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A SYSTEMATIC REVIEW ON *HELICOBACTER PYLORI* ANTIMICROBIAL RESISTANCE: GLOBAL TRENDS, CLINICAL IMPLICATIONS, AND FUTURE STRATEGIES

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Abstract – *Objective:* *Helicobacter pylori* remains one of the most prevalent bacterial infections globally. While *H. pylori* eradication reduces gastric cancer risk, increasing antimicrobial resistance (AMR) impairs the effective treatment with major geographic variability. This systematic review summarizes the global epidemiology, mechanisms of resistance, clinical consequences, and emerging strategies to address *H. pylori* AMR.
Materials and Methods: We systematically searched PubMed, Scopus, and Web of Science for articles published between 2000 and June 2025. Keywords included "*Helicobacter pylori*", "antimicrobial resistance", "clarithromycin", "metronidazole", "levofloxacin", "children", and "epidemiology". Inclusion criteria comprised English-language studies in human subjects reporting prevalence, mechanisms, or treatment outcomes related to resistance. Excluded were case reports, animal studies, and small series (<20 patients). Emphasis was placed on multicenter trials, surveillance reports, and systematic reviews.
Results: Analysis of included studies demonstrated that clarithromycin resistance exceeds 20-30% in many regions, particularly East Asia and Southern Europe, undermining traditional triple therapy. Metronidazole resistance is widespread, ranging from 30-70% globally, while levofloxacin resistance shows alarming upward trends. Amoxicillin and tetracycline resistance remain rare, while rifabutin retains activity against multidrug-resistant strains. Pediatric populations exhibit especially high clarithromycin and metronidazole resistance, with pooled prevalence exceeding 35% in some regions, limiting therapeutic options. Molecular mechanisms primarily involve point mutations in 23S rRNA, *rdxA/frxA*, and *gyrA* genes, while next-generation sequencing has identified additional candidate loci. Novel strategies, including bismuth-based quadruple therapy, vonoprazan-based dual regimens, and molecular-guided therapy improve outcomes. Adjunctive measures such as probiotics, antimicrobial peptides, and stewardship interventions offer further promise.
Conclusions: *H. pylori* AMR represents a critical barrier to eradication worldwide. Expanded global surveillance, rapid molecular diagnostics, and personalized therapy are urgently needed. Future research should prioritize pediatric-focused strategies, non-antibiotic alternatives, and equitable access to optimized regimens. Coordinated international action is essential to contain resistance and preserve the benefits of eradication.

Keywords: *Helicobacter pylori*, Antimicrobial resistance, Global rate, Clarithromycin, Metronidazole, Levofloxacin, Systematic review.

INTRODUCTION

Helicobacter pylori is one of the most widespread chronic bacterial infections, colonizing an estimated 4.4 billion individuals globally, with a prevalence of approximately 44% in adults and up to 35% in children and adolescents[1]. Prevalence remains highest in Africa (70%) and Latin America (60%), compared with 34% in Europe and 37% in North America[2]. Chronic infection is the primary cause of peptic ulcer disease and is strongly associated with mucosa-associated lymphoid tissue lymphoma and gastric adenocarcinoma. Indeed, the International Agency for Research on Cancer classifies *H. pylori* as a group I carcinogen, and pooled analyses demonstrate that eradication reduces gastric cancer incidence by nearly 40-50% and cancer-specific mortality by up to 36%[3,4].

Eradication regimens, typically combining a proton pump inhibitor (PPI) with two or more antibiotics, historically achieved cure rates exceeding 85-90%. However, rising antimicrobial resistance (AMR) has critically undermined these outcomes. Recent meta-analyses indicate primary resistance rates of 32-35% for clarithromycin, 55-60% for metronidazole, and 20-25% for levofloxacin globally, with resistance exceeding 40% for clarithromycin in many regions of Asia and Southern Europe[5]. These trends directly correlate with eradication failure and necessitate reconsideration of empirical strategies.

This systematic review synthesizes current evidence on *H. pylori* AMR, with emphasis on global epidemiology, pediatric populations, resistance mechanisms, and strategies to safeguard eradication efficacy.

