European Journal of Pediatrics (2019) 178:7–16
https://doi.org/10.1007/s00431-018-3282-z

REVIEW

Efficacy of *Lactobacillus*-supplemented triple therapy for *Helicobacter pylori* infection in children: a meta-analysis of randomized controlled trials

Hao-Ran Fang[1] · Guo-Qiang Zhang[1] · Jing-Yi Cheng[2] · Zhong-Yue Li[1]

Received: 27 July 2018 / Revised: 30 September 2018 / Accepted: 23 October 2018 / Published online: 16 November 2018

Abstract

Therapy-related side effects and severe antimicrobial resistance still remain an obstacle to *Helicobacter pylori* eradication. This meta-analysis aimed to investigate the efficacy of *Lactobacillus*-supplemented triple therapy on *H. pylori* eradication rates and therapy-related side effects in children. Five studies involving 484 pediatric patients were included in our analysis. The pooled relative risk (RR) for eradication rates in the *Lactobacillus* group versus the control group was 1.19 [95% confidence interval (CI) 1.07–1.33]. In subgroup analyses based on dose and duration of *Lactobacillus* supplementation, the pooled RRs for eradication rates were 1.36 (95% CI 1.15–1.60) in the high-dose group, 1.08 (95% CI 0.86–1.35) in the low-dose group, 1.24 (95% CI 1.06–1.46) in the long-term group, and 1.17 (95% CI 0.96–1.44) in the short-term group. With respect to side effects, *Lactobacillus* supplementation significantly reduced the incidence of diarrhea (RR = 0.30, 95% CI 0.10–0.85).

Conclusions: *Lactobacillus*, as an adjunct to triple therapy, can increase *H. pylori* eradication rates as well as reduce the incidence of therapy-related diarrhea in children. And a higher dose and a longer duration of supplementation may conduce to the positive impact of *Lactobacillus* on *H. pylori* eradication.

What is Known:

- *Probiotics-supplemented triple therapy may be beneficial in improving H. pylori eradication rates and reducing therapy-related side effects in children. However, not all probiotics are beneficial to H. pylori eradication and the pooled outcomes based on different probiotics may be erroneously extrapolated to other ineffective strains.*

What is New:

- *Lactobacillus, as an adjunct to triple therapy, can increase H. pylori eradication rates as well as reduce the incidence of therapy-related diarrhea in children.*

Keywords *Lactobacillus* · Triple therapy · *H. pylori* · Children · Meta-analysis

Abbreviations

CFU	Colony-forming unit
CI	Confidence interval
HpSA	*H. pylori* stool antigen test

Communicated by Peter de Winter

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00431-018-3282-z) contains supplementary material, which is available to authorized users.

✉ Zhong-Yue Li
lizhongyue1001@hotmail.com

Hao-Ran Fang
2258411656@qq.com

Guo-Qiang Zhang
zhangguoqiang.cqmu@gmail.com

Jing-Yi Cheng
1148591928@qq.com

[1] Department of Gastroenterology, Ministry of Eduaction Key Laboratory of Child Development and Disorders, Key Laboratory of Pediatrics in Chongqing, Chongqing International Science and Technology Cooperation Center for Child Development and Disorders, Children's Hospital of Chongqing Medical University, No.136, Zhongshan 2nd Road, Yuzhong District, Chongqing 400014, China

[2] Department of Child Health Care, Children's Hospital of Chongqing Medical University, Chongqing, China

NSAID	Nonsteroidal anti-inflammatory drug
RCT	Randomized controlled trial
RR	Relative risk
RUT	Rapid urease test
PPI	Proton pump inhibitor
UBT	Urea breath test

Introduction

Helicobacter pylori eradication in children should be supported by a clear benefit. For those with peptic ulcer, chronic idiopathic thrombocytopenic purpura, or intractable iron deficiency, testing for *H. pylori* is necessary and treatment should be advised for confirmed cases [1–3]. According to the ESPGHAN/NASPGHAN guidelines [1], a 14-day triple therapy or bismuth-based triple therapy is the first choice for *H. pylori* eradication in children based on results of antimicrobial sensitivity testing. If sensitivity testing is not available, a high dosage of PPI-amoxicillin-metronidazole therapy with or without bismuth should be used due to severe clarithromycin resistance worldwide. In addition to the anti-*H. pylori* regimens, investigating the prevalence of antibiotics resistance in the population, assessment of first-line therapy in regional centers, and emphasizing the necessity of adherence to the eradication therapy are also recommended strategies to improve eradication rates [1, 4, 5]. In despite of the increased eradication rates by using these strategies [5], concerns still exist regarding poor compliance caused by therapy-related side effects and severe antimicrobial resistance due to inappropriate use of antibiotics [6–8].

