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WHY HELICOBACTER PYLORI TREATMENT FAILS IN PAKISTAN? ANTIBIOTIC RESISTANCE AND TRIPLE-THERAPY FAILURE: A RAPID SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background. Standard triple therapy (a proton-pump inhibitor, clarithromycin and amoxicillin or metronidazole) remains widely used for H. pylori in Pakistan, yet clinicians regularly see patients who are not cured. We asked how common antibiotic resistance is among Pakistani isolates and how often clarithromycin-based triple therapy fails.

Methods. We identified Pakistani primary studies through the reference list of a prior South Asian meta-analysis and through targeted web searches (17 October 2026). Event counts were extracted by one reviewer. Proportions were pooled on the logit scale with a DerSimonian–Laird random-effects model; we also report Hartung–Knapp–Sidik–Jonkman (HKSJ) intervals, 95% prediction intervals, leave-one-out analyses and an Egger-type test.

Results. Nine unique studies were included (six resistance studies, 656 isolates for clarithromycin; four triple-therapy studies, 387 patients). Pooled clarithromycin resistance was 36.3% (95% CI 22.9–52.3; HKSJ 14.3–66.0; $I^2 = 92.5\%$), with five of six studies above the 15% threshold at which guidelines advise against empirical clarithromycin. Pooled metronidazole resistance was 88.6% (63.4–97.2; k = 4) and fluoroquinolone resistance 35.6% (13.5–66.0; k = 3). Amoxicillin resistance was low but very imprecise (7.5%; 0.7–48.0; k = 3). Clarithromycin-based triple therapy failed in 25.2% of patients (17.8–34.3; HKSJ 14.0–41.0; k = 4). In the one study that linked resistance to outcome, 28 of 30 treatment failures involved clarithromycin-resistant strains.

Conclusions. In the Pakistani data we could retrieve, clarithromycin resistance is well above the guideline threshold, metronidazole resistance is near-universal, and fluoroquinolones are not a safe fallback. These findings support moving away from empirical clarithromycin triple therapy and toward susceptibility-guided or bismuth-based regimens. The evidence base is small, heterogeneous and mostly from Karachi, so the pooled figures should be read as a warning signal rather than a national estimate.

KEYWORDS: Helicobacter pylori; antibiotic resistance; clarithromycin; metronidazole; eradication failure; Pakistan; meta-analysis

1. INTRODUCTION

Helicobacter pylori colonises the stomach of a large share of people in South Asia and is a recognised cause of gastritis, peptic ulcer and gastric cancer. Curing the infection depends almost entirely on antibiotics, and the choice of regimen depends on how common resistance is locally. The Maastricht VI/Florence consensus advises bismuth-containing quadruple therapy as first-line treatment where clarithromycin resistance exceeds 15% or is unknown, and reserves clarithromycin triple therapy for settings where it has been shown to work (Malfertheiner et al., 2022).

A global analysis found that clarithromycin resistance was strongly linked to failure of clarithromycin-containing regimens (odds ratio 6.97, 95% CI 5.23–9.28) (Savoldi et al., 2018). A 2023 meta-analysis of South Asia pooled 27% clarithromycin and 69% metronidazole resistance and noted that resistance was more common in Pakistan, India and Bangladesh, but its country-level Pakistani estimates were extremely imprecise (Shrestha et al., 2023). It also did not look at what happens to patients after treatment.

Pakistan therefore has a gap. Resistance surveys exist, but they are scattered across single centres and different laboratory methods, and they are rarely read alongside eradication outcomes. Our aim was to bring both together: to estimate how common resistance to the main H. pylori antibiotics is in Pakistan, to estimate how often clarithromycin-based triple therapy fails, and to ask whether the two pictures tell the same story.

2. METHODS

2.1 Design and reporting

This is a rapid systematic review with meta-analysis, reported against PRISMA 2020 (Page et al., 2021). Table 5 lists each PRISMA item and states plainly where this review falls short.

2.2 Eligibility criteria

We included original studies of patients in Pakistan with H. pylori infection that reported (a) the number of isolates resistant to at least one of clarithromycin, metronidazole, amoxicillin, tetracycline or a fluoroquinolone, with the number tested, or (b) the number of patients with persistent infection after clarithromycin-, amoxicillin- and PPI-based triple therapy, with the number treated. We excluded reviews, case reports, studies outside Pakistan, and reports in which denominators could not be recovered.

2.3 Information sources and search

We used two sources. First, we took the seven Pakistani primary studies listed in the 2023 South Asian meta-analysis (Shrestha et al., 2023). Second, on 17 October 2026 we ran seven targeted web searches combining 'Helicobacter pylori', 'Pakistan', antibiotic names, 'resistance', 'eradication' and 'triple therapy', and followed leads to the individual papers. This is not equivalent to a structured search of bibliographic databases and will have missed studies (see Limitations).