MATERIALS AND METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[6]. A systematic search of three electronic databases (PubMed, Scopus, and Web of Science) was performed to identify relevant literature published between January 2000 and June 2025. The search strategy combined Medical Subject Headings (MeSH) and free-text terms related to *Helicobacter pylori* and AMR, including "*Helicobacter pylori*," "AMR," "clarithromycin," "metronidazole," "levofloxacin," and "epidemiology,". Boolean operators and database-specific filters were applied to maximize the sensitivity and specificity of retrieval.

Two reviewers independently screened titles and abstracts for eligibility, followed by full-text evaluation. Disagreements were resolved through consensus. Inclusion criteria comprised: (i) original research articles or systematic reviews, (ii) studies conducted in human populations, (iii) English-language publications, and (iv) studies reporting AMR rates, mechanisms of resistance, clinical outcomes, or surveillance data. Multicenter trials and large surveillance studies were prioritized. Exclusion criteria were: (i) case reports or case series with fewer than 20 participants, (ii) animal-only studies, (iii) conference abstracts without full-text availability, and (iv) articles lacking primary data or resistance outcomes.

Data extraction focused on study design, geographic region, population characteristics (including pediatric subgroups), antibiotics evaluated, resistance prevalence, and diagnostic methodology (culture, molecular, or next-generation sequencing). Where available, trends in eradication rates and associations between resistance and treatment outcomes were also recorded.

RESULTS

Current Landscape of AMR

AMR in *H. pylori* has become a critical global health concern, with resistance rates to key antibiotics surpassing thresholds at which empiric therapy is likely to fail. A systematic review of 178 studies comprising 66,142 isolates across 65 countries has demonstrated that primary and secondary resistance to clarithromycin, metronidazole, and levofloxacin are ≥15% in most World Health Organization (WHO) regions[7]. Clarithromycin resistance, which is of particular concern given its role in standard triple therapy, remains highly variable across regions, with pooled prevalence exceeding 15% in Europe and rising steadily in Asia, especially in Southern and Eastern countries, whereas in the Americas and parts of Southeast Asia resistance rates are slightly lower but still often clinically significant[7]. Metronidazole resistance consistently demonstrates the highest prevalence, often above 50% in the Eastern Mediterranean, Africa, and the Western Pacific, and this severely undermines the utility of regimens that depend on this drug[8]. Levofloxacin resistance has also emerged as a major problem, with resistance rates approaching 20-25% in many regions and often even higher in patients with prior treatment exposure. In contrast, resistance to amoxicillin and tetracycline remains relatively uncommon, generally below 5-10% worldwide, although sporadic reports of increasing resistance are emerging, especially in Asia. Rifabutin resistance remains rare, which is consistent with its limited clinical use and the biological cost associated with mutations in its target gene[7]. Figure 1 demonstrates the geographic distribution of antibiotic resistance.

The WHO has recognized clarithromycin-resistant *H. pylori* as a high-priority pathogen for research and development of new antimicrobials, reflecting the threat posed to effective gastric cancer prevention strategies[9]. Global surveillance initiatives, such as the European Registry on *H. pylori* Management and regional molecular monitoring programs, have been crucial in documenting the temporal rise of resistance and its impact on eradication outcomes[10,11]. These alarming trends highlight the necessity for region-specific surveillance data, molecular resistance testing, and individualized treatment approaches, as the effectiveness of empiric regimens is now heavily constrained by local resistance profiles.

Mechanisms of Resistance

The molecular basis of *H. pylori* AMR is increasingly well understood and involves point mutations in target genes, inactivation of drug-activating enzymes, and, in some cases, efflux mechanisms or alterations in outer membrane permeability[12]. Clarithromycin resistance is most commonly mediated by point mutations in the 23S rRNA gene, particularly A2143G, A2142G, and A2142C, which prevent macrolide binding to the ribosomal peptidyl transferase center[13]. Additionally, less frequent variants, such as A2115G, G2141A, and C2147G, have also been identified, often through next-generation sequencing, and may contribute to heteroresistant phenotypes[14]. Resistance to metronidazole arises primarily through mutations or inactivation of *rdxA* and *frxA* genes, which encode nitroreductases responsible for prodrug activation[15]. These alterations prevent intracellular drug activation and lead to high-level resistance, although whole-genome sequencing studies suggest that additional redox-associated genes such as *fdxB* and *sodB* may play contributory roles[16]. Table 1 lists the primary genetic mutations and mechanisms implicated in *H. pylori* antibiotic resistance.

