Comparative effectiveness and tolerance of treatments for *Helicobacter pylori*: systematic review and network meta-analysis

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**ABSTRACT**

**OBJECTIVE**

To determine the most efficacious treatment for eradication of *Helicobacter pylori* with the lowest likelihood of some common adverse events among pre-recommended and newer treatment regimens.

**DESIGN**

Systematic review and network meta-analysis.

**DATA SOURCES**

Cochrane Library, PubMed, and Embase without language or date restrictions.

**STUDY SELECTION**

Full text reports of randomised controlled trials that compared different eradication treatments for *H pylori* among adults.

**RESULTS**

Of the 15,565 studies identified, 143 were eligible and included. Data on 14 kinds of treatments were available. Of 91 possible comparisons for the efficacy outcome, 34 were compared directly and the following treatments performed better: seven days of concomitant treatment (proton pump inhibitor and three kinds of antibiotics administered together), 10 or 14 days of probiotic supplemented triple treatment (standard triple treatment which is probiotic supplemented), 10 or 14 days of levofloxacin based triple treatment (proton pump inhibitor, levofloxacin, and antibiotic administered together), 14 days of hybrid treatment (proton pump inhibitor and amoxicillin used for seven days, followed by a proton pump inhibitor, amoxicillin, clarithromycin, and 5-nitroimidazole for another seven days), and 10 or 14 days of sequential treatment (five or seven days of a proton pump inhibitor plus amoxicillin, followed by five or seven additional days of a proton pump inhibitor plus clarithromycin and 5-nitroimidazole or amoxicillin). In terms of tolerance, all treatments were considered tolerable, but seven days of probiotic supplemented triple treatment and seven days of levofloxacin based triple treatment ranked best in terms of the proportion of adverse events reported.

**CONCLUSION**

Comparison of different eradication treatments for *H pylori* showed that concomitant treatments, 10 or 14 days of probiotic supplemented triple treatment, 10 or 14 days of levofloxacin based triple treatment, 14 days of hybrid treatment, and 10 or 14 days of sequential treatment might be better alternatives for the eradication of *H pylori*.

**Introduction**

Although *Helicobacter pylori* is thought to have infected humans for more than 58 000 years, it was first isolated in 1982.1-3 It is a Gram negative bacterium found on the luminal surface of the gastric epithelium.4 *H pylori* is a potentially curable cause of a diverse spectrum of diseases such as dyspepsia, peptic ulcer disease, gastric mucosa associated lymphoid tissue lymphoma, and gastric cancer.5,6 Surprisingly, a series of extra-gastric and even extra-digestive diseases, including haematological disorders such as idiopathic thrombocytopenic purpura and iron deficiency anaemia, cardiovascular diseases, as well as neurological disorders are associated with *H pylori*.7 On a global scale, *H pylori* is the most infectious human pathogen, affecting about 50% of the population.5 In northern Europe and North America, only one third of adults have this bacterium, whereas in southern and eastern Europe, South America, and Asia, more than 50% of people are estimated to be infected.8 *H pylori* occurs commonly in developing countries, whereas the infection rates are decreasing in developed countries,9 potentially indicating that socioeconomic status and living standards might play roles in the distribution of the infection.10,11 Initially, antibiotic treatment was popular and effective.11 In the early 21st century, European guidelines on the management of *H pylori* infection recommended a “standard triple treatment” composed of a proton pump inhibitor plus
clarithromycin, together with amoxicillin or metroni-
dazole.\textsuperscript{11} Ranitidine bismuth citrate based triple treat-
ment, including ranitidine bismuth citrate together 
with any two of amoxicillin, clarithromycin, and me-
tronidazole has proved to have similar efficacy as the 
standard triple treatment.\textsuperscript{11,12} However, in less than a
decade the effectiveness of the most commonly recom-
mended treatments declined to unacceptably low lev-
els, mainly as a result of the development of resistance 
to antibiotics.\textsuperscript{13}

Treatment regimens have been evolving to find the 
most effective approaches. Some researchers showed a 
sequential treatment consisting of five days of a proton 
pump inhibitor plus amoxicillin followed by five addi-
tional days of a proton pump inhibitor plus clarithro-
mycin and 5-nitroimidazole or amoxicillin to be an 
another alternative approach.\textsuperscript{14-16} A bismuth based quadruple 
treatment including bismuth, a proton pump inhibitor, 
and two antibiotics was also accepted as an alternative 
first line treatment in many studies.\textsuperscript{14,17} Concomitant 
treatment with a proton pump inhibitor and three dif-
ferent antibiotics also showed acceptable efficacy in 
some circumstances.\textsuperscript{17} In this regimen, all drugs are 
given concomitantly and not in sequence.\textsuperscript{17} Some 
researchers believe that the principal advantage of this 
regimen is the worldwide availability of antibiotics, 
compared with bismuth compounds.\textsuperscript{17} In addition, the 
antibiotic selection or duration of treatment of this reg-
imen is not standardised.\textsuperscript{17} Additionally, levofloxacin is 
an effective alternative to current standard antibiotics 
and tackles the primary resistance to macrolides and 
nitroimidazoles.\textsuperscript{18} Therefore several studies also recom-
mended a levofloxacin based triple treatment, contain-
ing a proton pump inhibitor, levofloxacin, and one 
antibiotic.\textsuperscript{18} Previous studies reported that adding pro-
biotics improved the effectiveness of \textit{H. pylori} eradica-
tion during standard triple treatment in some circum-
sances.\textsuperscript{19,20} Therefore a probiotic supplemented 
triple treatment has also been considered as a treat-
ment option.\textsuperscript{19} A novel hybrid treatment consisting of a 
dual treatment with a proton pump inhibitor and amox-
icillin for seven days, followed by a concomitant qua-
druple treatment with a proton pump inhibitor, 
amoxicillin, clarithromycin, and 5-nitroimidazole for 
another seven days produces high eradication rates and 
represents a promising first line treatment option.\textsuperscript{7} The 
standard triple treatment, ranitidine bismuth citrate 
base triple treatment, bismuth based quadruple treat-
ment, concomitant treatment, levofloxacin based triple 
treatment, and probiotic supplemented triple treatment 
can be used for seven days and can be extended to 10 or 
14 days. The sequential treatment is generally used for 
10 days and can be extended to 14 days. The hybrid 
treatment is commonly used for 14 days. According to 
previous meta-analyses, extending treatment delivery 
could enhance treatment effects in some circum-
sstances.\textsuperscript{21}

