

IS THERE A ROLE FOR DOXYCYCLINE IN A REGIMEN FOR ERADICATION OF *HELICOBACTER PYLORI* (*H. PYLORI*) INFECTION? A SYSTEMATIC REVIEW AND META-ANALYSIS

R.R. Molgan, Y. Niv

Adelson Faculty of Medicine, Ariel University, Ariel, Israel

Corresponding Author: Professor Yaron Niv, MD; email: nivyaron80@gmail.com; nivy@ariel.ac.il

Abstract – Objectives: Half of the world's population is infected with *H. pylori*, with higher prevalence in developing countries. *H. pylori* infection is associated with peptic ulcer disease, gastric adenocarcinoma, and gastric lymphoma; therefore, eradication is recommended in all diagnosed cases. We consider that successful eradication should exceed 90-95%, and for this, an efficient therapy including several antibiotics and a proton pump inhibitor is needed. Our study aims to assess the efficacy of doxycycline-containing regimens for *H. pylori* eradication.

Materials and Methods: English medical literature searches were conducted up to December 31, 2025. Searches focused on regimens containing doxycycline for the eradication of *H. pylori* in comparison with regimens without doxycycline. A meta-analysis was performed using Comprehensive Meta-analysis software (Version 4, Biostat Inc., Englewood, NJ, United States). Pooled odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated using a random-effects model. Heterogeneity was assessed using the Cochran Q test and the I^2 statistic. Potential publication bias was evaluated using funnel plots and statistical tests.

Results: We included 3 articles and 8 sub-studies in our meta-analysis that examined eradication rates of different regimens and compared doxycycline-based to non-doxycycline-based regimens, published up to December 31, 2025. The random-effects model was employed for the analysis. Doxycycline-based regimens were inferior to other regimens, with a mean OR for successful eradication of 0.641 (95% CI: 0.452 to 0.909; $p = 0.013$).

Conclusions: This systematic review and meta-analysis confirmed that doxycycline-based therapeutic regimens are less effective for *H. pylori* eradication than the other regimens studied.

Keywords: Systematic review, Meta-analysis, Doxycycline, *Helicobacter pylori*, Eradication.



INTRODUCTION

Helicobacter pylori (*H. pylori*) is a Gram-negative bacterium that colonizes the human stomach and is among the most prevalent chronic infections worldwide^{1,2}. Its prevalence is disproportionately higher in developing countries, where epidemiological studies have consistently linked transmission to poor sanitation, overcrowding, and limited access to clean water³⁻⁵. In both developing and developed regions, untreated *H. pylori* infection is almost universally associated with chronic gastritis and is a major cause of peptic ulcer disease and noncardia (distal) gastric cancer, with the disease burden significantly heavier in high-prevalence, resource-limited settings¹⁻⁴. Accordingly, eradication of *H. pylori* infection is a key therapeutic goal for peptic ulcer healing and gastric cancer prevention^{1,2}. However, the effectiveness of standard *H. pylori* eradication regimens has been increasingly compromised by rising antimicrobial resistance, resulting in higher treatment failure rates^{1,2}. Current international guidelines, therefore, recommend tailoring eradication therapy to local and individual resistance patterns. Given the global increase in resistance to clarithromycin, metronidazole, and fluoroquinolones, bismuth-based quadruple therapy is now endorsed as the preferred first-line regimen in most populations, including patients with penicillin allergy and those in resource-limited settings^{1,2}. Clarithromycin resistance is strongly associated with prior macrolide exposure⁶ and markedly reduces the effectiveness of standard triple therapy, resulting in unacceptably low eradication rates in many regions^{6,7}. Metronidazole resistance is highly prevalent worldwide, especially in developing countries⁷, and is primarily associated with alterations in bacterial nitroreductase activity⁶, reflecting the extensive use of nitroimidazoles for non-*H. pylori* infections⁷. At the population level, antimicrobial resistance surveillance relies on culture-based susceptibility testing and molecular detection of resistance-associated mutations, forming the basis for region-specific treatment recommendations⁷⁻⁹. At the individual level, resistance assessment may include phenotypic testing of gastric biopsies or molecular assays applied to gastric or stool samples, enabling personalized therapy and potentially improving eradication outcomes^{8,10}.