Fluoroquinolone resistance results from amino acid substitutions in the quinolone resistance-determining region of the *gyrA* gene, particularly at positions Asn87 and Asp91, with occasional involvement of *gyrB* mutations[16]. These substitutions alter the structure of DNA gyrase, reducing fluoroquinolone binding. Some resistant isolates, however, do not harbor canonical *gyrA* mutations, suggesting the involvement of alternative mechanisms, such as efflux pumps or compensatory chromosomal regulators. Amoxicillin resistance, while still relatively uncommon, is associated with mutations in the penicillin-binding protein genes, especially *pbp1A*, which reduce binding affinity for β-lactam antibiotics[14]. Alterations in outer membrane proteins and increased efflux activity may further modulate amoxicillin susceptibility. Tetracycline resistance, similarly uncommon, usually arises from mutations in the 16S rRNA gene at specific positions 926-928, which disrupt drug binding to the 30S ribosomal subunit[13]. Finally, rifabutin resistance, which is rarely observed in clinical isolates, has been linked to mutations in the *rpoB* gene encoding the β-subunit of RNA polymerase, although these mutations often impose significant fitness costs[17].

Insights from next-generation sequencing have broadened the understanding of these mechanisms, revealing novel resistance-associated mutations in genes not traditionally linked to antibiotic resistance, such as *infB* and *rpl22* in clarithromycin-resistant isolates, and identifying strains with phenotypic resistance in the absence of known mutations, underscoring the complexity of resistance determinants[16]. Whole-genome studies continue to expand the catalog of mutations and highlight the multifactorial nature of resistance, where point mutations, gene inactivation, efflux regulation, and compensatory adaptations interact to shape resistance phenotypes[18].