Treatment of this widespread infection remains an 
going challenge, given the estimated rates of infect-
ion in populations and the growing resistance of bacte-ia to antibiotics. Many treatment approaches have 
been developed, but it is unknown which eradication 
treatments are more effective and also tolerable. Previ-
ous meta-analyses of \textit{H. pylori} eradication treatments 
used conventional methods\textsuperscript{18,22-26} rather than network 
meta-analyses. In the conventional approach, only 
direct comparisons between treatments are possible 
where these have been reported in studies. This limits 
any conclusion about the relative efficacy and tolerance 
of treatments that have not been directly compared in 
existing studies.\textsuperscript{27} Network meta-analyses permit both 
direct and indirect comparisons across treatments, pro-
vided that a common comparator exists.\textsuperscript{27,28} We con-
ducted a systematic review and network meta-analysis 
to compare the efficacy and tolerance among different 
treatments for the eradication of \textit{H. pylori} infection.

\textbf{Methods}

\textbf{Data sources and searches}

On 20 December 2013 we searched the Cochrane 
Library, PubMed, and Embase using pre-established 
search terms that consisted of three parts (strategies for 
eradication treatment, \textit{H. pylori}, and a specific filter for 
randomised controlled trials). We used keywords in 
combination with both MeSH terms and text words. The 
search terms included (Helicobacter pylori OR Helico-
bacter OR Helicobacter infection OR Helicobacter* OR 
pylori OR Helicobacter pylori (MeSH)), and (eradication 
OR disease eradication (MeSH) OR treatment OR ther-
apy). We excluded second line, third line, rescue, or 
salvage treatments. There was no limitation on lan-
guage. To identify eligible studies we manually checked 
the reference lists of the included studies.

\textbf{Study selection}

Two researchers (BZL and CZ) initially screened the cita-
tion titles and abstracts. The full text versions of any 
study of potential relevance were then screened inde-
pendently in triplicate. Disagreements were resolved 
through discussions. If discrepancies still existed, we 
sought the opinions of another two researchers for 
further discussion.

Included studies were full text reports of randomised 
controlled trials that compared different treatments for 
the eradication of \textit{H. pylori}. The included studies met 
several criteria: comparisons among the following erad-
ication treatments: standard triple treatment, raniti-
dine bismuth citrate based triple treatment, bismuth 
based quadruple treatment, concomitant treatment, 
levofloxacin based triple treatment, probiotic supple-
mented triple treatment, sequential treatment, and 
hybrid treatment; mean or median age of patients with 
\textit{H. pylori} was more than 18 years; patients were free of 
comorbidities such as renal failure or cancer; eradica-
tion assessments were carried out at least four weeks 
after the end of treatment; only full articles were 
included to lower the risk of bias; and an intention to 
treat analysis had to be reported to present the fre-
quency of \textit{H. pylori} eradication. Exclusion criteria were: 
patients had received previous treatment for eradica-
tion of \textit{H. pylori}; abstracts presented at conferences and 
published abstracts; studies with interventions of
different length other than 7, 10, or 14 days; and letters, commentaries, editorials, and reviews. When multiple publications existed for the same study, we included the most comprehensive report or the publication with more complete outcome data.

**Patient involvement**
There was no patient involvement in this study.

**Data extraction and quality assessment**
Two authors independently extracted the data, which were recorded on a standard spreadsheet. Disagreements were resolved through discussions with two other researchers. To understand better the effects of the type or duration of treatment on eradication, we divided the treatments into 14 groups (table 1). Extracted data included the characteristics of the studies (title, publication year, country, and study design), characteristics of the patients (number of patients, age, number of men and women, assessment method for *H pylori* infection, observation interval between end of treatment and time *H pylori* eradication was confirmed), characteristics of the treatments (intervention, dosage, and duration), and outcomes (number of patients included in the intention to treat analysis, number of patients with successful eradication according to the intention to treat analysis, number of patients included in the analysis of adverse events, number of patients presenting with each of the most common adverse events). The primary outcome of this study was the efficacy of each eradication treatment, according to intention to treat analysis. The secondary outcome was the tolerance analysis, including the occurrence of adverse events in each eradication treatment. Two authors independently assessed the quality of evidence using both the Jadad scale and the Cochrane Collaboration’s tool for evaluating study bias. The resultant rankings are presented graphically.

**Data synthesis and analysis**
We used the traditional pairwise meta-analysis method to analyse direct treatment comparisons. A random effects model, which provides more conservative estimated effects, was applied. As all results were extracted as binary outcomes, we calculated the summary effect sizes as relative risks, with 95% confidence intervals. The statistical heterogeneity among studies was assessed by the Cochran’s Q test and the I² statistic. A P value of 0.10 or less for the Q test or an I² greater than 50% was suggestive of substantial between study heterogeneity. Publication bias was tested using funnel plots.

