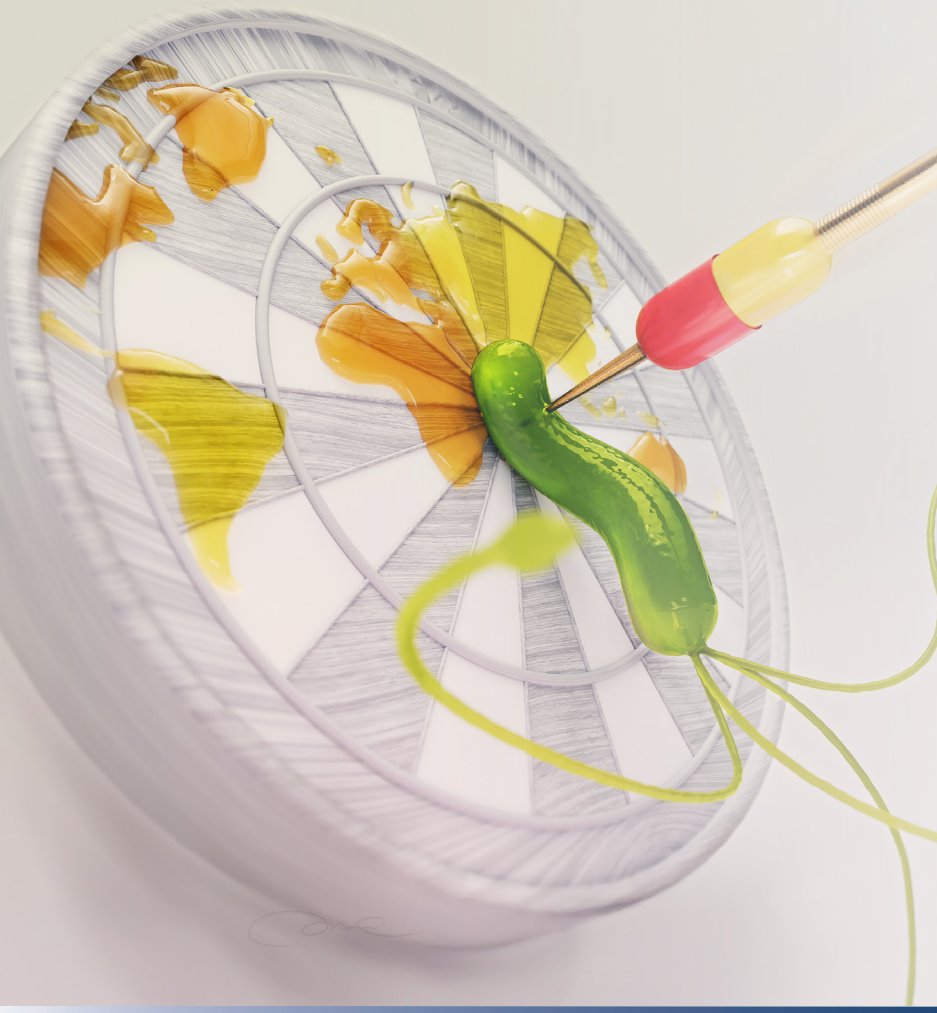
IARC WORKING GROUP REPORTS

POPULATION-BASED *HELICOBACTER PYLORI* SCREEN-AND-TREAT STRATEGIES FOR GASTRIC CANCER PREVENTION

GUIDANCE ON IMPLEMENTATION

EDITED BY JIN YOUNG PARK



IARC WORKING GROUP
REPORT NO. 12

International Agency for Research on Cancer
World Health Organization

Population-based *Helicobacter pylori* screen-and-treat strategies for gastric cancer prevention: guidance on implementation

Edited by Jin Young Park

IARC Working Group Report No. 12

IARC, 2025

Suggested citation.

Park JY, editor (2025). Population-based *Helicobacter pylori* screen-and-treat strategies for gastric cancer prevention: guidance on implementation (IARC Working Group Reports No. 12). Lyon, France: International Agency for Research on Cancer. Available from: https://publications.iarc.who.int/648. Licence: CC BY-NC-ND 3.0 IGO.

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IARC Library Cataloguing-in-Publication Data

Names: Park, Jin Young, editor.

Title: Population-based *Helicobacter pylori* screen-and-treat strategies for gastric cancer prevention: guidance on implementation / edited by Jin Young Park.

Description: Lyon: International Agency for Research on Cancer, 2025. | Series: IARC working group reports, n. 12 | Includes bibliographical references.

Identifiers: ISBN 9789283245285 (ebook)

Subjects: MESH: Stomach Neoplasms. | Helicobacter pylori. | Therapeutics. | Early Detection of Cancer. | Quality Assurance, Health Care.

Classification: NLM WI 320

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Acknowledgements

We would like to thank Ms Nadia Akel and Ms Karima Bendeddouche for their administrative assistance before and during the Working Group meeting, and Ms Viktoria Knaze and Dr Andrea Gini for their help as rapporteurs during the Working Group meeting.

We would like to thank the external reviewers – Dr Linda Rabeneck and Dr Uri Ladabaum – for taking the time to review specific chapters of the Working Group Report based on their individual expertise.

We thank the medical illustrator Dr Monal Yu-Hsuan Chang for designing the cover image.

We thank Dr Andrea Kay for her assistance in technical editing of the report.

The Working Group meeting and Report have been funded by the EUROHELICAN project. EUROHELICAN has been funded by the European Union under the EU4Health Programme.

Disclaimer

Co-funded by the European Union

EUROHELICAN

Accelerating gastric cancer reduction in Europe through *Helicobacter pylori* eradication

Executive summary

*Jin Young Park, Yi-Chia Lee, Paul Moayyedi, Iris Lansdorp-Vogelaar, M. Constanza Camargo, Bojan Tepeš, and David Forman, for the IARC Gastric Cancer Working Group**

The International Agency for Research on Cancer of the World Health Organization (IARC/WHO) convened a Working Group Meeting in February 2025 to provide guidance on the implementation of population-based *Helicobacter pylori* screen-and-treat strategies for adult populations to prevent gastric cancer.

The Working Group members included 35 experts from 20 countries and territories. There were two ad hoc contributors and one observer from the European Commission Joint Research Centre.

At a previous IARC Working Group Meeting, held in December 2013, in which *H. pylori* eradication was evaluated as a strategy for preventing gastric cancer [1], the Working Group recommended that countries explore the possibility of introducing population-based *H. pylori* screen-and-treat programmes. The Working Group emphasized the importance of conducting scientifically valid assessments of programme processes, feasibility, effectiveness, and possible adverse consequences when implementing such programmes [1].

However, practical guidance on implementation of such programmes at the population level has been lacking, which may have contributed to the relatively slow progress with piloting these strategies for gastric cancer prevention globally.

The 2025 Working Group Meeting and Working Group Report focused on providing detailed guidance for the implementation of population-based *H. pylori* screen-and-treat strategies for gastric cancer prevention, highlighting key aspects to consider and incorporate when implementing these programmes at the population level.

The global epidemiology of gastric cancer and *H. pylori*: current and future perspectives for prevention

Gastric cancer is a disease with high morbidity and poor prognosis although it is preventable. Most gastric cancer cases are attributable to chronic infection with *H. pylori*, and this burden is higher than that of any other cancer-causing infection, including human papillomavirus (HPV) and hepatitis B virus and hepatitis C virus combined. Although there exist concerted efforts globally for the elimination of cervical cancer and of viral hepatitis, there is a lack of interest and investment in gastric cancer prevention, except for a few countries with a high burden. The Working Group emphasized that, despite the decreasing trends in incidence and mortality rates observed in many countries, gastric cancer will remain a major global public health problem because of a substantial demographic-driven increase in new cases and deaths. Notably, the largest relative increases in the absolute numbers of new cases of gastric cancer and deaths from gastric cancer are predicted for countries with low and medium levels of the Human Development Index. These increases highlight the importance of coordinated global action for prevention efforts to reduce suffering and death from gastric cancer.

Current evidence from randomized controlled trials of the benefits and harms of population-based *H. pylori* screen-and-treat strategies for gastric cancer prevention and review of the existing recommendations, consensus reports, and guidelines

Existing guidelines, which focus on clinical management of *H. pylori* as a chronic infection, have generally become more assertive over time in their recommendations for population-based *H. pylori* screen-and-treat programmes for gastric cancer prevention. In a systematic review of randomized controlled trials of population-based *H. pylori* screen-and-treat strategies, in healthy *H. pylori*-positive individuals *H. pylori* eradication was associated with a 36% reduction in risk of developing gastric cancer, and in *H. pylori*-positive patients with gastric neoplasia undergoing endoscopic resection *H. pylori* eradication was associated with a 48% reduction in risk of recurrent gastric cancer. The available evidence from clinical trials also indicates that *H. pylori* eradication reduces the incidence of dyspepsia and reduces health-care costs. In addition, *H. pylori* eradication therapy does not appear to

increase the risk of oesophageal cancer or reflux symptoms. The Working Group acknowledged that the evidence related to benefits and potential harms comes mostly from high-risk countries and that information is limited for low-risk areas.

Examples of gastric cancer prevention efforts by WHO region

The Working Group described ongoing and planned gastric cancer prevention efforts grouped by WHO region: in Nigeria and Zambia (WHO African Region); Latin America and the Caribbean, the USA, and Arctic North America (WHO Region of the Americas); Europe (WHO European Region); Bhutan (WHO South-East Asia Region); and China, Japan, the Republic of Korea, the Matsu Islands, and Aotearoa New Zealand (WHO Western Pacific Region). In these subchapters, the need for preparatory steps before implementation of *H. pylori* screen-and-treat programmes was highlighted. These steps include setting up registries and infrastructure to collect information on gastric cancer, *H. pylori* prevalence, and antibiotic resistance patterns in the target populations. In addition, pilot studies in European countries highlighted the importance of population communication and awareness campaigns to increase participation in *H. pylori* screen-and-treat programmes and adherence to treatment.

Needs and readiness for the implementation of *H. pylori* screen-and-treat strategies for gastric cancer prevention locally

Assessment of needs and readiness is critical before implementing an *H. pylori* screen-and-treat programme. In areas with intermediate to high incidence of gastric cancer, a population-based *H. pylori* screen-and-treat programme should be considered a public health priority. In areas with a lower incidence of gastric cancer, *H. pylori* screen-and-treat programmes targeting intermediate-risk and high-risk groups will often be the best option for reducing the gastric cancer burden. Pilot projects, run before the implementation of a full programme, are crucial to assess the local level of readiness. For successful implementation of the programme, sustainable funding, governance, and leadership as well as additional infrastructure to support treatment delivery and overall programme implementation are required.

Considerations for choice of population-based *H. pylori* detection methods

The Working Group recommends that population-based *H. pylori* screening programmes use one or more of these three methods for *H. pylori* detection: the ^{13}C-

urea breath test (UBT), the stool antigen test (SAT), and the serology test. When selecting the screening test, the local context must be considered with respect to test performance, the prevalence of *H. pylori* infection, and other factors, such as infrastructure, participants' preferences, and costs. If serology is chosen for screening, a confirmatory UBT or SAT may be needed. Confirmation of success of *H. pylori* eradication, if undertaken, should be based on the UBT or the SAT at least 4 weeks after the completion of *H. pylori* therapy.

Considerations for choice of *H. pylori* treatment regimens

As participants enter the programme, they should be informed that the treatment is not uniformly successful in eradicating *H. pylori* infection or in preventing gastric cancer and that participation in the programme does not preclude routine medical care. *H. pylori* screen-positive individuals should receive information and counselling about the possible (generally mild) adverse events and the importance of completing the full course of treatment as prescribed. Screen-positive individuals should be treated with regimens informed by local *H. pylori* antibiotic resistance and treatment success rates. Bismuth-containing quadruple therapy is recommended as a first-line therapy, because it is unaffected by clarithromycin resistance and can overcome metronidazole resistance.

Antibiotic stewardship for population-based *H. pylori* screen-and-treat programmes, including testing of cure and monitoring of antibiotic resistance

The Working Group emphasized that population-based *H. pylori* screen-and-treat programmes for gastric cancer prevention should follow robust antibiotic stewardship principles, with oversight by a multidisciplinary group that monitors antibiotic use and resistance. When implementing a programme, a priori treatment success metrics should be established. *H. pylori* eradication rates should be assessed through systematic follow-up testing of treated individuals. *H. pylori* strains from a subset of participants should be tested for antibiotic resistance before and after programme implementation. The impact of increased exposure to antibiotics on the human microbiome, including the resistome, is not yet fully understood, and thus continued awareness, monitoring, and research are warranted. Further investment is needed to develop highly effective *H. pylori* therapies and vaccines. Policy-makers

implementing *H. pylori* screen-and-treat programmes must work to minimize the potential negative impacts of these programmes.

Process and outcome measures for improving the quality and equity of *H. pylori* screen-and-treat programmes for gastric cancer prevention

A population-based *H. pylori* screen-and-treat programme for gastric cancer prevention should adhere to the principles of an organized screening programme for effective and equitable outcomes across groups. The programme must be supported by an information system for data collection and generation of quality indicators. Quality indicators must be monitored to ensure and improve programme effectiveness, equity, safety, and cost–effectiveness. The Working Group emphasized that to ensure equity, at-risk communities should be involved in the design and governance of the *H. pylori* screen-and-treat programme.

How to optimize the cost–benefits of *H. pylori* screen-and-treat programmes for gastric cancer prevention

The Working Group concluded that the *H. pylori* screen-and-treat strategy is cost-effective (and may be cost saving) in high-risk settings. It is likely to be cost-effective even in low-risk settings. The optimal strategies (with respect to target population, *H. pylori* detection methods, age, confirmatory tests, and choice of treatment) depend on the local context. The Working Group emphasized the importance of decision modelling for making recommendations for the context-appropriate strategy based on information collected from local pilot projects. Long-term follow-up data on ancillary benefits and potential harms are needed to improve decision modelling, because these may play a significant role in the balance between the benefits, harms, and costs of *H. pylori* screen-and-treat programmes.

Conclusions

This Working Group Report, for the first time, comprehensively discussed and laid out essential considerations to be incorporated when implementing population-based *H. pylori* screen-and-treat strategies as an organized programme for gastric cancer prevention.

The Working Group emphasized that a population-based *H. pylori* screen-and-treat programme should be considered a public health priority in areas or populations

with elevated risk, for gastric cancer prevention. Assessment of needs and readiness at the local level by running pilot projects is essential before implementing the programme. Options for the screening test include the UBT, the SAT, and the serology test. The choice of treatment should be informed by local *H. pylori* antibiotic resistance data and eradication success rates, and the Working Group recommends bismuth-containing quadruple therapy as a first-line therapy. Ensuring and adopting robust antibiotic stewardship is of paramount importance for the success of the programmes, and further investment is urgently needed to develop highly effective *H. pylori* therapies and vaccines. The Working Group emphasized that *H. pylori* screen-and-treat programmes have the greatest chance of being equitable if the people with the highest rates of *H. pylori* infection participate and are successfully treated. Recognizing that the *H. pylori* screen-and-treat strategy is cost-effective for preventing gastric cancer, decision modelling is instrumental for recommending the context-appropriate strategy based on information collected from local pilot projects.

In the light of the increasing global burden of gastric cancer, driven by shifting epidemiological trends, the Working Group emphasized that prevention remains the most effective strategy for reducing this burden. Outlining essential considerations for implementing population-based *H. pylori* screen-and-treat programmes for gastric cancer prevention, this Working Group Report serves as a global reference for future development of evidence-based recommendations, best practice guidelines, and related quality assurance schemes.

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Abbreviations

ACG	American College of Gastroenterology
ACHED	Chilean Association of Digestive Endoscopy
AHMSG	African *Helicobacter* and Microbiota Study Group
ASEAN	Association of Southeast Asian Nations
ASR	age-standardized rate
AWaRe	Access, Watch, Reserve
BUPA	British United Provident Association
CAN*Help*	Canadian North *Helicobacter pylori*
CanSPUC	Cancer Screening Program in Urban China
CCSS	Caja Costarricense de Seguro Social
CDC	United States Centers for Disease Control and Prevention
CGC	cardia gastric cancer
CI	confidence interval
CISNET	Cancer Intervention and Surveillance Modeling Network
CONCORD	Global Surveillance of Trends in Cancer Survival
COX-2	cyclooxygenase-2
CT	computed tomography
DCEG	Division of Cancer Epidemiology and Genetics
DDD	defined daily dose
EAPC	estimated annual percentage change
ECHOS	Endoscopic Cohort and Histological OLGA Staging
EEA	European Economic Area
ELISA	enzyme-linked immunosorbent assay
EMR	endoscopic mucosal resection
EU	European Union
EUCanScreen	European Joint Action on Cancer Screening
EUROHELICAN	Accelerating Gastric Cancer Reduction in Europe through *H. pylori* Eradication
FIT	faecal immunochemical test
GC-GAP	Gastric Cancer Global Action Preparedness

GCPL	Gastric Cancer Precursor Lesions
GISTAR	Multicentric Randomized Study of *H. pylori* Eradication and Pepsinogen Testing for Prevention of Gastric Cancer Mortality
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HDI	Human Development Index
HELPER	*Helicobacter pylori* Eradication for Gastric Cancer Prevention in the General Population
HER2	human epidermal growth factor receptor 2
HOPE-Hp-GC	Hospital and Outpatient Prevention Program to Eradicate *H. pylori* and Gastric Cancer
HP	anti-*H. pylori* IgG antibody
Hp-AfricaReg	*H. pylori* Africa Registry
Hp-EuReg	European Registry on *H. pylori* Management
Hp-LATAMReg	Latin American Registry on the Management of *H. pylori* Infection
Hp-RESLA	*H. pylori*-antibiotics RESistance in Latin America
HPSS	United Kingdom *H. pylori* Screening Study
HPV	human papillomavirus
HR	hazard ratio
IARC	International Agency for Research on Cancer
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th revision
ICER	incremental cost–effectiveness ratio
IgG	immunoglobulin G
IL	interleukin
KNCSP	Korean National Cancer Screening Program
KNHIS	Korean National Health Insurance Service
LAC	Latin America and the Caribbean
LGIN	low-grade intraepithelial neoplasia
MALT	mucosa-associated lymphoid tissue
MISCAN	Microsimulation Screening Analysis
MITS	Mass Intervention Trial in Linqu, Shandong
NCGC	non-cardia gastric cancer
NCI	United States National Cancer Institute

NIH	United States National Institutes of Health
NNT	number needed to treat
NPV	negative predictive value
OGD	oesophago-gastro-duodenoscopy
OLGA	Operative Link on Gastritis Assessment
OLGIM	Operative Link on Gastric Intestinal Metaplasia Assessment
OPGE	Pan American Gastroenterology Organization (Organización Panamericana de Gastroenterología)
OR	odds ratio
OSCC	oesophageal squamous cell carcinoma
P-CAB	potassium-competitive acid blocker
PCR	polymerase chain reaction
PD-L1	programmed death-ligand 1
PG	pepsinogen
PHIA	Population-based HIV Impact Assessment
PPI	proton pump inhibitor
PPV	positive predictive value
QALY	quality-adjusted life year
RCT	randomized controlled trial
RR	relative risk
RUT	rapid urease test
SAT	stool antigen test
SEER	Surveillance, Epidemiology, and End Results
SIT	Shandong Intervention Trial
Th	T helper
TOGAS	Towards Gastric Cancer Screening Implementation in the European Union
UBT	urea breath test
UGCED	Upper Gastrointestinal Cancer Early Detection
UGIE	upper gastrointestinal endoscopy
UGIS	upper gastrointestinal series
WHO	World Health Organization

Introduction

Jin Young Park

Background

In 2013, a Working Group convened by the International Agency for Research on Cancer (IARC) [1] to consider strategies for gastric cancer prevention through *Helicobacter pylori* eradication recommended introducing population-based *H. pylori* screen-and-treat programmes in conjunction with a scientific assessment of the programme's processes, feasibility, effectiveness, and possible adverse consequences. Other international guidelines and consensus reports [2, 3] have also recommended the implementation of *H. pylori* screen-and-treat programmes, especially in high-risk areas for gastric cancer. The strategy has additional benefits in reducing the prevalence of other important clinical conditions, such as peptic ulcer disease, dyspepsia, iron-deficiency anaemia, and idiopathic thrombocytopenic purpura. It also provides a key opportunity to address the inequalities associated with gastric cancer, even in low-risk areas for gastric cancer.

Population-based *H. pylor*i screen-and-treat programmes are being implemented, albeit slowly, in some Asian settings with a high prevalence of *H. pylori* infection, such as in the Matsu Islands [4], in Japan (through national insurance coverage of *H. pylori* treatment) [5], and in Bhutan [6]. In particular, Bhutan recently initiated two national programmes for gastric cancer prevention as part of its Health Flagship Programme: (i) population-based *H. pylori* screen-and-treat programmes for people aged 18–75 years, and (ii) population-based screening for precancerous lesions using upper endoscopy for people aged 40–75 years [6]. Other countries, such as China, Japan, and the Republic of Korea, continue to focus their efforts on population-based screening for gastric cancer using national or regional endoscopic screening programmes.

Population-based *H. pylori* screen-and-treat programmes are also seen as important tools for gastric cancer prevention in European Union countries, especially for countries with a high burden of gastric cancer. These programmes were endorsed in the recently announced Europe's Beating Cancer Plan and in

subsequent recommendations on the prevention of gastric cancer from Science Advice for Policy by European Academies [7] and the European Council [8].

The outcomes of the implementation of population-based *H. pylori* screen-and-treat programmes in high-risk areas of Europe will be investigated in two European Union projects for gastric cancer prevention that have been launched recently: Accelerating Gastric Cancer Reduction in Europe through *H. pylori* Eradication (EUROHELICAN) and Towards Gastric Cancer Screening Implementation in the European Union (TOGAS).

Despite the international guidelines and recent initiatives and interest in implementing *H. pylori* screen-and-treat programmes in asymptomatic populations for gastric cancer prevention in various regions, no global guidance is currently available on how to successfully implement and evaluate such programmes at the population level.

Objectives and scope

As part of the EUROHELICAN project, IARC convened a 3-day Working Group Meeting bringing together an international, interdisciplinary group of experts to discuss best practices in the implementation of population-based *H. pylori* screen-and-treat strategies for adult populations for gastric cancer prevention.

This IARC Working Group Report addresses population-based *H. pylori* screen-and-treat strategies as specific interventions for the primary prevention of gastric cancer. The scope and objective of the Working Group Report need to be distinguished from existing guidelines or consensus that have been developed within the context of clinical management of chronic infection with *H. pylori* and are therefore oriented towards treatment of *H. pylori*-related clinical manifestations. In addition, such strategies should be distinguished from the secondary prevention of gastric cancer by early detection of precancerous lesions (i.e. precancers) or invasive cancers and their treatment, which is often termed “gastric cancer screening”. To avoid confusion, clarification is always required as to whether the term “screen-and-treat” or “screening and treatment” refers to *H. pylori* infection (as is the case in this publication) or to precancerous lesions.

The scope of the Working Group Meeting and this Working Group Report is not limited to Europe but covers all world regions, including various levels of the Human

Development Index and background burdens of disease, to ensure that the guidance is globally applicable.

Structure of the report

Chapter 1 describes the global epidemiology of gastric cancer and *H. pylori* infection, based on the latest estimates from IARC's GLOBOCAN and *Cancer Incidence in Five Continents* databases. **Chapter 2** summarizes the scientific evidence on the effect of population-based *H. pylori* screen-and-treat strategies for gastric cancer prevention and the currently available guidelines and recommendations on the strategies. **Chapter 3** presents various gastric cancer prevention efforts for each World Health Organization (WHO) region and highlights the gaps in knowledge and the future efforts that are needed.

The subsequent chapters detail programmatic aspects of the strategies for implementation at the population level. **Chapter 4** provides an overview of the needs and readiness to implement *H. pylori* screen-and-treat strategies locally, **Chapter 5** presents considerations for selecting *H. pylori* detection methods, and **Chapter 6** discusses considerations for choosing treatment regimens for population-based implementation of *H. pylori* screen-and-treat strategies. **Chapter 7** discusses antibiotic stewardship, focusing on the key principles to ensure the appropriate use of antibiotics to fight against the global threat of antimicrobial resistance. **Chapter 8** proposes process and outcome measures for improving the quality and equity of the strategies, and **Chapter 9** discusses how to optimize the cost–benefits of population-based *H. pylori* screen-and-treat programmes for gastric cancer prevention.

Definitions

In **Chapters 1** and **3**, incidence, mortality, trends over time, and absolute burdens across countries and regions with different levels of the Human Development Index are described in terms of the numbers of new cases and deaths, and age-standardized rates (ASRs, world standard population) are used for international comparisons to account for differences in age structures. In other chapters, such as **Chapters 4** and **8**, in which the planning aspects of the strategies are discussed, crude and age-specific rates are also used to reflect the actual experience of the specific population and the true magnitude of the health risks, and to highlight high-risk subgroups that may warrant intervention [9].

Although the Working Group wanted to avoid endorsing strict (bright-line) criteria based on ASRs to define high risk or low risk of gastric cancer, in this publication incidence rates (ASR) of < 10 per 100 000 person-years are used as indicative of “low” risk, and incidence rates (ASR) of ≥ 10 per 100 000 person-years indicate populations with “intermediate to high” risk.

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Chapter 1.

The global epidemiology of gastric cancer and *Helicobacter pylori*: current and future perspectives for prevention

Eileen Morgan, Gary Clifford, and Jin Young Park

Summary

- Gastric cancer remains and will remain a major global public health problem because of a substantial demographic-driven increase in burden, despite the decreasing incidence trends observed in many countries.
- The largest relative increases in the absolute numbers of new cases of gastric cancer and deaths from gastric cancer are predicted for countries with low and medium levels of the Human Development Index.
- The majority of gastric cancer cases are attributable to chronic infection with *H. pylori*, which is highly preventable. This highlights the importance of coordinated global action for prevention of *H. pylori* infection, to reduce suffering and death from gastric cancer.

1.1 Introduction

This chapter examines the global landscape of gastric cancer incidence and mortality in 2022. Overall comparisons of gastric cancer incidence and mortality rates between countries are presented using age-standardized rates (ASRs). This chapter focuses on variations in gastric cancer incidence and mortality rates in countries with different levels of the Human Development Index (HDI) using the databases of recorded data and estimates that are collected and disseminated by IARC. The trends in incidence of gastric cancer over time are presented for selected countries. Where possible, global patterns of incidence rates are examined for the two main subsites of gastric cancer: cardia gastric cancer (CGC) and non-cardia gastric cancer (NCGC). CGC, which occurs in the part of the stomach adjoining the gastro-oesophageal junction, and NCGC, which occurs in the distal regions of the stomach, have overlapping and distinct risk factors,

which warrant independent investigation. Predictions for the future global burden of these cancers and the preventable cases are made based on the current estimates. Finally, the global patterns of gastric cancer described in this chapter are presented in the context of the known risk factors for gastric cancer, with a focus on *H. pylori* infection and its contribution to the global burden of gastric cancer incidence.

1.2 Data sources and methods

This chapter explores the current patterns and trends of gastric cancer using the recorded trends and estimates hosted at IARC and distributed on the IARC Global Cancer Observatory platform [1]. Estimates of new gastric cancer cases and deaths from gastric cancer in 2022 in 185 countries and territories worldwide were extracted from the GLOBOCAN database. The sources and methods that were used to estimate country-specific incidence and mortality have been documented elsewhere [2]. Incidence and mortality across countries and regions with different HDI levels are described in terms of the numbers of new cases and deaths, as well as the ASRs, so that comparisons across countries can be made. *Cancer Incidence in Five Continents* Volume XII is an IARC publication that uses high-quality incidence data provided by population-based cancer registries [3]. This chapter provides the incidence patterns for the two main subsites of gastric cancer: CGC, which is defined as International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) code C16.0, and NCGC, which is defined as ICD-10 codes C16.1–C16.9, whereby cancers with overlapping or undefined topography were considered to be NCGC. In instances in which > 75% of all cases of gastric cancer in a population were coded as "not otherwise specified", which is defined as ICD-10 code C16.9, these were excluded from any subsite analyses. Sex- and age-specific proportions of CGC and NCGC subtypes were calculated for the countries in *Cancer Incidence in Five Continents*, and these proportions were then applied to the total number of estimated gastric cancer cases by 5-year age group, sex, and country in GLOBOCAN 2022. The ASRs of incidence and mortality (per 100 000 person-years) were calculated based on the world standard population [4], sex, and HDI level. Patterns by HDI level were examined to investigate variations in gastric cancer incidence and mortality in terms of the level of resources and societal development of countries. HDI was defined using the predefined four-tier distribution described in the United Nations Development Programme's Human Development Report 2021–2022 [5]. Trends in gastric cancer incidence over time were

examined using data from population-based cancer registries of cases diagnosed in 1980–2017 [3, 6, 7]. The numbers of new gastric cancer cases by 2050 were predicted using demographic projections assuming that rates as estimated in 2022 remained stable over the prediction period (2022–2050).

1.3 Global patterns of gastric cancer

Gastric cancer is the fifth most commonly diagnosed cancer and the fifth leading cause of cancer death worldwide, with an age-standardized incidence rate of 9.2 per 100 000 person-years and an age-standardized mortality rate of 6.1 per 100 000 person-years in 2022 [8]. In absolute numbers, an estimated 969 000 new cases of gastric cancer (4.8% of all cancer cases) were diagnosed and 660 000 deaths from gastric cancer (6.8% of all cancer deaths) occurred in 2022 [1].

A wide variation in gastric cancer incidence and mortality rates is observed across world regions (Fig. 1.1). The regions of eastern Asia (male ASR, 23.0 per 100 000 person-years; female ASR, 9.7 per 100 000 person-years; 521 000 new cases combined) and eastern Europe (male ASR, 16.2; female ASR, 7.7; 66 400 new cases combined) have the highest incidence rates. By World Health Organization (WHO) region, the Western Pacific Region has the highest incidence (ASR, 15.2; 543 757 new cases), followed by the European Region (ASR, 8.4; 161 553 new cases), the Eastern Mediterranean Region (ASR, 6.6; 37 781 new cases), the Region of the Americas (ASR, 6.4; 103 924 new cases), the South-East Asia Region (ASR, 4.4; 95 622 new cases), and the African Region (ASR, 4.1; 25 851 new cases) [1].

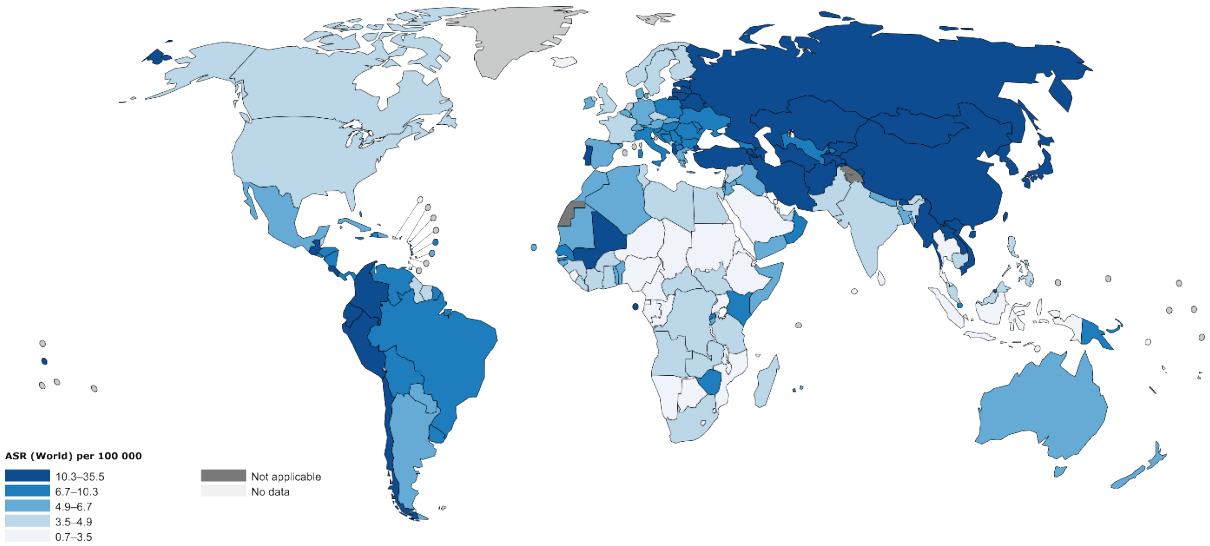


Fig. 1.1. Global incidence of gastric cancer in 2022 by country. ASR, age-standardized rate. Source: Ferlay et al. (2024) [1].

Of the top 25 countries for incidence of gastric cancer worldwide, Mongolia (male ASR, 53.0 per 100 000 person-years; female ASR, 21.9 per 100 000 person-years), Japan (male ASR, 40.9; female ASR, 15.9), and the Republic of Korea (male ASR, 38.4; female ASR, 16.9) have the highest incidence rates in both males and females (Fig. 1.2) [1]. Similar patterns in mortality are observed, with high mortality rates observed in countries with high incidence rates of gastric cancer. Japan and the Republic of Korea are exceptions to this pattern, because the mortality rates are about one quarter of the incidence rates observed in these countries. This is probably due to the introduction of radiographic screening in the 1960s in Japan, which was expanded to a nationwide screening programme in 1983 [9], and the introduction of an endoscopic-focused national screening programme in the Republic of Korea in 2000 [10], which have led to a shift in the stage at diagnosis and markedly improved the survival proportion of this cancer, which generally has a poor prognosis [11, 12].

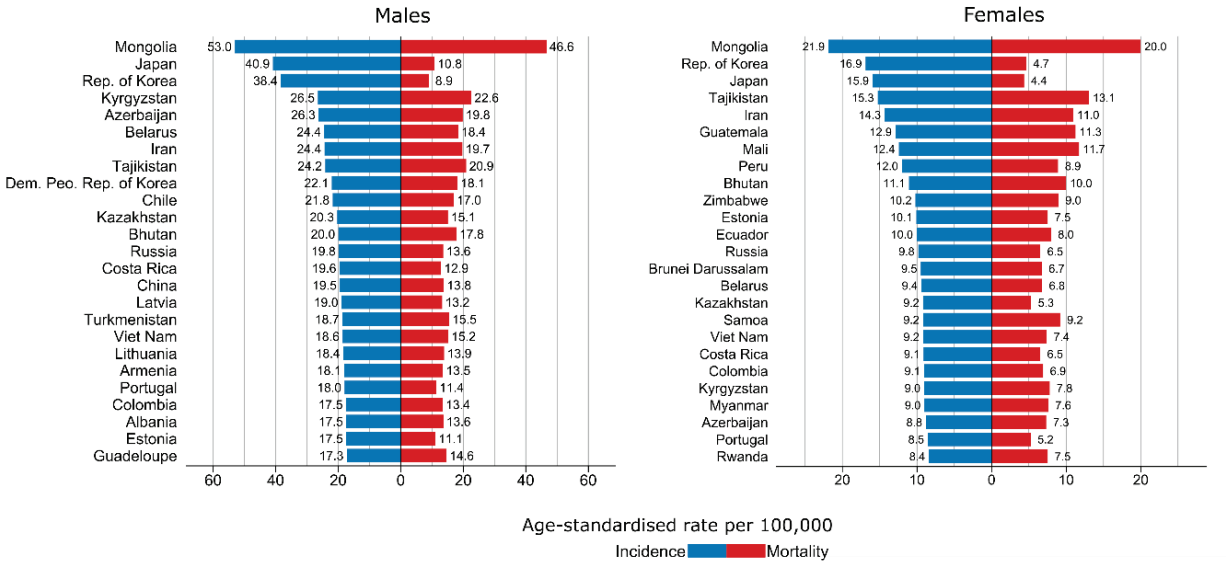


Fig. 1.2. Age-standardized incidence and mortality rates (per 100 000 person-years) for the 25 countries with the highest incidence rates of gastric cancer, from GLOBOCAN 2022. Source: Ferlay et al. (2024) [1].

The risk of gastric cancer varies substantially even within the same region (Fig. 1.3) [1]. Also, certain populations within low-incidence countries have a higher risk of gastric cancer, for example specific ethnic groups (see Chapter 4).

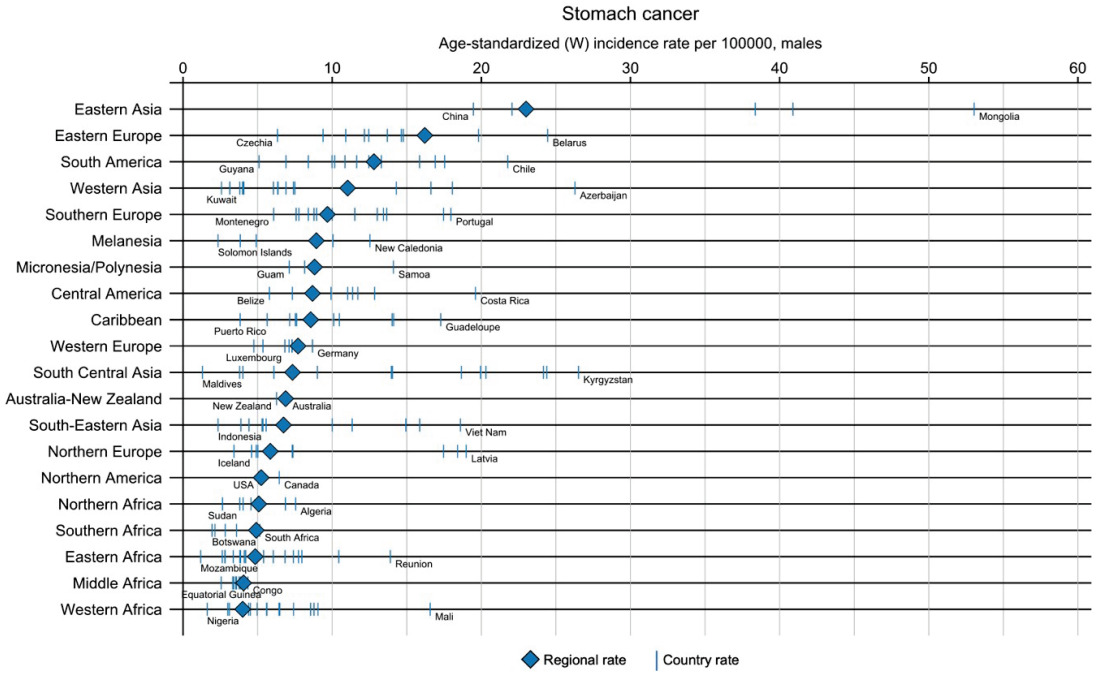


Fig. 1.3. Age-standardized incidence rates (per 100 000 person-years) of gastric cancer, in males, by world region. Source: Ferlay et al. (2024) [1].

Gastric cancer incidence was higher in areas with higher levels of HDI; 830 000 cases (85.7% of all gastric cancer cases) occurred in countries with high or very high HDI, compared with 138 000 cases (14.3% of all cases) in countries with low or medium HDI. This is driven by the high incidence rates in a few countries: the Republic of Korea and Japan in the group with very high HDI and China in the group with high HDI. China, the most populous of the countries with high or very high HDI, accounts for 43% of the cases of gastric cancer in the countries with high and very high HDI (359 000 cases), which is 37% of all gastric cancer cases worldwide. For mortality from gastric cancer, countries with low and medium HDI contribute to an important proportion of deaths from gastric cancer (18.4% of all gastric cancer deaths) relative to their contribution to the global gastric cancer burden (14.3% of all gastric cancer cases). This indicates a need to initiate dialogue to enable more affordable preventive strategies for gastric cancer to be made available in these countries.

1.4 Overview of gastric cancer incidence by subsite (cardia and non-cardia)

NCGC is the most common subtype of gastric cancer (853 000 cases), and this subtype contributes 82% of all gastric cancer cases worldwide, compared with CGC (181 000 cases), which contributes 18% of all cases. NCGC is consistently the more common subtype in all regions worldwide. The highest incidence rates of both subtypes are observed in East Asia (Fig. 1.4) [3]. Although both overlapping and distinct risk factors for the two subtypes have been identified, with much focus on the association of *H. pylori* infection and NCGC, there is increasing evidence for an association of *H. pylori* infection and CGC; about 62% of CGC cases in Asia could be attributable to *H. pylori* infection [14]. Given that the majority of the global NCGC and CGC burden is in East Asia [13], population-based *H. pylori* screen-and-treat strategies may have even larger beneficial effects in these high-risk settings.

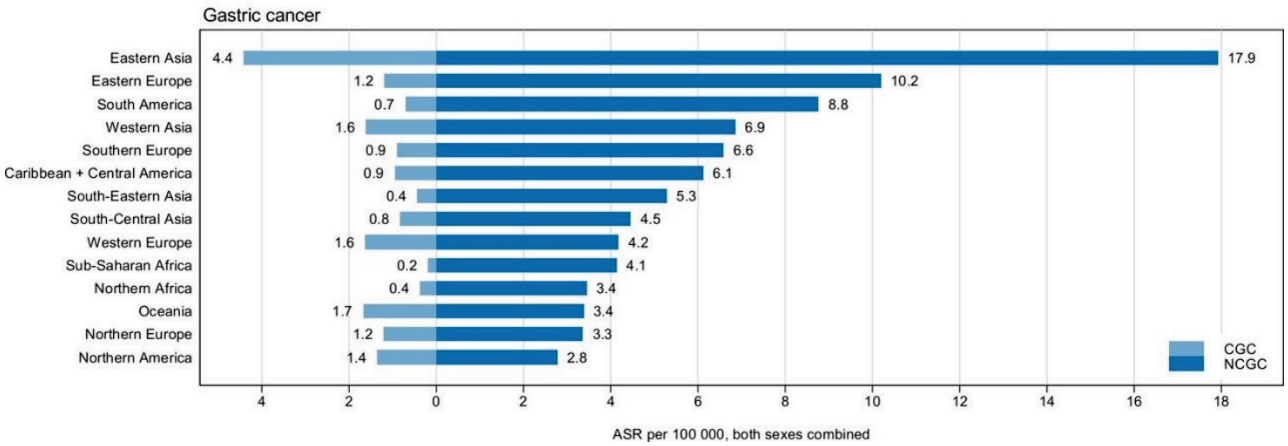


Fig. 1.4. Age-standardized incidence rates (per 100 000 person-years) of gastric cancer for each subsite, cardia gastric cancer (CGC) and non-cardia gastric cancer (NCGC), by world region. Source: Reproduced from Arnold et al. (2020) [13], © 2020 with permission from BMJ Publishing Group Ltd.

1.5 Trends in gastric cancer incidence over time

Fig. 1.5 shows the trends in the annual ASR of gastric cancer incidence in the countries for which data are available, and Fig. 1.6 shows the estimated annual percentage change (EAPC) of gastric cancer incidence rates in selected countries for the most recent 10 years (2008–2017). The decreasing prevalence of *H. pylori* infection as well as improved sanitation, changes in diet, and widespread use of antibiotics may have resulted in decreases in the incidence of gastric cancer, predominantly in countries with higher HDI [16]. During the most recent 10 years (2008–2017), gastric cancer incidence rates mostly decreased across countries, with incidence rates decreasing by more than 3% per year in several countries, including Bahrain, Costa Rica, Cyprus, Czechia, Denmark, Malta, Norway, Qatar, the Netherlands, the Republic of Korea, and the United Kingdom (England) [15].

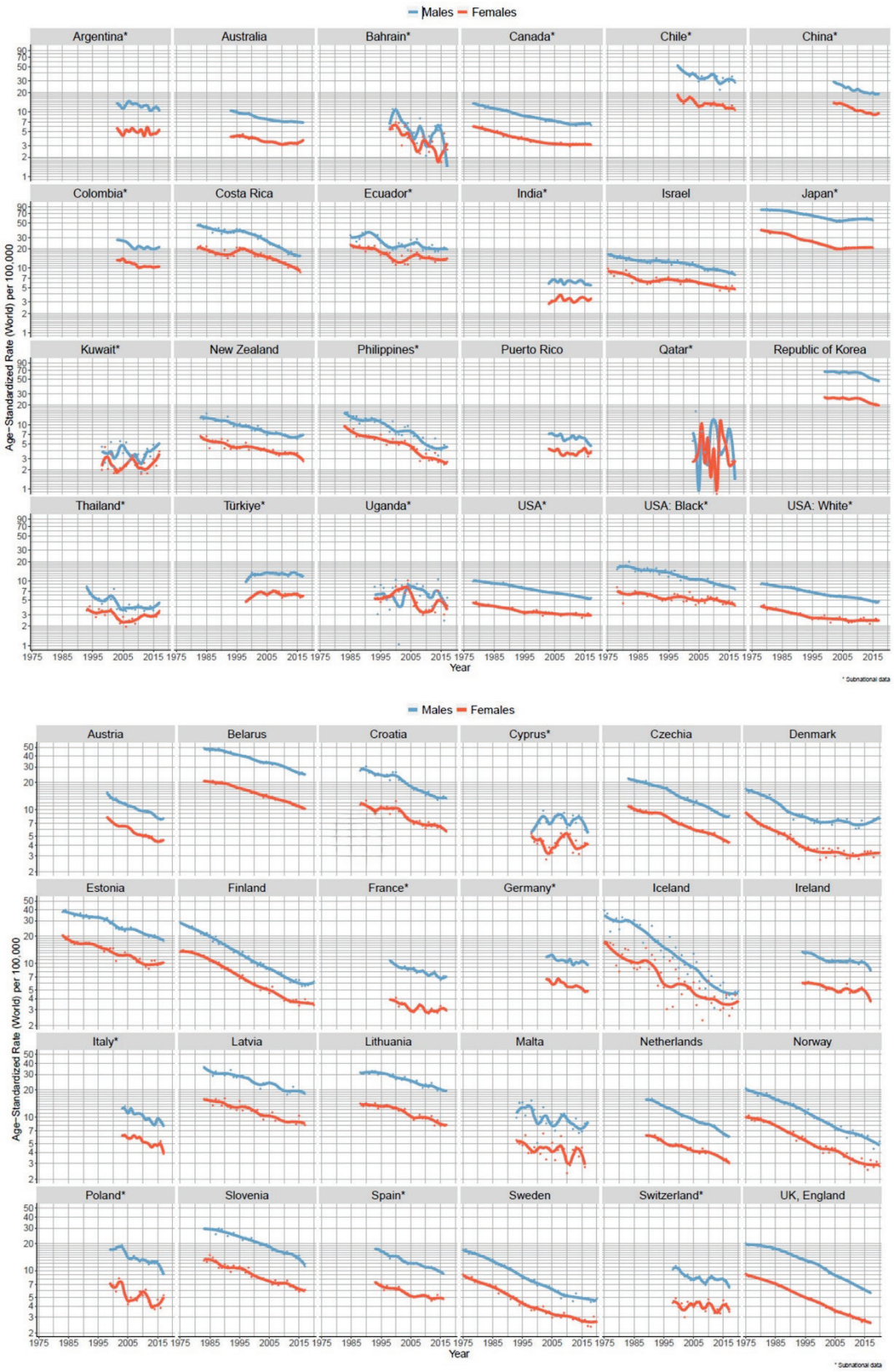


Fig. 1.5. Trends in age-standardized incidence rates (per 100 000 person-years) for gastric cancer in selected countries, 1980–2017. Source: Ervik et al. (2024) [15].

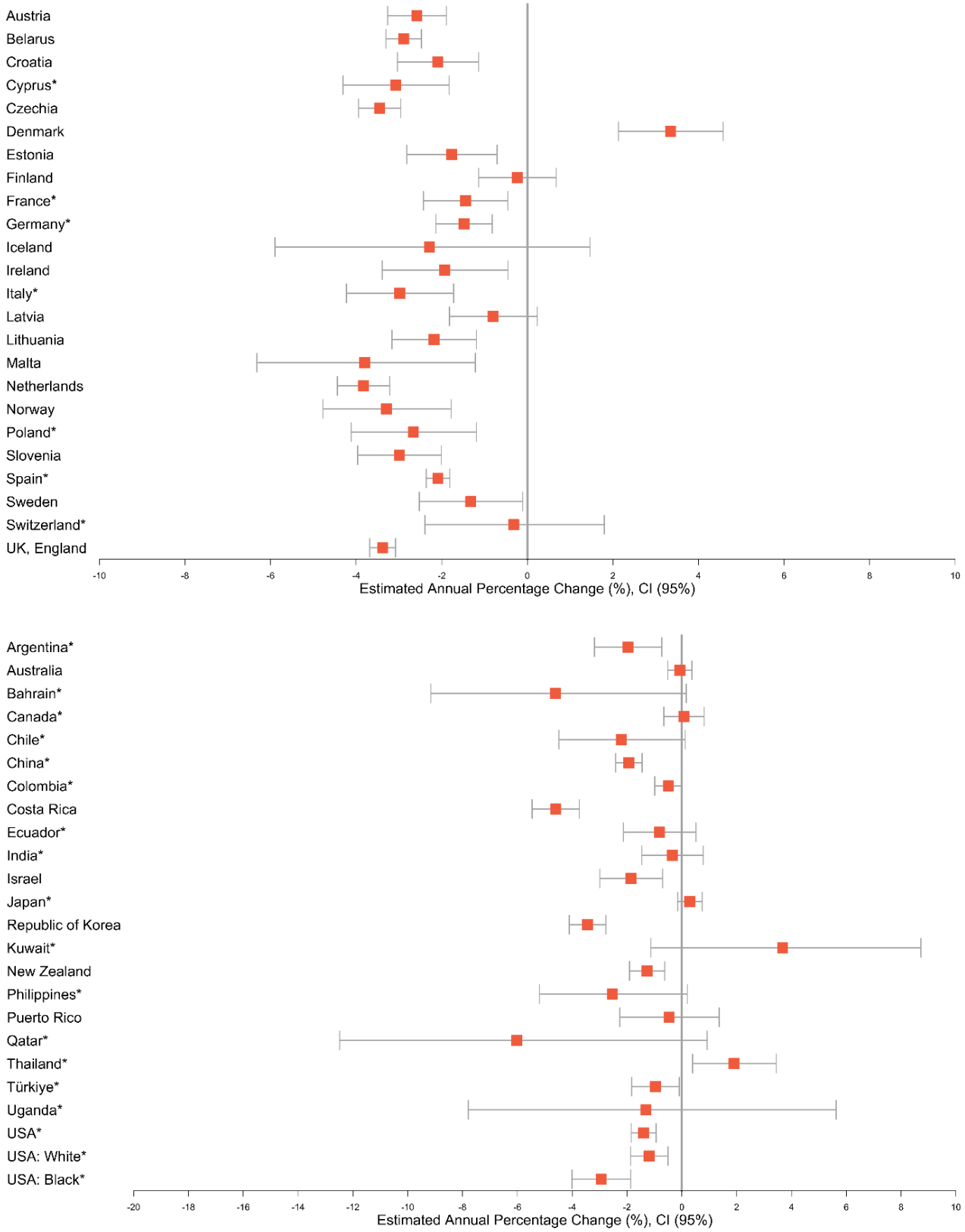
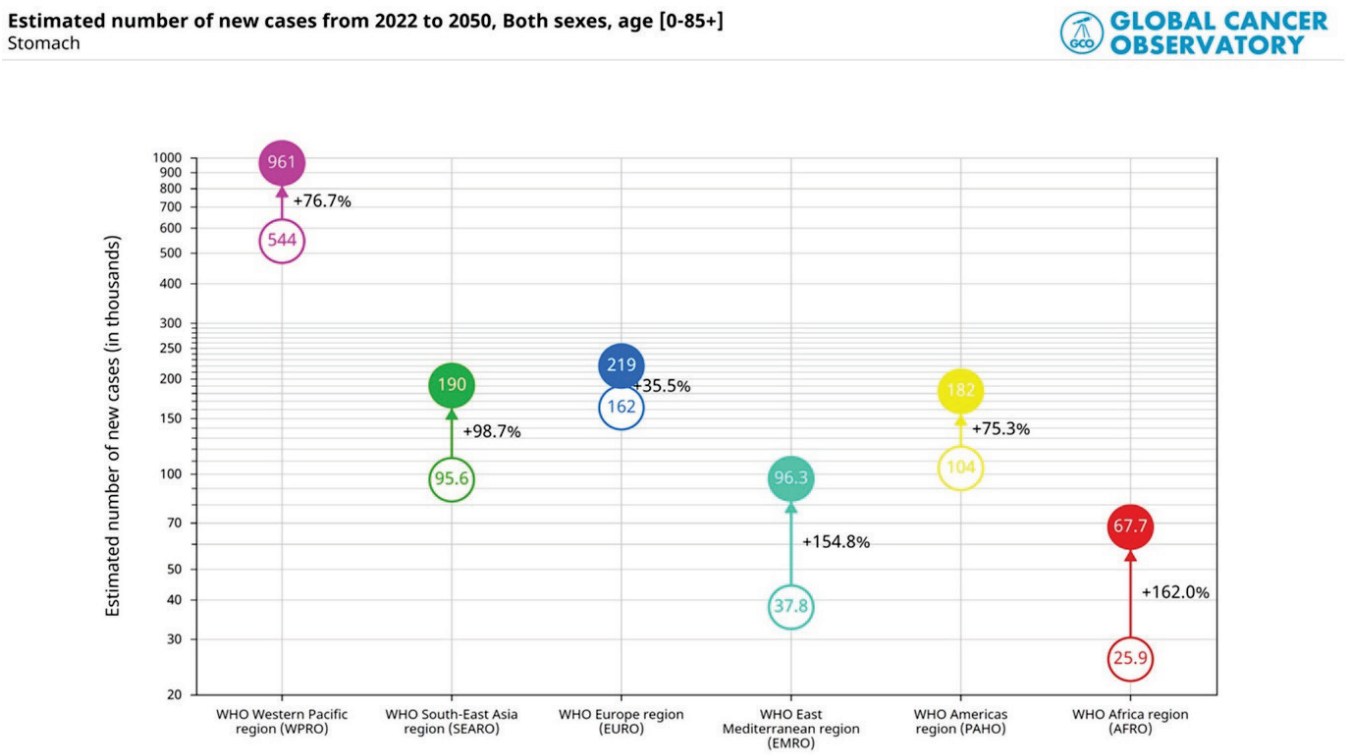


Fig. 1.6. Estimated annual percentage change (EAPC) of gastric cancer incidence rates for the most recent 10 years (2008–2017) in selected countries. CI, confidence interval. Source: Ervik et al. (2024) [15].

Previous studies have noted that the decreasing trends in gastric cancer incidence observed in some countries were more pronounced in older age groups, and an equivalent decrease has not always been seen in younger age groups [17, 18]. In younger populations (aged < 50 years) in 15 of 34 countries with both low and high incidence rates, increases in incidence have been observed [17]. In the same age group, increasing incidence rates of 1.3% per year in 1995–2013 for NCGC in non-Hispanic White Americans were reported using data from a population-based registry in the USA [19]. These increases were especially pronounced for women (EAPC, 2.6%). Although these observations are important, they require careful interpretation, because some of the observed increases may be due to the redistribution of unspecified tumours [13].

1.6 The burden of gastric cancer incidence and mortality by 2050

Although incidence rates of gastric cancer have been generally decreasing in countries, the absolute number of new gastric cancer cases is expected to increase because of demographic changes in populations (i.e. population growth and increasing longevity). Globally, it is predicted that there will be an 87.5% increase in the number of gastric cancer cases, assuming that current rates remain stable, from the 969 000 new cases estimated in 2022 to 1.82 million new cases estimated in 2050 [20]. By WHO region, the Western Pacific Region is expected to have the highest numbers of new cases and deaths in 2050 (961 000 new cases, 646 000 deaths) and the African Region to have the lowest numbers (67 700 new cases, 59 500 deaths). However, the largest relative increases are expected in the African Region, with increases of 162.0% in the number of new cases and 163.9% in the number of deaths (Fig. 1.7). The absolute number of new cases predicted in 2050 will be highest in countries with higher HDI (1.4 million cases) compared with countries with lower HDI (306 190 cases). The largest relative increases in new cases are predicted to occur in countries with low and medium HDI, with an increase of 153.2% in countries with low HDI and an increase of 114.0% in countries with medium HDI (Fig. 1.8A). The number of deaths from gastric cancer is predicted to increase by 94.7% by 2050, from the 660 000 deaths estimated in 2022 to 1.29 million deaths estimated in 2050. The largest relative increases in gastric cancer deaths are predicted to occur in countries with lower HDI, with an increase of 154.2% in countries with low HDI and an increase of 116.2% in countries with medium HDI, contributing about 271 195 deaths in 2050 (Fig. 1.8B).



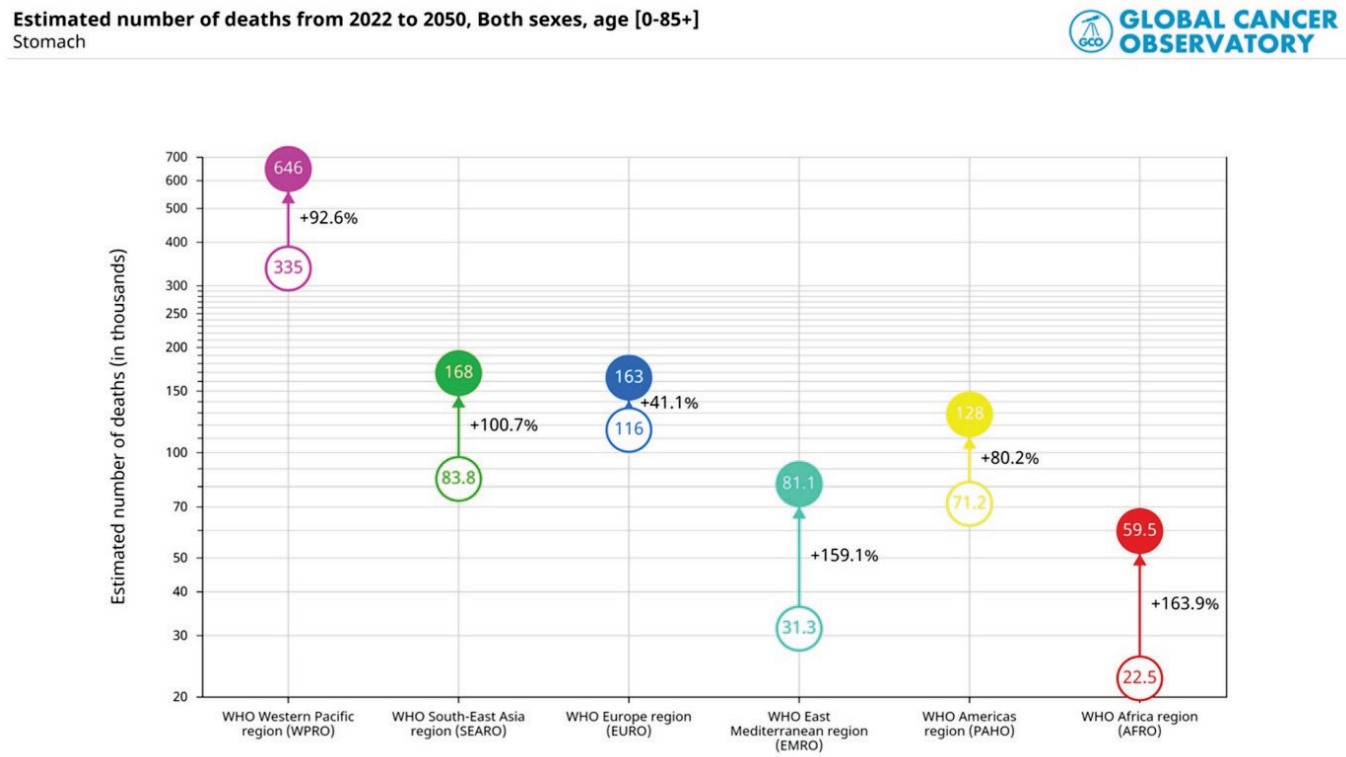


Fig. 1.7. Estimated number of (top) new cases of gastric cancer and (bottom) deaths from gastric cancer, 2022 to 2050, by WHO region. Source: Ferlay et al. (2024) [20].

These predictions are based on the assumption that current rates will remain stable. In many countries, a decrease in gastric cancer incidence and mortality has been observed, with an annual percentage decrease of ≥ 3% in many countries. However, even if the 3% annual decrease is assumed to be observed globally, there will still be a 50% increase in the predicted numbers of gastric cancer cases by 2050, with an estimated 1.45 million new cases.

Fig. 1.8. Estimated number of (top) new cases of gastric cancer and (bottom) deaths from gastric cancer, 2022 to 2050, by level of Human Development Index (HDI). Source: Ferlay et al. (2024) [20].

1.7 Lifetime estimates of expected and preventable gastric cancers

IARC estimated the numbers of expected and preventable gastric cancer cases for people born between 2008 and 2017 globally [21]. Based on data from GLOBOCAN 2022, the lifetime global burden of gastric cancer in these birth cohorts is expected to reach 15.6 million cases in the absence of any additional preventive efforts. By applying the reference-standard attributable fractions given in Table 1.1, it was estimated that about 76% of the gastric cancer burden in these birth cohorts was attributable to *H. pylori* infection and therefore was theoretically preventable.

Table 1.1. Proportions of non-cardia gastric cancer (NCGC) and cardia gastric cancer (CGC) attributable to *H. pylori* infection, by world region

Gastric cancer type and country or region	Gastric cancer cases		Controls		Odds ratio (95% CI)	Attributable fraction (%) (95% CI)
	Number	*H. pylori* positivity (%)	Number	*H. pylori* positivity (%)		
NCGC in China	500	94	500	76	5.9 (3.3–10.8)	78 (65–86)
CGC in China	500	92	500	76	3.1 (1.5–6.1)	62 (32–77)
NCGC in Australia, Europe, USA	230	93	803	61	15.0 (7.9–28.6)	87 (82–90)[a]

CI, confidence interval.
[a] Considered to be representative of the world outside China.
Source: Adapted from Gu et al. (2023) [22]. Reprinted by permission of Taylor & Francis Ltd (http://www.tandfonline.com).

The results showed Asia as the main contributor of the total estimated lifetime burden of gastric cancer in these birth cohorts, as expected, but also highlighted Africa and the Americas as the second most important regions to target for gastric cancer prevention in the future. The impact of demographic change is substantial, and it is expected that the gastric cancer burden will increase 4–8-fold across a lifetime in an average single birth cohort in Africa, mostly in sub-Saharan Africa, compared with the total number of cases estimated for the region in 2022. Africa is considered as an area of low gastric cancer incidence, despite having a very high prevalence of *H. pylori* infection; this is often referred to as the African enigma [23]. The data suggest that this may be a historical artefact of population structure, and indicate the need for local policy discussions and cancer control planning in the region to prevent increases in the numbers of gastric cancer cases linked to the substantial demographic changes expected in the future in Africa.

1.8 Risk factors for gastric cancer

The main risk factor for gastric cancer is chronic infection with *H. pylori*, which is classified by IARC as carcinogenic to humans (Group 1) [24, 25]. In 2021, the National Toxicology Program's 15th Report on Carcinogens added chronic infection with *H. pylori* to its list of substances that are known or reasonably anticipated to cause cancer in humans [26].

Chronic infection with *H. pylori* is responsible for the large majority of NCGC [22, 27, 28] (see Section 1.9). *H. pylori* infection causes a sequence of changes in the gastric mucosa: gastritis, atrophic gastritis, intestinal metaplasia, and dysplasia, which eventually leads to the development of cancer [29]. The global prevalence of *H. pylori* infection was 48% in an analysis of data from 62 countries [30], with substantial geographical variations. For example, the prevalence of *H. pylori* infection was highest in Africa, with a pooled estimate of 70%, and Oceania had the lowest prevalence (24%) [30]. These regional prevalence estimates indicated that 4.4 billion individuals worldwide had *H. pylori* infection in 2015 [30]. A recent review over various time periods showed that the crude global prevalence of *H. pylori* infection was 44% in adults and 35% in children and adolescents in 2015–2022 [31]. In adults, the prevalence of *H. pylori* infection has decreased by 16% during the past 30 years, but a corresponding decrease has not been observed in children and adolescents [31]. However, the reviews of the prevalence of *H. pylori* infection worldwide found substantial heterogeneity between studies, for example in terms of study design, diagnostic methods for *H. pylori* infection, population subgroups, and population age [31, 32].

In addition to *H. pylori* infection, the role of Epstein–Barr virus infection is implicated in about 10% of cases of gastric cancer [33, 34], but it is not known whether Epstein–Barr virus is a risk factor for gastric cancer that is independent of *H. pylori* infection, or whether it is a co-factor. Smoking and familial predisposition are also associated with increased risk of gastric cancer. Other modifiable risk factors that are linked to increased risk of gastric cancer include being overweight or obese (for CGC), consuming alcohol (≥ 3 alcoholic drinks per day), and consuming foods that have been preserved by salting, including pickled vegetables and salted or dried fish [35]. The interactive role of risk factors has also been investigated; for example, in Asian populations, the presence of *H. pylori* infection along with a high dietary salt intake was associated with a higher risk of gastric cancer compared with the absence of infection and a low salt intake [36].

An increased risk of gastric cancer was also found to be associated with the consumption of red meat and processed meat, and with the endogenous formation of nitrosamines; however, this association was observed only in people with *H. pylori* infection [37]. These results are based on small, mainly case–control studies; larger, prospective cohort studies are needed to confirm these findings.

1.9 Fraction of gastric cancer attributable to *H. pylori* infection

Accurate quantification of the fraction of gastric cancer attributable to *H. pylori* infection is highly dependent on obtaining accurate estimates of relative risk, and recent improvements in study designs have increased the accuracy of these estimates [22, 27]. First, *H. pylori* antibodies can spontaneously disappear during the carcinogenic process and thus require assessment in blood long before the development of gastric cancer, so that relative risks are higher in prospective study designs than in classic case–control studies. Second, the use of more sensitive immunoblotting, rather than the older enzyme-linked immunosorbent assay (ELISA) technology, has further increased the estimates of relative risk (and hence the attributable fraction) [27].

The significant relative risks for *H. pylori* infection were first established for NCGC, predominantly in studies in Australia, Europe, and the USA [25, 27, 38]. More recently, a large prospective study in China found significant associations not only for NCGC but also for CGC [14].

Based on relative risks and prevalence of *H. pylori* infection in gastric cancer cases from reference-standard studies (i.e. those testing for *H. pylori* by immunoblotting in samples > 10 years before gastric cancer diagnosis), the attributable fractions for cases of NCGC were recently estimated to be 87% in the low-risk settings for gastric cancer of Australia, Europe, and the USA and 78% in the high-risk setting for gastric cancer of China [22]. Furthermore, 62% of cases of CGC in China were also estimated to be attributable to *H. pylori* infection. The apparent discrepancy in the etiological role of *H. pylori* infection in CGC in China versus in Australia, Europe, and the USA, where earlier studies found no, or even inverse, associations of *H. pylori* infection and CGC [22], may be due to differences in the anatomical location of cancer, with CGC in Australia, Europe, and the USA tending to involve the distal oesophagus and CGC in East Asia involving the proximal stomach. Given the substantial role of *H. pylori* infection in CGC in China, which is the region that accounts for the majority of gastric cancer cases

worldwide, any beneficial effects of *H. pylori* eradication will extend beyond NCGC as a target for gastric cancer prevention.

Given the very high seroprevalence of *H. pylori* infection in gastric cancer cases, the attributable fractions assessed in these reference-standard studies remain highly sensitive to the presence of only a few false-negative results. Thus, even these current best estimates may still be underestimates, and the true attributable fractions for *H. pylori* infection, particularly for NCGC, could approach 100% if *H. pylori* exposure could be measured perfectly.

1.10 Global burden of *H. pylori*-attributable cancer

By extrapolating the subsite- and region-specific attributable fractions given in Table 1.1 to the worldwide gastric cancer burden, IARC estimated that 850 000 (4.3%) of all cancers diagnosed worldwide in 2020 were directly attributable to *H. pylori* infection; of these *H. pylori*-attributable cancers, NCGC contributed 94%, CGC contributed 4%, and gastric lymphoma contributed 2%. This cancer burden is higher than that of any other cancer-causing infection, including human papillomavirus (HPV) (730 000 attributable cases) and hepatitis B virus and hepatitis C virus combined (550 000 attributable cases). For these infections, WHO launched the Cervical Cancer Elimination Initiative (in 2020) [39] and the hepatitis elimination initiative (in 2016) [40]; this highlights the need to prioritize a global *H. pylori* prevention strategy.

In line with the geographical disparities in gastric cancer risk and burden discussed earlier, the majority (62%) of *H. pylori*-attributable cancers are diagnosed in East Asia, where the corresponding incidence rates are the highest in the world [28] (Fig. 1.9).

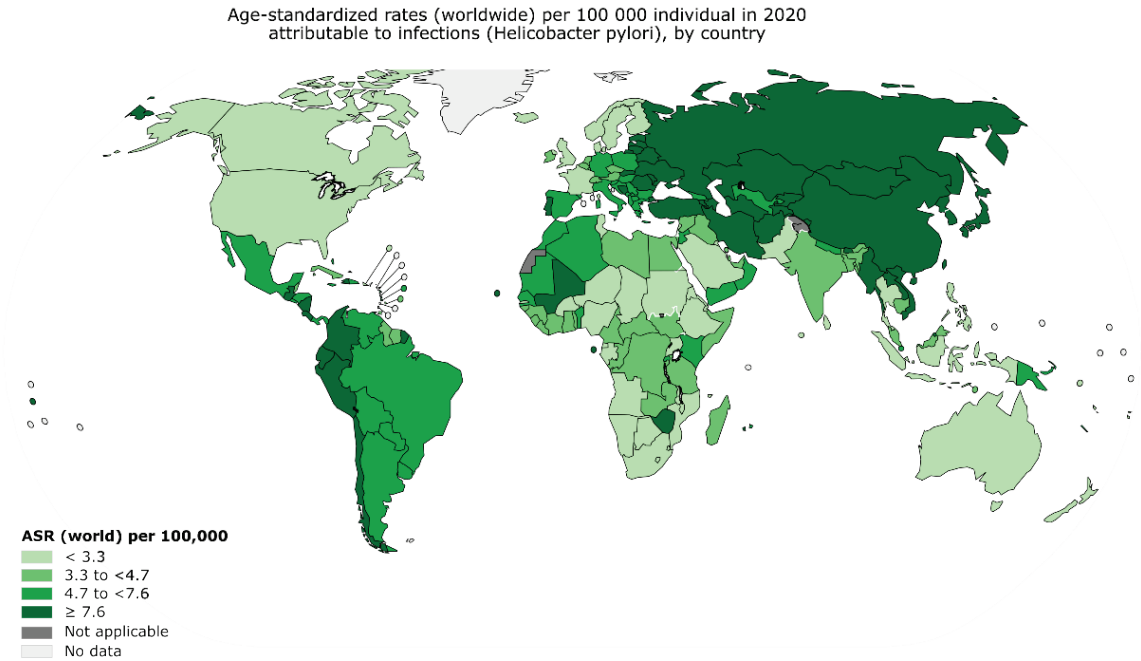


Fig. 1.9. Age-standardized incidence rate of *H. pylori*-attributable gastric cancer. ASR, age-standardized rate. Source: Reproduced from de Martel et al. (2019) [28]. © 2019 International Agency for Research on Cancer; licensee Elsevier.

1.11 Conclusions

These findings highlight that gastric cancer will remain a major global public health problem, with the projected demographic-driven increase in burden in low-risk areas in addition to the continuing burden in high-risk areas. Furthermore, these data highlight the potential public health impact of population-based *H. pylori* screen-and-treat approaches, which are evidence-based, relatively simple and effective, safe, and inexpensive to implement compared with cancer treatment, to reduce the *H. pylori*-attributable burden of gastric cancer.

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Chapter 2.

Current evidence from randomized controlled trials of the benefits and harms of population-based *Helicobacter pylori* screen-and-treat strategies for gastric cancer prevention and review of the existing recommendations, consensus reports, and guidelines

Paul Moayyedi, Peter Malfertheiner, Yuhong Yuan, and Alexander C. Ford

Summary

- Guidelines have generally become more assertive over time in their recommendations for population-based *H. pylori* screen-and-treat strategies.
- Recent guidelines have given divergent recommendations on the appropriateness of population-based *H. pylori* screen-and-treat strategies for gastric cancer prevention.
- In a systematic review of randomized controlled trials of population-based *H. pylori* screen-and-treat strategies, the Working Group identified eight trials, which involved 58 628 participants. The relative risk of gastric cancer in the *H. pylori* eradication arm was 0.64 (95% confidence interval, 0.48–0.84). The number needed to treat to prevent one case of gastric cancer was 228 (95% confidence interval, 158–514).
- *H. pylori* eradication was associated with reduced risk of recurrent gastric adenocarcinoma in patients with *H. pylori* infection (relative risk, 0.52; 95% confidence interval, 0.38–0.71). The number needed to treat was 18 (95% confidence interval, 14–30). This suggests that there is no “point of no return” for the prevention of gastric adenocarcinoma, provided that gastric adenocarcinoma has not already occurred before eradication therapy.
- There was no evidence that *H. pylori* eradication therapy increased the risk of oesophageal cancer or reflux symptoms.

- Population-based *H. pylori* screen-and-treat strategies reduce the incidence of dyspepsia and reduce health-care costs in people allocated to treatment compared with no treatment or placebo.
- More trials are needed in populations at lower risk of gastric cancer.

2.1 Introduction

The Correa hypothesis describes the series of histological changes that are the precursors to gastric adenocarcinoma [1]. The discovery that these changes were strongly associated with a then-new infectious organism, eventually named *H. pylori* [2], led to the possibility that treating this infection could reduce the incidence of gastric cancer. This possibility grew stronger after three seminal observational studies [3–5], which showed that *H. pylori* infection was associated with a strong risk of the future development of gastric adenocarcinoma. These studies and other findings led to *H. pylori* being classified by IARC as carcinogenic to humans (Group 1) [6]. Therefore, *H. pylori* gastritis was recognized as an essential trigger in the oncogenic cascade, which, over a period of decades, leads to gastric cancer in a subset of individuals with *H. pylori* infection [1, 7]. This concept opened the door for gastric cancer to be recognized as a disease with an infectious etiology, and for *H. pylori* eradication to represent a rational strategy for gastric cancer prevention [8]. There are no alternative targets for intervention in the complex interplay of the bacterium with the genetic determinants of the host. Furthermore, dietary interventions were not associated with consistent and substantial benefits for gastric cancer prevention [9]. It was not clear that treating *H. pylori* infection would reduce the incidence of gastric cancer, but about 20 years ago randomized trials and guidelines addressing this topic started to emerge. This chapter explores what these guidelines have concluded over this period, summarizes the evidence from randomized controlled trials (RCTs) that population-based *H. pylori* screen-and-treat strategies may reduce the risk of gastric cancer, and explores the other key harms and benefits of such screen-and-treat strategies.

2.2 Statements from existing guidelines and consensus reports

The landmark event that initiated the development of guidelines on population-based *H. pylori* screen-and-treat strategies was the convening in 2005 of an international working group that summarized and reviewed the available evidence on the relationship of *H. pylori* with gastric cancer and concluded that eradication of the infection had the

potential to prevent the disease. The data supporting this conclusion were obtained from animal experiments, cell biology studies, epidemiological studies, and clinical studies [10]. Guidelines addressing gastric cancer prevention by adopting *H. pylori* test-and-treat strategies soon followed. The first was the Maastricht III Consensus report, published in 2007 [11]. This consensus report evaluated existing evidence for *H. pylori*-related interventions and stated that population-based *H. pylori* screen-and-treat strategies were a promising approach, but the evidence was not sufficient to recommend this for populations, although the panel did recommend this for individuals at high risk of gastric cancer. The Asia–Pacific Consensus Guidelines on Gastric Cancer Prevention, published in 2008, were the first to recommend population-based screening for populations at high risk of gastric cancer [12]. These guidelines recommended against screening low-risk populations.

Since then, the development of guidelines has been a dynamic process, which has been influenced by several studies that have provided more evidence for the role of *H. pylori* eradication in gastric cancer prevention and have led to the extension of the statements and recommendations. Table 2.1 provides an overview of this progress, which is reflected by the key statements and recommendations published in the consensus reports and guidelines from 2007 to 2024.

The statements and recommendations in the Maastricht IV/Florence Consensus report [13], published in 2012, built on previous consensus groups that strongly recommended community *H. pylori* screen-and-treat strategies for gastric cancer prevention in areas with a substantial disease burden. This consensus report also proposed that screening should involve non-invasive testing for *H. pylori* infection [13]. In the Maastricht V/Florence Consensus report [14], published in 2017, the recommendation for the screen-and-treat approach in individuals with an increased risk of gastric cancer at the population level was enforced and extended by advising that communities at low and intermediate risk of gastric cancer were also included. The implementation of population-based screen-and-treat strategies became recognized as the main challenge, including how to administer *H. pylori* testing, which test to use, and what treatment should be given. Thus, this statement was made: “Public awareness campaigns for prevention of gastric cancer should be encouraged” [14].

Table 2.1. Consensus reports and guidelines on *H. pylori* screen-and-treat strategies for gastric cancer prevention

Consensus report (year) [reference]	Statements and recommendations
Maastricht III Consensus report (2007) [11]	• Eradication of *H. pylori* prevents development of pre-neoplastic changes of the gastric mucosa. • Eradication of *H. pylori* has the potential to reduce the risk of gastric cancer development. The optimal time to eradicate *H. pylori* is before pre-neoplastic conditions (atrophy, intestinal metaplasia) are present, probably in early adulthood. • *H. pylori* eradication for gastric cancer prevention is cost-effective in economic analyses. Feasibility studies are required to further evaluate the benefits and risks of this strategy. • The potential for gastric cancer prevention on a global scale is restricted by currently available treatments. • New treatments are required for a global strategy of *H. pylori* eradication to prevent gastric cancer. • *H. pylori* eradication for gastric cancer prevention in populations at risk should be evaluated and considered.
Asia–Pacific Consensus Guidelines (2008) [12]	• *H. pylori* screening and treatment is recommended for populations at high risk of gastric cancer. • *H. pylori* screening can be effective even in older age groups. • *H. pylori* screening is not recommended for low-risk populations.
Maastricht IV/Florence Consensus report (2012) [13]	• An *H. pylori* screen-and-treat strategy should be explored in communities with a substantial burden of gastric cancer. • *H. pylori* eradication to prevent gastric cancer should be undertaken in populations at high risk. • Validated serological tests for *H. pylori* and markers of atrophy (i.e. pepsinogens) are the best available non-invasive tests to identify individuals at high risk of gastric cancer.
Maastricht V/Florence Consensus report (2017) [14]	• *H. pylori* eradication for gastric cancer prevention is cost-effective in communities with a high risk of gastric cancer. • *H. pylori* eradication offers clinical and economic benefits other than gastric cancer prevention and should be considered in all communities. • A screen-and-treat strategy for *H. pylori* gastritis should be considered in communities with a low to intermediate risk of gastric cancer. • Public awareness campaigns for prevention of gastric cancer should be encouraged.
Bangkok Consensus report (2018) [15]	• Currently, community-based gastric cancer screening by endoscopy is not feasible in most ASEAN countries. • Community screening for *H. pylori* infection by non-invasive tests followed by eradication for gastric cancer prevention can be cost-effective depending on the disease burden in that community.
Taipei Global Consensus report (2020) [16]	• Young individuals would benefit most from *H. pylori* eradication because it cures *H. pylori*-related gastritis, reduces the risk of gastric cancer, and reduces transmission to their children. • The screen-and-treat strategy for *H. pylori* infection is most cost-effective in young adults for gastric cancer prevention in regions with a high incidence of gastric cancer. • The urea breath test or *H. pylori* stool antigen test are the preferred tests for mass screening, but a locally validated serology test may be considered. • Population-wide screening and eradication of *H. pylori* infection should be integrated or included in national health-care priorities to optimize the resources.

Table 2.1. Consensus reports and guidelines on *H. pylori* screen-and-treat strategies for gastric cancer prevention (continued)

Consensus report (year) [reference]	Statements and recommendations
Maastricht VI/Florence Consensus report (2022) [17]	• *H. pylori* eradication offers the chance for gastric cancer prevention at any age in adulthood. The magnitude of the benefit decreases with age. • Asymptomatic individuals older than 50 years are considered vulnerable and at increased risk of gastric cancer. • Screening modalities for gastric cancer prevention (non-invasive or endoscopic) combined with colorectal cancer screening is an opportunity. • Diagnostic tests used to screen *H. pylori* infection for the purpose of gastric cancer prevention should preferably be non-invasive. • If a serological method is used for *H. pylori* detection, a further test (urea breath test or stool antigen test) confirming current infection is required before initiating therapy. • Population-based *H. pylori* test-and-treat strategies provide additional benefits by preventing other gastroduodenal pathologies.
Chinese Consensus report (2022) [18]	• *H. pylori* should be screened and treated among family members living in the same household with patients who have gastric cancer or gastric mucosal pre-neoplastic lesions. • "Family-based *H. pylori* infection control and management" is an essential part of comprehensive *H. pylori* infection prevention and control strategies at the general public and community levels.
ACG Clinical Guideline (2024) [19]	• Broadly applied *H. pylori* screening and eradication for the primary prevention of gastric adenocarcinoma is not currently recommended in the general population in the USA. • Testing and treatment of *H. pylori* infection is appropriate in high-risk patient subgroups and in high-risk populations that involve defined ethnicities. • Serology for screening is not recommended.

ACG, American College of Gastroenterology; ASEAN, Association of Southeast Asian Nations.

The Bangkok Consensus report, published in 2018, stated that endoscopy-based gastric cancer screening was "not feasible" in most countries in the Association of Southeast Asian Nations (ASEAN) but considered non-invasive community screening for *H. pylori* infection followed by eradication to be cost-effective relative to the disease burden in that community [15]. The Taipei Global Consensus report, published in 2020, was the first global and comprehensive consensus report on population-based *H. pylori* screen-and-treat strategies for gastric cancer prevention [16]. In this consensus report, emphasis was placed on how to most effectively implement a population-based *H. pylori* screen-and-treat strategy. The urea breath test or the *H. pylori* stool antigen test (SAT) were the preferred tests, but locally validated serology tests were also considered to be appropriate [16].

The statements of the Maastricht VI/Florence Consensus report, published in 2022, provide the most recent comprehensive update of the evidence in support of *H. pylori*

test-and-treat strategies at the population level [17]. This consensus report also recommended the use of this prevention strategy at the individual level and for specific communities that are at increased risk. The report recommended adopting population-based *H. pylori* screen-and-treat strategies in all communities and suggested that the age group 50–69 years could be targeted at the same time as colorectal cancer screening was offered, in countries in which such programmes are in place [17].

A novel approach to gastric cancer prevention was proposed in the Chinese Consensus report, published in 2022 [18], which focused on family-based *H. pylori* infection testing and treatment as an important strategy to prevent intrafamilial transmission of the infection [20]. This consensus report deals with important considerations for a comprehensive prevention strategy with greater impact at the general public and community levels, particularly in regions with a high prevalence of *H. pylori* infection and a high incidence of gastric cancer.

However, there are other guidelines that do not recommend population-based *H. pylori* screen-and-treat strategies, particularly in areas with a low prevalence of gastric cancer. For example, in the most recent American College of Gastroenterology (ACG) Clinical Guideline, published in 2024, the primary prevention of gastric adenocarcinoma is not currently recommended in the general population in the USA [19].

Table 2.1 gives a summary of these guidelines. The most notable of these is the guideline from the USA on *H. pylori* management [19], which uses the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [21].

2.3 Evidence from randomized controlled trials for the efficacy of *H. pylori* eradication in *H. pylori*-positive individuals to prevent gastric adenocarcinoma

Recent guidelines have given divergent recommendations on whether population-based *H. pylori* screen-and-treat strategies should be used for gastric cancer prevention. These guidelines have used evidence from systematic reviews and meta-analyses that have examined this issue [22–25]. Overall, in these systematic reviews, the quality of the evidence supporting the efficacy of population-based *H. pylori* screen-and-treat strategies to prevent gastric adenocarcinoma was low. The low grade of the evidence was based on the modest number of gastric cancer events that were observed in the systematic review. Therefore, the Working Group updated this systematic review using the same methodology [24] to evaluate whether any new randomized trials would

change the estimate of effect and/or the quality of the evidence. Searches of MEDLINE (from 1947 to September 2024), Embase and Embase Classic (from 1947 to September 2024), and the Cochrane Central Register of Controlled Trials (CENTRAL) were conducted to identify potential studies. In addition, ClinicalTrials.gov was searched to identify unpublished trials, or supplementary data for potentially eligible studies. Also, conference proceedings (Digestive Disease Week, ACG, United European Gastroenterology Week, and Asian Pacific Digestive Week) from 2001 to 2024 were searched. Finally, a recursive search was performed, using the bibliographies of all obtained articles.

The RCTs that were considered to be eligible examined the effects of at least 7 days of eradication therapy on subsequent occurrence of gastric cancer in *H. pylori*-positive individuals who were otherwise healthy or in *H. pylori*-positive patients with gastric neoplasia, including dysplasia or early gastric cancer, who underwent endoscopic mucosal resection (EMR), compared with placebo or no eradication therapy. Eligible studies were required to have recruited adults (aged ≥ 18 years). In all studies, irrespective of design, a minimum duration of follow-up of 2 years was required, and at least two gastric cancers had to occur during follow-up. All end-points were extracted at the last point of follow-up at which they were reported.

All abstracts identified by the search were independently assessed for eligibility, and the data were extracted by two investigators (Yuhong Yuan and Alexander C. Ford). Any disagreements between the investigators were resolved through arbitration by a third investigator (Paul Moayyedi). There were no language restrictions. When multiple articles were identified for a single study, only the data from the latest publication from each eligible study were extracted. The primary outcome in the RCTs was the effect of *H. pylori* eradication therapy, compared with placebo or no eradication therapy, on subsequent occurrence of gastric cancer. Secondary outcomes in RCTs included the effect of eradication therapy on gastric cancer-related mortality and the effect on all-cause mortality.

The risk of bias was evaluated at the study level by two independent reviewers (Alexander C. Ford and Paul Moayyedi) using the Cochrane risk-of-bias tool for randomized trials [26]. Disagreements were resolved through arbitration by a third investigator (Yuhong Yuan). Data were pooled using a random-effects model [27] to give a more conservative estimate of the effect of *H. pylori* eradication therapy on future incidence of gastric cancer, allowing for heterogeneity between studies. Heterogeneity

was assessed using both the χ^2 test, with $P < 0.10$ used to define a significant degree of heterogeneity, and the I^2 statistic [28]. The effective sample size of any cluster-randomized trial in the data synthesis was reduced using the method described by Rao et al. [29]. The quality of the evidence was rated using the GRADE methodology, which evaluates the quality of the evidence in terms of risk of bias, inconsistency, directness of the evidence, precision of the data, and evidence of publication bias [30].

A total of 13 articles [31–43] were identified, which reported on eight separate RCTs comparing *H. pylori* eradication therapy [32] with placebo or no eradication therapy in 58 628 healthy *H. pylori*-positive individuals. Since the last systematic review on this topic [24], the number of *H. pylori*-positive participants included in RCTs had increased from 8323 to 58 628. *H. pylori* eradication was defined as any recognized dual, triple, or quadruple therapy regimen [17]. One RCT [44] was excluded because it randomized participants who had received the faecal immunochemical test (FIT) for colorectal cancer screening to either also receiving or not receiving a SAT. All individuals with a positive SAT result were offered treatment, and the gastric cancer rates in the screened arm were compared with those in the unscreened arm. Because the gastric cancer rates in individuals with *H. pylori* infection in the unscreened arm could not be determined, an *H. pylori*-positive population could not be evaluated [44]. All RCTs recruited healthy people from the community who did not have gastric neoplasia at baseline, except for one RCT in the Republic of Korea, which recruited healthy first-degree relatives of patients with gastric cancer [42]. All studies were conducted in East Asia, except for one study that recruited a population at high risk of gastric cancer in Colombia [34]. In the identified RCTs in healthy populations, the longest duration of follow-up was 26.5 years [37] and the shortest duration of follow-up was ≥ 4 years [43].

Overall, 258 (0.87%) gastric cancers occurred in 29 782 individuals with *H. pylori* infection who received eradication therapy, compared with 351 (1.2%) gastric cancers in 28 846 individuals who received placebo or no eradication therapy. The relative risk of subsequent occurrence of gastric cancer with eradication therapy versus placebo or no eradication therapy was 0.64 (95% confidence interval [CI], 0.48–0.84), with some heterogeneity between studies ($I^2 = 35\%$; $P = 0.15$) (Fig. 2.1). The number needed to treat (NNT) to prevent one case of gastric cancer was 228 (95% CI, 158–514). When the analysis was restricted to trials with a low risk of bias, the risk estimate did not change (relative risk [RR], 0.54; 95% CI, 0.41–0.72; $I^2 = 0\%$; $P = 0.43$). Note that the results from one recent well-conducted RCT were excluded from the analyses; this trial

considered *H. pylori* screening and treatment as a total strategy (rather than focusing only on participants with *H. pylori* infection), and the results of the trial were largely negative [44], which is probably related to a lack of power. The initial proportion of participants who were randomized seemed to be large (120 000 in each group), but only 26% received any screening (FIT with or without SAT). Fewer than 40% of the participants in the testing arm had *H. pylori* infection, and only about 70% were offered therapy. In retrospect, this amount of attrition meant that the trial was underpowered. In a post hoc analysis, *H. pylori* screening was associated with a lower gastric cancer incidence (but not mortality) when adjusting for patient characteristics, compared with FIT alone [44].

