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Global prevalence of *Helicobacter pylori* antibiotic resistance among children in the world health organization regions between 2000 and 2023: a systematic review and meta-analysis

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Abstract

Background *Helicobacter pylori* infection causes gastritis, peptic ulcers, and gastric cancer. The infection is typically acquired in childhood and persists throughout life. The major impediment to successful therapy is antibiotic resistance. This systematic review and meta-analysis aimed to comprehensively assess the global prevalence of antibiotic resistance in pediatric *H. pylori* infection.

Methods We performed a systematic search of publication databases that assessed *H. pylori* resistance rates to clarithromycin, metronidazole, levofloxacin, amoxicillin, and tetracycline in children. The WHO region classification was used to group pooled primary and secondary resistance estimates along with 95% confidence interval (CI). *H. pylori* antibiotic resistance rates were retrieved and combined with odds ratios (95% CI) to investigate the global prevalence and temporal trends. Subgroup analysis of the prevalence of antibiotic resistance was conducted by country, age groups, and susceptibility testing methods.

Results Among 1417 records obtained initially, 152 studies were selected for eligibility assessment after applying exclusion criteria in multiple steps. Ultimately, 63 studies involving 15,953 individuals were included comprising data from 28 countries in 5 WHO regions. The primary resistance rates were metronidazole 35.3% (5482/15,529, 95% CI: 28.7–42.6), clarithromycin 32.6% (5071/15,555, 95% CI: 27.7–37.9), tetracycline 2.1% (148/7033, 95% CI: 1.3–3.6), levofloxacin 13.2% (1091/8271, 95% CI: 9.3–18.4), and amoxicillin 4.8% (495/10305, 95% CI: 2.5–8.8). Raising antibiotic resistance was detected in most WHO regions.

Conclusions The escalating trend of *H. pylori* antibiotic resistance in children warrants urgent attention globally. National and regional surveillance networks are required for antibiotic stewardship in children infected with *H. pylori*.

Keywords *Helicobacter pylori*, Antibiotic resistance, Children, Epidemiology, Meta-analysis, WHO region

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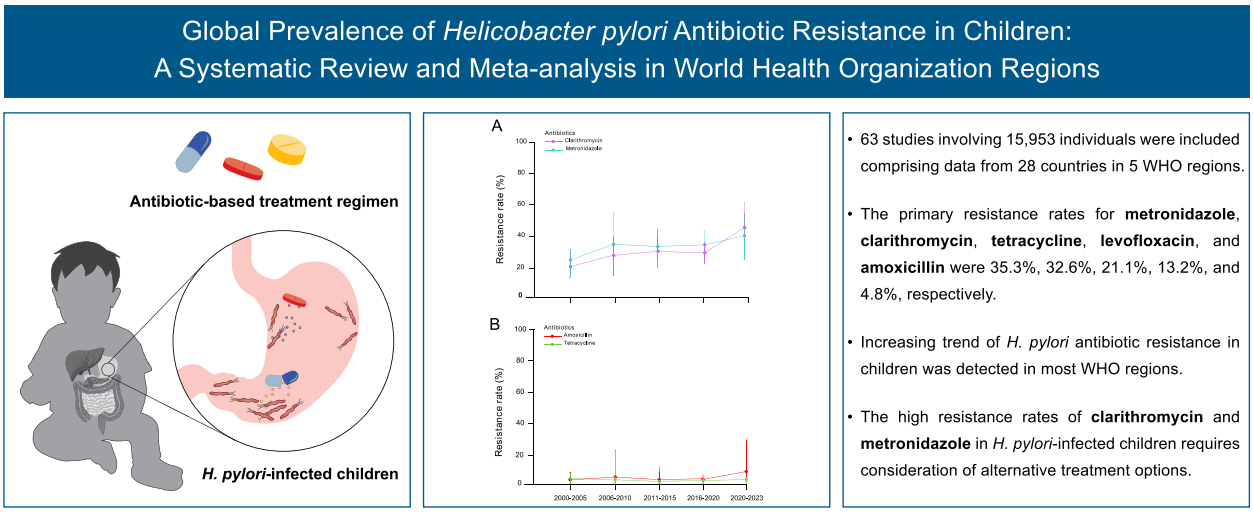
Graphical Abstract



Background

Helicobacter pylori (*H. pylori*) is a Gram-negative microaerophilic bacterium and major human pathogen etiologically related to gastritis, peptic ulcers, and gastric cancer. *H. pylori* infection affects over half of the global population with a higher incidence in developing countries [1]. The global prevalence of *H. pylori* infection in children was reported as 32.3% in a recent meta-analysis conducted in 2022 [2]. *H. pylori*-associated gastritis causes diminished acid production and adversely affects nutrient absorption contributing to malnutrition and growth issues in children [3]. Eradication of *H. pylori* infection stops the Correa cascade of histopathological progression to malignancy and reduces therefore the risk of developing gastric cancer [4]. The extent and severity of gastritis advance with age; the earlier in the course of the disease *H. pylori* eradication is accomplished, the greater likelihood of benefit. For instance, a clinical trial of *H. pylori* eradication, which spanned 26.5 years involving 808 individuals, reported a lower incidence of gastric cancer compared with their placebo counterparts (hazard ratio [5], 0.57; 95% CI, 0.33–0.98) [6].

Theoretically, effective monitoring and eradication of the infection in young adults would prevent transmission to their subsequent children constituting *H. pylori* eradication in children and young adults a potential cornerstone for preventing *H. pylori*-associated gastric cancer in adulthood [7]. Since *H. pylori* is an acknowledged carcinogen Class I by WHO, current guidelines for the management of *H. pylori* infection indicate that all *H. pylori* infections should be cured unless there are compelling reasons not to do so [8]. However, the optimal timeframe to initiate therapy in childhood remains unclear. The updated joint ESPGHAN-NASPGHAN guidelines recommended treatment initiation only in cases of severe disease, such as peptic ulcer disease [9]. One of the factors implicated in timing to treat children is the lack of simple highly effective therapy. Current popular eradication regimens primarily involve a combination of antimicrobials and antisecretory agents. These regimens have been hampered by increasing antimicrobial resistance. In addition, administration of multidrug treatments is frequently associated with side effects such as diarrhea, nausea, and vomiting as well as perturbation of the gut microbiota [10, 11]. Antibiotic resistance has emerged as one of the leading reasons for failure of *H. pylori* treatment in some areas, especially where antibiotic susceptibility testing is not performed before eradication therapy [12]. Current guidelines emphasize the importance of optimizing the success rate of first-line treatment in children, given the limited availability of antibiotics suitable for rescue therapy [13, 14]. The empirical use of clarithromycin and metronidazole can lead to the rise in *H. pylori* antimicrobial resistance and may also disrupt the gut microbiota, potentially leading to digestive and metabolic disorders [15]. Surveillance of the regional patterns of antibiotic resistance is crucial to implement the most efficacious treatment protocols that ensure superior patient outcomes. This systematic review and meta-analysis aims to identify knowledge gaps in the comprehension of antibiotic resistance patterns of *H. pylori* in children worldwide, and their clinical implications. The geographic

regions were classified according to the World Health Organization's (WHO) regional classification [16]. Furthermore, subgroup analyses were conducted based on age groups, diagnostic methods, and countries.

