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Helicobacter pylori Eradication as a Strategy for Preventing Gastric Cancer

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Helicobacter pylori Eradication as a Strategy for Preventing Gastric Cancer

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SECTION 4: CURRENT AND PLANNED STUDIES OF THE POTENTIAL OF *HELICOBACTER PYLORI* TREATMENTS FOR GASTRIC CANCER REDUCTION

Abbreviations

ASR	age-standardized incidence rate
BUPA	British United Provident Association
^{13}C-UBT	^{13}C-urea breath test
CAG	chronic atrophic gastritis
CI	confidence interval
CI5	*Cancer Incidence in Five Continents*
CYP	cytochrome P450
DDD	defined daily dose
ELISA	enzyme-linked immunosorbent assay
ESCC	oesophageal squamous cell carcinoma
FIT	faecal immunochemical test
FOBT	faecal occult blood test
G-17	gastrin-17
GORD	gastro-oesophageal reflux disease
GWAS	genome-wide association studies
HPSA	*H. pylori* stool antigen
HR	hazard ratio
IARC	International Agency for Research on Cancer
IgG	immunoglobulin G
MALT	mucosa-associated lymphoid tissue
MAPS	Management of precancerous conditions and lesions in the stomach
miRNA	microRNA
MG7-Ag	gastric carcinoma-associated antigen
MHLW	Japanese Ministry of Health, Labour and Welfare
NCI	United States National Cancer Institute
NCSP	National Cancer Screening Program of the Republic of Korea
NHI	National Health Insurance
NHS	National Health Service
OA	omeprazole–amoxicillin
OAM	omeprazole–amoxicillin–metronidazole
OCM	omeprazole–clarithromycin–metronidazole
OR	odds ratio
PAF	population attributable fraction
Pg	pepsinogen
PPI	proton pump inhibitor
QALYs	quality-adjusted life-years
RR	relative risk
RUT	rapid urease test
SNP	single-nucleotide polymorphism
Th1	T helper 1
Treg	regulatory T cell
UBT	urea breath test
UGIS	upper gastrointestinal series
WHO	World Health Organization

Summary of IARC Working Group Meeting on *Helicobacter pylori* eradication as a strategy for preventing gastric cancer

Jin Young Park, E. Robert Greenberg, Julie Parsonnet, Christopher P. Wild, David Forman, and Rolando Herrero, for the IARC *Helicobacter pylori* Working Group

The International Agency for Research on Cancer (IARC) of the World Health Organization convened a Working Group Meeting in December 2013 to review evidence regarding *Helicobacter pylori* treatment as a strategy for preventing gastric cancer, the third leading cause of cancer death globally. The burden of this disease is largely borne by populations in low- and middle-income countries, where resources for treating advanced cancer are limited, so cost-effective prevention strategies are needed. The Working Group members included 19 external experts and 11 IARC participants. Their review included presentations on the following topics: status of regional gastric cancer prevention efforts, health effects and consequences of *H. pylori* eradication, cost–effectiveness and feasibility of *H. pylori* screening and treatment programmes, and current and planned studies of the potential of *H. pylori* treatments for gastric cancer reduction.

Status of regional gastric cancer prevention efforts

In 2012, an estimated 1 million new cases of gastric cancer and 720 000 gastric cancer-related deaths occurred worldwide, the majority of them in East Asia, and nearly half in China. Many other countries, especially in Latin America and eastern Europe, also have relatively high rates of gastric cancer. Over the past four decades, incidence rates of gastric cancer have steadily declined in most populations, regardless of their background risk. Yet despite an anticipated continued reduction in rates of approximately 2% per year, the future burden of gastric cancer, in numbers of cases and deaths, is expected to rise as the world's population increases and ages.

Although gastric cancer has not been a public health priority worldwide, a few countries in East Asia with a high burden of the disease have implemented control efforts. The Republic of Korea, where the age-standardized gastric cancer incidence rate is the highest globally, has an established nationwide screening programme, which provides screening with either upper gastrointestinal series (barium swallow) or endoscopy every 2 years to individuals aged 40 years and older. In 2012, more than 12 million people were invited for screening, and about half participated. In Japan, gastric cancer prevention efforts have primarily focused on early detection using barium contrast imaging. However, screening has not been widely accepted by the target population, and less than 10% were screened in 2010. The emphasis is now shifting towards treating *H. pylori*, and in 2013 the Japanese government approved national health insurance coverage for antibiotic treatment for *H. pylori* infection in patients with endoscopically diagnosed chronic gastritis. In Changhua County, on the island of Taiwan, China, organized gastric cancer prevention is included in a community-based integrated screening programme that provides *H. pylori* stool antigen testing (as well as faecal immunochemical testing for colorectal cancer screening); individuals who test positive for *H. pylori* are offered endoscopic screening and antibiotic treatment.

In Latin America, Chile has introduced an opportunistic gastric cancer screening programme that focuses on symptomatic adults aged 40 years and older. The programme provides endoscopic examination for *H. pylori* detection, biopsy, and treatment. Other gastric cancer prevention activities in Latin America have mainly entailed opportunistic endoscopy screening conducted by private organizations, and they have resulted in limited population coverage.

Health effects and consequences of *H. pylori* eradication

IARC classified *H. pylori* as a Group 1 carcinogen in 1994, and reconfirmed this classification in 2009. Approximately 89% of non-cardia gastric cancer cases, representing 78% of all gastric cancer cases, are now estimated to be attributable to chronic *H. pylori* infection. Until relatively recently there were scant data from randomized clinical trials on the effectiveness of treating *H. pylori* infection to reduce cancer risk. In 2012, long-term follow-up results were reported from a randomized trial in Shandong, China, which found a statistically significant 39% reduction in gastric cancer risk [1], and in 2014, a meta-analysis of all reported randomized trials estimated a relative risk of 0.66 (95% confidence interval, 0.46–0.95) [2]. Two trials have assessed the effect of *H. pylori* treatment after endoscopic mucosal resection of early gastric cancer [3, 4]. One of the trials, in Japan, reported a statistically significant reduction in risk of metachronous gastric cancer [3]. Risk also appeared lower in a study in the Republic of Korea, but the result was not statistically significant [4]. Although these results of randomized trials indicate that *H. pylori* treatment lowers gastric cancer incidence by 30–40%, the available data do not permit precise estimation of overall benefits and possible adverse consequences, and the results may not be widely generalizable.

Programmes of treating *H. pylori* infection may have other health effects, both positive and negative. *H. pylori* is an important cause of peptic ulcer disease, and randomized trials of *H. pylori* treatment have shown that it significantly reduces risk of new ulcer development. In randomized trials conducted in the United Kingdom, community-based programmes of *H. pylori* treatment resulted in fewer visits to medical facilities for dyspepsia symptoms. There is also evidence that treating *H. pylori* can prevent anaemia. On the negative side, some studies have suggested that *H. pylori* has immunological and physiological benefits; thus, treatment to eradicate the organism might cause harm. A negative association between *H. pylori* infection and oesophageal adenocarcinoma seems to be well established in epidemiological studies.

Epidemiological studies also have suggested a negative association between *H. pylori* infection and asthma, eczema, and other immunological conditions, although the findings overall are inconsistent and sometimes conflicting. Studies suggesting that *H. pylori* infection may increase risk of other infectious diseases, including activation of latent tuberculosis, are thus far few in number, and their findings are not totally consistent. At the same time that *H. pylori* and ulcer disease have been disappearing from many populations, gastro-oesophageal reflux disease (GORD), Barrett oesophagus, and oesophageal adenocarcinoma have been increasing. Meta-analyses have provided differing results as to whether risk of GORD is increased in those treated for *H. pylori*. There are plausible physiological mechanisms by which *H. pylori* treatment could influence weight, but reported associations between *H. pylori* treatment and weight gain have been inconsistent and of relatively modest size.

At the population level, a programme of population screening and treatment for *H. pylori* could plausibly increase the prevalence of antibiotic-resistant pathogens within the community. In many countries, where indiscriminate use of antibiotics for human and veterinary purposes is common, it may be difficult to identify a particular effect of an *H. pylori* treatment programme against the background of resistance due to use of antibiotics for other purposes. Concern would be increased if the *H. pylori* treatment regimen contained antibiotics that are essential for treating serious human infections. At the individual level, treatment for *H. pylori* infection selects for organisms that are resistant to the antibiotics contained in the regimen used. *H. pylori* eradication treatment affects antibiotic resistance of normal bacterial flora and will also alter the intestinal microbiome; however, adverse health consequences have not been demonstrated.

Cost–effectiveness and feasibility of *H. pylori* screening and treatment programmes

Programmes of *H. pylori* screening and treatment are likely to be feasible and relatively affordable. An inexpensive blood test can be used to identify likely candidates for treatment; with a sensitivity of about 95% and a specificity of about 90%, this is not an ideal test but is perhaps acceptable for a population-based screening programme. The urea breath test and stool antigen test have at least as good sensitivity and higher specificity (better than 95%) for active infection, but the cost and complexity of testing are higher.

Treatment regimens that contain two or three inexpensive, generic antibiotics plus a proton pump inhibitor for 7–14 days can achieve greater than 80% success in eliminating *H. pylori* infection, although effectiveness will vary according to the profile of antibiotic resistance in the target population. Although the ideal approach would be a treatment chosen based on culture and susceptibility testing, the most feasible approaches for population-based treatment programmes will be either to use regimens that have been proven to be reliably effective in the area or to select a regimen based on the observed pattern of antimicrobial resistance in the target population.

Nine reports on health economic models have indicated that population *H. pylori* screening and treatment strategies are cost-effective using a threshold of US$ 50 000 per life-year saved. Some limitations of the published models are that they were based on observational epidemiological data rather than on the more recently published results of randomized trials evaluating *H. pylori* treatment to prevent gastric cancer, that most did not evaluate the cost savings from reducing dyspepsia in the population, that their estimates were based on years of life saved rather than quality-adjusted life-years, and that they did not consider possible deleterious effects of treatment. Also, the absence of data from low-income countries limits the utility of the analyses.

Gastric cancer is a multifactorial disease, and a combination of markers including host genetic factors, *H. pylori* virulence factors, and environmental factors such as diet may help to identify patients at risk. However, the value of using markers to stratify on risk among individuals and to guide public health interventions is not established.

Current and planned studies of the potential of *H. pylori* treatments for gastric cancer reduction

Several clinical trials that are currently under way should help to clarify whether and how to implement population-based *H. pylori* screening and treatment programmes. The largest of these was initiated in 2011 in Linqu County in China. The trial is enrolling 200 000 participants aged 25–64 years from a high-risk population and is allocating them in a randomized cluster design to treatment with anti-*H. pylori* quadruple therapy or to control (low-dose omeprazole and bismuth citrate). Participants will be followed up for 10 years.

In the United Kingdom, the *H. pylori* Screening Study (HPSS) began in 1997, and was designed to assess whether screening for and eradicating *H. pylori* infection in healthy men aged 35–69 years and women aged 45–69 years would reduce the incidence of gastric cancer. The target number of participants was 56 000, with a planned follow-up of 15 years or more after recruitment. Results should be available within the next few years.

A multicentre randomized study is proposed for Latvia, Belarus, and the Russian Federation, areas with a moderately high burden of gastric cancer. The objective is to evaluate whether serum pepsinogen and *H. pylori* testing are effective in identifying high-risk subjects to be referred for appropriate treatment with subsequent reduction in gastric cancer mortality. A pilot study in Latvia was launched in 2013 to test the study procedures, assumptions, and acceptability of the methods.

In the Republic of Korea, a multicentre, randomized controlled trial commencing in 2014 will evaluate the preventive efficacy and effectiveness of *H. pylori* treatment in reducing gastric cancer incidence among participants aged 40–60 years recruited from the nationwide cancer screening programme. The goal is to define the possible role of *H. pylori* screening and treatment in gastric cancer development within the context of a population-based screening programme. The trial is scheduled to run for 10 years, with biennial endoscopic follow-up.

Conclusions and recommendations

The Working Group recognizes that gastric cancer is a disease of high importance for global health, and it is likely to remain so for the foreseeable future unless effective control measures are implemented. The continuing high global burden of gastric cancer and the feasibility of treating its principal cause thus make it a logical target for intervention.

There is an acute need to commit more public health resources to gastric cancer control. The Working Group recommends that all countries consider including gastric cancer in their national cancer control programmes and that they conduct detailed assessments of its current and future human and economic impacts and of the potential value of prevention strategies. Collecting standardized data on *H. pylori* prevalence will be useful for predicting the future burden of gastric cancer and other *H. pylori*-associated conditions and may help to identify subpopulations that appear most likely to benefit from interventions.

Randomized clinical trials have found that *H. pylori* treatment is effective in preventing gastric cancer, and models indicate that *H. pylori* screening and treatment strategies would be cost-effective. However, uncertainties remain about the generalizability of results and about the cost–effectiveness and possible adverse consequences of programmes applied in community settings. The Working Group therefore recommends that countries explore the possibility of introducing population-based *H. pylori* screening and treatment programmes, but cautions that decisions as to whether and how to implement *H. pylori* testing and treatment must hinge on local considerations of disease burden, other health priorities, and cost–effectiveness analyses. Moreover, these programmes should be implemented in conjunction with a scientifically valid assessment of programme processes, feasibility, effectiveness, and possible adverse consequences.

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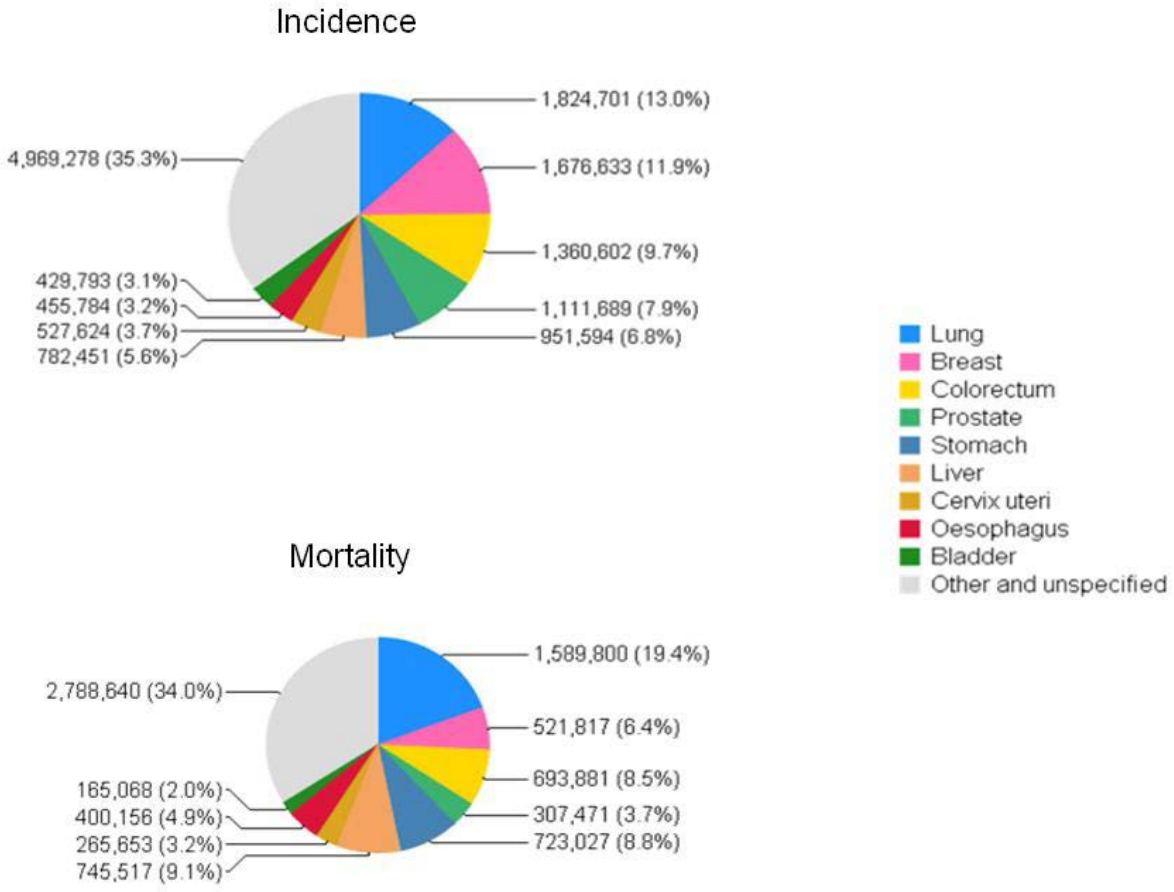
Introduction

The current and projected global burden of gastric cancer

David Forman and Mónica S. Sierra

Gastric cancer is now the fifth most common malignancy in the world, after lung, breast, colorectal, and prostate cancer. The most recent estimates from GLOBOCAN 2012 [1] indicate that nearly 1 million (951 594) new gastric cancer cases and 723 027 deaths occurred globally in 2012, accounting for 7% of the total new cancer cases and 9% of the total cancer deaths (Fig. 1).

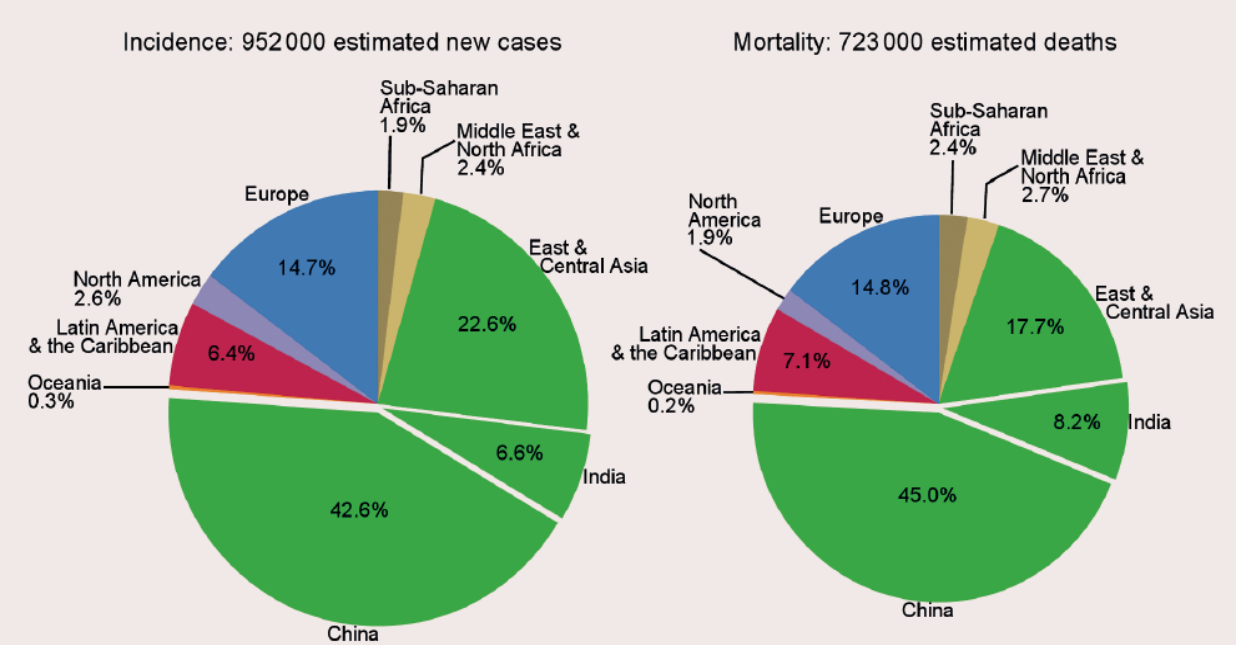
Fig. 1. Estimated frequency of new cancer cases and deaths worldwide in 2012, for both sexes combined. Source: Ferlay et al. (2013) [1].



The distribution of gastric cancer varies across geographical regions. In this chapter, we use the term “less developed regions” to include all regions of Africa, Asia (excluding Japan), Latin America and the Caribbean, Melanesia, Micronesia, and Polynesia, and the term “more developed regions” to include all regions of Europe, North America, Australia, New Zealand, and Japan. Among the 952 000 estimated new cancer gastric cancer cases that occurred worldwide in 2012, more than 70% (677 000 cases) were in less developed regions of the world and 29% (275 000 cases) were in more developed regions. Asia contributed approximately 74% (700 000 cases) to the global burden, and almost half of the cases in the world occurred in China alone (405 000 cases). Europe contributed about 17% (162 000

cases) to the global burden, whereas Latin America and the Caribbean contributed about 6% (61 000 cases) (Fig. 2).

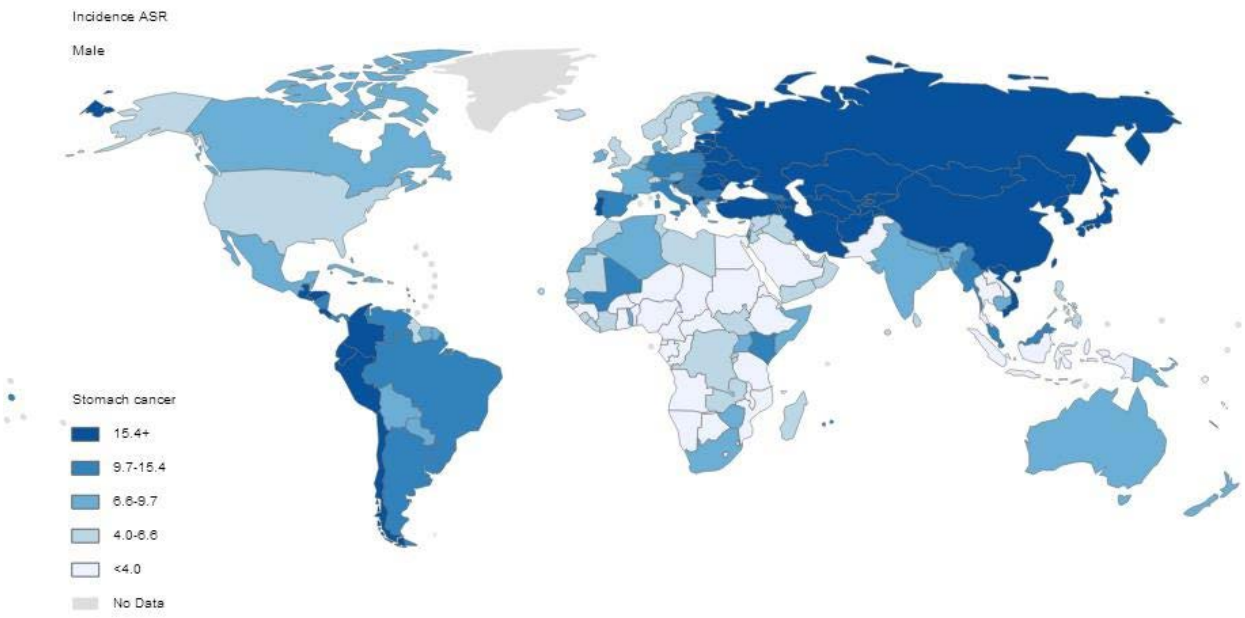
Fig. 2. Estimated numbers of new gastric cancer cases and deaths in 2012, with proportions by major world regions, for both sexes combined. Source: Stewart and Wild (2014) [2].



The geographical distribution of gastric cancer varies widely by sex. The estimated age-standardized (world) rates in 2012 among males were twice the rates among females (incidence per 100 000 person-years: 17.4 in males and 7.5 in females; mortality per 100 000 person-years: 12.7 in males and 5.7 in females). Among males, age-standardized incidence rates ranged from 1.3 in Mozambique to 62.3 in the Republic of Korea (Fig. 3A), whereas age-standardized mortality rates ranged from 1.2 in Mozambique to 37.1 in Mongolia (Fig. 3B). Similar distributions were observed in females; however, the age-standardized incidence and mortality rates were uniformly lower than the corresponding rates in males (Fig. 4A and 4B).

Fig. 3. (A) Estimated age-standardized (world) incidence rates of gastric cancer per 100 000 person-years by country among males in 2012. (B) Estimated age-standardized (world) incidence rates of gastric cancer per 100 000 person-years by country among females in 2012. Source: Ferlay et al. (2013) [1].

A



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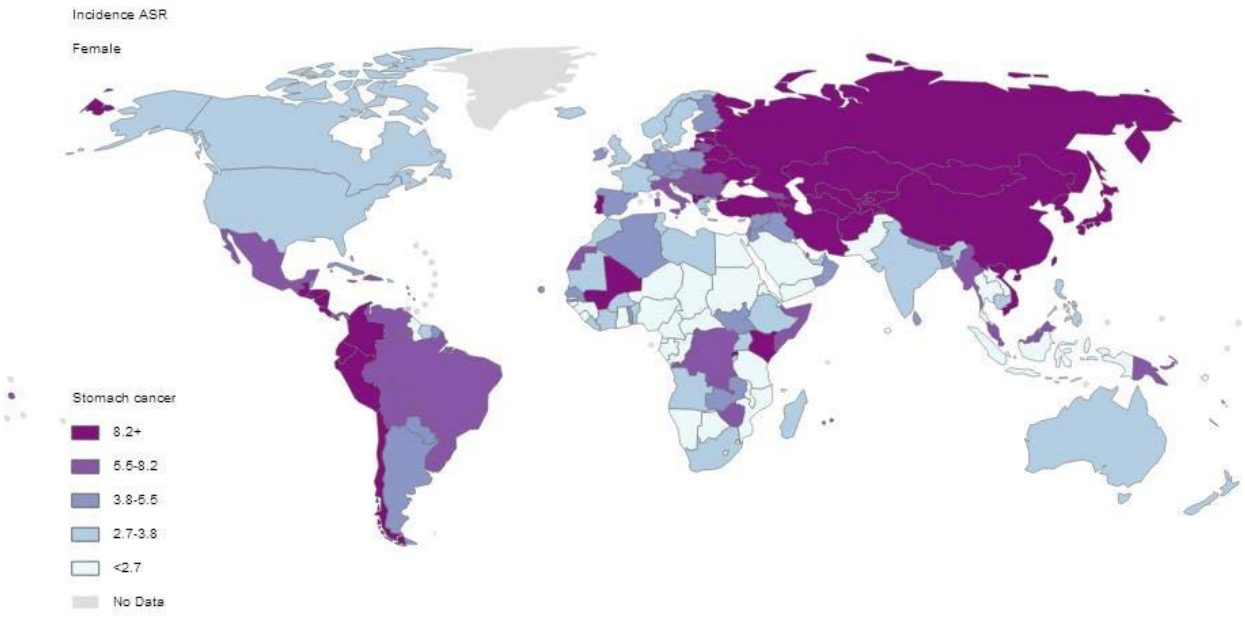
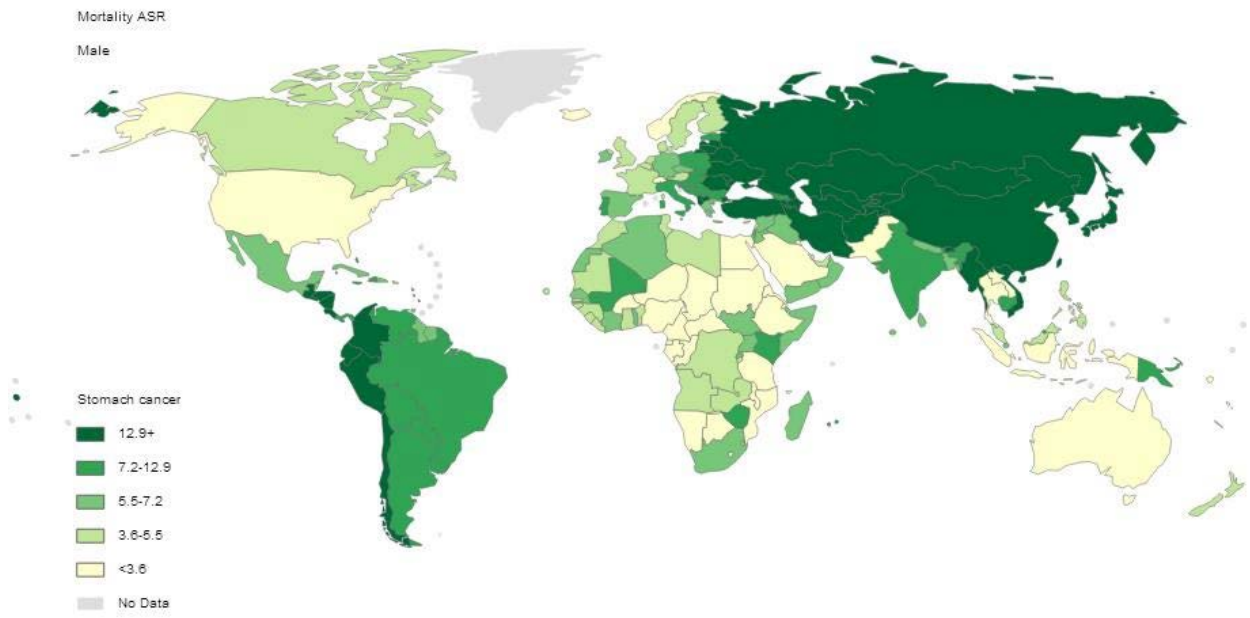


Fig. 4. (A) Estimated age-standardized (world) mortality rates of gastric cancer per 100 000 person-years by country among males in 2012. (B) Estimated age-standardized (world) mortality rates of gastric cancer per 100 000 person-years by country among females in 2012. Source: Ferlay et al. (2013) [1].

A



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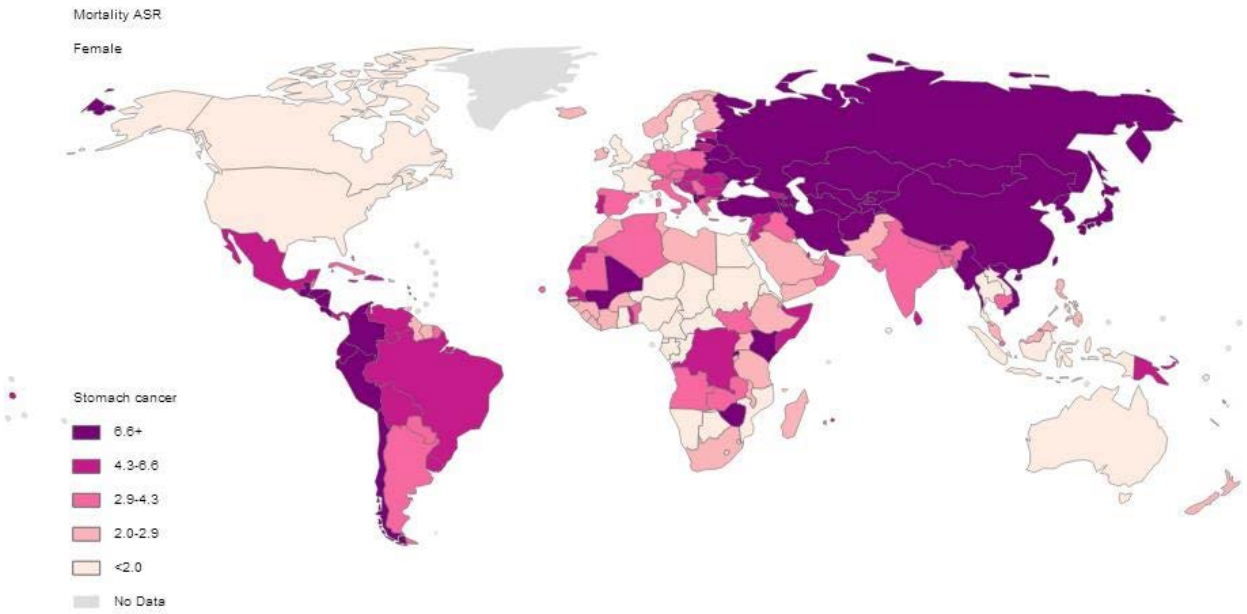


The global burden of gastric cancer described above must be interpreted with caution because it is based on estimates from GLOBOCAN 2012, which are subject to precision and data quality limitations. Although GLOBOCAN presents the best available estimates, they are dependent on the availability and quality of cancer incidence and mortality data for each country, and when such information is lacking (as in many developing countries), estimates are created using frequency data or rates of the neighbouring countries [1]. Therefore, it is important to consider in addition the more reliable incidence information derived directly from

population-based cancer registries. Every 5 years, IARC publishes data from selected population-based cancer registries with high-quality data in *Cancer Incidence in Five Continents* (CI5). The current CI5 volume (Volume X) includes 290 cancer registries from 68 countries with information on cancers diagnosed between 2003 and 2007 [3]. Table 1 summarizes the cancer registries with some of the highest and lowest gastric cancer rates in the world. For example, the incidence rates of gastric cancer among males in the Republic of Korea and Japan are almost 15 times the rates observed among White males in Florida in the USA.

Table 1. Cancer registries with high and low age-standardized (world) incidence rates of gastric cancer, males, 2003–2007

Registry	ASR	Registry	ASR
Republic of Korea, Daejeon	75.4	Libyan Arab Jamahiriya, Benghazi	4.9
Japan, Hiroshima	72.5	USA, Florida, White	4.9
India, Mizoram	50.6	Saudi Arabia, Riyadh, Saudi	4.4
Chile, Biobio	41.2	USA, Utah	4.0
USA, Los Angeles, Korean	39.4	Malaysia, Penang, Malay	3.5
Belarus	33.3	India, New Delhi	3.2
China, Jiashan	32.5	Kuwait	3.0
Russian Federation, St Petersburg	29.0	Egypt, Gharbiah	2.9
Costa Rica	26.5	Thailand, Khon Kaen	2.5
Colombia, Cali	26.0	Malawi, Blantyre	2.0

ASR, age-standardized (world) incidence rate per 100 000 person-years.

Source: Compiled from Forman et al. (2013) [3].

Overall, the patterns of gastric cancer incidence and mortality are very similar because prognosis after a diagnosis of gastric cancer is usually poor [4]. However, mortality rates in Japan and the Republic of Korea are considerably lower than incidence rates, which could reflect the impact of screening and early diagnosis in those countries.

1. Incidence trends over time

Cancer registry data can be used to analyse trends over time. Fig. 5 shows the trends in overall age-standardized (world standard population) gastric cancer rates for males and females for cancer registries included in all 10 volumes of CI5 between 1958 and 2007; plots represent age-standardized rates for each 5-year period (1960–2005). Over the 45-year period, the age-standardized incidence rates have steadily declined in nearly all populations. Trends for males and females in each population are very similar. The pattern is common for all selected areas regardless of the background risk of gastric cancer. For instance, in areas with historically high gastric cancer rates, such as Japan and Colombia, similar decreasing trends have been noted in more recent years.

The marked geographical variation of gastric cancer and the remarkable decline in incidence suggest that this decline may be related to the reduction of ubiquitous exposures worldwide.

Improvements in sanitation and preservation and storage of foods, changes in the prevalence of *Helicobacter pylori* infection, and use of antibiotics are thought to be responsible for these declines [4–6].

2. Cardia and non-cardia gastric cancer

There is increasing interest in the distribution of gastric cancers by subsite of the stomach because cancers arising from the most proximal cardia region and distal region (non-cardia) are likely to have different etiologies [4]. A pooled analysis of 12 case–control studies nested within prospective cohorts revealed that the risk of developing non-cardia gastric cancer among individuals who were *H. pylori* seropositive ≥ 10 years before cancer diagnosis was 6 times that among *H. pylori*-negative individuals [7]. GLOBOCAN 2012 estimates of the number of cardia and non-cardia gastric cancer cases revealed a variation by world region. For example, East Asia accounted for 61% of all non-cardia gastric cancers, whereas less than 3% of cases occurred in sub-Saharan Africa, North America, and Oceania (Table 2).

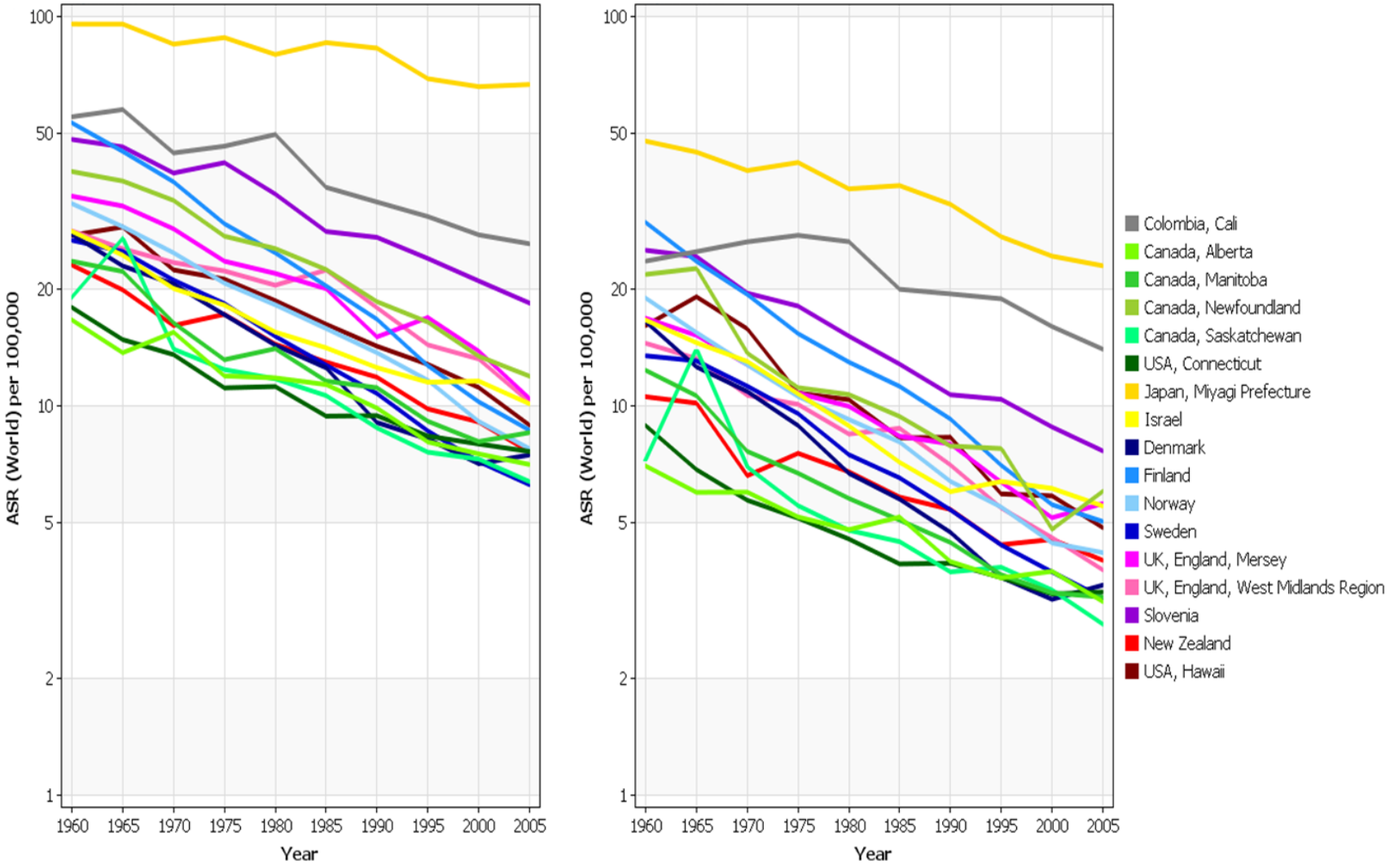
Table 2. Estimated numbers of gastric cancers and non-cardia gastric cancers by world region, 2012

Region	All gastric cancers	Non-cardia gastric cancers[a]
Sub-Saharan Africa	18 000	18 000
North Africa and West Asia	23 000	20 000
Central Asia	96 000	86 000
East Asia	587 000	504 000
South America	61 000	57 000
North America	25 000	17 000
Eastern Europe	70 000	62 000
North-western Europe	40 000	30 000
Southern Europe	30 000	27 000
Oceania	3 000	2 000
World	**954 000**[b]	**823 000**

[a] Estimated using proportions of non-cardia cancers within all microscopically verified gastric cancers within registries in *Cancer Incidence in Five Continents*, Volume X [3], stratified by region, sex, and age group (J. Ferlay, personal communication).

[b] The number for the world is slightly larger than the sum of the individual numbers, due to rounding error.

Fig. 5. Gastric cancer: age-standardized (world) incidence rates by 5-year period for cancer registries in all 10 volumes of *Cancer Incidence in Five Continents*: (left) males, all ages; (right) females, all ages. Source: Forman et al. (2013) [3].



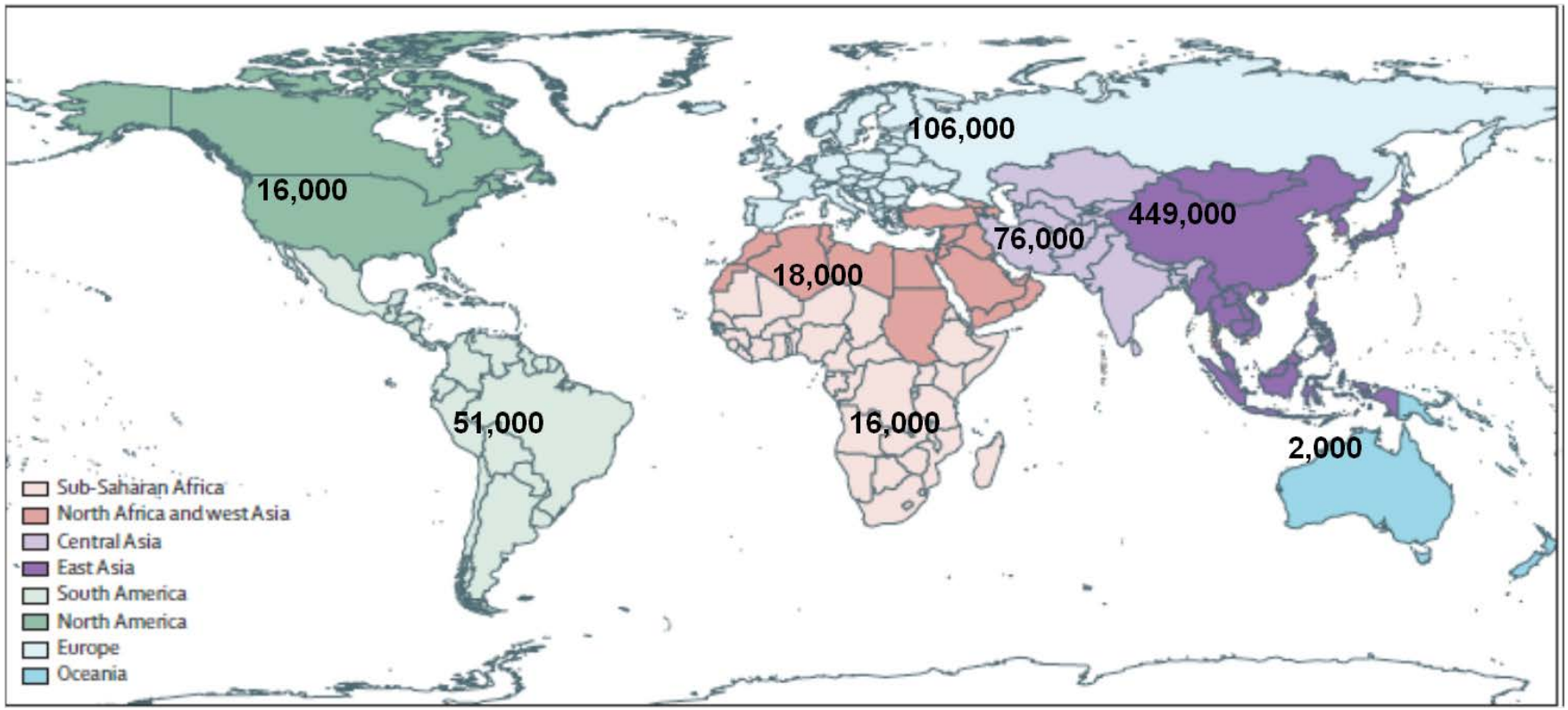
A recent analysis of gastric cancer incidence by subtype revealed a wide variation in the proportion of cardia gastric cancers worldwide [8]. For instance, in men the proportion of cardia cases among those with topography defined as cardia or non-cardia was 5.8% in the Republic of Korea, 13.1% in Ecuador, and 72.0% in Finland. Similar patterns were also described in women, even though the number of cancer cases was small.

3. Global burden of *H. pylori*-associated cancers

H. pylori infection has been classified by IARC as a human carcinogen [9]. Investigators have attempted to estimate the proportion of gastric cancer cases that could have been avoided if exposure to *H. pylori* infection was absent. De Martel et al. [10] estimated a population attributable fraction (PAF) by using the prevalence of *H. pylori* infection in gastric cancer cases of 90% (as measured by antibodies in blood serum with the enzyme-linked immunosorbent assay [ELISA]) and a relative risk of 5.9, and obtained a PAF estimate of 74.7%. If this PAF is applied to global incidence estimates from 2008, approximately 650 000 new gastric cancer cases would be attributable to *H. pylori* infection [10]. These estimates indicate that infection with *H. pylori* could be responsible for approximately 470 000 new cancer cases in less developed regions of the world and for 190 000 in more developed regions [10]. Plummer et al. [11] estimated a revised PAF based on a prevalence of *H. pylori* in gastric cancer cases of 94.6% (as measured by immunoblot [western blot] rather than ELISA) and a relative risk of 17.0, which resulted in a PAF of 89.0%. If this new PAF is applied to the GLOBOCAN 2008 estimates, approximately 774 000 new non-cardia gastric cancer cases would be attributable to *H. pylori* infection. If the most recent PAF estimate (89.0%) is applied to the GLOBOCAN 2012 estimates, approximately 734 000 non-cardia gastric cancer cases would be attributable to *H. pylori* infection. Fig. 6 shows the estimated annual burden of *H. pylori*-associated cancer by world region in 2012.

PAF estimates are largely dependent on accurate estimates of prevalence of *H. pylori* infection and the estimates of risk; uncertainties in these estimates inevitably lead to uncertainty in the PAF calculation. In spite of the inherent limitations of these calculations, they provide the most reasonable and up-to-date estimates of non-cardia gastric cancer attributable to *H. pylori* infection worldwide.

Fig. 6. Estimated annual burden of *Helicobacter pylori*-associated cancer by world region (2012).



4. Predicted burden of gastric cancer, 2012–2030

Assuming that the risk of gastric cancer remains stable in all countries, the global burden (annual number of new cases) of this form of cancer worldwide is expected to increase by 2030. The increase is expected to be driven primarily by the growth and ageing of the population (Table 3). However, if the currently observed decline in incidence rates remains at a constant level, then the global burden is estimated to be maintained at an approximately constant level.

Table 3. Predicted burden of gastric cancer, 2012–2030

Year	Annual number of new gastric cancer cases (millions)	
	Demographic effect	Demographic and –2.0% APC
2012	0.95	0.95
2015	1.03	0.97
2020	1.17	1.00
2025	1.34	1.03
2030	1.52	1.06

APC, annual percentage change.

Sources: Ferlay et al. (2013) [1] and J. Ferlay, personal communication.

5. Conclusion

In 2012 approximately 952 000 new gastric cancer cases occurred globally, of which 823 000 were at non-cardia sites. The main burden continues to fall in Asia, South America, and eastern Europe. In 2012 approximately 734 000 gastric cancers were estimated to be attributable to *H. pylori* infection. The burden of gastric cancer is likely to remain constant even with declining age-standardized incidence.

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Chapter 1.1

The role of endoscopic screening in gastric cancer control in the Republic of Korea

Il Ju Choi

Although the incidence of gastric cancer has declined in many countries during the past century, it is still the fifth most commonly diagnosed cancer and the third leading cause of cancer death globally [1]. In the Republic of Korea, about 30 000 gastric cancer cases are diagnosed per year, and this was the most common type of cancer until 2010 (when thyroid cancer took the top place) [2, 3]. In 2010, gastric cancer remained the leading type of incident cancer (19.6% of all cancers) in men and was the fourth most common cancer (10.0% of all cancers) in women. Mortality data in 2011 showed that gastric cancer is the third leading cause of cancer death (14.1% of all cancer deaths) in men and the second leading cause in women (12.7% of all cancer deaths) [3].

The 5-year relative survival rates for gastric cancer have increased over the past 15 years in the Republic of Korea (from 42.8% in 1993–1995 to 67.0% in 2006–2010) [3]. However, the age-standardized incidence (rate per 100 000 people) of gastric cancer did not show any significant changes during the past decade (67.2 in 2001 and 62.3 in 2010 for men; 26.2 in 2001 and 24.9 in 2010 for women) [3, 4].

1. National Cancer Screening Program

The National Health Insurance (NHI) programme of the Republic of Korea is a mandatory social insurance system that covers the whole population [5]. It is financed through contributions paid by the beneficiaries and their employers, as well as the government. Patients are allowed to choose medical service providers at their preference almost without restrictions, except for the payment of a certain level of premium. Providers are primarily paid by a fee-for-service system. Medical services are provided to very-low-income households through the Medical Aid programme to secure the minimum livelihood of those households.