The growing limitations of standard triple therapy in the context of rising antimicrobial resistance have led to the development of combination antibiotic regimens¹¹. As a result, multiple therapeutic strategies have been developed and evaluated, including bismuth-based quadruple therapy, non-bismuth concomitant and sequential regimens, high-dose dual therapies, and alternative combinations incorporating tetracycline or doxycycline^{1,11}. The systematic evaluation of different drug combinations is therefore essential to optimize eradication rates, overcome antibiotic resistance, and tailor treatment strategies to regional resistance patterns and individual patient characteristics^{1,12}. Differences in *H. pylori* eradication strategies between developed and developing countries reflect variations in antimicrobial resistance patterns, healthcare infrastructure, and access to diagnostic tools^{2,7}. In high-resource settings, guidelines increasingly advocate susceptibility-guided therapy or tailored approaches, although their widespread adoption remains limited^{8,12}. Conversely, developing regions face higher infection rates, extensive resistance to clarithromycin and metronidazole, and scarce access to susceptibility testing^{2,7}. Consequently, empirical regimens, particularly bismuth-based quadruple therapy, are often recommended as first-line treatments in resource-limited areas due to their efficacy and resistance robustness across diverse populations^{2,8,13,14}.

Rationale and Aim of the Study

In this meta-analysis, we aimed to compare the eradication success rates of *H. pylori* treatment regimens with and without doxycycline. Failure of doxycycline-containing regimens may indicate emerging resistance within the tetracycline antibiotic class, highlighting important implications for regimen selection and future treatment strategies.

MATERIALS AND METHODS

Identification of Studies and Data Extraction

For this meta-analysis, comprehensive searches were conducted across the MEDLINE, PubMed, Embase, and Google Scholar databases through December 31, 2025. The focus was on identifying

English-language human studies, utilizing the following search text and/or Medical Subject Headings (MeSH) terms: “*Helicobacter pylori*” OR “*H. pylori*” [All Fields] AND “doxycycline”. A manual search was also conducted, reviewing the bibliographies of retrieved original studies, review articles, and published editorials. This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for interventions¹⁵⁻¹⁷.

Selection Criteria – Primary Endpoints

Inclusion and exclusion criteria were established before initiating the study investigation. Eligible studies were incorporated into the meta-analysis if they were: a. published as complete articles with extractable data; b. written in English; and c. comparing eradication rates of doxycycline-based regimens with those of non-doxycycline regimens¹⁸⁻¹⁰. Critically, only comparison studies reporting results of eradication based on an acceptable test, such as a breath test or fecal antigen test (but not an IHC test), were considered. The primary endpoint was defined as the resolution of the OR and 95% Confidence Interval (95% CI) comparing successful eradication rates.

Statistical Analysis

Meta-analysis was performed using Comprehensive Meta-Analysis software (Version 4, Biostat Inc., Englewood, NJ, United States)¹⁶. The random-effects model was employed to calculate pooled ORs and 95% CIs, assuming that the true effects varied across studies due to inherent biological or methodological differences.

Heterogeneity, Sensitivity, and Publication Bias

Heterogeneity was assessed using the Cochran Q test and the I^2 Inconsistency index. Heterogeneity was considered present if the Q-test *p-value* was <0.10. I^2 values of 25%, 50%, and 75% represented low, moderate, and high inconsistency, respectively.

Sensitivity testing involved systematically excluding individual studies and recalculating the overall meta-analysis outcome to ensure the stability and robustness of the primary result. Publication bias was analyzed using a funnel plot, complemented by Begg-Mazumdar and Egger statistics¹⁷. Comparison-adjusted funnel plots were constructed to examine their symmetry. Meta-regression analysis was also performed to control for bias introduced by a single study.

RESULTS

Study Selection and Descriptive Characteristics

The literature search revealed 224 eligible papers, from which 3 articles contributing 8 sub-studies (data sets) were selected for the final meta-analysis after rigorous application of the exclusion criteria (Figure 1). Studies were excluded if they involved animals, lacked full-text availability, were not published in English ($n = 197$), or were editorials, reviews, duplicates, or did not meet the inclusion criteria ($n = 24$). The included studies were published up to December 31, 2025, and originated from 3 countries: Turkey, China, and Syria. These studies collectively involved 1,605 patients with *Helicobacter pylori* infection, comprising 773 men (48.17%) and 832 women (51.84%); 931 (58.00%) were treated with a doxycycline-containing regimen with 79.60% successful eradication, and 674 (42.00%) with a non-doxycycline regimen with 80.56% successful eradication ($p = 0.013$).

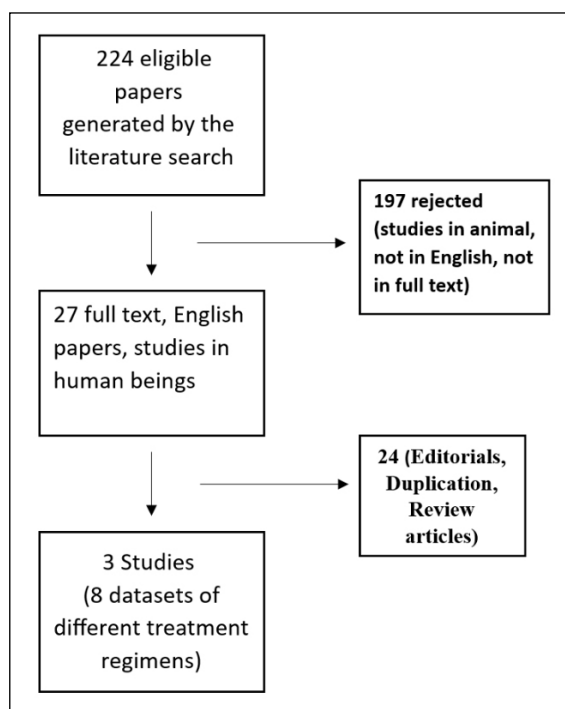


Figure 1. Flow chart of studies included in the meta-analysis.

