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GI CANCER

The Disease Burden of *Helicobacter pylori* Beyond Gastric Cancer: Quantifying the Forgotten Potential Benefits of Mass Eradication

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BACKGROUND & AIMS: Although *Helicobacter pylori* screen-and-treat has demonstrated effectiveness in preventing gastric cancer (GC), the impact on other diseases, such as peptic ulcer disease (PUD), dyspepsia, and gastric lymphomas, is often overlooked in guidelines and policy-analyses. This study quantifies the disease burden attributable to *H pylori* beyond GC. **METHODS:** A systematic literature search identified studies reporting the relative risk of developing PUD, dyspepsia, or gastric lymphomas due to *H pylori* to calculate the population attributable fraction (PAF) for each condition. The PAF represents the proportion of disease burden caused by *H pylori*. Preventable case numbers were calculated based on the risk reduction from eradication, both globally and specific for countries with varying *H pylori* prevalence. **RESULTS:** The proportions of PUD, dyspepsia, and gastric lymphoma attributable to *H pylori* (95% confidence interval) were 57% (44%–68%), 7% (2%–13%), and 33% (12%–53%), respectively, corresponding to 3.5 (2.7–4.2) million, 30 (7.1–52.2) million, and 12,000 (4200–19,100) cases potentially preventable through eradication, globally. Country-specific estimates varied with lowest PAFs (PUD, dyspepsia, gastric lymphomas) observed in the United States (35% [24%–47%], 3% [2%–13%], and 17% [5%–31%]) and highest in South Korea (63% [50%–73%], 9% [2%–15%], and 39% [14%–58%]). However, even in the United States, preventable case numbers remained substantial for PUD (134,000 [93,000–177,000]) and dyspepsia (860,000 [196,000–1.5 million]). **CONCLUSIONS:** Omitting PUD and dyspepsia as outcomes in studies on *H pylori* screen-and-treat may substantially underestimate benefits. Incorporating these diseases alongside GC into cost-effectiveness and policy analyses, therefore, may improve the evaluation of *H pylori* screen-and-treat programs. The actual benefit depends on the extent to which *H pylori* triggers an irreversible pathway to disease early in life.

Keywords: Stomach Cancer; *Helicobacter pylori*; Screening; Test-and-Treat; Peptic Ulcer Disease; Dyspepsia; Mucosa-Associated Lymphoid Tissue; MALT; Colorectal Cancer.

Multiple systematic reviews have demonstrated that eradication of *Helicobacter pylori* can decrease gastric cancer (GC) incidence and mortality.[1–3] Recently updated guidelines by the European Union, the American College for Gastroenterology, and the Asian Pacific Alliance on Helicobacter and Microbiota have, therefore, recommended *H pylori* screen-and-treat in populations with a high GC risk.[4–6] However, the risk threshold at what risk level the benefits of screening outweigh the harms remain unclear.[7] Even though *H pylori* is recognized to also be associated with other gastroduodenal pathologies by the Maastricht VI/Florence consensus report,[8] health policy analyses typically focus solely on GC as an outcome.[9] Because it is important to consider all diseases linked to *H pylori* to fully assess the potential harms and benefits, understanding the broader role of *H pylori* in the burden of other diseases could improve decisions on effective prevention strategies.

Recent research has given extensive consideration to the ancillary harms of *H pylori* screen-and-treat, particularly concerning antibiotic drug resistance. With antibiotic resistance reaching alarming levels worldwide,[10] any mass eradication program must be carefully evaluated. Continuous surveillance of resistance rates, such as those conducted by the European Registry on *H pylori*,[11] is, therefore, essential. Encouragingly, data from Taiwan show that long-term antibiotic resistance there did not increase after mass

Abbreviations used in this paper: **CI, confidence interval; CRC, colorectal cancer; GC, gastric cancer; NSAID, non-steroidal anti-inflammatory drugs; OR, odds ratio; PAF, population attributable fraction; PUD, peptic ulcer disease; RR, relative risk.**

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

While *Helicobacter pylori* screen-and-treat has demonstrated effectiveness in preventing gastric cancer, the impact on peptic ulcer disease (PUD) and dyspepsia is often overlooked in guidelines and policy analysis.

NEW FINDINGS

Globally, 57% of PUD and 7% of dyspepsia cases are attributable to *H pylori*, globally, corresponding to 3.5 million and 30 million cases potentially preventable through eradication. In the United States, eradication could prevent 134,000 PUD and 860,000 dyspepsia cases.

LIMITATIONS

The actual benefit of eradication depends on the extent to which *H pylori* triggers an irreversible pathway to disease early in life and needs to be further confirmed in clinical studies.

CLINICAL RESEARCH RELEVANCE

Omitting PUD and dyspepsia as outcomes in studies on *H pylori* screen-and-treat may substantially underestimate benefits. Incorporating these conditions in health policy and cost-effectiveness analyses may improve the evaluation of *H pylori* screen-and-treat.

BASIC RESEARCH RELEVANCE

Basic research is warranted to understand why *H pylori* causes (reversible) disease in some and none in others.

eradication of *H pylori*.[12] Although these risks have rightfully received much research attention, the potential additional benefits of *H pylori* screen-and-treat remain largely overlooked. Beyond its established role in gastric adenocarcinoma, *H pylori* is a recognized risk factor for several other upper-gastrointestinal diseases, including peptic ulcer disease (PUD), gastric lymphoma, and uninvestigated dyspepsia.[13] Furthermore, multiple studies have suggested a positive association between *H pylori* and colorectal cancer (CRC).[14,15] Despite this, the potential impact of *H pylori* screen-and-treat programs on the burden of these conditions remains unknown.

In this population attribution study, we aim to quantify the disease burden attributable to *H pylori* for PUD, gastric lymphoma, uninvestigated dyspepsia, and CRC. These estimates represent an important first step in understanding the full scope of benefits that *H pylori* screen-and-treat programs may offer.

