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Review Article

Prevention and Screening of Gastric Cancer by *Helicobacter pylori* Management: Synthesis of Existing Data

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Abstract

Gastric cancer (GC) is a preventable disease, and *Helicobacter pylori* infection is the most important controllable risk factor. Despite numerous studies confirming that eradicating *H. pylori* can reduce the risk of GC, there remains a significant gap between the fundamental and clinical knowledge and public health interventions. This article provides a review of the progress made in the last decade by gastroenterologists in understanding the carcinogenic effects of *H. pylori*. The authors also summarize the evidence demonstrating the beneficial effects of eradication of *H. pylori* on gastric precancerous lesions and GC, and outline current strategies for *H. pylori* management. Notably, a family-based approach to *H. pylori* management represents a novel strategy for future GC prevention and control, boasting numerous advantages and having the potential to play a crucial role in future policymaking.

Introduction

Gastric cancer (GC) is a major cause of cancer-related deaths worldwide. According to global cancer statistics,[1] 1,089,103 new cases of GC and 768,793 related deaths occurred in 2020, ranking fifth and third for cancer incidence and mortality, respectively. In China, GC causes a leading burden of 0.40 to 0.47 million deaths per year.[2,3] Over the last few decades, several key risk factors for the development of GC have been identified, including tobacco use, high salt intake, older age, and a family history of GC. Among these factors, *Helicobacter pylori* infection has been identified as the most important preventable and controllable risk factor owing to the nature of this highly virulent bacterium being able to be detected and treated, as emphasized in multiple international consensus reports.[4–6] In fact, China has a high prevalence of both *H. pylori* infection and GC. More than 40% (478,508 of 1,089,103) of GC cases worldwide were identified in China, which is alarmingly high given that China accounts for only 25% of the world's population. The fact that the *H. pylori* infection rate is 44% in the general Chinese population further confirms this trend. The high concordance of *H. pylori*-prevalent areas having high cancer incidence provides significant potential benefits and valuable opportunities to implement national GC prevention and control initiatives.

Although there exists substantial, high-quality research elaborating the effect and affordability of different GC prevention approaches, few systematic reviews have been performed to synthesize trial results and provide definite conclusions based on dynamic epidemiological changes in China. In this article, we aim to synthesize the latest evidence on the rationale of *H. pylori* management, the effect of various *H. pylori* management, and various established *H. pylori* management approaches. We hope our results will help focus future research directions and inform policymaking on GC prevention in China, as well as in other countries carrying a high cancer burden in the foreseeable future.

Rationale of *H. pylori* eradication for GC prevention

The relationship between *H. pylori* and stomach-related diseases has been a focus of gastroenterologists since its discovery by Barry J Marshall and J. Robin Warren in 1983.[7] The Correa cascade, a stepwise progression from atrophy to metaplasia, dysplasia, and ultimately gastric adenocarcinoma initiated by *H. pylori* infection, provides a useful framework for understanding the carcinogenic mechanisms involved.[8] In fact, most clinical investigations into the relationship between *H. pylori* and GC can be divided into three main topics (Fig. 1): (1) examining the correlation between *H. pylori* infection and GC, (2) assessing whether eradication of *H. pylori* can prevent the development of GC, and (3) determining the feasibility of eradicating *H. pylori* on a population scale as a preventive measure against GC.

Keywords: *Helicobacter pylori*; Gastric cancer; Prevention.

Abbreviations: ^{13}C-UBT, ^{13}C-urea breath test; AST, antibiotic sensitivity tests; GC, gastric cancer; GI, gastrointestinal; HpSA, *Helicobacter pylori* stool antigen; HR, hazard ratio; IM, intestinal metaplasia; P-CAB, potassium-competitive acid blockers; PPI, proton pump inhibitor; RCT, randomized controlled trial.

