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.

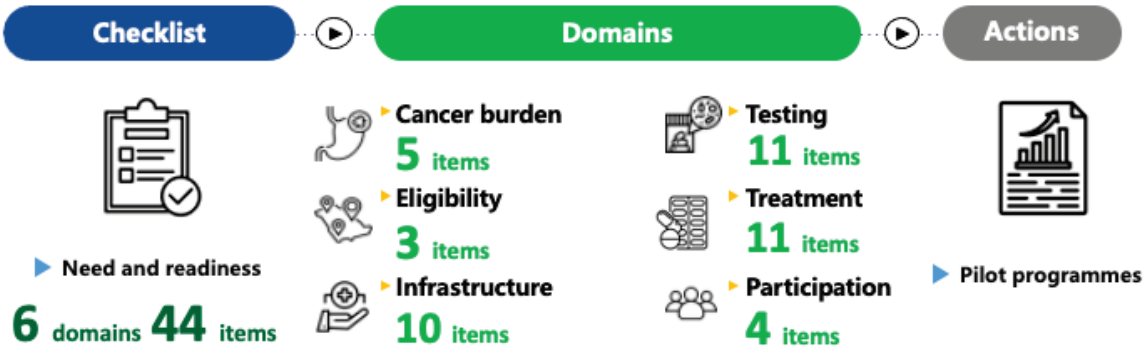

Fig. 4.1. Visual abstract.

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.

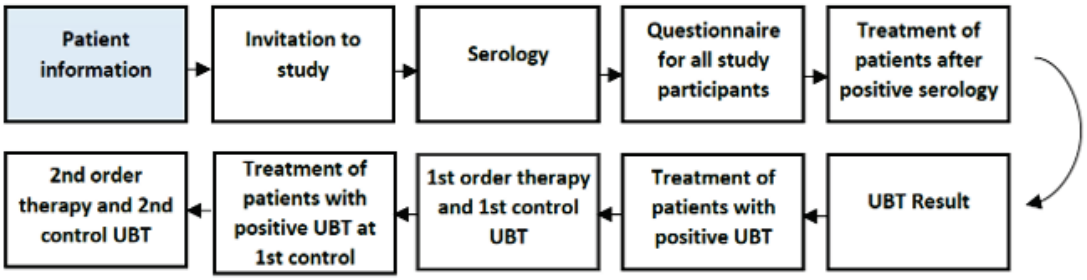

Fig. 4.2. Slovenia screen-and-treat programme. UBT, urea breath test. Source: Tepeš et al. (2024) [67].

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.