Methods

We systematically searched the literature to obtain estimates of the relative risk of developing PUD, dyspepsia, or gastric lymphomas due to *H pylori*. These estimates were used to calculate the population attributable fraction (PAF) for each condition, representing the proportion of disease cases caused by *H pylori*. We then used the PAFs and disease case data to estimate the absolute number of attributable cases and the number that could potentially be prevented through *H pylori* eradication. Because the PAF depends on the risk factor prevalence, estimates were calculated globally as well as area-specific for areas with varying *H pylori* prevalence levels. Although causation is debated, we also estimated the PAF and *H pylori*–attributable case numbers for CRC as a secondary outcome.

Obtaining Relative Risk Estimates

A systematic search was conducted to identify systematic reviews reporting relative risks (RRs) and odds ratios (ORs) for the association between *H pylori* and the development of PUD, dyspepsia, and gastric lymphomas with *H pylori*. The search term used MeSH terms including "helicobacter pylori," "odds ratio," "peptic ulcer," "dyspepsia," and "lymphoma" and was restricted to articles published before January 2025. More details on the search query can be found in the Supplementary Material. If multiple pooled RR/OR estimates were available for a given condition, the most comprehensive study, based on the number of included studies and populations, was selected for further analysis. If pooled RRs were not available from systematic reviews, RR estimates from individual studies were used based on the number of included cases.

Disease Case Data

The disease attribution of *H pylori* was investigated both on a global level and within the United States, the Netherlands, Slovenia, Taiwan, and South Korea. These countries were selected to reflect a range of *H pylori* prevalence levels.

Prevalence estimates for *H pylori* were drawn from recent systematic review evidence, with reported rates of 43.9% globally, 17.6% in the United States, 23.7% in the Netherlands, 34.1% in Taiwan, and 54.9% in South Korea.[16] As no systematic review estimates were available for Slovenia, a local study was used to provide an estimated prevalence of 25.1%.[17]

Global case numbers for PUD were obtained from the most recent global burden of disease data (Table 1). For uninvestigated dyspepsia, global case numbers were derived from prevalence estimates from a recent systematic review and population data from the World Bank.[18,19] The most recent estimates based on the Rome III and IV criteria were used to define cases. For gastric lymphoma, we estimated global case numbers using GC incidence data from the Global Cancer Observatory (GLOBOCAN). Consistent with prior literature,[20] we assumed that gastric lymphomas accounted for 5% of total GC incidence.

Country-specific case numbers were sourced from the same datasets wherever possible. Because these sources did not provide data for Slovenia, case numbers for PUD and dyspepsia were obtained from the SZBO database (Statistika zdravstvenih obiskov bolnikov, Statistics of Outpatients Visits) of the national public health organization (Nacionalni inštitut za javno zdravje, NIJZ) with 2023 as the reference year. These data were derived from patient visits to general practitioners. Data on gastric lymphoma were sourced from the Slovenian Cancer Registry (SLORA). Additionally, as registry studies on the incidence of gastric lymphoma were available for Taiwan and the Netherlands, these sources were used.[21,22]

Table 1. Area-Specific Estimates of the PAF due to *H pylori* and the Estimated Preventable Cases Under Various Assumptions of Preventive Effect

		Global	United States	Netherlands	Slovenia	Taiwan	South Korea
PUD	Cases	8,090,476	499,172	8476	2450	18,580	72,546
	PAF	57% (44%–68%)	35% (24%–47%)	42% (30%–54%)	43% (31%–55%)	51% (38%–62%)	63% (50%–73%)
	Attributable cases	4,635,960 (3,575,701–5,519,786)	176,918 (122,154–233,429)	3582 (2,557–4,572)	1060 (760–1,346)	9459 (7,054–11,593)	45,451 (36,091–52,854)
	Preventable cases, baseline (efficacy, 76%)	3,523,330 (2,717,533–4,195,037)	134,457 (92,837–177,406)	2722 (1,943–3,475)	806 (578–1,023)	7189 (5,361–8,811)	34,543 (27,429–40,169)
	Preventable cases, sensitivity analysis (efficacy, 50%)	2,317,980 (1,787,851–2,759,893)	88,459 (61,077–116,714)	1791 (1,279–2,286)	530 (380–673)	4729 (3,527–5,796)	22,726 (18,045–26,427)
Dyspepsia	Cases	553,724,795	36,840,639	715,180	98,308	1,043,028	2,533,918
	PAF	7% (2%–13%)	3% (1%–6%)	4% (1%–7%)	4% (1%–8%)	6% (1%–10%)	9% (2%–15%)
	Attributable cases	40,636,586 (9,577,001–70,206,811)	1,156,177 (263,356–2,065,635)	29,616 (6,800–52,485)	4233 (973–7,492)	60,152 (13,995–105,222)	228,260 (54,546–389,256)
	Preventable cases, baseline (efficacy, 76%)	30,233,620 (7,125,289–52,233,868)	860,195 (195,937–1,536,833)	22,035 (5,060–39,049)	3150 (724–5,574)	44,753 (10,412–78,285)	169,826 (40,582–289,607)
	Preventable cases, sensitivity analysis (efficacy, 50%)	20,318,293 (4,788,501–35,103,406)	578,088 (131,678–1,032,818)	14,808 (3,400–26,243)	2117 (487–3,746)	30,076 (6,997–52,611)	114,130 (27,273–194,628)
Gastric lymphoma	Cases	36,195	687	73	78	190	698
	PAF	33% (12%–53%)	17% (5%–31%)	21% (7%–38%)	22% (7%–39%)	28% (9%–46%)	39% (14%–58%)
	Attributable cases	12,091 (4,221–19,103)	117 (35–216)	16 (5–28)	17 (5–30)	53 (18–88)	269 (99–407)
	Preventable cases (efficacy, 75%)	9068 (3,165–14,327)	88 (26–162)	12 (4–21)	13 (4–23)	40 (13–66)	202 (74–305)
	Preventable cases (efficacy, 50%)	6045 (2,110–9,551)	58 (18–108)	8 (2–14)	9 (3–15)	27 (9–44)	134 (49–203)

NOTE. Numbers between brackets denote 95% CIs.