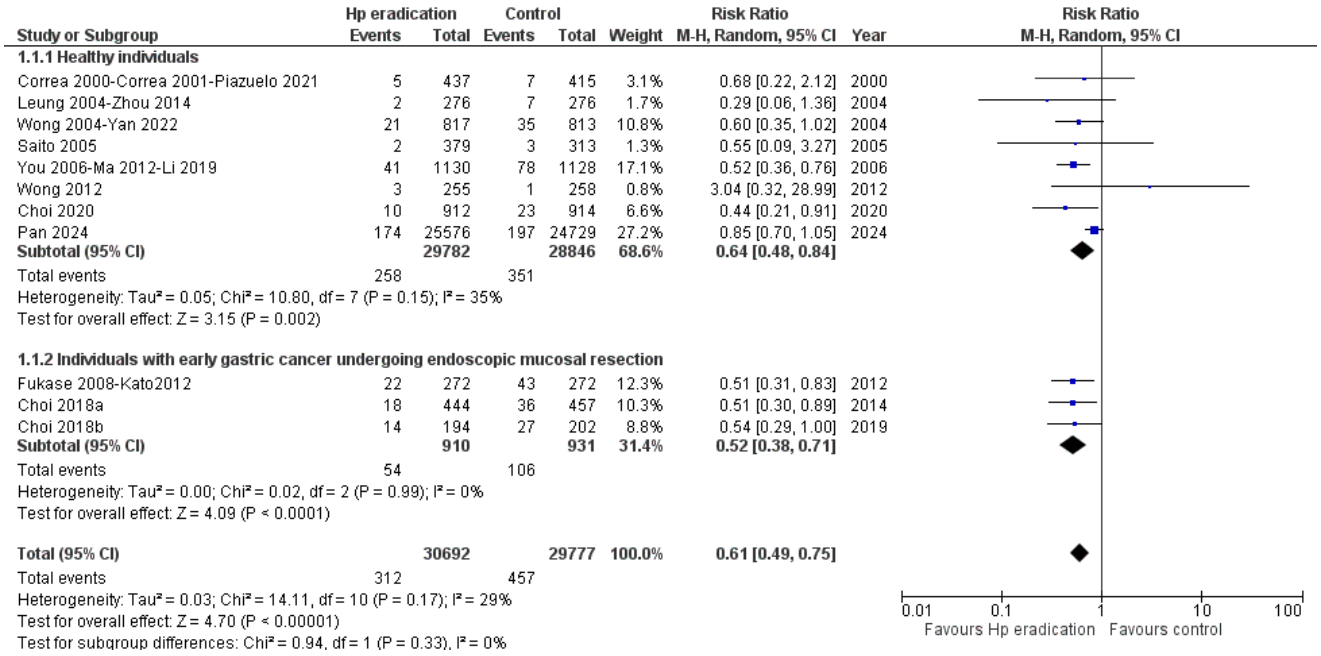

Fig. 2.1. Meta-analysis of population trials evaluating gastric cancer incidence in participants with *H. pylori* infection randomized to eradication therapy versus controls. CI, confidence interval; df, degrees of freedom; Hp, *H. pylori*; M-H, Mantel–Haenszel. Reproduced from Ford et al. (2025) [45].

There were five RCTs conducted in healthy *H. pylori*-positive individuals, which provided data on mortality from gastric cancer in 56 606 individuals [32, 35, 36, 40, 42]. The duration of follow-up in these five trials ranged from 9.2 years to 26.5 years. Overall, there were 124 (0.43%) deaths from gastric cancer in 28 730 individuals with *H. pylori* infection who were randomized to eradication therapy, compared with 156 (0.56%)

deaths from gastric cancer in 27 876 participants who were allocated to placebo or no eradication therapy. The relative risk of death from gastric cancer with eradication therapy compared with placebo or no eradication therapy was 0.78 (95% CI, 0.62–0.98) (Fig. 2.2), with no heterogeneity between studies (I^2 = 0%; P = 0.65). The NNT to prevent one gastric cancer death was 812 (95% CI, 470–8935).

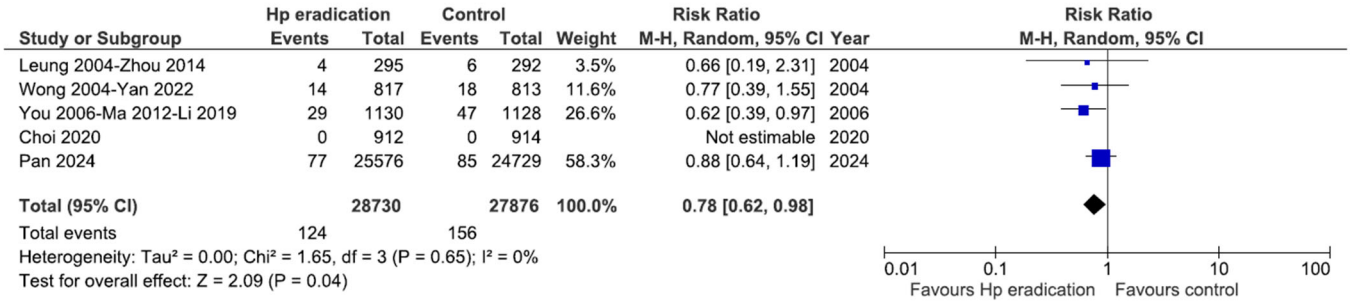

Fig. 2.2. Meta-analysis of population trials evaluating gastric cancer mortality in participants with *H. pylori* infection randomized to eradication therapy versus controls. CI, confidence interval; df, degrees of freedom; Hp, *H. pylori*; M-H, Mantel–Haenszel. Reproduced from Ford et al. (2025) [45]. © 2025 by the AGA Institute. Article available under the Creative Commons CC BY 4.0.

There were five RCTs that reported all-cause mortality in 7079 healthy *H. pylori*-positive individuals [34, 36, 37, 40, 42]. The duration of follow-up in these five trials ranged from 5 years to 26.5 years. In total, 420 (11.8%) of 3551 individuals with *H. pylori* infection who received eradication therapy had died by the last point of follow-up, compared with 426 (12.1%) of 3528 individuals who received placebo or no eradication therapy. The relative risk of death from any cause at the last point of follow-up with eradication therapy compared with placebo or no eradication therapy was 0.98 (95% CI, 0.87–1.11) (Fig. 2.3), with no heterogeneity between studies (I^2 = 0%; P = 0.49).

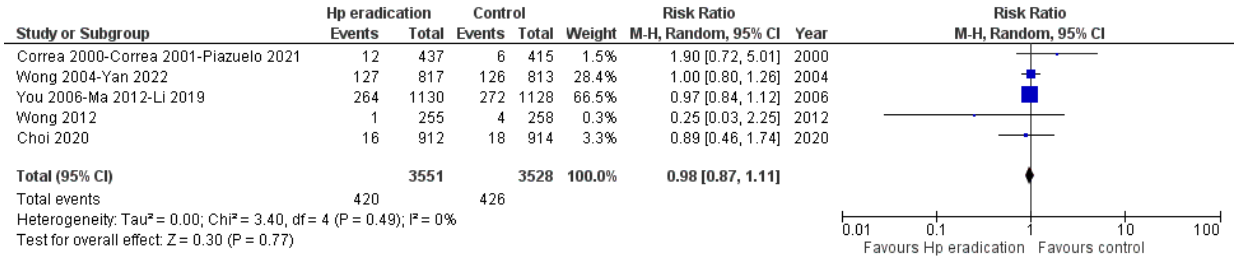

Fig. 2.3. All-cause mortality for randomized controlled trials evaluating *H. pylori* eradication therapy versus placebo or no treatment. CI, confidence interval; df, degrees of freedom; Hp, *H. pylori*; M-H, Mantel–Haenszel. Reproduced from Ford et al. (2025) [45]. © 2025 by the AGA Institute. Article available under the Creative Commons CC BY 4.0.

Some authors have recommended treating the young adult population because there may be a “point of no return”, at which pre-neoplastic changes are too advanced for *H. pylori* eradication to be effective at reducing the risk of gastric adenocarcinoma [46]. To answer this question, studies were identified in which patients with early gastric adenocarcinoma had been treated with EMR and then the patients with *H. pylori* infection were randomized to eradication therapy or placebo or no eradication therapy and were followed up to determine the recurrence of new cancer. Three RCTs [47–49] compared *H. pylori* eradication therapy with placebo or no eradication therapy in 1841 *H. pylori*-positive patients in this group. There were 54 (5.9%) recurrent gastric cancers in 910 patients who were randomized to eradication therapy, compared with 106 (11.4%) recurrent gastric cancers in 931 patients who were received placebo or no eradication therapy (RR, 0.52; 95% CI, 0.38–0.71; $I^2 = 0\%$; $P = 0.99$) (Fig. 2.1). The NNT was 18 (95% CI, 14–30). Minor heterogeneity was observed between the effect in the general population compared with those treated with EMR for early gastric cancer (subgroup heterogeneity, $P = 0.17$; $I^2 = 29\%$), suggesting from a statistical point of view that there was little evidence that the response to eradication therapy was worse in the group with early gastric cancer who were treated with EMR. The overall pooled effect for incidence of new gastric cancer was a relative risk of 0.61 (95% CI, 0.49–0.75) (Fig. 2.1). This is evidence that there is no “point of no return” for receiving *H. pylori* eradication therapy, provided that gastric cancer has not already developed.

Most studies reported adverse events associated with receiving *H. pylori* eradication therapy compared with placebo or no eradication therapy [31, 33–42, 44]. There were increased short-term adverse events associated with antibiotic use, but no severe or

long-term adverse events were reported. These data were not pooled because different antibiotic regimens were used that have different adverse event profiles, such as diarrhoea, altered taste, and nausea.

Overall, the GRADE quality of evidence that population-based *H. pylori* screen-and-treat strategies reduce the incidence of gastric adenocarcinoma is now moderate; the level of evidence was downgraded because of some modest heterogeneity between studies. There had previously been some concerns about imprecision, but the new trial data mean that this is no longer an issue.

2.4 Evidence from randomized trials for other harms and benefits of population-based *H. pylori* screen-and-treat strategies

H. pylori organisms have infected humans for many thousands of years [50]. It is reasonable to hypothesize that over this time mutualism may have evolved and the infection may confer some benefits to humans [51]. *H. pylori* infection has been inversely associated with gastro-oesophageal reflux symptoms and erosive oesophagitis [52], which reduce quality of life [53]. Gastro-oesophageal reflux symptoms have been associated with oesophageal adenocarcinoma [54], and having *H. pylori* infection has also been associated with a reduced risk of developing this malignancy [55]. Both gastro-oesophageal reflux and oesophageal adenocarcinoma are associated with affluent living conditions [56], and *H. pylori* infection is inversely associated with socioeconomic status [57]. Therefore, the apparent protective effect of *H. pylori* may relate to residual confounding by social class or other unmeasured confounding factors. Furthermore, in a recent large cohort study, *H. pylori* eradication was not associated with an increased risk of subsequent oesophageal adenocarcinoma [58].

Population-based *H. pylori* screen-and-treat strategies may have other benefits. RCTs have reported that treatment of *H. pylori* infection reduces the incidence of both gastric ulcer and duodenal ulcer [59]. A systematic review has also reported that *H. pylori* eradication therapy has a modest impact in reducing symptoms of functional dyspepsia in individuals with *H. pylori* infection [60]. Therefore, it is possible that a population-based *H. pylori* screen-and-treat programme could reduce peptic ulcer disease, dyspepsia symptoms, and dyspepsia-related clinician consultations, in addition to reducing gastric adenocarcinoma. This could help offset the cost of such a programme. Therefore, the potential harms and benefits of the programme in

population-based randomized trials of *H. pylori* screen-and-treat strategies were evaluated.

H. pylori *eradication and risk of oesophageal cancer*

In the meta-analyses described above, three RCTs reported on oesophageal cancer [32, 37, 40]. The duration of follow-up in these trials ranged from 11.8 years and 26.5 years. Overall, there were 56 oesophageal cancers in 27 523 individuals allocated to *H. pylori* eradication arms, compared with 49 oesophageal cancers in 26 670 individuals allocated to control arms (RR, 1.12; 95% CI, 0.76–1.64), with little heterogeneity between trials ($P = 0.85$; $I^2 = 0\%$) (Fig. 2.4). These trials did not report on the histology of oesophageal cancers, but given that all these trials were carried out in Asia it is probable that most were squamous cell carcinomas. There is no evidence from these trials that a population-based *H. pylori* screen-and-treat strategy leads to an increase in oesophageal adenocarcinoma.

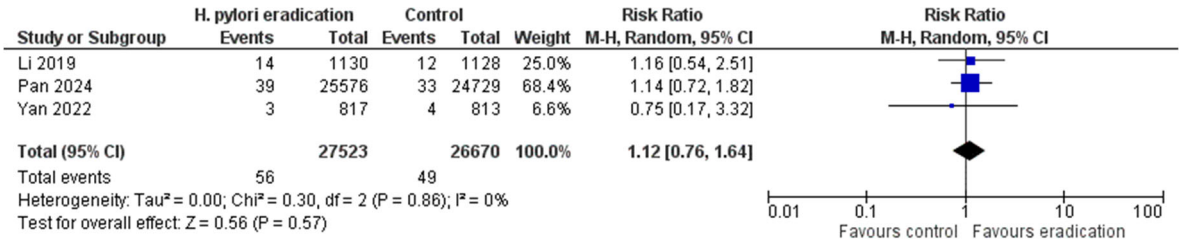

Fig. 2.4. Meta-analysis of population trials evaluating oesophageal cancer incidence in participants with *H. pylori* infection randomized to eradication therapy versus controls. M-H, Mantel–Haenszel.

H. pylori *eradication and risk of gastro-oesophageal reflux symptoms*

Population-based RCTs that reported on gastric adenocarcinoma did not describe reflux or dyspepsia symptoms in their populations. Three trials did evaluate this outcome: two in the United Kingdom [61, 62] and in from Denmark [63]. The trial in Denmark [63] was excluded because it randomized populations to receive screening or not receive screening. Because all participants with *H. pylori* infection in the screening arm were offered eradication therapy and there are no data on *H. pylori* infection status in unscreened participants, data on dyspepsia or reflux are inconclusive. In the other two RCTs [61, 62], 369 (18.9%) of the 1948 participants who were allocated to eradication therapy had heartburn at 2 years, compared with 411 (21.3%) of the 1934 participants in the control group, using the intention-to-treat approach (RR, 0.89; 95% CI, 0.77–1.04)

(Fig. 2.5). About 20% of participants in both trials were lost to follow-up at 2 years and were assumed to not have reflux at 2 years in the intention-to-treat analysis. The corresponding data for all evaluable patients were that 369 (23.2%) of the 1593 participants who were allocated to eradication therapy had heartburn at 2 years, compared with 411 (26.0%) of the 1581 participants in the control group (RR, 0.90; 95% CI, 0.75–1.07). Therefore, there was no signal suggesting that people who had been allocated to *H. pylori* eradication had more heartburn than controls after 2 years of follow-up.

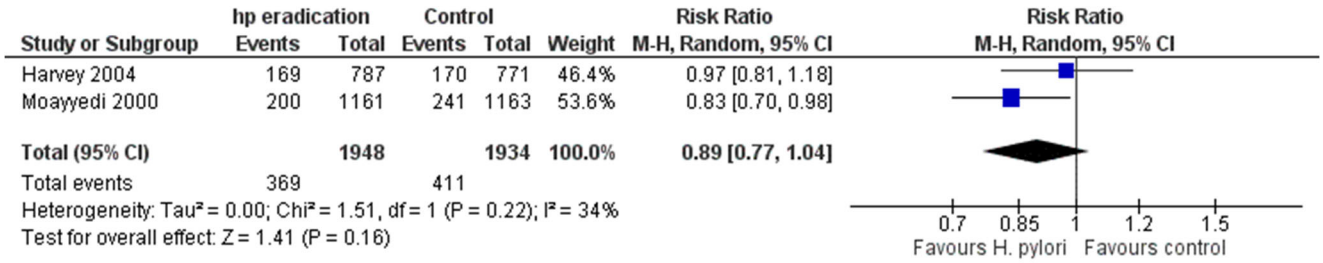

Fig. 2.5. Meta-analysis of population trials evaluating the prevalence of reflux symptoms in participants with *H. pylori* infection randomized to eradication therapy versus controls. CI, confidence interval; df, degrees of freedom; M-H, Mantel–Haenszel.

H. pylori *eradication and reduction of dyspepsia and peptic ulcer in population screening*

There were two RCTs [61, 64] that evaluated dyspepsia as an outcome after 2 years of follow-up. In total, 415 (21.3%) of the 1948 participants allocated to eradication therapy had dyspepsia at 2 years, compared with 500 (25.6%) of the 1934 participants in the control group, using the intention-to-treat approach (RR, 0.82; 95% CI, 0.74–0.92) (Fig. 2.6). About 20% of participants in both trials were lost to follow-up at 2 years and were assumed to not have dyspepsia at 2 years in the intention-to-treat analysis. The corresponding data for all evaluable patients were that 415 (25.7%) of the 1616 participants allocated to eradication therapy had dyspepsia at 2 years, compared with 500 (26.0%) of the 1582 participants in the control group, using the all-evaluable-participant approach (RR, 0.81; 95% CI, 0.73–0.91). One trial [61] reported that peptic ulcer disease was recorded in 4 participants who were allocated to *H. pylori* eradication therapy, compared with 13 participants in the placebo group, which is a statistically

significant reduction ($P = 0.04$). One trial in the United Kingdom [65] found that dyspepsia consultations were reduced by 35% over 2 years in those allocated to *H. pylori* eradication therapy and that this benefit persisted for 7 years [66], although the other trial in the United Kingdom [67] suggested that cost savings occurred after 10 years of follow-up. It is probable that a population-based *H. pylori* screen-and-treat programme would reduce the prevalence of dyspepsia in the community, and the resulting health-care cost savings could partly offset the cost of the programme.

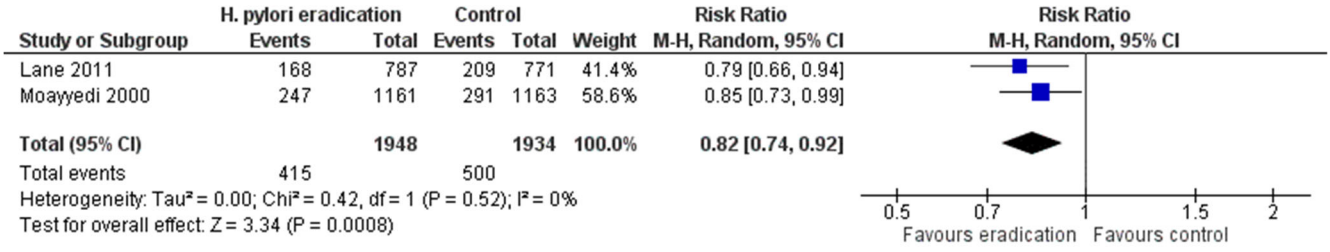

Fig. 2.6. Meta-analysis of population trials evaluating the prevalence of dyspepsia symptoms in participants with *H. pylori* infection randomized to eradication therapy versus controls. CI, confidence interval; df, degrees of freedom; M-H, Mantel–Haenszel.

2.5 Conclusions

There is now moderate-quality evidence that population-based *H. pylori* screen-and-treat strategies reduce the incidence of gastric adenocarcinoma. There are no data from countries in Europe and North America, and results from such trials are eagerly awaited. The NNTs described in this chapter, from meta-analyses of RCTs, are all from high-risk countries, and the NNTs will be much higher for low-risk countries. There is no evidence that these programmes increase the incidence of gastro-oesophageal reflux symptoms or oesophageal cancer. There is evidence that such programmes reduce the prevalence of dyspepsia in the community and reduce the associated health-care costs. If countries adopt population-based *H. pylori* screen-and-treat strategies, it will be important to assess the possible harms, because the data to date are not conclusive.

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Chapter 3.

Examples of gastric cancer prevention efforts by World Health Organization region

WHO African Region

Chapter 3.1.

Gastric cancer in Africa, with a focus on Nigeria and Zambia

Violet Kayamba and Stella Smith

Summary

- Gastric cancer is one of the leading causes of cancer mortality globally, but in Africa the exact rates are unknown.
- Nigeria and Zambia, both sub-Saharan African countries, do not have active population-based gastric cancer prevention programmes. However, what is within reach are strategies enabling eradication of *H. pylori* infection, which is a very common infection in both countries.
- Efforts are under way to improve data collection and to streamline optimal therapies for *H. pylori* eradication, guided by systematically obtained robust evidence.

This chapter summarizes and outlines past research on gastric cancer and *H. pylori* infection in two countries in sub-Saharan Africa: Nigeria and Zambia. It also highlights some ongoing projects and probable future prospects.

3.1.1 Gastric cancer incidence and mortality rates

Gastric cancer is the ninth most common cancer type in Africa. The estimated age-standardized rates (ASRs) are 4.0 per 100 000 person-years for incidence and 3.5 per 100 000 person-years for mortality [1]. It is projected that by 2045 the gastric cancer incidence rate in Africa will increase by more than 100% [1]. However, data on gastric cancer in Africa are estimates, because most countries do not have high-quality population-wide cancer registries [2]. This section provides an overview of gastric cancer in Africa, focusing on Nigeria and Zambia.

In Nigeria, gastric cancer is the 10th most common cancer type. The estimated ASRs are 1.8 per 100 000 person-years for incidence and 1.6 per 100 000 person-years for mortality [1, 3]. In Nigeria, gastric cancer accounted for 1.6% to 4.5% of all cancers reported in various studies in 1989–2010 [4, 5]. The relative frequency ratio of gastric

cancer ranged between 1.3% and 3.6% of all cancers, and it accounted for 14% to 48.4% of all gastrointestinal malignancies [6]. The incidence of gastric cancer in Nigeria has been reported to be higher in the southern regions of the country than in the northern regions [7–9]. Although the northern regions have a higher prevalence of *H. pylori* infection than the southern regions, access to diagnostic facilities is better in the southern regions, resulting in higher detection rates for gastric cancer cases [7, 10]. In Nigeria, a high proportion of patients with gastric cancer present with stage III and stage IV disease: 97% in the North West region, 94.3% in the North Central region, and 100% in a recent 15-year prospective study in the South West region [7, 8, 11]. Only a small percentage of patients with gastric cancer (2.6% to 5.6%) have been reported to present with early-stage disease [4, 7, 9].

In Zambia, gastric cancer is the eighth most common cancer type, with an estimated ASR of 3.9 per 100 000 person-years for incidence [1, 3]. It is projected that by 2050 the gastric cancer incidence rate in Zambia will increase by more than 150% [1, 3]. Endoscopy records in Zambia revealed a statistically significant increase in the number of gastric cancer cases over a period of 43 years (1977–2021) [12]. However, it remains unclear whether this finding reflects a true increase in gastric cancer incidence rates or is merely a reflection of better diagnostic and case-detection capabilities. There is growing evidence that current figures for gastric cancer incidence rates in Zambia are underestimates. An audit of records at the University Teaching Hospital in Lusaka, which is the largest referral hospital in the country, revealed that only 42% of clinically diagnosed cases of gastric cancer were included in the Zambia National Cancer Registry, which is the source for global estimates [13]. In the absence of a population-based cancer registry and good data management systems, the true burden of gastric cancer in Zambia is not known.

The estimated ASR for gastric cancer mortality in Zambia is 3.4 per 100 000 person-years [1, 3]. According to a hospital-based audit of gastric cancer outcomes in the country, the average survival rate after 1 year was 15% [14]. These poor outcomes were attributed mostly to late diagnosis, which was believed to be compounded by delays within the health-care system rather than being attributable to late patient presentation. This was the conclusion of a study in Lusaka in 2019, which found that the median time from onset of symptoms to endoscopic diagnosis of gastric cancer was 12 weeks (interquartile range, 4–32 weeks), although patients had their first consultation within 2 weeks (interquartile range, 0–4 weeks) of noticing symptoms [15]. The delay in

diagnosis was a result of a lack of endoscopy facilities in many parts of the country and difficulties faced by patients when travelling to health-care centres with more advanced facilities. In addition, the lack of specific symptoms for early gastric cancer posed a challenge to health-care providers, who had to decide when to send patients to centres with the facilities to carry out endoscopy, which were located at a distance from where the patients lived [15].

3.1.2 Age of onset and sex ratios of gastric cancer

In Nigeria, several studies have reported that the period of the fifth and sixth decades of life was the most common age of onset for gastric cancer, and the male-to-female ratio for gastric cancer in different studies ranged from 1.2:1 to 4:1 [4, 5, 7, 9, 11, 16–19].

In contrast, in Zambia, reports showed that about 25% of gastric cancer cases are detected in people younger than 45 years, which is considered to be early-onset gastric cancer. A crude analysis suggested that this high proportion of early-onset gastric cancer in Zambia was not due to the country's young population structure [20]. However, there has not been a systematically conducted population-wide analysis to confirm this finding. Therefore, it remains unclear to what extent the early onset of gastric cancer in Zambia could be explained by the young population structure of the country. In addition, there is little evidence of familial gastric cancer syndromes in Zambia. Studies have revealed that very low percentages of patients with gastric cancer have a family history of the disease [21]. In addition, only one third of the patients diagnosed with gastric cancer had the histologically diffuse type of gastric cancer, which is the type that is most associated with familial syndromes [21]. Further investigations are needed to validate these observations and to determine the factors driving the early onset of gastric cancer in Zambia. According to the Zambia National Cancer Registry, the male-to-female ratio for gastric cancer in Zambia is 1.1:1.

3.1.3 Health-care facilities for diagnosing gastric cancer

Endoscopy is the reference standard for the diagnosis of gastric cancer. Endoscopy services are scarce in most African countries and serve only a limited proportion of the population [22]. This is due to the high cost of establishing, running, and maintaining endoscopy units in health-care systems that are poorly resourced.

Nigeria currently has 13 population-based cancer registries and 20 hospital-based cancer registries, including the cancer registry at Lakeshore Cancer Center, which is

dedicated to cancer prevention and treatment [23]. The Nigerian National Systems of Cancer Registries was established in 2009, in collaboration with the Federal Ministry of Health, the Society of Oncology and Cancer Research of Nigeria, and the Institute of Human Virology of Nigeria to provide technical and scientific support, training, and capacity development to cancer registries in Nigeria [24]. However, health-care facilities in Nigeria are inadequate, which limits the comprehensive detection of gastric cancer cases. Often, education and community advocacy for early case detection are not readily available [23]. The major contributing factor is a lack of funding for disease diagnosis, resulting in a lack of equipment and limited numbers of trained personnel. In addition, the maintenance of these population-based cancer registries is inadequate because of a paucity of resources. This makes it difficult to know the exact number of gastric cancer cases in Nigeria. Another limitation is that most cancer registries in Nigeria do not report on *H. pylori* infection (Table 3.1.1), so it is difficult to link *H. pylori* infection to gastric cancer in Nigeria. In addition, most cancer registries in Nigeria collect only basic sociodemographic data and data on the type of cancer, with a few clinical presentations. There is no follow-up of the patients included in the registries.

Table 3.1.1. Characteristics of included studies describing gastric cancer incidence and *H. pylori* testing in cities or regions in Nigeria

Reference	City or region	Study period	Cancer population in study	Gastric cancer cases	Histologically confirmed (%)	*H. pylori* tested?	Registry type	Age group
Abdulkareem et al. (2009) [16]	Lagos and Sagamu	1995–2006	713	78	100	No	Hospital/ laboratory	All
Abdulkareem et al. (2010) [5]	Lagos	1995–2007	105	95	100	Yes; 15.5%	Hospital	Adults
Afuwape et al. (2012) [25]	Ibadan	2004–2009	Only gastric cancer cases were reported	49	73.5	No	Hospital	Adults
Ahmed et al. (2011) [7]	Zaria	1995–2009	Only gastric cancer cases were reported	179	100	Yes; result not reported	Hospital	Adults
Alatise et al. (2007) [9]	Ile-Ife	1989–2005	230	160	100	Yes; 36.3%	Hospital	All
Arodiwe et al. (2013) [26]	South East	1995–2010	335	4	0	No	Hospital	Adults

Table 3.1.1. Characteristics of included studies describing gastric cancer incidence and *H. pylori* testing in cities or regions in Nigeria (continued)

Reference	City or region	Study period	Cancer population in study	Gastric cancer cases	Histologically confirmed (%)	*H. pylori* tested?	Registry type	Age group
Awodele et al. (2011) [27]	Lagos and Ibadan	2005–2009	5094	221	0	No	Hospital	All
Bakari et al. (2010) [11]	Maiduguri	1989–2005	87	72	100	Yes; 7%	Hospital	Adults
Ekanem and Parkin (2016) [28]	Calabar	2009–2013	719	9	100	No	Regional	All
Fapohunda et al. (2020) [23]	Lagos	2015–2018	548	9	0	No	Hospital	All
Habeebu et al. (2017) [19]	Lagos	2009–2016	106	8	100	No	Hospital	Adults
Irabor and Afuwape (2012) [17]	Ibadan	1990–2008	Only gastric cancer cases were reported	286	89	Yes; none seen	Hospital	All
Komolafe et al. (2008) [29]	Ile-Ife	10 years; period not specified	1038	102	100	Yes; 63%	Hospital	All
Mandong et al. (2010) [4]	Plateau State	1985–2004	5706	205	100	No	Hospital	All
Nwafor and Nwafor (2018) [30]	Akwa Ibom State	2007–2015	1186	45	100	No	Hospital	All
Ray-Offor and Obiora (2021) [31]	Port Harcourt	2012–2021	622	17	100	Yes; 5.9%	Hospital	Adults
Oluwasola and Ogunbiyi (2003) [32]	Ibadan	18 years; period not specified	Only gastric cancer cases were reported	84	100	Yes; 17.9%	Hospital	Adults

Zambia does not have a population-based cancer registry that covers the whole country, and this lack results in inadequate collection of data on gastric cancer [13]. Theoretically, there is a system that is designed to facilitate the diagnosis and reporting of gastric cancer cases in the country. Evaluation for suspected cases is initially done at first-level public and private facilities. Centres that offer endoscopy services perform this procedure, and those that do not offer endoscopy arrange for patients to be referred to health-care centres with more advanced facilities. After endoscopy, biopsies from

suspicious lesions are sent for histological diagnosis. Upon histological confirmation of the cancer, patients are referred to the Cancer Diseases Hospital, which is the only institution in Zambia that has comprehensive cancer treatment capabilities. Records from the Cancer Diseases Hospital are then directly recorded into the Zambia National Cancer Registry. There is also provision for the Zambia National Cancer Registry to obtain cancer-related data directly from individual health facilities. If working efficiently, this system would facilitate timely diagnosis of gastric cancer. However, research has shown that the movement of patients from one level of care to another is not efficient, resulting in delayed diagnosis and poor data collection [15].

In Nigeria, a recent 15-year prospective study of patients with gastric cancer in a tertiary hospital in the South West region showed that 94.2% of the patients underwent endoscopy, and, among the 138 patients in the study, diagnosis was carried out by abdominal ultrasonography in 57.9% of cases, computed tomography (CT) in 23.9% of cases, and magnetic resonance imaging (MRI) in 2.9% of cases [8]. Another study in the South West region of Nigeria reported that flexible endoscopy was the only diagnostic method in 34.7% of cases and that 26.5% of cases received a combination of endoscopy and a barium-meal test. For 24.5% of cases, the barium-meal test was the only diagnostic tool used, and 14.3% of cases were diagnosed intra-operatively [25].

A report from two endoscopy centres to which patients in the southern regions of Nigeria are referred showed that endoscopy was carried out to diagnose gastric cancer in a small set of patients [31]. A study in the North Central region showed that diagnosis of gastric cancer was based primarily on the barium-meal test, endoscopy, and biopsy; other diagnostic methods used were CT and ultrasonography [7].

3.1.4 *H. pylori* infection

Globally, the major risk factor for gastric cancer is *H. pylori* infection. The prevalence of *H. pylori* infection in Nigeria is 87.7% [33] and in Zambia is 79%, with most infections being acquired before the age of 10 years [34]. In Zambia, acquisition of *H. pylori* infection occurs earlier in urban settings than in rural settings [34]. This is probably due to the higher population density in urban and peri-urban areas than in rural areas, resulting in close human-to-human contact, which is often associated with inadequate living conditions and compromised sanitation. In contrast, in Nigeria the prevalence of gastric cancer is higher in rural areas than in urban areas.

In the face of very high levels of exposure, the associations between exposure and disease can be difficult to observe. This is exemplified by studies in Nigeria and Zambia that have attempted to show an association between *H. pylori* infection and gastric cancer.

In a case–control study in Zambia, 88% of gastric cancer cases and 87% of controls had detectable *H. pylori* antibodies; this difference was not statistically significant [35]. In a similar case–control study, 79% of gastric cancer cases and 88% of controls had *H. pylori* antibodies; this difference was also not statistically significant [36]. Another study in Zambia used a multiplex assay to measure 13 different *H. pylori* antibodies. None of these antibodies were detected at statistically significantly higher levels in gastric cancer cases than in controls [35]. Similarly, a study in Nigeria showed that *H. pylori* infection was detected in only 18% of gastric cancer tissue specimens [32]. A 10-year retrospective study of upper gastrointestinal endoscopy cases in the southern regions of Nigeria reported that among cases with histologically confirmed gastric cancer, *H. pylori* was detected in only 1 case [31]. However, these studies do not prove that *H. pylori* is not driving gastric cancer in these countries. Rather, they show that there is an urgent need to conduct more robust, and possibly prospective, studies that will demonstrate a clear link between *H. pylori* infection and gastric cancer. In addition, some of these studies had design limitations that could have affected the results.

3.1.5 *H. pylori* treatment

Treatment for *H. pylori* infection typically involves a combination of antibiotics and gastric acid-reducing drugs. Currently, there are no continent-wide guidelines for *H. pylori* treatment in Africa, and most countries in Africa rely on international strategies that are backed by evidence from outside the continent.

In Nigeria, *H. pylori* resistance to metronidazole, clarithromycin, and amoxicillin is high [37]. In a report published in 2017, resistance to metronidazole was 99.1%, to amoxicillin was 33.3%, and to clarithromycin was 14.4% [38]. In a report published in 2020, all the isolates tested were resistant to metronidazole, 25% were resistant to clarithromycin, and 30% were resistant to amoxicillin [37]. Metronidazole is widely available and widely used in Nigeria as an antidiarrhoeal or antiparasitic drug, and it is also used for gynaecological infections. Antibiotics are widely available to buy over the counter. Drugs sold over the counter are not regulated like prescription medications, and many people do not have health insurance that can pay the high cost of prescription

drugs. Therefore, self-prescription of antibiotics, which is associated with inappropriate dosing, is quite high in Nigeria [38], and this is a good recipe for the development of antimicrobial resistance.

In addition, Nigeria has limited facilities for *H. pylori* culture and sensitivity testing. Because of the high cost of culture, most physicians prescribe drugs empirically. The most prescribed regimen is triple therapy. There is growing evidence that quadruple concomitant therapy or levofloxacin triple therapy should replace clarithromycin triple therapy in regions where clarithromycin resistance is > 15% [39].

In Zambia, the burden of *H. pylori* antimicrobial resistance is thought to be high. In a recent study, the prevalence of resistance to clarithromycin was 28%, suggesting that this drug should not be prescribed empirically for *H. pylori* infection [40]. There is evidence of other common bacterial infections being resistant to amoxicillin and metronidazole in Zambia, and therefore this is probably true for *H. pylori* infections as well. Bismuth salts, which are currently the preferred additions to therapeutic regimens, are not available in Zambia. The use of rifabutin (an antimycobacterial drug) may have a negative effect on the control of the tuberculosis epidemic, with disastrous consequences. Therefore, options for effective *H. pylori* eradication in Zambia are limited. There is an urgent need to (i) collect robust evidence of sensitivity patterns, and (ii) generate evidence-based treatment guidelines for *H. pylori* infection in Zambia.

3.1.6 *H. pylori* treatment as a strategy for gastric cancer prevention

Eradication of *H. pylori* infection is a proven strategy for reducing the risk of gastric cancer. To find ways of appropriately closing the gaps in the treatment of *H. pylori* infection, the African *Helicobacter* and Microbiota Study Group (AHMSG), in collaboration with the European Registry on *Helicobacter pylori* Management, established the *H. pylori* Africa Registry (Hp-AfricaReg), which currently involves four African countries, including Nigeria and Zambia. The Hp-AfricaReg is an observational study in which data are being collected from patients who test positive for *H. pylori* infection using the urea breath test, the stool antigen test, or the simple urease test. The patients are treated using the local standard of care, and success of eradication is confirmed at least 4 weeks after the completion of *H. pylori* treatment. However, in both Nigeria and Zambia, many patients do not return for repeat tests after they have been treated; this limits the amount of data collected. Once completed, the Hp-AfricaReg

database will provide clear evidence-based information on treatment outcomes for *H. pylori* infection in at least four countries in Africa.

3.1.7 The African enigma

The so-called African enigma was first described by Holcombe more than 30 years ago [41]. It stated that despite the high prevalence of *H. pylori* infection in Africa, the occurrence of associated diseases, such as peptic ulceration and gastric cancer, was low. Since then, this description has served as a basis for many studies. However, it was not based on systematically collected evidence. Therefore, the African enigma is thought of as a medical myth by some scientists [42]. Holcombe did not account for variations in *H. pylori* prevalence among African populations and did not consider limitations in case detection.

Some of the data that were used to come up with the conclusion of the African enigma were from the northern regions of Nigeria, and no data from other regions of Nigeria or Zambia were used. Current data from Zambia do not support the concept of the African enigma. A community survey in a peri-urban, high-density community in Lusaka reported that the prevalence of peptic ulceration was similar to prevalences in countries outside Africa [43]. A recent study revealed that < 1% of adults with *H. pylori* infection had normal gastric mucosa, providing evidence that the infection was not indolent [21]. In addition, the exact burden of gastric cancer in Nigeria and Zambia remains unknown; therefore, concluding that it is rare might be erroneous.

The population prevalence of serologically diagnosed gastric atrophy (most of which is due to *H. pylori* infection) was 11% in Zambian adults aged 55–59 years [34]. This is lower than the prevalences reported in countries with a high incidence of gastric cancer, such as Japan (17% in the age group 40–60 years) [44] and the Republic of Korea (43% in the age group 40–49 years) [45]. However, it is higher than the prevalences reported in countries with a low incidence of gastric cancer, such as Germany (4.1% in the age group 55–59 years) [46] and Finland (3.5%) [47]. In a hospital-based endoscopy study in Lusaka, the prevalence of serologically determined gastric atrophy in all adult age ranges was 30% [36]. Serological diagnosis of gastric atrophy was done by measuring the pepsinogen I/II ratio. However, both studies used the cut-off value of 3.0, which was not validated for the Zambian population.

The lack of a clear congruence between prevalence of *H. pylori* infection and prevalence of related gastric diseases has also been reported in other parts of the

world, including Asia and Latin America [48]. Therefore, the use of the term “African enigma” in relation to *H. pylori* infection is redundant.

3.1.8 Efforts to improve information on gastric cancer

Cancer registries and strategic plans

On 26 May 2024, the Federal Ministry of Health and Social Welfare of Nigeria launched the National Cancer Registry Regulations for Nigeria. The aims were to improve access to real-time data (by reporting cancer cases to centralized registries), to promote early detection through timely diagnosis and intervention, to help mitigate the impact of cancer on individuals and communities, and ultimately to improve the quality of health-care delivery in Nigeria. The launch included the publication of a document developed by the National Institute for Cancer Research and Treatment, in collaboration with the African Cancer Registry Network, IARC, and St. Jude Children’s Research Hospital (USA). After the launch, the Federal Government of Nigeria intends to focus on tackling cancer by cancer prevention activities, advocacy, social mobilization, treatment, supply chain management, data management, research, and finance.

In Zambia, similar efforts have been made with the launch of the National Cancer Control Strategic Plan 2022–2026. To improve diagnostics, Zambia now has the capacity to train endoscopists to a high standard; so far, 10 local endoscopists (qualified physicians and surgeons) have been trained. Some of these endoscopists have since gone on to practise in various institutions within Zambia. However, the impact of these efforts is limited by a lack of endoscopy equipment in health-care centres outside of Zambia’s main cities. Therefore, the diagnosis of gastric cancer remains a challenge.

Finding cost-effective methods of diagnosing gastric cancer early

Attempts have been made to find simple, more cost-effective ways of diagnosing gastric cancer early, in the absence of endoscopy. A simple bedside device to detect blood in gastric juice before endoscopy has been designed and tested [49]. The device, called the Sanguis-filum, is an inert, absorbent string coiled up in a gelatin capsule. The capsule is swallowed, and the string is left in situ for at least 30 minutes. Upon retrieval of the string, guaiacum powder is used to test for the presence of blood on the string. This device was tested on 200 volunteers, with a reported high acceptance rate. The Sanguis-filum was found to not be sufficiently accurate for use as a diagnostic tool for gastric cancer, because it had a low sensitivity. This is probably because not all cancers

would be actively bleeding at any one time. Therefore, better results would probably have been achieved if the string had been left in situ for longer. Other efforts are currently under way in Zambia to find alternatives to the endoscopic diagnosis of early gastric cancer.

Understanding the molecular characteristics of gastric cancer

To reduce mortality from gastric cancer in Zambia, work is being done to understand its molecular characteristics. In one study in Zambia, the proportion of gastric cancers overexpressing human epidermal growth factor receptor 2 (HER2) was 23% [50]. Tumours with HER2 overexpression respond to targeted therapy with the anti-HER2 antibody trastuzumab, and this approach is associated with improved survival [51]. Because Zambia has a high number of cases of advanced gastric cancer, routinely testing for HER2 may have a substantial impact on outcomes.

There is also evidence that a high proportion of gastric cancers exhibit loss of MutL homologue 1 (MLH1) expression, which is a marker of microsatellite instability [52]. This could be vital for future precision therapeutic approaches.

Programmed death ligand-1 (PD-L1) is an immune checkpoint inhibitor that is a promising prognostic and therapeutic target for gastric cancer. In a recent study in Zambia, the expression of anti-PD-L1 was evaluated in gastric cancers. Positive expression was detected in 14% of cases. This approach may improve the outcomes of patients with advanced gastric cancer in Zambia [53].

3.1.9 Future directions

Evidence shows that countries that have rolled out screening programmes for gastric cancer have higher detection rates and better outcomes for gastric cancer [54]. Currently, screening for gastric cancer is not possible in Africa. Work is under way to find affordable and applicable ways of either diagnosing gastric cancer early or preventing it altogether using effective *H. pylori* eradication. Because there is evidence that *H. pylori* infection is prevalent in Africa, the AHMSG was formed to spearhead activities and conduct high-quality research to provide evidence-based answers to the questions on *H. pylori*-induced gastric cancer in Africa.

The AHMSG currently has 16 board members from 10 African countries and several other members from 8 other countries. Several projects have been identified and will be

conducted within the AHMSG as funding becomes available. These are briefly described here.

Project 1: Understanding the true burden of H. pylori *infection and gastric cancer in Africa*

Very few countries in Africa have done population-wide studies on the prevalence of *H. pylori* infection. The model that was recently used in Zambia, in which archival blood samples from a Population-Based HIV Impact Assessment (PHIA) were used to accurately determine the national prevalence of *H. pylori* infection, could be used in other African countries. The PHIA project was supported by the United States President's Emergency Plan for AIDS Relief (PEPFAR) through the United States Centers for Disease Control and Prevention. The PHIA project has a presence in 15 African countries, including Nigeria. The PHIA survey had the resources to carry out systematically sampled door-to-door blood collection to study the burden of HIV. The AHMSG will use these stored samples to measure the presence of *H. pylori* antibodies and thereby determine the national prevalence of *H. pylori* infection in 15 countries in Africa. The AHMSG will also work in close liaison with diagnostic centres and cancer registries in Africa to understand the true burden of gastric cancer and *H. pylori*-related disease in the continent.

Project 2: A comprehensive survey of the available resources in AHMSG member countries

One of the limiting factors for information gathering in Africa is the lack of capacity to conduct credible research. The AHMSG recently conducted and published a survey on practices related to *H. pylori* treatment in Africa [55]. There are also plans to conduct another study, focused on research resources, to understand which centres can effectively collect and store biological samples and also perform culture and sensitivity testing.

Project 3: Evaluating the profile of antimicrobial resistance in the continent, with a specific focus on multidrug resistance and heteroresistance

The AHMSG is preparing a grant application aimed at determining the burden of antimicrobial resistance in Africa. This ambitious project will cover several African countries, providing robust data on *H. pylori* resistance.

Project 4: Participating in the Hp-AfricaReg

This descriptive observational study is collecting information on patient outcomes after treatment with the currently available standard of care. Four African countries have started the study.

Project 5: Multicentre randomized clinical trials

The information gathered from Project 3 and Project 4 will be used to design multicentre randomized clinical trials in Africa. This information will enable the formulation of evidence-based treatment guidelines that are applicable to Africa.

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WHO Region of the Americas

Summary

- The Americas contribute about 10% of the new cases of gastric cancer globally. The burden of gastric cancer is greatest in low- and middle-income countries and in specific racial and ethnic groups in high-income countries.
- The burden of *H. pylori* infection in the Americas varies across regions, with lower seroprevalence (< 25%) in North America and higher seroprevalence (~70%) in Central America, and across demographic groups within countries.
- The incidence of gastric cancer is increasing in young people in the USA.
- No primary or secondary preventive measures for gastric cancer have been established in the Americas.
- There is low public awareness of the risk factors and warning symptoms for gastric cancer.
- Several new and important research initiatives are under way in some countries, but only limited strategies for prevention and control are embedded into public health policies.

Chapter 3.2.

Gastric cancer prevention in Latin America and the Caribbean

Arnoldo Riquelme and M. Constanza Camargo

Summary

- Gastric cancer is a leading cause of cancer-related death in the Latin America and the Caribbean region, which contributes about 8% of the new cases globally. The burden of gastric cancer is greatest in the mountainous areas of the Pacific littoral.
- The most common anatomical subsite of gastric cancer in populations in Latin America and the Caribbean is *H. pylori*-driven non-cardia gastric cancer, and its late diagnosis is associated with poor outcomes.
- The burden of *H. pylori* infection in populations is high (> 60% in adults) and is relatively homogeneous across the region. Two multicentre studies in countries in Latin America and the Caribbean address *H. pylori* diagnosis and treatment schemes (Hp-LATAM-Reg) and *H. pylori* antibiotic resistance (Hp-RESLA).
- There are limited strategies for gastric cancer prevention and control embedded in public health policies in the region.
- Chile has taken a leading role in implementing demonstrative studies of prevention that could inform national and regional regulations to reduce gastric cancer mortality.

3.2.1 Introduction

Latin America and the Caribbean (LAC) is a region with a low to moderate risk of gastric cancer. LAC accounts for about 8% of new cases of gastric cancer globally [1]. The greatest burden of gastric cancer in LAC is concentrated in the mountainous areas of the Pacific littoral [2]. Based on the limited incidence data that are available, the risk of gastric cancer has been decreasing for several decades in both men and women in

LAC (Fig. 3.2.1) [3]. Gastric cancer is a leading cause of cancer-related deaths in LAC; it is responsible for about 58 000 deaths per year in the region [1].

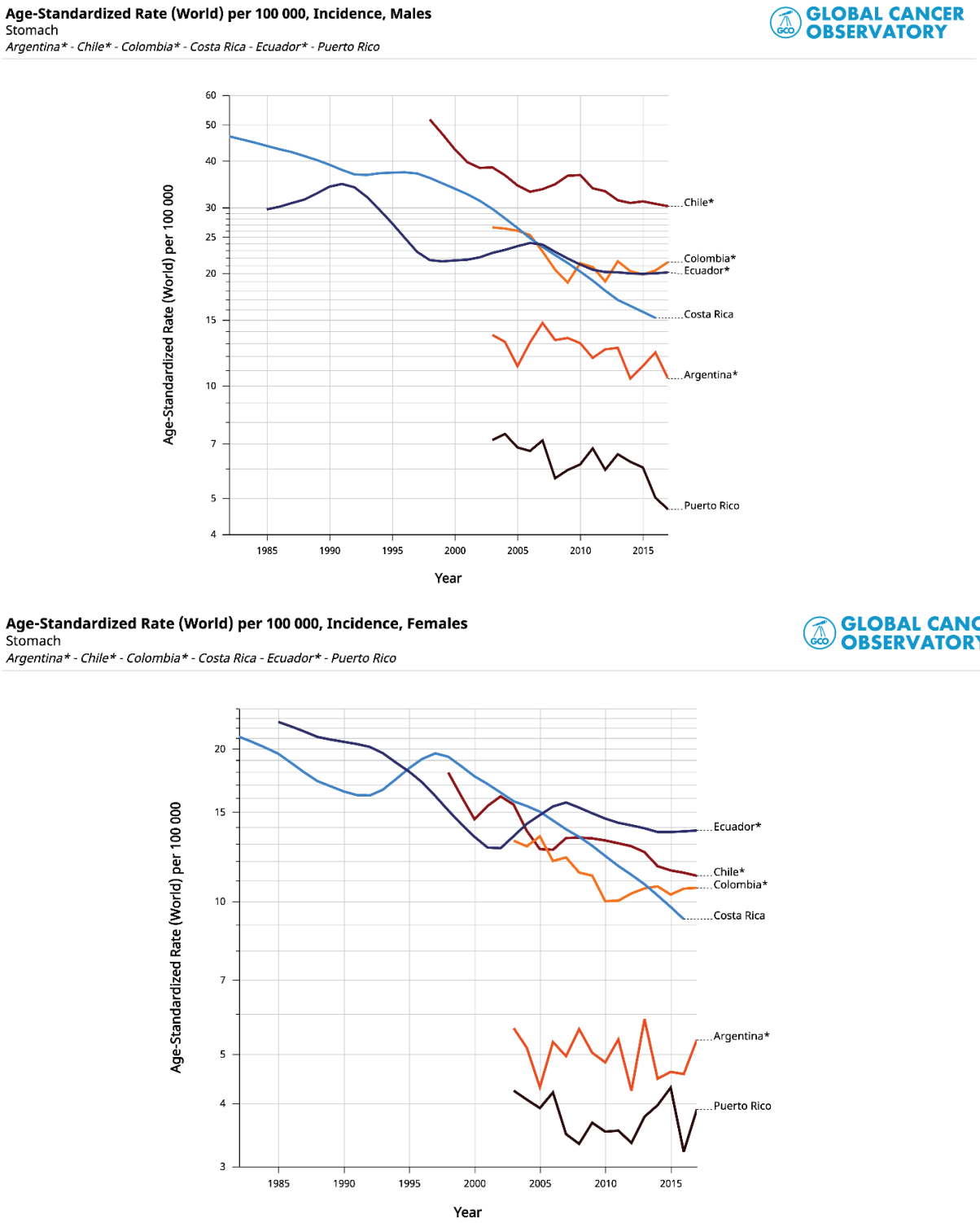
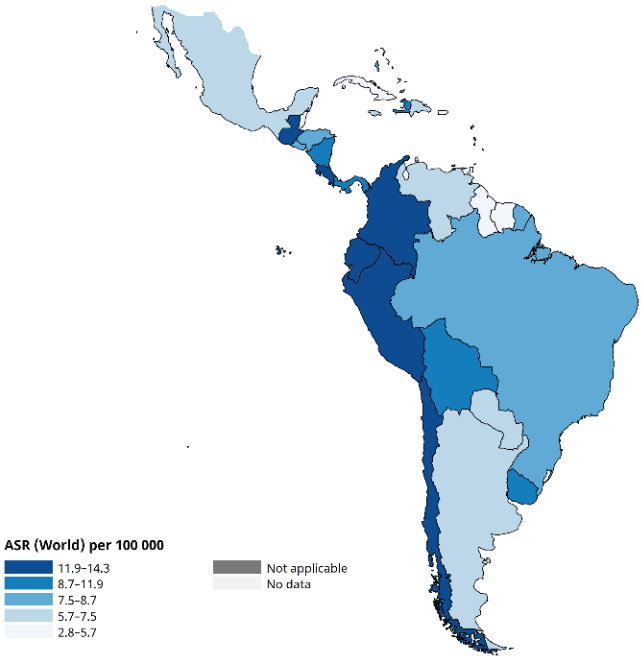


Fig. 3.2.1. Country-specific trends of gastric cancer incidence in (top) men and (bottom) women in Latin America and the Caribbean. * Subnational data. Source: Ervik et al. (2024) [3].

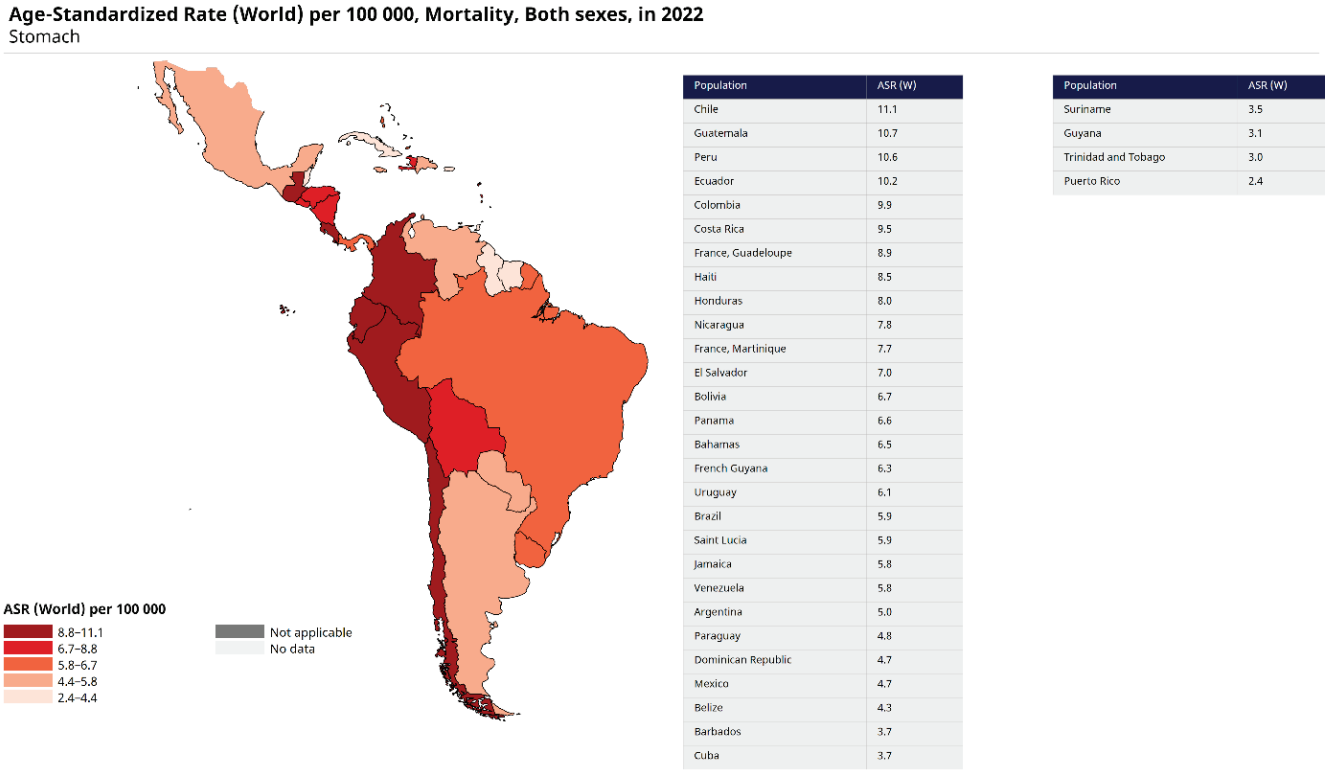
According to GLOBOCAN 2022, the countries in LAC with the highest overall gastric cancer incidence and mortality rates are Chile, Colombia, Costa Rica, Ecuador, Guatemala, and Peru (Fig. 3.2.2) [1]. The countries with the lowest gastric cancer incidence and mortality rates are Barbados, Belize, Guyana, Suriname, and Trinidad and Tobago. The Central America Four region (El Salvador, Guatemala, Honduras, and Nicaragua) is the largest low- and middle-income region in the Western Hemisphere, with a population of about 41 million; in addition, about 6 million people who now live in the USA have emigrated from the Central America Four region. Accurate mortality data are lacking for the Central America Four region, and underreporting hinders national and regional cancer control programmes [4]. The gastric cancer burden in the Central America Four region is projected to increase by 73% by 2030, primarily because of population growth and ageing, unless prevention strategies are implemented [4]. In contrast, the Caribbean has a heterogeneous incidence of gastric cancer, with an intermediate estimated incidence in Haiti (10 cases per 100 000 person-years) and a relatively low estimated incidence in the Dominican Republic (6 cases per 100 000 person-years) (Fig. 3.2.2) [1].

Age-Standardized Rate (World) per 100 000, Incidence, Both sexes, in 2022
Stomach



Population	ASR (W)
Peru	14.3
Chile	14.2
Costa Rica	14.0
Colombia	12.9
Ecuador	12.8
France, Guadeloupe	12.3
Guatemala	12.2
France, Martinique	10.8
Haiti	9.9
Uruguay	9.2
Nicaragua	9.1
Panama	8.8
Bolivia	8.7
French Guyana	8.6
Honduras	8.6
Saint Lucia	8.6
El Salvador	8.2
Bahamas	7.7
Brazil	7.6
Venezuela	7.5
Jamaica	6.9
Argentina	6.7
Paraguay	6.4
Mexico	6.3
Dominican Republic	6.2
Cuba	5.6
Barbados	5.0
Belize	4.8

Population	ASR (W)
Suriname	4.6
Guyana	4.5
Trinidad and Tobago	4.0
Puerto Rico	2.8



Population	ASR (W)
Chile	11.1
Guatemala	10.7
Peru	10.6
Ecuador	10.2
Colombia	9.9
Costa Rica	9.5
France, Guadeloupe	8.9
Haiti	8.5
Honduras	8.0
Nicaragua	7.8
France, Martinique	7.7
El Salvador	7.0
Bolivia	6.7
Panama	6.6
Bahamas	6.5
French Guyana	6.3
Uruguay	6.1
Brazil	5.9
Saint Lucia	5.9
Jamaica	5.8
Venezuela	5.8
Argentina	5.0
Paraguay	4.8
Dominican Republic	4.7
Mexico	4.7
Belize	4.3
Barbados	3.7
Cuba	3.7

Population	ASR (W)
Suriname	3.5
Guyana	3.1
Trinidad and Tobago	3.0
Puerto Rico	2.4

Fig. 3.2.2. Gastric cancer (A) incidence and (B) mortality in both sexes, age-standardized rates (ASRs) (world) per 100 000 person-years in Latin America and the Caribbean. Source: Ferlay et al. (2024) [1].

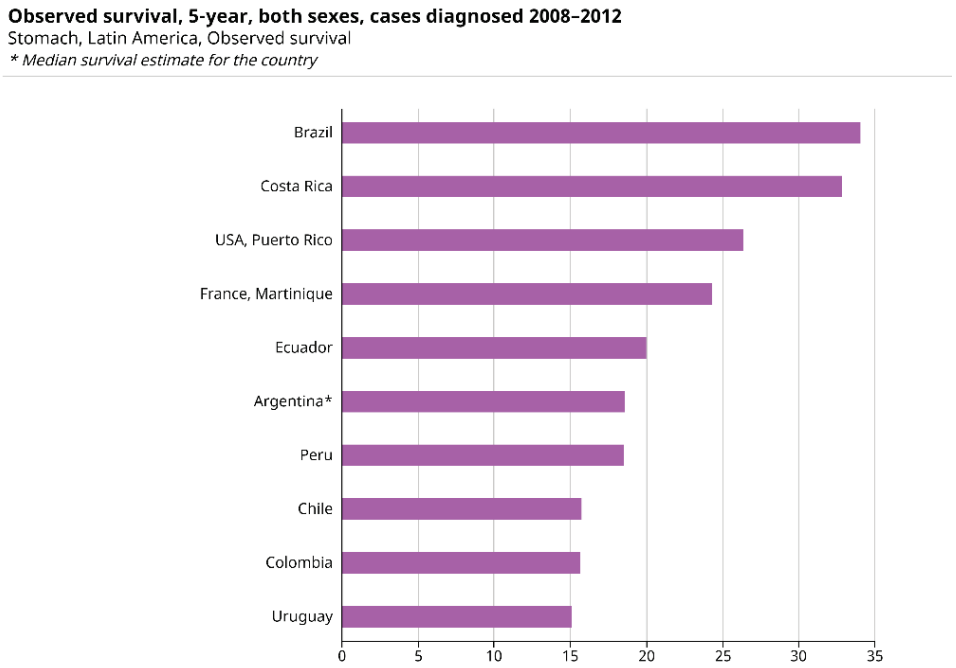


Fig. 3.2.3. Median 5-year observed survival of patients with gastric cancer in Latin America and the Caribbean, in both sexes combined. Source: Soerjomataram et al. (2023) [6].

The most common anatomical subsite of gastric cancer in populations in LAC is *H. pylori*-driven non-cardia gastric cancer [5]. In LAC, patients with gastric cancer are often diagnosed at an advanced stage of the disease, and the overall median 5-year survival rate is < 35% (Fig. 3.2.3) [6]. People in rural Central America have an even worse prognosis after a gastric cancer diagnosis, with a 5-year survival rate of < 10% [7].

The epidemiological pattern of gastric cancer is evolving. A trend analysis in Hispanic populations in Puerto Rico and 16 countries in LAC showed that gastric cancer mortality had increased slightly or was stable in people younger than 50 years [8]. This is consistent with an increasing incidence of non-cardia gastric cancer in young non-Hispanic White people and in Hispanic people in the USA, particularly in women [9]. Additional surveillance is needed in populations in LAC.

3.2.2 Risk factors for gastric cancer in populations in LAC

Improvements in hygiene and sanitation have contributed to the global decrease in the prevalence of *H. pylori* infection, and these factors still contribute to the varying prevalence of *H. pylori* infection across regions. The prevalence of *H. pylori* infection is about 50% in the population worldwide and is > 60% in most countries in LAC. Fig. 3.2.4 shows the prevalence of *H. pylori* infection and the age-standardized rates (world) of gastric cancer per 100 000 population in 2020 attributable to *H. pylori* infection in selected countries [10]. In a meta-analysis that included 22 studies in Latin America (in 14 countries) in 1987–2012, the prevalence of *H. pylori* infection was 69.3% in adults and 48.4% in children and adolescents [11]. In Chile, the historical seroprevalence of *H. pylori* infection was > 70% [12], but a recent study suggested that there has been a drastic decrease, with an observed prevalence of 29% in adults in urban areas, mainly related to water sanitization [13, 14]. In participants in the Hispanic Community Health Study/Study of Latinos, the overall weighted *H. pylori* seroprevalence was 57%, with a seropositivity of 38% in people born in the USA and a seropositivity of 62% in people born outside the USA [15].

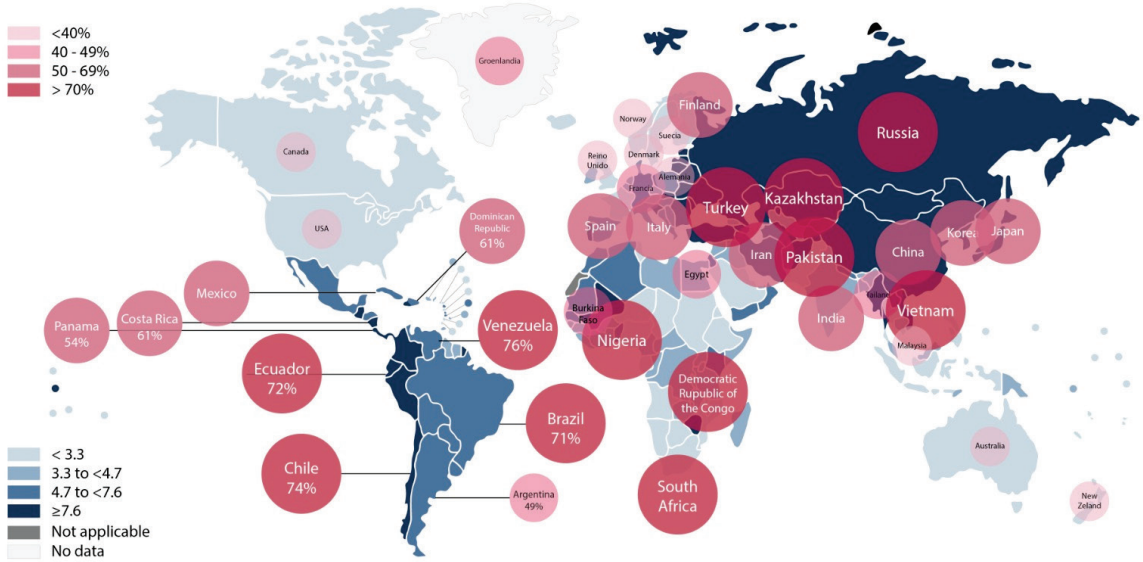


Fig. 3.2.4. Prevalence of *H. pylori* infection (in red) and age-standardized rates (world) of gastric cancer per 100 000 population (in blue) in 2020 attributable to *H. pylori* infection in selected countries. Compiled from Ferlay et al. (2024) [1]. Panel illustrated by Valentina Riquelme.

In Latin America, the associations of risk factors for gastric cancer are based on case–control comparisons. The specific factors that have been identified and their magnitudes of association are largely similar to those identified in other populations [5]. An association between altitude and gastric cancer incidence and mortality has been observed in the countries of western Latin America, located along the Pacific rim; this is known as the Andes enigma [2]. South American countries that are located along the Atlantic coast also have some populations at high risk of gastric cancer. For example, people in north-eastern Brazil have the highest rates of gastric cancer in the country [16]. These observed variations in risk may be attributed to differences in ancestry, salt intake, environmental factors, the prevalence of *H. pylori* CagA-positive strains, and the presence of other gastrointestinal coinfections [17].

3.2.3 Gastric cancer prevention in LAC

In most countries in LAC, health sectors have inadequate financial protection against health-care costs, and service delivery is fragmented [18]. Few health efforts in the region are focused on preventive medicine. Prevention strategies for gastric cancer are urgently needed in LAC to reduce the high social and economic costs of this disease.

An evidence-based strategic framework to achieve effective prevention and control of gastric cancer in the Americas was recently proposed, and this framework could guide immediate action [19]. In addition, under the umbrella of the World Code Against Cancer Framework, the 2023 Latin America and the Caribbean Code Against Cancer recommends screening and treatment for *H. pylori* infection in the context of specific public health programmes [20].

Gastric cancer prevention activities before 2013

The 2014 IARC Working Group Report on *H. pylori* eradication as a strategy for preventing gastric cancer [21] summarized the strategies used against gastric cancer in countries in LAC. At that time, only Chile, Costa Rica, Ecuador, the Bolivarian Republic of Venezuela, and Peru had explicit initiatives related to gastric cancer prevention. In Chile, the Ministry of Health initiated an opportunistic nationwide gastric cancer detection programme in 2006 that focused on symptomatic individuals. Also, *H. pylori* eradication (standard triple therapy) was recommended for any patient who had undergone oesophago-gastro-duodenoscopy (OGD) with a diagnosis of *H. pylori* infection and duodenal or stomach ulcer, atrophic gastritis, lymphoma, adenoma, gastric cancer, and/or a family history of gastric cancer [22]. In Ecuador, the Sociedad de Lucha Contra el Cáncer, a national non-profit organization, provides education about gastric cancer and specific recommendations for its treatment [23]. In Peru, the National Plan to Strengthen Cancer Prevention and Control in Peru, published in 2006, recommended (i) promoting research studies on methods for early detection of gastric cancer, including endoscopy; (ii) promoting the incorporation of early detection methods for gastric cancer and other cancers among health-care providers and the general public; and (iii) supporting actions to control *H. pylori* infection and to improve eating habits [24].

During the mid-1980s and the 1990s, as an international cooperation between the governments of Japan and of several LAC countries, gastric cancer screening programmes based on photofluorography were established in high-risk areas. In Peru, OGD examinations were conducted in > 30 000 symptomatic patients in 1985–2002. In the Bolivarian Republic of Venezuela, a screening programme conducted > 100 000 examinations in 1980–1989 in the high-risk region of Tachira [25]. Both of these programmes have been discontinued. In Costa Rica, the Cancer Early Detection Center in Cartago was opened in 1995, and 10 064 individuals were screened in 1996–1999 [26]. The impact evaluation of this intervention concluded that although X-ray mass

screening seems to be able to reduce mortality from gastric cancer, the high cost of the procedure may prevent this intervention from being scaled up to cover the entire country [27]. The Cancer Early Detection Center still operates as a patient care centre, as part of the Caja Costarricense de Seguro Social (CCSS). Residents in the target areas are invited for a gastrointestinal series, and individuals with an altered series and those referred (from within or outside the CCSS) for previous suspicious endoscopy findings have diagnostic OGDs. At the Cancer Early Detection Center, most cases of gastric cancer are diagnosed at an early stage of the disease, and they are treated by an expert multidisciplinary team.

Gastric cancer prevention activities after 2013

In recent years, the Pan American Gastroenterology Organization (Organización Panamericana de Gastroenterología; OPGE), in collaboration with organizations in Europe and North America, including the European Registry on *H. pylori* Management (Hp-EuReg), the Spanish Gastroenterology Association, and the United States National Cancer Institute, has led key regional initiatives related to the primary prevention of gastric cancer.

Local guidelines

In 2014, under the sponsorship of the Chilean Society of Gastroenterology, a consensus report on the management of *H. pylori* infection in Latin America was published by a multidisciplinary group of adult and paediatric gastroenterologists, epidemiologists, and scientists with expertise in *H. pylori* infection and associated diseases and evidence-based medicine [28]. In a parallel effort, the Chilean Association of Digestive Endoscopy (ACHED) published a consensus report on endoscopic diagnosis and follow-up of gastric premalignant lesions. The ACHED group recommended that (i) endoscopists should perform systematic biopsies and specific examinations to detect early lesions, (ii) pathologists should adopt the updated Sydney protocol and include the Operative Link on Gastritis Assessment (OLGA) or Operative Link on Gastric Intestinal Metaplasia Assessment (OLGIM) staging in the histopathological report, and (iii) endoscopy services and pathological anatomy services should implement administrative processes to ensure that patients receive notifications and appointments for endoscopies if needed [29]. These two consensus reports helped to launch several initiatives (described below) for the prevention and control of gastric cancer in LAC. The ACHED group is working on

an updated version of the guidelines on gastric premalignant conditions, to be published in 2025, which will incorporate new data.

The Latin American Registry on the Management of H. pylori *Infection*

In 2019, the Latin American Registry on the Management of *H. pylori* Infection (Hp-LATAMReg) was created, with the support of the Hp-EuReg and the Spanish Gastroenterology Association, to describe and evaluate the main *H. pylori* eradication therapies and their eradication rates, adherence, and side-effects in countries in LAC. Eight countries (Argentina, Chile, Colombia, Costa Rica, Ecuador, Guatemala, Mexico, and Peru) have joined the Hp-LATAMReg and have provided retrospective and prospective (2015–2023) information to the Hp-LATAMReg. In 2024, a preliminary analysis reported that 1378 individuals have been registered, including 1218 (88%) treatment-naive patients. Preliminary results showed that (i) most of the treatment regimens used were 14 days long (n = 1051; 96%) and administered high-dose proton pump inhibitors; (ii) dual therapy and bismuth-containing quadruple therapies were significantly more effective than standard triple therapy; (iii) the most frequently used diagnostic test was histology (66%), and the most frequently used tests to confirm eradication were the stool antigen test (39%) and the ^{13}C-urea breath test (29%) [30, 31]; and (iv) the eradication rates for several schemes were strongly associated with rates of *H. pylori* antibiotic resistance. Findings from the Hp-LATAMReg are already providing relevant information to enable updates of the national and regional guidelines for *H. pylori* treatment. For example, quadruple and dual therapies should be considered as the first-line treatment for *H. pylori* eradication in LAC.

H. pylori-*antibiotics RESistance in Latin America (Hp-RESLA)*

A systematic review and meta-analysis of studies in Latin America published up to October 2013 reported that the overall prevalence of *H. pylori* primary antimicrobial resistance among adults was 12% for clarithromycin, 53% for metronidazole, 4% for amoxicillin, 6% for tetracycline, 3% for furazolidone, 15% for fluoroquinolones, and 8% for dual clarithromycin and metronidazole resistance [32]. The prevalence of resistance varied substantially by country but not by year of sample collection. In 2019, a meta-analysis of studies on clarithromycin resistance in adults in Santiago, Chile, showed a higher prevalence of clarithromycin resistance (26%) and a suboptimal *H. pylori* eradication rate (63%) [33]. Another study in Santiago showed that levofloxacin

resistance was higher in women than in men (39% vs 13%; $P < 0.001$) [34]. Additional studies should be conducted to further explore potentially differential effects by sex. Accordingly, since 2019, the OPGE has supported Hp-RESLA, a multicentre study on molecular *H. pylori* antibiotic resistance in LAC, which aims to create a regional laboratory network for polymerase chain reaction (PCR), using gastric biopsies that were originally collected for rapid urease tests, and next-generation sequencing, using formalin-fixed, paraffin-embedded blocks.

GC-GAP index

The Gastric Cancer Global Action Preparedness (GC-GAP) study, led by the OPGE, aims to develop a preparedness index using published public policies against gastric cancer. Three rounds of Delphi panels were held, with the participation of 45 international experts. These experts represented all continents and included representatives from all the gastroenterology societies in the Americas (OPGE members), representing 98% of the population of the continent. The objectives of the three rounds were to define the domains, to define the indicators, and to adjust and agree on the final preparedness index. The index is made up of public policy domains and their respective indicators to classify countries according to their level of preparedness in each domain: low, intermediate, or high. Consensus (i.e. > 80% agreement) was reached on nine domains of public policies in favour of gastric cancer awareness, screening for risk factors and early-stage disease, availability of gastric cancer treatment, increasing the availability of drinking-water, and policies against *H. pylori* infection, obesity, tobacco use, and alcohol consumption. The use of a preparedness index will enable a standardized evaluation of public policies against gastric cancer in the Americas, including countries in LAC, based on global standards [35].

National activities in Chile

During the past decade, Chile has developed several initiatives and laws related to cancer prevention that may have a positive impact on gastric cancer. The 2015 Choose a Healthy Lifestyle programme promotes healthy eating, physical activity, outdoor lifestyles, and family life [36]. The 2016 Law of Food Labelling aims to reduce purchases of foods with sodium, sugars, saturated fats, or calories above the recommended limits ("high-in" foods) [37]. The 2022 Cancer Law aims for the integrated management of

patients with cancer [38]. In 2023, the Center for Cancer Prevention and Control was established to generate evidence that could guide public policies on cancer prevention and control [39].

As part of efforts for gastric cancer prevention, universal health coverage for gastric cancer and *H. pylori* infection includes access to therapy for all health-care systems and types of insurance [40]. The 2006 public health policy of offering OGD screening to symptomatic individuals aged ≥ 40 years has led to long waiting lists in several areas of Chile. To determine the best strategy to reduce these waiting lists, the Ministry of Health is conducting a pilot study using non-invasive biomarkers for risk stratification of gastric premalignant conditions and gastric cancer. The preliminary (unpublished) results of this study, using data on pepsinogen I/II ratios, immunoglobulin G (IgG), *H. pylori* serology, serum gastrin-17 levels, age, sex, and first-degree relatives with gastric cancer, showed an area under the receiver operating characteristic curve of 0.74, with a negative predictive value of 88% in the Maule region of Chile and of 90% in Santiago. This will enable the Ministry of Health to prioritize access to OGD in the next stage of the project. However, these findings are not sufficient to avoid OGD screening for patients on the waiting list, and they cannot be extrapolated to asymptomatic individuals in population-based studies.

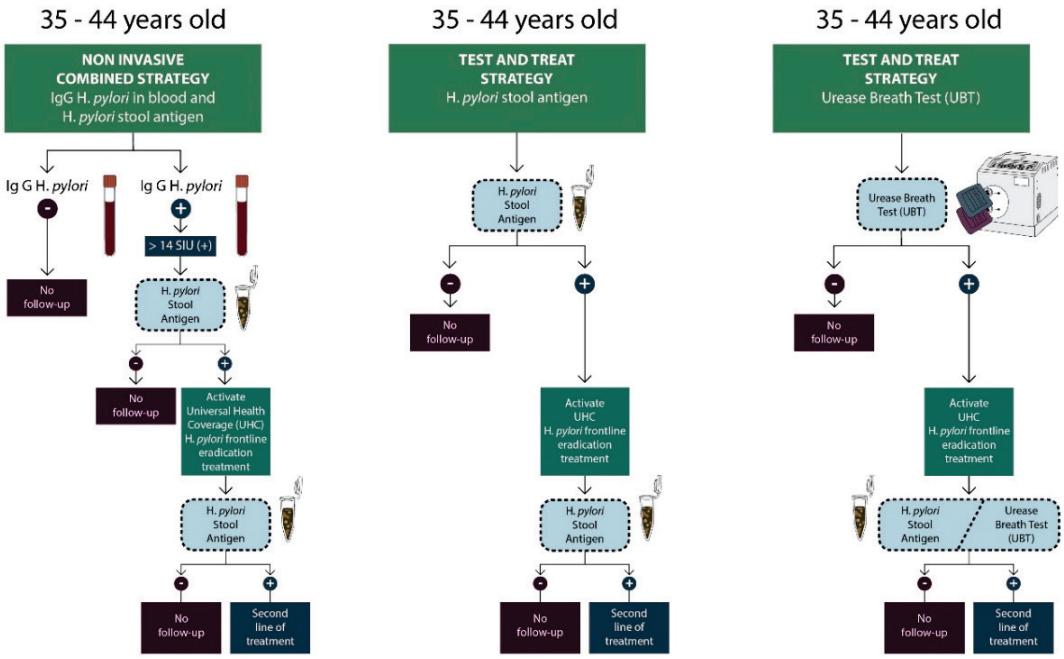


Fig. 3.2.5. Strategies for the non-invasive detection of *H. pylori* in an asymptomatic population aged 35–44 years. IgG, immunoglobulin G; UHC, universal health coverage. Reproduced from Corsi Sotelo et al. (2024) [41]. Copyright Elsevier 2024.

The Chilean consensus report for gastric cancer prevention [41], published in 2024, recommended a screen-and-treat strategy for *H. pylori* infection using non-invasive tests (primary prevention) for individuals aged 35–44 years (Fig. 3.2.5) and a combined strategy (IgG, *H. pylori* serology, and OGD) for individuals aged ≥ 45 years (primary and secondary prevention) (Fig. 3.2.6). This recommendation is aligned with the Maastricht VI/Florence Consensus report [42] and could be applicable in other high-risk countries in LAC.

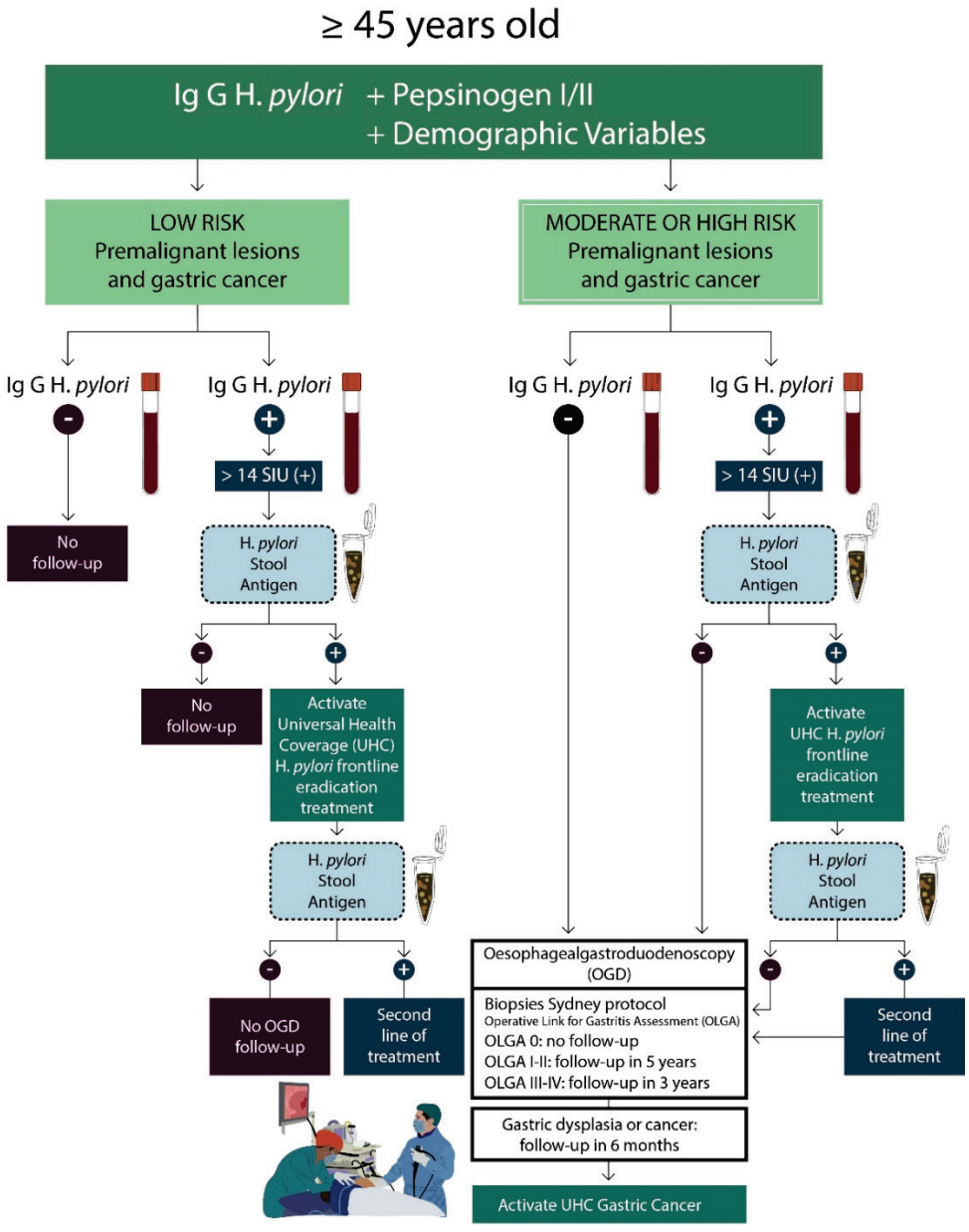


Fig. 3.2.6. Primary and secondary strategies for gastric cancer prevention in an asymptomatic population aged ≥ 45 years. IgG, immunoglobulin G; OGD, oesophago-gastro-duodenoscopy; OLGA, Operative Link on Gastritis Assessment; UHC, universal health coverage. Reproduced from Corsi Sotelo et al. (2024) [41]. Copyright Elsevier 2024.

ECHOS retrospective study

In the Endoscopic Cohort and Histological OLGA Staging (ECHOS) study, a retrospective cohort was assembled of 685 individuals who underwent > 2 OGDs with biopsies > 6 months apart in 2015–2021 and who had atrophic gastritis staged by OLGA and OLGIM [43]. In this study, OLGA and OLGIM stages III–IV were independently associated with a higher risk of progression to high-grade dysplasia and gastric cancer. A microsimulation model based on the ECHOS study and other data sets showed that surveillance of incidentally detected intestinal metaplasia every 5 years is associated with reduced gastric cancer incidence and mortality and is cost-effective from a health-care sector perspective [44]. These combined results support the role of endoscopic surveillance in patients in Latin America with advanced OLGA and OLGIM stages.

HOPE-Hp-GC study

In 2023, the Center for Cancer Prevention and Control launched the Hospital and Outpatient Prevention Program to Eradicate *H. pylori* and Gastric Cancer (HOPE-Hp-GC) study in Molina, a high-risk area in the Maule region of Chile. This study is based on the Chilean consensus report for gastric cancer prevention [41], and other centres in Chile and other countries in LAC will join this study in the near future. In the first level of the study, individuals aged < 40 years are screened for *H. pylori* infection using the urea breath test and are offered *H. pylori* eradication treatment using dual therapy or quadruple concomitant therapy for mass eradication. Currently, 3000 of the 50 000 inhabitants of Molina have been tested, and by the second year of the project, *H. pylori* positivity had decreased from 49% to 34%. In contrast, individuals aged 40–75 years are screened using *H. pylori* pepsinogen serology, considering individual baseline comorbidities to assess the level of gastric cancer risk, i.e. low risk or intermediate to high risk, followed by *H. pylori* treatment if the individual tests positive for *H. pylori* infection at the second level. Finally, individuals with intermediate to high risk of gastric cancer undergo OGD using the Sydney protocol, followed by an OLGA assessment, which is conducted after *H. pylori* treatment or directly if the individual tested negative for *H. pylori* infection. Individuals with intermediate to high risk of gastric cancer are followed up every 4 years for OLGA stages 0–I with persistent *H. pylori* infection and for OLGA stage II regardless of *H. pylori* status, and every 2 years for OLGA stages III–IV. Surveillance was not recommended for OLGA stages 0–I with no *H. pylori* infection; this

is in accordance with the updated ACHED protocol. In the preliminary results of OGDs performed in Molina, 12% were at OLGA stages III–IV. As part of this study, a new endoscopy unit was established at Molina Hospital, and this helped to reduce the waiting list for OGDs by 63%. In 2025, patients at OLGA stages III–IV will be offered follow-up endoscopy alongside the other study activities.

Recent and ongoing national activities in other countries in LAC

In the Bolivarian Republic of Venezuela, the Society Against Cancer (Sociedad Anticancerosa) launched a screening programme for premalignant lesions in first-degree relatives of patients with gastric cancer at Caracas Hospital in 2023. If this initiative is successful, it will be expanded to other areas of the country [45].

In Ecuador, the National Strategy for Comprehensive Cancer Care (2017–2023) recommended that screening for gastric cancer in the population aged > 50 years should be conducted using a combination of serology tests to determine *H. pylori* infection status and pepsinogen levels combined with OGD to detect gastric cancer. The intervals at which endoscopic studies should be done should be determined by the ABCD method [46].

3.2.4 Conclusions and future directions

In summary, gastric cancer prevention is an important public health programme in LAC. Continued and targeted prevention efforts are needed to reduce the morbidity and mortality burden of gastric cancer. Several new research initiatives are under way in key countries in LAC, but there are limited strategies for gastric cancer prevention and control embedded in laws and public health policies. Ongoing research work should inform future efforts and guide changes in regional and local clinical guidelines.

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Chapter 3.3.

Gastric cancer prevention research in the USA

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Summary

- In the USA, the burden of gastric cancer is low, but there are well-documented racial/ethnic and socioeconomic disparities, particularly in mortality.
- The epidemiological pattern of gastric cancer in the USA is evolving, with increasing incidence in young people, particularly in women.
- The USA has not implemented any gastric cancer prevention programmes targeting identifiable high-risk populations. However, upcoming management recommendations by professional medical societies may help to guide future research efforts and public health policies.
- The intramural programme of the United States National Cancer Institute has a research portfolio on gastric cancer that informs biological concepts, clinical practice, and public health policy.

3.3.1 Introduction

In the USA, the estimated number of new cases of gastric cancer in 2024 was about 27 000, and the overall 5-year relative survival for the period 2014–2020 was 36.4% [1]. These poor outcomes reflect the generally late stage of diagnosis of this preventable and curable cancer type. The lack of preventive strategies in the USA represents a major health-care disparity, because gastric cancer disproportionately occurs in minoritized communities and immigrant groups in the USA, such as Asian Americans, Hispanic Americans, Black Americans, and American Indian and Alaska Native people.

The epidemiological pattern of gastric cancer in the USA is evolving. According to data from the United States National Cancer Institute (NCI) Surveillance,

Epidemiology, and End Results (SEER) Program and the North American Association of Central Cancer Registries, the incidence of non-cardia gastric cancer is increasing in young non-Hispanic White people and Hispanic people, particularly in women [2, 3]. Consistent with these observations, gastric cancer mortality increased slightly or was stable in individuals younger than 50 years in Hispanic Americans and people from some Latin American countries [4]. The age-adjusted rates of total new gastric cancers in the USA in 2017–2021 showed a statistically significant increase, with an overall average annual percentage change of 1.98% (95% confidence interval [CI], 0.46–2.78%). The sex-specific average annual percentage change was 3.27% (95% CI, 2.26–4.00%) for women and 0.74% (95% CI, −0.65% to 1.74%) for men [5]. These findings demonstrate the importance of gastric cancer for public health in the USA.

3.3.2 Prevalence of *H. pylori* infection

The overall prevalence of *H. pylori* infection in the USA is estimated to be about 30–40% [6]. However, there are subpopulations in the USA that have higher rates of *H. pylori* infection. Some examples are given here.

- In a nested case–control study in Alaska Native people, 92% of the patients with gastric cancer and 82% of the control group were seropositive for *H. pylori* infection. A higher percentage of cases (95%) and controls (93%) were seropositive for CagA [7].
- Tribal members from the Navajo Nation have higher rates of *H. pylori* infection and gastric cancer. In a cross-sectional study, 57% of participants tested positive for *H. pylori*, and 79% of those who tested positive were positive for the *cagA* gene [8].
- A study evaluating the seroprevalence of *H. pylori* in the Hispanic community in the USA demonstrated an overall seropositivity rate of 57%, with substantially higher seropositivity rates in individuals who were not born in the USA and in those living in lower socioeconomic conditions [9].
- In a retrospective study of United States veterans with *H. pylori* testing data from 1999–2018, non-Hispanic Black people had an *H. pylori* positivity rate of 40%,

compared with 20% for non-Hispanic White people [10]. *H. pylori* infection was diagnosed in 26% of all individuals tested.

- A recent scoping review that combined data from 41 publications found that data on population-based *H. pylori* seroprevalence are lacking in the USA [11]. The *H. pylori* seroprevalence rates were highest in American Indian and Alaska Native people, followed by the Hispanic and non-Hispanic groups. The seroprevalence rates were lowest in the non-Hispanic White and Asian and Pacific Islander groups. Differences in age and birth cohort patterns emerged among racial/ethnic groups [11].

3.3.3 Gastric cancer prevention research

Attempts to increase the awareness of gastric cancer and to address both primary and secondary prevention have been made by local grass-roots initiatives, mainly in Alaska and in states with large immigrant populations, such as California, Florida, New Jersey, and New York.

Gastric cancer symposium in Anchorage, Alaska

In July 2019, a multiagency work group hosted a symposium in Anchorage, Alaska, that brought together internationally recognized experts and local leaders to evaluate issues related to gastric cancer in the Alaska Native population [12]. The goal of this symposium was to identify strategies to combat gastric cancer in the Alaska Native population that are scientifically sound, logistically realistic, and culturally acceptable. Key discussions included implementing clinical and community education, targeted screening and surveillance within clinical practice, and basic science and epidemiological investigations. The members of the scientific panel discussed the high prevalence of *H. pylori* infection in the Alaska Native population and the need for *H. pylori* treatment for people with a high-risk gastric pathology or a family history of gastric cancer. The members of the community panel discussed the risk factors for gastric cancer and noted the high prevalence in the Alaska Native population of known risk factors, such as *H. pylori* infection, smoking, and consumption of salted and smoked foods. The community panel thought that more information was needed about the risks associated with the lack of running water in homes, exposure to ground contaminants, and the use of iq'mik, which is a homemade chew that is

commonly used in some regions of Alaska and that mixes tobacco with fungus ash. They also thought that additional education for communities was needed to increase the understanding of gastric cancer, its risk factors, and the benefits of screening [12].

