# Chapter 3.10.

# Population-based *Helicobacter pylori* screen-and-treat strategy to prevent gastric cancer in the Matsu Islands

*Yi-Chia Lee*

## Summary

- A population-based *H. pylori* screen-and-treat programme is an approach that can be used when upper endoscopic screening is limited by low population participation and insufficient human resources.
- Implementing this approach as a pilot programme targeting a high-risk subpopulation can demonstrate its acceptability, feasibility, and sustainability within a country.
- The pilot programme can be expanded to larger populations with varying levels of risk after the benefits to the population have been demonstrated through rigorous scientific evaluation and the potential harms have been assessed.
- Eradication of *H. pylori* as a strategy can potentially help to achieve the goal of eliminating gastric cancer as a public health problem.

## 3.10.1 Gastric cancer epidemiology in the Matsu Islands

The Matsu Islands consist of five major islands and are located in the East China Sea. A substantial proportion of the population of the Matsu Islands are immigrants from Changle, Lienchiang, and Mawei counties in Fujian Province, China. In Fujian Province, the prevalence of *H. pylori* infection has been reported as 70% and the incidence rate of gastric cancer has been high. In 1988, the age-standardized mortality rate of gastric cancer in men was 153 per 100 000 person-years in Changle County [1]. By 2019, the crude incidence rate of gastric cancer remained high, at 28 per 100 000 person-years, with rates of 39.5 per 100 000 person-years for males and 16.5 per 100 000 person-years for females [2].

The residents of the Matsu Islands have long experienced high gastric cancer incidence and mortality rates. The geographical location of the Matsu Islands (Fig. 3.10.1) has amplified the problem, and substantial barriers to health-care access exist because of the limited transportation links and human resources. In 1985, the crude incidence rate of gastric cancer in the Matsu Islands was reported to be 100 per 100 000 person-years and remained at about 40 per 100 000 person-years until the initiation of an *H. pylori* screening programme in 2004. The age-standardized rate was about 30 per 100 000 person-years in 2000–2004, with rates of 50.3 per 100 000 person-years for males and 13.7 per 100 000 person-years for females [3].

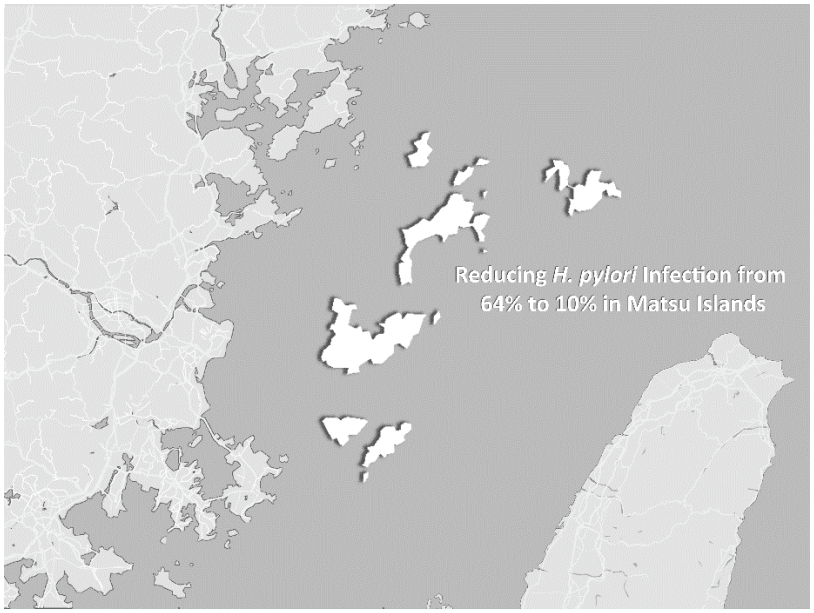


**Fig. 3.10.1.** Geographical location of the Matsu Islands. The Matsu Islands are located in the East China Sea and are composed of dozens of islands, including Nangan, Beigan, Juguang, and Dongyin. Note that nearby Fujian Province was also an area with prevalent *H. pylori* infection and a high incidence rate of gastric cancer. © Yi-Chia Lee.

## 3.10.2 Design of the gastric cancer prevention programme

A series of gastric cancer prevention programmes have been initiated in the Matsu Islands (Fig. 3.10.2), during three time periods. In 1995, an endoscopic screening programme was implemented using serological biomarkers, including pepsinogen testing, to identify high-risk individuals. People who tested positive would be referred for

upper endoscopic screening and histological sampling, which is a typical procedure for secondary prevention [5]. The sustainability of this programme had several challenges. First, the pepsinogen test was designed to detect premalignant conditions rather than gastric cancer, resulting in a high positivity rate of 43%, which exceeded the capacity of the available human resources providing endoscopy services. Second, the endoscopic referral rate was suboptimal because of the reluctance of participants to undergo an invasive procedure. Third, the endoscopic screening programme needed to be designed as a regular procedure rather than a one-time event, to capture new-onset early-stage cancer. These three challenges led to a low gastric cancer detection rate, and consequently the programme was terminated in 1999.