As a living microorganism, probiotic contributes to good health, when administered at adequate amounts [9]. Previous meta-analysis demonstrated that probiotics-supplemented triple therapy may be beneficial in improving *H. pylori* eradication rates and reducing therapy-related side effects in children [10]. However, it seemed that not all probiotics were beneficial to *H. pylori* eradication and the pooled outcomes based on different probiotics may be erroneously extrapolated to other ineffective strains [11]. An alternative solution is to pool data on a clearly defined species of probiotic, which has been substantially proven effective in inhibiting *H. pylori* in experimental studies.

Currently, numerous studies, in vitro and/or in animal models, have demonstrated that some specific *Lactobacillus* strains, including *Lactobacillus* GG, *L. acidophilus*, *L. casei*, and *L. reuteri*, could exhibit anti-*H. pylori* effects [12–24]. And a double-blind RCT involving 20 adult volunteers suggested that *H. pylori* colonization in vivo may be interfered by regular ingestion of *L. acidophilus*, and the urea breath test values decreased by approximately 10% 4 weeks after treatment [25]. However, researches in children that assessed the efficacy of *Lactobacillus*-supplemented triple therapy were surprisingly scant and conflicting as the sample size in each study was too small to reach a definite conclusion.

Given these considerations, we conducted this meta-analysis to investigate whether *Lactobacillus* supplementation can improve *H. pylori* eradication rates and reduce therapy-related side effects in children as well as explore the appropriate dose and duration of supplementation.

Methods

Cochrane Handbook for Systematic Reviews of Interventions [26] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) [27] were followed for conducting and reporting this systematic review and meta-analysis.

Search strategy

We searched Pubmed, Embase, and Cochrane Library for relevant studies (up to June 2018) with no language restrictions. The search strategy was based on a combination of the following terms: (probiotic OR probiotics OR *Lactobacillus* OR yogurt) and (*Helicobacter pylori* OR *H. pylori*) and (child OR children OR pediatric). As complementary, references of identified articles and previous reviews were manually searched as well.

Selection criteria

The results of initial search were reviewed by two independent reviewers (Fang and Cheng). Studies satisfying with the following requirements were included in our meta-analysis: (i) pediatric patients with *H. pylori* infection confirmed by generally accepted methods (histology, culture, RUT, UBT, or HpSA), (ii) randomized controlled trials compared at least two treatment groups including (a) eradication therapy (PPI and two antibiotics) with placebo or not and (b) the same eradication therapy with *Lactobacillus* supplementation, (iii) confirmation of eradication outcomes by UBT or HpSA at least 4 weeks after stopping antibiotics, and (iv) studies with full text providing the data of interest (eradication rate and/or side effect).

Data extraction

Two reviewers (Fang and Zhang) were in charge of independently extracting data, using a unitive data extraction form. The information extracted from eligible studies was as follows: source (first author, year of publication, country), age range, number of patients in each group, diagnostic methods of *H. pylori* infection for enrolling/rechecking patients, details of eradication therapy and probiotics regimen (including dose and duration), follow-up time, eradication rate (primary outcome), and side effect (secondary outcome). Consensus regarding data extraction was reached by discussion.

Quality assessment

The quality of included trials was evaluated in adherence to the Cochrane risk of bias assessment tool [26] including the following entries: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. Judgment of each entry was graded into three levels (low risk, unclear risk, and high risk). And the quality of evidence for key outcomes was assessed using GRADEpro GDT according to GRADE handbook [28]. Quality assessment was performed by two independent reviewers (Zhang and Cheng). Divergence regarding quality assessment was solved by discussion.

Statistical analysis

This meta-analysis was carried out using the RevMan 5.3 (The Nordic Cochrane centre, The Cochrane Collaboration) and Stata 12.0 (Stata Corporation). Dichotomous outcomes including eradication rates and side effects were analyzed based on intent-to-treat (ITT) principle and presented as relative risk (RR) with 95% confidence interval (CI). Heterogeneity among studies was evaluated by using chi-square test and I^2 statistic. $I^2 > 50\%$ and $P < 0.1$ were the indicators of significant heterogeneity. All data synthesis was performed using the random-effect model. For those with $I^2 > 50\%$ and $P < 0.1$, sensitivity test was conducted to detect the possible source of heterogeneity by excluding each study one by one and recalculating the pooled RR of the rest. For primary outcome, subgroup analyses based on dose and duration of *Lactobacillus* supplementation were performed to detect the impacts of dose and duration. Begg's and Egger's tests were used to detect potential publication bias. Considering the small number of included studies, publication bias was conducted only for the primary outcome. A P value < 0.05 was considered as statistically significant.