Qualitative Findings of Included Studies – A Systematic Review¹⁸⁻²⁰

Ozturk et al (2017)¹⁸ compared the eradication efficacy of a bismuth-containing sequential regimen vs. 5 different regimens without doxycycline in treatment-naïve *Helicobacter pylori*-positive patients with non-ulcer dyspepsia, using a prospective, randomized design. The doxycycline-containing sequential regimen (OA+OMDB), Omeprazole 20 mg b.i.d., and amoxicillin 1,000 mg b.i.d. for 5 days, followed by omeprazole 20 mg b.i.d., metronidazole 500 mg t.i.d., doxycycline 100 mg b.i.d., and bismuth subcitrate 600 mg b.i.d. for 5 days, achieved eradication in 32/54 patients, and compared with 5 different regimens without doxycycline:

1. Standard triple therapy for 10 days (OAC: Omeprazole 20 mg b.i.d., amoxicillin 1,000 mg b.i.d., clarithromycin 500 mg b.i.d) achieved eradication in 30/49 patients.
2. Bismuth-based quadruple regimen for 10 days (OTMB: omeprazole 20 mg b.i.d., tetracycline 500 mg q.i.d., metronidazole 500 mg t.i.d., bismuth subcitrate 600 mg b.i.d.), achieving eradication in 40/48 patients.
3. Bismuth-based quadruple therapy for 10 days (OACB: Omeprazole 20 mg b.i.d., amoxicillin 1,000 mg b.i.d., clarithromycin 500 mg b.i.d., bismuth subcitrate 600 mg b.i.d), achieving eradication in 39/51 patients.
4. Sequential therapy without bismuth (OA + OCM – First 5 days: omeprazole 20 mg b.i.d., amoxicillin 1000 mg b.i.d.; Second 5 days: omeprazole 20 mg b.i.d., clarithromycin 500 mg b.i.d., metronidazole 500 mg t.i.d.), achieving eradication in 34/47 patients.
5. Bismuth-containing sequential regimen (OA+OCMB – First 5 days: omeprazole 20 mg b.i.d., amoxicillin 1,000 mg b.i.d. Second 5 days: omeprazole 20 mg b.i.d., clarithromycin 500 mg b.i.d., metronidazole 500 mg t.i.d., bismuth subcitrate 600 mg b.i.d.), achieving eradication in 43/52 patients.

Doxycycline-containing sequential therapy was associated with lower eradication rates compared with other bismuth-based regimens. Internal validity was strengthened by a prospective randomized design, consecutive patient enrollment, standardized ¹⁴C-urea breath testing for objective outcome assessment, and multivariate analysis controlling for multiple cofactors, including smoking and gender. Key limitations include a relatively small sample size per arm, insufficient power to detect differences between regimens with <80% efficacy per Maastricht criteria, a single-center population, limiting generalizability, a lack of antibiotic resistance profiling and CYP2C19 polymorphism analysis, and the absence of longer-term recurrence data.

Zhou et al (2020)¹⁹ analyzed the efficacy and safety of bismuth-based quadruple eradication regimens for *Helicobacter pylori* infection according to previous antibiotic exposure in a large pro-

spective single-center cohort. The doxycycline-containing regimen included esomeprazole 20 mg twice daily, doxycycline 100 mg twice daily, furazolidone 100 mg twice daily, and colloidal bismuth tartrate 165 mg 3 times daily for 14 days, achieving successful eradication in 695/838 patients (including 85 patients treated as rescue therapy after previous eradication failure). Comparable eradication rates were observed with the non-doxycycline regimens:

1. Esomeprazole 20 mg b.i.d., amoxicillin 1,000 mg b.i.d., clarithromycin 500 mg b.i.d., and bismuth tartrate 165 mg t.i.d. with a successful eradication in 278/331 patients.
2. Esomeprazole 20 mg b.i.d., amoxicillin 1,000 mg b.i.d., furazolidone 100 mg b.i.d., and bismuth tartrate 165 mg t.i.d. with a successful eradication in 47/57 patients.