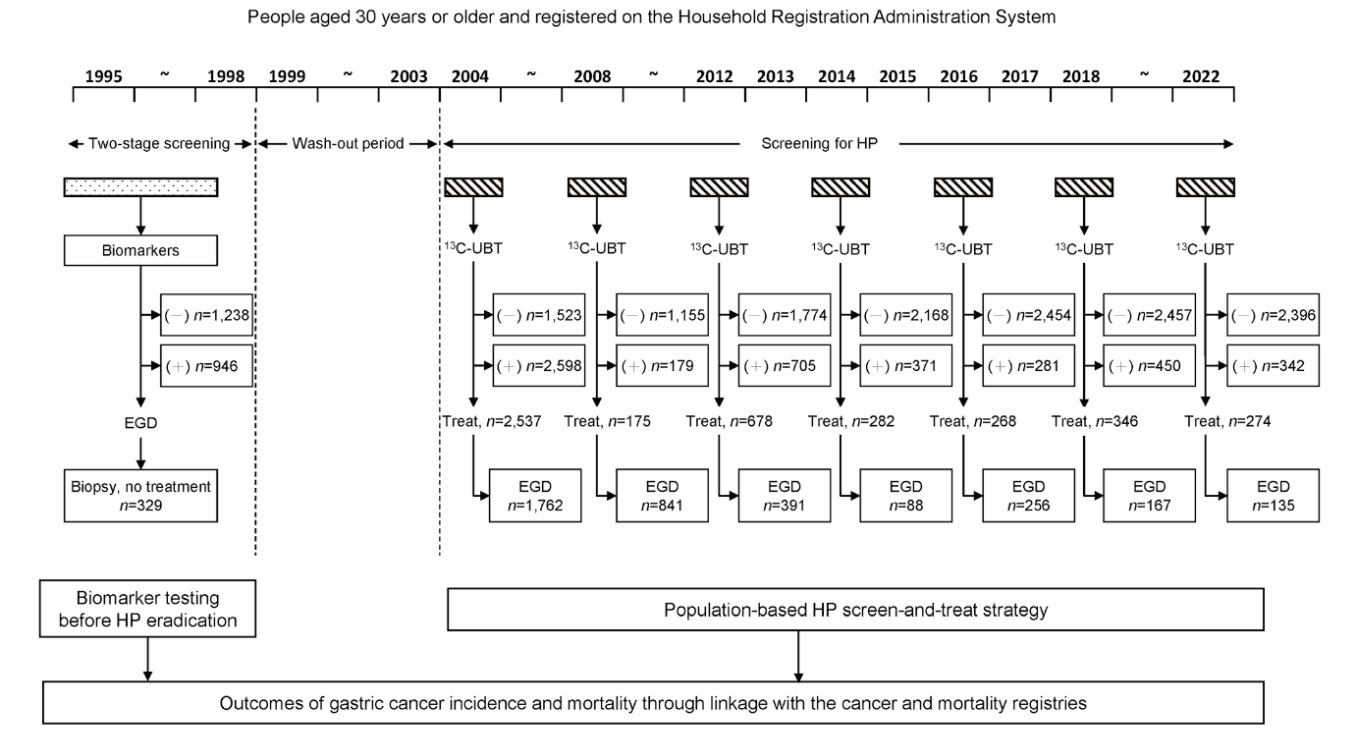


**Fig. 3.10.2.** Timeline of the gastric cancer prevention programmes implemented in the Matsu Islands. EGD, oesophago-gastro-duodenoscopy; $^{13}$C-UBT, $^{13}$C-urea breath test; HP, *Helicobacter pylori*. Adapted with permission from Chiang et al. (2021) [4]. Copyright © 2021, Chiang et al. Published by BMJ Publishing Group Ltd. Article available under the Creative Commons CC BY-NC 4.0.

However, for individuals who underwent endoscopic screening, a biopsy of the gastric mucosa was performed to assess the presence and severity of chronic non-

atrophic gastritis, atrophic gastritis, and intestinal metaplasia in the histology. From these histological changes observed over time, a multistate model showed that progression from normal gastric mucosa to chronic gastritis was significantly accelerated in individuals who tested positive for *H. pylori* infection [5, 6]. The results from the model suggested that eradicating *H. pylori* may reduce progression by 37% in the early stages of carcinogenesis. In addition, a randomized clinical trial conducted in Changle County, Fujian Province, China, published in 2004, enrolled 1630 individuals with *H. pylori* infection and demonstrated that *H. pylori* eradication reduced the risk of gastric cancer by 37% in participants who received eradication treatment compared with those who received a placebo [1]. Although results of the primary analyses were statistically non-significant, post hoc analyses indicated that the effect was significant in participants without premalignant gastric conditions [1]. These studies [1, 5, 6] laid the foundation for the subsequent primary prevention strategy.

In 2004, an *H. pylori* screen-and-treat programme targeting the general population was initiated in the Matsu Islands. The programme was implemented biennially to include new immigrants to the Matsu Islands and younger participants who reached the eligible age for screening. By 2024, eight rounds of the screen-and-treat programme had been completed. The programme's sustainability was attributed to the supportive framework established by the local government, the use of an easy-to-administer screening test, and effective eradication treatments, accompanied by higher population awareness about *H. pylori* as a pathogen in the stomach. Meanwhile, the involvement of a community-based integrated screening committee in the evaluation of the programme provided a strong scientific basis for pursuing support for continuous funding [7].

After the population-based *H. pylori* screen-and-treat programme had been implemented, the occurrence of gastric cancer gradually became rare, although gastric cancer still persists. Efforts to investigate effective methods for stratifying the post-eradication population based on the residual risk of gastric cancer have been continuing. This initiative has been integrated into the programme since 2015.

### 3.10.3 Recruitment and eligibility criteria

The population-based *H. pylori* screen-and-treat programme followed the principles of an organized screening programme by ensuring that everyone in the target population had an equal opportunity to participate in screening and that if a screening test result

was abnormal, the individual would receive the standardized management. The age of eligibility to enter this programme was set at 30 years or older, which was considered a frequent starting age for a primary cancer prevention programme, and the participant's household registration needed to be in the Matsu Islands. Pregnant or lactating women and individuals who had undergone total gastrectomy were excluded. Patients with major comorbid diseases were also excluded because of concerns about the feasibility of the use of multidrug antibiotic regimens if these patients tested positive.

### 3.10.4 Implementation

Eligible residents were invited via mail, telephone, social media, and newspapers to undergo screening for *H. pylori* using the $^{13}$C-urea breath test ($^{13}$C-UBT), which was found to have advantages over other detection methods because of its ease of administration, high accuracy, and high stability during transportation [8] (see Chapter 5). The participants' demographic data, lifestyle habits, and medical history were recorded in a structured questionnaire. The *H. pylori* screen-and-treat programme was included in a community-based integrated screening model (Box 3.10.1) [9].

**Box 3.10.1. A community-based integrated screening model**

Although single-disease screening strategies have documented benefits, it is worth integrating several of these strategies into a comprehensive screening programme to simultaneously detect multiple asymptomatic diseases, including both neoplastic and non-neoplastic chronic diseases. The benefits of this model include reducing the duplication of resources required for screening activities, enhancing attendance rates, and having the ability to identify possible associations between each test. For example, a model that integrates mammography, oral examinations, faecal occult blood tests, Pap smears, and biochemical blood tests into a single session has been implemented in the Matsu Islands since 2002, and this served as the platform for the *H. pylori* screen-and-treat approach.

