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Initially, six HTA panels (pharmaceuticals, acute sector, primary and community care, diagnostics and imaging, population screening, methodology) helped to set the research priorities for the HTA Programme. However, during the past few years there have been a number of changes in and around NHS R&D, such as the establishment of the National Institute for Clinical Excellence (NICE) and the creation of three new research programmes: Service Delivery and Organisation (SDO); New and Emerging Applications of Technology (NEAT); and the Methodology Programme.

This has meant that the HTA panels can now focus more explicitly on health technologies ('health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long term care) rather than settings of care. Therefore the panel structure has been redefined and replaced by three new panels: Pharmaceuticals; Therapeutic Procedures (including devices and operations); and Diagnostic Technologies and Screening.

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The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for the recommendations for policy contained herein. In particular, policy options in the area of screening will be considered by the National Screening Committee. This Committee, chaired by the Chief Medical Officer, will take into account the views expressed here, further available evidence and other relevant considerations.

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List of abbreviations

CI	confidence interval
CLO	Campylobacter-like organism
FCE	finished consultant episode
GP	general practitioner
HES	hospital episode statistics
IARC	International Agency on Research in Cancer
LYS	life-year saved
NSAID	non-steroidal anti-inflammatory drug
PAM	proton pump inhibitor, amoxicillin, metronidazole
PCM	proton pump inhibitor, clarithromycin, metronidazole
PCA	proton pump inhibitor, clarithromycin, amoxicillin
PPI	proton pump inhibitor
NICE	National Institute for Clinical Excellence
POST	patient-oriented simulation technique
RCT	randomised controlled trial
UBT	urea breath test

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

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Executive summary

Background

Helicobacter pylori is a Gram-negative bacterium that causes chronic inflammation of the stomach (gastritis). Such infection is a major cause of peptic ulcer disease and gastric cancer.

H. pylori infection fulfils many of the criteria for population screening. It can be detected by a simple test, and eradicated effectively. This speeds peptic ulcer healing and prevents recurrence, but the effect that eradicating *H. pylori* has on the risk of gastric cancer is unknown. Screening may not be cost-effective, given the decline in *H. pylori* prevalence and in gastric cancer, the scope for opportunistic eradication of *H. pylori* and the possibility of antibiotic resistance.

Objective

The objective of the study was to develop a discrete-event simulation model to evaluate the cost-effectiveness of population screening for *H. pylori* in England and Wales to prevent both gastric cancer and peptic ulcer disease.

Method

A model was developed using the 'patient-oriented simulation technique'. In this model, without screening most *H. pylori*-positive individuals remained asymptomatic, but a proportion developed dyspepsia and presented to primary care where testing and eradication therapy could be given. *H. pylori*-positive individuals were assigned increased risks of developing peptic ulcer disease and gastric cancer. In the screening scenarios, the population was invited to attend screening; those found to be *H. pylori*-positive were offered eradication therapy. The risk of developing peptic ulcer was considered to reduce immediately to that of *H. pylori*-negative individuals. The effect of eradication on gastric cancer risk was modelled by assuming a time lag before such risk reverted to *H. pylori*-negative levels. UK data were used where possible. The decline in gastric cancer incidence was taken into account by age cohort modelling.

Costs were NHS costs based at year 2000 prices. Discounting used base rates of 6% for both costs and benefits. The model was run for an 80-year period for the base case, to allow the impact of screening on gastric cancer risk to accrue. Sensitivity analyses were performed, to explore different scenarios and where there was uncertainty about the estimated values used in the model. Both incident and prevalent screening rounds were modelled, using the population of England and Wales. There were four age-related scenarios: screen all people aged 20–49 as a prevalent round and then 20-year-olds for the next 20 years as an incident round; screen those aged 30–49 as a prevalent round and then 30-year-olds for 30 years as an incident round; screen those aged 40–49 as a prevalent round and then 40-year-olds for 40 years as an incident round, and finally screen all 50-year-olds for 50 years as an incident round.

Results

Population screening would involve screening approximately 25 million individuals if uptake was 70%, with over 5 million people being treated. The number of deaths prevented falls with increasing age at screening, but so does the present value of costs because there would be less prevalent screening and costs are deferred.