2020 Gastric Cancer Summit at Stanford University

In March 2020, a summit was convened at Stanford University, in California, to bring together various groups from across the country to propose a framework for gastric cancer prevention that would be applicable to the USA, which has a population composed of diverse racial/ethnic groups with differing risks of gastric cancer [13]. The result of this summit was a white paper, which provided expert consensus statements that evolved from this summit [14]. The recommendations were as follows.

- Testing for *H. pylori* should be performed in the following individuals, irrespective of the presence of symptoms:
    - individuals with a family history of gastric cancer in a first-degree relative;
    - first-generation immigrants from regions with high prevalence of *H. pylori* infection; and
    - individuals belonging to racial/ethnic groups at increased risk of gastric cancer (Black Americans, Alaskan Natives, American Indians, Asian Americans, and Hispanic Americans).
- All individuals with a positive test result of active infection with *H. pylori* should be offered treatment.
- Testing to confirm eradication should be performed after treatment.
- Endoscopic screening with biopsies should be offered beginning at age 50 years to the following individuals:
    - individuals with a family history of gastric cancer in a first-degree relative;
    - first-generation immigrants from regions with high gastric cancer incidence; and

- individuals belonging to racial/ethnic groups at increased risk of gastric cancer (Black Americans, Alaskan Natives, American Indians, Asian Americans, and Hispanic Americans).

- If gastric intestinal metaplasia or more severe pathology is identified, endoscopic surveillance should be offered.

Additional Gastric Cancer Summits at Stanford University were held in November 2022 and November 2024 to continue the work of the initial summit. The progress that had been made in health policy and research was presented. Substantial progress has been reported, including additional societal guidelines addressing the primary and secondary prevention of gastric cancer in the USA. A conference summary of the November 2024 summit is currently being prepared for publication.

3.3.4 Existing guidelines from academic societies

Currently, there are no clear guidelines for gastric cancer prevention from any of the gastroenterology or cancer societies in the USA.

Recommendations

In the USA, most first-line treatments for *H. pylori* are clarithromycin-based triple therapy, with eradication rates of < 90% [15]. The low eradication rates are because clarithromycin resistance rates are > 30% [16]. In 2024, the American College of Gastroenterology updated its recommendations for *H. pylori* screening and treatment specifically for the primary and secondary prevention of gastric cancer [17]. The indications for an *H. pylori* screen-and-treat approach are as follows:

- current or history of gastric premalignant conditions;
- current or history of early gastric cancer resection;
- current or prior history of gastric adenocarcinoma;
- patients with gastric adenomas or hyperplastic polyps;
- individuals with a first-degree relative with gastric cancer;
- individuals at increased risk of gastric cancer, including certain non-White racial/ethnic groups, immigrants from regions or countries with high gastric

cancer incidence, hereditary cancer syndromes associated with an increased risk of gastric cancer;

- patients with autoimmune gastritis.

The American Society for Gastrointestinal Endoscopy recommendations [18], published in 2015, suggest:

- screening and treating for *H. pylori* in racial and/or ethnic groups at high risk of gastric cancer; and
- a screening oesophago-gastro-duodenoscopy (OGD) for gastric cancer to be considered in new immigrants to the USA from regions or countries with a high risk of gastric cancer, including South America, China, Japan, the Republic of Korea, and the Russian Federation, especially if there is a family history of gastric cancer in a first-degree relative [18].

However, these suggestions are not considered to be evidenced-based guidelines, are not well publicized, and do not contain critical guidance on what constitutes a screening OGD, which should include biopsies according to the Sydney protocol. New guidelines and clinical recommendations for gastric cancer screening are in preparation by the American Gastroenterological Association; however, they are currently under review and have not been published.

Clinical studies

A 2024 study evaluated community-based testing for *H. pylori* infection in a large immigrant, underserved (i.e. with limited access to services) population in South Florida [19]. Although this was a relatively small study, it demonstrates the feasibility of performing larger prospective studies evaluating the effectiveness of both primary and secondary prevention strategies that are needed for the United States Preventive Services Task Force and the gastroenterology societies to develop stronger guidelines for gastric cancer prevention in the USA.

The Gastric Precancerous Conditions Study (GAPS; ClinicalTrials.gov ID, NCT04191551), which is being performed at Stanford University, is a prospective observational study with two overarching objectives: (i) to improve the non-invasive identification of patients with gastric intestinal metaplasia, and (ii) to develop

biological markers to predict the subset of intestinal metaplasia that will progress to gastric cancer. Additional small pilot and feasibility studies for both primary and secondary prevention strategies are currently being planned at various centres throughout the USA, such as the City of Hope (Los Angeles, California), the University of Southern California, and Kaiser Permanente (California). The City of Hope has recently started a prospective pilot study called the Our Stomach Health Project. This is a prospective study to evaluate the feasibility of a cancer screening programme to assess the risk of gastric cancer in Asian Americans, Hispanic Americans, and Black Americans. Eventually, prospective, large, multicentre, federally funded studies will be needed to provide the level of evidence required to make substantial recommendations to implement in guidelines for gastric cancer prevention in the USA.

3.3.5 Current and planned research projects for gastric cancer prevention: the NCI perspective

The Division of Cancer Epidemiology and Genetics (DCEG) at the NCI is part of the intramural programme of the United States National Institutes of Health (NIH) and is a global research leader in cancer epidemiology. The DCEG's research portfolio informs biological concepts, clinical practice, and public health policy. DCEG investigators conduct transdisciplinary research that focuses mainly on risk factors for cancer and involves extensive collaborations within the NCI, within the NIH, and with national and international institutions. (This section does not include any research projects funded by the extramural programme of the NCI and other NIH centres; information on those projects can be found at https://reporter.nih.gov/.)

Given that a substantial proportion of gastric cancer cases and deaths can be avoided, DCEG investigators and other experts have proposed a strategic framework to achieve effective prevention and control of gastric cancer in the Americas [20]. This strategic framework can be used as a resource for making decisions on public policy and developing funding priorities.

For the fiscal year 2022, the NCI's financial commitment to gastric cancer research, for both the intramural and extramural programmes, was US$ 16 million [21]. However, the NCI is committed to advancing this research agenda and has taken some actions to guide it. In December 2021, the NCI convened the Clinical

Trials and Translational Research Advisory Committee (CTAC) ad hoc Gastric and Esophageal Cancers Working Group to advise on translational research strategies to most effectively advance this field. The working group report highlighted the importance of developing precision approaches for the prevention, screening, detection, surveillance, and treatment of gastric and oesophageal cancers [22]. In May 2024, the NCI hosted the first Think Tank on Advancing Gastric Cancer Prevention, a forum to enable a multidisciplinary group of gastric cancer experts to review the state of the science and to collaboratively identify the critical gaps in knowledge. This international meeting was organized to provide specific clinical and translational prevention strategies that will be practicable for use in the high-risk populations in the USA and in other countries with a low or moderate risk of gastric cancer.

In addition to the descriptive work on trends in gastric cancer incidence and mortality, the DCEG portfolio for gastric cancer research is wide-ranging. The Nutrition Intervention Trial in Linxian, China, showed that nutritional interventions can be effective in reducing gastric cancer mortality [23, 24], as did an independent cancer incidence trial in Shandong Province, China [25].

This section summarizes the recent activities of DCEG investigators in gastric cancer, with a particular focus on *H. pylori* and studies that have potential translational applications, including the creation of new resources.

Helicobacter pylori *Genome Project*

DCEG investigators, in collaboration with an international, multidisciplinary team, created an international biobank of clinically annotated genetic and epigenetic variations of *H. pylori*. The *Helicobacter pylori* Genome Project Research Network has quantified, with great resolution, the different inferred ancestral sources of *H. pylori* subpopulations and the recent and ongoing admixture among subpopulations [26]. Analyses currently under way are comparing strains from patients with different types of gastric disease to identify genetic and epigenetic bacterial features that determine human pathogenicity. Other studies are addressing antibiotic resistance, among other topics. This publicly available worldwide collection of complete genomes and epigenomes with high-quality metadata will become a major asset for *H. pylori* genomics and gastric cancer research.

Golestan Cohort Study

In 2004, researchers at the Digestive Disease Research Institute and Tehran University of Medical Sciences, IARC, and the NCI launched the Golestan Cohort Study. This 50 000-person prospective cohort study recruited a large fraction of the eligible population in Golestan Province in the Islamic Republic of Iran. Historically, the people of this region had high rates of oesophageal squamous cell carcinoma (OSCC). The population in this region has several distinctive lifestyle features, including a substantial fraction of the elderly population using opium, frequent consumption of very hot tea, and limited diversity in the diet. The study was designed principally to examine the etiology of OSCC, but Golestan Province also has high rates of gastric adenocarcinoma. Although rates of OSCC are decreasing in the population, gastric cancer remains a substantial public health problem and rates have been stable over the past two decades [27]. As in the populations with a high incidence of OSCC in central China, the population in Golestan Province has a high fraction of cardia gastric cancer, with a ratio of 1:1 with non-cardia gastric cancer. Cardia gastric cancer is often incorrectly thought of as a disease that occurs most frequently in White men in high-income, industrialized countries, but in fact most cardia gastric cancers occur in rural populations in Asia [28]. Previous *H. pylori* studies in north-eastern Islamic Republic of Iran have shown that infection with *H. pylori* is nearly universal in the population aged > 40 years and that most people have CagA-positive strains [29]. This study confirmed the direct association between *H. pylori* infection and the risk of both gastric cardia and non-cardia adenocarcinoma. Recently, the NCI, along with external collaborators, measured *H. pylori* antibodies, serum pepsinogens, and trefoil factor 3 concentrations in a large nested case–control study of gastric cancer in this cohort, to facilitate studies of other etiological and protective exposures. In addition to *H. pylori*, studies in this cohort have examined the relationship between gastric cancer risk and oral health [30], opium use [31], indoor air pollution [32], water source [33], diet [34, 35], and blood group [36].

Genetic susceptibility to gastric carcinogenesis

Genome-wide association studies of gastric cancer in populations with East Asian [37, 38] and European [39] ancestry, led by DCEG investigators and others, have

identified susceptibility variants for gastric carcinogenesis. However, studies in Hispanic and Latino people have been quite limited. DCEG investigators are leading a genome-wide association study in Hispanic and Latino people, with about 3500 cases and about 4500 controls from North, Central, and South America. In collaboration with intramural and extramural experts, a multi-ancestry analysis (i.e. meta-analysis and polygenic risk score) is planned, to better define the underlying architecture of genetic susceptibility to gastric cancer and to generate a more useful polygenic risk score for screening.

Gastric Cancer Precursor Lesions study

Studies of premalignant lesions may provide insights into cancer etiology and inform risk stratification. In 2017, investigators at the DCEG and the Pontificia Universidad Católica de Chile launched the Gastric Cancer Precursor Lesions (GCPL) study. This is a multidisciplinary project, based in Chile, to evaluate risk factors for intestinal metaplasia, a precancerous change of the mucosa of the stomach with intestinal epithelium that confers an increased risk of gastric cancer. Patients with intestinal metaplasia may benefit from endoscopic surveillance to enable diagnosis of cancer at an earlier stage. Therefore, potential non-invasive markers of intestinal metaplasia are being evaluated. A better understanding of the etiology of premalignant lesions may inform future efforts for gastric cancer prevention and control in the USA and globally. The GCPL study is evaluating risk factors that have been insufficiently studied, such as *H. pylori* genomics and non-*H. pylori* gastric microbiota and parasitic infections. The study is also evaluating potential non-invasive screening markers, including pepsinogens and polygenic risk scores.

Upper Gastrointestinal Cancer Studies in Shanxi Province, China

The Upper Gastrointestinal Cancer Studies in Shanxi Province, China, were started in 1985 to look for major susceptibility genes for upper gastrointestinal cancers and to identify the genetic changes associated with their development [40]. These studies have provided most of the biological materials and data for the DCEG's genome-wide association studies of OSCC and cardia and non-cardia gastric cancer in Asian people. Evaluation of somatic and germline molecular markers (including assessment of gene–environment interactions) in malignant and premalignant tissues is in progress.

3.3.6 Addressing gaps in health policy

The lack of national screening guidelines prompted participants of the 2020 Gastric Cancer Summit at Stanford University to write a white paper with recommendations for the primary and secondary prevention of gastric cancer in the USA [14] (see Section 3.3.3). In April 2022, these recommendations were submitted to the United States Preventive Services Task Force, which is responsible for producing all the national screening guidelines that health insurance companies are required to fully cover in health insurance policies for people living in the USA. In 2022, the recommendation for primary prevention by testing for *H. pylori* infection did not move into the final research plan stage and evidence review.

An additional important pathway to changing health policy and practice in the USA is to establish guidelines through the national medical societies, such as the American Gastroenterological Association, the American College of Gastroenterology, and the American Society for Gastrointestinal Endoscopy. These three societies are all actively considering updating guidelines for both primary and secondary prevention of gastric cancer as a result of recent national efforts, such as the Gastric Cancer Summit at Stanford University, the NCI's Think Tank on Advancing Gastric Cancer Prevention, and other gastric cancer-specific forums. The lack of evidence for prevention strategies in the USA is the primary reason that the country does not have meaningful guidelines for gastric cancer prevention.

Several non-profit organizations in the USA are dedicated to educating and influencing policy-makers at the federal, state, and local government levels about gastric cancer. These organizations include No Stomach for Cancer [41], the Gastric Cancer Foundation [42], and the Debbie's Dream Foundation [43]. These organizations focus on raising awareness of gastric cancer, lobbying government policy-makers to increase funding for gastric cancer research, and supporting patients and families affected by gastric cancer.

3.3.7 Conclusions and future directions

Gastric cancer remains a leading cause of mortality among certain racial, ethnic, and immigrant groups in the USA, but there are no structured national strategies for its prevention. In the USA, gastric cancer is slowly gaining attention as a preventable

disease, and the clinical societies are actively updating prevention guidelines. Community education would be an effective and feasible public health strategy to enhance knowledge and awareness of this lethal disease. Demonstrative studies on implementation of primary and secondary prevention strategies for gastric cancer in various high-risk populations are needed to inform public health policy and health-care delivery.

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Chapter 3.4.

Gastric cancer prevention in Arctic North America (Alaska, Canada, and Greenland)

Karen J. Goodman

Summary

- Indigenous people in Arctic North America have a higher burden of disease from *H. pylori* infection than non-Indigenous counterparts.
- This disease burden disparity is most striking when comparing gastric cancer frequencies in Indigenous groups with those in non-Indigenous residents of the same geographical region.
- Health jurisdictions in the region should prioritize the collection of accurate data on Indigenous identity and report gastric cancer frequencies specific to Indigenous groups.
- Although the disproportionately frequent occurrence of *H. pylori* infection and gastric cancer across Arctic communities has been observed for more than two decades, public health authorities in Arctic North America have not targeted this disparity in current cancer prevention strategies, nor have they implemented screen-and-treat programmes for gastric cancer prevention.
- A perceived obstacle to the implementation of gastric cancer prevention strategies is the lack of evidence of cost–effectiveness specific to Arctic Indigenous communities, given observations from treatment trials conducted in such communities of relatively frequent hesitancy to receive treatment, along with relatively frequent treatment failure and reinfection.
- In this setting, community-driven screen-and-treat projects offer the possibility of engaging high-risk communities in designing gastric cancer prevention activities that serve their goals and values and give them agency in public health initiatives.

3.4.1 Introduction

Alaska, Canada, and Greenland comprise the far northern region of North America and are dominated by vast Arctic landscapes that are sparsely populated by small Indigenous communities. The Indigenous Arctic coastal people, known as Inuit, established coastal communities across Alaska, Canada, and Greenland. Traditionally, other Indigenous North American groups, known as Alaska Natives in Alaska and First Nations in Canada, have lived in small Arctic communities that lie south of the tree line. Relatively large multiethnic urban populations of Alaska and Canada are concentrated near their southern borders.

Most Arctic Indigenous communities fare poorly on many health indicators compared with non-Indigenous counterparts, even though they live in high-resource countries [1]. According to the Indigenous-led Waapihk Research organization, the social determinants of Inuit health can be summarized as follows: (i) the geography and climate of the remote Arctic environment, with its extreme weather conditions, poses transportation barriers, induces a high cost of living, and limits access to health-care services and facilities; (ii) economic disparity, high unemployment, poverty, and inadequate housing are common, and limited access to education and employment exacerbates poverty; (iii) intergenerational trauma resulting from the legacy of colonial policies, such as forced relocations and cultural assimilation, has an impact on mental health, evidenced in higher rates of substance use, depression, and suicide; (iv) the loss of language, customs, and traditional knowledge and practices creates identity issues and a sense of cultural disconnect, which negatively affect mental health and well-being; and (v) inadequate health-care infrastructure, shortages of health-care professionals, high-cost medical services, and dependence on medical transportation to access treatment restrict health-care access [2]. These factors are now compounded by environmental deterioration caused by climate change. Although crisis conditions have been acknowledged internationally, the health and well-being of Arctic Indigenous communities has received insufficient attention at a global level [3].

In 1997, investigators affiliated with the United States Centers for Disease Control and Prevention (CDC) Arctic Investigations Program, based in Anchorage, Alaska, in collaboration with the Alaska Area Native Health Service, observed that the prevalence of *H. pylori* infection was 99% among 140 Yupik adults in three villages in western

Alaska, who also had a high prevalence of severe gastric mucosal abnormalities upon endoscopic examination [4]. Since then, accumulating evidence of the high prevalence of *H. pylori* infection and the corresponding gastric cancer risk among Indigenous populations of the circumpolar north has flagged this inequity as a major global health concern. In the ensuing years, gastric cancer prevention efforts in this region have focused on describing the burden of *H. pylori*-associated disease and generating evidence on the benefits of screen-and-treat strategies for Arctic Indigenous communities. In the meantime, public health authorities have left the responsibility for prevention and control of *H. pylori*-associated disease largely in the hands of primary care practitioners and gastroenterologists, with no systematic approach to reducing gastric cancer rates.

3.4.2 Descriptive epidemiology of gastric cancer in Arctic North America

In 1996, shortly before the first report on *H. pylori* infection prevalence in an Alaskan community, investigators from the Danish Cancer Registry, Statistics Canada, and the Alaska Area Native Health Service estimated standardized incidence ratios to compare cancer incidence rates in circumpolar Inuit with those in non-Indigenous comparison populations in Connecticut (USA), Canada, and Denmark [5]; the report revealed excess gastric cancer incidence in Inuit men.

In 2004, a report on cancer incidence in Greenlandic Inuit in 1973–1997, using data from the Danish Cancer Registry, described an increasing trend in gastric cancer incidence of 24% every 5 years in both sexes during the study period [6]. In 1988–1997, standardized gastric cancer incidence ratios comparing Greenlanders with the Danish population were 2.2 (95% confidence interval [CI], 1.4–3.4) for women and 2.9 (95% CI, 2.1–4.0) for men. Noting that gastric cancer incidence had decreased globally in the preceding decades, the authors stated that the increases observed in Greenland were unparalleled in industrialized countries. High levels of nitrosamine had been observed in the dried, unsalted fish preparations that are consumed in Greenland, but there was no indication of increased consumption of these traditional foods during a period in which the consumption of fruits and vegetables had increased. The authors stated that estimates of the seroprevalence of *H. pylori* in Greenland during the study period were not available. Similar increases in the rates of lung cancer incidence were not observed

in either sex in the study; therefore, increases in the prevalence of smoking were not likely to be responsible for the dramatic increases in gastric cancer incidence.

In 2008, an update using data from 1989–2003 was published by the Circumpolar Inuit Cancer Review Working Group [7]. This update showed that gastric cancer incidence rates in both Inuit men and Inuit women were about 4 times those in non-Indigenous comparison populations. A 2008 review summarized studies of Arctic Indigenous communities that estimated a consistently higher incidence of gastric ulcers relative to duodenal ulcers, as well as studies that estimated a consistently high prevalence of *H. pylori* infection [8]. Several data sources showed elevated gastric cancer rates among North American Indigenous populations compared with non-Indigenous counterparts [9–11].

A 2012 report analysed cancer patterns among Inuit across Canada in 1998–2007. Gastric cancer incidence rates were higher among Inuit men than among men in the rest of Canada [12].

In 2012, members of the Canadian *Helicobacter* Study Group assessed evidence on *H. pylori* infection in First Nations people and recent immigrants to Canada [13]. They noted that the prevalence of *H. pylori* infection had been decreasing across Canada and that this had changed the distribution of upper gastrointestinal diseases, including reduced frequency and severity of peptic ulcer disease. However, Indigenous people and recent immigrants in Canada continued to have high prevalence of *H. pylori* infection; thus, there remained an opportunity to investigate whether *H. pylori* infection is a treatable risk factor for malignancy in Canadian communities with high frequencies of both *H. pylori* infection and gastric cancer.

A 2014 systematic review of gastric cancer incidence, mortality, and survival in Indigenous populations worldwide revealed elevated rates of gastric cancer incidence and mortality in nearly all Indigenous Peoples compared with non-Indigenous counterparts in the same regions or countries, with increasing trends in incidence observed in some groups [14]. In populations for which there are data, the largest age-standardized incidence ratios were observed in Inuit residing in the circumpolar region, with age-standardized incidence ratios of 3.9 for men and 3.6 for women.

A retrospective cohort study used data from 1991–2014 to compare gastric cancer incidence in immigrants and non-immigrants living in the Canadian province of Ontario [15]. Investigators identified immigrants who were first eligible for the Ontario Health Insurance Plan at age ≥40 years and matched each of them to 5 non-immigrants by year of birth and sex. The study identified 415 gastric cancer cases in 209 843 immigrant women, 1872 cases in 1 049 215 non-immigrant women, 596 cases in 191 792 immigrant men, and 2998 cases in 958 960 non-immigrant men. Most of the immigrants came from the World Bank regions of East Asia and Pacific, South Asia, and Europe and Central Asia. The crude gastric cancer incidence rate was 22% higher in immigrant women than in non-immigrant women and 9% higher in immigrant men than in non-immigrant men. Adjusted hazard ratios were 1.29 (95% CI, 1.12–1.48) for women within 10 years of health insurance eligibility and 1.19 (95% CI, 1.01–1.40) beyond 10 years and 1.17 (95% CI, 1.04–1.31) for men within 10 years of health insurance eligibility and 1.00 (95% CI, 0.87–1.15) beyond 10 years. Female immigrants from the East Asia and Pacific region and the Europe and Central Asia region had the highest gastric cancer incidence rates compared with age-matched female non-immigrants, both before and after the 10-year mark. The same pattern was seen for male immigrants from the Europe and Central Asia region but not for male immigrants from the East Asia and Pacific region, in whom gastric cancer incidence rates were only higher compared with age-matched male non-immigrants during the first 10 years after health insurance eligibility.

The Alaska Cancer Registry reports statewide cancer statistics. Its most recent *Cancer in Alaska multi-year summary report*, published in 2017, reported incidence statistics for 2010–2014 and mortality statistics for 2005–2014 [16]. During this period, the diagnostic frequency rank of gastric cancer among all cancer sites was fourth among American Indian and Alaska Native men in Alaska and seventh among Alaska Native women in Alaska; gastric cancer was not in the top 10 most frequently diagnosed cancer sites among White men or women in Alaska. For cancer deaths, gastric cancer was the 11th most frequent cancer site among all men in Alaska and the ninth most frequent among all women in Alaska; it was third among Alaska Native men in Alaska and fourth among Alaska Native women in Alaska.

In 2017, a report using Yukon Cancer Registry data, *Cancer mortality trends, 1999–2013* [17], highlighted gastric cancer as the fourth most frequent cause of cancer death

in Yukon men and the fifth most frequent cause of death in Yukon women, even though gastric cancer is diagnosed much less frequently than many other cancers [18]. The report estimated the age-standardized mortality ratio, comparing gastric cancer mortality rates in Yukon in both sexes combined with those in Canada in 2008–2012, as 1.8 (95% CI, 1.1–2.6). However, according to the Yukon Government *Cancer incidence report, 2009–2016* [19], gastric cancer was the 14th most frequently diagnosed cancer among Yukon men and women combined, with incidence rates similar to those expected based on the rates in Canada. The report noted that the average gastric cancer incidence rates coupled with the higher-than-average gastric cancer mortality rates suggest that gastric cancer may be presenting relatively late in Yukon compared with the rest of Canada or that gastric cancer in Yukon is more aggressive. Given that Indigenous people are a minority in Yukon, comprising 22% of the territorial population [20], the lack of ethnicity-specific disease frequency estimates in the Yukon health statistics masks the burden of gastric cancer in the Indigenous population in Yukon.

In 2018–2021, published analyses of gastric cancer data from diverse Canadian cancer registries showed high age-standardized gastric cancer incidence rates in Indigenous residents of the western Canadian province of Alberta relative to non-Indigenous Albertans [21], in Indigenous residents of the Northwest Territories relative to non-Indigenous Canadians [22], and in low-income communities with a high concentration of Indigenous people, visible minorities, and immigrants [23]. Cancer registry data also revealed a younger age distribution of gastric cancer cases in the Northwest Territories and Yukon relative to Canada as a whole: the proportion of gastric cancer cases diagnosed in people aged < 60 years was 48% in the Northwest Territories in 1997–2015, > 40% in Yukon, and < 25% across Canada as a whole, during similar time periods [22]. Also, of the gastric cancer cases diagnosed in Indigenous residents of the Northwest Territories in 1997–2015, 16% occurred in people aged < 40 years, compared with < 2% across Canada as a whole [22].

In 2021, investigators affiliated with the CDC Arctic Investigations Program and the Alaska Native Tribal Health Consortium published a description of gastric cancer occurrence in 1990–2017 in Alaska Natives living in Alaska compared with the White population in the USA [24]. Greater proportions of gastric cancer cases in Alaska Natives were diagnosed at younger ages: 11% of cases in Alaska Natives and 3% of cases in White people in the USA ($P < 0.0001$) occurred in people aged < 40 years, and

37% of cases in Alaska Natives and 20% of cases in White people in the USA ($P < 0.0001$) occurred in people aged 40–59 years. Proportionally more gastric cancer diagnoses among Alaska Natives were distant-stage cancer (48% in Alaska Natives and 35% in White people in the USA; $P < 0.0001$). The age-adjusted gastric cancer incidence rate was substantially higher in the Alaska Native population (20.8 per 100 000 per year in Alaska Natives and 6.7 per 100 000 per year in White people in the USA; $P < 0.0001$). Although the gastric cancer incidence rate decreased in the White population in the USA during the study period, little change in incidence was seen in the Alaska Native population.

A 2021 article co-authored by health officials from across the circumpolar north described gastric cancer incidence and mortality trends using cancer incidence and mortality data for 1999–2016 from circumpolar cancer registries [25]. Only cancer registries in the USA enabled data to be stratified by ethnicity, although it should be noted that nearly 90% of the population of Greenland identifies as Inuit [26]. Among men, the highest age-standardized gastric cancer incidence rates were reported for Karelia, in the Russian Federation (40.8 per 100 000 per year), followed by Greenland (20.2 per 100 000 per year), which was slightly higher than the rate among Indigenous men in Alaska (18.6 per 100 000 per year) and nearly double the rate in North Jutland, in Denmark (11.5 per 100 000 per year). Among women, the highest age-standardized gastric cancer incidence rates were reported for Arkhangelsk, in the Russian Federation (17.7 per 100 000 per year), followed by Indigenous women in Alaska (10.3 per 100 000 per year), with Greenland in third place (8.8 per 100 000 per year). Standardized rate ratios were estimated by comparing age-adjusted incidence rates with those of the broader proximal geographical unit (Greenland compared with Nordic countries; Indigenous people in Alaska compared with White people in Alaska). Across circumpolar populations, the largest standardized rate ratios were reported for Alaska (men, 3.8; 95% CI, 2.7–5.4; women, 4.1; 95% CI, 2.6–6.4) followed by Greenland (men, 2.8; 95% CI, 1.9–4.6; women, 2.3; 95% CI, 1.3–4.8) for both men and women. The authors of this analysis concluded, “There is a need to address disparities observed among circumpolar subpopulations … [and doing so] could benefit from coordinated international action” [25].

3.4.3 Gastric cancer prevention activities in Alaska

Alaskan public health researchers published the results of the earliest intervention studies that used treatment to eliminate *H. pylori* infection in Arctic Indigenous communities [8]. These studies revealed high prevalence of antibiotic resistance, high rates of treatment failure, and high rates of reinfection. These challenges, which are not generally encountered in high-income countries, led to a 2015 expert commentary by members of the Circumpolar *H. pylori* Working Group, which has held annual meetings since 2007, convened by the CDC Arctic Investigations Program and the Statens Serum Institut in Copenhagen, Denmark. These experts concluded that studies were needed to determine whether there were population subgroups for whom screening and treatment of *H. pylori* infection was cost-effective for gastric cancer prevention, highlighting the lack of community-based intervention studies [27].

In 2019, in response to calls from outsiders for a screen-and-treat initiative to be implemented in Alaska to reduce gastric cancer rates among Alaska Native communities, researchers affiliated with the CDC Arctic Investigations Program and the Alaska Native Tribal Health Consortium explained their position [28], emphasizing the collaborative partnership between these two agencies, which had facilitated *H. pylori* research conducted since the 1990s in Alaska. They summarized the substantial benefit for Alaska Natives of research that has yielded Alaska-specific descriptions of *H. pylori* infection and associated disease, including recognition of the high prevalence of *H. pylori* infection, documentation of associated health disparities, laboratory-based surveillance of antimicrobial resistance, assessments of the utility of *H. pylori* detection methods for Alaskan residents, treatment trials showing high rates of treatment failure, and estimates of high reinfection rates among rural Alaska Native residents.

The Alaskan public health experts noted that their investigations provided data to aid clinical decision-making to clinicians and health leaders, resulting in early adoption of more effective therapies prescribed to eliminate *H. pylori* infection. The experts explained that recent goals were to find a way to identify *H. pylori*-positive people at highest risk of gastric cancer to target for *H. pylori* treatment, to develop and test markers to detect gastric cancer at earlier stages, and to develop pilot studies for early gastric cancer screening. The Alaskan public health experts concluded by emphasizing that no one other than Alaska Native health leaders should decide whether a specific

prevention strategy should be adopted for Alaska Native communities. They noted that the role of health professionals is to inform such decisions based on empirical evidence of the risks, the benefits, and the alternatives, without presuming to know what is best for others [28].

In July 2019, a multiagency workgroup hosted a 2-day symposium in Anchorage, bringing together internationally recognized experts and local leaders to identify the best strategies to combat gastric cancer among Alaska Natives [29]. The symposium organizers aimed to identify goals and actions that were scientifically sound, feasible, and culturally acceptable. The symposium connected scientists with the relevant expertise, Alaskan health providers, Alaska Native community and tribal leaders, and public health officials. The symposium attendees identified the gaps in knowledge specific to the Alaska Native population for the following questions: (i) what are the genetic, dietary, environmental, and behavioural risk factors for gastric cancer; (ii) who would benefit from oesophago-gastro-duodenoscopy (OGD) screening for gastric cancer; (iii) what is the best way to detect diffuse gastric cancer in its early stages, and how effective is endoscopy at doing so; (iv) why do some people develop gastric cancer at a very young age; and (v) what is the current epidemiology of *H. pylori* infection. The symposium identified goals and actions, calling for support of:

- ongoing interventions that target gastric cancer risk factors:
    - protocols for care providers to emphasize early referral of high-risk patients;
    - a statewide upper endoscopy protocol for biopsy sampling;
    - specialized training for pathologists and endoscopists to improve gastric cancer detection;
    - updated local *H. pylori* clinical guidelines;
    - surveillance OGDs for first-degree relatives of patients with gastric cancer and people diagnosed with gastric intestinal metaplasia; and
    - education on gastric cancer prevention and screening for communities of new gastric cancer cases.
- scientific projects to enhance knowledge of gastric cancer in the Alaska Native population:

- continued collaboration with Canadian research teams on *H. pylori* genomics;
- further investigation of gastric cancer markers to optimize risk stratification;
- further descriptive research on *H. pylori* infection epidemiology in Alaska Native communities;
- assessment of the effectiveness of treatment of dental caries in concert with *H. pylori* treatment;
- enrolment of patients with newly diagnosed gastric cancer and their families in studies designed to identify risk factors.

The participants in the Alaska symposium concluded that broad *H. pylori* screening and treatment would not be beneficial, because of the high prevalence of *H. pylori* infection and antibiotic resistance, high reinfection rates, and logistic challenges. The participants also concluded that a statewide OGD screening programme, similar to those in Japan and the Republic of Korea, was logistically, economically, and culturally unrealistic; instead, individuals at highest risk should be prioritized for screening [29].

In addition to surveillance of cancer rates, the Alaska Department of Health regularly updates its Comprehensive Cancer Control Program. For 2021–2025, it aimed to address social determinants of health by approaching cancer control through a health equity framework [30], focusing key initiatives on primary prevention, early cancer detection, care for patients with cancer, and promotion of health equity. It does not specifically mention gastric cancer or *H. pylori* infection.

3.4.4 Gastric cancer prevention activities in Canada

The Canadian government defines the Arctic region loosely, acknowledging as stakeholders Indigenous Peoples in Canada along with the governments of the three northern territories (Nunavut, Northwest Territories, and Yukon) and the three provinces with Arctic regions (Newfoundland and Labrador, Quebec, and Manitoba) [31]. Canada's borders contain 25% of the global Arctic, which makes up more than 40% of Canada's land-mass [32].

In 1997, Canadian gastroenterologists formed the Canadian *Helicobacter* Study Group to offer guidelines for clinical management of *H. pylori* infection, which were first published in 1998 and subsequently updated [33–38]. In 2002, members of this Study

Group published a review of the risks and benefits of treatment to eliminate *H. pylori* infection [39]. The Study Group did not recommend widespread testing for *H. pylori* infection, because of insufficient research on the cost–benefit for gastric cancer prevention, potential increases in antibiotic resistance, and potential negative health effects of eliminating *H. pylori* infection. The Study Group recommended that the clinical management guidelines designed in Canada be applied, with *H. pylori* infection diagnosed and treated in appropriately selected patients [39].

In 2002, Cancer Care Ontario, the cancer adviser to the government of the most populous Canadian province, organized a workshop to determine whether there was sufficient evidence to consider the promotion of *H. pylori* treatment for the purpose of cancer prevention and to identify critical areas for research [40]. The workshop participants concluded that despite widespread acceptance of the safety of treatment to eliminate *H. pylori* infection, current evidence did not warrant the implementation of population screening for *H. pylori* infection in populations at average risk of gastric cancer. They called, instead, for a demonstration project to estimate prevalence of *H. pylori* infection, evaluate the merits of screening, measure patient and physician participation, develop education materials, and establish a registry for monitoring and evaluation.

A 2009 report described an economic evaluation of *H. pylori* screening strategies for the prevention of gastric cancer [41], based on a Markov model that compared the lifetime cost and effectiveness of four *H. pylori* screening strategies (no screening, serology-based testing, stool antigen testing, and ^{13}C-urea breath testing) as part of a screen-and-treat initiative for gastric cancer prevention in a hypothetical cohort of 10 000 Canadian men aged 35 years with an *H. pylori* prevalence of 33% and a gastric cancer incidence rate of 6.6 per 100 000. Treatment consisted of the four-drug regimen recommended by the Canadian *Helicobacter* Study Group, with an estimated effectiveness of 87%. The estimated accuracy of each detection method was incorporated into the models; costs were valued in 2008 Canadian dollars. The analysis estimated incremental cost–effectiveness ratios per quality-adjusted life year of $29 800 for stool antigen testing, $33 000 for serology-based testing, and $50 400 for ^{13}C-urea breath testing. The report did not estimate the cost–effectiveness of screen-and-treat strategies for demographic groups in Canada with higher *H. pylori* prevalence, but it

would be reasonable to expect improved cost–effectiveness of these strategies in groups with relatively high gastric cancer incidence rates.

The 2014 Northwest Territories Health and Social Services report titled *Cancer in the Northwest Territories 2001–2010* did not include gastric cancer among the most frequent cancer sites for which estimated frequencies were reported [42]. However, a section on cancer prevention in this report focused on modifiable risk factors and mentioned tobacco smoking, consumption of red meat, and salt intake as risk factors for gastric cancer. This section included information on *H. pylori* infection, noting it as a major cause of gastric cancer and referencing ongoing research conducted by the Canadian North *Helicobacter pylori* (CAN*Help*) Working Group (see Section 3.4.6). The 2015 report *Charting our course: Northwest Territories cancer strategy 2015–2025* [43] emphasized three strategic priorities: strengthening initiatives that promote healthy lifestyles and behaviours, supporting programmes that aim to reduce the use of tobacco, alcohol, and other drugs, and supporting community-driven cancer awareness and prevention initiatives. The strategy did not include any specific mention of gastric cancer or *H. pylori* infection.

A section of Yukon *Cancer mortality trends, 1999–2013*, called “Avoiding cancer: infectious agents”, stated that *H. pylori* infection is the most important risk factor for gastric cancer, and that when *H. pylori* is present the risk of cancer is influenced by dietary factors, including an increased risk with a diet high in salt and a reduced risk with intake of fruits and vegetables. The report pointed out that treating *H. pylori* infection substantially reduces the risk of *H. pylori*-associated cancers. It emphasized that work done by the CAN*Help* Working Group identified *H. pylori* as a public health concern in the Canadian North and that this Working Group was collaborating with community members and decision-makers to identify ways to reduce the health risks associated with *H. pylori* infection (see Section 3.4.6) [17].

In 2022, the Government of Nunavut’s Department of Health published the report *Cancer in Nunavut: burden and trends, 2008–2017* [44]. The report described the cancer control interventions in Nunavut: the Tobacco Reduction Program, the Human Papillomavirus Immunization Program, and opportunistic screening for colorectal cancer and cervical cancer. It made no specific mention of gastric cancer or *H. pylori* infection.

Health Canada, the Canadian Ministry of Health, posts information on the health effects of tobacco, including its association with an increased risk of gastric cancer [45]. The Government of Canada's Action on Cancer [46] does not include information specific to gastric cancer, but it features *Cancer incidence in Canada: trends and projections (1983–2032)*, a website published by the Public Health Agency of Canada, which includes trends and projections for gastric cancer incidence [47]. This public information emphasizes that the overall gastric cancer incidence rate has been decreasing in Canada for decades; in fact, during 1998–2007, gastric cancer had the second most rapidly decreasing incidence rate of all cancers, after laryngeal cancer. The website does not mention demographic groups with above-average gastric cancer incidence or mortality rates. However, it does mention that *H. pylori* infection is a major risk factor for gastric cancer and lists additional gastric cancer risk factors, excluding ethnicity and place of birth: dietary habits, tobacco smoking, alcohol consumption, genetic factors, occupational exposure to dusty and high-temperature environments, exposure to radiation, and socioeconomic factors. It specifies that dietary risk factors include diets rich in starch, poor in protein quality, poor in fruits and vegetables, and high in salt and nitrate. This website explains decreases in gastric cancer incidence rates in Canada as follows: annual per capita consumption of fruits and vegetables in Canada has increased by more than 30% since the 1960s; the decrease in gastric cancer incidence rates may be due to decreased smoking, changes in diet, and, more recently, recognition and treatment of *H. pylori* infection.

3.4.5 Gastric cancer prevention activities in Greenland

In the published literature, there is little information of relevance to gastric cancer prevention in Greenland. A small number of studies focused on the descriptive epidemiology of gastric cancer or *H. pylori* infection. In addition to the gastric cancer data described above, reports published in 1997–2005 estimated prevalence of *H. pylori* infection at 61–77% in two small studies of dyspeptic adults, 47% in 71 population survey participants in Nuuk, and 58% in a population-based sample of 685 residents of Sisimiut [8]. The Greenland government contributes cancer data to NORDCAN [48]; NORDCAN tables show that age-standardized gastric cancer incidence rates in Greenland are 3.0 times the NORDCAN average rate in women and 4.4 times the NORDCAN average rate in men.

3.4.6 CAN*Help* Working Group community projects: community-driven gastric cancer prevention activities

Although Canada has no national or regional gastric cancer prevention programmes, a community-driven research programme with gastric cancer prevention goals shows how community-engaged research can be part of a multilevel approach to the development and implementation of effective gastric cancer prevention strategies for high-risk communities [49]. The CAN*Help* Working Group is an intersectoral research team of community partners in the Northwest Territories and Yukon (including community organizations, community leaders, government health officials, and health-care providers), health-technology industry representatives, and academic partners from diverse disciplines from the University of Alberta, which is the major academic centre closest to the Northwest Territories, in the southern province of Alberta, which shares a border with the Northwest Territories [50, 51]. The research programme was formed after leaders of Northwest Territories Indigenous communities voiced concerns about the cancer risk from *H. pylori* infection, which was being detected with high frequency among community members. Leaders of these communities advocated for research to reduce the cancer risk. In response, Northwest Territories health officials reached out to gastroenterologists at the University of Alberta for research support. These health officials sought information to improve health care for *H. pylori* infection, because public health physicians in the Northwest Territories were concerned about frequent treatment failure in patients treated for *H. pylori* infection. The health officials also recognized the need for information about the overall burden of disease from *H. pylori* in their jurisdictions.

Outreach from Northwest Territories health officials to gastroenterologists at the University of Alberta was facilitated by an agency called the Northern Health Services Network, which facilitates specialist care in Alberta for residents of northern territories. This infrastructure facilitated the development of community-driven gastric cancer prevention research projects that were supported by local, territorial, and out-of-territory health-care decision-makers and practitioners. The CAN*Help* community-driven projects were carried out in diverse Indigenous communities in the western Arctic region of Canada. These projects aimed to develop public health strategies for control of *H. pylori* infection, including strategies for the clinical management of *H. pylori* infection that are both cost-effective and culturally appropriate.

In 2007, the CAN*Help* Working Group launched its initial community project, the Aklavik *H. pylori* project [51], in Aklavik, Northwest Territories, a blended community of 500–600 predominantly Inuit and Gwich'in (Athabaskan) First Nations residents. After media reports of the successful project launch in Aklavik, leaders of the community of Old Crow, Yukon, approached the research team and requested that the research be extended to Old Crow, a Gwich'in (Athabaskan) First Nations community about 200 km north-west of Aklavik. The advocacy of Old Crow community leaders led to the inclusion of Yukon health officials in the CAN*Help* Working Group. Over the next decade, community-driven *H. pylori* projects were launched in four Northwest Territories communities and five Yukon communities.

Prevention research focused on gastric cancer end-points was not feasible, because of the small sizes of the territorial populations (the 2006 census population sizes were 41 000 in the Northwest Territories and 30 000 in Yukon) [52]. Furthermore, population-based data on the disease burden associated with *H. pylori* infection were not available for this region. Therefore, CAN*Help* projects focused on describing the *H. pylori*-associated disease burden and identifying effective treatments to eliminate *H. pylori* infection, and thus generated local evidence that was relevant to clinical decision-making about *H. pylori* infection for Arctic Indigenous communities [53, 54]. The projects included screening participants for *H. pylori* using ^{13}C-urea breath testing and treatment trials, with University of Alberta gastroenterologists overseeing treatment. In seven communities, CAN*Help* projects offered upper gastrointestinal endoscopy with gastric biopsies for pathological and microbiological assessments. In five of these communities, endoscopic examinations were done in endoscopy clinics that were set up temporarily in community health centres by technical support personnel and that were staffed by visiting gastroenterologists, endoscopy nurses, and service aides; endoscopies were done at the Inuvik Regional Hospital for CAN*Help* project participants in two Northwest Territories communities (Tuktoyaktuk and Inuvik). University of Alberta gastroenterologists advised local practitioners on follow-up care for abnormal endoscopy findings.

Early findings of the CAN*Help* projects showed that participating communities had high prevalence of *H. pylori* infection (59% of Indigenous participants who were screened using the urea breath test in all nine projects tested positive for *H. pylori* infection) and severe chronic gastritis [53], as well as more frequent visible mucosal

lesions in the stomach than in the duodenum [54]. CAN*Help* treatment trials showed that the clarithromycin-based three-drug therapy, recommended by Canadian clinical guidelines before 2016, had poor effectiveness compared with four-drug regimens [55]. Information from CAN*Help* projects was shared with local practitioners as it became available. The lead CAN*Help* gastroenterologist presented annual updates, along with the latest recommendations for management of *H. pylori* infection, at grand rounds for physicians in the Northwest Territories and Yukon. The public health physician at the Inuvik Regional Hospital, whose catchment area included the four participating Northwest Territories communities and other outlying communities, checked regularly with the lead CAN*Help* gastroenterologist about recommended treatment regimens and updated pharmacies serving the region on an ongoing basis about which regimens should be prescribed for elimination of *H. pylori* infection. Through these channels, findings from the community research projects were translated into improved clinical management of *H. pylori* infection and benefited Northwest Territories and Yukon residents who sought health care for *H. pylori*-associated complaints, whether or not they had participated in CAN*Help* projects.

In 2018, when Alberta Health Services updated *H. pylori* treatment guidelines under the direction of the lead CAN*Help* gastroenterologist, the Northwest Territories Chief Public Health Officer, also a member of the CAN*Help* Working Group, sought input from fellow Working Group members about the relevance of this update for the Northwest Territories population, about half of which is Indigenous. By that time, CAN*Help* community projects had generated a substantial amount of relevant information, which was used to adapt the updated Alberta guidelines for northern and Indigenous populations in Canada. These guidelines included the recommendation of surveillance of gastric precancerous lesions (intestinal metaplasia or severe atrophy) detected during gastroscopy in patients with gastric cancer risk factors, including Indigenous ethnicity, immigration from a high-incidence region, family history of gastric cancer, or intestinal metaplasia that is extensive or of incomplete cell type [56]. The guidelines were approved for circulation to clinicians by both the Northwest Territories Chief Public Health Officer and the Yukon Chief Medical Officer of Health.

CAN*Help* projects in three communities included a component aimed at assessing the long-term impacts of treatment to eliminate *H. pylori* infection. Of 310 participants from three communities with baseline pathology data from gastroscopy with gastric

biopsies collected in 2008–2013, 69 had follow-up pathology data from repeat gastroscopy with gastric biopsies collected in 2017 [57]. Compared with baseline data, the prevalence of *H. pylori* infection and precancerous gastric pathology was substantially lower at follow-up. Most participants who were *H. pylori*-positive at baseline and *H. pylori*-negative at follow-up had reduced severity of active, chronic, and/or atrophic gastritis at follow-up. In multivariable models of the probability of improved chronic gastritis and improved active gastritis, this probability was greatest among individuals who had reduced *H. pylori* density at follow-up. For chronic gastritis, the next strongest predictor was completion of treatment to eliminate *H. pylori* before follow-up. For active gastritis, the next strongest predictor was *H. pylori* density at baseline. In multivariable models of the probability of progression of atrophic gastritis and/or intestinal metaplasia, the strongest predictors were detection of *H. pylori* in gastric biopsies at baseline or follow-up (positively associated with progression) and treatment to eliminate *H. pylori* before follow-up (inversely associated with progression), whether or not the treatment was successful.

Across the CAN*Help* projects, participation rates in *H. pylori* screening varied widely by community. More consistently, on average across communities, about one third of participants who tested positive for *H. pylori* infection declined treatment and, among those dispensed treatment, about one third did not participate in follow-up testing to confirm treatment success. The CAN*Help* projects revealed challenges in participation for initiatives aimed at preventing gastric cancer by eliminating *H. pylori* infection. Although the number of participants with gastric pathology follow-up data was small, the substantial differences in comparison groups yield evidence that *H. pylori* treatment has the potential to reduce the risk of gastric cancer in Arctic Indigenous communities. Based on the available data, it is likely that most *H. pylori*-positive community members who participated fully in the treatment component of CAN*Help* projects had a sustained reduction in risk indicators for gastric cancer. This suggests that screening and treatment for *H. pylori* infection targeted to high-risk communities has the potential to reduce gastric cancer risk.

3.4.7 Conclusions

Consistent evidence from settings across Arctic North America shows that Indigenous people in this region have a higher burden of disease from *H. pylori* infection than non-

Indigenous counterparts. The disparity is most striking when comparing gastric cancer frequencies in Indigenous groups with those in non-Indigenous residents of the same geographical region; this reflects the importance of prioritizing the collection of accurate data on Indigenous identity and incorporating these data into the descriptive epidemiology of gastric cancer in the Arctic. Although the disproportionately frequent occurrence of *H. pylori* infection and gastric cancer across Arctic communities has been observed for more than two decades, public health authorities in Arctic North America have not targeted this disparity in current cancer prevention strategies, nor have they implemented screen-and-treat programmes for gastric cancer prevention. A perceived obstacle to the implementation of such strategies is the lack of evidence of cost–effectiveness specific to Arctic Indigenous communities, given observations from treatment trials conducted in such communities of relatively frequent hesitancy to receive treatment, along with relatively frequent treatment failure and reinfection. In this setting, community-driven screen-and-treat projects offer the possibility of engaging high-risk communities in designing gastric cancer prevention activities that serve their goals and values and give them agency in public health initiatives.

Acknowledgements

The author acknowledges collaborators who have informed her perspective on the content of this chapter, including those who have contributed Indigenous knowledge and insights pertaining to Indigenous health research and gastric cancer prevention activities in the Arctic: members of CAN*Help* project planning committees since 2007, with special thanks to Billy Archie, Velma Illasiak, and Gladys Edwards of Aklavik, Northwest Territories; Kathie Nukon and Paul Josie of Old Crow, Yukon; Winnie Greenland of Fort McPherson, Northwest Territories; Dalelyn Secord of Teslin, Yukon; Megan Williams, Vuntut Gwitchin Heritage Manager, Old Crow, Yukon; Crystal Lennie and Evelyn Storr of the Inuvialuit Regional Corporation, Inuvik, Northwest Territories; Lea Bill of the Alberta First Nations Information Governance Centre; Jessica Kolopenuk, Alberta Health Services Chair in Indigenous Health at the University of Alberta; Michael Bruce and colleagues of the CDC Arctic Investigations Program in Anchorage, Alaska; Timothy Thomas and colleagues of the Alaska Native Tribal Health Consortium; and Anders Koch of the Circumpolar *H. pylori* Working Group.

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WHO European Region

Chapter 3.5.

Gastric cancer prevention efforts in Europe (EUROHELICAN, TOGAS, and HPSS projects)

Bojan Tepeš, Mārcis Leja, Tamara Matysiak-Budnik, Mário Dinis-Ribeiro, David Forman, Janet Takens, and Zorana Maravic

Summary

- Four studies are currently under way in Europe: GISTAR, EUROHELICAN, TOGAS, and HPSS. An additional study is currently in the preparatory phase under the European Joint Action on Cancer Screening (EUCanScreen).
- The GISTAR study is a multicentre randomized trial in Latvia that is focusing on *H. pylori* eradication and pepsinogen testing as methods to reduce gastric cancer mortality in middle-aged people.
- Accelerating Gastric Cancer Reduction in Europe through *H. pylori* Eradication (EUROHELICAN), supported by the EU4Health programme, is assessing the feasibility, acceptability, and effectiveness of implementing a population-based *H. pylori* screen-and-treat programme in young adults (aged 30–34 years) in Slovenia.
- The Towards Gastric Cancer Screening Implementation in the European Union (TOGAS) study, also supported by the EU4Health programme, aims to evaluate three different approaches to gastric cancer screening: (i) an *H. pylori* screen-and-treat strategy in a young population (aged 30–34 years); (ii) upper endoscopic screening in individuals undergoing colonoscopy for colorectal cancer screening or surveillance; and (iii) long-term effects of *H. pylori* eradication, in a study in the GISTAR cohort (combining *H. pylori* detection and pepsinogen assessment).
- An *H. pylori* screen-and-treat study (European implementation study on simultaneous screening for gastric and colorectal cancers) within EUCanScreen

will address the potential of screening and treatment for *H. pylori* at the time of initiating colorectal cancer screening with a faecal immunochemical test (FIT).

- The United Kingdom *H. pylori* Screening Study (HPSS) has randomized 56 000 people aged 35–69 years (men) and aged 45–69 years (women) into screen-and-treat and control groups, with follow-up until 2024.
- Preliminary results from a survey conducted by the Thomas More University of Applied Sciences, Belgium, targeting representatives of policy-making authorities, suggest overall limited willingness and readiness among Member States of the European Union and the European Economic Area to implement gastric cancer screening.

Studies in the field of gastric cancer prevention through *H. pylori* screen-and-treat strategies are under way in Europe and are presented in this chapter. Four studies are currently under way in Europe: GISTAR, EUROHELICAN, TOGAS, and HPSS. An additional study is currently in the preparatory phase under the European Joint Action on Cancer Screening (EUCanScreen).

3.5.1 GISTAR

The GISTAR study (Multicentric Randomized Study of *H. pylori* Eradication and Pepsinogen Testing for Prevention of Gastric Cancer Mortality; ClinicalTrials.gov ID, NCT02047994) is a multicentre randomized study of *H. pylori* eradication and pepsinogen testing for gastric cancer prevention in middle-aged people. The study is run as a collaboration between the Institute of Clinical and Preventive Medicine of the University of Latvia and IARC [1]. The primary objective of the study is to determine whether *H. pylori* eradication combined with non-invasive screening and follow-up of precancerous lesions by measuring pepsinogen levels in the circulation reduces gastric cancer mortality in high-risk populations among individuals aged 40–64 years at enrolment.

The secondary objectives include analysis of the prevalence of *H. pylori* infection in the study populations, the success rates of *H. pylori* eradication therapy, the rates of resistance of *H. pylori* to the main antibiotics used in standard therapies, the potential

adverse effects of population-based eradication (including effects on the gut microbiome), and optimization of follow-up strategies, as well as a search for new biomarkers and optimization of the use of the available ones.

The key hypotheses of the GISTAR study are that: (i) *H. pylori* eradication in middle-aged people in a high-risk population with endoscopic follow-up of individuals with evidence of atrophic gastritis prevents gastric cancer mortality; (ii) *H. pylori* eradication is effective in preventing gastric cancer mortality even after the development of gastric mucosal atrophy; (iii) certain population subgroups can derive more benefit from *H. pylori* eradication and therefore could be targeted if general population eradication is not feasible; and (iv) a combination of biomarker screening and upper endoscopy is an appropriate strategy to prevent gastric cancer mortality in high-incidence areas.

The study flow chart in Fig. 3.5.1 shows the overall design of the study.

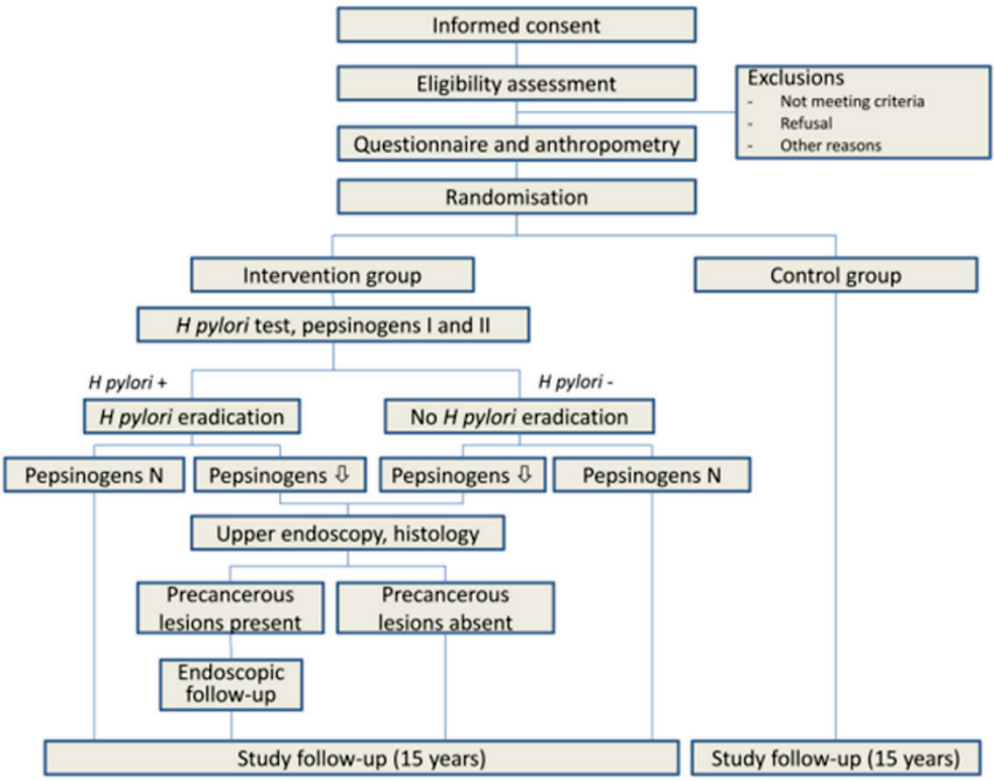

Fig. 3.5.1. Flow chart for the GISTAR study. Reproduced from Leja M et al. (2017) [1]. Copyright © 2017, Leja et al. Published by BMJ Publishing Group Ltd.

The recruitment centres for the main GISTAR study have been operating in regional cities and towns in Latvia. Apparently healthy, asymptomatic middle-aged participants (aged 40–64 years at recruitment) were enrolled in the study. Participants were interviewed to determine their socioeconomic status, lifestyle, environmental and occupational exposures, medical history, family history of disease, and dietary habits. Thereafter, participants were randomly assigned to either the intervention group or the control group.

The pilot study, which was designed to test the assumptions and tools, was followed by the general study. A total of 3447 participants were enrolled in the pilot study in 2013–2015; of those, 1724 were allocated to the intervention group and 1723 to the control group. Participants in the intervention group who tested positive for *H. pylori* infection (serology was used to detect the presence of the infection; whenever upper endoscopy was indicated, histology was considered as the confirmatory test) were offered *H. pylori* eradication treatment. Study participants with altered pepsinogen or gastrin-17 levels in the circulation were invited to undergo upper endoscopy. A randomly assigned subgroup with normal biomarker levels was invited to undergo upper endoscopy.

Based on the results of the pilot study, the general GISTAR protocol was modified. In particular, the primary detection method for *H. pylori* infection was changed from serology to the ^{13}C-urea breath test (because of a relatively high proportion of false-positive serology tests), and the use of biomarkers was optimized.

The GISTAR general study was run after the pilot phase. The data from the pilot study were included in the overall GISTAR study statistics. The recruitment to the study was completed by 31 August 2023. By then, 11 223 participants had been randomized in 11 recruitment centres (these are the combined numbers for the pilot study and the general study). Of those, 344 were excluded due to several reasons; therefore, the number of study participants for the follow-up is 10 882. GISTAR study cohorts are currently being used in the EUROHELICAN study 2 and in Pilot 3 within the TOGAS project, to address the potential long-term effects of *H. pylori* eradication therapy.

3.5.2 EUROHELICAN

Accelerating Gastric Cancer Reduction in Europe through *H. pylori* Eradication (EUROHELICAN), an ongoing project supported by the EU4Health programme, aims to reduce the gastric cancer mortality related to chronic infection with *H. pylori*. The project consists of the following actions [2]:

- Assessment of the feasibility, acceptability, and effectiveness of implementing an *H. pylori* screen-and-treat strategy programme in young adults (aged 30–34 years) in Slovenia at the population level; this is the first time that this type of assessment has been done in Europe.
- Assessment of the potential long-term effects of previous *H. pylori* screen-and-treat programmes in a middle-aged population in Latvia.
- Analysis of two randomly selected groups of people with *H. pylori* infection, one with *H. pylori* eradicated and one with *H. pylori* not eradicated, with a follow-up of 5–10 years.
- External evaluation of the two studies conducted in Slovenia and Latvia, performed by the University Hospital of Nantes, France.
- Development of a Working Group Report, prepared by IARC, aiming to establish a set of minimum standards for the implementation and evaluation of population-based *H. pylori* screen-and-treat strategies through an expert Working Group Meeting.

The prospective non-interventional study was launched in Slovenia in 2023. This study is a joint action of the Slovenia National Institute of Public Health and the Community Healthcare Centre Dr Adolf Drolc Maribor.

The main questions that the study aims to answer are:

- Is the proposed population-based *H. pylori* screen-and-treat strategy feasible and acceptable in a community health service setting?
- Is the proposed population-based *H. pylori* screen-and-treat strategy effective in a community health service setting?

- What is the profile of adverse events in the participants who have been treated, and how does this profile relate to the results of the *H. pylori* screen-and-treat strategy and the demographic characteristics of the participants?
- What is the relationship between the living conditions during childhood reported by the participants and the results of the *H. pylori* screen-and-treat strategy?
- What is the association between alcohol consumption or use of tobacco products reported by the participants and the results of the *H. pylori* screen-and-treat strategy?

Participants (n = 2000) are being randomly selected from young adults (aged 30–34 years) who are registered at the primary level of care at the Community Healthcare Centre Dr Adolf Drolc Maribor. They are tested for the presence of active infection with *H. pylori* using locally validated serology and the urea breath test (UBT) as a confirmatory test. Participants with *H. pylori* infection are offered bismuth-based quadruple therapy. Eradication of *H. pylori* infection is confirmed by the UBT at least 1 month after completion of treatment. Participants with a positive test result after the second UBT are retreated with a second-line modified bismuth-based quadruple therapy, and the success of eradication is verified with the UBT. Participants in whom two rounds of treatment have failed are referred to a gastroenterologist for susceptibility-based antibiotic therapy.

For each of the participants, compliance with testing and treatment, treatment outcomes, adverse events, and reasons for withdrawal of participation are monitored. The feasibility and sustainability of the proposed *H. pylori* screen-and-treat strategy will be evaluated using several key performance indicators that follow the structure of the five principal areas of feasibility. Several secondary participant outcomes will be also measured to provide additional evidence for and against the potential future implementation of a population-based *H. pylori* screen-and-treat programme in Slovenia.

The results of this study will enable the project to be scaled up to the national level and will serve as a model for the implementation of this strategy in the rest of Europe. The results will also contribute to the implementation of one of the goals of Europe's Beating Cancer Plan: preventing gastric cancers caused by *H. pylori* infection [3].

Finally, the real-world data from this study will be used in a Working Group Report, prepared by IARC, which will describe a set of minimum standards for the implementation of population-based *H. pylori* screen-and-treat programmes at the international level.

Interim results as of 30 September 2024 are as follows:

- Invitations sent, 4000 participants.
- Response rate, 1490 participants (37.2%).
- Exclusion criteria, 28 participants (2.1%).
- Serology, 1159 participants (147 participants positive; 12.7%).
- UBT, 54 participants (79.6% positive; 3.7% grey zone).
- Treatment started, 25 participants.
- Treatment completed, 13 participants (eradication rate, 92.3%).

The study will be enlarged by inviting other European countries to follow the same strategy as part of the TOGAS project (see Section 3.5.3) (Fig. 3.5.2).

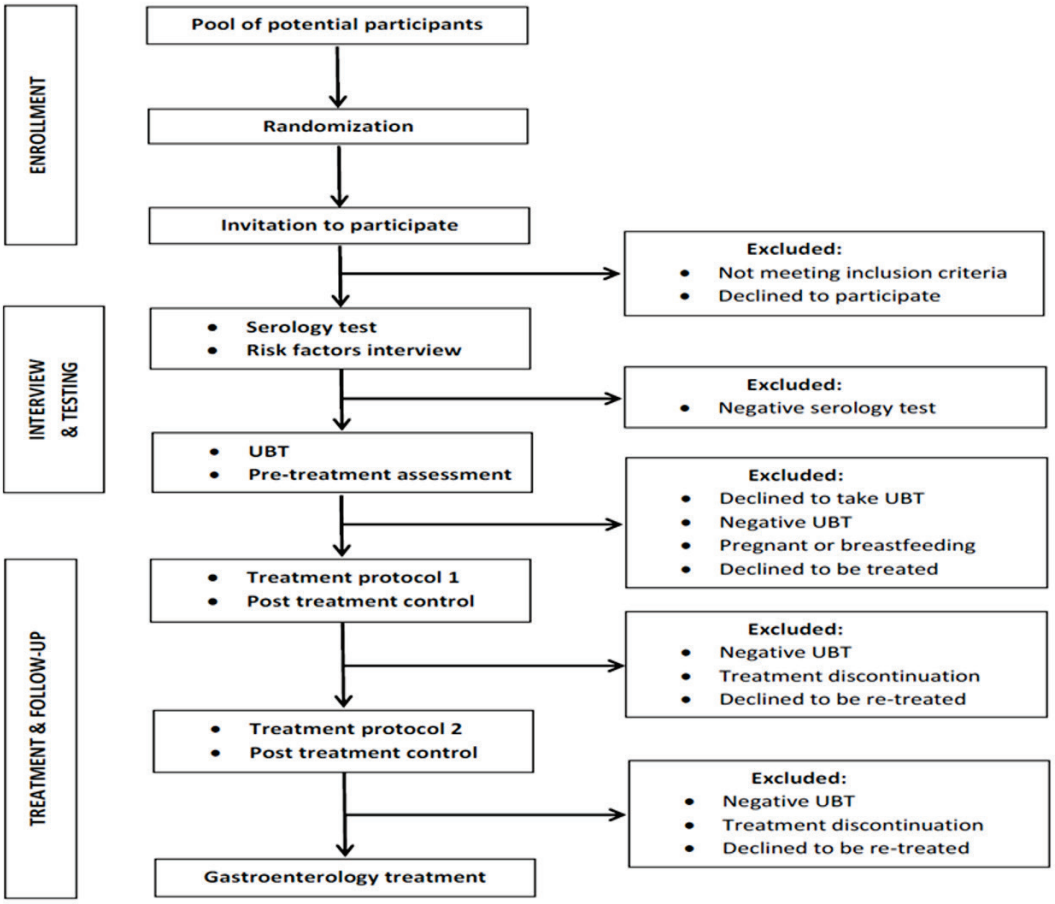

Fig. 3.5.2. Flow charts for the EUROHELICAN and TOGAS studies. UBT, urea breath test. Source: Tepeš et al. (2024) [4]

3.5.3 TOGAS

The Towards Gastric Cancer Screening Implementation in the European Union (TOGAS) project, which is also supported by the EU4Health programme, has been designed to provide the missing evidence that is needed for recommending appropriate implementation of gastric cancer screening across the European Union (EU) [5]. This includes the evaluation of various strategies that could be effective for reducing gastric cancer mortality in EU countries with varying burdens of gastric cancer and varying prevalence of *H. pylori* infection.

The results from this project will aid policy-makers in incorporating gastric cancer screening into their health-care priorities while balancing its effectiveness, feasibility, and acceptability with potential long-term adverse effects.

To achieve the set goals and generate additional information to fill the gaps in knowledge and understand the unmet needs for gastric cancer prevention, the following specific objectives have been designed:

- Assess the current situation and needs in EU Member States and target populations in the area of gastric cancer prevention.
- Assess the appropriateness of various gastric cancer screening modalities for use in the EU.
- Ensure that the TOGAS results are sustainable by using an effective dissemination strategy and coordinating the methodology with approaches used in the EU. This will involve gathering not only important data from the field studies but also critical information from the decision-makers, other stakeholders, and target populations. Furthermore, cost–effectiveness modelling of intervention strategies to reduce gastric cancer-related mortality will be performed to guide the decision-makers on the most appropriate and cost-effective strategy.

TOGAS pilot studies

Each of the pilot studies addresses a different aspect of gastric cancer prevention:

- Pilot 1: *H. pylori* screen-and-treat strategy in a young population in six EU countries.
- Pilot 2: Possibility of detection of gastric precancerous lesions and *H. pylori* infection by adding a systematic upper digestive endoscopy to screening upper endoscopies in individuals undergoing colonoscopy (in people aged 50–74 years) within colorectal cancer screening programmes or for surveillance in seven EU countries.
- Pilot 3: Assessment of potential long-term effects of *H. pylori* eradication therapy (using data from the GISTAR cohort).

Fig. 3.5.3 shows the design of the TOGAS pilot studies.

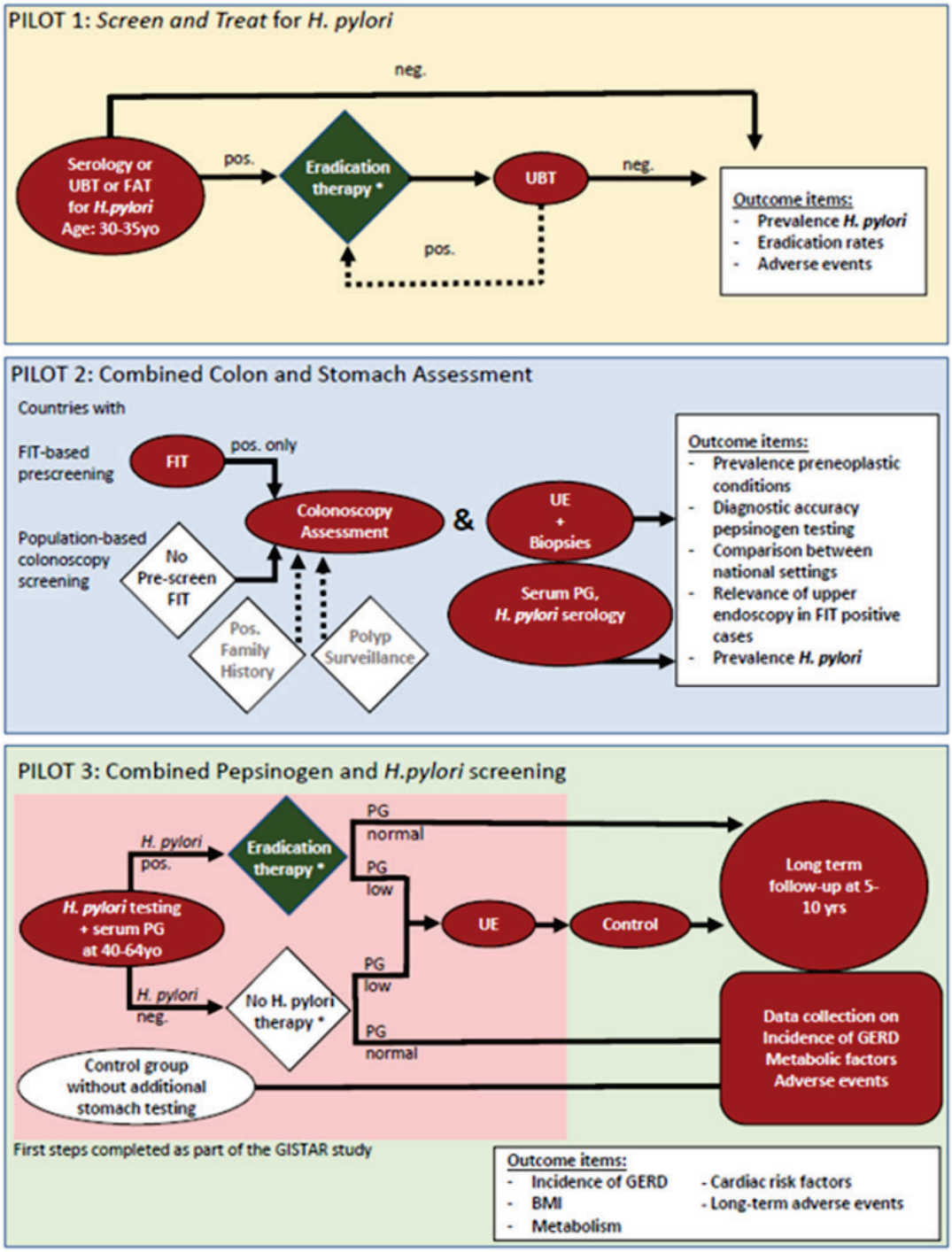

Fig. 3.5.3. TOGAS pilot studies. BMI, body mass index; FAT, faecal antigen test; FIT, faecal immunochemical test; GERD, gastro-oesophageal reflux disease; neg., negative; PG, pepsinogen; pos. positive; UBT, urea breath test; UE, upper endoscopy; yo, years old. Source: European Commission (2024) [6].

Pilot 1: H. pylori *screen-and-treat strategy in a young population in six EU countries*

In 2024, a prospective non-interventional population screen-and-treat study for *H. pylori* eradication as a method of primary prevention of gastric cancer was launched in six EU countries (Croatia, Ireland, Latvia, Poland, Romania, and Slovenia). A total of 13 600 randomly selected members of the population, aged 30–34 years, will be invited to participate in the study, with the aim of reaching at least 6800 study participants. This study is coordinated by the Slovenia National Institute of Public Health and uses the same protocol as the EUROHELICAN study (Fig. 3.5.2). Some centres are using serology and a confirmatory UBT as the method of *H. pylori* detection; in some other centres, the UBT is used only as the primary test. The first-line treatment is offered according to the local recommendations, mainly 14-day bismuth-based quadruple therapy or 10-day single-capsule bismuth, metronidazole, and tetracycline combination therapy; 14-day clarithromycin-based triple therapy is also used in some centres.

Pilot 2: Combined colon and stomach assessments

Screening for *H. pylori* infection and associated gastric lesions during upper digestive endoscopy performed in combination with screening colonoscopy is being addressed in Pilot 2. It is expected to include a total of 1600 participants in seven centres in Germany, France, Ireland, the Netherlands, Latvia, Lithuania, and Portugal.

Individuals presenting for screening or surveillance colonoscopy, including individuals with a positive faecal occult blood test (FOBT) or faecal immunochemical test (FIT) result, are invited to undergo a screening oesophago-gastro-duodenoscopy (OGD) in the same session. Patients who are undergoing colonoscopy for symptom investigation, individuals with genetic cancer syndromes, or people who have undergone an OGD within the past 3 years are excluded. The study protocol includes high standard operating procedures for OGD, such as the use of virtual chromoendoscopy, gastric biopsy sampling, imaging, and reporting, as well as histopathology assessment and serology testing.

The primary end-point of this study is the detection of gastric cancer or gastric pre-neoplastic lesions or conditions that need endoscopic surveillance or further therapy as defined by national and international guidelines. The secondary end-points include assessing the quality of the endoscopy, assessing the endoscopist's performance in

detecting other relevant gastric lesions, and identifying oesophageal or duodenal conditions.

On the day of the procedure, blood samples are obtained for the analysis of serum pepsinogens and *H. pylori* serology in order to provide input on the yield of serological screening for gastric lesions at the time of a screening colonoscopy, including the sensitivity, the specificity, and the area under the curve (AUC) of pepsinogens for the detection of advanced gastric precancerous lesions.

Pilot 3: Combined pepsinogen and H. pylori *screening*

Assessment of potential long-term effects is performed in participants who have been treated with *H. pylori* eradication therapy 5–10 years previously, and comparisons will be made with a matched group of study participants who have not been offered eradication treatment (i.e. participants recruited in the GISTAR cohort). Major concerns about negative effects of the eradication will be addressed, including potential increase in gastro-oesophageal reflux disease, negative metabolic effects (including increase in body weight), and laboratory parameters of cardiovascular risk patterns.

A total of 3000 study participants are expected to be recruited, and matched analyses with the data that were initially reported will be conducted.

European countries' willingness and readiness to implement gastric cancer screening

The TOGAS project aims to provide the knowledge needed to design and implement an effective gastric cancer prevention strategy in the EU. The results of this project will help policy-makers to incorporate gastric cancer screening into their cancer control strategies.

A European Commission report, *Cancer screening in the European Union*, prepared by the European Commission's Group of Chief Scientific Advisors, recommended that "the countries with the highest gastric cancer incidence and death rates should consider screening for *H. pylori*" [7]. Researchers from the Thomas More University of Applied Sciences, Belgium, in collaboration with partners from the TOGAS consortium, have evaluated the willingness and readiness of Member States to implement gastric cancer screening.

Methods

The willingness and readiness of Member States to implement gastric cancer screening were evaluated using an online survey, conducted in English. The survey targeted representatives of policy-making authorities in the Member States of the EU and the European Economic Area (EEA).

Invitations to participate were distributed in the newsletter of the European Commission Joint Research Centre, in emails to participants in the EUCanScreen project, and in announcements made during EU SANTE Working Group meetings. Given the specialized nature of the survey and the limited number of people capable of answering all the questions, reaching the target audience was challenging.

The survey was open from 29 February 2024 to 10 January 2025 and included questions on the following topics:

- Current practices with respect to gastric cancer screening [see Note 1 in Box 3.5.1].
- Plans for implementing a gastric cancer screening programme, the reasons for doing so, and the perceived desirability and feasibility of implementation [see Note 2 in Box 3.5.1].
- Availability of and reimbursement of costs for diagnostic tools and therapeutic options to reduce gastric cancer incidence, and medications used in regimens for *H. pylori* eradication [see Note 3 in Box 3.5.1].
- Readiness of the health-care system to implement gastric cancer screening [see Note 4 in Box 3.5.1].

A total of 27 policy advisers, legal advisers, medical professionals, and public health professionals from 19 Member States have completed the survey. The survey respondents represent ministries of health, cancer screening authorities, and other authorities with similar responsibilities [see Note 5 in Box 3.5.1].

Outcomes

- Currently, no EU or EEA Member State has a population-based gastric cancer screening programme [see Note 6 in Box 3.5.1]. Of 39 respondents from 16

Member States, 25 indicated that policy-makers in their country are not considering implementing such a programme.

- According to respondents from Belgium, Ireland, Latvia, Lithuania, and Portugal, there is an ongoing debate about the implementation of a gastric cancer screening programme [see Note 7 in Box 3.5.1].
- Respondents from Croatia, Italy, Lithuania, Portugal, and Slovenia deemed implementation of gastric cancer screening both desirable and feasible. The respondent from Greece found it desirable but not feasible, and the respondents from France and Ireland found it feasible but not desirable. The most common reason cited for finding screening undesirable was "gastric cancer is not a major problem in my country". The primary reason for considering screening unfeasible was "limited resources and higher priority for other cancer screening programmes".
- The most highly rated factors influencing the decision to implement gastric cancer screening include the gastric cancer incidence rate, the impact on mortality and incidence rates, and cost–effectiveness [see Note 8 in Box 3.5.1].
- In most responding countries, the diagnostic tools and therapeutic options to reduce gastric cancer incidence and the medications used in regimens for *H. pylori* eradication are available and the costs are reimbursed.
- According to the respondents, 14 Member States have guidelines for *H. pylori* eradication medications, and 6 have a policy or guideline for gastric cancer screening in high-risk groups or in patients with precancerous lesions [8].

Box 3.5.1. Notes

Note 1. The following questions were posed:

"Does your country or region currently have a gastric cancer screening programme?", followed by questions on the screening method used, the target group, the frequency, and available documentation.

"Does your country or region have a policy or guideline for gastric cancer screening in high-risk groups or surveillance of patients with precancerous lesions?", with among others the answer categories "Yes, surveillance of high-risk individuals (e.g.

family members of patients with precancerous lesions)" and "Yes, screening of high-risk individuals (e.g. family members of patients with gastric cancer)". This question was followed by questions on available documentation, method, target group, etc.

Note 2. The following questions were posed:

"Are policy-makers in your country considering implementing a population-based gastric cancer screening programme?", followed by a question on the screening method being considered to be used.

"Listed below are factors which might play a role in the decision to implement a gastric cancer screening policy or programme in your country or region. Please indicate the importance of each factor on a scale from 1 (not important at all) to 10 (very important)."

"Taking into account the importance of the factors related to gastric cancer screening in your country or region, do policy-makers in your country or region consider the implementation of a gastric cancer screening programme desirable?", followed by a question in which "desirable" was replaced by "feasible". Respondents who answered that the implementation of gastric cancer screening was not desirable or feasible were asked about the reasons why they think so.

Note 3. The following questions were posed:

"This question is about the availability of diagnostic tools and therapeutic options. Listed below are the diagnostic tools and therapeutic options to reduce gastric cancer incidence. Please indicate whether or not they are available for routine practice in your country or region."

For each of the available tools and options, a follow-up question on availability was posed. The same questions were asked for "medications used in regimens for *H. pylori* eradication". Included diagnostic tools and therapeutic options: upper gastrointestinal endoscopy, biopsy histology taken during upper gastrointestinal endoscopy, rapid urease test if taken during upper gastrointestinal endoscopy, antibiotic sensitivity testing for *H. pylori*, sedation (e.g. propofol deep sedation) during upper gastrointestinal endoscopy, blood test for pepsinogen I and pepsinogen II detection, upper gastrointestinal series (X-ray), C-urea breath test (UBT), *H. pylori* stool antigen test (SAT), *H. pylori* IgG group antibody detection in blood, medication

for *H. pylori* eradication (first-line therapy), and medication for *H. pylori* eradication (second-line therapy). Included medications: bismuth (e.g. subcitrate, subsalicylate), tetracycline (e.g. hydrochloride), combined bismuth–tetracycline–metronidazole capsule (e.g. Pylera), clarithromycin, amoxicillin, metronidazole, levofloxacin, rifamycins (e.g. rifampicin, rifabutin), and potassium-competitive acid blockers (P-CABs) (e.g. vonoprazan).

Note 4. The readiness of the health-care system was measured by posing questions on the existence of a governance structure dedicated to cancer screening programmes, a central IT platform for cancer screening data, funding, upper gastrointestinal endoscopy capacity, *H. pylori* eradication guidelines, etc.

Note 5. The survey was completed by 19 public health professionals, 13 policy advisers, 8 medical professionals, 2 researchers, 1 manager, and 4 professionals combining two of these functions; 22 respondents answered on behalf of a cancer screening authority, 15 on behalf of a ministry of health, 1 on behalf of both, and 9 on behalf of other relevant authorities. Complete responses were received from Belgium, Croatia, Czechia, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Latvia, Lithuania, Malta, the Netherlands, Portugal, Romania, Slovakia, Slovenia, and Spain. Incomplete responses were received from Austria, Denmark, and Hungary.

Note 6. A respondent from Denmark did indicate that Denmark does have a population-based gastric cancer screening programme. However, this was contested by the TOGAS consortium members who reviewed the report.

Note 7. Respondents from Italy (Marche Region), Latvia, and Slovenia indicated that the decision to start a pilot population-based gastric cancer screening programme has been made.

Note 8. Other answer categories were: diagnostic yield of current screening methods, gastric cancer mortality rate, expected adherence rate, costs of the programme, availability of resources in the health-care system such as human resources and infrastructure, number of short-term adverse events, number of long-term adverse events, number of late-stage diagnoses, and *H. pylori* prevalence.

Source: Compiled from Takens et al. (2025) [8].

Discussion

The results suggest limited willingness of EU and EEA Member States to implement gastric cancer screening. However, the Member States expressing interest in the implementation of screening tend to have a relatively high incidence of gastric cancer. This aligns with the recommendation that “the countries with the highest gastric cancer incidence and death rates should consider screening for *H. pylori*” [7].

Health-care systems in the surveyed Member States generally seem prepared to support the implementation of gastric cancer screening. However, certain components of the health-care infrastructure present challenges to widespread implementation. Future efforts should focus on addressing these hurdles to facilitate the adoption of effective

TOGAS general population survey

Initial insights into the willingness of European citizens to participate in gastric cancer screening were gathered from a general population survey conducted in 19 countries as part of the TOGAS project.

Currently, no effective screening method to prevent gastric cancer is available in Europe. Screening programmes depend on uptake. Therefore, before designing a gastric cancer screening programme, it is important to understand the willingness of the general population to participate and to understand any specific barriers or motivators to participation in screening. Surveys and preference studies for cancer screening programmes have previously been used to understand how such programmes can be optimized to maximize uptake. Digestive Cancers Europe, a TOGAS consortium member, designed and commissioned an online survey in 19 EU Member States to fulfil these objectives.

Methods

The willingness of citizens to participate in gastric cancer screening was evaluated using an online survey. The survey was conducted in 19 EU Member States among members of the general population aged 18–70 years in the local language of each country. The data were collected between February and July 2024 and were subsequently analysed at the Thomas More University of Applied Sciences, Belgium. There were at least 1000

respondents from each Member State; the number ranged from 1039 in Austria to 1123 in Poland. The data were weighted to achieve representativeness for age and sex.

The survey contained questions about various topics, including:

- knowledge about gastric cancer and gastric cancer testing;
- motivators and barriers to participation in screening;
- perceptions of different methods of gastric cancer screening; and
- attitudes towards *H. pylori* bacterial infection screening.

Preliminary outcomes

Awareness:

- Fewer than one third (31%) of respondents were aware of the risk factors for gastric cancer; country responses ranged from 20% in Belgium to 52% in Romania.
- Fewer than one quarter (24%) of respondents were aware of the symptoms of gastric cancer; country responses ranged from 17% in Belgium to 35% in Romania.
- Only 4% of respondents were familiar with the procedures involved for testing for risk of gastric cancer; a further 18% said they know a little about the procedures involved.

Motivators and barriers to participation in gastric cancer testing:

- The two main reasons that would motivate people to participate in gastric cancer testing were “being advised by their health-care provider to take part in testing” (47%) and “having symptoms that might indicate gastric cancer” (46%).
- The motivations differed significantly across countries. For example, whereas 68% of respondents in Slovenia said that being advised by their health-care provider to take part in testing would motivate them to do so, only 17% of respondents in Romania said the same.
- The two most important reasons that would prevent people from participating in gastric cancer testing were “concern about the possible discomfort associated with testing” (27%) and “financial constraints” (26%).

- In most Member States, “concern about the possible discomfort associated with testing” was the main barrier to participation. In Finland, Latvia, Poland, and Romania, “financial constraints” were the biggest barrier.

Perceived level of comfort of different screening methods:

- More than half (52%) of respondents expected a biopsy to be uncomfortable or very uncomfortable. The percentage of respondents who thought a biopsy would be uncomfortable was the highest in Croatia, at 64%, and the lowest in Germany, at 46%.
- Respondents were even more concerned about upper endoscopy. Most respondents (63%) expected an upper endoscopy to be uncomfortable or very uncomfortable. The percentage of respondents who thought an upper endoscopy would be uncomfortable was the highest in Finland, at 79%, and the lowest in Germany, at 53%.

Willingness to undergo gastric cancer testing:

- Overall, 57% of respondents said they would be willing to participate in gastric cancer testing, based on the information they had read.
- There were significant differences between certain countries. Respondents in Ireland showed the greatest willingness to undergo testing; 71% said they would, and only 8% said they would not. At the other end of the scale, in Hungary only 41% of respondents said they would be willing to undergo gastric cancer testing, and almost one quarter (24%) of respondents said they would not.
- By far the main reason people would be willing to participate in screening is that they would want to know if they had gastric cancer; 75% of respondents agreed with this.
- Of those respondents who said they were unwilling to undergo gastric cancer screening, the main reason was concern about the procedures being too invasive or uncomfortable; 46% of respondents agreed with this. In Croatia, this percentage was 62%. Other cited reasons included people trusting in their health and being convinced they do not have gastric cancer (21%) and not wanting to know if they had gastric cancer (15%).

Willingness to undergo *H. pylori* testing:

- Overall, 72% of respondents said they would be willing to undergo *H. pylori* testing, based on the information they had read. The willingness to participate varied from 61% in Hungary to 79% in Portugal.
- The main reason people would be willing to participate in *H. pylori* testing is to know whether they have an *H. pylori* infection; 70% of respondents agreed with this.
- Of those respondents who said they were unwilling to undergo *H. pylori* testing, the main reasons were concerns about the procedure being too invasive or uncomfortable (21%), being convinced they do not have an *H. pylori* infection (20%), and not wanting to know if they do (19%).

Overall willingness to participate in gastric cancer screening:

- After completing the survey and reading the information associated with it, 64% of respondents said they would be willing to participate in a gastric cancer screening programme; 11% said they would not, and 25% said they do not know. The willingness to participate varied from 54% in the Netherlands to 77% in Ireland.

Discussion

The preliminary results suggest that most citizens would be willing to participate in gastric cancer screening and *H. pylori* testing, once they understand what is involved. However, there is a substantial minority who say they would not participate or are undecided. In addition, current levels of awareness – of gastric cancer risk factors and symptoms and of gastric cancer screening – are relatively low. This reinforces the need for awareness campaigns and education to encourage widespread uptake of gastric cancer screening.

The barriers to participation appear to be more pronounced in certain countries. For example, in Hungary, nearly one quarter (24%) of respondents said they were unwilling to undergo gastric cancer testing. More research may be needed to understand the perceptions and beliefs of people in different countries to help overcome specific national barriers.

Concern about the possible discomfort of testing is a key barrier to participation; respondents were concerned about the uncomfortable nature of biopsy and, in particular, of upper endoscopy. This finding aligns with research in countries where gastric cancer screening is already in place, where concern about endoscopy appears to be a key barrier to participation. For example, in a study in China only 56.2% of respondents stated that they would schedule an endoscopy if they had symptoms; the main concern was pain and other discomfort associated with the procedure [9]. Understandably, very few people are currently aware of what gastric cancer testing entails. Education about the procedure and what to expect will need to be a significant focus in the rollout of gastric cancer screening in the EU. As always, health-care providers have an essential role in advising and educating their patients who are at the relevant age.

Concern about financial constraints is also a substantial barrier to participation, particularly in Finland, Latvia, Poland, and Romania. Reassurances that screening will be free at the point of delivery will need to be emphasized, reducing financial barriers.

In general, EU populations appear to be prepared to participate in gastric cancer screening, but there are clear barriers to uptake that will need to be addressed proactively through educational and awareness initiatives.

3.5.4 HPSS

One trial that is currently in progress is the United Kingdom *H. pylori* Screening Study (HPSS). This trial addresses the question “Does *H. pylori* screening and the treatment of individuals with positive test results prevent gastric cancer, and if so, to what extent?” The eradication treatment used in this trial 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 UK) and the British United Provident Association (BUPA) Foundation. In 1997–2006, 56 000 people aged 35–69 years (men) and aged 45–69 years (women) were randomized by week of attendance at one of 10 well-person screening clinics held by BUPA. All participants had to be United Kingdom residents and had to be registered with a National Health Service general practitioner, to enable their National Health Service records to be flagged so that automatic notifications would be sent to the study centre in the event of cancer registration or death.

Participants were randomly allocated, by week of attendance, to a screen-and-treat group or a control group. The standard analysis method for this study would be to compare the number of gastric cancer cases in the screened group and the control group, but the study protocol specified a more powerful statistical analysis. Because there is no expectation of an effect of treatment in *H. pylori*-negative participants, these participants can be ignored and the incidence of gastric cancer will be compared in the *H. pylori*-positive participants in the two randomized arms. Thus, the primary analysis for the trial will compare individuals in the treated and control arms who tested positive for *H. pylori* infection in the blood sample they provided at the time of randomization and who developed gastric cancer.

More detailed information about the trial design is provided in Chapter 4.5 (subsection 3) of IARC Working Group Report No. 8 [10]. It is anticipated that cancer registrations and death certifications in trial participants will be accrued until December 2024 and that analyses will be completed during 2025.

