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ORIGINAL ARTICLE

Sequential Therapy is Superior to Triple Therapy for *Helicobacter pylori* Infection in Children: A Meta-Analysis

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Abstract
Objectives To assess the efficacy and safety of 10-d sequential therapy compared to 5 to 14-d triple therapy for treating *Helicobacter pylori* infections in children according to the eradication rates.
Methods The Cochrane Library, MEDLINE, EMBASE, China National Knowledge Infrastructure databases, and other sources were searched in November 2014 without language restrictions. Randomized controlled trials (RCTs) that compared sequential therapy with triple therapy for *H. pylori* eradication in children were included. Dichotomous data were pooled to obtain the relative risk (RR) of the eradication rate with a 95 % confidence interval (CI).
Results Fourteen RCTs with 1698 participants (718 and 980 for sequential and triple therapy, respectively) were included. The intention-to-treat eradication rates were 73 % (95 % CI: 70–76) and 66 % (95 % CI: 64–70) for sequential and triple therapy, respectively. The pooled RR was 1.16 (95 % CI: 1.09–1.23), resulting in a number needed to treat of 16 (95 % CI: 10–48), favoring sequential therapy. Sequential therapy was superior to 7- and 10-d triple therapy. Sequential and triple therapy did not differ significantly in the overall risk of adverse effects.
Conclusions In children, sequential therapy appears to be superior to triple therapy for *H. pylori* eradication, although the eradication rates remain lower than the expected goal with both treatments. Factors-associated with a higher risk of eradication failure, such as compliance and antimicrobial resistance, remain insufficiently investigated. Therefore, further high-quality RCTs are needed to compare these different eradication treatment approaches.

Keywords *Helicobacter pylori* · Eradication · Sequential therapy · Meta-analysis

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Introduction

Helicobacter pylori is a highly prevalent chronic infectious pathogen in children, which can lead to chronic gastritis, atrophic gastritis, intestinal metaplasia, and a diverse spectrum of extra-gastric disorders [1, 2]. The successful eradication of *H. pylori* can dramatically reduce the rate of recurrence of peptic ulcers in children [3, 4]. Proton pump inhibitor (PPI)-based triple therapy has been recommended as a first-line eradication treatment in combination with an amoxicillin plus nitroimidazole regimen or an amoxicillin plus clarithromycin regimen for 7–14 d [5]. However, recently, the success of eradication using triple therapy has unexpectedly declined [1, 6]. Zullo et al. initially proposed a novel sequential treatment regimen for *H. pylori* infection, consisting of 5 d of treatment with a PPI and a single antibiotic (usually amoxicillin), followed by 5 d of treatment with a PPI and two different antibiotics (usually clarithromycin and nitroimidazole) [5, 7]. Two meta-analyses [8, 9] were performed to assess the efficacy of sequential therapy (ST) compared to triple therapy (TT) in children, and one of the two meta-analyses was later updated by their group [10].

The authors performed a review to compare the effect of a 10-d ST and TT on the *H. pylori* eradication rates in children; some new randomized controlled trials

(RCTs) have been included to update and further consolidate previous findings.

Material and Methods

This meta-analysis followed the guidelines from the Cochrane Handbook for Systematic Reviews of Interventions [11] and the meta-analyses (PRISMA) statement [12].

Included studies had to meet the following criteria using the PICOS approach: (i) Participants: children aged below 18 y who had *H. pylori* infection, confirmed using generally accepted methods (*i.e.*, bacterial culture, ^{13}C-urea breath test [^{13}C-UBT], histopathology, *H. pylori* stool antigen test, blood test, or rapid urease test); (ii) Intervention: ST; (iii) Comparison: TT; and (iv) Primary outcome: The *H. pylori* eradication rate, which was determined by a negative ^{13}C-UBT or other generally accepted methods by at least 4 wk post-treatment; Secondary outcomes: The rate of side effects (*e.g.*, abdominal pain, nausea, vomiting, diarrhea, taste disturbance, and constipation), compliance, and the need to discontinue *H. pylori* therapy; and (v) Study design: RCTs.

The authors performed an electronic search to identify relevant studies from the following databases in November 2014: The Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and China National Knowledge Infrastructure database. There was no language restriction, and the principal search text word terms and medical subject headings used were as follows: (i) *Helicobacter pylori* OR *H. pylori*; (ii) sequential treatment OR sequential therapy; (iii) children OR adolescents. The sets of terms (i), (ii), and (iii) were combined with "AND" operator. The reference lists from the included studies and key review articles were reviewed to identify other published or unpublished data that could be included.