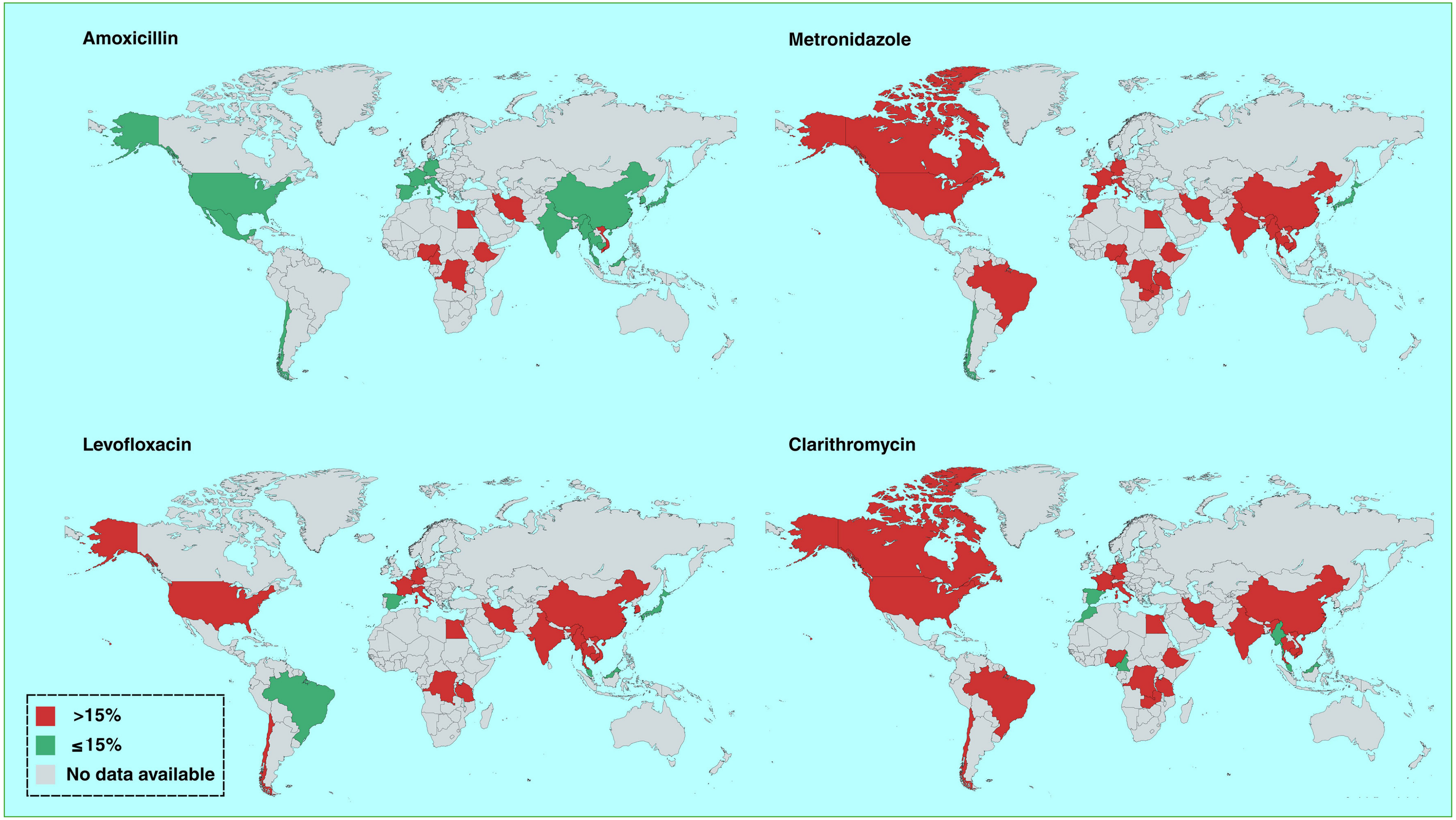

Figure 1. Geographic distribution of antibiotic resistance to clarithromycin, metronidazole, levofloxacin, and amoxicillin among adult populations. Data represent pooled prevalence estimates from multicenter surveillance studies and systematic reviews.

TABLE 1. MOLECULAR MECHANISMS OF *HELICOBACTER PYLORI* ANTIMICROBIAL RESISTANCE.

Antibiotic	Primary molecular mechanisms	Additional insights from genomic studies
Clarithromycin	Point mutations in 23S rRNA (A2143G, A2142G, A2142C)	Rare variants (A2115G, G2141A, C2147G); *rpl22* and *infB* involvement; heteroresistance
Metronidazole	Inactivating mutations in *rdxA* and *frxA*	Contributions from *fdxB*, *sodB*; oxidative stress adaptation; efflux activity
Levofloxacin	Mutations in *gyrA* QRDR (Asn87, Asp91); occasional *gyrB*	Resistant strains without QRDR mutations suggest efflux and regulatory mechanisms
Amoxicillin	Mutations in *pbp1A* and *pbp2* (penicillin-binding proteins)	Altered outer membrane proteins; possible efflux contribution
Tetracycline	Mutations in 16S rRNA at positions 926–928	Cases without 16S rRNA mutations suggest uptake and efflux influences
Rifabutin	Mutations in *rpoB* (RNA polymerase β-subunit)	Resistance rare; mutations often carry fitness costs

Clinical Implications

Rising AMR in *H. pylori* has profound and immediate clinical consequences for both first-line and rescue therapies, translating into lower eradication rates, greater patient morbidity, and increased healthcare expenditures[19]. Historically effective triple regimens combining a PPI with clarithromycin and either amoxicillin or metronidazole have shown progressively declining efficacy as clarithromycin resistance has risen above clinically acceptable thresholds in many regions. When clarithromycin resistance exceeds approximately 15%, empiric clarithromycin-based triple therapy commonly results in cure rates well below 80%, leading guideline panels to discourage its routine empiric use[20]. The increasing prevalence of metronidazole and levofloxacin resistance further compromises sequential and fluoroquinolone-based rescue regimens, resulting in a growing proportion of patients requiring multiple courses of therapy, endoscopic reassessment, and susceptibility testing[21]. These treatment failures are associated with persistent symptoms, continued risk of peptic ulcer complications, and, in populations targeted for gastric cancer prevention, diminished public-health benefit[22].

The clinical downstream effects also include measurable economic burdens. Failed eradication incurs direct costs from additional physician visits, diagnostic procedures, extended or repeated pharmacotherapy, and, in some systems, hospital admissions for complications[23]. Indirect costs arise from lost productivity and the broader societal impact of expanding antibiotic resistance[24]. Several high-quality cost-effectiveness analyses indicate that, in settings with high clarithromycin resistance, empiric bismuth-containing quadruple therapy or susceptibility-guided therapy becomes more cost-effective than repeated empiric clarithromycin regimens when accounting for eradication success and downstream costs[25,26].

