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Global eradication rates for *Helicobacter pylori* infection: systematic review and meta-analysis of sequential therapy



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Abstract

Objective To do a systematic review and meta-analysis of studies comparing sequential therapy for eradication of *Helicobacter pylori* with pre-existing and new therapies, thus providing a glimpse of eradication success worldwide.

Design Systematic review and meta-analysis.

Data sources Medline, Embase, and Cochrane Central Register of Controlled Trials up to May 2013; abstract books of major European, American, and Asian gastroenterological meetings.

Study selection Randomised controlled trials in previously untreated adults, in which sequential therapy was compared with a pre-existing or new therapy.

Results 46 randomised controlled trials were reviewed and analysed. 5666 patients were randomised to sequential therapy and 7866 to other (established and new) treatments. The overall eradication rate of sequential therapy was 84.3% (95% confidence interval 82.1% to 86.4%). Sequential therapy was superior to seven day triple therapy (relative risk 1.21, 95% confidence interval 1.17 to 1.25; $I^2=29.3%$; number needed to treat 6, 95% confidence interval 5% to 7%), marginally superior to 10 day triple therapy (1.11, 1.04 to 1.19; $I^2=67.2%$; NNT 10, 7 to 15), but not superior to 14 day triple therapy (1.00, 0.94 to 1.06; $I^2=54.3%$), bismuth based therapy (1.01, 0.95 to 1.06; $I^2=21.1%$), and non-bismuth based therapy (0.99, 0.94 to 1.05; $I^2=52.3%$). Data on eradication according to pre-treatment antimicrobial susceptibility testing were available in eight studies, and sequential therapy was able to eradicate 72.8% (61.6% to 82.8%) of the strains resistant to clarithromycin.

Conclusions Eradication rates with pre-existing and new therapies for *H pylori* are suboptimal. Regional monitoring of resistance rates should help to guide treatment, and new agents for treatment need to be developed.

Introduction

Helicobacter pylori infection causes peptic ulcers, gastric mucosa associated lymphoid tissue lymphoma, and gastric cancer.¹ Standard treatments for *H pylori* infection that have been endorsed by US as well as European scientific societies and by regulatory authorities rely on clarithromycin, metronidazole, or amoxicillin in conjunction with gastric acid inhibitors.^{2,3} The prevalence of resistance to clarithromycin and metronidazole has increased substantially in recent years, and a corresponding decrease has occurred in the eradication rate for *H pylori* infection,⁴ which has declined to unacceptable levels in most Western countries.⁵ A new treatment regimen that would achieve the eradication rates of 90% or greater seen at the advent of *H pylori* treatment is urgently needed.⁵ Such a regimen would need to have high efficacy against clarithromycin resistant and metronidazole resistant strains of *H pylori*, as these strains are increasingly encountered in routine clinical practice. As the response to eradication therapy is significantly related to the prevalence of primary resistance in the population, the choice of a treatment regimen should be based on the knowledge of the underlying prevalence of resistant strains in the community, which needs to be monitored.

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Supplementary tables
Supplementary figures

Sequential therapy, a new regimen administering antimicrobials in a given sequence rather than all simultaneously, has generated worldwide interest. This kind of treatment is not actually new, as it uses established drugs, all approved for eradication of *H pylori*. However, the administration strategy is innovative. The sequential regimen is a simple dual therapy including a proton pump inhibitor plus amoxicillin 1 g (both twice daily) given for the first five days, followed by a triple therapy including a proton pump inhibitor, clarithromycin 500 mg, and a nitroimidazole antimicrobial (all twice daily) for the remaining five days. Initial studies of sequential therapy suggested that its superiority over standard triple therapy might be due to improved eradication of clarithromycin resistant strains.^{6 7}

Recently, several randomised controlled trials have compared sequential therapy with other established and new therapies. These provide a glimpse into eradication rates for *H pylori* in the countries where those studies were conducted. The aim of this study was to assess the efficacy of sequential therapy compared with other eradication regimens, by doing a systematic review and meta-analysis of randomised controlled trials.

Methods

Search strategy and study selection

This meta-analysis was developed according to the PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement guidelines.⁸ We searched the medical literature by using Medline (1950 to May 2013), Embase (1980 to May 2013), and the Cochrane Central Register of Controlled Trials (May 2013). Randomised controlled trials examining the eradication rate of sequential therapy compared with other treatments were eligible for inclusion (box). We identified eligible studies with the terms “*Helicobacter pylori*”, “*H. pylori*”, “*H pylori*”, “*Campylobacter pylori*”, “*C. pylori*”, “*C pylori*”, “infection”, “dyspepsia”, “sequential”, “triple”, “concomitant”, “quadruple”, “treatment”, “therapy”, “omeprazole”, “lansoprazole”, “rabeprazole”, “pantoprazole”, “esomeprazole”, “bismuth”, “clarithromycin”, “metronidazole”, “tinidazole”, “amoxicillin”. We imposed no language restrictions. Two investigators (LG and NV) evaluated abstracts of the papers identified by the initial search for appropriateness, independently and in a blinded manner. Foreign language papers were translated where necessary. We also searched the abstract books from the British Society of Gastroenterology (2001-12), American Gastroenterological Association (2000-13), American College of Gastroenterology (2004-12), United European Gastroenterology Week (2000-12), European *Helicobacter pylori* Study Group (2000-12), and Asian Pacific Digestive Week (2003-12). We used bibliographies of all relevant studies identified to do a recursive search. In addition, we contacted authors to obtain unpublished data from their studies, whenever we deemed it necessary.

Outcome assessment

The primary outcome was the efficacy of sequential therapy compared with established and new therapies in eradicating *H pylori* infection. Secondary outcomes included safety and efficacy according to the antimicrobial resistance pattern, where reported.

Data extraction

Two investigators (LG and NV) assessed articles independently, using pre-designed data extraction forms. Disagreement between investigators was resolved by discussion with the other two

investigators (DV and CS). Data on eradication were based on intention to treat analysis. In addition, the following clinical data were extracted for each trial: country of origin, type of publication (article, abstract), proton pump inhibitor used, use of tinidazole (versus other nitroimidazole derivatives), duration of comparative eradication treatment, and adverse event rate.

Evaluation of risk of bias

We assessed risk of bias as described in the Cochrane handbook,⁹ by evaluating the random sequence generation, concealment of allocation, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. We considered randomised controlled trials as being at low risk of bias if all the domains except blinding of participants or personnel were properly assured. As the outcome (that is, eradication) was almost always assessed by objective means, we did not consider blinding to be crucial.