We analysed pooled data for all eradication treatments with random effects models, within a bayesian framework, using WinBUGS. Summary effect sizes were calculated as relative risks, with 95% credible intervals. To summarise the efficacy and tolerance of all treatments, we also calculated the absolute rates and relative ranks of different eradication treatments. The resultant rankings are presented graphically.

**Table 1 | General characteristics of treatments for eradication of *Helicobacter pylori***

| Treatment abbreviations | General characteristics |
|-------------------------|-------------------------|
| 7 days triple           | "Standard triple treatment": 7 days simultaneous PPI+clarithromycin+(amoxicillin or metronidazole) |
| 7 days concomitant      | 7 days simultaneous PPI+3 antibiotics (often amoxicillin, clarithromycin and 5-nitroimidazole) |
| 10 or 14 days sequential | 5 or 7 days simultaneous PPI+amoxicillin, followed by 5 or 7 days simultaneous PPI+clarithromycin+(5-nitroimidazole or amoxicillin) |
| 10 or 14 days triple    | 10 or 14 days simultaneous PPI+clarithromycin+(amoxicillin or metronidazole) |
| 10 or 14 days bismuth   | 10 or 14 days simultaneous PPI+bismuth compounds+2 antibiotics |
| 7 days bismuth          | 7 days simultaneous PPI+bismuth compounds+2 antibiotics |
| 10 or 14 days concomitant| 10 or 14 days simultaneous PPI+3 antibiotics (often amoxicillin, clarithromycin, and 5-nitroimidazole) |
| 7 days probiotic        | 7 days standard triple treatment supplemented with probiotics |
| 10 or 14 days probiotic | 10 or 14 days standard triple treatment supplemented with probiotics |
| 7 days ranitidine bismuth | 7 days simultaneous ranitidine bismuth citrate+amoxicillin, clarithromycin, and metronidazole |
| 10 or 14 days ranitidine bismuth | 10 or 14 days simultaneous ranitidine bismuth citrate+any 2 of amoxicillin, clarithromycin, and metronidazole |
| 7 days levofloxacin     | 7 days simultaneous PPI+levofloxacin+1 antibiotic |
| 10 or 14 days levofloxacin | 10 or 14 days simultaneous PPI+levofloxacin+1 antibiotic |
| 14 days hybrid          | 7 days simultaneous PPI+amoxicillin, followed by 7 days simultaneous PPI+amoxicillin+clarithromycin+5-nitroimidazole |

PPI=proton pump inhibitor.


Results

Study characteristics and quality assessment

Through literature searches, 15 565 studies were identified, of which 15 281 were excluded after screening of the titles and abstracts. The full texts of 284 remaining studies were reviewed. Overall, 143 studies were eligible and were included (see study inclusion flowchart in supplementary appendix 1, fig S1.1). These 143 studies covered 14 kinds of treatments (table 1). Of 91 possible comparisons between treatment regimens for the primary outcome, 34 were compared directly in the studies we identified. In total, 32 056 patients contributed to the efficacy analysis and 22 180 to the tolerance analysis. The average age of patients with H pylori was 47 years, and approximately 53% of participants were men. The baseline characteristics of the included studies are listed in supplementary appendix 1, table S1.1, and the citation details are given in supplementary appendix 2. The risk of bias summary and figure for included studies are listed in supplementary appendix 3. Some studies did not present details for randomisation, allocation concealment, and blinding.

Treatment efficacy

In total, the success of H pylori eradication was assessed for 14 treatments, presented in 143 studies, and data were available for 32 056 patients (intention to treat analysis). All commonly used treatments were assessed in at least one randomised controlled trial. Figure 1 graphically represents the network of eligible comparisons for the efficacy outcome of the network meta-analysis. For the efficacy outcome, the network meta-analysis estimations indicated that most treatments were better than the previously recommended seven days of standard triple treatment, the two exceptions being the seven days of levofloxacin based triple treatment and seven days of bismuth based quadruple treatment, which were comparable to the seven days of standard triple treatment (table 2 and fig 2). In the comparisons between seven days and 10 or 14 days of treatments, longer treatments in most cases were better, and this was the case for standard triple treatments, levofloxacin based triple treatments, probiotic supplemented triple treatments, and bismuth based quadruple treatments. For the concomitant treatments and ranitidine bismuth citrate based triple treatments, the efficacy of the shorter treatments was comparable to that of the longer treatments (see supplementary appendix 4, table S4.1).

In terms of eradication rates, all treatments, including the seven days of standard triple treatment, were still effective. Ranking on efficacy indicated that seven days of concomitant treatment was the highest, followed by 10 or 14 days of concomitant treatment, 10 or 14 days of probiotic supplemented triple treatment, 10 or 14 days of levofloxacin based triple treatment, 14 days of hybrid treatment, 10 or 14 days of sequential treatment, 10 or 14 days of ranitidine bismuth citrate based triple treatment, and 10 or 14 days of bismuth based quadruple treatment. Table 2 lists the eradication effects of each treatment compared with the seven days of standard triple treatment and supplementary appendix 4, table S4.1 presents the results across all other treatment comparisons. Despite the seven days of concomitant treatment ranking the highest, data on this treatment method was provided by only three studies and in 504 participants.

Heterogeneity in pairwise meta-analysis was generally moderate (see supplementary appendix 4, table S4.2). Similarly, no statistically significant inconsistency was indicated in most loops within the network for the efficacy outcome.