Methods

Search strategy

A comprehensive search strategy was conducted to identify relevant studies concerning antibiotic resistance of *H. pylori* among children. The protocol is available online (PROSPERO registration number: CRD42023453091; https://www.crd.york.ac.uk/) [17]. The search spanned six electronic databases covering the time frame from January 2000 to December 2023. The search string utilized relevant keywords and Medical Subject Headings (MeSH) terms for *H. pylori*, antibiotic resistance, and the pediatric population. We followed the PRISMA guidelines for systematic reviews and established inclusion and exclusion criteria prior to conducting our search [18]. The original search terms, selection criteria, and PICO elements are available in Additional file 1, Table S1-S3 [19–81].

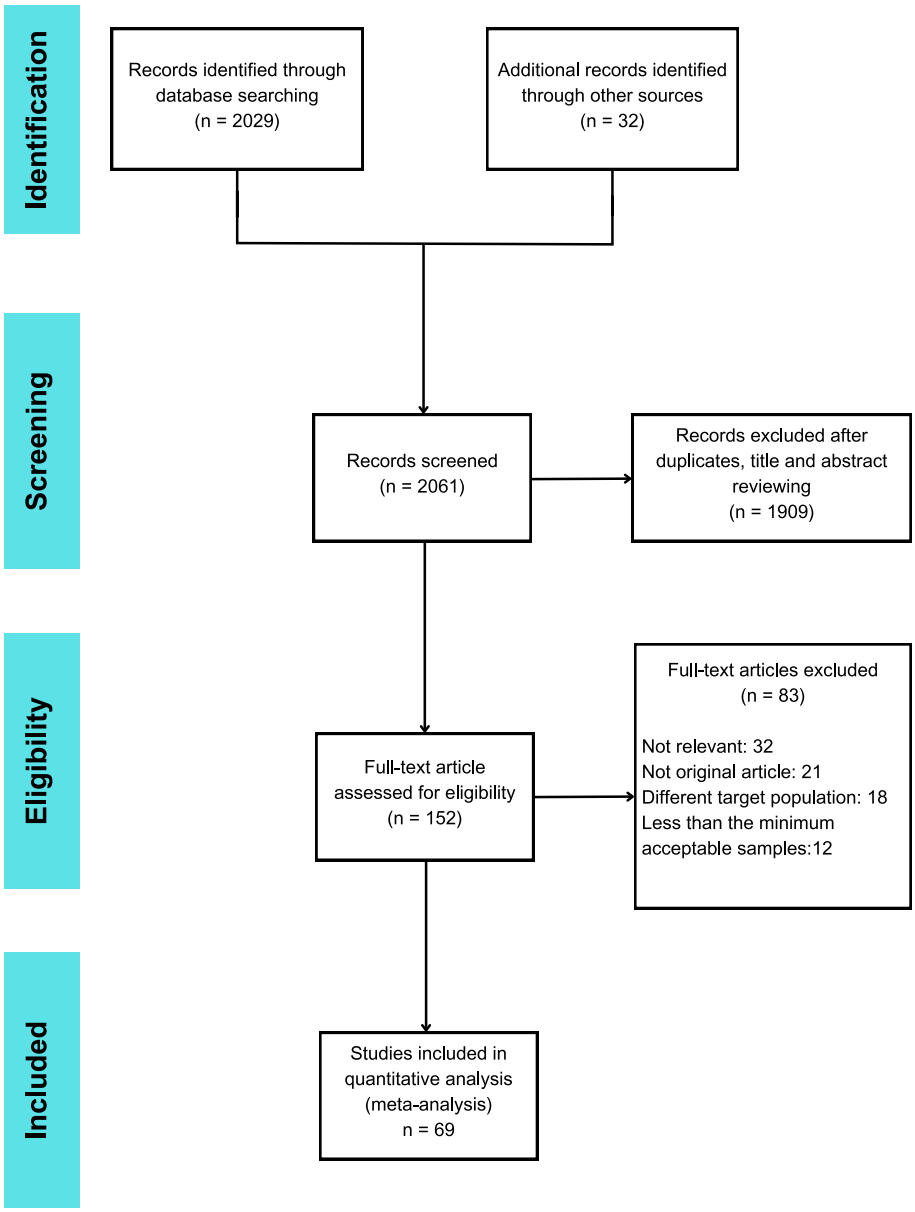


Fig. 1 Flowchart of the study selection process

Definitions

Patients were categorized as *H. pylori*-infected if they registered a positive outcome in any of the following tests: histology (histochemical and/or immunohistochemical staining), culture, stool antigen (monoclonal or polyclonal), urea breath test, or rapid urease test. The prevalence of resistance was established based on the results of culture and presented as the ratio of resistant isolates to the total number of isolates tested. In alignment with the most recent international consensus, we opted for a 15% threshold to designate a high rate of resistance [82, 83]. Minimum inhibitory concentration (MIC_{50}) and (MIC_{90}) values were defined as the lowest concentration of the antibiotic at which 50 and 90% of the isolates were inhibited, respectively. Both phenotypic assessments (E-test, agar dilution, and disk diffusion) and genotypic analyses (nucleic acid-based assays) were considered valid for the delineation of resistance.

Study selection and data extraction

The selection process followed a two-step approach, spearheaded by two authors (ASN, ANR). Initially, the relevance of studies was ascertained through scrutiny of titles and abstracts. Subsequently, full-text articles of potentially pertinent studies underwent thorough evaluation. To ensure accuracy, instances of duplicate publications or studies reporting the same cohort's data were managed by use of only the most recent data obtained. Instances of ambiguity regarding inclusion were resolved through consultations with a second reviewer (AY, MRZ). A PRISMA flow chart (Fig. 1) visually illustrates the search results, displaying the number of studies retrieved, articles inspected, and the rationale for exclusion [84]. Data extraction was independently undertaken by four reviewers (ASN, ANR, AS, MRZ), with any discrepancies resolved via consensus, involving a third reviewer (AY). Also, the quality appraisal of the encompassed studies was conducted independently by four reviewers (ASN, ANR, AS, AY) using an adapted version of the tool proposed by the Joanna Briggs Institute for critical appraisal of prevalence studies [85]. A summary of the quality assessment process and items considered for scoring the studies are described in Additional file 1, Table S4.

A meta-analysis of prevalence was performed, pooling estimates from diverse studies utilizing a random-effects model due to anticipated heterogeneity. Heterogeneity was quantified using the I^2 statistic, and subgroup analysis for categorical variables and meta-regression for continuous and dichotomous variables were carried out to identify potential sources.

To conduct the meta-analysis, the comprehensive meta-analysis (CMA) version 3 (Biostat Inc., USA) was used. Rates of resistance to clarithromycin, amoxicillin, metronidazole, tetracycline, levofloxacin, or a combination of these antibiotics were calculated from the total number of isolates from each study. These rates were then logit-transformed and pooled using a generalized linear mixed-effects model [86]. The relationship between antibiotic resistance and treatment failure was assessed by calculating a pooled odds ratio along with its corresponding 95% confidence interval (CI). Statistical significance was established at a threshold of a P value less than 0.05 [87].