In a double-blinded separate manner, two investigators (YH and XZ) performed the search, selected the studies, and performed quality assessment and data extraction using a predefined and standardized collection form to increase uniformity and reduce reporting bias. From each report, reviewers extracted basic information, details of treatment, confirming method for *H. pylori* infection, and side effects. The corresponding authors of the included studies were contacted for any missing data points. Any disagreements were resolved by a consensus decision between the two reviewers.

The Cochrane Collaboration's tool for assessing the risk of bias was used, which includes the following specific domains: Adequacy of sequence generation, allocation concealment and blinding of participants, personnel and outcome assessors, and incomplete outcome data. "Yes" indicates a low risk of bias, and "No" indicates a high risk of bias [13]. In addition, the authors assessed the presence of publication bias by visually inspecting funnel plot asymmetry and by applying Egger's test [14] for asymmetry.

The primary outcome was the relative risk (RR) of successful eradication of *H. pylori* based on intention-to-treat (ITT) when comparing ST to TT. Preplanned subgroup analyses were performed based on the duration of TT (5, 7, 10, or 14 d). The authors also performed subgroup analyses to compare the findings of RCTs available as full-text publications with those reported in abstract form only. The secondary outcome measures were the RR of side effects.

Heterogeneity was assessed by the I^2 statistic, which can be interpreted as the percentage of the observed variation between included studies that is attributable to heterogeneity rather than to chance. Values of 25, 50, and 75 % were used as outer limits for low, moderate and high heterogeneity, respectively [15]. If the I^2 value was >50 %, heterogeneity was considered to be significant. When there was a statistically significant heterogeneity of the primary outcome between studies, sensitivity analyses were performed to evaluate the differences in the quality of trials, resistance to clarithromycin, adherence, *etc*.

All the RRs were pooled using the fixed effects model (Mantel-Haenszel method), and a two-sided P value ≤ 0.05 was regarded as significant. Where significant heterogeneity was detected, a random effect model was additionally assessed, if appropriate. The data were analyzed using Review Manager (version 5.2; The Nordic Cochrane Center, The Cochrane Collaboration, 2011, Copenhagen, Denmark). The number needed to treat (NNT), with a 95 % confidence interval (CI) and the Egger's test, were calculated using the StatsDirect statistical software (version 2.7.9; StatsDirect, Altrincham, UK).

Results

A flow diagram illustrating the study retrieval method is shown in Fig. 1. Of the 104 potentially relevant studies, 14 RCTs were included in this meta-analysis [16–29]. Ten of 14 were full-text publications [16, 19, 21, 23–29], and four were published in abstract form [17, 18, 20, 22]. All the trials were published in English, except for three publications in Chinese [19, 24, 25]. The characteristics of the included studies are summarized in Table 1.

The selected trials included 1,698 randomized participants aged below 18 y. The sample sizes ranged 30–360 participants. The studies were performed in European countries (Belgium, France, Italy, Poland, Romania, and Turkey), Asia (China), and Africa (Kenya). Except for two multicenter trials [21, 26], all the studies were single-center trials.

The TT consisted of a PPI (Omeprazole or lansoprazole) and two antibiotics, except in two trials that included three antibiotics [18, 22]. One of the 14 RCTs [21] had a tailored

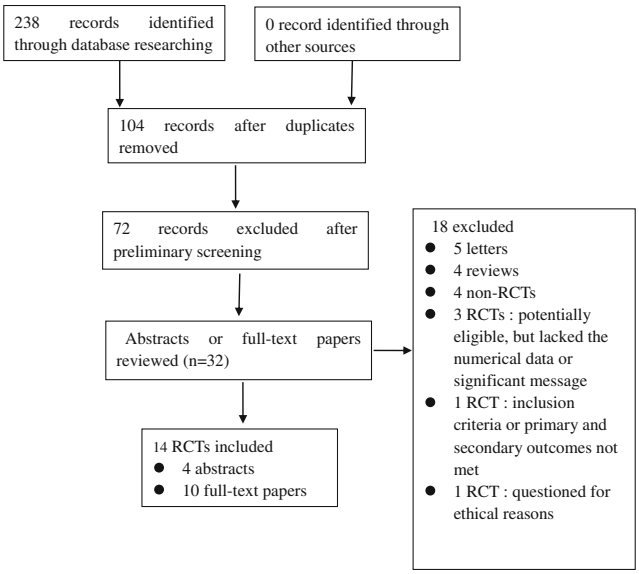

Fig. 1 Identification process of eligible RCTs to be included in the meta-analysis. *RCT* Randomized controlled trial