Statistical Analysis

Population attributable fraction. We estimated the proportion of disease attributable to *H pylori* using the PAF, as originally described by Levin (1953).[23] The PAF is a function of the RR of the disease (eg, PUD) associated with *H pylori* and the prevalence of *H pylori* (P_{Hp}) in the population:

$$\text{PAF} = \frac{P_{Hp} \cdot (RR - 1)}{P_{Hp} \cdot (RR - 1) + 1}$$

Depending on the exposure-disease relationship, the term "attributable" may have a causal interpretation. If causality between the exposure and the disease is demonstrated, the PAF is the estimated fraction of all cases that would not have occurred if there had been no exposure.[24] ORs were used as proxies for RR consistent with the rare disease assumptions.[25] Confidence intervals (CIs) will be calculated using the 95% CIs around the proxies for RRs. The PAFs were estimated as a function of the *H pylori* prevalence and presented at both global and country-specific levels.

Benefits of H pylori Eradication

The numbers of disease cases attributable to *H pylori* were estimated using the disease case data and the derived PAF values. For the base case analysis of PUD and dyspepsia, we estimated the number of preventable cases based on absolute risk reductions from randomized controlled trials. Specifically, for PUD, we used treatment efficacy of 76% as reported in a systematic review by Ford et al.[26] For dyspepsia, we used a treatment efficacy of 74.4% as reported from a meta-analysis in the International Agency for Research on Cancer (IARC) Working Group Report.[27] For gastric lymphoma, no such evidence was available. We, therefore, assessed the number of preventable cases for gastric lymphoma under 3 scenarios, assuming that eradication could prevent 50%, 75%, or 100% of the cases attributable to *H pylori*. Because the preventive effect may differ from the treatment effect, we also evaluated scenarios assuming 50% and 100% of cases could be prevented for both PUD and dyspepsia as sensitivity analyses.

Colorectal Cancer

The PAF for CRC was calculated using the same approach as the main analysis for PUD, dyspepsia, and gastric lymphomas. The search term included the MeSH term "colorectal neoplasms." Case numbers were sourced from GLOBOCAN for all regions, except for Slovenia, where data were obtained from the Slovenian Cancer Registry (SLORA).[28]

Results

Relative Risk Estimates

We identified 3 systematic reviews that assessed the increased risk of upper gastrointestinal conditions associated with *H pylori* infection.[29–31] For PUD, Papatheodoridis et al[29] reported a pooled OR of 4.05 (95% CI, 2.80–5.88), based on age-matched controlled studies, indicating a strong association between *H pylori* infection and PUD. In the case of uninvestigated dyspepsia, Ford et al[30] found a modest association, with an OR of 1.18 (95% CI, 1.04–1.33). Regarding gastric lymphoma, a recent systematic review concluded that the available evidence is insufficient to support pooled analyses.[32] However, data from Japanese case-control studies demonstrated an OR of 2.14 (1.30–3.54).[31]

Disease Proportion Attributable to H pylori

PUD had the highest estimated PAF, followed by gastric lymphoma and dyspepsia (Figure 1). The PAFs increased with higher prevalence of *H pylori*: at a 5% *H pylori* prevalence level, the PAFs (95% CI) for PUD, dyspepsia, and gastric lymphomas were 13% (8%–19%), 1% (0%–2%), and 5% (1%–11%), respectively; at a 75% *H pylori* prevalence level, the PAFs increased to 70% (57%–78%), 12% (3%–20%), and 46% (18%–66%), respectively (Figure 1).

Globally, an estimated 57% (95% CI, 44%–68%) of PUD cases were attributable to *H pylori*. Country-specific PAF estimates (95% CI) for PUD were 35% (24%–47%) in the United States, 42% (30%–54%) in the Netherlands, 43% (31%–55%) in Slovenia, 51% (38%–62%) in Taiwan, and 63% (50%–73%) in South Korea. In absolute numbers, approximately 4.7 million (95% CI, 3.6 million–5.5 million) PUD prevalent cases worldwide were linked to *H pylori*. As a result, the global number of preventable cases in our baseline analysis was around 3.5 million (2.7 million–4.2 million). Even if eradication efforts could prevent only 50% of the *H pylori* attributable cases, around 2.3 million (95% CI, 1.8 million–2.8 million) prevalent cases could potentially be avoided globally. Further country-specific estimates of the preventable case numbers under various scenarios of treatment effectiveness can be found in Table 1.

For dyspepsia, the global PAF of *H pylori* was estimated at 7% (95% CI, 2%–13%), corresponding to approximately 41 million (95% CI, 9.5 million–70.2 million) prevalent cases worldwide. Country-specific PAFs ranged from 3% (95% CI, 1%–6%) in the United States to 9% (95% CI, 2%–15%) in South Korea, representing about 1.2 million (95% CI, 263,000–2.1 million) cases in the United States and 228,000 (95% CI, 55,000–389,000) cases in South Korea attributable to *H pylori* (Table 1). The estimated number of preventable cases globally was 30 million (95% CI, 7 million–52 million), corresponding to 860,000 (95% CI, 196,000–1.5 million) cases in the United States and 170,000 (95% CI, 41,000–290,000) in South Korea.

The global estimated PAF for gastric lymphomas was 33% (95% CI, 12%–53%), corresponding to approximately 12,000 annual cases attributable to *H pylori* worldwide. Due to the low prevalence of the disease, the number of preventable cases at the country level was relatively small, reaching up to 117 (95% CI, 35–216) cases in the United States and 269 (95% CI, 99–407) in South Korea (Table 1), assuming that all attributable cases are preventable through eradication.

