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CLINICAL AT

Comparative Effectiveness of Multiple Different First-Line Treatment Regimens for *Helicobacter pylori* Infection: A Network Meta-analysis

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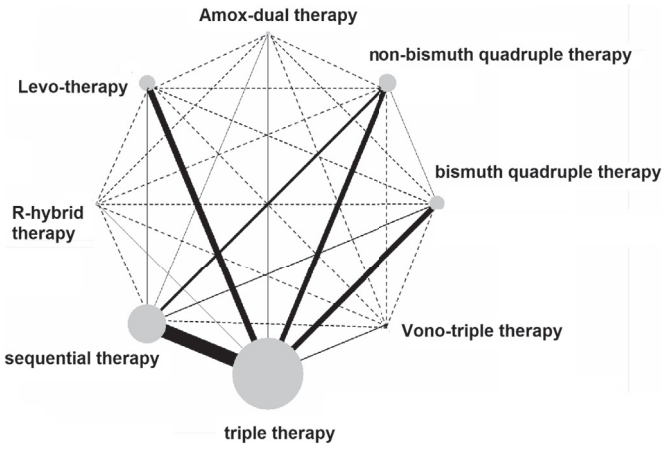
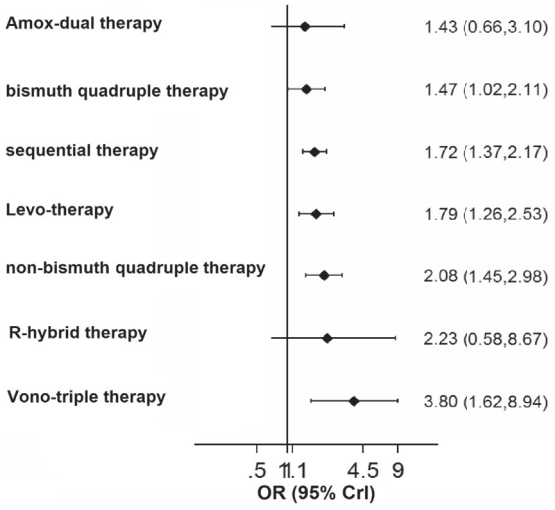
Network map of all 28 *H.pylori* first line treatment regimen comparisons (12 direct, 16 indirect).



Forest plot of *H.pylori* first line treatment regimens compared directly with triple therapy.



Abbreviations: Vono-triple therapy, Vonoprazan-containing therapy; R-hybrid therapy, reverse hybrid therapy; Levo-therapy, Levofloxacin-containing therapy; Amox-dual therapy, Amoxicillin high dose double therapy.

Gastroenterology

BACKGROUND & AIMS: A number of double, triple, and quadruple therapies have been proposed as first-line empiric treatments for *Helicobacter pylori* infection. However, knowledge of their worldwide and regional comparative efficacy is lacking. We examined the comparative effectiveness of all empirically used first-line regimens tested against standard triple treatment using a network meta-analysis of published randomized controlled trials. **METHODS:** Data extracted from eligible randomized controlled trials were entered into a Bayesian network meta-analysis to investigate the comparative efficacy of *H pylori* infection empiric first-line regimens and to explore their effectiveness rank order. The ranking probability for each regimen was evaluated by means of surfaces under cumulative ranking values. **RESULTS:** Sixty-eight eligible randomized controlled trials were included, giving a total of 92 paired comparisons with 22,975 patients randomized to 8 first-line regimens. The overall results showed that only vonoprazan triple therapy and reverse hybrid therapy achieved cure rates of >90%. Levofloxacin triple therapy performed best in Western countries (eradication rate 88.5%). The comparative effectiveness ranking showed that vonoprazan triple therapy had the best results, whereas standard triple therapy was the

least efficacious regimen (surfaces under cumulative ranking 92.4% vs 4.7% respectively; odds ratio, 3.80; 95% credible interval, 1.62–8.94). **CONCLUSIONS:** For first-line empiric treatment of *H pylori* infection, vonoprazan triple therapy and reverse hybrid therapy achieved high eradication rates of >90%. Levofloxacin triple therapy achieved the highest eradication rates in Western countries. Standard triple therapy was the least efficacious regimen in this network meta-analysis.

Keywords: Helicobacter pylori; Treatment; First-Line Regimens; Efficacy; Network Meta-Analysis.

CLINICAL AT

Helicobacter pylori infection is of worldwide concern, as it has been recognized as the main cause of gastritis, peptic ulcer disease, gastric mucosa–associated lymphoid tissue lymphoma and gastric cancer. In 2015, *H pylori* gastritis was formally recognized as an infectious disease, leading to the recommendation that all patients should receive treatment.[1] In 2018, the list of indications to test for the presence of the infection was greatly expanded.[2] In 2020, the Taipei Global Consensus emphasized the role of *H pylori* eradication in accomplishing the goal of reducing or eliminating deaths from gastric cancer.[3] Eradication of *H pylori* emphasizes the need for effective treatment. Despite more than a quarter century of work and many consensus conferences providing what were believed to be up-to-date treatment recommendations,[4,5] overall treatment success remains poor compared with other infectious diseases.[6] A number of different therapies have been introduced, including triple therapies consisting of a proton pump inhibitor (PPI), amoxicillin and clarithromycin, metronidazole, a fluoroquinolone, or rifabutin; bismuth quadruple therapy; PPI and amoxicillin dual therapy; and a group of 4 drug therapies consisting of a PPI, amoxicillin, clarithromycin, and metronidazole called sequential, concomitant, hybrid, and reverse hybrid therapies. The recent introduction of the potassium-competing acid blocker, vonoprazan, has rekindled interest in all of these therapies based on the observation that the marked acid suppression obtained resulted in an increase in efficacy with amoxicillin-containing regimens.

Until very recently, the approach to developing guidelines for first-line *H pylori* treatment has relied largely on results obtained from randomized controlled trials (RCTs) and relevant pairwise meta-analyses. The understanding that *H pylori* gastritis was fundamentally an infectious disease has resulted in the realization that the current approach to development and assessment of therapy for *H pylori* differs from that of other infectious diseases, which utilize the principles of antimicrobial stewardship. Antimicrobial stewardship evaluates effectiveness based on absolute cure rates rather than on results of RCTs and meta-analyses of empiric therapies.[7–9] Although pairwise meta-analyses form the basis for recent guidelines, none has included all of the currently available therapeutic interventions. Network meta-analysis (NWM) is an evidence synthesis tool for comparing RCTs with multiple treatments.[10–12] NWM incorporates both direct and indirect evidence in a collection of RCTs, thus providing information concerning the relative effects of 3 or more therapeutic interventions competing for a similar result. Although there has been a call to largely abandon comparative trials for *H pylori* infection therapy, except among those proven to be reliably highly effective locally, the role of NWM has not been explored. Our aim, therefore, was to study the comparative effectiveness of all current first-line dual, triple, and quadruple therapies for *H pylori* infection using NWM and to examine their comparative efficacy ranking in various parts of the world. These results might be useful to help future guidelines and clinical decision-making.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Helicobacter pylori infection has been formally recognized as an infectious disease, leading to the recommendation that all patients should receive treatment. A number of double, triple, and quadruple therapies have been proposed as first-line empiric treatments. However, knowledge of their worldwide and regional comparative efficacy is lacking. In this study, we used network meta-analysis to assess and rank the comparative effectiveness of current recommended *H pylori* therapies.

NEW FINDINGS

We obtained worldwide accurate and comprehensive results concerning the comparative efficacy of all current first-line dual, triple, and quadruple therapies. Overall, vonoprazan triple therapy was the most effective, whereas standard triple therapy was the least efficacious regimen, reflecting high percentages of antibiotic resistance.

