
Diarrhea	**5**	-0.73 [-1.05; -0.42]	**<0.001**	1.18 (p = 0.88)	0 %	0.0000
Nausea	**2**	/	/	/	/	/
Epigastric pain	**2**	/	/	/	/	/
Taste disturbance	**1**	/	/	/	/	/
Meteorism	**3**	-0.11 [-0.61; 0.39]	0.66	0.21 (p = 0.90)	0 %	0.0000
Urticaria	**2**	/	/	/	/	/
Vomiting	**2**	/	/	/	/	/
500 mg/day	**6**					
Eradication	**6**	0.14 [0.07; 0.20]	**<0.001**	1.88 (p = 0.87)	0 %	0.0000

Diarrhea	**5**	-1.40 [-2.33; -0.48]	**0.003**	11.2 (**p = 0.03**)	73.3 %	0.7192
Nausea	**4**	-0.66 [-1.05; -0.26]	**0.001**	0.63 (p = 0.89)	0 %	0.0000
Epigastric pain	**3**	-0.73 [-1.16; -0.30]	**<0.001**	0.17 (p = 0.92)	0 %	0.0000
Taste Disturbance	**3**	0.31 [-0.46; 1.09]	0.43	4.78 (p = 0.09)	53.2 %	0.2499
Meteorism	**1**	/	/	/	/	/
Urticaria	**1**	/	/	/	/	/
Vomiting	**2**	/	/	/	/	/

References:

[1] N. Viazis *et al.*, "A Four-Probiotics Regimen Combined with A Standard Helicobacter pylori-Eradication Treatment Reduces Side Effects and Increases Eradication Rates," *Nutrients,* vol. 14, no. 3, Feb 1 2022, doi: 10.3390/nu14030632.

[2] P. Qu *et al.*, "Saccharomyces boulardii Allows Partial Patients to Avoid Reusing Bismuth Quadruple for Helicobacter pylori Rescue Therapy: A Single-Center Randomized Controlled Study," *Front Cell Infect Microbiol,* vol. 12, p. 903002, 2022, doi: 10.3389/fcimb.2022.903002.

[3] J. Yu, Y. M. Lv, P. Yang, Y. Z. Jiang, X. R. Qin, and X. Y. Wang, "Safety and effectiveness of vonoprazan-based rescue therapy for Helicobacter pylori infection," *World J Gastroenterol,* vol. 29, no. 20, pp. 3133-3144, May 28 2023, doi: 10.3748/wjg.v29.i20.3133.

[4] K. Namkin, M. Zardast, and F. Basirinejad, "Saccharomyces Boulardii in Helicobacter Pylori Eradication in Children: A Randomized Trial From Iran," *Iranian Journal of Pediatrics,* vol. 26, no. 1, 2016/1// 2016, doi: 10.5812/ijp.3768.

[5] P. A. Cardenas *et al.*, "Effect of Saccharomyces boulardii CNCM I-745 as complementary treatment of Helicobacter pylori infection on gut microbiome," *Eur J Clin Microbiol Infect Dis,* vol. 39, no. 7, pp. 1365-1372, Jul 2020, doi: 10.1007/s10096-020-03854-3.

[6] M. Gotteland, L. Poliak, S. Cruchet, and O. Brunser, "Effect of regular ingestion of Saccharomyces boulardii plus inulin or Lactobacillus acidophilus LB in children colonized by Helicobacter pylori," *Acta paediatrica (Oslo, Norway: 1992),* vol. 94, no. 12, pp. 1747-51, 2005/12// 2005, doi: 10.1111/j.1651-2227.2005.tb01848.x.

[7] P. Minoretti, M. Liano Riera, A. Santiago Saez, M. Gomez Serrano, and A. Garcia Martin, "Probiotic Supplementation With Saccharomyces boulardii and Enterococcus faecium Improves Gastric Pain and Bloating in Airline Pilots With Chronic Non-atrophic Gastritis: An Open-Label Study," *Cureus,* vol. 16, no. 1, p. e52502, Jan 2024, doi: 10.7759/cureus.52502.

[8] K. Ozdil *et al.*, "Levofloxacin based sequential and triple therapy compared with standard plus probiotic combination for Helicobacter pylori eradication," (in eng), *Hepatogastroenterology,* vol. 58, no. 109, pp. 1148-52, Jul-Aug 2011, doi: 10.5754/hge11075.