Tolerance of treatments

Treatment comparison for total occurrence of adverse events

A total of 99 studies were included in the comparison of total occurrence rates of adverse events among the 14 treatments. Figure 3 graphically represents the network of eligible comparisons for the adverse event outcome of the network meta-analysis. Generally, the shorter the treatment time was, the lower the likelihood of adverse events. In our network meta-analysis comparisons, seven days of probiotic supplemented triple treatment and seven days of levofloxacin based triple treatment were significantly better than the seven days of standard triple treatment (table 3 and fig 4). These two treatments ranked the best in terms of tolerance. Risks of any adverse event ranged from 14-34% in the different treatments. However, the results should be interpreted with caution because most network meta-analysis comparisons between the various treatments did not reach statistical significance. Table 3 lists the comparisons of adverse events for each treatment with the seven days of standard triple treatment. All other comparisons are shown in supplementary appendix 5, table S5.1. The results of pairwise meta-analyses are also given in supplementary appendix 5, table S5.2.
Table 2 | Efficacy of treatment for Helicobacter pylori eradication compared with seven days of standard triple treatment, eradication rates for all treatments, and treatment effectiveness rank

| Treatments                      | No of studies comparing with 7 days triple | No of participants | Intention to treat | Network meta-analysis: risk ratio (95% CrI) | Direct comparison: risk ratio (95% CI) | Eradication rate (95% CrI) | Mean rank* (95% CrI) |
|--------------------------------|------------------------------------------|---------------------|--------------------|-------------------------------------------|----------------------------------------|----------------------------|----------------------|
| 7 days triple                  |                                          |                     |                    | 1.29 (1.22 to 1.35)                       | 1.39 (1.16 to 1.67)                       | 0.73 (0.71 to 0.75)       | 13.77 (11 to 14)      |
| 7 days concomitant             | 1                                        | 119                 |                    | 1.24 (1.19 to 1.29)                       | NA                                     | 0.79 (0.73 to 0.84)       | 11.52 (8 to 14)       |
| 10 or 14 days sequential       | 15                                       | 3713                |                    | 1.20 (1.16 to 1.23)                       | 1.22 (1.19 to 1.27)                       | 0.87 (0.85 to 0.90)       | 5.82 (4 to 8)         |
| 10 or 14 days triple           | 32                                       | 6844                |                    | 1.12 (1.08 to 1.15)                       | 1.08 (1.05 to 1.12)                       | 0.81 (0.78 to 0.84)       | 10.37 (9 to 12)       |
| 10 or 14 days bismuth          | 6                                        | 1188                |                    | 1.17 (1.12 to 1.21)                       | 1.27 (1.04 to 1.55)                       | 0.85 (0.82 to 0.89)       | 7.52 (5 to 10)        |
| 7 days bismuth                 | 8                                        | 1340                |                    | 1.08 (1.00 to 1.15)                       | 1.07 (1.00 to 1.15)                       | 0.79 (0.73 to 0.84)       | 11.52 (8 to 14)       |
| 10 or 14 days concomitant      | 0                                        | 0                   |                    | 1.24 (1.19 to 1.29)                       | NA                                     | 0.81 (0.78 to 0.84)       | 9.21 (6 to 12)        |
| 7 days probiotic               | 11                                       | 3992                |                    | 1.14 (1.07 to 1.20)                       | 1.14 (1.09 to 1.19)                       | 0.83 (0.78 to 0.87)       | 9.21 (6 to 12)        |
| 10 or 14 days probiotic        | 1                                        | 33                  |                    | 1.24 (1.17 to 1.29)                       | 1.13 (0.69 to 1.84)                       | 0.90 (0.85 to 0.94)       | 7.52 (5 to 10)        |
| 7 days ranitidine bismuth      | 11                                       | 3839                |                    | 1.12 (1.04 to 1.18)                       | 1.10 (1.04 to 1.16)                       | 0.82 (0.76 to 0.86)       | 10.06 (7 to 13)       |
| 10 or 14 days ranitidine bismuth| 0                                        | 0                   |                    | 1.17 (1.07 to 1.25)                       | NA                                     | 0.86 (0.78 to 0.94)       | 7.20 (3 to 12)        |
| 7 days levofloxacin            | 8                                        | 2329                |                    | 1.04 (0.95 to 1.11)                       | 1.01 (0.92 to 1.10)                       | 0.76 (0.69 to 0.81)       | 12.86 (11 to 14)      |
| 10 or 14 days levofloxacin     | 0                                        | 0                   |                    | 1.23 (1.16 to 1.29)                       | NA                                     | 0.90 (0.84 to 0.94)       | 9.21 (6 to 12)        |
| 14 days hybrid                 | 0                                        | 0                   |                    | 1.22 (1.11 to 1.29)                       | NA                                     | 0.89 (0.81 to 0.94)       | 4.71 (1 to 10)        |

CrI=credible interval; NA=not applicable.

*Rank was derived from eradication rate values for all studies, 1=best efficacy.