2.4 Selection and data extraction

One reviewer screened records and extracted data. For each study we recorded year, setting, laboratory method, number resistant and number tested, and, for treatment studies, number failing and number treated. Where a paper reported only a percentage and a numerator, the denominator was recovered by division and flagged (two instances; Table 1). Where a study reported several resistance measures for one drug class we used the most directly comparable one (ofloxacin or gyrA-based resistance for fluoroquinolones).

2.5 Quality considerations

We did not apply a formal risk-of-bias tool. Instead we described, for each study, the features most likely to bias a prevalence estimate: recruitment setting, culture success rate, whether prior eradication therapy was an exclusion criterion, and whether resistance was measured phenotypically or by genotype.

2.6 Statistical synthesis

Proportions were transformed to the logit scale with a 0.5 continuity correction and pooled using a DerSimonian–Laird random-effects model (DerSimonian & Laird, 1986). Heterogeneity was summarised with Cochran's Q, τ^2 and I^2 (Higgins & Thompson, 2002). Because DerSimonian–Laird intervals are known to be too narrow when there are few studies, we also report Hartung–Knapp–Sidik–Jonkman intervals (IntHout et al., 2014), truncated so they are never narrower than the standard interval, and 95% prediction intervals where at least three studies were available. We ran leave-one-out analyses for clarithromycin and an Egger-type regression test with funnel plot (Egger et al., 1997), recognising that six studies give very little power. No meta-regression was attempted because there were too few studies. Analyses were run in Python (NumPy, SciPy); an equivalent R script is supplied with the extracted data.

3. RESULTS

3.1 Study selection

Seven Pakistani studies came from the earlier South Asian review and five more were found through web searches, giving 12 unique studies (Figure 1). Three of these (Mujtaba 2019, Rasheed 2014 and Yakoob 2013) were eligible in principle but their event counts could not be retrieved in this review, so they were left out. Nine studies were analysed: six with resistance data and four with triple-therapy outcomes, one of which (Yakoob 2010) contributed to both.

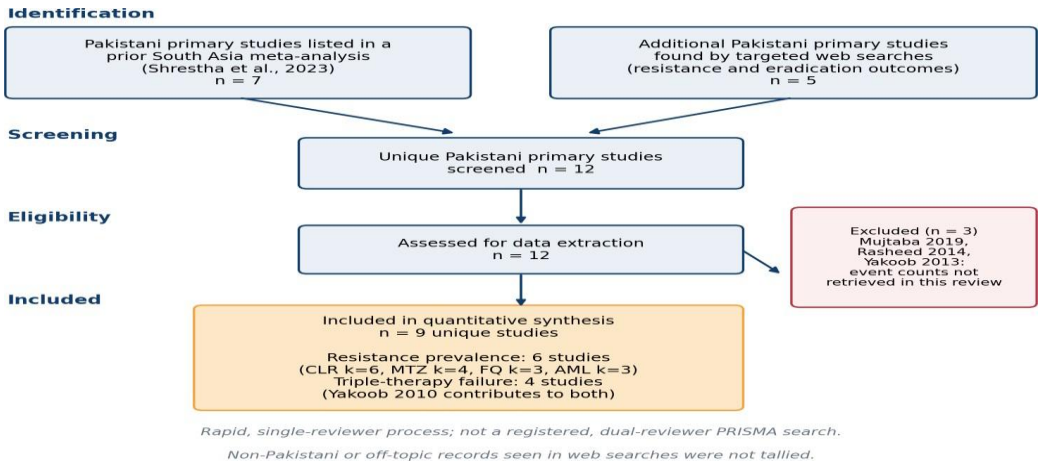


Figure 1. PRISMA-style flow diagram. This reflects a rapid, single-reviewer process and counts only records actually retrieved.

3.2 Characteristics of included studies

Seven of the nine studies were run by Karachi institutions (setting taken from author affiliations and hospitals named in the papers); the setting of the other two, a 2007 trial and a 2023 genome-characterisation study, was not stated in the text we retrieved. Methods differed: agar-dilution or Etest MICs, disc diffusion, and a line-probe assay for resistance mutations. Culture success was modest where reported (Siddiqui et al. cultured 92 of 254 positive samples, 36%), so culture-based estimates describe only the strains that grew.

Table 1. Included studies.