3.5.5 Future directions

There is an evidence gap between international recommendations and real data from application studies. Studies in the field of gastric cancer prevention through *H. pylori* screen-and-treat strategies are under way in Europe and are presented in this chapter. Certain aspects need to be addressed in studies to be planned for the future.

The optimal age for *H. pylori* screen-and-treat interventions should be still determined. The ongoing studies have suggested that the participation rate could be suboptimal in the young age group; however, a subfraction of individuals may have passed the “point of no return” by the age they are eligible for colorectal screening.

The potential combination of an *H. pylori* screen-and-treat strategy with colorectal cancer screening programmes, in particular with FIT screening, should be analysed for the implementation possibilities in Europe. Pilot 2 within the TOGAS project will address the prevalence of high-risk precancerous lesions at the time that the target population for colorectal cancer screening are undergoing colonoscopy. The possibility of combining FIT with *H. pylori* stool antigen testing will be further

addressed in a study (European implementation study on simultaneous screening for gastric and colorectal cancers) within EUCanScreen.

The risk of inducing an increased long-term gut resistome with *H. pylori* eradication regimens still needs to be addressed and monitored. Furthermore, the effects of an *H. pylori* screen-and-treat strategy on gastric cancer mortality as well as overall mortality need to be monitored; realistically, this could be done within implementation studies.

Public awareness campaigns about *H. pylori* infection and related diseases, especially gastric cancer, are needed, because knowledge among important stakeholders is still limited. The studies that are in progress in Europe can contribute some valuable data that can help in the organization and implementation of future national *H. pylori* screen-and-treat programmes. These programmes should be organized as cancer screening programmes [11] with a programme council and a steering committee at the national level and a network of primary care medical and laboratory facilities. A central data capture system should be provided for the assessment of quality indicators and programme monitoring.

In summary, implementation studies would be important to monitor effects and potential risks of population-based *H. pylori* screen-and-treat strategies.

Acknowledgements

Special thanks go to João Carlos Silva and Mário Dinis Ribeiro for their assistance in designing the survey.

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WHO South-East Asia Region

Chapter 3.6.

Gastric cancer prevention programme in Bhutan

Pempa Pempa and Guru Prasad Dhakal

Summary

- Gastric cancer is the leading cause of cancer in Bhutan, with a high mortality rate. Therefore, the Ministry of Health implemented a nationwide population-based *H. pylori* screening and endoscopic screening programme from 2020 to 2023 as part of the Health Flagship Programme.
- The programme screened 90.2% of the target population, providing 14-day triple therapy to individuals who tested positive for *H. pylori*, followed by eradication confirmation after 3 months.
- The cancer detection rate in the screening programme was 3.08 per 1000 people screened for *H. pylori*, with a positive predictive value for gastric cancer of 2.15% in individuals who underwent upper gastrointestinal endoscopy because of a positive *H. pylori* test result or other risk factors for gastric cancer.
- The programme used a multifaceted approach to raise awareness, including nationwide broadcasts, local sensitization programmes, leveraging schools to disseminate information, and a special high-level advocacy campaign in the most remote areas.
- Bhutan's experience in implementing a nationwide population-based cancer screening programme provides valuable insights into the effective implementation of public health interventions in resource-limited settings, highlighting several key lessons and strategies to address various challenges.

3.6.1 Rationale and the Health Flagship Programme

Bhutan is a small, mountainous country in the eastern Himalayas, with altitudes ranging from about 100 m to 7500 m above sea level. Almost 45% of the country lies at altitudes

of 3000 m and higher, and only about 5.3% lies at altitudes of lower than 600 m. Bhutan is a lower-middle-income country. It has a population of about 0.7 million, and 62.2% of the population resides in rural areas [1]. Some human settlement areas are still not connected with roads that are usable by motor vehicles, and places such as Lunana are officially 8 days' walking distance from the nearest road. Despite these challenges, Bhutan has made substantial progress in primary health care, including the implementation of successful initiatives in childhood immunization and improved maternal health. The crude childhood immunization coverage is about 97% [1, 2].

Bhutan's approach to education, health care, and the environment is guided by the Gross National Happiness principle. The constitution mandates free basic primary health care, which provides citizens with free health care from primary care to tertiary care, including referrals abroad when health-care services are unavailable in the country. Health-care services are provided through various levels of health-care facilities distributed across the 20 districts of the country. Bhutan has 54 hospitals, 186 primary health-care centres, 51 subposts, and 554 outreach clinics nationwide [2]. Only three hospitals in the country provide a certain level of tertiary health-care services, and these are designated as referral hospitals for three different regions of the country. Apart from a few selective private diagnostic centres, Bhutan does not have a single private hospital. The establishment of these selective private diagnostic centres was approved by the government in 2012 to provide diagnostic tests for health screenings for foreign workers, for immigration purposes, and to complement the workload of the diagnostic services in the public health facilities. Most of these diagnostic centres are located in the towns near the border with India in the southern districts, and their service fees are regulated by the Ministry of Health.

Until very recently, Bhutan had no health insurance system. The Royal Insurance Corporation of Bhutan Limited, the state-owned insurance company, recently launched a health insurance policy, which covers only medical treatment received abroad (in India).

Although Bhutan has made substantial strides in implementing public health initiatives, such as the expanded immunization programme and maternal health services across widely distributed health facilities, it faces substantial challenges in providing curative health care, because of the limited number of tertiary care hospitals.

For example, advanced cancer diagnosis and treatment facilities are available only at the National Referral Hospital, and some complex cancer cases need to be referred abroad for further treatment. The limited availability of and access to cancer care services in the country often result in advanced-stage cancer diagnoses, leading to poor health outcomes, high mortality rates, and substantial socioeconomic impacts. Cancer has been the third most common cause of death in Bhutan for the past 5 years. According to data from the Bhutan Cancer Registry for 2014–2018, cancer mortality rates were 30.7 per 100 000 people for males and 31.5 per 100 000 people for females [3]. The most common cancer types are gastric cancer in males and cervical cancer in females.

The analysis of lifestyle and dietary habits in the past two World Health Organization (WHO) STEPwise approach to noncommunicable disease risk factor surveillance (STEPS) surveys, in 2014 and 2019, has indicated some poor or deteriorating habits in the Bhutanese population [4–6]. Among adults in Bhutan, the prevalence of current tobacco use was 24.8% in 2014 and 23.9% in 2019, the prevalence of current alcohol consumption was 42.4% in 2014 and 42.9% in 2019, and the prevalence of insufficient intake of fruits and vegetables increased from 66.9% in 2014 to 86.4% in 2019. The mean population salt intake was 9 g per day in 2014 and 8.3 g per day in 2019. In addition, studies have shown a high prevalence of *H. pylori* infection in the population and have suggested that the high incidence of gastric cancer in the country could be attributed to a virulent strain of *H. pylori* [7, 8].

Given the limited cancer diagnosis and treatment services, the poor dietary and lifestyle habits in the population, and the high prevalence of *H. pylori* infection and gastric cancer, gastric cancer has become a substantial public health concern. In response, despite the absence of evidence on cost–effectiveness, the Royal Government of Bhutan has demonstrated a strong political commitment to addressing gastric cancer, along with two other preventable cancer types, cervical cancer and breast cancer, by implementing a rigorous population-based cancer screening programme, known as the Health Flagship Programme [9, 10]. The government allocated a budget of Nu 1109.572 million (US$ 13.095 million) to the Ministry of Health for the implementation of the Health Flagship Programme [9, 10].

3.6.2 Health Flagship Programme strategies

The Ministry of Health implemented the Health Flagship Programme from 2020 to 2023, based on the programme blueprint established by the Ministry of Health and the screening programme guideline [11]. The Health Flagship Programme Management Unit developed the guideline in consultation with the Technical Working Group for the Health Flagship Programme, which was made up of clinicians with relevant expertise, such as gastroenterologists, surgeons, oncosurgeons, pathologists, gynaecological oncologists, microbiologists, radiologists, and health communication specialists. The Technical Working Group was responsible for providing the necessary guidance for the effective implementation of the programme and reviewing its effectiveness. Because of the COVID-19 pandemic, the actual screening activities were implemented from 2021, and the primary implementing partners of the programme were the district health sectors in all districts and municipalities, mainly through primary health-care centres, subposts, and hospital community health departments. Primary health-care centres and subposts are the lowest level of health facilities, and these facilities do not have physicians. Primary health-care centres are staffed by at least one health assistant and a nurse, who takes care of public health interventions and minor clinical ailments. The screening strategy was issued as part of the national screening guideline, and the programme was rigorously monitored by the Prime Minister's Office.

The main strategies of the gastric cancer programme included:

- Expanding the *H. pylori* testing and endoscopy services in the country by
    - introducing the stool antigen test (SAT) for *H. pylori* infection to primary health-care centres;
    - expanding endoscopy services to the lower levels of health-care facilities.
- Enhancing advocacy and awareness of gastric cancer by
    - advocacy and capacity-building of health workers;
    - public awareness programmes designed to raise public awareness of the issue, persuade people to modify their risk factors, and encourage them to participate in screening programmes.
- Mass eradication of *H. pylori* infection in the Bhutanese population by

- using the SAT for *H. pylori* infection in people aged 18–75 years;
- an *H. pylori* eradication therapy programme (triple therapy and quadruple therapy) for people with positive SAT results.

- Endoscopic screening for gastric cancer by
  - upper gastrointestinal endoscopy (UGIE) for individuals aged 40–75 years with risk factors such as a history of atrophic gastritis, history of *H. pylori* infection, family history of gastric cancer, or history of dyspepsia with alarm features, and for individuals who use tobacco products and consume alcohol.

3.6.3 Implementation of the Health Flagship Programme

Expansion of H. pylori *testing, endoscopy, and histopathology services*

Before the Health Flagship Programme, *H. pylori* testing was performed on endoscopic biopsy samples using the rapid urease test (RUT). Later, the urea breath test (UBT) service was piloted in the three referral hospitals as an alternative method for *H. pylori* testing. The RUT could be used only on endoscopic biopsy samples, and the UBT was expensive and time-consuming. In addition to the requirement for an analyser, the cost per UBT was about 3–6 times the cost per SAT. Given the limitations of the RUT and the UBT for mass screening, the Health Flagship Programme adopted the SAT for mass population-based *H. pylori* screening [9, 10]. The SATs used for *H. pylori* testing included the H. PYLORI CHEK [12] and the H. PYLORI QUIK CHEK [13]. SAT kits were distributed to hospitals, primary health-care centres, and subposts.

Before the Health Flagship Programme, endoscopy services in Bhutan were limited to four centres: three referral hospitals and a military hospital in the capital city. Although outreach camps occasionally provided endoscopy services to other districts, permanent endoscopy services were available only in these four centres. In addition, the endoscopy equipment used was basic and lacked advanced features such as narrow-band imaging or i-scan. In 2021, the Health Flagship Programme established 12 endoscopy centres in 11 districts, covering all regions of Bhutan [9, 10]. This expansion improved the accessibility of routine endoscopy services at hospitals from 7.4% (4 of 54 hospitals) before the Health Flagship Programme to 22.2% (12 of 54 hospitals). This allowed 94.2% of the target population to be reached with UGIE [9]. All 12 centres have

advanced endoscopy equipment with narrow-band imaging and i-scan capabilities, enabling the early diagnosis of gastric cancer.

Before the Health Flagship Programme, histopathology laboratory services, which are essential for cancer diagnosis, were available in only two referral hospitals. The biopsy report turnaround time, calculated from the date of receipt of the sample to the dispatch of the report, ranged from 21 days to 47 days. As part of the Health Flagship Programme, a histopathology laboratory was established in another referral hospital, the Central Regional Referral Hospital, to improve the overall availability of histopathology services in the country; this has substantially reduced the biopsy report turnaround time [9, 10].

Advocacy and capacity-building of public service providers and health workers

For the effective implementation of the Health Flagship Programme, advocating for institutions and individuals, such as health service providers, health administrators, and local administrators, was treated as extremely important. Several rounds of sensitization programmes, including workshops and meetings on cancer screening initiatives, were conducted for these stakeholders. During the sensitization sessions, the stakeholders were informed about their roles and their accountability as crucial parties involved in the national initiative.

The primary focus was on building capacity among health workers through a wide range of training sessions covering prevention, early detection, protocols, skill enhancement, and data management. Knowledge gaps were identified and addressed through comprehensive training programmes [9]. All relevant health professionals, including health assistants at community health departments, primary health-care centres, and subposts, were trained to screen for *H. pylori* infection using the SAT kit. Nearly all of the 15 surgeons in the country and a gastroenterologist received basic training in UGIE, and some received advanced training in UGIE and early gastric cancer diagnosis. The endoscopy training was provided by the Khesar Gyalpo University of Medical Sciences in collaboration with Fukuoka University, Japan. This collaboration ensured that the training was of high quality and incorporated the latest advances and best practices in cancer screening and early detection.

Multifaceted public advocacy and awareness initiative

Public advocacy and awareness programmes were crucial components of the cancer screening initiatives, to ensure seamless implementation and the achievement of the objectives and outcomes. A multifaceted approach was adopted for the awareness initiative, to reach various target groups in the population (Table 3.6.1). The official launch of the programme, attended by the Honourable Health Minister, was broadcast nationwide on the Bhutan Broadcasting Service and was followed by an extensive panel discussion on the national television news channel.

Table 3.6.1. Public advocacy and awareness approaches used during the Health Flagship Programme in Bhutan[a]

Objective	Target groups	Methods
General awareness of the programme	General public, service providers	• Official launch of the programme • Panel discussion on a national television programme
Effective implementation of the programme	Management, local government, health service providers	• Sensitization programme • Screening guidelines • Official notifications • Executive orders
Enhanced awareness of cancer and the screening programme	General population	• Videos, narratives, infographics, pamphlets, posters • Public announcements and notifications • Panel discussions, talk shows • Health talks during the outreach camps
Improved programme coverage	General population, service providers	• High-level advocacy initiative in the most remote areas for unreached populations • Sensitization of students in schools

[a] The Health Flagship Programme is a nationwide population-based cancer screening programme initiated by the Ministry of Health from 2020 to 2023.

In addition to a series of talk shows and panel discussions about cancer and the related initiatives, which aired on national television and in social media, the awareness programme included short video clips, infographics, public notifications, and announcements about the screening schedules through various media channels. Announcing the screening schedules helped the public to plan their work in advance and enabled them to participate in the screening programme. In addition, before the

screening camps started, health professionals provided the necessary health education on gastric cancer to the public.

In rural areas, the resident populations are largely permanent, and health information can be effectively disseminated through the local administration's information-sharing mechanisms. However, in urban areas, the resident population is more mobile, which makes it challenging for the designated health facilities to trace their catchment populations and use the local administration's information-sharing mechanisms. In addition, health advocacy often failed to reach certain sections of the urban population because of the nature of their work, the presence of illiteracy, and the limited access to news and social media by some of the population. These challenges made it difficult to implement the screening programme effectively.

To address these challenges, a unique approach was taken that involved schools and schoolchildren in urban areas. Although students in schools are generally younger than the screening target age of 18 years, they played a crucial role in disseminating information about the screening programme to the target population, particularly their parents, family members, relatives, and neighbours. Sensitizing and educating students in urban areas about cancer and the cancer screening initiative substantially boosted coverage and helped to overcome the challenges in reaching the urban population.

High-level advocacy initiative

The high-level advocacy initiative for the residents of Lunana was led by one of Her Majesties the Queen Mothers. This initiative focused on reaching the most remote and underserved populations in the country. Lunana is a *gewog* (group of villages) with a population of about 700 and is located at an altitude of 3400 m above sea level, officially 8 days' walking distance from the nearest road. Her Majesty the Queen Mother and her entourage, including a complete team of health workers for advocacy and cancer screening, were flown to Lunana by helicopter for the event.

Lunana was chosen for the high-level advocacy initiative not because of its cancer prevalence or its population size but to emphasize the importance of the message about cancer care that needed to be conveyed to the entire Bhutanese population.

Before the event, health-care workers at the primary health-care centres in Lunana conducted extensive screening tests for *H. pylori* infection and assessed gastric cancer

risk factors, covering about 70% of the target resident population. Among those tested, 13% were found to be positive for *H. pylori* and were promptly started on eradication therapy.

During the event, UGIE services were offered to individuals who had been pre-identified and registered by the local primary health-care centres. A total of 113 people underwent UGIE, and 12 histopathology biopsies were collected for further analysis. Upon review, none of the biopsies indicated cancer or precancerous conditions.

This high-level advocacy initiative was a historic event for Lunana, because it was the first time that the community had experienced a specialized outreach medical camp that offered advanced services, such as endoscopy. This high-level event, held for a remote and unreached population, emphasized that every life matters and encouraged everyone to join the fight against this preventable cancer. The event also highlighted the potential for ongoing specialized health-care access in remote areas.

3.6.4 Community-based outreach camps

H. pylori screening, eradication therapy, and endoscopic screening were provided in both facility-based and camp-based settings. Most of the population (> 90%) were covered in outreach screening camps.

Registration of the target population and distribution of sample containers

The first task of the screening process was to list the target population by health facility catchment area. This task was assigned to the primary health-care centres, subposts, and hospital community health departments. After the district health office had scheduled the screening date for each catchment area, voluntary village health workers and *desuups* (volunteers) were mobilized to distribute sample containers. This ensured that individuals could bring their samples to the screening camp venue on the designated camp screening date. People who did not receive a sample container in advance could obtain one at the camp venue on the screening date or from nearby health facilities during official business hours.

People were advised to collect their samples so that they would be as fresh as possible on the scheduled screening date or within 2 days of this date. Individuals who could not attend the scheduled screening camp could visit their local health facilities during routine hours for *H. pylori* testing. This approach ensured maximum participation

and convenience for the community and enhanced the overall effectiveness of the screening programme.

H. pylori *testing*

Stool samples were collected from the screening camps or health facilities, and the demographic information and risk factor details for each individual were entered into the online cancer reporting system. A system-generated unique identity number was given to each sample. The reporting system, hosted on the DHIS2 software platform, includes features specifically for reporting cancer screening data. Every health facility (including primary health-care centres, subposts, and hospital community health departments) can access the system using their unique login credentials to enter, view, edit, and print data and reports. Laboratory, gynaecology, endoscopy, and pharmacy departments also have access to enter or view data on their reporting pages. The SAT results were uploaded to the system and were issued to individuals on the same day; this allowed people to collect the triple-therapy regimen if applicable. The district health office has access to the data for its district, and the Ministry of Health has access to nationwide data.

Before the online system was fully operational, data management was done using Excel; the data were later uploaded to the system. *H. pylori* tests were performed on the same day or within the recommended time limit using either the H. PYLORI CHEK or the H. PYLORI QUIK CHEK test. The H. PYLORI CHEK kit can be used to perform 94 tests (excluding positive and negative controls) and was used for the mass screening; this test was performed only by certified laboratory professionals. The H. PYLORI QUIK CHEK test was used for walk-in patients and for tests in distant places; this test can be performed by trained health assistants.

The H. PYLORI CHEK test uses an enzyme-linked immunosorbent assay (ELISA). The kit contains immobilized capture antibodies against *H. pylori* antigen. The conjugate consists of *H. pylori* antigen-specific antibodies coupled to horseradish peroxidase. If the antigen is present in the specimen, it binds to the conjugate and the immobilized capture antibody during incubation. After the addition of the substrate, a colour change is detected because of the formation of enzyme–antibody–antigen complexes. The results can be read using an ELISA reader or visually if an ELISA reader is unavailable. The main equipment required for the test is a centrifuge and a water bath. Test results can

be obtained in about 60 minutes. The sensitivity of this test was 91%, and the specificity was 100% [14].

The H. PYLORI QUIK CHEK test contains *H. pylori* antigen-specific antibodies (test line; “T”) and antibodies to horseradish peroxidase (control line; “C”). After the addition of the conjugate, *H. pylori* antigen in the sample binds to the antibody–peroxidase conjugate. The antigen–antibody–peroxidase complexes then migrate through a filter pad to a membrane, where they are captured by immobilized anti-*H. pylori* antibodies at the test line. The reaction window is visually examined for the appearance of vertical blue lines on the “C” and “T” sides after the addition of the substrate. Test results can be obtained in about 30 minutes. The sensitivity of this test was 92%, and the specificity was 91% [14].

The test kits require storage at 2–8 °C and must be brought to room temperature before testing. After use, the test kits should be returned to the storage temperature. Samples can be processed within 36 hours of collection if stored at room temperature. Fresh unpreserved samples can be stored at 2–8 °C for up to 96 hours, and frozen unpreserved samples can be stored at ≤ −10 °C for up to 14 days before they are tested [12].

Most of the tests were performed on the same day. When the public turnout for the mass screening exceeded expectations, especially in urban areas, tests were completed within 2 days on samples stored at 2–8 °C. The results were then uploaded to the online cancer reporting system, and individuals were informed via a text message alert on their mobile phones or via a telephone call to collect the triple-therapy medications from the screening camp or a pharmacy counter at any nearby health facility. Pharmacists or health assistants educated patients about the use of the triple-therapy medicines, the need for a follow-up test (3 months after completion of the treatment), and the importance of reporting any adverse drug reactions. Pharmacists were deployed to dispense medications to people who tested positive for *H. pylori* during the mass screening camps.

The district health office, through the primary health-care centres and hospitals, conducted a second round of testing 3 months after completion of the triple-therapy medication. Individuals who still tested positive for *H. pylori* on the second test were prescribed quadruple therapy. Because of metronidazole resistance in the community

[8], this drug was replaced by tinidazole in the quadruple-therapy regimen. The screening algorithm is shown in Fig. 3.6.1.

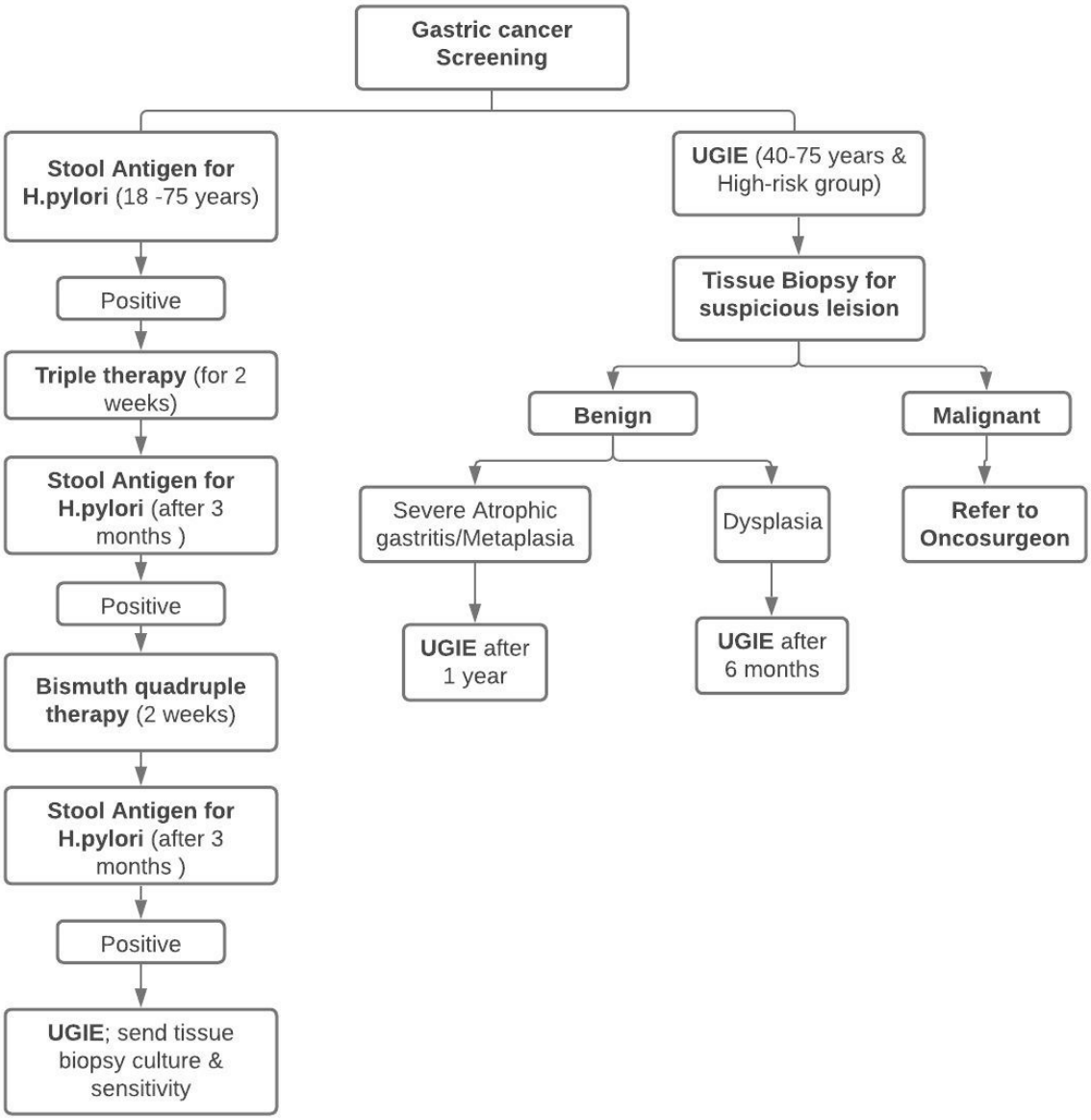

Fig. 3.6.1. Screening algorithm for *H. pylori* and gastric cancer used in Bhutan for the Health Flagship Programme. UGIE, upper gastrointestinal endoscopy.

Treatment for H. pylori *infection*

For the effective treatment of *H. pylori* infection, patients received triple therapy as a first-line treatment. This regimen includes clarithromycin (500 mg, twice a day), amoxicillin (1000 mg, twice a day), and pantoprazole (40 mg, twice a day). This regimen is administered for 14 days. Before starting treatment, patients were screened for any

penicillin allergy. For individuals with a confirmed allergy to penicillin, tinidazole (500 mg, twice a day) was prescribed as a substitute for amoxicillin. Patients were also advised to call the medical emergency hotline for assistance if they experienced any signs of a drug allergy.

If the triple therapy does not achieve eradication (confirmed by a follow-up test 3 months after completion of the treatment), quadruple therapy is recommended as the second-line treatment. This regimen includes tetracycline (500 mg, 4 times a day), bismuth subsalicylate (520 mg, 4 times a day) or bismuth subcitrate (120 mg, 4 times a day), pantoprazole (40 mg, twice a day), and tinidazole (500 mg, twice a day). Quadruple therapy is prescribed for an additional 14 days.

To improve compliance with the treatment regimen, several strategies were put in place, although further enhancements might have been beneficial. The focal pharmacists conducted random follow-ups with patients to ensure adherence to the prescribed regimen. At the 3-month confirmatory test, patients who tested positive were asked specific questions to verify compliance. The decision to proceed with quadruple therapy was contingent upon verification of treatment completion.

Only patients who were confirmed to have completed the treatment regimen in full were eligible for second-line treatment. For those who tested positive but had not completed the initial treatment as directed, a referral was made to the Hospital Therapeutic Committee. This committee reviewed each case individually and decided whether to repeat the first-line treatment or initiate the second-line treatment based on the patient's compliance and clinical response.

Endoscopic screening

Based on the risk factor assessment during the *H. pylori* screening and on the *H. pylori* test results, individuals aged 40–75 years with identified risk factors for gastric cancer were actively enrolled for UGIE screening [9, 10]. In addition, the screening guideline recommends UGIE for any patient irrespective of age and sex if clinically indicated, and for patients who are resistant to quadruple therapy (opportunistic diagnoses). UGIE outreach camps were scheduled for each community to screen all listed individuals. Endoscopy teams, along with the necessary equipment, were mobilized from the nearest established endoscopy centres.

All endoscopic findings were recorded in the online cancer reporting system and the health facility register book for each patient. Endoscopic biopsies obtained from suspicious lesions in the stomach and duodenum were sent to the nearest histopathology laboratory for laboratory confirmation. The histopathology biopsy reports were also entered directly into the system, allowing the referring endoscopist or the focal health worker to view the report and to follow up with the patient to arrange the necessary treatment or management. The screening algorithm is shown in Fig. 3.6.1.

3.6.5 Outcomes of the Health Flagship Programme

The Health Flagship Programme was implemented with sufficient resources to achieve the long-term goal of reducing gastric cancer incidence and mortality.

Key measurement metrics

Using the strategies outlined earlier, the Health Flagship Programme aimed to assess its outcomes by the end of the implementation period using the following key measurement metrics.

- Primary prevention programme:
    - ***H. pylori* screening coverage:** The proportion of individuals screened for *H. pylori* infection relative to the total population aged 18–75 years.
    - ***H. pylori* treatment coverage:** The proportion of individuals diagnosed with *H. pylori* infection who received triple therapy, compared with the total number of individuals who tested positive for *H. pylori* in the initial screening.
- Secondary prevention programme:
    - **Screening coverage:** The percentage of individuals who underwent UGIE compared with the total target population for gastric cancer screening.
    - **Cancer detection rate:** The proportion of cancers detected relative to the total number of individuals screened for gastric cancer.
    - **Positive predictive value:** The proportion of cancers detected among individuals aged > 40 years with a positive *H. pylori* test result or other identified risk factors for gastric cancer.

- **Proportion of advanced-stage cancers:** The percentage of advanced-stage cancers identified relative to the total number of cancers detected.

Screening results

A total of 410 546 individuals aged 18–75 years were registered for the gastric cancer screening programme across all 20 districts of the country. Of this target population, 370 225 individuals participated in *H. pylori* screening using the SAT, achieving a programme coverage rate of 90.2%. Among those tested, 119 854 individuals were found to be positive for *H. pylori* and subsequently received triple therapy, resulting in a national *H. pylori* positivity rate of 32.4%. The positivity rate varied across districts, ranging from 21.9% in Samtse District to 49.8% in Zhemgang District. A breakdown of *H. pylori* prevalence by district is shown in Fig. 3.6.2.

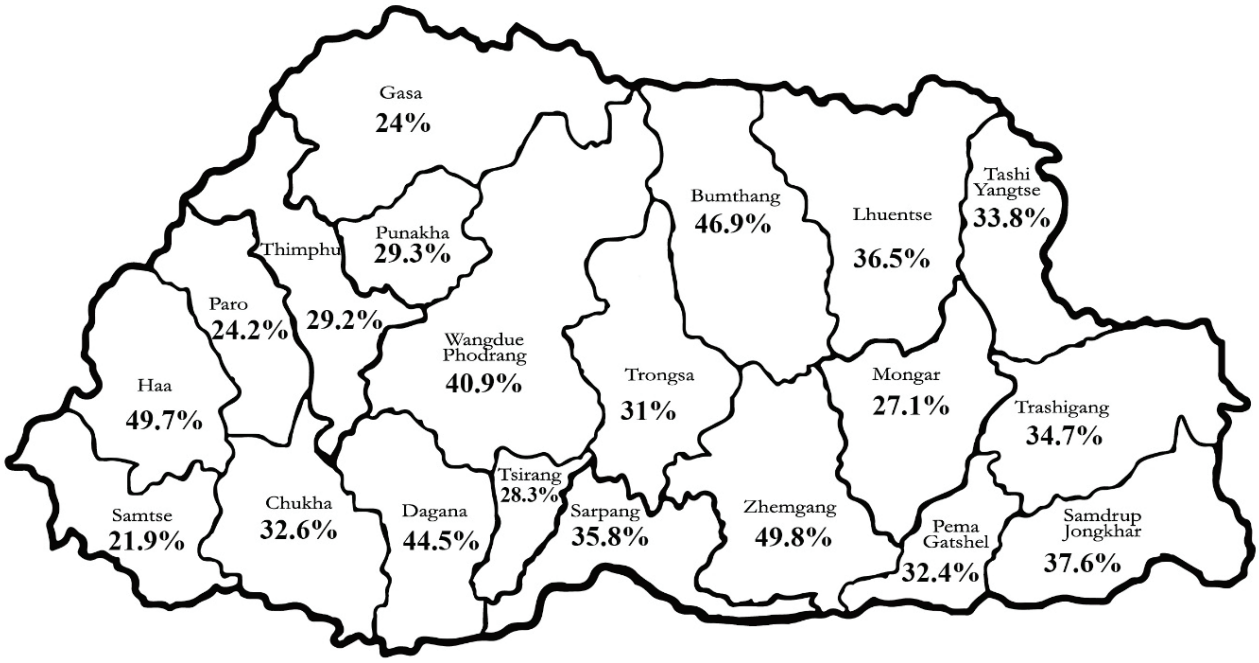

Fig. 3.6.2. *H. pylori* prevalence in districts in Bhutan measured using the stool antigen test during the Health Flagship Programme.

A confirmatory test was conducted for 32 262 individuals, representing 27% of those who tested positive for *H. pylori* and received eradication therapy. Of these, 7.92% still tested positive for *H. pylori*. The resistance to triple therapy varied between districts, with rates ranging from 2.16% to 22.13%. However, it is challenging to draw definitive conclusions about drug resistance, because these figures include all cases who tested positive on the repeat test regardless of treatment compliance (timely completion of the entire course of treatment).

After *H. pylori* screening and risk factor assessment for gastric cancer, 53 182 people aged 40–75 years underwent UGIE screening nationwide in 2021–2023. During this period, 11 637 endoscopic biopsies were taken from suspicious lesions for histopathological confirmation. Biopsies were performed on about 22% of individuals who underwent UGIE, and the biopsy rate varied between endoscopists. The guidelines recommended biopsies for any suspicious lesions, leading to a wide range in the biopsy rate, from 0.56% to 95.75%.

In 2021–2023, a total of 1142 cases of gastric cancer were identified nationwide, resulting in a cancer detection rate of 3.08 per 1000 people screened for *H. pylori* (Table 3.6.2). In comparison, according to data from the Bhutan Cancer Registry for 2019–2022, the overall age-adjusted incidence rate of gastric cancer was 25.1 per 100 000 people in males and 18.9 per 100 000 people in females. In addition, histopathological examination of the 11 637 biopsies identified 206 cases of low-grade dysplasia (1.77%), 42 cases of high-grade dysplasia (0.36%), and 40 cases of intramucosal carcinoma (0.34%). These conditions were found more commonly in districts with high biopsy rates, such as Lhuentse District and Mongar District.

Table 3.6.2. Gastric cancer detection rate by districts of Bhutan (per 1000 people screened for *H. pylori*) during the Health Flagship Programme[a]

District	Gastric cancer detection rate per 1000 people screened for *H. pylori* (2021–2023)
Bumthang	5.24
Dagana	3.35
Haa	14.12
Sarpang	2.28
Samdrup Jongkhar	2.27
Mongar	3.13
Chukha	1.20
Paro	6.57
Pema Gatshel	1.48
Punakha	7.60
Gasa	7.43
Lhuentse	8.47
Samtse	1.46
Trashigang	2.85
Thimphu	0.65
Trashiyangtse	9.16
Trongsa	6.63
Tsirang	2.01
Wangdue Phodrang	6.60
Zhemgang	5.21
National	**3.08**

[a] The Health Flagship Programme is a nationwide population-based cancer screening programme initiated by the Ministry of Health from 2020 to 2023.

From the number of cancers detected in individuals who underwent UGIE because of a positive *H. pylori* test result or other identified risk factors for gastric cancer, the positive predictive value for gastric cancer was found to be 2.15%.

The stage distribution of gastric cancer cases recorded by the oncology department at the National Referral Hospital indicated that 47% of the cases are classified as early stage (stage I–IIB), 43% as locally advanced (stage III), and 10% as advanced stage (stage IV) (Table 3.6.3).

Table 3.6.3. Proportions of gastric cancers by stage in Bhutan

Stage	Classification	Proportion (%)
Early	I	21
	IIA	20
	IIB	6
Locally advanced	III	43
Advanced	IV	10

3.6.6 Lessons learned from implementing a population-based cancer screening programme in Bhutan

Bhutan's population-based gastric cancer screening programme (2020–2023), implemented as part of the Health Flagship Programme, provided valuable insights into the effective implementation of public health interventions in resource-limited settings, highlighting several key lessons and strategies to address various challenges. Some of the main lessons learned and challenges addressed are as follows.

Lessons learned

Strong political commitment

Bhutan's nationwide gastric cancer screening initiative reflects a powerful political commitment to health. The Royal Government of Bhutan prioritized this programme, despite limited local cost–effectiveness evidence, by approving a substantial budget that enabled critical health infrastructure development and the widespread implementation of screening services.

Comprehensive strategy and collaboration

The programme's success was grounded in a comprehensive strategy and close collaboration with central and local government, health-care facilities, schools, and community leaders. These partnerships were essential for maximizing participation across diverse regions, including reaching remote populations.

Public awareness and education

Public engagement was substantially bolstered by a multifaceted advocacy campaign, which used television, social media, schools, and high-level outreach in

remote areas. The high-level advocacy initiative emphasized the importance of collective effort in fighting preventable cancers. Leveraging school students as information channels in urban areas was particularly effective for reaching mobile populations.

Trust between health-care providers and the public

The strong bond between health-care providers and the public in Bhutan was a key factor in the programme's success. Public trust in health-care workers made it easier to mobilize communities for screening, demonstrating the critical role of trust in successful public health interventions.

Infrastructure and resources

Expanding endoscopy centres and enhancing diagnostic equipment greatly increased the programme's reach. Bhutan's cold-chain storage capacity, complete with high-volume walk-in refrigerators and refrigerated vans, was essential for maintaining the quality of *H. pylori* test kits and ensuring the programme's effectiveness.

Data and technology integration

The implementation of an online cancer reporting system streamlined data management, enabling real-time updates. This system supported patient tracking, treatment management, and data-driven decision-making for optimizing screening strategies.

Challenges addressed

Logistics and cold-chain management

The SAT kits required a strict temperature range of 2–8 °C. This was tackled by storing kits in regional walk-in refrigerators and distributing them to health facilities based on their cold-chain capacity, using refrigerated vans. This approach was effective, although maintaining the cold chain was challenging in remote areas with limited road access.

Equipment transportation and infrastructure

Transporting sensitive endoscopy equipment and accessories to rural and remote areas required smart planning because of Bhutan's rugged terrain and lack of road connectivity in certain regions. Careful logistic coordination was essential for safely reaching these areas and setting up temporary screening facilities.

Human resource constraints

The limited health-care workforce in Bhutan is already stretched thin because of multiple public health initiatives. To expand capacity, nearly all surgeons were given basic training in UGIE, and some received advanced training in early gastric cancer detection. These trained surgeons were efficiently used through efficient mobilization and planning. In addition, primary health-care staff received specialized training to conduct rapid SAT screenings. These efforts helped expand service availability with a limited health workforce while managing the increased workload.

Community and cultural sensitivities

Bhutanese cultural practices, especially the preference for spiritual healing, posed a unique challenge, because individuals often delay seeking medical care. Recognizing the popular belief that medication and spiritual healing must go hand in hand, the programme included public sensitization efforts to encourage the integration of medical treatment with spiritual practices. This culturally sensitive approach helped reduce late-stage diagnoses by fostering trust and encouraging timely medical follow-up.

3.6.7 Future directions

Drawing on insights from Professor Prawase Wasi's "triangle that moves the mountain" [15], commitment to the continuation of such gastric cancer prevention efforts will be highly dependent on relevant high-quality evidence and strong political commitment. Insights from the recent programme will guide Bhutan to adopt the most efficient, cost-effective, and sustainable strategies for routine screening.

Enhancing national capacity and infrastructure for early gastric cancer diagnosis and treatment is Bhutan's foremost priority. Without this, population-based screening efforts will have a limited impact. In addition, although Bhutan's central clinical laboratory

currently monitors antibiotic resistance for commonly used antibiotics, developing and maintaining an antibiogram specific to the antibiotics used in *H. pylori* eradication therapy will help guide future treatment protocols.

With the data from the Health Flagship Programme and the National Health Survey, Bhutan plans to focus on evaluating the effectiveness of the programme, building evidence for cost-effective cancer screening, and refining its strategies in collaboration with the relevant national and international research agencies, such as IARC. This approach will not only support evidence-based decision-making in Bhutan but also contribute to the global understanding of gastric cancer.

Acknowledgements

The author would like to thank Dr Prabhat Pradhan and Dr Sonam Dargay from Jigme Dorji Wangchuck National Referral Hospital for their input when preparing this chapter.

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WHO Western Pacific Region

Summary

- Gastric cancer is still the most common in East Asian regions, including China, Japan, and the Republic of Korea. However, there are vast geographical and ethnic differences in the prevalence of *H. pylori* infection and in gastric cancer incidence within the Western Pacific Region, which affect the efforts on gastric cancer screening in different countries.
- In China, national gastric cancer screening programmes target high-risk regions, and challenges remain to expand the screening programme across the country, because of the huge population and vast territory. Future directions include developing more targeted prevention strategies based on risk prediction and advancing a comprehensive tiered prevention system for gastric cancer in China.
- Population-based gastric cancer screening programmes have been implemented in Japan and the Republic of Korea, which have high background incidence of gastric cancer, by endoscopy or barium studies. Screening with a 2-year interval is recommended in individuals aged ≥ 50 years or ≥ 40 years. Clinical trials have also been conducted to determine the role of *H. pylori* eradication in preventing metachronous gastric cancer and reducing risk of gastric cancer in first-degree relatives of patients with gastric cancer as well as at the population level in the Republic of Korea.
- *An H. pylori* screen-and-treat programme, as an alternative to a population-based endoscopy screening programme, has been implemented in the Matsu Islands in the East China Sea. The programme was initially a pilot programme, which was subsequently proven to have a positive impact. *H. pylori* eradication was associated with reduced rates of gastric cancer. Experiences gained from this pilot programme contributed to the expansion of the *H. pylori* screen-and-treat programme to the broader populations with varying gastric cancer risk levels.

- Aotearoa New Zealand is characterized by stark ethnic differences in *H. pylori* prevalence and gastric cancer incidence; for example, rates are higher in Māori people, Pacific people, and Asian people than in European people. Research into the stratification of the prevalence of *H. pylori* infection in the community by ethnicity, the feasibility of a screen-and-treat strategy, and the level of treatment resistance is expected to support the design of a future screen-and-treat pilot programme in New Zealand.

Chapter 3.7.

Gastric cancer prevention in China

Wen-Qing Li and Wai Keung Leung

Summary

- Gastric cancer is a major health burden in China. Both incidence rates and mortality rates are higher in males and in rural areas, increasing substantially in people aged > 40 years.
- *H. pylori* infection is responsible for three quarters of gastric cancer cases in China, with prevalence rates of 40–50%. Infection rates vary by region, with the highest rates in north-western China, and rates have decreased during recent decades.
- Large-scale randomized trials in high-risk areas of China have demonstrated that *H. pylori* eradication significantly reduces gastric cancer incidence and mortality. The recent Mass Intervention Trial in Linqu, Shandong provides evidence supporting population-based *H. pylori* screening and treatment for gastric cancer prevention in high-risk community settings.
- China has implemented national gastric cancer screening programmes targeting high-risk regions, which have shown effectiveness in reducing incidence and mortality. However, challenges remain in expanding screening to populations in need across the country.
- Future directions include developing more targeted prevention strategies based on risk prediction and advancing a comprehensive tiered prevention system for gastric cancer in China.

3.7.1 Overview of gastric cancer and *H. pylori* infection in China

Epidemiological characteristics and disease burden of gastric cancer

Incidence, mortality, and survival rates

China accounts for the highest proportion of gastric cancer cases globally, with 37% of the worldwide cases. In China, gastric cancer ranks fifth among cancer types in terms of cancer incidence and third in terms of cancer mortality. In 2022, about 358 700 new gastric cancer cases occurred in China, of which 246 600 were in males and 112 100 in females [1]. The gastric cancer incidence rate has decreased in recent years [2–4]. The overall crude incidence rate is 25.4 per 100 000 person-years, and the age-standardized incidence rate is 13.7 per 100 000 person-years. The overall crude mortality rate is 18.4 per 100 000 person-years, and the age-standardized mortality rate is 9.4 per 100 000 person-years [1].

Both incidence rates and mortality rates are more than twice as high in males as in females and are correlated with age, remaining relatively low in people aged < 40 years and increasing substantially in people aged > 40 years [5]. For males, the highest age-specific incidence rate (244.2 per 100 000 person-years) and mortality rate (265.8 per 100 000 person-years) are at ages 80–84 years. For females, the highest age-specific incidence rate (122.1 per 100 000 person-years) is at ages 80–84 years and the highest age-specific mortality rate (117.3 per 100 000 person-years) is at ages > 85 years. Although there was a decreasing trend in the age-standardized incidence rate of gastric cancer in China from 2000 to 2018, it remains one of the top five causes of cancer death in both males and females.

Regional differences are noticeable. The age-standardized incidence and mortality rates for gastric cancer are highest in north-western China and lowest in southern China [6]. In general, both incidence rates and mortality rates are higher in rural areas than in urban areas. In people aged ≤ 55 years, there is no substantial difference, but in people aged > 55 years, both incidence rates and mortality rates in rural areas markedly exceed those in urban areas [5].

About 35.2% of patients with gastric cancer in China survive more than 5 years after diagnosis. There is no substantial difference in survival rates between males and females. The 5-year survival rates decrease with increasing age for both males and

females, and there is a trend of sharper decreases in the older age groups, particularly for people aged > 74 years [7].

Economic burden

Gastric cancer imposes a heavy economic burden in China, accounting for about 10% of the total costs for cancer inpatient care in 2017 [5]. Costs for gastric cancer increased from ¥ 5.5 billion in 2008 to ¥ 23.8 billion in 2017, and the expenses were highest for patients with gastric cancer treated in grade 3 general hospitals [8]. In a recent study, the average hospitalization cost per patient was US$ 19 876, and the out-of-pocket expenses were US$ 10 605. The major contributors to the cost were radiation therapy (US$ 2716) and chemotherapy (US$ 6518), and surgical fees averaged US$ 724 per case [9].

Burden of* H. pylori *infection

Prevalence

In China, the prevalence of *H. pylori* infection was estimated to be 40.7–49.4%, based on several reports in recent years [10–13]. The infection rate varies substantially by region. A systematic review of studies in China in 1990–2019 found the highest infection rates in north-western (51.8%), eastern (47.7%), and south-western (46.6%) China. The prevalence of *H. pylori* infection was > 50% in Xizang Autonomous Region (66.4%), Guizhou Province (60.5%), and Gansu Province (57.2%) [10]. A nationwide, multicentre cross-sectional survey conducted in 2023 found similar geographical variations in the prevalence of *H. pylori* infection, with southern provinces generally having lower infection rates than northern and eastern regions [14]. In China, the distribution of household-based (Spearman correlation coefficient $r = 0.46$; $P = 0.01$) and individual-based ($r = 0.49$; $P = 0.007$) prevalence of *H. pylori* infection in province-level administrative divisions is significantly correlated with the incidence of gastric cancer (Fig. 3.7.1).

In China, the overall prevalence of *H. pylori* infection has decreased significantly during the past few decades. The infection rate was higher in 1983–1994 (58.3%; 95% confidence interval [CI], 50.7–65.5%) compared with the periods 1995–1999 (48.0%; 95% CI, 36.5–59.6%), 2000–2004 (51.1%; 95% CI, 43.7–58.5%), and 2005–2009 (48.7%; 95% CI, 45.6–51.8%), and the infection rate decreased to about 40% in 2015–

2019 [10]. This downward trend was consistent with a large-scale nationwide survey conducted in 2021, which reported an average *H. pylori* infection rate of 40.7% [12], and was also observed when the data were stratified by geographical region and by the diagnostic method used, such as serology or the urea breath test [10].

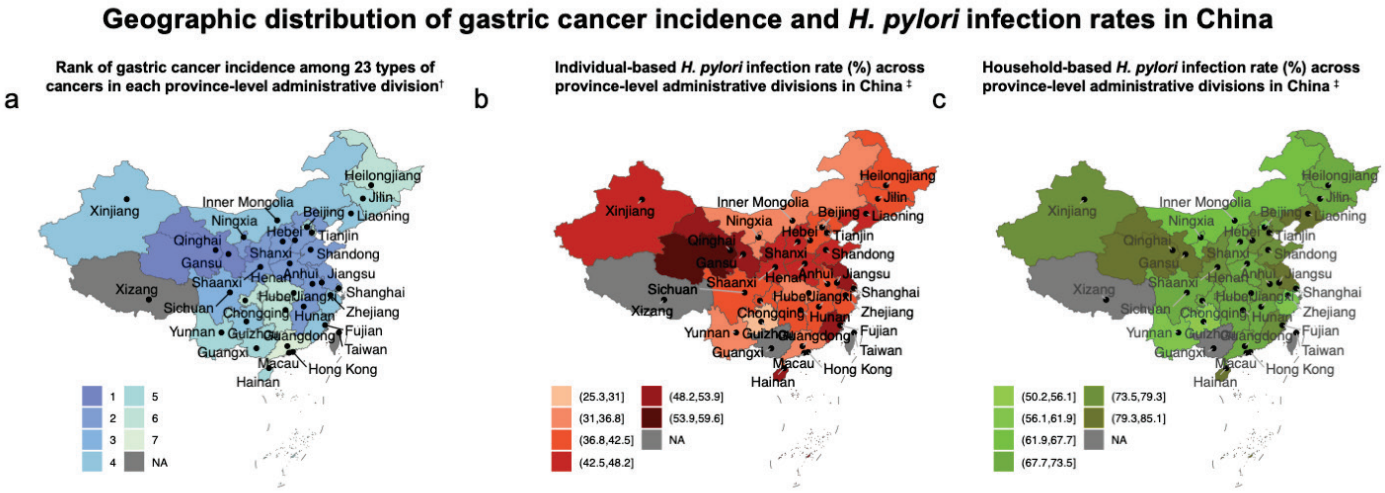

Fig. 3.7.1. Geographical distribution of gastric cancer incidence and *H. pylori* infection rates in China. The maps illustrate the geographical distribution of the rank of gastric cancer incidence among 23 types of cancer in province-level administrative divisions of China in 2018 (A) and the *H. pylori* infection rates in 2021 (B, C). The individual-based infection rate (B) and the household-based infection rate (C), defined as the percentage of households with *H. pylori* infection among all households, are derived from a large-scale national, family-based, cross-sectional survey conducted in 2021 across all 31 provinces of mainland China. The family-based *H. pylori* infection rates in China are significantly higher than the individual-based infection rates, with an average of 71.2% across 29 of 31 province-level administrative divisions (provinces, autonomous regions, or municipalities) in mainland China, ranging from 50.3% to 85.1%. Of these divisions, 26 had estimated family-based infection rates of > 60%, and 20 had rates of > 70%. Qinghai, Hainan, Gansu, Jiangsu, and Liaoning Provinces had family-based infection rates of > 80%. NA, not available. Compiled from (A) Zheng et al. (2022) [80] and from (B, C) Zhou et al. (2023) [12].

H. pylori infection rates also vary by age and sex. A nationwide survey reported a higher infection rate in adults (43.5%, aged ≥ 18 years) than in children and adolescents (20.6%, aged < 18 years) [12]. The average infection rate was slightly higher in males (44.9%; 95% CI, 43.6–46.2%) than in females (42.0%; 95% CI, 40.5–43.5%) [10]. The

difference in infection rates between males and females is seen in both children and adults.

Family cluster infection and intrafamilial transmission

In China, intrafamilial transmission of *H. pylori* infection is a frequent mode of transmission, especially in populations at high risk of gastric cancer [15, 16]. A family cluster infection, which is defined as a household with several family members with *H. pylori* infection, ranging from one to all family members, is a notable feature of *H. pylori* infection in both urban and rural China [12]. The risk factors for a family cluster infection of *H. pylori* are a large family size, multiple generations in a household, crowded conditions, having a large number of siblings, and poor household hygiene [12, 17–19]. The *H. pylori* infection rate in children is substantially influenced by the infection status of their parents [12]. In families in which both parents had *H. pylori* infection, the child infection rate was 34.3%, compared with 13.6% in families in which neither parent had *H. pylori* infection.

3.7.2 Primary prevention of gastric cancer in China

H. pylori infection was responsible for 340 000 new cancer cases in China (age-standardized incidence rate, 15.6 per 100 000 person-years) [20] and accounted for 74.5% of gastric cancer cases nationwide in 2018 [5]. Data from the China Kadoorie Biobank indicated that *H. pylori* infections were responsible for 78.5% of non-cardia gastric cancers and 62.1% of cardia gastric cancers in 2018 [21].

Since the 1990s, substantial efforts have been made to determine the efficacy and effectiveness of *H. pylori* treatment in preventing new cases of gastric cancer in several high-risk areas of China and globally [22, 23]. Nearly half of the available randomized trials were conducted in high-risk areas of mainland China, including Linqu County (Shandong Province; three trials) [24–28], Changle County (Fujian Province) [29, 30], and Yantai County (Shandong Province) [31, 32]. These trials have provided crucial evidence to support *H. pylori* eradication as a major primary prevention strategy for gastric cancer prevention (Table 3.7.1).

Table 3.7.1. Randomized controlled trials of *H. pylori* treatment for gastric cancer prevention in mainland China

Trial	Location	Follow-up period (years)	*H. pylori* eradication therapy regimen used	Pre-neoplastic lesions at baseline (%)	Eradication rate (%)[a]	Mean age at baseline (years), (range)	Sample size (gastric cancer cases)		Effect estimates (95% CI)[b]
							Treatment	Placebo/control	
Changle Trial [29, 30]	7 villages in Changle County, Fujian Province	26.5	Omeprazole 20 mg, co-amoxiclav 750 mg, and metronidazole 400 mg b.i.d. for 2 weeks	37.7[c]	83.7	42.2 (35–65)	817 (21)	813 (35)	EE1: 0.60 (0.35–1.02) EE2: 0.57 (0.33–0.98)
Intervention trial on *H. pylori* eradication and COX-2 inhibition [28]	12 villages in Linqu County, Shandong Province	5	Omeprazole 20 mg, amoxicillin 1000 mg, and clarithromycin 500 mg b.i.d. for 1 week	100.0[c]	63.5	53.0 (35–64)	258 (3)	255 (1)	EE1: 3.04 (0.32–28.99)
Yantai Trial [31, 32]	11 villages in Yantai County, Shandong Province	10	Omeprazole 20 mg, amoxicillin 1000 mg, and clarithromycin 500 mg b.i.d. for 1 week	45.5[d]	55.6	52.0 (35–75)	276 (2)	276 (7)	EE1: 0.29 (0.06–1.36)
Shandong Intervention Trial [24–26]	13 villages in Linqu County, Shandong Province	22.3	Omeprazole 20 mg and amoxicillin 1000 mg b.i.d. for 2 weeks	98.5[c]	73.2	46.8 (35–64)	1130 (41)	1128 (78)	EE1: 0.52 (0.36–0.76) EE2: 0.48 (0.32–0.71)
Mass Intervention Trial in Linqu, Shandong [34, 77]	980 villages in all 10 townships of Linqu County, Shandong Province	11.8	Omeprazole 20 mg b.i.d., tetracycline 750 mg t.i.d., metronidazole 400 mg t.i.d., and bismuth citrate 300 mg b.i.d. for 10 days	NR	72.9	42.5 (25–54)	52 026 (354)	50 304 (399)	EE1: 0.86 (0.74–0.99) EE2: 0.87 (0.75–1.00)

b.i.d., 2 times a day; CI, confidence interval; EE1, effect estimate 1; EE2, effect estimate 2; NR, not reported; t.i.d., 3 times a day.

[a] True intention-to-treat analysis, with eradication therapy assumed to have failed in all dropouts.
[b] Effect estimates for the risk of gastric cancer are derived from univariate analyses (effect estimate 1) and, if applicable, from multivariate analyses (effect estimate 2).
[c] Defined as gastric atrophy, intestinal metaplasia, or dysplasia.
[d] Defined as gastric atrophy or intestinal metaplasia, calculated from Leung et al. (2004) [31] (n = 435).

H. pylori *eradication as a measure for primary prevention: evidence from Linqu, Shandong Province*

From 1973 to 1975, a national survey on cancer mortality patterns identified geographical clusters of major malignant tumours and established high-risk areas for gastric cancer, which included Linqu (Shandong Province), Zhuanghe (Liaoning Province), Wuwei (Gansu Province), and Changle (Fujian Province). Linqu County, a rural area in Shandong Province in northern China, has one of the highest gastric cancer mortality rates in the world. This makes it an ideal location to investigate the effects of *H. pylori* eradication on reducing the risk of gastric cancer.

Shandong Intervention Trial

The Shandong Intervention Trial (SIT) (ClinicalTrials.gov ID, NCT00339768), which started in 1995, was one of the first randomized trials in China to evaluate the effects of *H. pylori* eradication on reducing the risk of gastric cancer [24–27, 33]. The trial, which involved 2258 *H. pylori*-seropositive individuals, adopted a 2 × 2 × 2 factorial design to evaluate the effect of *H. pylori* treatment, vitamin supplementation, and garlic supplementation on the prevalence of advanced precancerous gastric lesions. *H. pylori* treatment resulted in statistically significant decreases in the combined prevalence of severe chronic atrophic gastritis, intestinal metaplasia, dysplasia, or gastric cancer after 7.3 years (odds ratio [OR], 0.60; 95% CI, 0.47–0.75). By 2003, *H. pylori* treatment also had favourable effects on the average histopathological severity of gastric lesions and on the progression and regression of precancerous gastric lesions, but it did not reduce the combined prevalence of dysplasia or gastric cancer [24].

The SIT had an extended follow-up period and was the first study to report a statistically significant decrease in gastric cancer incidence after *H. pylori* treatment, at 14.7 years of follow-up (OR, 0.61; 95% CI, 0.38–0.96) [25]. Further follow-up substantiated the persistent benefits on gastric cancer incidence (OR, 0.48; 95% CI, 0.32–0.71) at 22.3 years of follow-up, and this study was the first to observe a marked reduction in gastric cancer mortality (hazard ratio [HR], 0.62; 95% CI, 0.39–0.99) [26]. Further evidence from the SIT has underlined the benefits of *H. pylori* eradication in the prevention of gastric cancer, even in people with severe gastric lesions [26].

Intervention trial on H. pylori *eradication and COX-2 inhibition*

Between 2002 and 2006, a randomized, placebo-controlled trial was conducted in Linqu to explore the effects of celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, and *H. pylori* eradication treatment on the progression of gastric lesions in a study with 1024 individuals and a 2 × 2 factorial design [28]. In this study, both *H. pylori* eradication (OR, 2.19; 95% CI, 1.32–3.64) and celecoxib treatment (OR, 1.72; 95% CI, 1.07–2.76) had beneficial effects on the regression of advanced gastric lesions, but there was no synergistic benefit when these two interventions were combined. During the 5-year follow-up period, neither *H. pylori* eradication nor celecoxib treatment was associated with the prevention of gastric cancer.

Community-based cluster-randomized trial of H. pylori *eradication with more than 180 000 participants*

Although previous randomized trials indicated that *H. pylori* treatment reduces gastric cancer incidence, those trials were conducted on a modest scale and accrued a limited number of events, leaving substantial knowledge gaps. In 2014, IARC noted that the currently available data were insufficient to precisely estimate the overall benefits and potential adverse consequences of *H. pylori* treatment and that large-scale, population-based *H. pylori* treatment programmes were needed. To address these uncertainties, in March 2011 research teams from China and Germany collaborated to initiate the Mass Intervention Trial in Linqu, Shandong (MITS) (Chinese Clinical Trials Registry ID, ChiCTR-TRC-10000979) [34, 35].

The MITS is a cluster-randomized, blinded mass intervention trial that enrolled all 980 villages in all 10 townships of Linqu and included 180 284 eligible people aged 25–54 years [34]. Individuals who were *H. pylori*-positive, as determined using the ^{13}C-urea breath test, received either 10-day quadruple anti-*H. pylori* treatment (in 493 villages; 20 mg of omeprazole 2 times a day, 750 mg of tetracycline 3 times a day, 400 mg of metronidazole 3 times a day, and 300 mg of bismuth citrate 2 times a day) or symptom alleviation treatment (in 487 villages; a single dosage of 20 mg of omeprazole and 300 mg of bismuth citrate). In a pilot study in the Linqu population, the combined resistance rate to tetracycline and metronidazole was only 5.3%. *H. pylori*-negative individuals did not receive any treatment.

The overall successful eradication rate was 72.9% (32 325 of 44 329 participants with known results from a second ^{13}C-urea breath test) in the participants who had received anti-*H. pylori* treatment, and 15.1% of the participants who had received symptom alleviation treatment were *H. pylori*-negative after treatment. Moderate adverse effects were reported in 1345 participants during the 10-day treatment. Severe intolerable events were not observed during the treatment, and no related adverse events were reported during the follow-up. During the 11.8 years of follow-up (2011–2022) of the 180 284 participants, 1035 incident gastric cancer cases were documented, including 354 cases in people who had received anti-*H. pylori* treatment, 399 cases in people who had received symptom alleviation treatment, and 282 cases in the *H. pylori*-negative group. Most of the gastric cancer cases occurred in non-cardia stomach sites (90.3%; 714 of 791 site-specified cases).

Based on the intention-to-treat analyses, individuals who received anti-*H. pylori* therapy had a statistically significant reduction in gastric cancer incidence compared with individuals who received symptom alleviation treatment (HR, 0.86; 95% CI, 0.74–0.99). Stronger effects were observed in individuals in whom *H. pylori* infection had been successfully eradicated (HR, 0.81; 95% CI, 0.69–0.96) than in individuals in whom the treatment had failed (HR, 1.02; 95% CI, 0.83–1.26). The beneficial effect of successful eradication was particularly noteworthy for individuals aged 25–45 years. Neither anti-*H. pylori* treatment (HR, 0.89; 95% CI, 0.72–1.11) nor successful eradication (HR, 0.81; 95% CI, 0.63–1.05) was associated with significantly decreased gastric cancer mortality rates during the 11.8 years of follow-up, although the effect estimates appeared similar to those for gastric cancer incidence rates. *H. pylori* eradication did not alter overall mortality or the risk of other individual cancers.

In the subgroup analysis, successful *H. pylori* eradication modestly reduced the cumulative risk of non-cardia gastric cancer (142 cases in 32 325 participants for successful treatment versus 284 cases in 50 304 participants for symptom alleviation treatment; HR, 0.80; 95% CI, 0.66–0.98) but did not reduce the risk of cardia gastric cancer (17 cases in 32 325 participants versus 25 cases in 50 304 participants; HR, 1.11; 95% CI, 0.60–2.05). In the MITS, in individuals aged < 45 years at baseline in whom *H. pylori* infection had been successfully eradicated, there was a reduction of 35% in gastric cancer incidence and a reduction of 43% in gastric cancer mortality.

As a large-scale community-based trial, the MITS confirmed the effect of *H. pylori* eradication with anti-*H. pylori* treatment. The comparatively modest protective effect of *H. pylori* treatment may be explained partly by the use of omeprazole and bismuth citrate in the comparison group instead of a pure placebo, the suboptimal (but still relatively successful) eradication rate in the individuals who received anti-*H. pylori* treatment (72.9%), and the relatively short follow-up period. Even so, the MITS provides evidence for implementing gastric cancer prevention by *H. pylori* eradication in the wider population, especially in regions or countries with a high burden of gastric cancer. The MITS strengthens the evidence base supporting the implementation of mass *H. pylori* screening and treatment from early adulthood as a public health policy and clinical practice for gastric cancer prevention in high-risk community settings.

H. pylori *eradication as a measure for primary prevention: evidence from other trials*

Beyond the findings from Linqu, other randomized trials have been conducted in China to examine the effects of *H. pylori* eradication on the evolution of gastric lesions and the risk of gastric cancer.

Yantai Trial

A randomized trial in Yantai (Shandong Province) investigated the effects of *H. pylori* eradication on the progression of intestinal metaplasia towards gastric cancer [31]. This study involved 587 individuals with *H. pylori* infection. Progression of intestinal metaplasia, which was defined as worsening severity of intestinal metaplasia at 5 years in either the antrum or the corpus or the development of neoplasia, was found in 52.9% of participants, and the progression rate was highest in individuals aged > 45 years with persistent *H. pylori* infection (62.8%) [31]. These findings highlight the protective role of *H. pylori* eradication against the progression of premalignant gastric lesions.

Changle Trial

The Changle Trial was initiated in 1994 and involved 1630 asymptomatic people with *H. pylori* infection. The primary outcome of this trial was the incidence of gastric cancer. Like with the SIT, in the initial 7.5-year follow-up of the Changle Trial no significant difference in gastric cancer incidence was observed between the treatment group and the placebo group, although a significant reduction in gastric cancer incidence was

observed in individuals without premalignant gastric lesions [29]. After 26.5 years of follow-up (1994–2020), the study reported that *H. pylori* eradication treatment did reduce the risk of gastric cancer (HR, 0.57; 95% CI, 0.33–0.98). Unlike the SIT, the Changle Trial only reported beneficial effects of *H. pylori* eradication for individuals without severe gastric mucosal lesions, and it did not observe a significant reduction in gastric cancer mortality risk from *H. pylori* eradication at 26.5 years of follow-up (HR, 0.76; 95% CI, 0.38–1.53) [30].

Health economics of H. pylori *screening and eradication*

Evidence from China has shown that the screen-and-treat strategy for *H. pylori* eradication reduces gastric cancer incidence and costs, which benefits high-risk populations. Zheng et al. identified that treating *H. pylori* infection was a cost-saving measure, which increased the number of quality-adjusted life years (QALYs) compared with no eradication treatment, particularly for close relatives of patients with gastric cancer [36]. Han et al. demonstrated that *H. pylori* screening followed by eradication treatment significantly decreased both the occurrence of gastric cancer and its associated expenses in asymptomatic individuals [37]. Chen et al. demonstrated that a population-wide approach in China involving screening and treating *H. pylori* infection was more cost-effective and efficient in preventing gastric cancer in the general asymptomatic population (individuals who tested positive for *H. pylori* but who were otherwise healthy) than a strategy without screening [38].

The optimal settings for implementing a screen-and-treat strategy in China have been explored. For example, one study reported that starting eradication treatment at age 20 years could enhance both health outcomes and economic savings [39].

Healthy lifestyles and nutrition supplementation as preventive tactics against gastric cancer

Regional studies in high-risk areas for gastric cancer in China have highlighted the potential role of healthy lifestyles and nutrition supplementation in primary prevention of gastric cancer. Findings from studies in Linqu (Shandong Province), Changle (Fujian Province), and Zhuanghe (Liaoning Province) have shown that dietary factors closely related to gastric cancer risk include high salt intake and consumption of acid-fried pancakes, fish sauce, and salty pork. Dietary habits such as consuming overheated

food and eating too quickly can also increase the risk of gastric cancer by causing physical irritation to the digestive tract mucosa, which promotes carcinogenesis. Cohort studies in Linqu found that a high-salt diet, low intake of fresh vegetables and fruits, and lower serum vitamin C levels were significantly associated with an increased risk of gastric cancer [40–42]. Conversely, consumption of allium vegetables (garlic, onion, leek, etc.) was inversely associated with the risk of gastric cancer, indicating a significant protective effect [43–45]. The 22.3-year extended follow-up of the SIT showed that gastric cancer incidence decreased significantly with vitamin supplementation (OR, 0.64; 95% CI, 0.46–0.91) but not with garlic supplementation (OR, 0.81; 95% CI, 0.57–1.13) [26]. Vitamin supplementation (HR, 0.48; 95% CI, 0.31–0.75) and garlic supplementation (HR, 0.66; 95% CI, 0.43–1.00) also significantly reduced gastric cancer mortality [26]. Lifestyle factors may also modify the effects of nutrition supplementation on gastric cancer risk [25, 46].

The Nutrition Intervention Trial in Linxian County (Henan Province), which is a high-risk area for oesophageal cancer, showed that supplementation with the antioxidant combination of selenium, vitamin E, and β-carotene significantly reduced gastric cancer mortality (relative risk [RR], 0.79; 95% CI, 0.64–0.99) [47]. A 10-year post-trial follow-up confirmed that these beneficial effects persisted for up to a decade (HR, 0.89; 95% CI, 0.79–1.00) [48].

3.7.3 Secondary prevention of gastric cancer in China

Major population-based national gastric cancer screening programmes

Since the 1980s, there have been sporadic gastric cancer screening programmes in China, led by various research teams. For example, endoscopic screening in Linqu (Shandong Province) in 1989–1990, which involved 3433 individuals, revealed the pervasive presence of precancerous gastric lesions and provided prospective follow-up data that substantiated the progression of these lesions to gastric cancer [49–52]. The Chinese government has promoted nationwide-level secondary prevention of gastric cancer, beginning with the Outline of Chinese Cancer Program (2004–2010). Subsequently, three major national programmes for gastric cancer screening have been conducted, which provide free gastric cancer screening for eligible residents: the Upper Gastrointestinal Cancer Early Detection (UGCED) programme for rural residents [53],

the Cancer Screening Program in Urban China (CanSPUC), and the Huai River Basin Cancer Early Diagnosis and Treatment Project (Table 3.7.2) [54, 55].

Table 3.7.2. Major population-based national gastric cancer screening programmes in China

Programme	Initiation year	Target population	Coverage	Achievements
Upper Gastrointestinal Cancer Early Detection programme for rural residents	2005	Individuals aged 40–69 years in selected high-risk rural areas	Organized screening in 249 counties or districts in 31 provinces, autonomous regions, or municipalities in mainland China, and opportunistic screening in 748 hospitals in 31 provinces, autonomous regions, or municipalities in mainland China	• Screened more than 2.6 million people; early diagnosis rate of 80% • Decreased gastric cancer incidence rates by 31% and mortality rates by 67% (based on evidence from Linqu, Shandong)
Huai River Basin Cancer Early Diagnosis and Treatment Project	2007	High-risk individuals aged 45–74 years, identified by questionnaire-based risk assessment	38 counties or districts in Henan, Jiangsu, Anhui, and Shandong Provinces in China	• Achieved high early diagnosis rates (70.33–76.55%) and treatment rates (87.89–96.41%) for upper gastrointestinal cancers • Decreased age-standardized gastric cancer mortality rates from 32.1 to 16.5 per 100 000 (2008–2018)
Cancer Screening Programme in Urban China	2012	High-risk individuals aged 45–74 years, identified by questionnaire-based risk assessment or pre-screening rapid test for *H. pylori*	75 cities in 30 provinces, autonomous regions, or municipalities in mainland China	• Completed risk assessments for nearly 4.5 million people and clinical screening for 1 million people • Included 143 000 people undergoing endoscopic screening by 2020, and detected 8953 cases (6.27%) of precancerous lesions and 290 cases (0.20%) of upper gastrointestinal cancers

Source: Adapted from Xia et al. (2023) [54].

Current parameters and procedures of gastric cancer screening programmes

Unlike Japan and the Republic of Korea, which have established nationwide screening for gastric cancer, China's national programmes have primarily targeted high-risk regions, with population selection typically relying on cluster sampling in each region.

Recent guidelines from the National Cancer Center of China recommend a starting age of 45 years and a stopping age of 74 years for gastric cancer screening [56]. Although the CanSPUC and Huai River programmes follow these age recommendations, the UGCED programme empirically targets individuals aged 40–69 years in most areas.

The Technical Plan for Early Diagnosis and Treatment of Cancer, published in 2011 [57], recommends two screening approaches for gastric cancer in China. The first approach, used before 2012, involved preliminary screening using serum pepsinogen testing and questionnaire surveys, followed by endoscopic screening for high-risk individuals aged 40–69 years. The second approach, adopted after 2012, involves direct gastro-endoscopy screening and tissue biopsy for residents aged 40–69 years in selected high-risk areas. The CanSPUC and Huai River programmes also use questionnaire surveys for risk assessments, which incorporated an individual's residential history in high-risk areas, personal history of precancerous lesions, family history, exposure to related risk factors, and *H. pylori* infection status.

Recommendations for screening frequency have evolved over time. According to the Technical Plan published in 2011, individuals with chronic atrophic gastritis, severe intestinal metaplasia, and low-grade intraepithelial neoplasia (LGIN) should be followed up with annual gastro-endoscopy. The Technical Plan for Screening and Early Diagnosis and Treatment of Upper Gastrointestinal Cancer (trial version 2020) [58] suggests that individuals with severe chronic atrophic gastritis, severe intestinal metaplasia, and LGIN identified during endoscopy screenings should have follow-up endoscopy at least once every 3 years. The latest guideline issued by the National Health Commission in 2024 [59] recommends endoscopy every 3 years for patients with atrophic gastritis or intestinal metaplasia that is limited to the gastric antrum or body, and annually if atrophy involves the gastric fundus or the entire stomach. For LGIN, endoscopy is recommended annually, and for high-grade intraepithelial neoplasia it is recommended every 3–6 months.

Assessment of endoscopic screening for gastric cancer: benefits and cost–effectiveness

Gastric cancer screening programmes in China have been demonstrated to be effective in reducing gastric cancer incidence and mortality. A 10-year follow-up study showed that endoscopic screening significantly reduced the incidence of non-cardia invasive

gastric cancer (RR, 0.66; 95% CI, 0.59–0.73) and the mortality from non-cardia gastric cancer (RR, 0.38; 95% CI, 0.33–0.45) and cardia invasive gastric cancer (RR, 0.58; 95% CI, 0.49–0.68) [60]. Another prospective study, in Linqu, also reported significant decreases in the incidence of and mortality from invasive gastric cancer, and it indicated that repeated endoscopy further reduced gastric cancer-specific mortality, with 5-year survival rates of 31.9% in the unscreened group, 73.4% in the group with single screening, and 90.2% in the group with repeated screening [61].

Balancing the costs and benefits of gastric cancer screening is essential to guide future government actions and policy-making. In high-risk areas of China, the incremental cost–effectiveness ratio (ICER) for various upper gastrointestinal cancer screening strategies ranged from US$ 1343 to US$ 3035 per QALY, compared with no screening over a lifetime [62]. A personalized screening strategy has been shown to be cost-effective for high-risk population subgroups [63]. The low uptake rate of upper gastrointestinal cancer screening can substantially reduce the benefits of endoscopic screening [64], and switching to endoscopy with sedation may increase participation [65].

3.7.4 Challenges and future directions

China still faces major challenges in prevention of gastric cancer, which remains one of the major threats to public health. Because *H. pylori* infection is the most established risk factor for gastric cancer, the efficacy and effectiveness of *H. pylori* eradication have been proven for the primary prevention of gastric cancer based on data from large intervention trials in high-risk areas. Secondary prevention for early detection and early diagnosis is widely accepted as the primary focus of current gastric cancer prevention efforts of both the local and central governments in China. Despite the progress that has been made in both primary and secondary prevention of gastric cancer, there are still knowledge gaps and challenges that need to be addressed. These challenges present opportunities for further advancement in these areas.

Primary prevention

Despite the recognized beneficial effect of *H. pylori* treatment for gastric cancer prevention, the implementation of the *H. pylori* screen-and-treat strategy, which focuses on detecting the presence of *H. pylori* infection and subsequently eradicating it when

detected, is mostly limited to certain symptomatic individuals or those with personal health concerns. There has been international interest in using *H. pylori* testing to screen asymptomatic individuals for gastric cancer prevention, but these practices are still relatively infrequent.

Systemic consequences after H. pylori *eradication treatment*

Although *H. pylori* eradication is proven to prevent gastric cancer and may benefit dyspepsia, peptic ulcer disease, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma, the broader health implications remain unclear. Reports from the SIT and the MITS have addressed concerns about *H. pylori* eradication inducing major individual cancers. Further studies are needed to understand its effect on oesophageal adenocarcinoma, Barrett oesophagus, and gastro-oesophageal reflux, although a recent population-based multinational cohort study did not lend support to the possibility of an increased risk of oesophageal adenocarcinoma after *H. pylori* eradication treatment [66]. In addition, potential benefits of *H. pylori* eradication, such as colorectal cancer prevention and improvements in the condition of children with hypochlorhydria, require investigation. *H. pylori* treatment has also been shown to alter gut microbiota and metabolomic profiles, with complex implications. Despite potential benefits, unaddressed concerns about adverse effects hinder the broader application of *H. pylori* eradication treatment, highlighting the need for a balanced approach to consider the unintended consequences of this treatment [67].

Antibiotic resistance

Antibiotic resistance is a burden for health care in China and is a major cause of *H. pylori* eradication failure. A multiregion study in China found high resistance rates to metronidazole (67.2%), clarithromycin (37.5%), levofloxacin (33.5%), rifampicin (14.2%), amoxicillin (6.8%), and tetracycline (3.5%) [68]. Resistance ranged from mono-resistance (34.2%) to sextuple resistance (0.3%) and was influenced by factors such as sex, age, and the presence of peptic ulcer [68]. A recent nationwide survey showed resistance rates of 50.8% to clarithromycin and of 47.2% to levofloxacin, with higher rates in women and people aged 40–60 years [14]. The high resistance rates to metronidazole, clarithromycin, and levofloxacin could be due to the increasing consumption of these antibiotics and cross-resistance to the corresponding antibiotics. In China, macrolides ranked third and quinolones ranked fourth for use of antibiotics

during 2018–2020 [69]. Although there are no definitive data on imidazole use, the long-term use of metronidazole since its introduction to China in the 1960s for treating anaerobic infections may have contributed to the high resistance rates observed today [70]. This extensive use has made metronidazole resistance particularly prevalent in China. Despite these challenges, the MITS reported a 72.9% elimination rate using tetracycline and metronidazole, with a combined resistance rate of 5.3%.

There are notable geographical variations in resistance rates in China. Northern provinces, such as Heilongjiang and Jilin, have high clarithromycin resistance rates (> 77.0%), and southern provinces, such as Hunan, have lower rates (27.8%) [14]. Levofloxacin resistance rates are higher in eastern coastal provinces and lower in southern regions [14]. These regional variations may be linked to differences in socioeconomic conditions, hygiene, availability of health care, and use of antibiotics [14].

Expert consensus and national guidelines on H. pylori *treatment for gastric cancer prevention*

Since 2017, there have been several expert consensus reports on *H. pylori* infection control in China, which generally highlight that the *H. pylori* screen-and-treat strategy is effective in reducing gastric cancer risk by slowing progression of inflammation. Key guidelines and initiatives from 2021–2023 have made recommendations for *H. pylori* screening and population intervention strategies (Table 3.7.3). A consensus report in 2021 introduced a novel family-based *H. pylori* infection control and management strategy [11]. In July 2023, the Chinese Center for Disease Control and Prevention issued a white paper on the prevention and control of *H. pylori* infection in China [71], which emphasizes population intervention strategies as the most effective national approach to reduce the disease burden of *H. pylori* infection and suggests an *H. pylori* screen-and-treat strategy in high-risk areas and a test-and-treat strategy in low-risk areas. The *H. pylori* screen-and-treat strategy involves proactively screening the predominantly healthy general population for *H. pylori* infection, followed by offering eradication treatment to individuals who test positive. In contrast, the test-and-treat approach is more targeted, involving testing individuals for the presence of *H. pylori* based on clinical suspicion or symptoms, and then providing eradication therapy only when *H. pylori* is detected. The white paper also advocates for establishing national

public health insurance funds to support population interventions for *H. pylori* infection as a primary preventive measure against gastric cancer.

Table 3.7.3. Recent expert consensus and national guidelines on *H. pylori* treatment for gastric cancer prevention in China

Year	Guidelines or consensus report [reference]	Lead organization	Key points
2023	White paper on the prevention and control of *H. pylori* infection in China [71]	Institute of Infectious Disease Control and Prevention, Chinese Center for Disease Control and Prevention	Advocates for population intervention strategies, including a screen-and-treat strategy in high-risk areas and a test-and-treat strategy in low-risk areas, with a focus on national public health insurance support and integration into the Healthy China 2030 initiative
2022	Chinese guideline for the screening, early detection, and early treatment of gastric cancer [56]	National Cancer Center	Recommends screening for *H. pylori* infection in high-prevalence areas using the urea breath test as the primary method, supplemented by serum antibody and stool antigen testing
2021	Chinese consensus report on family-based *H. pylori* infection control and management [11]	Changhai Hospital of Naval Medical University	Introduces family-based *H. pylori* infection control to prevent intrafamilial transmission and reduce medical expenses
2019	Consensus report on eradication of *H. pylori* and prevention and control of gastric cancer in China [13]	Changhai Hospital of Naval Medical University	Supports the *H. pylori* eradication strategy for gastric cancer prevention
2017	Consensus report on chronic gastritis in China [78]	Shanghai Institute of Digestive Disease	Highlights the importance of managing chronic gastritis to prevent progression to gastric cancer
2017	Fifth Chinese national consensus report on the management of *H. pylori* infection [79]	Chinese Study Group on *Helicobacter pylori* and Peptic Ulcer, Chinese Society of Gastroenterology	Emphasizes the effectiveness of an *H. pylori* screen-and-treat strategy to reduce gastric cancer risk by slowing progression of inflammation

Advancing precision primary prevention

The development of gastric cancer involves complex interactions between genetic susceptibility, environmental factors, and *H. pylori* infection. Most individuals with *H. pylori* infection do not develop gastric cancer, and even with successful eradication, some individuals develop cancer later [26]. This highlights the need for a targeted test-and-treat approach that focuses on populations at higher risk who may benefit most from early intervention. Cohort studies in high-risk areas of China have identified several risk factors for gastric cancer, such as *H. pylori* infection, poor dietary habits, and

unhealthy lifestyles. However, these findings have not yet been fully integrated into a comprehensive risk prediction framework. A nationwide, multicentre research initiative is needed to standardize information collection and follow-up, provide large-scale data to track the progression of gastric lesions, and identify target populations for primary prevention. Host characteristics, including genetic factors, should be considered to improve risk prediction and the effectiveness of prevention. Genetic factors have shown interactions with environmental factors and influence the efficacy of prevention. Jin et al. developed a polygenic risk score for gastric cancer in more than 21 000 Han Chinese individuals and showed that a healthy lifestyle significantly reduced cancer risk for individuals with high genetic risk [72]. A recent study further demonstrated that *H. pylori* treatment particularly benefited individuals with high genetic risk, suggesting that primary prevention be tailored for more effective outcomes [73].

Family-based H. pylori *infection control*

It is important to clarify whether *H. pylori* eradication, the most important measure for the primary prevention of gastric cancer, would be particularly effective in specific environmentally exposed subgroups [46]. Population-level research in China has demonstrated the effectiveness and efficacy of *H. pylori* eradication in preventing gastric cancer in high-risk areas. Families with shared lifestyles should be studied when defining exposed subgroups for intervention, because family cluster infection and intrafamilial transmission are features of *H. pylori* infection [74]. The novel concept of whole family-based *H. pylori* infection control and management has been reported as being effective and convenient in clinical practice because of better engagement of family members, higher eradication rates, lower reinfection rates, and cost–effectiveness [16, 74]. This approach has been recommended by the Chinese Study Group on *Helicobacter pylori* and Peptic Ulcer of the Chinese Society of Gastroenterology [11].

Secondary prevention

The Chinese government has made substantial efforts to implement nationwide cancer screening. However, endoscopic screening for the entire eligible population in China is unrealistic because of the large population size, lack of trained endoscopists and pathologists, inadequate facilities, socioeconomic disparities, and high costs. Although government-organized gastric cancer screening programmes are free, the current

annual investment of less than US$ 0.1 billion for five cancer screening programmes (for lung cancer, liver cancer, gastric cancer, colorectal cancer, and oesophageal cancer) is insufficient to cover the entire population. In addition, disparities in health-care access and the invasiveness of endoscopic examinations lead to low uptake rates and non-compliance, reducing the effectiveness of these programmes [53]. Efforts are needed to make screening programmes more affordable and accessible to underserved populations and to improve the quality of screening services. Incorporating evidence from well-designed studies for regular updates of screening programmes, including area selection, optimal ages, and screening intervals, is essential. This evidence-based approach will ensure better resource allocation and maximize the social and economic benefits. Currently, national organized gastric cancer screening covers only a fraction of eligible individuals in high-risk areas, with suboptimal early detection rates and substantial disparities in diagnosis and treatment. Opportunistic screening, conducted primarily by primary medical institutions, can complement current population-based programmes in high-risk rural and urban settings. Opportunistic screening is key to align with the goals of the Healthy China 2030 framework, which emphasizes reducing premature mortality from major chronic diseases through enhanced early diagnosis rates. Given the current constraints of insufficient resources and professional capacity, opportunistic screening presents a sustainable way of expanding gastric cancer screening to a wider population in China [75]. This approach, which is already part of the UGCED programme for rural residents, involves recommendations by health-care providers during routine consultations or self-referral by individuals. In 2021, opportunistic screening led to the detection of 56 677 cases of upper gastrointestinal cancer in 2.6 million screened individuals, with a detection rate of 2.2% [53].

The recent funding announcement by the National Health Commission encourages exploring sequential screening strategies for gastric cancer. This involves identifying new biomarkers for gastric mucosal lesion progression and integrating these with existing risk assessments to prioritize screening resources effectively [53, 72, 73, 76]. Translating these findings into practical screening tools, large-scale prospective studies, and cost–effectiveness evaluations is essential.

A comprehensive tiered prevention and control system for gastric cancer

The crucial roles of primary and secondary prevention for gastric cancer necessitate future efforts to establish a tiered prevention framework that is tailored to China's national context and is amenable to broad application. By targeting high-risk populations and subgroups who may benefit most from primary prevention, the framework would be able to delineate individual risk profiles subsequent to primary interventions. For people who would not evidently benefit from primary prevention, a refined secondary prevention strategy, informed by early diagnosis models for gastric cancer, would be provided. To further optimize the key components of the framework, an in-depth health economic evaluation combined with risk prediction and intervention efficacy assessment is needed. The framework is expected to serve as a cornerstone for enhancing government-led precision gastric cancer prevention protocols, informing health policy formulation and rational allocation of health-care resources. Such endeavours would pave the way for a scientifically grounded, advanced approach to gastric cancer prevention, thereby elevating the national response to this public health challenge.

3.7.5 Conclusions

Gastric cancer remains a major public health challenge in China, and *H. pylori* infection is a causal factor. Although *H. pylori* eradication has shown promising results in reducing gastric cancer incidence and mortality, its implementation at the national level should be scientifically devised, efficiently allocating medical resources, and pursued in a phased manner, starting with high-incidence areas before expanding to lower-incidence populations. Establishing national public health insurance funds for *H. pylori* interventions in high-risk areas embodies a governmental tactic to nurture gastric cancer prevention efforts. National cancer screening programmes in China have also been effective in early detection and reducing risks. However, challenges remain in fully implementing cancer prevention strategies nationwide, such as mobilizing investment, enhancing health awareness, boosting participation rates, and ensuring quality to prevent harms and overdiagnosis. Future directions for gastric cancer prevention in China should focus on addressing these knowledge gaps and improving implementation. This may encompass expanding research within the complex interplay of gastric cancer etiology, refining risk prediction models, and harnessing digital health technologies for more personalized and accessible prevention strategies.

China is committed to combating cancer, as outlined in the Healthy China Action – Implementation Plan for Cancer Prevention and Control (2023–2030). This plan, developed under the Healthy China Initiative and the Healthy China 2030 framework, emphasizes multidepartment collaboration, proactive prevention, and innovative cancer control models. Future endeavours encompass controlling cancer risk factors, enhancing prevention services, and improving access to anti-cancer medications, with the aim of reducing cancer incidence and mortality rates and increasing the 5-year cancer survival rate to 46.6% by 2030. Through multicentre and multidisciplinary efforts, China strives to achieve these goals and contribute to the global fight against cancer, ensuring better health outcomes for future generations.

Acknowledgements

The authors thank Zong-Chao Liu, Peking University Cancer Hospital, for his contribution to the preparation of this chapter.

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Chapter 3.8.

Gastric cancer prevention in Japan

Manami Inoue

Summary

- Gastric cancer incidence has drastically decreased in Japan because of reductions in its two major traditional risk factors, *H. pylori* infection and the intake of salt-preserved food.
- The high prevalence of these risk factors in older generations has led to gastric cancer occurring more frequently in patients in older age groups.
- Population-based gastric cancer screening has contributed to the high survival rate of gastric cancer in Japan compared with other countries.
- Given the ongoing transition to new generations with fewer risk factors for gastric cancer, Japan should consider a flexible transformation of its national gastric cancer prevention strategies and shift from a total-population approach to a high-risk population approach.
- Serological testing of anti-*H. pylori* IgG antibody in combination with pepsinogen I and II testing and eradication treatment are good candidates but have yet to be recommended, because the long-term effect of this approach on reducing gastric cancer incidence warrants verification.

3.8.1 Descriptive epidemiological trends

The incidence of gastric cancer in Japan, which was once the highest in the world, has decreased substantially in recent years. According to IARC's estimates for 2022, when ranked by age-standardized rates (world), gastric cancer was the fifth most common cancer type in Japan in terms of both incidence and mortality [1, 2]. In 2022, gastric cancer accounted for 12.6% of all cancer cases and 10.3% of all cancer deaths in

Japan, which is consistent with the global rates of 13.1% of all cancer cases and 6.6% of all cancer deaths.

The long-term trends (Fig. 3.8.1) show that the number of incident cases of gastric cancer in Japan has decreased drastically after a peak in about 2010–2015. In contrast, the number of gastric cancer deaths has remained stable, with a gradual decrease in recent years. The age-standardized rates (world) for both incidence and mortality have decreased constantly over time, with steeper decreases in recent years [1, 2].

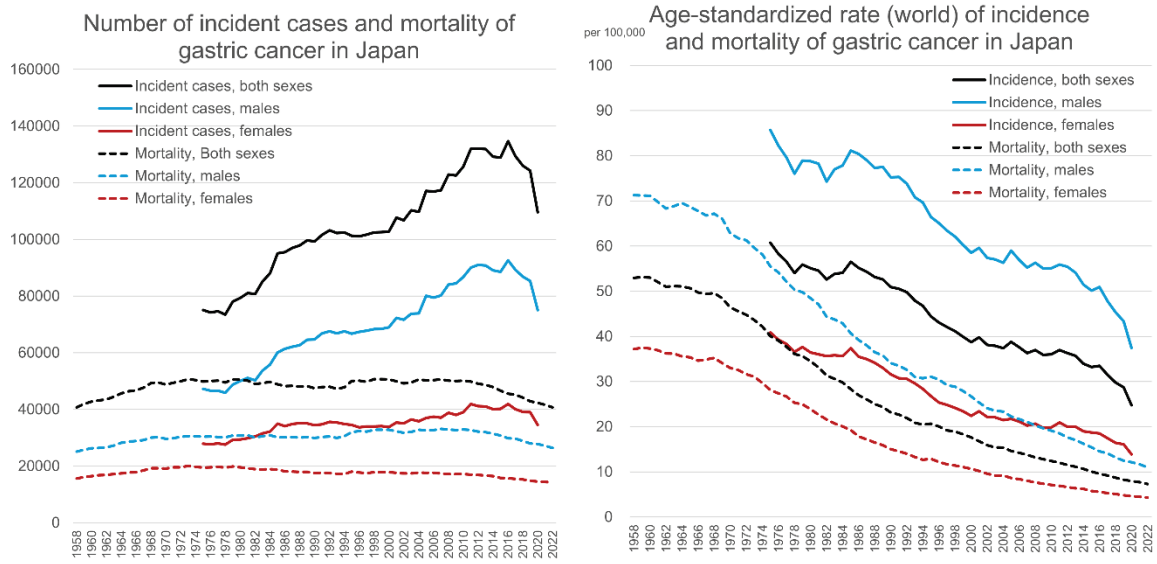

Fig. 3.8.1. Time trends of gastric cancer incidence and mortality in Japan. Compiled from Institute for Cancer Control (2024) [3] (incidence) and from Ministry of Health, Labour and Welfare (2024) [4] (mortality).