triple therapy regimen, which selected either clarithromycin or metronidazole according to the antimicrobial susceptibility testing. In one of the 14 RCTs [24], the two antibiotics used in TT had two regimens. In seven of the 14 RCTs, the duration of triple therapy was 7 d. In the remaining studies, the duration of triple therapy was 5 d [22], 10 d [19, 24–27, 29], or 14 d [18, 20, 25, 28]. In two of the RCTs [18, 26], the comparison groups had two arms. The participants were randomly assigned to one of three groups: an intervention group that received ST, a 7-d TT group and a 10-d TT group, or a 7-d TT group and a 14-d TT group. The objective of the index review was to compare ST with TT; thus, the TT arms were combined into a single TT group. However, in the subgroup analysis based on the duration of TT, ST was compared with the two different TTs. Another RCT compared ST with three TTs, differing only in the duration of the TT group (7, 10, and 14 d) [25]. The three TTs arms were combined into a single TT group, but in the subgroup analysis based on the duration of TT, ST was compared with the three different TT groups. The ST consisted of a PPI (Omeprazole or lansoprazole) and amoxicillin administered for the first 5 d, followed by a PPI and two antibiotics administered for another 5 d. Details of the ST and TT are presented in Table 2.

Only three of the 10 RCTs published as full-text publications were judged to have a low risk of bias [16, 23, 27]. The trials published in abstract form had a number of methodological limitations or lacked adequate information to assess the overall risk of bias (Table 3). The funnel plot of the RR from

Table 1 Characteristics of the RCTs included in the meta-analysis

Study ID (Country)	Publication type	Population age (y)	No. of patients	Test used to assess *H. pylori*	Sequential therapy (days)	Standard triple therapy (days)	Test used to assess eradication
Francavilla 2005 [16] (Italy)	Full-text	3.3–18	75	Two of 3: UBT, RUT, HA	5+5	7	UBT 8 wk
Lerro 2006 [17] (Italy)	Abstract	11.9–12.3 (Median)	50	HA, RUT, UBT	5+5	7	UBT 6 wk
Hurduc 2007 [18] (Romania)	Abstract	3–18	135	HA, UBT	5+5	7–14	UBT
Lu 2010 [19] (China)	Full-text	10.2±2.8 10.7±2.4 (Mean)	76	One of 2; blood test & UBT, RUT	5+5	10	UBT 4 wk
Baysoy 2010 [20] (Turkey)	Abstract	4–18	62	UBT, HA	5+5	14	UBT 8 wk
Bontems 2011 [21] (Belgium, France, Italy)	Full-text	2.7–17	165	HA, culture	5+5	7	UBT 8 wk
Anania 2011 [22] (Italy)	Abstract	4.8–14.1 5.8–16.7	30	Two of 3: UBT, HA, RUT	5+5	5	UBT 8 wk
Albrecht 2011 [23] (Poland)	Full-text	3–18	107	Two of 3: UBT, HA, RUT	5+5	7 (+3d placebo)	UBT 6–8 wk
Liu 2011 [24] (China)	Full-text	3–13 3.5–14 3–13	100	UBT, RUT	5+5	10	UBT 4 wk
Huang 2012 [25] (China)	Full-text	3–18	214	Two of 3: RUT, HA, culture	5+5	7–14	UBT 4 wk
Huang 2013 [26] (China)	Full-text	3–16	360	Culture or two of 3: HA, RUT, StAT	5+5	7–10	StAT 4 wk
Laving 2013 [27] (Kenya)	Full-text	0–16	104	HA	5+5	10	StAT &/or HA 6 wk
Baysoy 2013 [28] (Turkey)	Full-text	4–18	72	HA & one of 2: UBT, RUT	5+5	14	UBT 6–8 wk
Kutluk 2014 [29] (Turkey)	Full-text	3–18	148	RUT, HA	5+5	10	UBT 4–6 wk

UBT ^{13} C-urea breath test; *HA* Histopathology; *RUT* Rapid urease test; *StAT* Stool antigen test