Colorectal Cancer

Although causation is debated, 9 systematic reviews conducted between 2006 and the time of this study examined the association between *H pylori* and CRC.[15,33–40]

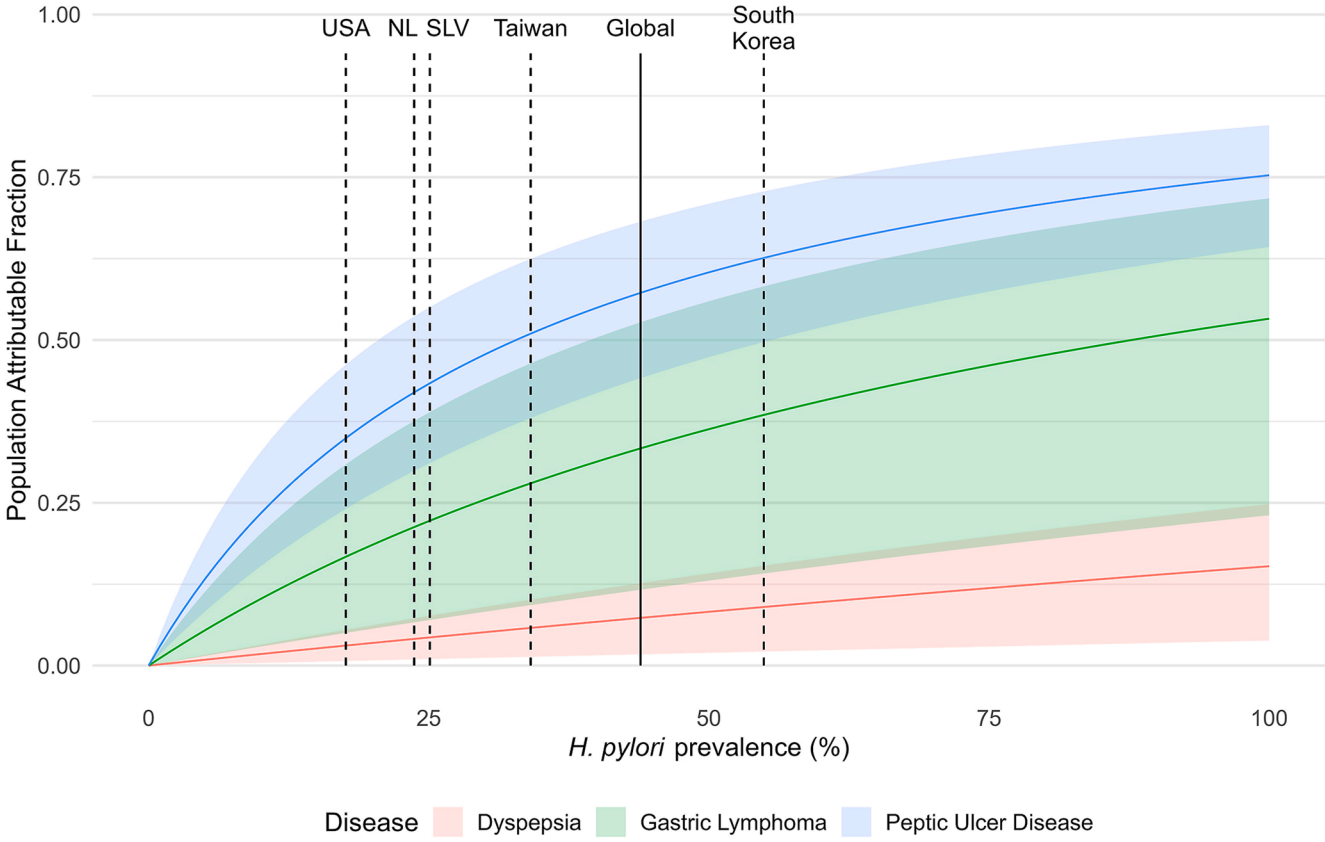

Figure 1. The PAF of dyspepsia, gastric lymphoma, and PUD indicates the proportion of cases attributable to *H pylori.* The *lines* indicate the point estimates and the *shaded areas* indicate the CIs. The *vertical lines* indicate the country-specific prevalence levels of *H pylori.* NL, Netherlands; SLV, Slovenia; USA, United States of America.

The estimated OR ranged from 1.27 (95% CI, 1.17–1.37)[36] to 1.80 (95% CI, 1.31–2.47).[40] The meta-analysis by Choi et al,[15] which included the largest number of studies (47 in total), reported an OR of 1.49 (95% CI, 1.37–1.62) and we used this to estimate the proportion of CRC cases attributable to *H pylori*. Globally, an estimated 18% (95% CI, 3%–44%) of CRC cases were attributable to *H pylori*, accounting for approximately 340,000 annual cases. Country-specific estimates of the PAF varied by country from 8% (95% CI, 1%–24%) in the United States to 21% (95% CI, 4%–49%) in South Korea (Figure 2). The estimated number of CRC cases linked to *H pylori* was 13,000 in the United States, 1900 in the Netherlands, 200 in Slovenia, 2300 in Taiwan, and 6000 in South Korea.

Discussion

This study indicated that infection with *H pylori* contributed substantially to the disease burden of PUD, dyspepsia, and gastric lymphoma. Globally, *H pylori* was estimated to be responsible for 57% of PUD cases, 7% of dyspepsia cases, and 33% of gastric lymphoma cases. These proportions corresponded to approximately 4.6 million cases of PUD, 41 million cases of dyspepsia, and 12,000 cases of gastric lymphoma caused by *H pylori*. These results suggest that mass eradication of *H pylori* could substantially reduce disease burden beyond GC. Because direct evidence of prevention is unavailable, the extent to which these cases can be prevented will depend on the effectiveness of *H pylori* eradication in reducing disease occurrence. However, even with the most conservative estimates of the effect of eradication obtained in this study, the number of preventable disease cases remained substantial. Although causality may be contested, it was also estimated that 18% of CRC cases may be attributable to *H pylori.*

Despite a global decrease in *H pylori* prevalence, the infection remains widespread.[16] As a result, *H pylori* continues to be the leading cause of PUD globally, with estimated PAFs exceeding 60% in countries like South Korea where *H pylori* prevalence is high. The strong association between *H pylori* and PUD is well-documented, as the bacterium triggers chronic inflammation that weakens the protective mechanisms of the gastrointestinal mucosa, increasing the susceptibility to ulcers.[41] In contrast, the lower PAF for dyspepsia suggests that, although *H pylori* contributes to symptoms in some individuals, many cases may be driven by other factors such as smoking, nonsteroidal anti-inflammatory drugs (NSAIDs) use, and psychiatric comorbidity.[42,43] The moderate attribution of *H pylori* to gastric lymphoma relates to the known role of *H pylori* in mucosa-associated lymphoid tissue (MALT) lymphoma development.[44] Taken together, these findings demonstrate the potential that mass *H pylori* eradication may have in the prevention of upper-gastrointestinal conditions in addition to GC.

