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REVIEW

Helicobacter pylori Eradication: Why Recurrence Risk Should Not Dictate Treatment Decisions

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Abstract: *Helicobacter pylori* infection is unequivocally associated with the development and progression of various digestive diseases. Clinical guidelines recommend eradication therapy for all eligible patients without contraindications. However, reports of high recurrence rates in earlier studies have raised concerns among clinicians and patients regarding the necessity of treatment, which has, to some extent, hindered the timely implementation of eradication strategies. This article provides a systematic review of the issue of *H. pylori* recurrence. A comprehensive analysis of literature retrieved from major databases such as PubMed, Web of Science, and Google Scholar, using keywords including "Helicobacter pylori", "recurrence", and "reinfection", indicates that the annual recurrence rate is significantly lower than previously thought, with modern epidemiological estimates ranging from 1.5% to 5.0%. The review further elucidates the underlying mechanisms of recurrence, identifies key modifiable risk factors, and highlights that optimizing eradication regimens and preventing intrafamilial transmission are central strategies for controlling recurrence. The conclusion emphasizes that concerns about recurrence should not preclude eradication therapy and offers a theoretical basis and practical directions for developing targeted prevention strategies in clinical practice.

Keywords: *Helicobacter pylori*, recurrence rate, reinfection, reactivation, risk factors

Introduction

Helicobacter pylori (*H. pylori*. HP) is the most prevalent Gram-negative pathogenic bacterium globally and continues to pose a significant public health threat.[1] Following infection, untreated *Helicobacter pylori* infection persists throughout the host's lifetime and rarely resolves spontaneously. Although most patients typically remain asymptomatic, persistent infection in certain individuals leads to chronic inflammation of the gastric mucosa, subsequently triggering chronic non-atrophic gastritis, atrophic gastritis, intestinal metaplasia, and dysplasia.[2,3] Extensive clinical and epidemiological evidence has firmly established its etiological role in a variety of gastrointestinal diseases, including chronic gastritis, peptic ulcers, gastric adenocarcinoma, and mucosa-associated lymphoid tissue (MALT) lymphoma.[4–6] Additionally, *H. pylori* infection has been linked to extragastric disorders (Figure 1), such as iron deficiency anemia, idiopathic thrombocytopenic purpura, and vitamin B12 deficiency.[3] Moreover, *H. pylori* infection has been shown to contribute to gastric cancer recurrence post-treatment through mechanisms such as autophagy.[7,8] Given its strong association with digestive diseases, key international consensus guidelines—such as the Maastricht VI/Florence Consensus, the Kyoto Global Consensus on *H. pylori* Gastritis, and the Fifth Chinese National Consensus on *H. pylori* management—recommend eradication therapy for all infected individuals, including asymptomatic carriers, unless contraindicated.[4,9,10]

Meanwhile, as global disease prevention and control systems improve, public awareness of *Helicobacter pylori* infection has significantly increased.[11–13] Concurrently, there has been a significant increase in the willingness to undergo proactive screening, along with a higher proportion of infected individuals opting for treatment.[14] Furthermore, clinicians have gradually reached a consensus on the necessity of implementing eradication therapy.[15] Although the global infection rate has been declining (with an average annual decrease of approximately 0.5%), the large infected population—estimated at about 4.4 billion worldwide—means that the demand for eradication therapy remains substantial.[16]

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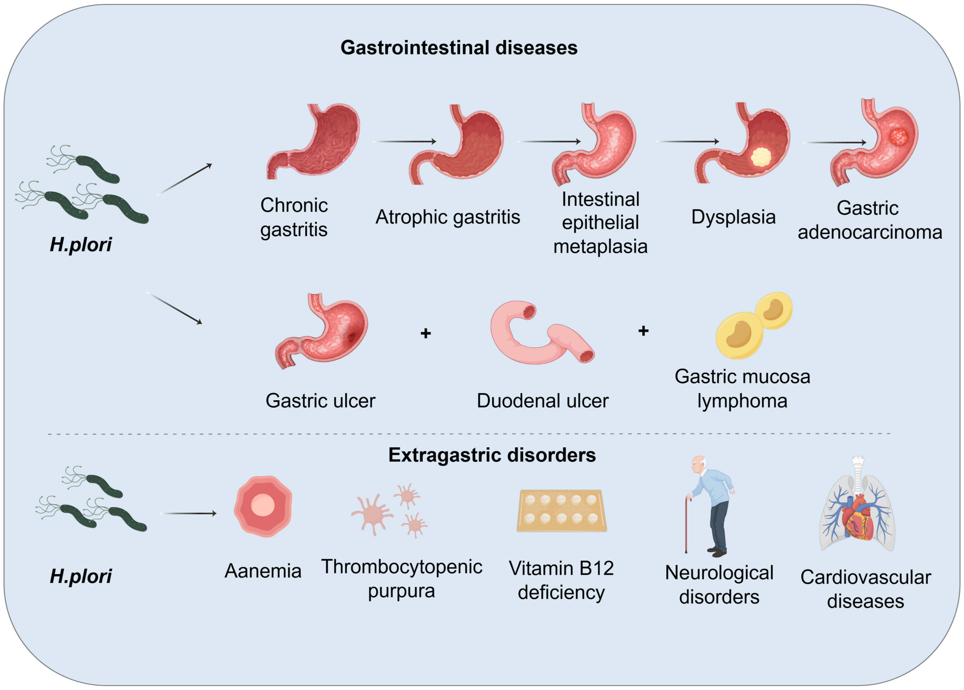