The programme followed a test–treat–retest–retreat sequence in case of initial eradication failure. Individuals who tested positive received eradication treatment. Initially, the regimen was prescribed as follows: a 7–14-day triple therapy consisting of 40 mg of esomeprazole once a day, 1000 mg of amoxicillin twice a day, and

500 mg of clarithromycin twice a day. The updated regimen, used since 2012, was a 10-day sequential therapy consisting of 30 mg of lansoprazole and 1000 mg of amoxicillin twice a day for days 1–5, followed by 30 mg of lansoprazole, 500 mg of clarithromycin, and 500 mg of metronidazole twice a day for days 6–10 or the 14-day triple therapy [10]. The eradication was confirmed 6–8 weeks after the completion of treatment by recalling people and testing for *H. pylori* using the $^{13}$C-UBT. Individuals for whom the initial treatment failed were retreated with a 10-day triple therapy consisting of 40 mg of esomeprazole once a day, 1000 mg of amoxicillin twice a day, and 500 mg of levofloxacin once a day. The eradication was confirmed again at 6–8 weeks after the completion of treatment. Individuals in whom eradication was not achieved after two courses of treatment underwent individualized treatment according to the results of antibiotic susceptibility tests.

Upper endoscopy was optional for participants with *H. pylori* infection, and whether it was offered was determined primarily based on clinical indications, including symptoms, a family history of gastric cancer, surveillance for gastric precancerous conditions, or the presence of antibiotic-resistant *H. pylori*. In addition to the identification of any lesions suspicious of being cancerous, endoscopic examination was used to evaluate the prevalence and severity of precancerous gastric lesions using the modified Sydney classification with biopsy of the antrum and the body, as acute inflammation (polymorphonuclear infiltrates), chronic inflammation (lymphoplasmacytic infiltrates), atrophic gastritis (loss of glandular tissue and fibrous replacement), and intestinal metaplasia (presence of goblet cells and absorptive cells). The severity of each category was rated as none, mild, moderate, or marked [11]. The histological results were subsequently classified according to the Operative Link on Gastritis Assessment (OLGA) and the Operative Link on Gastric Intestinal Metaplasia Assessment (OLGIM) criteria [12, 13]. The prevalence of precancerous gastric lesions could serve as a surrogate outcome for gastric cancer and support the programme's effectiveness, although the participants who underwent endoscopy may differ from the general participant population. The prevalence of peptic ulcer disease was a subsidiary outcome of the programme.

All tests and treatments were provided free of charge, supported by the programme funding. The endoscopic examination was reimbursed through the country's universal health insurance.

### 3.10.5 Outcome assessment

Screening data were recorded by the staff of the Bureau of Health of the Matsu Islands and analysed by the community-based integrated screening committee. Outcomes of incident gastric cancer and death from gastric cancer were ascertained from the Cancer Registry and the Death Registry. The population at risk was determined by searching the databases of the Household Registration Administration System (Fig. 3.10.2). The outcome assessment included the evaluation of short-term indicators, intermediate-term indicators, and long-term indicators (see Chapter 8). Because of the small population size of the Matsu Islands, the programme was initiated in 2004 to enrol all eligible individuals, to assess the acceptability and feasibility of the programme [8]. This assessment included evaluations of short-term indicators such as participation rate, test positivity rate, referral rate after positive test results, eradication rate, and endoscopic findings. The sustainability of the treatment effects was assessed, and a second round was scheduled for 2008 to evaluate the *H. pylori* prevalence and the *H. pylori* reinfection rate.

After the implementation of the programme, a cost–effectiveness analysis using the initial data was conducted to simulate the long-term effects on gastric cancer outcomes and the associated medical costs [14] (see Chapter 9). The results of these analyses were compared with the results of the pepsinogen-based endoscopic screening programme. The findings indicated that screening for *H. pylori* could be as effective as endoscopic surveillance in reducing the mortality rate associated with gastric cancer. However, starting the primary prevention programme earlier in life was more cost-effective than beginning the secondary prevention strategy at a later age; this supports the implementation of the primary preventive initiative.

To assess the real-world effectiveness of the preventive programme for the intermediate-term indicators, the prevalence of *H. pylori* infection, the *H. pylori* reinfection rate, and the screening coverage rate were evaluated. The prevalence of premalignant gastric conditions, including atrophic gastritis and intestinal metaplasia, was used as a surrogate outcome for gastric cancer.

The long-term indicators of gastric cancer incidence and mortality rates were evaluated using a quasi-experimental design, comparing the outcome variables before and after the mass screening. This evaluation made adjustments for history effects that

are unrelated to the screening programme, and for improvements that would have occurred with no active intervention, on the decreasing trend of gastric cancer. Taking the gastric cancer incidence rate as the example, data from the pre-intervention period (before 2004) were used to form the historical control group (or the natural history model) (see Chapter 9), considering the downward trends of gastric cancer incidence due to improvements in sanitation and hygiene, as well as the effects of opportunistic *H. pylori* treatment. The parameters estimated from this period were used to formulate the prediction model to estimate the expected number of gastric cancer cases. When the expected number of gastric cancer cases is compared with the observed number of cases, the effectiveness of the population-based *H. pylori* screen-and-treat programme in reducing gastric cancer incidence can be calculated: (1 − observed/expected number) × 100% [15]. The prevalence of peptic ulcer disease was evaluated in a similar manner.

The gastric cancer incidence and mortality trends could also be used to formulate another prediction model, by extending these trends to 2030. The goal was to predict when the intervention could effectively make gastric cancer a rare disease, such as with an age-standardized incidence rate of < 4 per 100 000 person-years [16].

### 3.10.6 Benefits of the programme

For the short-term indicators, the first round of screening in 2004 had a participation rate of about 83% for the $^{13}$C-UBT, with a baseline *H. pylori* infection rate of 64.2%. The second round of the programme was carried out in 2008. By this time, the *H. pylori* prevalence was about 15%; therefore, screening was carried out on a biennial schedule. By 2024, the programme had effectively reduced the prevalence of *H. pylori* infection to about 10% (Fig. 3.10.3) [4]. The referral rate to treatment was about 93%.

For the intermediate-term indicators, the programme's population-level effectiveness in reducing *H. pylori* prevalence was estimated to be > 80%. For individuals who had previously had successful *H. pylori* eradication therapy, the *H. pylori* reinfection rate was estimated to be about 0.35 per 100 person-years (Fig. 3.10.3). By 2024, the screening coverage rate was > 90% and the prevalence of *H. pylori* infection was 9.2%. Most people with *H. pylori* infection are new immigrants or younger participants who have recently become eligible for screening. For the surrogate outcomes of gastric histologies, the prevalence of both atrophic gastritis and intestinal metaplasia was reduced

(Fig. 3.10.4) [4]. The prevalence of atrophic gastritis decreased from 60% to about 2%, and the prevalence of intestinal metaplasia decreased from 32% to about 12%. The severity of the diseases also decreased, leading to diseases with high-grade OLGA and OLGIM stage becoming rare.