LIMITATIONS

The main limitation of this network meta-analysis is that *H pylori* resistance to antibiotics was not taken into account preventing the relevant sub-group analysis as the majority of included randomized controlled trials did not provide these data.

IMPACT

As increasing antibiotic resistance continues to emerge and impairs clinicians' ability to cure *H pylori* infection, the results of this network meta-analysis might suggest that a new approach concerning *H pylori* treatment is now needed and that the time for transitioning from trial and error to antimicrobial stewardship has arrived. This approach is expected to be useful in helping future guidelines and clinical decision-making.

Abbreviations used in this paper: **Amox-dual therapy, high-dose amoxicillin double therapy; CI, confidence interval; Levo-therapy, levofloxacin-containing therapy; MeSH, Medical Subject Heading; NWM, network meta-analysis; OR, odds ratio; PPI, proton pump inhibitor; RCT, randomized controlled trial; R-hybrid therapy, reverse hybrid therapy; SUCRA, surface under the cumulative ranking curve; Vono-triple therapy, Vonoprazan-containing therapy.**

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Methods

Identification of Studies and Data Extraction

To identify studies and extract data in this NWM we have followed the steps described in our previous publications (ie, identification, screening, eligibility, and inclusion).[13] The PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Scopus and Web of Science databases were searched up until November 2020 to identify human studies written in English using the following search text and/or Medical Subject Heading (MeSH) terms: *(helicobacter pylori* [MeSH Terms] OR (*helicobacter* [All Fields] AND *pylori* [All Fields]) OR *helicobacter pylori* [All Fields] OR *h pylori* [All Fields]) AND ((*therapy* [Subheading] OR *therapy* [All Fields] OR *treatment* [All Fields] OR *therapeutics* [MeSH Terms] OR *therapeutics* [All Fields]) OR (*therapy* [Subheading] OR *therapy* [All Fields] OR *therapeutics* [MeSH Terms] OR *therapeutics* [All Fields]) OR (*clinical protocols* [MeSH Terms] OR (*clinical* [All Fields] AND *protocols* [All Fields]) OR *clinical protocols* [All Fields] OR *regimen* [All Fields])) AND *eradication* [All Fields] AND *RCTs* [All Fields]. In addition, a manual search of all review articles, published editorials and retrieved original studies was done. This study was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) extension statement for interventions,[14] whereas the quality of evidence derived from pairwise and NWM was achieved by using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) working group modality.[15] Furthermore, we appraised the confidence in estimates derived from NWM, as described in our previous publication.[16]

Selection Criteria

We defined the inclusion and exclusion criteria before starting the study investigation. Appropriate studies were included in the meta-analysis provided that the following criteria were met: published as complete articles with data that could be extracted; written in English; were RCTs comparing different regimens, with at least 7-day treatment duration in all arms; 1 arm included patients allocated to clarithromycin-containing triple treatment (triple therapy); contained at least 50 patients per arm; treated patients were adults; and all therapeutic regimes were given as first-line treatment. Studies not meeting the above criteria and studies that had "double-counted" patients were excluded. In addition, RCTs comparing the same regimen in both arms with different doses or duration of the included drugs were excluded as irrelevant to the purposes of this study. In this NWM, the primary efficacy end point was *H pylori* eradication rate in an intention-to-treat analysis.

Statistical Analysis

For pair-based meta-analyses and heterogeneity estimation, we followed the methodology as described previously.[13] In addition to heterogeneity, we assessed inconsistency, as this is critical when conducting an NWM.[10–12] We constructed comparison-adjusted funnel plots and checked their symmetry to assess whether small-scale trials influence the efficacy results. Surfaces under cumulative ranking (SUCRA) values were used in intervention network charts to examine the cumulative ranking probability for each intervention concerning the efficacy achieved by this intervention compared with an ideal intervention showing the best efficacy without doubt, that is, SUCRA = 1, or 100% when expressed as a percentage.[10–12] Data were processed using software suitable for Bayesian NWM, namely, Stata, version 13.2 (StataCorp, College Station, TX)[10,11] and NetMetaX.[12] A P value $<.05$ reflects significance for all measurements except for heterogeneity, for which the corresponding value was 0.1.

Results

Characteristics of Studies

The process of study selection is shown in Figure 1. Of 1983 titles yielded by the initial search, 68 RCTs[17–84] were eligible for meta-analysis by fulfilling all inclusion criteria. There were 56 two-arm[17,18,20–51,54,56,58–68,70–73,76,78–80,84] and 12 [19,52,53,55,57,69,73,76,77,81–83] three-arm RCTs, including a total of 92 paired comparisons, which were grouped into 12 pairwise meta-analyses. The characteristics of the involved RCTs are shown in Supplementary Table 1. The studies were performed in various parts of the world and included 22,975 patients, who were randomized to 8 first-line treatment regimens, in alphabetical order:

1. Concomitant quadruple bismuth treatment (bismuth quadruple therapy);
2. Concomitant quadruple nonbismuth treatment (nonbismuth quadruple therapy);
3. High-dose amoxicillin double treatment (Amox-dual therapy);
4. Levofloxacin-containing treatment (Levo-therapy);
5. Reverse hybrid therapy (R-hybrid therapy);
6. Sequential quadruple treatment (sequential therapy);
7. Standard triple treatment (triple therapy); and
8. Vonoprazan-containing therapy (Vono-triple therapy).

Mean cure rates (95% confidence intervals [CIs]) achieved by these regimens are shown in Table 1. Concerning quality, some of the involved RCTs were double-blind, whereas the majority were open label with the accompanying limitations, mainly related to the lack of allocation concealment or blinding to the treatment arms. Consequently, the certainty of evidence was downgraded to a moderate level for most comparisons. This is depicted in the relevant Supplementary Figures 1*A* and *B*.

Network Map

The network map of the 8 therapeutic interventions (regimens) is depicted in Figure 2, which shows all 28 possible comparisons in this NWM, that is, 12 direct (Figure 2*A*) and 16 indirect (Figure 2*B*). In this map, the

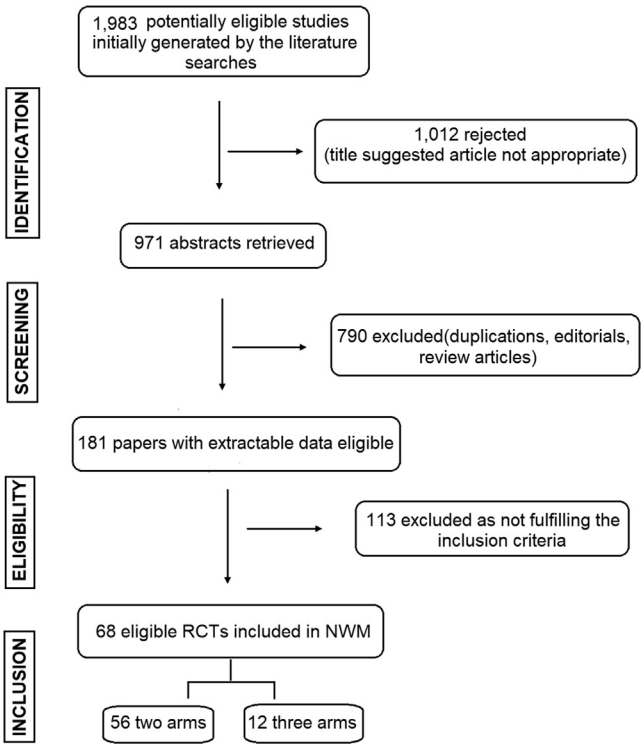


Figure 1. Flow chart of studies included in the network meta-analysis.