In 1996, the government of the Republic of Korea implemented the first 10-Year Plan for National Cancer Control [5]. The objective of the first term was to develop infrastructure by establishing cancer control programmes such as the Cancer Control Law and launching the National Cancer Center and regional cancer centres. The second term of the 10-year Plan for National Cancer Control began in 2006, to strengthen cancer control efforts at the government level and aimed at reducing the economic burden of cancer significantly by reducing cancer incidence and mortality through systemic cancer management [6].

The government of the Republic of Korea established the National Cancer Screening Program (NCSP) in 1999 in an effort to reduce the burden of cancer [7]. Until 2001, the NCSP provided Medical Aid recipients with screening free of charge for three types of cancer (gastric, breast, and cervical cancer). Since then, the target population and types of cancer covered have been expanded. NHI beneficiaries in the lower 20% income bracket were included in the NCSP in 2002 and those in the lower 30% in 2003. Liver cancer was included in 2003 and colorectal cancer in 2004. Since 2005, the NCSP has provided Medical Aid recipients and NHI beneficiaries in the lower 50% income bracket with screenings for five types of cancer (gastric, liver, colorectal, breast, and cervical cancer). NHI beneficiaries in the upper 50% income bracket receive screening services for the same five types of cancer from the NHI Corporation; however, they are required to pay 10% of the cost. Thus, currently

almost all people of eligible age in the Republic of Korea are provided with a cancer screening programme for free or at minimal cost.

The guidelines of the NCSP are listed in Table 1.1.1 [8, 9]. The NCSP provides gastric cancer screening every 2 years for those aged 40 years or older. Participants can choose either upper gastrointestinal series (UGIS) or endoscopy according to their preference. If UGIS is chosen and reveals any abnormal finding indicating gastric cancer, then endoscopy is provided to confirm what the abnormality is. Biopsy for any abnormal finding during endoscopy that requires histological evaluation is also covered by the NCSP.

In addition to these organized cancer screening programmes provided by the government, opportunistic cancer screening is widely available in the Republic of Korea. Organized cancer screening programmes use nationally implemented protocols that define a target population, screening interval, and follow-up strategies. However, opportunistic cancer screening programmes include a variety of options in terms of the target cancer, screening interval, and screening method, depending on the programmes chosen by the participants or their employers. All costs of opportunistic cancer screening are paid entirely by users, without a government subsidy.

Table 1.1.1. Guidelines of the National Cancer Screening Program of the Republic of Korea

Cancer	Target population	Interval (years)	Test
Gastric	Aged 40 years and older	2	Upper endoscopy or UGIS[a]
Liver	High-risk group[b] aged 40 years and older	1	Ultrasonography and AFP
Colorectal	Aged 50 years and older	1	FOBT[c]
Breast	Women aged 40 years and older	2	Mammography
Cervical	Women aged 30 years and older	2	Pap smear

AFP, α-fetoprotein; FOBT, faecal occult blood test; UGIS, upper gastrointestinal series.

[a] In the case of an abnormality on UGIS, endoscopy is recommended for further evaluation and biopsy.

[b] Patients at high risk for liver cancer include those with chronic hepatitis determined from serological evidence of infection with hepatitis B or C virus or liver cirrhosis.

[c] In the case of an abnormality on FOBT, colonoscopy or a double-contrast barium enema is recommended.

Sources: Suh et al. (2013) [8] and National Cancer Center (2013) [9].

2. Trends in gastric cancer screening

The target population of the NCSP consists of those insured by Medical Aid and the NHI programme [7]. The number of screened Medical Aid recipients increased from 238 762 in 2002 to 730 730 in 2011 [4]. The number of screened NHI beneficiaries increased from 533 343 in 2002 to 6 284 780 in 2011. In 2011, among the five cancers in the NCSP, gastric cancer was the most common type of cancer screened for (3 033 674). The overall rate of participation in the NCSP was 41.9% in 2011 (28.1% of Medical Aid recipients and 44.1% of NHI beneficiaries); this rate increases each year.

The NCSP and NHI cancer screening offered gastric cancer screening to 12 655 502 people in 2011; the actual number of participants was 5 820 296 (46.0%). This figure shows a significant increase compared with only 7.7% of the potential candidates in 2002.

Two types of cancer screening rates were used to estimate trends. “Lifetime screening rate” was defined as having experienced each type of screening test. The “screening rate with recommendation” category was assigned to participants who had undergone screening tests according to the protocols of the NCSP. The Korean National Cancer Screening Survey, a nationwide, population-based, cross-sectional survey, has been conducted annually by the National Cancer Center since 2004. Stratified multistage random sampling based on resident registration population data is conducted according to geographical area, age, and sex [8]. In 2004, lifetime screening rates and screening rates with recommendation for gastric cancer were 52.0% and 39.2%, respectively. These figures continuously increased, reaching 77.9% and 70.9%, respectively, in 2012. Thus, the estimated annual percentage change was a 4.0% increase for lifetime screening rate and a 4.3% increase for screening rate with recommendation [8]. One of the goals of the second-term 10-year Plan for National Cancer Control (2006–2015) was to increase screening rates with recommendation to 70% by 2015 [5]. For gastric cancer this goal was achieved ahead of time, in 2012.

3. Performance of gastric cancer screening: comparison of UGIS and endoscopy

In 2002, about 74.7% of participants underwent UGIS and 24.8% underwent endoscopy. In 2011, the proportions were reversed: about 70.8% of participants chose endoscopy.

Although the NCSP offers either UGIS or upper endoscopic examination as the initial screening method for gastric cancer, at the time the NCSP was initiated there was a lack of agreement on which screening method works better [10]. A study compared the cost and accuracy of UGIS and endoscopy for gastric cancer diagnosis using NCSP data from 2002–2004 [10]. Of the 1 067 378 people screened with UGIS, 892 gastric cancer cases were detected, and of the 436 268 participants screened with upper endoscopy, 1041 gastric cancer cases were detected. The probability of detecting gastric cancer through endoscopy was 2.9 times that through UGIS. The unit costs of screening using UGIS and endoscopy were similar in the Republic of Korea, at US$ 32.67 and US $34.89, respectively. Thus, the estimated cost of identifying one case of gastric cancer was US$ 53 000 using UGIS and US$ 16 900 using endoscopy, for a ratio of 3.7:1.

A more recent study evaluated the relative performance of UGIS and endoscopic screening using NCSP data from 2002–2005 [11]. Gastric cancer detection rates were 0.68 per 1000 UGIS and 2.61 per 1000 endoscopic screenings. The sensitivities of UGIS and endoscopic screening for detecting gastric cancer were 36.7% and 69.0%, respectively, and their specificities were 96.1% and 96.0%, respectively. Gastric cancer cases detected by endoscopic screening were at the localized stage in 45.7% of cases, whereas the figure for UGIS was 32.4%. Because tumour stage is the most important prognostic factor after cancer diagnosis, the performance of endoscopy can be considered to be far better than that of UGIS.

A recent study evaluated the cost–effectiveness outcomes of the gastric cancer screening programme of the NCSP using the target population who participated in the screening programme during 2002–2003 [12]. The study showed that incremental cost–effectiveness ratio estimates for life-years saved indicate that the gastric cancer screening programme in the Republic of Korea is cost-effective for both men and women. An upper limit of 75 or 80 years for screening age was suggested in men. Because endoscopy was a more cost-effective strategy than UGIS for both men and women, the study suggested that endoscopy should be recommended as the first-line method in the Republic of Korea.

Taking into account the improved quality of available equipment and the skill of endoscopists, endoscopic screening is expected to exhibit far better performance nowadays

compared with that seen 10 years ago during the initial periods of the NCSP. The issue of the upper limit for screening age should be evaluated in future studies.

4. Screening interval

The NCSP gastric cancer screening programme recommends biennial examination for both UGIS and endoscopy. Because there had previously been no adequate study evaluating the screening interval, a study investigated whether repeated endoscopy screening is an effective method for detecting early gastric cancer that can be treated by endoscopic resection [13]. Of the 18 414 patients who underwent opportunistic endoscopy at the National Cancer Center, 81 (0.44%) were found to have gastric cancer. The incidence of gastric cancer in the group that underwent repeated screening within 2 years was lower than that in the group that underwent infrequent screening (adjusted odds ratio, 0.45; 95% confidence interval, 0.26–0.77). In the group that underwent repeated screening within 2 years, the proportion of early gastric cancers was 96% (25 of 26), and endoscopic treatment for detected gastric cancer was possible in 54% (14 of 26) of these cases.

Another study evaluated the association of the interval between endoscopies with gastric cancer stage at diagnosis in 2485 gastric cancer patients referred to the National Cancer Center [14]. A significant benefit in cancer stage at diagnosis was observed in all interval groups (1-year, 2-year, 3-year, 4-year, 5-year, and > 5-year intervals) compared with never-screened patients. Compared with the 1-year interval group, the risk of advanced gastric cancer was increased in the 4-year and 5-year interval group, but not in the 2-year and 3-year interval groups. These data suggest that endoscopy intervals of 3 years or shorter show similar benefits.

Whether the 2-year screening interval can be applied for both UGIS and endoscopy, which have different performances in the context of the NCSP, has not yet been adequately evaluated. Moreover, it is unknown whether there are high-risk groups suitable for shorter screening intervals or a low-risk population for whom a longer screening interval is sufficient or who do not need screening at all.

5. Conclusions

The Republic of Korea has one of the highest incidence and mortality burdens from gastric cancer worldwide and has a unique programme for screening the general population. There are many aspects of the screening conditions and outcomes that require adequate evaluation to assess the gastric cancer screening programme in the setting of the Republic of Korea. One of the main issues is that the effect of screening on the gastric cancer mortality rate has not yet been proven, although a continuously decreasing trend in gastric cancer mortality is seen. Moreover, cost–effectiveness analysis should be performed using more recent data, which are derived from a much larger pool of participants and a high-quality endoscopy system. The adequacy of the screening interval and the age at which to begin and end screening also need validation. The incorporation of different screening strategies by risk stratification, or of primary prevention tools such as *Helicobacter pylori* eradication, is needed in the future to improve the performance and cost–effectiveness of the NCSP.

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Chapter 1.2

Strategy to eliminate gastric cancer deaths in Japan

Masahiro Asaka

In 2008, a randomized multicentre clinical study conducted in Japan revealed that eradication of *Helicobacter pylori* reduced the incidence of secondary gastric cancer by about two thirds after endoscopic mucosal resection of early gastric cancer, suggesting the usefulness of *H. pylori* eradication for prevention of gastric cancer [1]. However, that study also showed that *H. pylori* eradication did not completely eliminate gastric cancer. Thus, to achieve the elimination of gastric cancer in Japan, the important issue is how to combine primary prevention through *H. pylori* eradication with secondary prevention through surveillance. Fortunately, the Japanese Ministry of Health, Labour, and Welfare (MHLW) approved national health insurance coverage for eradication therapy in patients with gastritis caused by *H. pylori* infection (chronic active gastritis) on 21 February 2013, for the first time in the world [2].

1. Current status and characteristics of screening for gastric cancer in Japan

The concept of early gastric cancer was proposed in Japan in 1963 [3, 4]. At that time, early gastric cancer was defined as a lesion with infiltration of tumour cells limited to the mucosa or submucosa, irrespective of lymph node metastasis. The prognosis of early gastric cancer is far better than that of advanced cancer, with a 5-year survival rate of more than 90% in Japan [5, 6]. Therefore, many studies in Japan have focused on how to effectively diagnose early gastric cancer. As a result, early gastric cancer now accounts for nearly 60% of all gastric cancers detected in Japan [7]. In other countries, including the USA and countries in Europe, the 5-year survival rate of gastric cancer patients is reported to be only 10–25% [8]. This is not because treatment of gastric cancer in Japan is superior to that in other countries but because the detection rate of early cancer is much lower outside Japan [9]. It is also likely that the impressive 5-year survival results seen in Japan are in part attributable to lead-time and length-time bias as well as the possibility that some cancers are overdiagnosed [10].

In Japan, the prevention of cancer, including gastric cancer, has primarily focused on secondary measures for early detection of cancer, rather than on primary prevention aimed at elimination of the causes. Indirect barium contrast imaging has been used as the screening method for gastric cancer, but despite the long interest and emphasis, the screening rate was only 9.6% in 2010 [11]. Also, screening for gastric cancer based on barium contrast imaging does not have a high sensitivity for detecting early cancer [11] and is associated with considerable exposure to radiation. Furthermore, targeting all people aged 40 years or older for screening is a major problem as people aged younger than 50 years account for only about 3% of all gastric cancer patients in Japan [11]. Moreover, *H. pylori*-negative patients with minimal or no atrophy of the gastric mucosa are very unlikely to develop gastric cancer; thus, these patients are unlikely to benefit from annual barium contrast screening and are still exposed to the adverse effects of radiation.

2. Prevention of gastric cancer by eradication of *H. pylori*

Assessment of the design of a new prospective study on the basis of previous studies indicated that a clinical trial with a small sample size and short follow-up period should enrol patients with early gastric cancer who have undergone endoscopic mucosal resection, since they represent the population most likely to develop advanced gastric cancer. The annual incidence of gastric cancer has been reported to be only 0.1–0.4% in *H. pylori*-positive

patients with atrophic gastritis [12, 13], whereas the annual incidence of metachronous recurrence is far higher (3–5%) in patients who have undergone endoscopic surgery for early gastric cancer [14, 15]. The Japan Gast Study Group randomized multicentre clinical trial investigated the metachronous recurrence of gastric cancer in 544 patients who had undergone endoscopic treatment for early gastric cancer. They were randomly allocated to *H. pylori* eradication or non-eradication groups and were followed up by annual endoscopic examination for 3 years. As a result, metachronous recurrence was detected in 9 subjects from the eradication group and 24 subjects from the non-eradication group, and those in the eradication group had a significantly lower relapse rate ($P < 0.01$ according to intention-to-treat analysis) [1].

After the Japan Gast Study Group trial was completed and data obtained at 8–10 years were analysed, it was found that there was still a difference in the incidence of metachronous gastric cancer between the *H. pylori* eradication and non-eradication groups [16]. This indicates that the preventive effect of eradication therapy on gastric cancer persists for a long time.

3. Significance of health insurance coverage for *H. pylori* eradication therapy in Japan

Since it has become clear that most gastric cancer is due to *H. pylori* infection rather than lifestyle factors, it is time for major revision of the preventive strategies for gastric cancer. When it is suspected that a cancer is caused by infection, proactive preventive measures are likely to lead to a dramatic decrease in the incidence of that cancer, resulting in a significant decrease of cancer mortality. In Japan, preventive measures for liver cancer have been focused on hepatitis virus infection since 2002, leading to a reduction of mortality [17, 18]. However, the annual number of deaths from gastric cancer has remained at about 50 000 for the past few decades [19], suggesting that the current preventive measures are inadequate.

In 2009, the Japanese Society for *Helicobacter* Research published a guideline in which it is recommended that all *H. pylori*-infected people receive bacterial eradication therapy [20]. In response to this, the MHLW approved the extension of national health insurance coverage to *H. pylori* eradication therapy for three indications (i.e. patients with gastric mucosa-associated lymphoid tissue [MALT] lymphoma, patients who have undergone endoscopic surgery for early gastric cancer, and patients with idiopathic thrombocytopenic purpura [ITP]), in addition to patients with gastric and duodenal ulcers. This was the first time in the world that insurance coverage has been provided for *H. pylori* eradication therapy for indications other than gastric and duodenal ulcers and represents an innovative approach. Regarding the potential expansion of health insurance coverage for eradication therapy to include patients with chronic gastritis, the Japanese Society of Gastroenterology, the Japan Gastroenterological Endoscopy Society, and the Japanese Society for *Helicobacter* Research submitted a joint petition to the Minister of the MHLW. This public knowledge-based application led to the inclusion of *H. pylori* eradication therapy for patients with chronic gastritis on 21 February 2013. The MHLW notification states that eradication therapy is covered by the national health insurance scheme when a patient with endoscopically diagnosed chronic gastritis is positive for *H. pylori*. Thus, *H. pylori*-associated gastritis is the underlying cause of almost all gastric diseases; hence, treatment of this gastritis through bacterial eradication therapy is likely to prevent most gastric conditions, including gastric cancer.

4. Strategy to eliminate gastric cancer in Japan

The strategy to eliminate gastric cancer in Japan should be different for adolescents than for elderly people. This is because bacterial eradication in adolescents achieves nearly 100% prevention of gastric cancer, but the incidence of this cancer increases with age [21, 22]. The recommended strategy for adolescents is a test-and-treat approach, which includes *H.*

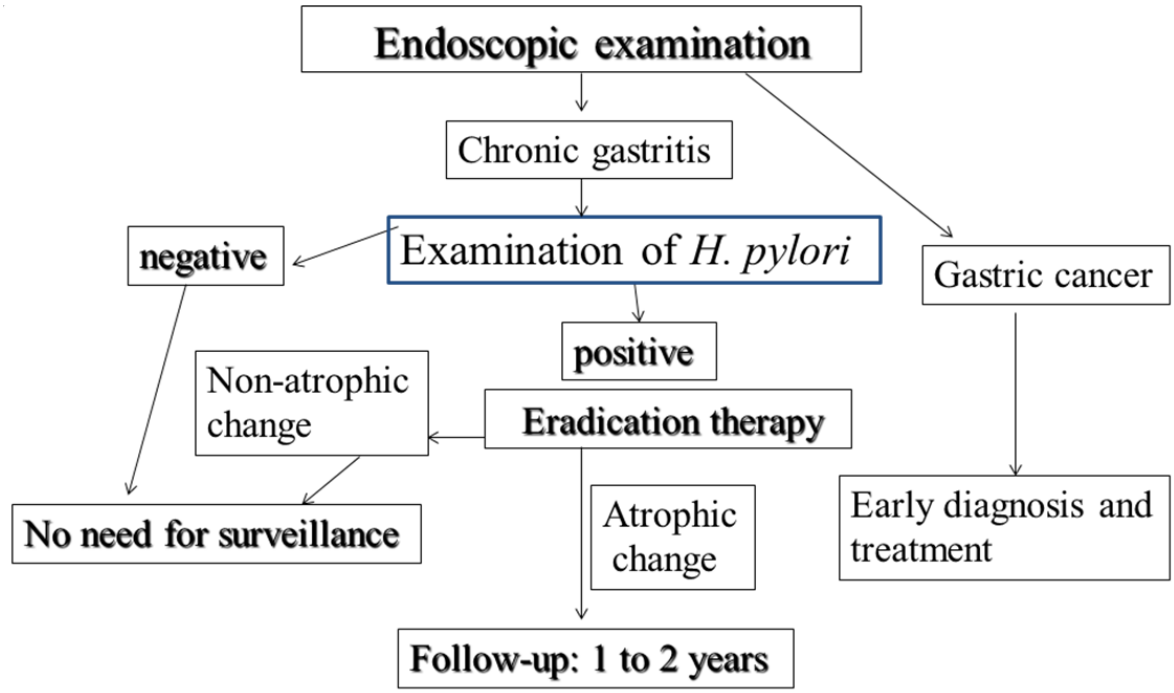
pylori testing of junior high school and high school students, followed by immediate *H. pylori* eradication therapy for those with a positive result. Eradication in adolescents should be able to prevent *H. pylori*-related diseases such as gastric ulcers and gastric polyps, as well as preventing the development of nearly 100% of gastric cancers. It is estimated that approximately 5% of all teenagers in Japan are positive for *H. pylori*, suggesting that the cost of this approach would not be so high. Some local governments have already scheduled free *H. pylori* testing for junior high school students [23].

The recent expansion of health insurance coverage allows individuals with symptoms such as gastric heaviness to present to a hospital for the diagnosis and treatment of *H. pylori*-associated gastritis. For a patient to obtain health insurance coverage, endoscopy must be performed first for the diagnosis of gastritis, and most patients seem to have chronic gastritis by the time they undergo endoscopy. It is expected that many cases of gastric cancer will be discovered during this endoscopic examination. This project thus includes a form of endoscopic screening supported by medical insurance. All patients in whom gastritis is diagnosed are supposed to receive *H. pylori* eradication therapy. In patients with obvious atrophic gastritis, periodic endoscopic follow-up is recommended every 1 or 2 years even after eradication therapy, whereas patients with no or mild atrophy and those who are negative for *H. pylori* infection can be followed up by optional screening instead of strategic screening (Fig. 1.2.1) [24].

In Japan, the success rate of *H. pylori* eradication therapy is decreasing every year because of the increase in bacteria resistant to clarithromycin, but secondary eradication therapy with metronidazole achieves a high success rate (> 95%). That may be because resistance to metronidazole is very low (about 5%) in Japan, where health insurance coverage for administration of metronidazole is limited and its use remains uncommon [20].

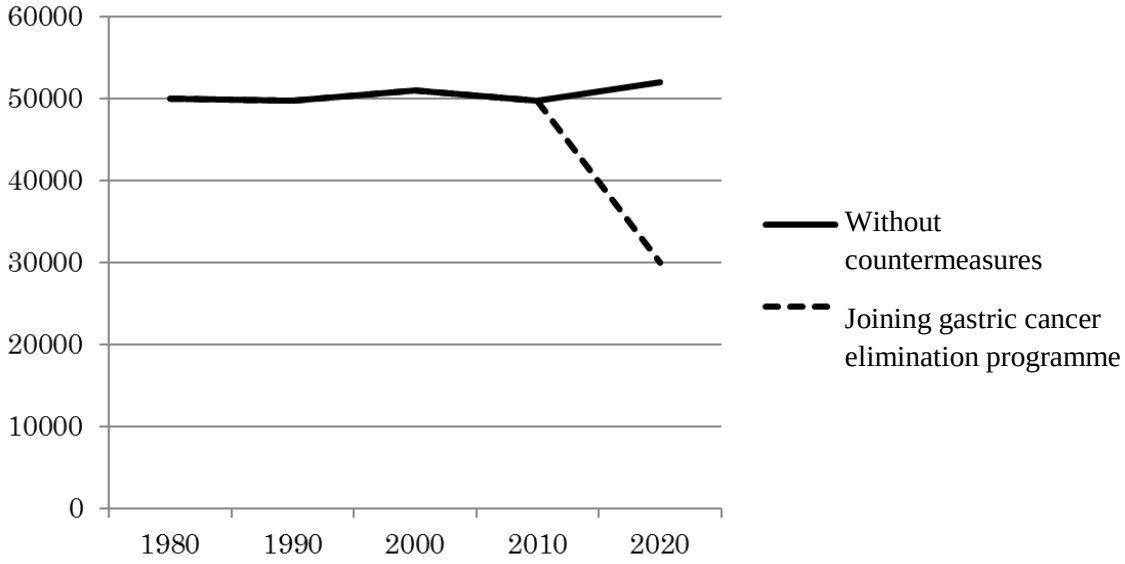
Although it is not clear to what extent the use of eradication therapy in patients with *H. pylori*-associated gastritis will inhibit the development of gastric cancer, a good model may be peptic ulcers, for which *H. pylori* eradication therapy was first covered by the Japanese national health scheme in 2000. Since then, the incidence of peptic ulcers has decreased dramatically, by about 60% over 10 years. In addition, the medical costs of treating ulcers have decreased by 47% during that period. Although it is unclear whether the results obtained with gastric cancer will be comparable to those for peptic ulcers, *H. pylori* eradication therapy (etiological treatment) for *H. pylori*-associated gastritis will lead to a long-term decrease of gastric cancer. Such treatment will inhibit the development of peptic ulcers and gastric polyps as well as gastric cancer, suggesting a greater reduction of medical costs than that achieved by providing insurance coverage for *H. pylori* eradication therapy in patients with peptic ulcers [25].

Fig. 1.2.1. Strategy to eliminate gastric cancer in Japan. Endoscopy must be performed first for the diagnosis of gastritis to obtain health insurance coverage in Japan. This project might include a form of endoscopic screening supported by medical insurance. All patients in whom gastritis is diagnosed are supposed to receive *Helicobacter pylori* eradication therapy. In patients with obvious atrophic gastritis, periodic endoscopic follow-up is recommended every 1 or 2 years even after eradication therapy. Source: Asaka et al. (2014) [24]. © Masahiro Asaka, Mototsugu Kato, Naoya Sakamoto, 2013.



There are two potential outcomes of the gastric cancer elimination project suggested here with regard to gastric cancer-related deaths in Japan. One is a definite decrease in the incidence of gastric cancer resulting from the widespread use of *H. pylori* eradication therapy (a direct effect of this therapy). The other is a decrease in the number of deaths resulting from an increase in the diagnosis of early gastric cancer owing to mandatory endoscopy at the time of presentation for chronic gastritis. The target would be to eventually increase the proportion of early gastric cancer from the current 60% to about 90%, which would make it possible to increase the 5-year survival rate for gastric cancer patients in Japan to approximately 90%. Because the baby boomer generation represents a huge population turning 65 and entering the cancer-prone years, the number of deaths from gastric cancer is likely to increase by 2020 if no countermeasures are taken. In contrast, if the gastric cancer elimination project is successful and about 50% of people with *H. pylori* infection receive eradication therapy, the number of deaths from gastric cancer will decrease to about 30 000 in 2020 (Fig. 1.2.2) [24].

Fig. 1.2.2. Anticipated gastric cancer deaths in Japan, with or without countermeasures. If the gastric cancer elimination project is successful and about 50% of people with *Helicobacter pylori* infection receive eradication therapy, the number of deaths from gastric cancer will decrease to about 30 000 in 2020. Source: Asaka et al. (2014) [24]. © Masahiro Asaka, Mototsugu Kato, Naoya Sakamoto, 2013.



5. Conclusion

In February 2013, national health insurance coverage for *H. pylori* eradication therapy to treat *H. pylori*-associated chronic gastritis became available in Japan. *H. pylori*-associated gastritis leads to development of gastric and duodenal ulcers and gastric polyps. Therefore, providing treatment for gastritis is likely to substantially decrease the prevalence of both gastric and duodenal ulcers and polyps. Because treatment for *H. pylori*-associated gastritis, which leads to atrophic gastritis and gastric cancer, is now covered by health insurance in Japan, a strategy to eliminate gastric cancer-related deaths by taking advantage of this innovation was planned. According to this strategy, patients with gastritis will be investigated for *H. pylori* infection and those who are positive will receive eradication therapy followed by periodic surveillance. If this strategy is implemented, deaths from gastric cancer in Japan will decrease dramatically after 10–20 years.

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Chapter 1.3

The regional status of current or planned gastric cancer prevention strategies in Taiwan, China

Yi-Chia Lee

Given the promising results of the gastric cancer prevention programme on Matsu Island over a 10-year follow-up period, the concept of this preventive strategy was disseminated to the health-care authorities on the main island of Taiwan, China. Starting in 2012, a prevention programme using modified screening design and eligibility criteria was implemented in a general population in Changhua County, Taiwan, China. This chapter provides a detailed rationale for this community-based study, addressing the burden of gastric cancer, design of the prevention programme, method of invitation to participants, screening test, antibiotic treatment, endoscopic examination, evaluation method, and future perspectives.

1. Gastric cancer burden in Taiwan, China

Gastric cancer was the seventh most common cancer in Taiwan, China in 2010 (sixth in males and seventh in females). The median age of gastric cancer occurrence is about 70 years. The time trends are shown in Table 1.3.1. The absolute numbers of incident cases and the incidence rates have increased gradually due to population ageing. The absolute numbers of deaths and the mortality rates are almost constant. Therefore, gastric cancer remains a significant public health burden in Taiwan, China.

Table 1.3.1. Time trends of gastric cancer in Taiwan, China for 1995–2010: number of people at risk, number of incident cases, number of deaths, and incidence and mortality rates of gastric cancer per 100 000 population

Year	Population	New gastric cancer cases	Gastric cancer deaths	Incidence rate	Mortality rate
1995	21 358 297	2849	2262	13.34	10.59
1996	21 527 195	3078	2519	14.30	11.70
1997	21 741 711	3194	2348	14.69	10.80
1998	21 927 683	3291	2443	15.01	11.14
1999	22 092 394	3386	2360	15.33	10.68
2000	22 276 672	3352	2374	15.05	10.66
2001	22 405 568	3502	2446	15.63	10.92
2002	22 520 776	3692	2433	16.39	10.80
2003	22 604 550	3356	2349	14.85	10.39
2004	22 689 122	3681	2500	16.22	11.02
2005	22 770 383	3487	2490	15.31	10.94
2006	22 876 527	3674	2398	16.06	10.48
2007	22 958 360	3691	2474	16.08	10.78
2008	23 037 031	3636	2292	15.78	9.95
2009	23 119 772	3848	2282	16.64	9.87
2010	23 162 123	3854	2261	16.64	9.76

2. Rationale for gastric cancer prevention in Taiwan, China

For the intermediate-risk population (in which the incidence rate of gastric cancer is about 16.6 per 100 000 people per year), two major issues may determine the applicability of gastric cancer prevention in Taiwan, China:

- When to screen?
- How to screen?

2.1 When to screen

The Matsu Island campaign against gastric cancer has suggested that the screen-and-treat approach for *Helicobacter pylori* infection may be an effective strategy for primary prevention in a high-risk population [1]. It is also known that, without previous opportunistic treatment, the frequency and the severity of *H. pylori*-associated precancerous lesions increase with age. Furthermore, the use of non-steroidal anti-inflammatory drugs/aspirin is higher in the older age range, which would be expected to have a synergistic effect with *H. pylori* infection on the risk of peptic ulcers and/or bleeding. To increase the yield rate of endoscopy as a tool for secondary prevention, it seemed reasonable to target the older population, in which the prevalence of latent *H. pylori* infection is lower and the burden of incident gastric pathology is higher. Therefore, it was planned to screen the general older adult population aged 50–69 years, in which the incidence rate of gastric cancer increases to about 30 per 100 000 person-years (Fig. 1.3.1). Those who were younger than 50 years would receive opportunistic testing and treatment, which is now common clinical practice in Taiwan, China. The other reason for screening the general older adult population was related to the delivery system described below (Section 2.2).

2.2 How to screen

The candidate screening tests will likely include the ^{13}C urea breath test (^{13}C-UBT) and the *H. pylori* stool antigen test (HPSA) [2]. In Taiwan, China, starting in 2004, the government initiated a mass screening programme for colorectal cancer (the leading incident cancer in Taiwan, China) using biennial faecal occult blood testing with a faecal immunochemical test (FIT) for the older adult population aged 50–69 years (extended to 50–74 years in June 2013). Mass screening, including the processes of invitation, distribution of FIT, testing of faecal sample, referral for colonoscopic examination, and histopathological diagnosis, were performed step by step by the local public health units, clinics, and hospitals in each municipality. All the screening results were transmitted via virtual private network to a central database, which is used to periodically generate standardized indicators for the central and local governments to monitor the screening performance. This established delivery system could serve as a strong basis for the implementation of a two-in-one, stool sample-based test panel for both colorectal cancer and gastric cancer. Therefore, it is insightful to use HPSA for mass screening. In addition to its easy incorporation into the established delivery system, the advantages of HPSA include its convenience, lower price, and reduced personnel needs.

3. Design of gastric cancer prevention programme in Changhua County, Taiwan, China

Changhua County, which is located in central Taiwan, China (Fig. 1.3.1), has a population of about 1 300 000. For the older adult population aged 50–69 years, the gastric cancer incidence rate in 2009 was about 29 per 100 000 person-years, and the gastric cancer mortality rate in 2011 was about 15 per 1000 000 person-years. In 2012, under the auspices of the Changhua County Public Health Bureau, a proof-of-concept study was conducted in Changhua County for gastric cancer prevention. For this population, HPSA was performed for the first time, designed as a once-in-a-lifetime test, and appended to the Changhua Community-based Integrated Screening programme [3]. This integrated screening programme has provided oral inspection for oral/throat cancer, mammography for breast

cancer, Pap smear for cervical cancer, and FIT for colorectal cancer by annually inviting 10 000 people to be screened. Among these 10 000, eligible people were further invited to participate in the screening for gastric cancer. The flow chart is shown in Fig. 1.3.2.

Fig. 1.3.1. Gastric cancer incidence rates (per 100 000 population in 2009), mortality rates (per 100 000 population in 2011), and mortality-to-incidence ratio (or case fatality rate) in the population aged 50–69 years in Taiwan, China. Numbers in parentheses represent the rankings of each city or county.

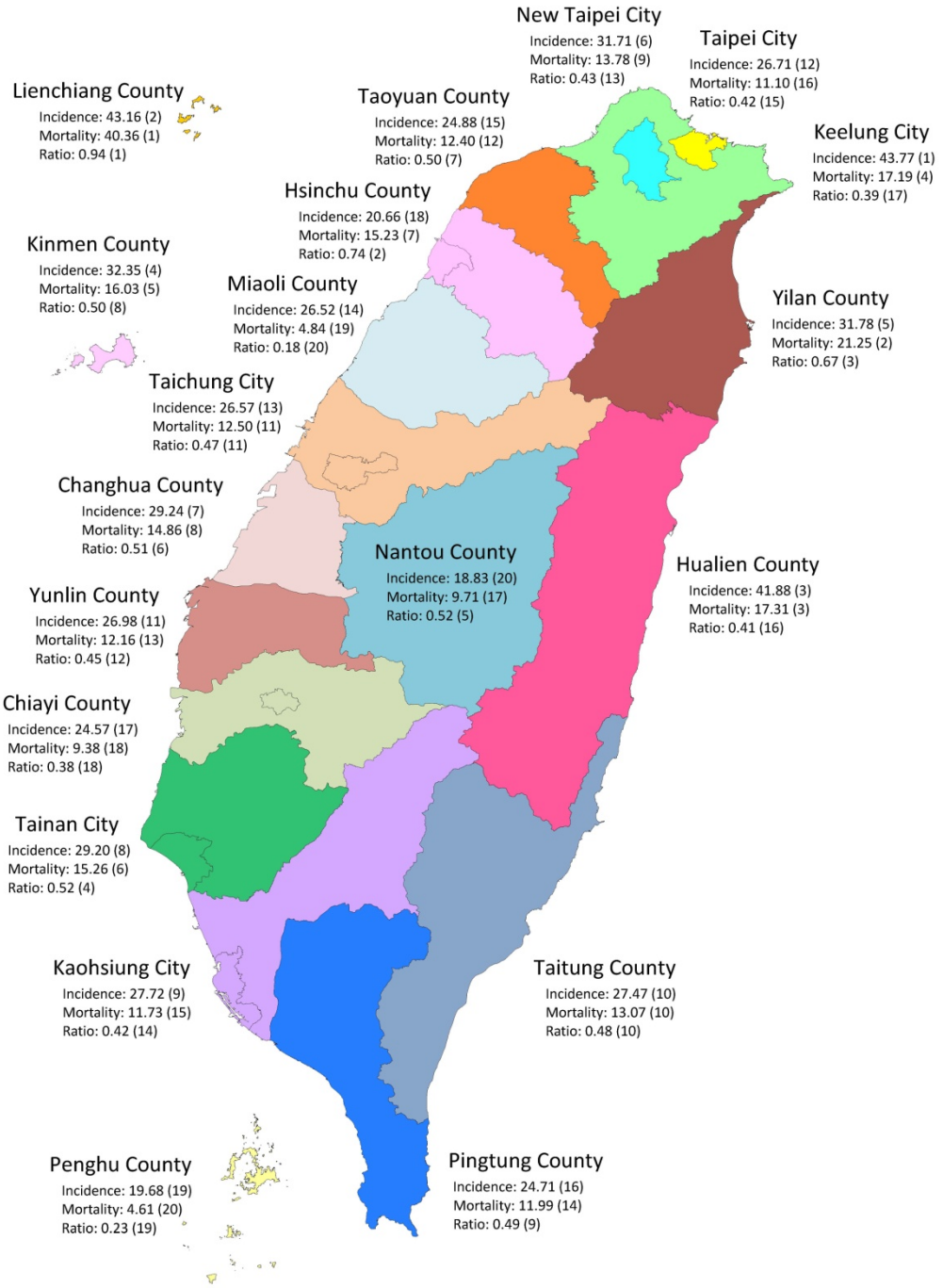
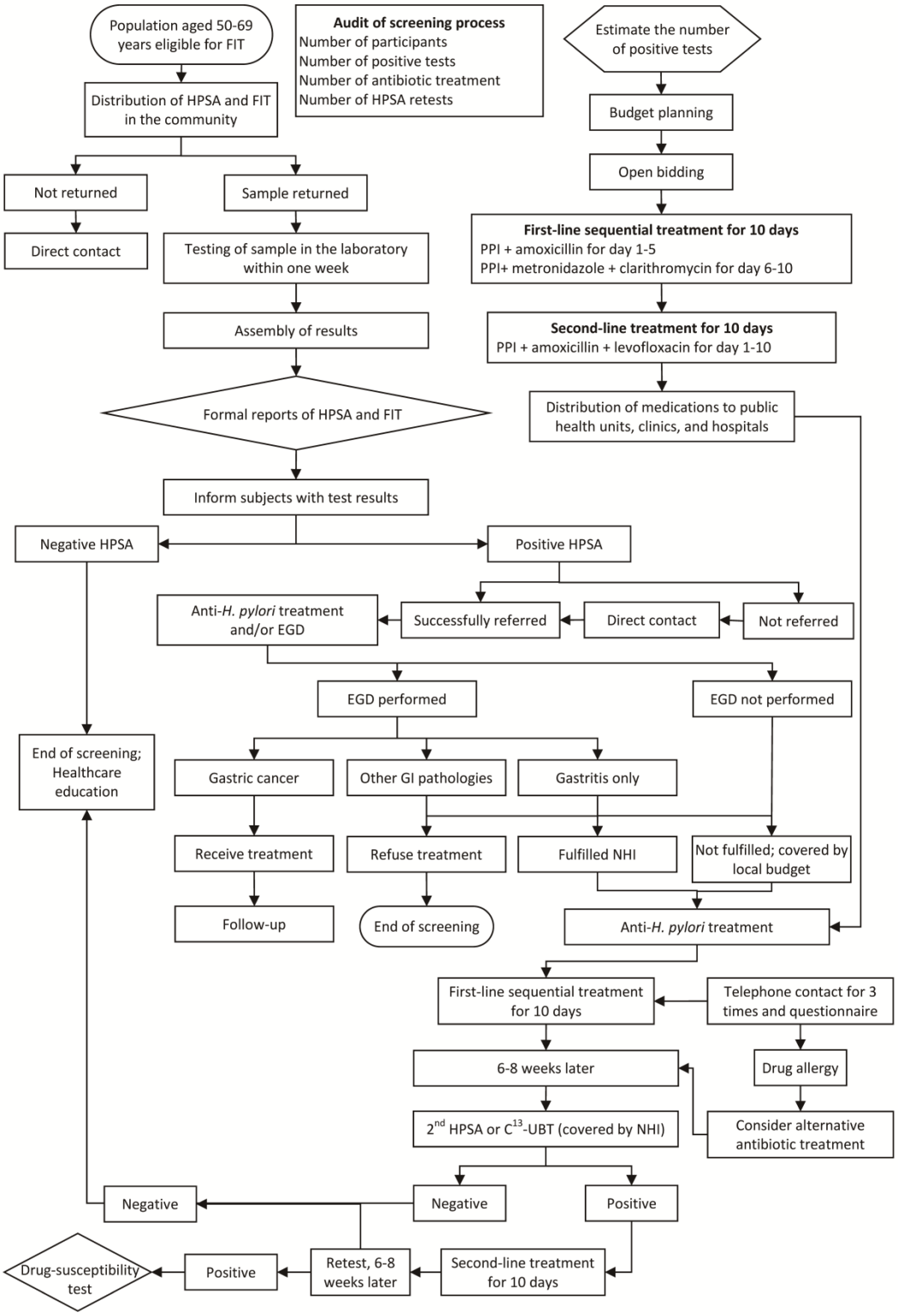


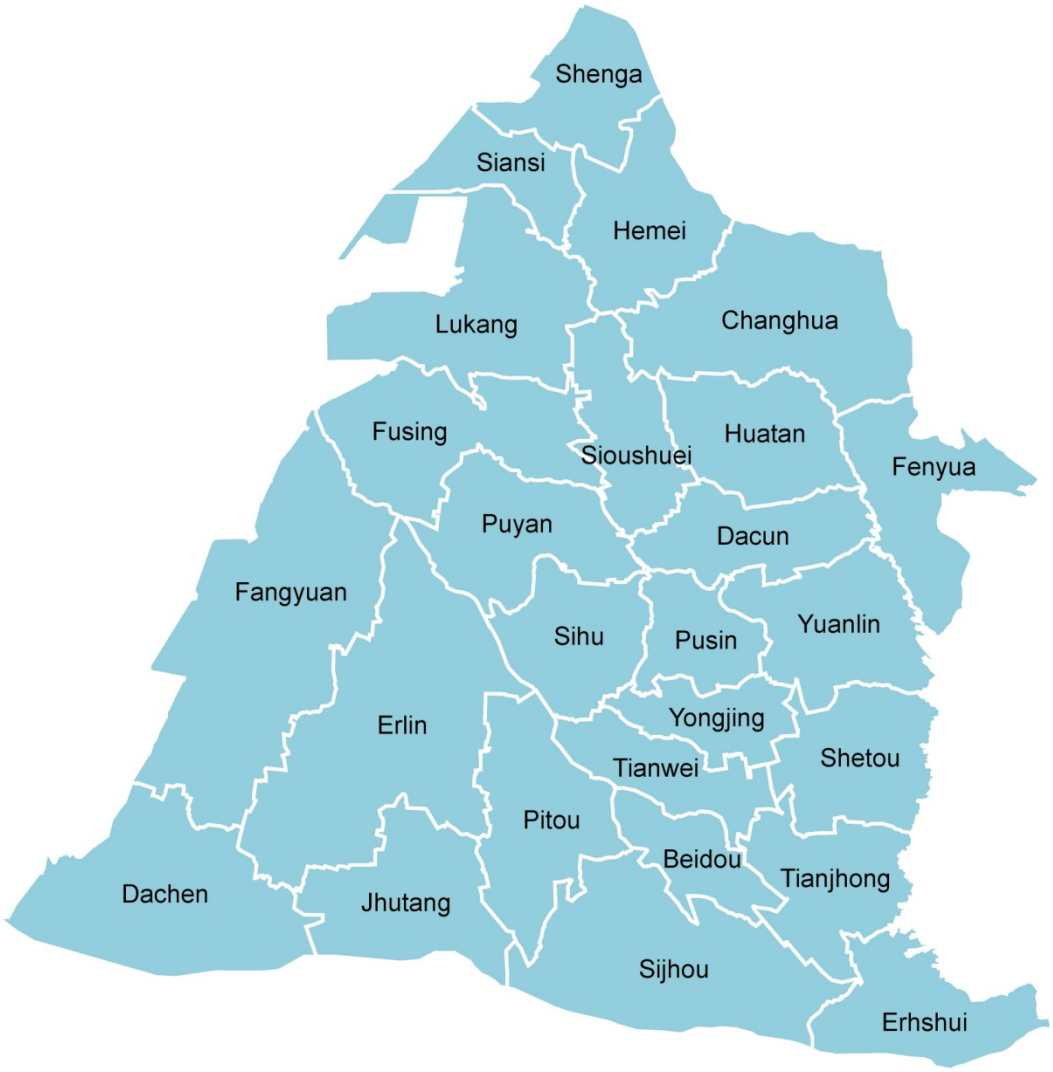
Fig. 1.3.2. Flow chart of the community-based screening for and treatment of *Helicobacter pylori* infection with the *H. pylori* stool antigen test (HPSA) in Changhua County in Taiwan, China (2013). Note that anti-*H. pylori* treatment could be reimbursed by the National Health Insurance (NHI) when active peptic ulcers were found by endoscopy. C^{13}-UBT, ^{13}C-urea breath test; EGD, esophagogastroduodenoscopy; FIT, faecal immunochemical test; GI, gastrointestinal; PPI, proton pump inhibitor.



4. Invitation method

Before the new screening strategy was implemented, a series of consensus meetings and educational programmes were held for primary care physicians and first-line health-care workers. Beginning on 21 April 2012, eligible participants were invited by telephone or postcard from 27 public health units covering a total of 26 townships in Changhua County (Fig. 1.3.3). A structured questionnaire was used to collect their medical and medication histories.

Fig. 1.3.3. The geographical locations of 26 townships in Changhua County in Taiwan, China.



5. *H. pylori* stool antigen test

Two diagnostic accuracy studies for HPSA were performed before it was widely implemented. The aims were:

- To evaluate the diagnostic accuracy of HPSA in identifying *H. pylori* infection.
- To evaluate the diagnostic accuracy of HPSA in detecting upper gastrointestinal lesions/cancers.

First, to evaluate the accuracy of HPSA in diagnosing *H. pylori* infection, a hospital-based study was conducted by recruiting 117 consecutive patients who were referred from the

primary care setting. These patients underwent two invasive tests (rapid urease test and histology) and three non-invasive tests (^{13}C-UBT, serology, and HPSA) for diagnosing *H. pylori* infection. The reference standard for a positive *H. pylori* infection was defined as positive results for at least two of the following three tests: ^{13}C-UBT, rapid urease test, and histology. The sensitivity and specificity of HPSA were estimated to be 88% and 99%, respectively, by taking into account about 1% of cases with trace-line readings. The specificity and positive predictive value of HPSA were significantly higher than those of the serological test. The second part of the same study consisted of a screening study based on 2720 participants, in which the concordance rate between the results of HPSA and ^{13}C-UBT was 91.7% and the kappa statistic was 0.78 [4].

Second, to evaluate the feasibility of combining HPSA with FIT and to determine the diagnostic accuracy in detecting upper and lower gastrointestinal tract lesions, a diagnostic accuracy study was also performed. A total of 3172 participants were recruited to undergo upper endoscopy and colonoscopy. The sensitivity and specificity of HPSA were 53% and 81%, respectively, for detecting upper gastrointestinal lesions, 60% and 81%, respectively, for detecting gastric lesions, and 78% and 76%, respectively, for detecting gastric cancer [5].

6. Antibiotic treatment

In 2012, individuals with positive HPSA results underwent endoscopic screening and antibiotic treatment, including:

- 7-day triple therapy (40 mg of esomeprazole once a day, 1 g of amoxicillin twice a day, and 500 mg of clarithromycin twice a day), and
- 10-day levofloxacin-based triple therapy (40 mg of esomeprazole once a day, 1 g of amoxicillin twice a day, and 500 mg of levofloxacin once a day) for individuals in whom initial treatment failed.

Based on experience from the Matsu Island gastric cancer prevention programme, the retest–retreatment practice was also included in this screening programme, with the hope of reducing the risk of antibiotic-resistant strains of *H. pylori*. HPSA was performed 6–8 weeks after the end of antibiotic treatment. For individuals whose test remained positive after two courses of antibiotic treatment, no further empirical treatment was given. Instead, a third-line treatment study was in progress, in which the optimal regimen was designed to overcome antibiotic resistance on the basis of phenotypic resistance (minimum inhibitory concentrations) and genotypic resistance (point mutations in the 23S ribosomal RNA and gyrase A genes).

In 2013, individuals with positive HPSA results would receive:

- 10-day sequential therapy (40 mg of esomeprazole and 1 g 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), and
- 10-day levofloxacin-based triple therapy (40 mg of esomeprazole once a day, 1 g of amoxicillin twice a day, and 500 mg of levofloxacin once a day) for individuals in whom initial treatment failed.

HPSA was performed 6–8 weeks after the end of antibiotic treatment. The purpose was to try to increase the first-line eradication rate. This evaluation is still in progress.

7. Phone call contact method

To increase the compliance with antibiotic treatment and evaluate the occurrence of side-effects, a phone call contact method was designed. This concept was derived from directly observed therapy for pulmonary tuberculosis, which remained an important public health problem in Taiwan, China. The first phone call contact would be made within 3 days after the

start of treatment. During the course of treatment, there would be at least three phone call contacts on different dates, and the results were recorded in a standardized questionnaire (Fig. 1.3.4). The method was applied to the 7-day triple therapy, 10-day sequential therapy, and 10-day second-line therapy.

8. Endoscopy

Individuals with positive HPSA results were referred to 15 local gastrointestinal clinics and 9 hospitals in Changhua County for antibiotic treatment and/or endoscopic diagnoses. The endoscopic diagnoses of gastrointestinal neoplasia were confirmed by histological results under routine medical practice.

9. Evaluation method

Standard screening indicators, including the participation rate, positive rate, referral rate, endoscopic findings, positive predictive value, and detection rate, were used to evaluate the applicability of this screening strategy within the community. The mass screening was to be conducted on an annual basis. The aims of the three successive rounds are as follows.