Results

Study identification and selection

The search and selection of studies are presented in Fig. 1. The initial search yielded a total of 312 records, of which 86 records were excluded for duplicates. After reading the title and abstract, additional 217 records were excluded. And nine potentially eligible articles [29–37] were assessed by reviewing the full texts, of which one [30] was excluded for not RCT and another three studies [31, 35, 37] for using probiotics other than *Lactobacillus*. Finally, five studies [29, 32–34, 36] consisting of 484 pediatric patients were included in our meta-analysis. No additional studies were included by manual searching.

Characteristics of included studies

The publication date of included studies ranged between 2005 and 2017. Two studies [32, 36] were conducted in Poland, one [29] in China, one [33] in Czech, and one [34] in Iran. The sample size of eligible studies ranged between 50 [34] and 205 [29] participants. All included studies used the same eradication regimen (amoxicillin, clarithromycin, and PPI) with various dose and duration. *Lactobacillus* strains were different among studies: (i) *L. acidophilus* and *L. rhamnosus* [36], (ii) *L. reuteri* [34], (iii) *L. casei* [33], (iv) *Lactobacillus* GG [32], (v) compound *Lactobacillus* without detailed information of contained strains [29]. The daily dose of *Lactobacillus* ranged between 1×10^9 CFU [34] and 10×10^9 CFU [33], and in one RCT, the dose was not available [29]. The duration of *Lactobacillus* supplementation ranged between 2 weeks [29, 32, 33] and 1 month [36]. The general characteristics of included studies are described in Table 1.

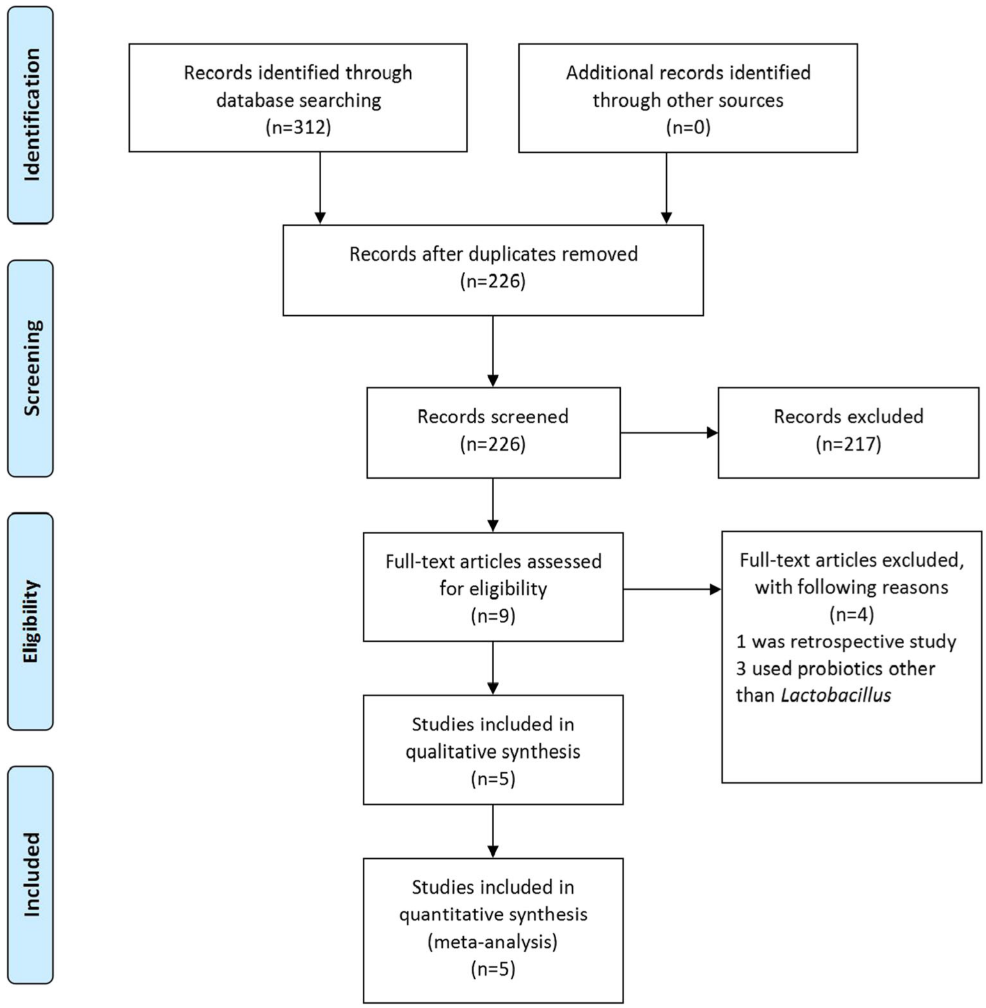
Risk of bias assessment of included studies