Figure 1 The pathogenic role of *Helicobacter pylori* in gastrointestinal diseases and extragastric disorders. Clinical and epidemiological evidence has clearly demonstrated its involvement in various gastrointestinal diseases, including chronic gastritis, peptic ulcers, gastric cancer, and mucosa-associated lymphoid tissue (MALT) lymphoma. Additionally, infection is associated with extragastric disorders such as iron deficiency anemia, idiopathic thrombocytopenic purpura, and vitamin B12 deficiency.

Nevertheless, some clinicians and patients continue to hesitate regarding *H. pylori* eradication therapy, often due to concerns over the high recurrence rates reported in prior studies. A 2020 nationwide multicenter survey conducted in China revealed that only 58.2% of gastroenterologists supported *H. pylori* screening, a stark contrast to the 84.2% support rate among non-gastroenterologists.[17] Further analysis revealed that 31.7% of physicians opposing screening cited concerns about high post-treatment recurrence rates as their primary reason. Their estimated recurrence rate (>5%) was considerably higher than the evidence-based clinical data (1–5%).[17–20] This misalignment in clinicians' perceptions may result in overly conservative treatment approaches, ultimately affecting patient outcomes.

Moreover, patients' concerns about recurrence following treatment can reduce their treatment adherence and potentially accelerate disease progression, for instance, in the multi-stage carcinogenesis process from chronic gastritis to atrophic gastritis, intestinal metaplasia, and ultimately to gastric cancer.[21] Additionally, another study has confirmed that *H. pylori* recurrence is closely linked to the recurrence of peptic ulcers and gastric lymphoma.[22] Once reinfection occurs, the previously alleviated ulcer and lymphoma conditions may also experience recurrence or further deterioration.[23,24]

Therefore, similar to antibiotic resistance, the recurrence of *Helicobacter pylori* remains a significant public health challenge in the management of its infection.[25] With the widespread application of eradication therapy, recurrence has become one of the key factors influencing overall treatment efficacy.[26] We aimed to conduct a systematic study of the recurrence rate of *Helicobacter pylori* and its associated risk factors can provide evidence-based guidance for clinical practice, help alleviate concerns about recurrence among both healthcare providers and patients, and further optimise treatment strategies, thereby holding significant clinical and public health value.

A systematic search was conducted across multiple electronic databases, including PubMed, Web of Science, and Google Scholar, with no restrictions on the publication date. The search employed the following keywords: "Helicobacter pylori" or "H. pylori" or "HP" and "recurrence" or "recrudescence" or "reinfection" or "recurrent" or "recurred" or "re-infect" *or* "relapse", to identify relevant original studies and reviews comprehensively. Subsequently, the source journals of the retrieved literature were systematically summarized.

Result

Definition and Classification of *Helicobacter pylori* Recurrence

HP infection recurrence refers to the situation where, after successful eradication with appropriate treatment, a patient tests positive for *Helicobacter pylori* after a certain period without antibiotics (at least one month) or acid suppressants/antacids (at least two weeks). Recurrence encompasses two distinct processes: reactivation and reinfection.[27,28] Reactivation specifically refers to the reactivation of the original bacterial strain that was not fully eradicated during the initial treatment.[29] In contrast, reinfection occurs when a patient is subsequently infected with genetically distinct strains following the complete eradication of the original bacterium (Figure 2).

Studies have shown that serological testing can indicate if an infection has recurred. After successful eradication, IgG antibody titers typically decline gradually over 12 to 18 months, with a sudden increase suggesting recurrence. This trend aligns with the results of invasive diagnostic methods, such as histological examination, rapid urease tests, or culture. Although a rapid rise in IgG antibody levels can serve as a serological marker for active infection recurrence, this method has certain limitations: first, continuous monitoring for up to 12 months is required to confirm eradication efficacy; second, it cannot distinguish between reactivation and reinfection. As a result, its clinical application remains limited.[30]