In the base case the cost-effectiveness of *H. pylori* screening improves with age and is under £10,000 per life-year saved (LYS) for all age groups, though over an 80-year follow-up. Lowering the discount rate for benefits significantly improves the cost/LYS to under £2000 in all groups. Increasing the time lag for reversion of gastric cancer risk to 20 years or increasing the level of opportunistic eradication reduces the relative advantage for screening. Screening at age 40 might be the most pragmatic policy, balancing cost-effectiveness and the feasibility of screening.

The cost/LYS for the base run at age 40 is £5866 falling to £1027 if the benefit is discounted at 1.5%. Screening by serology is more cost-effective than using the urea breath test. Using a less efficacious but cheaper eradication regimen is as

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cost-effective but with fewer deaths prevented. The cost-effectiveness is sensitive to the *H. pylori* prevalence, lag time, relative risk, cohort estimate and compliance. Moreover, cost/LYS rises to over £20,000 if there is a high level of opportunistic eradication of *H. pylori* in patients presenting with dyspepsia and a reduced efficacy of eradication on gastric cancer risk.

The benefits of screening take time to accrue and are very sensitive to the discount rate. At 6% rates the cost-effectiveness does not fall below £20,000 for 30 years.

Conclusion

Population screening for *H. pylori* is likely to be cost-effective with a cost/LYS of under £10,000 for the base assumptions, which compares favourably with other screening programmes. However the benefits take time to accrue and this cost/LYS is over an 80-year follow-up. Once-only screening at age 40 with a prevalent round for people aged 40–49 appears to be the most pragmatic policy. A major uncertainty is the effect of eradication of *H. pylori* on gastric cancer risk. The cost-effectiveness of *H. pylori* screening would be reduced if there were extensive *H. pylori* opportunistic testing of all dyspeptic individuals presenting to primary care.

Policy implications

A national *H. pylori* screening programme of prevalent 40 to 49-year-olds and incident 40-year-olds may be cost-effective. It would significantly reduce the incidence of peptic ulcers and gastric cancer at a relatively low cost to the NHS. However there is some uncertainty over some of the estimates, notably the efficacy of eradication in preventing gastric cancer and complicated ulcer, and concerning antibiotic resistance. A major drawback is the delay before benefits accrue. More evidence is needed before it can be recommended.

Research recommendations

Key issues that could be addressed include:

- The association between *H. pylori*, non-steroidal anti-inflammatory drugs (NSAIDs) and complicated peptic ulcer disease, in order to derive the independent relative risk of complicated ulcer in *H. pylori*-positive individuals compared with those who are *H. pylori*-negative. Case–control studies are needed; these could be undertaken relatively quickly.
- The efficacy of eradication of *H. pylori* on pre-cancerous pathological changes; the results of current trials concerning gastric metaplasia are awaited.
- The cost-effectiveness of a 'test and treat' policy for peptic ulcer disease (a trial funded by the Medical Research Council is currently underway), and the impact of such a policy on opportunistic screening.
- The model could be used to re-evaluate the cost-effectiveness of *H. pylori* screening in the light of updated data on the key parameters. If appropriate, a pilot *H. pylori* screening programme could be evaluated, probably screening all 40 to 49-year-olds as a prevalent round and then all individuals as they reach the age of 40. This would provide information on compliance, eradication and reinfection (in a sample), the impact on peptic ulcer disease and gastric pathology, and the impact of opportunistic testing in the non-screened group.

Finally, the model can be used to evaluate the effects of screening in other populations.

Chapter 1

Background and study aim

Background

Helicobacter pylori is a Gram-negative microaerophilic rod-shaped bacterium. It resides in the stomach and causes a chronic active inflammation,[1] and once acquired infection lasts several decades.[2] It is an important risk factor for both gastric cancer and peptic ulcer disease.