Table 2 Details of sequential therapy and triple therapy

Reference	Sequential therapy first 5 d	Dose (mg/kg/d)	Sequential therapy second 5 d	Dose (mg/kg/d)	Triple therapy	Dose (mg/kg/d)
Francavilla 2005 [16]	AMO	50	CLA	15	AMO	50
	OME	1	TIN	20	MET	15
			OME	1	OME	1
Lerro 2006 [17]	AMO	50	CLA	15	AMO	50
	OME	1	TIN	20	TIN	20
			OME	1	OME	1
Hurduc 2007 [18]	AMO	?	CLA	?	AMO	?
	OME	?	TIN	?	CLA	?
			OME	?	TIN	?
					OME	?
Lu 2010 [19]	AMO	40	CLA	15	AMO	40
	OME	0.8	TIN	15	CLA	15
			OME	0.8	OME	0.8
Baysoy 2010 [20]	AMO	?	CLA	?	AMO	?
	LAN	?	ORN	?	CLA	?
			LAN	?	LAN	?
Bontems 2011 [21]	AMO	50	CLA	15	AMO	50
	OME (Dose per day)	20 mg <30 kg	MET	20 mg	CLA or	15
		40 mg >30 kg	OME (Dose per day)	20 mg <30 kg	MET	20
				40 mg>30 kg	OME (Dose per day)	20 mg <30 kg
						40 mg >30 kg
Anania 2011 [22]	AMO	?	CLA	?	AMO	?
	OME	?	TIN	?	CLA	?
			OME	?	TIN	?
					OME	?
Albrecht 2011 [23]	AMO	50	CLA	20	AMO	50
	OME	1	TIN	20	CLA	20
			OME	1	OME	1
					PBO	
Liu 2011 [24]	AMO	30–50	CLA	15	AMO	30–50
	OME	0.9	MET	15–20	CLA or	15
			OME	0.9	MET	15–20
					OME	0.9
Huang 2012 [25]	AMO	50	CLA	20	AMO	50
	OME	0.8–1.0	MET	20	CLA	20
			OME	0.8–1.0	OME	0.8–1.0
Huang 2013 [26]	AMO	30	CLA	20	AMO	30
	OME	0.8–1.0	MET	20	CLA	20
			OME	0.8–1.0	OME	0.8–1.0
Laving 2013 [27]	AMO	50	CLA	15	AMO	50
	OME	1	TIN	20	CLA	15
			OME	1	OME	1
Baysoy 2013 [28]	AMO	50	CLA	15	AMO	50
	LAN	1	ORN	30	CLA	15
			LAN	1	LAN	1
Kutlok 2014 [29]	AMO	50	CLA	20	AMO	50
	LAN	1	MET	20	CLA	20
			LAN	1	LAN	1

AMO Amoxicillin (AMO; amoxicillin-clavulanate); *MET* Metronidazole; *CLA* Clarithromycin; *LAN* Lansoprazole; *OME* Omeprazole; *ORN* Ornidazole; *PBO* Placebo; *TIN* Tinidazole

Table 3 A summary table of review of authors' judgements for each risk of bias item for each study

Reference	Adequate sequence generation	Allocation concealment	Blinding	Incomplete data addressed (%)
Francavilla 2005 [16]	Yes	Yes	No	74/75 (99)
Lerro 2006 [17]	Unclear	Unclear	Unclear	50/50 (100)
Hurduc 2007 [18]	Unclear	Unclear	Unclear	135/135 (100)
Lu 2010 [19]	Unclear	Unclear	No	71/74 (93)
Baysoy 2010 [20]	Unclear	No	No	46/62 (74)
Bontems 2011 [21]	Unclear	Unclear	No	150/165 (91)
Anania 2011 [22]	Unclear	Unclear	Unclear	30/30 (100)
Albrecht 2011 [23]	Yes	Yes	Yes	103/107 (96)
Liu 2011 [24]	Yes	Unclear	No	93/100 (93)
Huang 2012 [25]	Unclear	Unclear	Yes	199/214 (93)
Huang 2013 [26]	Unclear	Unclear	No	318/360 (88)
Laving 2013 [27]	Yes	Yes	Yes	71/104 (68)
Baysoy 2013 [28]	Unclear	Unclear	Unclear	61/72 (85)
Kutulk 2014 [29]	Unclear	Unclear	Unclear	136/148 (92)

In all cases, an answer of 'Yes' indicates a low risk of bias, and an answer of 'No' indicates a high risk of bias

the 14 RCTs showed clear asymmetry favoring ST, as evidenced by the absence of trials in the lower right-hand portion of the triangle (Fig. 2). The result of the Egger's test (bias= −1.067905 [95 % CI: −2.804128 to 0.668318], *P* 0.205) provided no statistical evidence for publication bias. However, the sensitivity of the Egger's test was generally low in meta-analyses based on <20 trials [30]; thus, caution is necessary in interpreting the result.

There were 1698 participants (718 for ST and 980 for TT) enrolled in the included studies (Fig. 3). The eradication rate was 73 % (524/718) for ST (95 % CI: 70–76) and 66 % (651/980) for TT (95 % CI: 64–70). The pooled RR from 14 RCTs using the fixed model was 1.16 (95 % CI: 1.09–1.23), yielding a NNT of 16 (95 % CI: 10–48) favoring ST. However, the I^2 showed a moderate degree of heterogeneity (30 %).