References

1. Wilson JMG, Jungner G (1968). Principles and practice of screening for disease. Geneva, Switzerland: World Health Organization. Available from: https://iris.who.int/handle/10665/37650.
2. Li Y, Choi H, Leung K, Jiang F, Graham DY, Leung WK (2023). Global prevalence of *Helicobacter pylori* infection between 1980 and 2022: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 8(6):553–64. https://doi.org/10.1016/S2468-1253(23)00070-5 PMID:37086739
3. Nyssen OP, Bordin D, Tepes B, Pérez-Aisa Á, Vaira D, Caldas M, et al.; Hp-EuReg Investigators (2021). European Registry on *Helicobacter pylori* management (Hp-EuReg): patterns and trends in first-line empirical eradication prescription and outcomes of 5 years and 21 533 patients. Gut. 70(1):40–54. https://doi.org/10.1136/gutjnl-2020-321372 PMID:32958544
4. Hu Y, Wan JH, Li XY, Zhu Y, Graham DY, Lu N-H (2017). Systematic review with meta-analysis: the global recurrence rate of *Helicobacter pylori*. Aliment Pharmacol Ther. 46(9):773–9. https://doi.org/10.1111/apt.14319 PMID:28892184
5. Yan TL, Hu QD, Zhang Q, Li YM, Liang TB (2013). National rates of *Helicobacter pylori* recurrence are significantly and inversely correlated with Human Development Index. Aliment Pharmacol Ther. 37(10):963–8. https://doi.org/10.1111/apt.12293 PMID:23550618
6. Dixon MF, Genta RM, Yardley JH, Correa P (1996). Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. Am J Surg Pathol. 20(10):1161–81. https://doi.org/10.1097/00000478-199610000-00001 PMID:8827022
7. Rugge M, Meggio A, Pennelli G, Piscioli F, Giacomelli L, De Pretis G, et al. (2007). Gastritis staging in clinical practice: the OLGA staging system. Gut. 56(5):631–6. https://doi.org/10.1136/gut.2006.106666 PMID:17142647
8. Capelle LG, de Vries AC, Haringsma J, Ter Borg F, de Vries RA, Bruno MJ, et al. (2010). The staging of gastritis with the OLGA system by using intestinal metaplasia as an accurate alternative for atrophic gastritis. Gastrointest Endosc. 71(7):1150–8. https://doi.org/10.1016/j.gie.2009.12.029 PMID:20381801
9. He F, Wang S, Zheng R, Gu J, Zeng H, Sun K, et al. (2024). Trends of gastric cancer burdens attributable to risk factors in China from 2000 to 2050. Lancet Reg Health West Pac. 44:101003. https://doi.org/10.1016/j.lanwpc.2023.101003 PMID:38269331
10. Goodman KJ, Colquhoun A (2014). Principles of evidence-based cancer prevention strategies. In: IARC *Helicobacter pylori* Working Group (2014). *Helicobacter pylori* eradication as a strategy for preventing gastric cancer (IARC Working Group Reports No. 8). Lyon, France: International Agency for Research on Cancer; pp. 88–94. https://publications.iarc.who.int/391.
11. Teutsch SM (1992). A framework for assessing the effectiveness of disease and injury prevention. MMWR Recomm Rep. 41(RR-3):1–12. PMID:1313535
12. Brownson RC, Gurney JG, Land GH (1999). Evidence-based decision making in public health. J Public Health Manag Pract. 5(5):86–97. PMID:10558389
13. Malfertheiner P, Megraud F, Rokkas T, Gisbert JP, Liou J-M, Schulz C, et al.; European Helicobacter and Microbiota Study group (2022). Management of *Helicobacter pylori* infection: the Maastricht VI/Florence consensus report. Gut. 71(9):1724–62. https://doi.org/10.1136/gutjnl-2022-327745 PMID:35944925
14. European Commission (2022). Europe's Beating Cancer Plan Communication from the commission to the European Parliament and the Council. Brussels, Belgium: Directorate-General for Health and Food Safety. Available from: https://health.ec.europa.eu/system/files/2022-02/eu_cancer-plan_en_0.pdf.
15. Liou JM, Malfertheiner P, Lee YC, Sheu BS, Sugano K, Cheng HC, et al.; Asian Pacific Alliance on Helicobacter and Microbiota (APAHAM) (2020). Screening and eradication of *Helicobacter pylori* for gastric cancer prevention: the Taipei global consensus. Gut. 69(12):2093–112. https://doi.org/10.1136/gutjnl-2020-322368 PMID:33004546
16. Lansdorp-Vogelaar I, Sharp L (2013). Cost-effectiveness of screening and treating *Helicobacter pylori* for gastric cancer prevention. Best Pract Res Clin Gastroenterol. 27(6):933–47. https://doi.org/10.1016/j.bpg.2013.09.005 PMID:24182612
17. Dorji T, Wangmo S, Dargay S, Dorji N, Dorjey Y, Pradhan B, et al. (2024). Population-level cancer screening and cancer care in Bhutan, 2020-2023: a review. Lancet Reg Health Southeast Asia. 24:100370. https://doi.org/10.1016/j.lansea.2024.100370 PMID:38444883
18. Kowada A (2023). A population-based *Helicobacter pylori* eradication strategy is more cost-effective than endoscopic screening. Dig Dis Sci. 68(5):1735–46. https://doi.org/10.1007/s10620-022-07795-z PMID:36565366