The International Agency for Research in Cancer (IARC) have reviewed the considerable observational evidence and consider *H. pylori* to be a causal factor for gastric cancer.[3] The strongest support comes from six prospective studies which have used a nested case–control design on baseline blood samples to show that *H. pylori* infection (defined by serological status) is an important risk factor for gastric adenocarcinoma (excluding cardia lesions). The relative risk of *H. pylori* positivity varied from 1.1 to 6.0 and it has been suggested that between 30% and 90% of gastric cancers could be attributed to *H. pylori* infection.[4–6] Pooling of three of the studies and analysis of paticipants with a 15-year follow-up gave a even higher risk of 8.7 for gastric cancer.[7] The Eurogast study, an ecological investigation, showed a strong positive correlation between *H. pylori* prevalence and gastric cancer incidence in 15 countries.[8] Other risk factors for gastric cancer include a high salt intake, ingestion of nitrosamine precursors, and low anti-oxidant consumption.[9]

Although gastric cancer incidence and mortality have declined in Western countries over the last few decades,[10,11] this cancer remains an important public health problem. It ranks fifth in both men and women for cancer incidence and has accounted for 4% of all cancer cases in the UK.[12] Age-specific incidence rises continuously with age, and absolute numbers will rise because of the ageing of the population. Moreover survival is poor as patients present at a late stage: 70% are dead within 1 year, and the 5-year relative survival is only 10%. There has been little improvement over the last few decades. Screening methods using various cancer markers have been proposed but have not proved to be cost-effective.[13]

The pathogenesis of gastric cancer follows a multi-step pattern of progression, from gastritis to gastric atrophy, then to intestinal metaplasia and finally to gastric cancer.[14] Although the reduction in incidence of gastric cancer in patients given *H. pylori* eradication therapy is currently being studied, it will be another 15–20 years before results are available. However, studies of gastric atrophy[15] and intestinal metaplasia suggest that eradication may be of benefit.[16]

It is now well established that *H. pylori* is the major cause of peptic ulcer disease,[17] with over 90% of duodenal and 70% of gastric ulcers being associated with *H. pylori*; the rest are mainly found to be related to the use of non-steroidal anti-inflammatory drugs (NSAIDs). The most common clinical manifestation of peptic ulcer disease is dyspepsia, with its attendant burden of morbidity and NHS costs in diagnosis and treatment. More severe manifestations include perforation and haemorrhage, both of which can be fatal. A third of all acute gastrointestinal haemorrhages in one hospital-based incidence study were ascribed to peptic ulcer disease.[18] Mortality was 12%, being much higher in the elderly and those with comorbidity.[18] Peptic ulcer death has been classified as avoidable mortality; there were 876 deaths in the 25–64 age group and 1747 in the 65–74 age group in England in 1993–94.[19] *H. pylori* infection may interact with the use of NSAIDs to increase peptic ulcer disease risks.[20]

Traditional therapy of peptic ulcer disease with acid suppression does result in symptom relief and ulcer healing. However once treatment has been stopped, the relapse rate is 80–90% within 2 years.[21] Many studies have show that effective *H. pylori* eradication in patients with peptic ulcer (both duodenal and gastric) reduces relapse rates substantially to nearly zero.[22] Eradication also reduces the requirement for long-acting acid suppression. The US National Institutes of Health recommend that all patients with peptic ulcer, whether primary or recurrent, should be offered eradication.[23]

Successful eradication of *H. pylori* can be obtained by various combinations of two antibacterial agents with an antisecretory agent (a proton pump inhibitor (PPI) or an H_2 antagonist) or

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with bismuth, the so-called 'triple therapy'. Traditionally the most commonly used regimen was bismuth, metronidazole and tetracycline. Eradication rates, defined as the absence of detectable organisms 1 month after cessation of treatment, are variable at around 85%, the variation being partly caused by non-compliance.[24,25] The favoured regimen comprises a PPI with two antibiotics (selected from metronidazole, amoxicillin, clarithromycin) for 7 days, which gives eradication rates of 90–95%. Compliance, side-effects, and resistance to metronidazole are limiting factors. There have been occasional reports of lethal side-effects, such as pseudomembranous colitis and Stevens–Johnson syndrome.[26] Reinfection with *H. pylori* may occur.[27]

Worldwide, *H. pylori* is one of the most common infections and prevalence is related to socio-economic conditions.[28] In the developed world the incidence of infection in childhood is high (2–7% per annum) compared with the adult rate of about 0.5.[29] As there are very few spontaneous eradicators, the incidence reflects primary infection. Most infection is acquired in childhood. The observed increase in prevalence with age is largely due to cohort effects; successive cohorts in developed countries have a declining incidence because of improvement in social conditions.[30] Infection is very common in the UK with a prevalence as high as 50%.[31] It varies with age and geographical area, reflecting the transmission dynamics and the influence of period and cohort effects.