The pooled RRs from the trials published as full-text papers and abstracts using the fixed model were 1.19 (95 % CI: 1.11–1.27) and 1.00 (95 % CI: 0.89–1.13), respectively (Fig. 3). No evidence of heterogeneity was found in either comparison. Only the trials published as full-text publications found that ST had a statistically significant advantage.

The results of the trials based on the duration of TT are shown in Fig. 4. There was only a higher eradication rate when comparing the 7-d or 10-d STT (seven RCTs, *n*=830, RR: 1.22, 95 % CI: 1.13–1.32 and six RCTs, *n*=779, RR: 1.20, 95 % CI: 1.09–1.32). No such effect was found when compared to 14-d TT. No evidence of high heterogeneity was

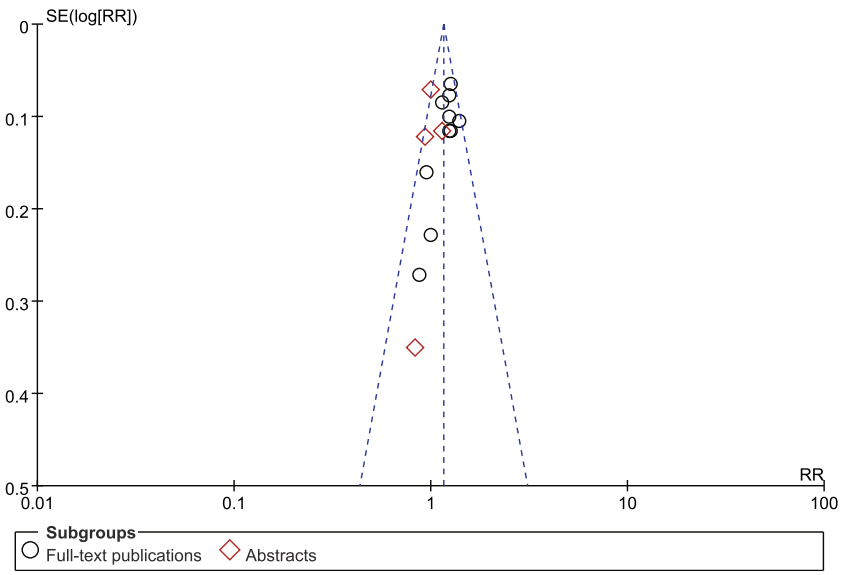

Fig. 2 Funnel plot of the included studies

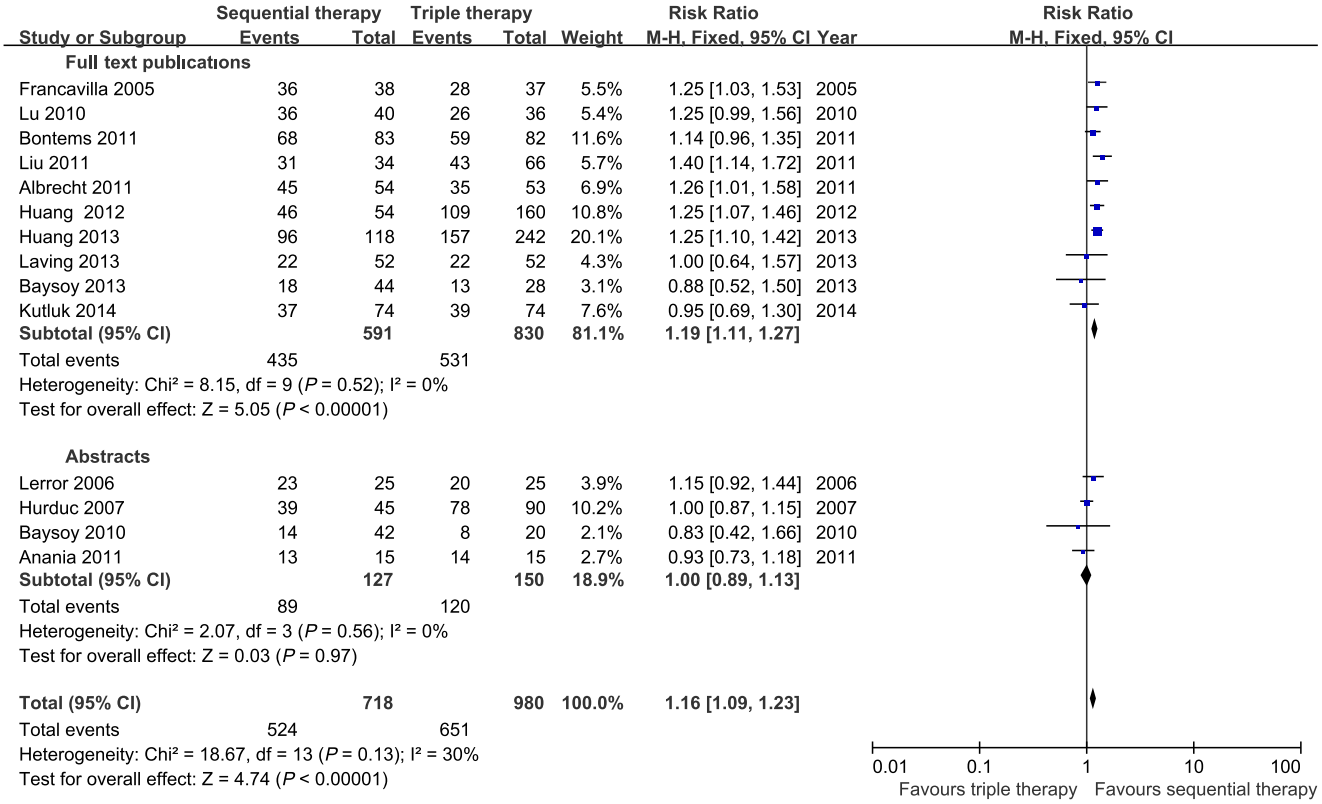

Fig. 3 Forest plot of eradication rates in children treated with sequential or triple therapy

found in the three comparisons. Only one RCT analyzed a 5-d STT, and since it was underpowered, no firm conclusion could be drawn.

Data regarding therapy-related adverse effects were available from eight of the included trials [16, 19–21, 23, 25, 26, 28] (Fig. 5). No significant differences between the study groups with respect to the overall risk of adverse effects were found (Eight RCTs, n=1131, RR: 1.05, 95 % CI: 0.85–1.30). No evidence of high heterogeneity was found. In addition, no significant differences between the study groups with respect to abdominal pain were found (Four RCTs, n=388, RR: 1.23, 95 % CI: 0.74–2.03).

The need to discontinue the eradication treatment was reported in five trials [16, 20, 21, 23, 24] (Seven patients; one in the ST group [20] and six in the TT group [20, 21, 24]).