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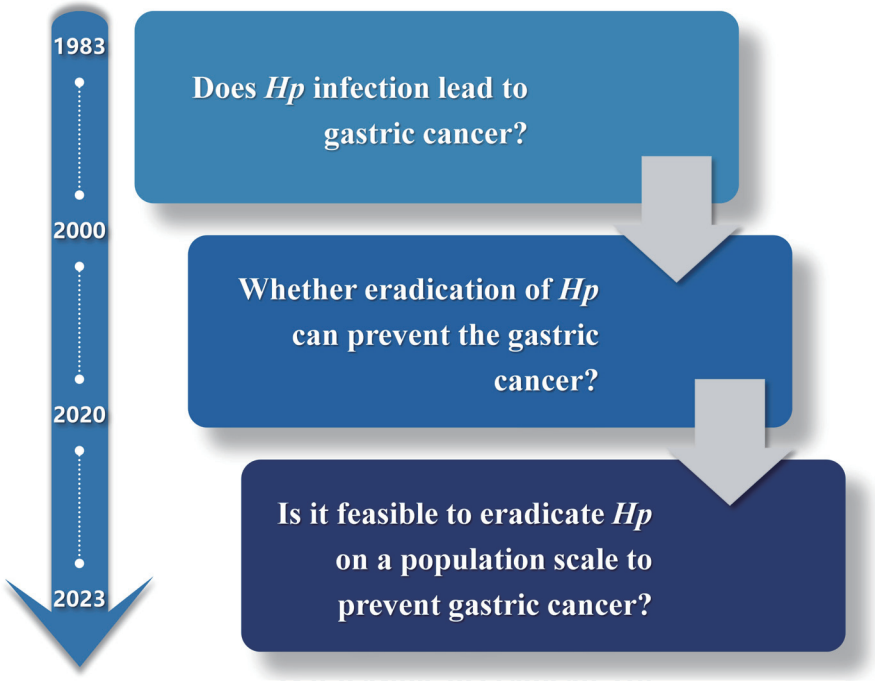

Fig. 1. Main topics of investigations of the relationship between *Helicobacter pylori infection* and gastric cancer. *Hp, Helicobacter pylori.*

Does H. pylori infection lead to GC (correlation between H. pylori infection and GC)?

During the period from the 1980s to the 2000s, numerous studies have directly or indirectly indicated a causal relationship between *H. pylori* infection and GC. For instance, in animal model trials in 1998, Watanabe[9] reported that 37% of Mongolian gerbils orally inoculated with *H. pylori* developed GC within 62 weeks. Epidemiological studies[10] conducted in 1991 also suggested that infection with *H. pylori* was associated with a 3.6-fold increased risk of GC, marking an important milestone in the understanding of *H. pylori*. Currently, it is recognized that up to 89% of noncardia gastric cancer cases can be attributed to chronic *H. pylori* infection,[11] while *H. pylori*-negative GC accounts for only 0.4–2.3% of cases.[12] This valuable recognition is intricately connected with relevant studies conducted during the late 20th century.

Could H. pylori eradication counteract the progression of precancerous lesions and block the development of GC?

In the 21st century, as consensus was reached regarding the carcinogenic potential of *H. pylori*, academic attention of medical specialists has gradually shifted to the effectiveness of *H. pylori* eradication on GC prevention, both for clinical utility and public health considerations. A number of high-quality randomized controlled trials (RCTs) were initiated in China (Yantai,[13] Shandong,[14] Fujian,[15] Taiwan[16]), and Korea,[17] and after years of follow-up, most of the findings were published between 2010 and 2020. As research deepened, understanding of the benefits of *H. pylori* eradication can be broadly divided into two stages.

Firstly, *H. pylori* treatment can block the progression of precancerous disease along the stepwise inflammatory pathway. A randomized double-blind, placebo-controlled trial[13] in China with 435 farmers infected with *H. pylori*, randomized to either therapy or placebo groups, demonstrated that treatment of *H. pylori* is protective against premalignant gastric lesions progression over a median of 10 years of follow-up. Gastric precancerous disease can also be reversed to lower-level lesions or even normal mucosa, as shown by a mass *H. pylori* chemoprevention program on Taiwan Matsu Island.[18] In this community-based study, the prevalence of gastric atrophy in 1,762 residents declined from 59.9% in 2004 (immediately before eradication) to 13.7% in 2008 (4 years after intervention), yielding an effectiveness of 77.2% in reversing gastric atrophy. Prior to 2017, the generally accepted point-of-no-return theory stated that by *H. pylori* eradication, the histological severity of intestinal metaplasia (IM) or dysplasia could not be reduced, nor the progression toward GC be halted or reversed, with this view adopted by the Maastricht consensus.[4] However, studies with longer follow-up periods have demonstrated significant regression in IM. Extending the follow-up period from 4 to 14 years for the previously mentioned mass eradication study in Matsu Island[16] revealed a decrease in the prevalence rates of both early and advanced-stage IM from 31.7 to 21.4% and from 11.8 to 1.8%, respectively. A subsequent meta-analysis[19] supported this conclusion, which has now been accepted in the guideline of latest version.[20] The development of GC involves a complex and protracted evolution over several years. Although studies with longer follow-up periods are more challenging to conduct due to financial and medical limitations, they typically yield more objective and robust conclusions, providing a more comprehensive understanding of disease progression and treatment efficacy.