Risk factors for acquisition are overcrowding and poor hygiene,[32] and sharing a bed with a sibling.[33] *H. pylori* has not been cultured from the environment; human faeco-oral and oro-oral spread are both postulated.

Determination of *H. pylori* status can be done simply and non-invasively, by serological testing[34] or using the urea breath test (UBT).[35] For the latter, isotopically labelled carbon dioxide is detected in the breath of *H. pylori*-positive individuals after ingestion of urea labelled with 14- or 13-carbon. In serological testing IgG antibodies are detected. The 'gold standards' are based on samples obtained at endoscopy, tested for production of urease, cultured for *H. pylori* or examined histologically. The sensitivity and specificity of both the breath test and the serological test are more than 90%. The serological test has advantages as it is easier to perform, it is less time-consuming and automated analysis is possible. Salivary tests and rapid blood tests do not perform as well as the serological one or UBT but might be considered in a screening context. [36,37]

Most *H. pylori*-positive individuals will remain asymptomatic thoroughout life with no symptoms of peptic ulcer disease and will die of causes unrelated to *H. pylori*.[38] A small proportion will develop gastric cancer. Others will develop symptoms of peptic ulcer, of whom a proportion will present with dyspepsia or other upper gastrointestinal symptoms to a primary care physician. Some will develop complications of ulcer such as haemorrhage; in a minority this will be fatal. Patients who have had one ulcer are at risk of recurrent ulcer and of future gastric cancer.

There are various diagnostic and treatment strategies depending on age and associated risk factors. In general patients under 45 should be offered empirical therapy by acid secretion-inhibitory agents, whilst those over 45 should undergo endoscopy to exclude malignancy. A proportion of *H. pylori*-positive individuals would be identified opportunistically and offered eradication therapy. It has been suggested that a strategy of screening dyspeptic patients under 45 prior to endoscopy may be worthwhile,[39] with eradication in those with proven ulcers ('test and scope'). Strategies of screening and eradication for *H. pylori* in dyspepsia ('test and treat') have been evaluated, and may be more cost-effective,[40,41] but the issue of screening the larger asymptomatic population has not been studied in the UK.

The case for screening for *H. pylori* rests on the public health burden of gastric cancer and peptic ulcer disease, and on the availability of a valid screening test for *H. pylori* and of effective eradication therapy. Against this is the fact that gastric cancer incidence and *H. pylori* prevalence are both declining. Although eradication leads to resolution and cure of peptic ulcer disease it is less clear whether precursors of gastric cancer, that is, gastric atrophy and intestinal metaplasia, can be reversed. A proportion of *H. pylori*-positive people who present with dyspepsia will be treated opportunistically with eradication therapy anyway. Any population-based screening programme would be an extensive undertaking, and the widespread use of triple therapy might lead to antibiotic resistance.

In the absence of a definitive clinical trial of *H. pylori* screening, modelling provides a risk-free approach to investigating whether population

screening would be likely to be cost-effective under various policies or strategies. It can define key parameters which could be used to design such a clinical trial, and identify those variables to which the cost-effectiveness of screening is sensitive. Modelling can evaluate the effects of screening for *H. pylori* on life expectancy, patient morbidity, and costs, and can incorporate the future effects of trends in gastric cancer.

