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Rapid testing and targeted population screening for *Helicobacter pylori*

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Executive Summary

Although a large proportion of all gastric cancers are associated with *H pylori* infection, not all *H pylori* infected individuals will go on to develop cancer; however it has been suggested that 60-80 per cent of gastric cancers could be prevented by *H pylori* eradication. In developing countries in Asia and South America, *H pylori* infection is associated with poor hygiene and high levels of infection (70-80% of *all* individuals are infected), and therefore rates of gastric cancer, are high. In Western countries, with improved hygiene, rates of *H pylori* infection have declined (10-20% infection rates) and accordingly rates of *H pylori* associated gastric cancer have also declined.

Numerous diagnostic methods are available for the detection of *H pylori* including non-invasive tests: rapid stool antigen test (enzyme-linked immunosorbant assay or immunochromatographic tests), urea breath test or serology. Invasive tests include the gold standard endoscopy followed by histology, endoscopy followed by culture or the rapid urease test. Rapid *H pylori* diagnostic tests are intended to provide a swift, accurate, non-invasive and inexpensive means of identifying individuals currently infected with *H pylori* which ideally would be able to be used in a point-of-care context in clinics or a general practitioner's office.

Diagnostic

Effectiveness values, compared to the reference standard histology, of the various immunochromotographic HpSA tests (ICTs) varied depending on the brand of test used and age of population tested. Sensitivity ranged from a poor 33 per cent to 100 per cent in individuals aged ≤ 45 years. The best sensitivity reported for an adult population not stratified according to age, was 83.8 %. Specificity ranged from 55 to 100 per cent. Overall, accuracy of the ICT HpSA tests ranged between 50-93 per cent. Of concern is the high number of false negatives that occurred with the use of the majority of the ICT HpSA tests (range16-66%). However, most studies using ICT HpSA tests reported *low* false positive numbers, indicating that a relatively small number of patients would receive inappropriate treatment.

Reported sensitivity values were consistently higher for the ELISA HpSA tests compared to the ICTs. Sensitivity and specificity of the ELISA HpSA tests compared to histology ranged from 87-95 and 67-100 per cent, respectively. Diagnostic accuracy of the ELISA HpSA tests was also consistently higher when compared to the ICT HpSA tests (range 87-93%).

Although it would appear that HpSA tests are not as accurate as UBT, they are as, or more cost-effective than UBT for the diagnosis of *H pylori*. In addition, for patients with dyspepsia, it appears that there is little difference in the cost-effectiveness of the two strategies of either empirical treatment with proton pump inhibitors or *H pylori* test-and-treat strategy. In addition, there appears to be little difference in the cost-effectiveness of the two non-invasive tests used: UBT or HpSA. However this situation may change with the falling prevalence of *H pylori* infection.

Screening

H pylori is a *necessary* but *not sufficient* causal factor for gastric cancer and therefore it has been suggested that a screening program for *H pylori* would be able to detect asymptomatic but infected individuals *before* they have developed atrophic gastritis. By treating these individuals with an appropriate antibiotic regime and eradicating the *H pylori* infection, it is anticipated that their risk of developing symptoms of dyspepsia, peptic ulcer disease or gastric cancer would be markedly reduced or eliminated.

There are no clinical guidelines for the screening or management of *H pylori* infection in Australia or New Zealand. However, the Asia-Pacific guidelines *do not* recommend screening for *H pylori* in populations considered to be at low-risk of gastric cancer, such as Australia and New Zealand.

A large community-based Danish study randomised controlled trial compared a screening to a no-screening strategy and compared rates of dyspepsia at 5-year follow-up. *H pylori* positive individuals (17.5%) in the screening arm were offered eradication therapy. After analysis of data, including only those individuals followed-up for the five years, there was an *insignificant decrease* in the rates of visits to a general practitioner due to dyspepsia (from 3.1% to 2.8%) and the number of sick leave days due to dyspepsia (from 2.2% to 1.9%) in the screened group but a *significant* ($p<0.001$) increase in both rates in the unscreened group (2.5% to 3.1% for GP visits and 1.6% to 2.5% for sick leave days).

The most recent screening cost-effectiveness study to be published used a Markov model which evaluated the economics of a population *H pylori* screening programme, and the use of various diagnostic techniques within this strategy, for the prevention of gastric cancer. Although UBT was more sensitive and specific than HpSA and serology, the most cost-effective strategy, depending on the willingness-to-pay threshold values, was either no screening or screening with HpSA tests.

It would appear in populations with a relatively low prevalence of *H pylori* infection, that a *targeted*, rather than a population screening strategy would be more effective for the resolution of dyspepsia symptoms and for the reduction in the costs associated with treating the condition.

In summary, rapid HpSA stool antigen tests are not as sensitive nor as specific as a urea breath test, however the ICT HpSA tests are relatively cheap, easy to perform in a clinic setting and give an instantaneous diagnosis. An advantage of HpSA tests is that unlike most *H pylori* diagnostic test, cessation of antibiotic and proton pump inhibitor treatment is not necessary before testing. HpSA tests appear to be a cost-effective option when compared to UBT in a "test-and-treat" scenario for patients presenting with symptoms of dyspepsia. The long term effect on rates of gastric cancer of screening for *H pylori* infection has yet to be established.

Helicobacter Pylori infection is associated with an increased risk of gastric cancer. This horizon scanning report has identified that immunochromatographic (ICT) and enzyme-linked immunosorbent assay (ELISA) rapid stool antigen tests for Helicobacter pylori may have potential as a diagnostic tool for this infection, but currently are not as sensitive or as specific as the urea breath test. HealthPACT did not find evidence to support the introduction of rapid stool antigen tests for screening for Helicobacter Pylori infection in the Australian and New Zealand population, and supports the current approach of a targeted 'test and treat' strategy for individual patients considered to be at risk of this infection.

Introduction

The National Horizon Scanning Unit, AHTA, School of Population Health and Clinical Practice, University of Adelaide, on behalf of the Medical Services Advisory Committee (MSAC), has undertaken an Horizon Scanning Report to provide advice to the Health Policy Advisory Committee on Technology (Health PACT) on the state of play of the introduction and use of rapid diagnostic tests and targeted population screening for *Helicobacter pylori*.

Several companies produce rapid stool antigen kits for the detection of *Helicobacter pylori*. These tests would be offered through either general practitioners or gastroenterologists. Rapid stool antigen tests are currently in limited use in Australia.

This Horizon Scanning Report is intended for the use of health planners and policy makers. It provides an assessment of the current state of development of rapid diagnostic tests and targeted population screening for *Helicobacter pylori*, its present use, the potential future application of the technology, and its likely impact on the Australian health care system.

This Horizon Scanning Report is a preliminary statement of the safety, effectiveness, cost-effectiveness and ethical considerations associated with rapid diagnostic tests and targeted population screening for *Helicobacter pylori*.

Description of the technology

Helicobacter pylori

In 2005, two Australian researchers Marshall and Warren were awarded the Nobel Prize for their 1983 work which demonstrated the causative association between the presence of *H pylori* and peptic ulcers and gastritis. In addition they established that peptic ulcers could be cured by the eradication of *H pylori* with antibiotics (Walker et al 2008). *H pylori* is a gram negative, rod-shaped bacterium which is capable of colonising the human gastric mucosa, causing chronic inflammation (Figure 1) (Beswick et al 2006). *H pylori* infection is usually acquired in childhood and may persist for the lifetime of the host (Beswick et al 2006; Lee et al 2008). Infection with one strain of *H pylori* does not infer immunity against infection with other strains. *H pylori* may be transmitted from person-to-person by the faecal-oral, oral-oral or gastro-oral routes (Johnston et al 2006).

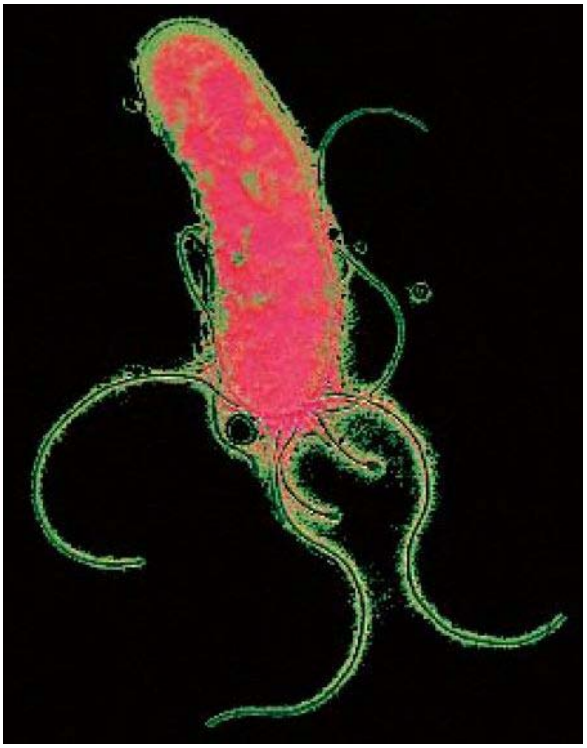


Figure 1 *Helicobacter pylori* (Moayyedi et al 2000b)

H pylori has a number of virulence factors which enable it to survive the harsh conditions of the gastric tract and to evade detection by the immune system. Although many of these factors have been identified, the precise mechanisms of adherence and pathogenesis that *H pylori* uses to colonise the gut are yet to be determined. Adherence via bacterial and host factors of *H pylori* to gastric epithelial cells is essential for colonisation and for the ability of *H pylori* to persist and cause disease. Adherence to the epithelium by *H pylori* induces a

host immune response, which may lead to one of two mutually exclusive outcomes (Figure 2):

- the protein complex NF-κB[1] is produced, which in turn results in the production of interleukin-8, initiating an inflammatory response. During the inflammatory response neutrophils are activated releasing antimicrobial reactive oxygen species. *H pylori* appear to be resistant to this antimicrobial activity, however the reactive oxygen species may induce tissue damage in the gastric mucosa leading to increased levels of apoptosis. Increased cell death is compensated by the proliferation of epithelial cells inducing chronic inflammation, which in turn may lead to hyperplasia or gastric cancer; or
- excess gastric acid is produced leading to tissue damage and ulceration (Beswick et al 2006).

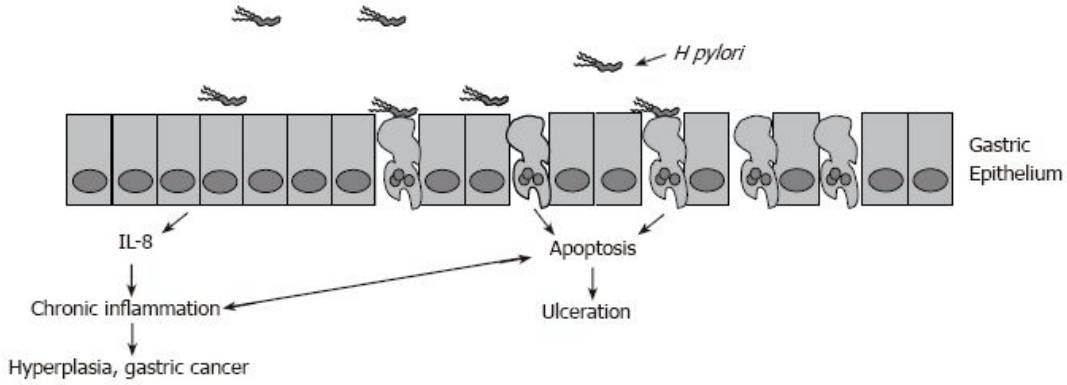


Figure 2 *H pylori* adheres to the gastric mucosa inducing cell death and chronic inflammation (Beswick et al 2006)

The causal link between the presence of *H pylori* infection and gastric cancer was established in 1991 by Parsonnet et al. Although 60-80 per cent of all gastric cancers are associated with *H pylori* infection, not all infected individuals will go on to develop cancer. It has been estimated that approximately 50 per cent of people world wide are infected with *H pylori*, however of these individuals, 10 per cent will develop gastric or duodenal ulcers and one per cent will develop gastric cancer (Beswick et al 2006; Walker et al 2008). When the 15-year outcomes of *H pylori* infected participants in the Parsonnet et al study were pooled with those from other studies, these individuals had a relative risk of 8.7 of developing gastric cancer (Roderick et al 2003a). In 1994, the World Health Organization and the International Agency for Research on Cancer declared the *H pylori* bacterium a class I carcinogen and although other risk factors for gastric cancer include high salt intake and low anti-oxidant consumption, it has been suggested that 60-80 per cent of gastric cancers could be prevented with the eradication of *H pylori* (Beswick et al 2006; Roderick et al 2003a; Walker et al 2008).

The factors that determine which individuals will go on to develop gastric cancer are determined by the host predisposition to infection, the genotype of the *H pylori* bacteria as well as environmental factors.

[1] NF-κB = nuclear factor kappa-light chain enhancer of activated B cells

In developing countries in Asia and South America, *H pylori* infection is associated with poor hygiene and high levels of infection (70-80% of *all* individuals are infected), and therefore rates of gastric cancer, are high. In Western countries, with improved hygiene, rates of *H pylori* infection have declined (United Kingdom 20% and United States 10% infection rates) and accordingly rates of *H pylori* associated gastric cancer have also declined (Walker et al 2008).

Several *H pylori* genes have been identified as candidate virulence factors in strains associated with causing gastric cancer. All strains of *H pylori* have the *vacA* gene, which is responsible for the formation of cytoplasmic vacuoles in gastric cells. However, not all strains induce vacuolation, indicating that there is a degree of genetic variation or polymorphism within the *vacA* gene. Two regions of this gene have been identified as being associated with gastric cancer: the signal (s) and the mid (m) region. In Western populations, gastric cancer is associated with *H pylori* strains carrying the *s1/m1* subtype of the *vacA* gene and is completely absent in individuals infected with strains expressing the *s2/m2* subtype (Ferreira et al 2008; Wen & Moss 2008). Two other genes, *cagA* and *cagPAI*[2], encode proteins associated with the development of gastric cancer. Although the *cagPAI* gene is important in the pathogenesis of *H pylori* it is only expressed in approximately 60 per cent of Western strains of the bacteria. Similarly, gastric cancer in Western populations is associated with *cagA*-positive rather than *cagA*-negative strains of *H pylori*. In addition, polymorphisms in the host genes encoding the pro-inflammatory interleukin-1 beta and interleukin-1 receptor antagonist have also been identified as factors associated with gastric cancer (Wen & Moss 2008). Polymerase chain reaction (PCR) may be used to accurately identify the *H pylori* genotype present in infected individuals and in so doing, more accurately predict those patients who are more likely to develop gastric cancer. However PCR is time consuming and as such is not currently used for routine *H pylori* diagnosis and is unlikely to be used for population screening (Megraud & Lehours 2007).

Many emerging therapies are being considered for the eradication of *H pylori*, however several of these therapies are currently unavailable in Australia. In Australia, recommended first and second line therapies include:

- 7 days triple therapy with proton pump inhibitors[3] (PPI), 500mg clarithromycin and 1000mg amoxicillin all twice daily;
- 7 days triple therapy with PPI, 500mg clarithromycin and 500mg metronidazole all twice daily;
- 14 days quadruple therapy with PPI twice daily, 120mg colloidal bismuth subcitrate, 500mg tetracycline and 400mg metronidazole all four times daily; or

[2] cag = cytotoxin-associated antigen
cagPAI = cytotoxin-associated antigen pathogenicity island

[3] Anti-ulcer medications which work by binding to H+/K+ ATPase, an enzyme which is found on the secretory surface of parietal cells. It inhibits the final transport of hydrogen ions (via exchange with potassium) into the gastric lumen. Examples of PPIs include omeprazole and lansoprazole.

- 10 days of therapy consisting of 5 days of PPI and 1000mg amoxicillin, followed by 5 days of PPI and 500mg clarithromycin all taken twice daily.

Recommended third line or salvage treatment for those who failed the above treatment options include:

- 14 days quadruple therapy with PPI and 200mg furazolidone twice daily, and 120mg bismuth subcitrate and 500mg tetracycline four times daily; or
- 14 days quadruple therapy with PPI, 1000mg amoxicillin, 150mg rifabutin and 500mg ciprofloxacin all taken twice daily (Stenström et al 2008).

Testing to ensure eradication of *H pylori* after treatment is recommended for patients with *H pylori* associated ulcers, those who have undergone resection for early gastric cancer, for those with *H pylori* associated MALT lymphoma or those with persistent dyspeptic symptoms. Treatment failure is often due to either poor patient compliance to the therapeutic regime or antibiotic resistance. It is also recommended that after two failed eradication attempts a sample of the infective *H pylori* strain should be collected and cultured for an antimicrobial sensitivity test. Using the results of this test, appropriate antibiotics may be chosen to successfully eradicate *H pylori* (Stenström et al 2008).

In Australia, the proven indications for the diagnosis and treatment of *H pylori* currently include:

- peptic ulcer disease (active or confirmed history);
- a test and treat strategy for patients with un-investigated dyspepsia who are <45 years of age without bleeding, anaemia, unexplained weight loss, progressive dysphagia, early satiety, recurrent vomiting, odynophagia, family history of gastric cancer or a previous oesophagogastric malignancy;
- low grade MALT lymphoma;
- after endoscopic resection of early gastric cancer; or
- first degree relative with gastric cancer (Stenström et al 2008).

Work is currently underway on the development of an *H pylori* vaccine (Vorobjova et al 2008). More interestingly, an Australian company is investigating the use of attenuated *H pylori* as a means of delivering vaccines against other organisms, including malaria and tuberculosis, due to its ability to adhere to and colonise the epithelial cells of the gut (Marshall & Schoep 2007).

The procedure

Although numerous diagnostic methods are available for the detection of *H pylori*, this Horizon Scanning report will focus on the use of the rapid, non-invasive stool antigen test. A number of these tests are currently available commercially, including monoclonal and polyclonal anti-*H pylori*-capture antibody enzyme immunoassays. Some authors have reported that the monoclonal stool antigen test for both the initial diagnosis and for the confirmation of *H pylori* eradication is superior to the polyclonal assays with a sensitivity and specificity of 93 and 96 per cent, respectively, compared to histology (Ricci et al 2007). In addition, rapid stool antigen tests may be either

an enzyme-linked immunosorbant assay (ELISA) or the newly developed immunochromatographic tests (ICTs) (Blanco et al 2008).

Stool antigen kits such as the monoclonal ImmunoCard STAT HpSA kit, an example of an ICT, require the collection of a stool sample, which may be stored at room temperature for 24 hours or for up to 72 hours at 4°C (Hirschl & Makristathis 2007). The ImmunoCard kit may be used on frozen samples and the kit itself should be stored at 2-8°C. A small stool sample (5-6mm) is transferred using an applicator stick into a diluent vial and vortexed for approximately 15 seconds. The tip of the diluent vial is then broken off to act as a dispenser and four drops are placed in the window at the lower end of the test strip (Figure 3).

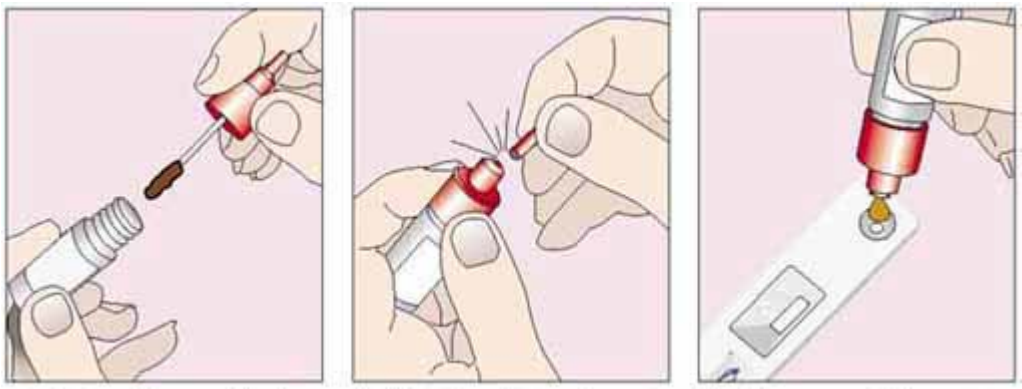


Figure 3 Sample preparation and use of the ImmunoCard STAT HpSA kit (Meridian Bioscience Europe 2009)

Results are available after a five minute incubation period with a single blue line indicating a negative result or an absence of *H pylori*, and a positive result, or presence of *H pylori* indicated by the presence of a blue land pink line (Figure 4). Each kit contains enough test strips for 20 samples as well as containing a positive control, allowing for batch testing of frozen samples (Meridian Bioscience Europe 2009). The Rapid HpStAR™ manufactured by Dako (Cambridge, UK) and the Certest, formerly known as Lettitest (Certest Biotec, Zaragoza, Spain) are ICTs similar to the ImmunoCard STAT HpSA kit.