To accurately distinguish between reactivation and reinfection, genotyping methods can be used. Common genotyping methods include multi-locus sequence typing (MLST), pulsed-field gel electrophoresis (PFGE), random amplified polymorphic DNA (RAPD), amplified fragment length polymorphism (AFLP), and whole-genome sequencing (WGS).[31] For instance, multi-locus sequence typing (MLST) can analyse primary cultures from gastric antrum biopsy specimens, determining the genotype of each isolated colony by detecting polymorphisms in housekeeping genes such as hspA and glmM. This reliably distinguishes between reactivation and reinfection.[30,32] However, its clinical application is hindered by operational complexity, high costs, and stringent laboratory requirements, making it currently unsuitable for widespread clinical use. In clinical practice, recurrence is often classified using a time-based threshold for ease of operation: infections occurring within one year after eradication therapy are considered reactivation, while those after one year are classified as reinfections.[33,34] However, this time-based classification method does not always accurately reflect biological reality. For example, drug-resistant strains may remain active even after one year; conversely, reinfection may occur within a short period of time in populations at high risk of exposure.[32]

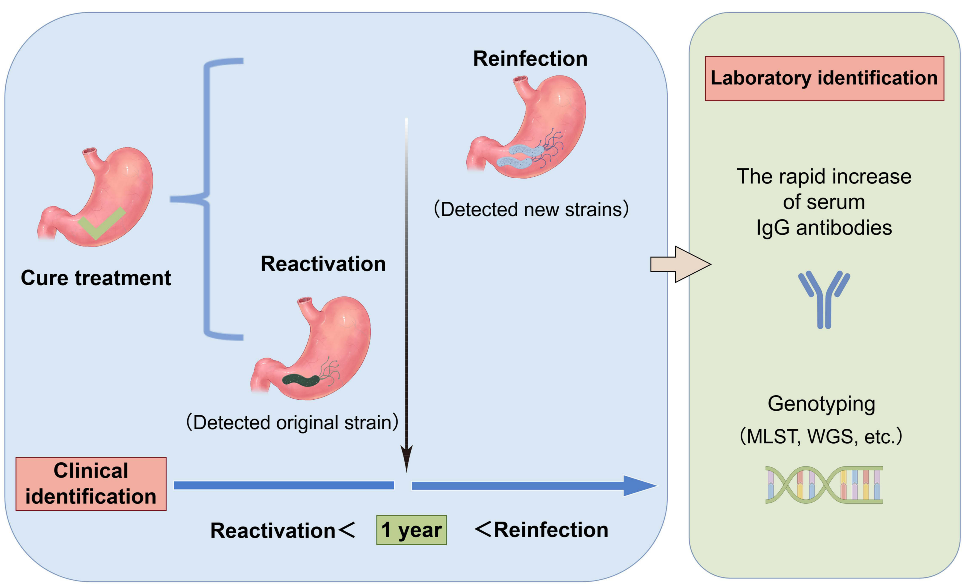

Figure 2 The distinction between reactivation and reinfection. *H. pylori* recurrence is categorised into two distinct types: reactivation (reactivation of the original strain) and reinfection (acquisition of a new strain). Genotyping serves as the gold standard for distinguishing between these mechanisms, whilst a rapid rise in serum IgG titres may also indicate recurrence; however, these methods prove difficult to implement widely. In clinical practice, a time-based criterion is commonly employed: recurrence within one year is typically classified as reactivation, whilst recurrence beyond one year is regarded as reinfection.

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Accurately distinguishing between reinfection and reactivation is clinically crucial. The incidence of reinfection is typically higher than that of reactivation, yet it is also more readily preventable Historically, most recurrence rate statistics have not distinguished between the two, leading to inflated overall recurrence rates in regions with high reinfection prevalence. This not only undermined confidence in eradication therapy but also obscured the fundamental differences in intervention strategies for each.[35,36] Reactivation primarily stems from incomplete bacterial eradication during initial treatment and can be prevented through optimised therapeutic regimens, improved patient compliance, and standardised clinical procedures. Preventing reinfection is comparatively more feasible, achievable through measures such as household-based simultaneous screening and treatment, promoting separate dining practices, and improving personal and environmental hygiene. These approaches effectively interrupt transmission routes and reduce reinfection risk.[32,37,38] However, only a few countries globally have reported data on *Helicobacter pylori* recurrence rates. Even in China, where the average annual reinfection rate of the bacterium is reported, studies that explicitly distinguish between reactivation and reinfection remain scarce.[18,39,40]

Current Status of Research on the Recurrence Rate of *Helicobacter pylori*

Global Recurrence Rate Overview

Global recurrence rates of *Helicobacter pylori* infection demonstrate substantial heterogeneity, closely linked to regional socioeconomic status. A meta-analysis (1988–2017) provides two key results: a pooled annual recurrence rate of 4.3%, and subgroup evidence from DNA fingerprinting studies showing recurrence is primarily driven by reinfection (3.1% per year) over reactivation (2.2% per year). Collectively, these rates have remained largely stable over the past 30 years.[41]