Compliance was assessed in six RCTs [16, 20–23, 29], and in all of these studies, compliance was claimed to be excellent, with no significant differences between the study groups.

Discussion

This meta-analysis shows that the ITT eradication rates of *H. pylori* were 73 % for ST and 66 % for TT in the pediatric population. However, ST did not obviously improve the eradication rates; the NNT for one additional child to be eradicated was 16. In addition, the absolute pooled eradication rate of ST did not reach the expected level (80 % in the intention-to-treat analysis and 90 % in the per-protocol analysis) [31], and the anti-microbial susceptibility may account for this. A recent review summarized the resistance rates for commonly used antimicrobial agents in different parts of the world and showed that clarithromycin-resistance is a major problem in most developed counties, with a few notable exceptions, such as in Scandinavia [32]. This has not been systematically assessed in the present review. However, only two RCTs [21, 29] provided related data on the eradication rate according to pre-treatment antimicrobial susceptibility testing. Since the response to eradication therapy is significantly related to the prevalence of primary resistance in the population, the choice of treatment regimen should be based on the knowledge of the underlying prevalence of resistant strains in the community, which need to be closely monitored.

Two previous meta-analyses [8, 9] have assessed the efficacy of ST compared to TT in children successively. However, the present meta-analysis further consolidates and adds to the evidence reported in previous meta-