Of all included studies, three studies [32–34] had adequate sequence generation and blinding, two studies [29, 36] were judged as unclear risk of randomization and blinding for limited relevant information described within articles. All but one [32] were judged as unclear risk of allocation concealment due to possible foreknowledge of forthcoming allocation by patients or study personnel. With respect to attrition and reporting bias, all included studies were judged as low risk for low rate of defaulters and completely reporting prespecified outcomes. Risk of bias summary was shown in Fig. 2.

Eradication rates

Data regarding eradication rates were available from five studies [29, 32–34, 36] involving 484 pediatric patients (243 in the experimental group and 241 in the control group) (Fig. 3). The eradication rates in the *Lactobacillus* supplementation group were significantly higher than the control group (84.0% vs 71.4%) and the pooled RR was 1.19 (95% CI 1.07–1.33, $I^2 = 25\%$). In subgroup analysis based on dose of *Lactobacillus* supplementation ($< 5 \times 10^9$ CFU/day, or $\geq 5 \times 10^9$ CFU/day), the eradication rates increased significantly in the high-dose group with *Lactobacillus* supplementation (2

Fig. 1 Search and selection of studies



RCTs, $n = 146$, 91.3% vs 64.9%, RR = 1.36, 95% CI 1.15–1.60, $I^2 = 0\%$), but not in the low-dose group (2 RCTs, $n = 133$, 65.2% vs 64.1%, RR = 1.08, 95% CI 0.86–1.35, $I^2 = 3\%$). In subgroup analysis based on duration of *Lactobacillus* supplementation (≤ 2 weeks, or ≥ 4 weeks), the eradication rates increased significantly in the long-term group with *Lactobacillus* supplementation (2 RCTs, $n = 110$, 94.5% vs 76.4%, RR = 1.24, 95% CI 1.06–1.46, $I^2 = 0\%$), but not in the short-term group (3 RCTs, $n = 374$, 80.9% vs 69.9%, RR = 1.17, 95% CI 0.96–1.44, $I^2 = 53\%$). Considering the significant heterogeneity in the short-term group, sensitivity analysis was conducted by omitting one study by Sykora et al. [33], and the recalculating RR was 1.10 (95% CI 0.96–1.27) with low heterogeneity ($I^2 = 10\%$).

Side effects

There were four studies [29, 32, 33, 36] involving 434 pediatric patients providing data regarding the incidence of total side effects. We found no significant difference between the *Lactobacillus* supplementation group and the control group with respect to the incidence of total side effects (17.9% vs 35.6%, RR = 0.47, 95% CI 0.19–1.17, $I^2 = 83\%$) (Fig. 4). In sensitivity analysis, the pooled RR had no material change with the results ranging from 0.34 (95% CI 0.10–1.16, $I^2 = 80\%$) to 0.72 (95% CI 0.42–1.25, $I^2 = 52\%$). With respect to specific side effects, *Lactobacillus* supplementation significantly reduced the incidence of diarrhea (3 RCTs, $n = 348$, 2.2% vs 9.5%, RR = 0.30, 95% CI 0.10–0.85, $I^2 = 0\%$), while not for taste disturbance (3 RCTs, $n = 348$, 3.9% vs 9.5%, RR = 0.46, 95% CI 0.19–1.14, $I^2 = 0\%$), and abdominal distension (2 RCTs, $n = 288$, 4.0% vs 3.6%, RR = 1.07, 95% CI 0.31–3.64, $I^2 = 0\%$) (Fig. 4). Other specific side effects were not included in quantitative analysis as data was only available from single trails. One study by Szajewska et al. [32] suggested that there was no significant difference with respect to the incidence of nausea, vomiting, constipation, and loss of appetite between study groups. Another study by Plewinska et al. [36] showed that the incidence of abdominal pain was significantly lower with probiotics supplementation ($n = 60$, 3.3% vs 23.3%, $P < 0.05$).