node size reflects the number of patients allocated to each treatment, whereas the edge thickness is in proportion to the precision, that is, the inverse of variance of each direct comparison.[10]

Direct and Indirect Pair Comparisons, Publication Bias

The network forest plot of Figure 3*A* shows the ORs (95% CIs) of all 92 individual direct pair comparisons grouped in 12 regimen pairwise meta-analyses. Of these, the comparisons of Vono-triple therapy vs triple therapy (OR, 3.80; 95% CI, 1.62–8.94), sequential therapy vs triple therapy (OR, 1.79; 95% CI, 1.26–2.53), nonbismuth quadruple therapy vs triple therapy (OR, 2.08; 95% CI, 1.45–2.98), bismuth quadruple therapy vs triple therapy (OR, 1.47; 95% CI, 1.02–2.11), and Levo-therapy vs triple therapy (OR, 1.79; 95% CI, 1.26–2.53) yielded significant results. In contrast, the comparisons triple therapy vs Amox-dual therapy, sequential therapy vs Amox-dual therapy, triple therapy vs R-hybrid therapy, nonbismuth quadruple therapy vs bismuth quadruple therapy, sequential therapy vs Levo-therapy, sequential therapy vs bismuth quadruple therapy and sequential therapy vs nonbismuth quadruple therapy yielded insignificant results. The evaluation of inconsistency showed insignificant overall results (P = .624), meaning that the comparative effect sizes that were obtained by these comparisons were consistent. The relevant funnel plot of Figure 3*B* appears symmetrical, meaning that there was no evidence of publication bias or small study effects.

The network forest plot (Figure 4*A*) shows ORs (95% credible intervals) of all 28 direct and indirect comparisons in this NWM (12 direct and 16 indirect). Figure 4*B* shows the efficacy order of the 7 comparators (Vono-triple therapy, nonbismuth quadruple therapy, bismuth quadruple therapy, sequential therapy, Levo-therapy, Amox-dual therapy, and R-hybrid therapy) against the reference treatment, that is, triple therapy. Of these comparators Vono-triple therapy, nonbismuth quadruple therapy, bismuth quadruple therapy, sequential therapy, and Levo-therapy yielded significant results against triple therapy, whereas Amox-dual therapy and R-hybrid therapy failed to reach significance.

League Matrix, Rankograms, and Surfaces Under Cumulative Ranking Values

The comparative efficacy ranking league matrix, showing the comparative efficacies of the 8 regimens included in this NWM, is shown in Figure 5*A*. This figure reflects all 28 comparisons (12 direct and 16 indirect) and shows that Vono-triple therapy had the best performance, followed by nonbismuth quadruple therapy, R-hybrid therapy, sequential therapy, Levo-therapy, bismuth quadruple therapy, Amox-dual therapy, and triple therapy, which was the least efficacious regimen. The respective rankograms are shown in Figure 5*B*, in close relationship with SUCRA values shown in Table 1. Thus, judging by ranking league matrix, rankograms, and SUCRA values, the global results showed that Vono-triple therapy (SUCRA value 92.4%) was the best choice, followed by nonbismuth quadruple therapy (68.8%), R-hybrid therapy (62.7%), Levo-therapy (53.6%), sequential therapy (49.7%), Amox-dual therapy (35.2%), and bismuth quadruple therapy (33.2%). Triple therapy (4.7%) was the least efficacious regimen.

Subgroup Analyses

Publication year effect. In order to explore the effect of the publication year, we performed subgroup analysis dividing the RCTs into 2 groups, that is, before and after 2010. In this way, we wanted to examine whether the gradually increasing incidence of clarithromycin-resistant strains of *H pylori* is reflected in the eradication rates of involved treatments, especially in triple-therapy effectiveness. The results showed that triple-therapy efficacy in RCTs before 2010 was better than after 2010, that is, a drop in SUCRA values from 20.3% to 6.2% (Figure 6*A* [before 2010] and *B* [after 2010]).

Regional effect. As not all of the 8 regimens were used in all parts of the world, for the purposes of this NWM, countries were grouped into the following 3 geographical areas: West, West Asia, and East Asia. Table 1 shows the relevant regional mean regimen cure rates, paired comparisons between regimens, and SUCRA values per regimen for these areas, together with overall data. In Western countries, R-hybrid therapy and Vono-triple therapy were not tested. Among the regimens tested, Levo-therapy showed the best performance (SUCRA 82.7%), followed by sequential therapy (SUCRA 78.4%),

Table 1. Overall and Regional Data, Including Cure Rates, Direct Pair Comparisons, and Surfaces Under Cumulative Ranking Values Concerning the Therapeutic Interventions Against *Helicobacter pylori* (Treatment Regimens) Included in This Network Meta-Analysis

Variable	Overall data	West	East Asia	West Asia
Cure rates, % (95% CI)				
Regimen				
Vono-triple therapy	91.4 (88.5–93.8)	—	91.4 (88.5–93.8)	—
Nonbismuth quadruple therapy	84.3 (82.7–85.8)	87.8 (84.0–91.2)	84.7 (82.8–86.4)	70.6 (63.5–77.1)
R-hybrid therapy	93.6 (90.4–96.8)	—	93.6 (90.4–96.8)	—
Levo-therapy	83.8 (82.1–85.4)	88.5 (86.5–90.5)	77.6 (74.3–80.7)	88.4 (84.6–91.1)
Sequential therapy	83.7 (82.7–84.7)	87.9 (86.3–89.3)	82.6 (81.1–84.1)	82.7 (78.9–86.1)
Amox-dual therapy	80.2 (75.3–84.4)	64.6 (51.7–76.8)	84.8 (80.3–88.6)	—
Bismuth quadruple therapy	81.3 (79.5–83.1)	81.2 (78.3–83.8)	87.3 (84.8–86.6)	71.2 (64.5–77.3)
Triple therapy	75.7 (74.9–76.4)	67.8 (66.3–69.3)	75.9 (74.7–77.8)	72.7 (67.7–77.3)
Pairwise comparisons, OR (95% CrI)				
Comparison				
Sequential therapy vs levo–therapy	0.96 (0.64–1.45)	0.94 (0.53–1.68)	2.13 (1.24–3.67)	0.51 (0.22–1.19)
Sequential therapy vs triple therapy	1.79 (1.26–2.53)	2.64 (1.83–3.80)	1.56 (1.20–2.03)	1.40 (0.87–2.23)
Nonbismuth quadruple therapy vs bismuth quadruple therapy	1.42 (0.87–2.33)	1.43 (0.60–3.39)	1.13 (0.63–2.01)	3.17 (0.90–11.18)
Bismuth quadruple therapy vs triple therapy	1.47 (1.02–2.11)	1.67 (1.05–2.67)	1.65 (0.94–2.91)	2.22 (0.88–5.57)
Sequential therapy vs nonbismuth quadruple therapy	0.83 (0.56–1.23)	1.10 (0.50–2.43)	0.68 (0.44–1.03)	0.98 (0.38–2.49)
Amox-dual therapy vs triple therapy	1.43 (0.66–3.10)	0.66 (0.18–2.47)	1.81 (0.86–3.82)	—
Levo-therapy vs triple therapy	1.79 (1.26–2.53)	2.81 (1.74–4.53)	0.75 (0.47–1.19)	2.72 (1.28–5.80)
Sequential therapy vs Amox-dual therapy	1.21 (0.54–2.69)	3.99 (1.01–15.69)	0.86 (0.40–1.87)	—
Vono-triple therapy vs triple therapy	3.80 (1.62–8.94)	—	3.68 (1.87–7.26)	—
Sequential therapy vs bismuth quadruple therapy	1.18 (0.77–1.79)	1.58 (0.87–2.80)	0.76 (0.43–1.34)	3.09 (1.18–8.13)
Nonbismuth quadruple therapy vs triple therapy	2.08 (1.45–2.98)	2.39 (1.15–4.94)	2.01 (1.41–2.87)	1.43 (0.59–3.45)
R-hybrid therapy vs triple therapy	2.23 (0.58–8.67)	—	2.23 (0.78–6.39)	—
Sucra, %				
Regimen				
Vono-triple therapy	92.4	—	94.1	—
Nonbismuth quadruple therapy	68.8	70.0	67.1	60.1
R-hybrid therapy	62.7	—	67.8	—
Levo–therapy	53.6	82.7	2.8	94.1
Sequential therapy	49.4	78.4	45.3	61.1
Amox-dual therapy	35.2	9.1	57.2	—
Bismuth quadruple therapy	33.2	44.7	50.5	2.4
Triple therapy	4.7	15.2	15.2	31.5