Statistical analysis

We assessed data for the primary outcome by using a random effects model,¹⁰ to give a conservative estimate of the 95% confidence intervals. Results were expressed as relative risk for success of *H pylori* eradication and as difference in eradication rates among patients assigned to sequential therapy versus other eradication regimens. We also used a random effects model to pool data for safety,¹⁰ and expressed them as relative risk for adverse events. We required at least three comparable study groups for every comparison for randomised controlled trials to be included in the meta-analysis. We also calculated prediction intervals at 95% confidence intervals for the primary outcome, as they might be considered a more appropriate future treatment summary.^{11 12}

We assessed heterogeneity between trials with the χ^2 test for heterogeneity at a significance level of $P < 0.1$. We also calculated the I^2 statistic.¹³ Its value ranges from 0% to 100%, with 0% representing no observed heterogeneity and larger values indicating increasing heterogeneity. We chose a value below 25% to represent low levels of heterogeneity.¹³ When the degree of statistical heterogeneity was greater than this cut-off between trial results for the primary outcome, we investigated possible explanations by using subgroup analyses according to country of origin, use of tinidazole as the nitroimidazole derivative in the sequential treatment, type of publication (abstract versus article), proton pump inhibitor used, duration of comparative treatment (when applicable), and trials with a high risk and unclear risk of bias versus a low risk of bias. As exploratory analyses, they may explain some of the observed variability between trials. We used the Cochran Q statistic to compare the relative risks between studies in the analyses.⁹

We used a random effects model to calculate eradication rates of regimens.¹⁰ We calculated proportions, their differences, and 95% confidence intervals by using the method recommended by Newcombe and Altman. We calculated the number needed to treat and 95% confidence intervals from the reciprocal of the risk difference of the meta-analysis. We used Stata version 10.1 to generate forest plots for primary and secondary outcomes with 95% confidence intervals, as well as funnel plots. We assessed funnel plots for evidence of asymmetry and possible publication bias or other small study effects, by using the Egger's linear regression and regarding a two sided P value of 0.10 or less as significant.¹⁴

Eligibility criteria

- Randomised controlled trials*
- Patients aged ≥ 18 years
- Patients never treated before for *Helicobacter pylori* infection
- Patients without significant comorbidity (for example, renal failure, hepatic failure, cancer)
- Helicobacter pylori* infection diagnosed (before and after treatment) using at least one of histology, rapid urease test, ^{13}C urea breath test, stool test, culture†
- Randomised controlled trials comparing sequential treatment‡ with other eradication regimens
- Eradication rate according to intention to treat analysis
- Eradication assessed at least four weeks after end of treatment

*Articles and/or abstracts reporting only interim analysis of randomised controlled trials were not included

†Articles and/or abstracts not reporting test used to diagnose infection and/or to follow-up infection were not included

‡Sequential treatment defined as proton pump inhibitors twice daily + amoxicillin 1 g twice daily for five days followed by proton pump inhibitors twice daily + clarithromycin 500 mg twice daily + nitroimidazole derivatives twice daily for next five days

Results

The search strategy we used identified 610 citations, of which we excluded 545 after examining the title and abstract. We retrieved and evaluated 65 articles in more detail. Of these, we excluded 19 for various reasons, leaving 46 randomised controlled trials that were eligible for inclusion,^{6 7 15-58} as shown in figure 1, 11 of which were abstracts.^{15 22 24 36 38 45 46 49 53 56 57} Fifteen studies included more than two arms.^{16 19 24 27 29 32-34 38 39 48-50 57 58} Three studies could not be included in the meta-analysis because our criteria required at least three comparable study groups for every comparison.^{32 47 54} Only four trials were at low risk of bias.^{7 32 51 55} The table shows detailed characteristics of the studies included in the systematic review and meta-analysis. Supplementary table A shows a complete evaluation of risk of bias.

Meta-analysis**Sequential therapy versus triple therapy lasting seven days**

Twenty two studies compared sequential therapy with a triple therapy regimen lasting seven days.^{6 15 16 18-26 30 33 36 38 39 42 43 46 48 52} No trial was at low risk of bias, and two trials did not report full data on the proton pump inhibitor used.^{24 48} As shown in figure 2, the pooled relative risk was 1.21 (95% confidence interval 1.17 to 1.25), favouring sequential treatment, the number needed to treat was 6 (95% confidence interval 5 to 7), and the 95% prediction intervals ranged from 1.10 to 1.33. We found evidence of heterogeneity ($I^2=29.3\%$; $P=0.098$), without funnel plot asymmetry (Egger's test coefficient -0.69 , 90% confidence interval -1.71 to 0.33 ; $P=0.257$).

In all, 2449 patients were treated with the sequential therapy compared with 2566 patients treated with triple therapy lasting seven days, and the eradication rate reported was 86.5% (95% confidence interval 82.9% to 89.7%) for the sequential therapy and 71.5% (68.4% to 74.5%) for the triple therapy. The difference in eradication rates was 15% (13% to 18%) favouring sequential treatment, and the 95% prediction intervals ranged from 9% to 22% (supplementary figure A), with evidence of heterogeneity ($I^2=34.0\%$; $P=0.061$).

Because of the heterogeneity, we did subgroup analyses according to country of origin, use of tinidazole in the sequential therapy, type of publication, and proton pump inhibitor used; we did not evaluate risk of bias, as all trials were at high or unclear risk of bias (supplementary table B). We found a slightly statistically significant effect in favour of sequential therapy in trials conducted in China, Italy, Korea, and Morocco.

One of these studies compared sequential therapy with both proton pump inhibitor-amoxicillin-clarithromycin and proton pump inhibitor-amoxicillin-metronidazole.⁴⁸ The eradication rate of sequential therapy was 24.0% (13.6% to 33.5%) higher than proton pump inhibitor-amoxicillin-clarithromycin and 15.9% (7.1% to 25.1%) higher than proton pump inhibitor-amoxicillin-metronidazole. One trial also compared sequential therapy with a modified triple therapy (and for this reason we did not include this arm in the meta-analysis) consisting of proton pump inhibitor twice daily, clarithromycin 500 mg twice daily, and amoxicillin 1000 mg three times daily for seven days. No significant difference in eradication rate was observed between the two treatments ($P=0.750$).³⁸

Data on adverse events were available in 18 trials.^{6 16 18-21 23 25 26 30 33 38 39 42 43 46 48 52} The pooled relative risk was 1.11 (0.97 to 1.27), indicating no significant difference, with no evidence of heterogeneity ($I^2=0\%$; $P=0.918$).