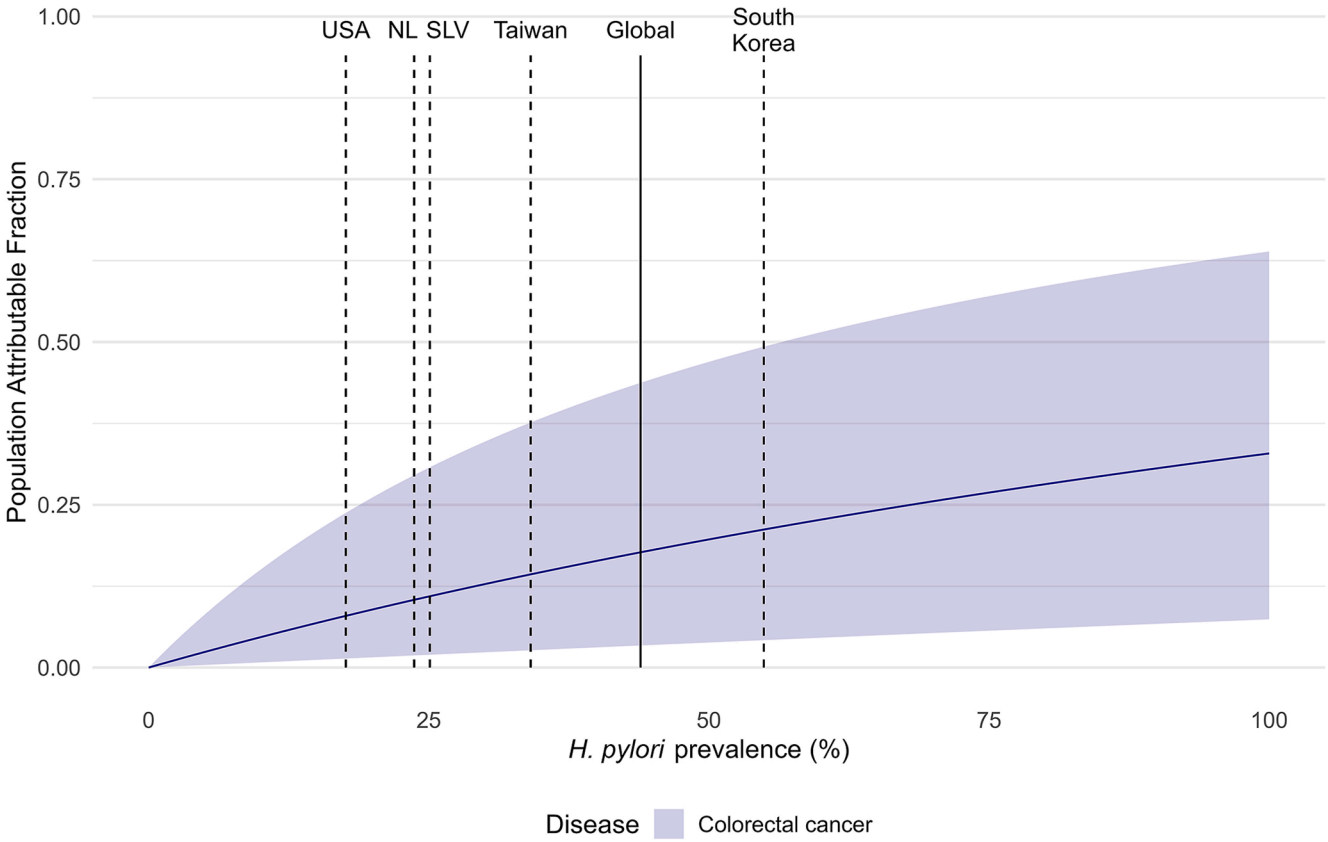

Figure 2. The PAF of CRC indicates the proportion of cases attributable to *H pylori.* The *lines* indicate the point estimates and the *shaded areas* indicate the CIs. The *vertical lines* indicate the country-specific prevalence levels of *H pylori.* Abbreviations as in Figure 1.

Although a substantial proportion of disease is attributable to *H pylori*, the actual benefit of eradication depends on its ability to prevent disease. If *H pylori* triggers an irreversible pathway to disease early in life, eradication at an older age may have reduced preventive effects. Although testing and eradicating *H pylori* has demonstrated benefits in symptomatic patients with PUD, dyspepsia, and gastric lymphoma,[26,27,30,45,46] evidence on its preventive impact in asymptomatic populations is limited. We, therefore, had to base the assumed preventive efficacy on the absolute risk reduction in randomized trials, which were conducted largely in symptomatic populations.[26,27] On a population-level, an *H pylori* screen-and-treat program in a high-risk region of Taiwan demonstrated a 67% reduction in total PUD incidence after mass eradication.[47] Given the reported *H pylori* prevalence of 65% in this population, our PAF estimation attributed 66% (95% CI, 54%–76%) of PUD cases to *H pylori*. The close alignment between the reported preventive effect and our estimated PAF suggests that *H pylori* does not trigger an irreversible pathway early in life. This implies that eradication may effectively prevent all PUD cases attributable to *H pylori,* indicating that our baseline estimates of preventable cases may be conservative. The corresponding benefits may be considerable from a clinical and economic point of view: in the United States, direct medical costs per PUD patient are estimated to be as high as 866 US$.[48] With 177,000 cases potentially preventable through *H pylori* eradication in the United States, the resulting cost reduction could approach 150 million US$. Similar evidence on the prevention of dyspepsia and gastric lymphoma is currently lacking. However, a randomized controlled trial in England investigating *H pylori* screen-and-treat found that healthcare costs for dyspepsia were lower in the eradication group than in the control group, suggesting a preventive effect.[49] Future clinical trials and pilot studies on *H pylori* screen-and-treat may benefit from including PUD, dyspepsia, and gastric lymphomas as secondary outcomes alongside GC.