Secondly, eradication of *H. pylori* has been shown to reduce the incidence of GC. In recent years, several high-quality meta-analyses have assessed the benefits of *H. pylori* eradication in preventing GC (Table 1).[21–27] These studies, with low heterogeneity, consistently demonstrate *H. pylori* eradication has a strong preventive effect on GC, with relative risks ranging from 0.46 to 0.66 for both primary and metachronous cancer. Ford's conclusion,[21] although limited to three trials, further indicates that *H. pylori* eradication not only reduces the incidence of GC, but also leads to a decrease in

Table 1. High-quality meta-analysis evaluating the association between *Helicobacter pylori* eradication and GC development

First author, year	Country	Database (timespan)	Sample size	Study inclusion	Enrolled targets	GC incidence			GC mortality		
						Effect	RR	Heterogeneity	Effect	RR	Heterogeneity
Ford AC, 2014[24]	UK	Medline (1946–2013); Embase (1947–2013); Cochrane central register	6,497	6 RCTs	Healthy asymptomatic infected Asian adults	1.6% vs. 2.4%	0.66	I^2 = 0%		NA	
Ford AC(a), 2020[21]	UK	MEDLINE (1947 to February 2020); Embase and Embase Classic (1947 to February 2020); Cochrane central register	8,323	7 RCTs	Healthy asymptomatic infected adults	1.6% vs. 3.0%	0.54	I^2 = 0%	1.14% vs. 1.87%	0.61	I^2 = 0%
Ford AC(b), 2020[21]	UK	Same as above	1,841	3 RCTs	Individuals after GC resection	4.5% vs. 9.3%	0.49	I^2 = 0%	NA		
Chen HN, 2016[22]	China	MEDLINE, EMBASE, Cochrane Library (up to March 2014)	7,955	8 RCTs	Individuals with normal mucosa or precancerous lesions	1.9% vs. 2.9%	0.64 (< IM RR = 0.25); (≥ IM RR = NS)	I^2 = 0%			
Sugano K, 2019[23]	Japan	MEDLINE and Ichushi-Web (up to December 2016)	31,106	32 (RCTs and cohort studies)	Individuals with normal mucosa, precancerous lesions, peptic ulcer, or GC undergone resection	1.9% vs. 3.6%	0.46	I^2 = 15%			
Lee YC, 2016[25]	China (Taiwan)	PubMed, Cochrane Library, ClinicalTrials.gov (up to May 2015)	48,064	24 (8 RCTs and 16 cohort studies)	Individuals with normal mucosa or after GC resection	1.2% vs. 1.7%	0.54	I^2 = 0%			
Doorakkers E, 2016[26]	Sweden	PubMed, Web of Science, Embase, and Cochrane Library (up to November 2015)	31,544	9 (1 RCT and 8 cohort studies)	General population	0.9% vs. 1.1%	0.46	I^2 = 32.3%			
Duan F, 2019[27]	China	MEDLINE, PubMed, EMBASE, the Cochrane Library, China National Knowledge Infrastructure, and Wanfang (January 1997 to January 2017)	40,740	13 (4 RCTs and 9 cohort studies)	Individuals with normal mucosa or precancerous lesions	0.13% vs. 0.14%	0.52	I^2 = 0%			

GC, gastric cancer; NA, not available; NS, not significant; RCT, randomized controlled trial; RR, risk ratio.