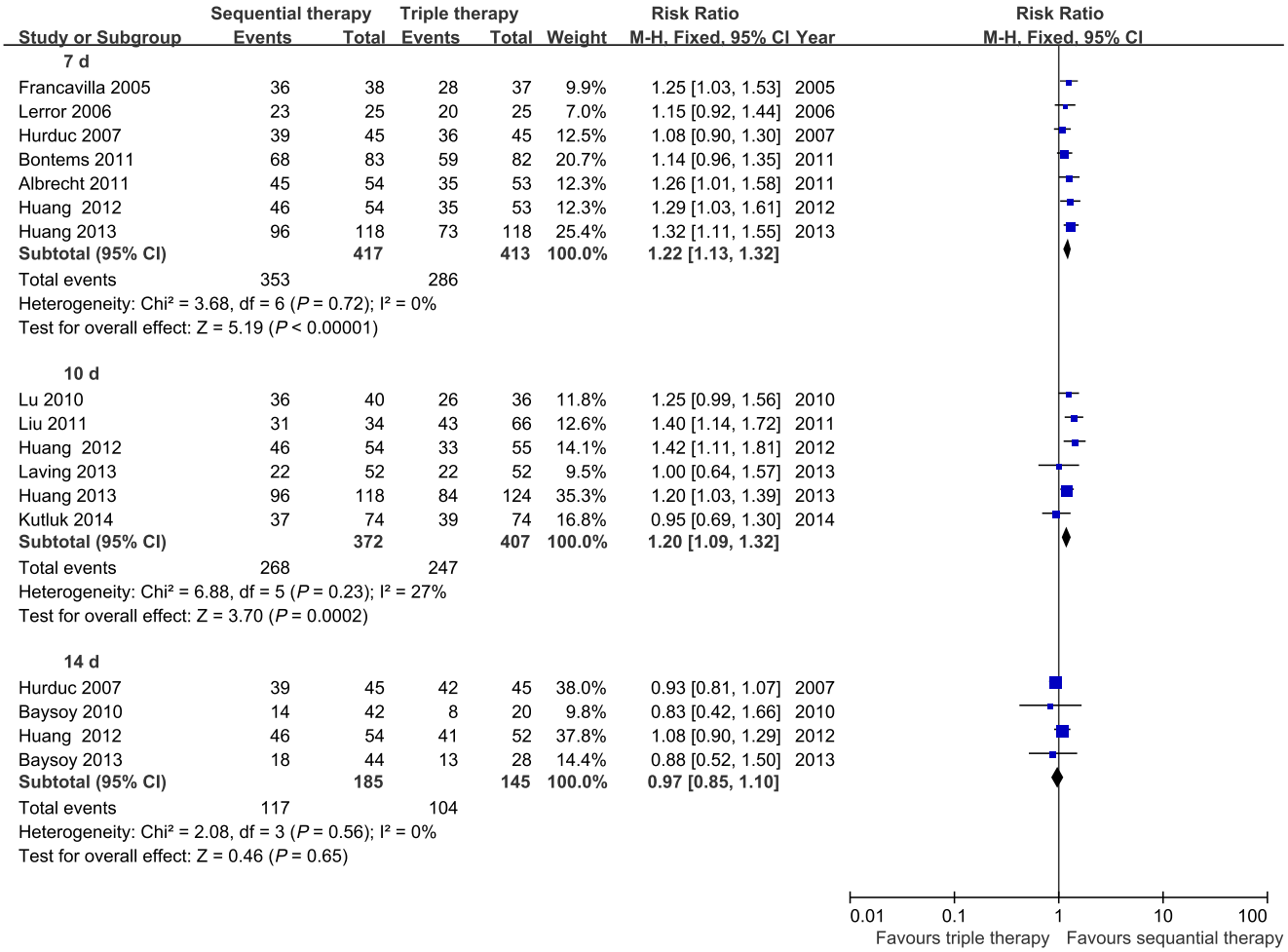

Fig. 4 Forest plots of eradication rates in children treated with sequential or triple therapy based on the duration of triple therapy

analyses conducted in children. First, the authors carefully analyzed the meta-analysis performed by Gatta et al. [8] who concluded that ST is superior to triple therapy for *H. pylori* eradication. However, this finding was only obvious in the adult population (10 RCTs, n= 3006, RR: 2.99, 95 % CI: 2.47–3.62). In the pediatric population, ST showed no statistically significant advantage in *H. pylori* eradication (Three RCTs, n=260, RR: 1.98, 95 % CI: 0.96–4.07). The eradication of *H. pylori* observed in adults was obviously higher compared to that in children studied in the present review. Second, the other meta-analysis performed by Horvath et al. [9], which was later updated by their group [10] and excluded data from one RCT for ethical reasons, found a significant difference between the ST and TT group with respect to the *H. pylori* eradication rates in the pediatric population (9 RCTs, n=813, RR: 1.11, 95 % CI: 1.03–1.20). Although the evidence was limited, the findings of the trials based on the duration of TT showed that ST was only superior to 7-d TT, which differs from the conclusion of the present analysis that ST is superior to 7- and 10-d TT. Neither the index analysis nor the two relevant aforementioned meta-analyses found significant differences in the rate of adverse effects between the ST and TT groups.

This meta-analysis has several potential limitations. First, determining the antimicrobial susceptibility is useful for choosing the best treatment option and/or for managing treatment failure, particularly with clarithromycin [1, 5]. However, only two RCTs [21, 29] provided the related data. Unfortunately, antimicrobial susceptibility testing is still not widely available in the United States and other countries; therefore, the availability of new kits that can perform susceptibility testing (*e.g.*, by using real-time polymerase chain reaction in stool) will likely make matters easier in the future [32]. Second, there was no available RCT data from North America or other regions, which may limit the generalizability. Third, not all studies conformed to the diagnosis standard of *H. pylori* infection that was