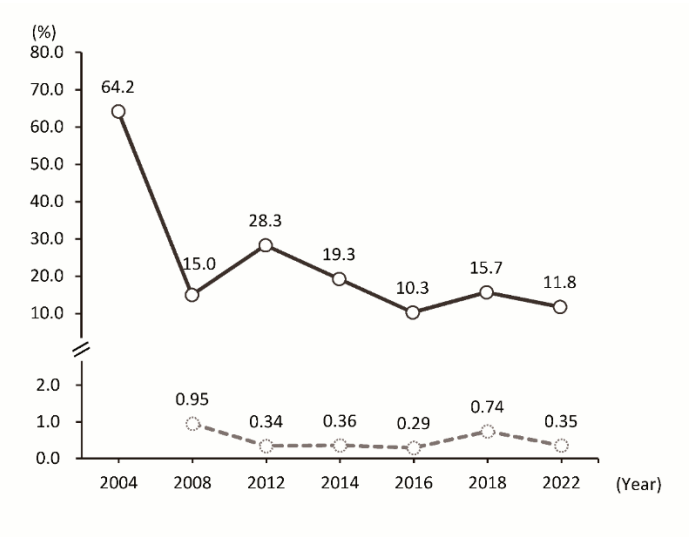


**Fig. 3.10.3.** Prevalence and reinfection rates of *H. pylori* infection in the Matsu Islands. The upper (solid) line shows the prevalence of *H. pylori* infection, and the lower (dashed) line shows the reinfection rates. Adapted with permission from Chiang et al. (2021) [4]. Copyright © 2021, Chiang et al. Published by BMJ Publishing Group Ltd. Article available under the Creative Commons CC BY-NC 4.0.

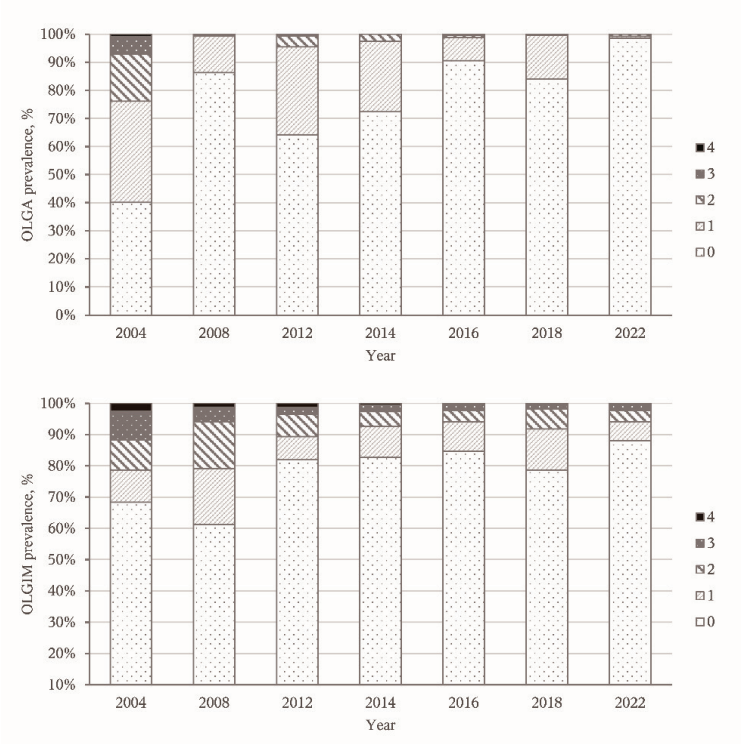


**Fig. 3.10.4.** Prevalence of precancerous gastric lesions according to the (top) Operative Link on Gastritis Assessment (OLGA) and (bottom) Operative Link on Gastric Intestinal Metaplasia Assessment (OLGIM) grading systems. Adapted with permission from Chiang et al. (2021) [4]. Copyright © 2021, Chiang et al. Published by BMJ Publishing Group Ltd. Article available under the Creative Commons CC BY-NC 4.0.

The results from the long-term indicators (i.e. the primary outcomes) showed a statistically significant reduction of 56% in the gastric cancer incidence rate until the end of 2021, compared with the pre-intervention period (Fig. 3.10.5). The gastric cancer mortality rate decreased by 36%, although this result was not statistically significant. Extrapolating these trends indicates that by 2030, reductions of 69% for gastric cancer incidence and of 57% for gastric cancer mortality would be expected. By 2030, the incidence rate of gastric cancer could potentially decrease to < 4 per 100 000 person-years, which is the threshold for considering that gastric cancer has been successfully eliminated as a public health problem [17]. For individuals who underwent endoscopy, the prevalence of active peptic ulcers decreased from 11% in 2004 to 3.6% in 2008, which is a reduction of 67.4% [15]. Since 2008, active peptic ulcers have become rare.