Heterogeneity among the studies was assessed using the I^2 statistic, with substantial heterogeneity deemed present when I^2 exceeded 50% [88]. In a sensitivity analysis, we removed outliers and influencing studies using the method reported by Viechtbauer and Cheung when three or more studies were present [89]. Indeed, evaluating publication bias in a meta-analysis is a crucial step in ensuring the robustness and credibility of the study findings. To assess the presence of publication bias, we employed several methods. First, we visually examined funnel plots, in which standard errors (SE) were plotted against logit-transformed prevalence rates. In these plots, individual study effect sizes were displayed on the horizontal axis, whereas a measure of study precision was represented on the vertical axis. In an ideal scenario where there is no publication bias, the funnel plot would assume a symmetrical shape, with smaller studies distributed widely at the bottom and larger studies concentrated towards the top. Any observed asymmetry in the funnel plot may raise suspicion of publication bias. In addition to the visual assessment, we conducted Egger's test, a statistical technique specifically designed to assess funnel plot asymmetry quantitatively. This test examines whether the regression line between effect sizes and their corresponding standard errors deviates significantly from zero. A significant intercept in Egger's test indicates the presence of publication bias. Notably, we set our significance threshold at $P > 0.05$ to determine the presence of bias [90].

Results

Our search analysis retrieved 1417 studies, comprising 1385 studies sourced from six databases (PubMed, Scopus, Medline, Cochrane, Embase, and Web of Science) and an additional 32 studies imported from Google Scholar. Following an initial review, a rigorous screening process led to the exclusion of 1265 studies. Subsequently, a detailed assessment of the full text of the remaining articles enabled the identification of 63 studies that emerged as candidates for in-depth analysis. This precise selection process, culminating in the

inclusion of these 63 studies, is visually encapsulated in (Fig. 1), providing an illustrative overview of the systematic journey through which these studies were identified and brought to final analysis. Also, publication bias was assessed for all studies by generating funnel plots and examining the dispersion of each study, as illustrated in Additional file 2, Fig. S1-S5.

The extensive scope of this study encompassed 63 countries, each strategically categorized into specific regions defined by the WHO (Additional file 2, Fig. S6). The distribution across these regions unveiled intriguing insights into the global landscape of *H. pylori* antibiotic resistance research. The European region emerged as the most widely represented area, with 30 studies represented in the analysis. Following closely, the Western Pacific region contributed data from 20 studies, underlining the pervasive concern of antibiotic resistance across this area. The Eastern Mediterranean region contributed eight studies, while the Americas provided data from four studies. However, the African region was underrepresented, with only one study included, which limits the global perspective of this meta-analysis. Further details and specifics about the involved studies, including the breakdown by country within each region, are accessible in Additional file 1, Table S5.

The final stage of the study encapsulated a diverse cohort of 15,953 individuals, encompassing children from around the world. The European region demonstrated the highest participation with 7462 individuals, followed by the Western Pacific region with 7202 participants. The Eastern Mediterranean and Americas regions contributed with 672 and 505 participants, respectively, whereas the African region was represented with 112 participants in this study. This inclusive participant pool, with an average age of 11.8 years (95% CI: 11.0–12.6), provided a comprehensive representation of the younger demographic, all under 18 years of age. This cohort's gender breakdown reveals that 41% of the participants are men and 59% of the participants are women. The patients' demographic and clinical features are summarized in Additional file 1, Table S6.

MIC

Some studies ($n=15$, 24.2%) specified MIC_{50} values used to define resistance. Based on the reports of all these studies, the amoxicillin breakpoint was 0.15 mg/L (ranged 0.015–1 mg/L), clarithromycin breakpoint was 8.0 mg/L in 94% of the studies (ranged 0.016–96 mg/L), levofloxacin breakpoint was 0.5 mg/L in 68% of the studies (ranged 0.064–2 mg/L), the breakpoint of metronidazole was 6.5 mg/L (ranged 0.094–40 mg/L), and the breakpoint of tetracycline was 0.5 mg/L in 80% of the studies (ranged 0.015–4 mg/L). Also, 16% of the studies ($n=10$) reported MIC_{90}. Amoxicillin's breakpoint was 0.8 mg/L (ranged 0.016–4 mg/L), clarithromycin's breakpoint was 55.7 mg/L (ranged 0.03–226 mg/L), and levofloxacin's breakpoint was 9 mg/L in 40% of studies (ranged 0.135–32 mg/L); metronidazole's breakpoint was 93.8 mg/L (ranged 0.256–256 mg/L) and the breakpoint of tetracycline was 0.6 mg/L in 80% of studies (ranged 0.047–2 mg/L).

MIC values were also analyzed based on the regions defined by the WHO. As illustrated in Additional file 1, Table S7, two studies examined MIC values in the Americas region, two studies in the Eastern Mediterranean region, eight studies in the European region, and three studies in the Western Pacific region presented their results.

A two-stage qualitative evaluation was performed on all included studies, and disagreements about the quality of the studies and the need for arbitration was recorded for three studies. The quality was high in 19 studies (30%), moderate in 34 (54%), and low in 10 (16%). The main factors limiting the overall quality were poor reporting of patients' demographic and endoscopy characteristics. Microbiological methods were standard for testing antibiotic resistance in most of the studies (78%). A summary of the scoring process and kappa values for each study is provided in Additional file 1, Table S8.

The rate of primary resistance to metronidazole was 35.3% (5482/15,529, 95% CI: 28.7–42.6), clarithromycin 32.6% (5071/15,555, 95% CI: 27.7–37.9), tetracycline 2.1% (148/7033, 95% CI: 1.3–3.6), levofloxacin 13.2% (1091/8271, 95% CI: 9.3–18.4), and amoxicillin 4.8% (495/10,305, 95% CI: 2.5–8.8), among all participants included in this study.

Table 1 Subgroup analysis of antibiotic resistance rate (95% CI) by time periods

Time period	AMX	MTZ	TET	CLA	LEV	MTZ + CLA
2000–2005	1.1 (0.5–2.2)	25.0 (16.4–36.3)	2.0 (1.5–2.7)	20.4 (12.1–32.3)	NA	8.5 (3.1–20.9)
2006–2010	6.7 (1.1–32.1)	35.7 (18.6–57.4)	2.5 (1.3–4.5)	27.7 (17.7–40.4)	NA	10.2 (0.6–16.8)
2011–2015	3.7 (1.5–9.1)	32.7 (19.2–49.9)	2.0 (0.2–17.0)	29.2 (21.0–38.9)	NA	15.0 (5.2–36.1)
2016–2020	2.7 (0.9–8.0)	33.5 (22.7–46.4)	2.4 (1.2–4.8)	27.7 (21.7–34.7)	7.2 (4.6–11.0)	13.3 (9.8–17.8)
2020–2023	16.1 (7.0–32.6)	38.5 (23.2–56.3)	2.7 (1.1–6.5)	49.5 (36.3–62.7)	23.4 (15.6–33.6)	23.8 (13.6–38.2)

NA no data available, *AMX* amoxicillin, *MTZ* metronidazole, *TET* tetracycline, *CLA* clarithromycin, *LEV* levofloxacin