19. Chiang TH, Chang WJ, Chen SL, Yen AM, Fann JC, Chiu SY, et al. (2021). Mass eradication of *Helicobacter pylori* to reduce gastric cancer incidence and mortality: a long-term cohort study on Matsu Islands. Gut. 70(2):243–50. https://doi.org/10.1136/gutjnl-2020-322200 PMID:32792335
20. Sugano K, Tack J, Kuipers EJ, Graham DY, El-Omar EM, Miura S, et al.; faculty members of Kyoto Global Consensus Conference (2015). Kyoto global consensus report on *Helicobacter pylori* gastritis. Gut. 64(9):1353–67. https://doi.org/10.1136/gutjnl-2015-309252 PMID:26187502
21. Rugge M, Genta RM, Malfertheiner P, Dinis-Ribeiro M, El-Serag H, Graham DY, et al.; RE.GA.IN (2024). RE.GA.IN.: the Real-world Gastritis Initiative – updating the updates. Gut. 73(3):407–41. https://doi.org/10.1136/gutjnl-2023-331164 PMID:38383142
22. Katelaris P, Hunt R, Bazzoli F, Cohen H, Fock KM, Gemilyan M, et al. (2023). *Helicobacter pylori* World Gastroenterology Organization global guideline. J Clin Gastroenterol. 57(2):111–26. https://doi.org/10.1097/MCG.0000000000001719 PMID:36598803
23. Thomas C, Mandrik O, Saunders CL, Thompson D, Whyte S, Griffin S, et al. (2021). The costs and benefits of risk stratification for colorectal cancer screening based on phenotypic and genetic risk: a health economic analysis. Cancer Prev Res (Phila). 14(8):811–22. https://doi.org/10.1158/1940-6207.CAPR-20-0620 PMID:34039685
24. Pashayan N, Morris S, Gilbert FJ, Pharoah PDP (2018). Cost-effectiveness and benefit-to-harm ratio of risk-stratified screening for breast cancer: a life-table model. JAMA Oncol. 4(11):1504–10. https://doi.org/10.1001/jamaoncol.2018.1901 PMID:29978189
25. Lin JS, Evans CV, Grossman DC, Tseng C-W, Krist AH (2018). Framework for using risk stratification to improve clinical preventive service guidelines. Am J Prev Med. 54(1S1):S26–37. https://doi.org/10.1016/j.amepre.2017.07.023 PMID:29254523
26. Oderda G, Ponzetto A, Boero M, Bellis D, Forni M, Vaira D, et al. (1997). Family treatment of symptomatic children with *Helicobacter pylori* infection. Ital J Gastroenterol Hepatol. 29(6):509–14. PMID:9513824
27. Sari YS, Can D, Tunali V, Sahin O, Koc O, Bender O (2008). *H pylori*: treatment for the patient only or the whole family? World J Gastroenterol. 14(8):1244–7. https://doi.org/10.3748/wjg.14.1244 PMID:18300351