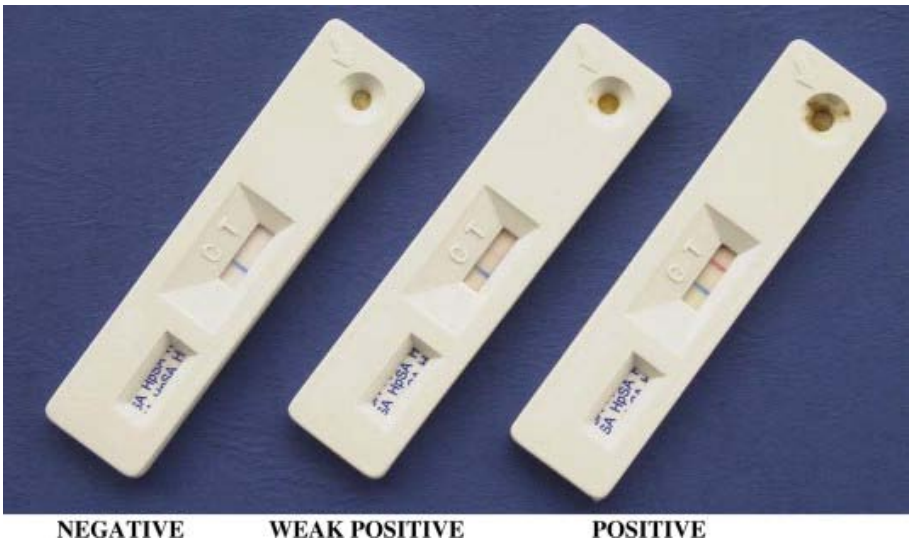


Figure 4 ImmunoCard Stat! HpSA stool antigen test (Ricci et al 2007)

Other stool antigen kits described in studies assessed in this Horizon Scanning report include the Premier Platinum HpSA kit (Meridian Bioscience Inc, Ohio, USA), the Amplified IDEIA Hp StAR kit (Dako, Cambridge, UK) and the Immunodiagnostik ELISA (Immunodiagnostik, Bensheim, Germany). These tests use the basic principles of ELISA assays: samples are prepared and dilated as required and added to an *H pylori*-antibody coated well in a micro-titre tray along with peroxidise-conjugated antibody. Plates are incubated at room temperature and unbound material is removed by washing. After the addition of an enzyme substrate the plates are incubated for a short period of time before a stop solution is added. Bound antigen-antibody complexes are indicated by a colour change detected by a spectrophotometer at a specific optical density (Chisholm et al 2004).

The stool antigen test has been proposed as an ideal tool for the testing of *H pylori* in children who may be unable to perform a urea breath test (Stenström et al 2008). Concerns have been raised about the performance of rapid stool antigen tests in populations with a low prevalence of *H pylori* infection. Positive predictive values (PPV) have been reported to be as high as 94-98 per cent in populations with high rates of *H pylori* infection (66%). In populations with a low prevalence of *H pylori* infection it has been estimated that the PPV could fall as low as 55-78 per cent. However, the study by Kuloğlu et al (2008) (see Effectiveness section) compared the effectiveness of the ICT test, Rapid Hp StAR of ascertaining *H pylori* infection in children pre- and post-eradication therapy and reported it to be as effective or better when measuring post-eradication infection, indicating that bacterial load may not be an issue when considering the use of a rapid stool antigen test. The diagnostic accuracy of this ICT test was 83 and 88 per cent pre- and post eradication therapy, respectively. The diagnostic accuracy of UBT in the same patient group was higher than the ICT diagnostic accuracy in both the pre-eradication (88%) and post-eradication patients (100%) (Kuloglu et al 2008).

It may be recommended in populations with a low prevalence of *H pylori* infection such as Australia and New Zealand that a positive stool antigen test is followed up by a urea breath test (Dzierzanowska-Fangrat et al 2006).

General practitioners may currently request a rapid stool antigen test be performed by pathology laboratories using the Medicare Benefits Schedule (MBS) item number 69494: For the detection of a virus or microbial antigen or microbial nucleic acid (Fee: $28.85 Benefit: 75% = $21.65 85% = $24.55). However, general practitioners are not eligible to claim an MBS rebate if this test is performed in a clinic setting. For point-of-care testing in a GP setting changes would need to be made to the MBS to allow clinicians to claim the MBS rebate for performing this test. Currently in Australia, the majority of pathology laboratories offer urea breath tests for the diagnosis of *H pylori* infection, with few laboratories offering HpSA tests (personal communication Medlab Diagnostics).

Intended purpose

Diagnostic tests

Rapid *H pylori* diagnostic tests are intended to provide a swift, accurate, non-invasive and inexpensive means of identifying individuals currently infected with *H pylori* which ideally would be able to be used in a point-of-care context in clinics or a general practitioner's office. Patients found positive by a rapid *H pylori* diagnostic test may require confirmation of diagnosis either by urea breath test or endoscopy, however for patients with suspected dyspepsia a "test and treat" strategy is recommended (Stenström et al 2008). Identification of *H pylori* positive patients may identify those at risk of developing gastric cancer.

Screening

The accepted criteria for the appraisal of the viability, effectiveness and appropriateness of population screening, as outlined by the UK Screening Committee, include, amongst others, the following points:

- the condition should be an important health problem;
- the natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage;
- there should be a simple, safe, precise and validated screening test;
- the test should be acceptable to the population;
- there should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals;
- there should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment;
- there should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public;
- the benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment) (NSC 2003).

Recommendations for or against a screening program are provided after consideration of the available evidence of the potential benefits of identifying and treating a health problem versus the cost and potential harms associated with the screening program, according to the above principles.

H pylori is a *necessary* but *not sufficient* causal factor for gastric cancer and therefore it has been suggested that a screening program for *H pylori* would be able to detect asymptomatic but infected individuals *before* they have developed atrophic gastritis. By treating these individuals with an appropriate antibiotic regime and eradicating the *H pylori* infection, it is anticipated that their risk of developing symptoms of dyspepsia, peptic ulcer disease or gastric cancer would be markedly reduced or eliminated. Thus a screening programme for *H pylori* would satisfy the majority of the above screening criteria, depending on the screening test used.

Population-based screening for gastric cancer is currently conducted in Japan, Korea and on Matsu Island in Taiwan, with annual reported prevalence rates of *H pylori* infection in these areas of 39, 54 and 54 per cent, respectively; however these countries have age-standardised rates of *H pylori* infection greater than 20 per 100,000. Australia and New Zealand have an estimated prevalence rate of *H pylori* infection of 38 per cent, and thus are considered to be low-risk countries for *H pylori* infection with an age-standardised incidence rate of *H pylori* infection of less than 10 per 100,000 (Fock et al 2008). Many authors consider that population screening in countries or regions of high-risk is worthwhile; however there is still some debate as to whether population or targeted screening for *H pylori* would be beneficial in low-risk countries (Fock et al 2008; Genta 2004; Leja & Dumitrascu 2007). The Maastricht III Guidelines recommend the testing for and the eradication of *H pylori* in individuals with symptoms of peptic ulcer disease and dyspepsia, in patients on non-steroidal anti-inflammatory drugs or long-term users of proton pump inhibitors (usually prescribed for symptoms of gastro-oesophageal reflux disease) and in first-degree relatives of patients diagnosed with gastric cancer (Leja & Dumitrascu 2007; Malfertheiner et al 2007). Inclusion of all these patient groups may constitute a large proportion of the population. Although the Maastricht III Guidelines do not recommend population screening in low-risk countries such as New Zealand and Australia, targeted screening for patients with symptoms of dyspepsia may be of benefit and *H pylori* eradication in these patients may reduce dyspepsia-related health care costs (Fock et al 2008). Concerns have been raised that a population test and treat strategy may result in increased antibiotic resistance (Fock et al 2008; Leja & Dumitrascu 2007).

Clinical need and burden of disease

Helicobacter pylori

The burden of *H pylori* infection within the population is difficult to ascertain as the majority of infections remain asymptomatic for long periods of time. A small cross-sectional study by Lin et al (1998) assessed the prevalence of *H pylori* in an Anglo-Celtic population in Melbourne. Subjects with Anglo-Celtic surnames were randomly selected from the telephone directory. Of a possible 1,042 subjects, 750 were contacted and 396 (53%) were considered eligible (aged between 20-80 years old and with both parents Caucasian). The response rate of eligible subjects was 69 per cent (n=273, mean age55.6 years). Subjects filled in a questionnaire which included demographic information and any experience of gastrointestinal symptoms. *H pylori* infection status was ascertained by an ELISA assay which detected *H pylori*-specific IgG antibodies. The overall sero-prevalence was 38 per cent. Sero-prevalence increased with age from 18 per cent in 20-30 years old (n=17) to 53 per cent in those >70 years old (n=45) ($p<0.0001$). Prevalence was higher in men (48%) than in women (30%) ($p<0.002$) and was associated with low-income ($p<0.0001$) and current smoking ($p=0.04$). Prevalence was not associated with a history of peptic ulcer disease (Lin et al 2004). However, it should be remembered that antibodies to *H pylori* can persist for long periods of time post-infection and therefore serological tests are not capable of distinguishing between an active *H pylori* infection and previous exposure to the bacterium.

This may result in a large number of false positives with patients receiving inappropriate treatment regimes (Dzierzanowska-Fangrat et al 2006; Hirschl & Makristathis 2007; Ricci et al 2007).

A later cohort study by Moujaber et al (2008) analysed a random number of serum samples (n=2,413) taken in 2002 from 37 diagnostic laboratories from around Australia using an *H pylori*-specific IgG ELISA. Samples were collected from individuals aged between 1 to 59 years old and samples were *not* stratified by racial origin. The overall sero-prevalence was 15.4 per cent (95% CI [13.9, 16.8]) and there was no statistical difference between genders. As with the study by Lin et al, sero-prevalence was found to increase with age ranging from four per cent in 1-4 years old to 23.3 per cent in those aged between 50-59 years. The lower sero-prevalence reported by Moujaber et al compared to that reported by Lin et al may be due to a difference in the sampled population or to a real decrease in the prevalence of *H pylori* in the community (Moujaber et al 2008).

A 2005 cross-sectional study by Windsor et al determined the prevalence of *H pylori* infection in two Western Australian Indigenous communities (Windsor et al 2005). Previous studies had established that *H pylori* infection was low in Indigenous communities despite well documented short-comings in health delivery to and the lower socio-economic status of these rural communities (Talley 2005). Fasting participants not on any antibiotic medication underwent a ^{13}C-urea breath test. A total of 520 participants from the different communities were studied (mean age 32.9 years, range 2-90 years). Of these, 250 subjects were recruited from an urban Perth community with a mean age of 35.6 years (range 3-75 years). The remaining 270 participants were recruited from Jigalong and the surrounding area, a rural and remote community 1,350 kms north-east of Perth. The mean age of this study group was 30.5 years (range 2-90 years). Overall, the prevalence of *H pylori* was 76 per cent with 395 of the 520 subjects having a positive breath test. Prevalence was higher in the remote community (91%) compared to the urban community (60%). The odds of being infected with *H pylori* in the rural group was six times greater than for those individuals living in the urban area (OR[4] 6.34; 95% CI [3.89, 10.33]), adjusted for age and sex. In addition, the odds of *H pylori* infection occurring in males was greater than for females (OR 1.61; 95% CI [1.02, 2.54], $p<0.001$). Unlike previous studies where prevalence increased with age, the prevalence of infection in both Indigenous communities remained constant after the age of 10 years. The high prevalence in both of these communities may support the screening of all indigenous children (Windsor et al 2005).

A large New Zealand birth cohort (n=1,037), recruited in Dunedin between 1972-73 was assessed at regular intervals up until the age of 26 years, with blood samples being taken at ages 21 and 26 years for *H pylori* testing. Of the total sample remaining at age 26 years (n=1,019), approval for blood sampling was gained for 882 participants (90%). Serum was stored frozen at -80°C until all samples could be analysed retrospectively using an *H pylori*-specific IgG ELISA. Sero-prevalence at age 21 years was 4.2 per cent (95% CI [2.7, 5.5]) and 6.3 per cent (95% CI [4.7, 7.9]) at age 26 years. The rates of sero-

[4] OR = odds ratio

conversion and sero-reversion[5] in individuals aged between 21 and 26 years were 0.53 and 0.11 per cent per person-year, respectively. Sixteen out of a possible 29 individuals sero-reverted from age 11 to 21 years, which was much higher than from age 21 to 26 years, when only one individual out of a possible 18 sero-reverted. In this cohort there was only a weak association with *H pylori* infection and low socio-economic status, however seropositivity was associated with lower educational attainment at 26 years of age (Fawcett et al 2005).

Dyspepsia and gastritis

In Australia in 2006-07 there were 15,440 hospital separations for dyspepsia (K30) and 46,930 hospital separations for gastritis and duodenitis (K29). These numbers do not indicate the actual number of patients and may include multiple hospital visits by the same patient. The average length of stay for each hospital separation was 1.0 and 1.3 days for dyspepsia and gastritis, respectively (AIHW 2009). In New Zealand during the period 2003-04, there were 643 public hospital separations for dyspepsia. Although the average length of stay was 1.8 days, 541 of these separations were day cases (data supplied by Analytical Services, New Zealand Ministry of Health).

Gastric cancer

MALT[6] lymphoma is a form of Non-Hodgkin's lymphoma; approximately eight per cent of all Non-Hodgkin's lymphomas are of the gastrointestinal MALT lymphoma type. *H pylori* has been established as the causative agent for the development of the gastric form due to the chronic inflammation associated with infection with the bacterium. It has been reported that 62 per cent of patients with low-grade MALT lymphoma will have complete remission within 12-months of *H pylori* eradication therapy (Kandulski et al 2008).

In Australia[7], there were 3,903 new cases of non-Hodgkin's lymphoma in 2005 with an age-standardised incidence rate of 18.4 per 100,000 (ICD-10 numbers C82-85, C96). There were 1,845 new cases of diffuse non-Hodgkin's lymphoma (C83). During 2006-07 there were 8,791 hospital separations for the same indication with an average length of stay of six days (AIHW 2009). In Australia during 2005, the age-standardised mortality rate from non-Hodgkin's lymphoma was 6.5 per 100,000, representing a total of 1,394 deaths (AACR 2008). In New Zealand in 2005[8], there were 694 new registrations of non-Hodgkin's lymphoma with an age-standardised incidence rate of 11.3 per 100,000 (ICD-10 numbers C82-85, C96). There were 335 new cases of diffuse non-Hodgkin's lymphoma (C83). In New Zealand during 2005, the age-standardised mortality rate from non-Hodgkin's lymphoma was 3.7 per

[5] Sero-conversion = the change of a serological test from negative to positive indicating the development of antibodies following an infection.
Sero-reversion = the change of a serological test from positive to negative.
[6] MALT = mucosa-associated lymphoid tissue
[7] Population of Australian at 30th June 2005 = 20,328,600 (http://www.abs.gov.au/)
[8] Population of New Zealand in 2005 = 4,100,600 (Analytical Services, New Zealand Ministry of Health

100,000, representing a total of 263 deaths (data supplied by Analytical Services, New Zealand Ministry of Health).

The majority of gastric malignant tumours are adenocarcinomas, classified as either intestinal or diffuse subtypes. The intestinal subtype is thought to develop slowly after acquisition of *H pylori* infection and is caused by chronic inflammation followed by atrophic gastritis and the development of intestinal metaplasia. The epithelium may undergo further changes in some individuals, resulting in the development of gastric dysplasia and finally gastric adenocarcinomas. Intestinal adenocarcinoma is the dominant subtype in countries with a high prevalence, increases significantly with age and is more common in males. The diffuse subtype may develop in the absence of atrophic gastritis, more commonly affects females and occurs in younger patients (Kandulski et al 2008; Lochhead & El-Omar 2008). Gastric adenocarcinomas may arise in the cardia region of the stomach and are referred to as proximal, and those carcinomas arising in the non-cardia region are referred to as distal (Lochhead & El-Omar 2008).

In Australia in the year 2005, there were 1,904 new cases of stomach cancer (C16) with an age-standardised incidence rate of 9.0 per 100,000. During 2006-07 there were 5,669 hospital separations for the same indication with an average length of stay of 7.2 days (AIHW 2009). In Australia during 2005, the age-standardised mortality rate from cancer of the stomach was 5.1 per 100,000, representing a total of 1,089 deaths (AACR 2008). In New Zealand in the year 2005, there were 341 new registrations of stomach cancer with an age-standardised incidence rate of 5.2 per 100,000. In New Zealand during 2005, the age-standardised mortality rate from stomach cancer was 3.7 per 100,000, representing a total of 256 deaths (data supplied by Analytical Services, New Zealand Ministry of Health). Maori and Pacific Islanders are at higher risk of gastric cancer (Fraser 2004).

Stage of development

Stool antigen tests

Stool antigen tests for the detection of *H pylori* infection are currently in limited use in Australia. Approval from Therapeutic Goods Administration of Australia is not required for the use of these diagnostic kits in a clinical setting. The uptake of this technology is likely to be reflected by the number of carbon-labelled urea breath tests (UBT) performed for patients presenting with symptoms of dyspepsia or peptic ulcer disease. The Medicare Benefits Schedule allows carbon-labelled urea breath tests to be performed to confirm *H pylori* colonisation or to monitor the success of *H pylori* eradication (item number 12533, fee $78.15). Australia-wide, the total number of services performed using this item number in the period January 2008 until December 2008 was 110,381, with the majority performed in New South Wales (58,266) (Medicare Australia 2009). The number of investigational endoscopies may also reflect the possible uptake of this technology, however endoscopies may be performed for several reasons and therefore the number of endoscopies performed would not be informative.

Screening for *H pylori*

Population or targeted population screening for *H pylori* infection is not currently carried out in Australia or New Zealand. Population-based screening for *H pylori*, as a means of screening for gastric cancer is currently conducted in Japan, Korea and on Matsu Island in Taiwan.

Existing comparators

Several methods are currently available for the diagnosis of *H pylori* and may be classified as either invasive: culture; histology; rapid urease test; or molecular tests, or non-invasive: urea breath test; stool antigen tests; or serology (Hirschl & Makristathis 2007). Most *H pylori* diagnostic tests, with the exception of the stool antigen test, require the cessation of treatment before testing is conducted. Antibiotics and bismuth use should cease four weeks prior to a rapid urease test or a urea breath test and proton pump inhibitors should cease one week prior to testing (Stenström et al 2008). The advantage of the stool antigen test is that antibiotic and PPI treatment may continue up to testing and that the test may be used to track the efficacy of treatment (personal communication, University of Sydney).

Invasive tests

Histopathology performed on biopsy specimens obtained by endoscopy was the original method used by Marshall and Warren to detect *H pylori* and is considered the *gold standard* for confirmation of *H pylori* infection. Sections of biopsy obtained tissue are made and stained with silver stain, Giemsa, haematoxylin eosine, Genta, toluidine blue or monoclonal antibodies to visualise the presence of *H pylori*. The results of histopathology are, however, highly dependent on the site of sample collection and biopsy specimens obtained from the greater curvatures of the middle body or the mid antrum appear to be more suitable for the detection of *H pylori* (Hirschl & Makristathis 2007). *In-situ* hybridisation with biotinylated probes and polymerase chain reaction (PCR) may also be conducted on biopsy samples or archival histology samples to ascertain virulence factors or clarithromycin resistance. The disadvantage of using PCR for the detection of *H pylori* compared to culture, histology and the rapid urease tests is that it is technically demanding and expensive. It is also highly sensitive and therefore may be subject to false-positive results by contamination. A further drawback is that a positive PCR result may not indicate a current infection as the DNA of dead organisms may be detected (Ricci et al 2007).

H pylori culture requires an endoscopy and the results can be highly variable depending on the conditions of transportation and sample processing. Culture of *H pylori* may be difficult to perform due to the bacterium's slow rate of growth and the rigorous conditions required for growth. Although the results of culture are highly specific, this technique tends to be used only in instances where the determination of antibiotic resistance or sensitivities needs to be ascertained, however culture may be useful in conjunction with PCR to identify specific subtypes or strains of *H pylori*. Some authors have reported instances of successful culture from biopsies (Granstrom et al 2008; Hirschl & Makristathis 2007; Stenström et al 2008).

The rapid urease test involves a gastric biopsy obtained by endoscopy. The most common commercially available test used is the CLOtest®, which is gel-based, however other paper-based (PyloriTek, ProntoDry HpOne) and liquid-

based (CPtest, EndoscHp) tests are available. The principle of the rapid urease test is the detection of *H pylori* urease enzyme activity in the biopsy sample by the conversion to ammonia, which increases the pH and is detected by the indicator phenol red (Figure 5). A yellow result indicates an absence of *H pylori*, with a pink result indicating the presence of *H pylori* in the biopsy sample. Test results may be obtained within 1-24 hours, depending on the number of *H pylori* present in the biopsy sample. All commercially available rapid urease tests have specificities ranging from 95-100 per cent and sensitivities between 85-95 per cent when compared to conventional histology. Low sensitivities are reported in patients with bacterial loads of less than 10^4 organisms (Ricci et al 2007).

