Chapter 5.

Considerations for choice of population-based *Helicobacter pylori* detection methods

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Summary

- For population-based *H. pylori* screen-and-treat programmes, non-invasive tests should be used.
- Non-invasive testing methods include the ^{13}C-urea breath test, the *H. pylori* stool antigen test, and serology tests, with confirmatory tests for people who test positive.
- Considerations for selecting *H. pylori* tests in population-based programmes should include test performance and predictive values, as well as practical factors such as support systems, participants' preferences, and costs.
- Confirmation of success of *H. pylori* eradication should rely on post-treatment testing using the ^{13}C-urea breath test or the stool antigen test at least 4 weeks after the completion of *H. pylori* therapy.

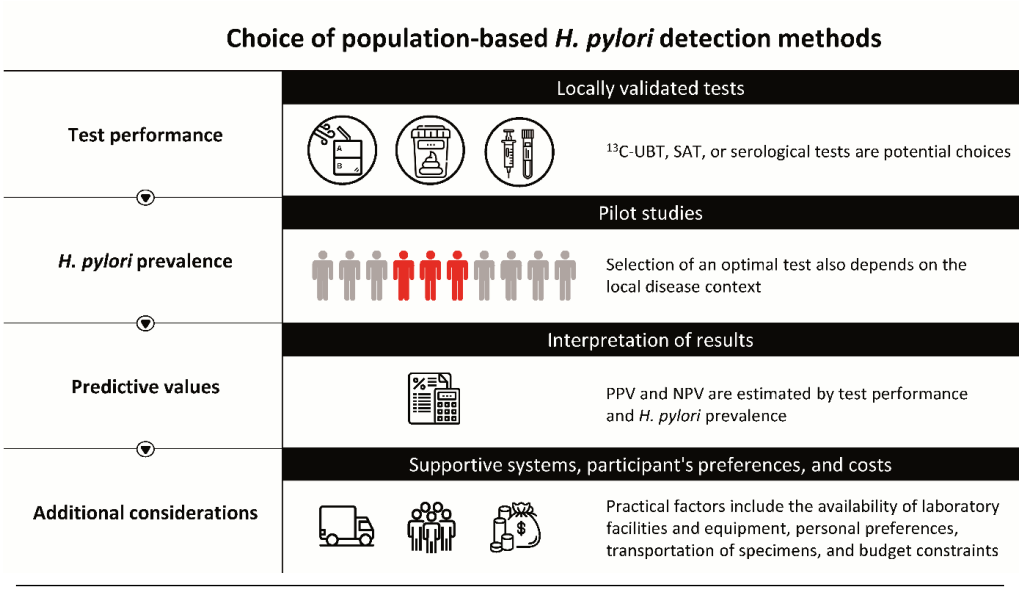

Fig. 5.1. Visual abstract. NPV, negative predictive value; PPV, positive predictive value; SAT, stool antigen test; UBT, urea breath test.

5.1 Introduction

H. pylori infection is usually clinically silent in most patients, and the only way to identify individuals with *H. pylori* infection is through testing. Although *H. pylori* infection consistently leads to chronic inflammation of the stomach mucosa, predicting who will develop clinically significant diseases remains challenging. Therefore, *H. pylori* eradication is recommended for anyone diagnosed with an active infection [1, 2]. Population-based *H. pylori* screen-and-treat programmes for gastric cancer prevention are recommended in countries with intermediate risk (i.e. a crude incidence rate of 10–20 new gastric cancer cases per 100 000 person-years) to high risk (i.e. > 20 new cases per 100 000 person-years), as stated in the Maastricht VI/Florence Consensus report [2], Europe's Beating Cancer Plan 2023–2033 [3], and the Taipei Global Consensus report [4].

The selection of the appropriate population testing methods is a crucial topic, and the methods selected may need to be tailored to the population characteristics and the health-care infrastructure. Diagnostic tests for *H. pylori* infection include non-invasive methods (urea breath test, stool antigen test, and serological tests) and endoscopy-based invasive methods (rapid urease test, histology, and bacterial culture). For population-based *H. pylori* screen-and-treat programmes, non-invasive tests should be used. Not only should the diagnosis of *H. pylori* infection be made using an accurate test; eradication should also be verified with a follow-up test, because the treatment rate is far from 100% with any treatment regimen.

This chapter provides an introduction to the potential choices for *H. pylori* testing and their underlying mechanisms (Section 5.2). In real-world applications, additional practical considerations are necessary (Section 5.3). It is possible that gastric cancers may already be present at the time of *H. pylori* testing and treatment (Section 5.4). An introduction to endoscopy-based, invasive tests for *H. pylori* infection in the middle-aged population is given in Section 5.5. In Section 5.6, methods for interpreting results across various population scenarios with differing prevalence of *H. pylori* infection are described, and predictive values are addressed. Conclusions and future directions are provided in Section 5.7.