disease-specific mortality. This finding highlights the importance of *H. pylori* treatment as a preventive measure and suggests directions for future investigations. In this section, the argument regarding the "point of unstoppable" persists, as demonstrated by Chen *et al*.[22] that eradication of *H. pylori* in lesions have progressed to IM does not significantly reduce the incidence of GC. However, Sugano study[23] found the benefit of eradication was strongly correlated with time to eradication, and the reduction in incidence after eradication was significantly greater ($p = 0.01$) in groups with long-term (> 5 years) follow-up (odds ratio of 0.32) compared with those with shorter follow-up (< 5 years). Hence, confirming the potential benefit of H. pylori eradication for preventing GC in IM patients is still required. It is important to note that most of the studies included in the current meta-analyses were conducted in East Asia. Given the variability of GC heterogeneity by ethnicity in multi-ethnic societies, caution should be exercised when extrapolating above conclusions in other populations without sufficient evidence.

Is it feasible to eradicate H. pylori on a population scale to prevent GC?

Clarifying the effectiveness of *H. pylori* eradication in preventing GC serves as a strong basis to support population-wide strategies as policy recommendations. The Taipei Consensus[28] published in 2020 discussed the feasibility of population-based screening, marking the gradual emergence of population-based screening as a mainstream issue for policy makers. However, a variety of factors must be considered when initiating a universal *H. pylori* screening program.

Target countries or areas

Mass screening for *H. pylori* infection should prioritize countries or regions with a high burden of both *H. pylori* infection and GC, since programs in highly *H. pylori*-infected regions could obtain higher screening efficiency and additional health benefits by identifying more *H. pylori*-infected participants with equal number of tests conducted. However, the carcinogenic effect of *H. pylori* infection does not show uniformity across global regions but is influenced by various factors, such as ethnicity and the type of infected strain. African and certain Asian countries, such as India, exhibit a high prevalence of *H. pylori* infection ranging from 63.5 to 87.7%,[29] surpassing the global average of 44.3%[30]; but their age-standardized GC incidence (4.5 per 100,000) is significantly lower than the world average of 11.10/100,000.[1] Population-wide eradication is only necessary and feasible in areas where *H. pylori* infection is clearly carcinogenic, that is, where both *H. pylori* infection and GC incidence are remaining in high levels. East Asia is known for its high incidence of GC; in particular, nearly 40% of GC cases seen globally occurred in China,[1] a typical country of both *H. pylori* and GC prevalence. A recent decision analysis synthesizing data from China's latest epidemiological surveys and trial results concluded that implementing a universal eradication program for *H. pylori* would be cost effective in reducing the cancer burden in the long term.[31] This program may serve as a reference for other countries or regions with similar epidemiological conditions. Recently, an effect of *H. pylori* eradication on the incidence of noncardia gastric adenocarcinoma was observed in a large diverse population in the USA.[32] In 716,567 individuals with a history of *H pylori* testing and/or treatment, the adjusted subdistribution hazard ratios (HRs) and 95% confidence intervals (CIs) of GC for *H pylori*-positive/untreated and treated individuals were 6.07 (4.20–8.76) and 2.68 (1.86–3.86), respectively, compared with *H pylori*-negative individuals.

Target populations

Different demographic characteristics of the target population can result in varying levels of benefit. Health economics evaluations[33,34] have consistently shown that *H. pylori* screening at a younger age (20–40 years) is more cost-effective owing to the higher efficacy of GC prevention. This can be attributed to the degree of mucosal damage at the time of intervention. *H. pylori* infection primarily occurs during childhood and adolescence and tends to persist in the absence of external intervention. Therefore, the age of the patient is considered an indicative factor of the duration of the infection and the extent and severity of the damage to the gastric mucosa. In 2016, a meta-analysis[22] consisting of 7,955 subjects concluded that after *H. pylori* eradication therapy, the relative risk of GC decreased by 12% in 2,115 participants with IM at baseline compared to controls, and by 75% in 1,337 participants without precancerous lesions or with only atrophy, indicating early eradication of *H. pylori* during the early stages of mucosal damage provides the greatest benefit. In other words, the earlier the eradication of *H. pylori*, the greater the benefit.

Although severe damage, such as advanced-stage IM and extensive dysplasia, is more commonly observed in older individuals, there are still significant benefits to performing *H. pylori* eradication in this population. A retrospective study conducted in Hong Kong, China, involving 73,237 patients who had undergone *H. pylori* eradication and were followed up for 7.6 years, revealed that the risk of GC was reduced by 18% among individuals over 60 years of age. Therefore, the eradication of *H. pylori* in elderly patients is to be encouraged.