Recent guideline updates reflect these realities. Contemporary recommendations from major gastroenterology societies emphasize optimized bismuth-based quadruple therapy as a preferred empiric first-line option in many settings and advocate for 14-day regimens to maximize efficacy[27]. Potassium-competitive acid blocker (PCAB)–based strategies, particularly vonoprazan combined with amoxicillin as high-dose dual therapy or with clarithromycin where susceptibility is known, have demonstrated higher and more consistent eradication rates in randomized trials and meta-analyses, including in some regions with elevated clarithromycin resistance, and are increasingly incorporated into guideline algorithms[28]. For patients with prior treatment failure, guidelines now strongly recommend susceptibility testing, either by culture or validated molecular assays, to guide rescue therapy, and reserve rifabutin-based regimens and novel combinations for carefully selected refractory cases[29]. Collectively, these changes underscore a shift from empiric, one-size-fits-all regimens toward tailored approaches that integrate local resistance epidemiology, rapid diagnostics, and optimized acid suppression to preserve eradication efficacy and limit further selection of resistant strains.

AMR in Children

The epidemiology and clinical management of *H. pylori* infection in pediatric populations present unique challenges, as infection is often acquired in childhood and AMR patterns in children both reflect and diverge from adult trends[30]. Systematic reviews and large pooled analyses published in recent years document substantial regional heterogeneity in pediatric resistance: clarithromycin and metronidazole resistance rates frequently exceed 30-40% in East Asia and other high-burden regions, while levofloxacin resistance is generally lower in children than in adults but is nevertheless non-negligible and increases following prior antibiotic exposure[31]. The high prevalence of dual and multi-drug resistance in some pediatric cohorts substantially reduces the likelihood of success with traditional pediatric regimens and complicates efforts to eradicate infection early in life to prevent long-term sequelae. Figure 2 illustrates the prevalence of *H. pylori* antibiotic resistance in pediatric populations.

Therapeutic decision-making in children is constrained by a narrower repertoire of approved antibiotic agents, concerns regarding adverse events and growth impacts, and ethical limitations on invasive diagnostic testing[31,32]. Unlike in adults, where empiric use of bismuth quadruple therapy or vonoprazan-amoxicillin regimens may be acceptable based on local resistance data, pediatric clinicians must weigh the benefits of eradication against potential harms of broader