5.2 Importance of test performance for population-based *H. pylori* testing

H. pylori testing is accomplished by measuring the concentration of $^{13}CO_2$ in exhaled air before and after the ingestion of a test meal, detecting *H. pylori* antigens in stool

samples, or detecting *H. pylori* antibodies in blood samples. For the selection of a population-based test, the test performance and predictive values should first be considered. Test performance is determined by diagnostic accuracy studies, which evaluate the sensitivity (test positive/true positive) and the specificity (test negative/true negative). The diagnostic accuracy of *H. pylori* tests is addressed in this section.

Urea breath tests

The urea breath test (UBT) is the cornerstone of non-invasive diagnosis of *H. pylori* infection. This diagnostic method exploits the urease activity of *H. pylori*. Participants ingest urea labelled with either ^{13}C or ^{14}C isotopes. Because of its radioactivity, ^{14}C is not suitable for population testing, because pregnant women may inadvertently participate in the programme. *H. pylori* urease hydrolyses the labelled urea ($^{13}CH_4N_2O$), resulting in the production of ammonia (NH_3) and labelled carbon dioxide ($^{13}CO_2$), and the $^{13}CO_2$ is absorbed into the bloodstream and subsequently exhaled. Measurement of the increase in the concentration of labelled $^{13}CO_2$ in the breath provides a direct indication of the presence of *H. pylori* infection. There are two analytical systems for the UBT: mass spectrometry and infrared spectrometry. The UBT has demonstrated high sensitivity and specificity, > 95% in most studies [5–7]. Participants should refrain from taking antibiotics for at least 1 month and from using proton pump inhibitors for at least 14 days before the UBT. Participants should fast for at least 2 hours before the test and should undergo pre-test and post-test assessments within a 30-minute interval. The UBT has been extensively validated in clinical settings not only for initial diagnosis but also for confirming eradication after treatment. In a meta-analysis, the UBT was found to be 10% more sensitive than stool and blood tests [7]. Given its non-invasive nature and its high diagnostic performance, the UBT is a commonly used method in clinical practice. In practice, there are two methods for collecting end-expiratory air: the tube method and the bag method (Box 5.1). Both methods offer advantages in sample stability during transportation compared with the stool antigen test.

Box 5.1. The tube method versus the bag method for the UBT

Both methods require correctly collecting the end-expiratory air and ensuring that the CO_2 concentration is sufficient. The tube method typically requires four tubes (two for pre-test assessments and two for post-test assessments). If the CO_2 concentration is

insufficient in one tube, there is another tube to test. The tube method may have a lower likelihood of air leakage, but it is associated with higher costs. A tube is more convenient than a bag for transportation between the collection point and the laboratory. The bag method involves collecting one bag for the pre-test assessment and another for the post-test assessment. This method is convenient to operate and collects a larger volume of gas, which allows for repeated testing. However, if the CO_2 concentration is insufficient initially, the participant should be called back and the UBT should be redone. Bags are less suitable than tubes for transportation, because of the higher likelihood of gas leaks.

Stool antigen tests

The stool antigen test (SAT), which detects *H. pylori* antigens in stool samples, offers a non-invasive and reliable diagnostic alternative. SATs use monoclonal antibodies to identify *H. pylori*-specific antigens in stool samples. Multiple studies and clinical trials have reported high sensitivity and specificity for SATs, with values > 90% [7–9]. In addition to population testing, the SAT has been proven to be particularly valuable in paediatric populations and for post-eradication verification, given its non-invasive nature and its high diagnostic accuracy [10, 11]. Like for the UBT, the intake of proton pump inhibitors, antibiotics, and bismuth-containing compounds can reduce the bacterial load and potentially lead to false-negative results [8]. Also, because monoclonal antibodies can only detect one epitope, the test performance depends on the conservation of the epitope and the nature of the circulating strains. The performance of SATs also depends on the timely processing of the stool sample and the storage temperature (< 8 °C). Delayed processing can lead to degradation of the antigen–antibody complexes and can lower the sensitivity of SATs. These factors mean that in real-life use the sensitivity of SATs is often < 90%. In a country with limited resources and many remote places, the above-mentioned limitations should be considered when choosing the SAT. A point-of-care SAT is now available as a rapid test, but it is not as sensitive as the enzyme-linked immunosorbent assay (ELISA) SAT.

Box 5.2. Molecular detection of *H. pylori* and resistance strains in stool samples