By age distribution, gastric cancer incidence and mortality show increases in both the number and the proportion of cases and deaths in people aged ≥ 75 years (Fig. 3.8.2). This is mainly due to the increasing rise in the number of cases and deaths in people aged ≥ 75 years, which indicates that gastric cancer will, in time, become a cancer type that is diagnosed predominantly in older people. Japan has become a “super-ageing society”. In 2007, > 21% of the population were aged ≥ 65 years. This percentage has continued to rise and is contributing in part to the increase in cases of gastric cancer [5].

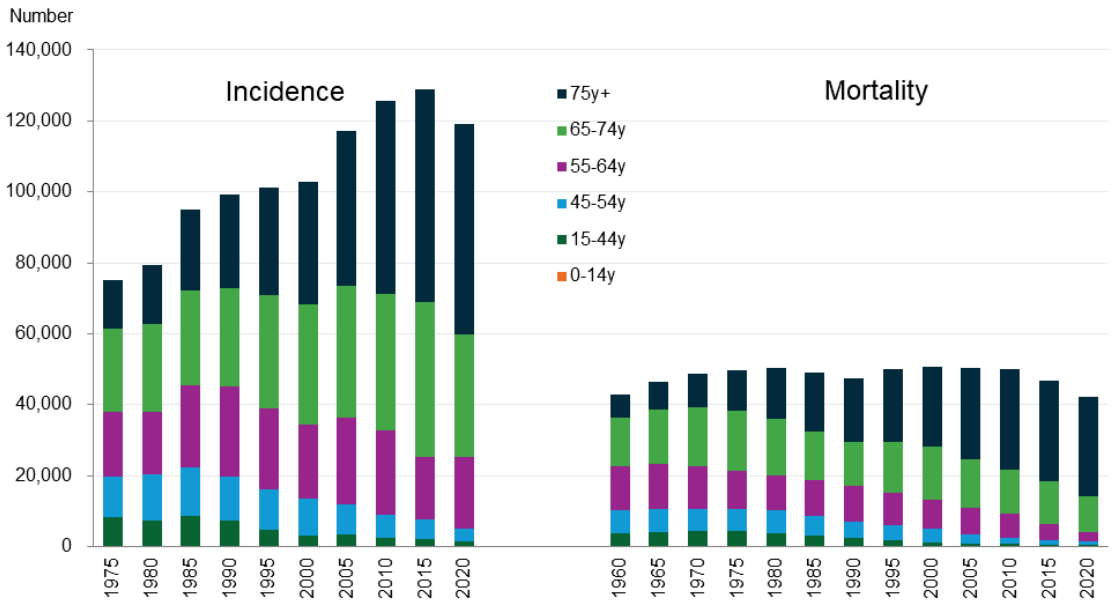

Fig. 3.8.2. Time trends of the number of gastric cancer cases and deaths in Japan in both sexes, by age group. Compiled from Institute for Cancer Control (2024) [3] (incidence) and from Ministry of Health, Labour and Welfare (2024) [4] (mortality).

3.8.2 Clinico-epidemiological features of gastric cancer

Gastric cancer in Japan has two notable characteristics. First, the occurrence is more common in the distal part of the stomach, which is in contrast to countries in North America and northern and western Europe, where occurrence in the proximal part of the stomach is more common. The latest global cancer registry data show that the subsite location in the distal portion has not changed substantially for decades and is substantially attributable to *H. pylori* infection [6].

Second, although the prognosis for gastric cancer is generally poor globally, better survival rates are observed in Japan. The ongoing Global Surveillance of Trends in Cancer Survival (CONCORD) programme has monitored global cancer survival rates for a long time, now involves more than 70 countries, and includes 75% of all cancer cases worldwide, with high representativeness. According to the latest CONCORD-3 report, the 5-year relative survival rate for patients with gastric cancer in 2000–2014 generally ranged from 20% to 40%, versus 60.3% in Japan [7]. This better overall survival in Japan is due to the high proportion of gastric cancers diagnosed at an early stage. In the National Cancer Registry Report 2020 [8], 59% of gastric cancers in Japan were

localized when they were diagnosed, which is relatively high compared with the 31.3% reported by the United States Surveillance, Epidemiology, and End Results (SEER) Program in 2020 [9].

3.8.3 Risk factors and prevention

The incidence of gastric cancer has decreased constantly in Japan (see Section 3.8.1), and the disease has now become a cancer of older people. Therefore, the question arises as to whether this trend is attributable merely to ageing or whether it is a birth cohort effect. However, in either case, *H. pylori* infection and intake of foods preserved by salting have made particular contributions to the history of gastric cancer in Japan.

H. pylori *infection*

H. pylori infection is the most important cause of gastric cancer, particularly non-cardia gastric cancer. *H. pylori* infection is generally acquired during childhood, typically before age 5 years. Therefore, infection status is strongly dependent on hygiene status during childhood, which is dependent mainly on eating behaviours, such as mouth-to-mouth feeding [10]. These factors during infancy greatly determine the infection rate in adulthood.

In Japan, which had the highest incidence rate of gastric cancer in the last century, the *H. pylori* infection rate has decreased with a birth cohort effect [11, 12]. The infection rate peaked at nearly 70–80% for people born in 1930–1940 and decreased with age to nearly 5% for people born in about 2000. Each respective birth cohort shows no marked change in infection rate with increasing age. Estimates in Japanese children and adolescents follow the trend seen in Japanese adults; the prevalence of *H. pylori* infection in children and adolescents was about 10% in individuals born in 1985 but decreased to < 3% in individuals born in 2011 [13] (Fig. 3.8.3).

Thus, gastric cancer prevention strategies must account for generational differences. National-level improvements in hygiene, including improvements in water and sewage systems, and in overall socioeconomic status, which are in turn generally influenced by a history of hygiene and health policy at the national level, will lead to a substantial decline in the overall prevalence of *H. pylori* infection in all age groups, even in countries with a high infection rate [14]. In Japan, *H. pylori* infection will eventually become a rare event, leading to an overall decrease in gastric cancer incidence.

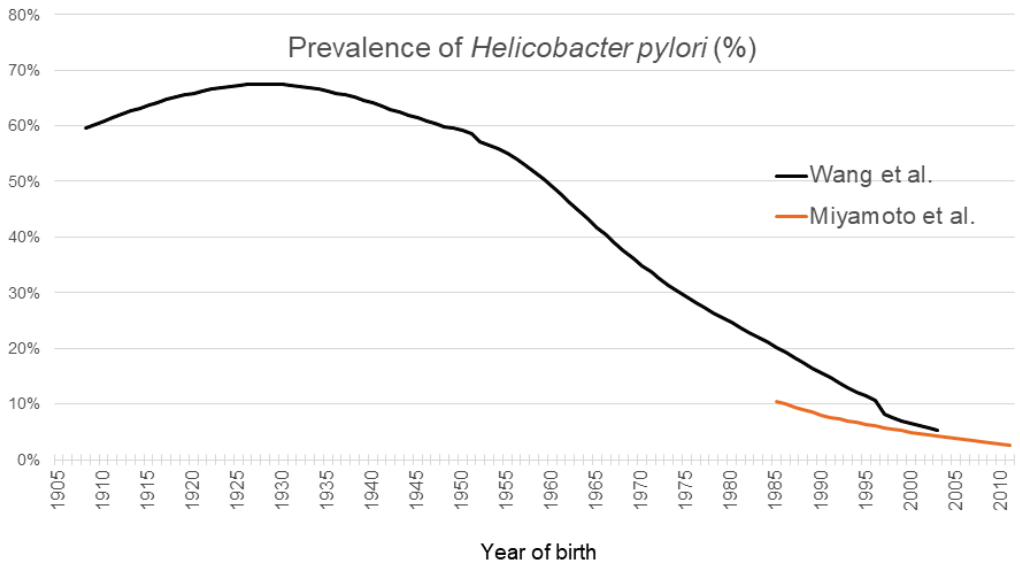

Fig. 3.8.3. Decreasing trend in the prevalence of *H. pylori* infection in Japan by birth year, 1908–2011. Compiled from Wang et al. (2017) [11] and Miyamoto et al. (2019) [13].

Intake of foods preserved by salting

Salt consumption, in general, is known to be linked not only to gastric cancer but also to hypertension and stroke [15]. These diseases are associated with the amount of salt intake and have historically been the major diseases in Japan. A high intake of foods preserved by salting increases the risk of gastric cancer but not the risk of stroke, which tends to be positively associated with the amount of salt intake [16, 17].

Salt reduction means reducing the amount of salt intake and the intake of highly salt-concentrated preserved foods. Salt-preserved foods were more commonly consumed before refrigeration became available [18, 19], and the dissemination of refrigeration has substantially affected the decrease in gastric cancer mortality in Japan. Expanded use of industrial refrigeration in both storage and transportation has led to increased consumption of fresh food and has reduced the need for salting and pickling, which are both positively associated with gastric cancer [18, 19]. Home refrigeration has shifted food preservation techniques from salt preservation to frozen storage [18, 19]. In Japan, the popularization of electric refrigerators in the 1960s was strongly inversely correlated with the decrease in gastric cancer incidence [18].

Japan has also achieved a decrease in salt consumption at the local community level. In the late 1950s, deaths from stroke in Japan were the highest in the world. It became apparent that the number of strokes in different parts of the country was directly related to the amount of salt consumed. The Japanese government initiated a campaign to reduce salt intake, and this eventually decreased over the subsequent decade. A resulting reduction in blood pressure was observed, along with a substantial reduction in stroke mortality [20] and eventually also in gastric cancer incidence and mortality.

3.8.4 Population-based gastric cancer screening

Gastric cancer screening in Japan began with indirect X-ray photography, which had been used in mass screening for pulmonary tuberculosis in the 1950s. The first population-based gastric cancer screening was conducted in Nagano Prefecture and Miyagi Prefecture in the late 1950s and 1960s [21] (Fig. 3.8.4).

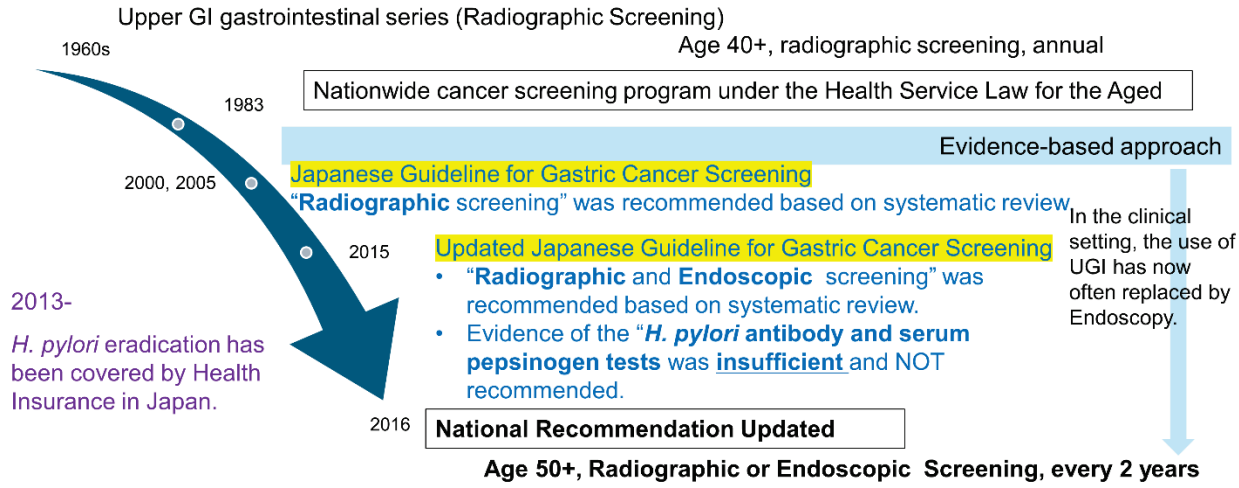

Fig. 3.8.4. Population-based gastric cancer screening in Japan. GI, gastrointestinal; UGI, upper gastrointestinal series. Compiled from Hamashima et al. (2018) [22] and Hamashima (2014) [23].

In the 1960s, in addition to the widespread use of the gastric cancer screening bus, the barium double-contrast method was introduced and was widely used as a gastric cancer screening method, with the establishment of gastric X-ray diagnostics. The number of participants undergoing gastric cancer X-ray screening increased steadily, partly as a result of the start of government subsidies in 1966. The project evolved into a

nationwide gastric cancer screening programme in 1983, under the Health Service Law for the Aged, and later was included in health promotion activities organized by municipalities, under the Health Promotion Act in 2008. The number of people undergoing gastric cancer X-ray screening continued to increase steadily. However, this increase started to slow down in about 1998, when gastric cancer screening was removed from the Geriatric Health Service and was moved to be part of the general financial responsibility of each municipality [21, 24].

The introduction of double-contrast radiography into gastric cancer screening made it possible to detect early gastric cancer. This technique continued to evolve, with improving diagnostic accuracy. In the Japanese Guidelines for Gastric Cancer Screening in 2005, it was reported to be the only screening modality to have reduced gastric cancer mortality [25]. By the late 1990s, radiography was gradually being replaced by endoscopy as the primary modality in the clinical setting.

Initially, the use of endoscopy in population-based screening for gastric cancer was not recommended because of a lack of evidence for effectiveness in reducing mortality [25]. However, after studies in Japan and the Republic of Korea, which provided evidence that gastroscopy screening effectively reduces mortality, the 2014 edition of the Japanese Guidelines for Gastric Cancer Screening [26] recommended endoscopy for both organized and opportunistic screening. This latest guideline recommends biennial endoscopic screening in individuals aged ≥ 50 years [22]. Each municipality is responsible for implementing its own population-based gastric cancer screening programme.

Even with the increasing proportion of municipalities adopting endoscopic screening, various issues have hindered implementation, including insufficient endoscopists, insufficient endoscopy processing capabilities, insufficient quality control systems, and budget constraints [27]. Further efforts are required to ensure the nationwide adoption of endoscopic gastric cancer screening, improve participation rates, and optimize diagnostic accuracy control.

3.8.5 Risk stratification approach

In Japan, groups at high risk of gastric cancer are commonly stratified by serological testing of anti-*H. pylori* immunoglobulin G (IgG) antibody (HP) in combination with pepsinogen I and II testing (PG) [28]. This method has attracted attention as a risk stratification tool, and its use has become more widespread in recent years, after national health insurance coverage in Japan was expanded in 2013 to include *H. pylori* eradication treatment for chronic gastritis. The approach stratifies Japanese people into four groups: (A) HP-negative and PG-negative, (B) HP-positive and PG-negative, (C) HP-positive and PG-positive, and (D) HP-negative and PG-positive. Compared with group A, the long-term risk of gastric cancer is highest in group D, followed by group C and group B [29].

Given the current variation in the prevalence of *H. pylori* infection by birth year (high in older age groups and low in younger age groups) and the efforts to address the inadequate endoscopy processing capacity in gastric cancer screening in Japan, it is worthwhile to considering a risk stratification approach by *H. pylori* infection status, in which screening is omitted or is conducted at longer intervals in individuals who have never had *H. pylori* infection. However, evidence for the effectiveness of this risk stratification method combined with endoscopy in the setting of population-based screening remains insufficient, and it is yet to be recommended.

3.8.6 *H. pylori* eradication for gastric cancer prevention

Eradication of *H. pylori* has drawn attention as a strategy to minimize gastric cancer risk. Since 2013, when eradication therapy for *H. pylori*-associated gastritis was included in national health insurance coverage (Box 3.8.1), a relatively large number of individuals with *H. pylori* infection have received this treatment, i.e. about 1.4–1.6 million people annually [30]. A recent systematic review and meta-analysis of published studies in Japan showed that eradication effectively prevents gastric cancer in the Japanese population irrespective of symptoms [33]. However, because of insufficient evidence on long-term effects after eradication, well-designed, extensive cohort studies are warranted to determine the long-term efficacy and safety of *H. pylori* eradication in reducing gastric cancer incidence at the population level [33].

The development of antimicrobial resistance and treatment failure fuel the global burden of *H. pylori*-associated gastric complications [34]. Antimicrobial susceptibility testing can improve the success rate of eradication treatment and avoid the spread of resistant bacteria due to inappropriate antibiotic use, and it has been included in the *H. pylori* diagnosis treatment guideline in Japan.

Box 3.8.1. History of health insurance coverage for *H. pylori* eradication therapy

In November 2000, based on the results of various clinical studies, *H. pylori* eradication therapy was approved in Japan for treating *H. pylori*-positive gastric and duodenal ulcers. This was the first time that eradication therapy was approved under Japan's public medical insurance system.

At about this time, it became clear that most gastric cancers are caused by *H. pylori* infection, and it was time for a substantial review of the *H. pylori* control measures. Since 2002, in Japan, measures to prevent liver cancer had focused on addressing hepatitis virus infections, resulting in a significant decrease in liver cancer mortality. However, the annual number of gastric cancer deaths had remained at about 50 000 for the past several decades, without substantial increases or decreases, suggesting that current prevention measures were inadequate. It was considered that primary prevention through *H. pylori* eradication therapy, as well as secondary prevention, should be promoted as a fundamental preventive method for gastric cancer.

In 2009, the Ministry of Health, Labour and Welfare approved the expansion of national health insurance coverage for *H. pylori* eradication therapy and added three new indications – gastric mucosa-associated lymphoid tissue (MALT) lymphoma, post-endoscopy treatment for early-stage gastric cancer, and idiopathic thrombocytopenic purpura – in addition to gastric and duodenal ulcers.

This was the first time in the world that *H. pylori* eradication therapy was covered by health insurance for indications other than gastric and duodenal ulcers. The Japanese Society of Gastroenterology, the Japanese Society for Gastrointestinal Endoscopy, and the *Helicobacter* Society of Japan jointly submitted a request to the Ministry of Health, Labour and Welfare to expand the insurance coverage of *H. pylori* eradication therapy for chronic gastritis. As a result, *H. pylori* eradication therapy for

patients with chronic gastritis became available on 21 February 2013.

After the insurance coverage had been extended, prescriptions for *H. pylori* eradication therapy were 5 times the previous numbers, with an estimated 1.5 million people being treated per year [30–32].

3.8.7 Conclusions and future directions

Gastric cancer incidence has drastically decreased in Japan because of reductions in its two major traditional risk factors, *H. pylori* infection and the intake of salt-preserved food. The high prevalence of these risk factors in older generations has led to gastric cancer occurring more frequently in patients in older age groups. Population-based gastric cancer screening has contributed to the high survival rate of gastric cancer in Japan compared with other countries. Given the ongoing transition to new generations with fewer risk factors for gastric cancer, Japan should consider a flexible transformation of its national gastric cancer prevention strategies and shift from a total-population approach to a high-risk population approach. Serological testing of anti-*H. pylori* IgG antibody in combination with pepsinogen I and II testing and eradication treatment are good candidates but have yet to be recommended, because the long-term effect of this approach on reducing gastric cancer incidence warrants verification.

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Chapter 3.9.

Gastric cancer prevention in the Republic of Korea

Il Ju Choi

Summary

- Gastric cancer had been the most commonly occurring cancer type in the Republic of Korea for a long time, but in 2021 it became the fourth most common cancer type, after a steady decrease in incidence since 2011.
- Since 2001, the nationwide gastric cancer screening programme in the Republic of Korea recommends screening with a 2-year interval for adults aged ≥ 40 years using mainly upper endoscopy. The screening programme, with upper endoscopy as the main modality, has been shown to reduce gastric cancer mortality.
- In randomized controlled trials conducted in the Republic of Korea, *H. pylori* treatment in high-risk groups (patients who underwent endoscopic resection for early gastric cancer or family members of patients with gastric cancer) reduced gastric cancer risk by 50%.
- A large-scale clinical trial (HELPER), currently under way in the Republic of Korea in collaboration with IARC, is investigating the efficacy of *H. pylori* eradication as a primary prevention strategy in the general population.

3.9.1 Gastric cancer statistics

In the Republic of Korea, cancer has been the leading cause of death since 1982 [1]. In 1996, the National Plan for Cancer Control was initiated to address this public health problem, and the fourth stage of the plan was initiated in 2021. The Korean Central Cancer Registry reports national cancer statistics annually, with a 2-year lag time. According to the 2021 statistics, published at the end of 2023, the age-standardized rate, standardized to the Korean 2020 standard population, showed that gastric cancer was the most frequently diagnosed cancer until 2018. In 2021, gastric cancer ranked as the

fourth most common cancer type, after thyroid cancer, colorectal cancer, and lung cancer (Fig. 3.9.1) [2]. In 2000–2011, the gastric cancer incidence rate (per 100 000 population) remained stable at > 80; since then, it has gradually decreased, by 4.4% each year, from 84.8 in 2011 to 55.3 (76.3 for men and 38.2 for women) in 2021. Compared with other parts of the world, the age-standardized rate of gastric cancer, adjusted using the Segi world standard population, was 27.5 per 100 000 person-years (38.9 per 100 000 person-years for men and 17.5 per 100 000 person-years for women) in 2021 [1].

The gastric cancer screening rate decreased during the COVID-19 pandemic in 2020, but it surged in 2021, which explains the rebound in gastric cancer incidence in the national cancer statistics [3, 4]. From the cancer incidence data up to 2021, gastric cancer is expected to be ranked the fifth most common cancer type in the Republic of Korea, because of the increasing incidence of breast cancer [5].

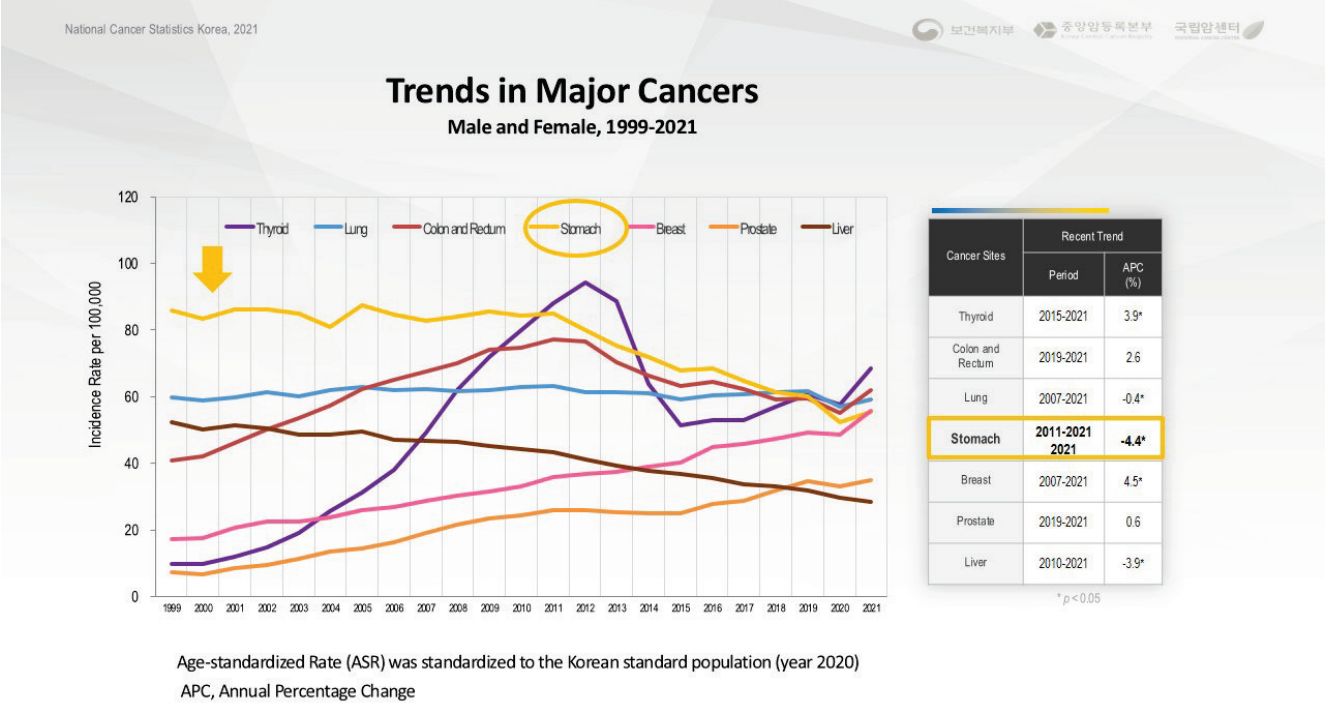

Fig. 3.9.1. Trends in the age-standardized incidence rates of the major cancer types in the Republic of Korea. Gastric cancer incidence rates were stable until about 2011. Since then, the incidence rate has decreased, and gastric cancer became the fourth most common cancer type in 2021. APC, annual percentage change. Compiled from Korean Statistical Information Service (2024) [2].

3.9.2 Gastric cancer stage distributions and mortality rates

The gastric cancer stage distribution in the Republic of Korea in 2019, according to the stage categories of the United States Surveillance, Epidemiology, and End Results (SEER) Program, was 64.3% for localized, 10.9% for regional, and 10.9% for distant stages. The prognosis worsened with increasing stage, with 5-year relative survival rates of 97.0% for localized, 62.1% for regional, and 6.4% for distant stages [6].

In 2021, the crude gastric cancer mortality rate (per 1000 000 population) was 14.1 (18.6 for men and 9.6 for women), and the age-standardized mortality rate was 5.9 (8.9 for men and 3.5 for women) [1]. The 5-year overall survival rate for patients with gastric cancer increased markedly, from 55.7% in 1999–2005 to 77.0% in 2013–2019 [7].

3.9.3 Introduction of the KNCSP for secondary prevention

In 1996, the Government of the Republic of Korea initiated a comprehensive 10-year cancer control plan. In 1999, the Korean National Cancer Screening Program (KNCSP) was launched to provide free-of-charge screening for gastric cancer, breast cancer, and cervical cancer via medical aid beneficiaries. In 2001, formal consensus guidelines for screening were developed for gastric cancer, liver cancer, colorectal cancer, breast cancer, and cervical cancer [8]. For gastric cancer, screening with a 2-year interval for adults aged ≥ 40 years is recommended using upper endoscopy or radiological evaluation (upper gastrointestinal series [UGIS]). The screening modality was chosen based on the participants' preferences and comorbidities [9]. Initially, most participants chose UGIS (74.7% in 2002); the proportion of endoscopy examinations gradually increased, to 70.8% in 2011 [10]. In 2015, the guidelines for gastric cancer screening were revised to place the upper age limit at 74 years and to recommend endoscopy over UGIS [11].

3.9.4 Gastric cancer screening rates

The lifetime screening rates for gastric cancer increased markedly, from 52.0% in 2004 to 76.7% in 2010 and 85.5% in 2018 [12]. The screening rates according to the guideline recommendations were lower than the lifetime screening rates: 39.2% in 2004, 65.1% in 2010, and 72.8% in 2018.

Data from the Korean National Cancer Screening Survey show that the organized screening rate for gastric cancer increased from 38.2% in 2009 to 70.8% in 2022,

whereas the opportunistic screening rate for gastric cancer decreased from 18.8% in 2009 to 4.5% in 2022 [13]. The increasing rate for organized screening can be explained by the very low out-of-pocket cost, because participants need to pay either 0% or 10% of total screening costs, according to their income levels. Therefore, the recent high participation rates for the organized screening programme have almost eliminated socioeconomic inequalities for gastric cancer screening in the Republic of Korea.

3.9.5 Effectiveness of the KNCSP in reducing gastric cancer mortality

The most important parameter for the effectiveness of gastric cancer screening is a reduction in mortality. A nested case–control study was performed using the KNCSP database and including the target population eligible for the screening programmes in 2002 and 2003 [14]. The study involved 54 418 patients with gastric cancer who died in 2004–2012 and living matched controls at a 1:4 ratio. Gastric cancer mortality decreased by 21% (odds ratio [OR], 0.79; 95% confidence interval [CI], 0.77–0.81) in the population who participated in screening compared with people who had never been screened. Gastric cancer mortality decreased by 47% among patients who underwent screening with endoscopy (OR, 0.53; 95% CI, 0.51–0.56). In contrast, no significant reduction in gastric cancer mortality was observed in individuals who underwent screening with UGIS (OR, 0.98; 95% CI, 0.95–1.01). The reduction in gastric cancer mortality increased as the number of endoscopy screenings per individual increased (OR for 1 screening, 0.60; 95% CI, 0.57–0.63; OR for 2 screenings, 0.32; 95% CI, 0.28–0.37; OR for ≥ 3 screenings, 0.19; 95% CI, 0.14–0.26). A significant reduction in gastric cancer mortality via endoscopy screening was observed in all the 5-year age groups in people aged 40–75 years but not in those aged ≥ 75 years [14].

Another cohort study of participants from four geographical areas in the Republic of Korea reported a 42% reduction in gastric cancer mortality among participants who underwent screening with endoscopy (hazard ratio [HR], 0.58; 95% CI, 0.36–0.94) compared with unscreened participants. Screening with UGIS did not significantly reduce gastric cancer mortality (HR, 0.91; 95% CI, 0.36–2.33) [15].

A nationwide population-based study using the Korean National Health Insurance Big Database included all patients with gastric cancer aged ≥ 40 years between 2004 and 2013. Patients with gastric cancer who participated in the gastric cancer screening programme (n = 116 775) showed a significantly better prognosis (41% decreased HR

for gastric cancer death) compared with those who did not participate in screening (non-screening group, $n = 74\,927$). In addition, medical care expenses were significantly lower in the screening group [16].

3.9.6 Gastric cancer stage migration

Stage migration of gastric cancer to earlier stages is a favourable outcome of the KNCSP. In a cohort consisting of 19 168 patients with gastric cancer, those who underwent endoscopy screening were significantly more likely to be diagnosed with a localized SEER cancer stage compared with those who were screened with UGIS (adjusted OR, 1.71; 95% CI, 1.55–1.89) or those who were not screened (adjusted OR, 2.10; 95% CI, 1.90–2.33) [17]. Another cohort study, including 18 414 individuals, evaluated the effects of repeated endoscopy screening on the early detection of gastric cancer [18]. The group of participants who underwent endoscopy screening within 2 years had a significantly higher proportion of early gastric cancer (96% vs 71%; $P = 0.01$) and were more frequently treated with endoscopic resection (54% vs 23%; $P = 0.007$) compared with those who did not undergo endoscopy screening within 2 years. The Korean Gastric Cancer Association reported nationwide survey data showing that the proportion of patients with early gastric cancer who had surgical treatment increased from 28.6% in 1995 to 63.6% in 2019 [19].

Data from the National Cancer Center showed that the proportion of early gastric cancer in surgically treated patients in the Republic of Korea increased from 39% in 2001 to 73% in 2016, whereas the proportion of early gastric cancer in the United States SEER data was almost stable at 23–26% from 2004 to 2016 [20].

3.9.7 Safety of gastric cancer screening and its effect on oesophageal cancer mortality

Endoscopy is a relatively safe procedure, but it sometimes leads to complications, such as bleeding or perforation. In a nationwide survey of about 2.1 million diagnostic endoscopies at 50 hospitals in 2013–2017, the incidence of bleeding was 0.012% and the incidence of perforation was 0.001% [21]. In addition, health insurance claims data in 2017 showed that in diagnostic upper endoscopies in outpatient departments the rate of bleeding was 0.028% and the rate of perforation was 0.003% [21]. The KNCSP for

gastric cancer, which uses endoscopy, is associated with fewer adverse events, and these are tolerated given the benefits of screening.

Oesophageal cancer usually has a poor prognosis, because of its rapid growth and early metastasis. It can be detected during gastric cancer screening using endoscopy or UGIS. A population-based cohort study using the KNCSP database included 16 969 patients diagnosed with oesophageal cancer in 2007–2014 [22]. Oesophageal cancer mortality decreased significantly, by 50%, in participants who were screened with endoscopy (adjusted HR, 0.50; 95% CI, 0.46–0.53). In contrast to findings for gastric cancer, screening with UGIS effectively reduced oesophageal cancer mortality (HR, 0.78, 95% CI, 0.75–0.84) [22].

3.9.8 *H. pylori* infection rates

H. pylori infection is the most important and easily modifiable risk factor for the development of gastric cancer. In 2016–2017, the seroprevalence of *H. pylori* infection in the asymptomatic Korean population aged > 18 years was 43.9% [23]. Over the past two decades, the *H. pylori* infection rate has decreased, from 66.9% in 1998 to 59.6% in 2005 and 54.4% in 2011. From 1998 to 2016–2017, *H. pylori* seroprevalence decreased in all age groups; the decrease was largest in the age group 30–39 years (from 74% to 29%) and smallest in the age group ≥ 70 years (from 67% to 52%) (Fig. 3.9.2) [23]. The proportion of patients with a history of *H. pylori* eradication increased, from 13.9% in 2005 to 19.3% in 2011 and 23.5% in 2017. The decrease in *H. pylori* seroprevalence and the increase in history of *H. pylori* eradication are expected to affect the incidence of gastric cancer in the Republic of Korea [23].

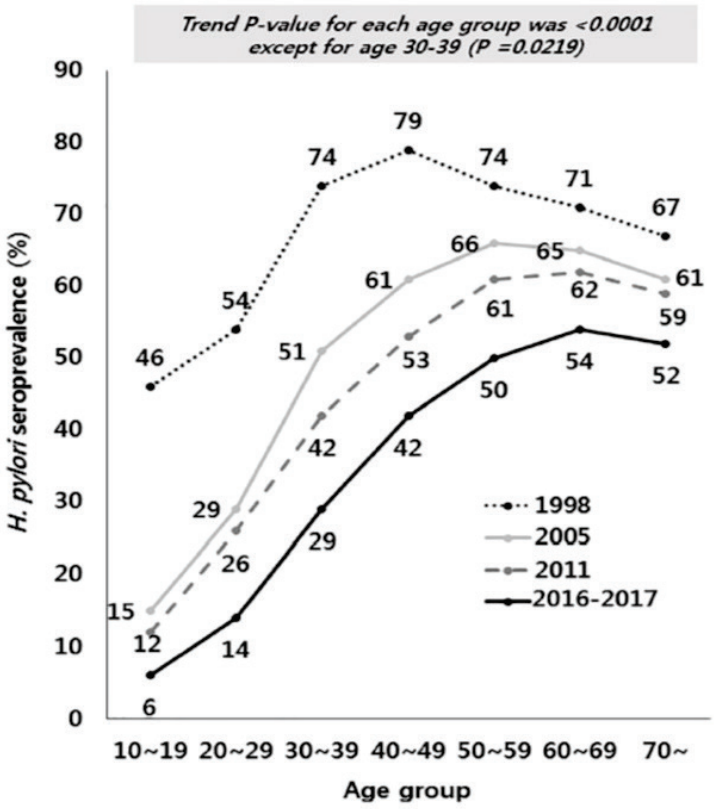

Fig. 3.9.2. Trends in the seroprevalence of *H. pylori* infection in asymptomatic individuals without a history of *H. pylori* eradication therapy, stratified by age group, in 1998, 2005, 2011, and 2016–2017. Adapted from Lim et al. (2018) [23]. © 2018 Lim et al. Article available under the Creative Commons CC BY 4.0.

3.9.9 *H. pylori* treatment trial for prevention of metachronous gastric cancer

The primary prevention strategy of eradicating *H. pylori* infection has not been incorporated into the KNCSP. However, the *Helicobacter pylori* Eradication for Gastric Cancer Prevention in the General Population (HELPER) trial, a large-scale clinical trial (see Section 3.9.11), is currently investigating this strategy in the general population in the Republic of Korea. This is because a primary prevention trial should be performed in a large-scale, long-term follow-up study. A study in a high-risk group can make a clinical trial feasible by reducing the size of the study population needed, reducing the follow-up duration required, and improving the compliance of the study participants.

The first such study was performed in a group at very high risk who underwent endoscopic resection for early gastric cancer, to show that eradicating *H. pylori* infection

could reduce the risk of the development of new gastric cancer (i.e. metachronous gastric cancer) [24]. A total of 396 patients were included in the study from 2003 to 2013. During the 13 years (median, 5.9 years) of follow-up, metachronous gastric cancer developed in 7.2% (14 of 194) of participants in the treatment group and in 13.4% (27 of 202) of participants in the placebo group (HR in the treatment group, 0.5; $P = 0.03$) (Fig. 3.9.3A) [24]. In the analysis according to the *H. pylori* eradication status after treatment, metachronous gastric cancer developed in 14.0% (32 of 228) of the patients with persistent *H. pylori* infection and in 5.4% (9 of 167) of the patients in whom *H. pylori* infection had been eradicated (HR in patients with eradicated infection, 0.32; $P = 0.002$).

The study also showed that improvement in the grade of atrophy in the gastric body was more frequent in the treatment group than in the placebo group (48.4% vs 15.0%; $P < 0.001$). In addition, improvement in the grade of intestinal metaplasia in the gastric body was more frequent in the treatment group than in the placebo group (36.6% vs 18.3%; $P < 0.001$) [24].

3.9.10 *H. pylori* treatment trial in first-degree family members of patients with gastric cancer

The second study in a high-risk group included first-degree relatives of patients with gastric cancer, who had an almost 3-fold increased risk of gastric cancer (OR, 2.92; 95% CI, 2.402–3.552) [26]. A total of 1838 participants with *H. pylori* infection were enrolled in this study in 2004–2011 [25]. During the 14 years (median, 9.2 years) of follow-up, gastric cancer developed in 1.2% (10 of 832) of participants in the treatment group and in 2.7% (23 of 844) of participants in the placebo group (HR in the treatment group, 0.45; $P = 0.03$) (Fig. 3.9.3B). In the analysis according to the *H. pylori* eradication status after treatment, gastric cancer developed in 2.9% (28 of 979) of the patients with persistent *H. pylori* infection and in 0.8% (5 of 608) of the patients in whom *H. pylori* infection had been eradicated (HR in patients with eradication of infection, 0.27; 95% CI, 0.10–0.70) [25].

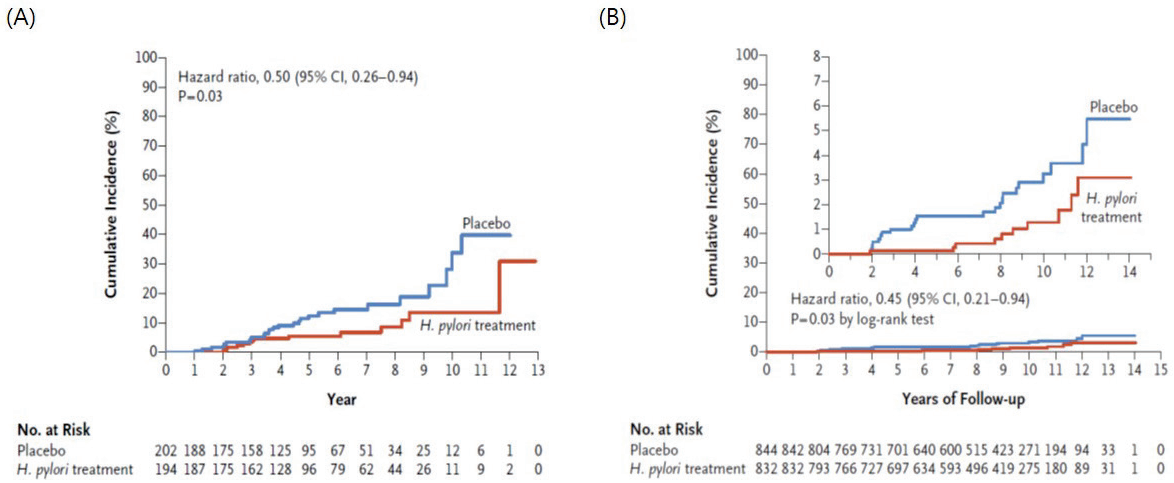

Fig. 3.9.3. Cumulative incidence of gastric cancer after treatment for *H. pylori* infection. (A) Kaplan–Meier curves for the cumulative incidence of metachronous gastric cancer starting 1 year after endoscopic resection of gastric cancer. During a median follow-up of 5.9 years, metachronous gastric cancer developed in 7.2% (14 of 194) of participants in the treatment group and in 13.4% (27 of 202) of participants in the placebo group. (B) Kaplan–Meier curves for the primary outcome of development of gastric cancer. During a median follow-up of 9.2 years, gastric cancer developed in 1.2% (10 of 832) of participants in the treatment group and in 2.7% (23 of 844) participants in the placebo group. The inset shows the same data on an enlarged *y* axis. (A) Reprinted from Choi et al. (2018) [24]. Copyright © 2024 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. (B) Reprinted from Choi et al. (2020) [25]. Copyright © 2024 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

H. pylori treatment with triple therapy of a proton pump inhibitor, clarithromycin, and amoxicillin, which has shown an eradication rate of about 70%, could reduce the risk of gastric cancer by 55% in family members of patients with gastric cancer in the absence of further rescue therapy. In the secondary outcome analysis, patients with confirmed eradication of *H. pylori* infection had a 73% lower risk of gastric cancer compared with those with persistent *H. pylori* infection [25]. Therefore, tests for successful *H. pylori* eradication should be performed to increase the effectiveness of gastric cancer prevention.

3.9.11 HELPER trial in the general population

In collaboration with IARC, a large population-based trial (the HELPER study) was initiated in 2014 to evaluate whether *H. pylori* treatment can reduce the risk of gastric

cancer in the asymptomatic general population in the Republic of Korea (ClinicalTrials.gov ID, NCT02112214). The study had screened *H. pylori* infection status in > 12 000 Korean individuals at average risk who had participated in the KNCSP until 2019. Individuals with *H. pylori* infection were randomized to receive either bismuth quadruple therapy for *H. pylori* eradication or placebo. The participants will undergo biennial endoscopy through the KNCSP for 10 years, and an interim analysis is planned after a 6-year follow-up period if two thirds of the expected target number of gastric cancers have developed by that time point. As of December 2024, about 35 cases of gastric cancer (> 60% of the target number) had been reported. The primary outcome of the trial is the incidence of gastric cancer in the treatment and placebo groups. The study will provide high-quality evidence on the *H. pylori* eradication strategy for gastric cancer prevention in the average-risk population in the Republic of Korea; the KNCSP will be modified according to the results of the trial.

3.9.12 Criteria for *H. pylori* treatment in the KNHIS

In 2024, *H. pylori* treatment was permitted by the Korean National Health Insurance Service (KNHIS) for patients with the following indications: (i) peptic ulcer disease (benign gastric ulcer and duodenal ulcer), (ii) low-grade mucosa-associated lymphoid tissue (MALT) lymphoma, (iii) post-treatment (endoscopic resection or surgical resection) status of early gastric cancer, (iv) idiopathic thrombocytopenic purpura, and (v) post-endoscopic resection status of gastric adenoma. *H. pylori* treatment for patients with post-treatment status has been included since 2018 based on the results of a randomized controlled trial of patients with early gastric cancer who underwent endoscopic resection [24]. The KNHIS does not yet cover *H. pylori* treatment for first-degree relatives of patients with gastric cancer or for healthy asymptomatic individuals with atrophic gastritis; however, *H. pylori* treatment can be prescribed if patients pay all the costs for the treatment. The indications for *H. pylori* treatment covered by the KNHIS are expected to expand based on the results of the HELPER study.

3.9.13 Trial of low-dose aspirin for prevention of metachronous gastric cancer

Aspirin is a promising chemopreventive drug for gastrointestinal tract cancers, particularly colorectal cancer. A meta-analysis reported that long-term aspirin use was associated with a reduced risk of gastrointestinal cancers, including gastric cancer [27]. The National Cancer Center started a randomized clinical trial to show that daily use of

low-dose (100 mg) aspirin for 5 years can reduce the risk of new gastric cancer in patients with early gastric cancer after endoscopic resection (ClinicalTrials.gov ID, NCT04214990). About 1700 participants will be recruited by 2025, and participants will be followed up until 2030.

3.9.14 Assessment of gastric cancer risk by evaluation of atrophy

Atrophic gastritis is the main risk factor for the development of gastric cancer. An objective and accurate assessment of the severity of gastric atrophy is essential for proper risk stratification. The most common methods include endoscopic evaluation, serological tests for pepsinogen I and II levels, and histological assessment.

Endoscopic assessment using the Kimura–Takemoto classification is a non-invasive method for evaluating gastric atrophy [28]. Interobserver variation for this assessment is high, especially among inexperienced endoscopists, and agreement rates can improve after training [29].

The pepsinogen test is a serological test. A serum pepsinogen I level of < 70 mg/mL and a serum pepsinogen I/II ratio of < 3 are accepted criteria for severe gastric glandular atrophy. This method is objective and non-invasive, but the absence of reference value standardization among commercially available test kits is a major limitation. Test results are usually affected by *H. pylori* status, age, sex, smoking, alcohol consumption, dietary habits, hormone levels, and use of medication [30, 31].

The updated Sydney system suggests using a visual analogue scale for biopsy specimens obtained from the antrum including the gastric angle and from the corpus for the histological assessment of atrophy or intestinal metaplasia [32]. Although histological assessment can be considered the reference standard for evaluation of gastric atrophy, interobserver agreement was low among gastrointestinal pathologists in the Republic of Korea, especially for atrophy (kappa value, 0.19 for atrophy; 0.52 for intestinal metaplasia) [33]. Interobserver variability can be reduced by consensus among pathologists and education.

The Operative Link on Gastritis Assessment (OLGA) and the Operative Link on Gastric Intestinal Metaplasia Assessment (OLGIM) have been suggested to estimate the risk of gastric cancer development using histological data from the updated Sydney system [34, 35]. In Korean patients with gastric cancer, high-risk stages (OLGA or

OLGIM stages III and IV) were associated with risk of intestinal-type gastric cancer but not with risk of diffuse-type gastric cancer [36]. In the general population in the Republic of Korea, the proportion of high-risk OLGA stages was 6.9% for ages < 40 years but increased gradually, to 23.0% for ages 40–49 years, 29.1% for ages 50–59 years, and 41.1% for ages 60–69 years [37]. A study in Italy with 1755 participants showed that OLGA stages III and IV could reliably predict gastric cancer development [38]. Therefore, a long-term prospective study in the Republic of Korea is urgently needed to evaluate the usefulness of the OLGA and OLGIM systems. The most accurate and cost-effective of the three methods for assessment of atrophy (endoscopic, serological, and histological) should be determined to effectively select high-risk groups from the general population in the Republic of Korea.

3.9.15 Future directions

H. pylori infection and gastric atrophy are two major factors to consider in the risk stratification of gastric cancer. In the Republic of Korea, most patients with gastric cancer have current or past *H. pylori* infection. However, the prevalence of *H. pylori* infection in the younger age group has continuously decreased. The current KNCSP for gastric cancer recommends endoscopy screening with a 2-year interval without risk stratification for adults aged ≥ 40 years. This policy may result in overutilization of medical resources, a high socioeconomic burden, or problems associated with overdiagnosis.

The following areas of research are urgently needed to modify the KNCSP by introducing the primary prevention strategy of *H. pylori* eradication into the current secondary prevention strategy. First, the effect of *H. pylori* eradication on gastric cancer incidence and mortality rates should be properly evaluated in high-quality clinical trials involving the general population. Second, proper estimation of the association of atrophy or intestinal metaplasia with risk of gastric cancer after *H. pylori* eradication should be performed. Third, the differential effects of *H. pylori* infection and gastric atrophy according to the histological type of gastric cancer should be determined, because intestinal-type and diffuse-type gastric cancers have different clinicopathological characteristics. Fourth, early-onset gastric cancer (i.e. at ages < 40 years) was also associated with *H. pylori* infection. The most appropriate age for screening and treatment of *H. pylori* infection needs to be determined.

In the Republic of Korea, the effects of endoscopy in gastric cancer screening programmes to reduce gastric cancer mortality have been well established. Further improvement of this secondary screening strategy by introducing surveillance based on gastric cancer risk factors, such as *H. pylori* infection and gastric atrophy, is required. The ongoing large prospective trial in the National Cancer Center, in collaboration with the HELPER trial and a prospective cohort study with well-defined endoscopic, histological, and serological data, will provide answers to many of these critical questions.

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Chapter 3.10.

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

Yi-Chia Lee

Summary

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

3.10.1 Gastric cancer epidemiology in the Matsu Islands

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

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

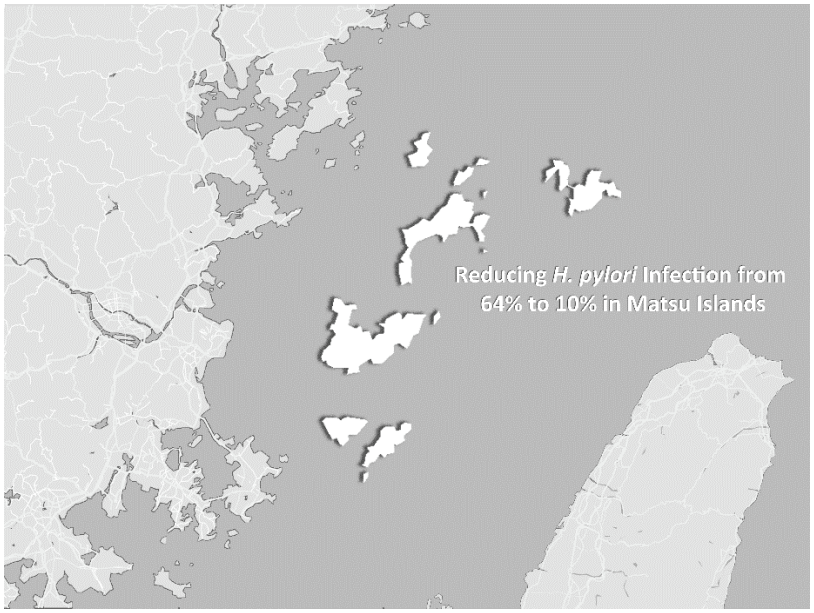

Fig. 3.10.1. Geographical location of the Matsu Islands. The Matsu Islands are located in the East China Sea and are composed of dozens of islands, including Nangan, Beigan, Juguang, and Dongyin. Note that nearby Fujian Province was also an area with prevalent *H. pylori* infection and a high incidence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

3.10.2 Design of the gastric cancer prevention programme

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

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

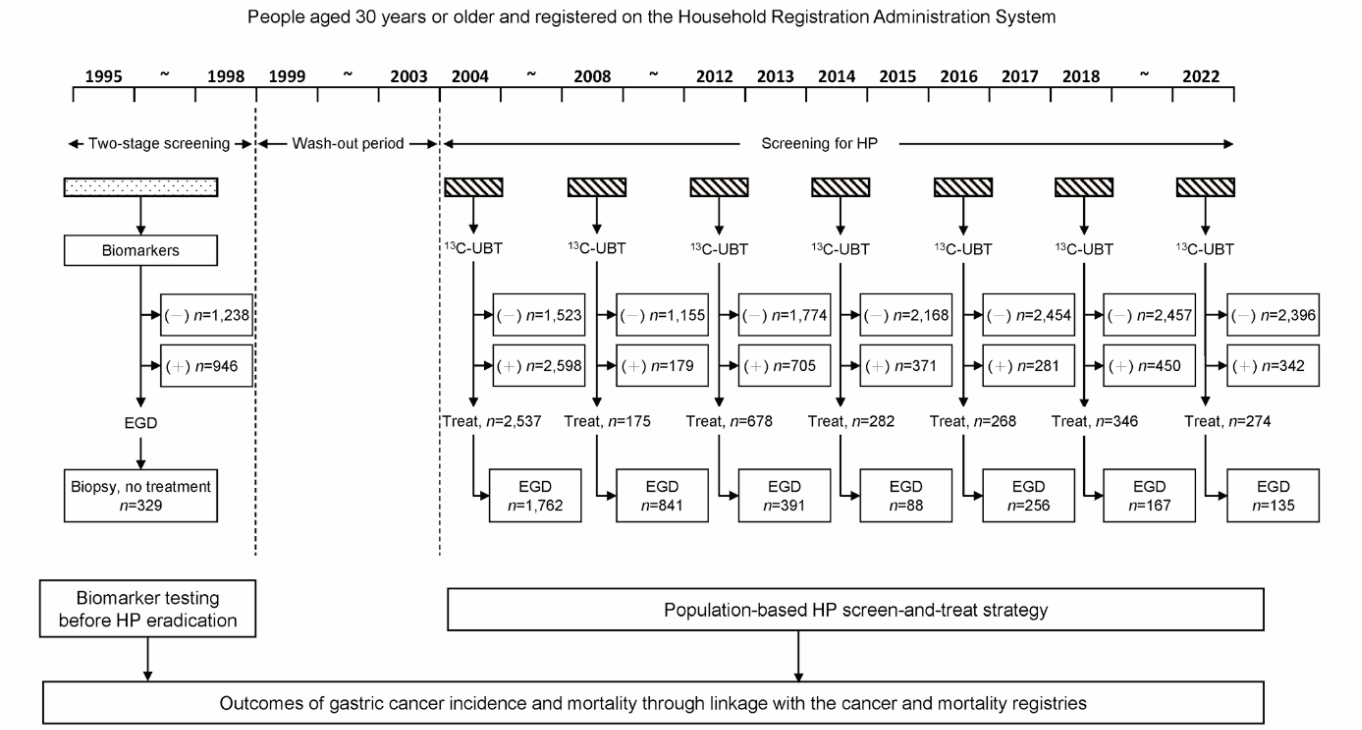

Fig. 3.10.2. Timeline of the gastric cancer prevention programmes implemented in the Matsu Islands. EGD, oesophago-gastro-duodenoscopy; ^{13}C-UBT, ^{13}C-urea breath test; HP, *Helicobacter pylori*. Adapted with permission from Chiang et al. (2021) [4]. Copyright © 2021, Chiang et al. Published by BMJ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

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

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

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

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

3.10.3 Recruitment and eligibility criteria

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

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

3.10.4 Implementation

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

Box 3.10.1. A community-based integrated screening model

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

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

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

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

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

3.10.5 Outcome assessment

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

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

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

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

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

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

3.10.6 Benefits of the programme

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

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

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

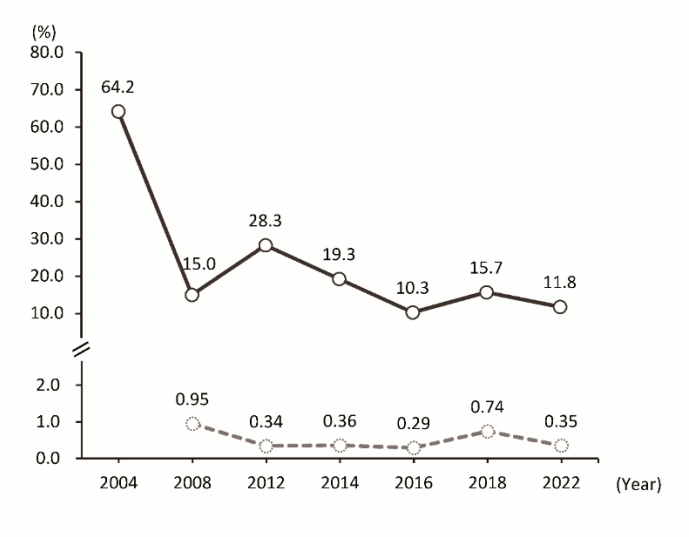

Fig. 3.10.3. Prevalence and reinfection rates of *H. pylori* infection in the Matsu Islands. The upper (solid) line shows the prevalence of *H. pylori* infection, and the lower (dashed) line shows the reinfection rates. Adapted with permission from Chiang et al. (2021) [4]. Copyright © 2021, Chiang et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

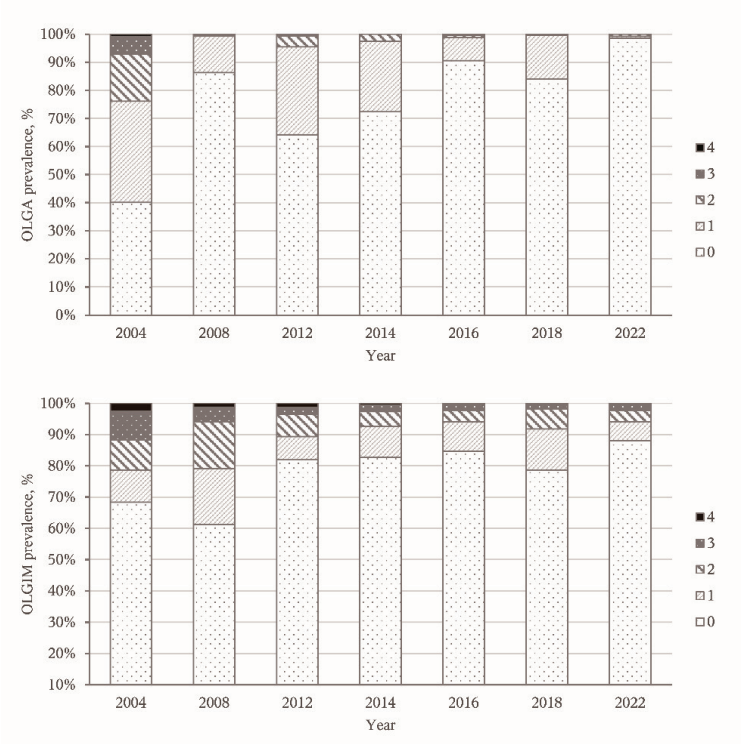

Fig. 3.10.4. Prevalence of precancerous gastric lesions according to the (top) Operative Link on Gastritis Assessment (OLGA) and (bottom) Operative Link on Gastric Intestinal Metaplasia Assessment (OLGIM) grading systems. Adapted with permission from Chiang et al. (2021) [4]. Copyright © 2021, Chiang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

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

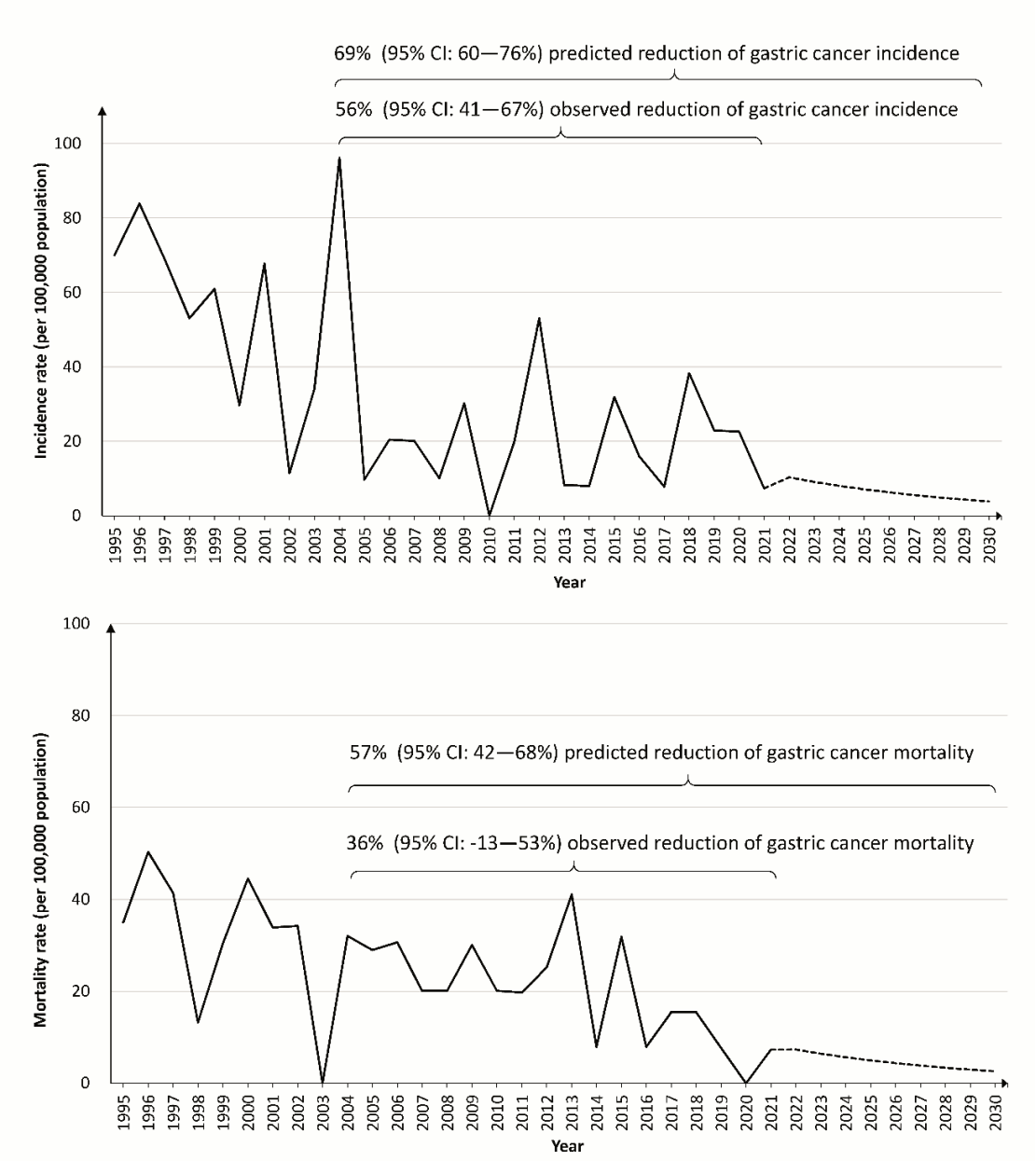

Fig. 3.10.5. Incidence and mortality rates of gastric cancer between 1995 and 2021, correlated with the start of the population-based screen-and-treat programme in 2004. The magnitude of risk reduction was determined by comparing the expected number of cases, based on the crude incidence rate (top) and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

3.10.7 Evaluation of possible harms

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

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

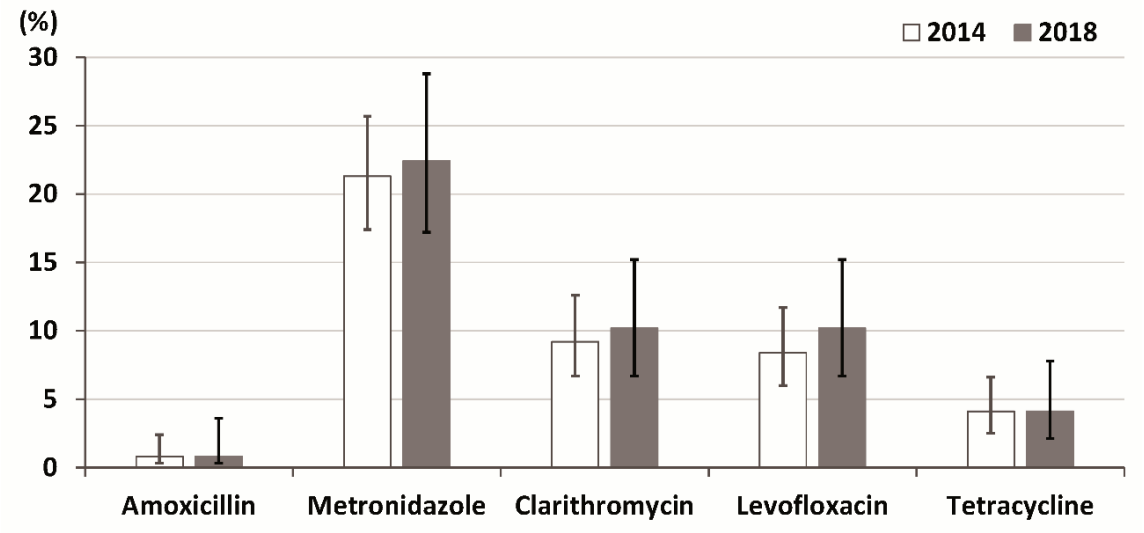

Fig. 3.10.6. Evaluation of the primary antibiotic resistance of *H. pylori* in the Matsu Islands; 95% confidence intervals are displayed on the bars. Adapted with permission from Chiang et al. (2021) [4]. Copyright © 2021, Chiang et al. Published by BMJ Publishing Group Ltd. Article available under the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

3.10.8 Extending the Matsu Islands experience to other communities

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

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

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

Box 3.10.2. Road to coverage by the health insurance system

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

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

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

3.10.9 Further planned activities and future directions

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

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

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

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

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

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

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

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

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Chapter 3.11.

Journey towards piloting a *Helicobacter pylori* screen-and-treat programme to address gastric cancer inequities in Aotearoa New Zealand

Andrea Teng

Summary

- The epidemiology of *H. pylori* infection in Aotearoa New Zealand is characterized by stark ethnic differences in prevalence of *H. pylori* infection and its sequelae, with higher prevalence of *H. pylori* infection and gastric cancer incidence and higher rates of hospitalization for peptic ulcer in Māori people, Pacific people, and Asian people than in European people.
- Māori people and Pacific people are currently less likely to be tested for *H. pylori* than European people, despite the higher risk of infection in these populations.
- A screen-and-treat approach targeted to a high-risk population is more cost-effective than implementing this approach in a low-risk population. Further cost–effectiveness modelling could support the evaluation of more specific targeting, choice of test, and choice of treatment where input data allow.
- Current research into the stratification of the prevalence of *H. pylori* infection in the community by ethnicity, the feasibility of a screen-and-treat strategy, and the level of treatment resistance in New Zealand is expected to support the design of a future screen-and-treat pilot programme.
- This chapter highlights some of the remaining questions that need to be addressed to support the development and implementation of a screen-and-treat pilot programme in New Zealand.

3.11.1 *H. pylori* infection and gastric cancer epidemiology

H. pylori *infection*

The epidemiology of *H. pylori* infection in Aotearoa New Zealand is characterized by stark ethnic differences in prevalence. In the asymptomatic population, the rate of seropositivity in Pacific people is 3 times that in European people, and the rate of seropositivity in Māori people (the Indigenous population) is twice that in European people, based on available studies from before 2000 [1]. Positivity rates from routine *H. pylori* testing also consistently follow this pattern. For example, in one largely primary care study, in 2013–2018, positivity rates were 38% in Pacific people, 21% in Māori people, and 8% in European people. Positivity rates were also high in Asian people (28%, which includes both East Asian and South Asian ethnicities) and Middle Eastern, Latin American, or African people (48%). The rates of testing for *H. pylori* were lowest in Māori people and Pacific people [2]. Table 3.11.1 summarizes the consistent pattern of ethnic inequities.

Table 3.11.1. Summary of ethnic inequities in *H. pylori* infection and its sequelae in Aotearoa New Zealand

Characteristic	Population			
	Māori	Pacific	Asian	European
Population size in 2023	887 493	442 632	861 576	3 383 742
H. pylori testing rates (per 1000 person-years), Auckland/Northland	6.4	7.2	20.8	11.8
Asymptomatic: relative rates of *H. pylori* seropositivity (before 2000)	1.9	3.4	–	1.0 (ref)
Symptomatic: *H. pylori* positivity rate (%)				
Auckland/Northland, 2015–2018	22	37	26	13
Canterbury, 2013–2018	21	38	28	8
Peptic ulcer hospitalization rate (per 100 000 person-years), 2015–2018[a]	51	63	22	15
Gastric cancer incidence rate (per 100 000 person-years), 2017–2021[b]	11.1	13.9	5.5	4.1
Gastric cancer mortality rate (per 100 000 person-years), 2017–2021[b]	7.4	8.5	3.0	2.6

[a] Age-standardized to the Māori census population in 2001.
[b] Age-standardized to the WHO world standard population.
Source: Compiled from McDonald et al. (2015) [1], Kubovy and Barclay (2022) [2], Hildred (2024) [3], and Teng et al. (2025) [4].

Sequelae

The age-standardized rates of gastric cancer in the New Zealand population are low in the international context. In 2015–2019, the rates were 8 per 100 000 person-years in males and 4 per 100 000 person-years in females, when age-standardized to the World Health Organization (WHO) world standard population [5]. The equivalent crude rate was 11 per 100 000 person-years in males and 6 per 100 000 person-years in females, with an overall rate of 8.5 per 100 000 person-years in 2015–2019 [5].

However, there are stark ethnic differences in gastric cancer incidence and mortality. The rates of gastric cancer in Māori people and Pacific people are 2.5–6.3 times those in European/Other people [6]; the rates in Asian people are somewhere in between [3]. In 2017–2021, gastric cancer incidence rates (per 100 000 person-years) were 15 in males and 8 in females in Māori people, 17 in males and 11 in females in Pacific people, and 8 in males and 4 in females in Asian people, compared with 6 in males and 3 in females in European/Other people, when age-standardized to the WHO world standard population (Fig. 3.11.1) [7]. Also, Māori people with gastric cancer are more likely than non-Māori people to have non-cardia gastric cancer [8] (about 80% vs 50%, if overlapping and undefined types of gastric cancer are excluded) [9] and diffuse-type gastric cancer [8].

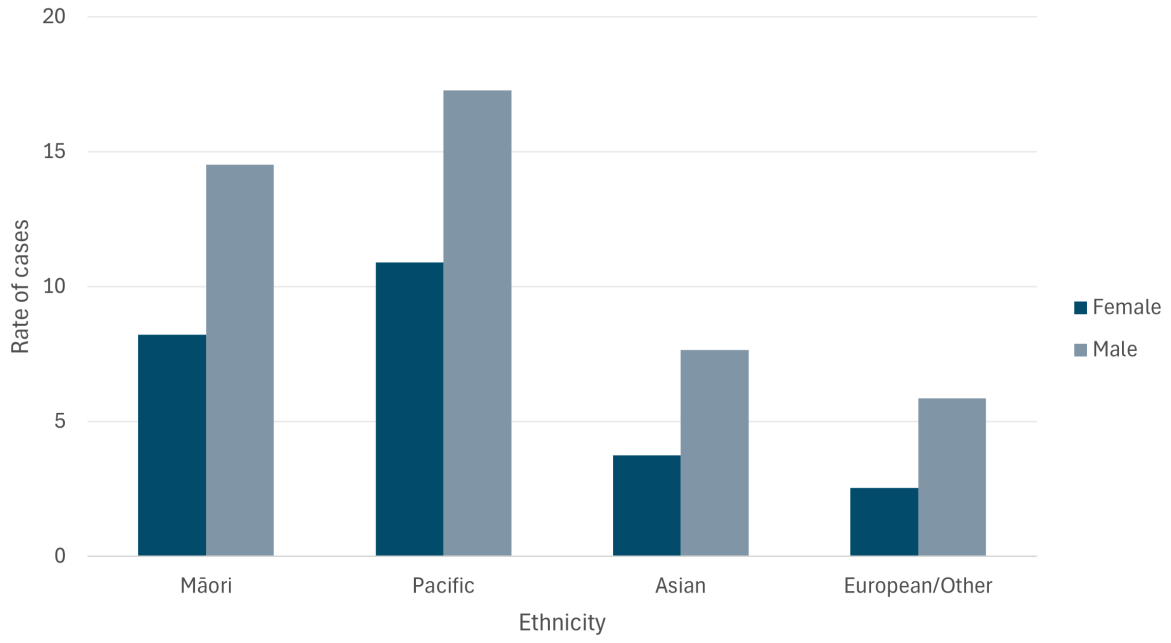

Fig. 3.11.1. Rate of gastric cancer registrations in 2017–2021 by ethnicity. Rate is per 100 000 person-years and is age-standardized to the WHO world standard population. Compiled from Te Whatu Ora/Health New Zealand (2024) [7].

In addition, rates of gastric cancer incidence and mortality are significantly higher in groups with the lowest socioeconomic positions. For example, in 2006–2011, in the lowest versus the highest equivalized household income quintile, the difference in gastric cancer incidence was 1.62 (95% confidence interval [CI], 1.03–2.56) in men and 1.81 (95% CI, 1.00–3.29) in women [10]. In 2017–2021, gastric cancer incidence rates (per 1000 000 person-years) were 10 in males and 6 in females living in areas with the highest levels of deprivation, compared with 6 in males and 3 in females living in areas with the lowest levels of deprivation (Fig. 3.11.2) [7].

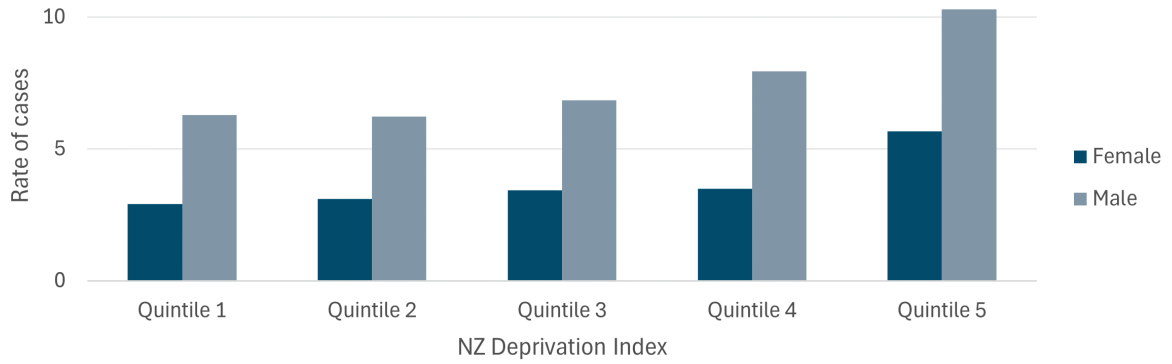

Fig. 3.11.2. Rate of gastric cancer registrations in 2017–2021 by New Zealand Deprivation Index quintiles. Rate is per 100 000 person-years and is age-standardized to the WHO world standard population. Compiled from Te Whatu Ora/Health New Zealand (2024) [7].

The incidence of peptic ulcers also varies by ethnicity. In 2015–2018, age-standardized rates of hospital admission for peptic ulcer in New Zealand (per 100 000 person-years) were 3.5 times as high in Māori people (50.8; 95% CI, 47.5–54.4) and 4.3 times as high in Pacific people (63.1; 95% CI, 57.9–68.6) as in European people (14.6; 95% CI, 13.8–15.4), and the admission rates in Asian people were intermediate (21.8; 95% CI, 19.7–24.1), when age-standardized to the Māori census population in 2001 [3].

Differential rates of *H. pylori* infection are the largest contributor to inequities in gastric cancer incidence in New Zealand [11], and this is probably also the case for peptic ulcers. The screen-and-treat approach for *H. pylori* is expected to be a useful tool to address existing gastric cancer inequities by ethnicity, and possibly also for groups with low socioeconomic position.

Gastric cancer risk factors

In addition to chronic *H. pylori* infection, other risk factors for gastric cancer in New Zealand are strongly patterned by ethnicity and socioeconomic position. For example, the population prevalence of smoking, obesity, and hazardous drinking is examined by the New Zealand Health Survey [12]. In 2022–2023, the percentage of adults who smoked every day was 17% in Māori people, 6% in Pacific people, 6% in European/Other people, and 3% in Asian people. The rates of obesity in adults were 67% in Pacific people, 48% in Māori people, 32% in European/Other people, and 14% in Asian people. The rates of hazardous drinking in adults were 25% in Māori people, 22% in Pacific people, 17% in European/Other people, and 5% in Asian people. These risk factors were also more common in adults living in areas with the highest levels of deprivation (unadjusted for ethnicity).

Hereditary risk

Higher rates of gastric cancer incidence in Māori people, particularly in younger age groups, have also been thought to be caused by an increased propensity towards mutation of the *CDH1* gene in particular family groups. A study has estimated that 6% of advanced gastric cancers in Māori people have a *CDH1* mutation [13], with higher rates found in younger age groups and for diffuse-type cancers. The rate of this mutation among European people in New Zealand with gastric cancer is less clear.

The impact of inherited genetic mutations appears to be particularly compounded by the presence of chronic *H. pylori* infection. Recent evidence from Japan shows an interaction between nine germline pathological variants and *H. pylori* infection. The lifetime risk of gastric cancer was strongly elevated in people with both *H. pylori* infection and one of these pathological variants (45% lifetime risk), compared with < 5% lifetime risk in people with no *H. pylori* infection and with one of these variants and 14.4% lifetime risk in people with *H. pylori* infection and none of these variants [14].

3.11.2 Inequities in current practice

Testing

In current primary care practice in New Zealand, the funded test for active *H. pylori* infection is the stool antigen test (SAT). The SAT is recommended in patients who present with one of the following risk factors [15]: history of peptic ulcer, family history of

gastric cancer, or dyspepsia and one of the following factors: aged ≥ 60 years; Māori, Pacific, Asian, or African ethnicity; or originating from an area with high (> 30%) prevalence of *H. pylori* infection (e.g. South Auckland, Porirua, East Cape; low- and middle-income countries, including in Asia). Urea breath tests are not publicly funded and are rarely used [2]. Serology is still widely used to test or screen for *H. pylori* and was more commonly used than the SAT until the end of 2018 [2].

Despite the higher prevalence of *H. pylori* infection in Māori, Pacific, Asian, and Middle Eastern, Latin American, or African people and the availability of ethnicity-specific guidelines, the rates of testing remain disproportionately low for Māori people and Pacific people [2–4], compared with testing rates for European people (who have low prevalence of *H. pylori* infection) [3]. In general, Māori people and Pacific people experience several barriers to primary care access and have the highest levels of unmet health-care needs [16]. Access to primary care in New Zealand usually requires co-payments (which differ between health-care providers), and funding for primary care has been found to have embedded historical inequity; unmet needs have been ignored, and services for Māori people have been systematically underfunded [17]. These underserved ethnic groups have the highest rates of gastric cancer incidence and are expected to gain the most (per-person) benefit from an *H. pylori* screen-and-treat approach, particularly if it is introduced with an equity focus [9].

Gastroscopy

Guidelines in New Zealand recommend referral for gastroscopy [15], for example when *H. pylori* treatment has failed, in people with persistent symptoms despite treatment, or in people with risk factors such as a first presentation of dyspepsia at age ≥50 years (or age ≥40 years in at-risk ethnic groups), a family history of gastric cancer onset at age < 50 years, severe or persistent dyspepsia despite treatment, previous peptic ulcer disease, coughing spells, or nocturnal aspiration. Despite the availability of ethnicity-specific guidelines, there are greater ethnic disparities in the rates of gastroscopy testing (e.g. in the use of rapid urease tests) than in primary care testing for *H. pylori* infection, suggesting even greater barriers to access to secondary care for Māori people and Pacific people compared with European people [2, 4]. These referral criteria do not guarantee access to gastroscopy, which varies geographically.

Treatment

Current treatment guidelines in New Zealand recommend triple therapy for 7–14 days with a proton pump inhibitor, amoxicillin, and clarithromycin (OAC) as a first-line treatment, with metronidazole as a potential substitute for either antibiotic [18]. Quadruple therapy is recommended as a second-line treatment in cases of eradication failure and comprises 2 weeks of a proton pump inhibitor, bismuth, tetracycline, and metronidazole [18]. This advice varies from the Maastricht VI/Florence Consensus report, which recommends first-line treatment with 14 days of bismuth-containing quadruple therapy in areas where clarithromycin resistance is > 15% (or unknown) and susceptibility testing is not available [19]. However, there is an urgent need to further investigate primary clarithromycin resistance rates, including by ethnicity [20].

Updated local information about clarithromycin and antibiotic resistance rates and *H. pylori* eradication rates would make a valuable contribution to the case for revising treatment guidelines in New Zealand [21]. This is particularly important given the increase in clarithromycin resistance globally. There is likely to be increasing resistance to first-line *H. pylori* treatment in New Zealand. In 2012, a small study (n = 73) in an area of New Zealand with a relatively high level of deprivation, in patients with positive gastroscopy specimens, reported 49% metronidazole resistance and 16% clarithromycin resistance [22] and 35% eradication failure of first-line treatment (OAC) in Māori people, Pacific people, and Asian people. A 2021 meta-analysis investigated antibiotic resistance of *H. pylori* in Australia and New Zealand [21] and reported a doubling of primary resistance to clarithromycin, to 16% (95% CI, 11–22%), after 2000 compared with before 2000.

Increasing antibiotic resistance and poor eradication rates make it vital to improve retesting with the SAT, i.e. 4–6 weeks after completion of treatment [20] in line with international guidelines [19]. Retesting is not in the current treatment guidelines in New Zealand, and its use remains low [4]. Retesting enables the use of second-line therapy to improve eradication rates and also could improve the usefulness of laboratory data for monitoring eradication rates. The guidelines for *H. pylori* treatment in New Zealand need to be revised and updated, and work on this is ongoing.

Ethnicity data quality

Accurate ethnicity data are crucial for equitable health care, and for targeted participation in a screen-and-treat strategy, but Māori people are undercounted in health data [23]. Improved protocols are needed for consistent, accurate ethnicity data collection.

3.11.3 Cost–utility modelling for population and targeted screen-and-treat approaches

Cost–utility modelling was applied to the New Zealand setting, using *H. pylori* infection and gastric cancer epidemiology data from 2011 [9]. An important contribution of this work is a comparison of the cost–effectiveness of *H. pylori* screen-and-treat approaches between Māori people (who have a moderate risk of gastric cancer) and the remaining population (who have low rates of gastric cancer on average; this remaining population also includes groups with a high risk of gastric cancer, such as Pacific people, who are likely to be a small proportion overall). The following model inputs were applied at different rates for Māori people and non-Māori people: (i) proportion of gastric cancer that is non-cardia gastric cancer, (ii) coverage of testing, (iii) eradication rate of triple therapy, and (iv) *H. pylori* seroprevalence. Two *H. pylori* screen-and-treat scenarios were evaluated based on the diagnostic test used: one analysis used serology (primary analysis), and the other used the SAT. The most relevant SAT results are reported here, given that serology is not recommended for diagnosing infection.

The SAT scenario cost NZ$ 369 million and resulted in 15 300 quality-adjusted life years (QALYs) gained in men and women aged 25–69 years, with lifetime follow-up. This resulted in an incremental cost–effectiveness ratio (ICER) of NZ$ 29 000 per QALY gained. If Māori people alone were targeted, the cost would be NZ$ 49 million and 4200 QALYs would be gained, which equates to a better-value ICER of NZ$ 13 700 per QALY gained.

The *H. pylori* screen-and-treat programme in the whole population had 4 times the absolute health gain (i.e. clinical effectiveness, QALYs) compared with targeting Māori people alone, but at more than 7 times the cost. However, the cost for targeting Māori people may be more than double if a programme were to include other known high-risk groups. The QALYs gained by Māori people were even greater in equity analyses in which life expectancy was set to the same level as that of non-Māori people [9]. The

greater cost–effectiveness in Māori people is likely to be similar in other groups with high rates of *H. pylori* infection and gastric cancer in New Zealand.

Although the modelled programme in the whole population was cost-effective, it was more cost-effective with a targeted approach for Māori people (Fig. 3.11.3) [9]. This supports the recommendation that high-risk groups would be a useful priority for implementation of this programme.

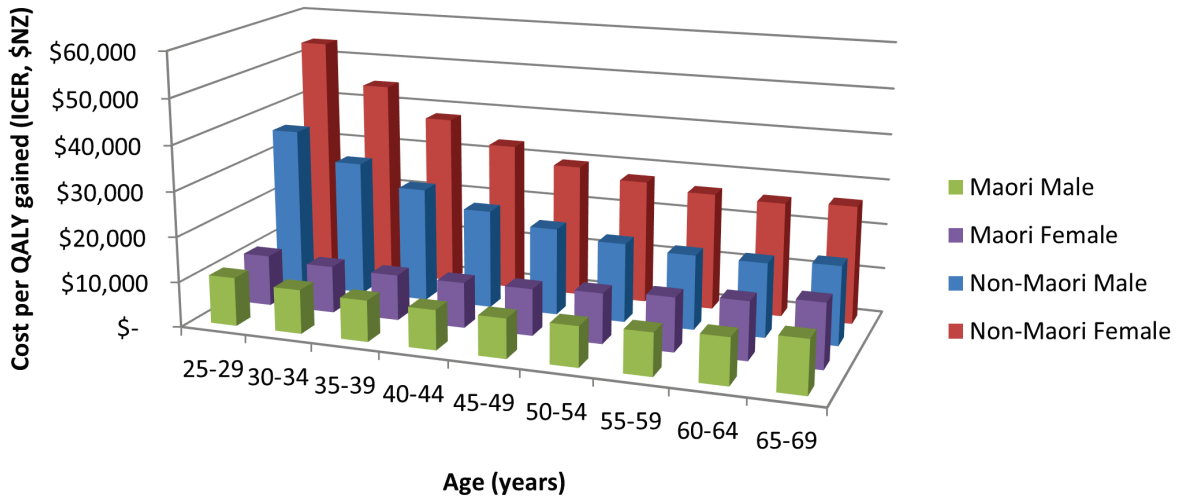

Fig. 3.11.3. Modelled cost–effectiveness of an *H. pylori* screen-and-treat programme in New Zealand in 2011 by ethnicity, sex, and age. ICER, incremental cost–effectiveness ratio; QALY, quality-adjusted life year. Reproduced from Teng et al. (2017) [9].

Further cost–effectiveness modelling would be useful to assess the costs and benefits of targeting additional high-risk groups and the impact of different testing and treatment modalities, such as the use of different types of tests, different treatment choices, and the inclusion of gastroscopy for participants who have clinical indicators of potential gastric cancer. This is possible as more precise model inputs become available, for example better estimates of *H. pylori* prevalence and eradication rates.

3.11.4 Prevention approaches being investigated

The New Zealand Cancer Action Plan 2019–2029 sets out a plan to develop a strategy to address *H. pylori* infection in priority populations [24]. Gastric cancer is one of the top 10 contributors to the life expectancy gap for both Māori people and Pacific people in New Zealand (compared with European people), and thus is a priority in the public health system.

Several research streams were in the field in mid-2024, with the aim of informing the future implementation of an *H. pylori* screen-and-treat pilot or programme. These studies are investigating (i) community estimates of *H. pylori* prevalence and a subsequent management pathway, in the *H. pylori* in Aotearoa New Zealand (ENIGMA) Study; (ii) a family-based index-case method focused on Indigenous people, recruiting participants for an *H. pylori* screen-and-treat study (Puku Ora Feasibility Study); and (iii) *H. pylori* antibiotic resistance rates using the polymerase chain reaction (PCR) for genetic markers and culture.

H. pylori *in Aotearoa New Zealand (ENIGMA) Study*

The objectives of the *H. pylori* in Aotearoa New Zealand (ENIGMA) Study are outlined in Box 3.11.1. In summary, the study's main objective is to investigate the ethnicity-specific distribution of *H. pylori* infection in New Zealand (using biological specimens), the risk factors for *H. pylori* infection (using survey data), and the overlap of *H. pylori* infection with risk factors for gastric cancer, along with testing markers of antibiotic resistance, and the effectiveness and acceptability of *H. pylori* case management. The study started recruiting in early 2024 and plans to report initial results in 2025.

Box 3.11.1. Objectives of the *H. pylori* in Aotearoa New Zealand (ENIGMA) Study

Primary objective

1. Measure the age-specific prevalence of *H. pylori* infection overall and among Māori people, Pacific people, and non-Māori, non-Pacific people in New Zealand, including by sex.

Secondary objectives

2. Examine potential risk factors for *H. pylori* infection for the total study population and by population subgroup, including their prevalence and distribution.
3. Measure the prevalence of potential co-factors, including virulence factors, that may be important in the pathogenesis of gastric cancer by *H. pylori* infection status.
4. Measure the prevalence of clarithromycin and antibiotic resistance by PCR from stool (faecal) samples.
5. Investigate the feasibility, acceptability, and costs of different *H. pylori* tests in the New Zealand setting.
6. Examine the acceptability, feasibility, and effectiveness of positive case management.

The study uses a cross-sectional survey design with a general community sample coverage, with participants selected by secondary sampling from past respondents to the New Zealand Health Survey. The aim was to include 1188 participants with equal numbers of Māori people, Pacific people, and people from the remaining European/Other groups, and equal numbers of people across 10-year age groups. Participants aged 12–69 years with no history of gastric cancer were eligible.

Participation involves responding to a survey by telephone, having a blood test at a local laboratory, and the option of submitting a stool sample (which has the added benefit of investigating a diagnosis of *H. pylori* infection). In the early stages of the study, about one third of participants were opting in for stool testing.

Any participant with a positive serology test result is followed up with an SAT sent to their home address (if the participant had not already opted in for this test). Participants collect the stool sample at home and submit it on the same day to a local community laboratory, where it is frozen. The sample is kept chilled for transportation to a centralized location for testing. Participants are asked to wait 15 days after the completion of any course of antibiotics or proton pump inhibitors (if appropriate) before they do the SAT.

For participants with a positive SAT result, case management is organized by a research nurse, who contacts participants by telephone to share the results, ask about the relevant medical history, and arrange treatment. A gastroenterologist writes the prescriptions, which are then sent to a local pharmacy. The participants collect the treatment, and the research nurse follows up to find out whether participants received the medication and have completed the treatment course. Retesting with the SAT is done to assess eradication at 6 weeks after completion of treatment. A holistic approach to case management has been taken and is carried out via a Māori health provider. This treatment pathway will be assessed by investigating rates of treatment, treatment completion, retesting, and eradication failure. Measures of acceptability and any barriers reported by participants will be assessed.

The key outcome measures from the study will be ethnicity-specific rates of participation, testing, *H. pylori* prevalence, treatment completion, and eradication, prevalence of clarithromycin resistance genes, and virulence factors.

The goal is for the findings to be generalizable nationally, but challenges to this include uncontactable participants, the geographical coverage of laboratory services relative to the population, and the low numbers of Pacific people in the primary sampling frame, which will necessitate additional recruitment pathways.

Puku Ora Feasibility Study

The Puku Ora Feasibility Study aims to take a Kaupapa Māori, holistic, strength-based approach to test the feasibility of an approach that addresses the health inequities between Māori people and non-Māori people in New Zealand in gastric cancer and colorectal cancer. A combined screening approach is used to screen and treat for *H. pylori* infection and to screen for colorectal cancer using a single stool sample, in a

Māori-specific context for people aged 45–60 years. Education and encouragement are given to promote participation in the National Bowel Screening Programme, for those who are not already participating. Participants older than 60 years and adults younger than 45 years are tested for *H. pylori* infection only. In mid-2024, this study was in its recruitment phase.