The estimated 18% proportion of CRC cases attributable to *H pylori* should be interpreted with caution. Although numerous systematic reviews have examined the association,[15,33,40] results may be subject to confounding and evidence on causation is inconclusive. Some animal studies suggest a causal link between *H pylori* infection and colorectal carcinogenesis, whereas studies using Mendelian randomization have not supported a causal effect.[50,51] Furthermore, a population cohort study from Scandinavia showed that *H pylori* eradication was not associated with a clear reduction in CRC incidence.[52] Confounder-adjusted cohort studies found hazard ratios of 1.7 and 1.9, which slightly exceeded the more conservatively assumed OR of 1.5 in our analysis.[52,53] A better understanding of the impact of *H pylori* eradication on CRC risk is needed before it can incorporated into health policy analyses.

Our results carry important implications for health policy. A review of modeling studies suggested that *H pylori* screen-and-treat is potentially cost-effective across various settings.[9] However, the balance between benefits and harms was less distinct in countries with moderate and low GC rates. Notably, most of the included studies only considered GC incidence as an outcome, overlooking the substantial additional benefits of reducing PUD and dyspepsia as outlined in our analysis. Future modeling studies could incorporate the disease burden estimates from our analysis to provide a more comprehensive cost-effectiveness assessment. This broader perspective could alter the conclusions regarding the cost-effectiveness of *H pylori* screen-and-treat, particularly in countries with a moderate GC incidence.

Strengths of this study include the comprehensive assessment of *H pylori*–related disease burden beyond GC, the provision of both global and country-specific estimates, and the implications for future health policy analyses. However, our analyses have several limitations. First, we had to make assumptions regarding the effect of *H pylori* treatment on disease prevention. Although eradication has demonstrated benefits in symptomatic patients,[30,45,46] its preventive effect in screening populations is supported by limited clinical trial evidence. Our study, therefore should be considered a first step in estimating the number of preventable cases. To account for uncertainty, we presented multiple treatment effect scenarios. Even under the most conservative assumptions–where treatment was assumed to reduce the burden of *H pylori*-induced conditions by only 50%–the number of preventable cases remained substantial, highlighting the need for further research in this area. However, the actual preventive effect may be closer to the more optimistic projections, given the demonstrated benefits of *H pylori* eradication in diagnosed PUD patients and the impact of mass eradication on PUD incidence in Taiwan.[26,47] Second, our study focused on the additional benefits of *H pylori* eradication without considering harms. Although some studies have hypothesized an increased risk of asthma and esophageal adenocarcinoma after *H pylori* eradication, these associations have been largely refuted, and we, therefore, did not include them in our analysis.[54,55] Harms related to potential increases in antibiotic drug resistance rates after mass eradication were also not examined in this study and should be considered in future research. In particular, long-term follow-up data on resistance rates in individuals with eradicated *H pylori* may help quantify the magnitude of this potential harm. Third, due to limited availability of granular data, we applied the same RR estimates across all countries, which does not account for regional differences in *H pylori* virulence. The prevalence of cytotoxin-associated gene A positive strains, known for higher pathogenicity, varies by region and is more common in East-Asia.[56] Furthermore, the use of either aspirin or NSAIDs further increases the risk of PUD in *H pylori*–infected individuals.[8] Regional differences in NSAID use could, therefore, modify the PAF of *H pylori.* In addition, host genetic factors, such as polymorphisms affecting inflammatory responses or mucosal defense mechanisms, may influence individual susceptibility to *H pylori*–associated disease.[57] If we had been able to incorporate these differences in strain virulence, NSAID use patterns, and host genetics, the variation in PAFs across countries may have been even greater than we observed. Fourth, we used ORs as proxies for RR following the rare disease assumption.[25] This assumption generally holds for diseases with a prevalence $<10\%$, which applies to all investigated conditions across all regions, except for dyspepsia in the United States (11%).[14] As a result, our estimates for dyspepsia in the United States may be slightly inflated. Finally, literature estimates of the RR of developing gastric lymphoma due to *H pylori* are difficult to assess due to low incidence of disease, resulting in large CIs around our estimates. Although we used the RR obtained in a recent case-control study with a relatively large number of cases,[31] an older study found a larger RR of 6.3 (95% CI, 2.0–19.9).[58] Therefore, our estimates for gastric lymphoma may be considered cautious.

Conclusions

Our study suggested that *H pylori* is responsible for 57% of PUD cases, 7% of dyspepsia cases, and 33% for gastric lymphoma cases globally. These proportions corresponded to approximately 4.6 million cases of PUD, 554 million cases of dyspepsia, and 12,000 cases of gastric lymphoma caused by *H pylori* globally. Omitting these conditions in studies on *H pylori* screen-and-treat could lead to a substantial underestimation of the potential benefits. Incorporating these diseases alongside GC into cost-effectiveness and policy analyses may, therefore, improve the evaluation of *H pylori* screen-and-treat programs. As the actual benefit depends on the ability to prevent disease, future clinical studies are needed to corroborate our findings.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2025.08.015.