Fig 2 | Forest plot of network meta-analysis results for treatment efficacy outcomes compared with seven days of standard triple treatment

Fig 3 | Network of eligible comparisons for treatment tolerance network meta-analysis. The width of lines is proportional to the number of studies compared in every pair of treatments, and the size of nodes is proportional to the total sample size of each treatment
Table 3 | Tolerance of treatment for Helicobacter pylori eradication compared with seven days of standard triple treatment, occurrence rates of adverse event for all treatments, and ranking of tolerance to treatment

| Treatments                  | No of studies comparing with 7 days triple | No of participants | Adverse events | Network meta-analysis: risk ratio (95% CrI) | Direct comparison: risk ratio (95% CrI) | Mean occurrence of adverse events (95% CrI) | Mean rank* (95% CrI) |
|-----------------------------|-------------------------------------------|--------------------|----------------|-------------------------------------------|------------------------------------------|-------------------------------------------|----------------------|
| 7 days triple               |                                           |                    |                | 1.19 (0.49 to 2.20)                        | 1.10 (0.70 to 1.73)                       | 0.26 (0.10 to 0.48)                        | 6.41 (3 to 10)        |
| 7 days concomitant          | 1                                         | 110                |                | 1.00 (0.85 to 1.18)                        | 0.99 (0.83 to 1.19)                       | 0.22 (0.17 to 0.27)                        | 6.42 (3 to 10)        |
| 10 or 14 days sequential   | 13                                        | 3216               |                | 1.10 (0.94 to 1.26)                        | 1.14 (1.01 to 1.28)                       | 0.24 (0.18 to 0.29)                        | 8.94 (5 to 12)        |
| 10 or 14 days triple       | 22                                        | 4560               |                | 1.08 (0.85 to 1.34)                        | 0.86 (0.75 to 1.01)                       | 0.23 (0.17 to 0.30)                        | 8.33 (4 to 13)        |
| 7 days bismuth             | 4                                         | 970                |                | 0.97 (0.69 to 1.32)                        | 1.04 (0.94 to 1.16)                       | 0.21 (0.14 to 0.30)                        | 6.14 (2 to 13)        |
| 10 or 14 days concomitant  | 0                                         | 0                  |                | 1.13 (0.83 to 1.48)                        | NA                                       | 0.24 (0.17 to 0.33)                        | 9.19 (3 to 13)        |
| 7 days probiotic           | 9                                         | 2158               |                | 0.65 (0.47 to 0.87)                        | 0.72 (0.49 to 1.06)                       | 0.14 (0.09 to 0.20)                        | 1.72 (1 to 4)         |
| 10 or 14 days probiotic    | 1                                         | 30                 |                | 1.59 (0.44 to 1.68)                        | 1.25 (0.41 to 3.77)                       | 0.34 (0.09 to 0.68)                        | 10.67 (1 to 14)       |
| 7 days ranitidine bismuth  | 6                                         | 943                |                | 1.06 (0.81 to 1.29)                        | 1.20 (1.06 to 1.56)                       | 0.25 (0.16 to 0.35)                        | 9.53 (3 to 14)        |
| 10 or 14 days ranitidine bismuth | 0                  | 0                  |                | 0.99 (0.64 to 1.42)                        | NA                                       | 0.21 (0.13 to 0.32)                        | 6.44 (2 to 13)        |
| 7 days levofloxacin        | 6                                         | 1413               |                | 0.69 (0.49 to 0.96)                        | 0.72 (0.54 to 0.95)                       | 0.15 (0.10 to 0.21)                        | 2.09 (1 to 5)         |
| 10 or 14 days levofloxacin | 0                                         | 0                  |                | 1.26 (0.83 to 1.79)                        | NA                                       | 0.27 (0.17 to 0.39)                        | 10.71 (3 to 14)       |
| 14 days hybrid             | 0                                         | 0                  |                | 1.22 (0.72 to 1.86)                        | NA                                       | 0.26 (0.15 to 0.41)                        | 9.83 (2 to 14)        |

CrI=credible interval; NA=not applicable.

*Rank was derived from occurrence rate of adverse event values for all studies, =best tolerance.

Treatment comparison for occurrence of adverse event subtypes

In terms of the number of patients presenting with epigastric or abdominal pain, occurrence rates in the network meta-analysis revealed that ranitidine bismuth citrate based triple treatments and 10 or 14 days of probiotic supplemented triple treatment might be relatively optimal choices (table 4). The lowest rates of taste alteration were reported with seven days of levofloxacin based triple treatment and bismuth based quadruple treatments. Headaches with or without vomiting were experienced less frequently during probiotic supplemented triple treatments and 10 or 14 days of levofloxacin treatment. Patients taking the probiotic supplemented triple treatments and seven days of levofloxacin based triple treatment reported experiencing diarrhoea less often. Again, findings should be interpreted with caution since most comparisons did not reach statistical significance (see supplementary appendix 5, tables S5.3, S5.5, S5.7, and S5.9). Credible intervals were not narrow in network meta-analysis comparisons and confidence intervals were wide in pairwise meta-analysis comparisons, reflecting the small number of studies available for these comparisons.

It was impossible to subdivide treatment groups further owing to the limited number of studies for each subgroup. However, we recognise that adverse events, particularly taste alteration, may differ by antibiotic choice. Clarithromycin may be one of the main contributors to risk of experiencing taste alteration: seven days of levofloxacin based triple treatment (proton pump inhibitor, levofloxacin, and amoxicillin) was compared with seven days of standard triple treatment (proton pump inhibitor, clarithromycin, and amoxicillin), and a lower risk for taste alteration was seen with levofloxacin instead of clarithromycin (data not shown).

Table 4 shows the occurrence rates and the relative ranks of treatments in terms of subtypes of adverse events. Supplementary appendix 5, tables S5.3-S5.10 list all the results of network meta-analysis and pairwise meta-analysis.