Sequential therapy versus triple therapy lasting 10 days

Fourteen studies compared sequential therapy with a triple therapy regimen lasting 10 days.^{7 16 17 19 24 27-29 39 44 45 51 53 57} Only two trials were at low risk of bias,^{7 51} and three trials did not report full data on the proton pump inhibitor used.^{24 45 57} As shown in figure 3, the pooled relative risk was 1.11 (1.04 to 1.19), slightly favouring sequential treatment, the 95% prediction intervals ranged from 0.89 to 1.39, and the number needed to treat was 10 (7 to 15). We found evidence of heterogeneity ($I^2=67.2\%$; $P=0.000$) but no funnel plot asymmetry (Egger's test coefficient 2.35, -1.96 to 4.90 ; $P=0.126$). In all, 1368 patients were treated with the sequential therapy compared with 1378 patients treated with triple therapy lasting 10 days, and the eradication rate reported was 84.3% (79.8% to 88.4%) for the sequential therapy and 75.3% (69.6% to 77.9%) for the triple therapy lasting 10 days. The difference in eradication rates was 9.0% (4% to 14%), favouring sequential treatment, the 95% prediction intervals ranged from -9% to 26% (supplementary figure B), with evidence of heterogeneity ($I^2=66.4\%$; $P=0.000$).

Because of the heterogeneity, we did subgroup analyses according to country of origin, use of tinidazole (instead of metronidazole) in the sequential therapy, risk of bias, type of publication, and proton pump inhibitor used (supplementary table C). We found a slightly statistically significant effect in favour of sequential therapy in trials conducted in China, Greece, India, Italy, and Spain.

Data on adverse events were available for 11 trials.^{7 16 19 27-29 39 44 45 51 53} The pooled relative risk was 0.94 (0.79

to 1.13), indicating no significant difference, with no evidence of heterogeneity ($I^2=0\%$; $P=0.642$).

Sequential therapy versus triple therapy lasting 14 days

Seven studies compared sequential therapy with a triple therapy regimen lasting 14 days.^{24 34 35 37 39 49 50} No trial was at low risk of bias, and one trial did not report full data on the proton pump inhibitor used.²⁴ As shown in figure 4J, the pooled relative risk was 1.00 (0.94 to 1.06), and the 95% prediction intervals ranged from 0.83 to 1.19. We found evidence of heterogeneity ($I^2=54.3\%$; $P=0.010$) but no funnel plot asymmetry (Egger's test coefficient -1.564, -3.46 to 0.33; $P=0.167$). In all, 1224 patients were treated with the sequential therapy compared with 1227 patients treated with triple therapy lasting 14 days, and the eradication rate reported was 80.8% (76% to 85.1%) for the sequential therapy and 81.3% (79.5% to 84.7%) for the triple therapy. The difference in eradication rates was -0.5% (-5% to 5%), and the 95% prediction intervals ranged from -16% to 15% (supplementary figure C), with evidence of heterogeneity ($I^2=61.1\%$; $P=0.003$).

Because of the heterogeneity, we did subgroup analyses according to country of origin, use of tinidazole in the sequential therapy, type of publication, and proton pump inhibitor used; we did not evaluate risk of bias, as all trials were at high or unclear risk of bias (supplementary table D). We found no statistically significant differences.

Data on adverse events were available for four trials.^{35 37 39 50} The pooled relative risk was 0.98 (0.73 to 1.33), indicating no significant difference, with evidence of heterogeneity ($I^2=47.8\%$; $P=0.125$).

Effect of duration of triple therapies on eradication rate

The analysis of the studies comparing triple therapies of different durations with sequential therapy allowed us to evaluate the effect of length of the triple regimens on the eradication rate. We found a significant trend (χ^2 for trend: $P<0.001$) between the duration of therapy and the success of treatment, even if the clinical gain was modest. Therapy lasting 14 days eradicated 9.8% (6.3% to 11.9%) and 6% (2.9% to 9.3%) more infections than therapy lasting seven and 10 days. We found no significant difference in eradication rate between therapy lasting seven and 10 days (3.8%, -0.1% to 5.8%).

Sequential therapy versus bismuth containing therapies

In three studies bismuth containing therapies lasted 14 days,^{27 40 49} whereas in two trials they had a 10 day duration.^{33 56} Different bismuth formulations were used, including colloid bismuth subcitrate, bismuth pectin, and other unspecified bismuth salts. In one of the studies lasting two weeks, furazolidone was given during the first week of treatment.⁴⁰ No trial was at low risk of bias.

The pooled relative risk was 1.01 (0.95 to 1.06) (fig 5J), and the 95% prediction intervals ranged from 0.89 to 1.14. We found evidence of low heterogeneity ($I^2=21.1\%$; $P=0.280$) and no evidence of funnel plot asymmetry (Egger's test coefficient 2.32, -0.32 to 4.9; $P=0.131$). The eradication rate with bismuth containing therapies, compared with the efficacy of sequential therapy, was not affected by the duration ($P=0.592$).

In all, 546 patients were treated with the sequential therapy compared with 545 patients treated with bismuth containing

quadruple therapy, and the eradication rate reported was 86.2% (82.1% to 89.8%) for the sequential therapy and 84.9% (78.8% to 90.1%) for the bismuth containing quadruple therapy. The difference in eradication rates was 1.3% (-4% to 5%), and the 95% prediction intervals ranged from -11% to 12% (supplementary figure D), with low heterogeneity ($I^2=22.3\%$; $P=0.272$).

Data on adverse events were available for four studies.^{27 33 40 56} The pooled relative risk was 1.08 (0.71 to 1.63), indicating no significant difference, with evidence of heterogeneity ($I^2=25.5\%$; $P=0.258$).

Sequential therapy versus non-bismuth quadruple therapy

Six studies compared sequential therapy with a non-bismuth containing quadruple therapy regimen (sometimes called concomitant therapy), including a proton pump inhibitor, amoxicillin, clarithromycin, and metronidazole.^{31 34 41 55 57 58} In four trials, non-bismuth quadruple therapy lasted 10 days,^{31 41 55 57} and in the remaining two it lasted five days,^{34 58} and one trial did not report full data on the proton pump inhibitor used.⁵⁷ Only one trial was at low risk of bias.⁵⁵

The pooled relative risk was 0.99 (0.94 to 1.05) (fig 6J), and the 95% prediction intervals ranged from 0.85 to 1.16. We found evidence of heterogeneity ($I^2=52.3\%$; $P=0.021$) and no evidence of funnel plot asymmetry (Egger's test coefficient 0.96, -0.72 to 2.65; $P=0.324$).

In all, 1039 patients were treated with sequential therapy compared with 1031 patients treated with concomitant therapy, and the eradication rate reported was 81.7% (76.1% to 86.7%) for sequential therapy and 81.3% (74.9% to 87%) for the non-bismuth containing quadruple therapy. The difference in eradication rates was 0.4% (-4% to 4%), and the 95% prediction intervals ranged from -14% to 13% (supplementary figure E), with evidence of heterogeneity ($I^2=55.3\%$; $P=0.014$).

Because of the heterogeneity, we did subgroup analyses according to country of origin, risk of bias, proton pump inhibitor used, duration of non-bismuth containing quadruple therapy, type of publication, and use of tinidazole in the sequential therapy (supplementary table E). We found a slightly statistically significant effect in favour of sequential therapy in trials conducted in Chile and Costa Rica.