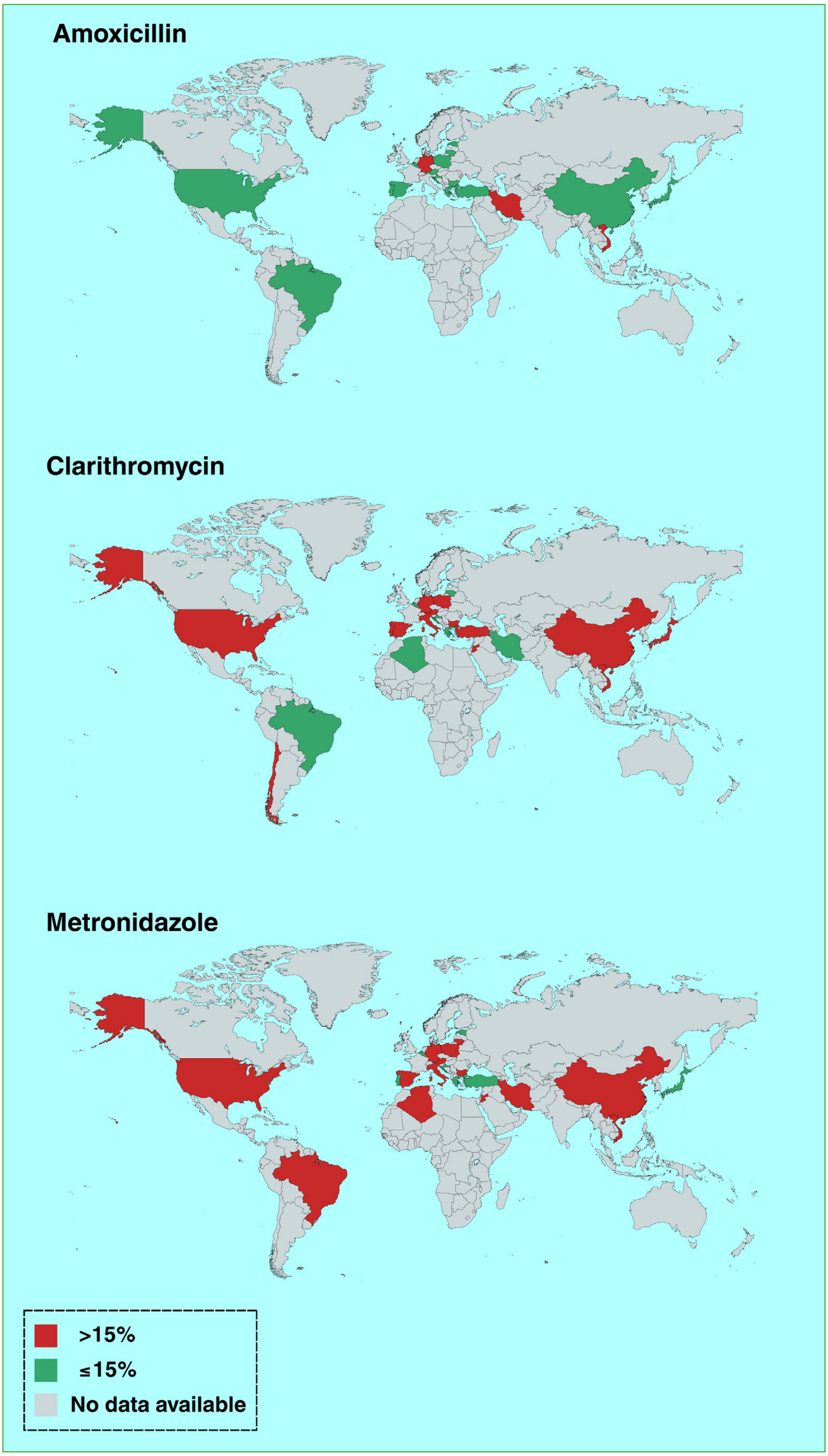

Figure 2. Pooled prevalence of antibiotic resistance to amoxicillin, metronidazole, and clarithromycin in pediatric *H. pylori* populations. Values reflect regional data from systematic reviews and large cohort studies.

antibiotic exposure and the limited pediatric safety data for newer agents[33]. Moreover, molecular susceptibility testing is less frequently available in routine pediatric practice, and obtaining gastric biopsy specimens for culture entails anesthesia and invasive endoscopy, which may not be justified for all clinical scenarios[31]. These factors have contributed to variability in guideline recommendations for children and to underuse of susceptibility-guided strategies in many settings.

Given these constraints, there is an urgent need for pediatric-focused surveillance networks and consensus treatment algorithms that reflect regional resistance patterns, age-appropriate dosing and safety, and pragmatic approaches to diagnosis and follow-up[34]. Noninvasive molecular tests that detect resistance-conferring mutations from stool or gastric juice and validated pediatric formulations of effective regimens would facilitate individualized therapy while minimizing unnecessary exposure[35]. In parallel, stewardship efforts that limit community macrolide and metronidazole overuse, frequent drivers of pediatric resistance, are essential[36]. Advancing coordinated surveillance, improving access to rapid, noninvasive susceptibility testing, and developing evidence-based pediatric treatment algorithms are therefore critical priorities to ensure that childhood infection is effectively and safely managed without exacerbating the global burden of AMR.

Strategies to Overcome Resistance

Efforts to overcome AMR in *H. pylori* increasingly focus on personalized therapeutic strategies, novel pharmacologic regimens, and adjunctive approaches that enhance eradication efficacy while preserving antibiotic stewardship[37]. Tailored therapy guided by susceptibility testing, whether by traditional culture or rapid molecular assays, consistently demonstrates higher eradication rates than empiric regimens in regions with high resistance prevalence[38]. The advent of Polymerase Chain Reaction (PCR)–based stool assays and next-generation sequencing (NGS) has facilitated noninvasive detection of clarithromycin and levofloxacin resistance mutations, thereby allowing individualized regimens without the need for invasive sampling[36]. Despite challenges in cost and accessibility, these approaches are poised to become the cornerstone of precision *H. pylori* therapy. Table 2 summarizes strategies to overcome *H. pylori* AMR.