Effectiveness versus harms

Figure 5 presents all eradication treatments ordered by their relative ranks for efficacy, showing the separate contributions to the overall results of efficacy and tolerance. We found that 7, 10, or 14 days of concomitant treatment, 10 or 14 days of probiotic supplemented triple treatment, 10 or 14 days of levofloxacin based triple treatment, 14 days of hybrid treatment, and 10 or 14 days of sequential treatment were among the most effective treatments, whereas seven days of probiotic supplemented triple treatment and seven days of levofloxacin based triple treatment performed better in the tolerance analysis. In figure 6, we ranked these eradication treatments according to both dimensions of efficacy and tolerance. Longer treatments in most cases were better for the efficacy outcomes and worse for adverse events, as most of these treatments lay in the upper left corner,

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whereas shorter treatments tended to have more optimal tolerance outcomes but lower efficacy as they appear mostly in the lower right corner of the figure.

Network assumptions, sensitivity analysis, and publication bias

The meta-regression with efficacy outcomes indicated that mean or median age, sex ratio, Jadad score, and observation interval between the end of treatment and the time *H pylori* eradication was confirmed did not lead to significant changes in the results.

Sensitivity analyses of the publication year and the risks of bias of the included studies did not show any major change in the primary outcome (see supplementary appendix 4, table S4.1). However, if we excluded studies in which any comparison group had a sample size of less than 10 or 14 days.

Table 4 | Occurrence rates and ranks for subtypes of adverse events according to treatments for *Helicobacter pylori* eradication

| Treatments | Abdominal or epigastric pain |
|-------------------------|-----------------------------|
| | Mean occurrence rate (95% CrI) | Mean rank* (95% CrI) | Mean occurrence rate (95% CrI) | Mean rank* (95% CrI) |
| 7 days triple | 1.04 (0.99 to 1.11) | 1.04 (0.99 to 1.11) | 1.04 (0.99 to 1.11) | 1.04 (0.99 to 1.11) |
| 7 days concomitant | 1.02 (0.97 to 1.07) | 1.02 (0.97 to 1.07) | 1.02 (0.97 to 1.07) | 1.02 (0.97 to 1.07) |
| 7 days bismuth | 1.06 (1.00 to 1.11) | 1.06 (1.00 to 1.11) | 1.06 (1.00 to 1.11) | 1.06 (1.00 to 1.11) |
| 7 days metronidazole | 1.01 (0.95 to 1.07) | 1.01 (0.95 to 1.07) | 1.01 (0.95 to 1.07) | 1.01 (0.95 to 1.07) |
| 7 days ranitidine | 1.02 (0.96 to 1.15) | 1.02 (0.96 to 1.15) | 1.02 (0.96 to 1.15) | 1.02 (0.96 to 1.15) |
| 10 or 14 days levofloxacin | 1.06 (1.00 to 1.11) | 1.06 (1.00 to 1.11) | 1.06 (1.00 to 1.11) | 1.06 (1.00 to 1.11) |
| 10 or 14 days metronidazole | 1.04 (1.00 to 1.07) | 1.04 (1.00 to 1.07) | 1.04 (1.00 to 1.07) | 1.04 (1.00 to 1.07) |
| 10 or 14 days bismuth | 1.08 (1.03 to 1.13) | 1.08 (1.03 to 1.13) | 1.08 (1.03 to 1.13) | 1.08 (1.03 to 1.13) |
| 10 or 14 days ranitidine | 1.11 (1.06 to 1.17) | 1.11 (1.06 to 1.17) | 1.11 (1.06 to 1.17) | 1.11 (1.06 to 1.17) |
| 10 or 14 days levofloxacin | 1.14 (1.05 to 1.23) | 1.14 (1.05 to 1.23) | 1.14 (1.05 to 1.23) | 1.14 (1.05 to 1.23) |
| 10 or 14 days bismuth | 1.16 (1.10 to 1.24) | 1.16 (1.10 to 1.24) | 1.16 (1.10 to 1.24) | 1.16 (1.10 to 1.24) |
| 10 or 14 days ranitidine | 1.16 (1.10 to 1.24) | 1.16 (1.10 to 1.24) | 1.16 (1.10 to 1.24) | 1.16 (1.10 to 1.24) |
| 10 or 14 days levofloxacin | 1.20 (1.10 to 1.30) | 1.20 (1.10 to 1.30) | 1.20 (1.10 to 1.30) | 1.20 (1.10 to 1.30) |
| Treatment | Efficacy (risk ratio 95% credible interval) | Occurrence of adverse events (risk ratio 95% credible interval) |

Footnote: Table 4 presents the occurrence rates and ranks for subtypes of adverse events according to treatments for *Helicobacter pylori* eradication.
Ranking for tolerance of Helicobacter pylori treatments in network meta-analyses

Fig 6 | Ranking for effectiveness and tolerance of Helicobacter pylori treatments in network meta-analyses

| Treatment Duration | Ranking for Efficacy | Ranking for Tolerance |
|--------------------|----------------------|-----------------------|
| 7 days bismuth     | 0                    | 1                     |
| 10 or 14 days probiotic | 2                | 2                     |
| 10 or 14 days levofloxacin | 3              | 3                     |
| 10 or 14 days sequential | 4            | 4                     |
| 10 or 14 days hybrid | 5               | 5                     |
| 10 or 14 days concomitant | 6          | 6                     |
| 24 days hybrid     | 7                    | 7                     |
| 7 days ranitidine bismuth | 8             | 8                     |
| 10 or 14 days triple | 9                | 9                     |
| 10 or 14 days probiotic | 10           | 10                    |
| 7 days levofloxacin | 11                   | 11                    |
| 7 days bismuth     | 12                   | 12                    |

Discussion

This network meta-analysis has four principal findings: the previously recommended seven days of standard triple treatment was the least effective in intention to treat analysis; prolonging the duration of treatments seems to enhance eradication rates; the concomitant treatments, 10 or 14 days of probiotic supplemented triple treatment, 10 or 14 days of levofloxacin based triple treatment, 14 days of hybrid treatment, and 10 or 14 days of sequential treatment seemed more effective than other kinds of treatments; prolonging treatment unsurprisingly seemed to increase the risk of adverse events. The two treatments that performed best in terms of adverse events were the seven days of probiotic supplemented triple treatment and seven days of levofloxacin based triple treatment.