Figure 5 The CLOtest indicating yellow for a negative and pink for a positive presence of *H pylori* (Trawax Pty Ltd 2009)

Non-invasive tests

The carbon-labelled (^{13}C or ^{14}C) urea breath test (UBT) was approved for public funding by the Medical Services Advisory Committee as a first line procedure for the detection of *H pylori* infection in June 2006 (MBS item number 12533, fee $78.15) (Johnston et al 2006). As with the rapid urease test, the UBT is based on the principle that the presence of *H pylori* in the stomach will result in urease activity, which will hydrolyse urea to form ammonia and bicarbonate. Patients ingest a carbon-labelled urea and if *H pylori* is present hydrolysis takes place and labelled CO_2 enters the blood stream before being exhaled by the lungs. Breath samples are collected into a CO_2 trapping agent for up to 20 minutes post-ingestion. If ^{14}C, a radioisotope, is used, detection requires a scintillation counter, whereas the use of the non-radioactive ^{13}C requires the use of a mass spectrometer or infra-red spectrometry. The sensitivity and specificity of the UBT, compared to histology, is high, ranging from 95-97 per cent (Ricci et al 2007). False positive results may occur when other urease-producing bacteria colonise the oral cavity or stomach (Johnston et al 2006).

Several serological tests are available, the most common of which is the enzyme-linked immunosorbent assay (ELISA). Most serological tests are based on the detection of specific anti-*H pylori* IgG antibodies in a patient's serum, however some test for the presence of IgA antibodies in saliva.

Serological tests require no specialised equipment and can be performed by most routine pathology laboratories. In addition, they are relatively inexpensive to perform. Depending on the population tested, reported sensitivities range from 90-97 per cent and specificity between 50 and 96 per cent when compared to histology. However, antibodies to *H pylori* can persist for long periods of time and therefore serological tests are not capable of distinguishing between an active *H pylori* infection and previous exposure to the bacterium. This may result in a large number of false positives with patients receiving inappropriate treatment regimes (Dzierzanowska-Fangrat et al 2006; Hirschl & Makristathis 2007; Ricci et al 2007).

The use of serum pepsinogen has also been investigated as a predictive marker of gastric mucosa disease. Pepsinogen is a precursor to the enzyme, pepsin which is produced in the stomach for the breakdown of ingested protein. Pepsinogen I and II (PGI/II) are produced by the gastric mucosa and although they are mainly excreted into the stomach lumen, approximately one per cent will diffuse into the blood stream and can be measured. Several studies have demonstrated that levels of PGII correlate with *H pylori* associated gastric inflammation in both the antrum and corpus (body) of the stomach, with levels increasing with the severity of inflammation. PGI levels are reduced when inflammation is localised in the corpus of the stomach (Figure 6) (di Mario & Cavallaro 2008; Dzierzanowska-Fangrat et al 2006). The ratio of PGI/PGII may be used as an indicator of gastric mucosa health, with the ratio decreasing with a progression from normal gastric mucosa to gastric mucosal atrophy. Cut-off ratio levels will vary from population to population depending on the prevalence of gastric mucosal disease. Testing for pepsinogen is relatively inexpensive and can be determined with the use of several immunoassays currently commercially available. Several authors have suggested that first – line population screening with pepsinogen assays would be a cost-effective method of identifying individuals at high-risk of *H pylori* infection, who may then be screened with more rigorous second-line diagnostic tests such as the UBT to confirm *H pylori* infection (Miki 2006).

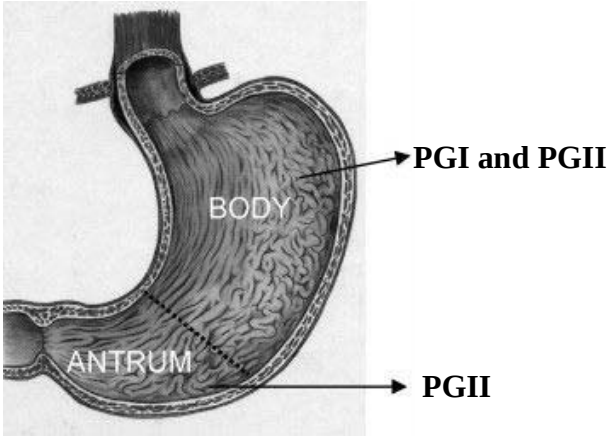


Figure 6 Site of pepsinogen secretion in the stomach (di Mario & Cavallaro 2008)

Clinical outcomes: *H pylori* diagnostic tests

A total of 173 *H pylori* diagnostic studies were identified in the stipulated search period. Due to the time restrictions placed on the writing of Horizon Scanning reports, exclusion criteria have been applied to these identified studies. Although a number of methods are available for the determination of *H pylori* infection, this Horizon Scanning report will focus on the use of rapid *H pylori* stool antigen (HpSA) tests. Forty-eight papers were identified in the 5-year search period, which reported on the use of HpSA tests. Even though ^{13}C or ^{14}C urea breath tests were approved for listing on the MBS schedule in 2006, histological results obtained via endoscopy are considered the gold or reference standard. Therefore only studies which describe the results of HpSA tests compared to endoscopy were included for analysis in this report. In addition, the prevalence of *H pylori* infection may affect the sensitivity, specificity and predictive values of a diagnostic test. Only studies conducted in developed countries with a similar population and demographic structure, and likely disease prevalence, as Australia and New Zealand were considered for inclusion.

Safety

Rapid HpSA tests are non-invasive and appear to be a safe diagnostic tests. None of the studies included for assessment reported any adverse events associated with the use of HpSA tests, however the potential harms of rapid HpSA tests when used for the diagnosis of *H pylori* infection arise from the number of false positives (patients receiving unnecessary antibiotic treatment and possibly further invasive confirmatory testing) and false negatives (patients receiving no treatment when they are in fact positive for *H pylori* infection).

Effectiveness

A total of seven studies assessing the effectiveness of rapid stool antigen HpSA were identified for inclusion in this assessment (Table 1). Three studies reported on the use of immunochromatographic (ICT) HpSA tests, two in adult populations with gastrointestinal symptoms (Demiray et al 2006; Krausse et al 2008) and one in children with non-specific abdominal symptoms (Kuloglu et al 2008). Two studies reported on the use of rapid ELISA HpSA tests both in adult populations with symptoms of dyspepsia (Adiloglu et al 2007; Calvet et al 2009). Two studies reported on the use of both ICT and ELISA HpSA tests. One of these studies was conducted on an adult population with various gastrointestinal symptoms (Blanco et al 2008). The remaining study was a low quality meta-analysis which combined studies conducted on adults and children (Gisbert et al 2006).

Effectiveness measure summarised in Table 2 varied widely not only between ICT and ELISA HpSA tests but also within the two different classes of tests.

ICT HpSA tests

Of the ICT HpSA tests, the most sensitive (those tests correctly identifying patients with *H pylori* infection), compared to the reference standard histology, was the Lettitest (83.8 %) (Blanco et al 2008). Although Krausse etal (2008) did report the sensitivity of the Rapid HpStAR as 100 per cent, this was only in patients ≤45 years old. Sensitivity was lower (72.7%) in patients >45 years and no overall sensitivity value was reported (level II diagnostic evidence).

The most specific (those tests correctly identifying patients without *H pylori* infection) ICT HpSA test was the Rapid Hp StAR test (90.9-100%), with the exception of the 55.5 per cent reported by Blanco et al (2008) (level III-2 diagnostic evidence).

Overall, accuracy of the ICT HpSA tests ranged between 50-93.3 per cent. The Rapid Hp StAR test appeared to perform better than other tests with three studies reporting an accuracy ranging from 74.5 to 93.3 per cent. Of concern is the high number of false negatives, ranging from 16.3 to 66.7 per cent, that occurred with the use of the majority of the ICT HpSA tests. However, the majority of studies using ICT HpSA tests reported low false positive numbers, indicating that a relatively small number of patients would receive inappropriate treatment. Blanco et al (2008) reported false positive values of 44.4 and 33.3 per cent for the Rapid Hp StAR and Lettitest tests, respectively, whilst other authors reported false positive values ranging from zero to 14.3 per cent.

Only the study by Kuloğlu et al (2008) compared the effectiveness of the ICT test, Rapid Hp StAR, to the reference standard of histology when ascertaining *H pylori* infection in children pre- and post-eradication therapy (level III-1 diagnostic evidence). The Rapid Hp StAR ICT test appeared to be as effective or better when measuring post-eradication infection, indicating that bacterial load may not be an issue when considering the use of a rapid stool antigen test. The diagnostic accuracy of this ICT test was 83 and 88 per cent pre- and post eradication therapy, respectively. However when UBT was used diagnostic accuracy was higher in both the pre-eradication (88%) and post-eradication patients (100%).

ELISA HpSA tests

Overall, reported sensitivity values were consistently higher for the ELISA HpSA tests compared to the ICT HpSA tests. Of the ELISA HpSA tests, the most sensitive was the Amplified IDEIA HpStAR test, with sensitivity values of 95 and 90.3 per cent reported by Blanco et al (2008) and Calvet et al (2009), respectively (level III-2 and III-1 diagnostic evidence, respectively). Only the study by Adiloglu et al (2007) reported a low sensitivity value (51.1%) using the optical density cut-off value as recommended by the manufacturer of the Premier Platinum HpSA kit (level III-2 diagnostic evidence). However, a “best cut-off” optical density was determined by receiver operating characteristic (ROC) curve analysis and sensitivity increased to 92 per cent, almost identical to the sensitivity reported by Blanco et al using the same kit (92.5%). Excluding the first analysis by Adiloglu et al, sensitivity of the ELISA HpSA tests compared to histology ranged from 87.3 to 95 per cent. The most specific ELISA HpSA test compared to histology was the Premier Platinum HpSA kit

(100%) in the hands of Adiloglu et al (2007), regardless of cut-off value used. Specificity of ELISA HpSA tests compared to histology ranged from 66.6 to 100 per cent. Diagnostic accuracy of the ELISA HpSA tests was also consistently higher when compared to the ICT HpSA tests, ranging from 86.6 to 92.6 per cent when the first analysis by Adiloglu et al is excluded.

Both ICT and ELISA HpSA tests

The meta-analysis conducted by Gisbert et al (2006) compared the use of HpSA tests to at least one other independent diagnostic method including endoscopy/ histology, UBT, serology, rapid urease test or culture. Although six of the 22 studies compared the results of HpSA tests to either serology, RUT and/or a UBT and *not* to histology, this meta-analysis was still included for assessment as it summarised a large number of studies. Sixteen of the studies compared HpSA tests to histological samples obtained by endoscopy. Of the 22 studies included in the meta-analysis, 13 assessed samples with tests which used both monoclonal and polyclonal antibodies, and nine studies used diagnostic kits which used monoclonal antibodies alone. None of the included studies used a polyclonal antibody test alone. Five of the included studies assessed samples obtained from children and the remaining 17 assessed adult patients. The meta-analysis also included the results from 12 studies which assessed *H pylori* status after eradication therapy, however only two used histology as a reference standard and therefore these results were not included for assessment.

Specificity and sensitivity values for all of the included studies are provided in Appendix C. The authors did conduct separate analyses excluding those studies that did not use histology as the gold standard and stated that the results were similar; however these results were not reported. The raw data from each study was provided in the paper, however due to the time constraints of writing an HS report, a meta-analysis by the evaluators of the 16 relevant comparative studies was not possible. The I-squared statistic for heterogeneity for sensitivity and specificity was 61 and 58 per cent, respectively, indicating a high degree of heterogeneity among the combined studies. This heterogeneity may reflect the combination of studies conducted on populations of children and adults. The authors reduced the I^2 statistic by the exclusion of outlier studies: Ignys et al in the I^2 calculation for sensitivity and Calvet et al in the I^2 calculation for specificity. For completeness these two studies should have been removed from *both* sensitivity and specificity I^2 calculations.

When all 22 studies were pooled the sensitivity of the HpSA tests was high at 94 per cent (range 68-99%, 95% CI [93, 95]) and the pooled specificity was excellent at 97 per cent (range 76-100%, 95% CI [96, 98]). Sensitivity and specificity were overall very high when the 16 studies which used histology as the gold standard were considered. Apart from the outlier of Ignys et al (69%), sensitivity of HpSA tests when compared to histology ranged from 88 to 98 per cent. Similarly, apart from the study by Calvet et al (76%), specificity of HpSA tests when compared to histology ranged from 90 to 100 per cent.

In summary, effectiveness results vary according to whether an ICT or ELISA HpSA test is used to detect *H pylori* infection. A direct comparison of results

is difficult to make due to the variation in brand of HpSA test used and the populations they were used on (e.g. adult vs child and differing gastro-intestinal symptoms). The ELISA tests appear to be more sensitive, however these assays are more time intensive and require the use of a laboratory based spectrophotometer. Although ICT HpSA tests can provide a rapid point-of-care diagnosis, the trade-off with the use of these tests is a decrease in sensitivity and diagnostic accuracy, which may result in patients receiving unnecessary treatment. The decision regarding which test to use needs to weigh up which of these factors is of greatest importance.

Table 1 Rapid stool antigen tests for the diagnosis of *H pylori* infection

Study	Diagnostic level of evidence	Study design	Population	Outcomes
Immunochromatographic (ICTs) HpSA tests				
Demiray et al (2006)	III-2	Cross classification of Rapid STRIP!HpSA and *H pylori* antigen cassette ICT HpSA tests compared to histology, RUT, UBT. Patients were considered positive for *H pylori* infection if UBT was positive or both RUT and histopathology were positive. Patients were considered negative if both RUT and histology were negative.	22 patients with upper gastro-intestinal bleeding, mean age 58 ± 18 years (range 20-86 years).	15/22 (68.2%) positive for *H pylori* infection by reference standard ICT HpSA tests Rapid STRIP!HpSA Sensitivity 9/15 (60%) Specificity 6/7 (86%) PPV 9/10 (90%) NPV 6/12 (50%) Accuracy 15/22 (68.2%) False positive 1/7 (14.3%) False negative 6/15 (40%) *H pylori* Antigen cassette Sensitivity 5/15 (33%) Specificity 6/7 (86%) PPV 5/6 (83%) NPV 6/16 (38%) Accuracy 11/22 (50.0%) False positive 1/7 (14.3%) False negative 10/15 (66.7%)
Krausse et al (2008)	II	Cross classification of Rapid Hp StAR ICT test compared to histology, RUT and culture. Patients were considered positive for *H pylori* infection if 1/3 reference standards were positive.	72 consecutive patients, mean age 58.4 ± 12 years (range 24-88 years), with gastrointestinal symptoms.	28/72 (38.9%) positive for *H pylori* infection by reference standard Age of patient Prevalence ≥65 years 46.7% 45-64 years 35.7% ≤45 years 31.3% ICT Rapid Hp StAR test 5/72 (6.9%) tests invalid Stratified according to age % ≤45yrs >45yrs Sensitivity 100 72.7 Specificity 90.9 80.0 PPV 80.0 72.7 NPV 100 80.0 Accuracy 93.3 76.9 Stratified according to diagnosis % Gast n=21 GU + DU n= 8 Norm n=38 Sens 70.0 71.4 88.9 Spec 90.9 100 79.3 PPV 87.5 100 57.1 NPV 76.9 33.3 95.8 Acc 81.0 75.0 81.6

HpSA = *H pylori* stool antigen tests, ELISA = enzyme-linked immunosorbant assay, ICT = immunochromatographic test, PPV = positive predictive value, NPV = negative predictive value, Gast = gastritis, GU + DU = gastric ulcer plus duodenal ulcer, Norm = normal mucosa

Kuloğlu et al (2008)	III-1	Cross classification of Rapid Hp StAR ICT test and UBT compared to histology. Patients were considered positive for *H pylori* infection if 1/3 reference standards were positive.	109 children and adolescents with abdominal symptoms, mean age 12.1 ± 3.1 years (range 5-17 years). N=25 <10 yrs n=84 ≥10 yrs	40/109 (36.6%) positive for *H pylori* infection by reference standard ICT Rapid Hp StAR test pre-therapy All ages % [95% CI] Sensitivity 65 [45.9, 77.8] Specificity 92.3 [84.1, 96.8] PPV 84 [75.3, 88.5] NPV 82 [73.2, 88.5] Accuracy 83% False positive 5/69 (7.2%) False negative 14/40 (35.0%) < 10 years % [95% CI] Sensitivity 67 [35.4, 87.9] Specificity 88 [63.9, 96.5] PPV 75.4 [53.4, 93.8] NPV 82.2 [61.2, 93.8] Accuracy 80% False positive 2/16 (12.5%) False negative 3/9 (33.3%) ≥ 10 years % [95% CI] Sensitivity 65 [46.9, 78.8] Specificity 94 [84.6, 98.1] PPV 87 [77.4, 93.1] NPV 82 [71.7, 89.2] Accuracy 83% False positive 3/53 (5.7%) False negative 11/31 (35.5%) UBT pre-eradication therapy All ages % [95% CI] Sensitivity 92.5 [80.2, 97.4] Specificity 85.5 [73.3, 91.9] PPV 79.3 [69.6, 85.7] NPV 95 [88.7, 98.1] Accuracy 88% False positive 10/69 (14.5%) False negative 3/40 (7.5%) < 10 years % [95% CI] Sensitivity 100 [70, 100] Specificity 94 [71.6, 98.8] PPV 90 [70, 97.8] NPV 100 [83.4, 99.6] Accuracy 96% False positive 1/16 (6.25%) False negative 0/9 (0.0%) ≥ 10 years % [95% CI] Sensitivity 90 [75.1, 96.6] Specificity 83 [70.7, 90.8] PPV 76 [64.8, 84.1] NPV 94 [85.4, 97.5] Accuracy 86% False positive 9/53 (17.0%) False negative 3/31 (9.7%)

Kuloğlu et al (2008) cont				Post-eradication therapy (n=17) ICT Rapid Hp StAR % [95% CI] Sensitivity 60 [23.1, 88.2] Specificity 100 [75.5, 100] PPV 100 [77.1, 99.4] NPV 86 [59.4, 96.9] Accuracy 88% False positive 0/12 (0.0%) False negative 2/5 (40.0%) UBT % [95% CI] Sensitivity 100 [56.5, 100] Specificity 100 [75.5, 100] PPV 100 [77.1, 99.4] NPV 100 77.1, 99.4] Accuracy 100% False positive 0/12 (0.0%) False negative 0/5 (0.0%)
ELISA HpSA tests				
Adiloglu et al (2007)	III-2	Cross classification of Premier Platinum HpSA ELISA compared to histology and RUT. Patients were considered positive for *H pylori* infection if both histology and RUT were positive.	102 consecutive patients with symptoms of dyspepsia for at least 3 months. Mean age 43.6 ± 14.2 years (range 19-73 years).	88/102 (86.3%) positive for *H pylori* infection by urease and histology reference standards. 7/102 (6.9%) were histology negative and urease positive and were excluded from analysis. Premier Platinum HpSA ELISA Manufacturer's cut-off OD 0.16 Sensitivity 45/88 (51.1%) Specificity 7/7 (100%) PPV 45/45 (100%) NPV 7/50 (14%) Accuracy 52/95 (54.7%) False positive 0/7 (0.0%) False negative 43/88 (48.9%) Best cut-off OD 0.048 Sensitivity 81/88 (92%) Specificity 7/7 (100%) PPV 81/81 (100%) NPV 7/14 (50.0%) Accuracy 88/95 (92.6%) False positive 0/7 (0.0%) False negative 7/88 (8.0%)

HpSA = *H pylori* stool antigen tests, ELISA = enzyme-linked immunosorbant assay, ICT = immunochromatographic test, PPV = positive predictive value, NPV = negative predictive value