Improving the eradication success rate

Effective control of GC relies on successful eradication of *H. pylori*. An RCT[15] conducted in Fujian, China in 2022 showed failure of first-line *H. pylori* therapy did not result in a statistically significant benefit in preventing GC over a 26.5-year follow-up period (HR = 0.46, $p = 0.289$) compared with those who achieved successful treatment (HR = 0.46, $p = 0.009$). Based on the experience gained from extensive screening initiatives,[17,35,36] the current success rate of eradicating *H. pylori* infection is limited, ranging from 70.1 to 78.2%, with considerable potential for further enhancement. Scientific and effective selection of first-line treatment regimens, along with timely adjustments based on regional variations, can significantly offset these deficiencies, and this is particularly crucial given the primary resistance rates to clarithromycin, metronidazole, and levofloxacin exceeding 15% in all regions.[37] As outlined in the VI consensus report,[20] the first-line algorithm for empirical *H. pylori* eradication in areas with low clarithromycin resistance includes bismuth quadruple therapy [proton pump inhibitor (PPI), bismuth, tetracycline, and metronidazole] and clarithromycin triple therapy (PPI, clarithromycin, and amoxicillin). In areas with high (> 15%) clarithromycin resistance, the recommended first-line treatments are bismuth quadruple therapy and nonbismuth quadruple therapy (PPI, clarithromycin, amoxicillin, and metronidazole). Triple therapy based on potassium-competitive acid blockers (also referred to as P-CAB) also demonstrated promising results in achieving high eradication rates among patients infected with clarithromycin-resistant strains.[38] Meanwhile, regular monitoring of treatment efficacy in at least a subset of the population is crucial for timely adjustment of the regimen before resistance compromises therapy effects, as empirical therapy failing to achieve a cure rate of at least 90% should be abandoned.[39]

The failed eradication of *H. pylori* has become a growing con-

cern because of the continuous increase in antibiotic resistance rates. The latest Chinese national guideline on *H. pylori*[40] recommends treatment based on the patient's history of antibiotic use in empirical treatment and the utilization of antibiotic sensitivity tests (ASTs) in individuals with a previous history of treatment failure. Data from China[41–43] suggests that personalized therapy guided by ASTs has a higher eradication rate compared with empirical treatment regimens, resulting in an average increase of 56–126 successful eradication cases per 1,000 patients. For refractory *H. pylori* infection (unsuccessful eradication after two consecutive standardized eradication treatments), the use of low-resistance antibiotics such as tetracycline and furazolidone yields better eradication outcomes.[40]

Compliance considerations

While symptomatic patients with *H. pylori* infection are more likely to undergo voluntary eradication, the majority of *H. pylori*-infected individuals from population screening programs are asymptomatic. This presents a significant challenge to the adherence of *H. pylori* management. For example, the implementation of a large-scale *H. pylori* screening program in Taiwan revealed that 20% of participants (3,764 of 18,821) did not respond to an invitation for a ^{13}C-urea breath test (^{13}C-UBT), and 17.31% of *H. pylori*-infected patients (5,493 of 6,643) refused the eradication therapy.[44] Another study demonstrated that 10% of patients prescribed *H. pylori* eradication regimen failed to take even 60% of their medications.[45] Consequently, ensuring compliance with screening and treatment protocols needs to be emphasized. (1) Compliance with *H. pylori* screening: Noninvasive screening tests, such as the ^{13}C-UBT, *Helicobacter pylori* stool antigen (HpSA) test, and serology testing, can help mitigate negative emotions and resistance to treatment. The ^{13}C-UBT is the most precise noninvasive screening method, but it necessitates fasting prior to testing and a 30 m wait between two expirations. Although serology tests are the most convenient, they are not able to differentiate between current and previous infections. The HpSA test is less commonly used for screening and is not well-received by the general population. Also, *H. pylori* infection status can be accurately assessed by magnetic controlled capsule endoscopy.[46] (2) Compliance with *H. pylori* therapy: The willingness to receive antibiotic therapy and the ability to adhere to the prescribed regimen are prerequisites for effective eradication. However, the incidence of short-term adverse events during treatment may discourage patients from receiving treatment, leading to lower levels of compliance.[47] The European Registry on *H. pylori* management conducted a prospective analysis of 22,492 patients who underwent eradication therapy and found that 23% of the patients experienced at least one adverse event during medication. The most common adverse reactions observed were taste disturbance (7%), diarrhea (7%), nausea (6%), and abdominal pain (3%).[48] Notably, the classic bismuth-based quadruple therapy regimen, which is widely used worldwide, was associated with a higher incidence of side effects of 37%. At the same time, long-term adverse events, such as antimicrobial resistance, constitute a potential concern for treated patients. (3) Compliance with follow-up retesting: In the context of increasing drug resistance, post-treatment retesting is becoming increasingly important. A negative test result would be considered as the official endpoint of treatment process. According to the fifth edition of the Chinese consensus on *H. pylori* eradication,[49] retesting should be performed 4–6 weeks after medication cessation to minimize the impact of residual drugs (such as PPIs, bismuth, and antibiotics) on test results.