Findings in context of recommendations for standard triple treatment

Some previous pairwise meta-analyses are aligned with our findings and showed that in some circumstances seven days of standard triple treatment is less effective than treatments such as seven days of probiotic supplemented treatment,7 10 days of bismuth based quadruple treatment,6 36 and sequential treatment.6 37 Seven days of standard triple treatment was consistently ranked last in our network meta-analysis. The most likely reason is growing resistance of Helicobacter pylori to clarithromycin and metronidazole.5 However, antibiotic resistance rates and thus efficacy will differ by region. One randomised controlled trial conducted in the United Kingdom and one in Hong Kong reported desirable eradication rates of over 90% with seven days of standard triple treatment. For those studies the resistance to clarithromycin was lower than 10%. In contrast, an extremely low eradication rate of 44-4% was reported in Turkey where the resistance rate to clarithromycin is reported to be over 40%.40 Therefore our analysis and other studies support the use of this standard triple treatment only in areas where clarithromycin resistance is lower than 15-20%.41

Other than comparisons with seven days of standard triple treatment, the number of studies that analysed each particular pair of treatments is still relatively small. Furthermore, for some treatments there was no direct comparative research. Consequently, traditional pairwise meta-analyses are limited in helping to summarise the most effective treatment among 14 kinds of treatments. The ability to estimate effectiveness in this work using network meta-analysis allows for more comprehensive assessment of treatment options than has been previously possible.

Detailed consideration of better performing treatments

Some treatments had relatively higher eradication rates in this study—for example, the concomitant treatments and hybrid treatment. However, relatively few studies assessed these treatments. Only three studies including 504 participants compared the efficacy of seven days of concomitant treatment with that of other treatments, and three studies including 940 participants compared 14 days of hybrid treatment with other treatments. Therefore the validity of conclusions drawn about these treatments is somewhat limited. There is a need for larger and well designed studies to assess less studied treatments so valid conclusions can be made about the most effective and least harmful treatments. This may be particularly relevant for treatments such as the seven days of concomitant treatment, which had the highest efficacy and yet no worse adverse events profile than many of the other 10 or 14 day treatments (fig 6).

Ten or 14 days of sequential treatment was another popularly studied treatment that performed well.5 37 As would be expected, this treatment was virtually identical to the seven days of standard triple treatment for risk of adverse events but did display improved efficacy of eradication. Differences between 10 or 14 days of concomitant treatment, 14 days of hybrid treatment, and 10 or 14 days of sequential treatment were not statistically significant, thus revealing similar efficacies of these regimens. The similar efficacy of concomitant, hybrid, and sequential treatments was also reported in a previously published pairwise meta-analysis.36
Our study demonstrated that adding probiotics to standard triple treatment had the positive consequence of enhancing efficacy, and previous systematic reviews reached the same conclusion. In addition, our study revealed that seven days of probiotic supplemented triple treatment performed the best in the tolerance analysis. Probiotics are viable microorganisms that have health benefits beyond general nutrition if ingested in sufficient numbers. They exhibit important and wide ranging in vitro antibacterial activity against enteric bacteria. Additionally, probiotics stimulate defensive acidogenic flora, induce lymphatic proliferation, modulate non-specific and specific immune responses to pathogens, as well as increase specific IgA responses, all of which are potential mechanisms for the efficacy and tolerance of probiotic supplemented treatment. However, several things should be considered before recommending probiotics in clinical practice. First of all, only seven studies used 10 or 14 days of probiotic supplemented triple treatment, and the sample sizes were small, ranging from 17 to 98 participants. The roles of probiotics in these studies are unclear, and different results may be due to the different timing of probiotic administration or to the duration of probiotic use. Different kinds of probiotics may also produce different effects. In addition, the quality of evidence from treatments including probiotic supplementation was generally poor, with only five of 17 studies clearly indicating that participants were blind to allocation. Lack of blinding is likely to influence compliance and reporting of adverse events, and in a large proportion of all included studies in this review a major weakness was the lack of or poor reporting about blinding of participants. Furthermore, the total adverse event rate for 10 or 14 days of probiotic supplemented triple treatment was only reported by small numbers of studies. Therefore, before we can safely conclude about the efficacy and tolerance profile of the probiotic supplemented triple treatments, more well designed double blind randomised controlled trials with large sample sizes should be conducted. Whether probiotics can help to improve efficacy of treatments such as the concomitant treatment, or other treatments, needs more research.