CrI, credible interval.

nonbismuth quadruple therapy (SUCRA 70.0%), bismuth quadruple therapy (SUCRA 44.7%), triple therapy (SUCRA 15.2%), and Amox-dual therapy (SUCRA 9.1%). In East Asia, Vono-triple therapy (SUCRA 94.1%) was the best performer, followed by R-hybrid therapy (SUCRA 67.8%), nonbismuth quadruple therapy (SUCRA 67.1%), Amox-dual therapy (SUCRA 57.2%), bismuth quadruple therapy (SUCRA 50.5%), sequential therapy (SUCRA 45.3%), and triple therapy (SUCRA 15.2%). In West Asia, Vono-triple therapy, R-hybrid therapy, and Amox-dual therapy were not tested. Among those tested, Levo-therapy performed best (SUCRA 94.1%), followed by sequential therapy (SUCRA 61.1%), nonbismuth quadruple therapy (SUCRA 60.1%), triple therapy (SUCRA 31.5%), and bismuth quadruple therapy (SUCRA 2.4%).

Discussion

Although *H pylori* is a worldwide concern affecting billions of people, the ideal eradication regimens remain unclear, despite 30 years of therapeutic experience worldwide. Therapy of *H pylori* is also not exempt from global increase in antimicrobial resistance that threatens the continued usefulness of currently available antimicrobials. A triple therapy combining a PPI with 2 antibiotics, most often amoxicillin and clarithromycin, had become less effective by 2000, but is still one of the most widely used first-line regimens worldwide, despite cure rates <80%.[85,86] Increased resistance to metronidazole and levofloxacin has resulted in them also becoming less effective when used empirically in triple therapies.[87–90] In contrast, as with

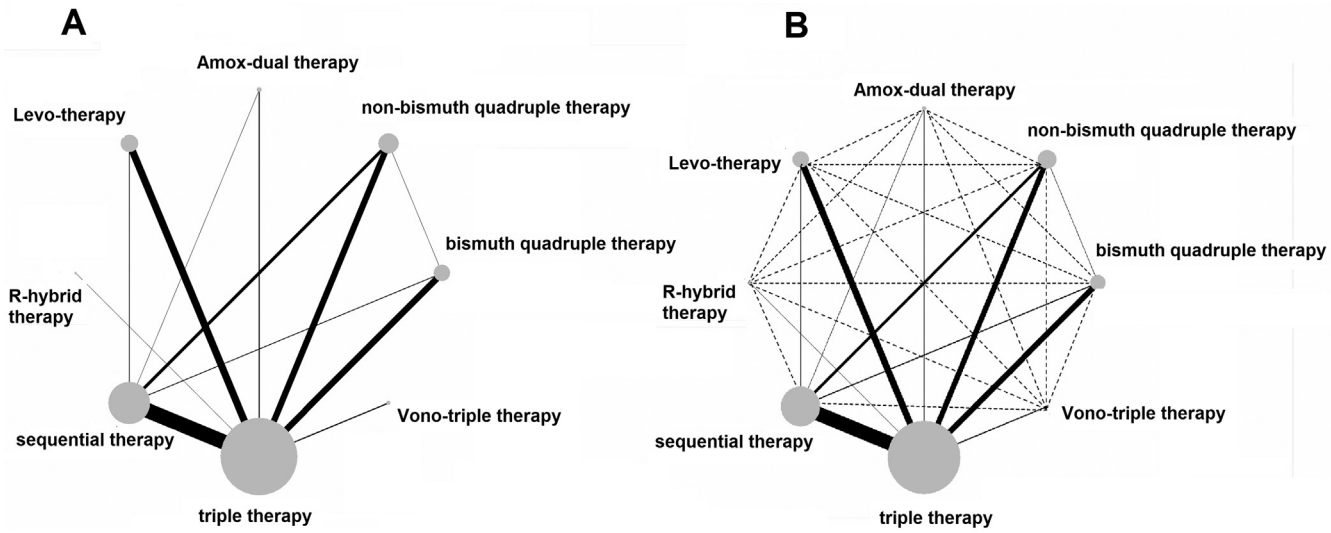


Figure 2. (*A*) Network map of the 12 direct regimen comparisons included in the RCTs. The node size reflects the number of patients allocated to each regimen, whereas edge thickness is in proportion to the precision, that is, the inverse of variance of each direct comparison. (*B*) Network map of all 28 comparisons in this NWM (12 direct [*solid lines*]) and 16 indirect (*interrupted lines*).

other infectious diseases, susceptibility-based therapies and empiric use of proven locally reliably effective therapies have been proved to be effective.[6]

This NWM examined the comparative effectiveness of 7 regimens against clarithromycin-containing triple therapy as first-line empiric *H pylori* therapy. The comparative overall efficacy of these regimens showed that Vono-triple therapy was the best (SUCRA 92.4%). R-hybrid therapy, despite good cure rate, failed to reach significance comparative efficacy, as shown in the relevant network forest plot. Vonoprazan is a novel acid suppressant that belongs to a group of potassium-competitive acid blockers,[91] and is currently available in Japan and recently in some other Asian countries. It is not yet available in Europe and the United States. It must be stressed, however, that despite good Vono-triple therapy performance in this NWM, the very high clarithromycin resistance in Japan has resulted in decreasing effectiveness of this regimen, with reported cure rates of <90%.[92] Thus, it has been reported that, in the presence of clarithromycin resistance, the cure rate is approximately 80% and therefore the majority of patients (estimated at 88%) receive clarithromycin unnecessarily, which contributes to global antimicrobial resistance.[93] This notion is supported by a recent report from