Molecular methods, such as polymerase chain reaction (PCR) and next-generation sequencing, are increasingly being used for detecting *H. pylori* DNA and identifying antibiotic resistance mutations directly from stool samples. Although these methods have not yet been implemented in population test-and-treat programmes, because of higher costs and lower availability, they offer better stability and valuable information for selecting effective treatments, usually after failure of first-line treatment. These advanced techniques provide high diagnostic accuracy, with sensitivities and specificities often > 95%, but the results are heterogeneous among the different studies [12–14]. The ability to detect specific mutations that confer resistance to antibiotics, such as clarithromycin and levofloxacin, is particularly crucial given the rising prevalence of antibiotic-resistant *H. pylori* strains. Molecular detection for these antibiotics has not yet been sufficiently validated in clinical trials, which have showcased excellent performance in both the diagnosis of *H. pylori* infection and the identification of resistance patterns [15]. This diagnostic approach is valuable in guiding the appropriate treatment regimens in the face of antibiotic resistance challenges [16]. However, PCR-based detection methods are limited when it comes to rare mutations, which may not be included in the panel. This limitation can be overcome by next-generation sequencing, which is more laborious and expensive, and the bioinformatics are more complex to validate. For other antibiotics, especially metronidazole, which is still one of the most frequently used antibiotics in *H. pylori* therapies, little is known about the molecular mechanisms that lead to resistance, and several genes or parameters seem to be able to contribute to resistance. Therefore, molecular models are not yet sufficiently reliable to detect or predict metronidazole resistance [17]. In general, molecular methods are not yet sufficiently validated and cost-effective to be used for population-level programmes.

Serological testing

Serological testing for *H. pylori* infection involves the detection of specific antibodies (immunoglobulin G) against *H. pylori* in the patient's serum. Because the gastric inflammation persists for decades, almost every individual with *H. pylori* infection has multiple, highly specific antibodies against *H. pylori* antigens in their blood. The most

used and best-characterized test formats are ELISA and western blotting, or a newer version called line blotting. The principal advantage of serology tests is the high sensitivity and technical specificity of these state-of-the-art tests. Given its simplicity, broad availability, and lower cost, ELISA is the preferred method for population-based screening. However, a major limitation is the inability to distinguish between current and past infections because of the prolonged presence of antibodies even after bacterial eradication, which lowers the clinical specificity [18–20]. Serology is used primarily for initial screening purposes (to be confirmed by the UBT) but cannot be used to determine successful eradication. Although western blotting may be considered too impractical for population-based testing, there may be circumstances in which it could be informative, for example if additional specificity is required or the responsiveness to individual antigens is of interest. The sensitivity and specificity of serology tests vary widely, typically ranging from 80% to 98% [20–22]. Because of the inability to differentiate current from past infection, serology tests are not recommended as the only method for diagnosing current *H. pylori* infection. The accuracy of serology tests depends on the choice and number of antigens used. Large-scale studies using multiple *H. pylori* antigens could show that the antibody frequencies against individual antigens are highly variable, depending on the antigens used. CagA is among the most immunogenic antigens, and almost every individual infected with a CagA-positive strain has high antibody titres against CagA. However, this depends on the geographical region, because, for example, in Europe and North America a substantial number of strains lack CagA [23]. Therefore, only locally verified serology tests with sensitivities and specificities of > 90–98% should be used in test-and-treat programmes as the first test, usually followed by the UBT for confirmation of current infection. Tests with lower performances should no longer be used. A properly validated and well-characterized serology test will always have a technical specificity of > 90%, and cross-reactivities are rare. State-of-the-art tests based on recombinant antigens are very sensitive and specific. Other antigens with highly prevalent antibodies are FliD and GroEL. If three or more antigens are combined, a sensitivity of nearly 100% can be achieved. In addition, some assay formats enable the distinction of the individual antibody responses (e.g. line blotting, Luminex). Such assays have become valuable in epidemiological studies to identify individuals in whom *H. pylori* infection was eradicated or who lost *H. pylori* infection by other means, and in determining the risk of *H. pylori*-associated diseases [24, 25], but these assays are more expensive and must be performed in specialized

laboratories, in which the required infrastructure (Dynablot instrument for line blotting or fluorescence-activated cell sorting [FACS] instruments for Luminex) to conduct and process the assays is available. An additional advantage of serological testing is the potential for the simultaneous assessment of gastric secretory function including testing for pepsinogen I and II (enzymes produced in the stomach), which could identify individuals with gastric atrophy [26].

5.3 Additional considerations

In addition to the test performance, several factors may influence the selection and effectiveness of diagnostic methods. Each health-care setting may prioritize these factors differently on the basis of local resources and health-care objectives, and this will influence the selection of diagnostic strategies [27]. The overall comparisons among the three tests are summarized in Table 5.1.

Support systems

Practical considerations about infrastructure play a crucial role in the choice of test, including the requirement for a laboratory, the equipment needed, and the transportation of test samples. For example, although the UBT is highly accurate, it requires a mass spectrometer or an infrared spectrometer, which may not be accessible in some clinical settings [28]. SATs are easier to administer and do not require such specialized equipment; this makes them suitable for settings with limited technical infrastructure [7], but they are not suitable for transportation. Although serology tests are less specific, they require only basic laboratory infrastructure [29]. The availability of equipment refers to the ease of acquiring the necessary test kits and materials, which are crucial for tests like the UBT and the SAT. Reagents and test kits must be reliably available. Disruptions in supply chains can significantly affect the availability of tests and the consistency of results. With respect to the transportation of specimens, the monoclonal SAT is temperature-sensitive, and samples should be stored at temperatures < 8 °C. In contrast, the UBT is stable and can be sent by mail, and the results can typically be analysed within 1 month. Rapid tests such as the UBT and the SAT can provide results within hours, which is advantageous for timely treatment decisions. In contrast, serological testing may take several days; this can potentially delay the next step for the confirmation of current infection for the initiation of treatment. Delays in treatment may affect the percentage of patients who accept treatment.