Parsonnet and colleagues, using a decision-tree model, have modelled *H. pylori* screening in a US population.[42] They found that once-only serological screening at age 50–54 had a cost-effectiveness ratio of $25,000 per life-year saved (LYS). This was a conservative estimate as future treatment costs of deaths prevented were included and the effect of screening on peptic ulcer disease was not included, though conversely they did not consider the effect of opportunistic eradication. The estimate varied by target group (sex, ethnicity) depending on base *H. pylori* prevalence, and on the efficacy of eradication in reducing gastric cancer risk. It was not sensitive to eradication rate, test performance, risk of cancer associated with *H. pylori*, prevalence and life expectancy. Such modelling needs to be applied to a UK population to take account of local prevalence and healthcare costs.

Aim of the study

The aim of the study was to develop a simulation model to investigate the potential effectiveness and cost-effectiveness of screening for *H. pylori* in reducing the mortality and morbidity from gastric cancer and peptic ulcer disease in England. Screening for *H. pylori* in the population was compared with no screening but with opportunistic testing for and eradication of *H. pylori* in patients with dyspepsia.

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Chapter 2
Methods

The simulation model

Davies and co-authors have already designed several simulation models using the 'patient-oriented simulation technique' (POST). The progress of patients with end-stage renal failure has been modelled,[43] and the effectiveness of screening for retinopathy in diabetes patients.[44] The POST is a very flexible approach which allows more realistic assumptions than do other published models. Sampling can be from any distribution, and individuals can be simultaneously at risk of developing disease and also receiving screening, so that screening can be introduced independently of the natural history. Also death from unrelated causes can be dealt with independently of screening and disease progression. An individual's experiences over time are divided into events (e.g. acquisition of *H. pylori*, development of ulcers) and each is assumed to take no time; the times between events, and whether or not they occur, are determined by prior events.

A simulation computer program was written in Borland Delphi. It was designed with a user-friendly interface so that the model could incorporate different population groups or changes to any of the sets of parameters. For example, it was possible to enter different screening scenarios, varying the sensitivities, specificities, screening intervals, compliance levels, population characteristics or treatment effectiveness levels.

The effect of screening on the natural history of *H. pylori*-related peptic ulcer disease and gastric cancer is shown in *Figure 1,* and *Table 1* shows how the distributions were sampled and amended after each event.

The simulation starts with a 'prevalent population'; this initial population is free of ulcer and cancer symptoms and has realistic levels of *H. pylori* in the different age and gender groups. As the simulation progresses, new patients may enter at the age of 20 (the 'incident population'), some already infected with *H. pylori*. Individuals can die from causes other than gastric cancer or peptic ulcer at any time. Some individuals acquire one or more duodenal or gastric ulcers and, of these, some get complications (such as haemorrhage) requiring hospitalisation, and a proportion of these die. A small proportion of individuals without *H. pylori* may become infected as adults, and a small proportion of those receiving eradication may be re-infected. Some patients acquire gastric cancer and the majority of these patients die as a result. In order to determine the effects of opportunistic testing and eradication, the model assumed that all individuals with diagnosed peptic ulcer disease, in primary care or hospital, were tested for *H. pylori*.

In population screening, individuals are invited for screening for *H. pylori* and eradication treatment if it is found. In the prevalent population screening round, all individuals who are between specified age bounds at the beginning of the simulation, are 'invited' for testing. In the continuing screening programme, individuals are 'invited' for testing when they reach a specified age (the incident round). Whether the 'invited' individuals attend the screening session depends on the level of compliance.

Screening tests are associated with a particular level of sensitivity and specificity. Those patients with false-negative test results do not have *H. pylori* eradication treatment, whereas the patients with false-positive results receive eradication treatment, thus incurring an unnecessary cost.

Treatment by triple therapy takes place, after a positive test, in two different circumstances: opportunistically after patients present with dyspepsia, and after screening. Whether individuals take the treatment is determined by their compliance.

The treatment changes the relative risk of disease, i.e. the probability of *H. pylori*-positive individuals acquiring the disease compared with *H. pylori*-negative individuals. In the simulation, this changes the time at which the disease is acquired. Smaller relative risks are associated with longer times to disease acquisition and vice versa. The projected time of acquisition may be later than the projected date of death of the individual, in which case the disease has been prevented.