Data on adverse events were available for four studies.^{31 41 55 58} The pooled relative risk was 0.92 (0.77 to 1.10), indicating no significant difference, with evidence of heterogeneity ($I^2=33\%$; $P=0.214$).

Data not included in meta-analysis

Sequential therapy versus levofloxacin based sequential therapy

Three studies compared sequential therapy with a modified sequential therapy in which levofloxacin was used instead of the clarithromycin used in the original scheme.^{29 32 47} Overall, 355 patients were randomised to sequential therapy and 356 patients were randomised to the modified sequential therapy. One study compared sequential therapy with a modified sequential therapy using levofloxacin at dosages of 500 mg daily and 1000 mg daily.³² Of the remaining two, one used levofloxacin at a dosage of 1000 mg daily,²⁹ and the other used it at a dosage of 500 mg daily.⁴⁷

In the studies using levofloxacin 1000 mg daily, 240 patients were randomised to standard sequential therapy and 240 to the levofloxacin based sequential therapy. The overall eradication

rates of sequential therapy and of levofloxacin based sequential therapy were 78.7% (73% to 83.7%) and 90% (85.4% to 93.4%), with a difference of -11.3% (-4.8% to -17.7%) in favour of modified sequential therapy. Adverse event rates were 24.4% (19.1% to 30.4%) with the standard sequential therapy and 24.3% (19.1% to 30.4%) with the levofloxacin based sequential therapy, with a non-significant difference of 0.1% (-7.8% to 7.6%).

In the studies using levofloxacin 500 mg daily, 240 patients were randomised to standard sequential therapy and 241 to the levofloxacin based sequential therapy. The overall eradication rates of sequential therapy and levofloxacin based sequential therapy were 79.5% (73.9% to 84.4%) and 89.6% (85% to 93.1%), with a difference of -10.1% (-3.6% to -16.5%) in favour of modified sequential therapy. Adverse event rates were 14.3% (10.1% to 19.4%) with the standard sequential therapy and 13.8% (9.7% to 18.9%) with the levofloxacin based sequential therapy, with a non-significant difference of 0.5% (-6.8% to 5.9%). The eradication rates of the modified sequential therapy using 1000 mg and 500 mg daily of levofloxacin were not significantly different (difference 0.4%, -5.1% to 5.9%).

10 day sequential therapy versus 14 day sequential therapy

Only two studies compared sequential therapy lasting 10 days with sequential therapy lasting 14 days.^{49 50} In all, 340 patients were randomised to the 10 day therapy and 340 to the 14 day therapy. The overall eradication rates of 10 and 14 day sequential therapy were 87.6% (83.6% to 90.9%) and 89.7% (85.9% to 92.7%), with a non-significant difference of -2.1% (-6.9% to 2.7%). Adverse events were reported in one study only,⁵⁰ and no significant difference was seen between treatments (difference 5.5%, -13.5% to 2.5%).

Sequential therapy versus hybrid therapy

Hybrid therapy is an evolution of sequential therapy that uses a proton pump inhibitor twice daily and amoxicillin 1 g twice daily for 14 days plus 500 mg clarithromycin and nitroimidazole derivatives, both twice daily, for the last seven days. Two randomised controlled trials compared sequential therapy with hybrid therapy: 300 patients were randomised to each treatment.^{54 58} The eradication rate was 81% (76% to 85.2%) for the sequential therapy and 86.6% (82.2% to 90%) for the hybrid therapy, with no significant difference (-5.6%, -11.6% to 0.2%).

Adverse event rates were 23% (18.3% to 28.1%) for the sequential therapy and 27% (22% to 32.2%) for the hybrid therapy, with no significant difference between the two therapies (-4%, -10.9% to 2.9%).

Eradication rate of sequential therapy according to antimicrobial resistance

Eight studies provided data on eradication according to pre-treatment antimicrobial susceptibility testing.^{6 7 31 32 36 41 44 50} Two studies were at low risk of bias.^{7 32} However, the number of patients with antimicrobial susceptibility testing was small and the 95% confidence intervals for eradication rates were wide, so caution is necessary in interpreting the following results.

Strains resistant to clarithromycin

The overall eradication rate of sequential therapy in patients harbouring strains resistant to clarithromycin was 72.8% (61.6% to 82.8%). In patients harbouring strains resistant to clarithromycin, sequential therapy achieved a significantly higher eradication rate than did triple therapy lasting seven (difference in eradication rate 49.6%, 27.7% to 66.9%) and 10 days (49.8%, 20.3% to 70.5%). However, compared with triple therapy lasting 14 days, non-bismuth containing quadruple therapy, or sequential therapy in which levofloxacin was used instead of clarithromycin, no significant difference was seen (supplementary table F).

Strains resistant to metronidazole

The overall eradication rate of sequential therapy in patients harbouring strains resistant to metronidazole was 86.4% (78% to 93%). In patients harbouring strains resistant to metronidazole, sequential therapy achieved a significantly higher eradication rate than did triple therapy lasting seven (difference in eradication rate 24.1%, 7.2% to 41.3%) and 10 days (17%, 2.1% to 32.7%). Triple therapy lasting 14 days achieved a slightly higher eradication than sequential therapy (difference in eradication rate 16.4%, 0.14% to 32.8%). However, when we compared sequential therapy with non-bismuth containing quadruple therapy or sequential therapy in which levofloxacin was used instead of clarithromycin, we found no significant difference (supplementary table G).

Strains resistant to both clarithromycin and metronidazole

The overall eradication rate of sequential therapy in patients harbouring strains resistant to both clarithromycin and metronidazole was just 37% (16.2% to 60.7%). Only sequential therapy in which levofloxacin was used instead of clarithromycin was able to overcome the resistance to both antimicrobials (supplementary table H).

Strains resistant to levofloxacin

Only one study tested primary resistance to levofloxacin.³² No significant difference in eradication rate was found between the sequential therapy and the "modified" sequential therapy (in which levofloxacin was used instead of clarithromycin), but the number of patients studied was extremely low (supplementary table I).

Overall eradication rate of sequential therapy

In the 46 randomised controlled trials, 5666 patients were randomised to receive sequential treatment, and the overall eradication rate, pooled with a random model, was 84.3% (82.1% to 86.4%). Supplementary figure F shows the eradication rates of sequential treatment according to the country of origin.

Discussion

The results of this meta-analysis clearly show that, for eradication of *Helicobacter pylori* infection, sequential therapy is superior to seven day triple therapy and similar to regimens of longer duration and those including more than two antimicrobial agents.

Implications of findings

H pylori infection has been shown to cause peptic ulcer disease, gastric mucosa associated lymphoid tissue lymphoma, and

gastric cancer.¹ A recent study estimated that the number of new cases of gastric cancer (non-cardia gastric carcinoma and gastric mucosa associated lymphoid tissue lymphoma) attributable to *H pylori* infection in 2008 was 470 000 in less developed regions and 190 000 in the more developed regions of the world.⁵⁹ Eradication therapy has been shown to improve outcomes in peptic ulcer disease as well as mucosa associated lymphoid tissue lymphoma, by reducing recurrence.⁵ Given the importance of eradicating *H pylori* infection in patients with ulcer disease, the infection should be treated optimally with a combination regimen that has an acceptably high eradication rate.