Calvet et al (2009)	III-1	Cross classification of Amplified IDEIA™ Hp StAR ELISA HpSA test compared to histology, RUT, UBT. Patients were considered positive for *H pylori* infection if 2/3 reference standards were positive.	209 patients with symptoms of dyspepsia. Mean age 48.2 ± 14.2 years.	10/209 (4.8%) patients had incomplete analysis of samples and were therefore excluded. 118/199 (59.3%) positive for *H pylori* infection by reference standard IDEIA Hp StAR % [95% CI] Sensitivity 90.3 [83, 95] Specificity 93 [84, 97] PPV 94.4 [88, 98] NPV 87.9 [79, 94] Accuracy 182/199 (91.5%) LR+ve 12.9 LR-ve 0.104 False positive 6/86 (7.0%) False negative 11/113 (9.7%) UBT % [95% CI] Sensitivity 90.3 [83, 95] Specificity 89.5 [81, 95] PPV 91.9 [83, 95] NPV 87.5 [78, 93] Accuracy 179/199 (89.9%) LR+ve 8.6 LR-ve 0.108 False positive 9/86 (10.4%) False negative 11/113 (9.7%)
Both ICT and ELISA HpSA tests				
Blanco et al (2008)	III-2	Cross classification of Premier Platinum HpSA EIA, Immunodiagnostik ELISA, Amplified, IDEIA™ HpStAR HpSA ELISA tests and *H pylori* Letitest, ImmunoCard STAT! HpSA, Rapid HpStAR™ ICT HpSA tests compared to histology, RUT, UBT. Patients considered positive for *H pylori* infection if 2/3 reference standards were positive.	98 adult patients with duodenal ulcer (39%), gastric ulcer (7.5%), erosive duodenitis (6.3%), erosive gastritis (6.3%), non-erosive antral gastritis (12.5%) and hiatus hernia (5%). Mean age of 80 *H pylori* positive patients 52.2 ± 20.2 years. Mean age of 18 *H pylori* negative patients 48.5 ± 18.4 years	80/98 (81.6%) positive for *H pylori* infection by reference standard ICT HpSA tests Letitest Sensitivity 67/80 (83.8%) Specificity 12/18 (66.6%) PPV 67/73 (91.8%) NPV 12/25 (48.0%) Accuracy 79/98 (80.6%) False positive 6/18 (33.3%) False negative 13/80(16.3%) ImmunoCard Sensitivity 42/80 (52.5%) Specificity 17/18 (94.4%) PPV 42/43 (97.7%) NPV 17/55 (30.9%) Accuracy 59/98 (60.2%) False positive 1/18 (5.6%) False negative 38/80 (47.5%) RAPID HpStAR Sensitivity 63/80 (78.8%) Specificity 10/18 (55.5%) PPV 63/71 (88.7%) NPV 10/27 (37.0%) Accuracy 73/98 (74.5%) False positive 8/18 (44.4%) False negative 17/80 (21.3%)

				ELISA HpSA tests Immunodiagnostik Sensitivity 69/79 (87.3%) Specificity 15/18 (83.3%) PPV 69/72 (95.8%) NPV 15/25 (60%) Accuracy 84/97 (86.6%) False positive 3/18 (16.7%) False negative 10/79 (12.7%) Premier Platinum Sensitivity 74/80 (92.5%) Specificity 13/18 (72.2%) PPV 74/77 (96.1%) NPV 15/21 (71.4%) Accuracy 89/98 (90.8%) False positive 3/18 (16.7%) False negative 6/80 (7.5%) Amplified IDEIA Sensitivity 76/80 (95.0%) Specificity 12/18 (66.6%) PPV 76/82 (92.7%) NPV 12/16 (75.0%) Accuracy 88/98 (89.8%) False positive 6/18 (33.3%) False negative 4/80 (5.0%)
Gisbert et al (2006)	IV	Meta-analysis of 22 studies. Cross classification HpSA tests compared to one or all of the following: endoscopy (histology), RUT, UBT, serology or culture. Studies used monoclonal and polyclonal (n= 13) or monoclonal alone (n=9) HpSA tests. One included study pre-selected patient samples post-endoscopy to be positive for *H pylori* (diagnostic yield study).	22 studies conducted on a European population. 5 studies conducted on children with remaining 17 studies conducted on adults.	16 studies with a total of 1,934 patients. Only studies which compared HpSA tests to the gold standard histology are included. Sensitivity range 69% [54, 81] to 98% [90, 100] Specificity range 76% [53, 92] to 100% [92, 100] 22 studies with a total of 2,499 patients, including studies which compared HpSA tests to non-gold standard RUT and UBT *H pylori* infection Mean prevalence of infection was 62% (range 28-100%) Sensitivity of HpSA test Range 0.68 to 0.99 (I^2 statistic* 61%) Pooled sensitivity [95% CI] 0.94 [0.93, 0.95] χ^2 = 53.64 (p=0.0001) Specificity of HpSA test Range 0.76 to 1.00 (I^2 statistic 58% Pooled specificity [95% CI] 0.97 [0.96, 0.98] χ^2 = 36.27 (p=0.0016)

HpSA = *H pylori* stool antigen tests, ELISA = enzyme-linked immunosorbant assay, ICT = immunochromatographic test
I^2 statistic – see glossary, PPV = positive predictive value, NPV = negative predictive value, LR+ve = positive likelihood ratio, LR-ve = negative likelihood ratio

Table 2 Summary of effectiveness measures of HpSA kits

	Population: Adult (A), Children (C)	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Acc (%)	FP (%)	FN (%)
ICT HpSA tests								
RAPID Hp StAR [1]	A (n=72)*	100, 72.7*	90.9, 80.0*	80.0, 72.7*	100, 80.0*	93.3, 76.9*		
	C (n=109)**	65.0, 60.0**	92.3, 100**	84.0, 100**	82.0, 86.0**	83.0, 88.0**	7.2, 0.0**	35.0, 40.0**
	A (n=98)	78.8	55.5	88.7	37.0	74.5	44.4	21.3
ImmunoCard STAT! HpSA [2]	A (n=98)	52.5	94.4	97.7	30.9	60.2	5.6	47.5
RapidSTRIP!HpSA [3]	A (n=22)	60.0	86.0	90.0	50.0	68.2	14.3	40.0
H pylori Antigen cassette [4]	A (n=22)	33.0	86.0	83.0	38.0	50.0	14.3	66.7
Lettitest	A (n=98)	83.8	66.6	91.8	48.0	80.6	33.3	16.3
Range		33.0-100	55.5-100	72.7-100	30.9-100	50-93.3	0.0-44.4	16.3-66.7
ELISA HpSA tests								
Amplified IDEIA Hp StAR [5]	A (n=98)	95.0	66.6	92.7	75.0	89.8	33.3	5.0
	A (n=199)	90.3	93.0	94.4	87.9	91.5	7.0	9.7
Premier Platinum HpSA [6]	A (n=98)	92.5	72.2	96.1	71.4	90.8	16.7	7.5
	A (n=102)***	51.1, 92***	100, 100***	100, 100***	14.0, 50.0***	54.7, 92.6***	0.0, 0.0***	48.9, 8.0***
Immunodiagnostik [7]	A (n=98)	87.3	83.3	95.8	60	86.6	16.7	12.7
Range		51.1-95	66.6-100	92.7-100	14.0-87.9	54.7-92.6	0.0-33.3	5.0-48.9
ICT and ELISA HpSA tests								
Meta-analysis	A + C (n=1,934)	range 69-98	range 76-100					

HpSA = *H pylori* stool antigen tests, Sens = sensitivity, Spec = specificity, ELISA = enzyme-linked immunosorbant assay, ICT = immunochromatographic test, PPV = positive predictive value, NPV = negative predictive value, Acc = accuracy, FP = false positive, FN = false negative, * Stratified according to age: first value ≤45 years, second value >45 years, ** Second values are post-eradication therapy, *** Study used 2 different optical density cut-off values for reading final results: first value = manufacturer's recommended cut-off, second value: best cut-off value (***)

1. DakoCytomation, Cambridge (UK), 2. Meridian Biosciences Inc (USA), 3. Meridian Biosciences Inc (USA), 4. Linear Chemicals (Spain), 5. Thermo Fischer Scientific (USA), 6. Meridian Biosciences Inc (USA), 7. Immunodiagnostik (Germany).

Potential cost impact: *H pylori* diagnostic tests

Cost Analysis

To perform an immunochromatographic HpSA test requires no infrastructure or specialised equipment, just the kit itself. To perform an ELISA HpSA test, samples need to be sent to a pathology laboratory that has access to an ELISA reader (spectrophotometer plate reader). The majority of pathology laboratories would have this equipment as it is used for a wide ranging number of assays. Several companies were contacted for the prices of the various HpSA kits, however at the time of writing only the prices of the following ICT kits were made available:

- Certest (Certest Biotec, Zaragoza, Spain) is distributed through Medlab Diagnostics (Sydney). A 20 test kit plus positive control may be purchased for A$160, or $8 per sample (personal communication Medlab Diagnostics).
- Dako Rapid Hp StAR (formerly manufactured by Dako, is now made and distributed by Oxoid Australia Pty Ltd, part of Thermo Fisher Scientific). Now known as Oxoid HP Faecal Antigen Test. A 20 test kit may be purchased for A$430, or $21.50 per sample (personal communication Medlab Diagnostics).

The Medicare Benefits Schedule allows carbon-labelled urea breath tests to be performed to confirm *H pylori* colonisation or to monitor the success of *H pylori* eradication (item number 12533, fee $78.15). General practitioners may currently request a rapid stool antigen test be performed by pathology laboratories using the MBS item number 69494: For the detection of a virus or microbial antigen or microbial nucleic acid (Fee: $28.85) (Medicare Australia 2009).

A "test-and-treat" strategy describes the process of testing for *H pylori*, usually with a non-invasive test, and the provision of an appropriate antibiotic regime as treatment. A large number of cost-effectiveness studies of "test-and-treat" strategies for various gastrointestinal disorders have been published, however many of these studies assessed the use of UBT rather than HpSA tests (e.g. You et al 2006), or were conducted in populations with high *H pylori* prevalence (e.g. You et al 2006) or assessed the cost-effectiveness of *H pylori* eradication (e.g. Moayyedi et al 2000b and Mason et al 2008).

Barton et al (2008) developed a cost-effectiveness decision analysis model for a hypothetical cohort of adult patients presenting to primary care in the United States with symptoms of dyspepsia. The authors generated many thousands of cohorts of 10000 individuals, each with randomly selected inputs. The resulting analysis generated a modelled distribution of cost effectiveness. *H pylori* prevalence was assumed to be 15 per cent, with a range of 3.4 to 33 per cent. Input data was ascertained from meta-analyses of the medical literature. Six patient management strategies were compared:

- baseline: patients receive antacid and no further investigation;
- treatment with H_2 antagonist or PPI for a month, with no follow-up;

- test for *H pylori* infection and treat positives with eradication therapy. Patients were tested with either serology, UBT or ELISA HpSA;
- endoscopy was performed. Patients underwent eradication therapy if a peptic ulcer or *H pylori* infection, via histology, was present. Patients negative for peptic ulcer or *H pylori* infection received a PPI;
- initial treatment with PPI followed by endoscopy; and
- UBT and treat followed by PPI and endoscopy.

Costs included in the analysis (in US dollars[9]) included clinical consultation $170, one month PPI therapy $100, H_2 receptor antagonist $112, antacid $8.49, eradication therapy $152, serology test $100, UBT $150, endoscopy $450 and biopsy in addition to endoscopy $100. The basic cost of a HpSA test was not documented. Quality adjusted life years were calculated over five years. The sensitivity and specificity of serology was assumed to be 85 per cent and the sensitivity and specificity of both the UBT and HpSA tests were assumed to be 95 per cent. The outcomes, stratified by age are summarised in Table 3 (Barton et al 2008).

For all patients, regardless of age, strategies involving initial endoscopy were dominated[10] by all empirical drug strategies. Treatment with antacid was the least effective option, as was treatment with H_2 receptor antagonists (marginal additional benefit at 30-years). In 30-year olds, PPI therapy was the most cost-effective strategy with an ICER of $9,740 however there was little difference between the two non-invasive "test-and-treat" strategies using UBT and HpSA, which both had an ICER of $10,800 in this group of patients. Interestingly, the two non-invasive tests had only a slightly better ICER than the use of PPI therapy followed by an endoscopy if required (ie if PPI treatment was ineffective), which had an ICER of $10,900. In 60-year olds, the two "test-and-treat" strategies using UBT and HpSA were the cost-effective with ICERs of $6,740 and $6,830 respectively (Barton et al 2008).

[9] Exchange rate as of 5th May 2009: 1 AUD = 0.736536 USD

[10] Empirical drug treatments "dominate" endoscopy by being less expensive and more effective (Moayyedi 2007)

Table 3 Cost-effectiveness of managing dyspepsia

Strategy	Average cost ($) per patient	QALYs	Diff cost ($)	Diff QALY	ICER ($) vs base
30-year olds					
Antacid	1,976	4.2004			
H2RA	2,897	4.2203	921	0.0199	46,300
PPI + endoscopy	3,591	4.3381	1614	0.1377	Dominated
Endoscopy (no biopsy)	3,986	4.3387	2009	0.1383	Dominated
PPI	3,340	4.3404	1364	0.140	9,740
UBT+ treat + PPI + scope	3,842	4.3488	1866	0.1484	Dominated
Endoscopy + biopsy	4,008	4.3496	2031	0.1492	Dominated
HpSA ELISA + treat	3,581	4.3497	1605	0.1493	10,800
UBT + treat	3,598	4.3511	1622	0.1507	10,800
PPI + scope + biopsy	3,656	4.3541	1679	0.1537	10,900
PPI + scope vs PPI			316	0.0137	23,100
60-year olds					
Antacid	2,842	4.2031			
H2RA	4,103	4.2281	1,260	0.0251	Dominated
PPI + endoscopy	4,298	4.3665	1,455	0.1635	Dominated
PPI	4,070	4.3680	1,227	0.1650	7,440
Endoscopy (no biopsy)	4,557	4.3712	1,714	0.1682	Dominated
HpSA ELISA + treat	4,087	4.3852	1,244	0.1821	6,830
UBT+ treat + PPI + scope	4,315	4.3852	1,473	0.1822	Dominated
Endoscopy + biopsy	4,486	4.3860	1,643	0.1830	Dominated
UBT + treat	4,087	4.3876	1,244	0.1845	6,740
PPI + scope + biopsy	4,334	4.3942	1,491	0.1911	7,800
PPI + scope vs UBT + treat			247	0.0066	37,500

H2RA = H_2 receptor antagonist, PPI = proton pump inhibitors, UBT = urea breath test, HpSA = H pylori stool antigen

For patients with non-ulcer dyspepsia, clinical practice guidelines recommend a "test-and-treat" strategy, however they do not recommend the diagnostic test that should be used. Elwyn et al (2007) constructed a cost-effectiveness decision analysis model using three non-invasive tests: serology, UBT and HpSA tests. The use of invasive endoscopy was not considered. Costs included in the analysis included test acquisition, staff time, *H pylori* eradication therapy, the estimated burden on health services of false negatives and false positives and the estimated cost of managing undiagnosed patients. The model consisted of a hypothetical population of 1,000 individuals presenting with symptoms of dyspepsia, where the prevalence of *H pylori* was assumed to be 25 per cent, similar to that of Australia. The basic cost of a

UBT, serology test and HpSA test was £20[11], £8.50 and £14, respectively. Cost of eradication therapy was estimated to be £30. The cost of a misdiagnosis, including the cost of a follow-up endoscopy, two months proton pump inhibitor therapy and an extra general practitioner visit was estimated to be £260 (range £0-£500). The sensitivities of UBT, serology and HpSA were assumed to be 97 (range 80-99%), 91 (range 80-95%) and 96 (80-97%) per cent, respectively. The specificities of UBT, serology and HpSA were assumed to be 96 (range 80-99%), 90 (range 70-90%) and 97 (80-97%) per cent, respectively. It was not stated by the authors whether an ICT or ELISA HpSA test was utilised, however based on the high sensitivity value utilised in the model it appears that the test was an ELISA HpSA test. The outcomes are summarised in Table 4. The most effective was the HpSA test with 968 true outcomes for a cost of £17,275 or a mean cost of £17.84 per true positive test. The ICER for the HpSA when compared to serology was £10. The HpSA test remained the most cost-effective test when one-way sensitivity analyses were performed with varying prevalence rates (20 and 40%). In addition, a one-way sensitivity analysis demonstrated that the faecal antigen test performed better than serology or UBT in the case of a misdiagnosis. The authors suggest that HpSA tests should replace UBTs in general practice, as although the UBT is as accurate it is more cumbersome to perform. Inaccuracies from testing with serology arise due to its inability to distinguish between an active and past *H pylori* infection (Elwyn et al 2007).

Table 4 ICER values of non-invasive *H pylori* diagnostic tests

	Cost/ 1000 tests (£)	Effectiveness (number of true outcomes)	ICER (£)
Serology test	16,600	903	18.38
Urea breath test	23,175	961	113.36
Faecal antigen test	17,275	968	Best

ICER = incremental cost-effectiveness ratio: for the least effective test, the ICER is equivalent to the mean cost per true positive. For the remaining tests, the ICER is calculated as the difference in cost divided by the difference in effectiveness.

A 2007 paper by Moayyedi explored the health economic aspects of *H pylori* infection. Not only is *H pylori* eradication an efficient way of healing peptic ulcers it is also cost-effective, and improves the quality of life of patients more effectively than acid suppression maintenance treatment. In patients diagnosed with functional dyspepsia, the impact of *H pylori* eradication is small, especially when compared to the impact of eradication on peptic ulcer disease, as not all dyspepsia is caused by *H pylori* infection, therefore not all patients benefit from eradication therapy. Treating dyspepsia patients with eradication therapy is still cost-effective in the countries such as the United Kingdom where the cost of eradication therapy is low but may not be cost-effective in the United States, where the cost of eradication therapy is much higher. Both of these scenarios assume that the patients had undergone an endoscopy for a definitive diagnosis. As dyspepsia is a common problem, not all patients will

[11] Exchange rate as of 5th May 2009: 1 AUD = 0.49 GBP

be able to undergo an endoscopy. To reduce the number of endoscopies performed, the "test-and-treat" strategy recommends that patients with symptoms of dyspepsia under the age of 50 years, who are unlikely to develop gastric cancer, should be offered a non-invasive test for *H pylori* and those that are positive given eradication therapy. Patients not infected with *H pylori* would be offered acid suppression with proton pump inhibitors as would positive patients that remained symptomatic after eradication therapy. An endoscopy in patients older than 50 years may be useful for the detection of early signs of gastric cancer. An *H pylori* test and treat strategy has been shown to reduce endoscopy workload that persists for at least five years (Moayyedi 2007).

Furthermore, in contrast to peptic ulcer disease and functional dyspepsia there are a number of randomised controlled trials that have evaluated the cost-effectiveness of the *H pylori* test-and-treat strategy using UBT compared to endoscopy. Results from these studies could not be pooled due to different unit costs being applied to each item of resource used. However, an individual patient data systematic review could be conducted and demonstrated that although endoscopy was more effective than *H pylori* test-and-treat in curing dyspepsia at one year, the effect was small (relative risk of remaining dyspeptic in endoscopy arm = 0.95; 95% CI [0.92, 0.99]). Endoscopy was more expensive, with *H pylori* test-and-treat strategy costing US$389 (95% CI [$275, $502]) less per patient. Compared to *H pylori* test-and-treat strategy, it is estimated that endoscopy cost US$9,000 per resolution of dyspepsia at one year (Moayyedi 2007). As demonstrated by the modelling studies discussed above, using HpSA tests is as, or more, cost-effective than using the UBT in the test-and-treat strategy.

As discussed by Barton et al (2008), the question of whether *H pylori* test-and-treat is more cost-effective than empirical acid suppression with proton pump inhibitors needs to be answered. A large Danish trial randomised 722 patients with symptoms of dyspepsia to empirical PPI therapy, *H pylori* test and treat, or empirical PPI therapy followed by *H. pylori* test and treat if symptoms did not resolve. The number of endoscopies performed was statistically significantly higher in the empirical PPI arm and health service dyspepsia costs were lower in the *H pylori* test and treat arms, however this was not statistically significant. Dyspepsia improvement was most marked in *H pylori* positive patients receiving eradication therapy. *H pylori* test-and-treat was more cost-effective than empirical PPI therapy in infected dyspepsia patients. However, as the population prevalence of *H pylori* decreases, infection will become a uncommon event and it is likely that empirical acid suppression will become the most appropriate management plan (Jarbol et al 2006; Moayyedi 2007).

In summary, for patients with dyspepsia, it appears that there is little difference in the cost-effectiveness of the two strategies of either empirical treatment with proton pump inhibitors or *H pylori* test-and-treat. However this situation may change with the falling prevalence of *H pylori* infection. There appears to be little difference in the cost-effectiveness of the two non-invasive tests used: UBT or HpSA.

Clinical outcomes: Targeted population screening

Only three screening studies were identified for inclusion (Table 5). The results of an initial screening strategy in two community based randomised controlled trials of eradication therapy were included (level IV screening evidence) and one study that compared screening for and eradication therapy of *H pylori* infection versus a control, non-screened population (level II screening evidence).