9.1 First round (2012–2013)

- To demonstrate proof of concept.
- To evaluate the eradication rate of a test–treat–retest–retreat strategy.

9.2 Second round (2013–2014)

- To optimize the efficacy of anti-*H. pylori* treatment.
- To establish the basis for a randomized trial to evaluate the efficacy of using this screening strategy.

9.3 Third round (2014–2015)

- To compare the eradication rate between the first round and the second round.
- To perform an economic modelling study to simulate the long-term outcome.
- To evaluate the reinfection rate of *H. pylori* after eradication.
- To launch a community-based randomized trial of screening and treating *H. pylori* infection integrated with colorectal cancer screening with the faecal occult blood test.

10. Results

10.1 First round (2012–2013)

A total of 6798 people aged 50–69 years were evaluated, of which 3621 eligible people were invited to participate. Among them, 941 (26%) were male and the mean age was 57.9 years. A total of 3454 (95.4%) participants returned an adequate stool test sample, and 1251 samples had positive HPSA results. Among the participants with positive results, 817 (65.3%) were referred to clinics or hospitals, 755 (92.4%) received antibiotic treatment, and 643 (78.7%) underwent upper endoscopic examination. Significant upper gastrointestinal lesions were found in 205 people (31.9%), including 7 erosive oesophagitis (grade C or D), 1 Barrett oesophagus, 4 oesophageal varices (form II or III), 189 peptic ulcers, and 2 gastric cancers. The positive predictive value was 31.9%, the detection rate for significant upper gastrointestinal lesions was 5.9% (205 of 3454), and the number of endoscopies required to find one gastric cancer was 322 [5]. The eradication rate of first-line treatment was approximately 88%.

Fig. 1.3.4. Questionnaire of the phone call contact method to improve the compliance and evaluate the side-effects related to anti-*Helicobacter pylori* treatment in Changhua County in Taiwan, China.

Questionnaire of the compliance and side effects to antibiotic treatment using the phone call contact method

Basic data of screenee:

Name	Study ID	Birthday	Gender	Telephone	Mobile phone

Treatment data:

Course of treatment	Starting date	Ending date

First contact	Date	Compliance	Allergic reaction	Nausea or vomiting	Headache or dizziness	Epigastric discomfort	Diarrhoea	Others	Management of side-effect

Second contact	Date	Compliance	Allergic reaction	Nausea or vomiting	Headache or dizziness	Epigastric discomfort	Diarrhoea	Others	Management of side-effect

Third contact	Date	Compliance	Allergic reaction	Nausea or vomiting	Headache or dizziness	Epigastric discomfort	Diarrhoea	Others	Management of side-effect

Name of Public Health Unit: _____

Name of phone call contact personnel: _____

10.2 Second round (2013–2014)

In 2013, 4009 eligible people were invited to participate. Among them, 1624 (40.5%) were male and 1325 (33.1%) tested positive for *H. pylori*. Patient referrals, endoscopies, and antibiotic treatment are under way. Preliminary results showed that 883 (66.6%) participants were referred for endoscopy and/or antibiotic treatment. A total of 877 (99.3%) people received antibiotic treatment. Among 647 (73.3%) individuals who also underwent endoscopy, 3 gastric cancers were found, and the number of endoscopies required to find one gastric cancer was 216.

11. Conclusion

Based on the experience from Matsu Island, a pilot study targeting the older adult population aged 50–69 years was conducted in Changhua County in Taiwan, China. Under the framework of the colorectal cancer screening programme, HPSA testing was performed with FIT for simultaneous detection of upper and lower gastrointestinal lesions. Both primary prevention (anti-*H. pylori* treatment) and secondary prevention (endoscopic screening) were implemented for gastric cancer. Preliminary results showed that this strategy was applicable and effective in detecting gastric cancer. Participants benefited from antibiotic treatment for peptic ulcer and chronic gastritis, and chemoprevention for gastric cancer. In 2012, another county in Taiwan, China (Yilan County) voluntarily adopted this screening strategy under the auspices of the local government. Using the pilot studies as the basis, a randomized community-based trial is in progress (NCT01741363).

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Chapter 1.4

The regional status of current or planned gastric cancer prevention strategies in Latin America

Catterina Ferreccio

Gastric cancer mortality rates are extremely high in some Latin American countries, such as Chile, Costa Rica, and Colombia, whereas the rates are low in other countries, like Mexico and Argentina the rates. Nevertheless, even in Mexico and Argentina there are areas or communities with high rates of gastric cancer, like Chiapas and southern Argentina, respectively.

1. Gastric cancer prevention in Latin America

Gastric cancer is an important health problem for most Latin American countries, yet no national programmes for the primary prevention of gastric cancer have been implemented or planned. In the area of secondary prevention of gastric cancer, the only Latin American country with a national programme is Chile, with its AUGE (Acceso Universal con Garantías Explícitas; Universal Access with Explicit Guarantees) plan. This programme guarantees endoscopic examination including *Helicobacter pylori* detection, biopsy, and treatment for symptomatic adults aged 40 years and older. Most activities for the secondary prevention of gastric cancer in Latin American countries have been conducted by private organizations and have been based on the detection of gastric cancer through endoscopy. These opportunistic programmes had subnational coverage (mostly local or regional) and lasted a few years or decades. Colombia, Mexico, and Paraguay have made efforts to develop a consensus on the histopathology of gastric cancer precursor lesions; nevertheless, this information has not yet been included in prevention programmes.

Practically all Latin American countries have coexisting populations with high and low risk of developing gastric cancer. These areas not only show differences in incidence and mortality but also show differences in the clinical and epidemiological characteristics of gastric cancer [1, 2]. Populations with high risk of gastric cancer are typically of low socioeconomic status and have high *H. pylori* prevalence; the high levels of *H. pylori* are reached at younger ages [3, 4]. In high-risk areas, gastric cancer is mainly of the intestinal type, is well differentiated, initiates in the distal part of the stomach, and is diagnosed at an advanced stage, and thus has a poor prognosis (5-year survival < 10%) [5]. In contrast, areas where risk of gastric cancer is low are the most affluent in each country and region and have low prevalence of *H. pylori*, most noticeably in younger generations [3]; patients present at early stages, have greater access to endoscopies and biopsies, and possibly have higher survival rates. In low-risk areas, gastric cancer tends to be located in the proximal part of the stomach, is less differentiated, affects younger patients, and is less associated with *H. pylori* [6]. In both high- and low-risk areas, men are affected more frequently than women, but the sex differential decreases in low-risk areas.

The current understanding is that *H. pylori* infection is the driving force for gastric cancer, especially in high-risk areas, and that in theory gastric cancer can be largely prevented. Prevention strategies in some countries include mass screening of the adult population or endoscopic examination of symptomatic individuals. For instance, Japan introduced screening in the 1960s and currently coverage is estimated at 30%; the programme is based on barium double-contrast radiography followed by endoscopy of suspicious images. This strategy has not been adopted in other countries as a nationwide strategy due to its high cost, the requirement of trained endoscopists and pathologists, its invasiveness, and the

uncertainties about its effectiveness [7]. Several authors have proposed shifting from secondary to primary prevention of gastric cancer based on *H. pylori* test-and-treat strategies [8, 9]. In Latin American countries, there are no national programmes for the primary prevention of gastric cancer [10]. This chapter reviews the gastric cancer prevention strategies that the governments and ministries of health in Latin American countries currently offer.

2. Gastric cancer prevention strategies by country

2.1 Argentina

In some areas of southern Argentina, gastric cancer mortality rates per 100 000 population reach 32 in men and 8 in women, whereas in Buenos Aires the corresponding rates are 8 and 3 [6]. Argentina does not have a national screening programme for gastric cancer or national guidelines for its management. The current programmes and management guidelines are limited to cervical, breast, skin, prostate, ovarian, lung, and paediatric cancers (http://www.msal.gov.ar/inc/index.php).

2.2 Belize

In Belize, there is a decreasing trend in gastric cancer mortality, with rates near 6 per 100 000 population and higher in men (6.2) than in women (1.0). There are no prevention programmes for gastric cancer; the only prevention programme is cervical cancer screening based on the Pap test [10].

2.3 Bolivia

The cancer prevention programme in Bolivia is in the early development stages and focuses on early detection of cervical cancer with Pap smears, covering about 12% of the population, and early detection of breast cancer with self-examination followed by clinical examination and mammography. Gastric cancer prevention is not included in the programme [10].

2.4 Brazil

In Brazil, as a general strategy for all cancers, prevention is focused on improving lifestyle factors (diet, tobacco use, alcohol consumption, physical activity) (http://www2.inca.gov.br/wps/wcm/connect/tiposdecancer/site/home/estomago/prevencao). Early detection programmes are offered for only cervical and breast cancers [10].

2.5 Chile

In Chile, the burden of gastric cancer is high, with mortality rates per 100 000 of 25.1 in men and 12.5 in women [11]. Gastric cancer prevention has been addressed by private and public initiatives. The first experience with mass endoscopic screening was conducted by Llorens from 1978 to 1986 in 42 492 individuals in Santiago [12], with support from the Japanese government. Llorens found a gastric cancer prevalence of 0.4% and 1.3% among asymptomatic and symptomatic subjects, respectively; in these groups, the percentages of gastric cancer at early stages were 15% and 11%, respectively. In 1995, the Ministry of Health of Chile conducted an endoscopic-based screening pilot programme in Santiago; the first 10-year (1996–2006) performance of this project was recently evaluated. The intervention area had a population of 223 708; 10 284 individuals (13 268 exams) were screened (~4.6 individuals per 1000 population per year), and 190 gastric cancer cases (8.5 per 100 000 population per year) were identified, of which 32.1% were at early stages (58.7% in women, 27.6% in men). The endoscopy detection rate was 1.4% (0.7% for men, 3.3% for women). It was estimated that 70 gastroscopies were required to identify one gastric cancer. The specific 5-year survival rate was 40% (53.2% in women, 33.3% in men) [13]. In 2006, the Ministry of Health initiated a nationwide gastric cancer detection programme, which is opportunistic and focuses on symptomatic individuals; it guarantees

endoscopic examination for any patient who fulfils some of the following criteria: individuals older than 40 years with epigastric pain lasting more than 15 days, heavy bleeding, anaemia, or weight loss of unknown origin, sensation of full stomach after eating, general feeling of weakness, tiredness, loss of appetite, dysphagia, history of gastrectomy more than 15 years earlier, and immediate family member with gastric cancer. *H. pylori* eradication is recommended "in any patient undergoing endoscopy, unless endoscopic examination is normal or the stomach mucosa presents only superficial and minimal lesions; eradication is also recommended in patients with duodenal or stomach ulcers, atrophic gastritis, lymphoma, adenoma, gastric cancer, and family history of gastric cancer". The recommended *H. pylori* eradication scheme is 500 mg of clarithromycin plus 1 g of amoxicillin plus 20 mg of omeprazole, all taken twice a day for 7 days [14].

2.6 Colombia

The gastric cancer mortality rate in Colombia is one of the highest in Latin America, with areas of high risk in the Andes Mountains and areas of low risk at the coast [15]. Colombia has an ambitious programme for cancer control, the Colombia National Cancer Control Program 2012–2020. The primary prevention goals, as in most other Latin American countries, are to reduce the prevalence of modifiable risk factors for cancer (tobacco use, physical inactivity, and unhealthy diet). The programme also addresses other factors, such as alcohol consumption and ultraviolet exposure, and includes human papillomavirus (HPV) vaccination; in addition, it seeks to reduce occupational oncogenic exposures to asbestos, silica, benzene, lead, and ionizing radiation. The programme for early detection is currently limited to cervical and breast cancers. There are no specific gastric cancer prevention strategies [10]. Investigators in Colombia, Mexico, and Paraguay have studied the reproducibility of the histopathology of gastric cancer precursor lesions, which could form the basis for a future Latin American consensus [16].

2.7 Costa Rica

Costa Rica also has one of the highest gastric cancer mortality rates in the region; gastric cancer occupies the second place among the main causes of cancer death in men and women [10]. The National Plan for Cancer Prevention and Control 2011–2017 includes, among the primary prevention measures, the control of lifestyle-related risk factors and of chemical exposures. The programme for early detection includes only cervical and breast cancers. There is no mention of any specific measure to prevent gastric cancer [17]. There was an initiative in 1995, supported by the Japanese government, in the high-risk area of Cartago, where the Centro de Detección de Cáncer Gástrico del Hospital Max Peralta initiated an endoscopy-based early detection programme for gastric cancer, following the Japanese model of X-ray screening, video endoscopy, and stomach biopsy. The programme included 6828 individuals, of whom 34% required endoscopy; 59 (0.86%) gastric cancer cases were identified, 55% of which were detected at early stages. The second round of screening, 2 years later, included 5046 participants, and 28 (0.55%) gastric cancer cases were identified; 80% of cases were at early stages. The 5-year gastric cancer survival rate was 85%, with an estimated reduction of 50% in gastric cancer mortality. Nevertheless, this programme was considered inapplicable to the country due to its high cost [18].

2.8 Cuba

Gastric cancer mortality rates in Cuba are relatively low in both men and women (7.2 and 3.6 per 100 000, respectively). Gastric cancer is the fifth most common cause of cancer death in men and is not among the 10 most common causes in women. Cuba has a national population cancer registry. Existing screening programmes cover cervical, breast, and colon cancers [10].

2.9 Dominican Republic

In the Dominican Republic, gastric cancer is the fifth most common cause of cancer death in men and is not among the 10 most common causes in women. Screening programmes exist for cervical and breast cancers [10].

2.10 Ecuador

A high-risk area for gastric cancer, Ecuador does not have a national gastric cancer prevention programme. There is a national programme for cervical cancer, which is provided by SOLCA (Sociedad de Lucha Contra el Cáncer del Ecuador), a non-profit national organization with representatives in most large cities in the country; they provide clinical guidelines for gastric cancer (http://www.solca.med.ec/).

2.11 El Salvador

In El Salvador, gastric cancer is the leading cause of cancer death in both men and women, with mortality rates per 100 000 of 17.2 in men and 12.3 in women. The only prevention programmes are for cervical and breast cancers.

2.12 Guatemala

Similarly to El Salvador, in Guatemala gastric cancer is the leading cause of cancer death in both men and women, representing 20% of all cancer deaths. The only screening programme is focused on cervical cancer.

2.13 Honduras

Honduras is also a high-risk country for gastric cancer, which is the leading cause of cancer death in men and the second most common cause in women [10]. Honduras does not have a specific gastric cancer prevention programme. The Ministry of Health issued a National Strategic Plan for the Prevention and Control of Cancer 2009–2013, which is limited to early detection and primary prevention of cervical cancer [19].

2.14 Mexico

Overall, Mexico has one of the lowest risks of gastric cancer of Latin American countries; nevertheless, it has areas like Chiapas, where gastric cancer mortality is twice the country's overall rate (8.0 and 3.9 per 100 000, respectively) [20]. The cancer priorities for 2007–2012 include screening for only cervical and breast cancers [21]. There is no mention of gastric cancer prevention in the package of guaranteed prevention and promotion services, which promotes healthy diet and seeks to control obesity and tobacco use; this package covers prevention of breast, cervical, and prostate cancers [22]. According to the Pan American Health Organization, Mexico offers colorectal cancer screening [10].

2.15 Nicaragua

Nicaragua has an intermediate risk of gastric cancer, with mortality rates per 100 000 of 12.9 in men and 8.0 in women. The only screening programme is focused on cervical cancer [10].

2.16 Panama

Gastric cancer mortality rates in Panama are similar to those in Nicaragua, with mortality rates per 100 000 of 13.1 in men and 7.4 in women. Panama has areas of high gastric cancer risk but does not have any specific intervention to prevent gastric cancer, although endoscopy is covered by the government as part of a medical workup. There are prevention programmes for cervical and breast cancers [10].

2.17 Paraguay

The only cancer prevention programmes in Paraguay are cervical cancer screening based on the Pap test and breast cancer screening based on self-examination.

2.18 Peru

A national programme exists for cervical cancer and breast cancer. With support from the Japanese government, Peru implemented esophagogastroduodenoscopy in 31 446 symptomatic patients between 1985 and 2002; gastric cancer prevalence was 3.19% in 1988 and 0.92% in 2002 [23]. In 2013, the "Plan Esperanza" (Hope Plan) was launched to prioritize the prevention of breast, cervical, and colon cancers (ftp://ftp2.minsa.gob.pe/normaslegales/2012/DS009_2012_SA_EP.pdf). In this plan, endoscopy is offered to patients with high suspicion of digestive cancer. There is a medical guide for gastric cancer, but it does not include prevention [24]. The PEAS (Plan Esencial de Aseguramiento en Salud; Health Insurance Essential Plan) covers the diagnosis of gastric cancer by funding one endoscopy and one biopsy [25]. The decree regarding cancer for the period 2012–2015 includes cervical, breast, and colon cancers in the area of early detection; gastric cancer is mentioned only in the diagnosis and treatment sections [26].

2.19 Puerto Rico

With low mortality rates for gastric cancer in both men and women (5.5 and 2.3 per 100 000, respectively), Puerto Rico does not have a prevention programme focused on gastric cancer. Screening programmes exist for breast, cervical, and colorectal cancers [10].

2.20 Suriname

In Suriname, gastric cancer mortality rates are very low in both men and women (4.0 and 1.7 per 100 000, respectively). The only screening programme is focused on cervical cancer [10].

2.21 Trinidad and Tobago

Gastric cancer mortality rates are low in Trinidad and Tobago in both men and women (7.5 and 3.0 per 100 000, respectively). The only screening programme is focused on cervical cancer [10].

2.22 Uruguay

Uruguay is a low-risk area for gastric cancer, and no intervention directed to prevent gastric cancer exists. The national cancer prevention programmes include early detection of breast, cervical, and colon cancers [10].

2.23 Venezuela

Venezuela has areas with high risk of gastric cancer, like the state of Táchira, but does not have a national intervention directed towards this cancer. From 1980 to 1989, a screening programme was conducted in this high-risk region, with the collaboration of the Japanese government. It was aimed at the population aged 35 years and older and was based on six-film indirect photofluorography using double contrast, to be repeated every1–2 years. During this period, 114 000 examinations were performed, identifying 445 cases of gastric cancer [27]. This programme was not extended to other regions and has now been discontinued; however, an endoscopic centre for early detection, diagnosis, and treatment of digestive cancers is maintained. The Venezuela Ministry of Health's cancer control programme has four specific components: cervical cancer screening based on the Pap test, breast cancer screening based on self-examination, prostate cancer screening based on digital exam of the prostate and prostate-specific antigen (PSA) testing, and cancer registry development; gastric cancer is not included [28].

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Chapter 1.5

The regional status of current or planned gastric cancer prevention strategies in Europe

Mārcis Leja

There are two major sets of guidelines addressing gastric cancer prevention strategies in Europe: the Maastricht IV guidelines on the management of *Helicobacter pylori* infection [1] and the MAPS (Management of precancerous conditions and lesions in the stomach) guidelines [2]. Both of these emphasize the need for gastric cancer risk stratification and propose strategies to decrease the burden of gastric cancer.

However, the guideline statements have been only partially taken up by clinical practice. Although mass eradication ("search-and-treat") in areas of high gastric cancer risk has been suggested by guidelines in Asia [3] and in Europe [1] and recent meta-analyses have confirmed the potential cost–effectiveness of this approach [4, 5], none of the high-risk countries in Europe has accepted this approach, because of the potential adverse events, including microbial resistance. Even though guidelines suggest pepsinogen detection as the best available approach for non-invasive selection of the group for further diagnostic workup [1–3], so far there are not sufficient data on the potential of these tests to decrease mortality due to gastric cancer to recommend their use in organized cancer screening programmes, at least in Europe and in Caucasian populations.

This chapter presents a summary of major gastric cancer prevention studies and gives insight into current and planned developments in the field. By considering the presence of Caucasian populations outside the geographical region of Europe, this review will also cover the activities in neighbouring territories, i.e. the Siberian part of the Russian Federation as well as Kazakhstan.

1. Improvements in endoscopy

There are substantial differences between the routinely performed upper endoscopies in the Far East (in particular, in Japan and the Republic of Korea) and in Europe and North America.

In Japan, detailed endoscopic evaluation with multiple photo-fixations following well-defined standards is the everyday practice. In Europe and North America, the standard biopsy strategy with five non-targeted biopsies according to the updated Sydney system is the recommendation if no visually detectable lesions are present (although this recommendation is frequently not followed in the community practice). The current guidelines do not recommend limiting the biopsy sampling to locations where visually detectable lesions can be identified, because of insufficient accuracy reported in previous studies [2]. However, the technologies are improving, and the targeted biopsy strategy is becoming more and more attractive. The current state of knowledge about identification of stomach lesions with the new visualization technologies has been reviewed recently [6].

Two (post-MAPS) studies to evaluate the possibilities of targeted biopsies with high-resolution endoscopy have recently been started in Europe: one with the narrow-band imaging (NBI) system by Olympus (principal investigator, M. Dinis-Ribeiro) and the other with the flexible spectral imaging colour enhancement (FICE) system by Fujifilm (principal investigator, I. Kikuste). The protocol of the NBI study is designed as a multicentre investigation, whereas the FICE study will be based in one centre or a few centres.

Several studies, including those mentioned here, will address the rationale for the surveillance intervals as suggested by the MAPS guidelines.

2. Histological risk stratifications

There are minor discrepancies present within the current guidelines with respect to the approach to biopsy sampling from a stomach mucosa without any visually detectable lesions: whereas traditionally, the updated Sydney classification requires a biopsy from the incisura of the stomach, the MAPS guidelines do not include this as part of the minimum requirements. Two studies are close to being completed and published: one being conducted in Magdeburg, Germany, and the other in Riga, Latvia. The preliminary results favour the use of the incisura biopsies. The remaining open issues are deciding whether subtyping of intestinal metaplasia and separate analysis of biopsies obtained from the major and minor curvature are rational.

New staging systems for gastric premalignant lesions – OLGA and OLGIM – have been suggested to simplify the clinical approach while using the same biopsy workup as for the Sydney system (i.e. five biopsies, including the incisura angularis). The Operative Link on Gastritis Assessment (OLGA) staging system is based on severity of atrophic gastritis, whereas the OLGIM system emphasizes the importance of intestinal metaplasia. The initially proposed OLGA system is based on pooling the atrophy scores in each part of the stomach into a simple OLGA stage, ranging from 0 to IV [7]. Because inter-observer agreement is better for intestinal metaplasia than for atrophy, the OLGIM system uses the same approach but stages intestinal metaplasia instead of atrophy [8].

The stage by itself does not allow a judgement to be made about the topography of the lesion revealed (in particular, for the lower stages), but it is considered to be linked to the issues of prognosis and management, since most of the cancer cases are expected to be associated with OLGA stages III and IV [9]. Such a stage distribution is also convenient for research purposes [10].

Several recent studies have evaluated the rationale for the staging systems and found them to be helpful in general. However, for the true validation of the systems, it is essential to conduct studies in high-risk areas demonstrating that cancer and dysplasia cases are associated with the advanced stages (III/IV) but not the early stages. Few such studies are currently under way.

A study in progress in the south of the Russian Federation (Stavropol and Cherkessk; coordinating investigator, V. Pasechnikov; principal investigator, S. Kotelevets) is recruiting patients referred for upper endoscopy and assessing them according to the OLGA staging system as well as pepsinogen testing (using the Biohit system). The initial patient sample includes 2965 individuals of Caucasian origin, with mean age 54 years (range, 18–92 years), 38.7% male patients, and *H. pylori* prevalence 74.7%. Decreased pepsinogen levels (decreased ratio of pepsinogen I to pepsinogen II; PgI/II < 3) have been found to correlate well with advanced OLGA stages (V. Pasechnikov, personal communication).

An additional follow-up study is being conducted in Latvia to access the endoscopy and pathology (OLGA/OLGIM) results in patients with decreased pepsinogen levels (the initial study is described elsewhere [11] and is briefly characterized in the text below). Individuals with decreased pepsinogen levels at study inclusion are invited for upper endoscopy with an appropriate biopsy workup. The results are expected by the end of 2014; the initial results suggest that high-risk lesions may be distributed in different OLGA/OLGIM stages, not limited to advanced stages.

3. Blood-sample-based gastric atrophy detection and its limitations

The traditional blood-sample-based (plasma or serum) indirect atrophy detection is based on pepsinogen measurement. A decreased PgI level – more precisely, a decreased PgI/II ratio – indirectly reflects the lower functional activity and, therefore, indirectly also the presence of atrophy in the stomach. Although previously reported [12] sensitivity results of pepsinogen levels for gastric cancer identification could be considered acceptable in screening settings, worse performance is reported in many of the studies. The results are better for detection of atrophy, i.e. sensitivity of 66.7–84.6% and specificity of 73.5–87.1% [13–16], but significantly lower sensitivity for detection of gastric cancer using the same cut-off values (36.8–62.3%) has been reported [17–19]. This would potentially result in missing half, or even more than half, of gastric cancer cases in settings of population-based screening.

Pepsinogen detection has been studied in Japan for decades; in Europe, the detection of pepsinogens has become available more recently. Different methods and different cut-off values have been used to define decreased circulating pepsinogen levels. Whereas a latex agglutination method (in a conventional clinical chemistry analyser) is used in most of the recent studies in Japan, enzyme-linked immunosorbent assay (ELISA) is the most common method in Europe and other parts of the world outside Japan. Although a relatively good correlation has been reported between the results obtained with these two methods, the absolute values differ; therefore, the results in absolute values cannot be translated between the different studies unless identical test systems are used in similar study populations [20]. Therefore, regional validation of the test system is absolutely essential.

More recently, an additional marker – amidated gastrin-17 (G-17) – has been suggested to characterize atrophy in the antral part of the stomach; G-17 is secreted exclusively by the G cells in the antral part of the stomach, and therefore G-17 levels are expected to be decreased in antral atrophy [21–23]. However, the concentrations of G-17 in the circulation are influenced by several factors, and as a result the sensitivity for diagnosing atrophy in the antral part of the stomach is unsatisfactory (15.4% in a fasting state and 30.8% after stimulation) [24].

4. Non-invasive GastroPanel testing for gastric cancer risk stratification – the Russian study

The GastroPanel system (Biohit, Finland) is a set of 4 plasma tests: PgI, PgII, G-17, and immunoglobulin G (IgG) group antibodies to *H. pylori* infection. Decreased pepsinogen levels have been found to correlate with increased risk of gastric cancer in Japan; however, such data were not previously available in a Caucasian population. A study in a population-based cohort of 9360 individuals recruited within the Health, Alcohol and Psychosocial factors in Eastern Europe (HAPIEE) study, aged 45–69 years at the time of recruitment, has been reported from Novosibirsk, a city in Russian Siberia. Within a follow-up period of 6 years, 25 gastric cancer cases were identified and included in the initial report. Every gastric cancer case was matched to two controls. In patients with decreased pepsinogen levels (PgI/II < 3), the odds ratio (OR) for developing gastric cancer was 4.31 (95% confidence interval, 1.49–12.45); however, decreased G-17 levels did not reach statistical significance to reveal gastric cancer risk. With respect to *H. pylori* positivity, statistical significance was not reached either, although seropositivity was high in both groups (80% in the cancer group and 69.4% in the control group) [25].

During the subsequent analysis several years later (follow-up period, 8 years), which has been reported in an abstract format so far, more cancer cases were revealed in the study group. A total of 60 gastric cancer cases and 120 controls were included in the case–control design. The odds ratio of PgI/II < 3 reached statistical significance as a risk factor for gastric cancer (odds ratio, 3.0; 95% confidence interval, 1.4–6.4) [26].

5. Blood-sample-based gastric atrophy prevalence studies

Three different types of prevalence studies have been reported. The most informative type are studies conducted in a representative population-based sample that is randomly selected and of sufficient size. The second type are studies conducted in generally healthy populations that are invited to participate in the intervention; some preselection bias cannot be excluded with this design. The third type are studies conducted either in a hospital-based population sample or in referrals for certain interventions, for example upper endoscopy. These three types of study are discussed here.

5.1 Population-based studies with random selection

The largest population-based cohort study (ESTHER) recruited a total of 9953 participants (45% male) aged 50–74 years in Saarland in south-western Germany between 2000 and 2002. PgI and PgII were detected in serum by the ELISA method (Biohit). With the cut-off values for atrophy PgI < 70 ng⁄mL and PgI/II < 3, the prevalence of atrophy in this cohort was 5.7% [27]. Recently, an additional analysis has been performed on the study population, suggesting the rationale of including anti-parietal cell antibody detection to the list of biomarkers [28].

The Kalixanda study, in Sweden, was a general-population based study (mean age, 54.0 years; 51.2% women; participation rate, 73% of the eligible population). Serum samples from 978 individuals were included in the analyses for pepsinogens and G-17 (GastroPanel); importantly, endoscopy with appropriate biopsy workup was performed in nearly all the cases. The cut-off value for pepsinogen tests to detect atrophy was PgI < 25 µg⁄L and/or PgI/II < 3. Based on the serum test results, multifocal (antrum and corpus) atrophic gastritis was revealed in 1.1% of people and corpus-limited atrophic gastritis in 5.4%; therefore, blood tests for atrophy revealed a 6.6% overall prevalence [29].

A different testing modality was used in a large population-based study in Latvia. Plasma samples from a total of 3564 individuals were available (median age, 54 years; 34% male). PgI and PgII were detected in plasma by the latex agglutination method (Eiken Chemical Co., Japan), and two different cut-off values were used: PgI ≤ 70 ng/mL and PgI/II ≤ 3 for atrophy of any grade; PgI ≤ 30 ng/mL and PgI/II ≤ 2 for advanced atrophy. With these criteria, the overall prevalence of atrophy was found to be 40.5%, whereas that of advanced atrophy was 13.3% [11].

Another population-based sample predominantly in a Caucasian population is available from Krasnoyarsk, a city in eastern Siberia (principal investigator, V. Tsukanov). A total of 801 subjects were involved (48.3% male; participation rate, 94.2% of the invited population). The Biohit ELISA test system was used to measure pepsinogen levels in serum, with cut-off values of PgI < 25 µg⁄L and PgI/II < 3. In this population with highly prevalent *H. pylori* infection (seroprevalence, 90%), the pepsinogen levels indicated the presence of atrophy in 10.9% of participants [30]. Recently, the same group reported the seroprevalence of atrophy in two Mongoloid populations in Siberia with high prevalence of *H. pylori* infection (about 94%) and high, but differing, incidence of gastric cancer; serological signs of atrophy were revealed in 5.3% of Evenks (total sample size, 527) and 9.4% of Tyvins (total sample size, 466) [31].

Using the same approach, a group from Novosibirsk has studied the prevalence of biomarkers characterizing atrophy in other regions of Russian Siberia (principal investigator, S.A. Kurilovich). The GastroPanel test system was used; a cut-off value of PgI < 25 µg/L was considered for corpus atrophy and fasting G-17 < 2 pmol/L for antral atrophy ([32] and S.A. Kurilovich, personal communication).

The prevalence of atrophy as detected with biomarker methods in several population samples from Russian Siberia is summarized in Table 1.5.1. The evidence from older studies, some of them based on population-selected individuals, was reviewed by Weck and Brenner in 2006 [33].

Table 1.5.1. Prevalence of atrophy as detected with biomarker methods in several population samples from Russian Siberia

Test results	Group description			
	Group 1	**Group 2**	**Group 3**	**Group 4**
	Novosibirsk, urban, Caucasians, 45–70 years	Yakutsk, urban, Caucasians, 60–90 years	Yakutsk, urban, indigenous, 60–90 years	Yakutsk, rural, indigenous, 45–70 years
	(*n* = 254)	(*n* = 81)	(*n* = 72)	(*n* = 90)
Corpus atrophy	9.1%	12.3%	15.3%	26.7%
Antral atrophy	13.6%	37.0%	36.1%	14.4%
H. pylori IgG	86.6%	72.2–74.1%	72.2–74.1%	72.2–74.1%

IgG, immunoglobulin G.

5.2 Studies in invited healthy individuals

A large cohort study in a population from Portugal, a high-risk region for gastric cancer in Europe, demonstrated the feasibility of the pepsinogen testing approach in a European population [34]. A total of 13 118 individuals were followed up for 5 years; 446 subjects (3.4%) had decreased pepsinogen levels. Of these, 274 underwent upper endoscopy; 6 cancer cases were detected, representing one cancer per 2200 tests or one incident case per 74 positive tests. However, 3 other cancer cases were detected in those with a negative pepsinogen test result. The Biohit ELISA test system with pepsinogen cut-off levels PgI < 70 ng/ml and PgI/II < 3 for detecting atrophy was used in this study [34].

Studies on large groups of invited individuals (medical professionals and the general population) have been conducted in Finland (principal investigator, P. Sipponen) by using the GastroPanel test system. The prevalence of lesions according to this non-invasive approach has not yet been reported.

5.3 Hospital/outpatient-department-based samples

In Europe, northern Italy has the largest experience in non-invasive testing with GastroPanel before referring patients with dyspeptic complains for endoscopy (principal investigator, F. di Mario). During 2003–2012, a total of 6000 subjects were investigated in the Padua region; 8% had results characteristic for atrophy, and 34% were *H. pylori*-infected. In 2011–2013, a total of 2000 people underwent testing in the Treviso region; atrophy was present in 4% and *H. pylori* infection in 26% (F. di Mario, personal communication).

A hospital/outpatient-department-based study was conducted in 818 dyspeptic patients of Caucasian origin aged 25–75 years in Novosibirsk in Russian Siberia. The GastroPanel test system was used; a cut-off value of PgI < 25 µg/L was considered for corpus atrophy and fasting G-17 < 2 pmol/L for antral atrophy. The results revealed corpus atrophy in 14.5% of patients and antral atrophy in 24.6% (A. Belkovets, personal communication).

In a recently reported hospital-based cohort in Kazakhstan, 835 patients (median age, 46.8; 43.4% male) were investigated with the GastroPanel test system. The seroprevalence of *H. pyl*ori infection was 62.3%. In 14.1% of the patients, the results were consistent with atrophic gastritis; in 8.6% the characteristic results for isolated antral gastritis were present, and in 5% for isolated corpus gastritis, but in 4 cases (0.4%) results for atrophic gastritis in both the antral and corpus parts of the stomach were present [35].

Currently, a study is in progress in Latvia to compare different pepsinogen tests (two ELISA tests and a latex agglutination test) in a hospital-based sample as well as to set the best cut-off values in a Caucasian population. The results obtained will be used and will be further validated in the GISTAR (Gastric cancer prevention study by predicting atrophic gastritis) study.

6. New biomarker developments

During the past decade there has been a growing interest in other biomarkers for the early detection of gastric cancer. Multiple studies have evaluated the role of host genetic polymorphisms to stratify risk of gastric cancer development; although an association is present, due to the insufficient strength of the association, these polymorphisms cannot be used as biomarkers. Extensive work has been conducted to study the potential role of microRNAs (miRNAs) as gastric cancer biomarkers, and several reviews have been published recently of the miRNAs that are upregulated or downregulated in gastric cancer [36–39]. There is potential that a panel of miRNAs may become a reliable marker for either detection or prediction of gastric cancer. New proteomic markers have been sought. In addition, recent studies suggest the potential of proteomic or miRNA marker expression in extracellular vesicles, including exosomes, microvesicles, retrovirus-like particles, and apoptotic bodies, as a cancer biomarker [40]. To date limited work has been conducted in this field, specifically with respect to gastric cancer, and the studies are still in progress. Here, more detailed information is provided about two potential biomarkers, on which studies have been published recently: cancer autoantibodies and volatile markers.

6.1 Cancer autoantibodies

Autoantibodies against tumour-associated antigens have been identified in several cancer types [41, 42]. The frequency of antibodies against particular tumour-associated antigens is rather low, typically ranging between 1% and 15%; therefore, a test-panel approach is being used to explore cancer-specific antibodies [43]. Recently such a search for a test panel was conducted in gastric cancer; a 45-autoantibody signature was found to discriminate gastric cancer from healthy controls with 59% sensitivity and 90% specificity [43]. Further work to increase the sensitivity of the panel is currently under way.

6.2 Volatile markers

Volatile components found in exhaled breath and identified either by gas chromatography coupled to mass spectroscopy or by nanosensor technology could become a reliable and easy-to-use tool for the detection of cancer [44]. A recent pilot study in patients from China suggested that a highly sensitive, cross-reactive, nanomaterial-based gas sensor could be used to identify and separate volatile marker patterns to distinguish between patients with gastric cancer and those with benign gastric conditions with 89% sensitivity, 90% specificity, and 90% accuracy [45]. However, geographical differences between the content of volatile substances do exist [46], and therefore local adaptation of the method (“training the electronic nose”) might be required.

Validation studies on gastric cancer-specific autoantibodies as well as volatile markers to be detected by sensor technologies are currently being designed in Europe (part of this work is expected to be combined with the GISTAR project).

7. Current European gastric cancer prevention efforts

Current gastric cancer prevention activities in Europe can be divided into (i) scientific projects and/or pilot projects and (ii) practical implementation activities.

7.1 Scientific field studies and/or pilot studies

A GISTAR study on preventing gastric cancer in a middle-aged population (40–64 years) was launched in 2013 (pilot study in Latvia) and is reviewed in more detailed separately.

GACSE (Gastric cancer screening in conjunction with colorectal cancer screening in Europe) is a multicentre study in subjects aged 50 years and older undergoing screening colonoscopy (coordinating investigator, P. Malfertheiner; principal investigator, M. Selgrad). These subjects will be invited to undergo blood sampling for PgI, PgII, G-17, and IgG group antibodies to *H. pylori* (GastroPanel). In countries where colonoscopy is not the primary method of colorectal cancer screening, blood samples will be taken when colonoscopy is planned for other clinical indications. Patients with pathological findings in the blood test will be invited for further investigations. Those with a positive *H. pylori* antibody test will be invited for confirmatory non-invasive testing (^{13}C urea breath test or faecal antigen test), and if the presence of the infection is confirmed, they will be offered eradication therapy consistent with European guidelines. The success of eradication will be investigated with non-invasive tests. Subjects with decreased pepsinogen levels will be referred for upper endoscopy with appropriate biopsy sampling, and will be followed up if confirmed to be positive for atrophy. Recruitment of 4300 subjects is expected to prove the expected 75% sensitivity of the biomarker test to detect atrophy [47]. Currently a pilot study is in progress in Magdeburg, Germany. It is planned that the following other countries will join the study: Italy, Hungary, Serbia, France, Croatia, Poland, Slovenia, and Israel.

A population-based sample in the age range 25–45 years is being recruited in Novosibirsk, Russian Siberia**.** A detailed questionnaire is being used, including information on gastrointestinal disease, and serum and full-blood samples are being collected and stored (the latter for DNA). The target of the recruitment is 3000 subjects; to date, approximately 200 have been enrolled. At present, pepsinogen tests are not scheduled (A. Belkovets, personal communication).

7.2 Practical implementation activities

7.2.1 Opportunistic GastroPanel screening in dyspeptic patients at the general practice level in northern Italy

Active promotion of stomach health is under way in northern Italy (principal investigator, F. di Mario). Individuals with dyspeptic symptoms at the general practice level are invited to undergo GastroPanel testing, and will be referred to a gastroenterology clinic if found to be positive for atrophy. The authors consider that the workload for the endoscopy units could be decreased in this way (F. di Mario, personal communication).

7.2.2 Screening plan for oesophageal and gastric cancers in Kazakhstan

Globally, there are no organized gastric cancer screening programmes functioning outside of Japan and the Republic of Korea. Kazakhstan, a country close to the European region with a high incidence of gastric cancer, has also made the decision to introduce biennial screening with upper endoscopy for oesophageal and gastric cancers for people in the age group 50–60 years. Although the national guidelines have not yet been finalized, such a programme was initiated in 6 of 16 regions of the country at the beginning of 2013, with the intention of

expanding to the entire country. However, the setup of the programme (lack of quality assurance in endoscopy and morphology, lack of clear evidence on the management of the lesions revealed) is unlikely to correspond to the criteria of an organized programme; therefore, the expectations that the target will be reached are low.

In conclusion, although several implementation activities are already under way, more research data and cost-efficacy estimates are required before any of the currently available or suggested tests can be recommended in organized cancer screening settings in Europe. However, the development is in progress, and it is highly likely that an effective screening test for gastric cancer and/or the related premalignant lesions could be established in Europe.

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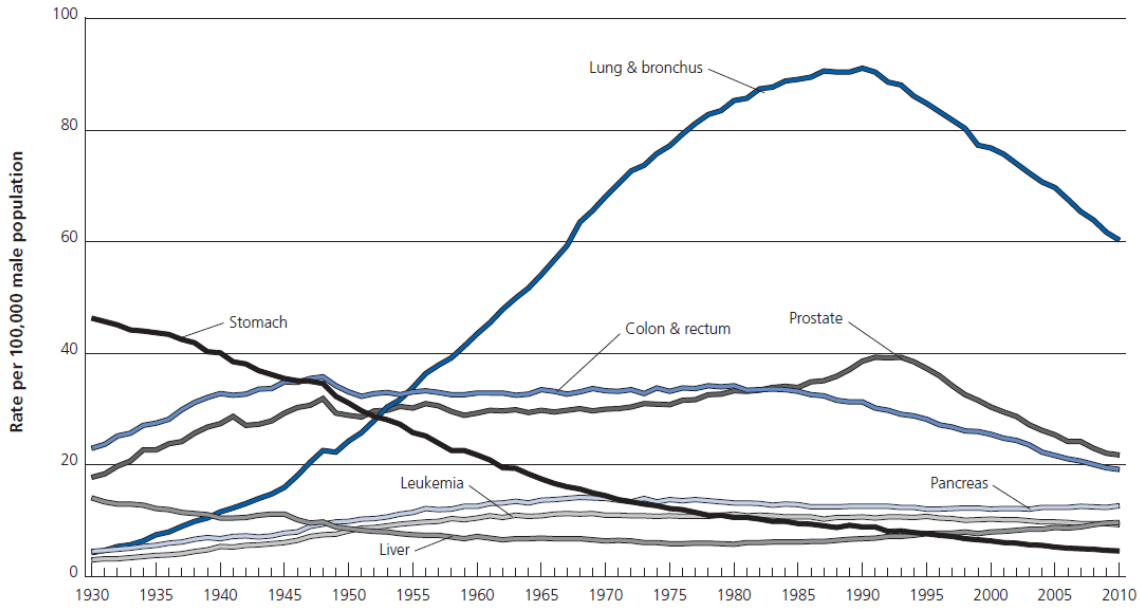
Chapter 1.6

Effect of *Helicobacter pylori* eradication on different subtypes of gastric cancer: perspective from a Middle Eastern country

Reza Malekzadeh

Gastric cancer is the fifth most common cancer and the third leading cause of cancer-related death in the world. Close to 1 million new cases of gastric cancer occur annually, and about 750 000 people die from this cancer each year [1]. The incidence of gastric cancer has declined dramatically during the past 50 years in the USA and western Europe without any specific preventive measures for gastric cancer (Fig. 1.6.1) [2]. This decline in the incidence of gastric cancer was also seen in populations in Japan [3] and other high-income countries [3].

Fig. 1.6.1. Age-adjusted cancer death rates in men by site for the USA in 1930–2010 (rates per 100 000, age-adjusted to the 2000 United States standard population). A sharp decline in the incidence of gastric (stomach) cancer is evident without any specific preventive measures for gastric cancer. Source: American Cancer Society (2014) [2].



This remarkable decrease in the incidence of gastric cancer is thought to be due to improvements in socioeconomic status, along with the almost universal use of refrigeration as the standard food preservation technique and the availability of sufficient vegetables and fresh fruits and a general improvement in the quality of drinking-water and nutritional status during the 20th century [3], with subsequent downward trends in the prevalence of *Helicobacter pylori* infection. This large reduction in the incidence of gastric cancer was achieved before the identification of its major etiological determinants, and during decades when this neoplasm was neglected in terms of research and prevention efforts [4].

At present, there is a wide variation in the incidence of gastric cancer across the globe. The Republic of Korea, China, Japan, and Costa Rica are considered high-risk areas, with an age-standardized incidence rate (ASR) per 100 000 person-years of more than 20 in men.

Intermediate-risk regions, with an ASR between 10 and 20, include countries like Turkey, Italy, and the Netherlands, and low-risk regions, with an ASR of less than 10, include India, Australia, the USA, and Canada [5].

1. Does *H. pylori* have a protective effect?

In spite of the sharp decline in the overall incidence of gastric cancer across the globe, several recent reports indicate an increasing incidence of gastric cardia adenocarcinoma, especially among Caucasians, which parallels an increasing incidence of the adenocarcinoma of distal oesophagus [6–11]. In the USA, the incidence rate for adenocarcinoma of the gastric cardia among White males is almost equal to the rate for non-cardia gastric neoplasm [7].There is now consensus that *H. pylori* is the most important risk factor for non-cardia gastric cancer, and there is accumulating evidence that cagA-positive strains of *H. pylori* may be inversely related to gastric cardia adenocarcinoma and oesophageal adenocarcinoma [12]. The protective effect of *H. pylori* has not been proven, but even after excluding the studies with selection or information bias, *H. pylori* infection is associated with a reduced risk of Barrett oesophagus [13–16].

If *H. pylori* could protect against gastric cardia cancer and oesophageal adenocarcinoma, then the strategy of *H. pylori* eradication for prevention of gastric cancer could be strongly questioned, especially in Caucasian populations. Therefore, an exact classification of gastric cancer subtypes is necessary. One major problem is the lack of consensus about the anatomical definition of gastric cardia cancer, which has been defined as tumours that originate 2 cm or 3 cm distal to the gastro-oesophageal junction, and it is quite plausible that an upward trend observed for incidence of gastric cardia adenocarcinoma is due to misclassification with distal oesophageal adenocarcinoma. Improvements are needed in the quality of data collected by cancer registries in various countries, and further studies are required to elucidate time trends in gastric cancer subsites (cardia and non-cardia) globally.

2. Patterns of gastric cancer incidence in the Islamic Republic of Iran

Gastric cancer is the most common cancer in the Islamic Republic of Iran, and the country includes all three categories of risk areas [17–23]. The southern and northern parts of the country are low- and high-risk areas, respectively, whereas the central region is an intermediate-risk area for gastric cancer. This marked variation in gastric cancer incidence provided an opportunity to study the etiology of gastric cancer in the Islamic Republic of Iran. The first obvious finding was that differences among the areas in the rate of *H. pylori* infection are small, and thus could not explain the large differences in gastric cancer incidence rates (Table 1.6.1) [24]. It has also been shown that in spite of the almost 2-fold higher risk of gastric cancer in men, sex differences in the prevalence of *H. pylori* infection in the Islamic Republic of Iran are minimal [25].

The high incidence rate of gastric cancer in Ardabil Province, in the north-west of the Islamic Republic of Iran, was found to be mainly due to higher rates of cardia cancer rather than non-cardia cancer; the ASR of cardia cancer is 26.4 in men and 8.6 in women [26]. The same is true for Golestan Province, in the north-east of the country, where up to 50% of gastric cancers are at the cardia subsite [27].This situation is in contrast to that in other high-risk areas, i.e. Japan and the Republic of Korea and some Latin American countries, where non-cardia cancers make up the majority of gastric cancers. The fraction of gastric cancers that are of the non-cardia subtype in low-risk areas of the Islamic Republic of Iran such as Khuzestan Province, in the south-west of the country, is 85%, which is much higher than that in Ardabil Province, in the north-west [28]. A recent study by Abdi-Rad et al. showed that the proportion of proximal gastric cancers in relation to mid and distal gastric cancers is increasing in Tehran, the capital city [29]. The high incidence of gastric cardia cancer in the northern part of the country coincides with a high incidence of squamous cell carcinoma of

the oesophagus, which may imply some common risk factors for these cancers [30]. This hypothesis has been supported by studies from other high-incidence areas, in northern China [31].

Table 1.6.1. Annual incidence of gastric cancer in the Islamic Republic of Iran, reported from different cancer registries, presented as age-standardized rate (ASR) per 100 000 person-years

Province	Region of the country	ASR		Cardia subtype as a proportion of all gastric cancers (%)	Reference
		Men	Women		
Ardabil	North-western	49.1	25.4	26.2	18
East Azerbaijan	North-western	26.0	11.6	NA	19
Golestan	North-eastern	27.8	8.3	50	20
Kerman	South-eastern	10.2	5.1	NA	21
Tehran	Central	19.8	10.0	NA	22
Islamic Republic of Iran (estimate)		26.1	11.1	NA	23

NA, not applicable.

Source: Malekzadeh et al. (2009) [24].