Active promotion of knowledge about *H. pylori*, including its potential gastrointestinal (GI) and extra-GI harms, as well as the benefits of eradication therapy, could be an effective approach to improving compliance among the public.[50] Specific ways to conduct public education include strengthening publicity through mass media and providing health education at the community and individual level. Physicians-targeted education is also important, as study found significant proportion (more than 30%) of physicians may have incorrect knowledge or inappropriate use of eradication regimens and antibiotic combinations.[48] Ensuring patients receive the appropriate treatments would be a powerful tool in overcoming public skepticism.

Existing *H. pylori* management strategies

In 1997, gastroenterologists from the European Helicobacter Study Group suggested performing *H. pylori* testing in patients over 45 years old who have dyspeptic symptoms. This recommendation was later established as a "test and treat strategy" in the Maastricht III consensus (Table 2),[5,51,52,53,54] which was published in 2007. The strategy does not necessitate physicians to engage in community-based surveillance to identify infected patients. Instead, it relies on testing patients who present to the hospital with GI symptoms for *H. pylori* infection and is therefore categorized as a passive screening measure. Despite the recommendation for implementing the strategy in highly infected areas, it has a limited target audience and efficacy in meeting the needs for *H. pylori* eradication in highly infected countries, and is unable to provide a sufficiently powerful intervention for reducing population infection levels.

The 2012 Maastricht IV Consensus[5] proposed a screen and treat strategy (Table 2) to effectively address the aforementioned issues by expanding the screening audience from solely outpatients to the entire population of a given region. In contrast to the test and treat approach, which depends on patients seeking care at clinics, this strategy involves policymakers making deliberate efforts to search and detecting *H. pylori* carriers within the community, making it an active screening strategy. Population-based mass eradication programs for *H. pylori* have been implemented in various regions, including Japan,[55] mainland China,[35] and Taiwan,[16] using both invasive testing (endoscopy) and noninvasive methods (e.g., ^{13}C-UBT). For example, from 2004 to 2018, a large-scale *H. pylori* screening program was conducted in Ma Zu, resulting in a notable reduction in the *H. pylori* prevalence from 64.2% to 15.0% in the local population.[16] Furthermore, this program led to a significant decrease in the incidence and mortality of GC by 53% and 25%, respectively, providing compelling evidence to confirm the effectiveness of "screen and treat" strategy in cancer prevention.

China is a vast country with a population of more than 1.4 billion individuals and nearly 500 million households, as per the seventh National Census.[56] Achieving population-wide *H. pylori* eradication often requires years or decades and re-infection among the selected population would be inevitable during the lengthy process of screening implementation if the screen and treat strategy is directly applied in China. In addition, the significant regional variation of infection rates across the country combined with the uneven distribution of medical resources, further weakens the feasibility of this strategy.