Antibiotic resistance studies

Several studies in New Zealand are investigating *H. pylori* antibiotic resistance in different clinical contexts, including the *H. pylori* in Aotearoa New Zealand (ENIGMA) Study. Rates of *H. pylori* antibiotic resistance in positive gastroscopy isolates are being investigated in the Wellington region. The study is recruiting symptomatic patients undergoing gastroscopy who have had a positive rapid urease test result. The aim of this study is to inform more precise treatment choice to improve eradication rates. Recruitment was completed in 2024, and DNA extraction and clarithromycin resistance gene testing have been done. The participants are being followed up to assess treatment completion and success of eradication. Similar methods are being applied to people with positive SAT results. Another study is investigating *H. pylori* antibiotic resistance in a similar clinical setting in Auckland.

3.11.5 Future directions

The following list provides some of the information needs and outstanding questions that would help to support the implementation of a screen-and-treat pilot or programme in New Zealand [20]. Chapter 4 gives further explanation about the needs and readiness in New Zealand.

Targeting:

1. Consensus on whether to aim for an untargeted population programme or focus on targeting high-risk groups. Targeting decisions could be informed by analysis of *H. pylori* prevalence and peptic ulcer and gastric cancer rates by age, sex, and ethnicity, including subgroups (e.g. East Asian and South Asian people), socioeconomic position, country of birth, family history, and other potentially relevant factors.
2. Consider expanding screen-and-treat processes to household members of positive cases detected through the initial inclusion criteria.

Testing:

3. Consensus on choice of diagnostic test (balancing ethnicity-specific acceptability, capacity of the health system, and costs), for example the SAT, serology then the SAT, or either with the urea breath test instead of the SAT. Consider where and how these tests will be done.
4. Determine the rates of reinfection in New Zealand and whether subsequent follow-up testing is needed.
5. Examine the acceptability of *H. pylori* screen-and-treat strategies for Māori people and Pacific people, and which methods of engagement would improve awareness and participation.

Treatment:

6. Up-to-date *H. pylori* treatment resistance information for current and alternative first-line and second-line therapies to inform improved national treatment guidelines:
    a. choice of first-line therapy (considering increasing resistance rates);
    b. introducing retesting as standard practice.
7. Develop a plan for assessing who is at high risk and should be referred for gastroscopy for diagnosis of gastric cancer. Will blood markers of gastric cancer risk be used? What are the service impacts of this for diagnosis of cancer?

Programme:

8. Cost–effectiveness analysis of different targeting, testing, treatment, and combination screening approaches.
9. Information on the pros and cons of delivering treatment and retesting via primary care or other more centralized or telehealth processes.
10. Development of an equitable process for invitation to screening, participation, and follow-up for treatment.
11. Consider how the screen-and-treat approach will be integrated with other screening programmes, for example in primary care like the cardiovascular risk

assessment, or combined with national-level colorectal cancer screening, lung cancer screening, or hepatitis screening.

12. Ongoing input from experts in Māori and Pacific health, migrant health, gastroenterology, primary health care, public health, microbiology, health service improvement, and epidemiology to support the development of a screen-and-treat model for New Zealand.

13. Commitment from funders and the public health system to introduce a pilot of the approach, with ongoing feedback informing improvements. This includes developing information technology to generate a system to provide a register, produce invitations, make bookings, carry out recall, and monitor outcomes.

New Zealand is well placed to make progress in addressing gastric cancer inequities, and an *H. pylori* screen-and-treat approach presents itself as a key tool. An equity approach to implementation will be key for reversing higher rates of gastric cancer in Māori people, Pacific people, and other high-risk groups. The next step is for funders and the public health system to invest in scaling up and piloting a risk-based target population *H. pylori* screen-and-treat strategy.

Useful research to support the next step includes investigation of sociodemographic risk factors to consider for risk-based targeting, sensitivity and specificity of testing approaches in New Zealand, which testing approach has the highest uptake by ethnicity, *H. pylori* eradication and resistance rates by ethnicity, and cost–effectiveness analysis of selected screen-and-treat approaches.

Acknowledgements

Thank you to Professor James Stanley for providing feedback on an early draft of this chapter.

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Chapter 4.

Needs and readiness for the implementation of *Helicobacter pylori* screen-and-treat strategies for gastric cancer prevention locally

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Summary

- Needs assessments are critical before implementing an *H. pylori* screen-and-treat programme for gastric cancer prevention and should include an assessment of recent local gastric cancer incidence and mortality rates (overall and for groups within the population), the prevalence of *H. pylori* infection, government support and commitment, the priorities of the population(s) targeted for intervention, and local testing and treatment facilities.
- In areas with intermediate to high incidence of gastric cancer, a population-based *H. pylori* screen-and-treat programme is recommended.
- In areas with lower incidence of gastric cancer, targeting *H. pylori* screen-and-treat strategies to intermediate-risk and high-risk groups within selected administrative or geographical units will often be the best option.
- Targeted *H. pylori* screen-and-treat programmes could also be considered for family members of individuals with *H. pylori* infection or gastric cancer.
- Pilot studies, run before the implementation of a full programme, are crucial to enable the local level of readiness to be assessed, on the basis of measures such as screening participation rates, positivity rates, treatment adherence, and treatment effectiveness. The results of the pilot study could be used to inform population decision modelling to determine the resource requirements and cost–effectiveness of the *H. pylori* screen-and-treat programme.
- Ongoing funding is required for *H. pylori* screen-and-treat programmes for gastric cancer prevention, and additional infrastructure is required. Adequate organization of the local testing and follow-up facilities for *H. pylori* screen-and-treat programmes

is essential, and the facilities and equipment required will depend on the choice of first-line screening test.

- Sound conclusions on the needs and readiness for implementing *H. pylori* screen-and-treat strategies require evidence-based policy analyses that weigh the specific costs and benefits for the target populations.

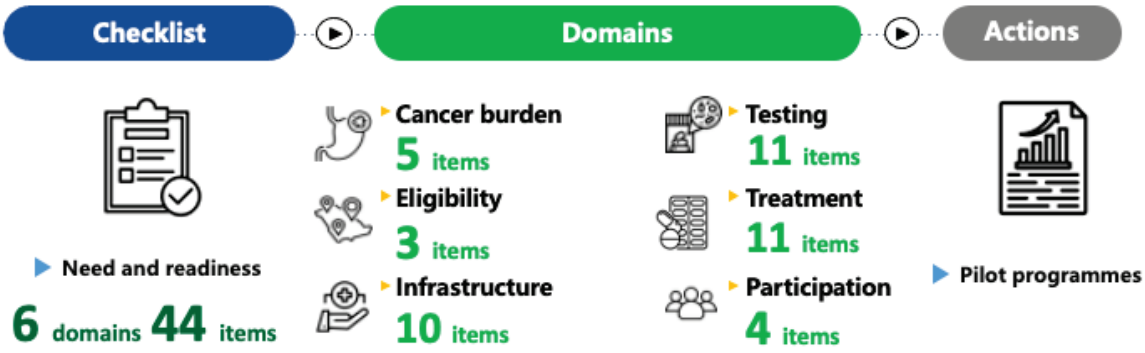

Fig. 4.1. Visual abstract.

4.1 Introduction

This chapter discusses the key considerations for assessing the needs and readiness for population-based *H. pylori* screen-and-treat strategies for gastric cancer prevention and provides a checklist for these strategies. The focus of this chapter is on assessing the readiness in the health-care system for the implementation of *H. pylori* screen-and-treat strategies. Chapters 8 and 9 discuss monitoring and evaluating *H. pylori* screen-and-treat strategies. Although *H. pylori* screen-and-treat strategies are considered here, rather than direct screening for gastric cancer, the principles used in these strategies correlate with the criteria outlined by Wilson and Jungner in *Principles and practice of screening for disease* [1].

As an initial consideration, the expected costs and benefits of the strategies proposed should be weighed against the alternative use of the available resources. Any decisions reached should be informed by the best available scientific evidence on the local epidemiology of *H. pylori* infection and its consequences, and the expected costs and benefits of specific strategies, along with the prioritization of the available resources according to the relevant social values. Because the expected costs and benefits, the

available resources, and the priorities vary across population settings, the strategies must be tailored to each local context.

In this chapter, the needs for implementing *H. pylori* screen-and-treat strategies are discussed in Section 4.2, identifying the target population is discussed in Section 4.3, and the readiness assessment is discussed in Section 4.4. Section 4.5 provides three examples of *H. pylori* screen-and-treat programme readiness. Performing pilot studies before the actual implementation of a strategy is crucial to enable the local level of readiness to be assessed, on the basis of measures such as screening participation rates, positivity rates, treatment adherence, and treatment effectiveness.

Box 4.1 summarizes the considerations to be made before *H. pylori* screen-and-treat programmes are initiated.

Box 4.1. Considerations for an *H. pylori* screen-and-treat programme for gastric cancer prevention

- Is there a need for an *H. pylori* screen-and-treat approach as a primary prevention strategy?
- Who should be targeted (the total population or specific high-risk groups)?
- The readiness assessment includes the following questions:
  - Are adequate resources available for *H. pylori* testing?
  - Are effective and affordable anti-*H. pylori* treatment regimens (and data on resistance) available?
  - Is there adequate infrastructure for providing the treatment and supporting the overall programme implementation?
  - Are strategies in place to maximize engagement of the target population?

4.2 Assessing need

Assessing the need for a gastric cancer prevention initiative based on an *H. pylori* screen-and-treat strategy requires gathering recent information (i.e. preferably from

within the past 5 years) on the local burden of disease. Identifying a need is relatively straightforward in areas with an intermediate to high incidence of gastric cancer and adequate medical resources. For other areas, the need may be limited to one or more high-risk demographic groups within the population with a high incidence of gastric cancer. This information could also be used for decision modelling to assess the harms versus the benefits and the cost–effectiveness of *H. pylori* screen-and-treat strategies in the local setting (see Chapter 9).

The needs assessment requires information on the prevalence of *H. pylori* infection, the prevalence of antibiotic-resistant *H. pylori* strains, *H. pylori* reinfection rates, the prevalence of *H. pylori*-associated gastric pathological changes, and gastric cancer incidence and mortality rates.

Prevalence of H. pylori *infection*

Estimating the total burden of *H. pylori* infection is not a trivial exercise, because most individuals with *H. pylori* infection are asymptomatic. Obtaining accurate estimates of the prevalence of *H. pylori* infection in a target population requires selecting a representative sample of that population. Where higher-risk population groups within a region are in a numerical minority, it may be necessary to oversample these groups to gain an accurate estimate of *H. pylori* infection prevalence. This situation is further complicated by the decreasing prevalence of *H. pylori* infection in most countries, particularly in the younger population [2].

The feasibility of population screening for estimating *H. pylori* infection prevalence is enhanced by the availability of accurate non-invasive tests (see Chapter 5). Estimates of *H. pylori* infection prevalence predict the fraction of the target population that will test positive and require treatment if *H. pylori* screen-and-treat strategies are used. This information is needed to estimate the costs and preventive impact of a screen-and-treat strategy, and it can also be used to estimate the size of the population at risk of *H. pylori*-associated disease. Comparisons of *H. pylori* infection prevalence between sociodemographic subgroups can help to identify groups with an elevated frequency of *H. pylori*-associated disease, to enable targeted preventive interventions.

Information on the prevalence and population distribution of the established virulence factors of *H. pylori* strains (such as CagA-positive or VacA s1m1 genotypes) may further

facilitate specific identification of high-risk groups, although evidence of the preventive effectiveness of this information in screen-and-treat strategies is limited, and the resources required for classifying strains based on virulence factors are not widely available.

Prevalence of antibiotic-resistant H. pylori *strains*

Estimates of the prevalence and distribution of *H. pylori* strains with antibiotic resistance patterns associated with reduced treatment effectiveness (e.g. clarithromycin or levofloxacin resistance) facilitate the estimation of treatment effectiveness for the target population, as well as the evidence-based selection of the best empirical therapy (see Chapters 6 and 7). However, testing for antibiotic resistance requires gastric tissue or stool samples for bacterial culture or molecular detection. In the future, molecular detection resources may facilitate the detection of antibiotic resistance of *H. pylori*; these resources include tests based on the polymerase chain reaction (PCR) technique, which were increasingly used in response to the COVID-19 pandemic. Data on eradication rates from registries, such as the European Registry on *Helicobacter pylori* Management, could be used to infer the frequency of antibiotic resistance rates in populations that are similar to those covered by the corresponding registry [3].

H. pylori *reinfection rates*

Because most *H. pylori* infections are acquired in childhood and generally go undetected, estimating the incidence of new infection is challenging and may not have short-term clinical relevance to gastric cancer prevention. However, the local reinfection rate should be monitored to ensure the lasting effect of the screen-and-treat programme, because the recurrence rate is closely associated with socioeconomic and sanitary conditions. Recurrence of *H. pylori* infection could occur through either reinfection or recrudescence. Reinfection is defined as infection with a new strain, whereas recrudescence usually refers to the reappearance of the original infection after an initially false-negative post-eradication result. In a meta-analysis of 132 studies in 45 countries or regions published in 1983–2017 that assessed the *H. pylori* status of adults after treatment to eliminate the infection, with a follow-up period of ≥ 12 months, the global recurrence rate was estimated as 4.3%, the reinfection rate as 3.1%, and the recrudescence rate as 2.2% [4]. The recurrence rate of *H. pylori* infection was inversely related to the Human Development Index (HDI) level and was directly related to the *H.*

pylori infection prevalence of the country [5]. Although it can be difficult to distinguish between reinfection and recrudescence of a suppressed infection falsely identified as cured, what is relevant for assessing screen-and-treat strategies is the average *H. pylori*-free duration after treatment and the average number of repeated therapy courses. Health-care systems that track diagnostic tests and prescriptions may yield information that can be used to estimate the average number of therapy courses after a positive *H. pylori* test, stratifying on treatment regimen and patient characteristics.

Prevalence of H. pylori*-associated gastric pathological changes*

Local descriptive studies of the severity of the gastric pathology associated with *H. pylori* infection, including the quantitative classification of chronic gastritis (updated Sydney classification system) [6], atrophic gastritis (Operative Link on Gastritis Assessment; OLGA) [7], and intestinal metaplasia (Operative Link on Gastric Intestinal Metaplasia Assessment; OLGIM) [8], facilitate the stratification of gastric cancer risk in the target population and within subgroups.

Gastric cancer incidence and mortality rates

Estimates of gastric cancer incidence and mortality rates are required to identify the burden of disease overall and within the target populations. Accurate estimates of gastric cancer rates require populations to have access to a diagnosis that is recorded in high-quality local cancer registries. The proportion of gastric cancer cases attributed to *H. pylori* infection in that region could add further information to the cancer incidence. The population attributable fraction depends on the prevalence of the infection in the population and the strength of its association with the cancer. A recent study in China showed that the population attributable fraction of *H. pylori* infection for gastric cancer has been decreasing since 2000 and is projected to decrease further by 2050 [9]. By 2050, *H. pylori* infection is predicted to be responsible for 40.7% of cardia gastric cancer and 62.1% of non-cardia gastric cancer [9]. In the long term, the trends in gastric cancer mortality rates, and the changes in mortality distributions, will constitute the evidence of the effectiveness of gastric cancer prevention efforts.

4.3 Who should be targeted?

After assessing needs, the next fundamental question when designing an *H. pylori* screen-and-treat programme for gastric cancer prevention is which population group to

target for prevention efforts, considering the epidemiology, the expected costs and benefits, the available resources, and the priorities of the stakeholders [10]. When the need for gastric cancer prevention initiatives has been demonstrated, prevention strategies should be based on the best available scientific evidence of the cost–effectiveness and practicality of the available options [11, 12] (see Chapters 8 and 9). This assessment requires information that is specific to and relevant to the target population.

Three different approaches are discussed here: (i) a population-based *H. pylori* screen-and-treat approach for gastric cancer prevention, (ii) a risk-based approach targeting high-risk subpopulations, and (iii) a family-based approach targeting family members of individuals with gastric cancer or *H. pylori* infection.

General population

Population-based *H. pylori* screen-and-treat programmes for gastric cancer prevention are recommended in countries with intermediate to high risk, as stated in the Maastricht VI/Florence Consensus report [13], Europe's Beating Cancer Plan 2023–2033 [14], and the Taipei Global Consensus [15]. The screen-and-treat programme usually applies to everybody in the population who is older than a certain age (e.g. 30 years or 40 years). A review that included 10 studies in countries with an *H. pylori* infection prevalence range spanning from low to high showed that screening for *H. pylori* infection to prevent gastric cancer in the general population cost < US$ 50 000 per life year gained across diverse populations (see Chapter 9); this finding was robust for differences in ethnicity as well as *H. pylori* infection prevalence [16]. Nevertheless, few population-wide *H. pylori* screen-and-treat programmes have been implemented for gastric cancer prevention. The only current population-wide *H. pylori* screen-and-treat programme is being implemented in Bhutan (see Chapter 3.6) [17]. A cost–effectiveness analysis study in Japan identified a population-wide *H. pylori* eradication strategy as the most cost-effective strategy for a national gastric cancer prevention programme, better than the current strategy, which is a secondary prevention-focused programme of biennial endoscopic screening [18]. A population-wide *H. pylori* eradication programme was launched in the Matsu Islands in 2004, and the incidence of gastric cancer has been reduced substantially [19] (Chapter 3.10). An example is given below of an *H. pylori* screen-and-treat pilot programme targeting people aged 30–34 years that was recently

implemented in Slovenia. This type of programme should be distinguished from the gastric cancer screening programmes in some countries in East Asia, such as Japan and the Republic of Korea, in which endoscopy or barium studies are used as the screening tool for gastric cancer rather than testing for *H. pylori* infection (see Chapters 3.8 and 3.9).

High-risk groups

Because not all groups in a population have the same risk of *H. pylori* infection or of gastric cancer, a strategy that targets higher-risk groups within a population with a lower incidence of gastric cancer may be more appropriate than targeting the general population. Several international guidelines recommend implementing *H. pylori* screen-and-treat programmes in adults to prevent gastric cancer in high-risk populations [13, 20, 21]; this recommendation is also supported by the World Gastroenterology Organization [22]. These alternative approaches are particularly important for countries in Europe and North America where the benefits of population-based *H. pylori* screen-and-treat programmes are relatively small because of low gastric cancer rates. A risk-based programme (also referred to as a risk-stratified or risk-tailored programme) has the potential to improve the balance of benefits and risks, to be more cost-effective, and to prevent more deaths with reduced resource use than population-wide screening [23, 24].

Lin et al. developed a conceptual approach to determine whether and how risk stratification should be incorporated into clinical guidelines [25]. The algorithm has six sequential questions:

1. Are there clinically relevant subpopulations?
2. Are there credible subgroup analyses for these subpopulations?
3. Do subgroup analyses show clinically important differences?
4. Do these differences result in variation of net benefit, or does the evidence only exist in people with a narrow spectrum of risk?
5. Can the subpopulations be easily identified?
6. Does a well-validated multivariable risk tool improve the identification of clinically relevant subpopulations compared with a simpler approach?

This framework allows for a systematic approach to determine whether and how to incorporate evidence for specific populations, and enables a consistent application of evidence and transparent communication about the derivation of risk-stratified recommendations. For *H. pylori* infection, it is likely that there will be limited evidence available for many population subgroups, in which case these questions may be used, instead, to identify the evidence gaps that need to be addressed.

There are no universal criteria for selecting target populations for risk-based *H. pylori* screen-and-treat programmes. Groups that are selected could represent demographic groups within a population in countries with a low risk of gastric cancer, such as Alaska Native people aged ≥ 50 years, and/or people living in the USA who emigrated there from countries with a high incidence of gastric cancer (see Chapter 3.3). Local epidemiology should be used to identify groups within a population that are most likely to benefit from the screen-and-treat programme.

For further research, there are two additional questions to be addressed: what are the comparative (i) clinical effectiveness and (ii) cost–effectiveness of targeting the general population versus targeting the high-risk population? Mathematical modelling remains an indispensable tool for estimating the long-term impact of an *H. pylori* screen-and-treat programme and for comparing different modalities and target groups.

Family-based programme

H. pylori infection is known to cluster in families. For a risk-based approach, an alternative to targeting the high-risk group would be to target family members of patients with gastric cancer or *H. pylori* infection. Testing and treating all *H. pylori*-positive family (or household) members to eliminate a source of reinfection in households, and to facilitate adherence to treatment, is a logical consideration [26, 27]. A meta-analysis comparing the effectiveness of whole family-based treatment versus single-infected-patient treatment showed that the *H. pylori* eradication rate was increased and the recurrence rate was decreased in family-based treatment compared with single-infected-patient treatment [28]. A family-based *H. pylori* treatment programme was recently introduced in China to prevent intrafamilial transmission; the results show that it appears to be an effective and practical strategy to control *H. pylori* infection [29]. In 2021, a Chinese expert panel presented a consensus recommendation for family-based *H. pylori* prevention and management to reduce the related disease burden [30]. A family-based

screen-and-treat strategy that targeted the family members of index cases in an Indigenous population in Taiwan, China, showed an increased *H. pylori* positivity rate in the family members who were tested and a lower reinfection rate among those who were treated, compared with testing and treating individuals [31]. Pre-screening education may be necessary for a more widespread implementation of family-based programmes; in a community-based study in six regions in China, poor adherence to treatment after testing was documented [32]. Family-based strategies present opportunities to eliminate sources of reinfection from households, and these strategies may also target individuals with a family history of gastric cancer in a first-degree relative, which is associated with 2–3 times the risk of gastric cancer. Most clinical consensus reports recommend treating *H. pylori* infection in individuals with a family history of gastric cancer, and this recommendation has been strengthened by data from a randomized *H. pylori* treatment trial [33].

Age group to target for H. pylori *screen-and-treat programmes*

According to the Taipei Global Consensus [15], the population-based screen-and-treat strategy for *H. pylori* infection is most cost-effective in young adults in regions with a high incidence of gastric cancer, and this strategy is recommended to be carried out before atrophic gastritis develops. In a subgroup analysis of a recent cluster-randomized controlled trial in China of community-based *H. pylori* eradication, successful *H. pylori* eradication modestly decreased gastric cancer incidence and mortality rates in treated people aged < 45 years but not in those aged ≥ 45 years [34]. In another randomized controlled trial, patients who underwent endoscopic resection of early gastric cancer and who received treatment for *H. pylori* infection had lower rates of metachronous gastric cancer [35]. In a population-based study in Asia, *H. pylori* treatment prescribed to people aged > 60 years reduced the risk of subsequent gastric cancer development, but these effects were more apparent ≥ 10 years after successful eradication [36].

There is no consensus on the optimal age for *H. pylori* treatment, and it is possible that the optimal age varies between populations. Other issues to consider when deciding on the optimal age for *H. pylori* treatment are differences in population age structure and age-specific risks for groups within a population, and whether the optimal age to screen may differ for some groups (e.g. Indigenous populations). Overall, the evidence supports

population-based *H. pylori* screen-and-treat programmes in adult populations, but the magnitude of the benefit may decrease with age [13].

The benefits of *H. pylori* treatment for asymptomatic children and adolescents have not yet been established; only a limited number of studies have addressed this topic [37]. On the assumption that it is better to eradicate *H. pylori* infection before the carcinogenic effects and advanced pre-neoplastic lesions have developed, several municipalities in Japan are offering *H. pylori* screening to teenagers [38–40]. In an *H. pylori* screening study in students aged 14–15 years, the intestinal microbiota was significantly affected by *H. pylori* infection [41]. Furthermore, in adolescents with *H. pylori* infection, the relative abundance of the Gram-negative *Prevotella* genus was found to be positively correlated with body mass index. In this study, the students are being followed up to evaluate the long-term effects on the intestinal microbiota of eliminating *H. pylori* infection. The 2018 guidelines of the Japanese Society for Paediatric Gastroenterology, Hepatology and Nutrition recommend against a screen-and-treat strategy for *H. pylori* infection in asymptomatic children to prevent gastric cancer, because there is no evidence to support this strategy [42]. However, these guidelines recommend considering treatment to eliminate *H. pylori* infection in children who have a family history of gastric cancer in a first-degree or second-degree relative and in whom active *H. pylori* infection has been found, which is in keeping with the family-based approach (see the previous section).

4.4 Readiness assessment

The implementation of an *H. pylori* screen-and-treat programme requires action at multiple levels: individuals and communities; health-care system units such as facilities and providers, as well as payers and central administration; and the public health authorities that are responsible for providing health information to the public. Table 4.1 provides a checklist for assessing needs and readiness at these different levels.

Table 4.1. Checklist to determine how ready a health system is to implement an *H. pylori* screen-and-treat programme for gastric cancer prevention

1. Needs for an *H. pylori* screen-and-treat programme for gastric cancer prevention		
Are the incidence and mortality rates of gastric cancer available for the target population?	Yes	No
Is the above information recent (within 5 years) and accurate?	Yes	No
Are the *H. pylori* infection prevalence estimates available for the target population?	Yes	No
Is the above information recent (within 5 years) and accurate?	Yes	No
Can the above information be stratified by subgroups (e.g. demographics, race/ethnicity, and socioeconomic position)?	Yes	No
2. Target population		
Have the eligibility criteria for an *H. pylori* screen-and-treat programme been defined, either for the general population or for specific subgroups?	Yes	No
Is the rationale for selecting the type of screening – whether general or risk-based – valid?	Yes	No
Is family-based screening a practical option, compared with individual screening?	Yes	No
3. Readiness for an *H. pylori* screen-and-treat programme for gastric cancer prevention		
Is there a public health authority or scientific assessment team in place to coordinate the programme?	Yes	No
Are the human resources available to implement the programme?	Yes	No
Can *H. pylori* screening be integrated into existing cancer screening programme platforms?	Yes	No
Is the public involved in the programme; for example by providing feedback on their experiences with the screening process?	Yes	No
Is funding available?	Yes	No
Is the health system ready to consider or adopt the *H. pylori* screen-and-treat programme for gastric cancer prevention?	Yes	No
Are the relevant data, such as screening data from a central database or incidence and mortality data from a population registry, available?	Yes	No
Are there quality control practices in place for a screen-and-treat programme for gastric cancer prevention?	Yes	No
Are the outcomes measurable?	Yes	No
Is the programme sustainable?	Yes	No
4. *H. pylori* testing		
Are *H. pylori* tests available, such as the ^{13}C-urea breath test, stool antigen test, and serological test?	Yes	No
Has the performance of the *H. pylori* test been validated in different settings?	Yes	No
Has a testing method been selected for implementation?	Yes	No
Do clinical societies support the *H. pylori* screen-and-treat programme for gastric cancer prevention?	Yes	No
Does the general public support the *H. pylori* screen-and-treat programme for gastric cancer prevention?	Yes	No
Have the providers for *H. pylori* tests been defined?	Yes	No
Are there quality control practices for testing in place?	Yes	No
Is cold-chain transportation available for biospecimens?	Yes	No
Are the costs of *H. pylori* tests affordable for the participants of the programmes or covered by the government?	Yes	No
Is there a payer for the *H. pylori* tests?	Yes	No
Is there a confirmatory test for *H. pylori* eradication?	Yes	No

Table 4.1. Checklist to determine how ready a health system is to implement an *H. pylori* screen-and-treat programme for gastric cancer prevention (continued)

5. *H. pylori* treatment		
Are there effective treatments available for *H. pylori* infection, including both generic and branded medications?	Yes	No
Are there any locally recommended treatment guidelines (last updated date)?	Yes	No
Do clinical societies endorse *H. pylori* treatment for both primary care and specialists?	Yes	No
Do patients endorse *H. pylori* treatment?	Yes	No
Is there a plan to assess treatment compliance?	Yes	No
Are the treatment costs affordable by the participants of the programmes or covered by the government?	Yes	No
Is there a payer available for *H. pylori* treatments?	Yes	No
Is the rate of *H. pylori* resistance to clarithromycin known in the target population, and is it accurate within the past 5 years?	Yes	No
Is the rate of *H. pylori* resistance to levofloxacin known in the target population, and is it accurate within the past 5 years?	Yes	No
Is the rate of *H. pylori* reinfection or recrudescence known in the target population, and is it accurate within the past 5 years?	Yes	No
Is there a follow-up plan in place for treatment failure?	Yes	No
6. Population engagement		
Is there a mechanism to monitor the participation rate in order to improve it?	Yes	No
Is there a mechanism to assess the attitudes of health-care professionals, including both primary care providers and specialists?	Yes	No
Is there a mechanism to assess the attitudes of the target population and the general public?	Yes	No
Are there awareness and engagement activities to involve the target population and the general public?	Yes	No

Infrastructure to support a population-based H. pylori *screen-and-treat programme for gastric cancer prevention*

It is crucial to carry out an assessment of resources before implementing an *H. pylori* screen-and-treat programme, including assessing the existing resources and those still needed. Adequate funding and human resources should be secured to enable the programme to be executed sustainably. To increase the participation rate, the screen-and-treat programme should be provided free of charge to all eligible participants. For risk-based interventions to be successfully developed and implemented, they need to be endorsed by health-care professionals and accepted by the communities and individuals targeted for screening.

Health-care systems vary across regions and countries. *H. pylori* screen-and-treat programmes are typically carried out within existing primary care or public health systems, which may lack experience in administering screening tests for *H. pylori* and

prescribing the appropriate treatment for people with the infection. In such situations, the appropriate testing facilities should be installed, and the health-care personnel who will be involved in the testing and treatment should be given the necessary training. A clear and defined pathway should be devised to give participants a simple way to register to be tested, to notify them of the test result, and to offer treatment if the test result is positive for *H. pylori* infection. This typically requires developing a new, secure electronic platform (or modifying an existing cancer screening programme platform, such as those used for colorectal or breast cancer screening) for registration, referral, reporting of results, and tracking of participants [43]. The system would ideally identify individuals who were due to be tested or treated and would gather data to be used to evaluate the process in real time and the programme's outcome indicators.

Testing facilities

The various testing options that are available for diagnosis of *H. pylori* infection are described in Chapter 5. Depending on the screening test selected, laboratory facilities equipped to handle the expected volume of tests must be made available. Although *H. pylori* serology and stool antigen tests do not usually require any special laboratory equipment, urea breath tests require infrared spectroscopy or mass spectrometry to measure the ^{13}C isotope. Implementing screen-and-treat strategies requires adequate dedicated laboratory space, equipment, and staffing; laboratory staff must be trained to provide standardized, uninterrupted, sustainable, and competent laboratory support services for screen-and-treat activities. To determine the scale of the laboratory facilities required, the available resources and the expected participation rates of the targeted individuals should be considered, as well as the options for building capacity gradually or all at once. Ongoing quality assurance and/or accreditation of test centres should be implemented to ensure the accuracy of the test results, the reported information, and the data archives.

In addition, infrastructure will be required to collect the relevant samples (blood, breath, or stool samples), either at dedicated testing centres or at the existing facilities. Samples should be collected in places that are convenient for the participants, and laboratory facilities should be easily accessible for delivery of samples, in particular because delays in transporting stool samples can lead to false-negative test results. If serology is used for testing, trained phlebotomists will be needed to take blood samples

to test for *H. pylori* antibodies. For urea breath tests, trained personnel are needed to administer the labelled urea and to collect breath samples according to a standard protocol. Moreover, assessment of local endoscopy capacity may be needed for performing additional endoscopy of some high-risk individuals identified by the programme.

Health-care providers

The health-care providers involved in the screen-and-treat programme should be trained and regularly updated on the latest local recommendations for the diagnosis and treatment of *H. pylori* infection. Locally available tests and follow-up protocols should be standardized across facilities. A clear referral and treatment pathway should be implemented, with standardized and structured responses to common outcomes (e.g. positive test results) and queries to minimize confusion and misunderstanding among participants.

A systematic review showed that risk stratification within population-based cancer screening programmes is largely acceptable to health-care professionals [44]. The review discussed many barriers to and facilitators of implementation, and emphasized the importance of training, public involvement, and effective communication, as well as the importance of providing evidence that justifies reducing screening for low-risk groups and managing resource limitations.

Treatment availability

A standard treatment protocol should be available for people who test positive for *H. pylori* infection, and this treatment should be provided free of charge to participants. Treatment can be provided at the primary care level or at dedicated screen-and-treat clinics. Updated local treatment recommendations should be made available and widely disseminated to the health-care providers responsible for treating individuals who test positive. Because of the general increase in *H. pylori* antimicrobial resistance [45], treatment recommendations should be updated periodically on the basis of local antibiotic resistance profiles, the treatment outcomes of programme participants, and the latest literature. For example, a recent meta-analysis of studies conducted in the Asia–Pacific region estimated resistance prevalences at 30% for clarithromycin, 61% for metronidazole, 35% for levofloxacin, 4% for tetracycline, and 6% for amoxicillin [46]. The

European Registry on *Helicobacter pylori* Management could be used as a reference for the prevalence of antimicrobial resistance in European countries [3]. Because the prevalence of *H. pylori* antibiotic resistance varies considerably across countries, local data are required to inform the best choice of antibiotics for a screen-and-treat programme. Alternative treatment options should be available for patients with allergies to antibiotics. The authorities responsible for the screen-and-treat strategies that are adopted should ensure an adequate supply of medications that are needed to treat people with *H. pylori* infection, including the medications needed to treat refractory cases. To ensure the success of screen-and-treat strategies, follow-up testing after treatment for *H. pylori* infection (by urea breath test or stool antigen test) should be available on a routine basis. Clear indications for referral for endoscopy should be included in the treatment guidelines (e.g. the presence of alarm symptoms or refractory infections).

Maximizing engagement

High levels of participation are crucial to the success of any cancer prevention programme, including any *H. pylori* screen-and-treat programme. Including representatives of the target population in the planning and evaluation of the programme is essential to design and maintain effective recruitment strategies. Information on *H. pylori* infection and the benefits and risks of a screen-and-treat programme should be prepared and delivered with the target population in mind. For the choice of where and how to deliver this content (e.g. media, pamphlets, workshops, via health professionals), the modalities that will have the greatest reach for the populations of interest should be considered.

During programme planning, media (i.e. TV, radio, printed and online media, and social media) should be engaged to raise public awareness of the importance of *H. pylori* infection as a cause of gastric cancer and other upper gastrointestinal diseases. Furthermore, media relations should be used to engage the public using various communication tools (e.g. press releases or statements). The general public, and especially the participants targeted, should be able to access additional information from dedicated programme websites. Additional research is needed on the acceptability of different testing modalities for target populations, and on the major barriers to

participation to be addressed in the design and implementation phases of any programme.

4.5 Examples of *H. pylori* screen-and-treat programmes

Community-driven projects in Arctic Canada

The community-driven research programme carried out by the Canadian North *Helicobacter pylori* (CAN*Help*) Working Group [47, 48] (see Chapter 3.4) demonstrates how community-engaged research can contribute the information that is required to assess the needs and readiness for effective gastric cancer prevention strategies. The relevant information generated by CAN*Help* projects is described below, and specific project findings are summarized in Table 4.2.

Table 4.2. Data for assessing readiness for a gastric cancer prevention test-and-treat initiative, CAN*Help* community projects, western Arctic Canada, 2007–2018

Community project data on *H. pylori*-associated disease burden

- Of 1082 Indigenous participants with data on *H. pylori* status, 60.5% tested positive for *H. pylori*.
- *H. pylori* infection occurred with gastric pathology indicative of increased risk of gastric cancer (severe chronic gastritis, atrophic gastritis, and intestinal metaplasia) more frequently in project participants than in a comparison population of patients who had gastric biopsies examined at the University of Alberta Hospital [49].
- Among 309 participants examined endoscopically, visible mucosal lesions were more frequent in the stomach than in the duodenum. The gastric-to-duodenal ratio was 2 for inflammation, 8 for erosions, and 3 for ulcers [50]. This pattern is associated with increased risk of gastric cancer.
- Pathological examination in 308 participants with gastric biopsies revealed normal gastric mucosa in 1 of 224 *H. pylori*-positive participants and 65 (77%) of 84 *H. pylori*-negative participants, with sharp contrasts in the prevalence of specific abnormalities between *H. pylori*-positive and *H. pylori*-negative participants, respectively: moderate–severe active gastritis, 50% and 0%; moderate–severe chronic gastritis, 91% and 1%; atrophic gastritis, 43% and 0%; intestinal metaplasia, 17% and 5%.
- In-depth pathological examination of gastric biopsies from 20 participants with intestinal metaplasia showed that all except 1 had the high-risk incomplete cell type.
- Frequencies of chronic digestive symptoms reported by participants did not differ notably by *H. pylori* status (adjusting for age, sex, ethnicity, proton pump inhibitor or acid suppressor use, non-steroidal anti-inflammatory drug use, smoking, and alcohol intake), with about half in either group reporting no symptoms; factors associated with reporting one or more chronic dyspepsia symptoms (excluding heartburn and reflux) were older age, female sex, non-steroidal anti-inflammatory drug use, smoking, and alcohol intake.

Cancer registry data on *H. pylori*-associated disease burden

- Increased gastric cancer incidence rates were observed in Indigenous residents of the Northwest Territories relative to Canada as a whole [51], Indigenous Albertans relative to non-Indigenous Albertans [52], and Indigenous populations relative to non-Indigenous counterparts worldwide [53].
- Gastric cancer is the fourth most frequent site for cancer mortality in Yukon men and the fifth most frequent site in Yukon women [54], in contrast to the 10th most frequent site in men and women across Canada [55].
- The proportion of gastric cancer cases diagnosed in people aged < 60 years was 48% in the Northwest Territories in 1997–2015 [51], > 40% in Yukon [54], and < 25% across Canada as a whole, during similar time periods [55].
- Also, of the gastric cancer cases diagnosed in Indigenous residents of the Northwest Territories in 1997–2015. 16% occurred in people aged < 40 years [51], compared with < 2% across Canada as a whole [55].

Table 4.2. Data for assessing readiness for a gastric cancer prevention test-and-treat initiative, CAN*Help* community projects, western Arctic Canada, 2007–2018 (continued)

Community project data on high-risk groups

Prevalence of *H. pylori* infection (by urea breath test or histology) by sociodemographic factors

	Number tested	Prevalence (%)	95% confidence interval (%)
Total	1352	54	51–65
Indigenous	1082	61	58–63
Non-Indigenous	202	16	11–22
Among 1082 Indigenous participants			
Aged 0–14 years	127	39	31–48
Aged 15–24 years	142	66	58–74
Aged 25–44 years	314	68	62–73
Aged 45–64 years	369	59	54–64
Aged 65–96 years	130	62	53–71
Female	636	57	53–60
Male	446	66	62–71
Inuit	331	63	57–68
Gwich'in First Nations	427	63	58–68
Among 813 Indigenous participants aged > 24 years			
	313	69	64–74
High school diploma or trade	325	64	58–69
Any higher education	139	47	39–56

Community project data on treatment effectiveness

- Two quadruple (4-drug) regimens evaluated had estimated effectiveness > 90%.
- Clarithromycin-based triple therapy was substantially inferior to quadruple therapies.
- Among 83 participants who were retested an average of 2.9 years after successful treatment, 71 (86%; 95% confidence interval, 76–92%) remained free of *H. pylori* infection.

Community project data on target population readiness for a test-and-treat programme

- Despite efforts to accommodate all community members who wished to be screened by urea breath test, the proportion screened varied widely across communities, from 10% to 80% among eight communities with < 1000 residents, averaging 33.
- Of 682 participants who tested positive for *H. pylori* by urea breath test, 31% did not accept the offer of treatment; this proportion was fairly consistent across communities, ranging approximately from 20% to 40%.
- Participants who returned for follow-up testing had excellent adherence to treatment.
- Of 473 participants to whom treatment was dispensed, 35% did not return for follow-up testing (and it is unknown whether they completed treatment).

Is there a need?

Information on the elevated risk of gastric cancer in populations with relevance to the target population was obtained from cancer registry data. Because the northern territories in Canada generally have < 5 gastric cancer cases per year, annual

frequencies of gastric cancer are not reported for these jurisdictions. A study that aggregated the Northwest Territories data from 1997–2015 (26 cases in Indigenous men, 16 cases in non-Indigenous men, 18 cases in Indigenous women, 3 cases in non-Indigenous women) estimated age-standardized incidence rates (per 100 000 person-years) of 13.8 (95% confidence interval [CI], 8.4–19.2) for Indigenous men and 7.7 (95% CI, 4.1–11.2) for Indigenous women, in contrast to 8.8 (95% CI, 3.9–13.7) for non-Indigenous men and 2.0 (95% CI, 0.0–4.3) for non-Indigenous women. This study compared these estimates with Canada-wide age-standardized incidence rates estimated from 2003–2012 data (16 872 cases in men and 9510 cases in women) of 7.0 (95% CI, 6.9–7.1) per 100 000 person-years in men and 3.2 (95% CI, 3.1–3.3) per 100 000 person-years in women [51]. CAN*Help* project data demonstrated a high burden of *H. pylori*-associated disease in the target population (Table 4.2).

Who should be targeted?

Although age-specific rates of gastric cancer are not reported for the target population, the proportion of gastric cancer cases diagnosed in people aged < 60 years was 48% in the Northwest Territories in 1997–2015 [51], > 40% in Yukon [54], and < 25% across Canada as a whole, during similar time periods [55]. Also, of the gastric cancer cases diagnosed in Indigenous residents of the Northwest Territories in 1997–2015, 16% occurred in people aged < 40 years [51], compared with < 2% across Canada as a whole [55]. This suggests a potential benefit of targeting young adults.

CAN*Help* project data demonstrated a prevalence of *H. pylori* infection of close to 40% in children aged < 15 years; this indicates that childhood transmission is common in participating communities. In adults, *H. pylori* infection prevalence was highest in the age group 15–44 years and was substantially lower in people who had received higher education compared with people who had not completed high school. *H. pylori* infection prevalence was about 60% in Indigenous participants compared with 16% in non-Indigenous participants, most of whom were teachers, nurses, and police officers from elsewhere in Canada residing temporarily in participating communities. *H. pylori* infection prevalence ranged from 56% to 66% in four communities in the Beaufort Delta region of the Northwest Territories and nearby northern Yukon in which participants were screened for *H. pylori* in 2008–2012; it ranged from 37% to 50% in four communities in southern Yukon in which participants were screened for *H. pylori* in 2016–2017. The

observed variations in *H. pylori* infection prevalence among populations, places, and times did not reveal subgroups of Indigenous community members who should be excluded from gastric cancer prevention initiatives, although few children aged < 15 years had pathological assessment, so there is little evidence on which to base a minimum age for a screen-and-treat strategy. In the absence of evidence of benefit to children, the relevant paediatric guidelines for managing *H. pylori* infection should take precedence [56].

Are adequate testing resources available?

The CAN*Help* projects demonstrated the successful implementation of non-invasive testing for *H. pylori* using the ^{13}C-urea breath test, with samples shipped from the northern territories for analysis in the laboratory at the University of Alberta. When the CAN*Help* projects began in 2007, Northwest Territories Health and Social Services provided breath tests to patients when health-care providers ordered *H. pylori* testing for diagnostic evaluation. However, this was not the case for Yukon Health and Social Services, which until recently used only serology testing to diagnose *H. pylori* infection. Currently, practitioners in both jurisdictions have been trained in the collection and transportation of breath samples for analysis in the southern Canadian provinces.

Are effective and affordable treatment regimens available?

Randomized treatment trials conducted within CAN*Help* projects identified regimens with good long-term effectiveness in trial participants and for which adherence to the regimen was also good (Table 4.2). Furthermore, follow-up of 69 participants examined by gastroscopy with gastric biopsies several years after treatment to eliminate *H. pylori* infection showed that most participants who had successful treatment at baseline remained infection-free at follow-up; the prevalence of precancerous gastric pathologies was also substantially lower at follow-up than at baseline. Furthermore, participants who were *H. pylori*-negative at follow-up had a higher frequency of improvement in precancerous gastric pathologies than those who were *H. pylori*-positive at follow-up. Overall, the available evidence suggests that most *H. pylori*-positive community members who participated fully in the treatment component of CAN*Help* projects had a sustained reduction in gastric cancer risk indicators.

Is the target population ready for a screen-and-treat strategy?

Data from the CAN*Help* projects show that motivation to participate in screening varied widely across communities (Table 4.2). Project data also reveal a participation challenge for initiatives involving treatment and verification of treatment success: close to one third of *H. pylori*-positive participants did not accept the offer of treatment, and about one third of those to whom treatment was dispensed were lost to follow-up. The queries of participants about chronic digestive complaints showed that complaints in the target population were similar to those in people without *H. pylori* infection; this circumstance would prevent most *H. pylori*-positive members of the target population from experiencing the immediate benefits of treatment.

Is there adequate infrastructure for providing the treatment and supporting the overall implementation of a screen-and-treat strategy?

The CAN*Help* projects demonstrated the feasibility of engaging local health-care practitioners and regional pharmacies to dispense treatment that was paid for by territorial and federal health insurance. The projects also demonstrated strong support from local, regional, territorial, and extraterritorial health officials for gastric cancer prevention activities that were sought by Indigenous communities in their jurisdictions.

Aotearoa New Zealand

Is there a need?

In Aotearoa New Zealand, the need for *H. pylori* screen-and-treat strategies to prevent gastric cancer in priority groups is clear. There are stark ethnic differences in the prevalence of *H. pylori* infection [57, 58] and the rates of gastric cancer [59] (see Chapter 3.11). Currently, gastric cancer incidence rates (per 100 000 person-years) are moderate (10–20) in Māori people (11) and in Pacific people (14), age-standardized to the World Health Organization (WHO) world population standard (2017–2021) but lower in Asian people (6) and European/Other people (4), i.e. non-Māori, non-Pacific, non-Asian people [60]. In another analysis, which was standardized to the 2001 Māori population, the gastric cancer incidence rates (per 100 000 person-years) were 13 for Māori people, 14 for Pacific people, 7 for Asian people, and 4 for Sole European people (in 2015–2018) [61]. The average age at diagnosis of gastric cancer is 10 years younger in Māori people and Pacific people than in European people [62, 63].

Who should be targeted?

Consensus is needed on the high-risk groups to target and whether a risk-based strategy is the best approach. This could be supported by more detailed analyses of the prevalence rates of gastric cancer, peptic ulcer, and *H. pylori* infection in potential priority and sociodemographic groups, under the direction of a broad advisory group that includes health experts representing Indigenous people, Pacific people, Asian people, and the migrant population (see Chapter 3.11). Agreement is needed on how to recruit individuals, the interaction with other screening programmes, which age groups to target, and whether to follow up household members, of what age, when someone has an infection. There is emerging interest in exploring an *H. pylori* screen-and-treat programme to prevent gastric cancer in New Zealand in Māori people [64].

Are adequate testing resources available?

Further consensus is needed on the choice of diagnostic test. The stool antigen test is a funded, recommended, and widely available test for assessing active *H. pylori* infection in New Zealand (see Chapter 3.11). Participants can drop stool samples off at local community laboratories across the country, where the samples are frozen and transported to a designated laboratory for testing. However, there may be concerns about the acceptability of this test in priority populations [64]. An alternative option would be to start with an initial (locally validated) serology test, and then follow up people who have a positive serology test result with a stool antigen test. Although the two-step model is more complicated, it is likely to be more affordable and may have fewer barriers to uptake. The *H. pylori* in Aotearoa New Zealand Study will investigate the uptake and the relative performance of serology (initial test) and stool antigen testing (optional or confirmatory test) (see Chapter 3.11). Further information (disaggregated by ethnicity and other factors) that is useful for testing decisions includes local validation of serology, local comparison of the sensitivity and specificity of testing approaches, and further understanding of the acceptability and uptake for different tests.

Tests that are not currently available may also be considered. Urea breath tests are not publicly funded in New Zealand and are thus used rarely and only in some centres [58]. The widespread adoption of breath testing would require additional investment, time, and planning. Home-based testing for stool antigens, as with rapid antigen testing, could also be considered if it becomes available and affordable.

Are effective and affordable treatment regimens available?

As has been seen globally, there are likely to be increasing rates of *H. pylori* clarithromycin resistance in New Zealand (see Chapter 3.11). There is an urgent need for study findings, including from studies currently under way, to report on *H. pylori* eradication rates and antibiotic resistance (e.g. clarithromycin resistance) to current first-line and second-line treatment combinations in New Zealand, and how this varies by ethnicity. This information should be used to update various New Zealand treatment guidelines (health pathways, formulary, Best Practice Advocacy Centre New Zealand) and to inform which treatments are publicly funded. Current guidelines are not consistent with the Maastricht VI/Florence Consensus report, which recommends first-line treatment with 14 days of bismuth-containing quadruple therapy if clarithromycin resistance is > 15% and susceptibility testing is not available [13].

Guidelines should also recommend retesting at 4–6 weeks after *H. pylori* treatment, to assess successful eradication. This would improve eradication rates via the use of second-line treatment and could support the monitoring of treatment effectiveness.

Is there adequate infrastructure for providing the treatment and supporting the overall implementation of a screen-and-treat strategy?

Advice on structured screening programmes in New Zealand is provided by an independent advisory group, the National Screening Committee, and funding and implementation require a government decision [65]. Organized cancer screening programmes are managed by the National Screening Unit in New Zealand, in the public health system (Te Whatu Ora/Health New Zealand). Previously, proposed screening programmes (e.g. lung cancer screening) have been piloted and evaluated by Te Whatu Ora/Health New Zealand, and this would be a useful approach for an *H. pylori* screen-and-treat strategy in the first instance, for example starting in one region (e.g. the northern region) and/or in a priority group. Implementation decisions would need to be made by a multidisciplinary team of experts about who will be invited, how people will be invited, the process for testing, who will treat participants (and whether this would include telehealth), and how each element will be publicly funded so that it is free to participants. A cost–effectiveness analysis of selected screen-and-treat approaches or modalities will be useful for decision-making. A single database or register would need to be developed to manage the process from invitation to final follow-up and would be used to monitor

and evaluate the progress. An important consideration will be the capacity of the health system to introduce and manage the new programme [66], including considerations about how the programme hopes to integrate with the stretched primary health-care system and how gastroscopy referrals will be managed for participants with red flags for gastric cancer.

There are groups in the New Zealand population who are at sufficiently high risk for gastric cancer to warrant a screen-and-treat approach. Piloting an *H. pylori* screen-and-treat programme for priority groups would enable solutions to be refined as the project is developed to address the current challenges outlined above. Funding appropriation would support the scale-up. Ongoing research can support these developments.

Slovenia (EUROHELICAN)

The goal of the EU4Health project Accelerating Gastric Cancer Reduction in Europe through *H. pylori* Eradication (EUROHELICAN) is to obtain new evidence to improve gastric cancer prevention by eradicating *H. pylori* infection, which is the most important risk factor (see Chapter 3.5). In contrast to the programmes in Arctic Canada and Aotearoa New Zealand, EUROHELICAN is a population-based pilot programme that is being implemented in people aged 30–34 years.

Is there a need?

The crude gastric cancer incidence rate in Slovenia is 28.5 per 100 000 person-years in men and 16.9 per 100 000 person-years in women.

Who should be targeted?

Participants aged 30–34 years were sampled using the Monte Carlo representative sampling method and are being enrolled at the Community Healthcare Centre Dr Adolf Drolc Maribor. Participant enrolment will provide data on responsiveness to the invitation, the current prevalence of *H. pylori* infection, the acceptability and success of treatment, and any adverse events during therapy. Data on the acceptability and feasibility of the proposed screen-and-treat strategy will be obtained from the medical personnel participating in the study, by using a survey conducted after the completion of patient enrolment. The sets of electronic forms and the sequences in which they are used are shown in Fig. 4.2. A total of 4000 individuals aged 30–34 years were invited,

with a participation rate of about 30% and a seropositivity rate of 13%. The study results are described in Chapter 3.5.

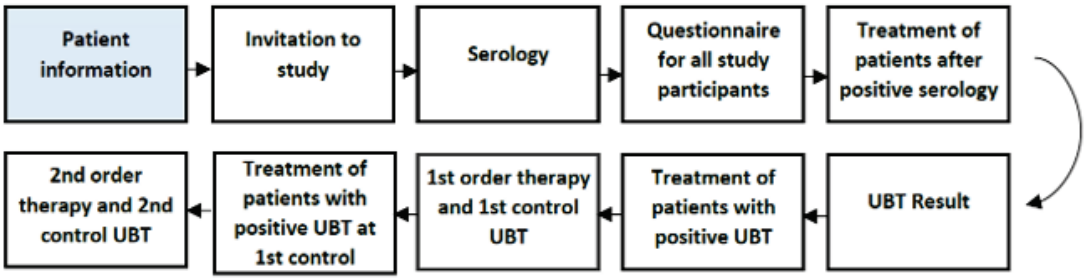

Fig. 4.2. Slovenia screen-and-treat programme. UBT, urea breath test. Source: Tepeš et al. (2024) [67].

Which test should be used to detect H. pylori *infection?*

Two-stage testing is being used to confirm an active infection; the first test used is serology, and a confirmatory urea breath test is used for participants with a positive serology test result.

Are effective and affordable treatment regimens available?

Participants with *H. pylori* infection are treated with bismuth-containing quadruple therapy, following the recommendation in the Slovenian Association for Gastroenterology and Hepatology guidelines.

Is there adequate infrastructure for providing the treatment and supporting the overall implementation of a screen-and-treat strategy?

The Slovenia National Institute of Public Health is the project leader and, in cooperation with the Community Healthcare Centre Dr Adolf Drolc Maribor, is investigating various aspects of the screening implementation by pilot testing the *H. pylori* screen-and-treat strategy. The study protocol was written in cooperation with the other project partners (the University of Latvia, Riga, Latvia; IARC, Lyon, France; and Nantes University Hospital, Nantes, France). An important part of the study is the analysis of participants' survey data on risk factors for *H. pylori* infection in childhood.

4.6 Conclusions

This chapter outlines an approach to assessing the needs and readiness for the implementation of *H. pylori* screen-and-treat strategies. Needs assessments are critical before the implementation of these strategies and should include an assessment of recent local gastric cancer incidence and mortality rates (overall and for groups within the population) and the prevalence of *H. pylori* infection. Widespread population-based *H. pylori* screen-and-treat strategies will be more cost-effective in areas with intermediate to high gastric cancer incidence than in areas with lower gastric cancer incidence. In areas with lower incidence of gastric cancer, targeting *H. pylori* screen-and-treat strategies to selected intermediate-risk and high-risk groups will often be the best option. Screening and treating could be considered for family members of individuals with *H. pylori* infection or gastric cancer.

Readiness for implementation includes having available testing resources, effective and affordable anti-*H. pylori* treatment, adequate infrastructure to support the overall implementation, and strategies to maximize engagement in the target population. It is essential to run a pilot study to assess the feasibility and acceptance of an *H. pylori* screen-and-treat programme. Additional infrastructure and ongoing funding would be needed to scale up and maintain a screen-and-treat programme. A sound cost–effectiveness analysis that weighs the specific costs and benefits for the target population, not limited to gastric cancer reduction, would help decision-makers to prioritize the resources required in the context of competing health priorities and local values.

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Chapter 5.

Considerations for choice of population-based *Helicobacter pylori* detection methods

Bojan Tepeš, Markus Gerhard, Wai Keung Leung, Jin Young Park, and Yi-Chia Lee

Summary

- For population-based *H. pylori* screen-and-treat programmes, non-invasive tests should be used.
- Non-invasive testing methods include the ^{13}C-urea breath test, the *H. pylori* stool antigen test, and serology tests, with confirmatory tests for people who test positive.
- Considerations for selecting *H. pylori* tests in population-based programmes should include test performance and predictive values, as well as practical factors such as support systems, participants' preferences, and costs.
- Confirmation of success of *H. pylori* eradication should rely on post-treatment testing using the ^{13}C-urea breath test or the stool antigen test at least 4 weeks after the completion of *H. pylori* therapy.

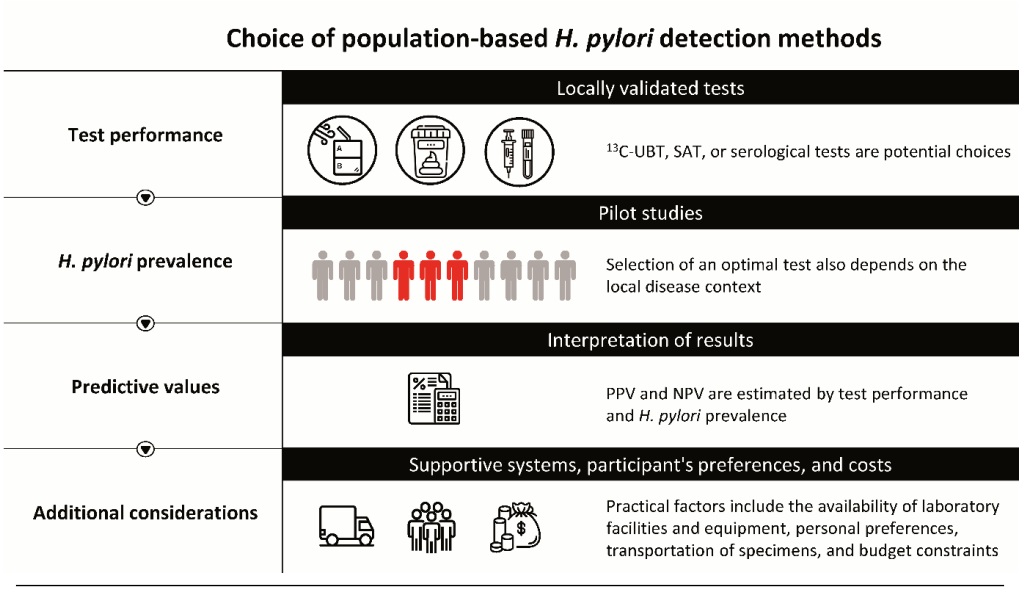

Fig. 5.1. Visual abstract. NPV, negative predictive value; PPV, positive predictive value; SAT, stool antigen test; UBT, urea breath test.

5.1 Introduction

H. pylori infection is usually clinically silent in most patients, and the only way to identify individuals with *H. pylori* infection is through testing. Although *H. pylori* infection consistently leads to chronic inflammation of the stomach mucosa, predicting who will develop clinically significant diseases remains challenging. Therefore, *H. pylori* eradication is recommended for anyone diagnosed with an active infection [1, 2]. Population-based *H. pylori* screen-and-treat programmes for gastric cancer prevention are recommended in countries with intermediate risk (i.e. a crude incidence rate of 10–20 new gastric cancer cases per 100 000 person-years) to high risk (i.e. > 20 new cases per 100 000 person-years), as stated in the Maastricht VI/Florence Consensus report [2], Europe's Beating Cancer Plan 2023–2033 [3], and the Taipei Global Consensus report [4].

The selection of the appropriate population testing methods is a crucial topic, and the methods selected may need to be tailored to the population characteristics and the health-care infrastructure. Diagnostic tests for *H. pylori* infection include non-invasive methods (urea breath test, stool antigen test, and serological tests) and endoscopy-based invasive methods (rapid urease test, histology, and bacterial culture). For population-based *H. pylori* screen-and-treat programmes, non-invasive tests should be used. Not only should the diagnosis of *H. pylori* infection be made using an accurate test; eradication should also be verified with a follow-up test, because the treatment rate is far from 100% with any treatment regimen.

This chapter provides an introduction to the potential choices for *H. pylori* testing and their underlying mechanisms (Section 5.2). In real-world applications, additional practical considerations are necessary (Section 5.3). It is possible that gastric cancers may already be present at the time of *H. pylori* testing and treatment (Section 5.4). An introduction to endoscopy-based, invasive tests for *H. pylori* infection in the middle-aged population is given in Section 5.5. In Section 5.6, methods for interpreting results across various population scenarios with differing prevalence of *H. pylori* infection are described, and predictive values are addressed. Conclusions and future directions are provided in Section 5.7.

5.2 Importance of test performance for population-based *H. pylori* testing

H. pylori testing is accomplished by measuring the concentration of $^{13}CO_2$ in exhaled air before and after the ingestion of a test meal, detecting *H. pylori* antigens in stool

samples, or detecting *H. pylori* antibodies in blood samples. For the selection of a population-based test, the test performance and predictive values should first be considered. Test performance is determined by diagnostic accuracy studies, which evaluate the sensitivity (test positive/true positive) and the specificity (test negative/true negative). The diagnostic accuracy of *H. pylori* tests is addressed in this section.

Urea breath tests

The urea breath test (UBT) is the cornerstone of non-invasive diagnosis of *H. pylori* infection. This diagnostic method exploits the urease activity of *H. pylori*. Participants ingest urea labelled with either ^{13}C or ^{14}C isotopes. Because of its radioactivity, ^{14}C is not suitable for population testing, because pregnant women may inadvertently participate in the programme. *H. pylori* urease hydrolyses the labelled urea ($^{13}CH_4N_2O$), resulting in the production of ammonia (NH_3) and labelled carbon dioxide ($^{13}CO_2$), and the $^{13}CO_2$ is absorbed into the bloodstream and subsequently exhaled. Measurement of the increase in the concentration of labelled $^{13}CO_2$ in the breath provides a direct indication of the presence of *H. pylori* infection. There are two analytical systems for the UBT: mass spectrometry and infrared spectrometry. The UBT has demonstrated high sensitivity and specificity, > 95% in most studies [5–7]. Participants should refrain from taking antibiotics for at least 1 month and from using proton pump inhibitors for at least 14 days before the UBT. Participants should fast for at least 2 hours before the test and should undergo pre-test and post-test assessments within a 30-minute interval. The UBT has been extensively validated in clinical settings not only for initial diagnosis but also for confirming eradication after treatment. In a meta-analysis, the UBT was found to be 10% more sensitive than stool and blood tests [7]. Given its non-invasive nature and its high diagnostic performance, the UBT is a commonly used method in clinical practice. In practice, there are two methods for collecting end-expiratory air: the tube method and the bag method (Box 5.1). Both methods offer advantages in sample stability during transportation compared with the stool antigen test.

Box 5.1. The tube method versus the bag method for the UBT

Both methods require correctly collecting the end-expiratory air and ensuring that the CO_2 concentration is sufficient. The tube method typically requires four tubes (two for pre-test assessments and two for post-test assessments). If the CO_2 concentration is

insufficient in one tube, there is another tube to test. The tube method may have a lower likelihood of air leakage, but it is associated with higher costs. A tube is more convenient than a bag for transportation between the collection point and the laboratory. The bag method involves collecting one bag for the pre-test assessment and another for the post-test assessment. This method is convenient to operate and collects a larger volume of gas, which allows for repeated testing. However, if the CO_2 concentration is insufficient initially, the participant should be called back and the UBT should be redone. Bags are less suitable than tubes for transportation, because of the higher likelihood of gas leaks.

Stool antigen tests

The stool antigen test (SAT), which detects *H. pylori* antigens in stool samples, offers a non-invasive and reliable diagnostic alternative. SATs use monoclonal antibodies to identify *H. pylori*-specific antigens in stool samples. Multiple studies and clinical trials have reported high sensitivity and specificity for SATs, with values > 90% [7–9]. In addition to population testing, the SAT has been proven to be particularly valuable in paediatric populations and for post-eradication verification, given its non-invasive nature and its high diagnostic accuracy [10, 11]. Like for the UBT, the intake of proton pump inhibitors, antibiotics, and bismuth-containing compounds can reduce the bacterial load and potentially lead to false-negative results [8]. Also, because monoclonal antibodies can only detect one epitope, the test performance depends on the conservation of the epitope and the nature of the circulating strains. The performance of SATs also depends on the timely processing of the stool sample and the storage temperature (< 8 °C). Delayed processing can lead to degradation of the antigen–antibody complexes and can lower the sensitivity of SATs. These factors mean that in real-life use the sensitivity of SATs is often < 90%. In a country with limited resources and many remote places, the above-mentioned limitations should be considered when choosing the SAT. A point-of-care SAT is now available as a rapid test, but it is not as sensitive as the enzyme-linked immunosorbent assay (ELISA) SAT.

Box 5.2. Molecular detection of *H. pylori* and resistance strains in stool samples

Molecular methods, such as polymerase chain reaction (PCR) and next-generation sequencing, are increasingly being used for detecting *H. pylori* DNA and identifying antibiotic resistance mutations directly from stool samples. Although these methods have not yet been implemented in population test-and-treat programmes, because of higher costs and lower availability, they offer better stability and valuable information for selecting effective treatments, usually after failure of first-line treatment. These advanced techniques provide high diagnostic accuracy, with sensitivities and specificities often > 95%, but the results are heterogeneous among the different studies [12–14]. The ability to detect specific mutations that confer resistance to antibiotics, such as clarithromycin and levofloxacin, is particularly crucial given the rising prevalence of antibiotic-resistant *H. pylori* strains. Molecular detection for these antibiotics has not yet been sufficiently validated in clinical trials, which have showcased excellent performance in both the diagnosis of *H. pylori* infection and the identification of resistance patterns [15]. This diagnostic approach is valuable in guiding the appropriate treatment regimens in the face of antibiotic resistance challenges [16]. However, PCR-based detection methods are limited when it comes to rare mutations, which may not be included in the panel. This limitation can be overcome by next-generation sequencing, which is more laborious and expensive, and the bioinformatics are more complex to validate. For other antibiotics, especially metronidazole, which is still one of the most frequently used antibiotics in *H. pylori* therapies, little is known about the molecular mechanisms that lead to resistance, and several genes or parameters seem to be able to contribute to resistance. Therefore, molecular models are not yet sufficiently reliable to detect or predict metronidazole resistance [17]. In general, molecular methods are not yet sufficiently validated and cost-effective to be used for population-level programmes.

Serological testing

Serological testing for *H. pylori* infection involves the detection of specific antibodies (immunoglobulin G) against *H. pylori* in the patient's serum. Because the gastric inflammation persists for decades, almost every individual with *H. pylori* infection has multiple, highly specific antibodies against *H. pylori* antigens in their blood. The most

used and best-characterized test formats are ELISA and western blotting, or a newer version called line blotting. The principal advantage of serology tests is the high sensitivity and technical specificity of these state-of-the-art tests. Given its simplicity, broad availability, and lower cost, ELISA is the preferred method for population-based screening. However, a major limitation is the inability to distinguish between current and past infections because of the prolonged presence of antibodies even after bacterial eradication, which lowers the clinical specificity [18–20]. Serology is used primarily for initial screening purposes (to be confirmed by the UBT) but cannot be used to determine successful eradication. Although western blotting may be considered too impractical for population-based testing, there may be circumstances in which it could be informative, for example if additional specificity is required or the responsiveness to individual antigens is of interest. The sensitivity and specificity of serology tests vary widely, typically ranging from 80% to 98% [20–22]. Because of the inability to differentiate current from past infection, serology tests are not recommended as the only method for diagnosing current *H. pylori* infection. The accuracy of serology tests depends on the choice and number of antigens used. Large-scale studies using multiple *H. pylori* antigens could show that the antibody frequencies against individual antigens are highly variable, depending on the antigens used. CagA is among the most immunogenic antigens, and almost every individual infected with a CagA-positive strain has high antibody titres against CagA. However, this depends on the geographical region, because, for example, in Europe and North America a substantial number of strains lack CagA [23]. Therefore, only locally verified serology tests with sensitivities and specificities of > 90–98% should be used in test-and-treat programmes as the first test, usually followed by the UBT for confirmation of current infection. Tests with lower performances should no longer be used. A properly validated and well-characterized serology test will always have a technical specificity of > 90%, and cross-reactivities are rare. State-of-the-art tests based on recombinant antigens are very sensitive and specific. Other antigens with highly prevalent antibodies are FliD and GroEL. If three or more antigens are combined, a sensitivity of nearly 100% can be achieved. In addition, some assay formats enable the distinction of the individual antibody responses (e.g. line blotting, Luminex). Such assays have become valuable in epidemiological studies to identify individuals in whom *H. pylori* infection was eradicated or who lost *H. pylori* infection by other means, and in determining the risk of *H. pylori*-associated diseases [24, 25], but these assays are more expensive and must be performed in specialized

laboratories, in which the required infrastructure (Dynablot instrument for line blotting or fluorescence-activated cell sorting [FACS] instruments for Luminex) to conduct and process the assays is available. An additional advantage of serological testing is the potential for the simultaneous assessment of gastric secretory function including testing for pepsinogen I and II (enzymes produced in the stomach), which could identify individuals with gastric atrophy [26].

5.3 Additional considerations

In addition to the test performance, several factors may influence the selection and effectiveness of diagnostic methods. Each health-care setting may prioritize these factors differently on the basis of local resources and health-care objectives, and this will influence the selection of diagnostic strategies [27]. The overall comparisons among the three tests are summarized in Table 5.1.

Support systems

Practical considerations about infrastructure play a crucial role in the choice of test, including the requirement for a laboratory, the equipment needed, and the transportation of test samples. For example, although the UBT is highly accurate, it requires a mass spectrometer or an infrared spectrometer, which may not be accessible in some clinical settings [28]. SATs are easier to administer and do not require such specialized equipment; this makes them suitable for settings with limited technical infrastructure [7], but they are not suitable for transportation. Although serology tests are less specific, they require only basic laboratory infrastructure [29]. The availability of equipment refers to the ease of acquiring the necessary test kits and materials, which are crucial for tests like the UBT and the SAT. Reagents and test kits must be reliably available. Disruptions in supply chains can significantly affect the availability of tests and the consistency of results. With respect to the transportation of specimens, the monoclonal SAT is temperature-sensitive, and samples should be stored at temperatures < 8 °C. In contrast, the UBT is stable and can be sent by mail, and the results can typically be analysed within 1 month. Rapid tests such as the UBT and the SAT can provide results within hours, which is advantageous for timely treatment decisions. In contrast, serological testing may take several days; this can potentially delay the next step for the confirmation of current infection for the initiation of treatment. Delays in treatment may affect the percentage of patients who accept treatment.

Table 5.1. Population tests for *H. pylori* infection

Test	Strengths	Weaknesses	Performance	Additional considerations
UBT	• Simple operation • Good performance • Can be used to test for active infection and evaluate for eradication success	• Higher direct and indirect costs (procedure time) • Requires fasting • Requires stopping PPI use for 2 weeks and antibiotic use for 4 weeks before testing	• Sensitivity and specificity > 95%	• Depends on the availability of mass spectrometry or infrared spectrometry • Requires trained technicians for analysis
SAT	• Simple operation • Good performance • Can be used to test for active infection and evaluate for eradication success • Point-of-care test is possible	• Requires stopping PPI use for 2 weeks and antibiotic use for 4 weeks before testing • Requires instruction about sample collection, storage, and transportation • Participants' preferences may be lower for stool sampling	• Sensitivity and specificity > 90%	• Can be performed together with FIT screening for colorectal cancer • Can be performed together with molecular testing for antibiotic resistance
Serological test	• Does not require modifications of medication before testing • The only method not influenced by current PPI intake • Widely available • Least expensive	• Does not reliably differentiate between active infection and previous infection • Cannot be used to confirm eradication • Needs to be carried out by professionals for blood sampling	• Technical sensitivity and specificity ranging from 80% to 98% • Clinical specificity is lower than for UBT and SAT because of inability to differentiate between current infection and past infection	• Can be performed together with other blood tests, such as pepsinogen testing • A positive test result should be confirmed by UBT or SAT • The test should be validated locally for optimal PPV and NPV

FIT, faecal immunochemical test; NPV, negative predictive value; PPI, proton pump inhibitor; PPV, positive predictive value; SAT, stool antigen test; UBT, urea breath test.

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Participants' preferences

Participants' preferences with respect to breath samples, stool samples, or blood samples can significantly influence their willingness to participate. In particular, participants may feel uncomfortable with providing stool samples [30], depending on geography, ethnicity, or religious background, or if they are unable to produce a sample during the visit to the health-care centre.

Costs

Budget considerations include not only the direct costs of the tests but also the broader economic impact, including the costs associated with false-positive or false-negative test results, which could lead to inappropriate treatments or delayed diagnosis. Therefore, budgetary constraints may necessitate a balance between the test accuracy and the related costs. For the same test, the costs can vary significantly depending on geographical location and health-care setting, which influence the accessibility and choice of diagnostic methods. Costs typically rank, from highest to lowest, in the order of the UBT, the SAT, and serological testing. In the Accelerating Gastric Cancer Reduction in Europe through *H. pylori* Eradication (EUROHELICAN) programme, which targets the young adult population with a lower prevalence of *H. pylori* infection in a European country (see Chapter 3.5), there is a notable cost disparity between the UBT and serological testing (the costs of the UBT are potentially many times those of the serology test). Using a two-step approach with a locally validated immunoglobulin G serology test as the first step and a confirmatory UBT as the second step may reduce overall testing costs compared with a one-step approach using the UBT (Fig. 5.2).

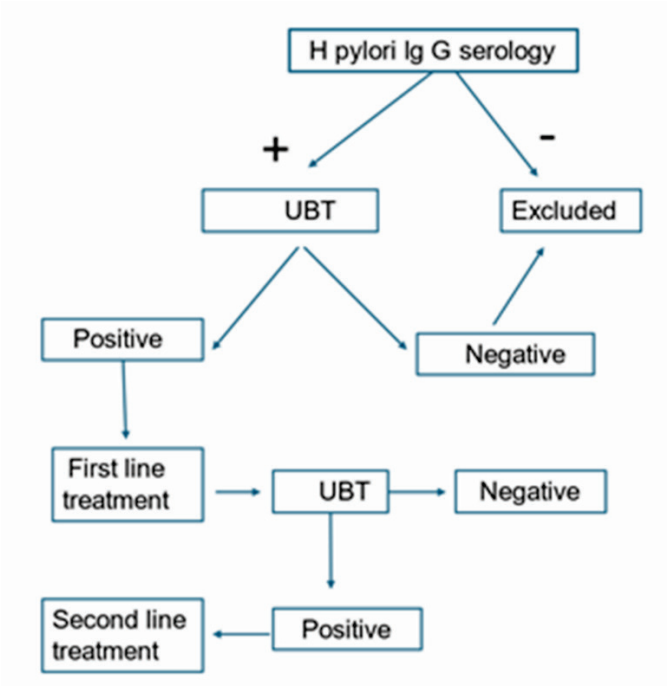

Fig. 5.2. A two-step approach for serological *H. pylori* testing and urea breath test (UBT) confirmation in a population-based *H. pylori* screen-and-treat programme in a setting with a low prevalence of *H. pylori* infection (as used in the EUROHELICAN and TOGAS projects). IgG, immunoglobulin G. Source: Tepeš et al. (2024) [31].

Testing after eradication treatments

H. pylori is classified as a class I carcinogen. It is an infectious disease that requires treatment and eradication for patients with an infection [1, 2]. *H. pylori* treatment regimens aim for eradication rates of > 90%, though actual eradication rates typically range between 80% and 90% [32]. Retesting after antibiotic treatment is important to confirm the successful elimination of the infection. This also reinforces the patient–doctor interaction in managing the disease. Without retesting, more-resistant strains may persist and spread within the community. The UBT and the SAT should be used as confirmatory tests for eradication [7]. In cases of treatment failure, additional lines of treatment may be prescribed until *H. pylori* infection is successfully eradicated [2].

5.4 Gastric cancer risk at the time of testing for *H. pylori* infection

The diagnostic tests used in the population-based *H. pylori* screen-and-treat programmes in younger and older adult populations may differ because of the differences in the risk of pre-neoplastic changes and gastric cancer. Economic capacities and medical facilities could also influence the approach to integrate *H. pylori* preventive measures with early detection of gastric cancer in a particular country. In young adults, *H. pylori* infection is often asymptomatic and typically results in chronic gastritis in most individuals with *H. pylori* infection. In older adults, additional considerations are needed because the intragastric damage may have progressed to a point where it is less reversible. *H. pylori* eradication reduces the risk of gastric cancer, but the magnitude of the effect is lower in older populations because of the high rate of pre-neoplastic changes in the gastric mucosa at older ages. The prevalence of advanced pre-neoplastic lesions (atrophic gastritis and intestinal metaplasia) in Europe in age groups > 50 years is up to 19% [33–35]. Measuring the levels of pepsinogens combined with *H. pylori* serological testing may provide additional information about pre-neoplastic conditions of the gastric mucosa [26]. A decreased pepsinogen I level or a low pepsinogen I/II ratio is indicative of atrophic gastritis, which is often associated with chronic *H. pylori* infection. The combination of two serology tests may be useful to triage the population for upper endoscopy on the basis of the risk of gastric cancer [36]. A drawback of pepsinogen testing is its low sensitivity for detecting gastric cancer and pre-neoplastic changes; this currently limits its readiness for implementation in preventive programmes. In a population-based screen-and-treat programme, additional endoscopy can be considered, according to medical judgement, for participants with a family history

of upper gastrointestinal cancer, for those with a history of oesophageal or gastric malignancy, or for those presenting with alarm symptoms and signs, such as unexplained iron deficiency anaemia, a palpable abdominal mass or lymphadenopathy, dysphagia, odynophagia, melaena, gastrointestinal bleeding, unintentional weight loss, or persistent vomiting [2].

5.5 Invasive tests for *H. pylori* infection

Invasive tests are generally not applicable to the *H. pylori* screen-and-treat approach, except when there is a concurrent endoscopy-based gastric cancer screening programme. When endoscopy is contemplated, gastric biopsy can be used for detection of *H. pylori* infection by the rapid urease test, histological examination, and bacterial culture. These necessitate endoscopic facilities, which involve higher initial set-up and maintenance costs. These methods require trained gastroenterologists and pathologists, which can be a limitation in resource-limited settings [37].

Rapid urease tests

The rapid urease test (RUT) is a simple and inexpensive rapid test, which detects the presence of urease activity. Two biopsies should be taken for the RUT, from the antrum and the corpus. The RUT contains urea, which would be broken down by *H. pylori* urease, leading to a pH change as reflected by the colour change of the pH indicator. The urease activity typically comes from *H. pylori* in the stomach, although false-positive test results are possible because of the presence of other bacteria. In general, commercial RUTs have a sensitivity of about 85–95% and a specificity of about 95–100% [38]. Results are available within minutes or sometimes hours, depending on the bacterial load present in the biopsy specimens. Rather than obtaining a further biopsy for PCR, the biopsies used for the RUT could be further used (after reading the results) for the detection of mutations associated with antibiotic resistance, using PCR [39]. However, RUTs can be falsely negative in patients with a recent intake of antibiotics or proton pump inhibitors, and in patients with upper gastrointestinal bleeding [40, 41]. Under these circumstances, additional gastric biopsies from the antrum and the corpus can be taken for histology, bacterial culture, or PCR.

Histology

Histology is a simple, economical, and widely available test for *H. pylori* infection. It is considered to be a standard protocol in routine upper endoscopy to evaluate gastric

inflammation and the presence of other pre-neoplastic lesions, such as atrophic gastritis and intestinal metaplasia. Although special staining techniques such as the Giemsa or Warthin–Starry stain could increase the detection of *H. pylori* infection, this bacterium is readily identified by the conventional haematoxylin and eosin stain. Because the density of *H. pylori* infection is not uniformly distributed in the stomach, taking multiple biopsies from both the antrum and the corpus can increase the diagnostic yield. Proper topographical staging of the severity of gastritis can be done using the Operative Link on Gastritis Assessment (OLGA) and the Operative Link on Gastric Intestinal Metaplasia Assessment (OLGIM) staging systems [42–44].

Culture

Two biopsies are obtained for bacterial culture, from the antrum and the corpus. Culture for *H. pylori* has to be performed with selective medium under microaerobic conditions for 5–7 days, because of the slow growth of the bacterium. Culture has a relatively low sensitivity compared with histology or even the RUT, and it is not widely available because of the need for equipment and expertise. However, bacterial culture is useful in determining antimicrobial susceptibility, particularly in patients in whom first-line eradication therapy failed or in regions with a high prevalence of antimicrobial resistance. Culture has a specificity of 100%, but its sensitivity shows substantial variation, ranging between 85% and 95%, depending on the expertise of the laboratory [2, 4]. The role of culture has increasingly been replaced by molecular detection methods, including PCR and direct sequencing (see Box 5.2), because of the low yield and the long turnover time for culture. However, PCR is not widely used because of the higher costs and lower availability [37].

5.6 Real-world examples of the use of tests in population-based *H. pylori* screen-and-treat programmes

In a population-based *H. pylori* screen-and-treat programme, the choice of the best approach depends on the availability of the different tests, the performance of each test, and the expected prevalence of *H. pylori* infection. A positive test result is interpreted using the positive predictive value (PPV) (true positive/test positive), and a negative test result is interpreted using the negative predictive value (NPV) (true negative/test negative). The population-based application of *H. pylori* testing includes the single-step and two-step approaches. The single-step approach uses either the UBT or the SAT.

The two-step approach involves initial serological testing, followed by the UBT (or the SAT) for those who test positive in the serology tests. These applications are demonstrated in the following real-world examples, which show how countries can adopt appropriate tests for their target populations with varying *H. pylori* infection rates. A highly sensitive screening serology test can be used to select individuals with potential *H. pylori* infection and avoid many (more expensive) UBTs, especially when the prevalence of *H. pylori* infection is < 30%.

Urea breath tests

The application of the UBT is illustrated using an example of a high-risk population with a high prevalence (~55%) of *H. pylori* infection [45, 46] (see Chapter 3.10). When the UBT (with a locally validated sensitivity and specificity of 95% [47]) is adopted, the PPV is estimated to be 96% and the NPV is estimated to be 94%. Among 100 participants, 54 who tested positive and 46 who tested negative will be observed (Fig. 5.3). This will include 52 true positives (54 × 96%) and 43 true negatives (46 × 94%). Consequently, in this scenario, only 5 cases (= 100 − 52 − 43) will be misclassified.

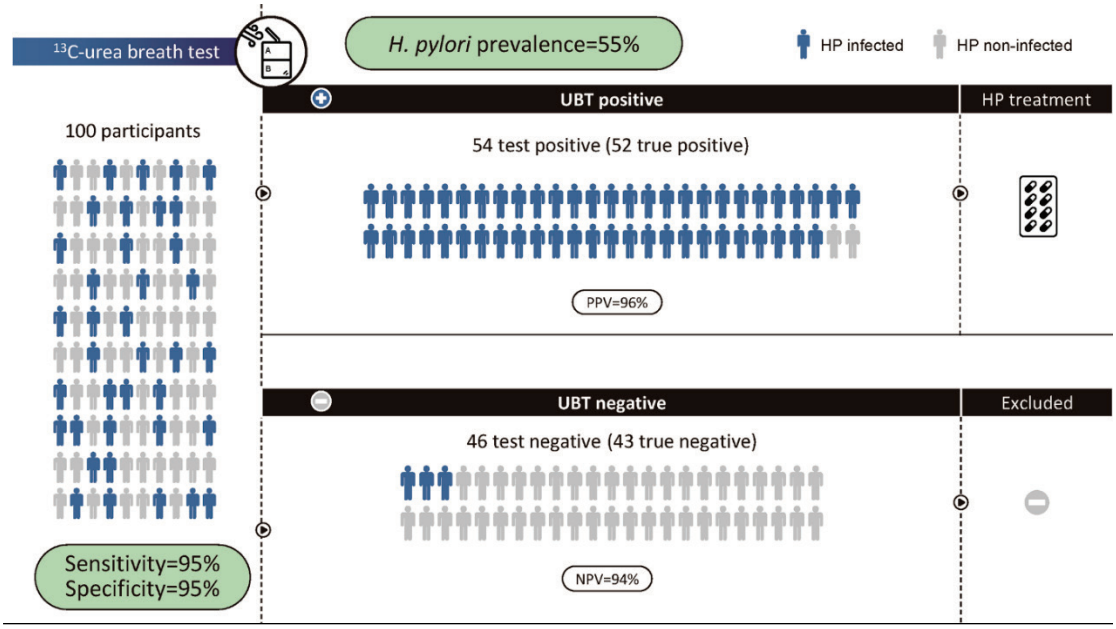

Fig. 5.3. Using the urea breath test (UBT) for *H. pylori* (HP) testing in a population-based *H. pylori* screen-and-treat programme in a setting with a high prevalence (55%) of *H. pylori* infection. NPV, negative predictive value; PPV, positive predictive value.

Stool antigen tests

The SAT has been shown to be valuable in population-based test-and-treat programmes in Bhutan [48] (see Chapter 3.6). The SAT can also leverage the established platform of colon cancer screening using faecal immunochemical tests for invitations and specimen transportation. This is illustrated in a middle-aged population with a prevalence of *H. pylori* infection of 38% [49]. When the SAT (with a locally validated sensitivity of 88% and specificity of 99% [50]) is adopted, the PPV is estimated to be 98% and the NPV is estimated to be 93%. Among 100 participants, 34 who tested positive and 66 who tested negative will be observed (Fig. 5.4). This includes 33 true positives (34 × 98%) and 61 true negatives (66 × 93%). Consequently, in this scenario, only 6 cases (= 100 − 33 − 61) will be misclassified.

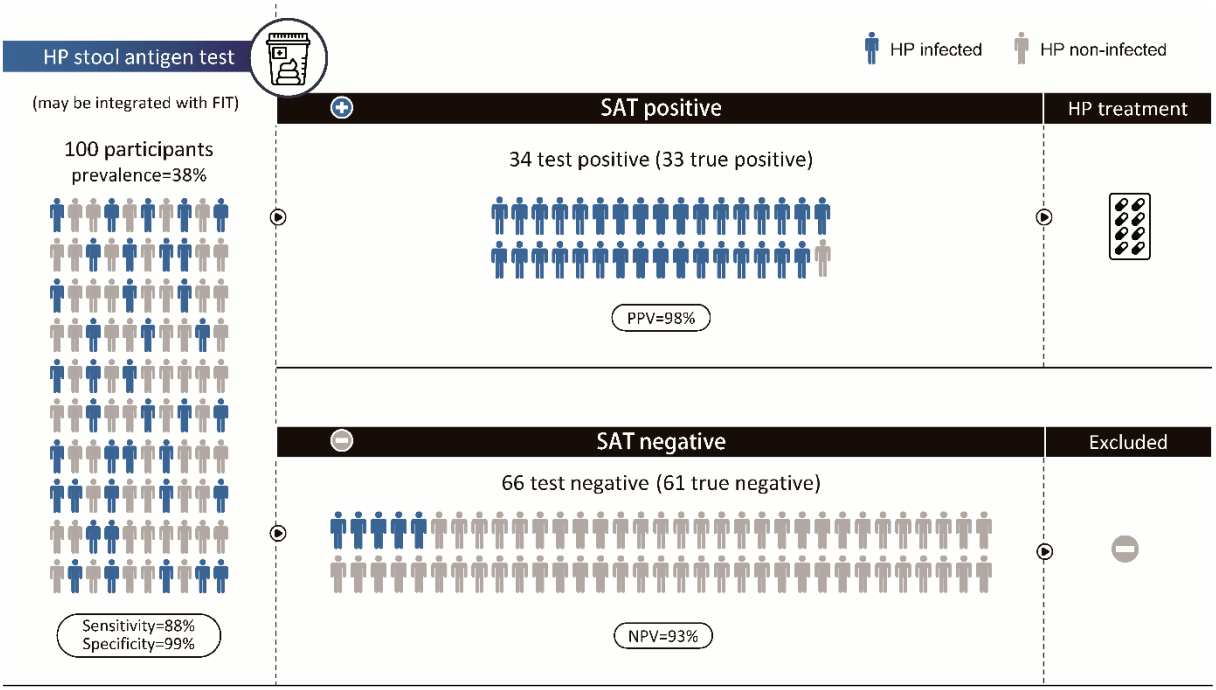

Fig. 5.4. Using the stool antigen test (SAT) for *H. pylori* (HP) testing in a population-based *H. pylori* screen-and-treat programme in a middle-aged population with an intermediate prevalence (38%) of *H. pylori* infection. FIT, faecal immunochemical test; NPV, negative predictive value; PPV, positive predictive value.

Serological testing

In a population-based programme, serological testing can be applied in a two-step approach, using a highly sensitive, but less expensive, ELISA for screening purposes, followed by confirmatory testing with the UBT or the SAT. Examples of this include the EUROHELICAN and Towards Gastric Cancer Screening Implementation in the European Union (TOGAS) projects (see Chapter 3.5) and the *H. pylori* in Aotearoa New Zealand (ENIGMA) Study (see Chapter 3.11). A high-performance and well-validated test should be chosen. This approach may be applicable, for example, in populations with lower prevalence of *H. pylori* infection, such as the programme for young adults (e.g. prevalence of 14%). When a serology test with a locally validated sensitivity of 95% and specificity of 90% is used, the PPV is estimated to be 61% and the NPV is estimated to be 99%. Among 100 participants, 22 who tested positive and 78 who tested negative will be observed (Fig. 5.5). This includes 13 true positives (22 × 61%) and 77 true negatives (78 × 99%). With the high NPV, almost all those who test negative are true negatives. Almost all participants with *H. pylori* infection will test positive, although there will be some positives because of past infection (previously treated) ($n = 9$). Therefore, this approach may reduce the reliance on the UBT compared with the single-step UBT approach, particularly when considering the costs (costs for 100 serology tests and 22 UBTs vs costs for 100 UBTs). However, the dropout rate for such a two-step approach should be considered.

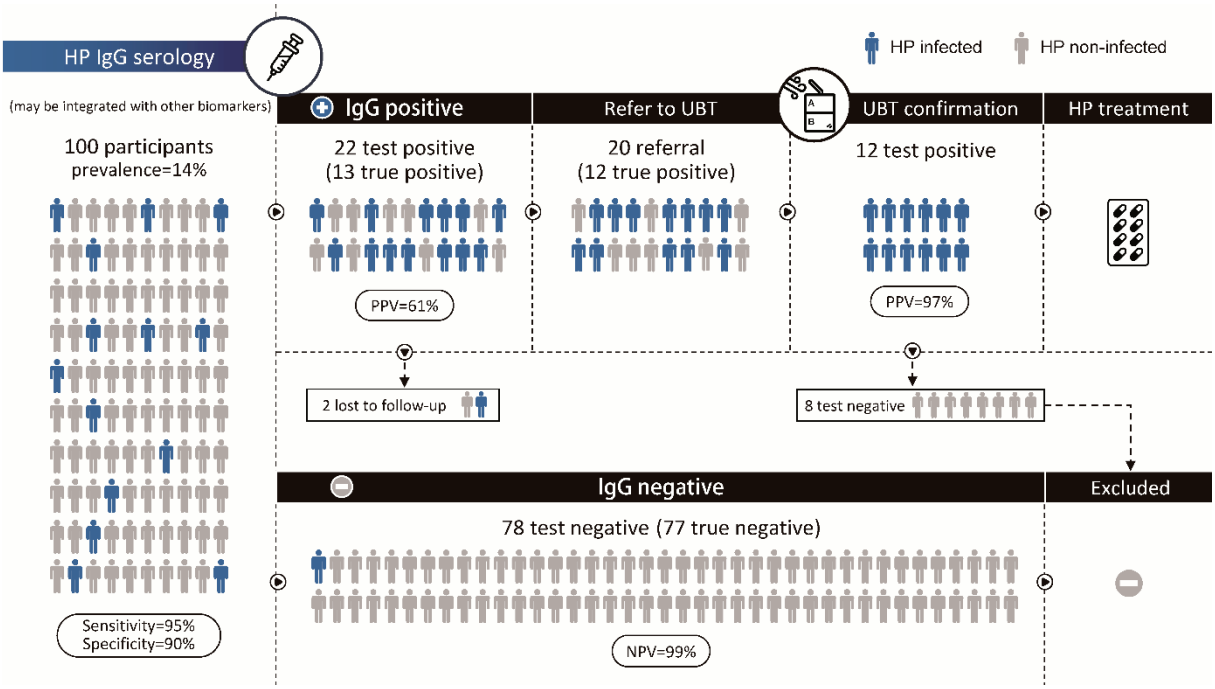

Fig. 5.5. Using a two-step approach for serological *H. pylori* (HP) testing in a population-based *H. pylori* screen-and-treat programme in a setting with a low prevalence (14%) of *H. pylori* infection. IgG, immunoglobulin G; NPV, negative predictive value; PPV, positive predictive value; UBT, urea breath test.