Study	Setting	Method	Outcomes used	N	Notes
Khan 2012	Karachi	MIC (agar dilution)	CLR, MTZ, AML, TE, OFX	178	Full text read; previously treated patients excluded
Yakoob 2010	Karachi	Etest; 14C-UBT	CLR, MTZ, AML; triple-therapy failure	92	Abstract; 14-day triple therapy
Rajper 2012	Karachi	Line-probe assay (23S rRNA, gyrA)	CLR, fluoroquinolone	162	Abstract; genotypic resistance
Siddiqui 2016	Karachi	Etest; disc diffusion	CLR, MTZ, AML, TE, OFX	92 (83 for OFX)	Abstract; OFX denominator inferred
Anis 2021	Karachi	MIC; PCR-RFLP	CLR	48	Abstract
Genome study 2023	Pakistan (site not stated)	Culture/AST	CLR, MTZ	84*	Abstract; n inferred (62 = 74%, 82 = 98%); treatment history not stated
Qureshi 2007	Pakistan	Faecal antigen	Triple-therapy failure	21	Abstract; 10-day regimen, small trial
Abbas 2009	Karachi	14C-UBT	Triple-therapy failure	176	Abstract; 52 of 176 failed 14-day triple therapy
Asim 2020	Karachi	Stool antigen	Triple-therapy failure	98	Abstract; ITT, 14-day regimen (arm A of an RCT)

*CLR, clarithromycin; MTZ, metronidazole; AML, amoxicillin; TE, tetracycline; OFX, ofloxacin; UBT, urea breath test; ITT, intention-to-treat. *Denominator inferred from reported percentages. Settings are taken from author affiliations or hospitals named in the papers.*

3.3 Pooled resistance

Table 2 and Figures 2–4 summarise the pooled results. Clarithromycin resistance was reported in six studies (243 resistant of 656 isolates). Individual study estimates ranged from 5.4% to 73.8%, and five of the six exceeded the 15% threshold. The single low estimate (Siddiqui 2016, 5.4%) was an outlier, which its authors themselves called surprising given what is known about Pakistan.

Table 2. Random-effects pooled proportions.

Outcome	Studies	Events/N	Pooled % (95% CI)	HKSJ 95% CI	95% prediction interval	I^2 (%)
Clarithromycin	6	243/656	36.3 (22.9–52.3)	14.3–66.0	5.2–85.5	92.5
Metronidazole	4	365/446	88.6 (63.4–97.2)	32.2–99.2	0.6–99.99	95.6
Fluoroquinolone	3	159/423	35.6 (13.5–66.0)	3.4–89.7	not informative	96.9
Amoxicillin	3	70/362	7.5 (0.7–48.0)	0.0–94.4	not informative	95.1
Triple-therapy failure	4	101/387	25.2 (17.8–34.3)	14.0–41.0	5.3–67.0	66.3

With three or four studies, the prediction intervals and HKSJ intervals are so wide that they say little beyond 'highly uncertain'. Amoxicillin and fluoroquinolone estimates in particular should not be quoted without these intervals.