Table 1 Characteristics of included studies

Source	Exp/Cont	Age range (year)	Diagnostic methods of *H. pylori* (initial/rechecking)	Eradication regimen	*Lactobacillus* regimen	Follow-up time	% Eradication (exp/cont)	% incidence of total side effects (exp/cont)
Plewinska, 2006, Poland	30/30	8–18	Histology, RUT/histology, RUT	Amoxicillin (50 mg/kg/day twice daily) for 10 days Clarithromycin (15 mg/kg/day twice daily) for 10 days PPI (0.5 mg/kg/day twice daily) for 10 days	*L. acidophilus* and *L. rhamnosus* (6×10^9 CFU/day) for 30 days	6 weeks	100.0/76.7	6.7/86.7
Shahraki, 2017, Iran	25/25	5–14	Histology/UBT	Amoxicillin (50 mg/kg/day twice daily) for 2 weeks Clarithromycin (15 mg/kg/day twice daily) for 2 weeks Omeprazole (1 mg/kg/day twice daily) for 1 month	*L. reuteri* (1×10^9 CFU/day) for 4 weeks	4 weeks	88.0/76.0	NA
Sykora, 2005, Czech	39/47	NA	Culture, histology, HpSA, RUT/HpSA, UBT	Amoxicillin (25 mg/kg twice daily) for 1 week Clarithromycin (7.5 mg/kg twice daily) for 1 week Omeprazole (20 mg/30 kg twice daily) for 1 week	*L. casei* (10×10^9 CFU/day) for 2 weeks	4 weeks	84.6/57.4	17.9/19.1
Zhu, 2017, China	105/100	3–14	UBT/UBT	Amoxicillin (NA)[a] for 2 weeks Clarithromycin (NA)[a] for 2 weeks Omeprazole (NA)[a] for 2 weeks	*Lactobacillus* (NA)[a] for 2 weeks	4 weeks	91.4/81.0	9.5 /23.0
Szajewska, 2009, Poland	44/49	5–17	RUT, histology, UBT/UBT	Amoxicillin (25 mg/kg twice daily) for 2 weeks Clarithromycin (10 mg/kg twice daily) for 2 weeks Omeprazole (0.5 mg/kg twice daily) for 2 weeks	*Lactobacillus* GG (2×10^9 CFU/day) for 2 weeks	4–6 weeks	67.6/68.8	45.5/63.3

CFU colony-forming unit, *HpSA H. pylori* stool antigen test, *NA* not available, *PPI* proton pump inhibitor, *RUT* rapid urease test, *UBT* urea breath test

[a] Dose is not available

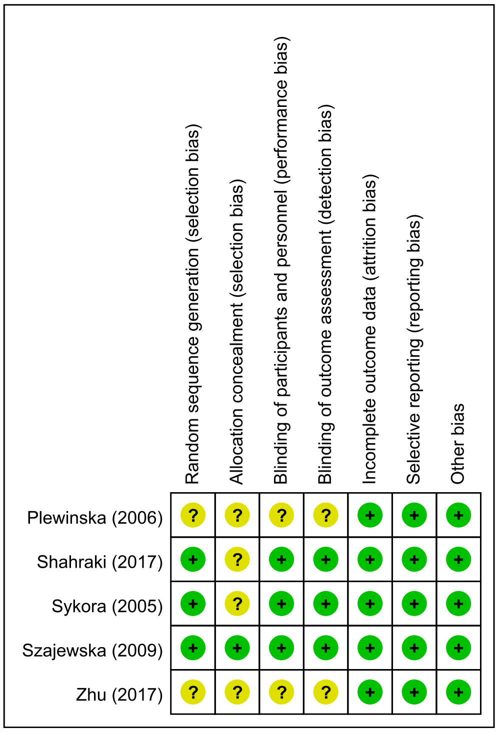


Fig. 2 Risk of bias summary (for assessment of each entry, green represents low risk of bias and yellow refers to unclear risk of bias)

Publication bias

The results of Begg's test and Egger's test suggested no significant publication bias ($P = 1.000$, $P = 0.747$, respectively).

Discussion

Summary of evidence

In our meta-analysis, the *H. pylori* eradication rate increased by approximately 13% with *Lactobacillus* supplementation. However, it was still below 90%, which was a recommended goal for avoiding further investigation and retreatment [38]. Furthermore, in subgroup analyses, the eradication rates increased significantly in the high-dose group ($\geq 5 \times 10^9$ CFU/day) and long-term group (≥ 4 weeks), but not in the low-dose group ($< 5 \times 10^9$ CFU/day) and short-term group (≤ 2 weeks), which indicated that a higher dose and a longer duration of *Lactobacillus* supplementation may improve the eradication efficacy.