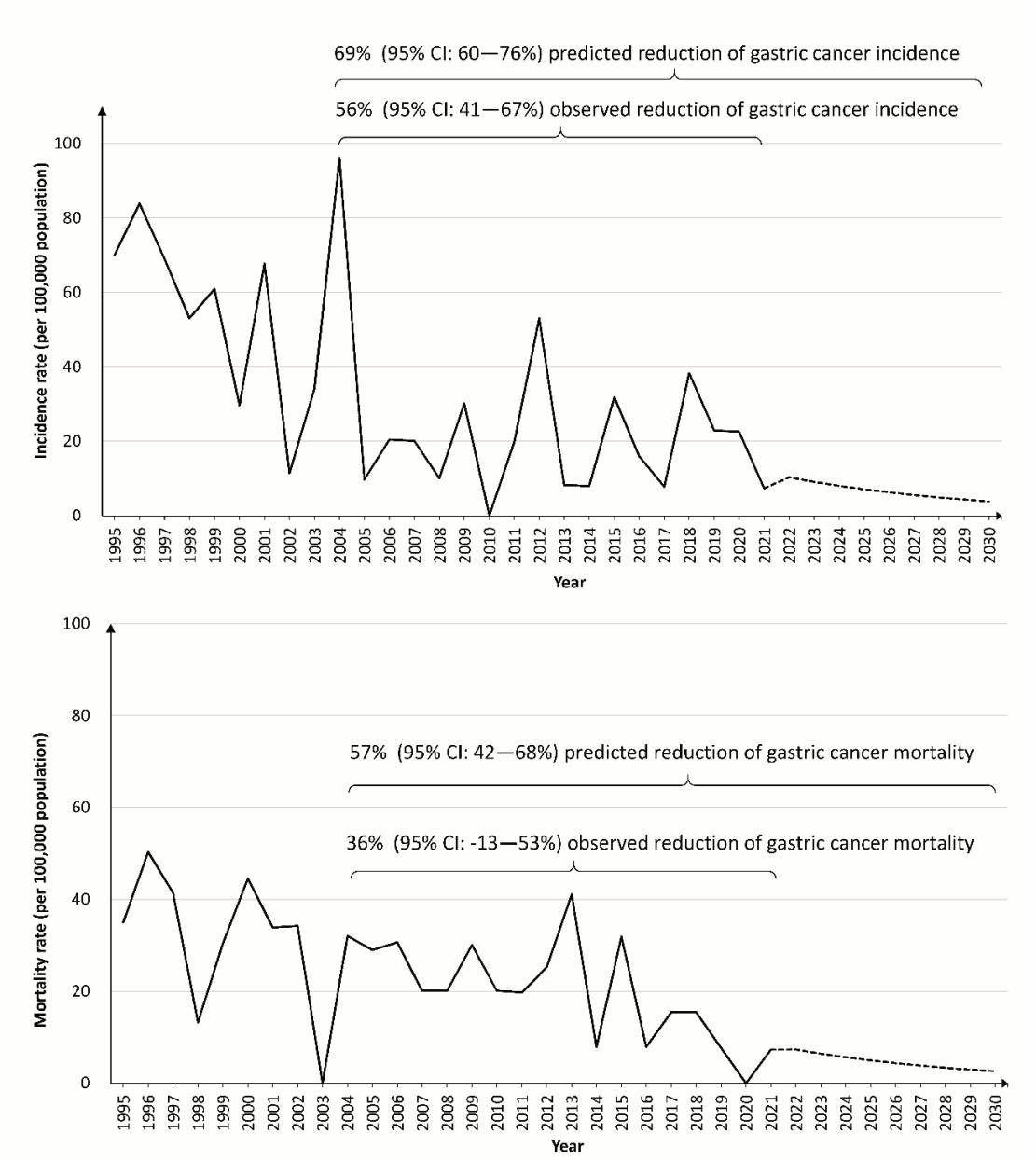


**Fig. 3.10.5.** Incidence and mortality rates of gastric cancer between 1995 and 2021, correlated with the start of the population-based screen-and-treat programme in 2004. The magnitude of risk reduction was determined by comparing the expected number of cases, based on the crude incidence rate (top) and the crude mortality rate (bottom) of gastric cancer between 1995 and 2003, with the observed number of cases during the population-based *H. pylori* screen-and-treat period. The dashed lines indicate the predicted trend to 2030 using Poisson regression models. CI, confidence interval. Adapted with permission from Chiang et al. (2021) [4]. 

### 3.10.7 Evaluation of possible harms

For the participants who received antibiotics, the most common adverse effects were taste distortion and diarrhoea, which each affected about 10% of participants. Fewer than 3% of participants discontinued the medication because of adverse effects [10]. No substantial adverse events were reported related to the endoscopic examination. Several approaches were used to evaluate the possible harms associated with widespread antibiotic eradication treatments.

First, for the antibiotic-resistant strains, in 2014 the resistance rate of *H. pylori* to amoxicillin was 0.8%, to metronidazole was 21.3%, to clarithromycin was 9.2%, to levofloxacin was 8.4%, and to tetracycline was 4.1%. By 2018, the resistance rate of *H. pylori* to amoxicillin was 1.0%, to metronidazole was 22.4%, to clarithromycin was 10.2%, to levofloxacin was 10.2%, and to tetracycline was 4.1%. The antibiotic resistance rates of *H. pylori* across four successive screening rounds did not show a statistically significant change (Fig. 3.10.6) [4], although there were modest increases in resistance rates to metronidazole, clarithromycin, and levofloxacin. Second, with respect to other diseases in the digestive tract, there was an initial increase in the prevalence of reflux oesophagitis [15], although the prevalence remained stable during the longer follow-up period [4]. Third, monitoring of the population cancer registry is ongoing for other cancer types. The incidence rates of oesophageal cancer (predominantly squamous cell carcinoma) and colorectal cancer before and after the mass eradication programme did not show statistically significant changes. In addition, the population microbiota in the Matsu Islands is being explored and compared with that of another, intervention-naive population [18].

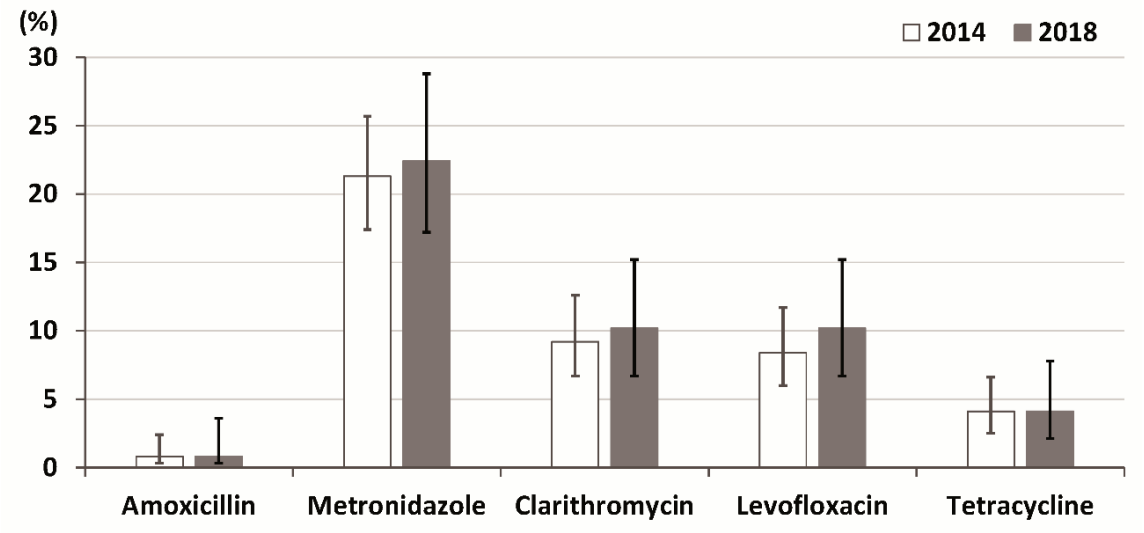


**Fig. 3.10.6.** Evaluation of the primary antibiotic resistance of *H. pylori* in the Matsu Islands; 95% confidence intervals are displayed on the bars. Adapted with permission from Chiang et al. (2021) [4]. Copyright © 2021, Chiang et al. Published by BMJ Publishing Group Ltd. Article available under the Creative Commons CC BY-NC 4.0.