Table 5.1. Population tests for *H. pylori* infection

Test	Strengths	Weaknesses	Performance	Additional considerations
UBT	• Simple operation • Good performance • Can be used to test for active infection and evaluate for eradication success	• Higher direct and indirect costs (procedure time) • Requires fasting • Requires stopping PPI use for 2 weeks and antibiotic use for 4 weeks before testing	• Sensitivity and specificity > 95%	• Depends on the availability of mass spectrometry or infrared spectrometry • Requires trained technicians for analysis
SAT	• Simple operation • Good performance • Can be used to test for active infection and evaluate for eradication success • Point-of-care test is possible	• Requires stopping PPI use for 2 weeks and antibiotic use for 4 weeks before testing • Requires instruction about sample collection, storage, and transportation • Participants' preferences may be lower for stool sampling	• Sensitivity and specificity > 90%	• Can be performed together with FIT screening for colorectal cancer • Can be performed together with molecular testing for antibiotic resistance
Serological test	• Does not require modifications of medication before testing • The only method not influenced by current PPI intake • Widely available • Least expensive	• Does not reliably differentiate between active infection and previous infection • Cannot be used to confirm eradication • Needs to be carried out by professionals for blood sampling	• Technical sensitivity and specificity ranging from 80% to 98% • Clinical specificity is lower than for UBT and SAT because of inability to differentiate between current infection and past infection	• Can be performed together with other blood tests, such as pepsinogen testing • A positive test result should be confirmed by UBT or SAT • The test should be validated locally for optimal PPV and NPV

FIT, faecal immunochemical test; NPV, negative predictive value; PPI, proton pump inhibitor; PPV, positive predictive value; SAT, stool antigen test; UBT, urea breath test.

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Participants' preferences

Participants' preferences with respect to breath samples, stool samples, or blood samples can significantly influence their willingness to participate. In particular, participants may feel uncomfortable with providing stool samples [30], depending on geography, ethnicity, or religious background, or if they are unable to produce a sample during the visit to the health-care centre.

Costs

Budget considerations include not only the direct costs of the tests but also the broader economic impact, including the costs associated with false-positive or false-negative test results, which could lead to inappropriate treatments or delayed diagnosis. Therefore, budgetary constraints may necessitate a balance between the test accuracy and the related costs. For the same test, the costs can vary significantly depending on geographical location and health-care setting, which influence the accessibility and choice of diagnostic methods. Costs typically rank, from highest to lowest, in the order of the UBT, the SAT, and serological testing. In the Accelerating Gastric Cancer Reduction in Europe through *H. pylori* Eradication (EUROHELICAN) programme, which targets the young adult population with a lower prevalence of *H. pylori* infection in a European country (see Chapter 3.5), there is a notable cost disparity between the UBT and serological testing (the costs of the UBT are potentially many times those of the serology test). Using a two-step approach with a locally validated immunoglobulin G serology test as the first step and a confirmatory UBT as the second step may reduce overall testing costs compared with a one-step approach using the UBT (Fig. 5.2).

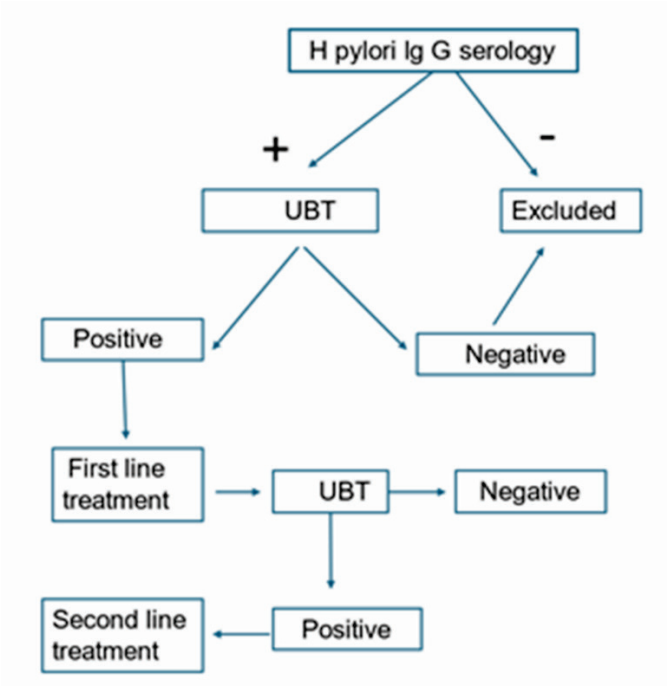

Fig. 5.2. A two-step approach for serological *H. pylori* testing and urea breath test (UBT) confirmation in a population-based *H. pylori* screen-and-treat programme in a setting with a low prevalence of *H. pylori* infection (as used in the EUROHELICAN and TOGAS projects). IgG, immunoglobulin G. Source: Tepeš et al. (2024) [31].