Internal validity was enhanced by the large prospective design, standardized $^{13}\text{C}/^{14}\text{C}$ urea breath testing, systematic documentation of prior antibiotic history over 2 years, and algorithmic regimen allocation based on clinical exposure patterns. Limitations include unequal group sizes, a single-center design, and the absence of antimicrobial susceptibility testing, precluding direct comparison with susceptibility-guided approaches.

Alhalabi et al (2021)²⁰ compared the eradication efficacy and safety of a doxycycline-based bismuth quadruple regimen vs. a levofloxacin-based concomitant regimen in patients with *Helicobacter pylori* infection. Patients treated with the doxycycline-based quadruple regimen (bismuth subsalicylate 524 mg four times daily, doxycycline 100 mg twice daily, tinidazole 500 mg twice daily, and esomeprazole 20 mg twice daily for 14 days) were compared with patients treated with levofloxacin concomitant regimen (levofloxacin 500 mg once daily, tinidazole 500 mg twice daily, amoxicillin 1,000 mg twice daily, and esomeprazole 20 mg twice daily for 14 days). Successful eradication was achieved in 30 of 39 patients vs. 32 of 39 patients, respectively. The difference in eradication rates between the two regimens did not reach statistical significance. Internal validity was enhanced by sealed-envelope randomization, blinded outcome assessment, compliant reporting, and an adequate power calculation (80% power). Limitations include small sample size, single-center design, reliance on patient-reported medication history, self-reported compliance, and absence of antibiotic susceptibility testing.

Meta-Analysis Outcomes

We included in our meta-analysis 3 articles and 8 sub-studies (data sets) examining eradication rates of different regimens and comparing doxycycline-based to non-doxycycline-based regimens, published up to December 31, 2025¹⁸⁻²⁰ (Figure 2, Table 1). The random-effects model was employed for the analysis. The studies in the analysis are assumed to be a random sample from a universe of potential studies, and this analysis will be used to make an inference about that universe. The mean effect size (OR) of successful eradication with doxycycline-based regimens is 0.641, 95% CI: 0.452 to 0.909, $p = 0.013$. The mean effect size across comparable studies could fall anywhere within this interval. The Z-value tests the null hypothesis that the mean effect size is 1.000 and yields a Z-value of -2492 with $p = 0.013$. Using a criterion alpha of 0.050, we reject the null hypothesis and conclude that in the universe of populations comparable to those in the analysis, the mean effect size is not precisely 1.000. The relevant funnel plot (Figure 3) suggests no significant publication bias ($p > 0.05$). The Q-statistic provides a test of the null hypothesis that all studies in the analysis share a common effect size. If all studies shared the same true effect size, the expected value of Q would be equal to the degrees of freedom (the number of studies minus 1). The Q-value is 12.155 with 7 degrees of freedom and $p = 0.096$. Using a criterion alpha of 0.100, we can reject the null hypothesis that the true effect size is the same in all these studies. The I-squared statistic is 42%, indicating that 42% of the variance in observed effects is due to variance in true effects rather than sampling error. If we assume that the true effects are normally distributed (in log units), we can estimate the prediction interval to be 0.263-1.562. The true effect size in 95% of all comparable populations falls in this interval (Figure 4). We measured sensitivity by excluding individual studies and recalculating the overall meta-analysis outcome. This process was repeated for each of the studies. Deviations from the primary result were not significant.

When studies were analyzed separately according to whether their OR was up to (and including) or above the median value (0.556), the results remained in the same direction and within the prediction interval, ranging from an OR of 0.391 (95% CI 0.254-0.611) to 0.928 (95% CI 0.702-1.226).