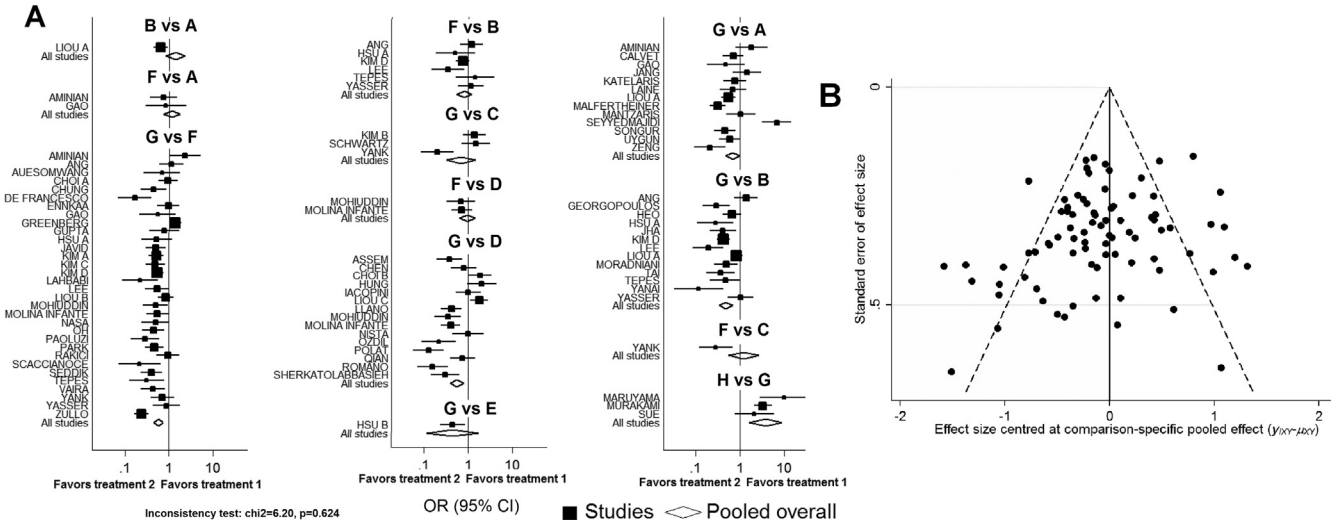


Figure 3. (*A*) Network *forest plot* illustrating all included pair comparisons grouped in 12 comparisons (OR; 95% CI) of regimens included in the RCTs. *Regimen labels:* A: bismuth quadruple therapy, B: nonbismuth quadruple therapy, C: high-dose amoxicillin double treatment, D: levofloxacin-containing treatment, E: reverse hybrid treatment, F: sequential treatment, G: triple therapy, H: vonoprazan-containing therapy. (*B*) Comparison-adjusted *funnel plot*. It appears symmetrical implying the absence of publication bias or small-study effects in the network.

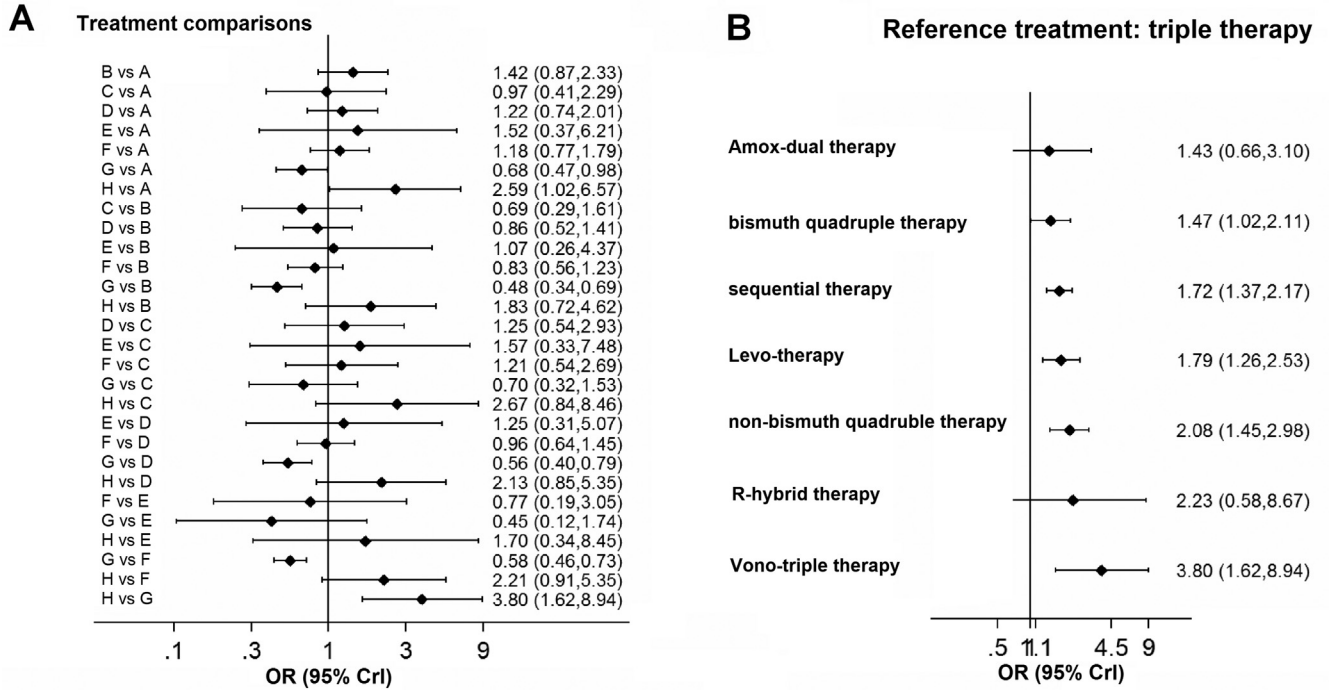


Figure 4. (*A*) Network *forest plot* (OR; 95% credible interval [CrI]) illustrating all 28 pair (direct and indirect) comparisons of regimens included in the RCTs. (*B*) Network *forest plot* depicting the efficacy of the regimens compared directly with the triple therapy reference regimen. Vertical line at OR = 1.0 indicates no regimen vs triple therapy difference. *Regimen labels:* A: bismuth quadruple therapy, B: nonbismuth quadruple therapy, C: high-dose amoxicillin double treatment, D: levofloxacin-containing treatment, E: reverse hybrid treatment, F: sequential treatment, G: triple therapy, H: vonoprazan-containing therapy.

Japan[94] that vonoprazan–amoxicillin dual therapy achieved *H pylori* eradication rates similar to Vono-triple therapy in regions with high clarithromycin resistance.

The regional subgroup meta-analyses showed that the rank order for each empiric intervention differed in various regions of the world as shown in Table 1. Thus, in Western countries, in accordance with overall results, triple therapy was the least efficacious regimen (cure rate, 72.4%; 95% CI, 71%–73.7%), stressing the need to avoid using this regimen as an empiric first-line treatment. However, it remains a very effective susceptibility-based therapy.[95] This notion is in agreement with recent reference guidelines[4] and indeed this recommendation already has a positive reflection in European clinical practice, as documented in a very recent publication concerning the *H pylori* European Registry.[5] The respective cure mean rates for Levo-therapy, sequential therapy, nonbismuth quadruple therapy, and bismuth quadruple therapy, were 88.5% (95% CI, 86.4%–90.4%), 87.9% (95% CI, 86,3%–89.3%), 87.8% (95% CI, 84%–91%), and 81.2% (95% CI, 78.3%–83.8%). However, taking into account the continuing rise of levofloxacin resistance and the potential adverse effects of quinolones, this regimen should rather be used primarily as rescue treatment.[4] Therefore, in Western countries, one of the remaining available regimens could be used as first-line treatment. In East Asia, Vono-triple therapy was the best regimen, whereas Levo-therapy did not perform well (cure rate, 77.6%; 95% CI, 74.3%–80.7%), most probably reflecting high levofloxacin resistance rates in this region.[96] On the contrary, Levo-therapy was the best in West Asia (cure rate, 88.4% (95% CI, 84%–6-91.1%), followed by nonbismuth quadruple therapy, sequential therapy, and triple therapy. Bismuth quadruple therapy was the least efficacious regimen in this area (mean cure rate, 70.5%; 95% CI, 63.8%–76.6%), thus contributing to low performance of this regimen in overall results. It must be noted, however, that in these areas there is often a problem of poor-quality drugs. Amox-dual therapy in East Asia achieved better results in comparison with Western countries (SUCRA, 57.2% and 9.1%, respectively). The reason for this difference is not clear, but it could be attributed to genetic polymorphisms in the enzyme CYP 2C19 status concerning potent acid suppression by PPIs.[97] Although relevant data were not accessible to this NWM, this hypothesis could probably explain the observed difference between these 2 regions.