However, substantial variations exist between countries and regions.[42] A marked disparity is observed between developed and developing nations: annual recurrence rates in developed countries are approximately 3.4%, whereas they can reach as high as 8.7% in developing countries.[18] This disparity stems from differential composition of recurrence types: reactivation predominates in developed regions, whereas reinfection drives recurrence in developing areas, which is in line with the aforementioned mechanisms of reactivation and reinfection.[43]

Multiple studies further corroborate this trend. A 2023 report from South Korea indicates that the annual recurrence rate after eradication is 3.9%, and the annual re-infection rate is 3.7%.[26] Representing developing nations, Mexico's Fourth National Consensus still reported a recurrence rate as high as 18.8%.[44] Of particular note, China has witnessed positive changes in its recurrence rates in recent years. The latest meta-analysis indicates that its annual reinfection rate has decreased to 1.5%–3.1%, below the global average.[41] This shift may be closely linked to improvements in socio-economic conditions and sanitation over the past decades. However, given China's vast territory, significant regional disparities persist.[18]

The infection and reinfection of *H. pylori* in children and adolescents pose a significant public health challenge, with recurrence rates higher than those observed in adults. A meta-analysis focusing on the global pediatric population reported an overall *H. pylori* recurrence rate of 19% and an annual recurrence rate of 13% in this group. Stratified analysis further revealed notable disparities: the annual recurrence rate among Asian children (17%) far exceeded that in Europe (6%), and rates in developing countries (18%) were significantly higher than in developed nations (5%). Moreover, the overall recurrence risk was inversely correlated with the Human Development Index. Recurrence risk also demonstrated a distinct age gradient, with rates of 30%, 14%, and 8% in children aged ≤5 years, ≤10 years, and 11–18 years, respectively. Notably, the reinfection rate (10%) was substantially higher than the recrudescence rate (6%), indicating that the acquisition of new pathogens serves as the primary pathway for recurrence. Therefore, actively preventing initial infection and reinfection in children, particularly in high-risk younger age groups, represents a fundamental strategy for controlling recurrence at its source.[34]

The Current Status of *Helicobacter pylori* Recurrence

Over the past five years, statistical data on *Helicobacter pylori* recurrence rates have primarily been derived from several large-scale, multicentre studies conducted in China, whilst other countries have reported comparatively fewer recent relevant data (Table 1). The specific situation is as follows: A multi-center study conducted in Gansu Province of China

Table 1 The Current Status of *Helicobacter pylori* Recurrence

No.	Region	Year	Sample Size (n)	Population Characteristics	Recurrence Rate (%)	Follow-Up Duration	Detection Method	Reference
1	Gansu, China	2024	81754	Outpatient and physical examination population	3.86%	10 years	13C or 14C-UBT	[45]
2	Hainan, China	2024	975	Adults	3.5%	3 years	13C or 14C-UBT	[33]
3	Gansu, China	2024	1733	Combined cardiovascular diseases	1-year recurrence rate: 1.3% 3-year recurrence rate: 3.5%	21 months	14C-UBT	[47]
4	China	2020	5193	Adults	Annual reinfection rate 1.5%	6–84 months	Specific details are unknown	[18]
5	South Korea	2024	996	Adults	Reactivation rate 3.9%, reinfection rate 3.7%	5 years	13C	[26]
6	Baoding, China	2020	218	Children	18.8%	1 year	13C or 14C-UBT	[48]

Abbreviation: 13C or 14C UBT, Urea breath test.

in 2024 (n=81,754) revealed an annual reinfection rate of 3.86% in physical examination and outpatient populations, but with marked gender disparity (male: 2.82% vs female: 5.44%; $P<0.05$),[45] This finding contradicts a 2012 Korean study reporting higher male reinfection risk, suggesting that gender-associated susceptibility may be modulated by geographical and demographic factors.[26,46] An independent cohort study from coastal Southern China in 2024 further confirmed a 3.5% overall recurrence rate at 1-year post-eradication (n=975), demonstrating alignment with the aforementioned epidemiological trends.[33] A 2024 South Korean research study revealed that among 996 patients receiving standard triple therapy between 2017 and 2022, the reactivation rate stood at 3.9% (9/228), while the reinfection rate was 3.7%.[26]

A 21-month study published in 2024 revealed that among patients with concomitant cardiovascular disease in Gansu Province (sample size: 1733 cases), the cumulative recurrence rate one year after eradication of *Helicobacter pylori* was 1.3%, with a cumulative recurrence rate of 3.1% over three years.[47]

In a 2020 study conducted in Baoding, China, among 218 children who were successfully followed up (accounting for 94.8% of the original cohort), 41 cases (18.8%) experienced *Helicobacter pylori* infection recurrence. This recurrence rate in children was substantially higher than that observed in adults, aligning with international trends of increased susceptibility among pediatric populations.[48]