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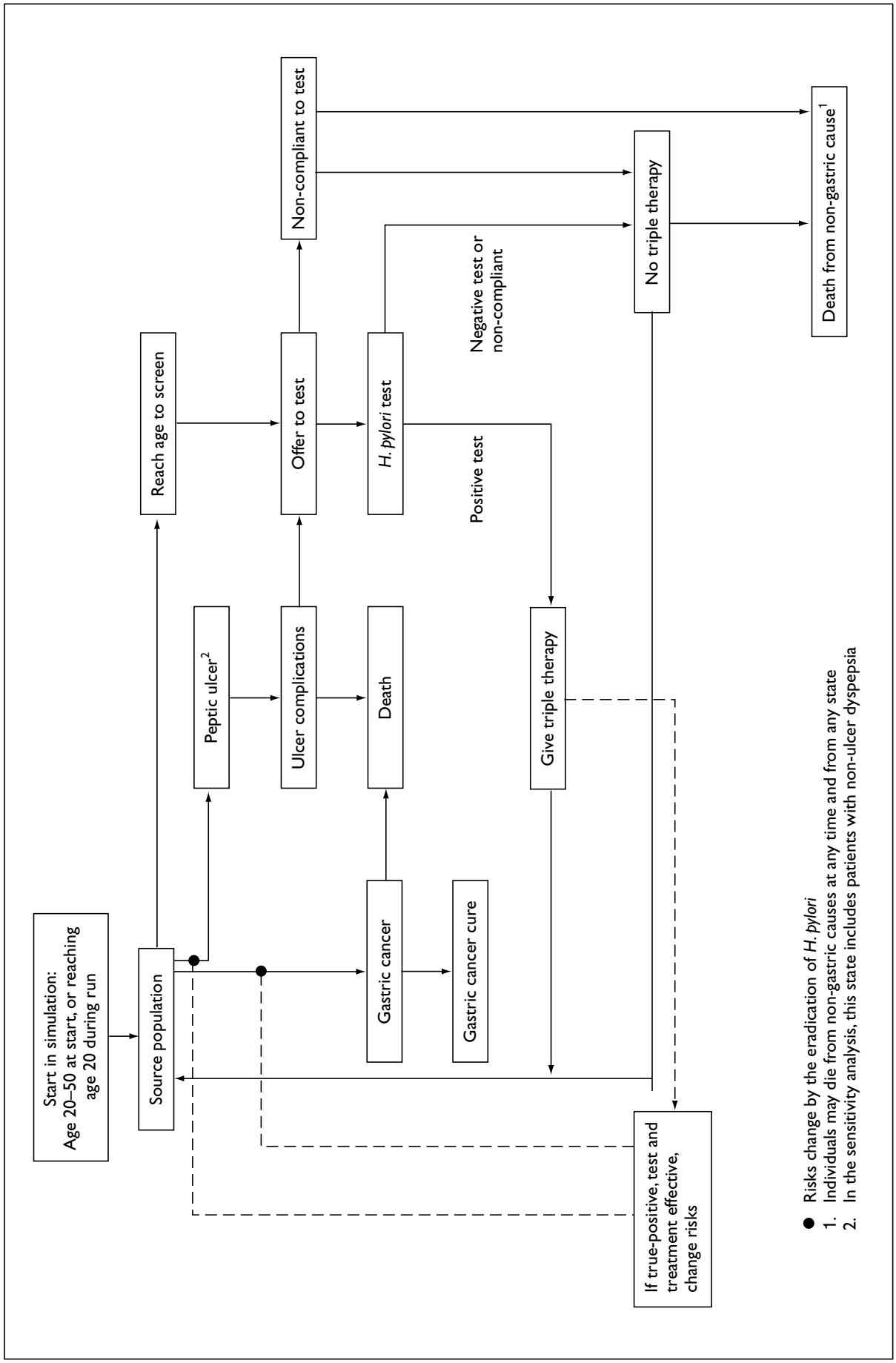

FIGURE 1 *Influence of a screening programme on the natural history and outcome of* H. pylori*-related peptic ulcer disease and gastric cancer*