References

1. Lee Y-C, Chiang T-H, Chou C-K, et al. Association between *Helicobacter pylori* eradication and gastric cancer incidence: a systematic review and meta-analysis. Gastroenterology 2016;150:1113–1124.e5.
2. Ford AC, Yuan Y, Park JY, et al. Eradication therapy to prevent gastric cancer in *Helicobacter pylori*-positive individuals: systematic review and meta-analysis of randomized controlled trials and observational studies. Gastroenterology 2025;169:261–276.
3. Ford AC, Yuan Y, Moayyedi P. *Helicobacter pylori* eradication therapy to prevent gastric cancer: systematic review and meta-analysis. Gut 2020;69:2113–2121.
4. European Health Union: Commission welcomes adoption of new EU cancer screening recommendations. European Commission, 2022.

5. Chey WD, Howden CW, Moss SF, et al. ACG clinical guideline: treatment of *Helicobacter pylori* infection. Am J Gastroenterol 2024;119:1730–1753.
6. Liou J-M, Malfertheiner P, Lee Y-C, et al. Screening and eradication of *Helicobacter pylori* for gastric cancer prevention: the Taipei global consensus. Gut 2020; 69:2093–2112.
7. Mülder DT, O'Mahony JF, Laszkowska M, et al. Recent US gastric cancer prevention recommendations: advances, unanswered questions, and the need for a unified approach. Gastroenterology 2025;169:545–550.
8. Malfertheiner P, Megraud F, Rokkas T, et al. Management of *Helicobacter pylori* infection: the Maastricht VI/ Florence consensus report. Gut 2022;71:1724–1762.
9. Lansdorp-Vogelaar I, Sharp L. Cost-effectiveness of screening and treating *Helicobacter pylori* for gastric cancer prevention. Best Pract Res Clin Gastroenterol 2013;27:933–947.
10. Yu Y, Xue J, Lin F, et al. Global primary antibiotic resistance rate of *Helicobacter pylori* in recent 10 years: a systematic review and meta-analysis. *Helicobacter* 2024;29:e13103.
11. Nyssen OP, Vaira D, Tepes B, et al. Room for improvement in the treatment of *Helicobacter pylori* infection: lessons from the European Registry on: *H. pylori*: management (Hp-EuReg). J Clin Gastroenterol 2022;56:e98–e108.
12. Chiang T-H, Chang W-J, Chen SL-S, et al. Mass eradication of *Helicobacter pylori* to reduce gastric cancer incidence and mortality: a long-term cohort study on Matsu Islands. Gut 2021;70:243–250.
13. Suerbaum S, Michetti P. *Helicobacter pylori* infection. N Engl J Med 2002;347:1175–1186.
14. Wernly S, Semmler G, Flamm M, et al. The association between *Helicobacter pylori* and colorectal neoplasia. Med Princ Pract 2023;32:77–85.
15. Choi DS, Seo SI, Shin WG, et al. Risk for colorectal neoplasia in patients with *Helicobacter pylori* infection: a systematic review and meta-analysis. Clin Transl Gastroenterol 2020;11:e00127.
16. Chen Y-C, Malfertheiner P, Yu H-T, et al. Global prevalence of *Helicobacter pylori* infection and incidence of gastric cancer between 1980 and 2022. Gastroenterology 2024;166:605–619.
17. Gubina M, Tepeš B, Vidmar G, et al. Prevalenca protiteles proti bakteriji *Helicobacter pylori* v Sloveniji v letu 2005. Slovenian Med J 2006;75.
18. Barberio B, Mahadeva S, Black CJ, et al. Systematic review with meta-analysis: global prevalence of uninvestigated dyspepsia according to the Rome criteria. Aliment Pharmacol Ther 2020;52:762–773.
19. World Population Prospects. In: Bank UNPDW, ed, 2024.
20. Juárez-Salcedo LM, Sokol L, Chavez JC, et al. Primary gastric lymphoma, epidemiology, clinical diagnosis, and treatment. Cancer Control 2018;25:1073274818778256.
21. Chang JS, Kuo S-H, Chu P-Y, et al. The epidemiology of gastric cancers in the era of *Helicobacter pylori* eradication: a nationwide Cancer Registry-based study in Taiwan. Cancer Epidemiol Biomarkers Prev 2019; 28:1694–1703.
22. Capelle LG, de Vries AC, Looman CWN, et al. Gastric MALT lymphoma: epidemiology and high adenocarcinoma risk in a nation-wide study. Eur J Cancer 2008; 44:2470–2476.
23. Levin ML. The occurrence of lung cancer in man. Acta Unio Int Contra Cancrum 1953;9:531–941.
24. Rothman KJ, Greenland S, Lash TL. Modern Epidemiology. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2008.
25. Greenland S, Thomas DC. On the need for the rare disease assumption in case-control studies. Am J Epidemiol 1982;116:547–553.
26. Ford AC, Delaney BC, Forman D, et al. Eradication therapy in *Helicobacter pylori* positive peptic ulcer disease: systematic review and economic analysis. Am J Gastroenterol 2004;99:1833–1855.
27. Moayyedi P, Malfertheiner P, Yuan Y, et al. Current evidence from randomized controlled trials of the benefits and harms of population-based *Helicobacter pylori* screen-and treat strategies for gastric cancer prevention and review of the existing recommendations, consensus reports, and guidelines. In: Park JY, ed. Population-based *Helicobacter pylori* screen-and-treat strategies for gastric cancer prevention: guidance on implementation (IARC Working Group Reports No. 12). Lyon, France: International Agency for Research on Cancer, 2025.
28. GLOBOCAN. Data and Methods. Volume 2024: IARC, 2024.
29. Papatheodoridis GV, Sougioultzis S, Archimandritis AJ. Effects of *Helicobacter pylori* and nonsteroidal anti-inflammatory drugs on peptic ulcer disease: a systematic review. Clin Gastroenterol Hepatol 2006;4:130–142.
30. Ford AC, Tsipotis E, Yuan Y, et al. Efficacy of *Helicobacter pylori* eradication therapy for functional dyspepsia: updated systematic review and meta-analysis. Gut 2022;71:1967–1975.
31. Ishikura N, Usui Y, Ito H, et al. *Helicobacter pylori* (HP) infection alone, but not HP-induced atrophic gastritis, increases the risk of gastric lymphoma: a case-control study in Japan. Ann Hematol 2019;98:1981–1987.
32. Doorakkers E, Lagergren J, Engstrand L, et al. Eradication of *Helicobacter pylori* and gastric cancer: a systematic review and meta-analysis of cohort studies. J Natl Cancer Inst 2016;108:djw132.
33. Zumkeller N, Brenner H, Zwahlen M, et al. *Helicobacter pylori* infection and colorectal cancer risk: a meta-analysis. *Helicobacter* 2006;11:75–80.
34. Zhao YS, Wang F, Chang D, et al. Meta-analysis of different test indicators: *Helicobacter pylori* infection and the risk of colorectal cancer. Int J Colorectal Dis 2008; 23:875–882.
35. Wu Q, Yang ZP, Xu P, et al. Association between *Helicobacter pylori* infection and the risk of colorectal neoplasia: a systematic review and meta-analysis. Colorectal Dis 2013;15:e352–e364.
36. Yang F, Xu YL, Zhu RF. *Helicobacter pylori* infection and the risk of colorectal carcinoma: a systematic review and meta-analysis. Minerva Med 2019;110:464–470.
37. Zuo Y, Jing Z, Bie M, et al. Association between *Helicobacter pylori* infection and the risk of colorectal