Testing after eradication treatments

H. pylori is classified as a class I carcinogen. It is an infectious disease that requires treatment and eradication for patients with an infection [1, 2]. *H. pylori* treatment regimens aim for eradication rates of > 90%, though actual eradication rates typically range between 80% and 90% [32]. Retesting after antibiotic treatment is important to confirm the successful elimination of the infection. This also reinforces the patient–doctor interaction in managing the disease. Without retesting, more-resistant strains may persist and spread within the community. The UBT and the SAT should be used as confirmatory tests for eradication [7]. In cases of treatment failure, additional lines of treatment may be prescribed until *H. pylori* infection is successfully eradicated [2].

5.4 Gastric cancer risk at the time of testing for *H. pylori* infection

The diagnostic tests used in the population-based *H. pylori* screen-and-treat programmes in younger and older adult populations may differ because of the differences in the risk of pre-neoplastic changes and gastric cancer. Economic capacities and medical facilities could also influence the approach to integrate *H. pylori* preventive measures with early detection of gastric cancer in a particular country. In young adults, *H. pylori* infection is often asymptomatic and typically results in chronic gastritis in most individuals with *H. pylori* infection. In older adults, additional considerations are needed because the intragastric damage may have progressed to a point where it is less reversible. *H. pylori* eradication reduces the risk of gastric cancer, but the magnitude of the effect is lower in older populations because of the high rate of pre-neoplastic changes in the gastric mucosa at older ages. The prevalence of advanced pre-neoplastic lesions (atrophic gastritis and intestinal metaplasia) in Europe in age groups > 50 years is up to 19% [33–35]. Measuring the levels of pepsinogens combined with *H. pylori* serological testing may provide additional information about pre-neoplastic conditions of the gastric mucosa [26]. A decreased pepsinogen I level or a low pepsinogen I/II ratio is indicative of atrophic gastritis, which is often associated with chronic *H. pylori* infection. The combination of two serology tests may be useful to triage the population for upper endoscopy on the basis of the risk of gastric cancer [36]. A drawback of pepsinogen testing is its low sensitivity for detecting gastric cancer and pre-neoplastic changes; this currently limits its readiness for implementation in preventive programmes. In a population-based screen-and-treat programme, additional endoscopy can be considered, according to medical judgement, for participants with a family history

of upper gastrointestinal cancer, for those with a history of oesophageal or gastric malignancy, or for those presenting with alarm symptoms and signs, such as unexplained iron deficiency anaemia, a palpable abdominal mass or lymphadenopathy, dysphagia, odynophagia, melaena, gastrointestinal bleeding, unintentional weight loss, or persistent vomiting [2].

5.5 Invasive tests for *H. pylori* infection

Invasive tests are generally not applicable to the *H. pylori* screen-and-treat approach, except when there is a concurrent endoscopy-based gastric cancer screening programme. When endoscopy is contemplated, gastric biopsy can be used for detection of *H. pylori* infection by the rapid urease test, histological examination, and bacterial culture. These necessitate endoscopic facilities, which involve higher initial set-up and maintenance costs. These methods require trained gastroenterologists and pathologists, which can be a limitation in resource-limited settings [37].

Rapid urease tests

The rapid urease test (RUT) is a simple and inexpensive rapid test, which detects the presence of urease activity. Two biopsies should be taken for the RUT, from the antrum and the corpus. The RUT contains urea, which would be broken down by *H. pylori* urease, leading to a pH change as reflected by the colour change of the pH indicator. The urease activity typically comes from *H. pylori* in the stomach, although false-positive test results are possible because of the presence of other bacteria. In general, commercial RUTs have a sensitivity of about 85–95% and a specificity of about 95–100% [38]. Results are available within minutes or sometimes hours, depending on the bacterial load present in the biopsy specimens. Rather than obtaining a further biopsy for PCR, the biopsies used for the RUT could be further used (after reading the results) for the detection of mutations associated with antibiotic resistance, using PCR [39]. However, RUTs can be falsely negative in patients with a recent intake of antibiotics or proton pump inhibitors, and in patients with upper gastrointestinal bleeding [40, 41]. Under these circumstances, additional gastric biopsies from the antrum and the corpus can be taken for histology, bacterial culture, or PCR.

Histology

Histology is a simple, economical, and widely available test for *H. pylori* infection. It is considered to be a standard protocol in routine upper endoscopy to evaluate gastric

inflammation and the presence of other pre-neoplastic lesions, such as atrophic gastritis and intestinal metaplasia. Although special staining techniques such as the Giemsa or Warthin–Starry stain could increase the detection of *H. pylori* infection, this bacterium is readily identified by the conventional haematoxylin and eosin stain. Because the density of *H. pylori* infection is not uniformly distributed in the stomach, taking multiple biopsies from both the antrum and the corpus can increase the diagnostic yield. Proper topographical staging of the severity of gastritis can be done using the Operative Link on Gastritis Assessment (OLGA) and the Operative Link on Gastric Intestinal Metaplasia Assessment (OLGIM) staging systems [42–44].