### 3.10.8 Extending the Matsu Islands experience to other communities

The success of the gastric cancer prevention programme in the Matsu Islands has led to the dissemination of its preventive strategy to other health-care authorities. Because these programmes involve much larger eligible populations, they have been implemented with more systematic approaches to both the process and the outcome measurements. Given that gastric cancer risk and health-care infrastructure vary between populations, a greater emphasis has been placed on standardizing programme quality to maximize efficiency. This began by assessing the needs and readiness for *H. pylori* screening in the population, taking into account six key domains: the disease burden, the eligibility criteria for screening, health-care infrastructure, testing, treatment, and participation (see Chapter 4). The first population was the residents living in Changhua County, with crude and age-standardized gastric cancer incidence rates of about 14 and 10 per 100 000 person-years, respectively, in 2008–2012 [3]. For colorectal cancer, the crude and age-standardized incidence rates were 58 and 41 per 100 000 person-years, respectively. A population-wide screening programme for colorectal cancer has been in place since 2004 using the faecal immunochemical test [19]. Within this established screening framework, almost all criteria across various

domains for needs and readiness for *H. pylori* screening have been met (see Chapter 4), especially because the cold-chain transportation of stool samples is already in place. However, for the colorectal screening programme, there is still room for improvement in the participation rates for faecal occult blood testing. The addition of a stool test for *H. pylori* infection, alongside the health benefits associated with *H. pylori* management, may increase people's willingness to participate in the screening programme.

In 2014, after a 2-year pilot programme [20], a pragmatic randomized clinical trial was launched in Changhua County for individuals aged 50–69 years at average risk of colorectal cancer [18]. Standardized quality indicators were used to ensure consistency in how the screening was conducted, interpreted, and managed across the 26 townships involved. This programme aimed to provide individuals with the benefits of *H. pylori* eradication treatment for gastric cancer prevention (primary prevention) while also enabling early detection of colorectal cancer (secondary prevention). In a comparison between 63 508 individuals invited for dual stool screening and 88 995 individuals invited for single faecal occult blood testing, the participation rate increased by about 14% for dual stool screening. At about 5.5 years of follow-up in the clinical trial, a 14% reduction in gastric cancer incidence was observed, although this was not statistically significant. However, after adjusting for participation rates and differences in the baseline characteristics of the populations, the dual stool screening approach demonstrated a statistically significant reduction of 21% in gastric cancer incidence. In the participants in each group (~31 000 per group), there was a statistically significant reduction of 32% in gastric cancer incidence [21]. It took two decades to progress from the initial explanatory clinical trial assessing the effect of *H. pylori* eradication, in 2004 [1], to a pragmatic clinical trial evaluating the impact of *H. pylori* screening on gastric cancer incidence, in 2024 [21]. Based on the scientific evidence and the expanded inclusion of *H. pylori* treatment in health insurance coverage (Box 3.10.2), the population-based *H. pylori* screen-and-treat approach has been rolled out as a service screening since 2024.

### Box 3.10.2. Road to coverage by the health insurance system

The traditional indication for *H. pylori* treatment was limited to patients with endoscopically proven peptic ulcers. The expansion of the screen-and-treat programme from the Matsu Islands to other communities highlighted the need to broaden the indications for *H. pylori* infection diagnosed by non-invasive testing. This proposal was submitted to the health insurance authority by the Gastroenterological Society on 1 November 2022 and was subsequently evaluated for cost–effectiveness and financial impact by the Center for Drug Evaluation at the request of the Health Promotion Administration. After the determination of appropriateness for coverage and the establishment of clinical guidelines, the results were reviewed by the Pharmaceutical Benefit and Reimbursement Scheme Joint Committee on 20 July 2024. This review involved discussions between policy-makers, the staff of the Food and Drug Administration, medical experts, and representatives of medical societies, insured people, and employers. Decisions about coverage are ultimately made based on evidence-based medicine, cost–effectiveness, affordability, and the overall improvement of public health outcomes. This policy was launched on 1 August 2024.

Continuous efforts have been made to identify high-risk populations by reviewing and stratifying gastric cancer incidence based on the annual cancer registration reports from across the country. The second population was Indigenous people, who are linguistically and culturally related to Austronesian peoples and reside primarily in remote and mountainous areas in Taitung County and Hualien County. The incidence rate of gastric cancer in Indigenous people is about 2–3 times that in non-Indigenous counterparts. In 2014, the crude and age-standardized gastric cancer incidence rates were about 25 and 23 per 100 000 person-years, respectively. Although there is a strong need for screening, the readiness for *H. pylori* screening had to overcome several challenges in various domains, particularly in the infrastructure for sending out invitations, test accuracy, reliable treatment, and uncertainties regarding participation. These barriers included administrative challenges, geographical distances, economic constraints, and cultural factors [22].

In 2018, screening and eradication of *H. pylori* were offered to individuals aged 20–60 years in Indigenous populations, using the $^{13}$C-UBT because of its stability during transportation [22]. This programme was specifically aimed at reducing health disparities related to gastric cancer, which are often more prevalent in populations with lower socioeconomic status, increased exposure to environmental risk factors such as *H. pylori* infection, lifestyle habits that facilitate *H. pylori* transmission within families, and greater barriers to accessing screening activities. To address these challenges, the programme was implemented alongside the development of an information technology system to manage the process and evaluate the outcomes, thus ensuring the quality of screening (see Chapter 8). As of 2023, the programme had successfully expanded from 16 to 55 Indigenous townships [23].

