Chapter 9.

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

Iris Lansdorp-Vogelaar, Duco T. Mülder, Mário Dinis-Ribeiro, Melissa McLeod, Jin Young Park, and Yi-Chia Lee

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.

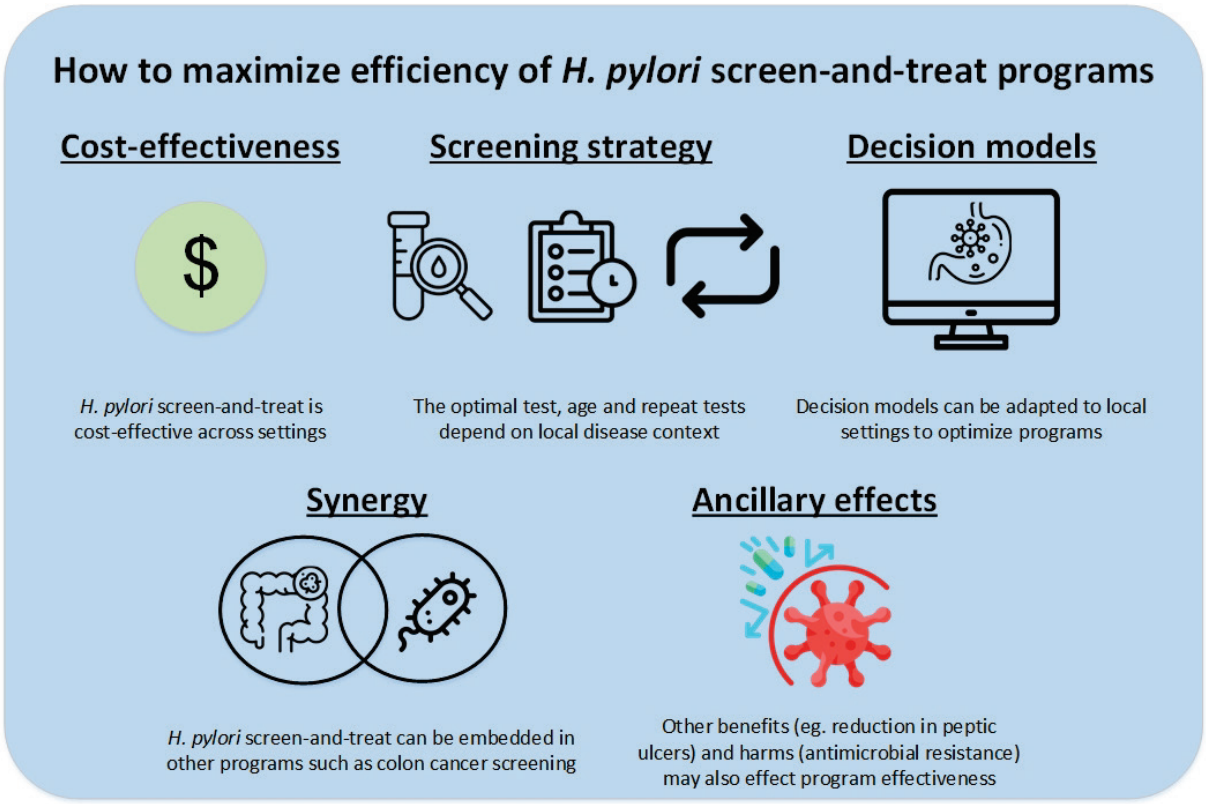

Fig. 9.1. Visual abstract.

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.

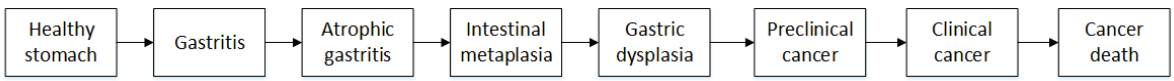

Fig. 9.2. Health states in gastric carcinogenesis according to the Correa cascade [10]. Arrows represent transitions between health states. In natural history models, transitions often depend on exposure to risk factors such as *H. pylori* infection.

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.

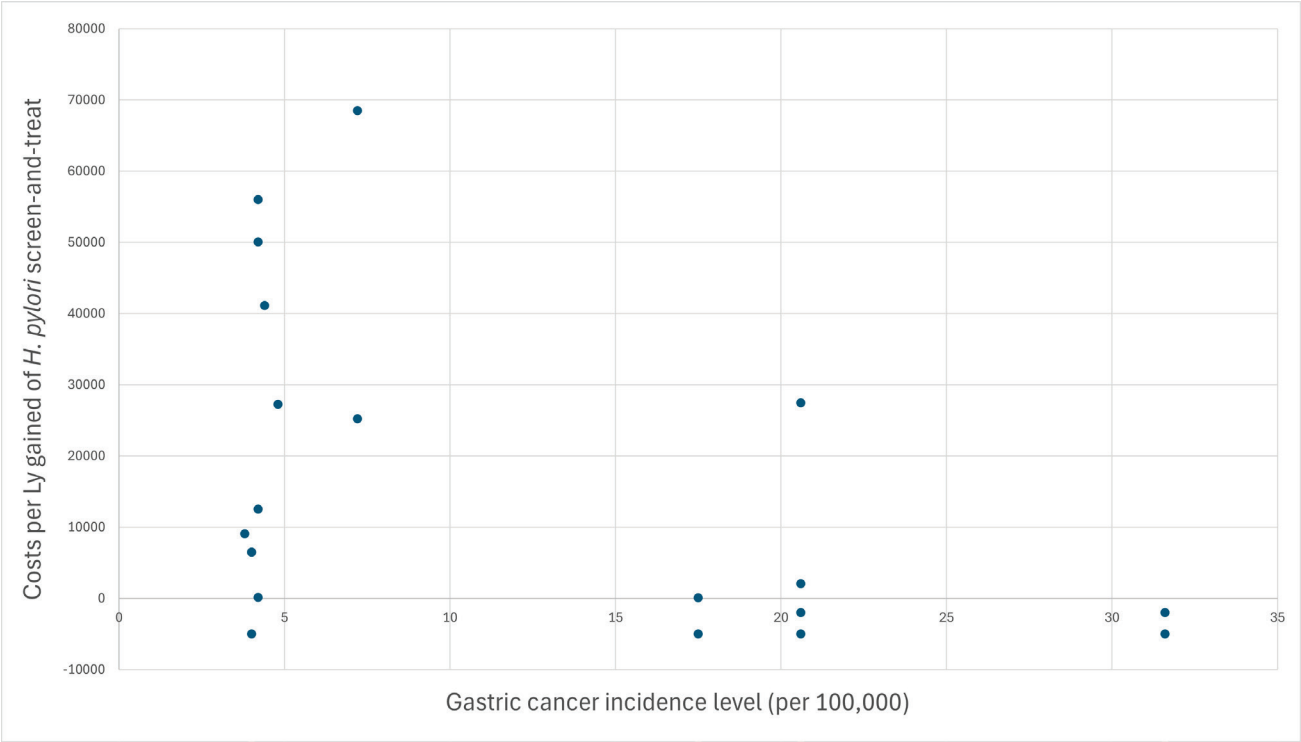

Fig. 9.3. Costs per life year (LY) gained (incremental cost–effectiveness ratio, ICER) plotted against the gastric cancer incidence level in the country of study. Studies demonstrating cost savings are artificially depicted as negative costs per LY gained.

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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