28. Zhao JB, Yuan L, Yu XC, Shao Q-Q, Ma J, Yu M, et al. (2021). Whole family-based *Helicobacter pylori* eradication is a superior strategy to single-infected patient treatment approach: a systematic review and meta-analysis. Helicobacter. 26(3):e12793. https://doi.org/10.1111/hel.12793 PMID:33675089
29. Ding SZ (2020). Global whole family based-*Helicobacter pylori* eradication strategy to prevent its related diseases and gastric cancer. World J Gastroenterol. 26(10):995–1004. https://doi.org/10.3748/wjg.v26.i10.995 PMID:32205991
30. Ding SZ, Du YQ, Lu H, Wang W-H, Cheng H, Chen S-Y, et al.; National Clinical Research Center for Digestive Diseases (Shanghai), Gastrointestinal Early Cancer Prevention & Treatment Alliance of China (GECA), Helicobacter pylori Study Group of Chinese Society of Gastroenterology, and Chinese Alliance for Helicobacter pylori Study (2022). Chinese consensus report on family-based *Helicobacter pylori* infection control and management (2021 edition). Gut. 71(2):238–53. https://doi.org/10.1136/gutjnl-2021-325630 PMID:34836916
31. Lei WY, Lee JY, Chuang SL, Bair M-J, Chen C-L, Wu J-Y, et al. (2023). Eradicating *Helicobacter pylori* via ^{13}C-urea breath screening to prevent gastric cancer in indigenous communities: a population-based study and development of a family index-case method. Gut. 72(12):2231–40. https://doi.org/10.1136/gutjnl-2023-329871 PMID:37197905
32. Kong Q, Li Y, Li R, Li Z, Zheng X, Wang Z, et al. (2022). Low compliance to post-screening recommendations in a family-based *Helicobacter pylori* screening and treatment program: a prospective cohort study. Helicobacter. 27(5):e12912. https://doi.org/10.1111/hel.12912 PMID:35816511
33. Choi IJ, Kim CG, Lee JY, Kim Y-I, Kook M-C, Park B, et al. (2020). Family history of gastric cancer and *Helicobacter pylori* treatment. N Engl J Med. 382(5):427–36. https://doi.org/10.1056/NEJMoa1909666 PMID:31995688
34. Pan KF, Li WQ, Zhang L, Liu W-D, Ma J-L, Zhang Y, et al. (2024). Gastric cancer prevention by community eradication of *Helicobacter pylori*: a cluster-randomized controlled trial. Nat Med. 30(11):3250–60. https://doi.org/10.1038/s41591-024-03153-w PMID:39079993
35. Choi IJ, Kook MC, Kim YI, Cho S-J, Lee JY, Kim CG, et al. (2018). *Helicobacter pylori* therapy for the prevention of metachronous gastric cancer. N Engl J Med. 378(12):1085–95. https://doi.org/10.1056/NEJMoa1708423 PMID:29562147