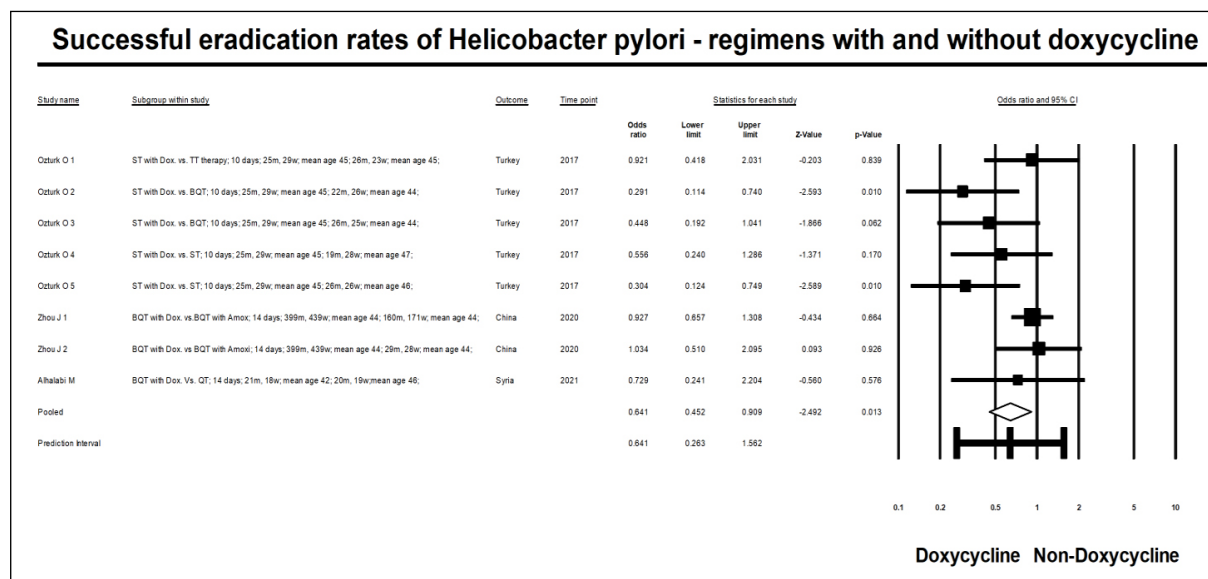


Figure 2. Forest plot illustrating OR and 95%CI for a successful *H. pylori* eradication with doxycycline-based regimens.

TABLE 1. COMPARISON OF THE SUCCESSFUL ERADICATION OF REGIMENS CONTAINING DOXYCYCLINE WITH REGIMENS WITHOUT DOXYCYCLINE.							
Author	Sub-study	Country	Year	X1	N1	X2	N2
Ozturk ¹⁸	ST with Dox. vs. TT therapy; 10 days; 25 m, 29w; mean age 45; 26m, 23w; mean age 45;	Turkey	2017	32	54	30	49
Ozturk ¹⁸	ST with Dox. vs. BQT; 10 days; 25m, 29w; mean age 45; 22m, 26w; mean age 44;	Turkey	2017	32	54	40	48
Ozturk ¹⁸	ST with Dox. vs. BQT; 10 days; 25m, 29w; mean age 45; 26m, 25w; mean age 44;	Turkey	2017	32	54	39	51
Ozturk ¹⁸	ST with Dox. vs. ST; 10 days; 25m, 29w; mean age 45; 19m, 28w; mean age 47;	Turkey	2017	32	54	34	47
Ozturk ¹⁸	ST with Dox. vs. ST; 10 days; 25m, 29w; mean age 45; 26m, 26w; mean age 46;	Turkey	2017	32	54	43	52
Zhou J ¹⁹	BQT with Dox. vs. BQT with Amox; 14 days; 399m, 439w; mean age 44; 160m, 171w; mean age 44;	China	2020	695	838	278	331
Zhou J ¹⁹	BQT with Dox. vs. BQT with Amoxi; 14 days; 399m, 439w; mean age 44; 29m, 28w; mean age 44;	China	2020	695	838	47	57
Alhalabi ²⁰	BQT with Dox. vs. QT; 14 days; 21m, 18w; mean age 42; 20m, 19w; mean age 46;	Syria	2021	30	39	32	39

Dox = Doxycycline; Amox = Amoxicycline; BQT = Bismuth quadruple therapy; QT = Quadruple therapy; ST = Sequential therapy; TT = Triple therapy; Men = m; Women = w.
 X1 = Number of patients treated with doxycycline-based regimens with successful eradication; N1 = Total number of patients treated with doxycycline-based regimens.
 X2 = Number of patients treated with non-doxycycline-based regimens with successful eradication; N2 = Total number of patients treated with non-doxycycline regimens.