Culture

Two biopsies are obtained for bacterial culture, from the antrum and the corpus. Culture for *H. pylori* has to be performed with selective medium under microaerobic conditions for 5–7 days, because of the slow growth of the bacterium. Culture has a relatively low sensitivity compared with histology or even the RUT, and it is not widely available because of the need for equipment and expertise. However, bacterial culture is useful in determining antimicrobial susceptibility, particularly in patients in whom first-line eradication therapy failed or in regions with a high prevalence of antimicrobial resistance. Culture has a specificity of 100%, but its sensitivity shows substantial variation, ranging between 85% and 95%, depending on the expertise of the laboratory [2, 4]. The role of culture has increasingly been replaced by molecular detection methods, including PCR and direct sequencing (see Box 5.2), because of the low yield and the long turnover time for culture. However, PCR is not widely used because of the higher costs and lower availability [37].

5.6 Real-world examples of the use of tests in population-based *H. pylori* screen-and-treat programmes

In a population-based *H. pylori* screen-and-treat programme, the choice of the best approach depends on the availability of the different tests, the performance of each test, and the expected prevalence of *H. pylori* infection. A positive test result is interpreted using the positive predictive value (PPV) (true positive/test positive), and a negative test result is interpreted using the negative predictive value (NPV) (true negative/test negative). The population-based application of *H. pylori* testing includes the single-step and two-step approaches. The single-step approach uses either the UBT or the SAT.

The two-step approach involves initial serological testing, followed by the UBT (or the SAT) for those who test positive in the serology tests. These applications are demonstrated in the following real-world examples, which show how countries can adopt appropriate tests for their target populations with varying *H. pylori* infection rates. A highly sensitive screening serology test can be used to select individuals with potential *H. pylori* infection and avoid many (more expensive) UBTs, especially when the prevalence of *H. pylori* infection is < 30%.

Urea breath tests

The application of the UBT is illustrated using an example of a high-risk population with a high prevalence (~55%) of *H. pylori* infection [45, 46] (see Chapter 3.10). When the UBT (with a locally validated sensitivity and specificity of 95% [47]) is adopted, the PPV is estimated to be 96% and the NPV is estimated to be 94%. Among 100 participants, 54 who tested positive and 46 who tested negative will be observed (Fig. 5.3). This will include 52 true positives (54 × 96%) and 43 true negatives (46 × 94%). Consequently, in this scenario, only 5 cases (= 100 − 52 − 43) will be misclassified.

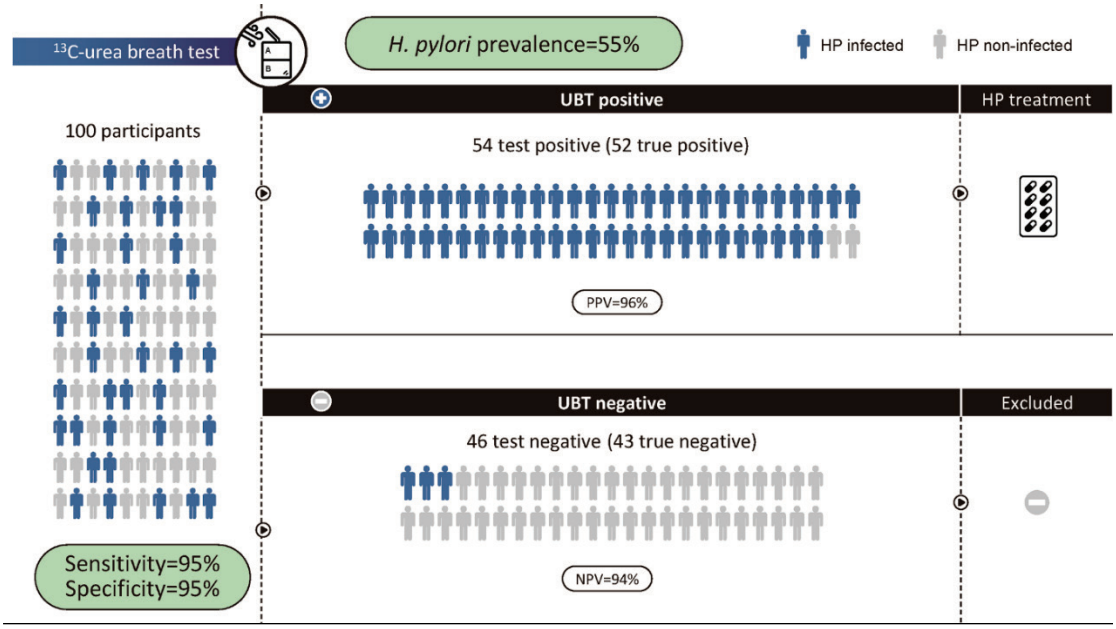

Fig. 5.3. Using the urea breath test (UBT) for *H. pylori* (HP) testing in a population-based *H. pylori* screen-and-treat programme in a setting with a high prevalence (55%) of *H. pylori* infection. NPV, negative predictive value; PPV, positive predictive value.