36. Leung WK, Wong IOL, Cheung KS, Yeung KF, Chan EW, Wong AYS, et al. (2018). Effects of *Helicobacter pylori* treatment on incidence of gastric cancer in older individuals. Gastroenterology. 155(1):67–75. https://doi.org/10.1053/j.gastro.2018.03.028 PMID:29550592
37. Saito H, Nishikawa Y, Masuzawa Y, Tsubokura M, Mizuno Y (2021). *Helicobacter pylori* infection mass screening for children and adolescents: a systematic review of observational studies. J Gastrointest Cancer. 52(2):489–97. https://doi.org/10.1007/s12029-021-00630-0 PMID:33761050
38. Akamatsu T, Ichikawa S, Okudaira S, Yokosawa S, Iwaya Y, Suga T, et al. (2011). Introduction of an examination and treatment for *Helicobacter pylori* infection in high school health screening. J Gastroenterol. 46(12):1353–60. https://doi.org/10.1007/s00535-011-0450-6 PMID:21853260
39. Kakiuchi T, Matsuo M, Endo H, Nakayama A, Sato K, Takamori A, et al. (2019). A *Helicobacter pylori* screening and treatment program to eliminate gastric cancer among junior high school students in Saga Prefecture: a preliminary report. J Gastroenterol. 54(8):699–707. https://doi.org/10.1007/s00535-019-01559-9 PMID:30770975
40. Kaji E, Yoden A, Otani M, Okuhira T, Aomatsu T, Tamai H, et al. (2020). *Helicobacter pylori* test-and-treat strategy for second-year junior high school students aimed at the prevention of gastric cancer in Takatsuki City. Helicobacter. 25(4):e12696. https://doi.org/10.1111/hel.12696 PMID:32352203
41. Kakiuchi T, Tanaka Y, Ohno H, Matsuo M, Fujimoto K (2021). *Helicobacter pylori* infection-induced changes in the intestinal microbiota of 14-year-old or 15-year-old Japanese adolescents: a cross-sectional study. BMJ Open. 11(7):e047941. https://doi.org/10.1136/bmjopen-2020-047941 PMID:34215607
42. Kato S, Shimizu T, Toyoda S, Gold BD, Ida S, Ishige T, et al.; Japanese Society for Pediatric Gastroenterology, Hepatology and Nutrition (2020). The updated JSPGHAN guidelines for the management of *Helicobacter pylori* infection in childhood. Pediatr Int. 62(12):1315–31. https://doi.org/10.1111/ped.14388 PMID:32657507
43. Lee YC, Chiang TH, Chiu HM, Su W-W, Chou K-C, Chen SL-S, et al.; Collaborators of Taiwan Community-based Integrated Screening Group (2024). Screening for *Helicobacter pylori* to prevent gastric cancer: a pragmatic randomized clinical trial. JAMA. 332(19):1642–51. https://doi.org/10.1001/jama.2024.14887 PMID:39348147
44. Taylor LC, Law K, Hutchinson A, Dennison RA, Usher-Smith JA (2023). Acceptability of risk stratification within population-based cancer screening from the perspective of healthcare professionals: a mixed methods systematic review and recommendations to support implementation. PLoS One. 18(2):e0279201. https://doi.org/10.1371/journal.pone.0279201 PMID:36827432
45. Savoldi A, Carrara E, Graham DY, Conti M, Tacconelli E (2018). Prevalence of antibiotic resistance in *Helicobacter pylori*: a systematic review and meta-analysis in World Health Organization regions. Gastroenterology. 155(5):1372–1382.e17. https://doi.org/10.1053/j.gastro.2018.07.007 PMID:29990487
46. Hong TC, El-Omar EM, Kuo YT, Wu J-Y, Chen M-J, Chen C-C, et al.; Asian Pacific Alliance on Helicobacter and Microbiota (2024). Primary antibiotic resistance of *Helicobacter pylori* in the Asia-Pacific region between 1990 and 2022: an updated systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 9(1):56–67. https://doi.org/10.1016/S2468-1253(23)00281-9 PMID:37972625
47. CAN*Help* Working Group (2024). Canadian North *Helicobacter pylori* Working Group mission statement. University of Alberta, Canada. Available from: http://www.canhelpworkinggroup.ca/.
48. Cheung J, Goodman K, Munday R, Heavner K, Huntington J, Morse J, et al.; CAN*Help* working group (2008). *Helicobacter pylori* infection in Canada's Arctic: searching for the solutions. Can J Gastroenterol. 22(11):912–6. https://doi.org/10.1155/2008/614538 PMID:19018336
49. Cheung J, Goodman KJ, Girgis S, Bailey R, Morse J, Fedorak RN, et al.; CAN*Help* Working Group (2014). Disease manifestations of *Helicobacter pylori* infection in Arctic Canada: using epidemiology to address community concerns. BMJ Open. 4(1):e003689. https://doi.org/10.1136/bmjopen-2013-003689 PMID:24401722
50. Fagan-Garcia K, Geary J, Chang HJ, McAlpine L, Walker E, Colquhoun A, et al.; CAN*Help* Working Group (2019). Burden of disease from *Helicobacter pylori* infection in western Canadian Arctic communities. BMC Public Health. 19(1):730. https://doi.org/10.1186/s12889-019-7065-x PMID:31185961
51. Colquhoun A, Hannah H, Corriveau A, Hanley B, Yuan Y, Goodman KJ; CAN*Help* Working Group (2019). Gastric cancer in northern Canadian populations: a focus on cardia and non-cardia subsites. Cancers (Basel). 11(4):534. https://doi.org/10.3390/cancers11040534 PMID:30991639