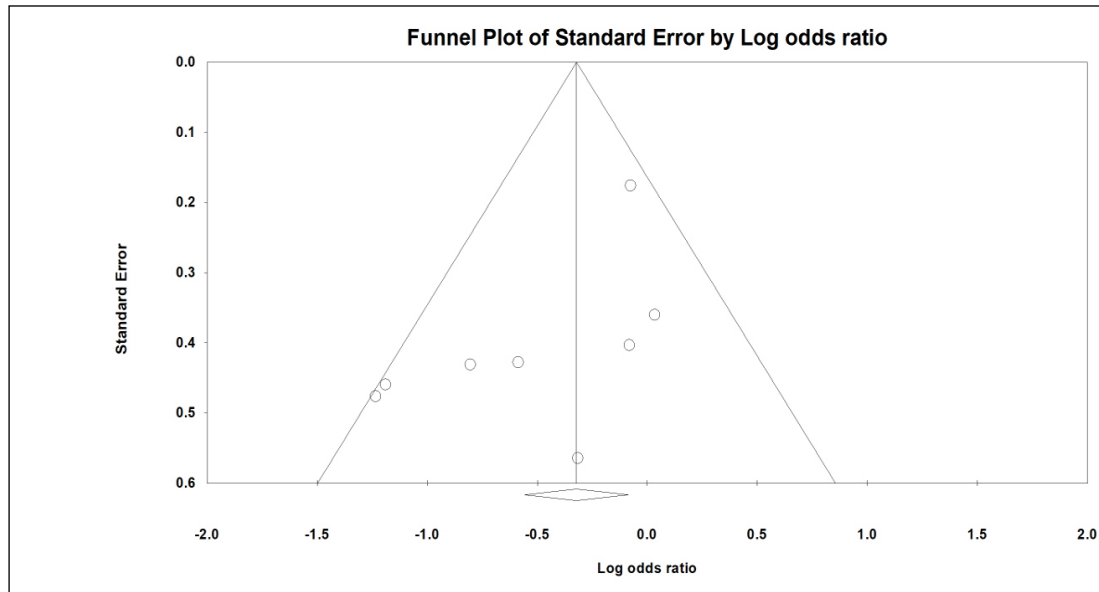


Figure 3. Funnel plot for publication bias of all the studies.

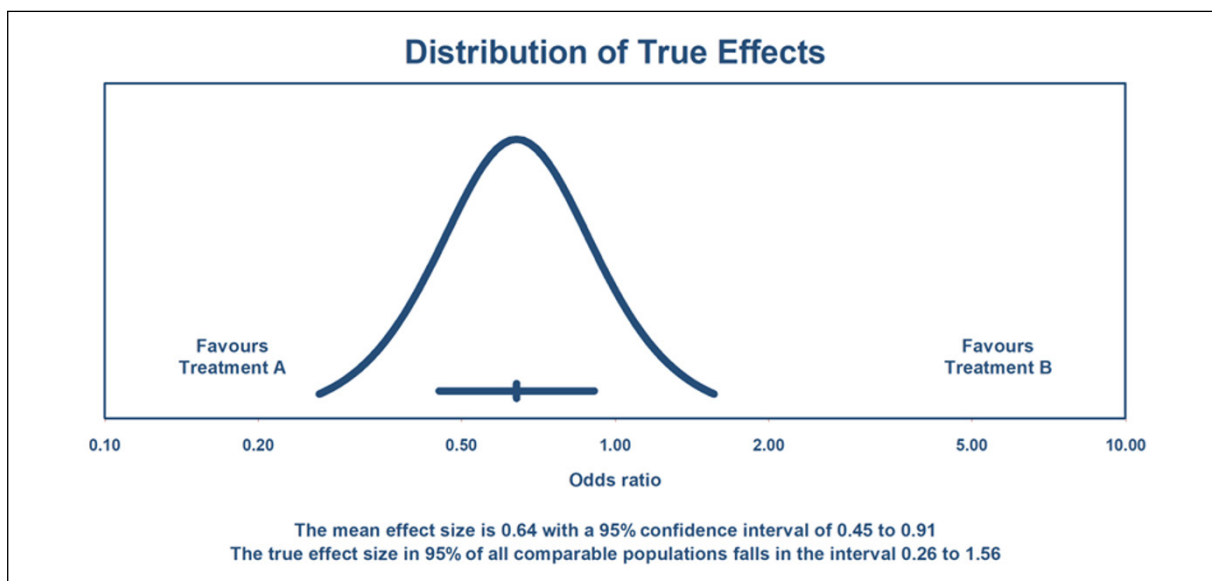


Figure 4. Range of true effects.

DISCUSSION

Quantifying the Eradication Rate in Doxycycline-Based Regimens

In the present meta-analysis, doxycycline-containing regimens were associated with lower overall eradication success than regimens that did not include doxycycline. The pooled analysis indicated a statistically significant disadvantage for doxycycline-based combinations, with moderate heterogeneity between studies. These findings suggest that doxycycline should not be assumed to provide a consistent additive benefit in contemporary *H. pylori* eradication strategies and may, in certain therapeutic combinations, reflect a less optimized treatment approach.

The present findings differ from those reported in an earlier meta-analysis²¹, which summarized older studies and suggested that doxycycline-containing regimens could achieve accept-

able eradication rates for *H. pylori*, particularly when a tetracycline-class antibiotic was required or when amoxicillin could not be used. However, the apparent discrepancy between that analysis and the current findings does not necessarily represent a biological contradiction. Rather, it likely reflects contextual differences between the bodies of evidence, including differences in the time periods in which the studies were conducted, the treatment regimens evaluated, the optimization of comparator therapies, and evolving antimicrobial resistance patterns. Among these factors, changes in global antimicrobial resistance patterns are likely to have played a particularly important role.