With respect to therapy-related side effects, *Lactobacillus* supplementation could significantly reduce the risk of diarrhea. However, there was no significant difference regarding total side effects between study groups.

All evidence for eradication rates and side effects was graded as moderate quality in our study, except for the evidence of eradication rates in the low-dose group and abdominal distension, which was graded as low quality for serious risk of bias and serious inconsistency among studies. The GRADE quality of findings was shown in Table S1 in detail.

Experimental proof supporting our findings

Role of *Lactobacillus* in *H. pylori* eradication has been substantially studied and the potential mechanisms are as follows: (i) producing antimicrobial substances: *Lactobacillus* strains produce lactic acid, which has an inhibitory effect on urease activity of *H. pylori* [14, 15, 24]. In addition, *L. acidophilus* can directly inhibit *H. pylori* by generating bacteriocins and autolysin [19, 22, 23]. And *L. reuteri* can secret reuterin to exert anti-*H. pylori* effects [14]. (ii) Competing for colonization: *L. acidophilus* exhibits good tolerance to gastric acid and is capable of attaching to gastric mucosa surface, potentially affecting *H. pylori* colonization [21]. Moreover, *L. reuteri* can interfere with the conglutination between *H. pylori* and epithelial cell receptor by producing cell surface protein [18]. And Myllyluoma et al. demonstrated that *H. pylori* adhesion in vitro can be inhibited by *Lactobacillus* GG, using the method of in situ immunofluorescence [13]. (iii) Stabilizing mucosal barrier: *Lactobacillus* strains stabilize mucosal barrier mainly through enhancing mucin secretion [16]. In addition, *Lactobacillus* GG can improve epithelial barrier and inhibit *H. pylori*-induced cell membrane leakage in vitro as well as improve NSAID-induced gastric mucosa damage in humans [13, 20]. (iv) Regulating immunologic response: *L. acidophilus* reduce gastric inflammation relating to *H. pylori* infection via suppressing the Smad7 and NFkappaB pathways [12]. *L. casei* can inhibit IL-8 secretion by independent inactivation of TNF-α pathway [17]. And *Lactobacillus* GG can also reduce *H. pylori*-induced IL-8 release in vitro [13].

Strengths and limitations

The main strength of our study was that we pooled the data based on a clearly defined species of probiotic (*Lactobacillus*), which has been substantially proven effective in inhibiting *H. pylori* in experimental studies. In addition, we adopted Cochrane risk of bias assessment tool for quality assessment of included studies and GRADE system for evaluating evidence of key outcomes. However, our study also has several limitations. First of all, our meta-analysis was conducted by pooling data from only five studies after an extensive literature search, which may reduce the credibility of our findings to some extent. However, to increase power was one of the reasons why we conducted this meta-analysis. Second, methodological quality of the included studies varied. Unclear risk of randomization and blinding may lead to a spurious result. Next, the diversity of population