3. Risk factors for gastric cancer

Gastric cancer is thought to be the result of continuous cell damage caused by lifelong exposure to different carcinogens. The intestinal histological subtype of gastric adenocarcinoma, the most common form of gastric cancer, develops in an inflammatory background induced by *H. pylori*-related chronic gastritis and progresses to atrophic gastritis, intestinal metaplasia, glandular dysplasia, and eventually adenocarcinoma [32, 33]. Several case–control studies and one cohort study in the Islamic Republic of Iran [34–37] have shown that in addition to *H. pylori* infection, environmental risk factors including tobacco use, opium use, high salt intake, and a diet with an insufficient level of antioxidants are involved in the pathogenesis of gastric cancer. Endogenous and host factors, including those related to male sex [38], and several genetic backgrounds are known risk factors, to a lesser extent [39, 40]. In addition to the well-established risk factors for gastric cancer, which are mainly applicable to classic non-cardia cancer, gastro-oesophageal reflux disease (GORD) and obesity have been shown to be two of the main risk factors for cardia cancer [41]. The association of these tumours with both the *H. pylori*-related pathway and GORD indicates that two distinct types of tumours arise from the anatomical cardia region [41].

4. *H. pylori* infection

The *H. pylori* infection rate is very high in the Iranian population (Table 1.6.2) [24]. In a population-based study in Ardabil Province in 2001–2002, more than 89% of adults aged 40 years or older were found to be infected [42, 43]. In Babol, on the coast of the Caspian Sea, *H. pylori* infection was reported in 78% of men and 82% of women, as determined by the urea breath test [44]. A population-based study on pastoral nomads revealed that 86% had *H. pylori* infection, diagnosed serologically [45]. In a large cross-sectional study in Tehran, the overall infection rate was 69%, which correlated positively with age, i.e. the highest prevalence was 79% in the age group 46–55 years [25]. Furthermore, the age at acquisition of *H. pylori* infection seems to be very low in the Islamic Republic of Iran. Based on a study in Shiraz, a southern region, 82% of children aged 9 months and 98% of children

aged 2 years were *H. pylori*-infected [46]. A higher prevalence of infection in children and adults and its correlation with age has also been reported in Rafsanjan, another southern region of the country [47].

Several virulence determinants of *H. pylori* have been recognized and linked to different outcomes of infection. The high-molecular-weight protein cagA encoded by cytotoxin-associated gene A (*cagA*) is present in 60–70% of *H. pylori* strains and has been shown to be related to a greater risk of gastric cancer in some populations [48]. In the Islamic Republic of Iran, the majority of *H. pylori*-infected people have cagA-positive strains. The prevalence ranges from 66% to 91% at different ages and in different geographical regions [48–50]. Despite the high prevalence of cagA-positive *H. pylori* in the Iranian population, its contribution to an excess cancer risk is unclear. A study attempting to clarify the role of cagA in the higher risk of gastric cancer in the Islamic Republic of Iran compared with its neighbouring country Iraq, where gastric cancer risk is low, found similar proportions of cagA-positive strains in both countries [49]. Another toxicity determinant of *H. pylori* is the vacA antigenic region [50]. One natural polymorphic type of this antigen, called vacA i-1, has been shown to be associated with increased gastric cancer risk in the Islamic Republic of Iran [51, 52]. Other antigenic determinants of *H. pylori*, such as dupA, have been studied in the Iranian population and have not shown any clear relationship with gastric cancer risk [53].

Table 1.6.2. Prevalence of *Helicobacter pylori* infection in population-based studies in the Islamic Republic of Iran (2001–2005)

Population (region), year studied	Prevalence	Number of subjects	Age (years), mean (SD)	Assessment method	Reference
Ardabil (north-western), 2001	All: 89%	M: 494 F: 517	53 (10)	Histology/rapid urease test	42, 43
Rafsanjan (southern), 2004	M: 72% F: 62%	M: 114 F: 86	48 (16)	Serology	48
Shiraz (southern), 2004	M: 81% F: 83%	M: 308 F: 284	8 months to 15 years	Stool antigen test	47
Tehran (central), 2005	All: 69%	M: 968 F: 1358	36 (14)	Serology	25

F, female; M, male; SD, standard deviation.

Source: Malekzadeh et al. (2009) [24].

5. Atrophic gastritis

Atrophic gastritis is a well-established precancerous lesion for gastric cancer [42]. As atrophic gastritis is an intermediate step in the carcinogenesis cascade of most intestinal-type tumours and some adenocarcinomas of the diffuse type, its prevalence in the population strongly correlates with the incidence of cancer. The prevalence of atrophic gastritis in high-incidence areas of gastric cancer in the Islamic Republic of Iran has been reported by few studies. In a population-based study of more than 1000 randomly selected, apparently healthy people in Ardabil Province, atrophic gastritis detected by histology was

found in 45%, 47%, and 22% of gastric antral, body, and cardiac biopsies, respectively [42, 43]. Later, in a case–control study in the same region, a strong association was shown between atrophic gastritis, defined by the lowest and second lowest quintiles of pepsinogen I/II ratios (PgI/II), and non-cardia gastric cancer, in multivariate analysis including GORD symptoms, smoking, and *H. pylori* serostatus, with odds ratio (95% confidence interval) of 21.47 (2.90–158.76) and 9.08 (1.1–75.29) for the lowest and second lowest PgI/II quintiles, respectively. A relationship was also noted in multivariate analysis between the lowest quintile of PgI/II (< 2.37) and a subgroup of gastric cardia cancer (odds ratio, 3.92; 95% confidence interval, 1.77–8.67) [41]. A high prevalence of serological atrophic gastritis has also been reported from Babol, in the northern part of the Islamic Republic of Iran: 51% and 53% in studied men and women, respectively – significantly higher than the values in Japan [44].

6. Prevention of gastric cancer

More than 85% of Iranian patients with gastric cancer are being diagnosed at advanced stages of the disease, and they may gain a borderline survival benefit from conventional surgical, chemotherapy, or radiotherapy methods [54]. Since the great majority of Iranian patients with gastric cancer have a current infection or a past history of *H. pylori* infection (94% and 83% for non-cardia and cardia cancers, respectively) [41], *H. pylori* infection is considered to be a necessary but not sufficient risk factor for non-cardia gastric adenocarcinoma [41]. Other well-established risk factors, including high salt intake, dietary factors, and tobacco and opium use, may promote gastric cancer development in an inflammatory background induced by *H. pylori* infection. Therefore, any preventive strategies against *H. pylori* infection would be a most reasonable action to reduce gastric cancer incidence. Theoretically, active immunization of young children against *H. pylori* would be ideal to prevent infection and its chronic consequences, including peptic ulcer disease and gastric cancer, but currently there is no commercial vaccine for clinical use.

If eradication of *H. pylori* could be done effectively, and at an early age, the chances for prevention of non-cardia gastric cancer would be much higher.

Eradication of current *H. pylori* infections in children and young adults may be the best option for gastric cancer prevention. This can be done in the earlier stages of infection, before the development of severe atrophic gastritis and intestinal metaplasia. Massive public eradication of *H. pylori* in adult populations with high infection rates and prevalent GORD and a predominance of gastric cardia cancer (i.e. the Islamic Republic of Iran) is impractical for several reasons, including the high costs of diagnostic tests and therapy on a national scale and the danger of development of multidrug-resistant microorganisms.

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Chapter 2.1

Effectiveness of *Helicobacter pylori* eradication

E. Robert Greenberg and Jin Young Park

Although incidence and mortality rates for gastric cancer have been declining in much of the world, it is still the third leading cause of cancer death globally (behind cancers of the lung and liver) [1] and is a major health problem in many countries of East Asia and Latin America [2]. Chronic infection with *Helicobacter pylori* causes gastric cancer as well as peptic ulcer disease, and together these two conditions cause an estimated 1 million deaths annually worldwide, with most of the burden borne by populations in low- and middle-income countries [1, 3]. Current guidelines from different regions differ as to whether asymptomatic adults should be screened and treated for *H. pylori* [4], and no countries have implemented *H. pylori* eradication programmes as a public health measure. Some of this inaction may reflect doubts about the effectiveness of *H. pylori* eradication in preventing gastric cancer, but there is also uncertainty about possible negative effects of mass antibiotic treatment and about the feasibility and economic costs of different eradication strategies [5].

This chapter addresses evidence relating to the effectiveness of *H. pylori* eradication in gastric cancer prevention; issues of possible negative effects, feasibility, and the cost–effectiveness of eradication programmes are the topics of subsequent chapters. Here, attention is focused on two topics: the importance of *H. pylori* infection in causing gastric cancer, and recent findings from randomized controlled trials of *H. pylori* eradication therapy for preventing gastric neoplasia.

1. *H. pylori* as a cause of gastric cancer

H. pylori infection is found throughout the world, and the prevalence of infection in adults varies from 20–50% in higher-income countries to more than 80% in many lower- and middle-income countries [6]. The infection is strongly associated with socioeconomic conditions, and transmission appears to occur through close personal contact, particularly within the family and typically in early childhood. Once established, infection usually persists throughout life unless treated. The prevalence of *H. pylori* infection has decreased in recent decades, particularly among children in developed countries, probably reflecting improvements in hygiene [7, 8].

The International Agency for Research on Cancer (IARC) classified *H. pylori* as a Group 1 carcinogen in 1994 based on a thorough review of relevant laboratory and epidemiological studies [9], and IARC reconfirmed this classification in 2009 [10]. Based on an aggregate review of the epidemiological literature, an estimated 75% of non-cardia gastric adenocarcinoma cases worldwide can be attributed to *H. pylori* infection [3]. However, *H. pylori* infection often clears spontaneously in chronically infected individuals when they develop gastric atrophy, a late stage in the carcinogenic process [11], and the enzyme-linked immunosorbent assay (ELISA) used in earlier epidemiological studies would classify some such participants as *H. pylori*-negative, even though they had been infected for most of their lives. A more recent large cohort study using a more sensitive anti-CagA immunoblot assay resulted in a risk estimate associated with *H. pylori* positivity (odds ratio [OR], 21.4; 95% confidence interval [CI], 7.1–64.4) that was 3-fold higher than that obtained with ELISA [12], and an analysis based on results of studies using immunoblot serology indicates that *H. pylori* infection accounts for 89% of all non-cardia gastric cancers [13]. In higher-risk countries such as the Islamic Republic of Iran and China, *H. pylori* infection is also strongly associated with cancers of the gastric cardia (see Chapters 1.6 and 4.1). Other identified risk

factors, such as tobacco use and high salt intake, appear to act primarily in conjunction with *H. pylori*.

2. Effectiveness of *H. pylori* eradication

Recognition of the causal role of chronic *H. pylori* infection in gastric cancer led some authors by 2005 to call for broad-scale programmes to eradicate the infection as a way to prevent the disease [14]. However, the proposal met with little support, perhaps because at the time there were scant data from randomized clinical trials on the effectiveness of this approach. Specifically, in 2005 results were available from just three randomized trials that together involved only 37 cases of gastric cancer [5] (Table 2.1.1), too few to provide an informative assessment of the effects of eradication on cancer occurrence. More recently, however, reports of two randomized trials have been published, in 2008 and 2012, which included 33 and 86 gastric cancer cases, respectively. Both trials showed a statistically significant reduction in risk among participants randomized to *H. pylori* eradication therapy [15, 16].

In 2008, the Japan Gast Study Group investigators reported the results of an open-label, randomized trial in which 544 *H. pylori*-infected patients who had undergone, or were about to undergo, endoscopic resection for early gastric cancer were randomized to *H. pylori* eradication therapy with amoxicillin, clarithromycin, and lansoprazole, or to standard care (control) [15]. The primary study end-point was new gastric cancer detected on follow-up at a site in the stomach other than that of the original resection. Biopsies of the stomach corpus at study entry showed moderate or severe atrophy in 75% of participants and intestinal metaplasia in 49%. On follow-up endoscopy, 75% of participants randomized to eradication therapy were *H. pylori*-negative, compared with 5% of those assigned to standard care. After 3 years of scheduled endoscopic follow-up, 9 new cancers were diagnosed in the group assigned to eradication therapy and 24 in the control group (OR, 0.35; 95% CI, 0.16–0.78, $P = 0.003$) [15].

The Japan Gast Study Group finding that *H. pylori* eradication was effective in reducing gastric cancer risk among patients with previous cancer and a high prevalence of gastric atrophy and intestinal metaplasia indicated that eradication need not occur early in the course of carcinogenesis to be effective, as had been suggested in a report from an earlier trial [18]. An editorial comment that accompanied the Japan Gast Study Group report recommended implementing large screening and eradication programmes in populations living in high-risk areas [23]. Other commentators stressed the clinical value of treating patients after gastric cancer resection, but they also raised concerns about the generalizability of the study results to patients without a history of cancer. A subsequent trial reported from the Republic of Korea used a similar design and noted about 40% fewer new cancers among patients randomized to antibiotic treatment compared with controls (10 vs 17), although the result was not statistically significant ($P = 0.15$) [24], and the authors concluded that the therapy was therefore ineffective.

Table 2.1.1. Published completed randomized trials and their follow-up studies that investigated the efficacy of *Helicobacter pylori* eradication on gastric cancer incidence

Completed trials of *H. pylori* treatment and subsequent gastric cancer						
Study details and registration number	**Participants**		**Follow-up**	**Gastric cancer outcomes**		
	Characteristics	**Number**		**Trial arm (*n*)**	**Placebo arm (*n*)**	**Effect estimate (95% CI)[a]**
Previous cancer patients						
Fukase et al. (2008) [15], Japan Gast study, Japan (UMIN000001169)	Men and women aged 20–79 years with early gastric cancer resected	272 *H. pylori* treatment, 272 standard care	3 years with gastroscopy	9	24	OR = 0.35 (0.16–0.78)
Choi et al. (2014) [17], Republic of Korea (NCT01510730)	Men and women aged 20–75 years with early gastric cancer resected	439 *H. pylori* treatment, 441 control	2.6–93.3 months (median, 38 months) with gastroscopy	10	17	Not reported (*P* = 0.15 by log-rank)
General population						
Wong et al. (2004) [18], China	Men and women aged 35–65	817 *H. pylori* treatment, 813 placebo	7.5 years	7	11	HR = 0.63 (0.24–1.62)
Leung et al. (2004) [19], China	Men and women aged 16–75 years	295 *H. pylori* treatment, 813 placebo	5 years	4	6	OR = 0.66 (0.19–2.31)

CI, confidence interval; HR, hazard ratio; OR, odds ratio; RR, relative risk.

[a] A report of further follow-up of the trial referenced above.

Table 2.1.1. Published completed randomized trials and their follow-up studies that investigated the efficacy of *Helicobacter pylori* eradication on gastric cancer incidence (continued)

Completed trials of *H. pylori* treatment and subsequent gastric cancer						
Study details and registration number	**Participants**		**Follow-up**	**Gastric cancer outcomes**		
	Characteristics	**Number**		**Trial arm (*n*)**	**Placebo arm (*n*)**	**Effect estimate (95% CI)[a]**
Colombian chemoprevention trial						
Correa et al. (2000) [20], Colombia	Men and women aged 29–69 years	491 *H. pylori* treatment, 485 placebo	6 years	3	2	RR = 1.48 (0.25–8.83)
Mera et al. (2005) [21], Colombia[a]	Men and women aged 29–69 years	394 *H. pylori* treatment, 401 placebo	12 years	5	4	Not reported
Shandong Trial (NCI-OH-95-C-N029)						
You et al. (2006) [22], China	Men and women aged 35–64 years	1130 *H. pylori* treatment, 1128 placebo	7.3 years	19	27	HR = 0.64 (0.35–1.15)
Ma et al. (2012) [16], China[a]	Men and women aged 35–64 years	1130 *H. pylori* treatment, 1128 placebo	14.7 years	34	52	OR = 0.61 (0.38–0.96)

CI, confidence interval; HR, hazard ratio; OR, odds ratio; RR, relative risk.

[a] A report of further follow-up of the trial referenced above.

In 2012, Ma and colleagues reported the long-term follow-up results of the Shandong Intervention Trial, a masked, randomized trial in which 2258 *H. pylori*-seropositive adults drawn from a general population in China were randomly assigned in a 2 × 2 × 2 factorial design to three interventions (2 weeks of *H. pylori* eradication therapy with amoxicillin plus omeprazole, garlic supplements for 7.3 years, supplemental vitamins for 7.3 years) or their controls [16]. Gastroscopies with stomach biopsies were scheduled to occur at study entry and at follow-up times of approximately 5 years and 9 years after randomization. The investigators had previously reported the results of the 9-year gastroscopy results, which indicated that antibiotic eradication therapy significantly reduced the prevalence of precancerous gastric lesions (OR, 0.60; 95% CI, 0.47–0.75) [22]. At that time there were 19 gastric cancers detected in participants assigned to eradication therapy and 27 in those assigned to control ($P = 0.14$). After the 9-year gastroscopy, participants remained under active clinical follow-up without protocol-specified endoscopy, and by 15 years after randomization there were a total of 34 gastric cancers in the participants assigned to *H. pylori* eradication and 52 in those assigned to the corresponding control (OR, 0.61, 95% CI, 0.38–0.96) [16].

A recent meta-analysis of all six published randomized trials of *H. pylori* treatment among asymptomatic infected individuals has yielded an estimated effectiveness of 34% (95% CI, 5–54%) in preventing new gastric cancer [25]. The Shandong Intervention Trial has provided much of this evidence supporting the strategy of testing and treating for *H. pylori*, but three issues complicate interpretation of the estimate of treatment effect size (a risk reduction of about 40%) reported from the trial.

First, the trial relied on a positive *H. pylori* serology (ELISA) to determine eligibility for randomization. Urea breath tests (UBTs) performed within 1 year after randomization indicated that 12.7–14.6% of participants assigned to the untreated control group were actually not currently infected with *H. pylori*. It is reasonable to assume that these participants, and a similar proportion of those assigned to eradication therapy, were not infected when they were randomized, despite being positive by ELISA testing.

Second, the eradication therapy regimen of amoxicillin and omeprazole was only moderately effective. Among participants in the eradication therapy arm, only 64% were UBT-negative after initial therapy [26]. The investigators offered retreatment with the same 2-week regimen to those who were UBT-positive after treatment, and upon retesting, 74% of the eradication group were UBT-negative. Even these figures provide an inflated estimate of the success of the eradication regimen, since they do not take into account the estimated 13% of the participants who were uninfected before receiving the study eradication therapy.

Third, there was a high risk of recurrent *H. pylori* infection after eradication therapy. UBT negativity in the treated group declined from 74% after completion of therapy to 47% by the year 7, midway through the entire period of follow-up. This represents an annual risk of recurrence of about 7%, assuming that risk was constant over the 7 years.

The net effect of these three aspects of the trial would be a dilution of the “ideal” effect of eradication therapy, i.e. the effect that would be observed if eradication therapy resulted in complete and sustained absence of *H. pylori* infection, and if everyone in the control group remained *H. pylori*-infected. In fact, there was contamination of both groups, in that about 13% of controls were not infected with *H. pylori*, and between 26% and 53% of the eradication group were not free of *H. pylori* infection during the first half of their follow-up period (presumably, more infections recurred during later follow-up). An estimate was made of how much the measured effectiveness of the intervention in this trial differed from the effectiveness that would be observed if the eradication regimen had been 100% successful and fully sustained, and if all of the controls had been *H. pylori*-negative. First, it was

assumed that the control group was contaminated due to inclusion of the 13% who were uninfected, and that the treated group was contaminated by inclusion of 40% who were actively infected (the midpoint between the UBT positivity at 1 year and 7 years). Applying these assumptions, the observed risk reduction of about 40% would translate into an "ideal" risk reduction of about 75%. This number is comparable to the observed 65% risk reduction in the Japan Gast Study Group trial, in which there was considerably less contamination of the two study groups. Of course, the estimate of an "ideal" protective effect rests on many assumptions that cannot be readily verified and are somewhat unrealistic (e.g. 100% success in eradication, no recurrence of infection), but it provides some perspective on the possible outcome of a programme that would use a much more effective eradication regimen than that used in the Shandong Intervention Trial.

3. Conclusions

In summary, given the strong causal link between *H. pylori* and non-cardia gastric cancer, the 3–4 billion people who are already infected with the organism represent a vast reservoir of potential cancer cases that will emerge in coming decades unless effective preventive measures are implemented. When viewed in the context of the epidemiological and laboratory evidence for the carcinogenic activity of chronic *H. pylori* infection, the recently reported results from randomized trials appear to provide compelling support for a large preventive effect of *H. pylori* eradication in gastric cancer. Nevertheless, important questions of programme costs, feasibility, appropriate target groups for intervention, and the potential harm of mass therapy with antibiotics must first be resolved before implementing large-scale programmes. The answers to these questions will likely require region-specific data and cost–benefit analyses. Important data are likely to emerge from randomized trials that are currently in progress or about to begin [5], and additional information could be obtained by initiating pilot programmes of *H. pylori* eradication in areas where gastric cancer risk is especially high.

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Chapter 2.2

Are there benefits of *Helicobacter pylori* infection?

Julie Parsonnet

The popular press has become captivated by the possibility that *Helicobacter pylori* – an established cause of ulcers and cancer – may actually provide some benefits to humans [1–4]. For example, articles in *The Economist*, *The New Yorker*, *Scientific American*, and *The New York Times Magazine* highlight the unintentional extinction of elements of the microbiome and the idea that *H. pylori* should be preserved. The argument has been made that *H. pylori*, a ubiquitous colonizer of human stomachs for many millennia, must provide some survival advantage. Certainly, other "normal flora" coexisting in humans are considered beneficial. Following on this teleological argument, since the prevalence of *H. pylori* has been decreasing rapidly over the past century, one might infer that its host benefits have also been decreasing. Either the diseases it putatively prevents are no longer a threat or the benefits that *H. pylori* imparts have been usurped by other organisms or exposures. In this chapter, the putative benefits of *H. pylori* are summarized, by dividing them into two categories: (i) immunological benefits and (ii) physiological benefits.

1. Potential immunological benefits of *H. pylori*

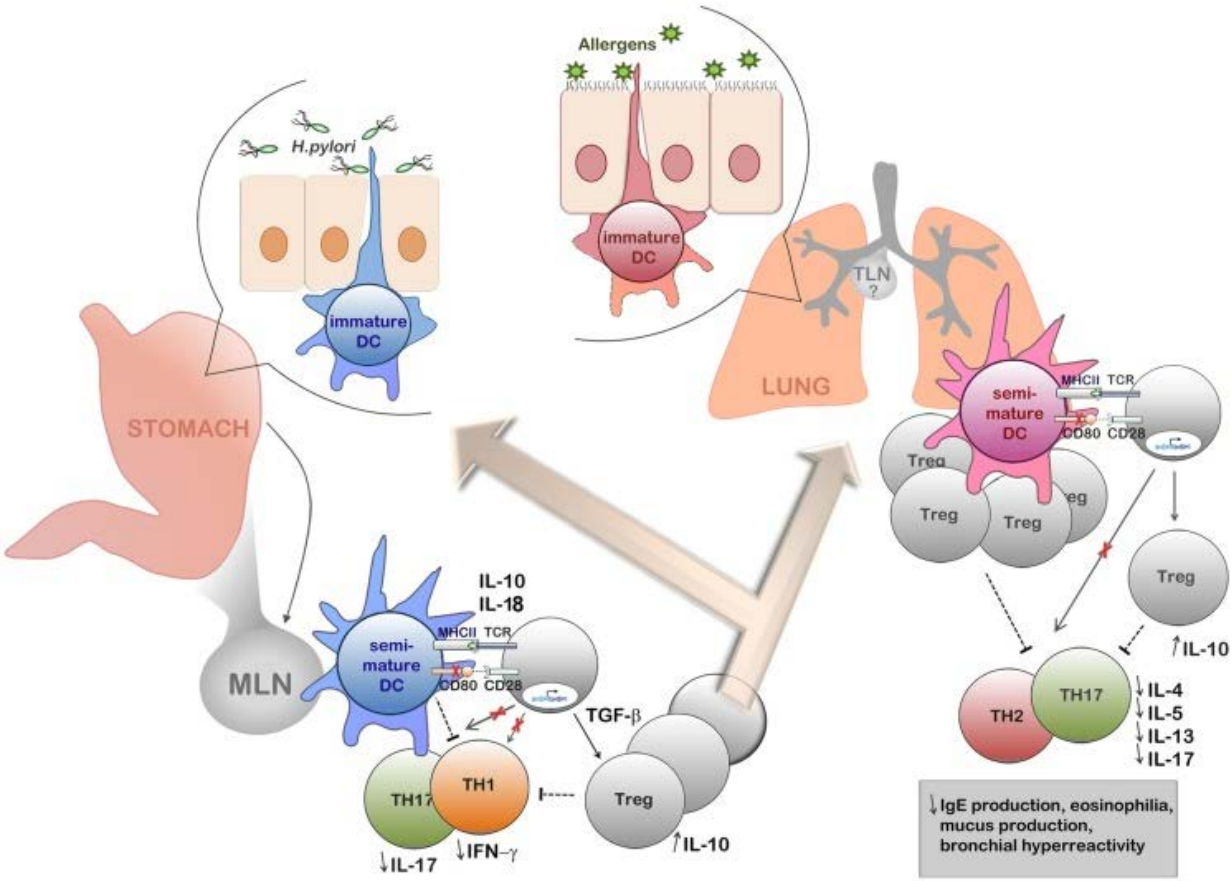
H. pylori is a potent stimulator of the innate and adaptive immune responses, both within the stomach and systemically. The gastric epithelium releases cytokines that attract and activate neutrophils and macrophages within the gastric epithelium [5, 6]. A variety of *H. pylori*-specific T cells can be found within the mucosa, including memory $CD4^+$ αβ T cells and a predominance of T helper 1 (Th1) and Th17 cells, and few Th2 cells. Despite the tendency towards a cellular response, individuals with *H. pylori* also have a strong humoral response with high levels of circulating antibodies – particularly immunoglobulin G (IgG), but also IgA. As infection becomes chronic, dendritic cells induce regulatory T cell (Treg) activity, resulting in downregulation of the Th1 and Th17 responses, contributing to persistence of infection [6]. This downregulation benefits both the host, by minimizing gastric damage, and the organism, by decreasing bacterium-specific killing (Fig. 2.2.1) [7].

1.1 Diseases of immune regulation

Because *H. pylori* has been decreasing in prevalence in the USA and western Europe at the same time as the prevalence of allergic diseases has been on the rise, some have speculated that *H. pylori* infection prevents immunologically mediated diseases. The first work on this topic dates from 2002, when Kosunen and colleagues noted an inverse relationship between IgE directed against inhalant antigens and *H. pylori* seropositivity [8]. Although others had previously reported inverse correlations between allergy and enteric pathogens, this study was the first to identify a specific *H. pylori* link. Subsequently, in 2007, Chen and Blaser reported that children with both asthma and allergic rhinitis in the Third National Health and Nutrition Examination Survey (NHANES III), a large, cross-sectional population-based study in the USA, were less likely than other children to have *H. pylori* antibodies [9]. Multiple studies – including cross-sectional, case–control, and cohort studies – followed thereafter, and three meta-analyses have concatenated the results (Table 2.2.1). The accumulated data indicate a negative association between *H. pylori* and allergy, although the results are inconsistent and even conflicting. The cohort studies – typically the most informative of studies – yielded the least convincing results: one study showed an association between *H. pylori* and wheezing but not other forms of atopy [10], a second showed an association with eczema but not wheezing [11], and a third showed less skin test reactivity in children with *H. pylori* but no association between *H. pylori* and symptoms [12].

The largest cross-sectional studies demonstrated consistent protection of *H. pylori* in asthma [13]. None of these studies, however, controlled for the many infectious and socioeconomic confounders that *H. pylori* infection – an organism closely linked to both socioeconomic status and poor childhood hygiene – may portend.

Fig. 2.2.1. Immunological link between *Helicobacter pylori* and asthma. DC, dendritic cell; IgE, immunoglobulin E; MLN, mesenteric lymph nodes; TLN, tracheal lymph nodes; Treg, regulatory T cell. Source: Arnold et al. (2012) [7]. Copyright © 2012 Arnold, Hitzler, and Müller.



The strongest linkages between *H. pylori* and allergies, and more specifically asthma, derive from physiological studies. In both animals and humans, Treg activity related to *H. pylori* infection can mitigate atopy, and particularly asthma. For example, in a mouse model, *H. pylori* infection skewed the immune response towards tolerance, protecting the mice against airway hyper-responsiveness, tissue inflammation, and goblet cell metaplasia, and preventing tissue infiltration with eosinophils, Th2 cells, and Th17 cells [7, 25]; these effects were mediated by Tregs. Moreover, dendritic cells exposed to *H. pylori* in vivo and in vitro enhanced Treg differentiation, indicating that *H. pylori*-reactive dendritic cells drive this tolerance. In 2013, Oertli and colleagues demonstrated that the tolerizing activity of dendritic cells can be induced with two *H. pylori*-associated proteins: γ-glutamyl transpeptidase and vacuolating cytotoxin [26]. Thus, a picture is beginning to hold together in which *H. pylori* proteins foster lipopolysaccharide stimulation of dendritic cells that in turn stimulate Tregs, decreasing gastric inflammation and systemically reducing allergic responses. It should be noted, however, that mice are not a natural host for *H. pylori*, and similar physiological studies in humans have not yet been conducted.

Table 2.2.1. Meta-analyses on protective effects of *Helicobacter pylori* on disease

Disease	Number of studies	Summary OR (95% CI)	Publication year	Reference
Asthma (meta-analysis a)	14	0.84 (0.73–0.96)	2013	14
Asthma (meta-analysis b)	19	0.81 (0.72–0.91)	2013	13
Asthma (meta-analysis c)[a]	5[b]	1.01 (0.82–1.24)	2012	15
Oesophageal cancer	16	0.97 (0.76–1.24) (squamous)	2013	16
	16	0.59 (0.51–0.68) (adenocarcinoma)		
Oesophageal cancer	9	1.10 (0.78–1.55) (squamous)	2008	17
	13	0.56 (0.46–0.68) (adenocarcinoma)		
Oesophageal cancer	5	0.80 (0.45–1.43) (squamous)	2008	18
	9	0.58 (0.48–0.70) (adenocarcinoma)		
Barrett oesophagus[c]	49	0.73 (0.60–0.88)	2012	19
Barrett oesophagus	9	0.50 (0.27–0.93)	2009	20
GORD[a]	19	0.64 (0.49–0.83)	2013	21
GORD after *H. pylori* eradication	12[d]	1.99 (1.23–3.22)	2013	21
GORD after *H. pylori* eradication	10[d]	0.81 (0.56–1.17) symptoms	2011	22
		1.13 (0.72–1.78) oesophagitis		
GORD after *H. pylori* eradication	6	1.11 (0.81–1.53) (RCTs)	2010	23
	5	1.37 (0.89–2.12) (cohort studies)		
Inflammatory bowel disease	23	0.64 (0.54–0.75)	2010	24

CI, confidence interval; GORD, gastro-oesophageal reflux disease; OR, odds ratio; RCTs, randomized controlled trials.

[a] All case–control studies.

[b] Overlap in these meta-analyses: 12 of 14 studies in meta-analysis a are included in meta-analysis b; 4 of 5 studies in meta-analysis c are included in meta-analysis b.

[c] Four unbiased studies had OR of 0.46 (95% CI, 0.35–0.63).

[d] All RCTs. There are 6 studies included in both analyses.

Invoking similar mechanisms to asthma, investigators have posited associations between *H. pylori* and other immune-mediated diseases, including eczema, allergic rhinitis, and inflammatory bowel disease [24]. Whether any of these diseases will truly be linked to absence of *H. pylori* remains to be seen.

1.2 Infectious diseases: tuberculosis and gastroenteritis

The putative inverse association between *H. pylori* and allergic diseases is thought to reflect downregulation of Th1 and Th17 pathways. However, other studies suggest that *H. pylori*

stimulates vigorous Th1 responses. Such responses have the potential to protect against infectious diseases. For example, *H. pylori*, by decreasing gastric acidity, could increase the risk of gastrointestinal infections. In two separate studies, however, the opposite was found to be true: *H. pylori* was negatively associated with symptomatic gastrointestinal infection. In a longitudinal cohort, household members with *H. pylori* infection were found to be less likely than uninfected household members to acquire gastroenteritis from a sick family member (odds ratio, 0.25) [27]. Moreover, in an experimental exposure to enteropathogenic *Escherichia coli* (EPEC), adults with *H. pylori* infection had attenuated symptoms of infection [28]. Similarly, pre-existing *H. pylori* was found to negatively correlate with activation of latent tuberculosis both in monkeys and in humans [29]. It was speculated that the neutrophil-activating protein of *H. pylori* could promote Th1 cytokines in response to tuberculosis and other antigens [29, 30]. Other investigators have not found similar protective effects of *H. pylori*, however. For example, field studies have associated *H. pylori* with increased risk of *Shigella* gastroenteritis and with severe cholera, although in both cases confounding could not be excluded [31, 32]. Further work on *H. pylori* immunity is needed to elucidate the balance between enhanced immunity and immune tolerance.

2. Potential physiological benefits of *H. pylori*

In addition to immunological effects, *H. pylori* causes profound changes in the gastric mucosa, including alterations in gastric hormone and acid secretion. Several diseases have been linked to the absence of these *H. pylori*-associated physiological effects.

2.1 Oesophageal diseases

At the same time that *H. pylori* and ulcer disease have been disappearing from many populations, the prevalence of gastro-oesophageal reflux disease (GORD), Barrett oesophagus, and oesophageal adenocarcinoma have been on the rise. These three diseases are thought to represent a continuum of the same process, with reflux leading to specialized metaplasia in the oesophagus (Barrett oesophagus), which can then ultimately give rise to oesophageal adenocarcinoma. Thus, risk factors for GORD will necessarily be risk factors for other diseases further down the chain. Risk factors for GORD, including obesity, cigarette smoking, hiatal hernia, advanced age, diets rich in nitrates, and male sex, have all, also, been linked to Barrett oesophagus and oesophageal adenocarcinoma [33]. More recently, however, investigators have linked the absence of *H. pylori* – and more specifically, the absence of CagA-positive *H. pylori* – to this pathophysiological pathway from damage to metaplasia to malignancy.

In general, two types of human studies inform the observed associations with oesophageal diseases: treatment trials (both randomized controlled trials and cohort studies) showing increases in GORD prevalence with *H. pylori* eradication, and observational studies linking infection to GORD, Barrett oesophagus, and oesophageal cancers. Results of these studies have yielded widely disparate results, particularly for GORD. Based in large part on a 2010 meta-analysis of 7 randomized clinical trials and 5 cohort studies, the Maastricht IV consensus statement concluded that “eradication of *H. pylori* in populations of infected patients, on average, neither causes nor exacerbates GORD” [34]. In contrast, a more recent meta-analysis assessing 12 randomized clinical trials and 12 cohort studies did find an increased risk of GORD in those treated for *H. pylori* [21].

Part of the disagreement may arise from the analytic criteria (per protocol vs intention to treat vs eradicated or not eradicated infection), the outcome used (symptoms vs oesophagitis), and the region of the world where the studies were conducted; studies from the Far East show the strongest association between lack of infection and GORD. However, a body of physiological data has accumulated over the past 10 years that supports a causal role for *H. pylori* in protecting against GORD. *H. pylori* is known to reduce acid secretion in

the stomach, over time. Since erosive oesophagitis is a consequence of acid secretion, the absence of acid should protect against GORD. Eradication of the organism can cause a rebound in acid production, which can explain the onset of erosive oesophagitis in predisposed individuals. Moreover, *H. pylori* is also linked to obesity (see below), although the data are far from definitive.

Studies on Barrett oesophagus and oesophageal adenocarcinoma show less variability than studies on GORD. Maastricht IV concluded that "there was a negative association between the prevalence of *H. pylori* and the severity of GORD and incidence of oesophageal adenocarcinoma". This conclusion conforms with many clinical studies as well as meta-analyses listed in Table 2.2.1.

Whereas the negative association between *H. pylori* and oesophageal adenocarcinoma is now becoming widely accepted, substantial uncertainty remains as to whether *H. pylori* also contributes to squamous cell carcinoma of the oesophagus. Neither the accumulated data nor physiological studies, however, yet provide coherent support for this association.

2.2 Obesity

H. pylori has long been linked to stunting in young children. When *H. pylori* eradication was also linked to GORD, investigators began to posit effects on adult weight and on causing the obesity epidemic. Given the day-to-day and time-to-time variability in weight, as well as the normal weight gain with increasing age (an estimated 0.5 kg per year), sample sizes required to conduct the ideal weight study would be quite large. Although the few randomized controlled trials conducted to date support the *H. pylori*–weight association, the differences are small and often difficult to interpret [35]. Certainly the magnitude of change observed to date is unlikely to account for the "obesity epidemic". Moreover, treatment of *H. pylori* eliminates a wide variety of colonizing infections; given the suspicion that the gut flora more generally influence weight, the lack of specificity of antibiotics renders imputing specificity of the *H. pylori* effect impossible. Yet, there are plausible physiological mechanisms by which *H. pylori* could influence weight. The most well studied is the rise in levels of ghrelin – a hormone that plays a role in appetite regulation – in patients after eradication of *H. pylori* infection [36, 37]. Other putative effects are alterations in leptin and other adipocytokines, increased appetite due to diminished abdominal pain, and differences in other aspects of the microbiome due to the presence of *H. pylori*.

3. Conclusions

Human beings are ecosystems of microorganisms. Is it far-fetched to imagine that changes in one member of the community, i.e. loss of *H. pylori*, might cause unpredictable alterations in the overall well-being of the entire ecosystem? The mere fact that *H. pylori* is disappearing from the human host without substantive intervention might indicate that, in many countries, it is providing little benefit. The large clinical trials of *H. pylori* eradication currently under way in China and Europe, if carefully monitored for a wide variety of outcomes, can provide more substantive insights on how *H. pylori* specifically and the entire human microbial ecosystem affect human health.

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Chapter 2.3

Potential impact of bacterial resistance after population-based *Helicobacter pylori* treatment

Francis Mégraud

The discovery of antibiotics was one of the most important breakthroughs of the 20th century. Life-threatening infectious diseases that had long been the main cause of human morbidity and mortality, especially in children, suddenly became curable.

However, there is always the other side of the coin. Very quickly bacteria began to adapt to these drugs by acquiring resistance mechanisms. Resistance to antibiotics is currently one of the most important challenges with which medicine is faced. One can now find bacteria resistant to virtually all existing antibiotics. Public health measures have been taken in many countries to limit the use of antibiotics or at least to use these drugs in a reasonable manner, thanks to education of the general population [1] and stewardship programmes in hospitals [2]. Therefore, the implementation of health programmes that lead to a massive use of antibiotics must be questioned. This chapter briefly reviews the basis of antimicrobial resistance, the relationship between antibiotic consumption and bacterial resistance, and the impact of antibiotic consumption on the composition of the microbiota.

1. Basis of antimicrobial resistance

Genetically speaking, antimicrobial resistance can be due either to point mutations or to mobile genetic elements. In resistance due to mobile genetic elements, plasmids, transposons, and integrons are the most threatening in terms of diffusion. Plasmids replicate independently of the chromosomes, support resistance mechanisms to several antibiotics, and can be transferred from bacterium to bacterium, usually between phylogenetically related bacteria but even sometimes in less-related bacteria. This horizontal transmission leads to outbreaks in the bacterial population. In contrast, resistance due to point mutation is only transmitted vertically to the descendants of the bacteria that acquired the mutation. Mutations arise by chance in a few bacteria in the bacterial population and are then selected by the antibiotic when it is used.

Antimicrobial resistance due to mobile genetic elements occurs mainly in Gram-negative bacteria other than *Helicobacter pylori*, for example Enterobacteriaceae, and affects mainly antibiotics from the β-lactam and aminoglycoside groups. It occurs more frequently in closed environments, such as hospitals where antibiotic consumption is very high and where immunosuppressed patients are present.

Fortunately, with regard to *H. pylori*, only point mutations and vertical transmission are involved. Mutations have been found for all antibiotics used to treat *H. pylori* (Table 2.3.1) [3–9], but they are clinically relevant essentially for macrolides and fluoroquinolones [10].

The question arises as to the stability of these mutations. Indeed, if the mutation has a cost for the bacterium, i.e. an impact on its growth and replication, or its “fitness”, then the mutation will not persist from generation to generation and the wild type, without the mutation, will make up the majority of the population [11]. Another possibility is the occurrence of compensatory mutations, which occur at other sites on the bacterial genome and compensate totally or partially for the loss of fitness of the resistant mutants [12]. Given the steady increase in macrolide resistance among *H. pylori*, it is most likely that the

mutations for macrolide resistance do not have a major impact on the fitness of the bacterium [13].

Table 2.3.1. Genes involved in point mutation or other genetic events leading to antibiotic resistance in *Helicobacter pylori*

Antibiotic group	Genes involved	References
Macrolides	*rrn* 23S	3
Metronidazole	*rdxA*, *frxA*	4
Quinolones	*gyrA*	5
Rifamycins	*rpoB*	6
Amoxicillin	*pbp-1*	7
Tetracycline	*rrn* 16S	8, 9

Source: Reproduced from Mégraud (2004) [10], with permission from BMJ Publishing Group Ltd.

Mechanistically speaking, point mutations lead to a modification of the antibiotic target, for example 23S ribosomal DNA for macrolides, which prevents the binding of the drug. In other cases, they cause a modification of the penetration of the drug. A mechanism comprising production of an enzyme to destroy the antibiotic outside of the cell has not been found in *H. pylori*. The presence of efflux pumps can, however, also be implicated for tetracycline and metronidazole.

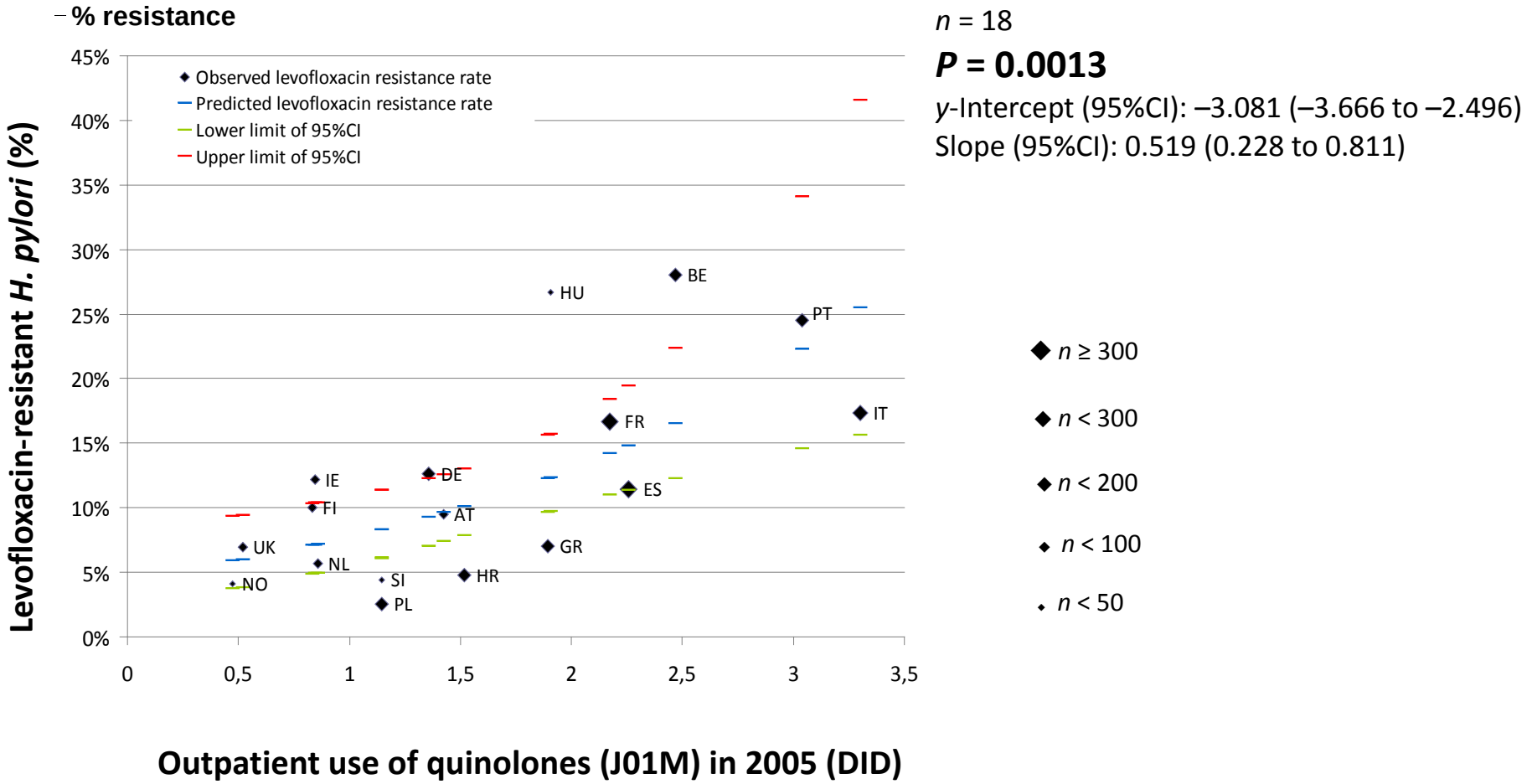
2. Relationship between antibiotic consumption and bacterial resistance

2.1 At the population level

The relationship between antibiotic use and bacterial resistance has been extensively studied in the context of hospitals, where horizontal transmission occurs. Resistance occurs frequently, but it is easy to implement interventions, i.e. to stop the use of the antibiotics in a relatively controlled environment, and then to have a strong argument of causality. It is more difficult to tackle the relationship in the community, where many determinants are not controlled – for example, the antibiotic residues present in food that are a consequence of the use of antibiotics in veterinary medicine – and where interventions are rarely performed.

A study was conducted to assess the resistance rates of *H. pylori* to certain antibiotics (macrolides, fluoroquinolones) and the link with outpatient antibiotic use in 17 European countries. Data for consumption were expressed as defined daily dose (DDD) per 1000 inhabitants per day, and *H. pylori* strains were collected in centres across Europe. A good correlation was obtained for fluoroquinolones (Fig. 2.3.1). The correlation was not statistically significant for macrolides when analysed together but was significant when only long-acting macrolides were considered [14].

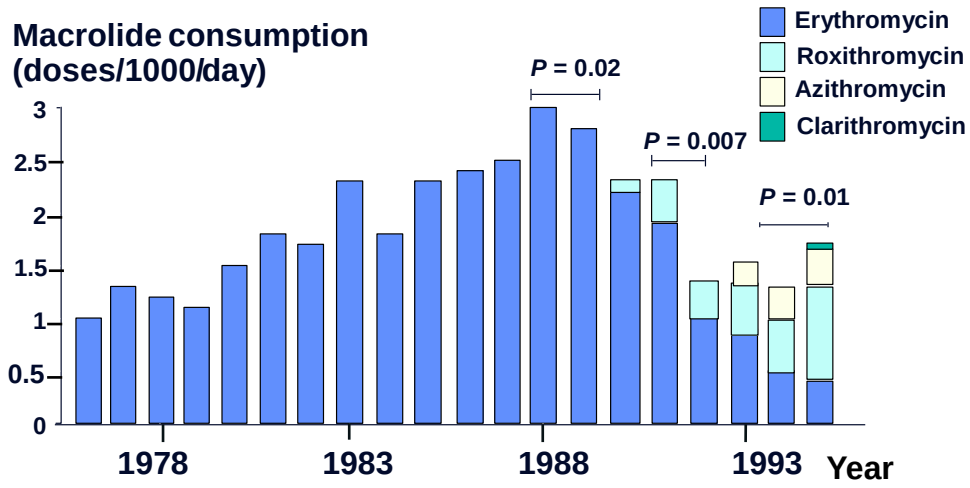
Fig. 2.3.1. Correlation between quinolone (J01M) use in 2005 and *Helicobacter pylori* resistance to levofloxacin in 2008–2009. CI, confidence interval; DID, defined daily dose per 1000 inhabitants per day. Country codes: AT, Austria; BE, Belgium; HR, Croatia; FI, Finland; FR, France; DE, Germany: GR, Greece; HU, Hungary; IE, Ireland; IT, Italy; NL, The Netherlands; NO, Norway; PL, Poland; PT, Portugal; SI, Slovenia; ES, Spain; UK, England only. Source: Reproduced from Mégraud et al. (2013) [14], with permission from BMJ Publishing Group Ltd.