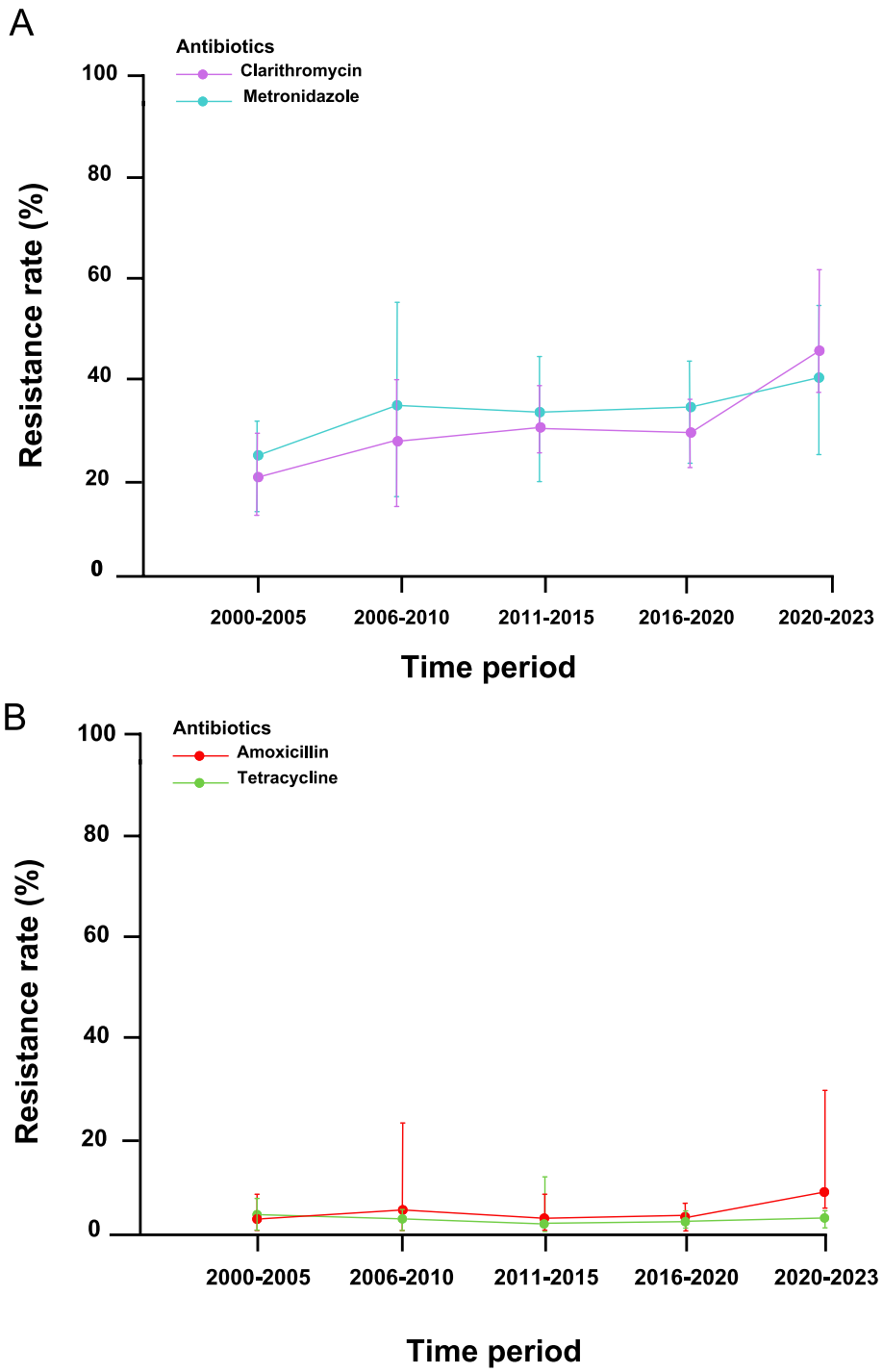


Fig. 2 The trends of resistance status of *H. pylori* in specified time intervals for clarithromycin and metronidazole (**A**), and for amoxicillin and tetracycline (**B**) are presented in separate lines. Error bars represent 95% CIs

Pooled prevalence of *H. pylori* secondary resistance

In total, there was secondary resistance information among 115 isolates. Accordingly, the rate of secondary resistance was reported as 69.3% (80/115, 95% CI: 33.8–90.9) for clarithromycin, 36.4% (42/115, 95% CI: 10.7–73.3) for levofloxacin, 45.8% (53/115, 95% CI: 34.6–57.5) for metronidazole, and 2.9% (33/115, 95% CI: 0.5–15.6) for tetracycline. The available data for the

rate of secondary resistance to amoxicillin was not sufficient to review and perform a meta-analysis. Therefore, we could not evaluate the rate of secondary resistance to amoxicillin.

Analysis of time trend

The time trend of *H. pylori* antibiotic resistance in children was analyzed. Spanning multiple time intervals, the analysis incorporated data from a diverse array of studies. Specifically, there were seven studies covering the 2000–2005 period, followed by eight studies during 2006–2010, 12 studies spanning 2011–2015, 16 studies encapsulating 2016–2020, and finally, 17 studies encompassing the interval of 2020–2023.

The data spans distinct time intervals from 2000 to 2023, capturing the evolving landscape of antibiotic resistance. As a result, there was a significant increase from 2000–2005 to 2020–2023, escalating from 1.1 to 16.1% for amoxicillin, 20.4 to 49.5% for clarithromycin, 25.0 to 38.5% for metronidazole, and 2.0 to 2.7% for tetracycline. The metronidazole + clarithromycin combination also demonstrated noticeable resistance fluctuations. These temporal shifts in resistance rates underscore the dynamic nature of resistance against antibiotics. Table 1 presents the temporal perspective of antimicrobial resistance rates across 5-year periods in *H. pylori*-infected children. Moreover, Fig. 2 depicts the linear diagram of antibiotic resistance changes based on selected time trends.

Country

In the European region, encompassing the largest number of studies, the resistance rate to amoxicillin was investigated in 14 countries and reported to be less than 5%, with Germany demonstrating the highest resistance rate with 20% (10/49, 95% CI: 11–34). In all countries except for Belgium and Croatia, the rate of resistance to clarithromycin was above 15%, among which Turkey exhibited the highest rate of resistance with 85% (83/98, 95% CI: 75–91). In the European region, levofloxacin displayed less than 15% resistance among children, except for Bulgaria, where the resistance rate was reported as high as 19% (57/299, 95% CI: 15–24). The rate of resistance to metronidazole was also above 15% in this region, except for Croatia 10%, (17/168, 95% CI: 6–16). In addition, the overall rate of tetracycline resistance in the European region was 1.8% (99/5511, 95% CI: 1.1–2.9), where Spain exhibited the highest rate of *H. pylori* resistance to tetracycline among children, with a rate of 8%.