Endoscopic approaches

In Asian countries with high gastric cancer incidence rates and sufficient economic and medical resources, endoscopic screening for early gastric cancer, along with diagnosis of *H. pylori* infection using invasive methods, may be an option. Nonetheless, the *H. pylori* screen-and-treat programme using non-invasive methods can still be run in younger age groups, in parallel with the endoscopic screening programme in older age groups. For example, in Japan and the Republic of Korea [51, 52], a nationwide gastric cancer screening programme is available for the early detection and surveillance of patients with premalignant lesions. These programmes have improved the detection rate of early gastric cancer in Japan (to 63.3%) and in the Republic of Korea (to 63.9%). A cost–benefit analysis in Japan identified a population-based *H. pylori* eradication strategy as the most cost-effective strategy for a national gastric cancer prevention programme, better than the current strategy, which is a secondary prevention-focused programme of biennial endoscopic screening [53].

5.7 Conclusions and future directions

For population-based *H. pylori* screen-and-treat programmes, non-invasive tests should be used. The choice of testing should initially prioritize test performance and the prevalence of *H. pylori* infection in the population, estimating the predictive values when interpreting results in clinical practice. For population-wide implementation, additional considerations may include the availability of support systems for testing, participants' preferences with respect to the test types, and economic factors. Confirmation of eradication is essential and should be performed at least 4 weeks after the completion of *H. pylori* therapy. Molecular detection of *H. pylori* holds promise in the future for the alternative selection of therapies with no risk or only a minor risk of being influenced by antibiotic resistance.

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Chapter 6.

Considerations for choice of *Helicobacter pylori* treatment regimens

Javier P. Gisbert and Peter Malfertheiner

Summary

- The design of population-based *H. pylori* screen-and-treat programmes must consider the impact they could have on the selection of antibiotic-resistant strains of *H. pylori* and other species, both at the individual level and at the societal–ecological level.

- The most common causes of the failure of treatment are poor compliance with therapy and/or *H. pylori* antibiotic resistance. Patients should receive counselling about the anticipated (generally mild) adverse events. Resistance rates vary remarkably between different geographical areas, and therefore the selection of therapeutic regimens needs to be adjusted according to the local resistance pattern. Several recent reviews have confirmed an increase in clarithromycin resistance rates in different areas around the world.

- *H. pylori* infection is an infectious disease, and therefore regimens should ideally be selected on the basis of antibiotic susceptibility determined at the individual patient level; if this information is not available, empirical regimens should be used that avoid (or have minimal risk of) antibiotic resistance. Local population-based data from surveillance registries will be of great help in this respect. Ultimately, the recommendations stated in each country's guidelines on *H. pylori* treatment should be followed.

- The main available eradication treatments for *H. pylori* worldwide include (i) clarithromycin triple therapy, (ii) classic bismuth-containing quadruple therapy (or the three-in-one single capsule), (iii) high-dose proton pump inhibitor–amoxicillin dual therapy, (iv) vonoprazan–amoxicillin dual therapy, and (v) non-bismuth-containing quadruple concomitant therapy.

6.1 General principles for choosing *H. pylori* treatment regimens

Factors to take into account when considering population-based H. pylori *eradication treatment*

An effective first-line eradication therapy is desirable, to avoid supplementary treatments and testing and to prevent the development of secondary resistance. In the context of population-based screening for and eradication of *H. pylori*, the challenges include dealing with clinically apparently healthy subjects, which requires a simple, well-tolerated therapy with few adverse events to support their motivation and adherence to treatment. In addition to effectiveness and tolerability, other issues that affect the treatment, such as the local availability of the treatment, the cost of the treatment, and the type of health system responsible for treatment, will play a critical role. Awareness campaigns on global, national, and regional scales will have an essential supportive role in disseminating knowledge about *H. pylori* therapy.

The design of these population-based *H. pylori* screen-and-treat programmes must also consider the impact they could have on the selection of antibiotic-resistant strains of *H. pylori* and other species, both at the individual level (i.e. the direct selection of surviving strains) and at the societal–ecological level (i.e. the type and quantity of antibiotic compounds entering the ecosystem could increase widespread resistance).

Therefore, programme design and treatment recommendations for *H. pylori* screening must fit the narrow criteria of being an acceptable compromise between the aims of cancer prevention (cost–effectiveness) and infection prevention (because population-based eradication reduces the sources of infection) with the containment of antimicrobial resistance.

Antibiotic resistance

The most common causes of the failure of reliably good or excellent regimens are, in addition to poor compliance with therapy, the presence of organisms that are resistant to one or more of the antimicrobial agents used [1].

Several studies have suggested a variety of miscellaneous factors that may be important in *H. pylori* eradication, including age, presentation (e.g. functional dyspepsia vs duodenal ulcer), and CagA status. However, these factors have typically been discovered in data-dredging studies in which resistance was not assessed [2].

Resistance rates vary remarkably between different geographical areas [3], and therefore the selection of therapeutic regimens needs to be adjusted according to the local resistance pattern. The prevalence of antibiotic resistance (mainly to clarithromycin) in various regions is correlated with the general use of antibiotics in the region, i.e. for infectious diseases other than *H. pylori* infection [4]. For example, the long-term use of clarithromycin as monotherapy, mainly for respiratory tract infections, has led to high clarithromycin resistance rates of *H. pylori* [4]. Several recent reviews have confirmed an increase in clarithromycin resistance rates in different areas around the world [4, 5, 6, 7, 8]. Metronidazole resistance plays a subordinate role, because metronidazole is not included in most triple therapies and this resistance can be overcome by the use of bismuth-containing quadruple therapy and by increasing the dose and duration of treatment [9].

The goal of H. pylori *eradication treatment*

The goal of any antimicrobial therapy is to reliably cure *H. pylori* infection in most patients [10]. Currently, as a general rule, it has been recommended that a regimen should not be used unless it reliably produces an eradication rate > 90% [10]. However, in the context of population-based *H. pylori* screen-and-treat programmes, it would be worth considering the use of treatments that are slightly less effective but are simpler, less expensive, and better tolerated and have minimal issues related to antibiotic resistance.

The reliable cure of *H. pylori* infection requires the use of antimicrobials to which local infections are susceptible. Physicians gain knowledge about the characteristics of the antibiotics and population antimicrobial resistance; this can be achieved using invasive and non-invasive methods. Antimicrobial susceptibility testing can be performed on *H. pylori* strains from patients with *H. pylori* infection by molecular testing in gastric biopsies, gastric juice samples, and possibly stool samples (most relevant for clarithromycin and levofloxacin) or by culture followed by an antibiogram, which provides susceptibility information for all relevant antibiotics. Several commercial kits are available that enable testing for clarithromycin (and possibly quinolone) susceptibility using polymerase chain reaction (PCR).

Another alternative, which is widely available to all, is to examine and regularly monitor the results of the eradication therapy (this monitoring is recommended to be routinely performed for all patients) and to share the data. Treatment failure with an

otherwise optimized therapy provides a strong indication of the presence of resistance, and that therapy should no longer be recommended and used unless local susceptibility is proven by culture or molecular testing.

In summary, *H. pylori* infection is an infectious disease, and therefore regimens should ideally be selected on the basis of antibiotic susceptibility determined at the individual patient level or by using eradication regimens that avoid (or have minimal risk of) antibiotic resistance. Establishing the collection of local population-based data from surveillance registries will be of great help in selecting the most effective therapies in the region.

Tailored versus empirical treatment

Resistance of *H. pylori* to antibiotics has reached alarming rates worldwide [11]. Local surveillance networks are required to select appropriate eradication regimens for each region. Tailoring treatment of *H. pylori* infection based on systematic antimicrobial susceptibility testing is useful to limit the increase in local, regional, and global antibiotic resistance by avoiding the use of unnecessary antibiotics. However, there is still a contentious debate about whether patients should systematically undergo an upper endoscopy for bacterial culture (or molecular techniques such as PCR) or even molecular tests in stool samples before the administration of *H. pylori* eradication treatment in clinical practice [10].

Ideally, the treatment for a bacterial infectious disease should be chosen based on antibiotic susceptibility testing, but the case of the infected stomach is very specific. Pre-treatment *H. pylori* susceptibility testing enables the selection of a regimen tailored by antimicrobial susceptibility. However, this is not always feasible in patients with *H. pylori* infection because, until very recently, this has required an invasive procedure (i.e. gastroscopy), which obviously is not indicated in population-based programmes such as those aimed at preventing gastric cancer in the general population [12]. In the past few years it has been reported that the genotypic testing of clarithromycin resistance from stool samples is an accurate, convenient, non-invasive, and rapid detection technology, which provides a definitive diagnosis of clarithromycin resistance and guides the rational selection of antibiotics [13, 14, 15]. However, the studies are still limited, some of their accuracy results are heterogeneous, and diagnostic kits are not available widely or in all settings worldwide [10].

Although some meta-analyses have found that, overall, first-line tailored therapy achieved higher eradication rates than empirical regimens, more recent meta-analyses have concluded that the benefit of susceptibility-guided treatment over empirical treatment of *H. pylori* infection could not be demonstrated in first-line therapy if the most up-to-date and effective quadruple regimens are prescribed [12, 16]. Thus, especially when bismuth-containing quadruple therapy is used as a first-line empirical therapy, there seems to be little need for routine upfront susceptibility testing for tailored treatment, as long as the local eradication success rate is high.

Therefore, a strategy that is also reasonable is that the selection of any empirical regimen be guided by regimen-specific eradication success rates locally. Thus, in many geographical regions, one must empirically choose therapy, and in this instance the best approach is to use regimens that have been proven to be reliably effective in a given area [2, 12]. That choice should take advantage of the knowledge of resistance patterns, obtained from local or regional antimicrobial surveillance programmes or based on local clinical experience with regard to which regimens are effective in that region. Ultimately, the recommendations stated in 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 to identify which antibiotics are likely to be successful and those for which resistance is probable [2].

6.2 Treatment options

First-line *H. pylori* eradication treatments that have been recommended in guidelines and consensus reports published worldwide are listed in Table 6.1. Table 6.2 summarizes the main available eradication treatment alternatives for *H. pylori* infection, including their constituents and their main strengths and weaknesses. The key principles that should guide the choice of *H. pylori* eradication therapy, in accordance with the World Gastroenterology Organization Global Guideline [3], are summarized in Box 6.1.

The eradication treatments that are currently in use are described and assessed below, along with their effectiveness, availability, and cost in each geographical area.

Box 6.1. Key principles that should guide the choice of *H. pylori* eradication therapy

1. Randomized controlled treatment trials and meta-analyses provide the highest level of evidence but are not available for many regions. Local audits of treatment outcomes are useful.
2. Treatment recommendations based on resistance patterns and outcome data from one region may not be applicable elsewhere, because of variations in resistance rates and other factors.
3. Generating high-quality local data and monitoring antibiotic resistance and treatment outcomes are priorities.
4. Ad hoc, unproven therapies should be avoided.
5. The main determinant of eradication success is pre-treatment antibiotic resistance.
6. Primary resistance to clarithromycin, metronidazole, and levofloxacin varies widely regionally.
7. Major determinants of primary resistance appear to be the magnitude and duration of community use of these antibiotics as monotherapy for other indications.
8. Prior personal exposure of a patient to these drugs is likely to result in resistance and increases the likelihood of treatment failure.
9. Primary clarithromycin resistance has been reported to have increased in many countries over relatively few years, although it has remained stable in other countries.
10. Primary or secondary resistance to amoxicillin and tetracycline are so rare that this does not affect treatment choices.
11. Because much treatment is given presumptively or after non-invasive *H. pylori* testing, the choice of therapy will be based on knowledge of the probable antimicrobial resistance patterns locally.
12. The availability of rapid, inexpensive point-of-care polymerase chain reaction (PCR) antimicrobial resistance testing may change individual treatment choices and facilitate surveillance of trends in resistance.
13. Compliance is a major modifiable determinant of eradication success and should be supported with clear verbal and written information.
14. Smoking has an adverse effect on eradication success.
15. Ideally, outcome assessment (confirmation of *H. pylori* eradication) should be done in all treated patients, although in practice this is not available in many places.
16. These key principles must be adapted regionally according to the available resources.

Source: Adapted from Katelaris et al. (2023) [3].

Table 6.1. First-line *H. pylori* eradication treatments recommended in guidelines and consensus reports worldwide[a]

Geographical area [reference]	Year of publication	Development organization	Recommended regimen
Africa [44]	2024	African Helicobacter and Microbiota Study Group	CTT (provided there was no previous exposure to macrolides and local resistance to clarithromycin is < 15%)
Belgium [45]	2023	Belgian *Helicobacter pylori* and Microbiota Study Group	Empirical treatment: BQT or CQT If clarithromycin has been excluded: CTT
Brazil [46]	2018	Núcleo Brasileiro para Estudo do *Helicobacter pylori* e Microbiota	First-line: CTT Alternatives: BQT, CQT
Canada [47]	2016	Canadian Association of Gastroenterology	In areas with high (> 15%) clarithromycin resistance: BQT or CQT In areas with low (< 15%) clarithromycin resistance: CTT
China [48]	2022	*Helicobacter pylori* Study Group of Chinese Society of Gastroenterology	BQT or HDDT
Egypt [49]	2019	Egyptian Association for Study of Gastrointestinal Diseases and Liver	CTT
Europe (Maastricht VI/Florence) [10]	2022	European Helicobacter and Microbiota Study Group	In areas with high (> 15%) or unknown clarithromycin resistance: BQT (if unavailable: CQT) In areas with low (< 15%) clarithromycin resistance: BQT or CTT
Germany [50]	2024	German Society of Gastroenterology, Digestive and Metabolic Diseases	BQT
Greece [51]	2020	Hellenic Society of Gastroenterology	CQT
Hong Kong Special Administrative Region, China [52]	2023	Hong Kong Society of Gastroenterology	CTT or BQT
India [53]	2022	Indian Society of Gastroenterology	In areas with high clarithromycin resistance: BQT In areas with low clarithromycin resistance: CTT

Table 6.1. First-line *H. pylori* eradication treatments recommended in guidelines and consensus reports worldwide[a] (continued)

Geographical area [reference]	Year of publication	Development organization	Recommended regimen
Indonesia [54]	2023	Directorate of Research and Community Service, Deputy for Strengthening Research and Development, Ministry of Research and Technology, Research Agency and National Innovation	CTT: this therapy should be implemented with caution in some regions in Indonesia with high (> 10%) clarithromycin resistance Alternatives: BQT and CQT
Ireland [55]	2024	Irish *Helicobacter pylori* Working Group	BQT (first-line treatment in the absence of clarithromycin susceptibility testing or where clarithromycin resistance has been confirmed) CTT (only if clarithromycin susceptibility has been confirmed)
Italy [56]	2022	Italian Working Group	BQT, CTT, or SEQ CTT only considered in areas with low (< 15%) clarithromycin resistance
Japan [57]	2019	Japanese Society for *Helicobacter* Research	CTT or PPI–amoxicillin–metronidazole or P-CAB–clarithromycin–amoxicillin or P-CAB–amoxicillin–metronidazole
Republic of Korea [58]	2021	Korean Society of Clinical Microbiology, Korean Society of Pathologists, and Korean Society of Gastroenterology	CTT, BQT, CQT, or SEQ
Latin America [59]	2014	Latin American Expert Group	CTT or SEQ
Malaysia [60]	2023	Expert panel	CTT Alternative: HDDT
Poland [61]	2023	Polish Society of Gastroenterology	BQT or CQT
Saudi Arabia [53]	2022	Saudi *H. pylori* Working Group	BQT Alternatives: CQT, SEQ with quinolones, hybrid therapy, HDDT, vonoprazan triple therapy
Spain [62]	2022	Spanish Association of Gastroenterology and Spanish Society of Digestive Pathology	BQT or CQT
Thailand [63]	2016	Expert panel	CTT Alternatives: CQT or SEQ

Table 6.1. First-line *H. pylori* eradication treatments recommended in guidelines and consensus reports worldwide[a] (continued)

Geographical area [reference]	Year of publication	Development organization	Recommended regimen
USA [64]	2024	American College of Gastroenterology	BQT when antibiotic susceptibility is unknown Rifabutin triple therapy or P-CAB dual therapy is a suitable empirical alternative
Viet Nam [53]	2022	Vietnam Association of Gastroenterology	BQT Alternative: PPI–amoxicillin–levofloxacin–bismuth
World Gastroenterology Organization [3]	2023	World Gastroenterology Organization	In areas with high clarithromycin resistance: BQT (or PPI–bismuth–amoxicillin–metronidazole) In areas with low clarithromycin resistance: CTT

BQT, classic bismuth-containing quadruple therapy (PPI, bismuth, tetracycline, metronidazole); CQT, non-bismuth-containing quadruple concomitant therapy (PPI, clarithromycin, amoxicillin, metronidazole); CTT, clarithromycin triple therapy (PPI, clarithromycin, amoxicillin); HDDT, high-dose dual therapy (PPI, amoxicillin); P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; SEQ, sequential therapy (PPI plus amoxicillin for 5–7 days followed by PPI plus clarithromycin and metronidazole for 5–7 days).

[a] Only guidelines published in English are included. Guidelines exclusively focused on children were excluded. If multiple guidelines have been published, only the most up-to-date publication was included.

Table 6.2. Main eradication treatment alternatives for *H. pylori* infection, including their constituents and their main strengths and weaknesses

Treatment name	Components and dosing	Duration (days)	Strengths	Weaknesses
Standard clarithromycin triple therapy	PPI (omeprazole 40 mg or equivalent/12 h) Clarithromycin (500 mg/12 h) Amoxicillin (1000 mg/12 h)	14	Simplicity Widely available Recommended by most guidelines in case of low clarithromycin resistance	Effectiveness reduced by clarithromycin resistance Requires the administration of 3 different drugs
Classic bismuth-containing quadruple therapy	PPI (omeprazole 20–40 mg or equivalent/12 h) Bismuth (120 mg/6 h or 240 mg/12 h) Tetracycline (500 mg/6 h) Metronidazole (500 mg/8 h)	10–14	Wide experience Effectiveness has remained constant over time Unaffected by clarithromycin resistance Can overcome metronidazole resistance	Requires the administration of 4 different drugs Complexity of dosing regimen Occasional unavailability of bismuth and/or tetracycline

Table 6.2. Main eradication treatment alternatives for *H. pylori* infection, including their constituents and their main strengths and weaknesses (continued)

Treatment name	Components and dosing	Duration (days)	Strengths	Weaknesses
			Low price	Three-in-one single capsule only available in a few countries High cost of three-in-one single capsule (in the USA)
High-dose PPI–amoxicillin dual therapy	PPI (omeprazole 40–80 mg or equivalent/6–8 h) Amoxicillin (750–1000 mg/6–8 h)	14	Simplicity Requires the administration of only 2 different drugs Widely available No resistance problems Good tolerance Low price	Heterogeneous results (Asian countries vs European countries) Potentially optimizable PPI and amoxicillin doses
Vonoprazan–amoxicillin dual therapy	Vonoprazan (20 mg/12 h) Amoxicillin (750–1000 mg/8–12 h)	7–14	Simplicity Requires the administration of only 2 different drugs No resistance problems Good tolerance Not dependent on the *CYP2C19* genotype	Heterogeneous results (Asian countries vs European countries) Pending optimization of the dosage and duration of both vonoprazan and amoxicillin Higher cost of vonoprazan vs PPI
Non-bismuth-containing quadruple concomitant therapy	PPI (omeprazole 20–40 mg or equivalent/12 h) Clarithromycin (500 mg/12 h) Amoxicillin (1000 mg/12 h) Metronidazole (500 mg/12 h)	14	Not clearly impaired by either clarithromycin or metronidazole isolated resistance Consistent good results in Europe	Effectiveness reduced by dual metronidazole–clarithromycin resistance Requires the administration of 4 different drugs Exposes the patient to at least 1 unnecessary antibiotic

h, hour or hours; PPI, proton pump inhibitor.

Standard clarithromycin triple therapy

Nowadays, the efficacy of the standard triple therapy that includes clarithromycin is seriously challenged in many parts of the world, where eradication rates have declined

to unacceptably low levels, largely related to the development of resistance to this antibiotic. This low efficacy compromises the design and development of any population-based 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 considered before implementing screening and treatment programmes.

The most recent data show that the triple therapy, which generally includes a proton pump inhibitor (PPI), clarithromycin, and either amoxicillin or metronidazole, has lost some efficacy and often enables the cure of only a maximum of 70% of the patients, which is less than the generally recommended rate of 90% and far below what should be expected for a bacterial infection [10]. The most important explanation for this decrease in the efficacy of the standard triple therapy 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 compared with only 18% in clarithromycin-resistant strains [17]. The global clarithromycin resistance rate in Europe has increased from 9% in 1998 [18] to > 20% in more recent years [4]. Resistance has increased in most parts of Europe, but it has now reached a prevalence of > 20% in most countries in central, western, and southern Europe, which is considered to be a high resistance rate [19].

A threshold of 15–20% was recommended to separate the regions of high and low clarithromycin resistance [10]. There are very few remaining areas with low clarithromycin resistance. Worldwide, with few exceptions, the presence of resistance prohibits the empirical use of triple therapies that contain clarithromycin. However, in the few areas with clarithromycin resistance rates of < 15% (and locally confirmed evidence of effectiveness of ≥ 90%), the standard PPI–clarithromycin-containing regimen may still be used as the first-line treatment (although bismuth-containing quadruple therapy is also a valid first-line alternative) [10]. In situations in which susceptibility testing is lacking or in areas with limited health-care resources, physicians must rely on evidence of local results (i.e. test-of-cure data).

In cases in which the clarithromycin-containing triple regimen has been selected to be used as the first-line treatment, different ways of improving its efficacy have been proposed. These include (i) increasing the dose of PPI (40 mg of omeprazole, or equivalent, twice a day) and (ii) increasing the duration of treatment (up to 14 days) [10].

However, these options will also increase the cost of treatment, which is a major issue in resource-constrained regions [3].

Finally, overall eradication rates with PPI–amoxicillin–clarithromycin and PPI–amoxicillin–metronidazole have been equivalent worldwide [20]. However, the combination with metronidazole instead of clarithromycin showed high efficacy in areas with a low incidence of metronidazole resistance (i.e. Japan), and could accordingly be recommended as a first-line therapy in these populations [20].

Classic 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. Therefore, as previously mentioned, no clarithromycin-based regimens should be recommended in areas with increasing clarithromycin resistance rates. In the context of increased resistance to antibiotics, quadruple therapy has the advantage of using the following compounds: (i) bismuth, for which the mechanism of action appears to be more like an antiseptic than like 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 can be overcome by increasing the dose and duration of treatment [9, 21]. Accordingly, classic bismuth-containing quadruple therapy has been recommended by most of the guidelines worldwide as an alternative first-line regimen to standard triple therapy in areas with low rates of clarithromycin resistance, and has been recommended as the first-line therapeutic option in areas with a high (> 15%) or unknown prevalence of clarithromycin resistance.

The major drawback of this therapy is the complex dosing regimen (some drugs are dosed 4 times a day). Thus, clinical trials of bismuth-containing quadruple therapy are needed to simplify the regimen to improve compliance. Several studies have shown that bismuth administered twice a day may be sufficient [22]. Subsequently, a bismuth-containing quadruple therapy using a three-in-one single capsule that contains bismuth subcitrate, metronidazole, and tetracycline has been demonstrated to decrease the pill burden and improve patient compliance [23].

In general, the treatment duration of bismuth-containing quadruple therapy should be 14 days. However, 10-day therapies have increasingly achieved very good and

consistent results in different geographical areas [24]. Furthermore, a meta-analysis [23] and several studies from the European Registry on *Helicobacter pylori* Management, including almost 4000 patients treated with 10-day single-capsule bismuth-containing quadruple therapy, demonstrated a cure rate of ≥ 90% [25, 26].

The safety and tolerability of the quadruple therapy have been similar to those of the standard triple therapy in several meta-analyses [27]. 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 situation for organized programmes in the general population. However, the limitations of this quadruple regimen are the unavailability of bismuth subcitrate worldwide and the current general unavailability of tetracycline in many countries. In addition, the three-in-one single-capsule presentation (marketed under the name Pylera) is only available on the market in a few countries worldwide.

High-dose PPI–amoxicillin dual therapy

In areas with high dual resistance (> 15%), a high-dose PPI–amoxicillin dual therapy may be an option, because it overcomes the issue of clarithromycin (and metronidazole) resistance, especially where bismuth, tetracycline, or the three-in-one single capsule are not available. Dosing frequency is essential for the efficacy of PPI–amoxicillin dual therapy, because amoxicillin has a time-dependent bactericidal effect. A meta-analysis including 15 randomized clinical trials found that PPI–amoxicillin administered 4 times a day achieved a significantly higher eradication rate than doses administered less frequently [28]. Some meta-analyses have demonstrated high (~90%) cure rates, with high-dose PPI–amoxicillin dual therapy being as effective as bismuth-containing quadruple therapy (and associated with fewer adverse effects) [29]. However, these favourable results obtained mainly in Asian countries have not been replicated in European countries (even when bismuth was added to this dual regimen), so this dual regimen cannot be recommended universally [30, 31].

Vonoprazan–amoxicillin dual therapy

Optimal eradication of *H. pylori* infection requires predictable and long-lasting inhibition of gastric acid secretion, especially throughout the night-time hours. Potassium-competitive acid blockers (P-CABs), which have been recently introduced and have a unique pharmacological profile, are better suited to combination treatment with one or

more antimicrobial agents [32]. P-CABs, such as vonoprazan, are characterized by a rapid onset of action and a predictable antisecretory profile that is not dependent on the *CYP2C19* genotype or the activation of parietal cells. This profile provides the opportunity to improve the management of *H. pylori* eradication treatments, particularly by simplifying complex eradication regimens and by potentially developing a very effective dual therapy [32].

Several systematic reviews and meta-analyses of randomized controlled trials have demonstrated that vonoprazan triple therapy is superior to PPI triple therapy in first-line treatment, with similar safety and patient tolerance levels [33]. Furthermore, several studies have shown a similar, or even higher, efficacy of vonoprazan–amoxicillin dual therapy compared with bismuth-containing quadruple therapy, and with better tolerance [34, 35]. However, it should be emphasized that the clinical experience with vonoprazan-based eradication regimens has been largely limited to East Asian countries. The eradication success rates with the vonoprazan regimens observed in the landmark trial in Europe and the USA were lower (79–85% in susceptible strains) than those observed in randomized clinical trials and observational studies in East Asia, perhaps due to differences in body mass index or parietal cell mass, among other factors, between the trial populations [36]. The same has been observed in other countries, such as Thailand, where dual therapies based on vonoprazan have yielded poorer outcomes that those in the studies carried out in East Asian countries [37]. Future research should focus on optimizing the dosage and duration of both vonoprazan and amoxicillin, especially in Europe and the USA.

Non-bismuth-containing quadruple concomitant therapy

This regimen combines a PPI, clarithromycin, amoxicillin, and metronidazole, which are administered together for at least 10 days [38]. In head-to-head trials against clarithromycin-resistant strains, concomitant therapy had superior outcomes (92%) compared with sequential therapy (62%) [38]. Concomitant therapy also works well in metronidazole-resistant, clarithromycin-susceptible cases because of its PPI–amoxicillin–clarithromycin component. Indeed, concomitant therapy was the only therapy other than bismuth-containing quadruple therapy that consistently achieved an eradication success rate of ≥ 90% in all European regions in the European Registry on *Helicobacter pylori* Management [25, 39]. 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 be < 90% when the prevalence of dual clarithromycin–metronidazole-resistant strains is > 15% [38]. Furthermore, with this regimen, all patients are exposed to at least one unnecessary antibiotic, whether it is clarithromycin in clarithromycin-resistant cases or metronidazole in metronidazole-resistant cases, which may contribute to global antimicrobial resistance. Thus, according to the Maastricht VI/Florence Consensus report and other consensus reports, in areas with high (> 15%) clarithromycin resistance, non-bismuth-containing quadruple concomitant therapy may be considered, but only if bismuth-containing quadruple therapy, and perhaps other treatments as well, is unavailable.

Other treatments

Rifabutin has generally been recommended as a rescue therapy after at least several *H. pylori* eradication failures [40]. Because of potential – although rare – severe adverse events with rifabutin-based regimens, these regimens should not be used as a first-line treatment [10].

Because of the high or rapidly rising prevalence of quinolone resistance in communities, and also because of the possible adverse events, fluoroquinolone-containing regimens should be reserved for rescue treatment [10].

6.3 The importance of compliance with and tolerance of treatment

Compliance is an important issue when *H. pylori* treatment is planned for inclusion in population-based screening. Therefore, for population-based screening, substantial efforts should be directed towards identifying a regimen that is easy for the participant to follow. Furthermore, adverse events are reported by ≥ 25% of patients [41]. The most frequent adverse events are taste disturbance (reported by 7% of patients), diarrhoea (7%), nausea (6%), and abdominal pain (3%) [41]. However, most of the adverse events are mild (< 1% are serious) and of limited duration, and their occurrence does not seem to interfere significantly with treatment compliance [41]. Nevertheless, patients should receive counselling about the anticipated adverse events, so that their occurrence does not cause cessation of therapy.

Adherence to a complex regimen is a particular problem when it is used in the general population, who are largely asymptomatic. They are less likely to adhere to the therapy if eradication treatment is not used to cure symptoms, and this could be a

challenge for a screening programme. If compliance with the regimen is poor, even the best-designed regimen will have a poor outcome. Therefore, another aspect of optimization is to identify the factors that determine compliance, such as dosing, duration, and adverse events. First, health-care providers must ensure that patients understand the rationale for treatment (principally to reduce the risk of gastric cancer). Second, because adherence to the therapy is associated with higher eradication rates [39], patients should receive counselling about the importance of completing the treatment regimen; taking a few extra minutes to provide patients with all the relevant information can prevent most of the issues associated with treatment failures [42]. The fact that *H. pylori* eradication therapy involves multiple drugs (and frequently multiple dosing intervals) makes patient education extremely important; therefore, written instructions with an appropriate language and literacy level should be provided. Finally, patients who smoke should be advised to stop, because active smoking is associated with *H. pylori* eradication failure [43].

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Chapter 7.

Antibiotic stewardship for population-based *Helicobacter pylori* screen-and-treat programmes, including testing of cure and monitoring of antibiotic resistance

Paul Moayyedi, Yi-Chia Lee, Markus Gerhard, and Francis Mégraud

Summary

- A population-based *H. pylori* screen-and-treat programme for gastric cancer prevention should follow robust antibiotic stewardship principles to minimize the risk of antibiotic resistance arising from the increased antibiotic use.
- An antibiotic stewardship checklist should be developed and implemented to ensure the appropriate use of antibiotics, guide best practices, and monitor the impact.
- *H. pylori* eradication rates can be assessed through routine follow-up testing of treated participants or by testing a representative subgroup to confirm treatment success.
- *H. pylori* isolates from a randomly selected subset of participants should be tested for antibiotic resistance. Establishing an antibiogram, which provides a summary of the susceptibility patterns of local bacterial isolates to various antibiotics, can aid in selecting effective drugs. The dosage and duration of treatment should also be carefully optimized to ensure efficacy and minimize the development of resistance.
- The impact of increased exposure to antibiotics through short-course eradication treatments in population-based programmes on antibiotic resistance in *H. pylori* and other human bacteria is not yet fully understood, and thus continued awareness and research are warranted.
- A prophylactic vaccine against *H. pylori* would be the ideal solution to the problems associated with antibiotic use in *H. pylori* screen-and-treat

programmes, but candidate vaccines are still in the preclinical stage of development.

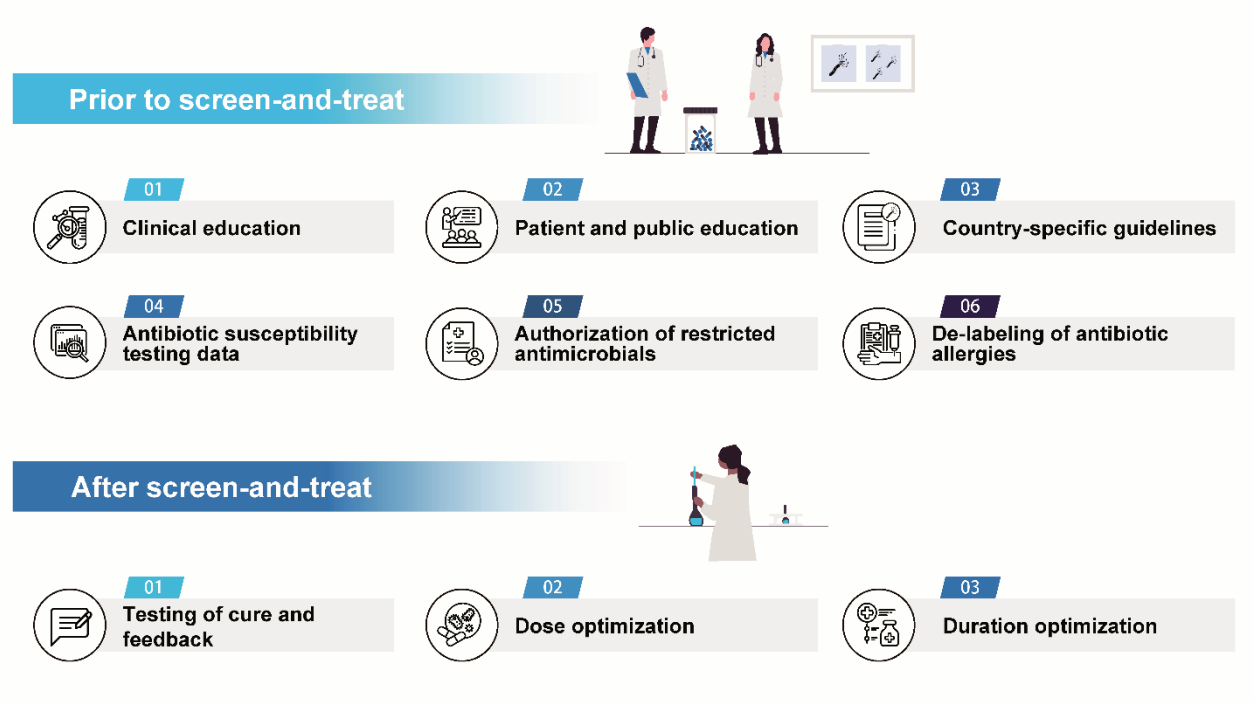

Fig. 7.1. Visual abstract.

7.1 Introduction

H. pylori infection is one of the most common chronic bacterial infections worldwide [1]. A systematic review of the global prevalence of *H. pylori* infection has shown a decrease in infection rates over time, from 53% (95% confidence interval [CI], 50–56%) before 1990 to 44% (95% CI, 42–46%) in 2015–2022 [2]. Multivariable regression analyses showed a decrease of 16% in the prevalence of *H. pylori* infection over the past three decades; a statistically significant decrease was observed in the Western Pacific, South-East Asia, and Africa. In the same study, the incidence of gastric cancer decreased in the countries in which the prevalence of *H. pylori* infection decreased. Another systematic review found that the decrease in the prevalence of *H. pylori* infection was mirrored by a decrease in the incidence of gastric atrophy, intestinal metaplasia, and dysplasia over time [3]. Although the global gastric cancer incidence rate is decreasing because of improved sanitation, which reduces the transmission of *H. pylori*, and opportunistic screen-and-treat practices for *H. pylori*, the absolute number of new cases of gastric cancer remains high in some

regions, and the risk of gastric cancer is increasing in younger generations. Together with the predicted increase in the number of new cases of gastric cancer driven by population ageing, this indicates that gastric cancer remains a substantial public health challenge [4].

The decreasing prevalence of *H. pylori* infection has been accompanied by an increased rate of antibiotic resistance. A systematic review of antibiotic resistance in World Health Organization (WHO) regions, published in 2018 [5], which included data from 2006–2016, highlighted considerable heterogeneity among regions (Fig. 7.2) and a trend towards increasing resistance during the study period. Another study, which reviewed data from 2018–2021, found a global *H. pylori* clarithromycin resistance rate of 32% (95% CI, 29–36%) in the 54 countries studied when both primary resistance (which develops before treatment) and secondary resistance (which occurs after initial treatment failure) were included [6]. In the Asia–Pacific region, data from 2016–2022 indicated resistance rates of 30% (95% CI, 28–33%) for clarithromycin, 35% (95% CI, 31–39%) for levofloxacin, and 61% (95% CI, 55–66%) for metronidazole; the resistance rates for tetracycline and amoxicillin remained low (4–6%) [7]. The prevalence of clarithromycin resistance was highest in Central Asia, and the prevalence of levofloxacin and metronidazole resistance was highest in South Asia [7]. A systematic review of 26 studies in Africa, of which only four were published in 2016 or later, found resistance rates of 29% (95% CI, 27–32%) for clarithromycin, 17% (95% CI, 13–22%) for levofloxacin, and 76% (95% CI, 74–77%) for metronidazole [8]. A high level of heterogeneity was observed in the studies in Africa, and the results did not differentiate between primary and secondary resistance. Differences in the methods used to determine antibiotic resistance, which included disc diffusion, the E-test, and molecular testing for resistance genes, may also contribute to the observed heterogeneity.

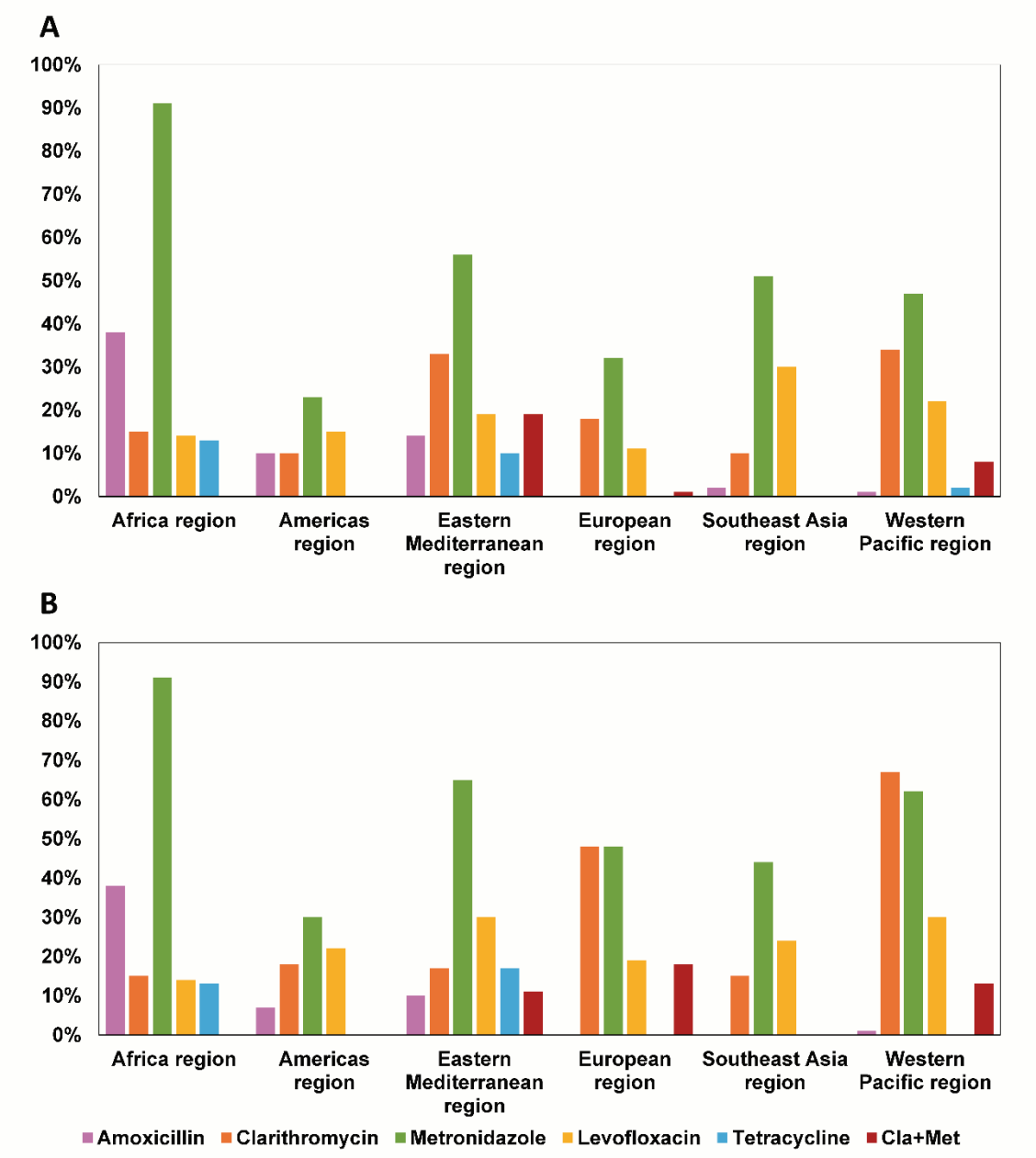

Fig. 7.2. Cumulative antibiograms of primary and secondary resistance of *H. pylori* in World Health Organization (WHO) regions in 2006–2016: (A) primary resistance rates of *H. pylori*; (B) secondary resistance rates of *H. pylori.* Primary resistance rates included individuals who had not yet received antibiotic treatment. Secondary resistance rates included individuals in whom one course of treatment had failed. In Africa, the antibiograms did not differentiate between primary and secondary resistance; therefore, the same data are presented in (A) and (B). These prevalence data were based on only three publications, from Cameroon, the Congo, and Senegal, and their representativeness should be interpreted with caution. Cla+Met, dual resistance to clarithromycin and metronidazole. Source: Compiled from Savoldi et al. (2018) [5].

Information on resistance rates in Latin America is also scant and out of date; the most recent publication was in 2014 [9]. The review reported primary resistance rates of 4% for amoxicillin, 12% for clarithromycin, 53% for metronidazole, 6% for tetracycline, 3% for furazolidone, 15% for fluoroquinolones, and 8% for dual resistance to clarithromycin and metronidazole.

In Europe, studies have been performed every 10 years; the most recent survey was in 2018. The primary resistance rates of *H. pylori* were 21.4% for clarithromycin, 15.8% for levofloxacin, and 38.9% for metronidazole [10]. The European Registry on *Helicobacter pylori* Management (Hp-EuReg) also provides data on antibiotic resistance [11]. In 2017–2020, the resistance rates observed in Europe were close to those reported in the 2018 survey [10], except for metronidazole (24.5% vs 38.9%).

The increasing rates of *H. pylori* antibiotic resistance are most probably caused by the global increase in antibiotic prescribing [12], which increased by 60% in 2000–2015 and has increased a further 16% since then, despite a decrease in antibiotic use during the COVID-19 pandemic [13]. A population-based *H. pylori* screen-and-treat programme will further increase antibiotic use. Therefore, any programme that is adopted must have robust antibiotic stewardship policies. This chapter evaluates the impact that *H. pylori* screen-and-treat programmes could have on population antibiotic use and suggests the antibiotic stewardship approaches that should be taken when choosing *H. pylori* eradication therapies and monitoring resistance.

Section 7.2 estimates the impact of population-based *H. pylori* screen-and-treat programmes on population antibiotic use. The importance of antibiotic stewardship is discussed in Section 7.3, with a checklist for assessing the antibiotic stewardship in a programme. Strategies for assessing *H. pylori* eradication rates and monitoring antibiotic resistance are discussed in Section 7.4, and real-world examples are provided in Section 7.5. Section 7.6 provides a perspective on the development of a vaccine against *H. pylori*.

7.2 Estimated impact of *H. pylori* screen-and-treat programmes on population antibiotic use

All screening programmes must balance harms against benefits, and one of the key disbenefits of a population-based *H. pylori* screen-and-treat programme is that it will inevitably increase antibiotic use. It is estimated that in 2021 antimicrobial resistance contributed to more than 4.7 million deaths, of which more than 1.1 million deaths

were directly attributable to antimicrobial resistance, and that these figures will increase to more than 8.2 million deaths and more than 1.9 million deaths per year by 2050 [14]. Population-based *H. pylori* screening and treatment could further add to this problem in any country that institutes such a policy. Therefore, it is important to try to estimate the potential impact of such programmes when introduced in various countries. The Working Group conducted a modelling exercise using a best-case scenario in which a programme would use two antibiotics and standard daily doses for 1 week in an eradication regimen, and would screen people aged 40–69 years (approximately modelling the randomized trials in this topic area [15–16]). It was assumed that 20% of the eligible population would be invited to be screened annually, to reduce the impact of antibiotic use each year, and that of those invited, 70% would attend, which is the best uptake rate that has been achieved by a new screening programme [17]. A recent systematic review was used to provide the estimates for the prevalence of *H. pylori* infection in each country, and data for the total population and the proportion of the population aged 40–69 years were taken from nationally available data [2]. The current total defined daily dose (DDD) [18] prescribed in each country in 2023 was estimated using published sources [13], and projections were made for how this would increase if a population-based *H. pylori* screen-and-treat programme was introduced in that country.

This modelling exercise showed that in most settings the proportional increase in antibiotic prescribing is modest (Table 7.1); most countries were projected to have a 1–3% increase in DDD prescribed. The exception is China, in which the DDD would increase by 11%. This is mainly due to the current low level of antibiotic prescribing in China, possibly because of stricter regulations [19] compared with most other countries. Therefore, the proportional increase would be greater in China than in other countries. The projected 7% increase in antibiotic prescribing in Colombia is driven mainly by the high proportion of individuals aged 40–69 years with *H. pylori* infection in that country.

Table 7.1. Estimated effect of population-based *H. pylori* screen-and-treat programmes on antibiotic use in some representative countries

Country or territory	Current annual DDD	Annual DDD after screening	Percentage increase
China	2 217 311 459	2 460 275 422	11.0
Japan	550 550 145	567 613 839	3.1
Taiwan, China	133 800 475	136 988 969	2.4

Table 7.1. Estimated effect of population-based *H. pylori* screen-and-treat programmes on antibiotic use in some representative countries (continued)

Country or territory	Current annual DDD	Annual DDD after screening	Percentage increase
Republic of Korea	634 371 001	647 400 989	2.1
United Kingdom	470 375 747	477 633 709	1.5
France	615 807 647	622 585 863	1.1
Spain	513 346 264	523 279 432	1.9
Poland	304 587 086	313 734 497	3.0
Greece	137 247 694	139 107 945	1.4
Canada	209 056 368	211 829 698	1.0
USA	2 783 138 735	2 805 058 634	0.8
Colombia	182 865 559	196 330 098	7.3
Brazil	1 466 232 682	1 494 255 989	1.9

DDD, defined daily dose.

Note: DDD refers to the assumed average maintenance dose per day for an antibiotic used in adults. For example, the DDD for amoxicillin is 1000 mg per day.

These estimates of increased antibiotic use are reassuring, but the assumptions made were optimistic. A more judicious approach would aim to maximize the chances of eradicating *H. pylori* infection in individuals while minimizing antibiotic exposure. Rather than attempting to eradicate *H. pylori* infection in every possible case, the focus should be on achieving the greatest benefit per dose of antibiotics used. It was assumed that only 20% of the eligible population would be invited annually and that only a 1-week course of antibiotics would be prescribed, whereas the currently recommended eradication treatments typically last 10–14 days [20]. This will approximately double the percentage increase in antibiotic prescribing described in Table 7.1. The proportion will increase even more if all participants are screened for treatment failure and offered further eradication therapy. Therefore, there can be no room for complacency if an *H. pylori* screen-and-treat programme is implemented, and it is important that antibiotic stewardship principles are followed. The benefits of *H. pylori* eradication treatment for associated diseases should be weighed against the potential disbenefits of increased antibiotic use, although the consequences may largely be theoretical. In existing programmes that target high-risk populations, the impact of the concern about antibiotic resistance has not yet been observed or fully understood (see Section 7.5), and decision analyses have not yet incorporated this point into model assumptions (see Chapter 9).

7.3 Antibiotic stewardship in *H. pylori* screen-and-treat programmes

There are numerous guidelines [21] on appropriate antibiotic use and antibiotic stewardship. Although these have some different nuances, all have similar approaches to minimizing antibiotic use. The purpose of antibiotic stewardship is to optimize the use of antibiotics to preserve their effectiveness, minimize adverse effects, and reduce the development of antibiotic resistance (Box 7.1).

Box 7.1. The five Ds of antibiotic stewardship

In population-based *H. pylori* screening programmes, communication between primary care physicians, gastroenterologists, and infection specialists is increasing to optimize antimicrobial use. Antibiotic stewardship is commonly guided by the **five Ds** principles [22]. These principles emphasize accurate **diagnosis** to ensure that antibiotics are prescribed correctly to individuals with *H. pylori* infection. Appropriate **drug** selection is guided by antibiotic resistance patterns and therapeutic evidence from clinical trials. Adequate **dosing** should adhere to the best therapeutic interval and timing before and after eating, to ensure efficacy, while considering patient health conditions, including the adjustment of hepatic and renal functions, and potential drug–drug interactions. Optimal **duration** helps to limit the development of resistance, minimize side-effects, and improve patient compliance. Full adherence to an antibiotic regimen is essential, because incomplete adherence can result in lower eradication rates and the potential selection of resistant strains. Treatment may be **discontinued** when the potential harms of (repeated) courses of antibiotics outweigh the clinical benefits or when there are competing health considerations, thereby reducing unnecessary antibiotic use and the risk of resistance.

Systematic review data [23] suggest that stewardship programmes are effective in reducing antibiotic use. Therefore, it is important that any population-based *H. pylori* screen-and-treat programme has an antibiotic stewardship team in place to advise and to monitor any impacts on antimicrobial use [24]. Such a team should involve people with expertise in gastroenterology, infectious diseases, clinical microbiology, epidemiology, and clinical pharmacy [25]. The key considerations for evaluating antibiotic stewardship in a population-based *H. pylori* screen-and-treat programme are outlined in Table 7.2, which presents a checklist of coordinated actions designed

to support the responsible and effective use of antimicrobials. Treatment of *H. pylori* infection is primarily empirical rather than definitive. Therefore, the first-line regimen should prioritize the most effective options (e.g. bismuth-containing quadruple therapy) while minimizing the risk of selecting for or driving the development of antibiotic-resistant strains. Treatment strategies should align with regional guidelines and the recommended benchmarks for successful eradication. Antibiotics with a higher potential for resistance – for example levofloxacin and rifabutin, which are not exclusively related to treatment of *H. pylori* infection – should be restricted for empirical use and require approval from infection specialists or guidance from antibiotic susceptibility testing, to enable definitive treatment. For antibiotics with a high eradication rate and low resistance potential, such as amoxicillin and tetracycline, it is crucial to verify the accuracy of the patient's allergic history. Systematic collection of test-of-cure data is needed to optimize the antibiotic regimen, including its dosage and duration.

First, to reduce adverse events, the ideal regimen would include only one antibiotic, because using multiple antibiotics to treat a single infection is not encouraged if monotherapy is sufficient [26]. Vonoprazan–amoxicillin dual therapy meets this goal, with acceptable eradication rates in East Asia [27], but eradication rates for this therapy have been suboptimal in other countries [28–29]. It is likely that in most countries at least two antibiotics will be needed to achieve acceptable eradication rates (see Chapter 6).

Table 7.2. Checklist for assessing antibiotic stewardship in a population-based *H. pylori* screen-and-treat programme

Before *H. pylori* screening and treatment
1. Clinical education
□ Is there an antibiotic stewardship team that includes experts from the gastroenterology, infectious disease, clinical microbiology, epidemiology, and clinical pharmacy departments?
□ Is there an initiative to enhance clinician education on screening tests and treatments?
□ Is there a system in place to maintain up-to-date knowledge on the practices and guidelines for antibiotic use?
2. Patient and public education
□ Is there an initiative to educate the patients and the public about the proper use of antibiotics for *H. pylori* infection?
□ Are there information technology or implementation resources available to communicate with the public?
□ Are the administrative and medical leadership committed to the programme?
3. Country-specific guidelines for the management of *H. pylori* infection
□ Are there guidelines available to standardize and reduce variation of the prescribing practices?
□ Are the guidelines evidence-based, and do they reflect the local epidemiology, treatment effectiveness, and drug availability?
□ Do the guidelines address diagnosis, drug selection, dosing, duration, and discontinuation of treatment?
□ Is there an available benchmark for appropriate antibiotic use that can be used for audit and feedback?
□ Is there an implementation strategy to encourage awareness and adherence to the guidelines?
□ Is there a mechanism to enable targeted education for physicians, in terms of audit and feedback?
4. Antibiotic susceptibility testing data (cumulative antibiogram)
□ Are the local antibiotic susceptibility testing data available?
□ Are human resources and microbiology laboratory services available, with appropriate quality controls for in vitro antibiotic susceptibility testing?
5. Prior authorization of restricted antimicrobials
□ Is there a mechanism that requires clinicians to obtain approval for specific antibiotics, such as levofloxacin and rifabutin, before they are released from the pharmacy for administration to individuals with *H. pylori* infection?
6. De-labelling of spurious antibiotic allergies
□ Is there a mechanism to clarify antibiotic allergies through dedicated allergy assessments, particularly for amoxicillin and tetracycline, which can distinguish individuals who are unlikely to react to an antibiotic challenge from those at substantial risk of an adverse allergic reaction?
After *H. pylori* screening and treatment
1. Testing of cure and feedback
□ Are the test-of-cure data available for participants who received antibiotic treatment?
□ Are the test-of-cure data available for clinicians who prescribed the antibiotic treatment?
□ Is an audit system in place, and is feedback provided when treatment does not adhere to the guidelines?
2. Antibiotic dose optimization
□ Is attention given to participant characteristics, such as age, weight, and renal and hepatic function, that can influence the appropriate dose and dosing interval?
□ Can the dose optimization be updated and incorporated into the clinical guidelines?
3. Antibiotic duration optimization
□ Is the treatment duration determined on the basis of local evaluation, with the participant's response to therapy being reassessed?
□ Can the duration optimization be updated and incorporated into the clinical guidelines?

Source: Modified from WHO (2021) [24].

Also, it is imperative not to choose antibiotics that would be ineffective because of high rates of antimicrobial resistance. This is the situation with clarithromycin, to which > 15% of *H. pylori* strains are resistant in many parts of the world [11]. The regimen that is most likely to be successful worldwide is bismuth-containing quadruple therapy, which involves a proton pump inhibitor, bismuth salts, tetracycline, and metronidazole, for 10–14 days [30]. *H. pylori* resistance to tetracycline is rare, and although the in vitro resistance rate is high for metronidazole, *H. pylori* appears to remain susceptible to this antibiotic in vivo [31–32]. In vitro metronidazole resistance has minimal effects on bismuth-containing quadruple therapy. Although the impact is greater with triple therapies, the impact remains limited with a 14-day treatment duration because of the accumulation of metronidazole in the mucus and its long half-life in the higher intragastric pH [33]. The regimen is complex, but single-capsule formulations that contain bismuth subcitrate potassium, metronidazole, and tetracycline are available [34], which may improve treatment compliance in population-based interventions in which simplicity is important. Although bismuth-containing quadruple therapy is more effective and carries a lower concern about antibiotic resistance, it may cause side-effects such as nausea, diarrhoea, a metallic taste, and temporarily black stools, which should be explained in advance and monitored throughout the treatment to improve compliance. Although amoxicillin and tetracycline show lower resistance rates, in some areas, such as Africa and the Eastern Mediterranean, primary resistance rates may be not trivial (Fig. 7.2). Continuous monitoring, particularly through updated time-trend analyses, is needed.

Second, an antibiotic stewardship committee would have to monitor eradication rates and resistance [35]. The challenge in implementing this approach is that it will require retesting at least a subset of participants, to assess successful eradication rates and monitor the development of antibiotic resistance. If this approach is implemented, individuals who remain *H. pylori*-positive should be offered second-line eradication regimens, and, if they are still positive, third-line treatments. This clinical approach would result in multiple courses of different antibiotics for a single infection, which has the potential to conflict with general antibiotic stewardship principles. However, the number of patients who require repeated treatments is likely to remain small provided that an effective initial treatment is selected. The approaches to deal with this conundrum are discussed in Section 7.4.

The recommendations outlined above are aligned with the WHO Access, Watch, Reserve (AWaRe) classification of antibiotics [36]. Antibiotics are classified into the Access, Watch, Reserve, and Not recommended groups based on the risk of selecting for bacterial resistance. Of the antibiotics used for treating *H. pylori* infection, amoxicillin, metronidazole, tetracycline, and doxycycline were classified into the Access category of antibiotics that showed lower resistance potential. Clarithromycin, levofloxacin, ciprofloxacin, cefuroxime, and rifabutin were classified into the Watch category of antibiotics that had a relatively high risk of selection of bacterial resistance. Minocycline was classified into the Reserve category of antibiotics that should be tailored for use in highly specific patients when alternatives have failed or were not suitable [37].

WHO periodically updates its priority pathogen list on the basis of evolving global health needs, scientific evidence, and public health challenges. In 2017, clarithromycin-resistant *H. pylori* was included in the WHO priority pathogens list for research and the development of new antibiotics [38], because *H. pylori* is a common infection worldwide, affecting both adults and children, and is associated with peptic ulcer and gastric cancer. The increasing prevalence of antibiotic resistance has led to suboptimal eradication rates. Guidelines advise against standard triple therapy if regional clarithromycin resistance is > 15% or if eradication rates are < 85% (see Chapter 6). However, in the 2024 update of the list [39], five antibiotic-resistant pathogens, including clarithromycin-resistant *H. pylori*, were removed. The removal of clarithromycin-resistant *H. pylori* from the priority list does not decrease the global concern about its burden, transmission, treatability, and prevention. Furthermore, this change may potentially lead to reduced emphasis on the monitoring of clarithromycin resistance. Treatment guidelines may still include clarithromycin as a first-line treatment without giving warnings about the high likelihood of treatment failure and the emergence of resistant strains, or without recommending suitable alternatives.

7.4 Strategies for assessing *H. pylori* eradication rates and monitoring antibiotic resistance

A population-based *H. pylori* screen-and-treat programme requires continuous monitoring to ensure that the desired outcome of the programme is being achieved. The primary aim of the programme is to reduce the incidence and mortality of gastric cancer with minimal adverse events, and it may take at least a decade before any

effects on gastric cancer outcomes become evident. Therefore, it is crucial to evaluate process measures that are immediately observable in a screening programme (see Chapter 8). These should include assessing the *H. pylori* eradication rate in the population targeted by the programme and monitoring the prevalence of antibiotic-resistant strains, both specific to *H. pylori* and in bacteria more broadly. To achieve the goals, the primary approach involves retesting either all or a subset of the participants who have received anti-*H. pylori* treatment, to confirm treatment success. This approach also includes selecting a subset of participants who tested positive for *H. pylori*, as well as those who were treated but retested positive, to assess antibiotic resistance. Concerns about bacterial resistance should be significantly lower if an effective treatment (such as bismuth-containing quadruple therapy and vonoprazan–amoxicillin dual therapy) has been administered and clarithromycin has not been prescribed (see Chapter 6).

*Testing of cure in participants who have received the anti-*H. pylori *treatment*

Two approaches can be taken to test participants who have received anti-*H. pylori* treatment. The most accurate approach to evaluating *H. pylori* eradication is to assess each individual population that undergoes screening and treatment. In this approach, all participants who meet the eligibility criteria for the programme would be tested and those with *H. pylori* infection would be offered antibiotic therapy with a follow-up test. Many methods are available for *H. pylori* testing [40], including non-invasive and invasive tests (see Chapter 5). For most countries, a non-invasive test, such as the urea breath test [41] or the stool antigen test [42] at least 1 month after the completion of therapy, can be used to assess eradication success.

The advantage of this approach is that it uses the largest sample size to assess the success of therapy and offers better generalizability. It also strengthens the patient–doctor interaction in the management of *H. pylori* infection. In addition, without the test-of-cure data, resistant strains are more likely to persist and spread within the community. The disadvantage of this approach is that it dramatically increases the cost and complexity of the programme, because it requires systems to be in place to inform participants of their results, check compliance, and offer alternative eradication therapies for individuals in whom eradication treatment fails. Providing the infrastructure needed to deliver such care, which becomes more

individualized with each round of treatment, would be expensive, and complex interventions at the population level are more likely to result in programme failure.

Other issues to consider with this approach are that a small but substantial proportion of the population would require treatment with multiple courses of differing antimicrobial regimens, and this will increase antibiotic exposure in this population [43]. There would also be a small proportion of the population who would still have *H. pylori* infection despite multiple attempts at treatment. This group may be left with anxiety that they have a carcinogenic infection that cannot be treated, and this may have an adverse psychological impact. Studies of breast cancer screening consistently find that women with breast abnormalities have increased anxiety and breast cancer-specific worry and distress [44]. There is some debate about whether these psychological impacts persist even after a negative diagnosis [45] or resolve [46]. These psychological effects may be influenced by the local disease burden and the community's perceived understanding of *H. pylori* infection.

Another approach that minimizes the potential harms of screening all individuals who receive therapy but still maintains the benefits is to screen a subgroup of those who have received therapy. A randomly selected subgroup would receive instructions, to check the success of therapy using the same methods as described in the first approach. The size of the subgroup selected would depend on the resources available and the size of the country offering screening, but it would usually be at the level of 10–20% of the population with *H. pylori* infection. The size of the subgroup also depends on the observed eradication rate in the population. If the eradication rate is high, a smaller sample size is required, but if the eradication rate is lower, a larger sample size is needed. The random selection would need to be stratified and weighted by region to ensure that vulnerable populations are not excluded or underrepresented. The advantage of this approach is that costs are lower, because fewer people would need follow-up. Also, fewer people would receive multiple antibiotic regimens and fewer people would have increased anxiety from knowing that they still have *H. pylori* infection despite having received therapy. The disadvantage of this approach is that if the proportion of the programme's population that is selected as the subgroup is not chosen appropriately, the estimate of the eradication rate may have wide confidence intervals. This problem can be overcome by continually monitoring the results and increasing the proportion tested as needed.

It could be argued that there are issues with not retesting the full population, given that no therapy is completely effective. For instance, after hypertension is detected, patients are prescribed antihypertensives and their blood pressure is rechecked until it falls within acceptable limits. However, *H. pylori* screening and treatment is not analogous to this, because blood pressure is a continuous measurement and can always be reduced, whereas some people will still have *H. pylori* infection despite any amount of antibiotic therapy. This group may experience heightened anxiety about what is a low absolute risk of developing malignancy. Screening for and treating *H. pylori* infection is more similar to screening for colorectal cancer using faecal immunochemical testing and offering colonoscopy to those who test positive. Good programmes introduce quality controls to minimize risks, but there is always a chance that polyps, or even colon cancer, may have been missed. Repeating the procedure more frequently is not practical, because it is prohibitively expensive and it increases the risks associated with colonoscopy. For an *H. pylori* screen-and-treat programme, testing the entire population would increase the cost of the programme and its complexity and would result in exposure to many antibiotics, and some participants would remain anxious despite the best efforts. This would prevent few gastric cancers and may not be justified. All participants entering any screening programme should be informed that there is never a 100% success rate in preventing the disease targeted by the screening.

The *H. pylori* screen-and-treat approach is also similar to screening for hepatitis B and C viruses for liver cancer prevention. Although the initial treatment may not always be effective, alternative treatments with a higher chance of success are available. The need to test for eradication may arise because of the observed eradication rate in the specific population, particularly after first-line treatment, when the eradication rate cannot be guaranteed to be high enough and effective second-line options are available. Depending on the health-care system, population screening can align with regular clinical practice, in which both the primary physician and the treated patient may need to know whether the treatment has been successful.

If a decision is made to test a subgroup of the population for therapy success and antibiotic resistance, the next question is how many years to wait before repeating the process. This refers to determining the frequency of testing of eradication rates and the emergence of resistance as part of a programme. The programme could be

either a continuous, rolling effort or an intermittent one. For countries that cannot afford a rolling programme, it is preferable to conduct intermittent testing of population samples. The interval should be determined based on the resources available for the programme. If resources are scarce, then an interval of 10 years, for example, may be all that is affordable. In higher-income countries, shorter intervals, such as every 2 years, would provide more timely information on whether eradication rates are decreasing and/or *H. pylori* antibiotic resistance rates are increasing.

Monitoring the antibiotic resistance

An important consideration in antibiotic stewardship is understanding which antibiotics are effective in curing infections; this is typically guided by the cumulative antibiogram (item 4 in Table 7.2) [47–48]. However, this raises the question of how to test for *H. pylori* antibiotic resistance. The reference standard would be gastric biopsy and culture, but this requires endoscopy and would be too expensive and invasive for many countries to implement. However, it may be feasible for countries that already offer population-based endoscopic screening, such as Japan [49] and the Republic of Korea [50]. Stool testing makes it possible to detect some of the *H. pylori* genetic mutations that confer antibiotic resistance by using real-time polymerase chain reaction (PCR) [51–53]. The stool PCR test has a low cost and is non-invasive, and testing could be done as a one-step process if stool antigen testing is also being used to assess eradication [54]. However, currently the sensitivity of the stool PCR test is not optimal, and only known mutations can be detected. For important antibiotics, such as metronidazole, both the mechanism of resistance and the significance of resistance mutations are unclear, and thus resistance cannot be determined by molecular methods. An alternative approach would be to use the string test method, which involves swallowing a capsule and, after retrieval of the capsule with a string, testing the gastric juice on the string, again with real-time PCR [55]. Public health programmes would need to determine whether this approach is feasible and applicable.

Treatment of *H. pylori* infection is generally based on empirical therapy rather than definitive treatment that is guided by susceptibility testing, as is done for other bacteria. However, it is still possible to conduct susceptibility testing before the antibiotic treatment. Invasive methods, including rapid urease testing, histology, culture, and antimicrobial susceptibility testing, cannot be adapted for population-

based screening for *H. pylori* infection in asymptomatic people, because they require upper digestive endoscopy. However, for countries that already conduct mass endoscopy screening to prevent gastric cancer, such as Japan [56] and the Republic of Korea [57], the antimicrobial susceptibility testing could be carried out at the same time as the gastric mucosa is evaluated. When endoscopic screening works together with *H. pylori* screening, this opportunity can be used to investigate the extent to which a population-based screen-and-treat approach has affected the levels of *H. pylori* antibiotic resistance.

The impact of population-based *H. pylori* screening on the general levels of antibiotic resistance, in bacteria other than *H. pylori*, can be measured using stool samples. Two hospital-based clinical trials used high-throughput DNA sequencing to evaluate the effects of antibiotic treatment on the dynamic changes in the gut microbiota and the resistome [58–59]. The number and abundance of microbial species (i.e. the diversity) and the antibiotic resistance genes of all bacteria (i.e. the resistome) were evaluated from stool samples taken before and after treatment for *H. pylori* infection, and the dynamic changes observed in the resistome are shown in Fig. 7.3. The results revealed a transient decrease in the diversity and an increase in the total resistome after antibiotic treatment, which may return to pre-treatment levels within about 2 months. Based on analyses of the minimum inhibitory concentration, the resistance rates of *Escherichia coli* and *Klebsiella pneumoniae* to levofloxacin, ciprofloxacin, ampicillin, and various cephalosporins temporarily increased 2 weeks after treatment. However, these rates returned to pre-treatment levels after 2 months and remained stable for up to 1 year. Collectively, the findings of these two studies provide some evidence against the concern about the long-term risks arising from antibiotic-resistant strains that might emerge in *H. pylori*-treated individuals, challenging the validity of this concern, which has yet to be demonstrated in practice. Nonetheless, there is a concern that the increased use of antibiotics may lead to more antibiotics entering the environment and negatively affecting ecosystems [60–61].

WHO promotes the One Health approach, which emphasizes an integrated strategy to achieve sustainable health outcomes for the entire ecosystem [62]. The One Health approach emphasizes addressing antibiotic resistance that can result from the overuse and misuse of antibiotics in various sectors, including human health

care, veterinary medicine, and agriculture, because these fields are closely interconnected. Improper practices may lead to an increase in antibiotic-resistant bacteria, which will make infections more difficult to treat. Consequently, a population-based *H. pylori* screen-and-treat programme should strictly adhere to robust antibiotic stewardship principles.

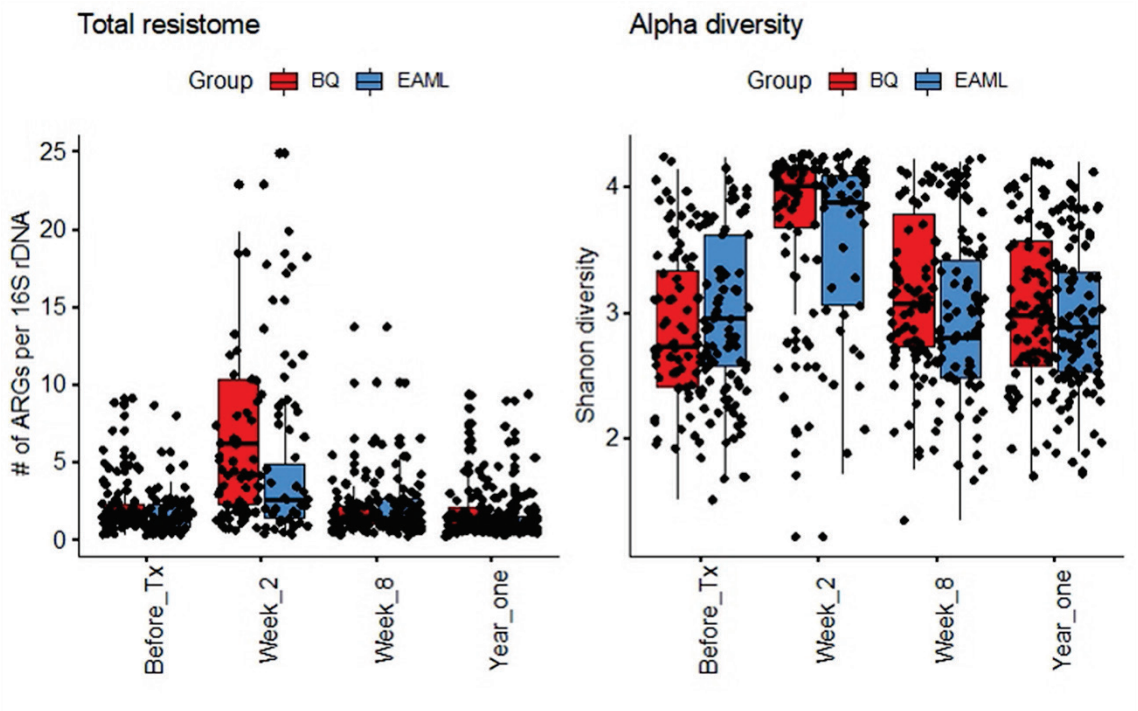

Fig. 7.3. The dynamic changes of the resistome before and after treatment (Tx) in a randomized clinical trial. Patients with *H. pylori* infection were randomized to receive second-line treatments of levofloxacin-based sequential quadruple therapy (esomeprazole, amoxicillin, metronidazole, and levofloxacin for 14 days; EAML) or bismuth-containing quadruple therapy (esomeprazole, bismuth, tetracycline, and metronidazole for 10 days; BQ). The abundance of antibiotic resistance genes (ARGs) at the type and subtype levels were normalized to the number of 16S ribosomal RNA (rRNA) genes for the quantification and downstream analysis of diversity indices. The treatments showed similar changes. The abundance of the total resistome was significantly increased 2 weeks after treatment, although the total resistome was similar to pre-treatment levels at 2 months (8 weeks) and 1 year. In the analyses, alpha diversity of the resistome showed consistent results. Source: Reprinted from Liou et al. (2023) [59]. Copyright 2023, with permission from Elsevier.

7.5 Examples of antibiotic stewardship in population-based *H. pylori* screen-and-treat programmes

There are existing *H. pylori* registries, such as the Hp-EuReg [63], which emphasize the value of structured, large-scale registries in tracking and understanding the epidemiology, management, and outcomes of *H. pylori* infection. The Hp-EuReg

collects data on empirical antibiotic prescriptions and cure rates for patients with *H. pylori* infection. Because the cure rate is highly dependent on *H. pylori* antibiotic resistance, this treatment-outcome registry may provide indirect estimates of the prevalence of *H. pylori* resistance to commonly used antibiotics [64–67].

In 2004, a community-based *H. pylori* screen-and-treat programme was implemented in the Matsu Islands, which are located in the East China Sea (see Chapter 3.10) [68]. A committee was established in collaboration with the Lienchiang County Bureau of Health and the Taiwan Community-based Integrated Screening Group [69]. This pilot programme lacked previous experience on the effectiveness of a 7-day triple therapy (esomeprazole, 40 mg once a day; amoxicillin, 1000 mg twice a day; and clarithromycin, 500 mg twice a day) in eradicating *H. pylori* infection in the general population. Therefore, routine retesting was included after the initial treatment to confirm treatment success, consistent with standard medical practices for *H. pylori* infection. If the retesting yielded positive results, retreatment was administered with a 10-day retreatment (esomeprazole, 40 mg once a day; amoxicillin, 1000 mg twice a day; and levofloxacin, 500 mg once a day). This approach sought to minimize the potential for selected antibiotic-resistant strains to remain in the community after the mass eradication, and to restrict them to a small, manageable subset of the population who would receive tailored therapies. Eradication rates with the initial therapy were 86.9% (95% CI, 84.7–89.1%) in all individuals who took medication and 88.7% (95% CI, 86.5–90.9%) in those who used at least 80% of the medication. The retreatment eradicated *H. pylori* infection in 91.4% (95% CI, 86.0–96.8%) of people who did not respond to the initial treatment. After one or two courses of antibiotic treatment, the *H. pylori* eradication rates were 97.7% (95% CI, 96.7–98.7%) in individuals who took medication and 98.8% (95% CI, 98.5–99.3%) in those who used at least 80% of the medication. This left a small subset of about 2% of participants who remained positive for *H. pylori* infection and required tailored management.

In addition, endoscopic biopsy for bacterial culture was performed on a subset of 624 individuals with *H. pylori* infection who had not previously received antibiotic treatment; it revealed modest changes in the rates of resistance to clarithromycin, metronidazole, and levofloxacin over time. The antibiotic susceptibility data (cumulative antibiogram) are shown in Chapter 3.10. The reinfection rate was < 1 per 100 person-years.

Another example is a community-based randomized clinical trial for *H. pylori* screening that was conducted in Changhua County under the platform of the Taiwan Colorectal Cancer Screening Program [15]. The trial targeted 240 000 residents aged 50–69 years who were eligible for colorectal cancer screening, and the trial protocol adhered to the antibiotic stewardship principles (see Table 7.2). Before initiating screening, the Changhua County Public Health Bureau established a steering committee of experts in public health, general medicine, gastroenterology, infectious diseases, and pharmacy. Local guidelines for the clinical management and surveillance of *H. pylori* infection were developed through a consensus among these experts [70]. To enhance clinicians' management of *H. pylori* infections, a series of educational activities was conducted that focused on the latest knowledge about antibiotic treatments. This initiative was supported by strong commitments from the administrative and medical leadership. Benchmarks, including for eradication rates, were set based on the experiences of the pilot, to enable the programme to be audited and to provide feedback after the programme was implemented (see Chapter 8). Monitoring of the antibiotic susceptibility data was planned in advance.

The central laboratory developed the antibiogram profile for the community in which the trial was being conducted by using biopsy samples collected from the participating hospitals. These samples were used both to test for antibiotic resistance genes and to test for minimum inhibitory concentration. These data were used to guide individualized treatments for individuals in whom treatment had failed, and also were periodically summarized and presented as percentages of *H. pylori* isolates that were resistant to commonly used antibiotics. This information was shared with the participating hospitals to enable them to optimize the first-line treatment strategies.

After the trial was implemented, the drug selection, dosage, and treatment duration were audited. Retesting was conducted in accordance with standard medical practice to evaluate treatment outcomes, aligned with the trial's pragmatic design. The first-line treatment used in the trial was a 10-day sequential therapy (days 1–5, esomeprazole, 40 mg once a day and amoxicillin, 1000 mg twice a day; days 6–10, esomeprazole, 40 mg once a day and clarithromycin, 500 mg plus metronidazole, 500 mg twice a day). Post-treatment *H. pylori* status was assessed using the stool antigen test at 6–8 weeks after the completion of treatment. Patients who remained test-positive received 10-day triple therapy (esomeprazole, 40 mg once a day; amoxicillin, 1000 mg twice a day; and levofloxacin, 500 mg once a day).

Individuals in whom eradication was not achieved after two courses of treatment received personalized treatment based on data from antibiotic susceptibility tests. In addition to the testing of cure, the antibiotic susceptibility testing data for *H. pylori* infection were assessed in a subset of participants who had endoscopic evaluation; this was used to optimize treatment protocols and address the potential changes in antibiotic resistance over time [11, 15].

For the test-of-cure data, after one or two courses of antibiotic treatment, the *H. pylori* eradication rates were 91.9% (95% CI, 91.3–92.5%) in all individuals who took medication and 97.6% (95% CI, 97.2–97.9%) in those who used at least 80% of the medication; 5.7% of individuals received more than one course of treatment. Among individuals in whom *H. pylori* eradication was successful, the reinfection rate was estimated as 0.3 per 100 person-years. For the antibiogram data from a total of 1110 individuals with *H. pylori* infection (Fig. 7.4), a stepwise increase in antibiotic-resistant strains was noted in all three groups: (i) individuals who had not yet received treatment; (ii) individuals in whom one course of treatment had failed; and (iii) individuals in whom two courses of treatment had failed and who required tailored management. The primary resistance rates over time mirrored the trends observed in the Asia–Pacific Region [7], with increases in resistance rates for clarithromycin, metronidazole, and levofloxacin, while resistance rates for amoxicillin and tetracycline remained stable.

The findings from this pragmatic clinical trial offer important insights into antibiotic stewardship in the context of an *H. pylori* screen-and-treat programme. First, the findings emphasize the importance of having the infrastructure in place to monitor whether antibiotic use aligns with the principles of antibiotic stewardship, supported by the commitment of health-care officials and professional leaders. Second, the findings from the antibiogram underscore the need to adopt more effective first-line treatment regimens. In this trial, the antibiotic resistance patterns aligned with the recommendations of the WHO AWaRe classification of antibiotics [36]. Resistance rates for clarithromycin and levofloxacin, compared with those for amoxicillin and tetracycline, showed a greater tendency to increase with treatment failures (Fig. 7.4A), which suggests that the empirical use of clarithromycin and levofloxacin may no longer be justified, particularly for retreatment. This highlights the need to consider bismuth-containing quadruple therapy as the most feasible option for initial treatment. Third, the prevalence of primary clarithromycin-resistant *H. pylori* infection

and levofloxacin-resistant *H. pylori* infection in treatment-naive patients has increased more over time compared with the prevalence of resistance to other antibiotics, probably because of the increased use of these antibiotics for other diseases (Fig. 7.4B). To implement an *H. pylori* screen-and-treat programme on a population scale, a simplified regimen that has fewer antibiotics, has a shorter duration, and uses antibiotics with a lower potential for emerging resistance, while maintaining efficacy, is needed to reduce overall antibiotic use.

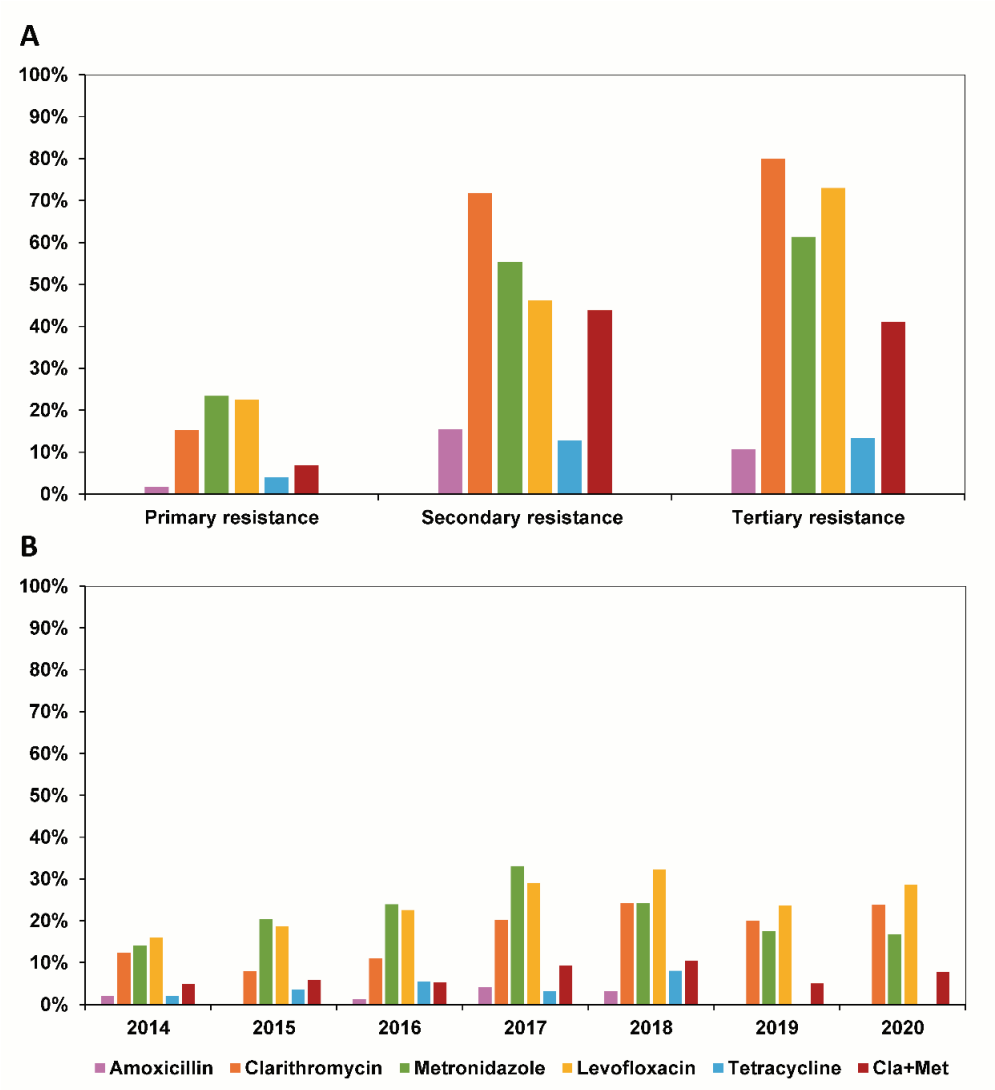

Fig. 7.4. Cumulative antibiograms of *H. pylori* for monitoring antibiotic resistance in a community-based randomized clinical trial to screen for *H. pylori* infection for gastric cancer prevention in 2014–2020: (A) primary, secondary, and tertiary resistance rates of *H. pylori*; (B) primary resistance rates of *H. pylori* over time. Primary resistance rates included individuals who had not yet received antibiotic treatment. Secondary resistance rates included individuals in whom one course of treatment had failed. Tertiary resistance rates included individuals in whom two courses of treatment had failed and who required tailored management. Cla+Met, dual resistance to clarithromycin and metronidazole. Source: Compiled from Lee et al. (2024) [15].

7.6 A prophylactic vaccine against *H. pylori*

Developing a prophylactic vaccine against *H. pylori* would be the ideal solution to the problems associated with antibiotic use in screen-and-treat programmes. In the USA, a cost–effectiveness analysis demonstrated that vaccinating children could prevent *H. pylori* infection and reduce the incidence of gastric cancer, which would save on long-term health-care expenses [71]. However, despite three decades of research on *H. pylori* vaccines, only a few candidates have reached the clinical trial stage and no single candidate induced long-lasting protection against *H. pylori* in terms of sterilizing immunity. Thus, no commercial vaccine is available on the market. This is because (i) *H. pylori* has developed several powerful strategies to evade both innate and adaptive immune responses upon infection [72–73], and (ii) the correlates of protection are still not known, which makes it challenging to guide clinical trials. The immune response to *H. pylori* infection is a complex interplay of innate and adaptive immune mechanisms that ultimately leads to chronic inflammation. *H. pylori* infection triggers the activation of various immune cells, including neutrophils, macrophages, and dendritic cells. This activation leads to the production of pro-inflammatory cytokines, such as interleukin-1β (IL-1β), IL-6, IL-12, and IL-23, which are crucial for the differentiation of T helper (Th) cells into Th1 and Th17 cells. The adaptive immune response to *H. pylori* involves the activation of specific T and B lymphocytes, leading to the production of antibodies and the generation of memory cells. CD4-positive T cells, particularly those that differentiate into the Th1 and Th17 subsets, play a crucial role in orchestrating the immune response against *H. pylori*. Recently, CD8-positive cells have been shown to be involved in early responses to infection and long-term immunological memory [74]. Moreover, *H. pylori* virulence factors, especially CagA, play a pivotal role in enhancing the immune response. *H. pylori* has also developed numerous immune evasion strategies that not only enable chronic persistence but also complicate the development of a vaccine against this pathogen [72]. One of the primary mechanisms of immune evasion used by *H. pylori* is the modulation of host immune responses, particularly through the induction of regulatory T cells and the suppression of effector T cell functions. This skewing of the immune response towards a more tolerogenic state enables *H. pylori* to persist in the gastric mucosa despite the presence of a robust immune response [73]. Such immune

evasion mechanisms must be overcome to develop efficacious vaccines, but they have mostly been neglected in previous approaches to vaccine development.

Thus, the efficacy of *H. pylori* vaccines in the preclinical stage has been variable and remains a major challenge. In addition, regulatory hurdles, including the need for rigorous testing and approval processes, can substantially delay the introduction of a new vaccine [75]. Vaccine candidates must demonstrate safety and efficacy in extensive clinical trials, which are expensive and time-consuming. Regulatory agencies require comprehensive data on immunogenicity, long-term protection, and potential adverse effects. The complexity of the immune response to *H. pylori* and the design of an effective vaccine pose additional challenges [76]. Previous vaccine trials have encountered issues including inadequate immune responses and adverse events, which have complicated the path to regulatory approval [77]. However, a phase III trial in children published in 2015 has shown some protectivity for the first years after vaccination [78]. Although the effect was not long-lasting and protection was only 71.8% after 1 year, this was the first human trial ever that showed that prophylactic immunization can protect against *H. pylori* infection, and it fuels the hope that optimized vaccines can provide better protection. This prophylactic vaccine candidate (developed by Kangwei Biological Technology) did not enter the market, and beyond this there are no advanced vaccine candidates in clinical development (clinicaltrials.gov, as at 11 November 2024). Therefore, a vaccine is currently not a viable option for preventing gastric cancer, and the only approach is to offer antibiotic therapy to people with *H. pylori* infection.

However, there are a few vaccine candidates that are in preclinical development. One approach, by a European consortium of nine partners funded under the Horizon Europe programme [79], uses highly conserved surface antigens together with novel delivery technologies for mucosal immunization to achieve a protective mucosal immune response. The lead candidate is anticipated to enter the first clinical trial in 2026. A potential therapeutic vaccine being developed by scientists in Umeå, Sweden, uses an approach based on the natural immunity generated against *H. pylori*. This project identified antibody species directed against the BabA protein, which mediates the binding of *H. pylori* to stomach epithelial cells. By immunizing with a BabA epitope, the researchers were able to elicit a blocking immune response, which prevents binding of *H. pylori* as well as cancer development in mice [80], even

without clearing the infection. This approach is still at the preclinical stage and will require substantial capital investment if it is to advance to a clinical proof of concept.

7.7 Conclusions

In a population-based *H. pylori* screen-and-treat programme, increased antibiotic use is expected. To reduce the risk of increasing antibiotic resistance within the population, it is essential to establish an antibiotic stewardship programme in advance, guided by a multidisciplinary team. The programme should provide comprehensive guidance on the appropriate use of antibiotics for *H. pylori* infection that reaches both clinicians and the public and includes perspectives on both individual-level management and broader policy-making. Data from *H. pylori* antibiotic susceptibility testing, similar to the antibiogram methods used for other common bacteria, along with the use of test-of-cure data as an indirect approach, can help reduce population exposure to ineffective antibiotics, thereby lowering the risk of selecting for and driving the emergence of antibiotic-resistant strains. Currently, an effective *H. pylori* vaccine that is suitable for population-based gastric cancer prevention programmes is not available. Therefore, policy-makers implementing *H. pylori* screen-and-treat programmes must work to minimize the potential negative impacts of these programmes. Adopting robust antibiotic stewardship measures is of paramount importance; these include carefully selecting eradication regimens, using retesting strategies after therapy, and continuously monitoring eradication rates and antibiotic resistance.

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Chapter 8.

Process and outcome measures for improving the quality and equity of *Helicobacter pylori* screen-and-treat programmes for gastric cancer prevention

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Summary

- A population-based *H. pylori* screen-and-treat programme for gastric cancer prevention should adhere to the principles of an organized screening programme for effective and equitable outcomes across groups.
- The programme should be supported by an information system for data collection and generation of quality indicators.
- Monitoring quality indicators enables ongoing improvements to the efficiency, effectiveness, and safety of a programme.
- An *H. pylori* screen-and-treat programme has the greatest chance of being equitable if the people with highest rates of *H. pylori* infection participate and are successfully treated, and monitoring this is important.