52. The Alberta First Nations Information Governance Centre (2018). First Nations – Health Trends Alberta. Stomach cancer among First Nations in Alberta. Available from: https://afnigc.ca/wp-content/uploads/2024/05/HTAFN-2018-03-27-Stomach-Cancer-FN.pdf.
53. Arnold M, Moore SP, Hassler S, Ellison-Loschmann L, Forman D, Bray F (2014). The burden of stomach cancer in indigenous populations: a systematic review and global assessment. Gut. 63(1):64–71. https://doi.org/10.1136/gutjnl-2013-305033 PMID:24153248
54. Government of Yukon (2019). Yukon Cancer Incidence Report, 2009–2016. Yukon Office of the Chief Medical Officer of Health. Whitehorse, Yukon, Canada: Department of Health and Social Services, Government of Yukon. Available from: https://open.yukon.ca/sites/default/files/yukoncancerincidencereport.pdf.
55. Statistics Canada (2021). Cancer incidence in Canada, 2018. Available from: https://www150.statcan.gc.ca/n1/daily-quotidien/210519/dq210519b-eng.htm.
56. Homan M, Jones NL, Bontems P, Carroll MW, Czinn SJ, Gold BD, et al.; on behalf of ESPGHAN/NASPGHAN (2024). Updated joint ESPGHAN/NASPGHAN guidelines for management of *Helicobacter pylori* infection in children and adolescents (2023). J Pediatr Gastroenterol Nutr. 79(3):758–85. https://doi.org/10.1002/jpn3.12314 PMID:39148213
57. McDonald AM, Sarfati D, Baker MG, Blakely T (2015). Trends in *Helicobacter pylori* infection among Māori, Pacific, and European birth cohorts in New Zealand. Helicobacter. 20(2):139–45. https://doi.org/10.1111/hel.12186 PMID:25403622
58. Kubovy J, Barclay ML (2022). *Helicobacter pylori* in New Zealand: current diagnostic trends and related costs. N Z Med J. 135(1562):48–55. https://doi.org/10.26635/6965.5761 PMID:36137766
59. Teng AM, Atkinson J, Disney G, Wilson N, Sarfati D, McLeod M, et al. (2016). Ethnic inequalities in cancer incidence and mortality: census-linked cohort studies with 87 million years of person-time follow-up. BMC Cancer. 16(1):755. https://doi.org/10.1186/s12885-016-2781-4 PMID:27669745
60. Te Whatu Ora/Health New Zealand (2024). Cancer data web tool. Available from: https://tewhatuora.shinyapps.io/cancer-web-tool/.
61. Hildred E (2024). Examining ethnic inequities in the management and health outcomes of *H. pylori* infection in New Zealand [thesis]. University of Otago. Available from: https://hdl.handle.net/10523/16512.
62. Signal V, Sarfati D, Cunningham R, Gurney J, Koea J, Ellison-Loschmann L (2015). Indigenous inequities in the presentation and management of stomach cancer in New Zealand: a country with universal health care coverage. Gastric Cancer. 18(3):571–9. https://doi.org/10.1007/s10120-014-0410-y PMID:25098927
63. Biggar M, Srinivasa S, Wickramarachchi B, Babor R, Poole GH, Hill AG (2011). Gastric cancer location and histological subtype in Pacific people and Māori defies international trends. N Z Med J. 124(1331):39–44. PMID:21725411
64. Signal V, Gurney J, Inns S, McLeod M, Sika-Paotonu D, Sowerbutts S, et al. (2020). *Helicobacter pylori*, stomach cancer and its prevention in New Zealand. J R Soc N Z. 50(3):397–417. https://doi.org/10.1080/03036758.2019.1650081
65. O'Hallahan J, Church E, Shaw C (2020). Cancer screening in New Zealand. J Cancer Policy. 23:100203. https://doi.org/10.1016/j.jcpo.2019.100203
66. National Advisory Committee on Health and Disability (2003). Screening to improve health in New Zealand: criteria to assess screening programmes. Wellington, New Zealand: National Health Committee. Available from: https://www.tewhatuora.govt.nz/assets/Our-health-system/Screening/screening_to_improve_health.pdf.
67. Tepeš B, Park JY, Knaze V, Leja M, Ražuka-Ebela D, Matysiak Budnik T, et al. (2024). EU Project 101079944, EUROHELICAN – Accelerating Gastric Cancer Reduction in Europe through *Helicobacter pylori* Eradication, Work Package 4, D4.1 Study manual. Available from: https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/projects-details/43332642/101079944/EU4H?order=DESC&pageNumber=1&pageSize=50&sortBy=title&keywords=EUROHELICAN&isExactMatch=true&programmePeriod=2021-2027&frameworkProgramme=43332642.