The lack of inconsistency strengthens the results of this NWM. In addition, by adopting strict inclusion criteria and excluding small RCTs, we avoided possible publication bias or the effects of small studies. However, some limitations should be mentioned. The main limitation is related to the fact that most of the involved RCTs were not double-blind but open-label, with all of the limitations concerning the lack of allocation concealments or blinding to the treatment arms. However, the open-label design was not likely to bias the results because in most studies, the methods of outcome measurement were objective and, in addition, the staff who performed the tests were blind to the treatment groups. A further limitation could be related to the fact that in this

A

Vono-triple therapy	0.55 (0.22,1.38)	0.59 (0.12,2.92)	0.47 (0.19,1.18)	0.45 (0.19,1.10)	0.38 (0.12,1.19)	0.39 (0.15,0.98)	0.26 (0.11,0.62)
1.83 (0.72,4.62)	**non-bismuth quadruple therapy**	1.07 (0.26,4.37)	0.86 (0.52,1.41)	0.83 (0.56,1.23)	0.69 (0.29,1.61)	0.70 (0.43,1.15)	0.48 (0.34,0.69)
1.70 (0.34,8.45)	0.93 (0.23,3.79)	**R-hybrid therapy**	0.80 (0.20,3.24)	0.77 (0.19,3.05)	0.64 (0.13,3.05)	0.66 (0.16,2.67)	0.45 (0.12,1.74)
2.13 (0.85,5.35)	1.16 (0.71,1.91)	1.25 (0.31,5.07)	**Levo-therapy**	0.96 (0.64,1.45)	0.80 (0.34,1.87)	0.82 (0.50,1.35)	0.56 (0.40,0.79)
2.21 (0.91,5.35)	1.21 (0.81,1.79)	1.30 (0.33,5.13)	1.04 (0.69,1.55)	**sequential therapy**	0.83 (0.37,1.84)	0.85 (0.56,1.29)	0.58 (0.46,0.73)
2.67 (0.84,8.46)	1.46 (0.62,3.42)	1.57 (0.33,7.48)	1.25 (0.54,2.93)	1.21 (0.54,2.69)	**Amox-dual therapy**	1.03 (0.44,2.42)	0.70 (0.32,1.53)
2.59 (1.02,6.57)	1.42 (0.87,2.33)	1.52 (0.37,6.21)	1.22 (0.74,2.01)	1.18 (0.77,1.79)	0.97 (0.41,2.29)	**bismuth quadruple therapy**	0.68 (0.47,0.98)
3.80 (1.62,8.94)	2.08 (1.45,2.98)	2.23 (0.58,8.67)	1.79 (1.26,2.53)	1.72 (1.37,2.17)	1.43 (0.66,3.10)	1.47 (1.02,2.11)	**triple therapy**

B

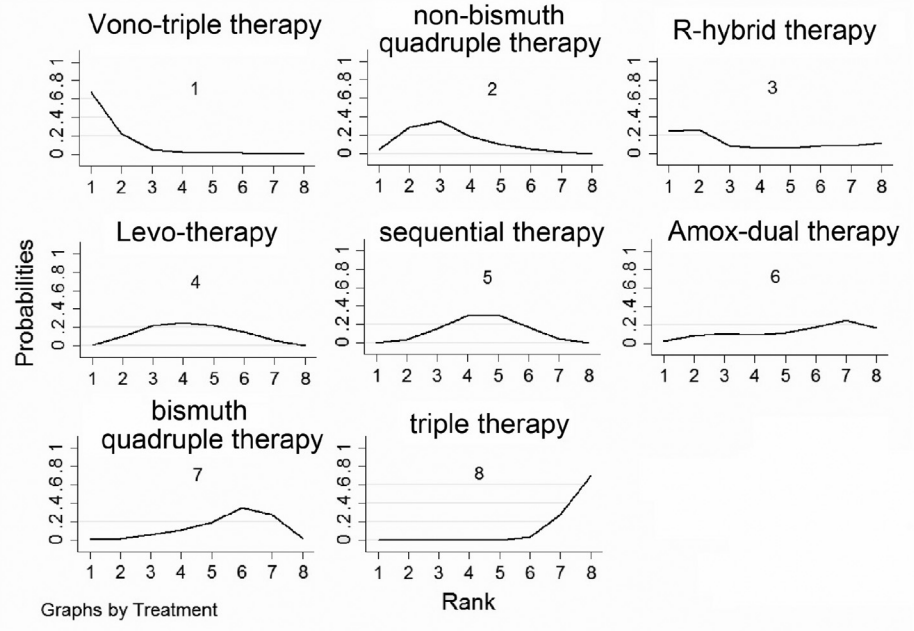
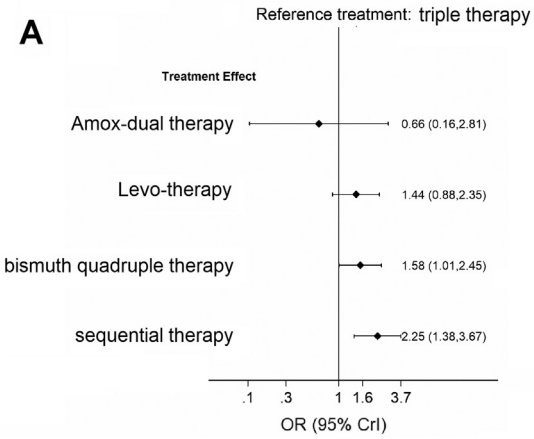


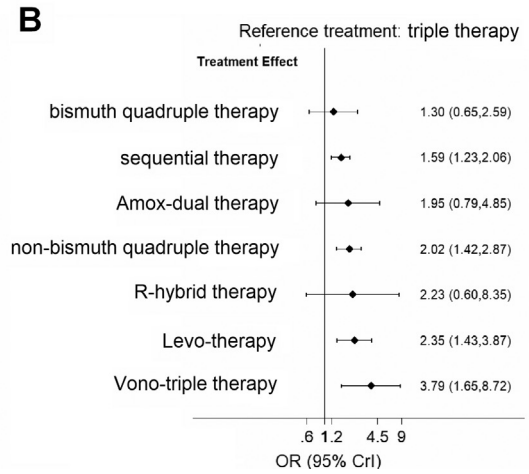
Figure 5. (*A*) SUCRA-based efficacy ranking league matrix showing the comparative efficacies of the regimens included in this network meta-analysis. Values below the regimens should be read from *row* to *column*, and above the treatments should be read from *column* to *row*. (*B*) *Rankograms* derived from relevant SUCRA values for the regimens evaluated in the included RCTs showing the cumulative rank order for each intervention (1–8).

NWM, *H pylori* resistance to antibiotics was not taken into account and the relevant sub-group analysis was not performed. We did not perform this sub-group analysis because the relevant information was not given in all included studies. However, by examining the role of the publication year, in the relevant sub-group analysis we derived an indirect answer concerning triple-therapy effectiveness over time, proving that triple-therapy efficacy in RCTs before 2010 was better than after 2010, that is, a substantial drop of SUCRA values (Figure 6), probably reflecting increasing antibiotic resistance. However, other explanations could be given, such as a general shift toward more effective regimens due to local recognition that standard triple therapies are less effective. Finally, a point of concern could be related to the fact that in this NWM, the primary end point was regimen efficacy, whereas safety was not taken into account. However, in most studies, adverse effect rates seemed broadly comparable across regimens, which eliminates the possibility that this could alter the messages of this NWM.