cancer: a systematic review and meta-analysis. Medicine 2020;99:e21832.
38. Ko HJ, Lin YC, Chen CC, et al. *Helicobacter pylori* infection and increased diabetes prevalence were the risks of colorectal adenoma for adults: a systematic review and meta-analysis (PRISMA-compliant article). Medicine (Baltimore) 2021;100:e28156.
39. Ma L, Guo W, Zeng Z, et al. Colorectal cancer risk in East Asian patients with *Helicobacter pylori* infection: a systematic review and meta-analysis. Medicine (Baltimore) 2023;102:e33177.
40. Xu H, Zhang Y, Guo Y, et al. Meta-analysis of the correlation between *Helicobacter pylori* infection and the risk of colorectal neoplasia. Altern Ther Health Med 2024;30:92–97.
41. Sung JJY, Kuipers EJ, El-Serag HB. Systematic review: the global incidence and prevalence of peptic ulcer disease. Aliment Pharmacol Ther 2009;29:938–946.
42. Ford AC, Marwaha A, Sood R, et al. Global prevalence of, and risk factors for, uninvestigated dyspepsia: a meta-analysis. Gut 2015;64:1049–1057.
43. Wauters L, Talley NJ, Walker MM, et al. Novel concepts in the pathophysiology and treatment of functional dyspepsia. Gut 2020;69:591–600.
44. Zullo A, Hassan C, Cristofari F, et al. Effects of *Helicobacter pylori* eradication on early stage gastric mucosa–associated lymphoid tissue lymphoma. Clin Gastroenterol Hepatol 2010;8:105–110.
45. Ford AC, Gurusamy KS, Delaney B, et al. Eradication therapy for peptic ulcer disease in *Helicobacter pylori*-positive people. Cochrane Database Syst Rev 2016;4:CD003840.
46. Zullo A, Hassan C, Andriani A, et al. Eradication therapy for *Helicobacter pylori* in patients with gastric MALT lymphoma: a pooled data analysis CME. Am J Gastroenterol 2009;104:1932–1937.
47. Lee Y-C, Chen TH-H, Chiu H-M, et al. The benefit of mass eradication of *Helicobacter pylori* infection: a community-based study of gastric cancer prevention. Gut 2013;62:676–682.
48. Barkun A, Leontiadis G. Systematic review of the symptom burden, quality of life impairment and costs associated with peptic ulcer disease. Am J Med 2010;123:358–366.e2.
49. Mason J, Axon ATR, Forman D, et al. The cost-effectiveness of population *Helicobacter pylori* screening and treatment: a Markov model using economic data from a randomized controlled trial. Aliment Pharmacol Ther 2002;16:559–568.
50. Luo F, Zhou P, Ran X, et al. No evident causal association between *Helicobacter pylori* infection and colorectal cancer: a bidirectional mendelian randomization study. Sci Rep 2023;13:18544.
51. Ralser A, Dietl A, Jarosch S, et al. *Helicobacter pylori* promotes colorectal carcinogenesis by deregulating intestinal immunity and inducing a mucus-degrading microbiota signature. Gut 2023;72:1258–1270.
52. Liu IL, Tsai CH, Hsu CH, et al. *Helicobacter pylori* infection and the risk of colorectal cancer: a nationwide population-based cohort study. QJM 2019;112:787–792.
53. Hsu W-Y, Lin C-H, Lin C-C, et al. The relationship between *Helicobacter pylori* and cancer risk. Eur J Intern Med 2014;25:235–240.
54. Wiklund A-K, Santoni G, Yan J, et al. Risk of esophageal adenocarcinoma after *Helicobacter pylori* eradication treatment in a population-based multinational cohort study. Gastroenterology 2024;167:485–492.e3.
55. Wang Q, Yu C, Sun Y. The association between asthma and *Helicobacter pylori*: a meta-analysis. *Helicobacter* 2013;18:41–53.
56. Yamaoka Y, Kato M, Asaka M. Geographic differences in gastric cancer incidence can be explained by differences between *Helicobacter pylori* strains. Intern Med 2008;47:1077–1083.
57. El-Omar EM, Carrington M, Chow W-H, et al. Interleukin-1 polymorphisms associated with increased risk of gastric cancer. Nature 2000;404:398–402.
58. Parsonnet J, Hansen S, Rodriguez L, et al. *Helicobacter pylori* infection and gastric lymphoma. N Engl J Med 1994;330:1267–1271.

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Data Availability
All data used in this study are available in the article.