Contradictory results were sometimes observed for the same treatments between studies included in this review: the same regimen may prove to be extremely effective in one geographical area but have disappointing results in another, indicating that each treatment might have its own preferred application condition and limitations. For instance, sequential treatment proved ineffective in patients with dual resistance to clarithromycin and imidazole, and concomitant treatment seemed to be a better choice. The difference in the rates of antibiotic resistance in different geographical areas, especially the resistance to clarithromycin and metronidazole between groups is probably one of the main explanations for contrasting results. In addition, even in the same geographical region, differences in results may occur, making it challenging to identify the “best” treatment. However, a large portion of the included studies did not conduct antibiotic resistance or sensitivity tests before allocation of treatments, and some studies tended to only mention the antibiotic resistance rates in their countries in general. This could cause selection bias and a baseline difference in resistance to antibiotics between groups. Because of the lack of information on antibiotic resistance, it was not possible for us to conduct a meta-regression analysis or a subgroup analysis to evaluate the extent to which each study’s antibiotic resistance rates contribute to heterogeneity of treatment effects.

Strengths and weaknesses of this review
First and foremost this study is the most comprehensive and systematic comparative meta-analysis of eradication treatments for \textit{H pylori}. After rigorous and detailed searching, we identified 143 studies including 32056 patients to contribute data to this work. Moreover, using the network meta-analysis, we were able to assess multiple treatments and to provide a rank order for treatments based on their capacity to eradicate \textit{H pylori} and the likelihood to cause adverse events.

Our study has several limitations. The quality of included studies is the principal limitation in any findings generated through meta-analysis. In addition to the lack of information about random sequence generation, blinding, and other useful information, a large portion of studies did not assess the antibiotic sensitivity or resistance of \textit{H pylori}. Thus a baseline difference in resistance to antibiotics between groups cannot be ruled out. Different types or rates of antibiotic resistance might account for some degree of discrepancy between different study outcomes. Additionally, the treatments were divided into 14 kinds and studies varied in terms of proton pump inhibitor type, antibiotic agents, drug doses, and administration frequency. Other key information on potential effect modifiers such as smoking rates and alcohol consumption were generally not well reported in the studies. These factors may affect the clinical outcomes in the network analysis and cause inconsistency and heterogeneity. Although we used a loop specific method and found most loops to be consistent, we cannot rule out the possibility of inconsistency because of the presence of many underpowered and correlated tests in using this method. Moreover, because of the great variety in terms of study design, antibiotic type, dose, and administration frequency of the drugs, and the poor reporting of potential effect modifiers such as smoking and alcohol use, we could not account for all factors in the meta-regression and subgroup analyses. Our results are limited in this regard. In addition, evidence in this network meta-analysis largely originated from countries in East Asia, the Middle East, and Europe, with fewer from other regions. The better treatment regimens identified in this work may therefore not be applicable to other regions such as South East Asia, South America, middle Asia, and Africa, and further studies from these regions are welcomed. Furthermore, treatments such as hybrid and concomitant treatments have not been extensively studied. The numbers of studies and the sample sizes
focusing on these treatments were small. Because of small numbers of studies reporting on many treatments, any conclusions made here are based on limited information. The bias from the small numbers of studies could act in either direction to exaggerate or under-estimate effect sizes. Moreover, many included studies did not provide information on the reasons for patients’ withdrawal, or poorly reported the adverse events. In less researched treatments, assessment of separate adverse events is limited by small numbers of such events, and so overall adverse events may represent a more reliable impression of treatment harms.

Implications
Balancing the evidence of greater effectiveness and the accompanying increasing risk of harms with longer duration of treatment is a crucial problem in the treatment of H pylori infection and should have a bearing in clinical practice guidelines that might result from this work. The concomitant treatments, 10 or 14 days of probiotic supplemented triple treatment, 10 or 14 days of levofloxacin based triple treatment, 14 days of hybrid treatment, and 10 or 14 days of sequential treatment performed better in terms of efficacy. The credible intervals in outcome ranks were wide, indicating overlapping degrees of effectiveness for many treatments; therefore, a choice of any treatment should also be based on other factors, such as status of local antibiotic resistance, costs, availability of medicines, and safety. Although most of the differences in adverse events were not statistically significant, there is a trend for greater occurrence with longer treatment.

The important problem of local resistance to antibiotics needs to be tackled in future work, with studies quantifying local resistance rates. In particular, the efficacies of the same treatment with different antibiotics could be examined.

A major challenge in interpreting results from these many studies is that the resistance profile by region is likely to be different, meaning that one single “most effective” treatment is unlikely to be identified across the world, as the treatments will need to be tailored to regional resistance profiles. An important limitation with the included studies is that the resistance was not measured and also only a small proportion of the studies originated in South East Asia, South America, middle Asia, or Africa. The efficacy results here must be interpreted in this context and will be more relevant to those regions contributing large numbers of studies to the analysis. Consequently, we are unable to draw conclusions about the “best” treatment for regions where few studies have been conducted; and even for those regions with many studies, findings are limited by the unquantified antibiotic resistance of study populations.

Conclusions
This comprehensive network meta-analysis showed that the previously widely used seven days of standard triple treatment, although effective, was out-performed in effectiveness by most other treatments. Treatments such as the concomitant ones, the 10 or 14 days of probiotic supplemented triple treatment, 10 or 14 days of levofloxacin based triple treatment, 14 days of hybrid treatment, and 10 or 14 days of sequential treatment might be optimal alternatives. Prolonging the duration of treatments for longer than seven days seems to significantly enhance eradication rates but may increase the rates of adverse events. However, different regions are likely to have different features of H pylori resistance to antibiotics and findings from the smaller number of studies that have examined these apparently more effective treatments may not apply to other locations. H pylori eradication was more often studied in regions such as China, South Korea, southern Europe, and the Middle East, with relatively few in other areas. Therefore, more well designed randomised controlled trials in different countries, with large sample sizes and that include tests for antibiotic resistance are crucial to enable assessment of these varying treatments.

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