The triple treatment including a proton pump inhibitor, clarithromycin, and amoxicillin or metronidazole to treat *H pylori* infection, proposed at the first Maastricht conference,⁶⁰ has become universal since all the consensus conferences and guidelines around the world recommended it. However, the most recent data show that this combination has lost efficacy, with an eradication rate ranging from 71% in the United States to 60% in Western Europe.^{5 61 62} The eradication rate is uniformly less than the 80% target set at the beginning and well below what should be expected for treatment of an infectious disease.⁶³⁻⁶⁵

One of the main reasons for this poor performance is the increasing number of strains of *H pylori* that are resistant to antibiotics. A recent European multicentre survey found that primary resistance (that is, the resistance found in patients infected but never treated) for clarithromycin was 17.5% (an increase in comparison with earlier surveys^{66 67}), resistance to levofloxacin had already reached 14.1%, and the resistance to metronidazole remained stable at 34.9%.⁴

Investigators in different parts of the world have made several attempts to find new regimens as a more effective alternative to traditional triple therapies. One of these is sequential therapy.⁶⁸ Analysis of the first studies showed promising results, with eradication rates consistently higher than 90%.^{69 70} However, the number of studies was small and most of them were done in Italy. Since then, several randomised controlled trials have been carried out in different parts of the world comparing sequential therapy with traditional and novel treatments, providing a glimpse into current eradication rates with new and old treatments.

Our results show that sequential therapy is clearly superior to the triple therapy regimen administered for seven days. But when a comparison was made with triple therapy lasting 10 days, the results were less clear-cut. Although the estimate of the effect size was better for the sequential therapy, prediction intervals were not significant, suggesting that future trials may not be able to observe a superior effect. When the comparison was made with triple therapy lasting 14 days and with bismuth based and non-bismuth based quadruple therapies, the sequential regimen was not significantly superior to any of these treatments.

Pre-treatment susceptibility data were also available in eight studies.^{6 7 31 32 36 41 44 50} Previous data suggested a high eradication rate with sequential therapy in strains resistant to clarithromycin.^{6 7} Our data show that sequential therapy was able to eradicate 72.8% of strains resistant to clarithromycin. In the head to head comparisons, sequential therapy achieved significantly better results only when compared with triple therapy lasting seven or 10 days; we found no significant differences in other comparisons. For the strains resistant to metronidazole, the pooled eradication rate was 86.4%; however, as in the previous case, sequential therapy achieved significantly better results only when compared with triple therapy lasting seven or 10 days. For the strains resistant to both clarithromycin

and metronidazole, only sequential therapy in which levofloxacin was used instead of clarithromycin was able to significantly overcome the resistance to both antimicrobials. Data on resistance and eradication should, however, be interpreted with caution owing to the small number of patients included in the trials.

If we consider the studies that could not be included in the meta-analysis (our criteria required at least three comparable study groups for every comparison), the modified levofloxacin based sequential therapy showed eradication rates of about 90% and was able to achieve a high eradication rate in strains resistant to clarithromycin, metronidazole, or both. Recently, a new therapy consisting of proton pump inhibitor, amoxicillin 1 g, levofloxacin 500 mg, and tinidazole 500 mg, all given twice daily for five days, has been shown to reach a high eradication rate.⁷¹ However, the prevalence of primary resistance to levofloxacin found by the authors in this study was quite low (7.9%) compared with that reported by a recent multicentre survey in southern Europe (13.1%).⁴ Large well conducted trials that include areas of high resistance are required before this treatment can be considered effective. A hybrid therapy consisting of proton pump inhibitor and amoxicillin 1 g twice daily for 14 days plus clarithromycin 500 mg and tinidazole 500 mg twice daily for the last seven days gave an eradication rate of 86.6%. Additional studies confirming these findings are awaited. Finally, two studies compared sequential therapy lasting 10 and 14 days. The first was a large multicentre, open label, randomised trial, conducted in six centres in Taiwan,⁵⁰ and the treatment efficacy was similar between the sequential therapy lasting 10 days (87%) and that lasting 14 days (90.7%) ($P=0.153$). The second study, a randomised controlled trial conducted in Turkey and published only as an abstract, also found no significant difference.⁴⁹

Recently published data are in line with the poor eradication rates found by our systematic review. In a meta-analysis, bismuth based quadruple therapy failed to show an improvement in eradication rate compared with the triple therapy.⁷² A large randomised, open label, non-inferiority, phase III trial conducted at 39 sites in Europe compared the efficacy and safety of 10 days' therapy with omeprazole plus a single three in one capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline (quadruple therapy) with seven days of triple therapy in adults. The eradication rate, according to the intention to treat analysis, was 80% (95% confidence interval 73.9% to 84.9%) for quadruple therapy compared with only 55% (48.6% to 62.1%) for the triple therapy.⁶¹ Another meta-analysis, using a fixed effect model, showed that non-bismuth based quadruple therapy was superior to the triple therapy. However, by adopting a more conservative analysis (random effect model), we observed that the prediction interval ranged from 0.92 to 1.40, suggesting that future trials may not be able to detect a superior effect.⁷³ As the response to eradication therapy is related to the prevalence of primary resistance in the population, the choice of a treatment regimen should be based on a knowledge of the underlying prevalence of resistant strains in the community and on the patient's history (no treatment or previous treatments).⁷⁴ National monitoring studies such as one started (but later discontinued) in the United States may help clinicians to choose the appropriate therapy.⁷⁵

One of the studies included in our meta-analysis was a multicentre trial conducted in several South American countries.³⁴ We decided to pool eradication data separately for each country. As recently shown,⁷⁶ a significant dispersion can be seen across the countries, highlighted by the values of I^2 . Part of this dispersion could possibly be due to the differing

prevalence of resistant organisms in the individual countries. The analysis by country shows that in Colombia, Mexico, and Nicaragua, no significant difference existed between treatments tested. In the other three countries, the results were different: in Chile, the non-bismuth based quadruple therapy was inferior to the triple therapy lasting 14 days and to sequential therapy; in Costa Rica, sequential therapy was superior to the non-bismuth based quadruple therapy; and in Honduras, triple therapy lasting 14 days was superior to sequential therapy.