Factors Associated with Reactivation

Pathogen-Related Factors

Antibiotic resistance: In recent years, the issue of antibiotic resistance has continued to escalate, with a particularly marked increase in *Helicobacter pylori* strains resistant to clarithromycin and levofloxacin. This has become one of the key factors contributing to treatment failure and disease recurrence.[49] Resistant strains can survive during eradication therapy and subsequently proliferate, leading to reactivation, which severely compromises treatment efficacy and patient prognosis.[50] The mechanisms of its reactivation may primarily involve the following two pathways:

Firstly, the spherical transformation mechanism: Under environmental stressors such as antibiotic pressure, gastric pH fluctuations, or oxygen concentration changes, and host obesity, *Helicobacter pylori* transforms into environmentally resistant coccoid forms, entering a dormant state (Figure 3).[51,52] This morphological adaptation comprises two subtypes: Type A represents an irreversible terminal death state, while Type B maintains low metabolic activity, including sustained urease synthesis, protein expression, and virulence gene transcription.[53] It is worth noting that type B spherical

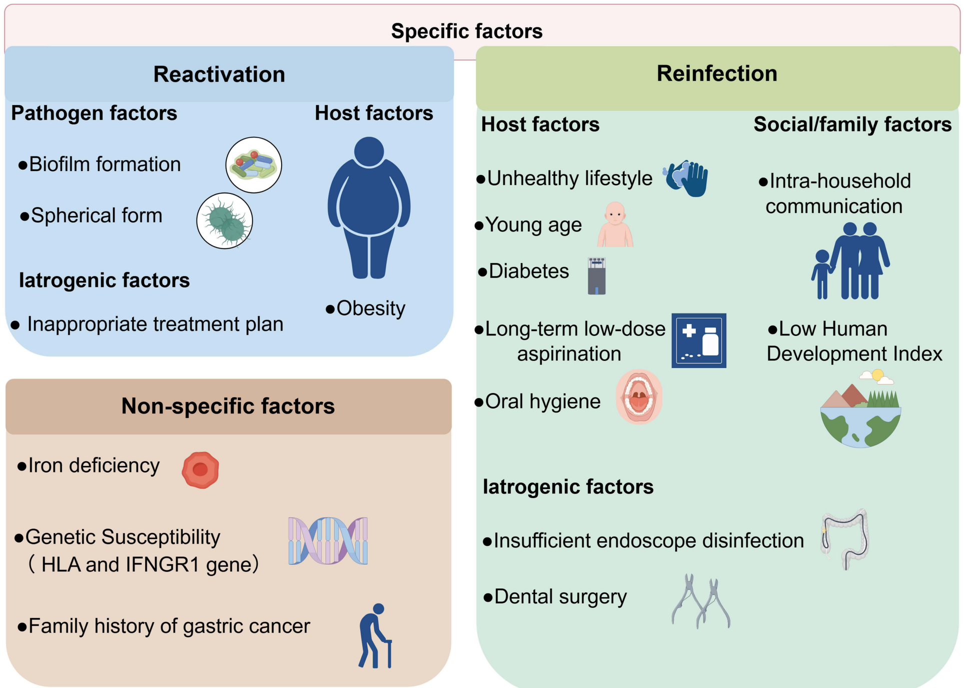

Figure 3 Factors associated with *Helicobacter pylori* reactivation and reinfection. Reactivation of infection is influenced by pathogen factors (biofilm formation and spherical form), host factors (obesity), and inappropriate treatment plans. Reinfection is associated with host factors (unhealthy lifestyle, diabetes, long-term low-dose aspirin use, poor oral hygiene), social factors (intra-household transmission and low Human Development Index), and iatrogenic factors (insufficient endoscope disinfection and dental procedures). Non-specific factors such as iron deficiency, genetic susceptibility (HLA-DQ and IFNGR1 polymorphisms), and a family history of gastric cancer complicate the distinction between reactivation and reinfection.

morphology can reversibly transform into spiral morphology when conditions improve, re-colonising the gastric mucosa and causing reactivation.[54]

Secondly, the biofilm formation mechanism: *Helicobacter pylori* secretes extracellular polymeric substances to form biofilms, whose physical barrier effect significantly compromises antibiotic penetration.[55] Clinical studies demonstrate that when standard triple therapy (amoxicillin + clarithromycin + omeprazole) is combined with the biofilm-disrupting agent N-acetylcysteine (NAC), eradication rates significantly improve ($P<0.05$).[56,57] Furthermore, in mouse experiments, the NAC pretreatment group showed a reduction of approximately 1 logarithmic unit in the *Helicobacter pylori* load (the number of colony-forming units per gram of gastric tissue) in the mice.[58] Biofilms promote recrudescence through dual pathological effects: (1): providing physical sanctuary for dormant bacterial subpopulations; (2): impeding antibiotic diffusion into microenvironments, ultimately leading to eradication failure and reactivation.[31,59]