Based on a survey of 20 studies in the Western Pacific region, it was revealed that the rate of resistance to

Table 2 Global pooled prevalence of antibiotic resistance by country in the WHO regions

WHO region	Antibiotic, country (no. of studies)	Pooled prevalence, %	95% CI
African	Clarithromycin		
	Algeria (1)	13	(7–19)
	Metronidazole		
	Algeria (1)	37	(29–45)
Americas	Amoxicillin		
	USA (2)	7	(5–10)
	Brazil (1)	10	(7–13)
	Clarithromycin		
	USA (2)	27	(10–54)
	Brazil (1)	20	(12–30)
	Chile (1)	27	(13–47)
	Levofloxacin		
	Chile (1)	29	(15–49)
	Metronidazole		
	USA (2)	36	(22–53)
	Brazil (1)	40	(30–51)
	Tetracycline		
	USA (1)	0	(0–21)
Eastern Mediterranean	Amoxicillin		
	Iran (7)	28	(9–60)
	Clarithromycin		
	Jordan (1)	26	(19–35)
	Iran (7)	25	(11–45)
	Levofloxacin		
	Jordan (1)	7	(4–13)
	Metronidazole		
	Jordan (1)	50	(41–59)
	Iran (6)	61	(39–79)
	Tetracycline		
	Iran (5)	5	(1–16)
European	Amoxicillin		
	Belgium (1)	0	(0–1)
	Bulgaria (4)	2	(0–12)
	Croatia (1)	0	(0–1)
	Germany (1)	20	(11–34)
	Israel (3)	10	(7–16)
	Italy (1)	0	(0–1)
	Poland (4)	0	(0–4)
	Slovenia (1)	1	(0–7)
	Spain (2)	4	(0–68)
	Turkey (1)	0	(0–10)
	Clarithromycin		
	Austria (1)	34	(27–41)
	Belgium (2)	11	(9–14)
	Bulgaria (4)	22	(14–33)
	Croatia (1)	12	(8–18)
	Germany (2)	32	(15–56)

Table 2 (continued)

WHO region	Antibiotic, country (no. of studies)	Pooled prevalence, %	95% CI
	Israel (4)	27	(12–51)
	Italy (1)	18	(10–30)
	Lithuania (1)	33	(29–39)
	Poland (5)	47	(25–67)
	Slovenia (1)	23	(16–33)
	Spain (2)	45	(34–57)
	Turkey (1)	85	(75–91)
	Levofloxacin		
	Austria (1)	0	(0–4)
	Belgium (2)	7	(5–9)
	Bulgaria (1)	19	(15–24)
	Israel (2)	2	(0–6)
	Poland (3)	3	(0–14)
	Slovenia (1)	3	(0–9)
	Spain (2)	0	(0–4)
	Turkey (1)	14	(8–24)
	Metronidazole		
	Austria (1)	23	(17–30)
	Belgium (2)	19	(12–29)
	Bulgaria (4)	22	(14–33)
	Croatia (1)	10	(6–16)
	Germany (2)	43	(18–72)
	Israel (4)	30	(25–36)
	Italy (1)	25	(15–38)
	Lithuania (1)	45	(40–50)
	Poland (5)	41	(35–48)
	Slovenia (1)	20	(14–29)
	Spain (3)	22	(12–38)
	Turkey (1)	62	(50–72)
	Tetracycline		
	Austria (1)	0	(0–4)
	Belgium (2)	1	(0–9)
	Bulgaria (4)	3	(2–4)
	Israel (3)	5	(2–11)
	Italy (1)	0	(0–1)
	Poland (5)	2	(0–15)
	Slovenia (1)	0	(0–7)
	Spain (1)	8	(4–16)
	Turkey (1)	0	(0–10)

Table 2 (continued)

WHO region	Antibiotic, country (no. of studies)	Pooled prevalence, %	95% CI
Western Pacific	Amoxicillin		
	China (5)	1	(0–9)
	Japan (3)	0	(0–3)
	Singapore (1)	7	(3–16)
	Taiwan (3)	7	(1–33)
	Vietnam (5)	38	(16–69)
	Clarithromycin		
	China (5)	43	(31–57)
	Japan (3)	31	(15–52)
	Singapore (1)	30	(20–42)
	Taiwan (3)	16	(9–27)
	Vietnam (5)	76	(61–87)
	Levofloxacin		
	China (8)	15	(9–26)
	Japan (1)	19	(13–27)
	Taiwan (1)	8	(5–13)
	Vietnam (3)	48	(35–52)
	Metronidazole		
	China (8)	69	(61–76)
	Japan (3)	43	(7–89)
	Singapore (1)	28	(18–39)
	Taiwan (3)	14	(6–31)
	Vietnam (5)	38	(24–55)
	Tetracycline		
	China (2)	3	(0–29)
	Japan (1)	0	(0–3)
	Taiwan (3)	0	(0–4)
	Vietnam (5)	7	(2–27)

amoxicillin was 5.5% (201/3649, 95% CI: 1.8–15.5), clarithromycin 49.1% (3504/7137, 95% CI: 38.0–60.2), levofloxacin 22.0% (1427/6488, 95% CI: 14.4–31.9), metronidazole 46.9% (3347/7137, 95% CI: 1.9–8.5), and tetracycline 4.1% (39/954, 95% CI: 1.9–8.5). These values were 7.1% (32/453, 95% CI: 5.1–9.9) and 37.4% (208/556, 95% CI: 10.4–75.5), 23.5% (106/453, 95% CI: 14.1–36.5), and 22.3% (150/672, 95% CI: 10.4–41.5), 43.1% (195/453, 95% CI: 38.6–47.7), and 55.6% (299/537, 95% CI: 33.0–47.3), respectively, for amoxicillin, clarithromycin, and metronidazole for the Americas and Eastern Mediterranean regions. Meta-analysis for two antibiotics, tetracycline and levofloxacin in the Americas region and levofloxacin in the Eastern Mediterranean region was not performed, due to a confined number of studies. In addition, only one country in Africa provided data on the antibiotic resistance of *H. pylori* in children, and the result included 13% resistance to clarithromycin and 37% resistance to metronidazole in Algeria. A report of the resistance rate to the mentioned antibiotics by country is available in Table 2.