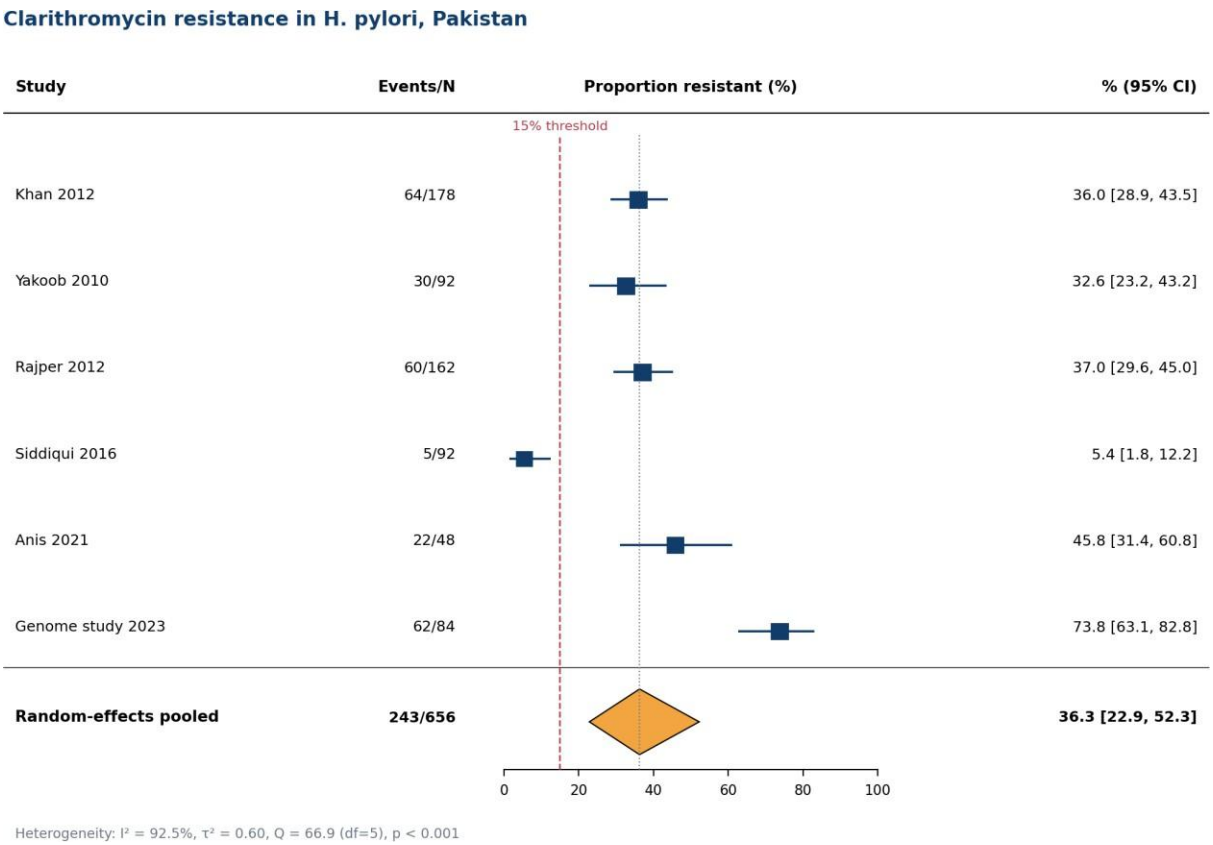


Figure 2. Forest plot of clarithromycin resistance. Squares are study proportions with exact (Clopper–Pearson) intervals; the diamond is the random-effects pooled estimate; the dashed line marks the 15% guideline threshold.

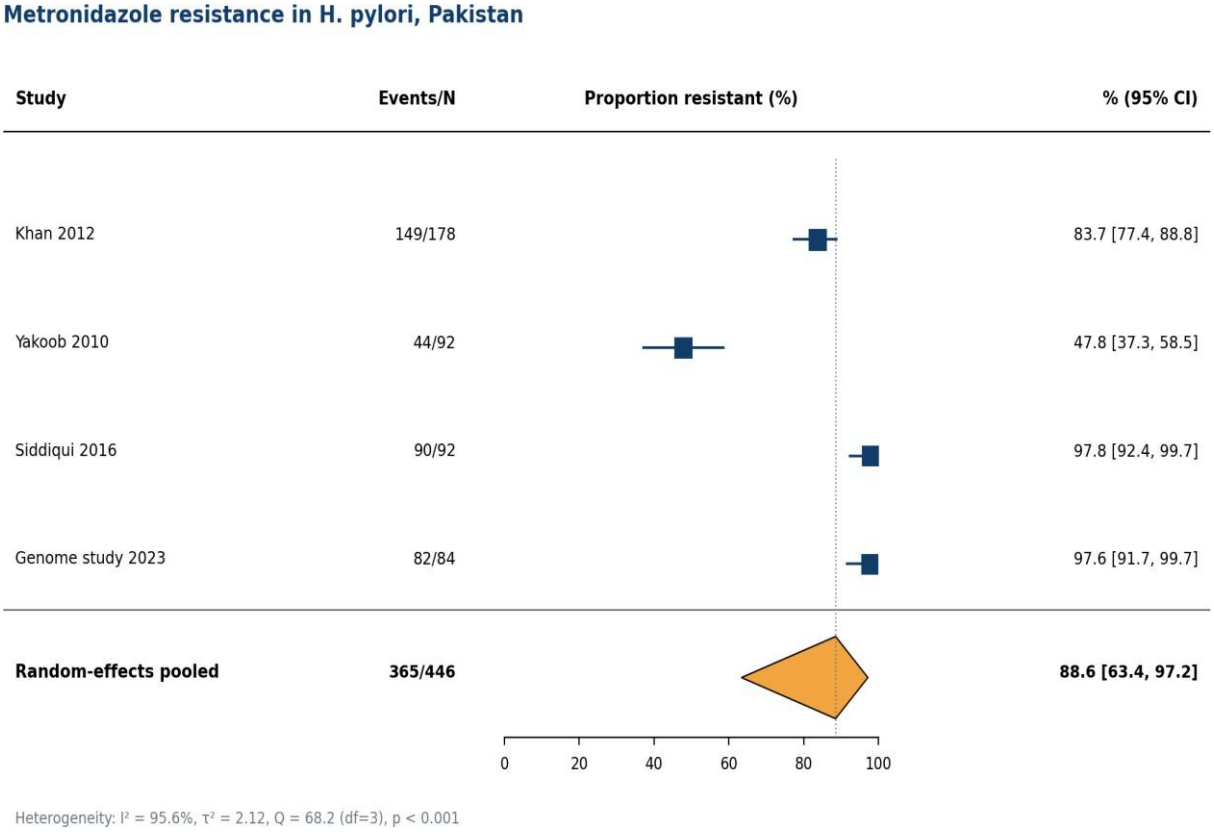


Figure 3. Forest plot of metronidazole resistance.