Host-Related Factors

Obesity:Recent studies suggest a potential association between obesity and reactivation. A higher prevalence of coccoid-form has been observed in the gastric mucosa of obese individuals. The altered gastric microenvironment in obesity may promote the morphological of *H. pylori* transformation of into its coccoid form. This shift aligns with the previously described spherical transformation mechanism of the bacterium, potentially enhancing its survival capacity under adverse conditions and thereby increasing the risk of reactivation.[52,60,61]

Iatrogenic Factors

Inappropriate selection of treatment regimens constitutes one of the primary iatrogenic factors contributing to *Helicobacter pylori* recurrence. Failure to adopt highly effective regimens tailored to local resistance patterns—such as persisting with standard triple therapy in regions with high resistance rates, where recurrence rates typically exceed those of bismuth-containing quadruple therapy—or prescribing unreasonable treatment durations may result in incomplete bacterial eradication, subsequently leading to "reactivation after a period of time".[62,63] However, this perspective remains contentious. Some studies indicate no significant difference in long-term recurrence rates between different treatment regimens following successful eradication.[64] Such discrepancies may stem from variations in study design, follow-up duration, or definitions of recurrence.

Factors Associated with Reinfection

Host-Related Factors

Hygiene and Behavioural Habits

Poor hygiene and lifestyle habits significantly increase the risk of reinfection, such as sharing utensils or personal items with infected individuals.[33,65] Furthermore, inadequate intake of fruit and vegetables may lead to deficiencies in antioxidants like vitamin C.[66] Other factors considered to elevate reinfection risk include dining in environments with substandard sanitation, consuming untreated water, frequent eating out, irregular meal patterns, and regular consumption of preserved foods.[33]

Host Susceptibility

(1) Age: Age is a well-established non-modifiable factor associated with reinfection. Numerous studies have demonstrated significantly higher reinfection rates among children compared to adults. For example, children under 10 years of age may have a one-year reinfection rate as high as 20%, while this rate decreases to approximately 8% in those over 10 years old, suggesting that younger age is an independent risk factor for reinfection.[67] A 2020 study from Baoding, China, further supports this trend: among 218 successfully followed-up children (94.8% of the cohort), 41 (18.8%) experienced reinfection-substantially higher than rates typically reported in adults, and consistent with international pediatric data. The core reason may lie in children's immune systems not yet being fully matured, rendering them more susceptible to developing immune tolerance towards *Helicobacter pylori* and consequently exhibiting weaker bacterial clearance capabilities. This tolerance may prevent the establishment of effective immune memory during initial infection, thereby increasing the risk of reinfection.[68] Moreover, children are particularly susceptible to infection through household transmission.[28]

(2) Metabolic Disorders: Metabolic diseases, especially diabetes mellitus, are closely linked to reinfection. Diabetic patients are not only more susceptible to initial infection but also exhibit significantly higher reinfection rates. This may be attributed to delayed gastric emptying in diabetic individuals. Chronic hyperglycemia can trigger inflammatory responses and immune dysregulation, leading to peripheral neuropathy and gastrointestinal dysmotility, including gastroparesis, thereby compromising the gastric mucosal defense and facilitating bacterial re-colonization.[33,69]

(3) Long-term oral administration of low-dose aspirin: Low-dose aspirin is widely used clinically for the prevention of cardiovascular and cerebrovascular events, but its long-term use may cause damage to the gastrointestinal mucosa and increase the risk of bleeding. Research indicates that prolonged low-dose aspirin therapy correlates with an elevated three-year reinfection rate following *Helicobacter pylori* eradication, though it exerts no significant effect on the one-year r reinfection rate. This phenomenon may relate to the salicylate produced through aspirin hydrolysis in vivo, which alters gastric environmental factors (such as pH) thereby facilitating HP penetration through the mucus layer and enabling colonisation.[47]

(4) The oral microbiota constitutes a significant factor influencing *Helicobacter pylori* infection and reinfection. Research has confirmed that HP can colonise the oral cavity of infected individuals, representing a major risk factor for gastric infection and post-treatment reinfection.[70] Oral diseases such as periodontitis, gingivitis, and dental plaque can disrupt the oral microbiota.[71] HP-positive patients with concomitant periodontitis exhibit higher reinfection rates following eradication therapy compared to those without periodontal disease.[72,73] Furthermore, HP positivity is detectable in approximately 40–50% of dental plaque samples. Plaque not only provides a protective barrier for microorganisms, impeding the bactericidal effects of antibiotics, but may also serve as a reservoir for reinfection. Notably, HP within dental plaque proves exceptionally difficult to eradicate completely, further facilitating the persistent presence of *Helicobacter pylori* and reinfection.[19,74]

Social and Family Factors

Family Clustering

High-frequency close contact with infected persons (kissing/shared meals) and exposure to contaminated water/food facilitate pathogen transmission.[39,75] Household transmission is further established as a pivotal reinfection pathway, particularly in regions with suboptimal sanitation infrastructure where intrafamilial cross-infection prevails.[38,76] It is also the primary cause of high reinfection rates.