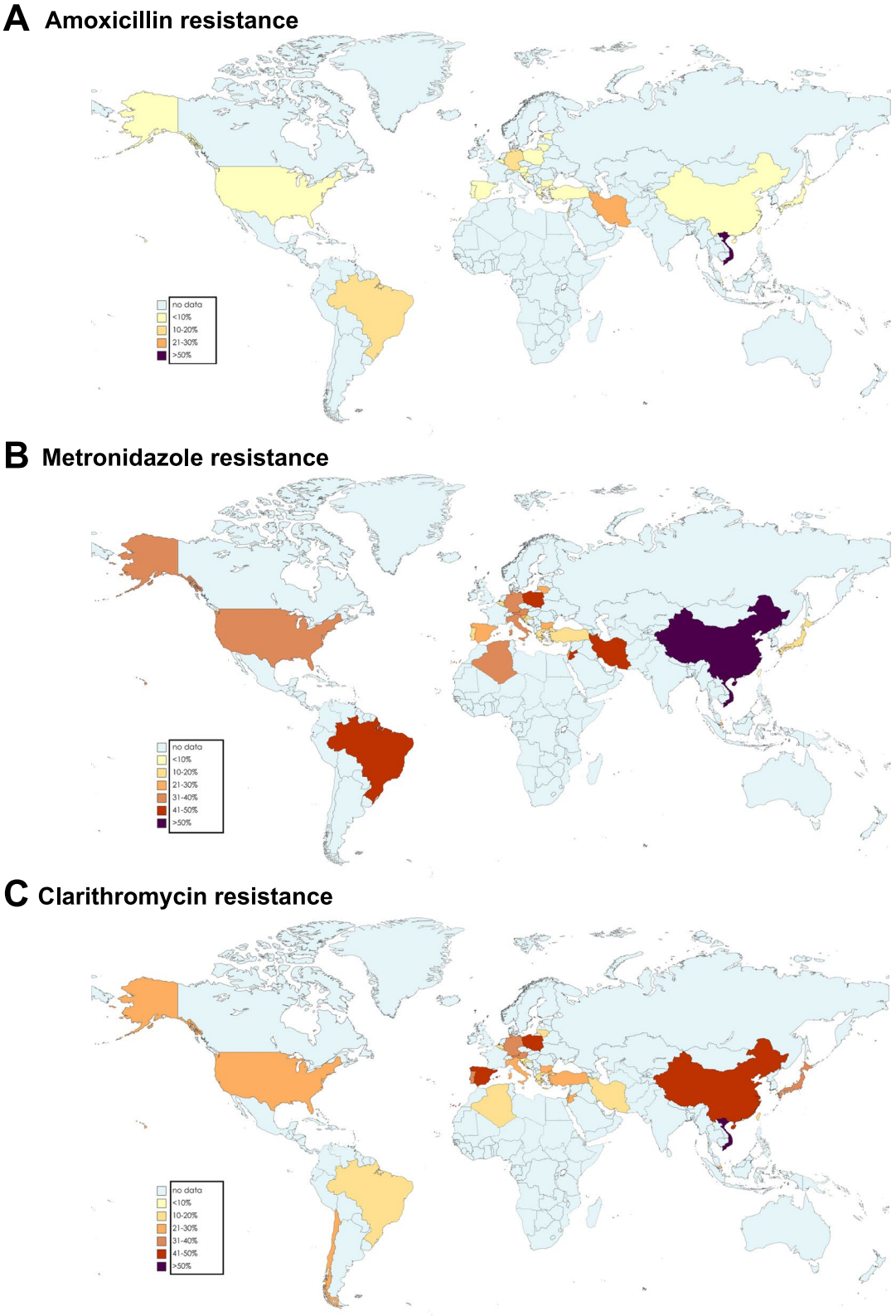


Fig. 3 Estimated pooled prevalence of antibiotic resistance for amoxicillin (**A**), metronidazole (**B**), and clarithromycin (**C**) of *H. pylori* among children from 28 countries in 5 WHO regions during (2000–2023) (created with mapchart.net)

Table 3 Antibiotic resistance rate according to regions determined by WHO

WHO region	Single-antibiotic resistance									
	AMX		MTZ		TET		CLA		LEV	
	Rate, %	95% CI	Rate, %	95% CI	Rate, %	95% CI	Rate, %	95% CI	Rate, %	95% CI
Americas	7.1	(5.1–9.9)	43.1	(38.6–47.7)	NA	NA	23.5	(14.1–36.5)	NA	NA
Eastern Mediterranean	37.4	(10.4–75.5)	55.6	(33.0–47.3)	5.3	(1.1–22.2)	22.3	(10.4–41.5)	NA	NA
European	2.2	(1.0–4.7)	25.2	(21.0–29.9)	1.8	(1.1–2.9)	28.0	(22.1–34.7)	4.2	(2.2–8.0)
Western Pacific	5.5	(1.8–15.5)	46.9	(36.0–58.1)	4.1	(1.9–8.5)	49.1	(38.0–60.2)	22.0	(14.4–31.9)
	Multi-antibiotic resistance									
	CLA + LEV		MTZ + CLA		MTZ + LEV		CLA + MTZ + LEV			
	Rate, %	95% CI	Rate, %	95% CI	Rate, %	95% CI	Rate, %		95% CI	
European	NA	NA	12.8	(9.0–17.8)	NA	NA	2.3		(1.1–4.8)	
Western Pacific	2.7	(0.5–13–6)	13.0	(9.5–17.6)	5.1	(2.1–11.5)	7.5		(6.8–8.3)	

CI confidence of interval, *NA* no data available, *AMX* amoxicillin, *MTZ* metronidazole, *TET* tetracycline, *CLA* clarithromycin, *LEV* levofloxacin, *WHO* World Health Organization

Furthermore, Fig. 3 illustrates the antibiotic resistance rates for metronidazole, amoxicillin, and clarithromycin within countries that have contributed their data on a global scale.

Multi-antibiotic resistance was also investigated based on the regions declared by the WHO, and the rate of resistance to metronidazole + clarithromycin was 12.8% (1437/11,226, 95% CI: 9.0–17.8) in the European region and 13% (773/5945, 95% CI: 9.5–17.6) in the Western Pacific region. Also, resistance to clarithromycin + levofloxacin and metronidazole + levofloxacin was 2.7% (150/5555, 95% CI: 0.5–13.6) and 5.1% (277/5432, 95% CI: 2.1–11.5), respectively, in the Western Pacific region. The triple resistance rate to clarithromycin + metronidazole + levofloxacin was observed as 2.3% (127/5525, 95% CI: 1.1–4.8) and 7.5% (22/300, 95% CI: 6.8–8.3), respectively, in the European and Western Pacific region. Table 3 presents a summary of single-antibiotic and multi-antibiotic resistance rates based on WHO regions.

Age

A total of seven studies presented data in the specified intervals for metronidazole, clarithromycin, and levofloxacin. The age-dependent patterns of antibiotic resistance, emphasizing the potential impact of age on *H. pylori* resistance to various antibiotics are presented in Table 4.

Antibiotic susceptibility testing

In total, 37 studies used E-test, 7 studies used disk diffusion method, 12 studies used the agar dilution method, 4 studies used polymerase chain reaction (PCR), and for 3 studies testing details were unavailable. According to the multivariate meta-regression analysis model, studies using PCR showed a much lower prevalence of resistance to metronidazole, amoxicillin, and tetracycline than studies using agar dilution method (Additional file 1, Table S9). Furthermore, studies that applied E-test exhibited a lower prevalence of metronidazole resistance compared to those that used agar dilution method. Moreover, disk diffusion method revealed a much higher resistance rate to tetracycline, metronidazole, and amoxicillin in comparison to agar dilution method.

Table 4 Comparison of antibiotic resistance against *H. pylori* in different age groups

Age range, year	Metronidazole		Clarithromycin		Levofloxacin	
	Rate, %	95% CI	Rate, %	95% CI	Rate, %	95% CI
0–5	42.6	(22.8–65.1)	51.0	(28.3–73.4)	NA	NA
5–10	61.5	(29.1–86.1)	37.8	(29.3–47.0)	16.5	(7.4–32.8)
10–15	52.3	(21.2–81.7)	25.4	(17.8–34.9)	13.7	(8.3–21.7)

Meta-analysis was conducted on the resistance rate reported in only seven studies within these ranges

NA no data available

Heterogeneity assessment

No significant heterogeneity was observed in any of the general analyses among the five selected antibiotics and in all analyses conducted, and the value of I^2 was reported to be less than 50%. However, after grouping the studies based on the countries where the study was conducted, as well as based on age and time periods grouping, the amount of heterogeneity decreased significantly. I^2 values for each analysis is also depicted in Additional file 2, Fig. S7-S21.