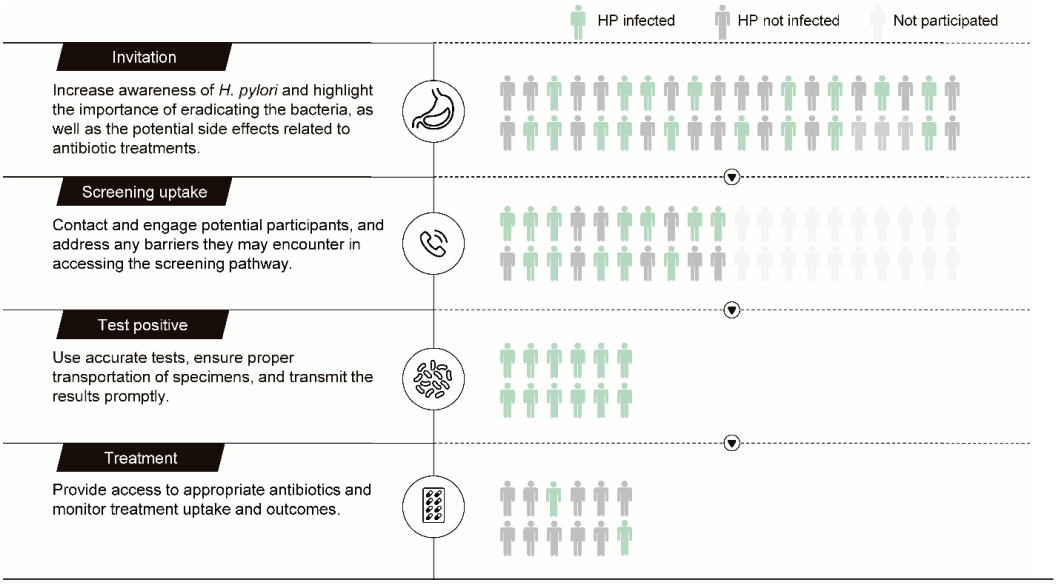

Fig. 8.1. Visual abstract. HP, *H. pylori*.

8.1 Introduction

In 2022, scientists from IARC published an international consensus statement on the essential and desirable criteria for an organized cancer screening programme [1]. According to the World Health Organization, screening programmes are only likely to achieve a high coverage of the at-risk population and deliver the desired impact at the population level when they are implemented using an organized approach [2]. Moreover, organized screening programmes spend health-care resources in a more cost-effective manner [3].

Although the *H. pylori* screen-and-treat strategy for gastric cancer prevention is not formally a cancer screening programme, because it focuses on screening for and treating *H. pylori* infection rather than gastric cancer [4], it has many commonalities with cancer screening programmes. To be effective, both gastric cancer screening and screening for *H. pylori* infection should follow the public health principles of disease screening. Because the goal is cancer prevention, it is logical to use cancer screening programmes as models. An effective *H. pylori* screen-and-treat strategy should adhere to the principles of cancer screening. Members of the advisory board of the IARC Cancer Screening in Five Continents (CanScreen5) project have identified 16 essential criteria for organized cancer screening programmes, which include having a protocol for the screening programme and providing continuing training of service providers [1]. Nine of the 16 criteria are concerned with the quality assessment of the programme, including monitoring and evaluation according to programme indicators. This list underlines the importance of quality assessment and is also applicable for *H. pylori* screen-and-treat strategies.

This chapter describes the required quality indicators that need to be collected to enable diligent quality assessment, monitoring, and evaluation of *H. pylori* screen-and-treat programmes. Centralized information systems play an important role in this process by storing detailed histories of the participants, including screening results, information about follow-up tests, and treatment data, which facilitate the continuity of care (Section 8.2). Quality indicators can be generated based on various follow-up periods before analysis, including short-term indicators (Section 8.3), intermediate-term indicators (Section 8.4), and long-term indicators (Section 8.5). The potential harms associated with screening are explored in Section 8.6. Section 8.7 provides an outline of how monitoring of quality indicators, disaggregated by ethnicity and

socioeconomic position, can be used to improve equitable health outcomes, with real-world examples.

8.2 Information systems

When an *H. pylori* screen-and-treat programme is implemented, data items are generated from different stages of the programme over time. This generally requires an information system to collect the data. Attention should be given to local data protection regulations and rules on obtaining consent from participants for their data to be collected and potentially linked to other data sets. Data can be analysed weekly, monthly, or yearly to generate the quality indicators that assist in auditing and monitoring the performance of the programme, including identifying eligible people, ascertaining screening test results, tracking the follow-up for participants with positive test results, and evaluating the effectiveness of the programme (Fig. 8.2). These indicators should be part of the ongoing quality improvement cycle in which this information is used to improve the performance of the *H. pylori* screen-and-treat programme. These indicators should include measures of the completion of the key steps in the pathway, adherence to best practices within these steps, and timeliness, and they should be measured for the total eligible population and with stratification by key demographic variables.

In the system, emphasis should be placed on ensuring the effective treatment of infections. Screening programmes may initially focus on testing but can face challenges in ensuring follow-up treatment [2]. This includes promptly communicating *H. pylori* test results to individuals who are diagnosed, providing access to the appropriate antibiotics, and monitoring treatment uptake and outcomes. The system should also identify bottlenecks in the screening workflow to ensure that the number of individuals invited does not exceed the available treatment capacity.

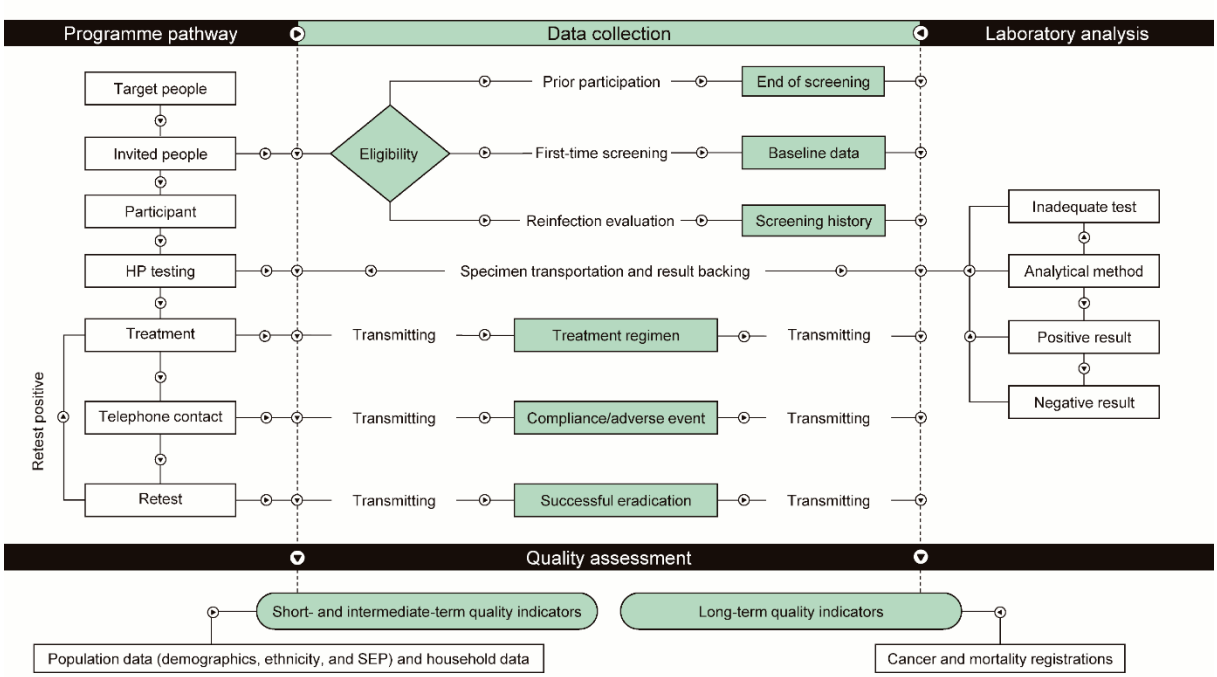

Fig. 8.2. An information system for data collection and generation of screening quality indicators. The system transmits the secure data collected from the *H. pylori* (HP) screening pathway and laboratory analyses to generate quality indicators. This is a real-world example from a population-based *H. pylori* screen-and-treat programme in Indigenous communities [5]. Bottlenecks can be identified when the system generates timely messages for quality control. Stratified analyses can be conducted for individuals who were screened, based on demographic data, geography, ethnicity, and socioeconomic position (SEP). Data can also be collected from individuals who either were not screened or did not adhere to the testing and treatment process, to evaluate the effectiveness of the programme.

H. pylori screening and treatment is a method of infectious disease control for primary prevention of gastric cancer, rather than a direct tool for early cancer detection. If one member of a household is screened and treated and other members are not, there may be a risk of reinfection within the household. Therefore, cascading testing to other household members may be considered when the targeted individual has an *H. pylori* infection (see Chapter 4). Developing such a family-based index-case method may require linking screening data with household data [5]. Information systems can also integrate with local infectious disease surveillance systems to monitor and prevent antibiotic resistance resulting from population-based antibiotic use.

8.3 Short-term indicators

Table 8.1 lists a set of recommended quality indicators for evaluating a population-based *H. pylori* screen-and-treat programme. It includes definitions for short-term

indicators, intermediate-term indicators, and long-term indicators and the required data to measure each indicator.

Short-term indicators are measurable outcomes that can be observed and assessed shortly after implementing a programme, to ensure that the programme is operating efficiently and adhering to the required standards. Details related to person, place, and time should be systematically recorded, including information about the individuals involved (e.g. demographics, eligibility criteria, and socioeconomic position), the geographical location of the programme, and the time frame during which the screening activities take place. Accurate documentation of these details facilitates the analyses of the performance of the programme and supports evaluation of its effectiveness.

Invitation coverage

An effective invitation is a critical first step in initiating the subsequent screening and treatment processes. Invitation coverage is an indicator that measures how well the target population is being reached. The population list and contact information should be made available. The quality of these population lists will vary, depending on how the data were collected. Therefore, there will be variability in who the data will and will not capture; for example, the data may not include immigrant populations, people who leave the country, and people who have died. The aim should be to obtain as complete a list as possible, so that the measures of coverage will be as accurate as possible. The process for invitation to screening should enable a high invitation rate to everyone eligible for the screening. This can be a particular concern if the invitation data set has limited coverage or fails to accurately identify certain subpopulations with lower socioeconomic positions and whose contact information is incomplete or inaccurate. Invitation coverage provides a measure of the quality of the register or contact list and can provide an indication of how complete the contact information list is.

When the total population list is unavailable, the proportion of the eligible population invited can be estimated by comparing the number of invitations sent with an estimated target population size. This estimation can be based on methods such as conducting household surveys within the community or collaborating with local organizations, schools, workplaces, and community groups to approximate the size of the eligible population.

Screening participation

Screening participation in its broadest sense provides a measure of the proportion of individuals who take up the invitation to screening. However, the screening participation is also a measure of how successful the programme has been in contacting and engaging participants and in addressing any barriers there may be in accessing the screening pathway. Variations in screening participation (e.g. by region, ethnicity, and socioeconomic position) can indicate the magnitude of the barriers to accessing the programme. Improvements to eliminate barriers require partnership and close engagement with high-risk groups from the outset, and targeted investment to address cost, time, distance, and other barriers [6]. Also, certain test types may have differential acceptability and uptake in different cultural groups; this may need further assessment [7]. The potential side-effects of antibiotic treatments and differences in personal medical histories should be considered, and individuals should make an informed choice and should not be unduly influenced towards participation. To enhance participation in screening, several interventions can be implemented, including general messaging and recruitment strategies, and the impact of these interventions can and should be monitored.

General messaging can increase public awareness of the importance of eliminating *H. pylori* infection for decreasing the burden of associated diseases, such as gastric cancer, peptic ulcer disease, and dyspepsia. The GISTAR study in Latvia (see Chapter 3.5) has shown that only a minority of the general population aged 40–64 years are motivated to participate in interventions for gastric cancer prevention [8]. Communication strategies can be designed to educate the target population and medical professionals and/or to deal with the misbeliefs or barriers related to *H. pylori* infection and gastric cancer prevention. The most frequent reasons reported as barriers to testing included not seeing the benefit of being tested or the need to be tested, and feeling healthy [8].

A range of potential communication tools and channels can be used, including programme websites, television, radio, print and online newspapers, opportunistic conversations with health-care providers, community gatherings and workshops, and social media (Box 8.1). The tools and channels to be used should be selected on the basis of the likely level of reach for the target population, i.e. those at highest risk within a population (to ensure equity), as well as health-care workers in different

health-care institutions, medical communities, scientific and research communities, and policy-makers and decision-makers at the national, regional, and local levels. By carefully selecting the communication channels used, Slovenia increased the rate of participation in colorectal cancer screening from 50% to 66% [9]. Engagement efforts, ideally including co-designed activities, should bring together policy-makers, health-care providers, community members, and the population groups that face the highest barriers to screening.

As an example of this, the invitation letters in the pilot programmes in Slovenia (EUROHELICAN and TOGAS) are labelled and signed by the Community Healthcare Centre (Ljubljana or Maribor) and the Slovenia National Institute of Public Health (see Chapter 3.5). Additional email invitations are signed in the same manner. Communication activities and campaigns may be carried out through mass media and both external and internal advertising spaces, including health institutions and public places. Increased participation can also be achieved by involving famous people and programme ambassadors. In addition, a tailored communication approach should be developed for people with disabilities, including those with visual or hearing impairments.

Box 8.1. Monitoring and evaluation of communication activities

Social media platforms can reach a vast audience, allowing for the dissemination of information about the importance of *H. pylori* screening, its benefits, and how to access services. Continuous monitoring and evaluation of communication activities is essential, because these are ongoing processes. Indicators may include data on click-throughs, retention, shares, and others. Feedback is collected regularly, using the built-in measuring systems of social media channels. For example, social media analytics tools can show the reach and engagement of a post. Meta Business Suite measures activities on Facebook and Instagram, and X (Twitter) Analytics measures tweets, engagement, and impressions. The use of different social media channels enables evaluation and constant feedback. Analytical tools, process evaluation, and feedback reciprocally enhance each other.

Recruiting strategies may include sending invitation letters, providing explanatory leaflets, using secure messaging, using mobile applications, making telephone calls,

and giving face-to-face presentations. If there is a functioning postal system, the invitation letter should contain relevant information about the purpose and goals of the programme, along with basic information about the positive aspects of the *H. pylori* screen-and-treat strategy for gastric cancer prevention. The stakeholders should collaborate to design and implement a screening programme to ensure that public messaging reaches groups with different socioeconomic positions equitably [10]. There is evidence that having the invitation letter signed by a health professional and sending text messages or telephone reminders can improve screening coverage overall and for underserved populations [11–12]. The information leaflet, which includes key messages about the programme, gastric cancer, *H. pylori* infection, and the importance of treatment, should be distributed to identified stakeholders and project partners. Co-designing programme information resources with participants is important to ensure that the messages will reach those at the highest risk [10].

If the postal system is limited, alternative methods of delivery of invitations should be considered. A health-care provider's mobile application provides convenience through features such as easy appointment scheduling, access to screening services, and timely reminders [13]. Telephone outreach and face-to-face presentations may yield a higher participation rate than mailed letters, but this can also be the most expensive approach in terms of human resources [14] and so it may be reserved for individuals who have not responded to multiple previous contact attempts. Conferences and symposiums for scientific, medical, research, and governmental audiences should be used to disseminate the project results and inform the attendees about the project's goals during its implementation.

Screening participation may vary depending on the type of tests used; this is influenced by factors such as preparation requirements, cultural perceptions, and costs (see Chapter 5). For example, in a screening trial in Taiwan (China), the participation rate was 50% when the *H. pylori* stool antigen test was combined with the faecal immunochemical test (FIT) [15–16], whereas the screening participation could reach 80% when ^{13}C-urea breath tests were used in Indigenous communities [5]. When serology tests are used for screening, the proportion of participants who miss confirmatory testing should be evaluated.

Testing indicators

Testing indicators include the test positivity rate and the rate of inadequate tests (Table 8.1). Despite the high diagnostic accuracy of ^{13}C-urea breath tests and monoclonal stool antigen tests, inadequate testing can occur (see Chapter 5). When individuals providing breath samples are not coached on the optimal exhalation technique or are incapable of executing it, the sample may have an insufficient CO_2 concentration for the ^{13}C-urea breath test [5]. The *H. pylori* stool antigen test can be affected by inadequate faecal sampling and improper temperature conditions during specimen transportation and the time before analysis, leading to false-negative results [17]. The test positivity rate may indicate whether the programme is reaching those who would benefit most, and it can serve as a guide for appropriate resource allocation [5, 18]. Because *H. pylori* is an infectious disease that is often transmitted within families, the programme may contact family members of individuals with positive test results, to increase the likelihood of test positivity [5, 19]. It is also important to provide counselling at the time of testing about the significance of treating *H. pylori* infection.

Table 8.1. Recommended quality indicators for evaluating a population-based *H. pylori* screen-and-treat programme

Quality indicators[a]	Required data[b]	Definitions[c]
Short-term indicators		
Invitation coverage	(1) Number of people invited to screening (2) Number of eligible people	Proportion of people who receive an invitation among the eligible people
Screening participation	(1) Number of participants (2) Number of invited people	Proportion of participants among the people invited
Test positivity rate	(1) Number of test positives for *H. pylori* (2) Number of participants	Proportion of test positives among participants
Rate of inadequate tests	(1) Number of inadequate test results (2) Number of *H. pylori* tests	Proportion of inadequate test results among participants
Rate of missed confirmatory testing	(1) Number of missed confirmatory tests (2) Number of *H. pylori* serological tests	Proportion of missed confirmatory testing among participants receiving *H. pylori* serological tests

Table 8.1. Recommended quality indicators for evaluating a population-based *H. pylori* screen-and-treat programme (continued)

Quality indicators[a]	Required data[b]	Definitions[c]
Referral rate to treatment	(1) Number of participants referred for treatment (2) Number of test-positives for *H. pylori*	Proportion of participants referred for treatment among those who test positive
Rate of antibiotic prescriptions	(1) Number of participants prescribed antibiotic treatment (2) Number of participants referred for treatment	Proportion of participants prescribed antibiotic treatment among *H. pylori*-positive participants referred for treatment
Successful eradication rate	(1) Number of successful eradications (2) Number of participants prescribed antibiotic treatment	Proportion of successful eradication among participants prescribed antibiotic treatment
Adverse event rate	(1) Number of serious adverse events (2) Number of participants treated for *H. pylori*	Proportion of serious adverse events among the treated participants
Rate of stopping treatment because of adverse events	(1) Number of participants stopping treatment because of adverse events (2) Number of participants treated for *H. pylori*	Proportion of treated participants who stop treatment because of adverse events
Intermediate-term indicators		
Screening coverage	(1) Number of people who participate in the screening test (2) Number of eligible people	Proportion of eligible individuals who participate in screening
H. pylori prevalence	(1) Number of people with *H. pylori* infection (2) Number of eligible people	Proportion of people with *H. pylori* infection among eligible people
H. pylori reinfection rate	(1) Number of people with *H. pylori* reinfection (2) Number of people who have been successfully treated for *H. pylori* (3) Follow-up time	Rate of people with *H. pylori* reinfection among people who have been successfully treated during a follow-up period (per 100 person-years or 1000 person-years)
Long-term indicators		
Gastric cancer incidence rate	(1) Number of eligible people newly diagnosed with gastric cancer (2) Number of eligible people (3) Follow-up time	Rate of newly diagnosed gastric cancer during a follow-up period (per 100 000 person-years)

Table 8.1. Recommended quality indicators for evaluating a population-based *H. pylori* screen-and-treat programme (continued)

Quality indicators[a]	Required data[b]	Definitions[c]
Gastric cancer mortality rate	(1) Number of eligible people whose death was related to gastric cancer (2) Number of eligible people (3) Follow-up time	Rate of death related to gastric cancer during a follow-up period (per 100 000 person-years)

[a] Stratify the indicators by population subgroup, and establish benchmarks tailored to different populations.
[b] The numerator is (1), and the denominator is (2) or (2) × (3).
[c] The definition is equal to (1) divided by (2), or (1) divided by (2) × (3) when follow-up time is required.

Treatment indicators

Treatment indicators include several key measures: the proportion of individuals referred for treatment among those who test positive, the proportion of antibiotic prescriptions adhering to guidelines that are given to people who are referred for treatment, the proportion of successful eradication among people who were prescribed antibiotic treatment, the proportion of serious adverse events among the treated participants, and the proportion of treated participants who stop treatment because of adverse events.

About 30% of participants who test positive for *H. pylori* may not seek treatment, because of the absence of symptoms, concerns about the pill burden associated with treatment, and worries about potentially needing an endoscopy because of their positive *H. pylori* test results [16]. Antibiotic treatments for *H. pylori* infection are the core elements of gastric cancer prevention (see Chapter 6). Successful eradication is generally reported based on the intention-to-treat (all patients who were prescribed medication) and per-protocol (those who used ≥ 80% of the prescribed medication) principles [20]. Substantially lower eradication rates can be identified in some subpopulations as a result of high prevalence of antibiotic resistance [5, 21]. Disparities in antimicrobial resistance may be addressed by revising the first-line therapy and offering bespoke treatment regimens for any identified target populations. Consideration should also be given to monitoring disparities in the completion of treatment and any barriers to treatment completion, including variations in the presence of adverse events and the acceptability of treatment, in relation to the predefined quality benchmarks (Box 8.2). Adverse events related to the treatment can be common and include abdominal pain, diarrhoea, dyspepsia, and poor appetite, but serious adverse events are generally rare.

Box 8.2. Quality benchmarks

Quality benchmarks for screening programmes help programme managers to understand typical performance levels and identify areas for improvement. These benchmarks are established from guidelines and recommendations from relevant health-care organizations, previous studies, or experts in the field, along with the analysis of historical data from previous programmes. For example, the *European guidelines for quality assurance in colorectal cancer screening and diagnosis* established the quality benchmarks for colorectal cancer screening [22]. Communities can assess whether their screening programmes align with current best practices and whether they are designed to achieve optimal health outcomes. Continuous knowledge updates are vital to determine the most effective performance levels while maintaining an optimal balance between benefits and harms [23].

8.4 Intermediate-term indicators

Intermediate-term indicators are measurable outcomes that reflect the progress and impact of a programme over the medium term; this can provide insights into the effectiveness of the programme before the long-term outcomes can be measured. These indicators may include screening coverage, *H. pylori* prevalence, and *H. pylori* reinfection rate (Table 8.1). Screening coverage is defined as the proportion of eligible individuals who participate in screening. It is considered an intermediate-term indicator because it reflects the extent of participation by the target population in the screening programme, and it serves as a step towards achieving the long-term health outcomes. As screening coverage increases, the prevalence of *H. pylori* infection (the proportion of eligible individuals with *H. pylori* infection) typically declines [24]. With repeated screenings, particularly among a subset of participants who have been successfully treated for at least 2 years, the *H. pylori* reinfection rate can be evaluated and expressed per 100 person-years or 1000 person-years. It can be as low as < 1 per 100 person-years, particularly when lifestyle education is also provided to reduce the risk of *H. pylori* transmission [5, 25]. Reinfection rates may be higher in high-risk communities; for example, very high reinfection rates have been reported in Alaska [26]. Higher reinfection rates associated with ethnicity and socioeconomic position may lead to prioritizing family-based or community-wide invitation approaches in a programme [5].

8.5 Long-term indicators

Long-term indicators are measurable outcomes that assess whether the programme has achieved its ultimate goal; they primarily include gastric cancer incidence and mortality rates (see Chapter 2 for the summaries of explanatory clinical trials). These rates, which incorporate a time component, are calculated based on the incidence of newly diagnosed gastric cancer cases and deaths related to gastric cancer during the follow-up period (Table 8.1). Data can be obtained through cancer registries and death registries to minimize the loss to follow-up. Reductions in the gastric cancer mortality rate from *H. pylori* screening and treatment are observed after decreases in the gastric cancer incidence rate, because of the primary prevention nature [24, 27].

When the programme is continued for about 5–10 years, depending on the baseline incidence rates, gastric cancer outcomes can be evaluated using various approaches (Fig. 8.3). In the context of a population-based programme operating as part of health-care policy or public health initiative, gastric cancer outcomes can be compared between individuals who were invited to participate in the *H. pylori* screen-and-treat approach and those who were not invited. Comparisons can also be made between participants who completed the *H. pylori* screening and non-participants, as well as between individuals with *H. pylori* infection in whom the infection was successfully eradicated and those who remain untreated or experience unsuccessful treatment. Evaluations of programme effectiveness may need to account for non-adherence to the invitation, resulting from self-selection bias, as well as variations in the baseline characteristics of the participants [16].

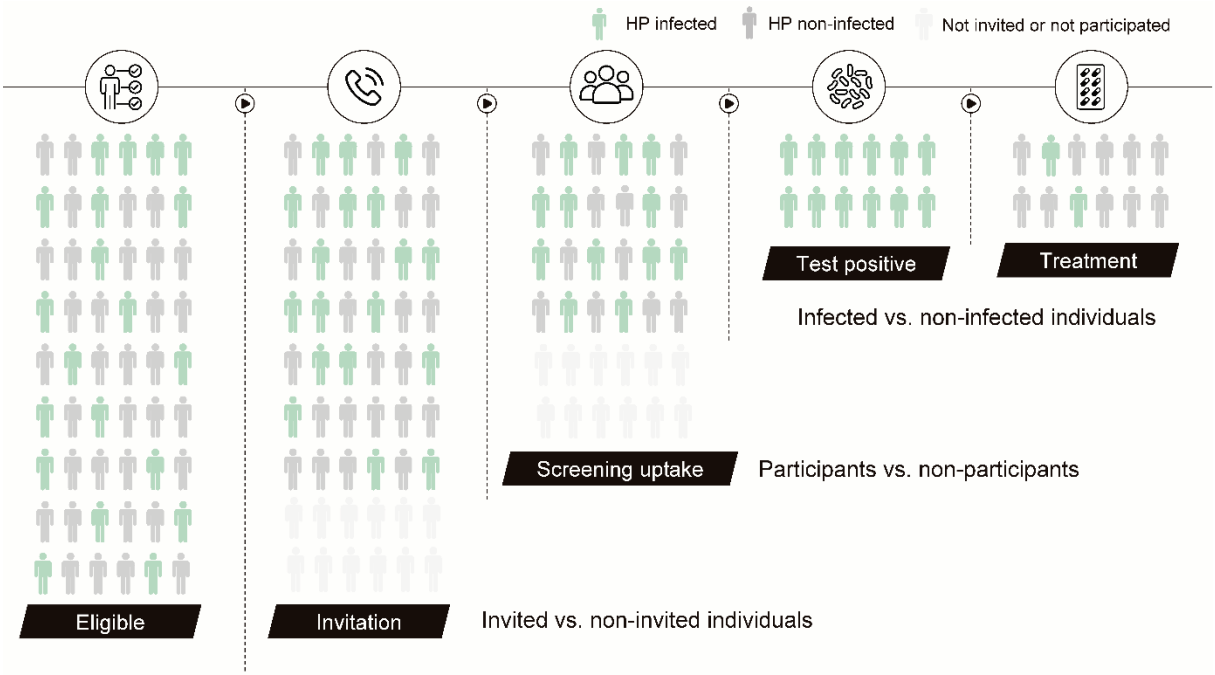

Fig. 8.3. Outcome evaluations for gastric cancer incidence and mortality rates in a population-based screen-and-treat programme for *H. pylori* (HP) infection. This is an example from a pragmatic clinical trial [16]. The assessment can be conducted at several levels within the screening intervention pathway, including comparisons between individuals who were invited and those who were not invited, between participants and non-participants, and between patients who have been successfully treated for *H. pylori* infection and those who still have *H. pylori* infection.

Alternatively, with sufficient screening coverage, programme effectiveness can be estimated by comparing gastric cancer incidence and mortality rates before and after the initiation of the programme. Historical trends can also be accounted for by using a natural history model to project the trends in gastric cancer incidence and mortality before the programme (see Chapter 9). This projection generates expected rates without intervention, which can then be compared with the observed outcomes (see Chapter 3.10).

Monitoring long-term outcomes by demographic variables is crucial to understand whether an *H. pylori* screen-and-treat programme is meeting its equity goals. These goals include achieving equal or better access and participation in all groups compared with the most privileged groups. The long-term aim is to reduce gastric cancer incidence and mortality rates to be as low as those in the most privileged groups. This may require progress to be measured directly against measures of equity through the absolute differences and relative risks of incidence and mortality. The programme may also yield benefits in the prevention of peptic ulcer disease and

other *H. pylori*-related diseases, which can be evaluated in a similar manner using hospital electronic health records or health insurance databases [24, 28]. In a well-functioning programme, the current inequities in rates of peptic ulcer disease and gastric cancer in the target population would be expected to be reduced in the long term. In regions such as the high-risk population living in the Matsu Islands (see Chapter 3.10), an *H. pylori* screen-and-treat programme has been implemented and reached the stage of evaluating long-term outcomes for gastric cancer [24].

8.6 Exploring the potential harms

Concerns about the potential harms of *H. pylori* screening mainly revolve around the effects of antibiotic use (see Chapters 2 and 7), because an intervention based on antibiotic treatment will increase antibiotic use [29]. Potential harms may include the impact on the digestive tract because of changes in gastric acidity, alterations in the diversity of gut microbiota, and the development of antibiotic resistance. The oesophagus is presumed to be the most susceptible site for acid reflux, and the colorectum is presumed to be the most susceptible site for changes in the gut microbiota. However, the associations between treatment of *H. pylori* infection and the risk of cancer at these sites have not yet been supported by observational studies [30–34] or population-based randomized trials [16, 35]. Antibiotic treatment for *H. pylori* infection may affect the gut microbiota [36], although research suggests that these changes are temporary and the gut microbiota largely return to the pre-treatment state over time [33, 37].

The increasing trends of antibiotic resistance are a global concern because of high selection pressure from the increasing use and misuse of antibiotics. Gathering data on *H. pylori* resistance from endoscopic biopsies and stool samples may offer the advantage of selecting the antibiotic regimens with the highest eradication rates (e.g. > 90%) while minimizing the population's exposure to less-effective antibiotics [38–39]. When new *H. pylori* eradication regimens are developed, their potential to induce the gut resistome may be considered. Monitoring general increased antibiotic resistance in any bacteria, in addition to *H. pylori*, in the population may involve tracking the number of individuals who present with resistant bacterial strains overall, the number of hospitalizations for infectious diseases in the population, and the number of deaths from infectious diseases in the general population.

8.7 Real-world examples of monitoring to improve equitable outcomes

Monitoring all the quality indicators outlined in this chapter by a range of demographic variables (e.g. geographical region, age, sex, race or ethnicity, socioeconomic position, homelessness and other housing factors) is important to assess the reach, quality, and timeliness across the screening pathway and to implement quality improvement activities where required. This is also necessary to ensure equitable health outcomes (Box 8.3) and programme effectiveness. To monitor by demographic variables, these variables must be accessed through existing data sources or collected as part of the screening programme. To meet standard quality requirements, screening requires strategies to overcome barriers related to cultural differences, administrative challenges, geographical constraints, and economic disparities. Equity recognizes that people with different levels of advantage require different approaches and resources to obtain equitable health outcomes [40].

Box 8.3. Cancer health inequalities and cancer inequities

Cancer health inequalities refer to the differences in risk factors, cancer incidence, cancer stages at diagnosis, and treatment outcomes among different population groups. Differences can be associated with factors such as geographical location, race or ethnicity, socioeconomic position, access to health-care services, education level, and environmental factors. For example, elevated gastric cancer incidence and mortality rates are found in almost all Indigenous peoples relative to the corresponding non-Indigenous populations in the same region or country. Cancer inequities are those differences that are unnecessary and avoidable but are also considered to be unfair and unjust [41].

The incidence of gastric cancer and the prevalence of *H. pylori* infection are disproportionately higher in people with lower socioeconomic positions [42–43], Indigenous populations [5, 44–46], other ethnic groups [45, 47], and immigrants from areas with higher prevalence of *H. pylori* infection [48]. These same groups frequently experience some of the greatest barriers to accessing organized screening and health care [5, 24, 49]. They are often not well served by the existing health system and may have historically low rates of participation in screening. Yet the same high-risk groups have the most to gain by participation in a population-based *H. pylori* screen-and-treat programme, in terms of reduced risk of gastric cancer.

Equity in access into and through screening can be achieved by system change and by designing equity into the programme, not only by individual behaviour change [50]. To successfully introduce and develop the screen-and-treat approach from an equity perspective requires effort, expertise, and engagement with the populations of interest. The aim is a participant-centred approach that is “easy” for people, in which all interactions, including invitation, testing, treatment, and follow-up, are accessible and culturally safe. Enrolling individuals who are experiencing homelessness in screening for infectious diseases may require tailored strategies to address challenges such as unstable living conditions, limited access to health care, and mistrust of medical systems [51].

Other axes should also be considered for monitoring, particularly where they are correlated with *H. pylori* infection and its sequelae; examples are rurality, region, sex, and other factors. Pertinent demographic information in line with the agreed equity

goals of the programme should be collected from the outset, so that quality indicators can be reported across ethnicity, socioeconomic position, and other appropriate variables [5, 46].

The Indigenous people living in Taiwan (China), which include 16 ethnic groups, are Austronesian and constitute about 600 000 individuals, accounting for 3% of the population of the island. There are 55 designated Indigenous townships traditionally inhabited by Indigenous peoples, with similar historical and cultural characteristics. The age-standardized incidence rate of gastric cancer is about 23 per 100 000 person-years overall, and the rate among Indigenous people is almost double that among non-Indigenous people residing in the same regions. Since 2018, a population-based *H. pylori* screen-and-treat programme has been implemented, targeting individuals aged 20–60 years who reside in 17 Indigenous townships [46]. Although the programme aimed to increase enrolment among Indigenous people, it is open to both Indigenous and non-Indigenous individuals, to ensure equal access to screening.

In 2023, this programme expanded to 55 Indigenous townships. By the end of 2024, about 30 000 participants were included [5]. This expansion can be attributed to the endorsement of Indigenous health providers in the programme, funding support for screening and treatment, monitoring of quality indicators, use of telemedicine for instant consultations, and increased awareness through various approaches, including social media platforms, telephone contacts, and face-to-face invitations [5]. The benchmark was set at 60% for the *H. pylori* screening participation rate, 40% for the test positivity rate, 60% for the referral rate to treatment, and 80% for the successful eradication rate. The average performance achieved was 80% for screening participation, 44% for test positivity rate, 83% for referral rate to treatment, and 91% for successful eradication rate, with greater variability in the screening participation and test positivity rates between townships. The test positivity rate among Indigenous individuals (~60%) was notably higher (by 2–3-fold) than that in their non-Indigenous counterparts living in the same township. Consequently, the test positivity rate in each township may reflect the effectiveness of the invitations and the level of screening participation among Indigenous individuals.

In Aotearoa New Zealand, the *H. pylori* in Aotearoa New Zealand (ENIGMA) Study (see Chapter 3.11) is investigating the prevalence of *H. pylori* infection by inviting, in equal numbers, Māori people (the Indigenous population), Pacific people,

and individuals from other ethnic groups aged 12–69 years from across the country to be screened and treated for *H. pylori* infection. Participants have a serology test at their local laboratory and are invited to do a stool antigen test if the result of the serology test is positive. The study will report ethnic differences in rates of contact or invitation, participation (for serology and stool antigen tests), seropositivity, treatment, eradication, retesting, adverse effects, and antibiotic resistance. The treatment pathway is being delivered by a Māori health-care provider and has been designed in partnership with this provider to enable a culturally centred approach to be taken. An earlier cost–utility analysis compared the cost–effectiveness of the *H. pylori* screen-and-treat approach by ethnicity and showed a much greater cost–effectiveness for Māori people than for non-Māori people [52]. Current research aims to inform the design of a wider screen-and-treat pilot study in New Zealand, to address the unfair and avoidable high rates of gastric cancer among Māori people and Pacific people.

8.8 Conclusions

Population-based *H. pylori* screening and treatment is a multistep process. To ensure its effectiveness, it is necessary to assess a range of quality indicators at each stage and to facilitate the continuous monitoring and improvement of overall performance. Advances in information technology enable the timely collection and assessment of the recommended process and outcome measures, to ensure consistently high screening standards across regions and groups with varying gastric cancer burdens and health-care infrastructure. It is particularly important to increase public awareness about the significance of eliminating *H. pylori* infection to reduce the burden of associated diseases, such as gastric cancer, peptic ulcer disease, and dyspepsia. Effective programmes are designed in partnership with high-risk groups; these programmes invest in improving participation within these populations from the outset, and they are also responsive to the differences identified through programme monitoring, such as inequities in the rates of invitation, participation, eradication, and programme outcomes. An *H. pylori* screen-and-treat programme has the greatest chance of being equitable, effective, and efficient if the people with the highest rates of *H. pylori* infection participate and are successfully treated. This requires attention across the screen-and-treat pathway to ensure that all interactions are accessible and culturally safe.

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Chapter 9.

How to optimize the cost–benefits of *Helicobacter pylori* screen-and-treat programmes for gastric cancer prevention

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Summary

- Decision models consistently demonstrate that an *H. pylori* screen-and-treat programme is a cost-effective intervention to prevent gastric cancer even in settings with a low incidence of gastric cancer (age-standardized rate < 10 cases per 100 000 person-years).
- The optimal strategy (i.e. which test, what age range, total population vs high-risk population only, and once-only vs repeat testing) varies across settings.
- Before implementation, pilot studies should be conducted to provide essential information about the local conditions of the *H. pylori* screen-and-treat programme, such as the prevalence of *H. pylori* infection, testing participation, and treatment efficacy.
- Data from pilot studies, combined with data on demographics and costs, can inform decision models to optimize *H. pylori* screen-and-treat strategies in local settings.
- Organizers of screening programmes can consider embedding an *H. pylori* screen-and-treat strategy into existing preventive care protocols, such as those for colorectal cancer screening, to enhance the efficiency of care.
- Ancillary effects of *H. pylori* eradication, such as prevention of other gastric diseases and antimicrobial resistance, may affect the cost–effectiveness of screening programmes. These effects should be considered in decision modelling and should be monitored in *H. pylori* screen-and-treat pilot programmes to obtain data on the long-term effects.

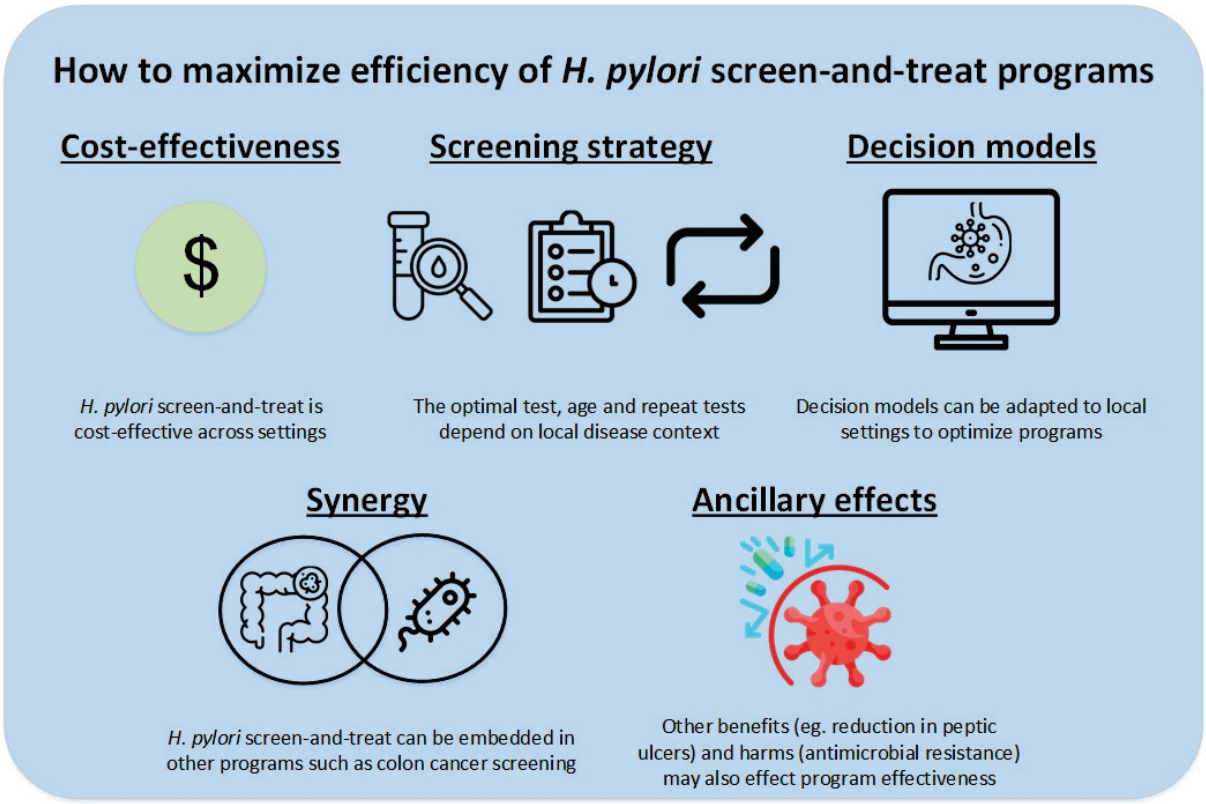

Fig. 9.1. Visual abstract.

9.1 Introduction

According to the widely adopted Wilson and Jungner criteria for screening, the costs of any screening programme should be economically balanced with expenditure on medical care as a whole [1]. Therefore, the implementation of an *H. pylori* screen-and-treat programme should be carried out with the aim of maximizing the benefits with respect to the costs. This chapter guides health policy-makers through the optimization of the efficiency of *H. pylori* screen-and-treat programmes.

The chapter starts by delving into the role of decision modelling in the optimal implementation of *H. pylori* screen-and-treat programmes (Section 9.2) and then outlines the information that needs to be collected to enable effective decision modelling for the local context (Section 9.3). Section 9.4 discusses the currently available international evidence on the cost–effectiveness of *H. pylori* screen-and-treat programmes and the optimal strategies for their implementation (i.e. which test, what age range, etc.). Section 9.5 outlines the potential synergies when combining *H. pylori* screen-and-treat programmes with existing preventive interventions. Section 9.6 addresses the ancillary

benefits and harms of *H. pylori* screen-and-treat strategies and considers the broader public health implications.

9.2 The need for decision modelling and cost–effectiveness assessments

The previous chapters of this report have provided evidence that population-based *H. pylori* screen-and-treat strategies are effective in reducing the burden of gastric cancer. However, as also pointed out in the European Commission recommendations for cancer screening [2], the benefits of *H. pylori* screen-and-treat programmes are highly dependent on the local gastric cancer burden. Moreover, the optimal strategy for an *H. pylori* screen-and-treat programme will depend on the local resources available and the prioritization of the programme among other health prevention interventions. However, it is not feasible to perform clinical studies that address all the variables and dimensions necessary to evaluate the benefit of every possible strategy to estimate which strategy is optimal. Therefore, it is important to find different methods to translate the findings of clinical studies to local settings, to estimate whether an *H. pylori* screen-and-treat programme would provide good value for money in the local setting and under what conditions; for this process, decision modelling is often used.

Decision modelling is a structured process that is used to predict the outcome of certain scenarios, and it can offer valuable insights to policy-makers and stakeholders. Decision models provide an overview of the potential outcomes (e.g. the benefits, harms, and resource requirements) of specific interventions, and thus provide valuable insights during the decision-making and implementation phases of preventive interventions. An example of the value of decision modelling is the role that the Microsimulation Screening Analysis (MISCAN) model for colorectal cancer played during the implementation of the successful colorectal cancer screening programme in the Netherlands (Box 9.1) [3].

Box 9.1. Decision modelling during the implementation of the colorectal cancer screening programme in the Netherlands

In 2009, the Health Council of the Netherlands recommended that a national colorectal cancer screening programme using biennial faecal immunochemical testing (FIT) should be implemented. The choice of the test and the cut-off level for a positive test were based on decision modelling carried out using the MISCAN model for colorectal cancer, which showed that FIT screening at low cut-off levels was the most cost-effective

strategy. The advice of the Health Council was followed by a preparation phase in which the MISCAN model was used to estimate the annual resources required for the programme, to enable the potential gaps in resource capacity to be identified. In 2014, the implementation of the programme revealed that the chosen FIT was not performing as expected, resulting in long waiting lists for colonoscopy. The MISCAN model was then used to evaluate the optimal way to address the pressure on the colonoscopy capacity; as a consequence, the cut-off level for a positive FIT result was adjusted. Since then, the colorectal cancer screening programme in the Netherlands has been considered to be one of the most successful programmes in the world in terms of its organization, participation, and yield of screening.

Decision modelling should also be used in the decision-making phase of *H. pylori* screen-and-treat programmes to establish for the local setting whether the benefits of the programme outweigh its harms and whether the required resources are economically balanced with the net benefits. In addition, decision modelling can be used in this phase to suggest an optimal approach to implementing the *H. pylori* screen-and-treat programme, i.e. for which groups within the population, at what age, with what test, and so on [4]. Which strategy will be optimal in each setting will depend on the predicted benefits (e.g. the gastric cancer incidence and mortality prevented), the harms (e.g. false-positive test results, overtreatment, and side-effects of treatment), the resource requirements (e.g. the number of breath tests and the number of antibiotic treatments), and the costs, as well as the balance between these aspects of the programme. This information can be used by policy-makers to make an informed decision about whether the *H. pylori* screen-and-treat programme provides good value for money and whether it should be implemented. The decision should also consider the wider implications of *H. pylori* screen-and-treat programmes, such as a potential increase in antibiotic resistance. Unfortunately, it is very challenging to account for the impact of antibiotic resistance, because very little is known about which bacterial species would be affected by population-based *H. pylori* treatment and whether this would result in an increase in serious infections.

If a positive decision on implementation has been made, decision models can then be used in the preparatory phase before implementation, to estimate the annual resource requirements for laboratory testing, drug availability, endoscopic follow-up

capacity, and so on, to help in the planning of the *H. pylori* screen-and-treat programme. Different roll-out schedules can be compared to best accommodate any resource constraints, and potential bottlenecks in implementation can be identified and tackled where necessary. During implementation, decision modelling can be used to compare the outcomes of the programme (and their distribution over population subgroups) with the expectations from the modelling that was carried out beforehand and/or any pilot studies. Decision modelling can also be used to evaluate how best to adjust the programme if it does not perform according to expectations. Finally, modelling can be used to make predictions about the long-term benefits of the programme. This is especially important in the light of the long lag time between the implementation of an *H. pylori* screen-and-treat strategy and the actual reduction in gastric cancer incidence and mortality.

These various uses clearly indicate the potential added value of decision modelling in the decision-making and implementation process of an *H. pylori* screen-and-treat programme. However, decision models are only helpful if the information they provide is correct. Therefore, it is important to either choose a model that has already been validated or validate a new model. Model validation consists of putting model predictions through several checks, which constitute different levels of validity [5]. For validity level 1 (face validity), model assumptions and predictions correspond to the current science and evidence, as judged by experts in the field. Validity level 2 (internal validity) checks whether the model behaves as intended and compares the model predictions with the data the model has been based on. Most models meet these two requirements for validity. However, validity level 3 (external validity) and validity level 4 (predictive validity) are used much less often and are more important. In both these types of validation, a model is used to simulate a real scenario, such as a clinical trial, and the predicted outcomes are compared with the real-world ones. The difference is that for predictive validity, a model is used to forecast events before the events have been observed. For decision-making purposes, policy-makers should ideally use information from models that have passed at least validity levels 1–3.

However, even well-constructed models are not necessarily right. Especially in situations with sparse data, multiple model assumptions may all give a good fit to the data. Nevertheless, the implications that these different assumptions can have on the effectiveness and cost–effectiveness of interventions can be substantial. An example of such a situation arose in colorectal cancer modelling [6]. Three models were all fitted to

the same data on adenoma prevalence and colorectal cancer incidence, but their predicted impact on the benefits of colorectal cancer screening was substantially different. The lack of longitudinal data on the adenoma–carcinoma sequence made it impossible to reliably estimate its duration and thus the protective effect of screening. It was not until new evidence about the effectiveness of colonoscopy screening became available that the differences could be resolved. Therefore, it is important to continuously compare models with newly available evidence and to update them where necessary.

In the meantime, it is important to perform sensitivity analysis on uncertain model parameters to assess the robustness of the conclusions from the modelling to its assumptions. A special form of sensitivity analysis involves performing comparative modelling with other, independently developed models. Whereas within-model sensitivity analyses assess the uncertainty in model parameters, between-model analyses also assess uncertainty in structural model assumptions (Box 9.2).

Box 9.2. Model comparisons in CISNET

The Cancer Intervention and Surveillance Modeling Network (CISNET) is a consortium sponsored by the United States National Cancer Institute. Investigators in CISNET independently develop decision models and compare the estimated effects of screening interventions between models. If models that differ in structure have the same results, the conclusions may be more robust. CISNET models have been compared for many diseases, such as colorectal cancer [7], breast cancer [8], and lung cancer [9], and have been used to inform screening guidelines around the world. Gastric cancer models in CISNET are under development. Using validated CISNET models for health policy analyses provides additional robustness to the obtained findings.

To enable valid decision modelling, it is important to build decision-modelling capacity in local settings and to collect the necessary data for building the model. Adherence rates to screening invitations and eradication treatment are key drivers of model outcomes. Because these rates often differ in the local setting from those assumed in models, these aspects need input from pilot programmes. Therefore, every country considering the implementation of an *H. pylori* screen-and-treat programme should first perform pilot studies before implementing the programme. These pilot studies provide essential information about the local conditions of the *H. pylori* screen-and-treat programme, such as the prevalence of *H. pylori* infection and testing participation.

Countries should then use this information in valid decision models to estimate the resource and budget impact of implementing the *H. pylori* screen-and-treat programme in their local setting. Section 9.3 addresses which data elements are essential and what tools are available to build local decision-modelling capacity.

9.3 Natural history models and data specifications for decision models

Decision models rely on robust natural history models, which describe the progression of a disease over time, from its inception through various precursor states to its ultimate outcome. The parameters of the model are used to quantify the transitions between health states and should be based on observed data. This section starts by describing the clinical assumptions and methodology that are typically used in gastric cancer natural history models. Then the types of data required to conduct country-specific modelling for health policy analyses are described.

Gastric cancer natural history models

The Correa cascade is the most widely accepted model for the progression from precursor lesions to gastric adenocarcinoma of the intestinal type, encompassing the stages of gastritis, atrophic gastritis, intestinal metaplasia, and gastric dysplasia (Fig. 9.2) [10]. Multiple systematic reviews of endoscopy studies indicate significant differences in the prevalence of these precursor lesions [11–13], with a higher prevalence of precursors in countries with a high burden of gastric cancer [13]. In addition to affecting the onset of precursor disease, exposure to risk factors, such as *H. pylori* infection, smoking, and diet, may also influence disease progression [14]. However, there is no systematic evidence that precursor progression rates differ internationally other than through these factors, which enables the generalization of this progression across countries [15]. Therefore, gastric cancer natural history models often assume similar progression rates when adjusted for risk factors.

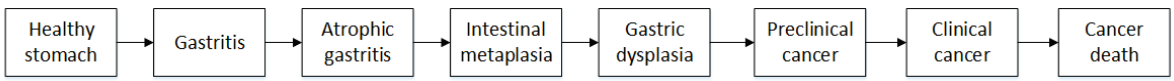

Fig. 9.2. Health states in gastric carcinogenesis according to the Correa cascade [10]. Arrows represent transitions between health states. In natural history models, transitions often depend on exposure to risk factors such as *H. pylori* infection.

Although the Correa cascade is widely accepted, the exact proportion of gastric cancer cases that progress through this cascade remains unclear, particularly for cancers with diffuse-type histology, which remain poorly understood [10]. Nonetheless, it is important to note that both intestinal and diffuse-type gastric cancers are strongly associated with *H. pylori* infection [16]. These uncertainties should be considered when interpreting modelling estimates because they influence the modelled proportion of cancers that are attributable to *H. pylori* infection and the potential impact of eradication strategies.

The transitions in the natural history models are quantified using mathematical approaches, such as the Markov model, the semi-Markov model, and microsimulation models. Although these models differ in their assumptions and complexity, they all aim to derive parameters that accurately reflect real-world data. Through calibration to the age-specific gastric cancer incidence and mortality rates, these parameters can be adjusted to reflect local disease contexts.

Developing a decision model for the local context

The aim of decision modelling is to extrapolate the findings of clinical studies to different settings and strategies. However, for valid extrapolation to a local setting, two requirements need to be met: (i) the evidence for the effectiveness of screening is available for settings that are comparable to the local situation, and (ii) good-quality data are available to inform the model parameters in the local setting. Given that most trial evidence on the long-term benefits of *H. pylori* screen-and-treat programmes comes from studies in Asia (see Chapter 2), long-term model results for the non-Asian context should be interpreted with caution.

With respect to data availability, access to more elaborate and detailed data enables more precise estimations. Data requirements can generally be categorized into three main groups: demographic data, disease and testing data, and outcome data (Table 9.1).

Developing and calibrating decision models are complex and time-consuming tasks that require specialized expertise in statistical modelling and epidemiology. Instead of developing independent decision models, health policy-makers are advised to collaborate with established modelling consortia, such as CISNET (see Box 9.2) or the Decision Analysis in R for Technologies in Health (DARTH) group [18]. CISNET is aiming to develop a web interface for its decision models for stakeholders around the

world to use to estimate the impact of different gastric cancer prevention interventions in their local context. Courses offered by institutions, such as the Netherlands Institute for Health Sciences [19], the Society for Medical Decision Making [20], and the Heidelberg Health Economics Summer School [21], could help to enhance the general understanding of decision modelling and the interpretation of the results of such web-based models.

Table 9.1. General data requirements for cost–effectiveness modelling

Category	Data required
Demographic data[a]	Birth tables
	Life tables (life expectancy)
Disease and testing data[a]	Prevalence of *H. pylori* infection by age
	Gastric cancer incidence by localization (cardia vs non-cardia) and histology (intestinal vs diffuse) by age
	Observed cancer stage distribution
	Stage-specific cancer survival
	Testing participation in pilot studies (initial participation and treatment adherence)
Outcome data	Costs of and costs associated with the test and the procedure
	Treatment costs (stage-specific, ideally split by phase of care)
	Estimates of disutility per test procedure[b]
	Stage-specific estimates of disutility to gastric cancer

[a] Data should be reported stratified by variables of interest, such as sex, geographical region, socioeconomic status, or migration history.

[b] Disutility in the context of an *H. pylori* screen-and-treat strategy refers to the negative aspects of the screening for individuals, such as physical discomfort related to antibiotic treatment and mental distress about the cancer risk [17]. If unavailable, proxies based on existing literature could be considered for use in decision modelling.

9.4 Current evidence from decision modelling for *H. pylori* screen-and-treat strategies

Although decision modelling should always be re-evaluated for optimization to the local context, some lessons can be learned from existing decision-modelling studies. In particular, when results are found to be robust across settings with different prevalence

of *H. pylori* infection and risk of gastric cancer, it is likely that these results are generalizable to the local setting.

Generally, most decision modelling in the academic literature on *H. pylori* is limited to one aspect of decision modelling: cost–effectiveness analysis. A cost–effectiveness analysis presents the costs and effects of an intervention compared with an alternative using cost–effectiveness ratios. The denominator of the ratio measures the health gain from the intervention, and the numerator measures the costs of obtaining that health gain. Health gains are often expressed as life years gained or quality-adjusted life years (QALYs) gained. Interventions that have a better balance between costs and life years gained (i.e. provide better value for money) are preferred over alternative interventions and are considered cost-effective. An intervention is considered to be cost saving if it results in health gains and the costs of obtaining that health gain are actually negative. Negative costs occur if the future health-care savings from gastric cancer prevention exceed the initial investment for an *H. pylori* screen-and-treat strategy.

Although traditional cost–effectiveness analyses often focus on cost–effectiveness as the primary output, there is a growing body of literature on cost–effectiveness analysis methods that can additionally consider the distributional and equity impacts of interventions [4, 22]. Two key examples of these methods are distributional cost–effectiveness analysis and extended cost–effectiveness analysis.

Distributional cost–effectiveness analysis involves modelling an intervention by population subgroup, incorporating a measure of opportunity cost, and then using relative and absolute measures of inequality to identify the service configuration that maximizes health while also minimizing “unfair” health inequality [23]. This method has been used to examine different invitation strategies for the United Kingdom bowel cancer screening programme [24].

Extended cost–effectiveness analysis is an approach that has been developed to address equity concerns relating to medical impoverishment in low- and middle-income countries, where most health care is funded through out-of-pocket payments [25, 26]. In addition to assessing the distribution of health gains by income levels, it measures non-health benefits by quantifying the amount of household expenditure averted through a publicly financed programme (with associated changes to intervention uptake and outcomes), as well as a measure of the financial risk protection afforded (and the distribution of this across the strata of wealth) if the intervention was funded through public financing. Extended cost–effectiveness analysis has been used across a range of

interventions in low- and middle-income countries, including, but not limited to, tuberculosis treatment [25], tobacco taxation [27], rotavirus vaccine [28, 29], and provision of clean water and improved sanitation [30].

Evidence for the cost–effectiveness of H. pylori *screen-and-treat strategies for gastric cancer prevention*

This section summarizes the current evidence from decision modelling with respect to *H. pylori* screen-and-treat strategies. First, studies are considered that assess the cost–effectiveness of an *H. pylori* screen-and-treat strategy compared with no intervention. Then, studies are evaluated that compare different *H. pylori* screen-and-treat strategies to evaluate which strategies provide better value for money than others.

Four reviews have assessed the cost–effectiveness of *H. pylori* screen-and-treat strategies [31–34]. Three reviews included studies from countries all over the world, with very different prevalence of *H. pylori* infection and burden of gastric cancer [31, 32, 34]. One review specifically focused on the cost–effectiveness in countries in Europe, North America, and Oceania with lower burdens of *H. pylori* infection and gastric cancer [33]. All four reviews concluded that an *H. pylori* screen-and-treat strategy is cost-effective in reducing gastric cancer incidence and mortality. Since the most recent review, which included studies until 2021, five additional studies have been published that evaluate the cost–effectiveness of *H. pylori* screen-and-treat strategies to prevent gastric cancer (Table 9.2). Four of these studies found that *H. pylori* screen-and-treat strategies resulted not only in life years gained from gastric cancer prevention but also in cost savings compared with no testing. In the fifth study, *H. pylori* screen-and-treat strategies were not found to save costs, but they still resulted in a favourable balance between the additional costs and benefits compared with no testing. Of the 18 studies included in the reviews, only two found that *H. pylori* screen-and-treat strategies resulted in net cost savings compared with a situation without testing. In these studies, cost savings from preventing dyspepsia were also considered in addition to those from preventing gastric cancer.

Table 9.2. Overview of studies on the cost–effectiveness of *H. pylori* screen-and-treat strategies published after the most recent reviews until 2021

Reference	Country	Population simulated	Strategies evaluated	Test characteristics	Test costs	Costs per LY or QALY
Oh et al. (2022) [40]	USA	Cohort of people aged 40 years	^{13}C-UBT and PCR	^{13}C-UBT sensitivity: 96% ^{13}C-UBT specificity: 93% PCR sensitivity: 100% PCR specificity: 98%	^{13}C-UBT: US$ 76 PCR: US$ 604	^{13}C-UBT: US$ 116 PCR: US$ 2373
Yousefi et al. (2023) [37]	Islamic Republic of Iran	Population aged ≥ 20 years	Endoscopy, serology, ^{13}C-UBT, and SAT	Serology sensitivity: 90% Serology specificity: 80% ^{13}C-UBT sensitivity: 96% ^{13}C-UBT specificity: 93% SAT sensitivity: 94% SAT specificity: 92%	Serology: US$ 5 ^{13}C-UBT: US$ 17 SAT: US$ 3	Serology: cost saving ^{13}C-UBT: US$ 78 SAT: cost saving
Feng et al. (2022) [92]	China	Cohort of people aged 20 years	^{13}C-UBT annually, every 3 years, every 5 years, or once only	^{13}C-UBT sensitivity: 96% ^{13}C-UBT specificity: 94%	^{13}C-UBT: US$ 21	Once only: cost saving
Kowada and Asaka (2022) [93]	Japan	Population aged 20–80 years	Serology	Sensitivity: 93% Specificity: 99.5%	Serology: US$ 8	Cost saving: US$ 494, depending on age
Wang et al. (2022) [94]	China	Population aged 40–69 years	Serology	Sensitivity: 93% Specificity: 90.5%	¥30	Cost saving

LY, life year; PCR, polymerase chain reaction; QALY, quality-adjusted life year; SAT, stool antigen test; UBT, urea breath test.

The gastric cancer burden plays an important role in evaluating the cost–effectiveness of *H. pylori* screen-and-treat strategies. When the burden of disease is high, more deaths can be prevented with the same number of tests, resulting in a more favourable balance between the benefits and the resources required. The four recent studies showing that *H. pylori* screen-and-treat strategies resulted in cost savings from preventing gastric cancer were all performed in countries with an age-standardized rate (ASR) of gastric cancer incidence of > 10 per 100 000 person-years: China (2 studies), Japan (1 study), and the Islamic Republic of Iran (1 study). Nevertheless, also in countries with a low incidence of gastric cancer (i.e. ASR < 10 per 100 000 person-

years) [35], *H. pylori* screen-and-treat strategies have been found to be cost-effective. As mentioned earlier, one review specifically focused on the cost–effectiveness of *H. pylori* screen-and-treat strategies in countries in Europe, North America, and Oceania with a low incidence of gastric cancer [33]. This review included nine studies on *H. pylori* screen-and-treat strategies. Despite the differences in model assumptions, the studies were quite consistent in their findings that *H. pylori* screen-and-treat strategies are cost-effective in reducing gastric cancer mortality in the investigated countries. Except for one study, all the studies found that the costs were < US$ 25 000 per life year or QALY gained. These findings suggest that *H. pylori* screen-and-treat strategies may provide good value for money around the world. Although *H. pylori* screen-and-treat strategies were found to be cost-effective across all settings, the costs per life year gained were typically lower in the studies performed in high-risk areas (Fig. 9.3). One study explicitly studied the impact of prevalence of *H. pylori* infection and burden of gastric cancer on the cost–effectiveness of *H. pylori* screen-and-treat strategies [36]. This study concluded that in countries with intermediate to high gastric cancer incidence (in this study, ASR ≥ 17 per 100 000 person-years), *H. pylori* screen-and-treat strategies would be cost saving. However, the study also showed that even in countries with low gastric cancer incidence (in this study, ASR of 6 per 100 000 person-years), *H. pylori* screen-and-treat strategies resulted in a favourable balance between costs and health benefits.

None of the reviews included here have performed formal quality assessments of the decision-modelling studies mentioned, and the Working Group has not engaged in such an endeavour. Nevertheless, the consistency of the findings that *H. pylori* screen-and-treat strategies are cost-effective across studies provides additional confidence in the validity and robustness of these findings.

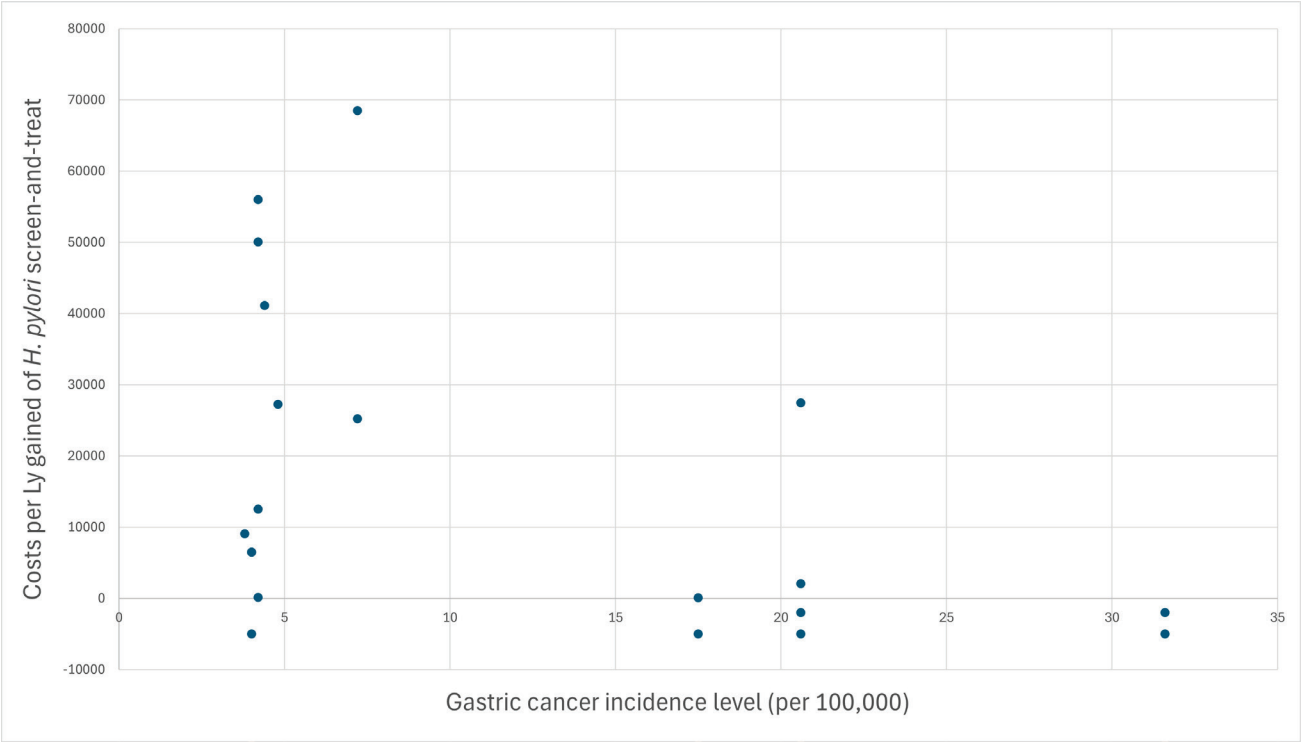

Fig. 9.3. Costs per life year (LY) gained (incremental cost–effectiveness ratio, ICER) plotted against the gastric cancer incidence level in the country of study. Studies demonstrating cost savings are artificially depicted as negative costs per LY gained.

Optimizing the cost–effectiveness of H. pylori *screen-and-treat strategies for gastric cancer prevention*

As can be seen in the previously mentioned reviews and in Table 9.2, studies differ with respect to the tests used for *H. pylori* testing (serology, urea breath test [^{13}C-UBT], or stool antigen test [SAT]; see Chapter 5), the age range of testing, and/or the test frequency (once-only or repeat testing). When *H. pylori* screen-and-treat strategies are implemented, decisions need to be made about these aspects and about the treatment regimen for eradication (see Chapter 6): which drugs to use, whether to eradicate all *H. pylori* or only CagA-positive *H. pylori*, whether to perform confirmation of eradication, and whether to perform resistance testing before eradication. This section summarizes the results of decision-modelling studies that compare these attributes to inform policy-makers on which strategies provide the best value for money, i.e. which approach is most cost-effective.

Comparative cost–effectiveness of different H. pylori *tests*

Three studies directly compared the ^{13}C-UBT with serology testing, and two of these studies also considered the SAT [37–39]. In all three studies, a strategy based on the ^{13}C-UBT was associated with higher costs than serology testing. However, the ^{13}C-UBT was also more effective in preventing gastric cancer incidence and mortality and thus resulting in more life years gained. In one study, these extra benefits weighed favourably against the extra costs [37]. In the other two studies, the incremental costs per QALY exceeded the willingness-to-pay threshold, implying that the ^{13}C-UBT did not provide good value for money compared with serology testing [38, 39]. Both the studies that compared the SAT with serology testing and the ^{13}C-UBT concluded that the SAT was more effective than serology testing. One study also found the SAT to be less expensive [37], and the other found it to be highly cost-effective [39].

Another study compared the ^{13}C-UBT with polymerase chain reaction (PCR) testing of gastric biopsies and concluded that PCR testing is cost-effective for gastric cancer prevention [40]. However, PCR testing of gastric biopsies is an invasive strategy. Moreover, serology testing and the SAT were not considered in this analysis. If these strategies had been considered, this may have resulted in a less favourable balance between the costs and benefits (QALYs gained) of PCR testing compared with these strategies.

In conclusion, there is limited evidence on the optimal test for *H. pylori* screen-and-treat strategies for gastric cancer prevention, with only four decision-modelling studies that performed direct comparisons between tests. These studies suggest that the SAT may be preferred over serology testing from a cost–effectiveness perspective. However, in general all tests were found to be cost-effective for gastric cancer prevention compared with no testing, and none of the tests consistently dominated in all of the analyses. This finding suggests that the choice of the test may be based on the local setting and resource considerations rather than on cost–effectiveness.

Comparative cost–effectiveness of H. pylori *screen-and-treat strategies at different ages*

Six studies compared the cost–effectiveness of *H. pylori* screen-and-treat strategies in different age groups in the population [36, 41–45]. Two studies concluded that it was optimal to test for *H. pylori* infection at a young age (20 years or 30 years), because *H. pylori* testing in older cohorts was both less effective and less cost-effective [36, 41].

Both these studies were performed in high-incidence settings (ASR ≥ 20 per 100 000 person-years). The other studies, mostly conducted in low-incidence settings (ASR < 10 per 100 000 person-years), also found *H. pylori* testing to be more effective at these younger ages, but this effectiveness was accompanied by higher costs per life year gained. Therefore, they suggested ages for *H. pylori* testing of between 40 years and 50 years. These findings suggest that in low-incidence settings, *H. pylori* screen-and-treat strategies might not be cost-effective in younger birth cohorts, whereas they may be cost-effective in high-incidence settings. However, an important caveat with these findings is that many studies compared different screening ages across different birth cohorts. Given the high correlation between birth cohort and gastric cancer risk, this may indicate that it is more cost-effective to screen older birth cohorts, rather than older people. Therefore, more studies on the optimal age of screening within the same birth cohort are needed.

Comparative cost–effectiveness of once-only versus repeat testing for H. pylori

The evidence on repeat *H. pylori* screen-and-treat strategies was even more limited. The purpose of repeat testing may be to account for infection or reinfection or for failed eradication therapy. Two studies evaluated repeat *H. pylori* screen-and-treat strategies [36, 41]. The studies considered different intervals (varying from 1 year to 10 years) and frequencies (one repeat vs multiple repeats) for repeat testing. Both studies concluded that the extra benefits of repeat testing did not outweigh the extra resources required. Evidence on reinfection rates is scarce, although the rates are estimated to be < 1% [46]. In the absence of strong evidence, policy-makers can best implement a once-only *H. pylori* screen-and-treat strategy. However, pilot studies within these programmes, in which a subset of individuals are rescreened after 5–10 years, should be considered to fill this important gap in knowledge and to inform future modelling.

Comparative cost–effectiveness of different management strategies of individuals who screen positive for H. pylori

None of the cost–effectiveness analyses of *H. pylori* screen-and-treat strategies compared different eradication therapy regimens or the benefits of resistance testing before initiating treatment. However, one study addressed the incremental cost–effectiveness of confirmatory testing of successful eradication [47], and one study addressed restricting treatment to only those individuals who tested CagA-positive [48].

The first study explicitly compared serology testing with and without confirmatory testing 6 weeks after eradication therapy [47]. Under the assumption that the initial eradication therapy had an effectiveness of 80%, the scenario with the confirmatory test resulted in more life years gained than the serology-only strategy, but it had substantially higher costs. This finding suggests that in settings in which the eradication rate of the initial therapy is > 80%, confirmatory testing is not cost-effective. However, without confirmatory testing in at least a sample of the population, it is not possible to establish the *H. pylori* eradication rate (see Chapter 6).

The other study evaluated the cost–effectiveness of screening for and treating either all *H. pylori* strains or only CagA-positive strains [48]. Testing and treating only individuals with CagA-positive infection reduced the number treated, the number of cases of anaphylaxis, and the overall costs of the screen-and-treat strategy, but it also reduced the number of cancers prevented and the life years gained. In all countries for which it was evaluated, the incremental cost–effectiveness ratio for treating all *H. pylori* strains compared with treating only CagA-positive strains was < US$ 25 100 per life year gained. These results suggest that it is better to screen for and treat all *H. pylori*, rather than only CagA-positive *H. pylori*.

9.5 Synergies with other existing preventive interventions

Combining programmes to enhance the efficiency of care

It is well established that some screening programmes lead to improved survival of patients with cancer. However, to achieve this benefit, the participation of asymptomatic individuals in screening is of paramount importance. A one-stop-shop approach to screening for multiple cancers has been hypothesized to lead to increased participation by reducing time and cost [49]. In Israel, a proof of principle of such an approach has been implemented. The satisfaction with the approach was high (> 8 on a 10-point scale), and in the first year of the programme three quarters of the cancers were detected through the screening, and most of them were in early stages [50]. However, these results should be interpreted with caution, because the patients were self-referrals and only 26% of the patients returned for repeat screening.

An alternative approach for achieving synergies between preventive interventions is by combining *H. pylori* screen-and-treat strategies with primary prevention interventions, such as combining smoking cessation interventions with lung cancer screening [51] or combining human papillomavirus (HPV) vaccination with cervical cancer screening [52].

Similarly, for gastric cancer, combined preventive interventions with existing screening and primary prevention programmes could be envisaged.

Combining H. pylori *screen-and-treat programmes with colorectal cancer screening*

One potential synergistic approach for *H. pylori* screen-and-treat programmes is the combination with colorectal cancer screening. Many colorectal cancer screening programmes around the world are based on the non-invasive collection of stool samples, and this would combine well with the SAT. The feasibility of a combined approach has been established both in Asia [53] and in Europe [54]. One study demonstrated that *H. pylori* antigen measurement can be performed in FIT stool samples with a similar test performance to that of the standard SAT [54]. Because FIT is widely used in clinical practice, this approach may conveniently enable dual prevention of cancer in both the upper and lower gastrointestinal tracts.

The SAT has been combined with FIT to screen both upper and lower gastrointestinal lesions in a population with a high prevalence of digestive tract diseases [53]. Three scenarios were compared in a hospital cohort: using the SAT in all individuals, using the SAT only in those with a negative FIT result, or using the SAT only in those with a negative colonoscopy result. The sensitivity of the SAT for detecting gastric cancer did not differ and was about 50%. In this study, three quarters of gastric cancers were diagnosed as stage I–II disease. In the same study but within a validation community cohort, the positive predictive value for upper gastrointestinal lesions using the SAT was about 32%.

A randomized clinical trial in which about 150 000 people were invited to participate in either the SAT plus FIT or FIT alone demonstrated that the participation rate increased by about 14% for FIT combined with the SAT compared with FIT alone [55]. This implies that combined screening attracts a larger proportion of individuals to engage in the screening programme. Therefore, using the existing FIT screening framework may be advantageous (Table 9.3).

Table 9.3. Potential advantages of using the FIT programme as the foundation for offering screening and treatment for *H. pylori* infection for gastric cancer prevention

Category	Potential advantage
Eligibility	The eligibility criteria for FIT are shifting towards younger ages, at which *H. pylori* treatment is considered to be of greater benefit.
Invitation	Stool sample-based tests are more acceptable and accessible for people compared with invasive procedures such as endoscopy.
Participation	The participation rate for FIT may be increased by adding *H. pylori* stool antigen tests.
Testing	Both tests use stool samples, making it easy to distribute them together.
Management	The management of *H. pylori* infection has been well established.
Cost–effectiveness	The direct and indirect costs of *H. pylori* testing can be reduced by leveraging the established FIT screening platform.

FIT, faecal immunochemical testing.

The effectiveness of using the FIT programme to offer *H. pylori* screen-and-treat strategies depends on the screening age. Although most colorectal cancer screening programmes begin at age 50 years [56], the best age to apply *H. pylori* screen-and-treat strategies is uncertain. Some studies have suggested that treating *H. pylori* infection has the most impact before the onset of precursor lesions or when precursor lesions are less severe [57]. If this is the case, it seems likely that the optimal *H. pylori* screening age is lower than the starting age of colorectal cancer screening. However, the continuation of the current trend towards starting colorectal cancer screening earlier could lead to more potential for synergistic effects in future screening programmes.

The randomized clinical trial that evaluated the addition of the SAT to FIT included participants with an average age of 58 years [55]. In this trial, an invitation to the *H. pylori* screen-and-treat programme reduced gastric cancer incidence by 14% among invited individuals, although the reduction was not statistically significant. However, in post hoc analyses, adjusted for non-adherence to the invitation, a statistically significant reduction of 21% in gastric cancer incidence was observed [58]. These analyses should be considered exploratory because of the potential healthy-screenee bias. Nevertheless, these findings suggest that an intervention age of 50 years may not be too late to achieve meaningful reductions in gastric cancer risk.

This Working Group Report is focused on an *H. pylori* screen-and-treat approach as a strategy for gastric cancer prevention. However, a section on synergistic approaches

would not be complete without also considering alternative strategies for gastric cancer prevention, which can be combined with existing preventive initiatives. In addition to combined faecal testing, colorectal cancer screening provides a second synergistic approach to gastric cancer prevention, by directly combining upper gastrointestinal endoscopy with colonoscopy, either for primary screening or after a positive FIT result. This approach has been evaluated in decision-modelling analyses in regions with intermediate risk (i.e. ASR of 10–20 per 100 000 person-years) and found to be cost-effective [35, 59–61]. Pilot studies are currently being conducted at a European level to clinically evaluate this approach, for example in the Towards Gastric Cancer Screening Implementation in the European Union (TOGAS) study [62] (see Chapter 3.5). This approach has the additional advantage that the entire upper gastrointestinal segment can be visualized, allowing the identification of individuals at risk of oesophageal adenocarcinoma (i.e. Barrett oesophagus) [61].

Combinations with alternative interventions to reduce gastric cancer

Another option to enhance the efficacy of an *H. pylori* screen-and-treat approach is to combine the *H. pylori* serological assessment with another blood-based assessment of the gastric mucosa, i.e. testing for pepsinogens. This has been explored extensively in Japan in the ABCD method [63] and has also been evaluated in a multicentre randomized study in Latvia [62] (see also Chapter 3.2). The ABCD method uses the positivity of serological assessment of pepsinogen I and pepsinogen II together with a negative test for *H. pylori* antibodies as a marker of long-term exposure to gastric atrophic changes. The study in Latvia planned to randomize about 30 000 individuals to either no intervention or an *H. pylori* screen-and-treat approach in combination with serological determination of pepsinogen levels and endoscopic follow-up of individuals who test positive for pepsinogen [62].

Combining H. pylori *screen-and-treat strategies with primary prevention interventions*

Common risk factors (e.g. smoking and obesity) exist between digestive cancers and other cancers, as well as cardiovascular or metabolic causes of death. These commonalities may well justify the exploration of an even broader approach of merging primary prevention initiatives with cancer screening programmes. *H. pylori* infection is associated with an unhealthy diet and other lifestyle factors. Combining *H. pylori*

eradication with interventions to encourage diet and lifestyle modifications could benefit overall health and help prevent multiple diseases.

9.6 Ancillary effects of *H. pylori* screen-and-treat strategies

Previous chapters have outlined the proven impact of *H. pylori* screen-and-treat strategies on reducing the burden of gastric cancer. However, *H. pylori* infection is also associated with other malignant and benign diseases. Conversely, *H. pylori* eradication may have negative ancillary effects, of which antimicrobial resistance is the most substantial concern. This section discusses the ancillary benefits and harms of *H. pylori* screen-and-treat strategies and their potential effects on the cost–effectiveness of screening programmes (Table 9.4).

Table 9.4. Overview of the ancillary effects of *H. pylori* eradication relevant to cost–effectiveness

Condition	Postulated effect on cost–effectiveness	Magnitude of the effect on the cost–effectiveness of *H. pylori* screen-and-treat strategies
Peptic ulcer disease	Positive	Demonstrated and substantial impact, because of relatively high disease incidence.
Gastric lymphomas	Positive	Demonstrated impact. Impact may be modest because of rarity of disease.
Dyspepsia	Positive	Demonstrated and substantial impact, because of relatively high disease incidence.
Iron-deficiency anaemia	Positive	Demonstrated impact on patients with *H. pylori* infection. Impact on cost–effectiveness is unclear.
Colorectal cancer	Positive	Despite association between *H. pylori* infection and colorectal cancer, impact of eradication on colorectal cancer incidence is unclear.
Antimicrobial resistance	Negative	Large potential impact, because of its broader population health effects. Magnitude of the effect is unclear.
Oesophageal cancer	Negative	Strong evidence that *H. pylori* eradication does not affect oesophageal cancer.
Asthma	Negative	No evidence that *H. pylori* eradication affects asthma prevalence.

Ancillary benefits of H. pylori *screen-and-treat strategies*

Because *H. pylori* infection is associated with diseases other than gastric cancer, *H. pylori* eradication may also prevent these other conditions and, as a consequence, affect the cost–effectiveness of interventions. Although Section 9.2 suggested that *H. pylori* screen-and-treat strategies are cost-effective across settings, the balance between the benefits and harms may be less clear in countries with a low incidence of gastric cancer. Consequently, the ancillary benefits of *H. pylori* screen-and-treat strategies are

particularly relevant for informing policy discussions in countries with a low risk of gastric cancer (see also Chapter 2).

Peptic ulcer disease

Peptic ulcer disease significantly impairs well-being and aspects of health-related quality of life, and it is associated with high costs for employers and health-care systems [64]. The global incidence of peptic ulcer disease is estimated to be 0.03–0.17% per year, with a lifetime risk of 5–10% per person [65, 66]. *H. pylori* infection has been identified as one of the primary causes of peptic ulcer disease. Therefore, an *H. pylori* screen-and-treat approach is the recommended treatment for patients diagnosed with peptic ulcer disease [67]. Despite this, the evidence on the preventive effect of *H. pylori* screen-and-treat programmes on incidence of peptic ulcer disease is limited. A study showed that population-based *H. pylori* screen-and-treat programmes reduced the incidence of peptic ulcer disease by 67% (95% confidence interval [CI], 52.2–77.8%) [68], and a modelling study showed that the reduction in incidence of peptic ulcer disease affected the cost–effectiveness of *H. pylori* eradication programmes [43].

Gastric lymphomas

Gastric lymphomas, such as mucosa-associated lymphoid tissue (MALT) lymphomas, are a rare type of cancer. Therefore, many aspects of this neoplasm are controversial. *H. pylori* infection has been identified as a cause, and case–control studies have shown an association between *H. pylori* infection and gastric lymphomas [69]. About 60–70% of gastric MALT lymphomas that are associated with *H. pylori* infection regress after antibiotic treatment [70]; this provides compelling evidence for the benefits of *H. pylori* eradication in preventing these gastric malignancies. Although a reduction in gastric lymphomas after *H. pylori* eradication is anticipated, the magnitude of this reduction on a population level would be limited because of the rarity of this disease.

Dyspepsia

Multiple reviews have demonstrated that *H. pylori* eradication could provide a small benefit to patients with non-ulcer dyspepsia (indigestion or heartburn) [71, 72]. Although trial evidence on the preventive effect of the *H. pylori* screen-and-treat strategy on dyspepsia is limited, modelling studies have shown that additional savings from prevented cases of dyspepsia could substantially improve the cost–effectiveness of *H. pylori* eradication, particularly in low-risk countries [44, 73].

Iron-deficiency anaemia

Iron-deficiency anaemia is a common nutritional deficiency and may also be caused by *H. pylori* infection. The pooled odds ratio for developing iron-deficiency anaemia is estimated to be 2.22 (95% CI, 1.52–3.24) [74]. Another review estimated that treating *H. pylori* infection significantly improved haemoglobin, serum iron, and serum ferritin concentrations [75]. Although these results suggest that *H. pylori* eradication could be effective in improving anaemia in patients with *H. pylori* infection, the magnitude of the potential preventive effect is unclear.

Colorectal cancer

Although multiple systematic reviews have demonstrated an association between *H. pylori* infection and colorectal cancer, evidence on causality is weak. One review found an odds ratio of 1.70 (95% CI, 1.64–1.76), and another review found an odds ratio of 1.44 (95% CI, 1.26–1.65) [76, 77]. However, these studies do not prove a causal link between *H. pylori* infection and colorectal cancer. Although some studies in animals indicate a potential causal relationship, other studies based on Mendelian randomization do not support this causation [78, 79]. Furthermore, there are no studies demonstrating that eradicating *H. pylori* infection reduces the incidence of colorectal cancer. Therefore, it is unclear whether *H. pylori* eradication has any effect on colorectal cancer incidence.

Ancillary harms of H. pylori *screen-and-treat strategies*

Antimicrobial resistance

None of the current cost–effectiveness analyses have considered the impact of widespread *H. pylori* screen-and-treat strategies on antimicrobial resistance. Several studies have shown that antimicrobial resistance has a substantial impact on morbidity, mortality, and costs of infectious diseases worldwide [80, 81]. If widespread antibiotic use in an *H. pylori* screen-and-treat strategy leads to increases in antimicrobial resistance, the current cost–effectiveness may be overestimated (see Chapter 7). Given the current uncertainties about antimicrobial resistance, observational evidence is needed before cost–effectiveness models can incorporate antimicrobial resistance into their estimates.

Oesophageal cancer

The current evidence does not support the hypothesis that population-based *H. pylori* screen-and-treat strategies increase the risk of oesophageal cancer. Because of diverging trends in gastric cancer and oesophageal cancer incidence [82], it has been suggested that there may be a protective effect of *H. pylori* on oesophageal cancer. A systematic review found a statistically significant negative association between *H. pylori* infection and oesophageal cancer [83]. However, a recent large multinational cohort study demonstrated that the incidence rate of oesophageal adenocarcinoma did not increase over time after *H. pylori* eradication [84]. These results suggest that *H. pylori* eradication may be safe from the perspective of oesophageal cancer (see Chapter 2) and thus may not affect the cost–effectiveness.

Asthma

It has been proposed that being exposed to infections in the early phase of life is essential for the normal maturation of the immune response [85]. The "disappearing microbiota" hypothesis suggests that the reduction in certain types of microbiota, such as *H. pylori*, therefore contributes to the development of some diseases, such as allergic asthma [86]. However, a systematic review concluded that the corresponding evidence for an association between *H. pylori* infection and asthma prevalence is weak in both children and adults [87]. Therefore, the current evidence does not support the notion that the eradication of *H. pylori* would affect the risk of asthma or that it would affect the cost–effectiveness of *H. pylori* screen-and-treat programmes.

9.7 Gaps in the evidence

H. pylori infection is known to be the major contributor to gastric cancer. Efforts to combat *H. pylori* infection should replicate the success seen in other primary prevention programmes that target the elimination of well-known risk factors, such as HPV, hepatitis B virus, and hepatitis C virus [88]. As this chapter shows, modelling suggests that *H. pylori* screen-and-treat strategies are cost-effective interventions across various settings. Decision models should be used to extrapolate these findings and optimize the efficiency of the programmes according to the local cancer burden. However, some gaps in the evidence remain. Addressing these could further optimize the allocation of health-care resources.

Current questions about the cost–effectiveness of H. pylori *screen-and-treat strategies for gastric cancer prevention*

Although more than 23 cost–effectiveness analyses have been performed for *H. pylori* screen-and-treat strategies, considerable gaps in knowledge still exist. First, none of the cost–effectiveness analyses have considered the impact of widespread *H. pylori* screen-and-treat strategies on antimicrobial resistance. Second, only two cost–effectiveness studies have considered additional benefits of *H. pylori* screen-and-treat strategies on peptic ulcer disease and dyspepsia [89, 90]. The impact of these ancillary benefits and harms on the cost–effectiveness of *H. pylori* screen-and-treat strategies could be considerable (see Section 9.6). Finally, none of the cost–effectiveness analyses have examined the impact of *H. pylori* screen-and-treat programmes on health inequalities between subgroups of the target population, such as racial or ethnic minorities or those with lower socioeconomic positions.

Most of the studies included in this chapter have only estimated the cost–effectiveness of one particular strategy for *H. pylori* screen-and-treat programmes. The maximum number of strategies considered did not exceed five. However, many questions remain about the most cost-effective approach to implementing *H. pylori* screen-and-treat programmes. This includes questions about which test to use, what age range to screen, with what frequency to screen, with what treatment regimen to eradicate, and whether to test for resistance before treatment or for successful eradication after treatment.

Questions about the implementation of H. pylori *screen-and-treat strategies for gastric cancer prevention*

Cost–effectiveness is only one part of the financial question for a screening programme; the budget impact of the strategy is at least as important. An intervention can be highly cost-effective or even cost saving (i.e. better health outcomes at lower costs). However, the savings occur later on, and the investments are needed before the start of the programme. To date, no studies have been performed to help policy-makers gain insights into the annual resource requirements of *H. pylori* screen-and-treat programmes.

In addition to cost–effectiveness and budget impact, the feasibility and successful implementation depend on access to health-care facilities and the availability of trained personnel and follow-up care. A decision analysis measures not only costs and benefits

but also the intermediate aspects of the screening process, such as the number of *H. pylori* tests needed, the number of antibiotic treatments needed, hospital visits, and so on. This information will help policy-makers prepare to ensure the availability of resources and health professionals who are adequately trained to perform their role in the *H. pylori* screen-and-treat programme. Such information is especially important in the light of recent shortages of health-care personnel and antibiotics [91].

Future directions

New observational evidence and comprehensive decision-modelling analyses can play a role in filling the knowledge gaps identified here. These studies, which capture both the negative and positive ancillary effects of *H. pylori* screen-and-treat strategies, could provide a final verdict on the balance between the benefits, the harms, and the resources required for these strategies. They could be used to evaluate the optimal way to implement the programmes and could provide policy-makers with estimates of what resources are needed for the successful implementation of the programme. In Europe, the first step in this direction is being taken with the TOGAS project and the European Joint Action on Cancer Screening (EUCanScreen). Both these projects combine local pilot studies with decision modelling to provide policy-makers throughout Europe with essential information to enable them to make informed decisions about *H. pylori* screen-and-treat programmes.

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Disclosures of interests

Javier P. Gisbert reports that his unit at Hospital Universitario de La Princesa benefited from research funding from Juvisé Pharmaceuticals.

Mārcis Leja reports owning shares in the Digestive Diseases Centre, and that his unit at the University of Latvia benefits from non-monetary support from Eiken Chemical Co.

Zorana Maravic, in her capacity as CEO of Digestive Cancers Europe (DiCE), reports that DiCE benefits from research funding from several pharmaceutical companies.

Peter Sasieni reports having been a member of Roche's Scientific Advisory Board. This was determined not to present a conflict of interest for the present IARC meeting, since there was no reported involvement with the topics under review.

Stella Smith, in her capacity as President of the African Helicobacter and Microbiota Study Group, reports that the Group benefited from research support from Richen Force Ltd.