In 2021, a group of Chinese scholars proposed a novel approach,[52] a family-based *H. pylori* management strategy (Table 2), to prevent and control *H. pylori* infection at the community level. It supplements the first two existing strategies and focuses on countries with

Table 2. Comparison of existing *Helicobacter pylori* management strategies

Strategy	Test and treat	Screen and treat (also called "search and screen" strategy)	Family-based control and management
Aims	GC prevention and dyspeptic symptom control	GC prevention	GC prevention and intrafamily spread interruption
Target populations	Uninvestigated dyspeptic patients with no alarm symptoms	Populations with a high incidence or high risk of GC. intermediate or high incidence of GC.	Cohabitants and family members of H. pylori-infected patients
Target areas	*H. pylori*-prevalent regions (>20%)	Incidence of GC higher than 15–20 per 100,000.	Both high and low prevalent regions
Type of strategy	Passive	Active	Either active or passive
Recurrence	Moderate	Moderate	Low
Eradication rates	>80%	>80%	>90%
Cancer prevention effect	Low to Moderate	High	Moderate to high
Cost	Low	High	Moderate
Benefit-cost ratio	Moderate to high	Moderate to high	High
Compliance	Moderate	Moderate	Potentially high (awaiting evidence)
H. pylori detection ability	Moderate	Moderate	Moderate (slightly higher)
Formal inception, year	Maastricht II[53] and III[51] Consensus Report, 2000–2006	Maastricht IV Consensus Report[5] and Kyoto global consensus report,[54] 2006–2015	Chinese Consensus Report on Family-Based *H. pylori* Infection,[52] 2022

H. pylori detection ability refers to the number of *H. pylori*-infected participants identified under conducting an equal number of tests. GC, gastric cancer; *H. pylori*, *Helicobacter pylori*.

high rates of GC and limited per capita resources. This approach is not designed to function autonomously from the previous two strategies, but rather serves to enhance their efficacy and applicability in real-world settings. The family strategy, integrated with the test and treat approach, encompasses screening, treatment, and follow-up care for family members after identifying an *H. pylori*-carrier during outpatient visit, with aims to enhance family engagement, awareness, and contain the probability of bacterial transmission within the household. When used in conjunction with the screen and treat approach, the family screening strategy entails modifying the basic *H. pylori* screening unit from individuals to the entire family, with all family members being screened before moving on to the next household. The primary difference between family-based screening and conventional strategies lies in the order of individual screening during the procedure, despite the ultimate objective being unchanged of testing the entire population.[57] The latest guideline from China provided feasible eradication treatment for completing the family screening strategy.[40] Also, compared with a genetic cause, *H. pylori* has a larger role in GC development.[58]

The advantages of family-based strategy (Table 2) are: (1) Applicability in both high and low infection areas. The phenomenon of *H. pylori* family clustering has been demonstrated in various regions worldwide,[58–61] indicating the universal suitability of the family-based strategy across regions and ethnicities. (2) Blocking intrafamily transmission. Eliminating the source of *H. pylori* infection in households can reduce the risk of children acquiring the bacterium and provide long-term benefits to newborns. A meta analysis[62] confirmed that *H. pylori* family management strategies have higher success rates in eradicating *H. pylori* infection and lower rates of recurrence compared with traditional individual-based approaches. (3) Higher patient compliance, as family management strategies are intrinsically linked to the health of household members and cohabitants, trial participants may exhibit greater enthusiasm and higher levels of compliance for undergoing screening. This may lead to a swifter implementation of the program. (4) Higher cost-effectiveness, according to a health economics analysis, family-based strategies were more cost-effective than screen-and-treat strategies, with a cost of $9.18 per quality-of-life year gained, as opposed to $12.08 for the latter.[63] (5) Better *H. pylori* detection, as the efficiency of screening would be enhanced by searching along the *H. pylori* intrafamilial transmission chain, compared with random selection. The family-based strategy has a potentially higher yield for detecting *H. pylori*-infected individuals, with approximately 4.02% more infections identified with equal numbers of tests conducted.[64]

Conclusions

GC is a preventable disease, and *H. pylori* infection is the most important controllable risk factor, serving as an essential step toward effective prevention and control of GC. Despite numerous studies confirming that eradicating *H. pylori* reduces the risk of GC, there remains a significant gap between fundamental and clinical knowledge and public health interventions. A family-based approach to *H. pylori* management represents a novel strategy for future GC prevention and control, boasting numerous advantages and having the potential to play a crucial role in future policy making. In addition, secondary screening measures for GC based on *H. pylori* represent a critical focus of attention (Table 3).[65–81] Both primary and secondary preventive strategies are crucial components of effective GC management. Much like the indispensable nature of both legs in bipedal locomotion, either strategy cannot be overlooked without compromising the overall efficacy of the treatment.