In the randomised controlled trial conducted by Hansen et al (2008), 20,011 individuals were invited to participate and were randomised. Of these, 5,749 were randomised to the *H pylori* screening and eradication group and 6,781 were randomised to the unscreened group. Subjects were followed-up at one and five years with a questionnaire to assess symptoms of dyspepsia and quality of life. In the screened group, 17.5 per cent were positive for *H pylori* infection and offered eradication therapy. A random sample of 200 individuals tested for *H pylori* infection four weeks post-eradication therapy found that eradication was successful in 95 per cent of cases.

The baseline rate of dyspepsia was slightly higher in the screened group (24.8%) compared to the unscreened group (21.0%), however at one-and five-year follow-up, rates of dyspepsia were similar in both groups (slightly higher than 20%). When adjusted for the imbalance at baseline, the odds ratio for *not* having dyspepsia for the screened group compared to the unscreened group was 1.27 (95% CI [1.14, 1.41]) at one-year, however this was markedly reduced at five-years (OR 1.04, 95% CI [0.93, 1.16]). When looking at *only* those individuals who completed the 5-year follow-up, rates of dyspepsia in the screened and unscreened groups were 23.5 and 19.8 per cent at baseline. Rates of dyspepsia for those individuals who dropped out of the study were much higher at baseline in both the screened (32.6%) and unscreened groups (27.7%), however re-analysis of data for only those individuals followed-up for the five years did not change the overall result. For those individuals symptomatic for dyspepsia at baseline, there was no significant difference in the risk of remaining dyspeptic in the screened (51%) and unscreened (54%) groups (p=0.15).

At baseline, a higher rate of GP visits and sick leave days due to dyspepsia was observed in the screened group (3.6% and 2.6%, respectively) compared to the unscreened group (3.2% and 2.1%, respectively). At five-year follow-up the rates for GP visits and sick leave days due to dyspepsia decreased in the screened group (2.8% and 1.9%, respectively) but remained stable or increased in the unscreened group (3.1% and 2.5%, respectively). Interestingly, at baseline, those individuals who did not complete the five-year follow-up had a higher rate of visits to the GP and sick leave days due to dyspepsia in the screened (5.4% and 5.0%, respectively) and unscreened (4.6% for both). After re-analysis of data including only those individuals followed-up for the five years, there was an *insignificant decrease* in the rates of GP visits (from 3.1% to 2.8%) and the number of sick leave days (from 2.2% to 1.9%) in the screened group but a *significant* (p<0.001) increase in both rates in the

unscreened group (2.5% to 3.1% for GP visits and 1.6% to 2.5% for sick leave days). There was no difference between the screened and unscreened groups in the prescription rate of ulcer drugs.

An analysis of the costs for the two arms of the randomised trial, including costs for medication, endoscopy, hospitalisation and GP consultations, revealed that the total mean cost was 68 Danish Kroner[12] higher in the unscreened group than the screened group. The mean cost per individual invited to be screened for *H pylori* infection was 349 Kroner.

In summary, the authors concluded that although population screening had a small effect on the rate of dyspepsia and a small but significant effect on the rate of GP consultations and sick leave days for dyspepsia, a blanket *H pylori* population screening intervention would result in increased costs due to *H pylori* screening and eradication therapy (Hansen et al 2008).

The Bristol Helicobacter study commenced in 1996 and recruited patients until 1999 and patients were followed up for two years post-treatment Almost 30,000 general practice patients were approached to participate in this study, with 38.3 per cent consenting to undergo screening for *H pylori* infection with UBT (level IV screening evidence). There was no pre-selection of patients with pre-existing gastrointestinal symptoms. Of those patients screened, approximately 16 per cent were found to be positive for *H pylori* infection and were randomised to receive either eradication therapy or placebo. Many of those patients found to be *H pylori* positive had a range of pre-existing gastrointestinal symptoms including monthly acid reflux (18.5%), monthly heartburn (28%) and monthly epigastric pain (25%) (Harvey et al 2004; Lane et al 2002). The number of primary care consultations for dyspepsia was reduced by 35 per cent in the eradication group compared to placebo (odds ratio 0.65, 95% CI [0.46, 0.94], p=0.021). These results translated to a number needed to treat of 30, that is 30 patients with *H pylori* infection would have to be treated to prevent one person consulting their general practitioner for dyspepsia. Although consultations for dyspepsia were reduced, the costs to the National Health Service were £84.70 greater per participant in the eradication group, of which £83.40 was the cost of the eradication therapy (Lane et al 2006). The Bristol study did not assess the effect of *H pylori* screening on the development of gastric cancer. These results give an indication of the effectiveness of eradication therapy in *H pylori* positive patients, rather than the effectiveness of screening for *H pylori* infection. The authors of these three studies suggest targeted screening (i.e. patients presenting with symptoms of dyspepsia) may be preferable to population screening for *H pylori* infection.

A similar study was conducted in the Leeds/ Bradford area of the United Kingdom (level IV screening evidence) (Moayyedi et al 2000a). Although the results of this study were reported in the year 2000, well beyond the scope of the search period of this Horizon Scanning report, a follow-up of this study was reported in 2007, and therefore the initial results were included for completeness. Of the 8,407 patients screened, 28 per cent were found to be positive for *H pylori* infection and were randomised to receive either eradication therapy (n=1,161) or placebo (n=1,163). Approximately 44 per cent of the patients found to be positive for *H pylori* had reported symptoms of

[12] Exchange rate as of 13th May 2009:1 AUD = 4.17615 DKK

dyspepsia. Seventy-six per cent of participants returned for a 2-year follow-up. Eradication was successful in 74 per cent of the treatment group compared to five per cent of the placebo group. At follow-up, symptoms of dyspepsia or gastro-oesophageal reflux were reported in 28 pre cent of the treatment group and 33 per cent of the placebo group (absolute-risk reduction 5%, 95% CI [1, 10]). *H pylori* treatment had no effect on the quality of life and was therefore deemed to have a small benefit. The secondary analysis of the Leeds study conducted by Ford et al (2007) assessed the effect on health-care seeking behaviour when individuals were made aware of their *H pylori* status. Of the 6,078 original patients found to be negative for *H pylori*, 1,353 were randomised to a placebo PPI and antibiotics regime, whilst a further 1,355 were informed of their *H pylori* negative status. Primary health-care records of all patients were reviewed at 2-year follow-up. Individuals made aware of their *H pylori* negative status were less likely to seek health care for dyspepsia (relative risk =0.81, 95% CI [0.67, 0.97]) than those in the placebo arm. Lower costs were incurred by the group made aware of their infection status with a mean saving per person of £11.02, 95% CI [-3.52, 25.56]. The authors concluded that population screening may reduce dyspepsia-related health-care costs in those individuals found to be *H pylori* negative as well as in those found to be *H pylori* positive (Ford et al 2005).

In summary, it would appear in populations with a relatively low prevalence of *H pylori* infection, that a targeted, rather than a population screening strategy would be more effective for the resolution of dyspepsia symptoms and for the reduction in the costs associated with treating the condition. In line with many established guidelines, patients presenting to their general practitioner with symptoms of dyspepsia should be tested for *H pylori* infection and treated if found to be positive. No studies were identified that reported on the impact of screening for *H pylori*, the subsequent eradication of infection and its long term impact on the incidence of gastric cancer. Studies such as this would require a long-term follow-up.

Table 5 Population screening for *H pylori* infection

Study	Screening level of evidence	Study design	Population	Outcomes
Hansen et al (2008)	II	Randomised controlled trial. All individuals in the *H pylori* screening group were screened using an in-office test (FlexPack HP, Abbott Laboratories). All *H pylori* positive individuals were confirmed using UBT. Those positive by both tests were offered eradication therapy.	20,011 individuals aged 40-64 years, living in the city of Odense were randomised to the *H pylori* screen and treat group (n=5,749) or the unscreened control group (n=6,781).	1,008/5749 (17.5%) of screened group +ve for *H pylori* 989/1008 (98.1%) underwent eradication therapy, eradication success rate 95% **Screened** Base: N 5749; Dyspepsia % 24.8; GP visit (%) 3.6; Leave (%) 2.6; *H pylori* +ve Dys (%) 27.8; *H pylori* –ve Dys (%) 23.6 1-yr: N 5339; % 92.9; Dyspepsia % 20.5; OR 1.27 5-yr: N 4821; % 83.9; Dyspepsia % 20.5; OR 1.04; GP visit (%) 2.8; Leave (%) 1.9; *H pylori* +ve Dys (%) 22.5; *H pylori* –ve Dys (%) 20.0 **Unscreened** Base: N 6781; Dyspepsia % 21.0; GP visit (%) 3.2; Leave (%) 2.1 1-yr: N 6222; % 91.8; Dyspepsia % 21.8 5-yr: N 5612; % 82.8; Dyspepsia % 20.0; GP visit (%) 3.1; Leave (%) 2.5
Lane et al (2002, 2004, 2006)	IV	Screening conducted as part of eradication therapy RCT. All eligible patients were screened with UBT. *H pylori* +ve patients randomised to eradication therapy or placebo. Screening component of study is a case series.	27,536 urban-based patients aged 20-59 years from 7 primary care centres were invited to participate. 10,714 (38.9%) attended for screening and 10,537 were eligible for screening.	1636/10537 (15.5%) *H pylori* positive Age (years) / *H pylori* % +ve / Adjusted OR [95% CI] 20-29: 1.0 / 1.0 30-39: 15.1 / 2.81 [1.87, 4.2] 40-49: 31.0 / 5.07 [3.12, 8.24] 50-59: 53.0 / 7.82 [5.53, 11.04] Sex / *H pylori* % +ve / Adjusted OR [95% CI] Male: 48.8 / 1.0 Female: 51.2 / 0.87 [0.76, 1.0]
Moayyedi et al (2000)	IV	Screening conducted as part of eradication therapy RCT. All eligible patients were screened with UBT. *H pylori* +ve patients randomised to eradication therapy or placebo. Screening component of study is a case series.	32,929 urban-based patients aged 40-49 years from 36 primary care centres were invited to participate. 9,262 attended for screening and 8,407 evaluated at baseline.	2329/8407 (27.7%) *H pylori* positive

UBT = urea breath test, OR = odds ratio, Dys = dyspepsia

Although many studies were identified by the search strategy as screening studies, they were primarily conducted in Asian countries, such as China and Japan, which have a high prevalence of *H pylori* infection and a corresponding high incidence of gastric cancer. It is difficult to translate the results of these screening studies to Australia and New Zealand due to the differences in prevalence of both *H pylori* infection and gastric cancer. The majority of these studies were aimed at identifying gastric cancer rather than *H pylori* infection as a precursor of gastric cancer. For example, the meta-analysis conducted by Miki (2006) correlated sensitivity and specificity results from the measurement of serum pepsinogen (PG I and PG I/II ratio) (data not shown). The meta-analysis suggests that in countries with a high incidence of gastric cancer, the pepsinogen I/II ratio could be used as a screening strategy to identify individuals at high-risk of developing gastric cancer, who would then undergo more rigorous gastric cancer assessment in the form of an endoscopy (Miki 2006). A small study (n=444) conducted by Sun et al (2008) in the Liaoning Province of China, correlated changes in serum pepsinogen I/II ratios to changes in gastritis as observed by endoscopy and also concluded that the ratio could be used to identify individuals at high-risk of gastric cancer (Sun et al 2008). This smaller 2008 study was part of a large case series conducted on 6,990 residents of the province, aged 11-82 years (level IV screening evidence). All participants underwent serum pepsinogen analysis and endoscopy. In addition, *H pylori* status was determined by histological examination or by the detection of IgG antibodies to *H pylori.* Although 5,285 individuals tested positive for *H pylori*, the results were presented in terms of their correlation with serum pepsinogen levels and the correlation of pepsinogen levels to changes in the gastric mucosa. Pepsinogen I and II levels were higher in the *H pylori* positive individuals when compared to *H pylori* negative subjects (PG I 88.7 μg/L vs 81.4 μg/L, $p = 0.000$ and PG II 11.4 μg/L vs 8.4 μg/L, $p = 0.000$). The PG I/II ratio was lower in the *H pylori* positive group (7.7 vs 9.6, $p= 0.000$) (Sun et al 2007). The evidence–based Japanese guidelines for gastric cancer screening assessed four potential population screening methods: photofluorography[13], endoscopy, serum pepsinogen and *H pylori* antibody testing. Interestingly this systematic review reported that there was insufficient evidence to support *H pylori* detection as a means of population screening for gastric cancer, instead recommending the use of photofluorography (Hamashima et al 2008).

[13] Photofluorography = photography of images produced on a fluorescent screen by X-rays

Potential cost impact: Targeted population screening

As outlined in the effectiveness section, many cost-effectiveness papers have been published describing the results of either modelling of screening studies or population screening studies, which have been conducted in countries of high *H pylori* prevalence such as China and Japan (Lee et al 2007; Xie et al 2008a; Xie et al 2008b; Yeh et al 2009). As the prevalence of disease will affect the success of a screening programme, and also due to differences in the health systems described, these economic studies will not be presented in this Horizon Scanning report.

The most recent cost-effectiveness study to be published is a Markov model evaluating the economics of a *H pylori* screening programme, and the use of various diagnostic techniques within this strategy, for the prevention of gastric cancer (Xie et al 2009). Unfortunately at the time of writing this report, this study had been published as an E-publication and only the abstract was available for evaluation. A Markov model was constructed for the detection of *H pylori* infection in a hypothetical cohort of 10,000 Canadian men aged 35 years. The model compared the lifetime cost and effectiveness of four strategies for *H pylori* detection: no screening, serology using an ELISA, HpSA tests and UBT. The primary outcome measured was the incremental cost-effectiveness ratio between the screening strategies and the no-screening strategy. Base-case analysis and probabilistic sensitivity analysis were performed using the point estimates of the parameters and Monte Carlo simulations, respectively. Compared with the no-screening strategy in the base-case analysis, the ICER was C$29,800[14] per QALY for the HpSA, C$33,000per QALY for the serology ELISA and C$50,400 per QALY for the UBT. A sensitivity analysis revealed that the no-screening strategy was more cost effective if the willingness to pay[15] was <C$20,000 per QALY, while the HpSA had the highest probability of being cost effective if the willingness-to-pay was >C$30,000 per QALY. Serology and the UBT were not cost-effective strategies over a wide range of willingness-to-pay values. The authors concluded that, although the UBT had the highest sensitivity and specificity values of all the diagnostic technologies evaluated, the most cost-effective strategy, depending on the willingness-to-pay threshold values, was either no screening or the HpSA tests.

Leivo et al (2004) conducted an economic analysis to evaluate the costs and benefits of population screening for *H pylori* infection in Finland. The cost-benefit analysis used a computer-based decision tree and the primary decision analysis compared two intervention strategies: to screen for *H pylori* and treat all those who are positive, or no screening but test and treat those individuals who present with clinical symptoms. For both strategies, the model estimated

[14] The current exchange rate as of 18th May 2009 is: 1 CAD = 1.13589 AUD

[15] Willingness to pay refers to the value of a good to a person that they are willing to pay, sacrifice or exchange for it. In health economics it is a measurement technique in order to establish the *maximum* that respondents are willing to pay when they are confronted with hypothetical scenarios about the health intervention under evaluation. Willingness to pay is one of the methods being used to assign money to health outcomes in cost-benefit analysis.

the discounted *H pylori*-related accumulative health care costs from screening age to death. The baseline case estimates cost-benefit for individuals screened aged 15-45 years. The main outcome measure was the incremental health-care cost per individual invited for screening in addition to the incremental cost per treated *H pylori* infection as a consequence of screening. Only direct health-care costs were considered. Input data for the model, including the sensitivity and specificity of serology for *H pylori* detection, were ascertained from a population-based screen and treat program (n=5,288) conducted in a semi-urban community in south-west Finland (Salomaa et al 1998). The prevalence at screening was 13 per cent, with a 76 per cent screening participation rate and a 91 per cent eradication therapy compliance rate.

The cost per person invited to be screened was US$69[16] in the screening group and US$43 in the no-screening group, therefore the incremental cost per case was US$26 for the screening strategy. The incremental cost per case was highest in those aged 15 at time of screening ($36) and lowest in those aged 45 years at time of screening, with a *cost-saving* of $6. The incremental cost per treated *H pylori* infection due to screening was US$412. Although *H pylori* screening was more favourable in older individuals and the estimated cost per screenee was considered to be acceptable, the authors raised concerns about the effect of *H pylori* eradication on gastro-oesophageal reflux disease and oesophageal adenocarcinoma (Leivo et al 2004).

A 2003 study evaluated the cost-effectiveness of population screening for *H pylori* infection for the prevention of gastric cancer and peptic ulcer disease. The study was conducted in a primary care setting in England and Wales. The aim of this study was to ascertain the costs of population screening for *H pylori* in different aged populations, to prevent gastric cancer and peptic ulcer disease and to consider the impact on life-years saved. The four screening populations were: 20 to 49 years and as the simulation model progresses, all new 20-year-olds can enter the model; 30 to 49 years and all new 30-year-olds; 40 to 49 years and all new 40-year-olds; and all new 50-year-olds. A screening and treat only those found to be *H pylori* positive strategy was compared to no-screening strategy. However patients in the no-screened group who presented with clinical symptoms of dyspepsia were offered eradication therapy. The model was populated with UK data where possible, obtained from the peer-reviewed literature: sensitivity and specificity of serology and UBT, relative risk of developing a peptic ulcer or gastric cancer if *H pylori* positive, and the efficacy of eradication therapy. The economic perspective of the study was that of the health care payer, in this case the United Kingdom National Health Service. Costs included screening, eradication and costs averted to provide costs per life years saved (cost/LYS) for preventing gastric cancer and peptic ulcer disease. A sensitivity analysis was performed.

Adult population screening with an uptake of 70 per cent in the United Kingdom would involve screening approximately 25 million individuals, with approximately five million found to be positive and undergoing eradication therapy. The study found that the number of deaths from gastric cancer

[16] The authors used the1999 exchange rate of US$1.00 = 5.54 Finnish Markka. The current exchange rate as of 14th May 2009 is: 1 USD = 4.38290 FIM

prevented falls as the age at screening increases. Screening existing 20- to 49-year-olds and incident 20 year –olds would prevent 17,440 deaths, screening 30- to 49-year-olds and incident 30-year-olds would prevent 17,360 deaths, screening 40- to 49-year-olds and new 40-year-olds would prevent 16,263 deaths and screening 50-year-olds would prevent 13,156 deaths. The number needed to treat per death prevented at age 20 was 312, with 313 at age 30, 333 at age 40 and 404 at age 50 years. Screening existing 40- to 49-year-olds and new 40-year-olds would result in a cost per life-year saved of £5,866 in comparison with no screening programme. Details of the cost per life-year saved with the other age screening options were not provided. Serology was found to be more cost-effective than UBT. The sensitivity analysis indicated that increasing the age of the screening population, increasing the risk of peptic ulcers and gastric cancer amongst people with H. pylori, and increasing the *H pylori* prevalence decreased the cost-effectiveness of screening. Lowering the prevalence of *H pylori*, increasing the opportunistic eradication and lag, and altering the cancer and peptic ulcer disease outcomes increased the cost-effectiveness of screening to more than £10,000 per life year saved.

The authors considered that screening at age 40 years balanced cost-effectiveness and the feasibility of implementing a screening program and was therefore the most realistic option. Although they concluded that population screening in this age group was likely to be cost-effective, the benefits would take time to accrue. As in previous studies, concerns were raised over the effects of *H pylori* eradication. In addition, the cost-effectiveness of screening for *H pylori* would be reduced with an increase of opportunistic testing and treating of patients presenting with clinical symptoms of dyspepsia (Roderick et al 2003a; Roderick et al 2003b).

Social and ethical issues

The potential use of tests for the detection of *H pylori* included in this assessment fall into two groups: diagnostic tests intended to provide a swift, accurate, non-invasive and inexpensive means of identifying infected individuals; and population-based screening programs. The ethical issues related to these two uses are quite different and will be dealt with separately.

Diagnosis

A rapid, non-invasive and inexpensive test to identify individuals with *H pylori* infection in a clinical setting raises a number of ethical issues. First, there are questions related to the choice of test. The tests described in this Horizon Scanning Report vary in their diagnostic accuracy (specificity and sensitivity) and their cost. Ideally, a suitable test would be cheap and have high sensitivity and specificity. In this case, less than ideal conditions mean that trade-offs need to be made between diagnostic accuracy, which may impact on 1) the benefits and harms for known individuals i.e. those receiving the tests and 2) costs, which concern benefits and harms for the community overall by way of the most efficient use of resources. A full ethical assessment of the most appropriate balance between accuracy and cost for these tests is beyond this report.