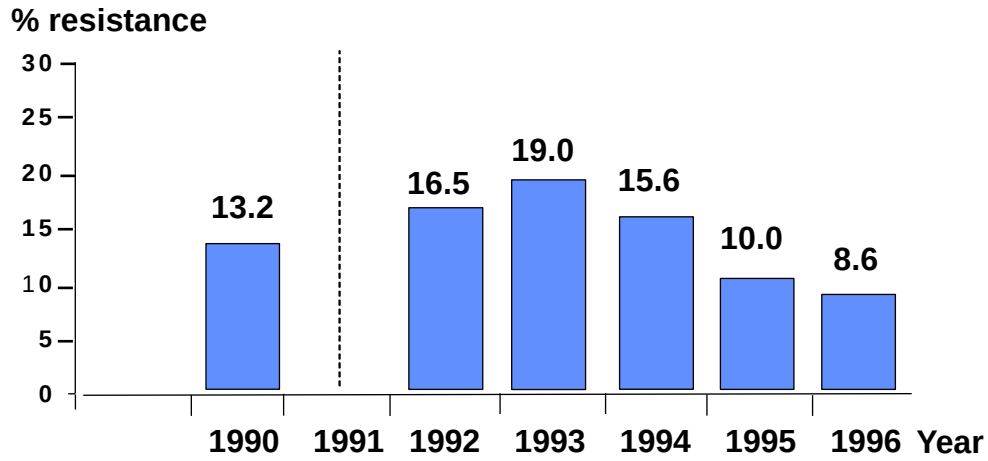
Another major study in this area was carried out in Finland, where Seppälä et al. studied the effect of macrolide consumption on erythromycin resistance of *Streptococcus pyogenes*. After an increase in macrolide resistance of *S. pyogenes*, the policy on outpatient antibiotic use was changed throughout the country in the early 1990s, especially concerning limitations of macrolide use for respiratory and skin infections. After this decision, *S. pyogenes* resistance to erythromycin was monitored over 7 years (53 900 isolates). The researchers observed a decrease in the DDD per 1000 inhabitants per day from 2.40 to 1.38, and the percentage of *S. pyogenes* macrolide resistance decreased by almost 50%, but only after a 5-year delay (16.5% in 1992; 8.6% in 1996) (Fig. 2.3.2) [15].

Fig. 2.3.2. (A) Evolution of macrolide consumption by outpatients in Finland (1976–1995). Consumption is expressed in terms of defined daily doses per 1000 inhabitants per day. (B) Evolution of *Streptococcus pyogenes* resistance to erythromycin in Finland (1990 and 1992–1996). Source: From Seppälä et al. (1997) [15], copyright © 1997 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

A



B



The results of these two studies, one ecological and the other an interventional study, point out that a positive relationship exists between antimicrobial use and development of resistance.

2.2 At the individual level

The impact of the standard clarithromycin-based triple therapy on *H. pylori* has been well documented over the years. Indeed, when this treatment fails, approximately 60–70% of the strains test resistant to clarithromycin [16]; when levofloxacin is used instead of clarithromycin, about 50% of the strains test resistant to fluoroquinolones when the treatment fails [17]. An increase in metronidazole resistance is also observed under such circumstances.

Besides *H. pylori* resistance, it is also important to consider the resistance induced by *H. pylori* eradication therapy on other bacteria, especially the faecal flora. Currently, very few studies are available. They were conducted mainly in Sweden and concern essentially the consequences of the standard clarithromycin-based triple therapy. In a study of the stool, throat, and nostril flora of 85 patients who received clarithromycin, metronidazole, and omeprazole for 1 week, the researchers focused on four bacterial species. A dramatic increase in resistance was observed 2 weeks after the start of treatment among all strains that were previously susceptible: Streptococci (80%), Staphylococci (72%), Enterococci (67%), and Bacteroides (27%). After 1 year, the probability of persistence of resistant organisms was 51% for Streptococci, 39% for Staphylococci, 14% for Enterococci, and 14% for Bacteroides [18].

That study confirmed the results previously obtained on throat flora only, where Streptococci and *Neisseria* sp. were chosen as indicator organisms and a follow-up was carried out 1 year and 3 years after patients received the same eradication treatment. Resistance was found to increase after treatment in all cases except one; after 1 year, resistance was still higher than at inclusion, but it reverted to baseline levels after 3 years [19].

Another study showed that anti-*H. pylori* treatment selects for highly resistant Enterococci, which were able to persist for 3 years in 3 out of 5 patients [20].

These data indicate that anti-*H. pylori* treatment has an important and long-lasting impact on resistance of normal bacterial flora.

3. Impact of antibiotic consumption on the composition of the microbiota

The few studies that have been performed on this topic were based on standard culture methods and not the current metagenomics approach. Two studies were performed in Sweden in the 1990s. In the first study, 14 patients received omeprazole–amoxicillin (OA) for 10 days and were compared with 14 who received a placebo. In the second study, 14 patients received omeprazole–amoxicillin–metronidazole (OAM) and 16 received omeprazole–clarithromycin–metronidazole (OCM), both groups for 7 days.

Significant alterations were seen in the saliva microbiota of the patients who received OA. The number of viridans streptococci increased, and the number of *Haemophilus* sp. decreased. The anaerobic microflora was significantly reduced. Levels returned to normal after 35 days. In the group who received OAM, similar results were observed, with an additional increase in the numbers of yeasts. The same was true for the OCM group.

Concerning the intestinal microbiota, in the OA group, in addition to the emergence of resistant enterobacteria, yeasts emerged. With OAM and OCM treatment, there was also a significant increase in the numbers of Enterococci, Enterobacteria, and Peptostreptococci. Anaerobic bacteria such as Bifidobacteria and Clostridia were significantly suppressed. These alterations returned to normal 4 weeks after treatment in the OAM group but persisted for the OCM group [21].

Another study, performed in Germany, investigated the impact of OCM on the intestinal microflora of 57 patients and 21 controls [22]. The researchers also observed a decreased colonization with non-spore-forming anaerobic bacteria and an increased colonization with yeasts including *Candida albicans*, and with Clostridia, after treatment. *Clostridium difficile* was detected in 3 cases but without associated diarrhoea.

Although *C. difficile* enterocolitis has rarely been described after *H. pylori* eradication therapy, this is a potential issue to consider in implementing a mass eradication programme.

4. Conclusion

There is evidence of a positive correlation between antibiotic consumption and bacterial resistance to the corresponding antibiotic, as well as a negative impact on the normal flora, which is now considered as a specific organ, given its impact in many diseases.

Unfortunately, even the countries with the strictest policy, like the Netherlands, have seen an increase in antibiotic prescription over the past decade, especially because of the ageing of the population [23]. A mass *H. pylori* eradication campaign would no doubt add greatly to this burden.

However, the precise impact of eradication measures should be calculated in each country, according to the prevalence of the infection, to see what the real additive effect would be. In Germany, for example, only an estimated 15% of antibiotics are, in fact, used directly by humans, whereas 85% are used for veterinary medicine [24].

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Chapter 3.1

Principles of evidence-based cancer prevention strategies

Karen J. Goodman and Amy Colquhoun

1. What evidence can be used for evidence-based disease prevention strategies?

In the formulation of evidence-based disease prevention strategies, the expected costs and benefits of proposed strategies must be evaluated against the alternative use of available resources. In particular, it must be decided whether spending the required resources for a particular intervention is preferable to using these resources for other priorities. Such decisions should be informed by the best available scientific evidence on the expected costs and benefits of specific strategies, along with prioritization of available resources according to relevant social values. Expected costs and benefits, as well as available resources and priorities, vary across population settings; thus, strategies must be tailored to each local context. This chapter summarizes key principles articulated in authoritative texts on evidence-based disease prevention.

1.1 What is considered "best evidence"?

Evidence for evidence-based practice has been defined as "knowledge derived from a variety of sources that has been subjected to testing and has been found to be credible" [1]. Rycroft-Malone et al. (2004) stated that this knowledge can be gained from a variety of sources, including: research evidence; professional knowledge or clinical experience; patients, clients, and carers; and local context [2]. Skovgaard et al. (2007) pointed out that what is considered "best, current available knowledge" varies but is sought to [3]:

- Estimate the need and potential for interventions
- Demonstrate "what works"
- Guide efficient implementation
- Single out action plans that will be more cost-effective than feasible alternatives.

1.2 What types of evidence should be considered?

Brownson et al. (2011) highlighted three levels of evidence to consider in evidence-based public health [4]:

- Type 1: whether something should be done, based on analytic data illustrating the importance of the health condition and its link with some preventable risk factor as well as the magnitude, severity, and preventability of the condition.
- Type 2: whether a specific action can be identified, based on the relative effectiveness of specific interventions to address a particular health condition.
- Type 3: how an intervention should be implemented, based on an understanding of the context of an intervention, including social, cultural, economic, and political factors.

When considering various types of evidence for disease prevention strategies, it may also be valuable to note differences between evidence used to inform medicine and evidence that is typically used to inform public health. Brownson et al. (1999) described evidence-based medicine as "the delivery of optimal individual patient care through the integration of current best evidence on pathophysiological knowledge, cost effectiveness, and patient preferences" [5]. They noted that much of the evidence used to support medicine is based on randomized controlled trials. In contrast, they stated that evidence-based public health is "the development, implementation, and evaluation of effective programs and policies in public health through application of principles of scientific reasoning" and noted that public health interventions typically rely on evidence from quasi-experimental or observational studies.

2. Disease prevention strategies: development and implementation

Teutsch (1992) presented an idealized model for developing and implementing prevention strategies [6]:

1. Basic research produces prevention technologies that may reduce morbidity and/or mortality.
2. Controlled experimental studies estimate the efficacy of the resulting prevention technologies.
3. Community-based studies estimate the effectiveness and cost of prevention strategies based on efficacious prevention technologies, first in demonstration settings and then in routine community settings.
4. Improvements in methods to increase prevention effectiveness are incorporated iteratively.

Similarly, Greenwald et al. (1995) listed five phases of cancer control research [7]:

1. Hypothesis development
2. Methods development
3. Controlled intervention trials
4. Defined population studies
5. Demonstration and implementation.

Defined population studies should be done after an intervention has been shown to be effective in a controlled comparison study. Demonstration and implementation should proceed only after a prevention strategy has passed through the first four phases; there should be clear scientific evidence from controlled trials demonstrating the extent of benefit, and information from defined population studies about the practical implementation and cost–effectiveness in a relevant geographical region. Identification of these five research phases reveals the level of evidence available to support a cancer control intervention, with the strength of the scientific evidence corresponding to the highest phase achieved. As noted by Teutsch (1992), pressure to move rapidly from basic and applied research to widespread implementation before the appropriate evaluation studies can be completed leads to gaps in evidence of the efficacy, effectiveness, safety, or economic impact of potential prevention strategies [6]. Generally, however, there should be accurate estimates of the efficacy and safety of prevention strategies before evaluation in population settings to ensure that they have the expected impact [8].

3. Disease prevention strategies: assessing evidence

Skovgaard et al. (2007) presented three types of evidence that together form the evidence base for disease prevention [3]:

Type I. Descriptions and analyses of the determinants of health and disease and their distribution.
These help when answering questions like:

- What do we know about the cause of a given state of health, its distribution, and possible consequences of preventive interventions to individuals and groups?
- Do we know enough to design actions with the aim of intervening?
- Which target populations should be selected?
- Which interventions might work for the selected target populations?

Type II. Assessments of the relative effectiveness of preventive interventions.
These help when answering questions like:

- What is the quality of knowledge about the effects of potential preventive interventions that is available to guide new practice and decision-making?
- What works best on whom?

Type III. Accounts of the best possible design and implementation of interventions in specified contextual circumstances.
These help when answering questions like:

- Is the proposed intervention well suited to the target group?
- What is required for its implementation (organization of services, personnel qualifications, partnerships)?
- How can user involvement and activity be ensured?

The best evidence for prevention does not consist of studies that establish causality under optimal conditions. Instead, the need is for real-world investigations of the impact of prevention strategies under typical conditions. Moving evidence into practice requires assessing whether effective interventions conducted as research trials can be re-created under less-ideal, everyday circumstances. The following questions proposed by Skovgaard et al. (2007) are useful in guiding such assessments [3]:

1. What proportion of the target group would be willing and able to participate in the intervention?
2. Which negative and positive effects can be expected?
3. Will those expected to execute the intervention actually commit themselves?
4. To what degree will the intervention be performed as prescribed?
5. Can the intervention and its effects be maintained over time?

Teutsch (1992) presented a framework for assessing the effectiveness of disease prevention strategies, including [6]:

- Identification of efficacious and effective strategies to reduce disease and promote health.
- Identification of potential consequences of those strategies, including social, legal, ethical, and economic considerations.
- Estimation of the economic impact of a prevention strategy.
- Identification of optimal methods for implementing effective strategies.
- Evaluation of the impact of prevention programmes.

3.1 Assessing efficacy

As elaborated by Teutsch (1992), evaluating efficacy requires critical review of relevant studies that have been done, with the goal of assessing the quality of the science and the magnitude of the impact [6]. In health research, the highest-quality study design for efficacy is considered to be a randomized trial. Many prevention technologies are not subjected to this level of scrutiny, however, because of the prohibitive costs. Consequently, less-desirable studies are often used to assess efficacy.

3.2 Assessing effectiveness

Once a prevention strategy is known to be efficacious, the next question is: How well does it work in the real world? Effectiveness characterizes the success of the prevention strategy in target populations, allowing for the practical aspects of delivering it to people as part of their routine activities. Effectiveness is influenced by problems of access, follow-up, quality assurance, and individual behaviour in the social context. Effectiveness studies must be done in the community settings targeted for disease prevention. High-quality assessment of the effectiveness of prevention strategies comes from community demonstration projects. The safety of potential prevention strategies must also be evaluated, to identify undesired consequences, such as adverse effects, including anxiety created by highlighting potential health risks. Effectiveness studies can be used to assess the difference between the attributable fraction, interpreted as the proportion of disease cases that would be prevented by removing an exposure to which they are attributable, and the prevented fraction, which

estimates the proportion of disease cases prevented given the actual implementation of a prevention strategy.

3.3 Economic assessments

Teutsch (1992) also reviewed principles of economic assessments of preventions strategies, which are needed to evaluate expected costs and benefits of potential prevention strategies [6]. Useful cost–effectiveness analysis fulfils basic criteria:

- Prevention strategies are compared against alternatives, for example doing nothing, using other methods, or addressing different problems.
- The perspective is explicit (e.g. societal, employer, government, insurer), given that the perspective determines which costs are included in the analysis and how benefits are valued.
- Results produce quantified measures that weigh benefits against costs:
    - Cost–effectiveness: cost unit per prevented health event, for example dollars per year of life saved.
    - Cost–benefit: cost unit expended per cost unit of benefit achieved.
    - Cost–utility: cost unit of utility measures such as number of life-years saved.
- Weighting factors used to adjust cost–utility measures are explicit due to their subjective nature (e.g. the length of life a person would be willing to forgo if they could be freed of the morbidity).
- The method used for discounting is explicit and reasonable in accounting for benefits that accrue in the future against costs incurred in the present.

Standard methods for economic impacts of prevention strategies are needed to compare results across studies of these impacts: compared studies must be comparable on perspective, costs included, how benefits are valued, and methods of adjustment and discounting. Many good cost–effectiveness studies of *Helicobacter pylori* elimination for gastric cancer prevention have been done, but there is little standardization of methods across these studies.

4. Disease prevention strategies: who should be targeted, and who should be involved?

Ockene et al. (2007) described the following levels of intervention [9]:

- *Individual-level interventions:* one-to-one interactions between a patient and a provider, also well suited for including the family in addressing the health needs of the individual.
- *Social, family, and community network interventions:* strategies that target social groups in community settings, such as recreation centres, workplaces, schools, places of worship, and so on; interventions that target the family and social networks can facilitate behavioural changes at the individual level.
- *Community-level interventions:* strategies that target communities defined by geography, race, ethnicity, sex, illness, and so on, with a common interest such as a service agency, workplace, school, clinic, or policy-makers; such strategies include broad environmental, regulatory, and policy changes.

Coherent recommendations for evidence-based disease prevention must target explicitly those expected to implement the preventive practices. It must be clear whether messages are aimed at public health officials, health-care decision-makers, clinicians, or individuals at risk. Ockene et al. (2007) called for the integration of evidence-based clinical and community strategies to improve health [9]. Disease prevention initiatives can be more effective when based on coordinated efforts of clinical and community-based interventions to take full advantage of opportunities for prevention; thus, targeted health threats should be approached from a multilevel perspective, through partnerships across health systems,

communities, academia, business, and the media. Strategies that integrate preventive services across clinical and public health sectors align with a social–ecological perspective that recognizes behaviours and health to be influenced by multiple levels, from the individual to families to larger groups and, ultimately, to populations and ecosystems. When intervention strategies target each level of influence in a complementary manner, support is provided to those at risk at many different points, such as schools, clinics, and workplaces, thereby expanding their potential impact.

Example 1. Ockene et al. (2007) characterized the Massachusetts Tobacco Control Program as a comprehensive coordinated disease prevention programme, which incorporated clinical and community strategies, linking activities in clinical settings, the media, community agencies, academic institutions, and local and state policy-makers [9]. It included:

- An innovative media campaign to change public opinion and community norms
- Community mobilization to change local laws and health regulations
- Comprehensive tobacco treatment programmes based in clinics and community settings.

Example 2. A community-driven research programme with gastric cancer prevention goals demonstrates how community-engaged research can be part of a multilevel approach to develop and implement effective prevention strategies. The Canadian North *Helicobacter pylori* (CAN*Help*) Working Group is an intersectoral and interdisciplinary team comprising community organizations and residents, health-care providers, health technology industry representatives, and academic researchers. The research programme was initiated after concerns were voiced by Aboriginal communities about cancer risk from *H. pylori* infection. These communities, located in the Yukon and Northwest Territories of Canada, advocated for research to find solutions and were supported by health officials who sought information to improve health care for *H. pylori* infection. The research programme uses a collaborative and participatory approach in pursuit of the following aims:

- To obtain representative data from diverse Arctic communities for developing public health strategies for control of *H. pylori* infection in the circumpolar north.
- To conduct policy analysis to identify cost-effective *H. pylori* management strategies that are ethically and cultural appropriate for the target population.
- To develop knowledge exchange strategies that help participating communities understand *H. pylori* health risks, available solutions, and unsolved challenges for reducing these risks.

5. Gaps in the evidence for evidence-based gastric cancer prevention

The Circumpolar *H. pylori* Working Group (Brian J. McMahon, Michael G. Bruce, Anders Koch, Karen J. Goodman, Vladislav Tsukanov, Gert Mulvad, Malene L. Borresen, Frank Sacco, David Barrett, Steven Westby, and Alan Parkinson) has produced a manuscript entitled “Expert commentary on the diagnosis and treatment of *Helicobacter pylori* infection in Arctic regions with a high prevalence of infection”, which reaches the following conclusions about the adequacy of evidence for evidence-based gastric cancer prevention strategies:

- Treatment of *H. pylori* infection should be limited to conditions for which there is strong evidence of benefit in terms of reduced morbidity/mortality:
    - peptic ulcer disease
    - mucosa-associated lymphoid tissue (MALT) lymphoma.
- A test-and-treat strategy for individuals with dyspepsia should not be used in Arctic regions with high prevalence of *H. pylori* infection.
    - Most individuals in these areas will have been infected during their lifetime.
    - Particularly in instances where serology is used to test, most individuals, whether or not infected, will have a positive test.

    - Evidence shows that:
        - The proportion of individuals treated successfully can be as low as 50%.
        - Antimicrobial resistance is high.
        - Re-infection rates are high.
- Indications for treatment of *H. pylori* are inconclusive for individuals with severe gastritis that is not associated with heavy alcohol consumption or use of non-steroidal anti-inflammatory drugs; randomized controlled trials are needed to estimate the benefit of treating such individuals.
- Researching the local costs and benefits of alternative *H. pylori* management practices will lead to improvements in the evidence base for local policies.
- Additional studies of the following sort are needed:
    - Community intervention trials designed for accurate estimation of the effect on the risk of gastric cancer of screening and treating for *H. pylori* within subgroups defined by factors that may modify this effect.
    - Studies designed to estimate effects on gastric cancer risk of screening and treating asymptomatic individuals with a strong family history of gastric cancer.
    - Studies to identify bacterial and host factors that may better identify *H. pylori*-infected persons who benefit most from treatment.

6. Summary and key messages

- Prevention strategies should be tailored to the local context because of variation in available resources, priorities, intervention costs, and intervention effectiveness (variations in screening accuracy, treatment effectiveness, prevented fraction).
- Pressure to move too rapidly to widespread implementation leads to gaps in evidence of the efficacy, effectiveness, safety, and economic impact of potential prevention strategies.
- Disease prevention initiatives can be more effective when they expand opportunities for prevention through partnerships across health systems, communities, academia, business, and the media.
- Community-engaged research can be part of a multilevel approach to develop and implement effective prevention strategies.

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Chapter 3.2

Potential regimens for the mass eradication of *Helicobacter pylori* infection

Javier P. Gisbert and E. Robert Greenberg

It was more than 30 years ago that *Helicobacter pylori* was discovered and 20 years ago that standard triple therapy – a proton pump inhibitor (PPI) plus two antibiotics – was established in clinical practice for the eradication of this infection [1]. Nowadays, the efficacy of triple therapy is seriously challenged in many parts of the world, where eradication rates have declined to unacceptably low levels, largely related to development of resistance to clarithromycin [2]. It is this low efficacy that compromises the design and development of any mass screening and treatment programme for the prevention of gastric cancer. Moreover, the risk of causing a direct or ecological increase in the existing antibiotic resistance rates of *H. pylori* and other agents must be taken into consideration before implementing screening and treatment programmes.

In this context of mass screening and eradication of *H. pylori*, the most efficient treatment regimen may not be the same as for routine clinical management of symptomatic *H. pylori* patients. Efficacy must be considered, but other issues affecting the treatment, such as cost, tolerability, and simplicity (and therefore compliance), gain an even more important role [3]. Moreover, design of these programmes must be concerned with the impact they may have on the selection of antibiotic-resistant strains from *H. pylori* and other species, at both the individual level (direct selection of surviving strains) and the societal–ecological level (the type and quantity of antibiotic compounds entering the ecosystem may increase widespread resistance).

Programme design and treatment recommendations in *H. pylori* screening must, therefore, fit the narrow criteria to be an acceptable compromise between cancer prevention aims (cost–effectiveness) [4] and infection prevention (mass eradication reduces sources of infection), with the containment of antimicrobial resistance [5].

1. The problem of antibiotic resistance: a worldwide perspective

The most common causes for the failure of reliably good or excellent regimens are poor compliance with therapy and/or the presence of organisms resistant to one or more of the antimicrobial agents used [3, 6]. Several studies have suggested a variety of miscellaneous factors that might be important in *H. pylori* eradication, including age, presentation (e.g. functional dyspepsia vs duodenal ulcer), and CagA status [7, 8]. However, these candidates have typically been discovered in data-dredging studies in which resistance was not assessed [9].

Resistance rates vary remarkably in different geographical areas, and therefore the selection of therapeutic regimes needs adjustments according to the local resistance pattern. The prevalence of antibiotic resistance (mainly to clarithromycin, metronidazole, and levofloxacin) in various regions is correlated with the general use of antibiotics – for infectious diseases other than *H. pylori* infection – in the region [10–12]. For example, the long-term use of clarithromycin as monotherapy, mainly for respiratory tract infections, has led to high *H. pylori* clarithromycin resistance rates [10]. This explains why those countries in northern Europe that have a strict policy for antibiotic use still have a low prevalence of resistance [13]. The resistance against amoxicillin is virtually zero, with few exceptions, and thus it does not represent a concern for its use in treatment regimens [14].

A systematic review performed in 2010 analysed the clarithromycin resistance rates in different areas around the world [15]. On a global scale, resistance was detected in 17% of the cases. The resistance rates differed significantly between Europe (11%), Asia (19%), and the Americas (29%). A recent European multicentre study [12] showed that resistance rates in Europe for adults were 17% for clarithromycin and 35% for metronidazole. In Europe, there are also huge differences between geographical areas, mainly between southern and northern Europe [16]. The same occurs in various regions of Asia, with low rates in Malaysia and high rates in Japan [16].

2. Tailored versus empirical treatment

Ideally, the treatment for a bacterial infectious disease should be chosen based on culture and susceptibility testing. Pretreatment *H. pylori* susceptibility testing allows the selection of a regimen tailored by antimicrobial susceptibility. However, this is not always feasible in *H. pylori*-infected patients because it requires an invasive procedure (i.e. gastroscopy), which obviously is not indicated in mass programmes such as those aimed at preventing gastric cancer in the general population [4]. Thus, if these programmes are implemented, one must empirically choose therapy, and in this instance the best approach is to use regimens that have been proven reliably effective in a given area [9, 17, 18]. That choice should take advantage of the knowledge of resistance patterns obtained from local or regional antimicrobial surveillance programmes and/or based on local clinical experience with regard to which regimens are effective locally [9]. In the end, the recommendations stated by each country's guidelines on *H. pylori* treatment should be followed. Finally, the history of the patient's prior antibiotic use and any prior therapies will help identify which antibiotics are likely to be successful and those for which resistance is probable [9].

As Graham et al. have accurately stated, "All other things being equal, data from any area or region regarding the effects of resistance on outcome can be used reliably to predict outcome in any other area" [9]. Thus, strains with similar patterns of resistance in Spain, the USA, the Islamic Republic of Iran, China, and so forth should be expected to respond alike, so that if one knows the results with susceptible strains and with resistant strains in one place, one can reasonably predict the outcome of therapy anywhere [9].

In summary, a first-line eradication regimen should be based on what works best in a defined geographical area and must take into account the prevalence of antimicrobial resistance in that region [18].

3. The importance of compliance with and tolerance of treatment

Compliance is an important issue, mainly when *H. pylori* treatment is planned to be included in the context of population-based screening (such as mass programmes to prevent gastric cancer in the general population) rather than clinical management. Furthermore, side-effects are reported by approximately 50% of patients. Therefore, in this setting, significant effort should be directed towards identifying a regimen that is short and easy for the patient to follow [19].

If compliance with the regimen is poor, even the best-designed regimen will have a poor outcome, so another aspect of optimization is to identify the factors that determine compliance, such as dosing, duration, and side-effects [20]. The fact that *H. pylori* therapy involves multiple drugs (and frequently multiple dosing intervals) makes patient education extremely important. It is worth considering direct counselling about the regimen and the need to be compliant, as well as providing handouts with the objectives and the details of the regimen [9]. Measures to enhance compliance improve eradication success and are meaningful when large numbers of patients are treated. At a minimum, patients should

receive counselling about the anticipated side-effects and the importance of completing the treatment regimen [21]. A few extra minutes can prevent most of the issues associated with treatment failures [20]. In this respect, it is well known that adherence to the therapy is associated with high eradication rates: patients taking 60% or more of the prescribed therapy have a higher treatment success compared with patients with a poor compliance (96% vs 69%) [22].

Adherence to treatment is a very important consideration, which partially depends on the complexity of the therapeutic regimen. For example, the ingestion of multiple medications, up to 4 times a day in some regimens, can cause problems with adherence. Moreover, confusion may be caused when treatments or drug intake change during the regimen.

4. Standard triple therapy

The triple therapy including PPI–clarithromycin and amoxicillin or metronidazole proposed at the first Maastricht conference to treat *H. pylori* infection has become universal since it was recommended by all the consensus conferences held around the world [23].

However, the most recent data show that this combination has lost some efficacy and often allows the cure of only a maximum of 70% of the patients, which is less than the 80% rate aimed for at the beginning and far below what should be expected for a bacterial infection [2]. In some European countries, the success rates are disappointingly low [24], with values of only 25–60% [25, 26]. At present, as a general rule, it has been recommended that a regimen should not be used unless it reliably produces an eradication rate greater than 90% (per-protocol) [20]. An effective (i.e. > 90%) first-line therapy has been considered mandatory for avoiding supplementary treatments and testing, and more importantly for preventing the development of secondary resistance. However, desirable qualities of an optimal regimen may differ between that used to treat “sick” patients (such as ulcer patients), where eradication effectiveness will be paramount, and that used in mass programmes to prevent gastric cancer in the general population, where compliance, tolerance, ease, cost, and avoiding the emergence of resistance will be important.

There are several explanations for the decrease in efficacy of the standard triple therapy: compliance, high gastric acidity, high bacterial load, and type of strains, but by far the most important is the increase in *H. pylori* resistance to clarithromycin. Pooled data from 20 studies involving 1975 patients treated with standard triple therapy showed an eradication rate of 88% in clarithromycin-sensitive strains versus only 18% in clarithromycin-resistant strains [10].

The global clarithromycin resistance rate in Europe increased from 9% in 1998 [27] to 18% in 2008–2009 [12]. Resistance has increased in most parts of Europe, but it has now reached a prevalence of greater than 20% in most countries in central, western, and southern Europe, which is considered a high resistance rate. In northern European countries, prevalence is less than 10%, which is considered a low resistance rate [14]. Following the European Medicines Agency recommendation on evaluation of medicinal products indicated for treatment of bacterial infection, three categories of bacterial species can be defined, according to their susceptibility to a given antibiotic: usually susceptible (0–10% resistant), inconstantly susceptible (10–50% resistant), and usually resistant (> 50% resistant). *H. pylori* now falls into the second category for clarithromycin resistance, except in northern Europe and Thailand [28].

To take into account the confidence intervals of the prevalence obtained and the regional differences in a given country, a threshold of 15–20% was recommended to separate the regions of high and low clarithromycin resistance. Thus, in areas with clarithromycin resistance of less than 10–15% (i.e. the Netherlands, Sweden, Ireland, Germany, Malaysia,

and the south of Taiwan, China), it is still possible to use the standard triple therapy to achieve a per-protocol eradication rate greater than 80–90% [18]. Accordingly, it has been stated (e.g. Maastricht IV conference) that "in areas of low clarithromycin resistance, clarithromycin-containing treatments are recommended for first-line empirical treatment (although bismuth-containing quadruple therapy is also an alternative)" [23]. However, it was stated that "PPI–clarithromycin-containing triple therapy without prior susceptibility testing should be abandoned when the clarithromycin resistance rate in the region is more than 15–20%" [23].

In case the clarithromycin-containing triple regimen is selected to be used as the first-line treatment, different ways of improving its efficacy have been proposed. These are outlined below.

4.1 Increasing the dose of PPI

There is indirect and direct evidence that high-dose PPI can improve the cure rates of *H. pylori* treatment. Indirect evidence comes from old multiple studies showing that high-dose PPI was necessary for the efficacy of dual therapies and the meta-analysis showing that twice-a-day PPI was better than a single daily dose in triple therapy [29]. Direct evidence comes from a meta-analysis showing that high-dose PPIs increase cure rates by about 6–10% compared with standard doses [30]. A subanalysis of these data showed that the maximal effect was seen in the studies comparing high doses of the more potent second-generation PPIs (i.e. 40 mg of esomeprazole twice a day) with a standard dose of a first-line PPI, also twice a day [30]. The rationale for this finding is that the difference in the degree of gastric secretion between arms is more important when using double doses of more potent PPIs. According to the data of that subanalysis, increasing the dose of PPI from, for example, 20 mg of omeprazole twice a day to 40 mg of esomeprazole or rabeprazole twice a day may increase cure rates by 8–12% [30].

PPIs undergo hepatic metabolism mainly via the cytochrome P450 (CYP) pathways and the isoforms CYP2C19. There are interindividual differences in the activity of CYP2C19, which may affect the pharmacokinetic behaviour and clinical efficacy of PPIs [31, 32]. Indeed, the CYP2C19 phenotype is categorized into three groups: extensive or rapid metabolizer, intermediate metabolizer, and poor metabolizer. The proportion of CYP2C19 rapid metabolizers was proven to be higher in Europe and in North America, whereas the proportion was lower in the Asian population [33]. Significantly higher eradication rates of *H. pylori* have been observed in patients with the poor or intermediate metabolizer phenotype, compared with extensive metabolizers [34]. Thus, initial genotyping for this enzyme would be ideal before *H. pylori* therapy, since higher dosage in extensive metabolizers is likely to improve the clinical efficacy of PPIs for *H. pylori* therapy. Obviously, this approach is unrealistic in clinical practice, so it is conceivable that all patients, especially in Europe and North America, should receive high-dose PPI therapy to circumvent the high rate of CYP2C19 rapid metabolizers.

Finally, as for the different available PPI molecules, a recent meta-analysis disclosed that the efficacy of omeprazole- and lansoprazole-based first-line triple therapies at the standard doses was dependent on CYP2C19 genotype status, which appeared not to affect the efficacy of the regimens including rabeprazole [35]. In line with this finding, two other recent meta-analyses have demonstrated that esomeprazole and rabeprazole provide better overall *H. pylori* eradication rates, especially in CYP2C19 extensive metabolizers [36, 37].

4.2 Increasing the duration of treatment

Several meta-analyses have been carried out and have yielded very similar results: a 10-day treatment improves the eradication rate by 4%, and a 14-day treatment improves the eradication rate by 5–6%, compared with a 7-day treatment [38–40]. More recently, a

Cochrane review confirmed that, in general, increasing the duration of PPI-based triple therapy increases *H. pylori* eradication rates, and that specifically for a PPI–clarithromycin–amoxicillin regimen, prolonging the treatment duration from 7 days to 10 days or from 10 days to 14 days is associated with a significantly higher eradication rate; thus, the optimal duration of therapy for this regimen was considered to be 14 days [41].

With 14-day therapy, the combination remains effective until clarithromycin resistance exceeds approximately 15%, whereas 7-day therapy is compromised by clarithromycin resistance that exceeds 5%. Currently, there are few regions in the world where clarithromycin resistance is less than 15% (i.e. the 14-day regimen is still useful in such areas as northern Europe and Thailand) [9].

Although the difference in efficacy between short and long regimens is statistically significant, it may be considered relevant or not, according to other factors such as cost, mainly when the perspective of mass eradication in large populations is considered. Furthermore, although some authors have reported a benefit of prolonging the duration of triple therapy, others – from the Republic of Korea [42] and Turkey [43] – could not demonstrate an advantage for this strategy. Thus, prolonging *H. pylori* triple therapy seems to increase – overall – eradication rates, but whether it represents a clinically useful strategy should be locally evaluated.

4.3 Using metronidazole instead of amoxicillin as the second antibiotic

The Achilles heel of metronidazole-containing triple therapy is metronidazole resistance, and metronidazole-containing triple therapy now rarely is used except as a tailored therapy or in Japan, where the general use of metronidazole has been strongly discouraged by the government because of possible genotoxicity [9]. In any case, a previous meta-analysis [44], updated for the Maastricht IV conference, did not find statistically significant differences in eradication rates for PPI–clarithromycin–metronidazole (71%) and for PPI–clarithromycin–amoxicillin (65%) when the same dose of clarithromycin was used [23].

5. Bismuth-containing quadruple therapy

From a microbiological standpoint, the most rational way to overcome antibiotic resistance would be the use of a combination of drugs for which resistance does not appear to be a problem, so, as previously mentioned, no clarithromycin-based regimens should be recommended in geographical areas with increasing clarithromycin resistance rates. In this context, bismuth-containing quadruple therapy (PPI, bismuth, metronidazole, and tetracycline) seems to be an attractive alternative treatment [13]. Accordingly, bismuth-containing quadruple therapy has been recommended by the Maastricht IV Consensus Report [23] and by the Second Asia-Pacific Consensus Guidelines for *H. pylori* infection [45] as an alternative first-choice regimen to standard triple therapy in areas with a low rate of clarithromycin resistance, and has been recommended as the first-line therapeutic option in areas with a high prevalence of clarithromycin resistance.

As Mégraud has accurately stated, in the context of increased resistance to antibiotics, quadruple therapy has the advantage of using the following compounds [13]: (i) bismuth, whose mechanism of action appears to be more like an antiseptic than an antibiotic, and for which no resistance has been described; (ii) tetracycline, an antibiotic for which resistance is rarely encountered; and (iii) metronidazole, for which resistance in vitro exists at a high prevalence in most countries around the world, but the clinical impact of this resistance is limited and it can be overcome by increasing the dose and duration of treatment (in addition, the quadruple regimen overcomes clarithromycin resistance). Thus, if this quadruple regimen is used at full doses and for 14 days, one can expect greater than 90% treatment success irrespective of the level of metronidazole resistance [46–48]. Indeed, a meta-

analysis of 91 treatment arms concluded that if nitroimidazole resistance is present, a nitroimidazole-containing regimen should be avoided or a quadruple regimen should be given for more than 1 week [49]. Therapy for 7 days, and probably for 10 days, is very susceptible to metronidazole resistance [46]. Accordingly, it has been recommended that the duration be 14 days whenever metronidazole resistance is known or suspected [20].

Several meta-analyses comparing the outcomes of triple therapy and bismuth-containing quadruple therapy found similar eradication rates for both regimens when used as first-line therapies for *H. pylori* infection [50–52]. However, many of these comparative studies predate the emergence of high rates of clarithromycin resistance.

Bismuth-containing quadruple therapy is the treatment most in need of clinical trials to simplify the regimen to improve compliance. Recent studies in China have shown that twice-a-day bismuth may be sufficient [48, 53]. Furthermore, studies in Italy have suggested that twice-a-day therapy (at the noon and evening meals) may be sufficient, which would allow the total dosage to be cut in half, likely with improved compliance [54, 55].

Recently, a novel bismuth-containing quadruple therapy using a single three-in-one capsule containing bismuth subcitrate, metronidazole, and tetracycline has been proposed to decrease the pill burden and improve patient compliance. The value of this regimen is based on two randomized clinical trials, one performed in North America [56] and the other in Europe [57], where the three-in-one capsule treatment was compared with the standard regimen of omeprazole, amoxicillin, and clarithromycin. The intention-to-treat results in the North American trial were 86% for the bismuth-containing regimen and 80% for the standard triple regimen; for the European trial, they were 80% and 55%, respectively. The apparent lower success rate in the European trial can be linked to protocol violations. In contrast to many other trials, the protocol was very stringent in requesting two negative urea breath tests at a 1-month interval. Unfortunately, some missing second urea breath test results led these cases to be considered as failures. Considering one urea breath test result instead of two, the eradication rate was 93% for the bismuth-containing quadruple regimen versus 68% for the standard triple regimen. Finally, it should be emphasized that despite the high level of metronidazole resistance in both trials, this did not influence the results significantly.

It is interesting to look at the difference between the eradication rates of a clarithromycin-based regimen versus a bismuth-based regimen in the two trials: 6% in the North American trial and 25% in the European one [13]. One possible explanation may be the difference in duration of treatment (7 days in Europe and 10 days in North America). However, the most likely reason appears to be the higher resistance to clarithromycin in Europe than in North America between the two trials carried out 10 years apart [13].

Another international multicentre study, which was not a comparative trial, was carried out to evaluate the impact of metronidazole in vitro resistance on the efficacy of three-in-one capsule treatment in vivo [58]. A total of 170 patients were included, and the metronidazole resistance rate was 33%. The overall eradication rate by modified intention-to-treat was 93%, with no significant difference between metronidazole-resistant cases (93%) and metronidazole-susceptible cases (95%).

The safety and tolerability of the quadruple therapy, which is still one of the unjustified concerns about the quadruple therapy, have been similar to those of the standard triple therapy in several meta-analyses [50–52]. Regarding safety, in the context of *H. pylori* eradication, the doses of bismuth currently used in the quadruple regimen are relatively low and are administered for a short time period, leading to blood levels lower than 50 mg/L, considered to be at the threshold for potential bismuth toxicity [59].

Finally, because the bismuth-containing quadruple therapy is an inexpensive regimen, it is often preferred in situations where the cost of therapy is the main concern, which may be the case for mass programmes in the general population. However, limitations of this quadruple regimen are the unavailability of bismuth salts worldwide, and the fact that many countries are currently also experiencing a general unavailability of tetracycline.

6. Non-bismuth-containing quadruple therapies

"Sequential" treatment consists of the administration of a 5-day induction phase of amoxicillin plus PPI followed by 5 days of PPI, clarithromycin, and metronidazole (all given twice a day) [60, 61]. "Concomitant" treatment combines these four drugs given together for at least 10 days [62–64]. Although non-bismuth-containing quadruple therapy is not ideal because it contains clarithromycin, it has been shown that clarithromycin resistance could be overcome in several cases. Indeed, the success rate of non-bismuth-containing quadruple therapies with clarithromycin-resistant strains was relatively high [60]. Thus, non-bismuth-containing quadruple schemes have been recommended as first-line therapy in areas with high clarithromycin resistance (> 15–20%), mainly where bismuth-containing quadruple therapy is not locally available [23].

6.1 Sequential therapy

Sequential therapy was developed in Italy in 2000 as a replacement for triple therapy [65, 66]. Until 2008, most of the studies on this therapeutic strategy had been conducted in Italy. In 2007, a randomized controlled trial showed a significant advantage of 10-day sequential therapy over 10-day triple therapy (eradication rate, 91% vs 78%), and the sequential therapy was highly effective against clarithromycin-resistant strains [67]. A pooled data analysis with evidence from Italian studies showed promising eradication rates higher than 90%, even in patients with risk factors for failure of triple therapy (clarithromycin or metronidazole resistance, functional dyspepsia, smoking, or the absence of the *CagA* gene) [68]. Indeed, several meta-analyses evidenced the advantage of sequential therapy over triple therapy [69–71]. Accordingly, it was suggested in 2007 by the American College of Gastroenterology Guidelines [72] and the European Maastricht Consensus (Maastricht III) [73], as well as in 2009 by the Second Asia-Pacific Consensus Guidelines [45], that sequential therapy was a promising therapy, but it required further evaluation outside Italy before a generalized change in first-line *H. pylori* treatment was recommended.

In 2010, a critical review of the published evidence highlighted several concerns in previous meta-analyses, such as lack of validation outside of Italy, low-quality studies, or insufficient information on the effect on antibiotic-resistant strains [60]. In 2011, a large, multicentre trial from Latin America showed no advantage of 10-day sequential therapy over 14-day triple therapy [74]. In 2012 and 2013, an updated meta-analysis in children and two systematic reviews in adults dealing with sequential therapy were published [75–77]. From 2008 to 2013, cure rates of sequential therapy in studies conducted in Asia, Europe, and Latin America remained significantly better than those of triple therapy, but mean eradication rates dramatically dropped by 15% compared with those in Italian trials before 2008. A recent multicentre study performed in Taiwan, China, comparing 14-day sequential and triple therapy definitely showed the limitations of sequential therapy, since the efficacy of this regimen was impaired by both clarithromycin and metronidazole resistance [78]. Finally, a recent meta-analysis showed a mean cure rate of 84% for 10-day sequential therapy, which was superior to that of 7-day triple therapy and marginally superior to that of 10-day triple therapy but not superior to that of 14-day triple therapy [61]. Currently, 10-day sequential therapy cannot be considered a good therapeutic option to overcome antibiotic resistance, and its failure might be expected when the prevalence of dual – clarithromycin plus metronidazole – resistant strains is greater than 5%.

6.2 Concomitant therapy

The term “concomitant” therapy, which implies that all the antibiotics are administered together, is actually a misnomer because all treatments for *H. pylori*, with the exception of sequential therapy, are in fact concomitant therapies, but this will be the term used hereafter as it has been widely used. The concept of this regimen consists of converting standard triple therapy to a quadruple therapy by the addition of 500 mg of metronidazole or tinidazole twice a day. In 1998, two groups of investigators, one in Germany and the other in Japan, proposed that a PPI, amoxicillin, clarithromycin, and nitroimidazole be given concurrently as a four-drug, three-antibiotic, non-bismuth-containing quadruple regimen [79, 80]. Despite the short duration of therapy (5 days on average), this approach provided, at that time, high cure rates (90% by intention-to-treat). It fell into oblivion after a few years of research, but resurfaced in 2010 as an alternative therapy to triple and sequential therapy [63, 64].

Meta-analyses have shown that the outcome of concomitant therapy is duration-dependent [63, 64], which was confirmed in a recent head-to-head comparison of 5-day and 10-day concomitant therapies in Thailand, where 5-day therapy proved unsatisfactory [81], and by failure of 5-day concomitant therapy in Latin America [74] and the Republic of Korea [82]. In a recent study, 14-day concomitant therapy achieved the best intention-to-treat results (92%) [83] compared with studies evaluating 10-day concomitant therapy (86–87%) [84, 85]. Finally, it has recently been demonstrated that a 14-day high-dose concomitant regimen is highly effective for *H. pylori* eradication, achieving cure rates greater than 90% both by per-protocol and by intention-to-treat, and that this optimized regimen is more effective than the standard (10-day) one [86].

The Achilles heel of concomitant therapy is dual metronidazole–clarithromycin resistance. Thus, the efficacy of concomitant therapy was not impaired by either clarithromycin or metronidazole isolated resistance, but it is expected to fall below 90% when the prevalence of dual clarithromycin–metronidazole-resistant strains is greater than 15% [9]. Accordingly, concomitant therapy may be the preferred initial empirical therapy for areas and patient groups in which dual resistance is unlikely but is not recommended as a first-line empirical regimen where metronidazole resistance is likely greater than 60%, such as China, the Islamic Republic of Iran, India, or Central and South America, or in populations at high risk of dual resistance (i.e. after clarithromycin or metronidazole treatment failures) [9]. These recommendations are in agreement with suboptimal results in Latin America [74], the Republic of Korea [82, 87], and Turkey [88], where clarithromycin-resistant, but especially metronidazole-resistant, *H. pylori* strains are very prevalent. Likewise, they match with good to excellent results in southern Europe and some Asian countries, where rates of clarithromycin resistance range from low (9%) to high (40%) figures but metronidazole resistance remains in relatively low figures (< 30–40%).

If a non-bismuth-containing quadruple regimen is going to be used, a relevant question is whether a sequential or a concomitant regimen should be preferred. Recently, several studies have evaluated the efficacy of sequential and concomitant non-bismuth-containing quadruple therapies against clarithromycin- and metronidazole-resistant strains. Georgopoulos et al. addressed this issue nicely [89], and their results have been adapted [90] to exhibit the most recent evidence [83, 84, 91–93]. Concomitant and sequential therapies were successful against dual-resistant strains in 78% (18 of 23) and 33% (9 of 27) of the cases, respectively. Furthermore, a recent meta-analysis comparing sequential and concomitant therapy has shown a significant advantage of concomitant therapy [94]. Overall, solid evidence points towards concomitant therapy being a more reasonable therapeutic option in areas with a high incidence of clarithromycin and/or metronidazole resistance [89], but, as previously stated, it is expected to fail when the prevalence of dual clarithromycin–metronidazole-resistant strains is greater than 15% [9]. Finally, it should be taken into

account that concomitant therapy is less complex than sequential therapy, as the concomitant regimen does not involve changing drugs halfway through.

6.3 Treatment as an ecological/societal factor for future resistance

The societal consequences of the massive use of antibiotics should also be taken into account, as a positive correlation between antibiotic consumption and bacterial resistance to the corresponding antibiotic, as well as a negative impact on the normal flora (microbiota), has been reported [95]. Studies performed in Sweden have shown the impact of the standard clarithromycin-based triple therapy on the resistance of some bacteria present in the flora from saliva and intestine [95]. Samples showed an increase in amoxicillin minimum inhibitory concentrations (MICs) for *Streptococcus* sp., *Staphylococcus* sp., and *Enterococcus* sp., and an increase in clarithromycin MICs also for *Enterobacteriaceae* and *Bacteroides* sp., whereas a suppression of other anaerobic bacteria occurred. Persistence of high-level clarithromycin-resistant enterococci was found for 3 years in 3 of 5 patients in a long-term follow-up [96, 97]. Thus, when mass eradication in large populations is considered, it should be taken into account that the ecological impact of regimens such as the non-bismuth-containing quadruple regimens – which involve simultaneous administration of three broad-spectrum antibiotics such as amoxicillin, clarithromycin, and metronidazole – can be expected to be quite negative, with the selection of multiresistant strains despite a heavy antibiotic load received by the patients [13]. The acquired resistances in these patients may become a major societal concern as they, in turn, become infection sources, spreading the resistant strains. Finally, the ecological burden of antibiotic waste into the environment, both from unused pills and from excretion by the treated patient, may increase the appearance and selection of resistant strains [98].

7. Conclusion

In summary, a treatment recommendation to follow a *H. pylori* screening programme must take into consideration several factors, such as cost–effectiveness, simplicity, safety, direct selection of resistance, and ecological impact. Although a wide screening programme will probably have to recommend different regimens for different areas, bismuth-containing quadruple therapy positions itself as the most viable candidate in most regions.

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Chapter 3.3

Feasibility and cost–effectiveness of population-based *Helicobacter pylori* eradication

Paul Moayyedi

Wilson and Jungner described a classic set of criteria for a successful screening programme [1], and it has previously been shown that *Helicobacter pylori* screening and treatment to prevent gastric cancer fulfils most of these conditions [2]. This chapter focuses on whether a population *H. pylori* test-and-treat strategy (i.e. testing for the bacterium non-invasively and treating infected individuals) is likely to be feasible and cost-effective.