Stool antigen tests

The SAT has been shown to be valuable in population-based test-and-treat programmes in Bhutan [48] (see Chapter 3.6). The SAT can also leverage the established platform of colon cancer screening using faecal immunochemical tests for invitations and specimen transportation. This is illustrated in a middle-aged population with a prevalence of *H. pylori* infection of 38% [49]. When the SAT (with a locally validated sensitivity of 88% and specificity of 99% [50]) is adopted, the PPV is estimated to be 98% and the NPV is estimated to be 93%. Among 100 participants, 34 who tested positive and 66 who tested negative will be observed (Fig. 5.4). This includes 33 true positives (34 × 98%) and 61 true negatives (66 × 93%). Consequently, in this scenario, only 6 cases (= 100 − 33 − 61) will be misclassified.

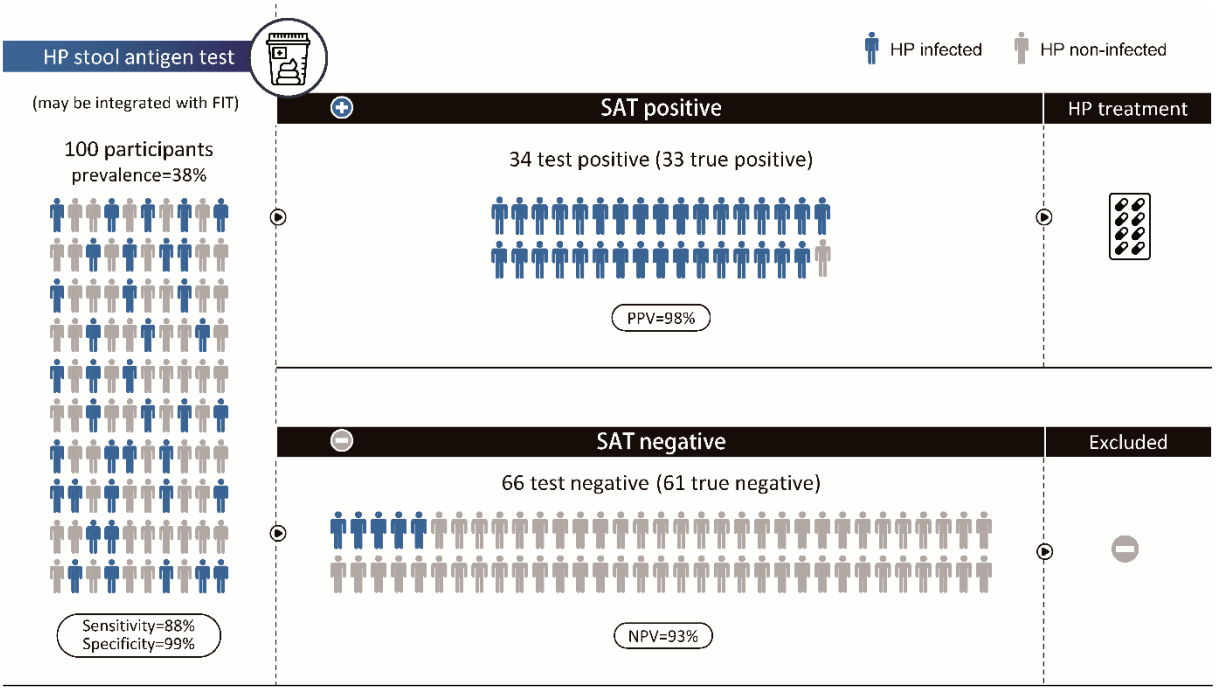

Fig. 5.4. Using the stool antigen test (SAT) for *H. pylori* (HP) testing in a population-based *H. pylori* screen-and-treat programme in a middle-aged population with an intermediate prevalence (38%) of *H. pylori* infection. FIT, faecal immunochemical test; NPV, negative predictive value; PPV, positive predictive value.

Serological testing

In a population-based programme, serological testing can be applied in a two-step approach, using a highly sensitive, but less expensive, ELISA for screening purposes, followed by confirmatory testing with the UBT or the SAT. Examples of this include the EUROHELICAN and Towards Gastric Cancer Screening Implementation in the European Union (TOGAS) projects (see Chapter 3.5) and the *H. pylori* in Aotearoa New Zealand (ENIGMA) Study (see Chapter 3.11). A high-performance and well-validated test should be chosen. This approach may be applicable, for example, in populations with lower prevalence of *H. pylori* infection, such as the programme for young adults (e.g. prevalence of 14%). When a serology test with a locally validated sensitivity of 95% and specificity of 90% is used, the PPV is estimated to be 61% and the NPV is estimated to be 99%. Among 100 participants, 22 who tested positive and 78 who tested negative will be observed (Fig. 5.5). This includes 13 true positives (22 × 61%) and 77 true negatives (78 × 99%). With the high NPV, almost all those who test negative are true negatives. Almost all participants with *H. pylori* infection will test positive, although there will be some positives because of past infection (previously treated) ($n = 9$). Therefore, this approach may reduce the reliance on the UBT compared with the single-step UBT approach, particularly when considering the costs (costs for 100 serology tests and 22 UBTs vs costs for 100 UBTs). However, the dropout rate for such a two-step approach should be considered.