Second, there are questions related to consent. Informed consent requires that clinicians give a full account of reasons for why the patient is being tested, the likely implications of having the test for their future health and well-being, and any risks and harms arising from the test. *H pylori* testing is undertaken for two related reasons: directly to treat an infection in an individual with symptoms that have led them to present to the doctor and, indirectly, to prevent the development of gastric cancer. Clinicians should obviously tell patients the first reason for the test, in that it is being undertaken to detect a possible cause of their presenting symptoms. It is less obvious that clinicians will tell patients about the association between *H pylori* infection and gastric cancer, absent the need to persuade an uncertain patient to have the test. The grounds for *not* fully disclosing the rationale presumably are that patients will not be interested, or alternatively that they may become unnecessarily concerned about their future chances of developing cancer, and that allaying these fears may be time-consuming on the clinician's behalf. Such responses may be pragmatic but they are difficult to justify ethically. All other things being equal, patients being tested for *H pylori* should receive a full account of the rationale for the test.

Screening

There is considerable body of literature on the ethical assessment of screening programs (Holland 2007). Much of it builds on the classic work of Wilson and Jungner (Wilson & Jungner 1968) and Muir Gray (Gray 2001), both of whom documented the key principles for mass screening programs. The principles provide a set of straightforward guidelines for screening, grounded in

assessments of the importance of the health problem, the availability and acceptability of screening tools and treatment for the health problem, scientific understanding of the condition, and a favourable economic balance between the costs and benefits of screening. From an ethical point of view, the key points of difference between screening programs and diagnostic tests are that screening tests populations of healthy individuals, most of whom will not benefit from the program and where there is considerable potential for harm to those inappropriately diagnosed. Thus, there is a heavy burden on those who would introduce a screening program to be confident that the benefits of the program will outweigh the harms for the *whole* population screened.

In the case of population screening for *H pylori*, weighing the benefits of the program against potential harms is difficult. The intent of a population screening program would be to prevent the development of gastric cancer by detecting asymptomatic but infected individuals *before* they have developed atrophic gastritis, and this is clearly a substantial benefit for the small proportion of individuals who move from asymptomatic infections to gastric cancers. However, the burdens on the much larger group who do not fall into this category are significant, both in terms of unnecessary treatments and anxiety and distress associated with the knowledge that they may have been at risk of developing gastric cancer. For most people in this group, the likely benefit of earlier diagnosis would be offset by the fact that they would likely be diagnosed later through identification of when they become symptomatic. However, because we do not know the proportion of individuals who develop gastric cancer *without* symptoms of dyspepsia that may have led to earlier identification of *H pylori* infection, making any judgment about the balance between harms and benefits of the screening program is difficult.

Training

No training would be required in the use of a rapid stool antigen HpSA test. Immunochromatographic HpSA tests may be conducted in a clinic or general practitioner environment as a point-of-care test, however stool samples taken for analysis by ELISA HpSA tests are required to be sent to a pathology laboratory for processing. Equivocal results may require further investigation by other diagnostic methods.

Clinical Guidelines

There are no clinical guidelines for the screening or management of *H pylori* infection in Australia or New Zealand. Evidence- based clinical practice guidelines for the investigation, management and treatment of *H pylori* infection in adults have been produced by the American College of Gastroenterology and the European Helicobacter Study Group, which produced the updated Maastricht III consensus report (Malfertheiner et al 2007; Stenström et al 2008). In addition, a multi-disciplinary group formulated the 2008 Asia-Pacific evidence-based guidelines for the prevention of gastric cancer, which included screening and treatment for *H pylori* infection (Fock et al 2008). In 2000, consensus statements and evidence-based guidelines for the management of *H pylori* infection in children were produced by two groups in North America and Europe[17] (Day et al 2004).

The Asia-Pacific guidelines *do not* recommend screening for *H pylori* in populations considered to be at low-risk of gastric cancer, such as Australia and New Zealand. However the guidelines recommend the screening for, and eradication of, *H pylori* in populations considered to be at high-risk of gastric cancer, which may include the indigenous populations of Australia and New Zealand.

In Australia, as outlined in the Introduction to this report, the indications for the diagnosis and treatment of *H pylori*, based on the Maastricht III consensus report include:

- peptic ulcer disease (active or confirmed history);
- a test and treat strategy for patients with un-investigated dyspepsia who are <45 years of age without bleeding, anaemia, unexplained weight loss, progressive dysphagia, early satiety, recurrent vomiting, odynophagia, family history of gastric cancer or a previous oesophagogastric malignancy;
- low grade MALT lymphoma;
- after endoscopic resection of early gastric cancer; or
- first degree relative with gastric cancer.

[17] The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology and Nutrition (ESPGHAN)

Using the test results an appropriate antibiotic regime may be chosen to eradicate *H pylori*. Post-eradication therapy testing is also recommended as treatment failure may occur due to poor patient compliance to the therapeutic regime or antibiotic resistance. It is also recommended that after two failed eradication attempts a sample of the infective *H pylori* strain should be collected and cultured for an antimicrobial sensitivity test. (Stenström et al 2008).

A cross-sectional survey conducted by Day et al (2004) found that the evidence-based clinical guidelines for the management of *H pylori* infection in children are not strictly adhered to in Australasia. The recommendations are as follows:

- the aim of investigations in dyspeptic children should be directed to ascertaining the cause of the underlying symptoms, and not just to see whether *H pylori* is present or not;
- non-invasive testing of all children and treatment of those with positive non-invasive test results is not recommended;
- upper gastrointestinal endoscopy with biopsies is the optimal investigation for children with undiagnosed significant upper gastrointestinal symptoms or suspected peptic ulceration;
- non-invasive testing (especially urea breath testing) is not appropriate as an alternative to upper gastrointestinal endoscopy (as H. pylori infection is relatively uncommon compared to other causes of upper gastrointestinal symptoms), but that urea breath testing may be an appropriate test by which to confirm eradication;
- screening for infection in asymptomatic individuals is not indicated;
- testing for H. pylori is only appropriate when treatment would be considered when test results are positive; and
- eradication treatment is absolutely indicated in peptic ulcer disease and MALT-lymphoma but that in other situations where H. pylori infection is identified one should only offer treatment after full discussion of the potential risks and benefits with the parents or caregivers (Day et al 2004).

Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology.

Horizon Scanning forms an integral component of Health Technology Assessment. However, it is a specialised and quite distinct activity conducted for an entirely different purpose. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.

An Horizon Scanning Report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost effectiveness of a technology.

In the context of a rapidly evolving technology, an Horizon Scanning Report is a 'state of play' assessment that presents a trade-off between the value of early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

This report provides an assessment of the current state of development of rapid testing and the targeted population screening for *Helicobacter pylori*, its present and potential use in the Australian public health system, and future implications for the use of this technology.

Availability and Level of Evidence

A total of seven studies assessing the effectiveness of rapid stool antigen HpSA were identified for inclusion in this assessment. Three studies reported on the use of immunochromatographic (ICT) HpSA tests, two in adult populations with gastrointestinal symptoms (one level II (Krausse et al 2008) and one level III-2 (Demiray et al 2006) diagnostic level of evidence) and one in children with non-specific abdominal symptoms (diagnostic level III-1 evidence (Kuloglu et al 2008)). Two studies reported on the use of rapid ELISA HpSA tests both in adult populations with symptoms of dyspepsia (one level III-1 (Calvet et al 2009) and one level III-2 (Adiloglu et al 2007) diagnostic evidence). Two studies reported on the use of both ICT and ELISA HpSA tests. One of these studies was conducted on an adult population with various gastrointestinal symptoms (level III-2 diagnostic evidence) (Blanco et al 2008). The remaining study was a low quality meta-analysis which combined studies conducted on adults and children. Usually a meta-analysis would be afforded the highest level of evidence, however this depends on the strength of the evidence of the included studies. This meta-analysis presented the results of at least one study which pre-selected patient samples post-endoscopy to be positive for *H pylori* and is therefore a study of diagnostic

yield. The meta-analysis must therefore be classified as the lowest level of evidence of the studies it assessed (level IV diagnostic evidence) (Gisbert et al 2006).

Only three studies assessing the effectiveness of population screening for *H pylori* infection were identified for inclusion in this assessment. One large-scale community-based study compared a population screened for and eradication therapy of *H pylori* infection versus a control, non-screened population (level II screening evidence) (Hansen et al 2008).Two studies reported on the results of large scale community-based randomised controlled trial of *H pylori* eradication therapy, both of which had an initial screening strategy (level IV screening evidence) (Harvey et al 2004; Moayyedi et al 2000a). Although these two studies were outside the search period stipulated for this report, follow-up studies were reported within the search period, therefore the original studies were assessed for completeness.

Search Strategy used for the Report

The medical literature (Table 7) was searched utilising the search terms outlined in Table 6 to identify relevant studies and reviews, until March 2009. In addition, major international health assessment databases were searched.

Table 6 Search terms utilised

Search terms
MeSH
(Helicobacter pylori AND infection) OR (Helicobacter pylori AND diagnosis) OR (Helicobacter pylori AND mass screening) OR (Helicobacter pylori AND stomach neoplasms)
Text words
Limits
English, Human

Table 7 Literature sources utilised in assessment

Source	Location
Electronic databases	
AustHealth	University library
Australian Medical Index	University library
Australian Public Affairs Information Service (APAIS) - Health	University library
Cinahl	University library
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	University library
Current Contents	University library
Embase	Personal subscription
Pre-Medline and Medline	University library
ProceedingsFirst	University library
PsycInfo	University library
Web of Science – Science Citation Index Expanded	University library
Internet	
Australian Clinical Trials Registry	http://www.actr.org.au/default.aspx
Current Controlled Trials metaRegister	http://controlled-trials.com/
Health Technology Assessment international	http://www.htai.org
International Network for Agencies for Health Technology Assessment	http://www.inahta.org/
Medicines and Healthcare products Regulatory Agency (UK).	http://www.mhra.gov.uk/index.htm
National Library of Medicine Health Services/Technology Assessment Text	http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat
National Library of Medicine Locator Plus database	http://locatorplus.gov
New York Academy of Medicine Grey Literature Report	http://www.nyam.org/library/grey.shtml
Trip database	http://www.tripdatabase.com
U.K. National Research Register	https://portal.nihr.ac.uk/Pages/NRRArchive.aspx
US Food and Drug Administration, Center for Devices and Radiological Health.	http://www.fda.gov/cdrh/databases.html

Sources of further information

An ongoing trial, comparing the performance of the Certest immunochromatographic HpSA test to a primary standard of dual gastric biopsies (one from each pole of the stomach), is being conducted at the Repatriation General Hospital Concord, New South Wales. The principal investigator is Professor Peter Katelaris. All patients undergoing an endoscopy in the Gastroenterology Unit are invited to join the trial. Patients present with a wide range of symptoms so there is no strict delineation of the sample population. No limitations have been placed on age (currently ranging from 16-92 years) or ethnic background. At this point in time, 25 patients have

enrolled in the study and the trial intends to enrol a total of 100 patients (personal communication, University of Sydney).

The German Institute for Medical Documentation and Information (DIMDI) prioritised the following topic in 2008 but are yet to complete their assessment: "What medical and economical benefit has the examination of the helicobacter pylori population via urea respiratory test in primary diagnostics compared to invasive and non-invasive methods?"

A 12-month observational study was registered on the Australian Clinical Trials Register in 2007, and although the study was anticipated to start in January 2008, recruitment has yet to commence (ACTRN12607000521426). The study intends to enrol 80 consecutive patients admitted to the emergency unit of the A. Cardarelli Hospital of Naples during a 12-month period for peptic ulcer disease complicated by haemorrhage after assumption of nonsteroidal anti-inflammatory drugs (NSAIDs), in an effort to ascertain the prevalence of *Helicobacter pylori* infection. This observational study intends to provide further information on the role of *H pylori* in the pathogenesis of peptic ulcer disease complicated by haemorrhage in patients chronically or occasionally treated with NSAIDs (ACTR 2007).

A double-blind, parallel assignment, placebo controlled, randomised trial is currently underway in Hong King examining chemoprevention of gastric cancer by intervention with the *H pylori* and cyclo-oxygenase pathway (NCT00498134). Laboratory research indicated that an abnormally high expression of the enzyme cyclooxygenase-2 was found in gastric cancer and inhibition of this enzyme by a specific cyclooxygenase-2 inhibitor could kill gastric cancer cells. This second chemoprevention study aims to assess the addition of this specific cyclooxygenase-2 inhibitor together with eradication of *H pylori* on the prevention or reduction of the risk of gastric cancer and to assess whether the combination can reverse pre-cancerous lesions in the stomach in the high-risk population. The proposed site is Shangdong, China with very high prevalence of pre-cancerous lesions in asymptomatic *H pylori* carriers. We plan to recruit 1500 *H pylori* positive subjects for this randomised placebo-controlled study. *H pylori* carriers will be randomized to receive treatment for the infection or placebo, followed by specific COX-2 inhibitor or placebo for 3 years. The study is expected to be completed by April 2013 (CCT 2009).

Novartis Vaccines in Germany are conducting a study to examine the efficacy and safety of an *H pylori* vaccine in *H pylori*-negative adults compared to placebo (NCT00736476). This study is expected to be completed in October 2009 (CCT 2009).

Conclusions

The causal link between the presence of *H pylori* infection and gastric cancer was established in 1991 by Parsonnet et al. Although 60-80 per cent of all gastric cancers are associated with *H pylori* infection, not all infected individuals will go on to develop cancer. It has been estimated that approximately 50 per cent of people world wide are infected with *H pylori*; of these individuals 10 per cent will develop gastric or duodenal ulcers and one per cent will develop gastric cancer (Beswick et al 2006; Walker et al 2008). It has been suggested that a large proportion of gastric cancers could be prevented with the eradication of *H pylori* (Beswick et al 2006; Roderick et al 2003a; Walker et al 2008). In Australia, recommended first and second line therapies for *H pylori* infection include 7-14 days treatment with various combinations of antibiotics and proton pump inhibitors (Stenström et al 2008).

Numerous diagnostic methods are available for the detection of *H pylori* including the rapid, non-invasive stool antigen test, which may be either an enzyme-linked immunosorbant assay (ELISA) or one of the newly developed immunochromatographic tests (ICTs) (Blanco et al 2008). Other methods include invasive tests: culture, histology, rapid urease test or molecular tests. Other non-invasive tests include: urea breath test or serology (Hirschl & Makristathis 2007). Most *H pylori* diagnostic tests, with the exception of the stool antigen test, require the cessation of antibiotic and proton pump inhibitor treatment before testing is conducted.

Rapid *H pylori* diagnostic tests are intended to provide a swift, accurate, non-invasive and inexpensive means of identifying individuals currently infected with *H pylori* and ideally would be used in a point-of-care context in clinics or a general practitioner's office. The stool antigen test has been proposed as an ideal tool for the testing of *H pylori* in children who may be unable to perform a urea breath test. General practitioners may currently request a rapid stool antigen test be performed by pathology laboratories, however, GPs are not eligible to claim an Medicare Benefits Schedule rebate if this test is performed in a clinic setting. For point-of-care testing in a GP setting changes would need to be made to the MBS to allow clinicians to claim the MBS rebate for performing this test.

In developing countries in Asia and South America, *H pylori* infection is associated with poor hygiene and high levels of infection (70-80% of *all* individuals are infected), and therefore rates of gastric cancer are high. In Western countries, with improved hygiene, rates of *H pylori* infection have declined (United Kingdom 20% and United States 10% infection rates) and accordingly rates of *H pylori* associated gastric cancer have also declined (Walker et al 2008).

Diagnostic

None of the studies included for assessment reported any adverse events associated with the use of rapid stool antigen or HpSA diagnostic tests, however the potential harms of rapid HpSA tests when used for the diagnosis of *H pylori* infection arise from the number of false positives (patients

receiving unnecessary antibiotic treatment and possibly further invasive confirmatory testing) and false negatives (patients receiving no treatment when they are in fact positive for *H pylori* infection).

Of the ICT HpSA tests, the most sensitive (those tests correctly identifying patients with *H pylori* infection), compared to the reference standard histology, was the Lettitest (83.8 %) (Blanco et al 2008). The most specific (those tests correctly identifying patients without *H pylori* infection) ICT HpSA test was the Rapid Hp StAR test (91-100%), with the exception of one study that reported a specificity of 55.5 per cent (Blanco et al 2008).

Overall, accuracy of the ICT HpSA tests ranged between 50-93 per cent. Of concern is the high number of false negatives that occurred with the use of the majority of the ICT HpSA tests (range16-66%). However, the majority of studies using ICT HpSA tests reported *low* false positive numbers, indicating that a relatively small number of patients would receive inappropriate treatment.

Reported sensitivity values were consistently higher for the ELISA compared to the ICT HpSA tests. Of the ELISA HpSA tests, the most sensitive was the Amplified IDEIA HpStAR test (95 and 90%). Sensitivity and specificity of the ELISA HpSA tests compared to histology ranged from 87-95 and 67-100 per cent, respectively. Diagnostic accuracy of the ELISA HpSA tests was also consistently higher when compared to the ICT HpSA tests (range 87-93%).

A “test-and-treat” strategy describes the process of testing for *H pylori*, usually with a non-invasive test, and the provision of an appropriate antibiotic regime as treatment. A cost-effectiveness decision analysis model conducted in the United States reported that in 30-year olds, PPI therapy was the most cost-effective strategy with an ICER of US$9,740 however there was little difference between the two non-invasive “test-and-treat” strategies using UBT and HpSA, which both had an ICER of $10,800 in this group of patients. In 60-year olds, the two “test-and-treat” strategies using UBT and HpSA were cost-effective with ICERs of $6,740 and $6,830 respectively (Barton et al 2008).

Elwyn et al (2007) constructed a cost-effectiveness decision analysis model using three non-invasive tests: serology, UBT and HpSA tests. The most cost-effective was the HpSA test with 968 true outcomes for a cost of £17,275 or a mean cost of £17.84 per true positive test. The ICER for the HpSA when compared to serology was £10. The HpSA test remained the most cost-effective test when one-way sensitivity analyses were performed with varying prevalence rates (20 and 40%). In addition, a one-way sensitivity analysis demonstrated that the faecal antigen test performed better than serology or UBT in the case of a misdiagnosis.

In summary, the ELISA HpSA test appears to be more sensitive, however these assays are more time intensive and require the use of a laboratory based spectrophotometer. Although ICT HpSA tests can provide a rapid point-of-care diagnosis, the trade-off with the use of these tests is a decrease in sensitivity and diagnostic accuracy, which may result in patients receiving unnecessary treatment. It would appear that although HpSA tests are not as accurate as UBT, they are as, or more cost-effective than UBT for the

diagnosis of *H pylori*. In addition, for patients with dyspepsia, it appears that there is little difference in the cost-effectiveness of the two strategies of either empirical treatment with proton pump inhibitors or *H pylori* test-and-treat. However this situation may change with the falling prevalence of *H pylori* infection. There appears to be little difference in the cost-effectiveness of the two non-invasive tests used: UBT or HpSA.

Screening

H pylori is a *necessary* but *not sufficient* causal factor for gastric cancer and therefore it has been suggested that a screening program for *H pylori* would be able to detect asymptomatic but infected individuals *before* they have developed atrophic gastritis. By treating these individuals with an appropriate antibiotic regime and eradicating the *H pylori* infection, it is anticipated that their risk of developing symptoms of dyspepsia, peptic ulcer disease or gastric cancer would be markedly reduced or eliminated.

There are no clinical guidelines for the screening or management of *H pylori* infection in Australia or New Zealand. However, the Asia-Pacific guidelines *do not* recommend screening for *H pylori* in populations considered to be at low-risk of gastric cancer, such as Australia and New Zealand.

A large community-based Danish study randomised 5,749 individuals to *H pylori* screening and eradication and 6,781 were randomised to no screening. In the screened group, 17.5 per cent were positive for *H pylori* infection and offered eradication therapy. At follow-up, rates of dyspepsia were similar in both groups but when adjusted for an imbalance in dyspepsia at baseline, the odds ratio for *not* having dyspepsia for the screened group compared to the unscreened group was 1.27 (95% CI [1.14, 1.41]) at one-year, however this was markedly reduced at five-years (OR 1.04, 95% CI [0.93, 1.16]). For those individuals symptomatic for dyspepsia at baseline, there was no significant difference in the risk of remaining dyspeptic in the screened (51%) and unscreened (54%) groups (p=0.15). After re-analysis of data including only those individuals followed-up for the five years, there was an *insignificant decrease* in the rates of GP visits due to dyspepsia (from 3.1% to 2.8%) and the number of sick leave days due to dyspepsia (from 2.2% to 1.9%) in the screened group but a *significant* (p<0.001) increase in both rates in the unscreened group (2.5% to 3.1% for GP visits and 1.6% to 2.5% for sick leave days) (Hansen et al 2008).