### 3.10.9 Further planned activities and future directions

The statistically significant reduction of 50% in gastric cancer incidence in the long-term cohort in the Matsu Islands and the projected reduction of about 70% by 2030 have confirmed the feasibility and applicability of adopting the *H. pylori* screening and eradication programme to decrease the gastric cancer burden. In the post-eradication period in the Matsu Islands, three noteworthy issues emerged, prompting the development of additional strategies.

First, the population in the Matsu Islands was dynamic, characterized by continuous immigration of individuals from other high-risk communities who potentially had a higher prevalence of *H. pylori* infection. This led to a persistent 10% prevalence of *H. pylori* infection despite the repeated mass screening efforts. In addition, the proportion of the population who were registered in the Matsu Islands but lived elsewhere increased, and these individuals potentially fell outside the coverage of screening services. However, the gastric cancer incident cases and deaths continue to be counted for the Matsu Islands [3]. This may contribute to the slower decrease in gastric cancer incidence and mortality rates. To address this issue, further extending the preventive strategies should be considered, to increase the regional coverage of screening services. This extension should be guided by gastric cancer statistics and corresponding data on *H. pylori* prevalence, coupled with cost–effectiveness analyses with outcome simulations [7].

Second, although *H. pylori* infection was highly associated with the occurrence of gastric cancer, *H. pylori* eradication was not able to completely eliminate the risk of

gastric cancer in cases in which chronic infection had existed for decades. Post-*H. pylori* eradication gastric cancer has become a topic of interest. To identify individuals with a residual risk of developing gastric cancer and to allocate the limited endoscopic resources, an effective endoscopic surveillance method is needed to enhance the early detection rate of gastric cancers. Although pepsinogen testing demonstrated effectiveness in predicting atrophic gastritis or intestinal metaplasia in the pre-eradication period [24], its accuracy would be reduced after *H. pylori* eradication. This reduced accuracy is partly because the improved histological findings and enhanced integrity of the gastric mucosal barrier may lead to decreased pepsinogen backflow to the circulation, complicating the interpretation of the pepsinogen test results, and also because the genetic damage may persist despite histological improvement [25, 26].

Third, the grading of gastric histology may aid in risk stratification [27], although this may have limitations, such as lower coverage rates because it involves an invasive procedure, sampling variability in the location and number of biopsies from normal-appearing mucosa, and variability in histological interpretation for atrophic gastritis and intestinal metaplasia. Ongoing projects are using big medical data and artificial intelligence to assist with histological grading (ClinicalTrials.gov ID, NCT05762991) and to assess the value of additional pepsinogen testing at the time of *H. pylori* testing (ClinicalTrials.gov ID, NCT03793335). The direct quantitative measure of genetic damage has also been shown to be promising in stratifying the residual risk [25]. These projects aim to improve the early detection rate of gastric cancers by incorporating individual-level characteristics, in addition to population screening for *H. pylori* infection, with the ultimate goal of reducing deaths related to gastric cancer.

### 3.10.10 How applicable are the lessons learned from the Matsu Islands?

The campaign against gastric cancer in the Matsu Islands, although small in scale, can serve as an example of how to start to intervene to reduce the burden of gastric cancer. It could act as a pilot programme that may be extended to larger populations with varying risk levels. Lessons learned from this programme can be generalized in several ways. First, regions facing similar challenges in health-care access, limited medical resources, and a high disease burden because of geographical barriers could benefit from adopting a similar approach. The initial considerations included infrastructure development, health-care workforce training, and community engagement (see the

checklist in Chapter 4). The execution of the programme should follow the organized screening principles of invitation, testing, referral to treatment, eradication treatment, and selected endoscopic examination for individuals who are clinically indicated (see Chapter 8). Second, the emphasis on the non-invasive screening test and effective eradication treatments in this programme can be generalized to other health-care contexts where human resources for endoscopy services are limited. In addition, the use of non-invasive methods can improve participants' acceptance and compliance. Third, the screening programme requires scientific evaluation. Outcome evaluation is invaluable, because evidence-based knowledge can be generated from the outcomes of the screening service, and this knowledge could be applicable to the broader context of health-care delivery.