Discussion

The present systematic review and meta-analysis provides several novel insights into the prevalence and patterns of antibiotic resistance in *H. pylori*-infected pediatric populations, with focus on regional differences as categorized by WHO regions. Unlike previous studies, our analysis offers a detailed comparison of resistance rates for key antibiotics, including metronidazole, clarithromycin, tetracycline, levofloxacin, and amoxicillin, specifically within the pediatric population. We also highlight the significant variability in antibiotic resistance across different WHO regions, emphasizing the influence of geographic origin, socioeconomic factors, and healthcare practices. Additionally, our study draws attention to the differences in methodologies, particularly the variations in MIC breakpoints used to evaluate antibiotic resistance. These methodological differences likely contribute to the discrepancies observed in resistance rates between regions and underscore the importance of standardized approaches in resistance monitoring. These findings provide a more nuanced understanding of *H. pylori* resistance in children and underscore the need for tailored treatment strategies that consider regional resistance patterns and methodological consistency. Specifically, the European region was shown to be the primary source of data regarding antibiotic resistance, followed by the Western Pacific, Eastern Mediterranean, Americas, and African regions.

The presented data provides insightful details regarding the extent of resistance for clarithromycin, metronidazole, and amoxicillin. Evidently, the global resistance pattern highlights clarithromycin as the most prominent antibiotic conferring resistance and was particularly conspicuous in the Western Pacific region with a resistance rate of 49% [70–72]. Subsequently, this region exhibits a relatively elevated resistance trend for metronidazole, notably pronounced with a resistance rate of 47% [31, 38]. Consistently, MIC_{50} and MIC_{90} breakpoints for clarithromycin and metronidazole are higher in the Western Pacific region, which emphasize the validity of the performed analysis. However, amidst these trends, amoxicillin stands out as a marked exception as the available data suggests that amoxicillin has maintained its effectiveness with a resistance rate of less than 10% in different regions (except for the Eastern Mediterranean region with a resistance rate of 37%) [38, 48]. This might indicate the potential significance of amoxicillin prescription in treatment regimens targeting *H. pylori* in children [42, 91].

The disk diffusion method tends to yield higher resistance rates compared to other methods, primarily due to its broader categorization criteria. This method relies on the measurement of inhibition zones around antibiotic-impregnated disks placed on an agar plate inoculated with the bacterial agent. The interpretation of these zones can be subjective, and the cutoff values for resistance are sometimes less stringent, leading to a higher likelihood of categorizing an isolate as resistant. While disk diffusion can serve as a standard method for several bacterial species, due to specific growth requirements of *H. pylori*, this method may not always work well for this pathogen and can lead to false positives [92]. This contrasts with methods like E-test or agar dilution assay, which provide more precise measurements of MICs and typically have more defined thresholds for resistance classification. Additionally, PCR-based methods, while valuable for their specificity and ability to detect known resistance-associated mutations, have limitations in sensitivity, especially for detecting resistance beyond clarithromycin. PCR primarily targets specific genetic mutations known to confer resistance, such as those in the 23S rRNA gene for clarithromycin resistance [5, 92]. Nevertheless, it may overlook additional resistance mechanisms or mutations in various genes that confer resistance to antimicrobial agents such as metronidazole or levofloxacin [93, 94]. The resistance of *H. pylori* to antibiotics such as levofloxacin and metronidazole is commonly caused by a variety of genetic alterations, including insertion, deletion, and frameshift mutations. Thus, traditional PCR that typically detects specific and known point mutations may not work as an applicable technique for the detection of mutations involved in resistance to levofloxacin and metronidazole [95]. For instance, resistance to metronidazole is often due to multiple mutations occurring in *rdxA* gene, such as insertion of transposable elements like mini-IS605 and deletion of adjacent sequences, which are not point mutations and thus not easily detectable by standard PCR methods [96]. This limitation can lead to an underestimation of resistance rates for antibiotics other than clarithromycin, making it less comprehensive than phenotypic methods that evaluate the overall bacterial response to antibiotics.

A subgroup analysis of antibiotic resistance rates across distinct age groups revealed the resistance dynamics within pediatric populations. The resistance rate varies based on the age ranges and antibiotics, with the

highest rate of metronidazole resistance among children aged 5–10 years old with a rate of 61.5%, while the highest rate of clarithromycin resistance is in the age range of 0–5 years old with a rate of 51.0%. Age-specific treatment techniques should be taken into consideration due to the documented variances in resistance levels across different age groups, which may be caused by differences in immune system development and microbiota. Moreover, a noteworthy aspect arises from the examination of secondary resistance rates. This highlights the evolving nature of resistance mechanisms, particularly for such antibiotics as clarithromycin, levofloxacin, and metronidazole [59, 77]. These observations emphasize the pivotal importance of maintaining an efficient approach to treatment methodologies. This, in turn, reiterates the imperative nature of exercising prudence in antibiotic administration to effectively mitigate the progression of secondary resistance development [53, 97].

Savoldi and colleagues [98] conducted a systematic review and meta-analysis in 2018 on antibiotic resistance rates in both adults and children across WHO regions. Their work included 178 studies analyzing data from 53,583 patients. According to their findings, the resistance rates for clarithromycin and metronidazole in the Americas region were 19% and 40% in children, respectively. However, our study demonstrated that these rates were 24% and 43%, respectively. In the Eastern Mediterranean region, the resistance rates for clarithromycin and metronidazole were reported as 10% and 81%, respectively, while our study presented higher rate of resistance in clarithromycin but lower rate in metronidazole, 22% and 56%, respectively. Compared to their data, our study recorded lower rate of clarithromycin resistance (49% vs. 85%) but higher rates of levofloxacin resistance (22% vs. 17%) and comparable metronidazole resistance (46% vs. 43%) in the Western Pacific region. These differences might be partially due to the inclusion of higher number of studies in the present work, which entirely focused on *H. pylori* infection in children and encompassed a longer time trend. Results of the present meta-analysis contrasted the resistance rates to amoxicillin, levofloxacin, and clarithromycin in Western Pacific region with those found in Savoldi et al. [98] study. The investigation's findings suggest that patterns of antibiotic resistance are always evolving, particularly with raising rates of resistance to metronidazole and levofloxacin. Interestingly, the increase in the resistance rate of levofloxacin was higher than that of metronidazole, which might suggest levofloxacin to be more commonly used in treatment regimens within this region [21, 73].

Compared to the data from Savoldi et al. [98] study in the European region, our study exhibits higher resistance rates for clarithromycin (28% vs. 24%) and for metronidazole (25% vs. 20%). The resistance rates for amoxicillin, tetracycline, and levofloxacin are also slightly higher in our study. Additionally, Koletzko et al. [99] provided an overview of primary antibiotic resistance prevalence in children living in the European region in a prospective multicenter study. The study included 1233 patients from Northern (3%), Western (70%), Eastern (9%), and Southern Europe (18%). The initial resistance rate to clarithromycin, metronidazole, and amoxicillin was 24%, 25%, and 0.6%, respectively. However, the resistance rates for these antibiotics in the European region are reported in our study as 28.0%, 25.2%, and 2.2%, respectively. This indicates that over the past 17 years, there has been a 4% and 2% increase in clarithromycin and amoxicillin resistance rates, respectively, while the metronidazole resistance has hardly raised (0.2%) [99, 100]. It can be extrapolated that precise and constant antibiotic stewardship programs and prescription monitoring in the European region have been effective in preventing a sudden increase in resistance rates.