Limitations of study

When considering the results of this meta-analysis, some limitations should be acknowledged. As with any systematic review and meta-analysis, the results rely on the quality and reporting of the trials. Most of the studies included had problems with concealment of allocation and blinding, which are important safeguards against bias in randomised controlled trials.⁷⁷ Allocation concealment seeks to prevent selection bias by concealing what treatment the next patient will receive before and until assignment.⁷⁷⁻⁷⁸ In contrast, blinding seeks to prevent performance and detection bias by protecting the sequence after assignment.⁷⁷⁻⁷⁹ Empirical studies show that the effects of experimental interventions measured as odds ratios are exaggerated on average by 21% if allocation concealment is unclear or inadequate and by 18% if trials are not reported as "double blind."⁷⁸⁻⁸⁰⁻⁸³ We also found significant heterogeneity, and subgroup analyses failed to identify plausible explanations. Subgroup analyses are entirely observational in their nature and have the limitations of any observational investigation, including possible bias through confounding by other study level characteristics.⁹ Therefore, the presence of heterogeneity without plausible explanations, as well as the presence of only a few trials at low risk of bias, affects the quality and the strength of the evidence.⁸⁴ The applicability of the results should also be viewed with caution, as information regarding the efficacy of the sequential therapy in several Western countries is lacking. No studies have been reported from Canada, and few southern European countries are represented. One open label, randomised controlled trial is ongoing in the United States, comparing triple therapy containing clarithromycin and lasting 10 days with sequential therapy.⁸⁵ Finally, data on the response of treatments according to pre-treatment sensitivity was available in a minority of the overall patients studied, not allowing a thorough analysis of the results.

Conclusion

Sequential therapy is superior to seven day triple therapy and similar to regimens of longer duration or including more than two antimicrobial agents. The search for a new agent to treat *H pylori* is important and should continue, but until such an agent is discovered, any single therapy is unlikely to be effective all over the world.

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What is already known on this topic

Triple treatments including a proton pump inhibitor, clarithromycin, and amoxicillin or metronidazole have lost efficacy, which is now uniformly less than the 80% target set initially

Several attempts have been made to find new regimens as a more effective alternative to treat *H pylori*

One such regimen is sequential therapy, originally found to give eradication rates consistently higher than 90%

What this study adds

The overall efficacy of sequential therapy is 84.3% (95% confidence interval 82.1% to 86.4%)

This is superior to seven day triple therapy and similar to regimens of longer duration or including more than two antimicrobial agents

The search for more effective eradication regimens or for new agents to treat *H pylori* should therefore continue

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Table

Table 1 | Characteristics of studies included in systematic review and meta-analysis

Author and year	Country	Publication	Comparison*	Test to diagnose†	Follow-up (weeks)	Test to follow-up†	Culture	PPI‡
Zullo et al 2003 ⁶	Italy	Full paper	TT-7	H/R/ ¹³ C-UBT	6	H/R/ ¹³ C-UBT	Yes	R
Focareta et al 2003 ¹⁵	Italy	Abstract	TT-7	R	6	¹³ C-UBT/ST	NA	E
De Francesco et al 2004 ¹⁶	Italy	Full paper	TT-7/TT-10	H/R/ ¹³ C-UBT	6-8	H/R/ ¹³ C-UBT	NA	R
De Francesco et al 2004 ¹⁷	Italy	Full paper	TT-10	H/R/ ¹³ C-UBT	6-8	¹³ C-UBT	NA	R
Zullo 2005 et al ¹⁸	Italy	Full paper	TT-7	H/R	4-6	H/R	NA	R
Scaccianoce et al 2006 ¹⁹	Italy	Full paper	TT-7/TT-10	H/R	4-6	¹³ C-UBT	NA	E
Vaira et al 2007 ⁷	Italy	Full paper	TT-10	H/R/C/ ¹³ C-UBT	4 and 8	¹³ C-UBT	Yes	P
Choi et al 2008 ²⁰	South Korea	Full paper	TT-7	B	8	¹³ C-UBT/B	NA	O
Ma et al 2008 ²¹	China	Full paper	TT-7	¹⁴ C-UBT/R	4	¹⁴ C-UBT/R	NA	O
Wu et al 2008 ²²	China	Abstract	TT-7	H	4-6	¹³ C-UBT	NA	R
Hu et al 2009 ²³	China	Full paper	TT-7	R/H	4	¹³ C-UBT	NA	E
Park et al 2009 ²⁴	South Korea	Abstract	TT-7/TT-10/TT-14	UBT/R/H	4	UBT/R/H	NA	Different
Zhao et al 2009 ²⁵	China	Full paper	TT-7	H	4	¹³ C-UBT	NA	P
Paoluzi et al 2010 ²⁶	Italy	Full paper	TT-7	H/R/C-UBT/ST	8	H/R/ST/C-UBT	NA	E
Aminian et al 2010 ²⁷	Iran	Full paper	TT-10/BCT	R	8	ST	NA	O
Liang et al 2010 ²⁸	China	Full paper	TT-10	¹⁴ C-UBT/R	4	¹⁴ C-UBT/R	NA	R
Molina-Infante et al 2010 ²⁹	Spain	Full paper	TT-10/ST with levofloxacin 500 bd	C-UBT/R/H	8	C-UBT	NA	O
Song et al 2010 ³⁰	China	Full paper	TT-7	¹⁴ C-UBT/H	4	¹⁴ C-UBT	NA	O
Wu et al 2010 ³¹	Taiwan	Full paper	NBQT	R/H/C	6	¹³ C-UBT/R/H/C	Yes	E
Romano et al 2010 ³²	Italy	Full paper	ST with levofloxacin 250 bd/500 bd	¹³ C-UBT/H/R	6 and 10	¹³ C-UBT	Yes	O
Gao et al 2010 ³³	China	Full paper	TT-7/ BCT	R/H	4-6	¹³ C-UBT	NA	R/O
Greenberg et al 2011 ³⁴	South America	Full paper	TT-14/NBQT	¹³ C-UBT	6-8	¹³ C-UBT	NA	L
Kim et al 2011 ³⁵	South Korea	Full paper	TT-14	¹³ C-UBT/R/H	4	¹³ C-UBT	NA	P
Gatta et al 2011 ³⁶	Italy	Abstract	TT-7	H/R/C/ ¹³ C-UBT	4	¹³ C-UBT	Yes	E
Wu et al 2011 ³⁷	China	Full paper	TT-14	¹³ C-UBT/R/H	4	¹³ C-UBT/R/H	NA	E
Franceschi et al 2012 ³⁸	Italy	Abstract	TT-7/high dose amoxicillin TT-7	¹³ C-UBT	6	¹³ C-UBT	NA	L
Choi et al 2012 ³⁹	South Korea	Full paper	TT-7/TT-10/TT-14	C-UBT/R/H	4	C-UBT/H	NA	R
Fakheri et al 2012 ⁴⁰	Iran	Full paper	BCT	R/H	8	¹⁴ C-UBT	NA	P
Huang et al 2012 ⁴¹	Taiwan	Full paper	NBQT	C/R/H	6	C-UBT/B	Yes	L
Oh et al 2012 ⁴²	South Korea	Full paper	TT-7	R/H	4	¹³ C-UBT	NA	R
Park et al 2012 ⁴³	South Korea	Full paper	TT-7	¹³ C-UBT/R/H	4	¹³ C-UBT	NA	R
Chung et al 2012 ⁴⁴	South Korea	Full paper	TT-10	H/R/C	4	¹³ C-UBT	Yes	L
Kalapothakos et al 2012 ⁴⁵	Greece	Abstract	TT-10	¹³ C-UBT/R/H	8	¹³ C-UBT	NA	Different
Singh et al 2012 ⁴⁶	Malaysia	Abstract	TT-7	R/H	6	C-UBT	NA	R
Qian et al 2012 ⁴⁷	China	Full paper	ST with levofloxacin 500 od	R/ ¹³ C-UBT	4	¹³ C-UBT	NA	E
Lahbabi et al 2012 ⁴⁸	Morocco	Full paper	TT-7 AC/TT-7 AM	H/PCR	12	¹³ C-UBT	NA	NR
Harmandar et al 2012 ⁴⁹	Turkey	Abstract	TT-14/BCT/ST-14	B	4	B/ ¹⁴ C-UBT	NA	P
Liou et al 2012 ⁵⁰	Taiwan	Full paper	TT-14/ST-14	¹³ C-UBT/R/H/C/S	6	¹³ C-UBT	Yes	L
Javid et al 2013 ⁵¹	India	Full paper	TT-10	R/H	4	R/H	NA	P
Seddik et al 2013 ⁵²	Morocco	Full paper	TT-7	H	4-6	¹³ C-UBT	NA	O
Yep-Gamarra et al 2013 ⁵³	Peru	Abstract	TT-10	B	4	B	NA	O
Sardarian et al 2013 ⁵⁴	Iran	Full paper	Hybrid	H/R	8	¹⁴ C-UBT	NA	P