Table 3. Screening models or strategies for GC that includes indicators of *Helicobacter pylori* infection

Model	Country	Target population	Sample size	Indicators included in the model	Discrimination
Prediction models					
Ikeda F, 2016[65]	Japan	General Japanese population	2,446	PG, *H. pylori*	0.77
Taninaga J, 2019[66]		Healthy population	1,431	*H. pylori* serology testing and chronic atrophic gastritis, sex, age, and body mass index, white blood cell counts, neutrophil ratio, lymphocyte ratio, eosinophil ratio, monocyte ratio, basophil ratio, platelet count, hemoglobin, mean corpuscular volume, and hemoglobin A1c, gastric, or duodenal ulcers including scars, GERD, or Barrett's esophagus and postgastrectomy	0.736–0.874
Charvat H, 2016[67]	Japan	Japanese residents	19,028	Age, family GC history, smoking, salted food, PG, *H. pylori*	0.768
Murphy JD, 2022[68]	USA	Healthy individuals across Japan, China, and Korea	1,422	Sex, age, UreA, *Hp* 0305, *Hp* 1564, PGs	0.738
Ishikura N, 2021[69]	Japan	Participants of the Hospital Epidemiology Research Program	3,678	Age, ABCD classification defined by *H. pylori* and PGs, smoking, alcohol consumption, fruit and vegetable intake, and 3 GWAS-identified SNP polymorphisms	0.77–0.78
Song M, 2018[70]	USA	Finnish male smokers	21,895	PGI, *H. pylori*	NA
Lee TY, 2015[71]	China	Patients with Peptic Ulcer Disease from Taiwan	278,898	Age, sex, ulcer site, ulcer complication, *H. pylori* eradication, NSAIDs duration, surveillance endoscopy	0.78
Diagnostic models					
Tu, 2017[72]	China	Population from high GC mortality area	9,002	PGI, PGII, PGR, G-17, *H. pylori* IgG	0.803
Iida M, 2017[73]	Japan	General Japanese population	2,444	Age, sex, *H. pylori* and atrophic gastritis, Hemoglobin A1c, Current smoking	0.79
So JBY, 2021[74]	Singapore	Singapore Chinese population	682	miRNAs, Age, *H. pylori*, PG, CA199, CEA	0.849–0.890
Cai QC, 2019[75]	China	Chinese individuals with a 'high risk' of GC	14,929	Age, *H. pylori*, sex, pickled food, fried food, PG, G-17	0.73–0.76
Tao W, 2020[76]	China	Chinese individuals with precancerous lesions	383	Age, sex, tap water drinking, *H. pylori* infection, GC family history, PGs	
Park CH, 2016[77]	Japan	Consecutive Japanese patients	562	Age, sex, PGs, *H. pylori*	NA
Liu MM, 2018[78]	China	Patients with gastric diseases	620	34 variables including age, BMI, sex, *H. pylori* infection	0.62–0.74
Ji L, 2020[79]	China	General residents	7,773	Positive family history of GC in first-degree relatives, PG, *H. pylori*, age	NA
Lin JT, 1995[80]	China	Subjects underwent endoscopy from Taiwan	686	Peptic ulcer, PGI, *H. pylori*	0.84
Kaise M, 2011[81]	Japan	Medical health checkup population	1,446	TFFs, PGs, *H. pylori*	0.812–0.893

BMI, body mass index; CA199, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; G-17, gastrin-17; GC, gastric cancer; GERD, gastroesophageal reflux disease; *H. pylori*, *Helicobacter pylori*; NA, not available; PG, pepsinogen; TFF, trefoil factor; urea, urease subunit a.

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Conflict of interest

Prof. Zhaoshen Li has been an editor-in-chief of *Cancer Screening and Prevention* since August 2021. Prof Yiqi Du has been an executive associate editor of *Cancer Screening and Prevention* since December 2022. Xianzhu Zhou has no other conflict of interests related to this publication.

Author contributions

Contributed to study concept and design (YD and ZL), acquisition of the data (XZ and YD), assay performance and data analysis (XZ and YD), drafting of the manuscript (XZ and YD), critical revision of the manuscript (YD and ZL), supervision (YD and ZL). All authors have made a significant contribution to this study and have approved the final manuscript.

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