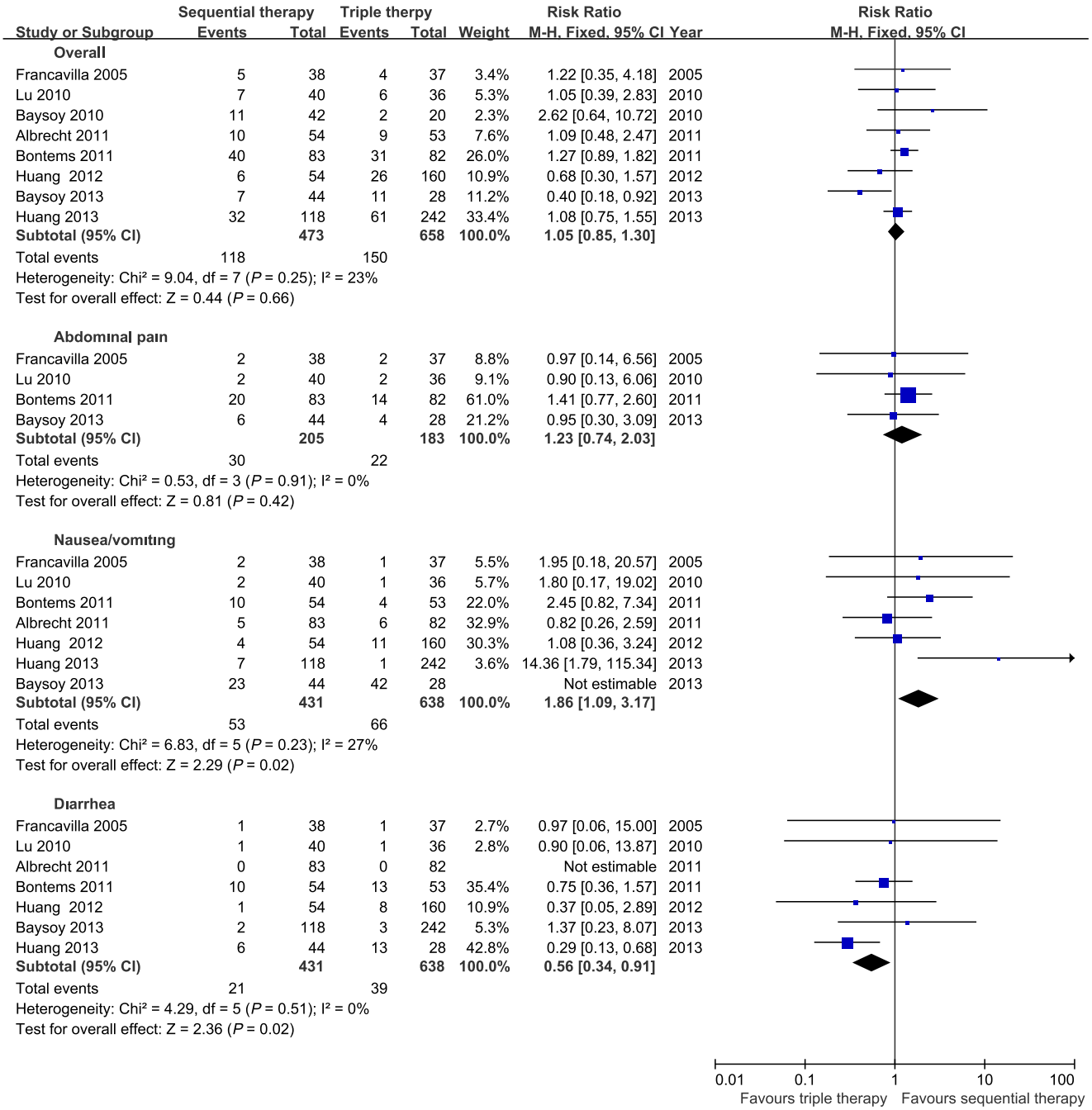

Fig. 5 Forest plots of *H. pylori* eradication therapy-related adverse effects in children treated with sequential therapy or triple therapy

recommended and based on a positive histopathology plus a positive rapid urease test, or a positive culture [5]. Fourth, adherence to the treatment regimen is difficult to measure, and incomplete data are provided in the studies on compliance. Lastly, the strength of the present conclusions may be reduced by the varied methodological quality of the included RCTs.

Conclusions

This meta-analysis provides evidence that 10-d ST is superior to either 7- or 10-d TT. However, the improvement was only moderate, and the absolute pooled eradication rate of ST did not reach the expected level. Factors-associated with a higher risk of eradication failure, such as compliance and

antimicrobial resistance, remain insufficiently investigated. Therefore, further high-quality RCTs are needed to compare these different eradication treatment approaches.

Conflict of Interest None.

Source of Funding None.

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