(continued)

Author and year	Country	Publication	Comparison*	Test to diagnose†	Follow-up (weeks)	Test to follow-up†	Culture	PPI‡
McNicholl et al 2013 ⁵⁵	Spain	Full paper	NBQT	¹³ C-UBT/R/H/C	4	¹³ C-UBT/H	NR	O
Liu et al 2013 ⁵⁶	Hong Kong	Abstract	BCT	H/R	8	¹³ C-UBT	NA	E
Ang et al 2013 ⁵⁷	Singapore	Abstract	TT-10/NBQT	R/H/ ¹³ C-UBT	4	¹³ C-UBT	NA	NR
Zullo et al 2013 ⁵⁸	Italy	Full paper	NBQT/hybrid	H/R	6	¹³ C-UBT	NA	O

bd=twice daily; NA=not assessed; NR=not reported; od=once daily; PPI=proton pump inhibitor.

*BCT=bismuth containing therapies; hybrid=PPI twice daily and amoxicillin 1 g twice daily for 14 days plus 500 mg clarithromycin and nitroimidazole derivatives, both twice daily, for last 7 days; NBQT=non-bismuth quadruple therapy; ST-14=sequential therapy lasting 14 days; TT-7=triple therapy lasting 7 days; TT-10=triple therapy lasting 10 days; TT-14=triple therapy lasting 14 days.

†B=biopsy based test; C=culture; C-UBT=urea breath test; H=histology; PCR=polymerase chain reaction; R=rapid urease test; S=serology; ST=stool test.

‡E=esomeprazole; L=lansoprazole; O=omeprazole; P=pantoprazole; R=rabeprazole.

Figures

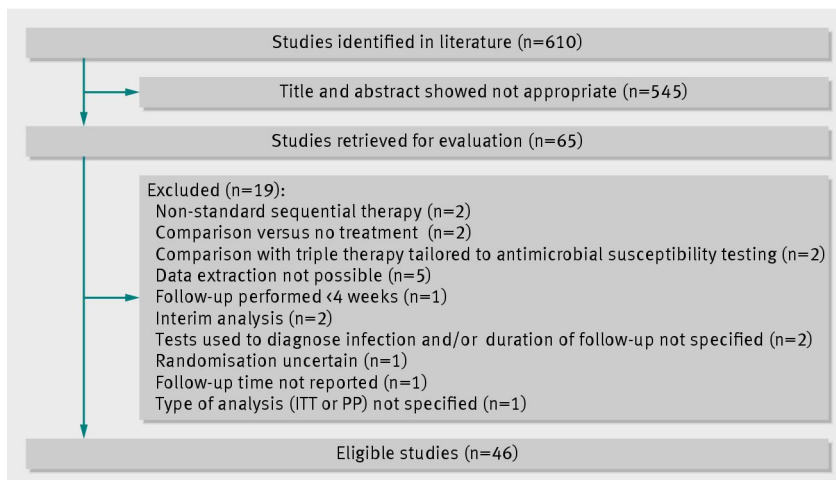


Fig 1 Flow diagram of systematic review. ITT=intention to treat; PP=per protocol.