Two large studies conducted in the United Kingdom screened general practice patients for *H pylori* infection with UBT. Patients found to be positive for *H pylori* infection were randomised to receive either eradication therapy or placebo. In one study, the number of primary care consultations for dyspepsia was reduced by 35 per cent in the eradication group compared to placebo (odds ratio 0.65, 95% CI [0.46, 0.94], p=0.021), however the costs to the NHS were £84.70 greater per participant in the eradication group, of which £83.40 was the cost of the eradication therapy (Lane et al 2006). In the remaining eradication RCT, eradication was successful in 74 per cent of the treatment group compared to five per cent of the placebo group at 2-year follow-up. However, symptoms of dyspepsia or gastro-oesophageal reflux were only slightly reduced in the treatment group (28%) compared to placebo (33%,

absolute-risk reduction 5%, 95% CI [1, 10]). Eradication therapy did not resolve dyspepsia symptoms in all patients. It would be recommended that patients presenting with symptoms post-eradication be investigated further to ascertain the cause of symptoms.

These results give an indication of the effectiveness of eradication therapy in *H pylori* positive patients, rather than the effectiveness of screening for *H pylori* infection. Interestingly, individuals made aware of their *H pylori* negative status were less likely to seek health care for dyspepsia (relative risk =0.81, 95% CI [0.67, 0.97]) than those in the placebo arm, indicating that population screening may reduce dyspepsia-related health-care costs in those individuals found to be *H pylori* negative as well as in those found to be *H pylori* positive (Ford et al 2005).

In summary, it would appear in populations with a relatively low prevalence of *H pylori* infection, that a *targeted*, rather than a population screening strategy would be more effective for the resolution of dyspepsia symptoms and for the reduction in the costs associated with treating the condition. In line with many established guidelines, patients presenting to their general practitioner with symptoms of dyspepsia should be tested for *H pylori* infection and treated if found to be positive. No studies were identified that reported on the impact of screening for *H pylori*, the subsequent eradication of infection and its long term impact on the incidence of gastric cancer. Studies such as this would require a long-term follow-up.

The most recent screening cost-effectiveness study to be published is a Markov model evaluating the economics of a *H pylori* screening programme, and the use of various diagnostic techniques within this strategy, for the prevention of gastric cancer (Xie et al 2009). The model compared the lifetime cost and effectiveness of four strategies for *H pylori* detection: no screening, serology using an ELISA, HpSA tests and UBT. Compared with the no-screening strategy in the base-case analysis, the ICER was C$29,800 per QALY for HpSA, C$33,000per QALY for serology and C$50,400 per QALY for UBT. Serology and the UBT were not cost-effective strategies over a wide range of willingness-to-pay values. The authors concluded that, although the UBT had the highest sensitivity and specificity values of all the diagnostic technologies evaluated, the most cost-effective strategy, depending on the willingness-to-pay threshold values, was either no screening or the HpSA tests.

Leivo et al (2004) conducted an economic model to evaluate the costs and benefits of population screening for *H pylori* infection in Finland. The cost per person invited to be screened was US$69 in the screening group and US$43 in the no-screening group, therefore the incremental cost per case was US$26 for the screening strategy. The incremental cost per case was highest in those aged 15 at time of screening ($36) and more favourable in older individuals with a *cost-saving* of $6 in those aged 45 years at time of screening. The incremental cost per treated *H pylori* infection due to screening was US$412.

A 2003 study evaluated the cost-effectiveness of population screening for *H pylori* infection for the prevention of gastric cancer and peptic ulcer disease in the United Kingdom. This study found that the number of deaths from gastric cancer prevented decreases as the age at screening increases. Screening

existing 40- to 49-year-olds and new 40-year-olds would prevent 16,263 deaths and would result in a cost per life-year saved of £5,866 in comparison with no screening programme. Serology was found to be more cost-effective than UBT. The sensitivity analysis indicated that increasing the age of the screening population, increasing the risk of peptic ulcers and gastric cancer amongst people with H. pylori, and increasing the *H pylori* prevalence *decreased* the cost-effectiveness of screening. Lowering the prevalence of *H pylori*, increasing the opportunistic eradication and lag, and altering the cancer and peptic ulcer disease outcomes *increased* the cost-effectiveness of screening to more than £10,000 per life year saved (Roderick et al 2003a; Roderick et al 2003b).

In summary, rapid HpSA stool antigen tests are not as sensitive nor as specific as a urea breath test, however the immunochromotographic HpSA tests are easy to perform in a clinic setting, give an instantaneous diagnosis and are relatively cheap. HpSA tests appear to be a cost-effective option when compared to UBT in a "test-and-treat" scenario for patients presenting with symptoms of dyspepsia. In population screening studies conducted on Western populations, reported rates of *H plyori* infection ranged from 16-28 per cent, with many of these individuals presenting with existing symptoms of dyspepsia. Most studies concluded that targeted screening of individuals presenting with symptoms of dyspepsia was a more cost-effective option than population screening. Whether rapid HpSA tests, especially immunochromotographic ones, are a cost-effective screening tool remains to be seen. In addition, the long term effect on rates of gastric cancer of screening for *H pylori* infection has yet to be established.

Appendix A: Levels of evidence

Level	Intervention [1]	Diagnostic accuracy [2]	Prognosis	Aetiology [3]	Screening Intervention
I [4]	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among consecutive persons with a defined clinical presentation[6]	A prospective cohort study[7]	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among non-consecutive persons with a defined clinical presentation[6]	All or none[8]	All or none[8]	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial[9] ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study[10] ▪ Interrupted time series without a parallel control group	Diagnostic case-control study[6]	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)[11]	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

Tablenotes

[1] Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b).

[2] The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes (Medical Services Advisory Committee 2005, Sackett and Haynes 2002).

[3] If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (ie. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilised.

[4] A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review *quality* should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

[5] The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting et al 2003).

[6] Well-designed population based case-control studies (eg. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice (Mulherin and Miller 2002).

[7] At study inception the cohort is either non-diseased or all at the same stage of the disease. A randomised controlled trial with persons either non-diseased or at the same stage of the disease in *both* arms of the trial would also meet the criterion for this level of evidence.

[8] All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

[9] This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C with statistical adjustment for B).

[10] Comparing single arm studies ie. case series from two studies. This would also include unadjusted indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C but where there is no statistical adjustment for B).

[11] Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question eg. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

Source: Hierarchies adapted and modified from: (Bandolier editorial 1999; Lijmer et al 1999; NHMRC 1999; Phillips et al 2001)

Appendix B: Profiles of studies

Helicobacter pylori rapid diagnostic test studies

Diagnostic level of evidence	Study	Location	Study design	Study population	Outcome assessed	Length of follow-up
III-2	Adiloglu, A.K. Isler, M. Goren, I. Candir, O. Senol, A. Onal, S. Karahan, N. (2007)	Isparta, Turkey	Cross classification of Premier Platinum HpSA ELISA compared to histology and RUT. Patients were considered positive for *H pylori* infection if both histology and RUT were positive.	102 consecutive patients with symptoms of dyspepsia for at least 3 months. Mean age 43.6 ± 14.2 years (range 19-73 years).	*H pylori* infection	N/A
III-2	Blanco, S. Forné, M. Lacoma, A. Prat, C. Cuesta, M.A. Latorre, I. Viver, J.M. Fernández, G. Molinos, S. Domínguez, J. (2008)	Barcelona, Spain	Cross classification of Premier Platinum HpSA EIA, Immunodiagnostik ELISA, Amplified, IDEIA™ HpStAR HpSA ELISA tests and *H pylori* Letitest, ImmunoCard STAT! HpSA, Rapid HpStAR™ ICT HpSA tests compared to histology, RUT, UBT. Patients were considered positive for *H pylori* infection if 2/3 reference standards were positive.	98 adult patients with duodenal ulcer (39%), gastric ulcer (7.5%), erosive duodenitis (6.3%), erosive gastritis (6.3%), non-erosive antral gastritis (12.5%) and hiatus hernia (5%). Mean age of 80 *H pylori* positive patients 52.2 ± 20.2 years. Mean age of 18 *H pylori* negative patients 48.5 ± 18.4 years.	*H pylori* infection	Patients considered positive for *H pylori* infection underwent further testing 6-weeks post-eradication therapy. H pylori status was confirmed using UBT as the reference standard, therefore results are not presented.
III-1	Calvet, X. Sánchez-Delgado, J. Montserrat, A. Lario, S. Ramíez-Lázaro, M.J. Quesada, M. Casalots, A. Suárez, D. Campo, R. Brullet, E. Junquera, F. Sanfeliu, I. Segura, F. (2009)	Barcelona, Spain	Cross classification of Amplified IDEIA™ Hp StAR ELISA HpSA test compared to histology, RUT, UBT. Patients were considered positive for *H pylori* infection if 2/3 reference standards were positive.	209 patients with symptoms of dyspepsia. Mean age 48.2 ± 14.2 years.	*H pylori* infection	N/A

III-2	Demiray, E. Yilmaz, Ö. Şarkiş, C. Soytürk, M. Şimşek, I. (2006)	Izmir, Turkey	Cross classification of Rapid STRIP!HpSA and *H pylori* antigen cassette ICT HpSA tests compared to histology, RUT, UBT. Patients were considered positive for *H pylori* infection if UBT was positive or both RUT and histopathology were positive. Patients were considered negative if both RUT and histology were negative.	22 patients with upper gastro-intestinal bleeding, mean age 58 ± 18 years (range 20-86 years).	*H pylori* infection	N/A
IV	Gisbert, J.P. de la Morena, F. Abraira, V. (2006)	Madrid, Spain	Meta-analysis of 22 studies. Cross classification HpSA tests compared to one or all of the following: endoscopy (histology), RUT, UBT, serology or culture. Studies used monoclonal and polyclonal (n= 13) or monoclonal alone (n=9) HpSA tests. One included study pre-selected patient samples post-endoscopy to be positive for *H pylori* (diagnostic yield study).	22 studies conducted on a European population. 5 studies conducted on children with remaining 17 studies conducted on adults.	*H pylori* infection	Some studies assessed *H pylori* status post-eradication therapy, however only 2 studies confirmed status with endoscopy/ histology, therefore results are not presented.
II	Krausse, R. Müller, G. Doniec, M. (2008)	Kiel, Germany	Cross classification of Rapid Hp StAR ICT test compared to histology, RUT and culture. Patients were considered positive for *H pylori* infection if 1/3 reference standards were positive.	72 consecutive patients, mean age 58.4 ± 12 years (range 24-88 years), with gastrointestinal symptoms.	*H pylori* infection	N/A

III-1	Kuloğlu, Z. Kansu, A. Kirsaçhoğlu, C.T. Üstündağ, G. Aysev, D. Ensari, A. Küçük, N. Ö. Girgin, N. (2008)	Ankara, Turkey	Cross classification of Rapid Hp StAR ICT test and UBT compared to histology. Patients were considered positive for *H pylori* infection if 1/3 reference standards were positive.	109 children and adolescents with abdominal symptoms, mean age 12.1 ± 3.1 years (range 5-17 years).	*H pylori* infection pre- and post-eradication therapy.	30-day eradication therapy post-diagnosis with follow-up testing 4-6 weeks after treatment cessation.

HpSA = *H pylori* stool antigen tests, RUT = rapid urease test, UBT = urea breath test, ICT = immunochromotographic test, ELISA = enzyme-linked immunosorbant assay, N/A = not applicable

Helicobacter pylori screening studies

Screening level of evidence	Study	Location	Study design	Study population	Outcome assessed	Length of follow-up
II	Hansen, J.M. Wildner-Christensen, M. Hallas, J. Schaffalitzky de Muckadell, O.B. (2008)	Odense, Denmark	Randomised controlled trial. All individuals in the *H pylori* screening group were screened using an in-office test*. All *H pylori* positive individuals were confirmed using UBT. Those positive by both tests were offered eradication therapy.	20,011 individuals aged 40-64 years, living in the city of Odense were randomised to the *H pylori* screen and treat group (n=5,749) or the unscreened control group (n=6,781).	*H pylori* infection. Symptoms of dyspepsia and quality of life assessed at 1- and 5-year follow-up.	1 and 5 years
IV	Lane, J.A. Murray, L.J. Noble, S. Egger, M. Harvey, I.M. Donovan, J.L. Nair, P. Harvey, R.F. (2002, 2004, 2006)	Bristol, UK	Screening was conducted as part of a RCT of eradication therapy. All eligible patients were screened with UBT. If positive for *H pylori* patients were randomised to eradication therapy or placebo. Therefore screening component of study is a case series.	27,536 urban-based patients aged 20-59 years from 7 primary care centres were invited to participate. 10,714 (38.9%) attended for screening and 10,537 were eligible.	*H pylori* infection	N/A
IV	Moayyedi, P. Feltbower, R. Brown, J. Mason, S Mason, J. Nathan, J. Richards, I.D.G. Dowell, A.C. Axon, A.T.R. Leeds HELP Study Group (2000)	Bradford and Leeds, UK	Screening was conducted as part of a RCT of eradication therapy. All eligible patients were screened with UBT. If positive for *H pylori* patients were randomised to eradication therapy or placebo. Therefore screening component of study is a case series.	32,929 urban-based patients aged 40-49 years from 36 primary care centres were invited to participate. 9,262 attended for screening and 8,407 evaluated at baseline.	*H pylori* infection	N/A

UBT = urea breath test, FlexPack HP, Abbott Laboratories

Appendix C: Glossary

Allele: alternative form of a gene. One of the different forms of a gene that can exist at a single locus.

Apoptosis: programmed cell death.

Dyspepsia: the impairment of the power of function of digestion, usually applied to epigastric discomfort following meals.

Dysplasia: abnormality of development, in pathology, alteration in size, shape and organisation of adult cells.

False positive rate: complement of test specificity.

False negative rate: complement of test sensitivity.

Gastritis: inflammation of the stomach.

ICER: The incremental cost-effectiveness ratio, or ICER, represents the additional cost of one unit of outcome gained (a QALY, LYG or infection averted) by a healthcare intervention or strategy, when compared to the next best alternative, mutually exclusive intervention or strategy. The ICER is calculated by dividing the net cost of the intervention, by the total number of incremental health outcomes prevented by the intervention (HealthEconomics.nl 2009).

I-squared statistic: the I^2 statistic is a measure of the total variation across studies due to heterogeneity, expressed as a percentage. I^2 tells us whether or not the variation is larger than what would be expected by chance. The I^2 statistic does not depend on the number of studies included in the meta-analysis. An I^2 greater than 50% is considered large enough to question whether the studies should have been combined in a meta-analysis (ie there is too much heterogeneity) (Perera & Heneghan 2008).

Likelihood ratios: The likelihood ratio incorporates both the sensitivity and specificity of the test and provides a direct estimate of how much a test result will change the odds of having a disease. The likelihood ratio for a **positive** result (LR+) tells you how much the odds of the disease increase when a test is positive. The likelihood ratio for a **negative** result (LR-) tells you how much the odds of the disease decrease when a test is negative. The likelihood ratio of a positive test result (LR+) is sensitivity divided by 1- specificity. The likelihood ratio of a negative test result (LR-) is 1- sensitivity divided by specificity.

$$LR^{+} = \frac{sensitivity}{1 - specificity} \qquad LR^{-} = \frac{1 - sensitivity}{specificity}$$ (Simon 2008)

Negative predictive value (NPV): The proportion of patients with a negative test result who are correctly diagnosed ie the number of true negatives divided by the total number who tested negative.

PCR: Polymerase chain reaction: Amplification of a DNA sequence using primers, one complementary to the (+)- strand at one end of the sequence to be amplified and the other complementary to the (-)- strand at the other end. Because the newly synthesized DNA strands can subsequently serve as additional templates for the same primer sequences, successive rounds of primer annealing, strand elongation, and dissociation produce rapid and highly specific amplification of the desired

sequence. PCR also can be used to detect the existence of the defined sequence in a DNA sample.

Polymorphism: the occurrence in a population (or among populations) of several phenotypic forms associated with alleles of one gene or homologs of one chromosome. See genetic polymorphism.

Positive predictive value (PPV): The proportion of patients with a positive test result who are correctly diagnosed ie the number of true positives divided by the total number who tested positive.

QALY: The quality adjusted life year (**QALY**) is a unit commonly used to measure health gain (or health effects), where the duration of the survival is adjusted by the patients quality of life. This is done by multiplying the duration of survival with a utility weight that represents the quality of life of the health state experienced during that time (HealthEconomics.nl 2009).

Reference standard: an independently applied test that is compared to the diagnostic test being evaluated in order to ascertain the accuracy of the new diagnostic test. Required for the verification of true negatives and true positives.

Screening: the performance of tests on asymptomatic individuals in order to detect a disease or medical condition at an earlier stage than would otherwise be the case. A screening test is not intended to be diagnostic, an individual with a positive or suspicious result must be referred for diagnosis and treatment.

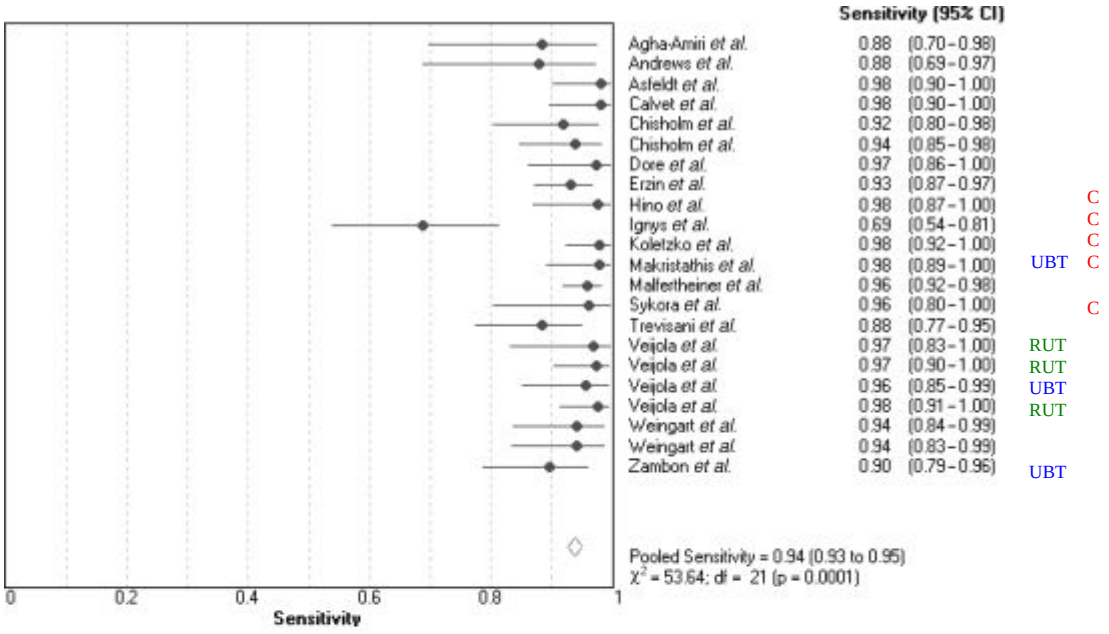
Sensitivity: the ability of a test to correctly identify those individuals with the disease or the proportion of individuals who have the disease who also returned a positive test result for the disease.

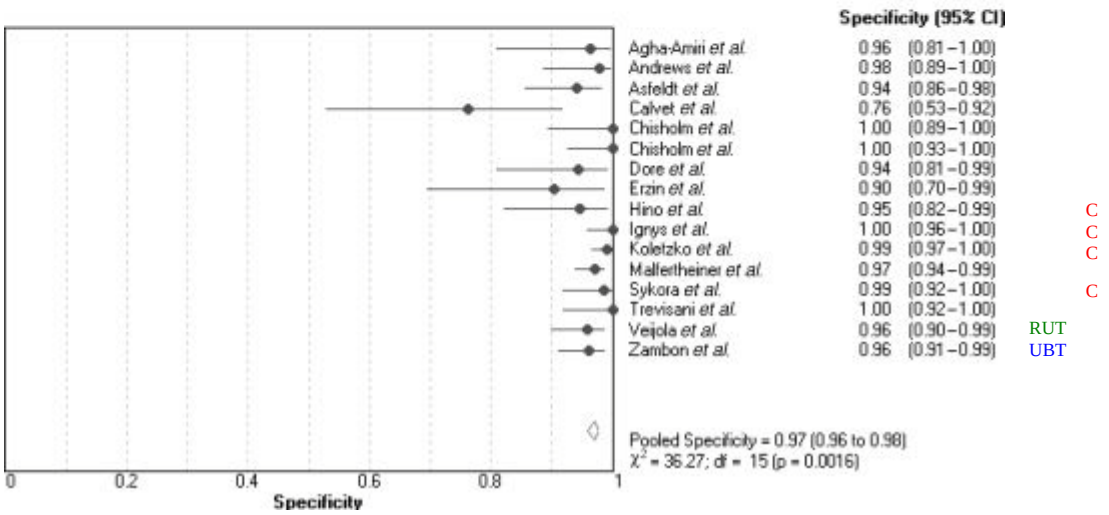
Specificity: the ability of a test to correctly identify those individuals who do not have the disease or the proportion of individuals who do not have the disease who also returned a negative test result for the disease.