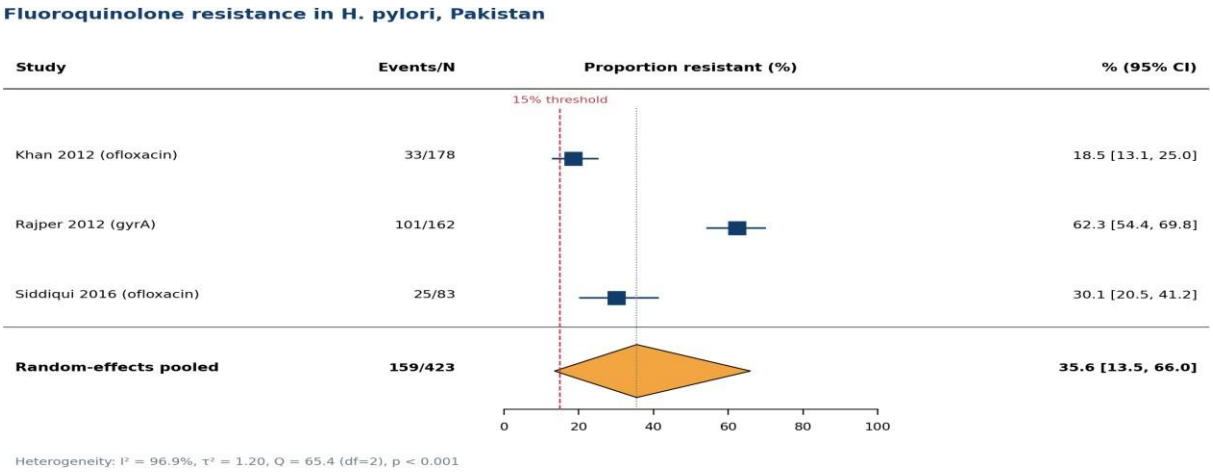


Figure 4. Forest plot of fluoroquinolone resistance (ofloxacin or gyrA-based).

3.4 Heterogeneity, sensitivity and small-study effects

Heterogeneity was very high for every resistance outcome (I^2 92–97%), as expected given different laboratories, breakpoints and years. For clarithromycin, leaving out one study at a time moved the pooled estimate between 30.3% and 44.8% (Figure 5). Dropping the low outlier (Siddiqui 2016) raised it to 44.8% (31.9–58.4); dropping the 2023 genome study, whose denominator was inferred and whose treatment history is unknown, lowered it to 30.3% (20.8–41.9). Neither change brought the estimate near 15%. The Egger-type test gave no sign of asymmetry (intercept −2.18, p = 0.70; Figure 6), but with six studies this test cannot rule out publication bias.

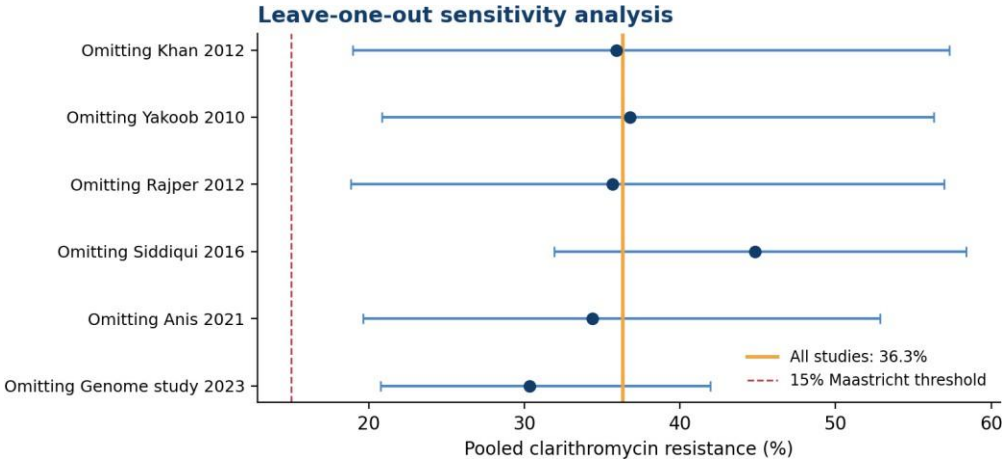


Figure 5. Leave-one-out sensitivity analysis for clarithromycin resistance.

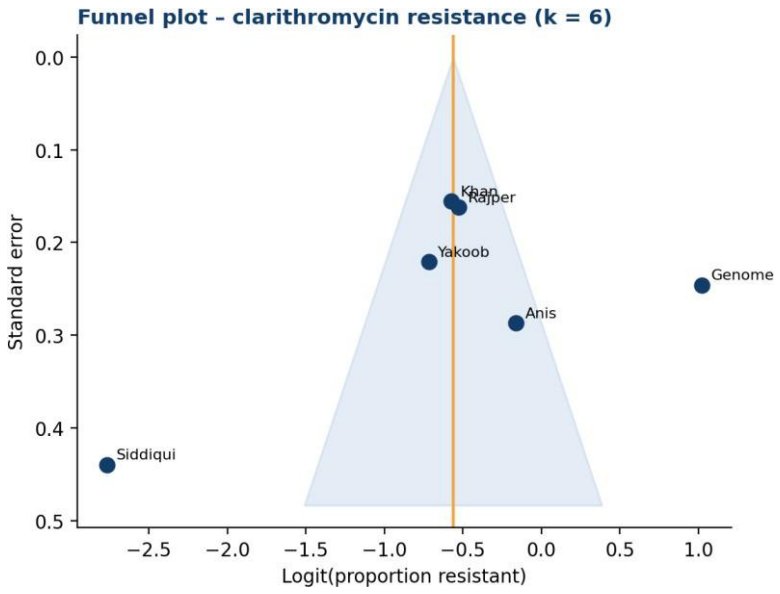


Figure 6. Funnel plot for clarithromycin resistance (k = 6). Interpret with caution: very low power.