Most studies included in the earlier meta-analysis were conducted between the 1990s and early 2010s²¹. During that period, antimicrobial resistance patterns of *H. pylori* differed substantially from those observed today, and resistance rates to several commonly used antibiotics were generally lower. Over the past two decades, however, multiple epidemiological investigations and global meta-analyses have documented a substantial increase in resistance to key antibiotics such as clarithromycin, metronidazole, and fluoroquinolones across most regions⁷. Subsequent surveillance studies have confirmed continued increases in resistance and marked geographic variability in antimicrobial susceptibility patterns²²⁻²⁴. These trends have been associated with declining eradication rates for previously effective regimens and have prompted substantial modifications to recommended treatment strategies worldwide.

Critical Appraisal of Included Data and Sources of Heterogeneity

The aggregated data suggest less universal success for doxycycline-based regimens, and the quantitative analysis revealed low heterogeneity ($I^2 = 42\%$). The studies included in this meta-analysis varied in design, population characteristics, and therapeutic strategies, which may partly explain the variability observed across treatment outcomes. The available evidence was derived from prospective randomized trials as well as prospective cohort analyses conducted in single-center settings. Some studies incorporated randomized treatment allocation and standardized diagnostic methods, such as urea breath testing or stool antigen testing to confirm eradication, which strengthens the internal validity of the reported outcomes^{18,19}. However, differences in treatment regimens, including variations in antibiotic combinations, treatment duration, and the clinical context of therapy (first-line vs. rescue treatment), may have influenced eradication success across studies. Additional variability may have arisen from differences in patient populations and regional treatment practices. Furthermore, most studies did not include detailed antimicrobial susceptibility testing, limiting the ability to directly assess the influence of local resistance patterns on treatment efficacy¹⁸⁻²⁰. Together, these methodological and clinical differences represent important sources of heterogeneity that should be considered when interpreting the pooled estimates of doxycycline-containing eradication regimens.

Clinical Implications and Future Therapeutic Strategies

The present meta-analysis provides a quantitative synthesis of the available comparative evidence regarding doxycycline-containing regimens for *H. pylori* eradication. By pooling data from clinical studies, this analysis provides a clearer assessment of the relative effectiveness of doxycycline-based therapies compared with alternative treatment strategies, an area where direct comparative evidence has historically been limited.

The findings suggest that doxycycline-containing regimens may achieve less consistent eradication success than other commonly used treatment approaches. This observation has potential clinical relevance, particularly in the context of ongoing efforts to optimize eradication strategies in the face of evolving antimicrobial resistance patterns. The moderate heterogeneity observed across studies ($I^2 = 42\%$) likely reflects differences in treatment regimens, patient characteristics, prior antibiotic exposure, and regional resistance patterns.

Taken together, these results contribute to the current evidence base by providing a contemporary quantitative estimate of the relative performance of doxycycline-containing regimens and by clarifying their potential role in modern *H. pylori* treatment strategies.

Limitations

Potential limitations should be considered in this review: (1) Only English-language literature was included, potentially leading to selection bias. (2) The meta-analysis included studies that used different regimens, which may cause heterogeneity. (3) Our data involved patients from only 3 countries, all of which are developing countries, indicating a possibility for variation in results across other geographical areas, ethnic groups, or resistance of *H. pylori* to different antibiotics.

The included studies employed different methods for *H. pylori* diagnosis, treatment, or repeated tests to assess eradication success. In addition, the recurrence rate (recrudescence or reinfection) could not be considered. The studies involved different types of *H. pylori* bacteria, including CagA-positive and CagA-negative strains, with varying virulence.

CONCLUSIONS

This systematic review and meta-analysis confirmed that doxycycline-based therapeutic regimens are less effective for *H. pylori* eradication than the other regimens studied.

Acknowledgments

None to declare.

Financial Disclosure or Funding

None to declare.

Conflict of Interest

The authors have declared no conflicts of interest.

Authors' Contributions

Both authors performed the following according to CRediT: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, supervision, validation, writing original draft, review, and editing.

Data Availability

Additional data are available from the corresponding author upon reasonable request.

ORCID ID

Yaron Niv: 000-0003-4397-2531

REFERENCES

1. Chey WD, Howden CW, Moss SF, Morgan DR, Greer KB, Grover S, Shah SC. ACG clinical guideline: treatment of Helicobacter pylori infection. *Am J Gastroenterol* 2024; 119: 1730-1753.
2. Katelaris P, Hunt R, Bazzoli F, Cohen H, Fock KM, Gemilyan M, Malfertheiner P, Megraud F, Piscocoy A, Quach D, Vakil N, Vaz Coelho LG, LeMair A. World Gastroenterology Organisation global guidelines: Helicobacter pylori. *J Clin Gastroenterol* 2021; 55: 93-120.
3. Hooi JKY, Lai WY, Ng WK, Suen MMY, Underwood FE, Tanyingoh D, Malfertheiner P, Graham DY, Wong VWS, Wu JCY, Chan FKL, Sung JJY, Kaplan GG, Ng SC. Global prevalence of Helicobacter pylori infection: A systematic review and meta-analysis. *Gastroenterology* 2017; 153: 420-429.
4. Salih BA. Helicobacter pylori infection in developing countries: the burden for how long? *Saudi J Gastroenterol* 2009; 15: 201-207.
5. Andreev DN, Khurmatullina AR, Maev IV, Bordin DS, Abdulkhakov SR, Kucheryavyi YA, Belyi PA, Sokolov FS. The prevalence of Helicobacter pylori infection in the adult population of Russia: a systematic review and meta-analysis. *Epidemiologia* 2025; 6: 47.