Human Development Index/Sanitation Conditions

Socioeconomic dimension: The Human Development Index (HDI), as a composite measure of life expectancy, educational attainment and per capita income, exhibits a significant inverse correlation with *Helicobacter pylori* reinfection rates.[18] Low income restricts access to healthcare, limited education diminishes health awareness, while poor living conditions degrade environmental quality. These factors interact synergistically to heighten reinfection risk.[19,77] Multiple studies further indicate that factors closely associated with low HDI—such as residence in midwestern China, lower educational attainment, and minority ethnicity—are independent risk factors for *Helicobacter pylori* reinfection.[18]

Healthcare-Related Factors

In addition, procedural factors in clinical settings may also contribute to reinfection through iatrogenic transmission. Inadequate cleaning or disinfection of endoscopic equipment has been identified as a potential route for transmission, leading to reinfection. Moreover, patients undergoing dental procedures or gastrointestinal endoscopy have been shown to exhibit significantly higher reinfection rates.[19] These findings underscore the importance of rigorous infection control measures in medical and dental practices to minimize the risk of healthcare-associated transmission.

Non-Specific Factors

Non-specific factors refer to those whose influence cannot be definitively attributed to either reactivation or reinfection, or which may impact both simultaneously.

Nutritional Status

Both iron deficiency (ID) and iron deficiency anaemia (IDA) are closely associated with *Helicobacter pylori* infection.[78] Iron plays a crucial role in the proliferation and oxidative metabolism of numerous tissues and cells.[79] Research indicates that low serum ferritin levels may constitute a risk factor for treatment resistance and recurrence following eradication therapy in children with HP infection. Furthermore, low haemoglobin and serum iron levels are also recognised as significant factors influencing the efficacy of eradication treatment in infected paediatric patients.[80]

Genetic Susceptibility

The human leukocyte antigen (HLA) system, particularly HLA class II molecules (including DP, DQ, and DR), plays a vital role in adaptive immune responses by presenting exogenous antigens to CD4+ T helper cells.[81] A case-control study in Egypt reported that 78.6% of patients with recurrent infection carried the HLA-DQ-rs3920AG genotype, which conferred a 9.8-fold increased risk of recurrence compared to other genotypes.[82] The report also indicates that HLA-II gene polymorphism influences the risk of host-specific recurrence.

Other studies have shown that children infected with *Helicobacter pylori* exhibit elevated levels of IFN-γ, an inflammatory cytokine that enhances the host's ability to clear the bacterium and provides a degree of protective effect.[83] The IFN-γ receptor gene, IFNGR1, is located on chromosome 6q23-q24 and comprises seven exons. Polymorphisms within this gene may increase the risk of gastric mucosal cell damage in *Helicobacter pylori*-infected patients and reduce the efficiency of cellular immune responses, thereby further elevating susceptibility to the bacterium.[84] Consequently, IFNGR1 gene polymorphisms are considered a potential risk factor for recurrent *Helicobacter pylori* infection in children.[48]

Family History and Gender

Patients with a family history of gastric cancer have a significantly increased risk of recurrence, possibly due to inherited susceptibility and shared environmental exposures.[18] In addition, some studies have suggested a gender-related difference in recurrence rates, though the underlying mechanisms remain unclear.[46]

Strategies for Preventing *Helicobacter pylori* Recurrence

Against the backdrop of widespread eradication therapy, persistently high infection rates are closely linked to recurrence issues. However, large-scale epidemiological investigations into *Helicobacter pylori* recurrence have been relatively limited in recent years, with recurrence rate data still largely relying on earlier statistical findings.[18,19] Previous studies failed to distinguish between "reactivation" and "reinfection", leading to an overestimation of recurrence risk. This has caused some clinicians and patients to harbour excessive concerns about post-eradication recurrence, even favouring conservative treatment strategies. In reality, most factors associated with reinfection can be effectively prevented through intervention, while reactivation can be significantly reduced by optimising treatment regimens. Specific measures are outlined below:

(1) Preventing reactivation: optimising initial eradication to reduce the risk of recurrence: Achieving successful eradication during the initial treatment phase is paramount, as studies indicate that higher eradication rates correspondingly lower the risk of reactivation.[85] Therefore, it is essential to enhance systematic training for non-specialist physicians and primary care practitioners, promoting standardised diagnostic and treatment protocols to comprehensively improve eradication success rates. In clinical practice, clinicians should formulate individualised treatment plans based on regional antibiotic resistance patterns and patient characteristics.[86,87] Comprehensive assessment must incorporate multiple factors including familial gastric cancer history, *Helicobacter pylori* infection status among household members, relevant diagnostic findings, prior eradication regimens, treatment duration, proton pump inhibitor type, and antibiotic combinations. Based on this, for regions with the necessary conditions, it is recommended to further improve the Hp culture and drug sensitivity tests of the patients' gastric mucosa, and accordingly provide the most optimal antibiotic combination regimen.[88,89] This holistic evaluation enables the development of highly effective, personalised eradication strategies.