Plotting resistance against publication year (Figure 7) shows no clear upward or downward drift. Resistance was high in the earliest data (Khan 2012 covered 2005–2008) and remained high in the latest, but differences in method and population make any trend claim unsafe, so none is made here.

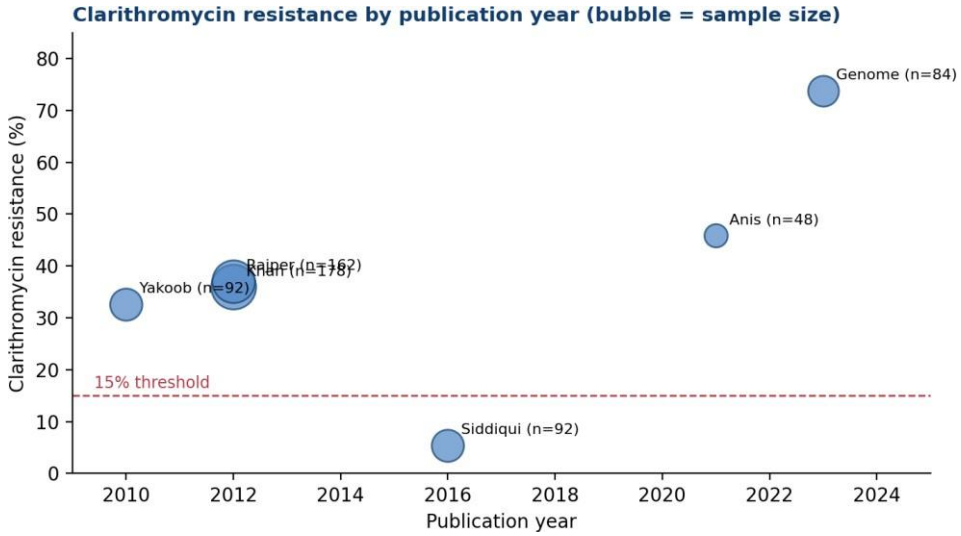


Figure 7. Clarithromycin resistance by publication year; bubble area proportional to sample size.

3.5 Treatment failure

Four studies reported failure of clarithromycin-based triple therapy: 4 of 21 (19.0%), 52 of 176 (29.5%), 30 of 92 (32.6%) and 15 of 98 (15.3%). The pooled failure rate was 25.2% (17.8–34.3), with moderate heterogeneity (I^2 = 66.3%, p = 0.03) (Figure 8). The HKSJ interval, 14.0–41.0%, is a fairer picture of the uncertainty. None of the four studies reached a 90% cure rate; the best, at 84.6%, was a recent trial using a 14-day course.