TABLE 1 *The distributions sampled, descheduled, or rescheduled at each event. Reproduced from Davies* et al. Health Care Man Sci *2002;**5**:249–58, by permission of Kluwer Academic Publishers*

Event	Distributions sampled	Distributions changed
New patients at start of simulation or on entry at age 20	Time to death – non-gastric cancer or ulcer Time to duodenal ulcer (depends on *H. pylori* status) Time to gastric ulcer (depends on *H. pylori* status) Time to gastric cancer (depends on *H. pylori* status) Time to screening If not *H. pylori*-positive, time to infection	
Duodenal ulcer*	Probability of complication Probability of death If not dead, time to duodenal ulcer (depends on *H. pylori* status)	If *H. pylori*-positive and with eradication, increase time to gastric ulcer and gastric cancer
Gastric ulcer*	As for duodenal ulcer	If *H. pylori*-positive and with eradication, increase time to duodenal ulcer and gastric cancer
Gastric cancer	Time to gastric cancer death	Remove: – time to duodenal ulcer – time to gastric ulcer – time to screening – time to infection or reinfection
Screen	If *H. pylori* eradicated, time to reinfection	If *H. pylori*-positive and with eradication, increase time to gastric ulcer, duodenal ulcer and gastric cancer
H. pylori infection or reinfection		Reduce time to gastric ulcer, duodenal ulcer and gastric cancer
Death		Remove all times

* *These were multiplied by a constant in scenarios that took account of opportunistic screening for non-ulcer dyspepsia*

Treatment methods are associated with a level of efficacy. Unsuccessful treatments do not eradicate *H. pylori* and thus do not alter the patient's *H. pylori* status. If, however, *H. pylori* is successfully eradicated, then the relative risk of acquiring future peptic ulcers is changed immediately. The way in which the time to cancer is determined is described below.

The effect of *H. pylori* eradication on peptic ulcer disease

Details about the association between *H. pylori* and peptic ulcer disease are presented in appendix 1, and appendix 2 shows how this was taken into consideration in the simulation.

The risk of peptic ulcer disease appears to be related to age and gender (see *Figure 2*). There is no consistent trend over time and so incidence by age and sex for *H. pylori*-negative individuals is assumed to remain constant for the foreseeable future. *H. pylori* is known to increase the risk of peptic ulcer.[1]

Based on incidence by age, gender and *H. pylori* status, the simulation projects the time to the first gastric and duodenal ulcer. The times to second and subsequent ulcer, are sampled from the same distributions, depending on each individual's current *H. pylori* status. The complications, including haemorrhage and perforation, are derived from hospital episode statistics (HES) data for 1994–97, and the mortality data, for 1994–96, are from the Office of National Statistics, with primary care incidence details from the GP Morbidity Survey (*Figure 2*).[45] If *H. pylori* is successfully