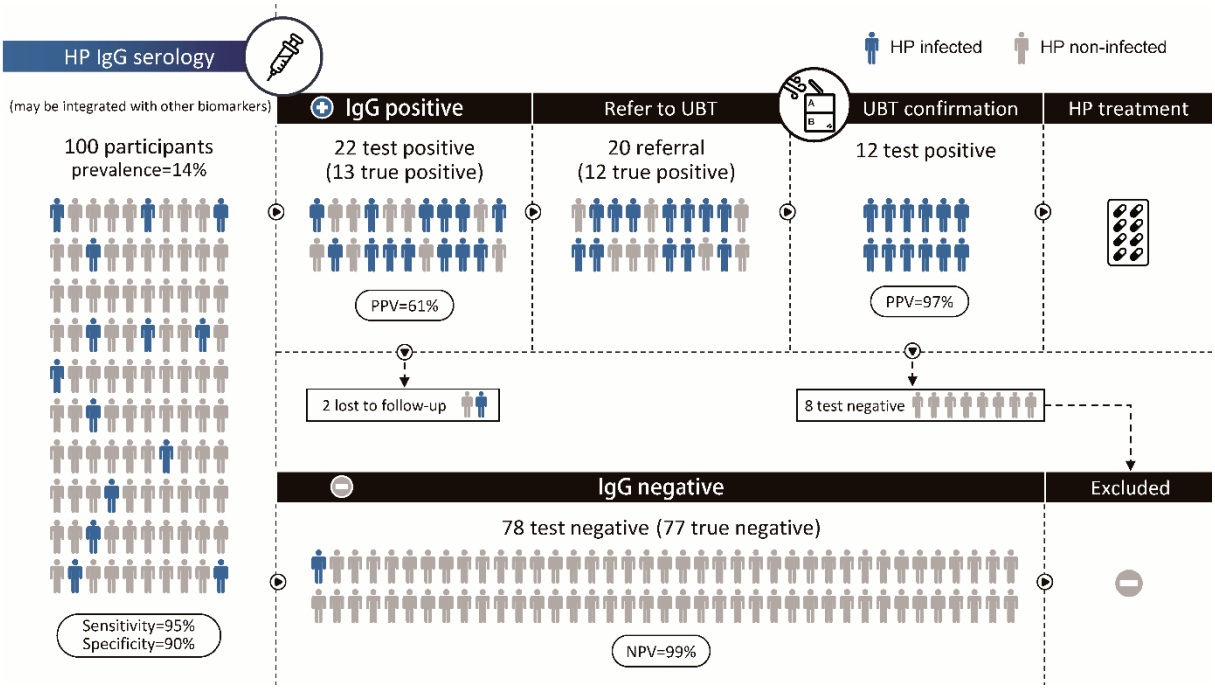

Fig. 5.5. Using a two-step approach for serological *H. pylori* (HP) testing in a population-based *H. pylori* screen-and-treat programme in a setting with a low prevalence (14%) of *H. pylori* infection. IgG, immunoglobulin G; NPV, negative predictive value; PPV, positive predictive value; UBT, urea breath test.

Endoscopic approaches

In Asian countries with high gastric cancer incidence rates and sufficient economic and medical resources, endoscopic screening for early gastric cancer, along with diagnosis of *H. pylori* infection using invasive methods, may be an option. Nonetheless, the *H. pylori* screen-and-treat programme using non-invasive methods can still be run in younger age groups, in parallel with the endoscopic screening programme in older age groups. For example, in Japan and the Republic of Korea [51, 52], a nationwide gastric cancer screening programme is available for the early detection and surveillance of patients with premalignant lesions. These programmes have improved the detection rate of early gastric cancer in Japan (to 63.3%) and in the Republic of Korea (to 63.9%). A cost–benefit analysis in Japan identified a population-based *H. pylori* eradication strategy as the most cost-effective strategy for a national gastric cancer prevention programme, better than the current strategy, which is a secondary prevention-focused programme of biennial endoscopic screening [53].

5.7 Conclusions and future directions

For population-based *H. pylori* screen-and-treat programmes, non-invasive tests should be used. The choice of testing should initially prioritize test performance and the prevalence of *H. pylori* infection in the population, estimating the predictive values when interpreting results in clinical practice. For population-wide implementation, additional considerations may include the availability of support systems for testing, participants' preferences with respect to the test types, and economic factors. Confirmation of eradication is essential and should be performed at least 4 weeks after the completion of *H. pylori* therapy. Molecular detection of *H. pylori* holds promise in the future for the alternative selection of therapies with no risk or only a minor risk of being influenced by antibiotic resistance.

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