H pylori treatment continues to be a challenge, as antibiotic resistance continues to emerge and impair clinicians' ability to cure *H pylori* infection. A recent consensus recommended that clarithromycin, metronidazole, and levofloxacin should not be used empirically unless proven to be reliably effective locally.[2] Under these circumstances, a new approach concerning *H pylori* treatment is needed and, toward this end, there are views supporting the notion that it is now time for transitioning from trial and error to



Treatment	SUCRA(%)
sequential therapy	93
bismuth quadruple therapy	64.7
Levo-therapy	56.1
triple therapy	20.3
Amox-dual therapy	15.9



Treatment	SUCRA(%)
Vono-triple therapy	89.8
Levo-therapy	69.5
R-hybrid therapy	59.7
non-bismuth quadruple therapy	58.6
Amox-dual therapy	54
sequential therapy	37
bismuth quadruple therapy	25.3
triple therapy	6.2

Figure 6. (*A*) *Forest plot* and the relevant SUCRA values concerning the efficacy of the regimens compared directly with the reference regimen (triple therapy) in RCTs published before 2010. (*B*) The respective values for RCTs published after 2010.

antimicrobial stewardship, as in other infectious diseases.[6] This approach requires therapy to be restricted to optimized therapies proven to be reliably highly effective in the local population (eg, cure rate of $\geq$95%) and therefore comparisons should be restricted to regimens that meet these criteria.

In conclusion, for first-line empiric *H pylori* infection treatment, Vono-triple therapy and R-hybrid therapy achieved high eradication rates of >90%. Levo-triple therapy achieved the highest eradication rates in Western countries. The comparative effectiveness ranking results showed that Vono-triple therapy was the best regimen showing the highest SUCRA value, whereas standard triple therapy was the least efficacious regimen. However, Vono-triple therapy, although the most effective first-line regimen, was tested in Japan only and more studies from various parts of the world are needed.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://doi.org/10.1053/j.gastro.2021.04.012.

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Conflicts of interest
These authors disclose the following: David Y. Graham is a consultant for RedHill Biopharma and Phathom Pharmaceuticals regarding novel *Helicobacter pylori* therapies. He has received research support for culture of *H pylori* and is the principal investigator of an international study of the use of antimycobacterial therapy for Crohn's disease. Francis Megraud received research support from Aptalis Pharma, bioMerieux, and Mobidiag and is consultant for Phathom Pharmaceuticals. Peter Malfertheiner has received consulting fees from Aboca, Bayer, Danone, Mayoly Spindler, and Malesci. Javier P. Gisbert has served as a speaker, a consultant and advisory member for or has received research funding from Mayoly, Allergan, Diasorin, Phathom and Gebro Pharma. The remaining authors disclose no conflicts.

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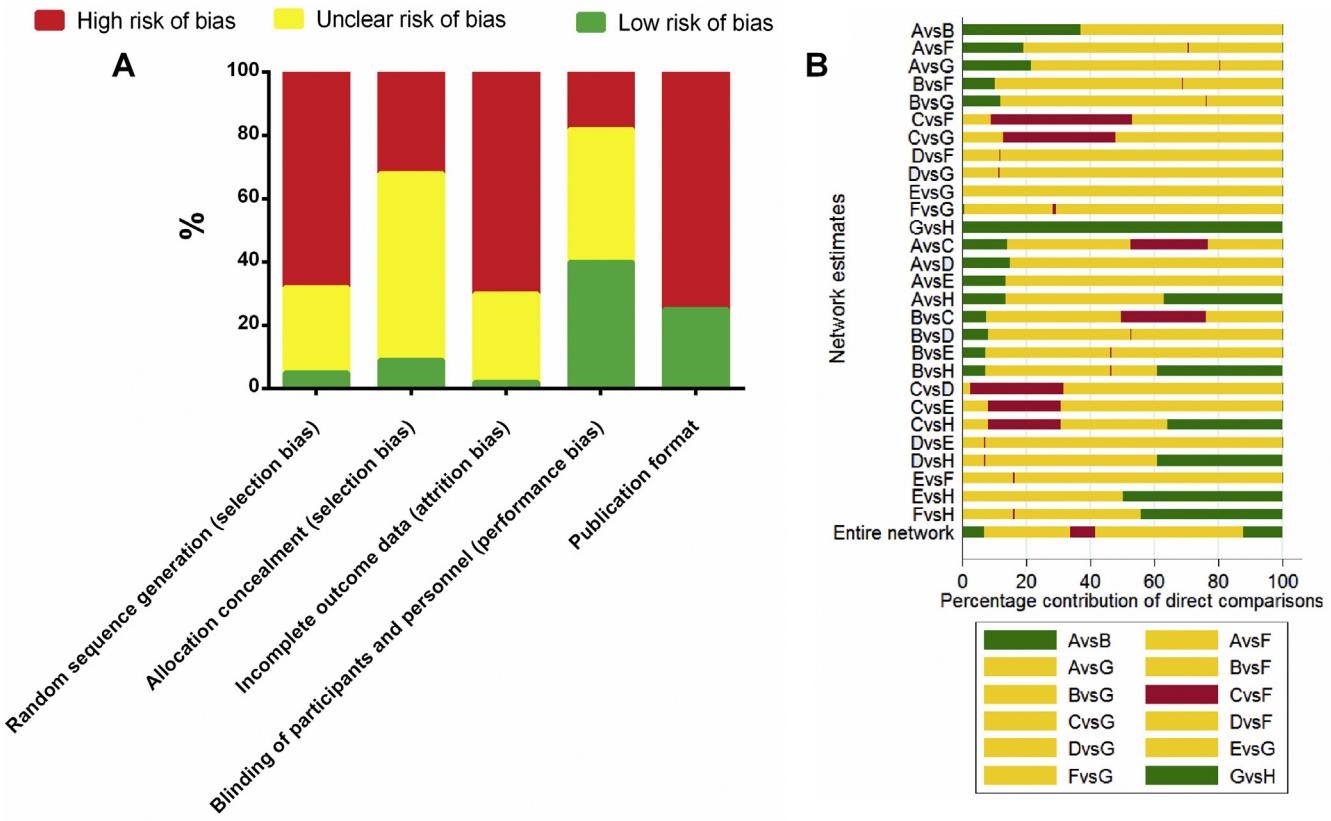

Supplementary Figure 1. (*A*) *Risk of bias graph* depicting each risk of bias item presented as percentage across all included studies. (*B*) *Network bar graph* depicting the risk of bias for each network estimate in the entire network (*upper panel*) and for the direct comparisons (*lower panel*). *Regimen labels:* A: bismuth quadruple therapy, B: nonbismuth quadruple therapy, C: high-dose amoxicillin double treatment, D: levofloxacin-containing treatment, E: reverse hybrid treatment, F: sequential treatment, G: triple therapy, H: vonoprazan-containing therapy.