In the European and Western Pacific regions, applying a combination of clarithromycin and amoxicillin treatment remains an efficient option for treating *H. pylori* infection in children, based on our data analysis. Sequential therapies, bismuth-based therapy, or amoxicillin combined with metronidazole could be considered for those infected with clarithromycin-resistant strains. Our study also found that a combination of clarithromycin and metronidazole may still be effective in eradicating *H. pylori* infection in American children with susceptible strains [100]. In Africa, the present study demonstrated even lower amoxicillin and metronidazole resistance rates for *H. pylori* compared to the other two continents (13.0% and 37.1%, respectively) [19]. Reports from Africa suggest that sequential therapies and the combination of amoxicillin with high doses of metronidazole might be effective for *H. pylori* eradication [100]. However, there were some inconsistencies in reported resistance rates, which could be attributed to children with more severe course of disease being more likely to undergo testing, thereby increasing the likelihood of detecting resistant strains of the bacteria [101, 102]. Aside from *H. pylori* resistance mechanisms, differences in antibiotic consumption among distinct continents and countries worldwide contribute to the discrepancies in antimicrobial resistance patterns [102]. Therefore, as the prescription of empirical treatment regimens remain the predominant option for pediatric patients [100, 103], we emphasize the necessity for further cohort studies on larger pediatric populations across different geographical areas to identify peculiarities regarding antimicrobial resistance patterns and increase the efficacy of empirical eradication strategies for *H. pylori* infection management.

Recently, the alarming surge in antibiotic resistance has raised global concerns. This increase could potentially be attributed to the indiscriminate use of antibiotics, especially during the COVID-19 pandemic. The pandemic-driven increase in antibiotic consumption, often as a precautionary measure or due to secondary infections, raises important questions about its potential impact on antibiotic resistance [104]. As the world grapples with the aftermath of the pandemic, it becomes imperative to evaluate post-COVID effects on antibiotic resistance and the emergence of multidrug-resistant organisms (MDRO) [105, 106]. According to recent research, an antibiotic prescription may affect the resistance burden once for 4 years, and thus, continuous use could lead to a never-ending cycle [106–108].

Within our research, we demonstrated that certain WHO regions are characterized by higher resistance levels to amoxicillin and tetracycline. While these antibiotics exhibited lower levels of resistance compared to clarithromycin, metronidazole, and levofloxacin, they still displayed relatively high levels of resistance in certain areas of the Eastern Mediterranean and Western Pacific. In the Eastern Mediterranean region, amoxicillin resistance has been reported as 37.4%, primarily due to its high consumption in Iran, which has caused a significant increase in resistance rates in this region [24, 25, 27, 108]. Although tetracycline has a resistance rate of 5.4%, it is still the highest compared to other regions [26, 28]. Similarly, in the Western Pacific region, Vietnam has contributed to the higher rate of amoxicillin resistance, which is reported to be 38% [63, 81]. The rate of tetracycline resistance is also reported to be 7% in Vietnam, further contributing to the overall increase in resistance rates [66, 77]. Therefore, these countries warrant revisiting their treatment regimens and deploying different antimicrobial stewardship strategies to prevent further increases in resistance rates.

This study has several limitations that should be acknowledged. First, there is the potential for publication bias, as studies with significant results are more likely to be published, possibly skewing the reported resistance rates. Additionally, the availability of data for certain antibiotic combinations and resistance patterns is restricted, particularly for less commonly used antibiotics such as levofloxacin and tetracycline. The comprehensiveness of our search strategy may also be constrained by the integrity of the search terms and databases used, potentially leading to the omission of relevant studies, especially those published in non-English languages or in less accessible journals. Furthermore, there is a regional asymmetry in the data, with some regions, such as Africa and the Americas being underrepresented, which might affect the generalizability of our findings. Lastly, the heterogeneity of methodologies across the included studies, such as variations in antibiotic susceptibility testing methods, may introduce variability in the results, impacting the comparability of the resistance rates reported. These limitations underscore the necessity for ongoing, standardized research to accurately monitor global patterns of *H. pylori* resistance in children and to develop effective, region-specific treatment strategies.

Conclusions

All in all, this study highlights the global prevalence of *H. pylori* antibiotic resistance in children, a population often overlooked in resistance research. The findings reveal significant regional variations, with the Western Pacific region showing the highest resistance rates, particularly to clarithromycin. This underscores the urgent need for ongoing research and monitoring in this area. Furthermore, the results highlight a significant worry; more than 15% of kids worldwide show resistance to clarithromycin. This exceeds the expected threshold for prescriptions that are usually administered, as the most recent Maastricht recommendations indicate [109]. The study also emphasizes the significance of developing new treatment strategies and alternatives to current antibiotics to effectively manage *H. pylori* infections in children. These efforts are crucial to addressing the rising challenge of antibiotic resistance and ensuring effective treatment options remain available.

Abbreviations

AMX	Amoxicillin
CI	Confidence interval
CLA	Clarithromycin
CMA	Comprehensive meta-analysis
H. pylori	*Helicobacter pylori*
LEV	Levofloxacin
MeSH	Medical subject headings
MIC	Minimum inhibitory concentration
MTZ	Metronidazole
NA	No data available
PCR	Polymerase chain reaction
SE	Standard error
TET	Tetracycline
WHO	World health organization

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-024-03816-y.

Additional file 1: Tables S1–S9. Table S1. The original search terms used in the present study. Table S2. Eligibility criteria. Table S3. PICO table for meta-analysis. Table S4. Quality assessment of included studies. Table S5. Geographic distribution of the studies and number of participants according to the WHO regions. Table S6. Demographic and clinical features of patients. Table S7. A report of MIC 50 and MIC 90 values for the investigated antibiotics according to WHO regions. Table S8. Description of scoring process used by the authors to evaluate included studies along with a measure of inter-rater agreement (kappa). Table S9. Subgroup analysis of the prevalence of antibiotic resistance based on antibiotic susceptibility testing method in children.

Additional file 2: Figs. S1–S21. Fig. S1-S5. Funnel plots of the meta-analysis on overall *H. pylori* primary resistance to antibiotics. Fig. S6. Geographical distribution of the 6 WHO regions and member states for each region. Fig. S7-S21. Summary forest plot of the odds ratios associating treatment failure and antibiotic resistance among children around the world and each WHO region.

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Authors' contributions
AS-N, AN-R and AY contributed to the literature review, collected, extracted and verified the data. AS-N did the statistical analyses and prepared the first draft of the manuscript. AY contributed to conceptualization, methodology, project administration, study design, funding acquisition, and critically edited the manuscript. TMM, TR, MD, AS, MRZ, YY and ET revised the manuscript. All authors read and approved the final manuscript.

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Data availability
All data generated or analyzed in this study are included in the manuscript and supplements. Applications and additional requests for information should be made to Abbas Yadegar (babak_y1983@yahoo.com).

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable; this manuscript does not include any details, images, or videos relating to an individual person.

Competing interests
The authors declare no competing interests.

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