6. Graham DY, Fischbach L. Helicobacter pylori treatment in the era of increasing antibiotic resistance. *Gut* 2010; 59: 1143-1153.
7. Savoldi A, Carrara E, Graham DY, Conti M, Tacconelli E. Prevalence of antibiotic resistance in Helicobacter pylori: a systematic review and meta-analysis in World Health Organization regions. *Gastroenterology* 2018; 155: 1372-1382.
8. Malfertheiner P, Megraud F, Rokkas T, Gisbert JP, Liou JM, Schulz C, Gasbarrini A, Hunt RH, Leja M, O'Morain C. Management of Helicobacter pylori infection: The Maastricht VI/Florence consensus report. *Gut* 2022; 71: 1724-1762.
9. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Infect Dis* 2018; 18: 318-327.
10. Mégraud F, Lehours P. Helicobacter pylori detection and antimicrobial susceptibility testing. *Clin Microbiol Rev* 2007; 20: 280-322.
11. Thung I, Aramin H, Vavinskaya V, Gupta S, Park JY, Crowe SE. The global emergence of Helicobacter pylori antibiotic resistance. *Aliment Pharmacol Ther* 2016; 43: 514-533.
12. Fallone CA, Moss SF, Malfertheiner P. Reconciliation of recent Helicobacter pylori treatment guidelines in a time of increasing resistance to antibiotics. *Gastroenterology* 2019; 157: 44-53.
13. Fiorini G, Zullo A, Saracino IM, Gatta L, Pavoni M, Vaira D. Pylera and sequential therapy for first-line Helicobacter pylori eradication: a culture-based study in real clinical practice. *Eur J Gastroenterol Hepatol* 2018; 30: 621-625.
14. Liou JM, Fang YJ, Chen CC, Bair MJ, Chang CY, Lee YC. Concomitant, bismuth quadruple, and 14-day triple therapy in the first-line treatment of Helicobacter pylori: a multicentre, open-label, randomised trial. *Lancet* 2016; 388: 2355-2365.
15. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med* 2009; 6: e1000097.
16. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Method* 2010; 1: 97-111.
17. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315: 629-634.
18. Ozturk O, Doganay L, Colak Y, Yilmaz Enc F, Ulasoglu C, Ozdil K, Tuncer I. Therapeutic success with bismuth-containing sequential and quadruple regimens in Helicobacter pylori eradication. *Arab J Gastroenterol* 2017; 18: 62-67.
19. Zhou JJ, Shi X, Zheng SP, Tang D, Cai T, Yao Y, Wang F. Efficacy of bismuth-based quadruple therapy for eradication of Helicobacter pylori infection based on previous antibiotic exposure: a large-scale prospective single-center clinical trial in China. *Helicobacter* 2020; 25: e12755.
20. Alhalabi M, Alassi MW, Alaa Eddin K, Cheha K. Efficacy of two-week therapy with doxycycline-based quadruple regimen versus levofloxacin concomitant regimen for Helicobacter pylori infection: a prospective randomized controlled trial. *BMC Infect Dis* 2021; 21: 642.
21. Niv Y. Doxycycline in eradication therapy of Helicobacter pylori: a systematic review and meta-analysis. *Digestion* 2016; 93: 167-173.
22. Liou JM, Chen CC, Chang CM, Chen MJ, Fang YJ, Lee JY. Long-term changes of gut microbiota, antibiotic resistance, and metabolic parameters after Helicobacter pylori eradication: a multicentre, open-label, randomised trial. *Lancet Infect Dis* 2019; 19: 1109-1120.
23. Mégraud F, Coenen S, Versporten A, Kist M, Lopez-Brea M, Hirschl AM, Andersen LP, Goossens H, Glupczynski Y. Helicobacter pylori resistance to antibiotics in Europe and its relationship to antibiotic consumption. *Gut* 2013; 62: 34-42.
24. Xie DD, Xu WX, Zhang ZZ, Huang F, Dai XB. Epidemiological surveys, antibiotic resistance, and related risk factors of Helicobacter pylori in Quanzhou, China: a cross-sectional study. *Sci Rep* 2025; 15: 4410.