1. Feasibility of population *H. pylori* test and treat

For a screening programme to be feasible, there must be a diagnostic test and a therapy that is affordable and acceptable to the population. Facilities should be available to conduct a population *H. pylori* test-and-treat strategy; the diagnostic test should be accurate and the treatment effective. Population *H. pylori* test and treat fulfils these criteria when compared with other screening programmes that are currently available in most developed countries, such as cervical cancer screening [3] and colorectal cancer screening [4].

The most readily available test for *H. pylori* is serology. This is inexpensive, and many commercial kits are available [5]. The infrastructure needed to administer this test is in place in most countries as serology is widely used for a variety of medical investigations. The test is likely to be acceptable to the population as people are used to undergoing blood tests. Screening projects such as prostate-specific antigen testing to screen for prostate cancer [6] have not found a blood test a barrier to recruitment. The median sensitivity for commercial *H. pylori* serology tests is more than 90% and the median specificity greater than 80% [7]. This is not ideal but is acceptable for a population screening programme. If greater accuracy is needed, then the stool antigen test has sensitivities and specificities greater than 95% [8]. Subjects in most countries may find stool samples less pleasant to deal with than providing a serum sample, but faecal occult blood testing programmes have been instituted in the United Kingdom and Canada to detect early colorectal cancer, without any major problems [9]. Stool antigen tests are more expensive than serology and are therefore likely to be less cost-effective than serology. Carbon urea breath tests (UBTs) have also been used in screening studies [10]; although these are the non-invasive gold standard in terms of accuracy [11, 12], the ^{13}C-UBT is expensive and the ^{14}C-UBT involves exposing the person being screened to radiation (although at one tenth of the dose needed for a chest X-ray). Overall, most have considered that serology is the most cost-effective and acceptable test to use in a screening programme [13].

The therapy most commonly used to treat *H. pylori* infection is a proton pump inhibitor (PPI) combined with clarithromycin and either amoxicillin or metronidazole, each given twice a day for 1–2 weeks – so-called PPI–clarithromycin-based triple therapy. Initial reports suggested that these regimens would eradicate the infection in more than 90% of cases [14], but over time eradication rates have fallen, and now this regimen often achieves rates below 80%, possibly due to the increased prevalence of clarithromycin resistance. Another alternative is bismuth salts combined with tetracycline, PPI, and metronidazole for 1 or 2 weeks – so-called quadruple therapy. This achieves eradication rates in excess of 80% [15], and metronidazole resistance has only a modest impact on efficacy. Both types of regimen are tolerable, and PPI triple therapy has the advantage of being simple to take. Quadruple therapy is more complex, and in the context of a population eradication strategy this could

be a major concern. In addition, bismuth salts are not widely available worldwide. More recently, non-bismuth quadruple regimens, administered either sequentially or concomitantly, have been demonstrated to be more effective than the standard triple therapy [16, 17].

Currently, therefore, *H. pylori* screening and treatment is certainly feasible. However, work is needed to establish the best test and the most appropriate therapy to apply.

2. Cost–effectiveness of population *H. pylori* test and treat

A screening programme also needs to be affordable, and the benefits of the strategy must justify the costs. In 1996, Parsonnet et al. first reported a health economic model that suggested population *H. pylori* test and treat could be a cost-effective strategy to prevent gastric cancer [18]. This chapter reviews the literature on health economic models published since then that have evaluated population *H. pylori* screen-and-treat programmes compared with “do nothing”, with a view to reducing mortality from gastric cancer. The search strategy that was used to identify studies is given in Annex 1.

Nine eligible studies were identified [18–26], and the model methodology and results are summarized in Tables 3.3.1 and 3.3.2. The models studied a variety of populations and made different assumptions, but all found population *H. pylori* screening and treatment to be cost-effective using a threshold of US$ 50 000 per life-year saved. Most studies evaluated screening using serology, and the three that also assessed the carbon UBT all found this approach to have an unacceptable incremental cost–effectiveness ratio compared with serology [22, 23, 26]. Most studies also assessed PPI triple therapy as the treatment of choice for *H. pylori* infection, although one evaluated bismuth-based quadruple therapy [26]. All studies also found this result to be robust to the majority of reasonable assumptions and the main determinants of cost–effectiveness related to the efficacy of eradication therapy to prevent gastric cancer. Models usually made the assumptions from previous systematic reviews of case–control studies, and none evaluated evidence from systematic reviews of randomized controlled trials. Savings related to dyspepsia were rarely considered in these models, and none of the studies used data from randomized controlled trials.

Table 3.3.1. Summary of economic models that have evaluated population *Helicobacter pylori* screening and treatment to prevent gastric cancer

Reference	Country	Perspective taken	Population	Duration of follow-up	*H. pylori* test evaluated	*H. pylori* eradication	Factors important in model	Cost-effective?	ICER
18	USA	Third-party payer	Three ethnic groups in USA (White, African American, Japanese) at age 50–54 years (base case)	Lifetime	Serology	PCM	Age at which screened, prevalence of gastric cancer, efficacy in preventing gastric cancer (base case 30% RRR)	Yes	US$ 25 000
19	USA	Third-party payer	USA at age 50–54 years (also looked at other country data)	Lifetime	Serology, treat CagA-positive only	PCM	Age at which screened, prevalence of gastric cancer, efficacy in preventing gastric cancer (base case 30% RRR)	Yes (but no more than regular serology)	US$ 23 900
20	USA	Third-party payer	White men at age 40 years (also African American, Hispanic, and Japanese)	Lifetime	Serology	Unclear	Age at which screened, prevalence of gastric cancer, efficacy in preventing gastric cancer (base case RR = 3.6)	Yes	US$ 6264

ICER, incremental cost–effectiveness ratio; LYS, life-year saved; PCA, PPI–clarithromycin–amoxicillin; PCM, PPI–clarithromycin–metronidazole; PPI, proton pump inhibitor; QALY, quality-adjusted life-year; RR, relative risk; RRR, relative risk reduction; UBT, urea breath test; WTP, willingness to pay.

Table 3.3.1. Summary of economic models that have evaluated population *Helicobacter pylori* screening and treatment to prevent gastric cancer (continued)

Reference	Country	Perspective taken	Population	Duration of follow-up	*H. pylori* test evaluated	*H. pylori* eradication	Factors important in model	Cost-effective?	ICER
21	United Kingdom	Third-party payer	United Kingdom at age 40–49 years	Until age 85 years	Serology	PCM	Prevalence of gastric cancer, efficacy in preventing gastric cancer (base case 30% RRR), savings related to dyspepsia costs	Yes	Dominant (saves US$ 9 per person screened and 130 LYS per 10^5 people screened)
22	United Kingdom		United Kingdom at age 40–49 years	Lifetime	Serology (and UBT)	PCM	Efficacy in preventing gastric cancer (base case 30% RRR), savings related to dyspepsia	Yes	US$ 8800
23	Singapore	Third-party payer	Singaporean Chinese at age 40 years	Lifetime	Serology (and UBT)	PCA	Prevalence of gastric cancer, efficacy in preventing gastric cancer (base case RR = 3.6)	Yes	US$ 25 881 (5700–120 000) 75% certain cost-effective at US$ 50 000 threshold

ICER, incremental cost–effectiveness ratio; LYS, life-year saved; PCA, PPI–clarithromycin–amoxicillin; PCM, PPI–clarithromycin–metronidazole; PPI, proton pump inhibitor; QALY, quality-adjusted life-year; RR, relative risk; RRR, relative risk reduction; UBT, urea breath test; WTP, willingness to pay.

Table 3.3.1. Summary of economic models that have evaluated population *Helicobacter pylori* screening and treatment to prevent gastric cancer (continued)

Reference	Country	Perspective taken	Population	Duration of follow-up	*H. pylori* test evaluated	*H. pylori* eradication	Factors important in model	Cost-effective?	ICER
24	Taiwan, China	Societal	Residents of Matsu Islands between China and Taiwan, China	Lifetime	UBT	PPI triple therapy	Age at which screened, prevalence of gastric cancer, efficacy in preventing gastric cancer (base case 30% RRR)	Yes	US$ 17 044
25	China	Third-party payer	Chinese at age 20, 30, or 40 years	Lifetime	Serology	Unclear	Unclear what RRR of *H. pylori* eradication to prevent gastric cancer	Yes	< US$ 1600/LYS for each scenario
26	Canada	Third-party payer	Singaporean Chinese at age 40 years	Lifetime	Serology (positive stool antigen and UBT)	Bismuth-based quadruple therapy	Prevalence of gastric cancer, efficacy in preventing gastric cancer (base case RR = 3.6)	Yes	US$ 33 000 (stool antigen test most cost-effective → 95% certain that screening cost-effective if WTP US$ 40 000 per QALY gained)

ICER, incremental cost–effectiveness ratio; LYS, life-year saved; PCA, PPI–clarithromycin–amoxicillin; PCM, PPI–clarithromycin–metronidazole; PPI, proton pump inhibitor; QALY, quality-adjusted life-year; RR, relative risk; RRR, relative risk reduction; UBT, urea breath test; WTP, willingness to pay.

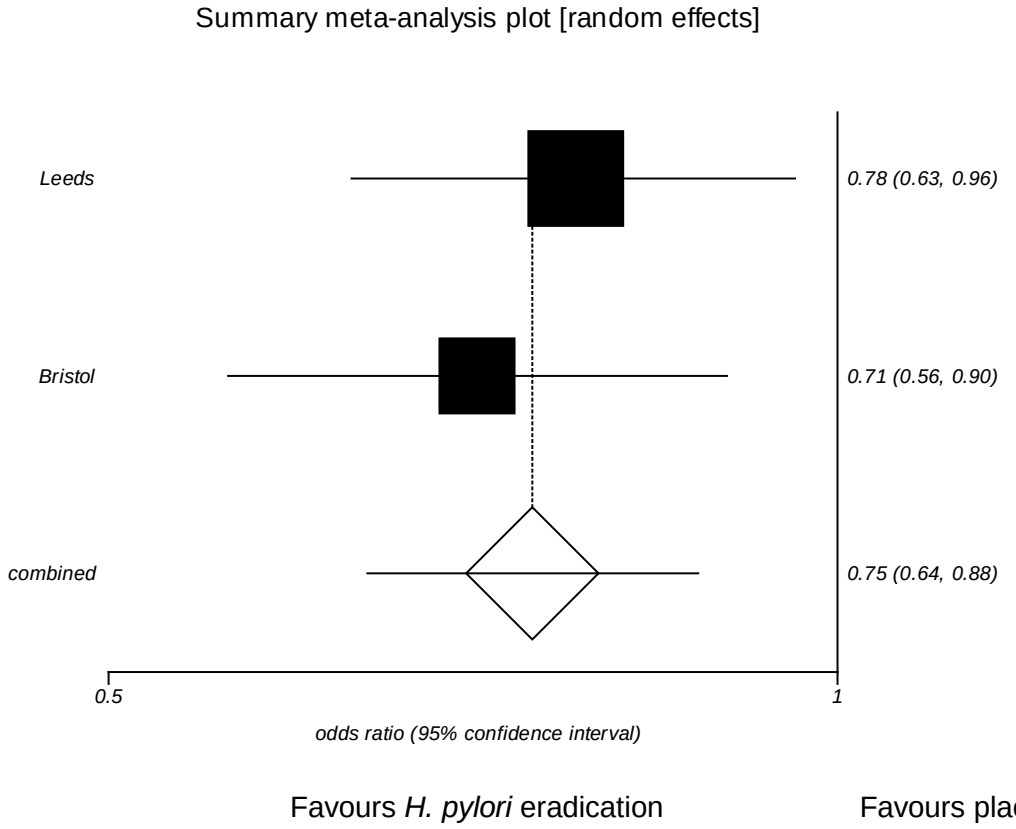
Table 3.3.2. Summary of the methodology of economic models for population *Helicobacter pylori* screening and treatment to prevent gastric cancer

Reference	Type of model	Systematic review of literature?	Discounting	Method of incorporating uncertainty	Type of analysis	Dyspepsia cost savings considered?
18	Markov	No	3%	One-way sensitivity analysis	C/LYS	No
19	Markov	No	3%	One-way sensitivity analysis	C/LYS	No
20	Markov	No	3%	One-way sensitivity analysis	C/LYS	No
21	Markov	No	5%	One- and two-way sensitivity analyses	C/LYS	Yes
22	DES	No	6%	Probabilistic	C/LYS	Peptic ulcer only
23	Markov	No	3%	Probabilistic	C/QALY	No
24	Markov	No	3%	Probabilistic	C/LYS	No
25	Markov	No	3%	One-way sensitivity analysis	C/LYS	No
26	Markov	No	3%	Probabilistic	C/QALY	No

C, cost; DES, discrete event simulation; LYS, life-year saved; QALY, quality-adjusted life-year.

Two randomized controlled trials have evaluated the reduction in dyspepsia in *H. pylori*-positive subjects randomized to eradication therapy or placebo in the context of a population screen-and-treat strategy [10, 27]. Both studies were in the United Kingdom in approximately 3900 subjects, and each showed a significant reduction in dyspepsia symptoms in those randomized to eradication therapy at 2 years, with overall 25% reduction in odds (Fig. 3.3.1). Interestingly, neither study showed an increase in reflux symptoms [10, 28]. This is important as some studies have suggested that *H. pylori* eradication may increase the risk of gastro-oesophageal reflux, and this would be a major concern for a population screen-and-treat programme.

Fig. 3.3.1. Impact of population *Helicobacter pylori* screening and treatment on dyspepsia after 2 years. Data are from two studies in the United Kingdom, one in Leeds (Moayyedi et al. (2000) [10]) and one in Bristol (Lane et al. (2006) [27]).



This reduction in dyspepsia is likely to translate into lower health-service-related dyspepsia costs. The first of the above-mentioned studies reported that *H. pylori* screening and treatment given to subjects aged 40–49 years was cost saving at 10 years due to reduction in dyspepsia costs associated with the strategy [29]. The other population *H. pylori* screening and treatment trial, evaluating a wider age range of subjects, also found that *H. pylori*-positive subjects randomized to eradication therapy had a significantly lower number of primary care visits for dyspepsia [30]. It is important to emphasize that savings related to dyspepsia in the community have not often been considered in cost–effectiveness models, and none have used data from randomized controlled trials. Considering these cost savings may make such programmes even cheaper and mean that population *H. pylori* screening and treatment could be cost-effective in a wide variety of settings. Another aspect that has not been considered is the health benefits of population screening and treatment in terms of prevention of morbidity and mortality from bleeding peptic ulcer [31]. This, again, is likely to make any population *H. pylori* screening and treatment programme even more cost-effective.

Other limitations of the current health economic literature are that less than half of studies conduct a probabilistic analysis to evaluate the uncertainty in the data modelled, and even fewer present the data in a way that is meaningful to health-care decision-makers. One study that did present the data in this way reported that there is 75% certainty that population *H. pylori* screening and treatment is cost-effective for the Singaporean Chinese population using a threshold of US$ 50 000 per life-year saved [23]. This type of analysis is needed for other populations using other assumptions relevant to local populations. Most models evaluated screening programmes from a third-party payer's perspective. Although this is a valid approach, it could be argued that societal costs are more important for a

national screening programme. One economic model did take this perspective and also found population *H. pylori* screening and treatment to be cost-effective [24]. Finally, it is important to emphasize that nearly all models reported benefit in terms of life-years saved. This will overestimate the benefit of the programme as most of the life-years saved will be in the elderly, many of whom have other comorbidities that may limit their quality of life. The standard economic approach to this problem is to evaluate benefit in terms of quality-adjusted life-years (QALYs). Two studies, with similar methodologies and the same research team, did report benefit in terms of QALYs and did find population *H. pylori* test and treat cost-effective in both Singapore and Canada [23, 26]. Assigning QALYs at a given age can be a challenge as data in some populations are lacking, but this approach should be used more in modelling exercises in this area.

3. Conclusion

Current data would suggest that population *H. pylori* screening and treatment is feasible and cost-effective in preventing gastric cancer. Future economic models should use current systematic review data on the efficacy of *H. pylori* eradication to prevent gastric cancer. These models should also incorporate health-care-related savings due to dyspepsia reduction in the population and should assess health benefits in terms of QALYs. Uncertainty in the data should be evaluated using probabilistic analyses, and there is no model currently published that fulfils all these criteria.

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Annex 1. Search strategy for economics of *Helicobacter pylori* test and treat to prevent gastric cancer

1. *Helicobacter pylori*.mp. or *Helicobacter pylori*/
34 734

2. Gastric Cancer.mp. or Stomach Neoplasms/
78 492

3. Markov Chains/ or Models, Statistical/ or Markov.mp.
84 830

4. Economics, Medical/ or Cost-Benefit Analysis/
69 498

5. 3 or 4
150 856

6. 1 and 2 and 5
53

Chapter 3.4

The role of biomarkers of gastric cancer risk to target interventions

Javier Torres

Gastric cancer is currently the fifth most common malignancy in the world, behind cancers of the lung, breast, and colorectum, and with about 1 million new cases in 2012. Gastric cancer is also the third leading cause of cancer death in both sexes worldwide, with an estimated 723 000 deaths in 2012. More than 70% of these deaths occurred in developing countries, mostly in Asia and Latin America, and this figure is expected to increase, largely due to ageing of the populations in low- and middle-income countries. Gastric cancer is one of the leading cancers in many areas of Latin America, particularly in Central America and in the Andean countries.

1. Gastric cancer and *H. pylori* infection

The main risk factor for distal gastric cancer is infection with *Helicobacter pylori*, the first bacterium recognized as oncogenic [1]. *H. pylori* infects the gastric mucosa during childhood and establishes a chronic long-lasting inflammation that, if not treated, remains for decades. This persistent inflammation of the gastric mucosa will eventually cause gastric cancer in less than 3% of the infected individuals. An improved understanding of the natural history of the infection will enable the development of tests for an early diagnosis, or even better, the identification of patients at risk of developing gastric cancer. *H. pylori* colonizes the gastric mucosa, where it expresses an array of proteins that allow it to establish a persistent infection. Most of these factors interact with receptors in gastric epithelial cells to signal different cellular pathways that eventually lead to changes in the expression of genes involved in inflammation, cellular proliferation, invasion, and metastasis. Inflammation may also lead to chronic long-lasting exposure to reactive oxygen species and reactive nitrogen species, which cause DNA damage, genetic instability, and gene mutations, eventually leading to carcinogenesis. Decades of gastric inflammation may also induce epigenetic changes, such as methylation of genes, that would also lead to carcinogenesis. Virulence factors such as CagA, VacA, or LPS interact and modulate cellular signalling pathways (c-MET, SHIP, SRC, PAR1, NF-κB, COX-2, etc.) to induce a pro-inflammatory response, or alter tight junctions and cell polarity, and finally favour metastasis [2]. A pro-inflammatory response would result in increased mucosal levels of cytokines such as IL-1 or IL-8, TNF-α, or PGE2 [3, 4].

2. Considerations

All the bacterial or cellular factors described above represent potential biomarkers for risk, early diagnosis, or prognosis for gastric cancer, but there are important considerations in the selection of candidates. The utility of biomarker tests is optimized when they are applied in the right context. The association of genetic polymorphisms with gastric cancer risk largely depends on ethnicity, and thus it should be determined which single-nucleotide polymorphisms (SNPs) apply to a population before using them as biomarkers. Age is also important, and most markers for unregulated inflammatory response, such as altered microRNA (miRNA), DNA methylation, or altered glycomics and proteomics, would be more useful in older adults, when precancerous lesions are more likely (probably after age 40 years). Infection with *cagA*-positive strains was found to be significantly associated with precancerous lesions in individuals with type A blood group, but not in those with other ABO groups [5]. In a patient with family history of gastric cancer, “test and treat” for *H. pylori* infection would be advised, even in the absence of biomarkers. Gastric cancer is a multifactorial disease, and a proper combination of markers, including host genetic factors

(e.g. polymorphisms in inflammation-associated genes, age), *H. pylori* virulence factors (e.g. *cag* pathogenicity island, *cagA* and *vacA* genes), or environmental factors (e.g. diet, salt intake), may improve their utility to identify patients at risk.

3. The challenge for biomarkers in cancer

After decades of investigation for biomarkers useful in cancer, very few biomarkers have become useful in the clinic; the Early Detection Research Network of the United States National Cancer Institute (http://edrn.nci.nih.gov/) is an organization that promotes and supports studies for the discovery and validation of cancer biomarkers, and after hundreds of millions of dollars have been invested for about 10 years, none of the biomarkers studied have yet been approved for clinical use [6]. In fact, very few cancer biomarkers already in clinical use have high sensitivity and specificity, and for many of them, whether they really improve cancer outcome is currently questioned. In the coming decades, the incidence of gastric cancer in developing countries will increase, largely because of ageing of the population [7]. It is in these countries where identification of patients at risk and early disease detection are most needed, but it is also in these countries where resources for health are limited. Thus, biomarker tests for these regions must be non-invasive, simple, and cheap, which makes the task of discovery and development even harder [8].

4. Biomarkers for distal gastric cancer: *H. pylori*

A major difference between gastric cancer and other tumours is that a bacterial infection is the strongest risk factor for most of the cases, initiating the cascade of events that set up the initial conditions for other risk factors to further increase the risk of cancer development. The importance of this is that, hypothetically, by eradicating the infection with antimicrobial therapy, it would be possible to prevent most of the gastric cancer cases; unfortunately, this is not that simple. *H. pylori* infects more than 50% of the world's population, and in developing countries the prevalence is as high as 80% in adults [9]; still, less than 3% of those infected will ever develop gastric cancer. In addition, it has been argued that early infection may protect against autoimmune diseases during adulthood, probably by "training" the immune system [10, 11]. Furthermore, evidence has been presented to show that eradication of *H. pylori* increases the risk of oesophageal cancer [12]. Still, *H. pylori* is estimated to increase the risk of gastric cancer 3–6-fold [13, 14], and detection of the infection is then a marker of risk. Several studies have found that serological detection of *H. pylori* may be improved if combined with the serological detection of virulence factors like CagA, particularly for pre-neoplastic lesions [14–18]. A meta-analysis concluded that searching for CagA in addition to *H. pylori* infection may confer additional benefit by identifying patients at greater risk for gastric cancer [19]. However, CagA-positive strains are so common in Asia that its detection may not help to distinguish patients at increased risk for gastric cancer [20, 21]. Recently, a multiplex assay to detect antibodies to several other *H. pylori* proteins has been tested in a high-risk region of China, and showed that assessment of additional virulence factors may improve the ability to identify patients at risk for gastric cancer [22].

5. Regional gastric cancer mortality rates

The regional gastric cancer mortality rate is a geographical marker for populations at risk and an important criterion in the selection of populations at greater need of targeted intervention programmes. According to GLOBOCAN 2012 estimates, Asia, eastern Europe, Central America, and Andean countries in South America are the regions with the highest mortality rates [23]. Large clinical trials for eradication in populations with high mortality rates have been performed in China and Colombia [24, 25]; both showed a significant effect in preventing development of cancer and in regression of pre-neoplastic lesions. Even within high-risk countries, screening in high-risk groups might be more effective, as shown in a study in Singapore, where screening limited to Chinese men aged 50–70 years [26] was

highly cost-effective and the endoscopic screening of 199 000 subjects prevented 743 gastric cancer deaths and saved 8234 absolute life-years.

6. Pepsinogens

It is accepted that in the case of intestinal gastric cancer, gastric atrophy represents the earliest pre-neoplastic lesion detectable [27, 28], and histological detection after endoscopy and biopsy has been used in the identification of such cases. Pepsinogen I (PgI) and pepsinogen II (PgII) are produced by cells from the gastric mucosa, and gastric atrophy alters the production of pepsinogens, which can be measured in serum [29]. Accordingly, serological levels of PgI and PgII have been shown to be a reliable marker for atrophy in the gastric mucosa, and the pepsinogen test is currently considered to be a "serological endoscopy" [30]. Most studies to date on the utility of the pepsinogen test have been performed in Asian countries, where evidence shows that it is a useful serological test to identify patients with gastric atrophy. In a pooled analysis of Japanese studies in a total of about 300 000 individuals, the pepsinogen test resulted in a sensitivity of 77% and a specificity of 73% [31] for gastric atrophy, suggesting that the test is reliable as a marker for the identification of individuals at risk of progression to intestinal gastric cancer. Additional studies have shown that a PgI/II ratio > 3.0 results in a sensitivity of 93% and a specificity of 88% for the absence of atrophy, and patients with these values might be excluded from further screening studies [32]. The utility of the test might be improved if combined with serology for *H. pylori* infection. In a follow-up study in 9000 Japanese individuals, those with both *H. pylori* positivity and low pepsinogen levels had a risk of developing gastric cancer 6–8 times that of those negative for both tests. Furthermore, individuals negative for *H. pylori* but positive for pepsinogens showed a higher risk than those only *H. pylori*-positive, presumably because in advanced atrophy *H. pylori* can no longer grow, and disappears [33]. The synergistic effect of *H. pylori* and pepsinogens has been confirmed in longitudinal cohort studies. A study in 2859 Japanese individuals determined gastric atrophy by the pepsinogen test (PgI ≤ 70 ng/mL and PgI/II ≤ 3.0) in a basal sample and followed up individuals for a median of 9.3 years. Basal serological atrophy increased the risk of developing gastric cancer (hazard ratio [HR], 3.74; 95% confidence interval [CI], 2.13–6.57), and the risk increased when both pepsinogens and *H. pylori* were positive (HR, 11.23; 95% CI, 2.71–46.51); still, the highest risk was in the group who were positive for pepsinogens but negative for *H. pylori* (HR, 14.81; 95% CI, 2.47–88.8) [34]. Another study in 4655 asymptomatic Japanese individuals followed up for 7.7 years reported that in contrast to the group who were *H. pylori*-negative and pepsinogen-negative, patients who were *H. pylori*-positive and pepsinogen-negative had a hazard ratio of 7.13, but those who were *H. pylori*-positive and pepsinogen-positive had a hazard ratio of 14.85 to develop gastric cancer during the follow-up period; the group who were *H. pylori*-negative and pepsinogen-positive had a hazard ratio of 61.85 [27]. Similarly, a study in 1501 Chinese individuals, followed up for 14 years, found that abnormal pepsinogen levels were associated with increased risk of gastric cancer (relative risk [RR], 4.22; 95% CI, 1.91–9.33), but in individuals with both *H. pylori* infection and abnormal pepsinogen levels, risk of developing gastric cancer was even higher (RR, 27.46; 95% CI, 3.34–225.4) [35].

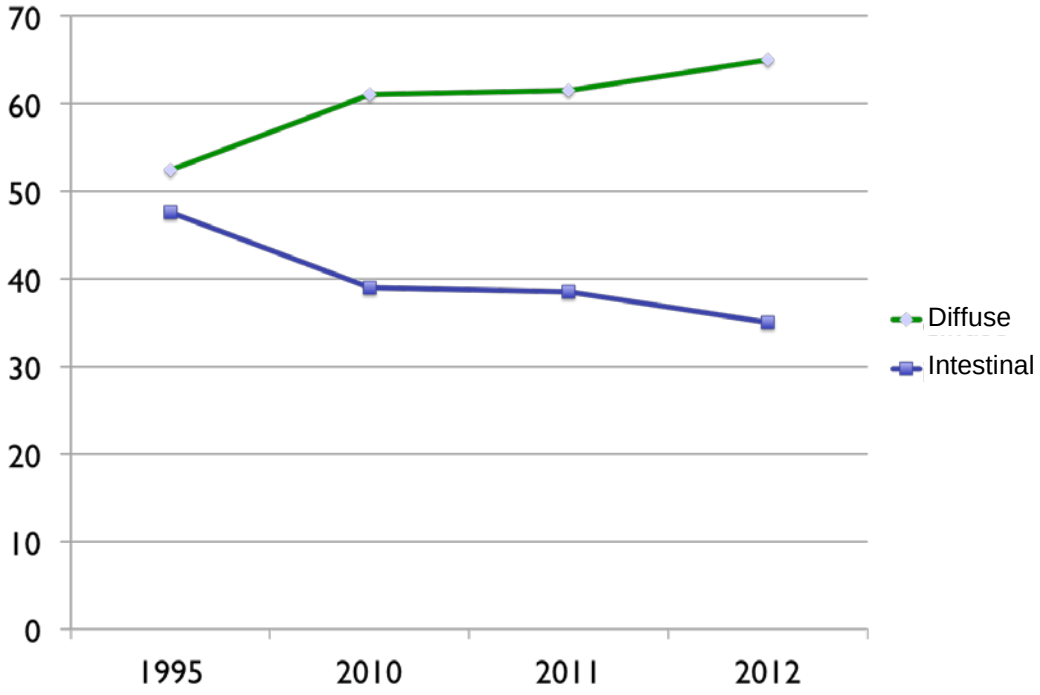
Limited studies have evaluated pepsinogen levels in countries outside of Asia. One performed in Finland screened 22 436 men by PgI level, with a cut-off value of PgI < 25 ng/mL [36]. The study found 2196 individuals with low PgI levels, and endoscopy was performed in 1344 of them, finding moderate to severe atrophic corpus gastritis in 78%. In contrast, in 136 men with PgI > 50 ng/mL, only 2.2% presented atrophic gastritis. Among the 1344 individuals with low PgI levels, neoplastic lesions were found in 63, and early cancer in 7; these were cured by surgical removal, showing the importance of early detection to prevent death. Pepsinogen levels were also validated as serum biomarkers in a study that included a subsample of 284 patients from the Eurohepygast cohort [37]. In that study, only the PgI/II ratio was useful to identify patients with atrophy, and a cut-off value of 5.6 showed

a sensitivity of 65% and a specificity of 77.9% for *H. pylori*-related corpus-predominant or multifocal atrophy. The association of low levels of PgI with gastric cancer rates was studied in 17 populations (mostly European), and it was found that low PgI levels were associated with areas of high rates of gastric cancer [38]; this association was observed in men but not in women. A study nested in the European Prospective Investigation into Cancer and Nutrition evaluated 233 gastric cancer cases diagnosed after enrolment and 910 controls; atrophic gastritis was considered when basal PgI levels were < 22 ng/mL [39]. PgI levels < 22 ng/mL were found in all gastric cancer patients, with an odds ratio of 3.3, which in the case of non-cardia gastric cancer increased to an odds ratio of 6.5. In cardia gastric cancer cases with low PgI levels, the risk increased to an odds ratio of 11.0. A study in Thailand reported that patients with gastric cancer presented lower PgI/II ratios than patients in the gastritis control group (odds ratio [OR], 2.3; 95% CI, 1.10–4.80) [40]. These studies indicate that the pepsinogen test accurately detects gastric cancer, due to the fact that most patients still present with gastric atrophy [41].

Few studies have been performed in Latin America, and most of them with a small sample size. In Mexico, a study in 205 patients identified chronic atrophic gastritis by histology in 70% of the cases, and PgI < 25 ng/mL identified those cases with a specificity of 100% but a sensitivity of only 6%, whereas PgI/II < 2.5 had a specificity of 96% but a sensitivity of 14% [42]. In that study, serology for CagA resulted in a sensitivity of 83% and a specificity of 41%. In contrast, a study in Costa Rica, a country with one of the highest mortality rates for gastric cancer, conducted in 501 dyspeptic patients reported that PgI/II < 3.4 resulted in a sensitivity of 91.2% but a positive predictive value as low as 11.2% to identify atrophic body gastritis [43]. The study also suggested that serology for CagA antibodies may improve the efficacy to detect atrophic gastritis. Differences between these two Latin American studies are that the gastric cancer mortality rate in Costa Rica is about 2.6 times that in Mexico, and that in Mexico the study was performed in asymptomatic subjects, whereas in Costa Rica dyspeptic patients were included. Still, the contrasting results between the two countries are hard to explain. In another study, conducted in Mexico in 180 healthy volunteers, atrophy was measured in multiple biopsies from antrum and corpus. The performance of PgI/II ratio varied according to the cut-off value; with a cut-off value of 6.7, the test showed a sensitivity of 75% and a specificity of 71.2%, whereas a cut-off value of 3.2 resulted in a sensitivity of 25% and a specificity of 95.7% [44]. Thus, more studies are needed in Latin America to better establish the performance of the test and to define cut-off values for the population.

The use of the pepsinogen test has some limitations that need to be considered. Since the test detects atrophic gastritis, it is not effective for screening of diffuse gastric cancer, and performance would vary depending on the proportion of diffuse gastric cancer in the population. This is important because in countries with the highest gastric cancer mortality rates, like Honduras, the proportion of the diffuse type in relation to the intestinal type seems to be increasing [45]; this tendency has also been observed in Mexico (Fig. 3.4.1) and Paraguay (J. Torres, unpublished observations). Also, in regions with low gastric cancer incidence, which is the case in many countries, the test would have a low positive predictive value [46].

Fig. 3.4.1. Trends in proportion (%) of diffuse and intestinal gastric cancer in Mexico (1995–2012).



The prevalence of pre-neoplastic lesions would also affect the performance of the test. A systematic review of the prevalence of intestinal metaplasia in 29 countries on five continents found that prevalence of intestinal metaplasia ranges from 3% in Argentina to 55% in New Zealand [47], i.e. a difference of almost a factor of 20 between the country with the lowest and the country with the highest prevalence. Autoimmune diseases can also cause chronic atrophic gastritis, like when anti-gastric parietal cell antibodies (APCA) are present. This was addressed in a study in 9684 Germans, where pepsinogens, APCA, and *H. pylori* antibodies were measured in serum [48]. Atrophic gastritis was diagnosed with a low PgI/II ratio, and the study showed a significant correlation between low PgI/II and APCA, a correlation that was even stronger in *H. pylori*-negative subjects (OR, 11.3) than in *H. pylori*-positive patients (OR, 2.6), illustrating that the pepsinogen test may also detect gastric atrophy not associated with *H. pylori* infection. The Asia-Pacific conference stated with moderate agreement that “low pepsinogen level and low PgI/II ratio may be useful as a marker to identify populations at high risk for gastric cancer” [49], whereas the European guidelines for the management of precancerous conditions stated, also with moderate agreement, that “serum pepsinogens levels can predict extensive atrophic gastritis”, although only 50% of the national societies mentioned that this would be applicable in their countries [50]. In addition, the pepsinogen test is still too expensive to use in community-based screening programmes, particularly in countries in Latin America and Asia that present the highest mortality rates. Still, pepsinogen tests currently represent the most reliable and practical test to screen populations and identify those who deserve close follow-up by means of invasive endoscopic methods.

7. Gastrin-17

Serum gastrin-17 (G-17) is produced by G cells in the antrum, and circulating gastrin has been suggested as a serological marker to distinguish antral atrophic gastritis from corpus atrophic gastritis [29, 51]. In particular, patients with atrophic antral gastritis present with low levels of circulating G-17. However, the relationship between G-17 and gastric physiology is complicated; *H. pylori* may induce a pan-gastritis, and when atrophy affects the body, it

usually also affects the antrum, so that in *H. pylori*-positive patients, a low G-17 level is associated with atrophy in both antrum and corpus [29]. The G-17 level increases substantially in gastric cancer and does not help to distinguish early from advanced cancer [52]. Gastrin circulates as several bioactive peptides, and all need to be measured for a proper diagnosis; however, available antibodies fail to efficiently identify all forms. Other important technical drawbacks are that G-17 has a very short half-life and that available commercial kits vary extensively in their performance, with more than half displaying inaccurate performance [53]. Finally, it should be considered that abnormal gastrin levels occur also in other gastrinomas, such as Zollinger–Ellison syndrome. Considering the above and the fact that adding G-17 to the pepsinogen and *H. pylori* tests does not significantly improve efficacy, G-17 would not be recommended for screening programmes.

8. Current national programmes in Asia

Japan and the Republic of Korea, the Asian countries with the highest gastric cancer mortality rates, have national or regional screening programmes to identify early gastric cancer cases. Japan uses barium X-ray as a government-sponsored nationwide programme in asymptomatic individuals older than 40 years. In the Republic of Korea, the National Cancer Screening Program recommends biennial screening for individuals older than 40 years, with direct upper-gastrointestinal series or endoscopy. In China, there is no nationwide screening programme, and early detection relies on opportunistic screening; also, barium-meal and serum pepsinogen tests are not commonly used because of cost and availability [54].

9. Novel approaches

There are several recent studies searching for markers that may distinguish normal individuals from those with pre-neoplastic lesions, which take advantage of what is being learned about the natural history of gastric cancer. Although they are still far from clinical use or from being recommended in population screening programmes, such markers should be considered for studies in large groups in regions with high gastric cancer mortality rates, particularly in Asia and Latin America, to better elucidate their potential use in a particular population.

The gastric inflammation caused by *H. pylori* induces the release of several pro-inflammatory mediators, among which the most studied include IL-1β, IL-8, TNF-α, IL-10, and IL-6 [3, 4]. A study in 226 consecutive patients, 150 of whom were receiving acid inhibitory treatment for reflux disease, found that serum IL-8, IL-6, and IL-1β levels were significantly higher in patients with atrophic gastritis [55]. The authors of that study constructed an index using the IL-8-to-pepsinogen ratio and reported that this index was significantly better than serum gastrin or pepsinogen levels alone at correctly classifying atrophic gastritis cases. A recent study also showed that high levels of IL-8 were significantly associated with risk of gastric cancer (OR, 2.1), although increased levels of IL-1β, IL-2, IL-4, IL-6, IL-10, TNF-α, or IFN-γ were not [56]. Many studies have looked for polymorphisms in inflammation-related genes, among which IL-1β and its antagonist IL-1RN have been extensively studied, although with conflicting results. A meta-analysis found a consistent association of the IL-1β-511 SNP with gastric cancer in Caucasians but not Asians [57], whereas another meta-analysis reported that this SNP was associated with the intestinal but not the diffuse type of gastric cancer [58]. Still, another recent meta-analysis failed to identify any significant correlation of the SNPs in both IL-1β and IL-1RN with gastric cancer [59]. Studies in a Latin American population have also found a lack of association of IL-1β with gastric cancer, although genotypes TNF-β-252G/G and HSP70-1C/G were found as risk markers for gastric cancer [60]. Polymorphism in IL-8 has also been reported to be associated with gastric cancer risk, and an SNP in the promoter -251A was reported as associated with risk of intestinal gastric cancer, and the -251T SNP as associated with risk of diffuse gastric cancer [61]. A recent

meta-analysis concluded that the IL-8-251 AA genotype is associated with risk of gastric cancer, particularly of the intestinal type, in Asian populations but not in other groups [62]. IL-10 as a modulator of inflammatory mediators plays a major role in inflammation-driven gastric cancer, and SNPs in the gene have been studied in gastric cancer. In fact, meta-analyses have found that IL-10-592 AA [63] and IL-10-819 TT [64] are associated with a reduced risk of gastric cancer in Asian populations.

The study of the role of miRNAs in the regulation of gene expression is an expanding field, and cancer is not the exception. In cancer development, miRNAs may function as oncogenes or as tumour suppressor genes since they regulate cell proliferation, apoptosis, differentiation, and even inflammation, all important in the genesis of gastric cancer. The miRNAs can help identify individuals at risk, as exemplified in Japanese [65] and Chinese [66] populations, where the rs2910164 (G > C) SNP in miR-146a was associated with susceptibility to gastric cancer. SNPs in miR-196a-2 [67], miR-27a [68], and miR-378 [69] have also been found to be associated with susceptibility to gastric cancer in Chinese populations. The analysis of circulating miRNA offers a promising non-invasive alternative to test for susceptibility to gastric cancer, although it should be considered that a single polymorphism may be associated with risk for different tumours and candidates should be evaluated for acceptable specificity and sensitivity. Clearly, much has been learned about genetic polymorphisms as risk factors for gastric cancer in Asia, particularly Japan and China, but an effort should be made to study this in other human groups with high gastric cancer mortality rates, including other countries in Asia and Latin America. Another factor to consider is that when analysing the utility of gene alleles as biomarkers for gastric cancer risk in different human groups, it should be noted that allele frequencies vary widely across populations, which may affect the statistical power of allele differences to detect an effect on risk [70].

The human intestinal microbiota has been shown to play a major role in health and disease, and its study has been suggested as a potentially useful biomarker to identify individuals at risk of diseases like diabetes, obesity, inflammatory bowel disease, or even colon cancer [71]. The study of microbiota in the stomach may also show some utility as a marker of risk or prognosis for gastric cancer. It has also been suggested that when *H. pylori* infection leads to atrophy and hypochlorhydria, the gastric environment becomes more permissive to colonization with other bacteria, which in turn may increase the inflammatory and immune response of the gastric mucosa, and modulate mucosal damage and the development of pre-neoplastic lesions. Initial attempts to characterize microbiota in gastric cancer samples have reported no significant differences with dyspeptic controls [72]. Given the diversity of microbiota structure across individuals and across populations, regional studies are needed to gain insight into its diversity in each population.

Several studies have been performed on the identification of candidate proteomic and glycomic biomarkers circulating in plasma, which report molecules able to distinguish gastric cancer or pre-neoplastic lesions from gastritis [73–76], and these constitute potential biomarkers for use in the screening of individuals at risk for gastric cancer.

10. Other considerations

It should be kept in mind that gastric cancer is a multifactorial disease and that a proper combination of markers may improve their utility to identify patients at risk. The utility of a biomarker test is optimized when it is applied in the right context. The association of genetic polymorphisms with gastric cancer risk largely depends on ethnicity, and thus it should be determined which SNPs apply to a population before using them as biomarkers. Age is also important, and most markers for unregulated inflammatory response, altered miRNA, DNA methylation, altered glycomics or proteomics, would be more useful in adult ages when precancerous lesions are more likely (e.g. after age 40 years). Blood group background may

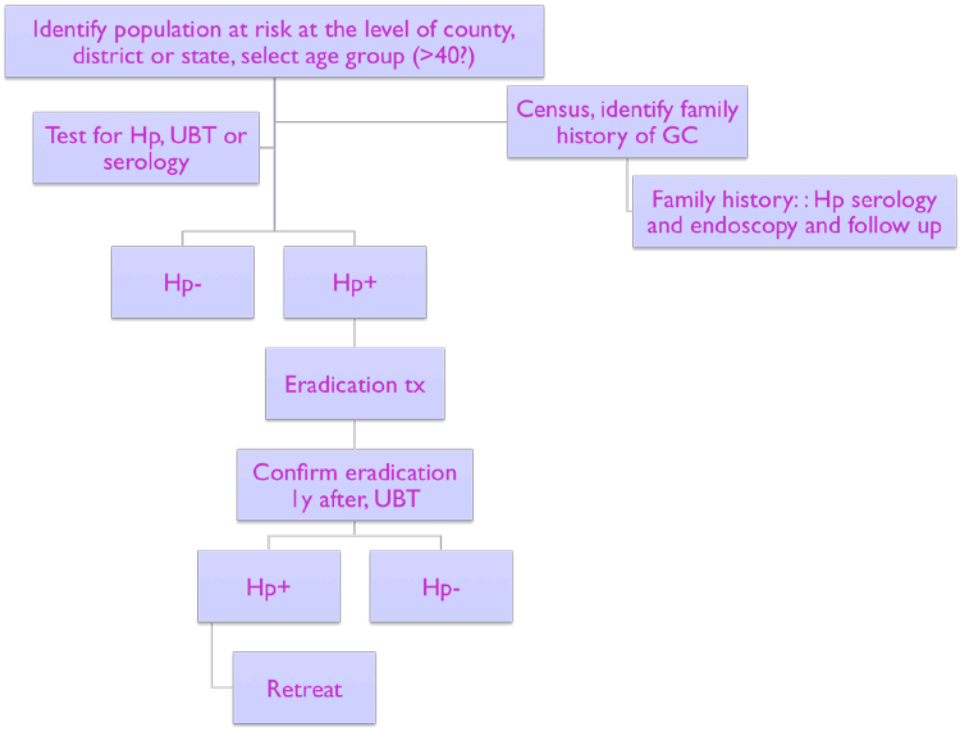
also influence outcome; infection with *cagA*-positive strains was found to be significantly associated with precancerous lesions in individuals with type A blood group, but not in those with other ABO groups [5]. At present none of the suggested biomarkers for gastric cancer has been approved for clinical use, and they are even farther from being ready for use for large-scale screening. However, in a patient with family history of gastric cancer, “test and treat” for *H. pylori* infection would be advised, even in the absence of other biomarkers.

When planning for a community screening programme, important points to consider are that the test should be validated for accuracy and high predictive value in the population being studied, and it should be non-invasive, simple, cheap, and accessible. The serological test for *H. pylori* is widely available and inexpensive, and serological tests for gastric atrophy are also available, and although not yet inexpensive, they offer the opportunity to test both in the same minimally invasive sample.

11. Suggested strategies for Latin America

In Latin America, no population strategies have been suggested so far, despite the fact that the region contains areas with gastric cancer mortality rates among the highest in the world. A first approach should consider that the pepsinogen test has not proven as efficient in Latin America as in Asia to detect atrophy. Also important is the reported increasing trend in different countries of the diffuse type of gastric cancer, for which no precancerous lesions have been described yet. Still, an initial selection by country and by district or county might help better target screening programmes. Latin America is a region with limited resources for public health, and an initial screening should be simple and cheap. Probably, after initial selection of districts, screening could be performed in adults older than 40 years for *H. pylori* using either serology or the urea breath test, and then eradication treatment could be given, as suggested in Fig. 3.4.2.

Fig. 3.4.2. Suggested minimal screening in the Latin American region. GC, gastric cancer; Hp, *Helicobacter pylori*; UBT, urea breath test; tx, therapy; y, year.



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Chapter 3.5

Current and ongoing research projects related to gastric cancer prevention: perspective of the United States National Cancer Institute

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Gastric cancer rates make it the third leading cause of cancer death worldwide, and new diagnoses may top 1 million per year in the near future. In the USA, as in many economically developed countries, total gastric cancer incidence rates continue a steady decline, with a concomitant decrease in gastric cancer mortality. In contrast to this overall encouraging trend, severable notable concerns remain. First, the incidence and mortality rates for gastric cancer have declined in all racial/ethnic groups, but Hispanic and non-White United States residents have rates almost twice those seen in non-Hispanic Whites. Second, the incidence rate trends for cardia gastric cancer may not have declined in parallel with those of non-cardia gastric cancer, but the difficulty of separating cardia and oesophageal adenocarcinoma makes this difficult to assess. Third, the declines in total gastric cancer may not be apparent in all age groups [1]. A significant increase in non-cardia gastric cancer incidence rates at certain subsites has been detected in United States Whites aged 25–39 years [2]. These findings demonstrate some of the remaining concerns about gastric cancer in the USA. But the United States National Cancer Institute (NCI) also has a commitment to advance cancer research globally, where gastric cancer remains a major cause of cancer death, and this is reflected in the recent formation of the NCI Center for Global Health (http://www.cancer.gov/aboutnci/globalhealth). The NCI financial commitment to gastric cancer research peaked in fiscal year 2009 at US$ 15.4 million (http://www.cancer.gov/researchandfunding/snapshots/stomach).

The NCI Intramural Research Program conducts many primary research projects in international settings (http://www.cancer.gov/researchandfunding/intramural), and this has been particularly true for gastric cancer. The intramural programme includes basic scientists, population scientists, clinical scientists, and translational scientists working in interdisciplinary teams. The programme conducts a wide range of gastric cancer studies, including studies of etiology (e.g. [3, 4]) and an expanding portfolio examining the role of Epstein–Barr virus [5, 6], but this chapter summarizes the recent activities of the NCI intramural programme that examine gastric cancer with a particular focus on prevention.

1. Extended follow-up of gastric cancer prevention trials

In 1985, NCI and the Cancer Institute, Chinese Academy of Medical Sciences initiated two companion randomized placebo-controlled intervention trials to test whether supplementation with vitamins and minerals could be used to prevent upper gastrointestinal cancer in a nutrient-deficient high-cancer-incidence population in Henan Province, China [7]. The larger trial (General Population Trial) included nearly 30 000 apparently healthy subjects aged 40–69 years and randomized them to one of four vitamin and mineral combinations using a partial factorial design such that one half of the subjects received each of the four interventions. The smaller trial (Dysplasia Trial) enrolled 3318 subjects who had previously been diagnosed with oesophageal dysplasia via balloon cytology. This method has relatively low sensitivity and low specificity [8, 9] but will result in a population group with higher-than-average cancer risk. The Dysplasia Trial used a non-factorial design to test the use a commercial multivitamin plus β-carotene. The intervention portion of both trials concluded in 1991, and the results were published at that time [10, 11]. All subjects remain under follow-up to this day, and the cohort has been used extensively to address numerous etiological

hypotheses. Recently, the trial was re-analysed after 10 years (General Population Trial) or 20 years (Dysplasia Trial) of additional follow-up, to assess the durability of the intervention effects and to test for any late occurring effects. At the end of intervention, the General Population Trial showed that a combination of selenium, α-tocopherol, and β-carotene significantly reduced the incidence of gastric cancer by 21% and total mortality by 9%. Re-analysis of the data after continued follow-up showed that this effect was highly durable and that even 10 years after supplementation ended, subjects were at 11% lower risk of developing gastric cancer [12]. Observational studies examining serum concentrations at study baseline suggest that selenium is the most likely agent to confer this benefit, since higher baseline selenium was associated with lower risk of gastric cancer [13], whereas β-carotene showed no association [14] and higher α-tocopherol serum concentrations were associated with elevated risk [15]. The Dysplasia Trial showed that multivitamins had no effect on cancer risk either at the end of the trial [11] or during extended follow-up [16].