(2) Preventing reinfection: reinfection predominantly occurs via oral-oral, faecal-oral, or contaminated water sources, being particularly prevalent in regions with high infection rates.[38] To effectively prevent reinfection, public awareness campaigns on personal hygiene should be intensified to enhance preventive measures. At the public health level, improvements in basic sanitation facilities, safeguarding drinking water and food safety, alongside systematic health education initiatives, are essential to significantly reduce exposure and reinfection risks. In clinical practice, strict adherence to disinfection protocols for medical instruments such as endoscopes is paramount in preventing nosocomial transmission.[19] Furthermore, given the potential for the oral cavity to serve as a reservoir for *Helicobacter pylori*, long-term management strategies should incorporate oral hygiene promotion measures to reduce the likelihood of gastric reinfection.[90]

(3) Identifying high-risk individuals and developing targeted follow-up strategies: Although certain factors associated with reinfection (such as genetic susceptibility and metabolic disorders) are difficult to intervene upon, they remain valuable in risk stratification. For instance, children, diabetic patients, individuals with cardiovascular disease, obese persons, those with a family history of gastric cancer, or carriers of high-risk HLA genotypes should be incorporated into personalised follow-up management plans following eradication therapy. Such plans may encompass more frequent monitoring, enhanced patient education, and initiation of retreatment strategies when necessary, thereby effectively reducing the long-term risk of reinfection.

(4) Research indicates that patients receiving probiotic supplementation during and following quadruple therapy exhibit a significantly reduced "reactivation rate of *Helicobacter pylori* infection within 12 months".[91] The mechanism may lie in probiotics' ability to restore gut microbiota balance and prevent the re-colonisation of pathogenic bacteria.[92,93] In particular, Lactobacillus and Bifidobacterium strains inhibit the adhesion of *Helicobacter pylori*, mitigate inflammatory responses, and promote gastric mucosal repair.[94]

Conclusion and Future Prospects

The recurrence of *Helicobacter pylori* infection is a key issue faced by both patients and physicians in clinical decision-making, and is often misunderstood as an unavoidable outcome. In reality, recurrence, including reactivation and reinfection results from a combination of factors, including bacterial survival strategies (such as coccoid transformation and biofilm formation), host-specific characteristics (such as age, genetic predisposition, and metabolic comorbidities), and environmental exposures. Although certain factors—such as age, genetic background, and coccoid conversion—are non-modifiable, recurrence can still be effectively prevented through targeted interventions addressing modifiable determinants and by optimizing treatment strategies.

This review is subject to several inherent limitations. The comprehensive analysis may be constrained by the potential omission of the most recent high-quality epidemiological data and the inclusion of some outdated references on molecular mechanisms. Furthermore, the field at large is challenged by the relative scarcity of robust epidemiological studies on recurrence and a relatively limited number of mechanistic investigations at the molecular level, which together may constrain the breadth of the discussion.

Future research should therefore advance along two key directions. First, molecular investigations are needed to elucidate the underlying biological mechanisms of recurrence and to develop rapid diagnostic tools capable of distinguishing between recrudescence and reinfection. Second, well-designed prospective cohort studies are essential to construct more accurate recurrence prediction models, thereby supporting individualized treatment decisions and follow-up strategies in clinical practice. For clinicians, optimizing initial eradication regimens and reducing antibiotic resistance through rational prescribing are fundamental steps. As a key actionable measure, hospitals are encouraged to develop the capacity for routine *H. pylori* susceptibility testing where feasible, enabling clinicians to select the most effective, tailored antibiotic therapy based on the results. For patients, it is critical to understand that recurrence does not negate the value of treatment.

In conclusion, concerns regarding recurrence should not preclude patients from receiving indicated eradication therapy. A more constructive approach involves scientifically evaluating the distinct risk factors for recrudescence and reinfection to implement targeted preventive strategies. Through such tailored measures, recurrence risk can be substantially reduced at its source. When managed with evidence-based eradication and follow-up protocols, infection need not be feared for its potential to recur. Standardized treatment remains essential to reduce long-term gastrointestinal disease burden, and apprehension about recurrence should not deter clinicians or patients from pursuing this effective intervention.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have declared that no conflict of interest exists.

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