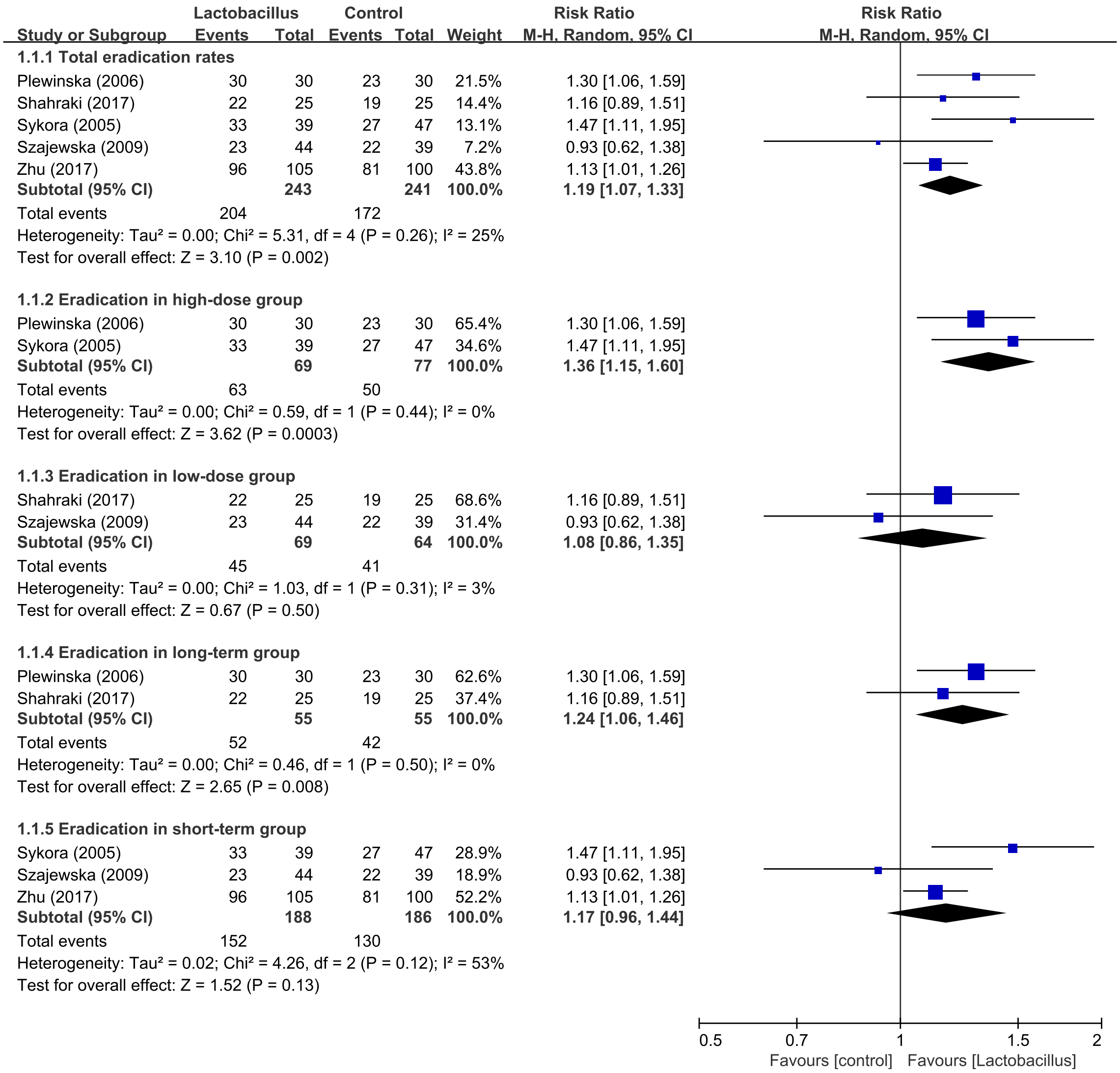


Fig. 3 Effects of *Lactobacillus* supplementation on *H. pylori* eradication rates

characteristics and various dose/duration of *Lactobacillus* supplementation may result in clinical heterogeneity among studies. Thus, we conducted subgroup analyses and adopted the random-effect model to try to account for such variability. In addition, other important outcomes including severity of side effects, and patient compliance were not evaluated in our analysis as relevant data was quite limited within included studies.

Agreement and disagreement with other studies

It was confirmed in our study that *Lactobacillus* supplementation had a beneficial impact on *H. pylori* eradication in children, which was consistent with previous studies [39–41]. A network meta-analysis by Feng et al. [42] pointed out that *Lactobacillus casei* was most appropriate for *H. pylori* eradication in children. However, the results were not convincing enough for ranking the probiotics based on only single trails. Subgroup analysis based on dose of *Lactobacillus* supplementation suggested that a higher dose may enhance the efficacy of *H. pylori* eradication, but Zhang et al. [43] drew inconsistent conclusions. The rational explanations for this pattern are as follows: (i) the pooled RR in those studies was based on different species of probiotics, which may result in erroneous conclusions, (ii) the patients of those studies were mainly adults, and the pooled results in adults cannot be directly extrapolated to children. Besides, duration of supplementation is also an important confounding factor in *H. pylori* eradication. Our subgroup analysis suggested that a longer duration of *Lactobacillus* supplementation may be beneficial in *H. pylori* eradication, and a meta-analysis by Lv et al. [44] also drew similar conclusions.