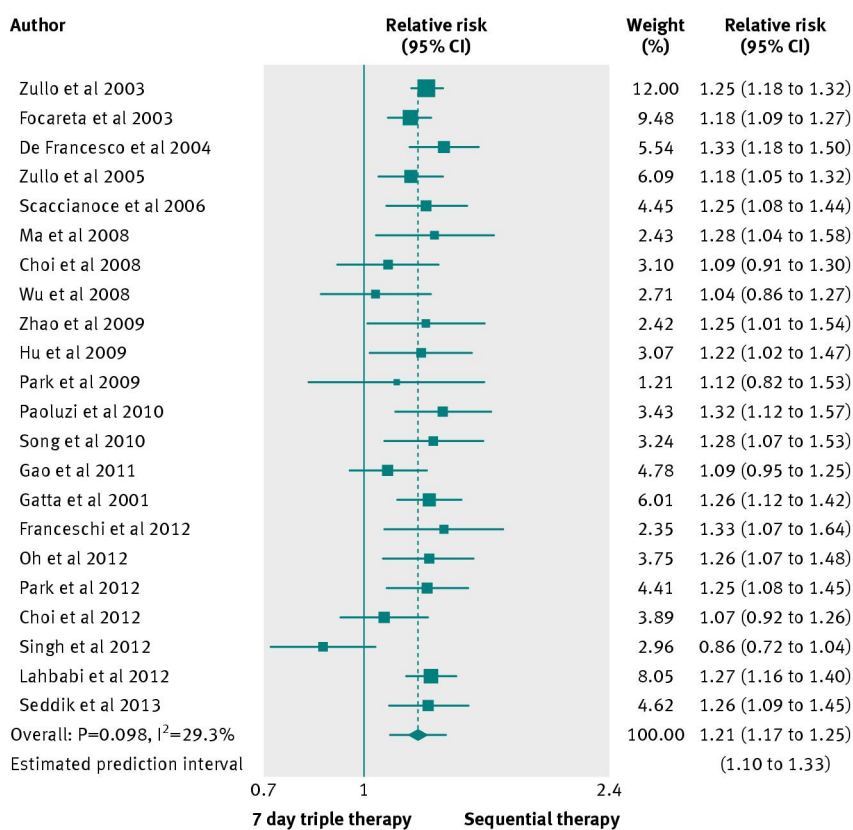


Fig 2 Forest plot of sequential therapy versus seven day triple therapy

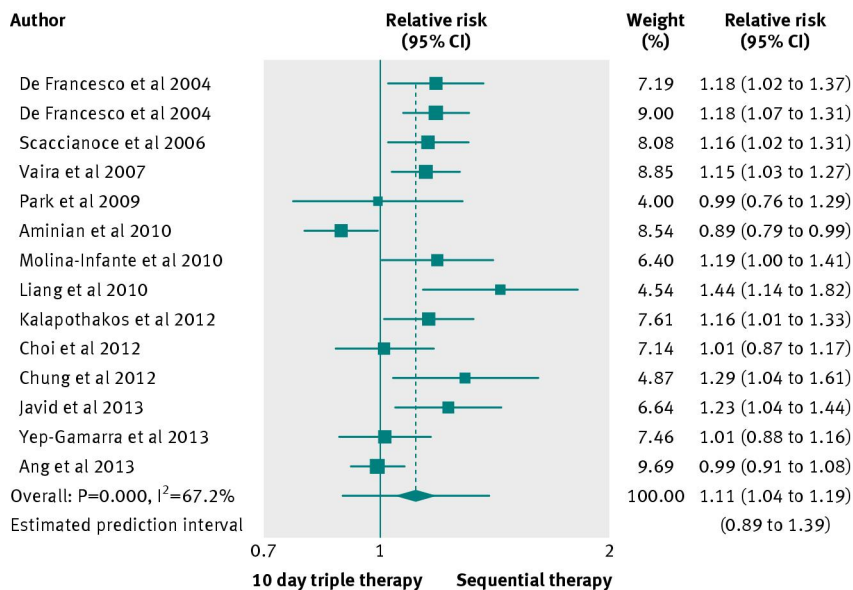


Fig 3 Forest plot of sequential therapy versus 10 day triple therapy

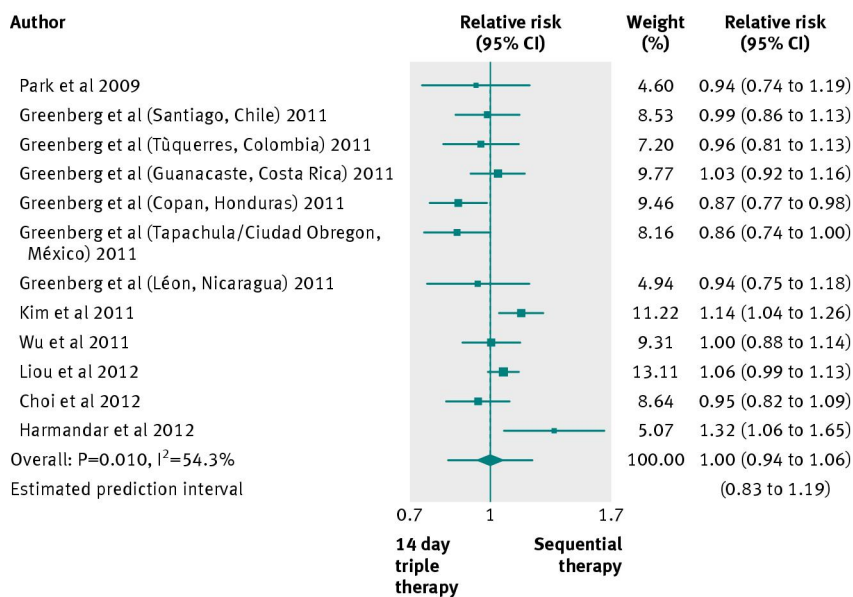


Fig 4 Forest plot of sequential therapy versus 14 day triple therapy

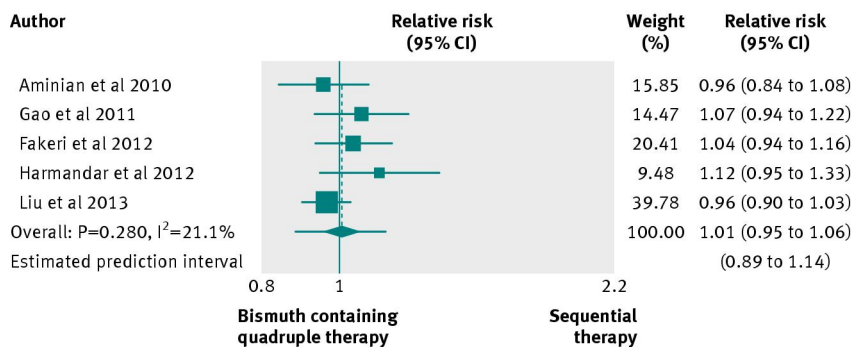


Fig 5 Forest plot of sequential therapy versus bismuth containing therapies

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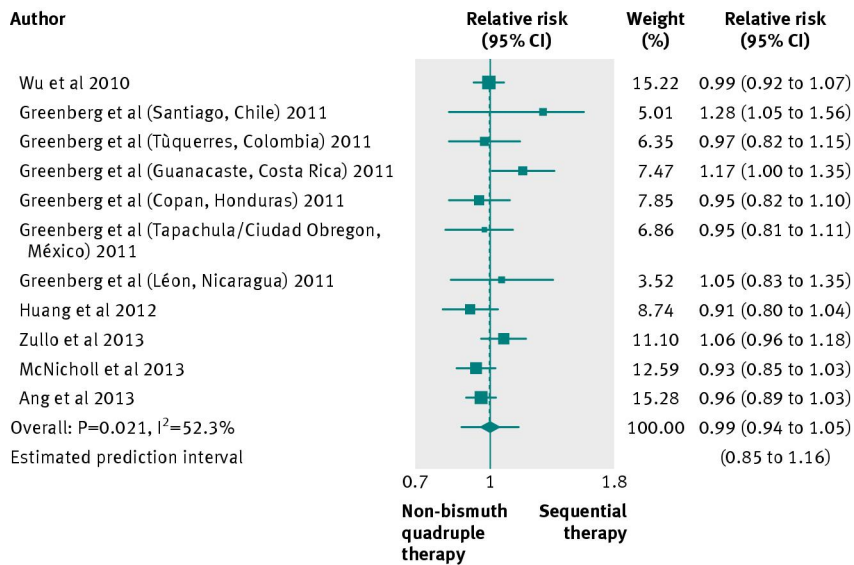


Fig 6 Forest plot of sequential therapy versus non-bismuth containing quadruple therapy

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