New pharmacological regimens have also shown promise. High-dose dual therapy consisting of a potent acid inhibitor (PPI or vonoprazan) combined with amoxicillin has achieved eradication rates comparable to quadruple regimens in several randomized controlled trials[39]. Bismuth-containing quadruple therapy remains highly effective, particularly in areas with dual or multidrug resistance, and is recommended as a first-line option in many updated guidelines. Vonoprazan-based regimens, including triple and dual therapies, have consistently outperformed standard PPI regimens in clinical trials, especially in clarithromycin-resistant populations, due to more potent and sustained acid suppression that enhances antibiotic activity[40].

Adjunctive measures may further mitigate resistance-driven failures. Probiotics have been evaluated as adjuvants to therapy, with meta-analyses indicating modest improvements in eradication and reductions in treatment-related side effects[41]. Experimental strategies, including antimicrobial peptides and bacteriophage therapy, are under early investigation, offering the prospect of non-traditional therapeutics with reduced potential for cross-resistance[42].

Antimicrobial stewardship remains a fundamental pillar of resistance mitigation. Rational prescribing that limits unnecessary use of macrolides, fluoroquinolones, and metronidazole in the community can reduce background resistance rates and preserve treatment efficacy[43]. Integrated stewardship programs, combined with surveillance and diagnostic testing, represent a sustainable strategy to protect the utility of available drugs. Ultimately, a combination of individualized therapy, novel regimens, adjunctive innovations, and stewardship initiatives is required to curb the escalating threat of resistance and restore consistent eradication outcomes.

CONCLUSIONS

The future management of *H. pylori* requires coordinated global action to address the accelerating challenge of AMR. Expansion of regional and international surveillance systems, with real-time monitoring of resistance patterns, will be essential to guide evidence-based empiric

TABLE 2. STRATEGIES TO OVERCOME *HELICOBACTER PYLORI* ANTIMICROBIAL RESISTANCE.

Strategy	**Examples and evidence**	**Clinical impact**
Tailored therapy	Culture-guided therapy; PCR-based stool tests for 23S rRNA and *gyrA* mutations; next-generation sequencing	Higher eradication rates compared to empiric regimens; reduced retreatment
New regimens	High-dose amoxicillin + vonoprazan dual therapy; bismuth quadruple therapy; vonoprazan-based triple therapy	Effective in regions with high clarithromycin and metronidazole resistance; superior acid suppression enhances efficacy
Adjunctive approaches	Probiotics, antimicrobial peptides, bacteriophage therapy	Improved eradication and reduced side effects; novel agents may bypass classical resistance pathways
Antimicrobial stewardship	Restricting unnecessary macrolide, fluoroquinolone, and metronidazole use	Slows emergence of resistance; preserves efficacy of available therapies

therapies and inform policy[19]. Incorporation of rapid molecular diagnostics, particularly non-invasive assays capable of detecting resistance mutations directly from stool or gastric fluid, offers the potential for widespread adoption of personalized, susceptibility-guided treatment in routine practice.

Advances in precision medicine are expected to further refine eradication strategies, combining host, bacterial, and pharmacogenomic data to tailor therapy. Beyond antibiotics, novel approaches such as therapeutic vaccines, antimicrobial peptides, and microbiota-modulating interventions represent promising avenues to reduce reliance on traditional regimens[44].

Ultimately, the growing burden of *H. pylori* resistance cannot be contained by clinical innovation alone[45]. Stewardship policies, equitable access to diagnostics and effective regimens, and sustained international collaboration will be required to preserve the benefits of eradication in preventing gastric cancer and ulcer disease. A coordinated, multidisciplinary response is critical to ensure that effective eradication remains achievable in the coming decades.

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Authors’ Contribution

AS-N and AY contributed to the literature review, collected, extracted, and validated the data. AS-N worked on the first draft of the manuscript. MRZ edited the manuscript. AY contributed to conceptualization, methodology, project administration, study design, funding acquisition, and critically edited the manuscript. All authors approved the final version of the article.

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Conflicts of interest

The authors declare no conflicts of interest.

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