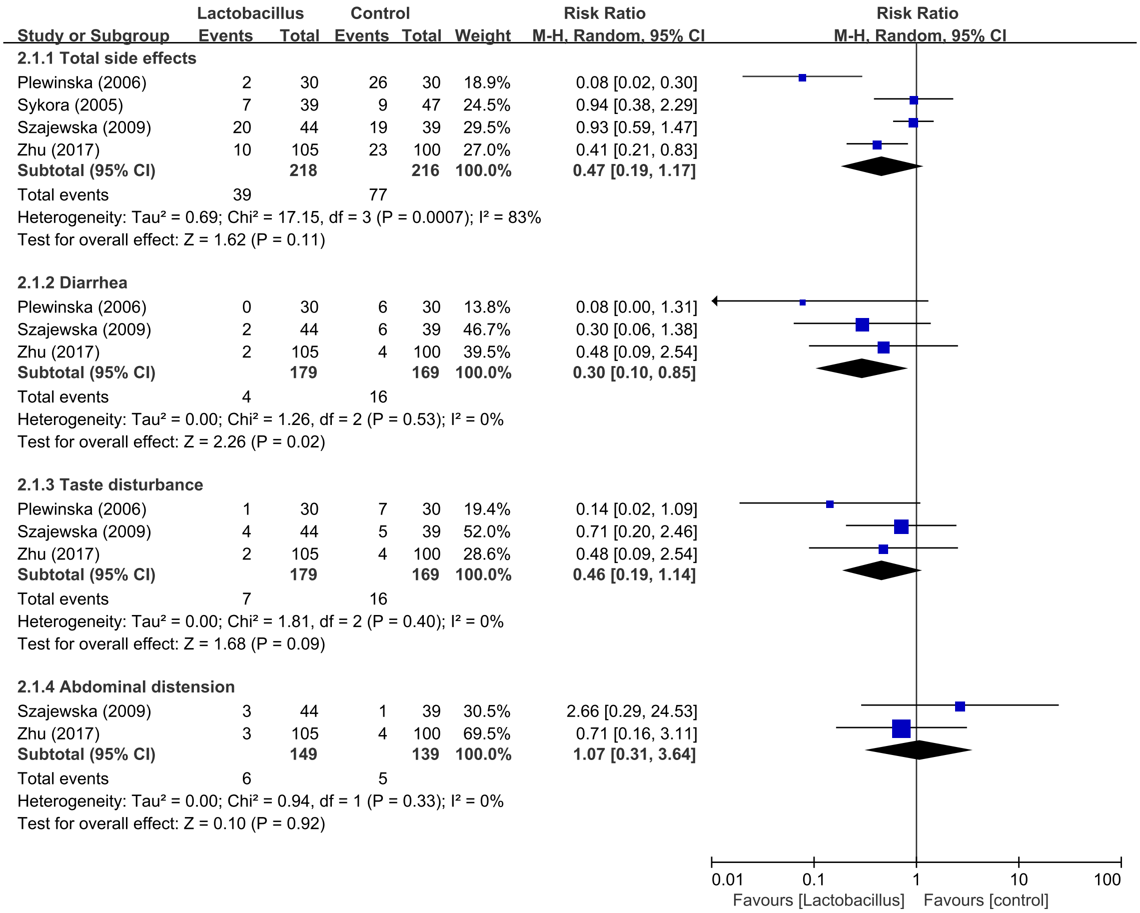


Fig. 4 Effects of *Lactobacillus* supplementation on *H. pylori* eradication therapy-related side effects (total and specific)

However, the results were inconsistent with another two studies [43, 45], which showed increased eradication rates in both short-term and long-term groups. The above explanations for inconsistency of subgroup analysis based on dose of supplementation between our study and previous studies also applied to this pattern.

Our results regarding therapy-related side effects partially supported the conclusion of previous studies in children [10, 42], that is, probiotics supplementation can reduce the incidence of diarrhea. But *Lactobacillus* supplementation did not significantly reduce the incidence of total side effects in our study, which was in accordance with the study by Zheng et al. [39] in adults. Considering the limited included studies and significant heterogeneity regarding total side effects in our analysis, further well-designed and large-scale RCTs are warranted.

In conclusion, the current moderate-quality evidence suggested that *Lactobacillus*, as an adjunct to triple therapy, can increase *H. pylori* eradication rates as well as reduce the incidence of therapy-related diarrhea in children. And a higher dose and a longer duration of supplementation may conduce to the positive impact of *Lactobacillus* on *H. pylori* eradication.

Authors' contributions H-RF: study design, search and selection of articles, data extraction, statistical analysis, drafting the manuscript; G-QZ: data extraction, quality assessment, statistical analysis, revising the manuscript; J-YC: search and selection of articles, quality assessment, statistical analysis; Z-YL: study design, statistical analysis, drafting, and revising the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Not applicable for this manuscript.

Informed consent Not applicable for this manuscript.

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