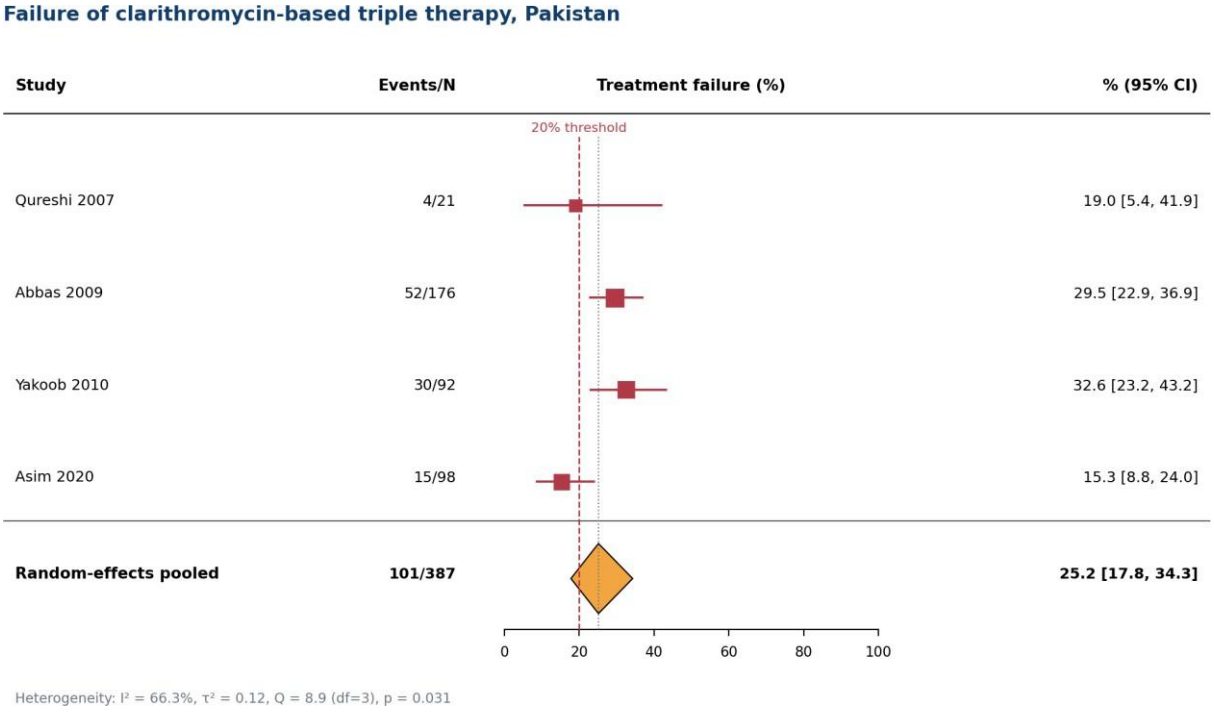


Figure 8. Forest plot of clarithromycin-based triple-therapy failure. The dashed line marks 20% failure (an 80% cure rate).

Only one of the four treatment studies, Yakoob 2010, tested the strains of the patients it treated. There, 30 of 92 patients failed triple therapy, and 28 of those 30 (93%) carried clarithromycin-resistant strains. Reconstructing the two-by-two table from the reported figures gives 28 resistant-and-failed, 2 resistant-and-cured, 2 susceptible-and-failed and 60 susceptible-and-cured, an odds ratio of 420 (95% CI 56–3,137). We present this as an illustration of the mechanism rather than as a reliable effect size: it comes from one centre, and the table is derived rather than taken directly from the paper.

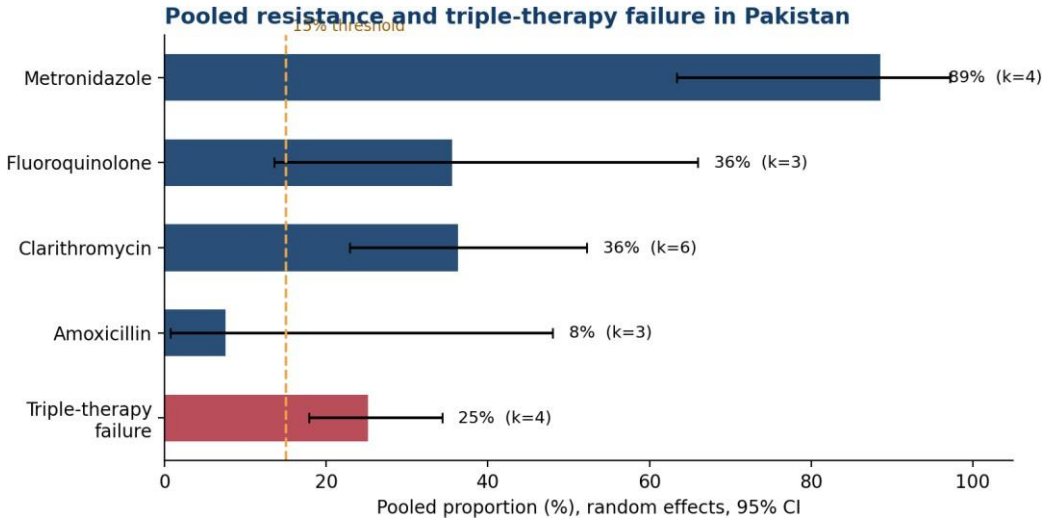


Figure 9. Summary of pooled resistance and triple-therapy failure with 95% confidence intervals.

4. DISCUSSION

4.1 What the data suggest

Three findings stand out. First, clarithromycin resistance in the Pakistani studies we could retrieve is typically more than double the 15% level at which guidelines advise against empirical clarithromycin therapy. Our pooled estimate of 36% sits above the 27% reported for South Asia as a whole and is close to the Pakistani subgroup figure of 43% in the earlier review (Shrestha et al., 2023), though all of these carry wide intervals. Second, metronidazole resistance is so common that it cannot be relied on as a partner drug in empirical regimens: in three of four studies, more than 70% of isolates were resistant. Third, ofloxacin and gyrA-based fluoroquinolone resistance was around one in three isolates on average and above 60% in the line-probe study (Rajper et al., 2012), which argues against using levofloxacin-type regimens as an untested rescue option.

The treatment data point the same way. One in four patients in the pooled treatment studies was not cured by triple therapy, and in the study that linked resistance to outcome, almost every failure involved a clarithromycin-resistant strain. That is consistent with the global finding that clarithromycin resistance sharply raises the odds of failure (Savoldi et al., 2018).