The Peking University School of Oncology and NCI conducted a multifactorial intervention trial in 3365 subjects from Shandong Province, a region with extraordinarily high rates of gastric precancerous lesions and gastric cancer. The trial tested one-time *Helicobacter pylori* treatment and long-term use of vitamin or garlic supplements. The eradication therapy showed statistically significant decreases in the combined prevalence of severe chronic atrophic gastritis, intestinal metaplasia, dysplasia, and gastric cancer 5 years and 9 years after treatment, but there was no effect of the nutritional interventions [17]. Subsequent analysis after additional follow-up showed a significant reduction of gastric cancer incidence with *H. pylori* treatment and now revealed that the 7.3 years of treatment with vitamin C, vitamin E, and selenium significantly reduced mortality due to gastric and oesophageal cancer combined [18], a secondary trial end-point.

Beyond the important findings of the Shandong Trial on *H. pylori* eradication, these trials suggest that in some populations, likely those with deficiencies, nutritional interventions may be an effective method of reducing gastric cancer incidence. Fortification programmes for numerous vitamins and minerals are used in many parts of the world. Demonstration projects to test population-level fortification to prevent gastric cancer would provide further insight and may lead to important reductions in the incidence of this cancer.

2. *H. pylori* serology and cancer risk

Several cohort studies have been pursued to examine the strength of the association between *H. pylori* serology and gastric cancer in different settings. The results suggest that positive *H. pylori* serology carries greater apparent relative risk in the Finnish population, which has lower background infection rates [19], than in China, where the large majority of the population tests positive for evidence of past or current *H. pylori* infection [20]. Recently, some of the populations have been retested to assess whether use of a serological test that covers a broad array of antigens [21] can provide additional risk information.

Several areas of the world that have high rates of oesophageal squamous cell carcinoma (ESCC) also have high rates of gastric cardia adenocarcinoma. The risk factors for gastric cardia cancer in these areas tend to show some overlap with risk factors for ESCC and to be distinct from the apparently reflux-induced gastric cardia cancers in populations that have higher rates of oesophageal carcinoma, such as those in Europe, North America, and Australia. NCI has conducted *H. pylori* serology studies in Linxian, China, where gastric cardia cancer predominates 5:1 over non-cardia gastric cancer [20], and in the Shanghai Women's Health Study [22], where, as is more common in China and elsewhere, non-cardia cancer predominates 9:1 over cardia gastric cancer. In these studies, it was found that *H. pylori* seropositivity conveys similarly elevated risks for cardia and non-cardia gastric cancer [20]. This is quite distinct from the situation in Europe, North America, and Australia, where *H. pylori* seropositivity may be associated with lower risk of cardia cancer [19].

To fully assess the role of *H. pylori* in human health, NCI has also extended some of these serology studies beyond its original focus on gastric cancer. With the Linxian General Population Nutrition Intervention Trial cohort, the association of *H. pylori* seropositivity with ESCC was examined, and no association was observed [20]. And a similar null result was observed for ESCC in the Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort [23]. Other studies from NCI have examined the association of *H. pylori* seropositivity with pancreatic cancer, which showed mixed results [24, 25], and most recently with biliary tract cancer, which showed a substantially increased risk (unpublished data).

3. Other seromarkers for gastric cancer risk

In populations with high incidence rates, endoscopic screening programmes have the potential to reduce disease-specific gastric cancer mortality, but few health systems have the wherewithal to support endoscopic screening of all at-risk individuals. Therefore, serological markers have been of interest to allow for lower-cost triage of subjects who may be at the highest risk for gastric cancer. A large number of studies have tested the association between serum pepsinogen concentrations and gastric cancer risk in both cross-sectional and prospective studies, although there have been no randomized controlled trials of serum pepsinogens as a screening method that tested whether this can reduce mortality due to gastric cancer. NCI has examined serum pepsinogens in three prospective studies (the Nutritional Intervention Trial, the Shanghai Women's Health Study cohort, and the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort) and showed strong associations, similar to other groups. At least 13 groups have examined the association with gastric cardia cancer [26] and many dozens for non-cardia cancer [27], although many of these studies have not been prospective, which may be less informative with regard to the utility as an early detection method. It appears that serum pepsinogen I (PgI) concentration may be of greatest use in the few years before cancer diagnosis, but that serum pepsinogen II (PgII) concentration and PgI/II ratio may have independent value over a longer period [22, 28]. Furthermore, many previous studies have used dichotomization of pepsinogen concentrations as risk markers, but this may substantially reduce the predictive power of these markers, given the apparent linear association between the PgI/II ratio and gastric cancer risk [28].

If additional markers with independent predictive powers can be identified, the predictive power of these tests may be improved. Recently, NCI tested the association between upper gastrointestinal cancer risks and serum concentrations of ghrelin, a gastric hormone that may stimulate gastric acid, regulate energy balance, and control appetite. The study showed strong associations that are independent of pepsinogen concentrations for multiple upper gastrointestinal malignancies [29, 30]. Replication in additional studies will be crucial to test whether serum ghrelin should be added to future trials of gastric cancer screening methodologies.

4. Gastric cancer genetics

Hundreds of studies have examined whether common genetic variants alter gastric cancer risk. But the utility of hypothesis-driven testing of single-nucleotide polymorphisms has been called into question, and many reported associations have not been confirmed in subsequent studies [31]. Genome-wide association studies (GWAS) have dramatically improved the problem of non-replication. NCI is currently pursuing a comprehensive set of GWAS studies of upper gastrointestinal cancers in multiple ethnic groups. The first publication examined the top hits for ESCC and gastric cancer in a study of ethnic Chinese subject [32]. That study found that for populations in central China, a single genomic locus at 10q22 had the strongest association with risks for both ESCC and gastric cardia cancer, but

no association with non-cardia cancer. Several subsequent studies have confirmed this finding. Despite a relatively high odds ratio of 1.57 per allele for gastric cardia cancer in that study, common variants are unlikely to be used as a risk-stratifying exposure. The utility of common genetic variants for individual risk prediction has been explored in depth, and even in the situation where a large number of variants have been confirmed, these are unlikely to be useful for this purpose [33, 34]. The 10q22 genomic region harbours the *PLCE1* gene, which has been linked to altered risk of cancer at several sites and with different carcinogens in animal models. It remains possible that these associations will lead to additional etiological insights. A deeper examination of the data for cardia and non-cardia gastric cancer is in process with NCI collaborators from China and other parts of East Asia. NCI is also pursuing a GWAS for gastric cancer in subjects of European/Caucasian descent, and results will be published in the near future.

NCI laboratories have also explored other aspects of gastric cancer genetics, including a detailed examination of gene expression differences between cardia and non-cardia tumours [35]. In addition, microRNAs show promise as early detection markers or therapeutic targets, and some early work in characterizing gastric cancer miRNAs has been carried out at NCI [36].

5. Conclusion

This chapter has summarized current and ongoing research projects related to gastric cancer prevention in the NCI intramural portfolio. Promising results from nutritional intervention trials suggest that nutritional fortifications should be further explored for their potential to reduce the incidence of gastric cancer in addition to trials of *H. pylori* eradication. Gastric cancer screening may be appropriate in some populations, and work with serum pepsinogens and ghrelin suggests that serological markers could play a role in risk stratification as an adjunct to an endoscopic screening programme, but at present this strategy remains unproven through cancer control trials. Ongoing work at NCI in genetics has revealed interesting findings with regard to gastric cancer susceptibility, but the translation potential of this works remains to be developed. NCI intramural programme investigators continue work in gastric cancer prevention research and aim to make substantial contributions in reducing the suffering and death due to this all-too-common disease.

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Chapter 4.1

Current gastric cancer prevention strategies in Linqu County, a high-risk area in Shandong Province, China

Wei-Cheng You

Nearly 1 million new gastric cancer cases occur annually worldwide, 40% of them in China [1–3]. The prognosis of gastric cancer varies markedly by the stage of cancer; the 5-year relative survival rate can reach 90% for cancers detected in stage I but is less than 5% for those detected in stage IV [4]. Therefore, efforts have been made in China to detect gastric cancer in the early stages and develop primary prevention strategies.

There is a considerable geographical variation in the incidence of gastric cancer in China, with higher incidence rates in the northern and central regions of the country. Linqu County, in Shandong Province in north-eastern China, is a rural area with one of the highest gastric cancer incidence rates. The age-adjusted (world standard) mortality rate per 100 000 per year for gastric cancer in Linqu County was 70 for men and 25 for women in 1973–1975, accounting for 42% of the total cancer deaths in that region [5]. Since 1983, epidemiological studies of early detection of gastric cancer have identified risk factors including *Helicobacter pylori* infection, *H. pylori* virulence factors, genetic susceptibility, dietary factors, and interactions among risk factors associated with gastric cancer and precancerous gastric lesions. Based on the accumulated evidence, three intervention trials have been conducted in the high-risk population in Linqu County since 1995.

1. Early detection of gastric cancer in Linqu County, a high-risk area for gastric cancer

In 1989–1990, endoscopic mass screening was conducted among 3400 adults aged 35–64 years in Linqu County. A total of 13 gastric cancers were detected in this screening (detection prevalence rate, 0.38%), of which 64% were in stage I or II [6]. To assess whether endoscopic screening could be made more cost-effective by identifying subjects at highest risk, a study evaluated using the ratio of pepsinogen I to pepsinogen II levels (PgI/II) in serum as a risk marker, but it was found to not be sensitive or specific enough [7]. From 2008 to 2011, a further study examined the impact of PgI/II compared with direct endoscopy in the early detection of gastric cancer in 2290 residents aged 40–69 years in Linqu County, and found that endoscopy had a higher detection rate than PgI/II for gastric cancer (odds ratio [OR], 2.83; 95% confidence interval [CI], 1.34–5.98) and for early gastric cancer/high-grade intraepithelial neoplasia (OR, 2.12; 95% CI, 1.12–4.02). The sensitivity and specificity of PgI/II for detection of gastric cancer were 76.5% and 41.9%, respectively [8].

To identify more specific and sensitive biomarkers for gastric cancer detection, a human gastric carcinoma-associated antigen (MG7-Ag)-specific monoclonal antibody was developed [9]. A total of 2710 participants aged 35–64 years received an endoscopic examination. Serum samples were collected to detect MG7-Ag by serum-based immuno-polymerase chain reaction (immuno-PCR) assay. Among 2710 participants, 148 (5.46%) were determined to be MG7-Ag-positive. The sensitivity of the MG7-Ag immuno-PCR assay for the detection of gastric cancer was 77.5% (31 of 40 gastric cancer cases); the specificity was 95.62% (2553 of 2670 non-gastric cancer subjects), and the accuracy was 73.12%. A total of 24 gastric cancer cases were in stage I or II, of which 17 (70.8%) were MG7-Ag-positive [10].

Since the above-mentioned studies revealed that direct endoscopy is more effective than the PgI/II ratio scheme in detection of gastric cancer, 3018 residents of Linqu County aged 40–69 years were screened in 2013, and 38 (1.26%) cases of gastric cancer were detected. Among those gastric cancer cases, 78.95% were in early stages. Since 2008, a nationwide oesophageal cancer and gastric cancer screening programme by endoscopy has been implemented, supported by the Chinese Ministry of Health. A total of 110 counties in 26 provinces are enrolled in this project so far. In 2013, a total of 189 329 residents aged 40–69 years were screened by endoscopy, and 3040 (1.61%) oesophageal and gastric cancers were detected, of which 2201 (72.40%) of gastric cancer cases were in early stages.

2. Randomized controlled intervention trials to prevent gastric cancer by eradication of *H. pylori* in Linqu County, Shandong Province

Half of the world's population is infected with *H. pylori*. Accumulated evidence from epidemiological and experimental studies during the past three decades strongly suggests that *H. pylori* infection causes chronic inflammation of gastric mucosa and increases the risk of gastric cancer [11, 12].

A major risk factor for gastric cancer and its precursors in Linqu County is thought to be *H. pylori* infection; 72% of adults (68% of men and 75% of women) and 50–85% of children aged 3–12 years are infected with *H. pylori* [13, 14]. The prevalence of *H. pylori* infection is nearly 3-fold higher among children in Linqu County than among children in Cangshan County (also in Shandong Province), a low-risk area for gastric cancer.

In an endoscopic survey among 3400 adults in Linqu County, 33% had intestinal metaplasia and 20% had dysplasia [6]. The prevalence of *H. pylori* positivity varied markedly by histological status; the infection rate was 55%, 60%, 87%, and 78%, respectively, for those with superficial gastritis, mild chronic atrophic gastritis (CAG), severe CAG, and more advanced lesions. The odds ratio for each of the advanced lesions remained significantly higher after adjusting for sex, age, and cigarette smoking. The subjects with different gastric lesions were subsequently observed for 5 years, and the risk of progression to dysplasia and gastric cancer was 80% higher among subjects with *H. pylori* infection [15]. The prevalence patterns and longitudinal outcomes indicated that *H. pylori* infection primarily enhanced the transition from superficial gastritis to mild and then to severe CAG, consistent with an important role of *H. pylori* infection during the early stages of gastric carcinogenesis.

The effects of treatment of *H. pylori* infection on gastric cancer prevention and the histological changes of precancerous gastric lesions were studied in Linqu County. In late 1995, a total of 3411 subjects were randomized in a 2 × 2 × 2 factorial design according to their *H. pylori* status and received eradication therapy, vitamins plus minerals, or garlic supplements, or their placebos. After the treatment, repeated endoscopies were conducted in 1999 and 2003, and clinical follow-up continued until 2010. The trial yielded a statistically significant 40% decrease in the prevalence of severe CAG, intestinal metaplasia, and dysplasia as well as favourable effects on gastric cancer prevention. In total, 19 of 1130 subjects in the active *H. pylori* treatment arm were diagnosed with gastric cancer in 2003, compared with 27 of 1128 subjects in the placebo arm (OR, 0.60; 95% CI, 0.47–0.75) [16]. At the 15-year follow-up of this cohort, 34 gastric cancer cases had accrued in the treatment group compared with 52 in the placebo group, supporting that *H. pylori* eradication can reduce gastric cancer incidence (OR, 0.61; 95% CI, 0.39–0.96) [17].

From 2002 to 2006, another factorial-designed, randomized, and placebo-controlled trial was conducted in Linqu County to evaluate the effect of a selective COX-2 inhibitor (celecoxib), alone or combined with anti-*H. pylori* treatment, on the progression of precancerous gastric lesions. Of the 1024 participants aged 35–64 years who received the initial anti-*H. pylori* treatment or placebo, 919 completed the 24-month treatment with celecoxib or placebo. The

H. pylori eradication rate was 78.1%. Eight gastric cancer cases were diagnosed during the trial, and no significant difference in gastric cancer incidence was found between each treatment group and the placebo group. However, the proportion of regression of precancerous gastric lesions was significantly higher in the anti-*H. pylori* group than in the placebo group (59.3% vs 41.2%; OR, 2.19; 95% CI, 1.32–3.64) and was higher in the celecoxib group than in the placebo group (52.8% vs 41.2%; OR, 1.72; 95% CI, 1.07–2.76) [18].

Although these intervention trials support that eradication of *H. pylori* can reduce the incidence of gastric cancer, the sample sizes in the trials were relatively small and thus the results are unconvincing for community-based eradication. Based on a series of epidemiological studies over the past 30 years in Linqu County, a large population-based intervention trial with nearly 200 000 residents was launched in 2011 in this high-risk area for gastric cancer. The study is a collaboration between Peking University Cancer Hospital & Institute and the International Digestive Cancer Alliance/Technical University of Munich, Germany. The purpose of this study is to provide valid evidence whether gastric cancer can be prevented by the eradication of *H. pylori* in a population at high risk, so as to inform implementation of gastric cancer prevention in more areas with high risk of gastric cancer nationwide.

So far, this large intervention trial is proceeding well. The results of this study will have worldwide public health implications, especially for countries with a high incidence of gastric cancer. This trial is also expected to provide a great opportunity to evaluate the influence of *H. pylori* eradication on the incidence of gastro-oesophageal junction cancer. In addition, this trial will generate a biorepository for biomarker identification and molecular biological studies in the intermediate assessment of the impact of the intervention trial.

Because of the evidence from the two intervention trials in Linqu County and another trial in Changle, a consensus was generated by a small group of influential physicians and scientists in a Summit Workshop on Frontiers in Cancer Chemoprevention organized by the Chinese Academy of Science and held 17–18 October 2013. The eradication of *H. pylori* in the adult population of three or four counties with a high risk of gastric cancer in China is a priority in gastric cancer prevention and is highly recommended by this group. The costs of this examination of *H. pylori* infection and anti-*H. pylori* therapy in the selected population should be covered by the insurance of the Chinese government.

3. Conclusion

Evidence derived from studies during the past 30 years strongly supports *H. pylori* infection as a risk factor for gastric cancer, one of the leading causes of cancer death worldwide. Understanding how and when to undertake eradication of *H. pylori* for gastric cancer prevention, particularly in *H. pylori* prevalent areas and in populations at high risk for gastric cancer worldwide, is an important health priority that is currently being investigated in China.

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Chapter 4.2

Multicentre randomized study of *Helicobacter pylori* eradication and pepsinogen testing for prevention of gastric cancer mortality (Gastric cancer prevention study by predicting atrophic gastritis; GISTAR)

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Gastric cancer is an important global public health issue in eastern European regions, where the burden of the disease is substantial. The methods used for gastric cancer screening in Asia (Republic of Korea and Japan), including photofluorography (barium swallow) and upper endoscopy, are not suitable for organized cancer screening programmes outside East Asia because of the comparatively lower burden of the disease, cost issues, and acceptance.

Considering the incidence of gastric cancer in parts of the world other than East Asia (e.g. eastern Europe, South America) and the generally delayed diagnosis (with the exception of the Republic of Korea and Japan), non-invasive screening for gastric cancer or premalignant lesions that precede cancer development would be the approach of choice to decrease the burden.

There is sufficient epidemiological and experimental evidence that supports a causal link between *Helicobacter pylori* and gastric cancer. A population-based screen-and-treat strategy for *H. pylori*, the microorganism directly related to gastric cancer in high-risk areas, has been recommended in the guidelines in Asia [1] and Europe [2]. Two recent meta-analyses have suggested the cost–effectiveness of such an approach [3, 4].

However, to date no country with high gastric cancer incidence has included mass eradication of *H. pylori* in the setting of an organized screening programme; although *H. pylori* eradication started to be reimbursed in Japan from February 2013, it is not yet a part of the organized screening programme. There is still limited evidence from clinical trials to prove whether *H. pylori* eradication with antimicrobial therapy is the approach of choice in entire infected populations or only in selected groups to reduce the risk of gastric cancer, and whether eradication at advanced stages of atrophy is effective among these patients. In addition, the potential risks of wide antibiotic use have been studied less thoroughly in these studies.

During the past decades, substantial work either in Asia or Europe has been applied to study serological markers for identification of premalignant lesions in the stomach, in particular atrophy and intestinal metaplasia. Pepsinogens, the pro-enzymes of pepsin, are the most extensively studied biomarkers. Acceptable performance of pepsinogen tests to detect atrophy has been reported: sensitivity ranging from 66.7% to 84.6% and specificity ranging from 73.5% to 87.1% [5–8]. At the same time, substantially lower sensitivity for gastric cancer detection (36.8–62.3%) has been reported when the same cut-off values are used [9–11]. This would potentially result in missing about half of gastric cancer cases in a population-based screening setting.

Pepsinogen testing for the identification of subpopulations at increased risk for gastric cancer development has been recommended by the guidelines in Asia [1] and Europe [2, 12]; however, this method has not been accepted for organized screening in any country.

In recent years, there has been a growing interest in developing new biomarkers with potential application in gastric cancer screening. These efforts include, but are not limited to, proteomic and microRNA marker panels.

In addition, some less-traditional applications for gastric cancer have been suggested recently. Autoantibodies against tumour-associated antigens have been identified in several cancer types [13, 14], including gastric cancer. A 45-autoantibody signature was found to discriminate gastric cancer patients from healthy controls with 59% sensitivity and 90% specificity [15].

Volatile components detected either by gas chromatography coupled with mass spectroscopy or with nanosensor technology have also been studied in gastric cancer; a recent pilot study suggested the possibility of using a highly sensitive, cross-reactive, nanomaterial-based gas sensor to identify and separate volatile marker patterns between gastric cancer patients and those with benign gastric conditions with 89% sensitivity, 90% specificity, and 90% accuracy [16].

Yet, there is insufficient evidence available about how effective these different tests are as gastric cancer prevention strategies in organized cancer screening settings.

It is therefore proposed to conduct a multicentre randomized trial in Latvia, Belarus, and the Russian Federation, areas with a high burden of the disease, with the main objective of evaluating whether *H. pylori* screening followed by eradication in participants with positive results and endoscopy of those with serological evidence of atrophic gastritis can reduce gastric cancer mortality. The proposed trial will also investigate retrospectively whether biomarkers of chronic atrophic gastritis can select groups of subjects who require treatment to achieve comparable gastric cancer reduction. Ultimately, this study will have the potential to find effective prevention strategies through identifying appropriate target groups that could derive the most benefits from the treatment.

1. Key hypotheses

Hypothesis 1
H. pylori eradication in subjects positive for the infection with endoscopic follow-up of those with evidence of atrophic gastritis in the middle-aged population group in high-risk areas prevents gastric cancer mortality.

Hypothesis 2
H. pylori eradication is effective to prevent gastric cancer mortality even after the development of gastric mucosal atrophy.

Hypothesis 3
Certain subgroups (e.g. individuals with atrophy determined by pepsinogen testing, *cagA*-positive individuals) can derive more benefit from *H. pylori* eradication, and therefore could be targeted if general population eradication is not feasible.

Hypothesis 4
Combination of biomarker screening (e.g. pepsinogen testing, volatile marker testing) and upper endoscopy is an appropriate strategy in high-cancer-incidence areas to prevent cancer-related mortality.

2. Objectives

The aim of this study is to search for new intervention strategies to decrease mortality from gastric cancer in high-risk areas, either by testing in screening settings already established

methods or by searching for new biomarkers with potential application in gastric cancer screening.

The **primary objective** of the study is to determine whether *H. pylori* screening followed by eradication in positive subjects and endoscopic follow-up of those with serological evidence of atrophic gastritis reduces mortality from gastric cancer in a high-risk population among subjects aged 40–64 years.

The **secondary objectives** are:

1. To determine retrospectively whether biomarkers of chronic atrophic gastritis or other related conditions can select the group of subjects who require treatment to achieve gastric cancer reduction comparable to the primary objective.
2. To evaluate the rationale for volatile marker testing in exhaled breath for early identification of lesions in the stomach as well as other conditions related to increased risk.
3. To evaluate the role of diet, lifestyle factors, and environmental factors in the development of gastric lesions.
4. To evaluate the impact of *H. pylori* eradication on selected medical conditions potentially associated with the infection (e.g. obesity, inflammatory bowel disease, dementia, circulatory diseases, and oesophageal diseases).

3. Methods

Approximately 30 000 men and women will be recruited into a randomized study. Eligible subjects aged 40–64 years at study entry who are residents in areas with high gastric cancer incidence will be invited to participate in the trial by visiting one of the study clinics set up specifically for this trial.

For eligible participants who agree to participate and sign the informed consent, a risk factor questionnaire will be administered and a complete medical evaluation will be performed at baseline.

Participants will be randomly assigned to either Group 1 (50%) or Group 2 (50%). Among those assigned to Group 1, *H. pylori* screening by detecting immunoglobulin G (IgG) group antibodies in plasma/serum and pepsinogen testing will be performed. According to the results of the tests, participants will be assigned to *H. pylori* eradication treatment or upper endoscopy. Participants with serological evidence of atrophic gastritis (low pepsinogen I/II ratio) will undergo upper endoscopy with appropriate biopsy sampling as well as further follow-up with endoscopy according to the MAPS (Management of precancerous conditions and lesions in the stomach) guidelines. *H. pylori*-positive individuals will be offered standard eradication treatment as appropriate. From subjects in this group, breath samples will also be collected by research nurses or junior physicians, for the study of volatile markers.

Participants assigned to Group 2 (50%) will constitute the control group, after having had a medical evaluation at the time of recruitment. During the follow-up period, this group will be offered a consultation with a specialist when required due to clinical symptoms.

Participants in both Group 1 and Group 2 will be offered faecal occult blood testing (FOBT) as a benefit of study participation. Any participants with a positive FOBT result will be referred for colonoscopy.

All the trial participants, including those in Group 2, will be followed up at least for 15 years to collect systematic information on medical conditions, in particular gastric cancer and cause of death. A follow-up telephone call or alternative communication will be made every 5 years for outcome assessment.

The general study will be preceded by a pilot study to test the assumptions as well as the tools and functionality of the study infrastructure. On completion of the pilot phase, the required infrastructure and tools planned in the general study will be adapted accordingly.

4. End-points

The primary end-point for this trial will be the difference in mortality from gastric cancer between Group 1 and Group 2 at 15 years or when enough cases have accumulated to demonstrate a statistical difference between the groups.

In addition to the difference in gastric cancer mortality between the two groups, other end-points required to achieve the secondary objectives are:

- The difference in gastric cancer incidence between Group 1 and Group 2
- The difference in all-cause mortality between Group 1 and Group 2
- The difference in incidence and mortality of medical conditions between Group 1 and Group 2
- The sensitivity and specificity of pepsinogen tests to detect atrophy
- The proportion of gastric cancers arising in patients with non-atrophic versus atrophic gastritis
- The proportion of cancers arising in patients with atrophy but negative for *H. pylori* infection
- The difference in incidence of gastric cancer between the group with successful eradication and those within Group 1 who refused eradication therapy or in whom eradication therapy failed
- The proportion of gastric cancer cases identified during scheduled follow-up endoscopy out of the total number of cases in the follow-up group
- The differences in the test performance and disease prevalence between ethnic groups
- The performance (sensitivity, specificity, overall accuracy) of the volatile marker testing approach to diagnose gastric cancer as well as premalignant lesions in the stomach.

5. Statistical analysis

The estimates of differences in gastric cancer-related mortality between the groups have been based on the cancer incidence in eastern Europe (e.g. Belarus) according to the GLOBOCAN 2008 data [17].

With 90% power and a significance level of 5%, significant differences between the groups are expected to be achieved after 15 years of follow-up.

6. Pilot study

Before embarking on the large-scale intervention, a 2000–3000-subject pilot study will be conducted in one or more potential sites. To date the pilot has been launched in Latvia. All the procedures described for the main study will be implemented during the pilot, except the long-term follow-up. The general objectives of the pilot study are to test the assumptions, the appropriateness of the chosen tools, and the infrastructure before the launch of the general study.

The **objectives** of the pilot study are:

1. To test the assumptions defined for the study, as far as the short-duration pilot can address these (e.g. the mortality-related assumptions cannot be addressed with the pilot).

2. To test the appropriateness of the chosen tools (e.g. questionnaire, approach to the study population recruitment, laboratory investigations).
3. To test the appropriateness of the chosen infrastructure for the study (e.g. online data capture system; infrastructure for sample procurement, transportation, and storage; result reporting).

The **concrete aims** of the pilot study are to evaluate:

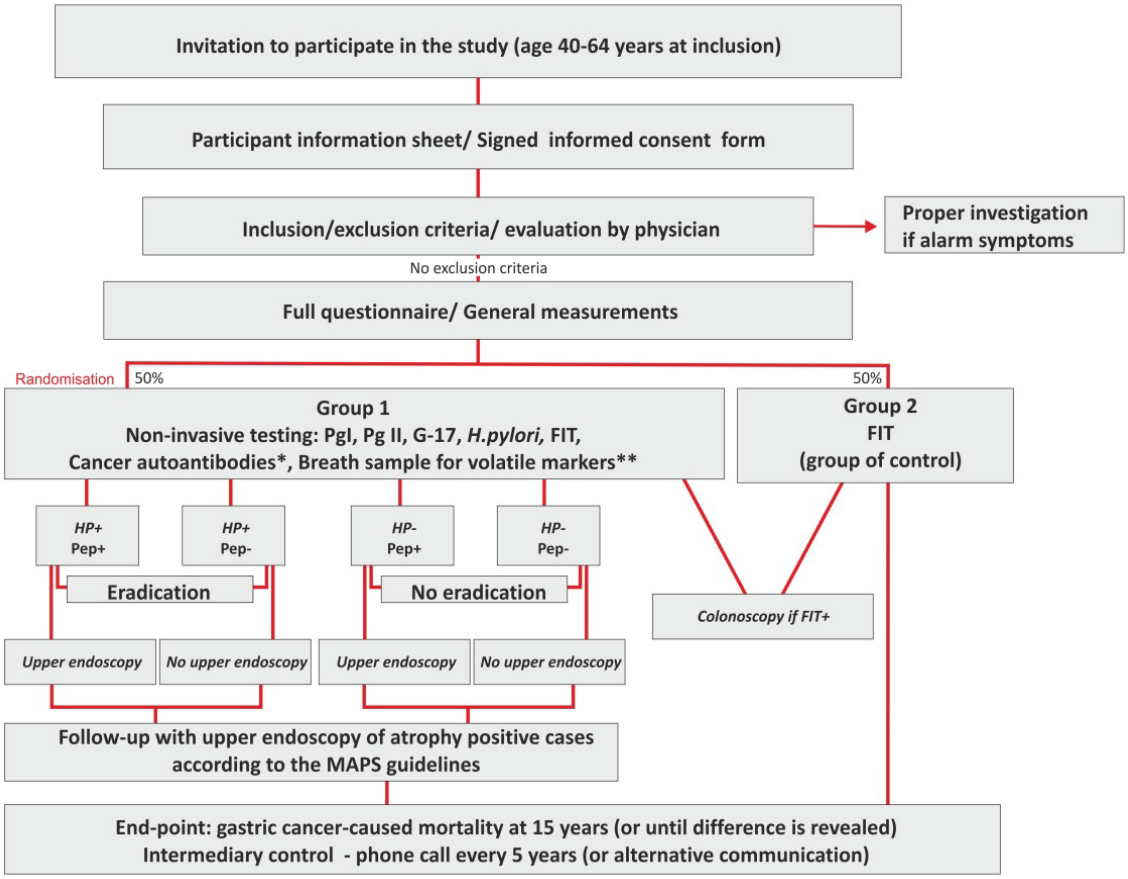
1. The acceptance rate of the target population to participate in the study
2. The proportions of male and female participants
3. The proportions of participants in the different age groups
4. The number of cases that could be recruited by a stationary or mobile recruitment centre per day or per week
5. The prevalence of alarm symptoms or other exclusion factors for the study in the study population
6. The prevalence of *H. pylori* in the study population
7. The sensitivity and specificity of pepsinogen tests as measured by different methods (latex agglutination, enzyme-linked immunosorbent assay [ELISA]) to detect moderate to severe atrophy in the stomach
8. The rationale of gastrin-17 test use for identification of atrophy in the antral part of the stomach in the general study
9. The rationale of cancer autoantibody test panel use for identification of gastric cancer cases in the general study
10. The acceptance rate to undergo *H. pylori* eradication if the infection is positive
11. The acceptance rate to undergo upper endoscopy if the pepsinogen test is positive
12. The adherence to the *H. pylori* eradication treatment
13. The efficacy of a 10-day triple clarithromycin-containing eradication regimen
14. The differences between the target populations in different recruitment sites
15. The differences in acceptance rates by age and sex
16. The feasibility of the data capture system
17. The feasibility of the approach for randomization
18. The feasibility of the laboratory testing approach
19. The adherence to the upper endoscopy protocol
20. The feasibility of sample logistics, including cross-border transportation
21. The ability to comply with the local legal requirements
22. The impact of eradication on short-term outcomes, including biomarkers.

In contrast to the general study, the pilot will also include a gastric-cancer specific autoantibody panel and detection of gastrin-17. Also, the performance of different pepsinogen tests (different methods) will be compared in the pilot study.

For the purpose of measuring the sensitivity and overall accuracy of the non-invasive tests, a group of controls with normal blood test results will be also referred for upper endoscopy.

The design of the pilot study is reflected in Fig. 4.2.1.

Fig. 4.2.1. General design of the pilot study. FIT, faecal immunochemical test; G-17, gastrin-17; *HP*, *Helicobacter pylori*; MAPS, Management of precancerous conditions and lesions in the stomach; Pep, pepsinogen; PgI, pepsinogen I; PgII, pepsinogen II. * All patients with positive gastric cancer-related autoantibodies will be referred for upper endoscopy. ** Based on volatile marker test results, referral for upper endoscopy will be done only if specific panel characteristics for gastric cancer are revealed.



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Chapter 4.3

Effect of *Helicobacter pylori* eradication on gastric cancer prevention in the Republic of Korea: a randomized controlled clinical trial

Il Ju Choi, Jin Young Park, and Rolando Herrero

The incidence of gastric cancer in the Republic of Korea is currently the highest in the world and has remained stable for decades without geographical variation across the country. In the most recent statistics, from 2010, gastric cancer remains the leading cause of cancer in the Republic of Korea and is the third leading cause of cancer death in men (age-standardized incidence rate, 62.3 per 100 000 person-years; age-standardized mortality rate, 20.7 per 100 000 person-years) [1]. In the Republic of Korea, the seropositivity rate of *Helicobacter pylori* in 2005 was 59.6% among subjects older than 16 years who had neither a history of *H. pylori* eradication nor current gastrointestinal symptoms [2].

Considering the high prevalence of *H. pylori* in the Republic of Korea, *H. pylori* screening and eradication may potentially reduce gastric cancer incidence and mortality. The National Cancer Screening Program (NCSP) currently provides *universal* secondary prevention by providing endoscopic or radiological screening every 2 years rather than primary prevention measures for *H. pylori* eradication.

The International Agency for Research on Cancer (IARC) classified *H. pylori* as a Group 1 carcinogen in 1994 [3], and reconfirmed this evaluation in 2009 [4]. In many geographical regions, consensus guidelines for *H. pylori* management have been reported [5–9]. Strongly supported by data from the literature, these guidelines consistently recommend *H. pylori* eradication for patients with peptic ulcer diseases and mucosa-associated lymphoid tissue (MALT) lymphoma. However, for prevention of gastric cancer, recommendations for *H. pylori* eradication are not consistent among the guidelines, except for eradication after endoscopic resection of gastric cancer. The second Asia-Pacific guidelines recommended a screen-and-treat strategy for *H. pylori* infection in communities with a high incidence of gastric cancer [8].

However, guidelines for the Republic of Korea, which were revised in 2013, do not provide any statement regarding *H. pylori* management for the general population. Based on the available evidence, these guidelines only provided a strong recommendation for *H. pylori* eradication after endoscopic resection of early gastric cancer and weak recommendations for patients with atrophic gastritis or intestinal metaplasia and a family history of gastric cancer [5].

Standard triple therapy consisting of a proton pump inhibitor (PPI), amoxicillin, and clarithromycin is recommended as a primary regimen for *H. pylori* eradication in the Republic of Korea [5]. However, there has been a decreasing rate of *H. pylori* eradication with standard triple therapy in the Republic of Korea since 2000. Eradication success rates have been reported to be 74.0–80.4% with a 14-day triple therapy [10, 11] and 64.9–76.9% with a 7-day triple therapy [11–13]. The decreasing rates of *H. pylori* eradication by standard triple therapy may be due to the high rate of clarithromycin resistance. Meanwhile, bismuth-containing quadruple therapy, which is recommended as a secondary regimen for *H. pylori* eradication, remains effective, with higher success rates than standard triple therapy. The success rates of *H. pylori* eradication by secondary quadruple therapy have been reported to be 85.1–96.3% with a 14-day treatment and 81.6–83.5% with a 7-day treatment [14–16].

To address the issues of population-based prevention strategies, it is proposed to conduct a multicentre, double-blind, randomized controlled trial in the Republic of Korea to evaluate the effect of *H. pylori* eradication to prevent gastric cancer in middle-aged adults. The study will also evaluate the effects of *H. pylori* eradication on the incidence of gastric dysplasia and other conditions that may be associated with *H. pylori* infection. Possible adverse events caused by antibiotic treatment as well as the role of environmental and host genetic factors in the development of gastric cancer and its precursors, and as modifiers of the treatment, will also be assessed. All participants will be followed up for at least 10 years to assess the gastric cancer incidence in both the intervention and placebo groups, as well as in the *H. pylori*-negative group.

1. Objectives of the study

H. pylori infection is an important cause of gastric cancer. Therefore, the hypothesis is that the risk of gastric cancer can be reduced by eradication of *H. pylori* infection in individuals in the Republic of Korea. The **primary objective** of the study is to determine whether *H. pylori* eradication reduces gastric cancer incidence in a population of subjects aged 40–60 years in the Republic of Korea.

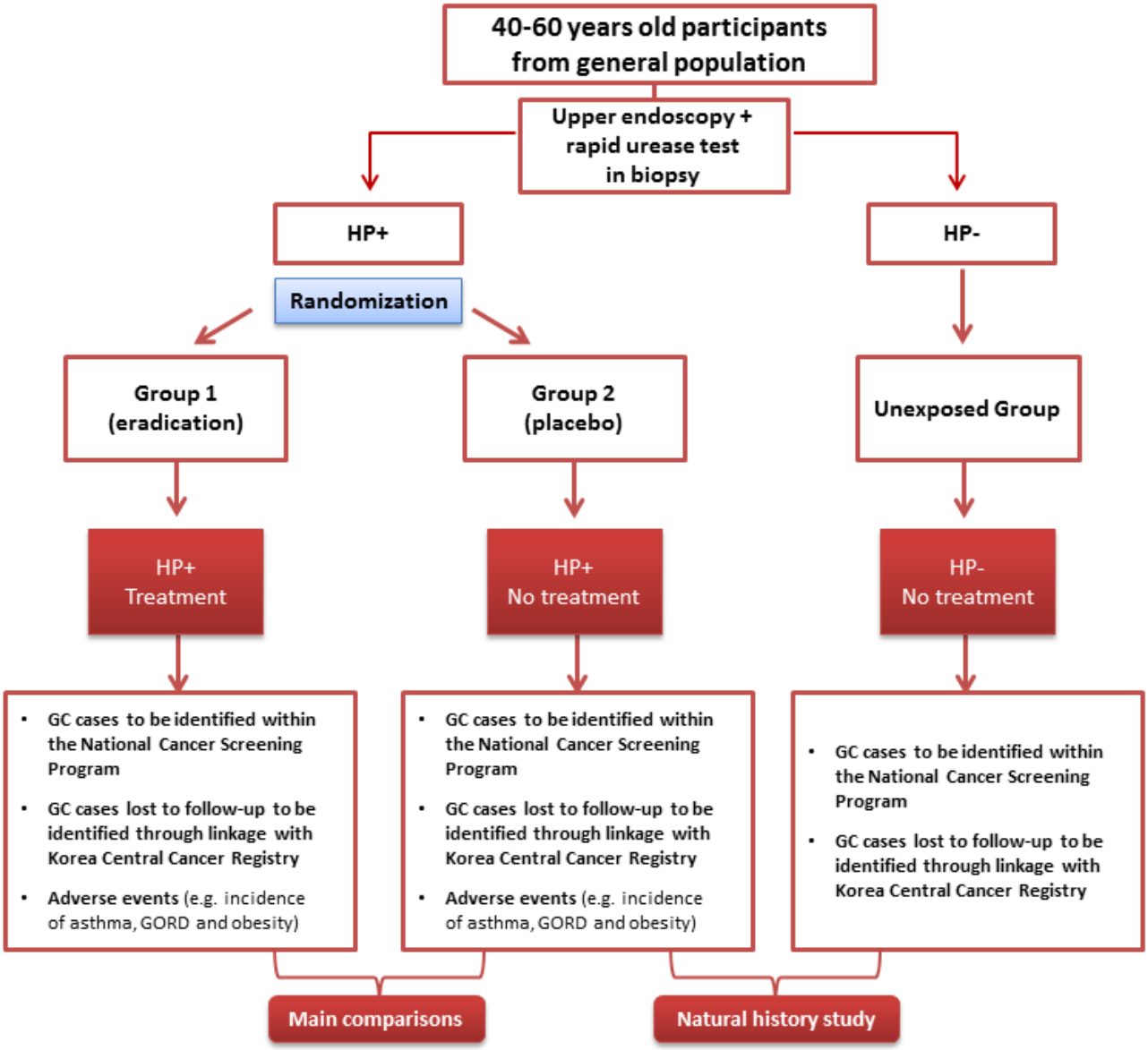
The **secondary objectives** are:

1. To determine whether *H. pylori* eradication reduces the incidence of gastric dysplasia
2. To assess adverse events caused by antibiotic treatment for *H. pylori* eradication
3. To evaluate the impact of *H. pylori* eradication on the occurrence of selected medical conditions potentially associated with the infection or its eradication
4. To assess whether the *H. pylori* treatment results in similar incidences/mortalities of gastric cancer compared with the unexposed group without *H. pylori* infection
5. To assess differences in gastric cancer incidence and mortality between the groups with successful eradication and with persistent *H. pylori* infection
6. To assess the impact of *H. pylori* eradication on precancerous lesions (atrophy score and intestinal metaplasia)
7. To investigate the role of cofactors for gastric cancer development among untreated *H. pylori*-positive subjects (e.g. demographics, dietary differences, lifestyles, host genetic factors, and inflammatory markers).

2. Overview of the study design

This is a population-based, double-blind, randomized controlled clinical trial that will be conducted in seven designated hospitals participating in the NCSP in different administrative districts in the Republic of Korea. The overview of the study design is illustrated in Fig. 4.3.1. Men and women aged 40–60 years at entry who were invited to the NCSP in the Republic of Korea will be asked to participate in this trial until a total of 11 000 individuals have been recruited. Eligible participants who agree to participate and sign informed consent will provide a medical history, undergo a physical examination, and be administered a detailed lifestyle questionnaire. The subjects will be excluded if they meet any of the following criteria: (i) a previous history of gastric cancer, (ii) a family history of gastric cancer in a first-degree relative, (iii) other organ cancers within 5 years, (iv) indication of *H. pylori* eradiation such as peptic ulcer or MALT lymphoma, or (v) other serious medical illnesses or conditions that preclude adequate participation. All participants will undergo upper endoscopy at entry, and a standard collection of gastric biopsies will be performed for histology and *H. pylori* diagnosis. *H. pylori* status will be determined through the rapid urease test (RUT) and histological examination on endoscopic biopsy specimens. The pathological results of biopsy specimens will be reported based on the updated Sydney system [17].

Fig. 4.3.1. Overview of the study design. GC, gastric cancer; GORD, gastro-oesophageal reflux disease; HP, *Helicobacter pylori*.



Subjects who are *H. pylori*-positive (~6600 with a *H. pylori* prevalence estimate of 60%) will be randomly assigned to either the intervention group (Group 1) (50%) or the placebo group (Group 2) (50%). For those assigned to Group 1, an eradication treatment with a 10-day course of a bismuth-based quadruple therapy will be provided. The regimen consists of 500 mg of metronidazole (3 times a day), 500 mg of tetracycline (4 times a day), and 300 mg of bismuth (4 times a day), and a PPI (twice a day) for 10 days. Participants assigned to Group 2 will receive a placebo with an identical shape. This regimen has been selected due to the low eradication rates (< 80%) in the Republic of Korea of the standard triple therapy, which consists of a PPI, amoxicillin, and clarithromycin [12, 18]. Currently, clarithromycin resistance rates of *H. pylori* are greater than 20% in the Republic of Korea [19, 20]. Both the Maastricht IV/Florence Consensus Report [6] and recent guidelines for the Republic of Korea for *H. pylori* infection [5] recommend a bismuth-containing quadruple therapy as a first-line treatment regimen for *H. pylori* eradication in areas with high clarithromycin resistance (clarithromycin resistance rate > 15–20%). Eradication success rates of a

bismuth-containing quadruple therapy have been reported to range from 83% to 100% as a first-line therapy and from 91% to 100% as a second-line therapy (National Cancer Center data, personal communication). This regimen was therefore chosen for *H. pylori* eradication in this study.

Randomization will be performed using a permuted block design stratified by sex and the centre location. Both participants and investigators will be blinded to the interventions. Participants with no evidence of *H. pylori* infection or baseline chronic atrophic gastritis will constitute the "unexposed group" as a comparison group for investigating the natural history of the *H. pylori*-infected or treatment group. Data will be entered into the Internet-based eVelos system operated by the National Cancer Center, which serves the research team through a centralized platform.

All the trial participants will be followed up within the NCSP with endoscopy every 2 years for at least 10 years. Gastric cancer cases will be identified during a biennial endoscopic follow-up appointment for those who participated in the screening programme. For those lost to endoscopic follow-up, gastric cancer cases will be identified through a record linkage with the Korea Central Cancer Registry. At the first follow-up visit during routine screening, two biopsies will be collected (antrum and body) for blinded assessment of the presence of *H. pylori* using the RUT method. After 10 years, at the end of the study, endoscopic biopsies to assess the presence of precancerous lesions will be obtained, and interviews and specimens similar to those obtained during the enrolment visit will be obtained. It is anticipated that approximately 90% of all participants will undergo upper endoscopy every 2 years as part of the NCSP, assuming an active follow-up schedule.

3. Statistical considerations

The expected number of gastric cancer cases was calculated based on the assumption of a reduction in gastric cancer incidence due to the intervention of at least 47%. The assumption for the effect size is based on the available literature [21] as well as on the most recent Japanese study of early gastric cancer patients, which reported a hazard ratio of 0.497 (95% confidence interval, 0.297–0.831) after a maximum of 10 years of follow-up in the eradicated group for the incidence of metachronous gastric cancer after endoscopic resection [22]. Applying a significance level of 5% and a statistical power of 90%, 104 gastric cancer cases would be needed. Overall gastric cancer incidence (men and women combined) in an *H. pylori*-positive population in the Republic of Korea was calculated as 165 cases per 100 000 population each year, using the most recent 5-year follow-up data from the NCSP. *H. pylori* prevalence was estimated to be 60% in adults aged 40–60 years in the Republic of Korea [2], and a relative risk of gastric cancer for *H. pylori*-positive to *H. pylori*-negative patients was assumed to be 6, based on available evidence from the literature [23]. Assuming a 10% follow-up loss, it was estimated that the total sample size of 11 000 (6600 *H. pylori*-positive participants in both Groups 1 and 2 plus 4400 participants in the *H. pylori*-negative group), with all participants to be followed up for 10 years, would meet the requirement of the study design to investigate the differences of at least 47% in the gastric cancer incidence rate between the treatment and placebo groups.

The primary analysis will be based on intention to treat; therefore, all randomized subjects will be included in the analysis regardless of compliance with treatment. Information on interruptions, changes, or discontinuation of treatments will be documented and used to perform additional analyses that are restricted to subjects who completed the treatments. A per-protocol analysis will also be performed with data obtained from subjects who complete this trial. Independent statisticians will prepare the interim unblinded reports for the independent data and safety monitoring committee, which will oversee participant safety and the quality of the trial. The study will be coordinated jointly by the National Cancer Center in the Republic of Korea and the Prevention and Implementation Group at IARC.

4. Ethical considerations

The current guidelines in the Republic of Korea do not include routine *H. pylori* testing and eradication, except for patients with a history or treatment of early gastric cancer, and those with peptic ulcer or MALT lymphoma [5]. The randomized clinical trial design is considered to be ethically sound for the following reasons:

1. The impact of eradication on gastric cancer incidence in the Republic of Korea has not been completely elucidated.
2. *H. pylori* treatment is not a standard practice in the Republic of Korea for the general population; therefore, the National Health Insurance does not cover the cost of treatment.
3. All participants are recruited within the context of the NCSP in the Republic of Korea, which provides active surveillance every 2 years for detection of cancer at an early stage, when it is curable.
4. *H. pylori* infection will be treated in participants with early gastric cancer, peptic ulcer (benign gastric ulcer or duodenal ulcer), and MALT lymphoma detected during the endoscopic follow-up visit, as indicated in the guidelines.