Vacuolation: formation of vacuoles.

Appendix C: Additional study information

Sensitivity and specificity data obtained from studies included in the meta-analysis by Gisbert et al (2006). Those studies which did not use histology as the reference standard are indicated by the method used (either urea breath test or rapid urease test). Studies conducted in children are indicated by the letter C, with the remaining studies conducted on adults





Appendix D: HTA internet sites

AUSTRALIA

- Centre for Clinical Effectiveness, Monash University
  http://www.mihsr.monash.org/cce/

- Health Economics Unit, Monash University
  http://chpe.buseco.monash.edu.au

AUSTRIA

- Institute of Technology Assessment / HTA unit
  http://www.oeaw.ac.at/ita/welcome.htm

CANADA

- Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) http://www.aetmis.gouv.qc.ca/site/index.php?accueil

- Alberta Heritage Foundation for Medical Research (AHFMR)
  http://www.ahfmr.ab.ca/publications.html

- Canadian Agency for Drugs and Technology in Health (CADTH)
  http://www.cadth.ca/index.php/en/

- Canadian Health Services Research Foundation
  http://www.chsrf.ca/about/index_e.php

- Centre for Health Economics and Policy Analysis (CHEPA), McMaster University http://www.chepa.org

- Centre for Health Services and Policy Research (CHSPR), University of British Columbia http://www.chspr.ubc.ca

- Health Utilities Index (HUI)
  http://www.fhs.mcmaster.ca/hug/index.htm

- Institute for Clinical and Evaluative Studies (ICES)
  http://www.ices.on.ca

DENMARK

- Danish Institute for Health Technology Assessment (DIHTA)
  http://www.dihta.dk/publikationer/index_uk.asp

- Danish Institute for Health Services Research (DSI)
  http://www.dsi.dk/engelsk.html

FINLAND

- FINOHTA http://www.stakes.fi/finohta/e/

FRANCE

- L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES) http://www.anaes.fr/

GERMANY

- German Institute for Medical Documentation and Information (DIMDI) / HTA http://www.dimdi.de/dynamic/en/

THE NETHERLANDS

- Health Council of the Netherlands Gezondheidsraad http://www.gr.nl/adviezen.php

NEW ZEALAND

- New Zealand Health Technology Assessment (NZHTA) http://nzhta.chmeds.ac.nz/

NORWAY

- Norwegian Centre for Health Technology Assessment (SMM) http://www.kunnskapssenteret.no/

SPAIN

- Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"I/Health Technology Assessment Agency (AETS) http://www.juntadeandalucia.es/salud/orgdep/aetsa/default.asp

- Catalan Agency for Health Technology Assessment (CAHTA) http://www.gencat.net/salut/depsan/units/aatrm/html/en/Du8/index.html

SWEDEN

- Swedish Council on Technology Assessment in Health Care (SBU) http://www.sbu.se/en/

- Center for Medical Health Technology Assessment http://www.cmt.liu.se/

SWITZERLAND

- Swiss Network on Health Technology Assessment (SNHTA) http://www.snhta.ch/

UNITED KINGDOM

- NHS Quality Improvement Scotland http://www.nhshealthquality.org/nhsqis/qis_display_home.jsp?pContentID=43&p_applic=CCC&pElementID=140&pMenuID=140&p_service=Content.show&

- National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA) http://www.ncchta.org/

- University of York NHS Centre for Reviews and Dissemination (NHS CRD) http://www.york.ac.uk/inst/crd/

- National Institute for Clinical Excellence (NICE) http://www.nice.org.uk/

UNITED STATES

- Agency for Healthcare Research and Quality (AHRQ) http://www.ahrq.gov/clinic/techix.htm

- Harvard School of Public Health – Cost-Utility Analysis Registry http://www.tufts-nemc.org/cearegistry/index.html

- U.S. Blue Cross/ Blue Shield Association Technology Evaluation Center (TEC) http://www.bcbs.com/tec/index.html

References

AACR, A. (2008). *Cancer in Australia: an overview, 2008,* Australian Institute of Health and Welfare & Australasian Association of Cancer Registries, Canberra. http://www.aihw.gov.au/publications/can/ca08/ca08.pdf.

ACTR (2007). [Internet]. Australian Clinical Trials Registry. Available from: http://www.anzctr.org.au/default.aspx [Accessed 11th March, 2009].

Adiloglu, A. K., Isler, M. et al (2007). 'Quantitative correlation of Helicobacter pyloris stool antigen (HpSA) test with the severity of H. pylori-related gastritis', *Tohoku Journal of Experimental Medicine,* 212 (2), 159-167.

AIHW (2009). *Principle diagnosis data cubes and Cancer incidence data cubes* [Internet]. Australian Institute of Health and Welfare. Available from: http://www.aihw.gov.au/dataonline.cfm [Accessed 16th April, 2009].

Bandolier editorial (1999). *Diagnostic testing emerging from the gloom?* [Internet]. Bandolier. Available from: http://www.jr2.ox.ac.uk/bandolier/band70/b70-5.html [Accessed 2004].

Barton, P. M., Moayyedi, P. et al (2008). 'A second-order simulation model of the cost-effectiveness of managing dyspepsia in the United States', *Med Decis Making,* 28 (1), 44-55.

Beswick, E. J., Suarez, G. & Reyes, V. E. (2006). 'H pylori and host interactions that influence pathogenesis', *World Journal Of Gastroenterology,* 12 (35), 5599-5605.

Blanco, S., Forne, M. et al (2008). 'Comparison of stool antigen immunoassay methods for detecting Helicobacter pylori infection before and after eradication treatment', *Diagnostic Microbiology And Infectious Disease,* 61 (2), 150-155.

Calvet, X., Sanchez-Delgado, J. et al (2009). 'Accuracy of diagnostic tests for Helicobacter pylori: a reappraisal', *Clin Infect Dis,* 48 (10), 1385-1391.

CCT (2009). [Internet]. Current Controlled Trials. Available from: http://controlled-trials.com/ [Accessed 11th March, 2009].

Chisholm, S. A., Watson, C. L. et al (2004). 'Non-invasive diagnosis of Helicobacter pylori infection in adult dyspeptic patients by stool antigen detection: does the rapid immunochromatography test provide a reliable alternative to conventional ELISA kits?' *Journal of Medical Microbiology,* 53 (7), 623-627.

Day, A. S., Mitchell, H. M. & Bohane, T. D. (2004). 'Management guidelines for Helicobacter pylori infection: Utilization by paediatric gastroenterologists in Australasia', *Journal Of Paediatrics And Child Health,* 40 (4), 195-200.

Demiray, E., Yilmaz, O. et al (2006). 'Comparison of invasive methods and two different stool antigen tests for diagnosis of H pylori infection in patients with gastric bleeding', *World J Gastroenterol,* 12 (26), 4206-4210.

di Mario, F. & Cavallaro, L. G. (2008). 'Non-invasive tests in gastric diseases', *Digestive and Liver Disease,* 40 (7), 523-530.

Dzierzanowska-Fangrat, K., Lehours, P. et al (2006). 'Diagnosis of Helicobacter pylori infection', *Helicobacter,* 11, 6-13.

Elwyn, G., Taubert, M. et al (2007). 'Which test is best for Helicobacter pylori? A cost-effective model using decision analysis', *British Journal of General Practice,* 57 (538), 401-403.

Fawcett, J. P., Barbezat, G. O. et al (2005). 'Helicobacter pylori serology in a birth cohort of New Zealanders from age 11 to 26', *World Journal of Gastroenterology,* 11 (21), 3273-3276.

Ferreira, A. C., Isomoto, H. et al (2008). 'Helicobacter and gastric malignancies', *Helicobacter,* 13, 28-34.

Fock, K. M., Talley, N. et al (2008). 'Asia-Pacific consensus guidelines on gastric cancer prevention', *J Gastroenterol Hepatol,* 23 (3), 351-365.

Ford, A. C., Forman, D. et al (2005). 'A community screening program for Helicobacter pylori saves money: 10-year follow-up of a randomized controlled trial', *Gastroenterology,* 129 (6), 1910-1917.

Fraser, A. (2004). 'Helicobacter pylori: a historical perspective 1983-2003', *New Zealand Medical Journal,* 117 (1194), U896.

Genta, R. M. (2004). 'Screening for gastric cancer: does it make sense?' *Alimentary Pharmacology & Therapeutics,* 20 (S2), 42-47.

Gisbert, J. R., de la Morena, F. & Abraira, V. (2006). 'Accuracy of monoclonal stool antigen test for the diagnosis of H-pylori infection: A systematic review and meta-analysis', *American Journal Of Gastroenterology,* 101 (8), 1921-1930.

Granstrom, M., Lehours, P. et al (2008). 'Diagnosis of Helicobacter pylori', *Helicobacter,* 13, 7-12.

Gray, M. (2001). *Evidence-Based Healthcare: How to Make Health Policy and Management Decisions*. 2nd edition Churchill Livingstone, London.

Hamashima, C., Shibuya, D. et al (2008). 'The Japanese guidelines for gastric cancer screening', *Japanese Journal of Clinical Oncology,* 38 (4), 259-267.

Hansen, J. M., Wildner-Christensen, M. et al (2008). 'Effect of a community screening for Helicobacter pylori: A 5-yr follow-up study', *American Journal of Gastroenterology,* 103 (5), 1106-1113.

Harvey, R. F., Lane, J. A. et al (2004). 'Randomised controlled trial of effects of Helicobacter pylori infection and its eradication on heartburn and gastro-oesophageal reflux: Bristol helicobacter project', *BMJ,* 328 (7453), 1417.

HealthEconomics.nl (2009). *Health Economics and Pharmacoeconomics Glossary of Terms* [Internet]. Pharmacoeconomics group of the Pharmaco-epidemiology Department of the University of Groningen. Available from: http://www.healtheconomics.nl/W/HealthEconomics.nl [Accessed 6th May, 2009].

Hirschl, A. M. & Makristathis, A. (2007). 'Methods to detect Helicobacter pylori: From culture to molecular biology', *Helicobacter,* 12, 6-11.

Holland, S. (2007). *Public Health Ethics*. Cambridge University Press, Cambridge.

Jarbol, D. E., Kragstrup, J. et al (2006). 'Proton pump inhibitor or testing for Helicobacter pylori as the first step for patients presenting with dyspepsia? A cluster-randomized trial', *Am J Gastroenterol,* 101 (6), 1200-1208.

Johnston, R., Vu, T. et al (2006). *Carbon-labelled urea breath tests for the diagnosis of Helicobacter pylori infection,* The Medical Services Advisory Committee, Canberra. http://www.msac.gov.au/internet/msac/publishing.nsf/Content/4753418A5C8F33DDCA25745E000A3933/$File/1085%20-%20Carbon-labelled%20urea%20breath%20tests%20Report.pdf.

Kandulski, A., Selgrad, M. & Malfertheiner, P. (2008). 'Helicobacter pylori infection: a clinical overview', *Dig Liver Dis,* 40 (8), 619-626.

Krausse, R., Muller, G. & Doniec, M. (2008). 'Evaluation of a rapid new stool antigen test for diagnosis of Helicobacter pylori infection in adult patients', *Journal of Clinical Microbiology,* 46 (6), 2062-2065.

Kuloglu, Z., Kansu, A. et al (2008). 'A rapid lateral flow stool antigen immunoassay and C-14-urea breath test for the diagnosis and eradication of Helicobacter pylori infection in children', *Diagnostic Microbiology And Infectious Disease,* 62 (4), 351-356.

Lane, J. A., Harvey, R. F. et al (2002). 'A placebo-controlled randomized trial of eradication of Helicobacter pylori in the general population: study design and response rates of the Bristol Helicobacter Project', *Control Clin Trials,* 23 (3), 321-332.

Lane, J. A., Murray, L. J. et al (2006). 'Impact of Helicobacter pylori eradication on dyspepsia, health resource use, and quality of life in the Bristol helicobacter project: randomised controlled trial', *British Medical Journal,* 332 (7535), 199-202.

Lee, Y. C., Lin, J. T. et al (2008). 'Is eradication of Helicobacter pylori the feasible way to prevent gastric cancer? New evidence and progress, but still a long way to go', *Journal of The Formosan Medical Association,* 107 (8), 591-599.

Lee, Y. C., Lin, J. T. et al (2007). 'Cost-effectiveness analysis between primary and secondary preventive strategies for gastric cancer', *Cancer Epidemiology Biomarkers & Prevention,* 16 (5), 875-885.

Leivo, T., Salomaa, A. et al (2004). 'Cost-benefit analysis of Helicobacter pylori screening', *Health Policy,* 70 (1), 85-96.

Leja, M. & Dumitrascu, D. L. (2007). 'Should we screen for Helicobacter pylori to prevent gastric cancer?' *Digestive Diseases,* 25 (3), 218-221.

Lijmer, J. G., Mol, B. W. et al (1999). 'Empirical evidence of design-related bias in studies of diagnostic tests.' *Journal of the American Medical Association,* 282 (11), 1061 - 1066.

Lin, F. Y. H., Sabri, M. et al (2004). 'Development of a novel microfluidic immunoassay for the detection of Helicobacter pylori infection', *Analyst,* 129 (9), 823-828.

Lochhead, P. & El-Omar, E. M. (2008). 'Gastric cancer', *British Medical Bulletin,* 85, 87-100.

Malfertheiner, P., Megraud, F. et al (2007). 'Current concepts in the management of Helicobacter pylori infection: the Maastricht III consensus report', *Gut,* 56 (6), 772-781.

Marshall, B. & Schoep, T. (2007). 'Helicobacter pylori as a vaccine delivery system', *Helicobacter*, 12 (S2), 75-79.

Mason, J. M., Raghunath, A. S. et al (2008). 'Helicobacter pylori eradication in long-term proton pump inhibitor users is highly cost-effective: economic analysis of the HELPUP trial', *Aliment Pharmacol Ther*, 28 (11-12), 1297-1303.

Medicare Australia (2009). *Medicare Benefits Schedule* [Internet]. The Australian Government. Available from: http://www.medicareaustralia.gov.au/provider/medicare/mbs.jsp [Accessed 16th April, 2009].

Megraud, F. & Lehours, P. (2007). 'Helicobacter pylori detection and antimicrobial susceptibility testing', *Clin Microbiol Rev*, 20 (2), 280-322.

Meridian Bioscience Europe (2009). *ImmunoCard STAT! HpSA* [Internet]. Available from: http://www.mdeur.com/products/750720.htm [Accessed 7th April, 2009].

Miki, K. (2006). 'Gastric cancer screening using the serum pepsinogen test method', *Gastric Cancer*, 9 (4), 245-253.

Moayyedi, P. (2007). 'The health economics of Helicobacter pylori infection', *Best Practice & Research In Clinical Gastroenterology*, 21 (2), 347-361.

Moayyedi, P., Feltbower, R. et al (2000a). 'Effect of population screening and treatment for Helicobacter pylori on dyspepsia and quality of life in the community: a randomised controlled trial. Leeds HELP Study Group', *Lancet*, 355 (9216), 1665-1669.

Moayyedi, P., Soo, S. et al (2000b). 'Systematic review and economic evaluation of Helicobacter pylori eradication treatment for non-ulcer dyspepsia. Dyspepsia Review Group', *BMJ*, 321 (7262), 659-664.

Moujaber, T., MacIntyre, C. R. et al (2008). 'The seroepidemiology of Helicobacter pylori infection in Australia', *International Journal Of Infectious Diseases*, 12 (5), 500-504.

NHMRC (1999). *Familial aspects of cancer: A guide to clinical practice*, National Health and Medical Research Council, Commonwealth of Australia, Canberra, ACT.

NSC (2003). *Criteria for appraising the viability, effectiveness and appropriateness of a screening programme* [Internet]. UK National Screening Committee. Available from: http://www.nsc.nhs.uk/pdfs/criteria.pdf [Accessed 30th September, 2008].

Perera, R. & Heneghan, C. (2008). 'Interpreting meta-analysis in systematic reviews', *Evid Based Med*, 13 (3), 67-69.

Phillips, B., Ball, C. et al (2001). *Levels of Evidence and Grades of Recommendations* [Internet]. Centre for Evidence-Based Medicine, Oxford, UK. Available from: Available from: http://www.cebm.net/levels_of_evidence.asp [Accessed 28th January, 2004].

Ricci, C., Holton, J. & Vaira, D. (2007). 'Diagnosis of Helicobacter pylori: invasive and non-invasive tests', *Best Pract Res Clin Gastroenterol*, 21 (2), 299-313.

Roderick, P., Davies, R. et al (2003a). *The cost-effectiveness of screening for helicobacter pylori to reduce mortality and morbidity from gastric cancer and peptic ulcer disease: a discrete event simulation model,* National Coordinating Centre for Health Technology Assessments, Southampton. http://www.hta.ac.uk/fullmono/mon706.pdf.

Roderick, P., Davies, R. et al (2003b). 'Cost-effectiveness of population screening for Helicobacter pylori in preventing gastric cancer and peptic ulcer disease, using simulation', *J Med Screen,* 10 (3), 148-156.

Salomaa, A., Kosunen, T. U. & A., A. (1998). '"Screen and treat Helicobacter pylori gastritis" project in a western community', *Gut,* 43 (Suppl 2), A112.

Simon, S. (2008). *What is a likelihood ratio?* [Internet]. Children's Mercy Hospitals and Clinics. Available from: http://www.childrens-mercy.org/stats/definitions/likelihood.htm [Accessed 29th April, 2009].

Stenström, B., Mendis, A. & Marshall, B. (2008). 'Helicobacter pylori: the latest in diagnosis and treatment', *Australian Family Physician,* 37 (8), 608-612.

Sun, L. P., Gong, Y. H. et al (2008). 'Follow-up study on a high risk population of gastric cancer in north China by serum pepsinogen assay', *Journal Of Digestive Diseases,* 9 (1), 20-26.

Sun, L. P., Gong, Y. H. et al (2007). 'Serum pepsinogen levels and their infiuencing factors: A population-based study in 6990 Chinese from North China', *World Journal Of Gastroenterology,* 13 (48), 6562-6567.

Talley, N. J. (2005) In *Medical Journal of Australia, 182, 2; 2005; 205-206,* Vol. 182, pp. 205-206.

Trawax Pty Ltd (2009). *CLOtest* [Internet]. Available from: http://www.trawax.se/produkt.html [Accessed 7th April, 2009].

Vorobjova, T., Watanabe, T. & Chiba, T. (2008). 'Helicobacter pylori immunology and vaccines', *Helicobacter,* 13, 18-22.

Walker, M. M., Teare, L. & McNulty, C. (2008). 'Gastric cancer and Helicobacter pylori: the bug, the host or the environment? - art. no. 169', *Postgraduate Medical Journal,* 84 (990), 169.

Wen, S. & Moss, S. F. (2008). 'Helicobacter pylori virulence factors in gastric carcinogenesis', *Cancer Lett.*

Wilson, J. M. G. & Jungner, G. (1968). *Principles and practices of screening for disease. Public health paper,* World Health Organization, Geneva.

Windsor, H. M., Abioye-Kuteyi, E. A. et al (2005). 'Prevalence of Helicobacter pylori in Indigenous Western Australians: comparison between urban and remote rural populations', *Medical Journal of Australia,* 182 (5), 210-213.

Xie, F., Luo, N. et al (2008a). 'Cost-effectiveness analysis of Helicobacter pylori screening in prevention of gastric cancer in Chinese', *International Journal Of Technology Assessment In Health Care,* 24 (1), 87-95.

Xie, F., Luo, N. & Lee, H. P. (2008b). 'Cost effectiveness analysis of population-based serology screening and 13C-Urea breath test of Helicobacter pylori to prevent gastric cancer: A Markov model', *World Journal of Gastroenterology,* 14 (19), 3021-3027.

Xie, F., O'Reilly, D. et al (2009). 'Illustrating economic evaluation of diagnostic technologies: comparing Helicobacter pylori screening strategies in prevention of gastric cancer in Canada', *J Am Coll Radiol*, 6 (5), 317-323.

Yeh, J. M., Kuntz, K. M. et al (2009). 'Exploring the cost-effectiveness of Helicobacter pylori screening to prevent gastric cancer in China in anticipation of clinical trial results', *International Journal of Cancer*, 124 (1), 157-166.

You, J. H., Wong, P. L. & Wu, J. C. (2006). 'Cost-effectiveness of Helicobacter pylori "test and treat" for patients with typical reflux symptoms in a population with a high prevalence of H. pylori infection: a Markov model analysis', *Scand J Gastroenterol*, 41 (1), 21-29.