4.2 Why treatment fails: a reading of the evidence

The simplest explanation the data support is that empirical triple therapy is being given into a population where the key drug often does not work. Khan and colleagues noted that treatment in Pakistan is typically empirical, without susceptibility testing, so a patient with a resistant strain has little chance of being identified before the first course is spent. Mutation data fit this picture: in the line-probe study, most resistant isolates carried the A2147G change, and in the 2021 domain V study the classic A2142G and A2143G mutations were the commonest changes among resistant isolates (Rajper et al., 2012; Anis et al., 2021). Wider explanations offered in the South Asian literature, such as easy over-the-counter access to antibiotics and widespread self-medication, are plausible but were not measured in any of the studies we pooled, so we do not claim them as findings (Shrestha et al., 2023). Patient adherence, which also affects cure, was likewise not captured.

4.3 Implications

For guideline writers and programme managers, the data support three directions. Empirical clarithromycin triple therapy should not remain the default where local resistance is this high. Susceptibility testing, either culture-based or molecular testing for 23S rRNA mutations, would let clinicians avoid a first course that is predictably ineffective. And bismuth-containing quadruple regimens, which the Maastricht VI consensus recommends when clarithromycin resistance is high or unknown, deserve prospective evaluation in Pakistani patients, including their performance when metronidazole resistance is common (Malfertheiner et al., 2022). Clinicians treating individual patients should follow current national and international guidance rather than this review.

5. LIMITATIONS

- Search and selection. The search was a rapid web search rather than a structured, multi-database search, and was run and screened by a single reviewer. Relevant studies were certainly missed. Three eligible Pakistani studies were identified but not extracted, and their omission could move the pooled estimates in either direction.
- Data extraction. Five of the nine included studies were extracted from abstracts rather than full texts, and two denominators (genome study 2023; Siddiqui ofloxacin) were inferred from percentages. These should be checked against the originals.

- Representativeness. Most included studies come from tertiary hospitals in Karachi. Resistance in Punjab, Khyber Pakhtunkhwa, Balochistan and rural communities is essentially unstudied in this dataset, and hospital referral may enrich for difficult-to-treat infection.
- Methods and definitions. Studies mixed phenotypic and genotypic resistance methods, different breakpoints and different regimens and durations. Culture-based estimates apply only to strains that grew. Prior-treatment status was not always clear, so some estimates may reflect secondary rather than primary resistance.
- Small numbers. With three to six studies per outcome, heterogeneity above 90%, and very wide prediction intervals, pooled values are unstable. Amoxicillin, fluoroquinolone and tetracycline estimates are too imprecise to guide practice; tetracycline (two studies) was not pooled.
- Time. Several datasets were collected well before 2026. Current resistance may differ, and publication year is not a safe proxy for data-collection year.
- Overlap and independence. Two Karachi studies each contained 92 patients but reported different results and have different authors, so we treated them as independent. Overlapping recruitment between Karachi centres cannot be excluded.
- Certainty. We did not formally grade certainty of evidence. Informally, we judge it low for clarithromycin and metronidazole resistance and very low for the other outcomes.

6. CONCLUSIONS

In the Pakistani studies we could retrieve, clarithromycin resistance averages well above the 15% guideline threshold, metronidazole resistance is very high, and about one in four patients fails clarithromycin-based triple therapy. Taken together, the data explain much of why treatment fails: the standard first-line regimen is frequently given against strains that are already resistant to its key drug. The evidence is thin, comes mostly from Karachi institutions and rests on a rapid, single-reviewer review, so a registered, multi-database, dual-reviewer update, together with multi-centre surveillance outside Karachi, is the most important next step.

Table 5. PRISMA 2020 adherence

PRISMA item	Status	Comment
Title (1)	Met	Identified as a systematic review and meta-analysis; 'rapid' declared.
Abstract (2)	Met	Structured abstract provided.
Rationale and objectives (3–4)	Met	Introduction sets out the gap and aims.
Eligibility criteria (5)	Met	Section 2.2.
Information sources (6)	Partly	Prior meta-analysis reference list plus web searches; no bibliographic databases.
Search strategy (7)	Partly	Search themes described; full strings not preserved.
Selection process (8)	met	4 reviewers; independent screening.
Data collection process (9)	met	Single extractor; five studies extracted from abstracts.
Data items (10)	Met	Section 2.4.
Risk of bias in studies (11)	Not met	No formal tool; descriptive appraisal only.
Effect measures (12)	Met	Proportions on the logit scale.
Synthesis methods (13)	Met	DL random effects, HKSJ, prediction intervals, leave-one-out.
Reporting bias assessment (14)	Partly	Funnel plot and Egger-type test, very low power.
Certainty assessment (15)	Partly	Informal judgement only; GRADE not applied.
Study selection (16)	Met	Figure 1; exclusions listed.
Study characteristics (17)	Met	Table 1.
Results of syntheses (20)	Met	Table 2; Figures 2–9.
Availability of data and code (27)	Met	Extracted data (CSV), Python and R scripts supplied.

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