5. Conclusions

Despite much evidence supporting the association between *H. pylori* infection and gastric cancer, it remains controversial whether *H. pylori* eradication may reduce or prevent gastric cancer occurrence in the general population. Moreover, recent reports suggest that *H. pylori* plays a mixed role in human health and is not a major risk factor for all-cause mortality [24]. Currently, there are two opposite viewpoints on this issue. One is “It’s time to eradicate gastric cancer by treating *H. pylori*” [25]; the other is “Stop killing beneficial bacteria by antibiotic overuse”, which raised concerns about permanent changes in our protective microflora [26]. The results of several ongoing studies on the effectiveness of *H. pylori* eradication are now being eagerly awaited [27]. It is anticipated that it will be possible to find answers to those critical and important issues by conducting a well-designed, multicentre study in the Republic of Korea, coordinated by the National Cancer Center in collaboration with IARC. Success of this primary prevention strategy for gastric cancer in the general population may benefit not only those in the Republic of Korea but also those in high-risk countries where endoscopic surveillance is not under consideration for decreasing gastric cancer burden.

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Chapter 4.4

Community-based *Helicobacter pylori* eradication with two sequential antibiotic regimens for the residents and migrants in a high-risk area for gastric cancer

Yi-Chia Lee

In Taiwan, China, programmatic gastric cancer prevention was started in 2004 for a high-risk population on an offshore island (Matsu Island), applying a strategy of mass eradication of *Helicobacter pylori*. This chapter provides a detailed rationale for this population-based study, addressing the burden of gastric cancer, design of the preventive programme, method of invitation to participants, screening test, antibiotic treatment, endoscopic examination, evaluation method, and the updated results.

1. Gastric cancer burden in Matsu Island

Matsu Island is an archipelago of five major islands in the Taiwan Strait, located about 100 miles from the coast of Taiwan, China, near the northern coast of Fujian Province in mainland China (Fig. 4.4.1). The population of Matsu Island was about 5000 in 1995 and gradually increased to about 10 000 by 2008. Before 2004, the incidence rate of gastric cancer in Matsu Island was about 50 per 100 000 person-years (Table 4.4.1), which was 3–5 times the incidence rate in the main island of Taiwan, China. The mortality rate of gastric cancer was about 26 per 100 000 person-years, yielding a mortality-to-incidence ratio of about 0.5. An effective preventive strategy was urgently needed for this high-risk population.

2. Design of a gastric cancer preventive programme in Matsu Island

To prevent gastric cancer in Matsu Island, a secondary preventive programme was implemented during 1995–1998. The intervention applied a two-stage design. The first stage comprised a standardized questionnaire and serum pepsinogen measurement, aiming to identify high-risk subjects, and the second stage included endoscopic examination for subjects with a positive serum pepsinogen measurement [2, 3]. However, the sensitivity and specificity of pepsinogen measurement in identifying subjects with premalignant lesions were estimated to be 62% and 70%, respectively. Because the programme's effectiveness was low, it was ended in 1999. During 1999–2003, no intervention for gastric cancer prevention was administered. Also during this period, accumulated evidence showed that *H. pylori* infection was the major cause of gastric cancer [4, 5], which prompted the planning of a mass eradication programme.

Fig. 4.4.1. Location of Matsu Island and prevalence of *Helicobacter pylori* infection. Matsu Island is an archipelago of five major islands; the prevalence of *H. pylori* infection on each island is specified. Note that Fujian Province in mainland China was also an area with prevalent *H. pylori* infection and a high gastric cancer incidence rate. Source: Lee et al. (2013) [1].

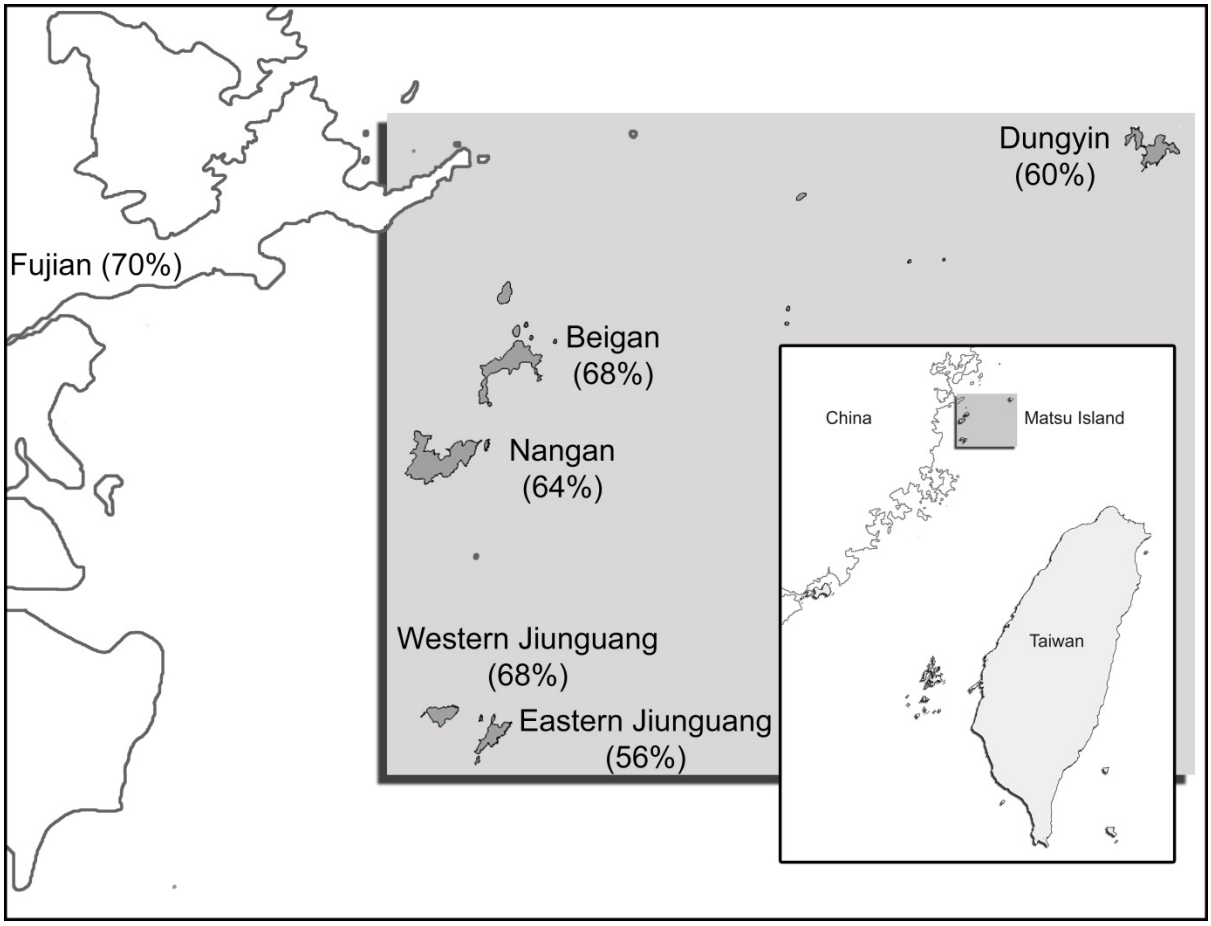

Table 4.4.1. Number of people at risk, number of incident cases, number of deaths, and incidence and mortality rates of gastric cancer in Matsu Island, 1995–2010

Year	Population	New gastric cancer cases	Gastric cancer deaths	Incidence rate[a]	Mortality rate[a]
1995	5711	4	2	70.04	35.02
1996	5959	5	3	83.91	50.34
1997	7240	5	3	69.06	41.44
1998	7536	4	1	53.08	13.27
1999	6560	4	2	60.98	30.49
2000	6733	2	3	29.70	44.56
2001	8851	6	3	67.79	33.89
2002	8763	1	0	11.41	0
2003	8806	3	0	34.07	0
2004	9359	9	3	96.16	32.06
2005	10 345	1	3	9.67	29.00
2006	9786	2	3	20.44	30.66
2007	9965	2	2	20.07	20.07
2008	9961	1	2	10.04	20.08
2009	9919	3	3	30.25	30.25
2010	9944	0	2	0	20.11

[a] Rates are per 100 000 person-years.

Source: Adapted from Lee et al. (2013) [1].

In 2004, under the auspices of the Taiwanese Ministry of Health, a mass eradication programme for *H. pylori* was launched (NCT00155389), aiming to prevent gastric cancer and reduce its mortality rate in this population [6]. This prospective cohort study applied quasi-experimental, before-and-after study design, designating the whole population of Taiwan, China as an external comparator group. The main outcome measure was the impact of mass eradication on the changes of premalignant gastric lesions and gastric cancer, which was obtained by comparing data from the periods before and after the mass eradication programme in the same population. The eligible age range for participation in the study was 30 years and older (n = ~5000), registered in the Matsu Island population list. It should be noted that the Matsu Island population was not a closed population; some subjects registered in the population list may have migrated to the main island of Taiwan, China. These migrants from Matsu Island were also invited to participate in screening. Pregnant or lactating women, patients with major concomitant diseases, and those who had undergone gastric surgery were excluded. To date, three rounds of mass screening have been conducted in this population: in 2004–2005, 2008–2009, and 2012–2013.

3. Invitation method

During 1999–2003, a multiple-disease screening programme was launched that included non-neoplastic diseases (e.g. diabetes mellitus, hypertension, and hyperlipidaemia) and neoplastic diseases (e.g. cervical, breast, and colorectal cancers), but not gastric cancer. This programme was called the Matsu Community-Based Multiple Screening Program [7]. In this multiple-disease screening programme, potential participants were contacted by telephone and then received a pamphlet by mail that invited them to visit their local screening centres.

In 2004, the mass eradication programme, which included the first stage with the ^{13}C-urea breath test (^{13}C-UBT) and a structured questionnaire, and the second stage with endoscopic examination, was appended to the multiple-disease screening programme. The questionnaire included sociodemographic characteristics; cigarette smoking, alcohol consumption, and exercise habits; personal and familial history of major diseases; and intake frequency of salted foods, pickled foods, meat, and fruit.

4. ^{13}C-UBT and antibiotic treatment

The sensitivity and specificity of ^{13}C-UBT in diagnosing *H. pylori* infection were estimated to be 97.8% and 96.8%, respectively [8]. During the first round (2004–2005) and second round (2008–2009) of mass screening, individuals with positive ^{13}C-UBT results underwent endoscopic screening and antibiotic treatment, including:

- 7-day triple therapy (40 mg of esomeprazole once a day, 1 g of amoxicillin twice a day, and 500 mg of clarithromycin twice a day), and
- 10-day levofloxacin-based triple therapy (40 mg of esomeprazole once a day, 1 g of amoxicillin twice a day, and 500 mg of levofloxacin once a day) for individuals in whom initial treatment failed.

The ^{13}C-UBT was done 6–8 weeks after antibiotic treatment. For individuals whose results remained positive after two courses of antibiotic treatments, no further empirical treatment was given.

During the third round (2012–2013), those who tested positive were invited to participate in a randomized controlled trial (NCT01607918) that compared two first-line antibiotic regimens, including:

- 14-day triple therapy (30 mg of lansoprazole twice a day, 1 g of amoxicillin twice a day, and 500 mg of clarithromycin twice a day, for 14 days), and
- 10-day sequential treatment (30 mg of lansoprazole and 1 g 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).

Individuals in whom initial treatment failed received 10-day levofloxacin-based triple therapy (30 mg of lansoprazole twice a day, 1 g of amoxicillin twice a day, and 500 mg of levofloxacin once a day).

5. Endoscopy

Biopsy specimens from the antrum (from the greater and lesser curvatures 2–3 cm from the pylorus) and specimens from the corpus (one from the lesser curvature and one from the greater curvature at the mid-corpus) were obtained during endoscopy. Specimens were graded using a visual analogue scale (the modified Sydney classification) to rate the severity of each category as none (0), mild (1), moderate (2), or marked (3). Three subcategories were added to describe the types of inflammatory cell infiltrates, including acute inflammation, chronic inflammation, and mucosa-associated lymphoid tissue (MALT). The presence and severity of gastric dysplasia were also graded as none, indefinite for dysplasia, low-grade dysplasia, and high-grade dysplasia.

6. Evaluation method

Knowing that new immigrants or the younger generation would enter this cohort or meet the eligibility criteria, an inter-screening interval of 4 years was scheduled. The follow-up period was set as at least 12 years. The aims of the three successive rounds were as follows.

6.1 First round (2004–2005)

- To demonstrate proof of concept.
- To evaluate the eradication rate of a test–treat–retest–retreat strategy in the community.
- To perform an economic modelling study to simulate the long-term outcome.

6.2 Second round (2008–2009)

- To evaluate the effectiveness of intervention in terms of changes in the prevalence/incidence rate of *H. pylori* infection, premalignant gastric lesions, gastric cancer, and other upper gastrointestinal lesions (e.g. peptic ulcers and reflux oesophagitis).
- To evaluate the reinfection rate of *H. pylori* after eradication.

6.3 Third round (2012–2013)

- To optimize the eradication rate of antibiotic treatment.
- To evaluate the impact of mass eradication on the drug-resistance pattern of *H. pylori* after two courses of interventions.

7. Results

7.1 First round (2004–2005)

A total of 4121 participants participated, and 2598 (63%) tested positive for *H. pylori* infection. Endoscopy was performed for 1762 *H. pylori*-positive individuals, and 4 gastric cancers were found. The eradication rates with first-line therapy were 86.9% and 88.7% by intention-to-treat and per-protocol analyses, respectively. Rescue therapy eradicated infection in 91.4% of 105 non-responders. The overall eradication rate was 97.7% after two courses of antibiotic treatments [6]. Using the first-round result as the base case, a cost–effectiveness analysis was performed to predict long-term effectiveness. The results showed that mass eradication was cost-effective. The incremental cost–effectiveness ratio for once-only mass eradication at age 30 years versus no screening was US$ 17 044 per life-year gained. Sensitivity analyses showed that the cost–effectiveness was subject to the rate of reinfection, the endoscopic detection rate of early gastric cancer, and the age at initial screening [9].

7.2 Second round (2008–2009)

In this round, mainly those who had participated in the first round were invited, to evaluate the effectiveness in reducing premalignant gastric lesions and the reinfection rate of *H. pylori*. A total of 1334 subjects participated (1152 who had participated in the first round, and 182 new participants). Overall, the prevalence rate of *H. pylori* infection was 13.4% (9.7% of the group of first-round participants who were retested in the second round, and 36.8% of the group of new participants). During 2004–2008, the incidence of reinfection was 1% (95% confidence interval [CI], 0.6–1.4%) per person-year. Of the 1762 residents who had undergone a baseline histological assessment in 2004, 841 underwent endoscopy in the second round and 1 gastric cancer was found. To evaluate the effectiveness of the intervention, three different analyses were used, as follows [1]:

- A comparison of the prevalence and incidence rates between the periods before and after the mass eradication.

- A comparison of the severity scores of intragastric histology before and after the mass eradication.
- A comparison of the observed and predicted data using the time trends before and after the mass eradication.

First, the prevalence and incidence rates were compared by comparing data between the 5-year periods before and after chemoprevention. The results showed that the effectiveness of reducing the incidence of gastric atrophy was significant, at 77.2%, whereas the reduction in intestinal metaplasia or dysplasia was not significant. The reduction in gastric cancer incidence was 25%. The reduction in peptic ulcer disease was 67.4%, whereas the incidence of oesophagitis was 6% after treatment.

Second, the changes in the intragastric histology were evaluated. The descriptive results are shown in Tables 4.4.2–4.4.6. These results showed significant improvement in the severity scores for acute inflammation, chronic inflammation, MALT, and gastric atrophy, but no change in the severity score for intestinal metaplasia. Regression analyses showed that successful eradication of *H. pylori* was associated with a significant decrease in histological scores; however, this effect was modified by the individual's age. Histological regression after the eradication of *H. pylori* infection was more prominent in young adults. The impacts of individual factors were also evaluated, using multiple logistic regression analyses. The factors of interest included age, smoking, alcohol consumption, metabolic risk factors, and first-degree relatives with gastric cancer. The results consistently showed that greater age was associated with the occurrence of intestinal metaplasia after *H. pylori* treatment.

Third, taking into consideration the improved sanitation and hygiene applied during the study period, the data on gastric atrophy, intestinal metaplasia, and the incidence and mortality rates of gastric cancer between 1995 and the end of 2003 (the historical control data) were used to formulate the Poisson regression model. Then, the occurrence of premalignant gastric lesions and gastric cancer between 2004 and the end of 2008 was predicted, if no screening was implemented. The results consistently showed that the effectiveness of reducing the incidence of gastric atrophy was significant, at 61%. No significant benefit was seen for intestinal metaplasia, gastric cancer incidence, or gastric cancer mortality.

Table 4.4.2. Scores of acute polymorphonuclear infiltrates in Matsu Island before chemoprevention (first data, in 2004) and after chemoprevention (second data, in 2008). An excess of cases below the diagonal line indicates an improvement in histological scores between the two rounds of eradication.

Baseline score	Follow-up score of acute polymorphonuclear infiltrates (antrum, body)																
	(0,0)	(0,1)	(0,2)	(0,3)	(1,0)	(1,1)	(1,2)	(1,3)	(2,0)	(2,1)	(2,2)	(2,3)	(3,0)	(3,1)	(3,2)	(3,3)	Total
(0,0)	52	0	0	1	1	1	0	0	0	2	0	0	0	0	0	0	57
(0,1)	9	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	10
(0,2)	5	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	7
(0,3)	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
(1,0)	125	1	0	0	12	5	0	0	2	1	1	0	0	0	0	0	147
(1,1)	111	3	1	0	6	5	0	0	2	3	1	0	0	0	1	0	133
(1,2)	24	1	0	0	0	1	0	0	0	1	0	0	0	0	0	0	27
(1,3)	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10
(2,0)	93	1	0	0	6	1	0	0	0	0	0	0	0	0	0	0	101
(2,1)	131	1	0	0	6	5	0	0	1	1	0	0	0	0	0	0	145
(2,2)	74	3	0	0	4	3	0	0	1	0	1	0	0	0	0	0	86
(2,3)	6	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	8
(3,0)	7	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	10
(3,1)	34	1	0	0	5	1	0	0	0	0	0	0	0	0	0	0	41
(3,2)	25	0	0	0	1	3	0	0	0	0	0	0	0	0	0	0	29
(3,3)	24	0	0	0	0	2	0	0	0	1	0	0	1	0	0	0	28
Total	732	13	1	1	45	29	0	0	6	9	3	0	1	0	1	0	841

Table 4.4.3. Scores of chronic lymphoplasmacytic infiltrates in Matsu Island before chemoprevention (first data, in 2004) and after chemoprevention (second data, in 2008). An excess of cases below the diagonal line indicates an improvement in histological scores between the two rounds of eradication.

Baseline score	Follow-up score of chronic lymphoplasmacytic infiltrates (antrum, body)																
	(0,0)	(0,1)	(0,2)	(0,3)	(1,0)	(1,1)	(1,2)	(1,3)	(2,0)	(2,1)	(2,2)	(2,3)	(3,0)	(3,1)	(3,2)	(3,3)	Total
(0,0)	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
(0,1)	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
(0,2)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(0,3)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(1,0)	0	0	0	0	8	0	0	0	0	0	0	0	0	0	0	0	8
(1,1)	7	0	0	0	8	15	0	0	1	0	0	0	0	1	0	0	32
(1,2)	0	0	1	0	4	2	1	0	0	0	0	0	0	0	0	0	8
(1,3)	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	2
(2,0)	0	0	0	0	4	3	0	0	0	2	0	0	0	0	0	0	9
(2,1)	23	0	0	0	59	61	0	0	4	25	11	1	0	3	5	0	192
(2,2)	27	5	1	0	89	160	14	0	9	76	32	1	0	5	10	3	432
(2,3)	0	0	0	0	2	11	3	0	0	4	5	0	0	0	2	0	27
(3,0)	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1
(3,1)	2	0	0	0	8	8	0	0	1	3	1	0	0	0	0	0	23
(3,2)	4	1	0	0	15	26	0	0	2	15	4	1	0	0	1	2	71
(3,3)	1	0	0	0	9	13	1	0	0	7	2	0	0	1	0	0	34
Total	65	6	2	0	207	302	19	0	17	132	55	3	0	10	18	5	841

Table 4.4.4. Scores of gastric atrophy in Matsu Island before chemoprevention (first data, in 2004) and after chemoprevention (second data, in 2008). An excess of cases below the diagonal line indicates an improvement in histological scores between the two rounds of eradication.

Baseline score	Follow-up score of gastric atrophy (antrum, body)																
	(0,0)	(0,1)	(0,2)	(0,3)	(1,0)	(1,1)	(1,2)	(1,3)	(2,0)	(2,1)	(2,2)	(2,3)	(3,0)	(3,1)	(3,2)	(3,3)	Total
(0,0)	54	1	0	0	7	7	0	0	0	2	1	0	0	0	0	0	72
(0,1)	4	2	0	0	1	1	0	0	0	0	0	0	0	0	0	0	8
(0,2)	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
(0,3)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(1,0)	184	6	0	0	45	8	0	0	0	0	0	0	0	0	0	0	243
(1,1)	131	8	3	0	38	15	2	0	1	1	0	0	0	0	0	0	199
(1,2)	23	5	0	0	8	2	0	0	0	0	0	0	0	0	0	0	38
(1,3)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(2,0)	51	2	0	0	12	4	0	0	3	0	0	0	0	0	0	0	72
(2,1)	65	6	0	0	31	15	1	0	0	0	1	0	0	0	0	0	119
(2,2)	39	4	1	0	12	6	3	0	0	0	0	0	0	0	0	0	65
(2,3)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(3,0)	2	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	4
(3,1)	9	0	0	0	2	1	0	0	0	0	0	0	1	0	0	0	13
(3,2)	3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	4
(3,3)	0	1	0	0	2	0	0	0	0	0	0	0	0	0	0	0	3
Total	566	35	4	0	160	60	6	0	4	3	2	0	1	0	0	0	841

Table 4.4.5. Scores of mucosa-associated lymphoid tissue in Matsu Island before chemoprevention (first data, in 2004) and after chemoprevention (second data, in 2008). An excess of cases below the diagonal line indicates an improvement in histological scores between the two rounds of eradication.

Baseline score	Follow-up mucosa-associated lymphoid tissue score (antrum, body)																
	(0,0)	(0,1)	(0,2)	(0,3)	(1,0)	(1,1)	(1,2)	(1,3)	(2,0)	(2,1)	(2,2)	(2,3)	(3,0)	(3,1)	(3,2)	(3,3)	Total
(0,0)	217	11	7	0	7	3	0	0	3	1	0	0	3	1	0	0	253
(0,1)	23	1	0	0	6	0	0	0	1	0	0	0	0	0	0	0	31
(0,2)	16	1	0	3	1	0	0	0	0	0	0	0	1	0	0	0	22
(0,3)	7	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	10
(1,0)	122	0	1	1	9	1	0	0	4	0	0	0	1	2	0	0	141
(1,1)	22	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	24
(1,2)	8	4	0	0	1	0	0	0	1	0	0	0	0	0	0	0	14
(1,3)	6	1	1	0	1	0	1	0	0	1	0	0	0	0	0	0	11
(2,0)	140	9	1	0	9	0	0	0	7	1	0	0	3	0	0	0	170
(2,1)	13	0	1	0	1	0	0	0	2	0	0	0	0	0	0	0	17
(2,2)	15	1	0	0	2	0	0	0	0	0	0	0	0	0	0	0	18
(2,3)	2	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	3
(3,0)	85	2	0	0	3	0	0	0	1	1	0	0	3	0	0	0	95
(3,1)	16	2	0	0	2	0	0	0	0	0	0	0	0	0	0	0	20
(3,2)	4	3	0	0	1	0	0	0	0	0	0	0	0	0	0	0	8
(3,3)	3	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	4
Total	699	38	13	4	45	6	1	0	19	4	0	0	11	3	0	0	841

Table 4.4.6. Scores of intestinal metaplasia in Matsu Island before chemoprevention (first data, in 2004) and after chemoprevention (second data, in 2008). Similar case numbers above and below the diagonal line indicate no change in histological scores between the two rounds of eradication.

Baseline score	Follow-up score of intestinal metaplasia (antrum, body)																
	(0,0)	(0,1)	(0,2)	(0,3)	(1,0)	(1,1)	(1,2)	(1,3)	(2,0)	(2,1)	(2,2)	(2,3)	(3,0)	(3,1)	(3,2)	(3,3)	Total
(0,0)	442	6	4	0	74	4	2	0	34	3	0	1	5	1	2	0	578
(0,1)	4	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	5
(0,2)	3	0	0	0	1	0	0	1	1	1	0	0	0	0	0	0	7
(0,3)	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	2
(1,0)	26	1	1	0	20	1	1	0	14	2	1	0	3	0	1	0	71
(1,1)	2	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	4
(1,2)	2	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	3
(1,3)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(2,0)	22	0	0	0	16	2	0	0	19	2	1	0	5	1	0	0	68
(2,1)	1	0	0	0	1	1	0	0	2	0	0	0	0	0	0	0	5
(2,2)	0	0	0	0	2	0	0	1	1	1	0	0	0	0	0	0	5
(2,3)	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2
(3,0)	9	0	0	0	18	0	2	0	24	0	2	0	6	2	3	2	68
(3,1)	1	0	0	0	0	0	1	0	1	0	0	0	1	0	0	0	4
(3,2)	1	0	1	0	0	0	1	0	1	0	0	0	0	1	0	0	5
(3,3)	0	0	0	0	2	1	0	1	3	0	1	0	4	0	1	1	14
Total	514	7	6	0	138	10	7	3	101	9	5	1	25	5	7	3	841

7.3 Third round (2012–2013)

The main purpose of the third round was to optimize the efficacies of antibiotic treatment and to evaluate the issue of antibiotic resistance. A total of 2518 Matsu Island residents participated (1480 who had participated in the first or second round, and 1038 new participants). A total of 713 people had positive ^{13}C-UBT test results. The overall prevalence rate of *H. pylori* infection was 28.3% (15.7% for former participants, and 46.2% for new participants). Using the data for 2008–2012, the reinfection rate was estimated to be 0.67% (95% CI, 0.45–0.98%) per person-year.

Among the 713 *H. pylori*-positive individuals, 509 received antibiotic treatment, 391 received endoscopic examinations, and 382 received drug-susceptibility testing. No gastric cancer was found. The preliminary results showed that two antibiotic regimens had similar efficacy rates (about 87% and 89% for intention-to-treat and per-protocol analyses, respectively). As shown in Table 4.4.7, preliminary data indicated that the drug-resistance patterns in the Matsu Island population were 1.0% for amoxicillin, 8.2% for clarithromycin, 3.8% for levofloxacin, 21.6% for metronidazole, and 0.3% for tetracycline, which were similar to those in Taiwan, China [10].

In the third round, 362 adolescents (junior high school students; mean age, 14.4 years) were also invited to receive the *H. pylori* stool antigen (HPSA) test, and the prevalence rate of *H. pylori* infection in this group was 19.3%. Antibiotic treatment was not prescribed for these adolescents.

Table 4.4.7. Impact of mass eradication of *Helicobacter pylori* on the prevalence rate of antibiotic-resistant strains in Matsu Island in 2013, compared with different geographical areas in Taiwan, China, in the absence of mass screening

Location	Antibiotic				
	Amoxicillin	**Clarithromycin**	**Levofloxacin**	**Metronidazole**	**Tetracycline**
Matsu Island	1.0%	8.2%	3.8%	21.6%	0.3%
Northern Taiwan, China	3.2%	8.1%	9.4%	21.8%	1.1%
Central Taiwan, China	4.1%	10.3%	8.7%	23.9%	2.0%
Southern Taiwan, China	1.5%	9.4%	13.8%	32.4%	2.2%
Eastern Taiwan, China	0.9%	3.6%	2.7%	15.2%	4.5%

8. Conclusion

This cohort study demonstrated that mass eradication of *H. pylori* infection was applicable in a population in which *H. pylori* infection was prevalent and the incidence rate of gastric cancer was high. Significant benefit has been found in reducing gastric atrophy and the risk of peptic ulcer disease. It was anticipated that a substantial chemoprevention-mediated reduction in gastric atrophy would lead to a further reduction in the incidence and mortality of gastric cancer, provided that the follow-up period was sufficiently long and the Correa pathway of pathological events leading to gastric cancer is valid. This study also lent support to the concept of a “point of no return” at which the older participants who were more likely to

harbour intestinal metaplasia or dysplasia were less likely to benefit from anti-*H. pylori* treatment for gastric cancer prevention. For the older adult population, endoscopic surveillance was needed. Given the routine retest–retreatment practice, the drug-resistance patterns did not show significant change in this population after two rounds of mass eradication.

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Chapter 4.5

The treatment of *Helicobacter pylori* infection of the stomach in relation to the possible prevention of gastric cancer

Nicholas J. Wald

Although the incidence of gastric cancer is declining throughout the world, it remains a common and serious global health problem. A strong association between the risk of gastric cancer and *Helicobacter pylori* infection, as judged by the assessment of *H. pylori* antibody status, was first identified in prospective studies in 1991 [1]. Subsequently, the International Agency for Research on Cancer judged the bacterium to be a cause of gastric cancer [2].

1. *H. pylori* infection and gastric cancer

H. pylori infection of the stomach is also common throughout the world. The infection is usually acquired in childhood, and is associated with living in relatively crowded conditions. Its role in the etiology of gastric cancer probably involves co-factors, such as increased salt consumption.

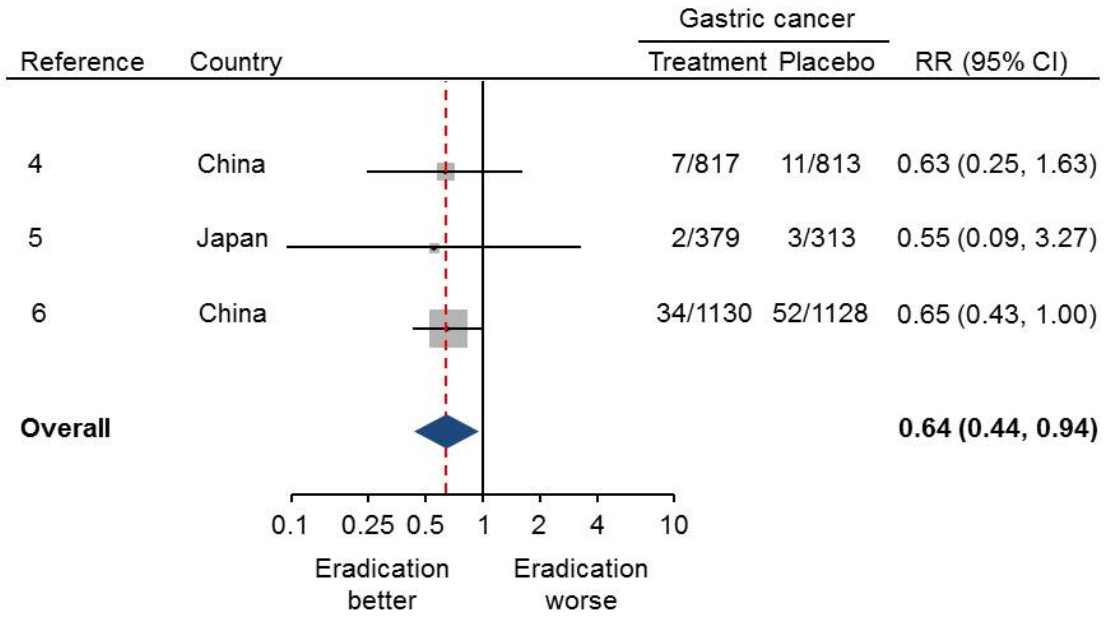
Interestingly, whereas a meta-analysis of 12 prospective studies [3] showed a relative risk of 2.4 (95% confidence interval [CI], 2.0–2.8) between *H. pylori*-positive status and gastric cancer, the relative risk was higher in individuals who were tested for infection more than 10 years before the development of the cancer (relative risk, 5.9) compared with those who were infected 10 years or less before the development of the cancer (relative risk, 2.4). The explanation for this difference is that *H. pylori* infection tends to be lost with the atrophic gastritis that the organism causes. In other words, the bacterium over many years destroys its own habitat.

From the relative risk estimates available, it can be concluded that in most parts of the world most cases of gastric cancer are attributable to *H. pylori* infection.

2. Published trials of *H. pylori* eradication and gastric cancer

Three placebo-controlled trials of eradication therapy of *H. pylori* have been performed in relation to the incidence of gastric cancer [4–6]. Two of the studies were performed in China, and one in Japan. Fig. 4.5.1 shows that the summary relative risk was 0.64 (95% CI, 0.44–0.94). This summary estimate is dominated by the results from one study [6] with 34 cases of gastric cancer in the treated group and 52 in the placebo group, compared with 9 and 14, respectively, in the two other studies. Another randomized controlled trial reported after 5 years [7] and 10 years [8] of follow-up, but after 10 years there were fewer cases of cancer reported (9) than after 5 years (10). Because of this surprising result, this study was not included in the meta-analysis, but the relative risk was 0.65 (95% CI, 0.19–2.28) after 5 years and 0.29 (95% CI, 0.06–1.36) after 10 years.

Fig. 4.5.1. Randomized placebo-controlled trials of eradication therapy on the incidence of gastric cancer in *Helicobacter pylori*-positive subjects. CI, confidence interval; RR, relative risk.



There are two published randomized placebo-controlled trials of eradication therapy in patients with precancerous stomach lesions. One trial yielded a relative risk of 1.48 (95% CI, 0.25–8.83) [9]. The other trial had a four-group factorial design using two treatments: *H. pylori* eradication treatment and the use of a COX-2 inhibitor (celecoxib) [10]. The incidences of gastric cancer were as follows: placebo, 1/258; *H. pylori* treatment plus COX-2 inhibitor, 3/255; *H. pylori* treatment plus placebo, 3/255; and placebo plus COX-2 inhibitor, 2/256. The relative risk based on the groups without use of the COX-2 inhibitor is 3.04 (95% CI, 0.32–28.99), and the relative risk based on all the data (6/510 vs 3/514) is 2.00 (95% CI, 0.50–7.97). Fig. 4.5.2 shows that the combined relative risk for these two trials is 1.79 (95% CI, 0.60–5.33).

Two randomized trials have been performed on *H. pylori* eradication therapy on the incidence of second gastric cancers, one in Japan and the other in the Republic of Korea [11, 12]. The two trials resulted in 19 second gastric cancers in the treated group compared with 41 in the control group (see Fig. 4.5.3). The relative risk estimate was 0.47 (95% CI, 0.28–0.80).

Fig. 4.5.2. Randomized placebo-controlled trials of eradication therapy on the incidence of gastric cancer in *Helicobacter pylori*-positive subjects with precancerous lesions. CI, confidence interval; RR, relative risk.

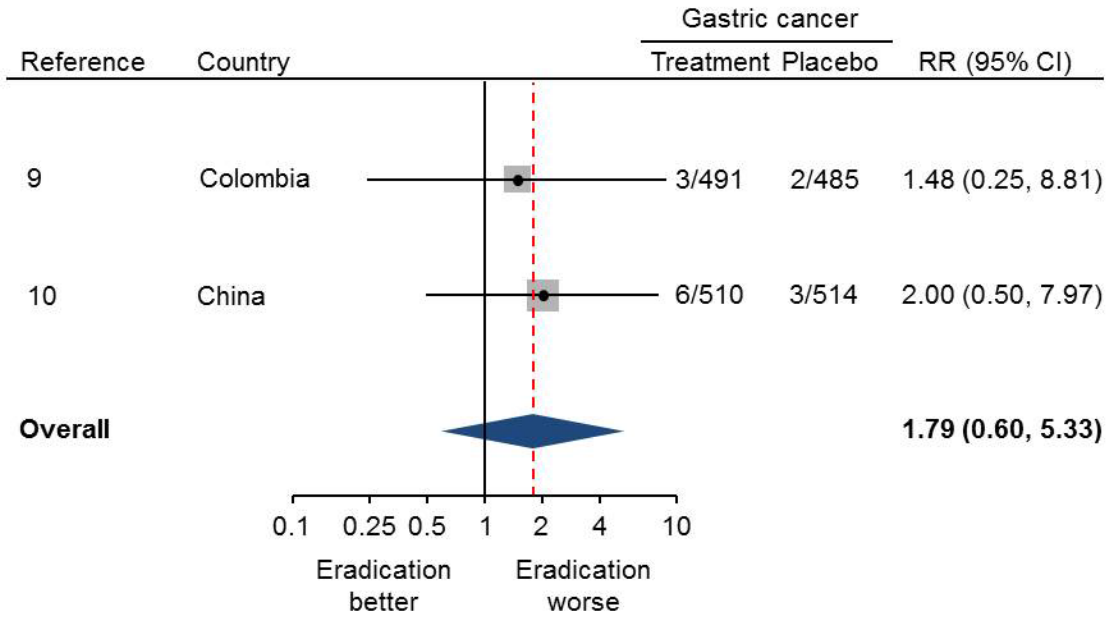
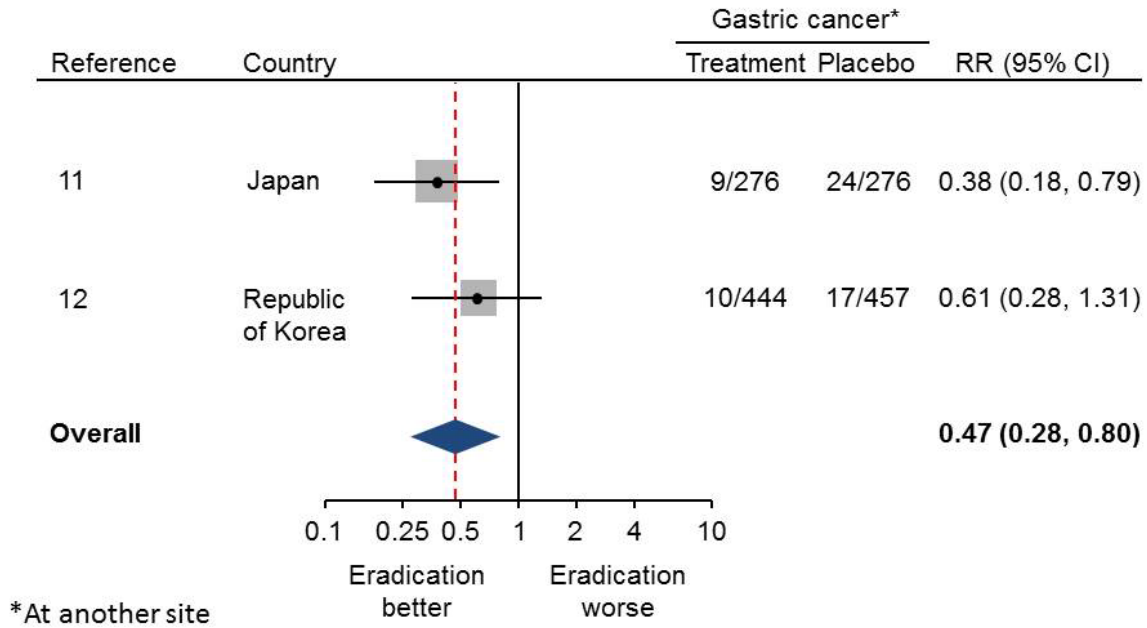


Fig. 4.5.3. Randomized placebo-controlled trials of eradication therapy on the incidence of a second gastric cancer in *Helicobacter pylori*-positive subjects. CI, confidence interval; RR, relative risk.



Three studies compared the number of second gastric cancers between patients in whom *H. pylori* had been successfully eradicated after treatment and patients in whom the treatment had failed to eradicate *H. pylori*; relative risks of 0.59 (95% CI, 0.30–1.19) [13], 0.53 (95% CI, 0.32–0.87) [14], and 0.45 (95% CI, 0.23–0.86) [15] were observed. However, these studies were not randomized controlled trials, so the possibility of selection bias cannot be excluded.

These results, taken together, suggest that treating *H. pylori* infection of the stomach protects against gastric cancer, but they do not provide conclusive evidence, mainly because they are dominated by the results of one trial [6]. Given that other randomized trials are in progress, it would be prudent to defer any conclusion as to the benefit of *H. pylori* eradication therapy on gastric cancer until further evidence is available from these trials.

3. The *H. pylori* Screening Study

One trial in progress is the *H. pylori* Screening Study (HPSS) being conducted in the United Kingdom, which addresses the question: Does *H. pylori* screening and the treatment of those with positive results prevent gastric cancer, and if so, to what extent? The anti-*H. pylori* treatment used was 30 mg of lansoprazole, 400 mg of metronidazole, and 250 mg of clarithromycin, all taken twice a day for 7 days. The trial was funded by the Cancer Research Campaign (now part of Cancer Research United Kingdom) and the British United Provident Association (BUPA) Foundation. Men aged 35–69 years and women aged 45–69 years were randomized by week of attendance at a Well Person Screening Clinic conducted by BUPA. All individuals had to be United Kingdom residents, registered with a National Health Service (NHS) general practitioner, so that their NHS records could be flagged and an automatic notification sent to the study centre in the event of cancer registration or death.

Fig. 4.5.4 shows the expected numbers of people with gastric cancer in the trial according to randomized allocation (screened, or control), and among the screened group, the expected numbers found to be negative and positive for *H. pylori* antibody. It also shows the expected numbers of individuals with gastric cancer in the absence of treatment. Fig. 4.5.5 shows the expected numbers with treatment assuming a 3-fold relative risk. Comparison of cases in the screened and control groups would be the standard analysis, but a more powerful statistical analysis was specified in the protocol. As there is no expectation of an effect in *H. pylori*-negative people, one can ignore these and compare gastric cancer incidence in *H. pylori*-positive people in the two randomized arms (see Fig. 4.5.6). The standard nested case–control analysis compares 62 versus 85 cases of gastric cancer (Fig. 4.5.5), which would yield a *P* value of borderline statistical significance (0.06). The more powerful statistical analysis (Fig. 4.5.6) compares 22 versus 45 cases, which yields a highly statistically significant difference ($P = 0.005$).

In this trial, people were recruited from 10 United Kingdom screening centres between 1997 and 2006. They were randomly allocated, by week of attendance, at each screening centre, to a screen-and-treat group or a control group. Since recruitment took place over a decade, the number of randomization groups is large, avoiding the loss of statistical power that can arise from cluster randomized trials. The nested case–control design, within the randomized trial, provides an efficient approach, which is further enhanced by limiting the analysis to individuals in the treated and control arms of the trial who develop gastric cancer and were *H. pylori*-positive on the blood sample they provided at the time of randomization. Follow-up will continue for a further 5 years or more to achieve the required statistical power necessary for the trial results to be informative.

Fig. 4.5.4. *Helicobacter pylori* Screening Study (HPSS): Study design and expected numbers of gastric cancers in the absence of treatment.

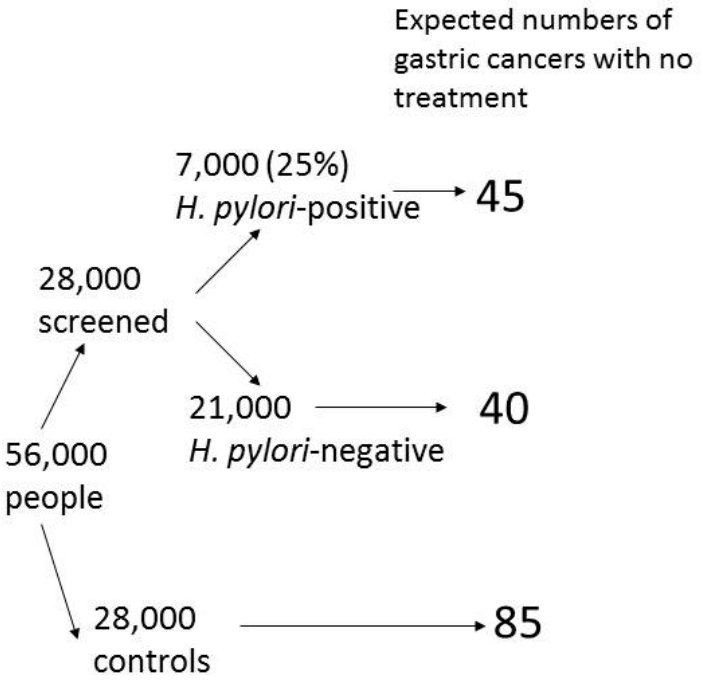


Fig. 4.5.5. *Helicobacter pylori* Screening Study (HPSS): Study design and expected numbers of gastric cancers with treatment.

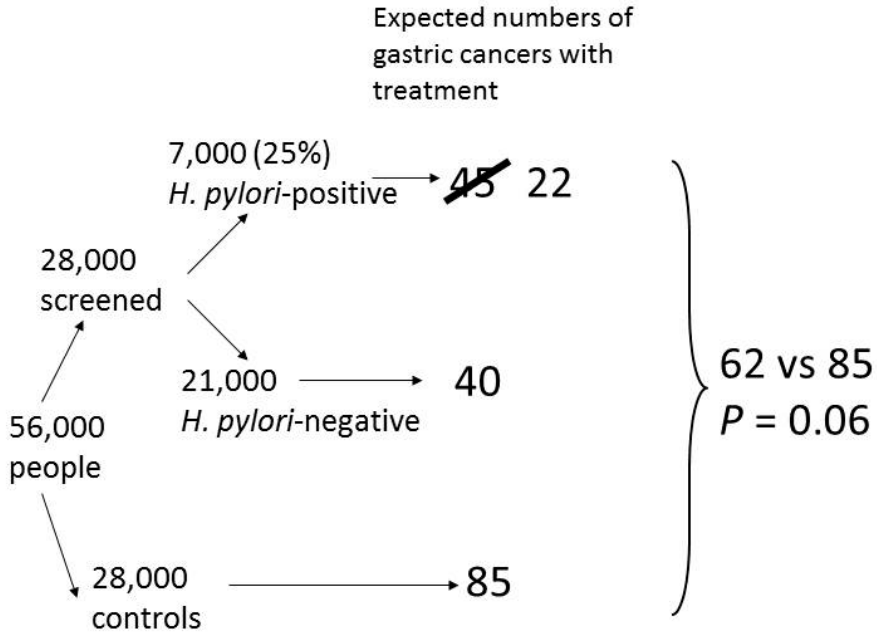
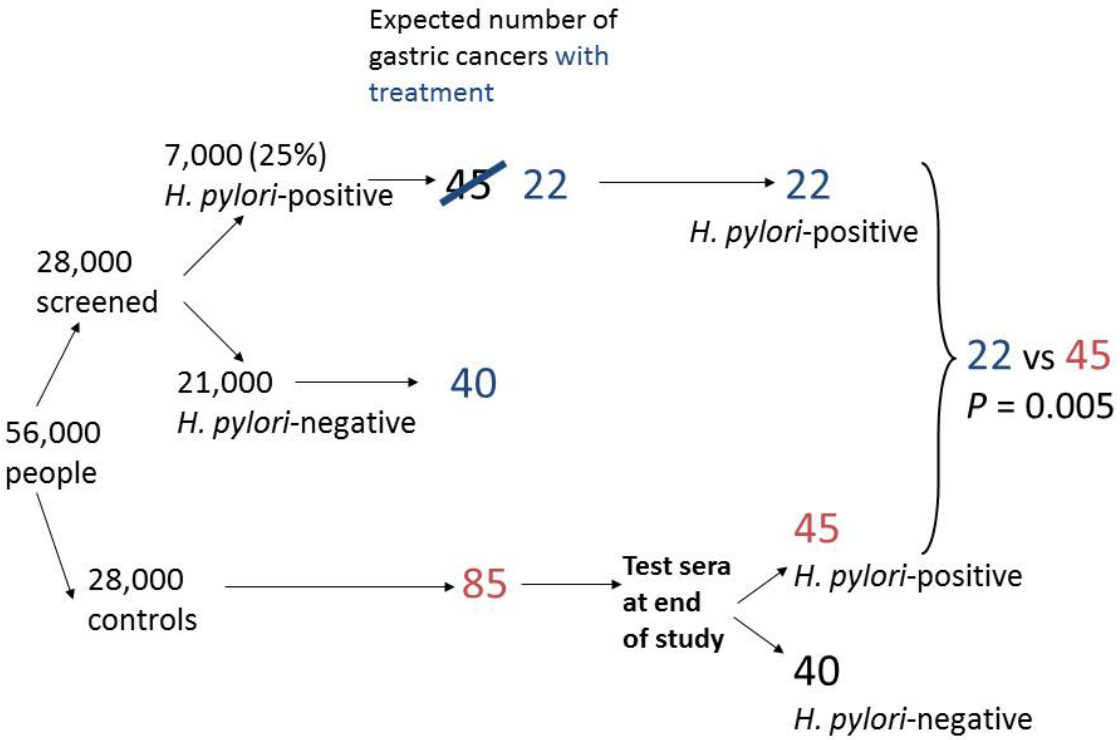


Fig. 4.5.6. *Helicobacter pylori* Screening Study (HPSS): Study design and expected numbers of gastric cancers with treatment using statistical analysis, with enhanced power.



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Disclosures of interests

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