Supplementary Table 1. Characteristics of the Triple Therapy-Controlled Randomized Controlled Trials Included in This Network Meta-Analysis

Study, first author	Publication year	Country	Study design	Total no. of patients included	Regimens compared
Georgopoulos[17]	2013	Greece	RCT-2 arm	257	Triple therapy vs nonbismuth quadruple therapy
Heo[18]	2014	China	RCT-2 arm	348	Triple therapy vs nonbismuth quadruple therapy
Liou[19]	2016	China	RCT-3 arm	1620	Triple therapy vs nonbismuth quadruple therapy vs bismuth quadruple therapy
Tai[20]	2015	China	RCT-2 arm	200	Triple therapy vs nonbismuth quadruple therapy
Kim[21]	2016	Korea	RCT-2 arm	601	Triple therapy vs sequential therapy
Moradniani[22]	2017	Iran	RCT-2 arm	214	Triple therapy vs nonbismuth quadruple therapy
Murakami[23]	2016	Japan	RCT-2 arm	650	Triple therapy vs Vono-triple therapy
Maruyama[24]	2017	Japan	RCT-2 arm	141	Triple therapy vs Vono-triple therapy
Sue[25]	2018	Japan	RCT-2 arm	106	Triple therapy vs Vono-triple therapy
Kim[26]	2012	Korea	RCT-2 arm	208	Triple therapy vs Amox-dual therapy
Katelaris[27]	2002	Australia	RCT-2 arm	268	Triple therapy vs bismuth quadruple therapy
Calvet[28]	2002	Spain	RCT-2 arm	339	Triple therapy vs bismuth quadruple therapy
Jang[29]	2005	Korea	RCT-2 arm	149	Triple therapy vs bismuth quadruple therapy
Mantzaris[30]	2002	Greece	RCT-2 arm	149	Triple therapy vs bismuth quadruple therapy
Laine[31]	2003	USA	RCT-2 arm	275	Triple therapy vs bismuth quadruple therapy
Uygun[32]	2007	Turkey	RCT-2 arm	212	Triple therapy vs bismuth quadruple therapy
Songur[33]	2009	Turkey	RCT-2 arm	206	Triple therapy vs bismuth quadruple therapy
Zheng[34]	2010	China	RCT-2 arm	170	Triple therapy vs bismuth quadruple therapy
Malfertheiner[35]	2011	Germany	RCT-2 arm	440	Triple therapy vs bismuth quadruple therapy
Choi[36]	2008	Korea	RCT-2 arm	460	Triple therapy vs sequential therapy
De Francesco[37]	2004	Italy	RCT-2 arm	347	Triple therapy vs sequential therapy
Greenberg[38]	2011	Latin America	RCT-2 arm	974	Triple therapy vs sequential therapy
Javid[39]	2013	India	RCT-2 arm	272	Triple therapy vs sequential therapy
Kim[40]	2011	Korea	RCT-2 arm	409	Triple therapy vs sequential therapy
Lahbabi[41]	2013	Colombia	RCT-2 arm	209	Triple therapy vs sequential therapy
Liou[42]	2013	China	RCT-2 arm	840	Triple therapy vs sequential therapy
Nasa[43]	2013	India	RCT-2 arm	231	Triple therapy vs sequential therapy
Oh[44]	2012	Korea	RCT-2 arm	246	Triple therapy vs sequential therapy
Paoluzi[45]	2010	Italy	RCT-2 arm	180	Triple therapy vs sequential therapy
Park[46]	2012	Korea	RCT-2 arm	326	Triple therapy vs sequential therapy
Rakici[47]	2014	Turkey	RCT-2 arm	343	Triple therapy vs sequential therapy
Scaccianoce[48]	2006	Italy	RCT-2 arm	213	Triple therapy vs sequential therapy
Seddik[49]	2013	Turkey	RCT-2 arm	281	Triple therapy vs sequential therapy
Vaira[50]	2007	Italy	RCT-2 arm	300	Triple therapy vs sequential therapy
Zullo[51]	2003	Italy	RCT-2 arm	1049	Triple therapy vs sequential therapy

Supplementary Table 1. Continued

Study, first author	Publication year	Country	Study design	Total no. of patients included	Regimens compared
Kim[52]	2019	Korea	RCT-3 arm	1142	Triple therapy vs sequential therapy vs nonbismuth quadruple therapy
Tepes[53]	2016	Slovenia	RCT-3 arm	356	Triple therapy vs sequential therapy vs nonbismuth quadruple therapy
Auesomwang[54]	2018	Thailand	RCT-2 arm	120	Triple therapy vs sequential therapy
Hsu[55]	2014	Taiwan	RCT-3 arm	307	Triple therapy vs sequential therapy vs nonbismuth quadruple therapy
Schwartz[56]	1998	USA	RCT-2 arm	129	Triple therapy vs Amox-dual therapy
Gao[57]	2010	China	RCT-3 arm	215	Triple therapy vs sequential therapy vs bismuth quadruple therapy
Assem[58]	2010	Egypt, Saudi Arabia	RCT-2 arm	300	Triple therapy vs Levo-therapy
Chen[59]	2010	China	RCT-2 arm	189	Triple therapy vs Levo-therapy
Choi[60]	2011	China	RCT-2 arm	197	Triple therapy vs Levo-therapy
Hung[61]	2009	China	RCT-2 arm	300	Triple therapy vs Levo-therapy
Iacopini[62]	2005	Italy	RCT-2 arm	164	Triple therapy vs Levo-therapy
Liou[63]	2010	China	RCT-2 arm	432	Triple therapy vs Levo-therapy
Nista[64]	2006	Italy	RCT-2 arm	200	Triple therapy vs Levo-therapy
Ozdil[65]	2011	Turkey	RCT-2 arm	190	Triple therapy vs Levo-therapy
Polat[66]	2012	Turkey	RCT-2 arm	150	Triple therapy vs Levo-therapy
Qian[67]	2012	China	RCT-2 arm	231	Triple therapy vs Levo-therapy
Romano[68]	2010	Italy	RCT-2 arm	375	Triple therapy vs Levo-therapy
Yasser[69]	2013	Palestine	RCT-3 arm	203	Triple therapy vs sequential therapy vs nonbismuth quadruple therapy
Jha[70]	2019	Indian	RCT-2 arm	138	Triple therapy vs nonbismuth quadruple therapy
Llano[71]	2013	Colombia	RCT-2 arm	317	Triple therapy vs Levo-therapy
Chung[72]	2012	Korea	RCT-2 arm	159	Triple therapy vs sequential therapy
Molina-Infante[73]	2010	Spain	RCT-3 arm	460	Triple therapy vs sequential therapy vs Levo-therapy
Seyyedmajidi[74]	2013	Iran	RCT-2 arm	198	Triple therapy vs bismuth quadruple therapy
Sherkatolabbasieh[75]	2017	Iran	RCT-2 arm	192	Triple therapy vs Levo-therapy
Aminian[76]	2010	Iran	RCT-3 arm	321	Triple therapy vs sequential therapy vs bismuth quadruple therapy
Mohi-Ud-Din[77]	2018	India	RCT-3 arm	300	Triple therapy vs sequential therapy vs Levo-therapy
Ennkaa[78]	2018	Qatar	RCT-2 arm	206	Triple therapy vs sequential therapy
Gupta[79]	2018	India	RCT-2 arm	350	Triple therapy vs sequential therapy

Supplementary Table 1. Continued

Study, first author	Publication year	Country	Study design	Total no. of patients included	Regimens compared
Yanai[80]	2012	Japan	RCT-2 arm	119	Triple therapy vs nonbismuth quadruple therapy
Lee[81]	2016	China	RCT-3 arm	425	Triple therapy vs sequential therapy vs nonbismuth quadruple therapy
Yang[82]	2015	Taiwan	RCT-3 arm	450	Triple therapy vs sequential therapy vs Amox-dual therapy
Ang[83]	2015	Singapore	RCT-3 arm	457	Triple therapy vs sequential therapy vs nonbismuth quadruple therapy
Hsu[84]	2015	Taiwan	RCT-2 arm	440	Triple therapy vs R-hybrid therapy