## References


1. Wong BC, Lam SK, Wong WM, Chen JS, Zheng TT, Feng RE, et al.; China Gastric Cancer Study Group (2004). *Helicobacter pylori* eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. JAMA. 291(2):187–94. https://doi.org/10.1001/jama.291.2.187 PMID:14722144
2. Fujian Cancer Prevention and Control Office (2023). Fujian Cancer Registry annual report [in Chinese]. Available from: https://wjw.fujian.gov.cn/xxgk/gzdt/mtbd/202404/t20240417_6431437.htm.
3. Health Promotion Administration (2024). Cancer registry data [in Chinese]. Available from: https://wjw.fujian.gov.cn/xxgk/gzdt/mtbd/202404/t20240417_6431437.htm.
4. Chiang TH, Chang WJ, Chen SL, Yen AM, Fann JC, Chiu SY, et al. (2021). Mass eradication of *Helicobacter pylori* to reduce gastric cancer incidence and mortality: a long-term cohort study on Matsu Islands. Gut. 70(2):243–50. https://doi.org/10.1136/gutjnl-2020-322200 PMID:32792335
5. Liu CY, Wu CY, Lin JT, Lee YC, Yen AM, Chen TH (2006). Multistate and multifactorial progression of gastric cancer: results from community-based mass screening for gastric cancer. J Med Screen. 13(Suppl 1):S2–5. PMID:17227633
6. Correa P (1992). Human gastric carcinogenesis: a multistep and multifactorial process – first American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. Cancer Res. 52(24):6735–40. PMID:1458460
7. Chiang TH, Cheng HC, Chuang SL, Chen Y-R, Hsu Y-H, Hsu T-H, et al. (2022). Mass screening and eradication of *Helicobacter pylori* as the policy recommendations for gastric cancer prevention. J Formos Med Assoc. 121(12):2378–92. https://doi.org/10.1016/j.jfma.2022.08.012 PMID:36085264
8. Lee YC, Wu HM, Chen TH, Liu T-Y, Chiu H-M, Chang C-C, et al. (2006). A community-based study of *Helicobacter pylori* therapy using the strategy of test, treat, retest, and re-treat initial treatment failures. Helicobacter. 11(5):418–24. https://doi.org/10.1111/j.1523-5378.2006.00432.x PMID:16961802
9. Chen TH, Chiu YH, Luh DL, Yen M-F, Wu H-M, Chen L-S, et al.; Taiwan Community-Based Integrated Screening Group (2004). Community-based multiple screening model: design, implementation, and analysis of 42,387 participants. Cancer. 100(8):1734–43. https://doi.org/10.1002/cncr.20171 PMID:15073864
10. Liou JM, Chen CC, Chang CY, Chen M-J, Chen C-C, Fang Y-J, et al.; Taiwan Gastrointestinal Disease and Helicobacter Consortium (2016). Sequential therapy for 10 days versus triple therapy for 14 days in the eradication of *Helicobacter pylori* in the community and hospital populations: a randomised trial. Gut. 65(11):1784–92. https://doi.org/10.1136/gutjnl-2015-310142 PMID:26338825
11. Dixon MF, Genta RM, Yardley JH, Correa P (1996). Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. Am J Surg Pathol. 20(10):1161–81. https://doi.org/10.1097/00000478-199610000-00001 PMID:8827022
12. Rugge M, Meggio A, Pennelli G, Piscioli F, Giacomelli L, De Pretis G, et al. (2007). Gastritis staging in clinical practice: the OLGA staging system. Gut. 56(5):631–6. https://doi.org/10.1136/gut.2006.106666 PMID:17142647
13. Capelle LG, de Vries AC, Haringsma J, Ter Borg F, de Vries RA, Bruno MJ, et al. (2010). The staging of gastritis with the OLGA system by using intestinal metaplasia as an accurate alternative for atrophic gastritis. Gastrointest Endosc. 71(7):1150–8. https://doi.org/10.1016/j.gie.2009.12.029 PMID:20381801
14. Lee YC, Lin JT, Wu HM, Liu T-Y, Yen M-F, Chiu H-M, et al. (2007). Cost-effectiveness analysis between primary and secondary preventive strategies for gastric cancer. Cancer Epidemiol Biomarkers Prev. 16(5):875–85. https://doi.org/10.1158/1055-9965.EPI-06-0758 PMID:17507609
15. Lee YC, Chen TH, Chiu HM, Shun C-T, Chiang H, Liu T-Y, et al. (2013). The benefit of mass eradication of *Helicobacter pylori* infection: a community-based study of gastric cancer prevention. Gut. 62(5):676–82. https://doi.org/10.1136/gutjnl-2012-302240 PMID:22698649
16. Singh D, Vignat J, Lorenzoni V, Eslahi M, Ginsburg O, Lauby-Secretan B, et al. (2023). Global estimates of incidence and mortality of cervical cancer in 2020: a baseline analysis of the WHO Global Cervical Cancer Elimination Initiative. Lancet Glob Health. 11(2):e197–206. https://doi.org/10.1016/S2214-109X(22)00501-0 PMID:36528031
17. WHO (2020). Global strategy to accelerate the elimination of cervical cancer as a public health problem. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/publications/i/item/9789240014107.
18. Lee YC, Chiang TH, Chiu HM, Wu M-S, Yeh Y-P, Hsiu-Hsi Chen T; Collaborators of the Taiwan Community-Based Integrated Screening Group (2021). Community-based gastric cancer screening

coupled with a national colorectal cancer screening program: baseline results. Gastroenterology. 160(6):2159–2161.e4. https://doi.org/10.1053/j.gastro.2021.01.008 PMID:33444571
19. Lee YC, Hsu CY, Chen SL, Yen AM-F, Chiu SY-H, Fann JC-Y, et al. (2019). Effects of screening and universal healthcare on long-term colorectal cancer mortality. Int J Epidemiol. 48(2):538–48. https://doi.org/10.1093/ije/dyy182 PMID:30184208
20. IARC *Helicobacter pylori* Working Group (2014). *Helicobacter pylori* eradication as a strategy for preventing gastric cancer (IARC Working Group Reports No. 8). Lyon, France: International Agency for Research on Cancer. Available from: https://publications.iarc.who.int/391.
21. Lee YC, Chiang TH, Chiu HM, Su W-W, Chou K-C, Chen SL-S, et al.; Collaborators of Taiwan Community-based Integrated Screening Group (2024). Screening for *Helicobacter pylori* to prevent gastric cancer: a pragmatic randomized clinical trial. JAMA. 332(19):1642–51. https://doi.org/10.1001/jama.2024.14887 PMID:39348147
22. Bair MJ, Chuang SL, Lei WY, Chen C-L, Tian H-W, Chiang T-H, et al. (2020). Planning mass eradication of *Helicobacter pylori* infection for indigenous Taiwanese peoples to reduce gastric cancer. J Gastroenterol Hepatol. 35(4):609–16. https://doi.org/10.1111/jgh.14898 PMID:31677184
23. Lei WY, Lee JY, Chuang SL, Bair M-J, Chen C-L, Wu J-Y, et al. (2023). Eradicating *Helicobacter pylori* via $^{13}$C-urea breath screening to prevent gastric cancer in indigenous communities: a population-based study and development of a family index-case method. Gut. 72(12):2231–40. https://doi.org/10.1136/gutjnl-2023-329871 PMID:37197905
24. Chiang TH, Chiu SY, Chen SL, Yen AM-F, Fann JC-Y, Liu C-Y, et al. (2019). Serum pepsinogen as a predictor for gastric cancer death: a 16-year community-based cohort study. J Clin Gastroenterol. 53(5):e186–93. https://doi.org/10.1097/MCG.0000000000000992 PMID:29369241
25. Asada K, Nakajima T, Shimazu T, Yamamichi N, Maekita T, Yokoi C, et al. (2015). Demonstration of the usefulness of epigenetic cancer risk prediction by a multicentre prospective cohort study. Gut. 64(3):388–96. https://doi.org/10.1136/gutjnl-2014-307094 PMID:25379950
26. Chiang TH, Maeda M, Yamada H, Chan C-C, Chen SL-S, Chiu SY-H, et al. (2021). Risk stratification for gastric cancer after *Helicobacter pylori* eradication: a population-based study on Matsu Islands. J Gastroenterol Hepatol. 36(3):671–9. https://doi.org/10.1111/jgh.15187 PMID:32671873
27. Rugge M, Genta RM, Malfertheiner P, Dinis-Ribeiro M, El-Serag H, Graham DY, et al.; RE.GA.IN (2024). RE.GA.IN.: the Real-world Gastritis Initiative – updating the updates. Gut. 73(3):407–41. https://doi.org/10.1136/gutjnl-2023-331164 PMID:38383142