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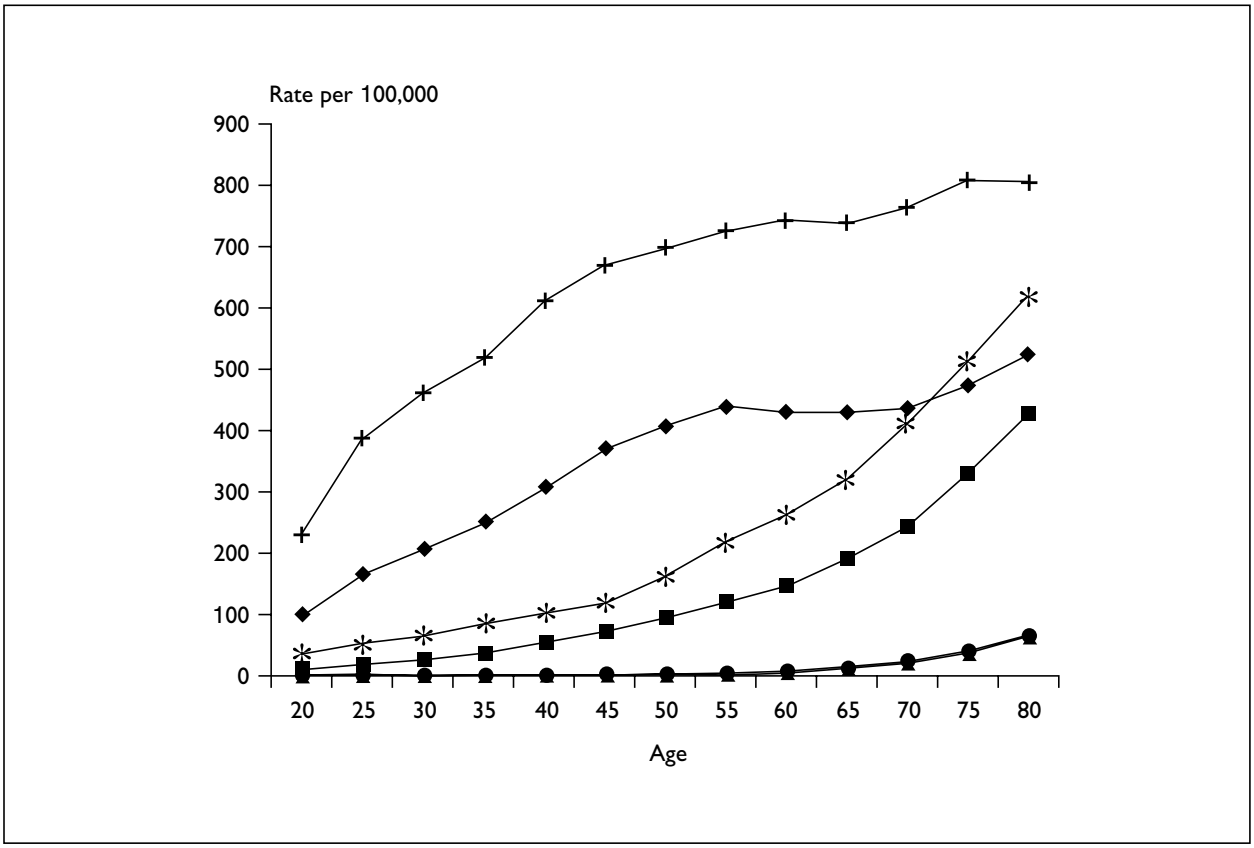

FIGURE 2 *Peptic ulcers: rate per 100,000 in primary care,[45] complications leading to hospitalisation and death rates (+, male ulcers; ◆, female ulcers; ✳, male hospitalisation; ■, female hospitalisation; ●, male death; ▲, female death). Reproduced from Davies* et al. Health Care Man Sci *2002;**5**:249–58, by permission of Kluwer Academic Publishers*

eradicated, then the relative risk of acquiring future peptic ulcers is changed immediately to *H. pylori*-negative levels.

The rates of peptic ulcer disease in *H. pylori*-positive individuals were derived by partitioning the ulcer rates based on relative risk and prevalence of *H. pylori*. In our base case, the probability of acquiring peptic ulcer complications or dying from ulcers was not affected by *H. pylori* status over and above a threefold risk of developing a peptic ulcer.[46] A recent meta-analysis has shown that the relationship between *H. pylori* and NSAIDs and peptic ulcer disease is complex. Both of the former are strong independent determinants of ulcer risk, with an odds ratio of nearly 20; in the presence of the other factor each increases the risk by an additional factor of 3.5.[20] However, for bleeding ulcers NSAIDs had a four-fold effect on risk and *H. pylori* about two-fold (in studies where serological testing was used); when both were present the risk increased six-fold suggesting synergism but not an independent multiplicative effect. Prior eradication of *H. pylori* prevents the complications of NSAIDs in patients newly starting these drugs and who have a history of ulcer or dyspepsia.[47] The risks of acquiring gastric or duodenal ulcers were regarded as independent of each other and of the risk of acquiring gastric cancer. This is a simplification as there is some evidence to suggest that patients who have a duodenal ulcer are at lower risk of gastric cancer and those with gastric ulcer are at higher risk.[48] However in the model only a small proportion of cancers arise in patients with a previous ulcer as most are treated following opportunistic testing of all patients with diagnosed ulcers.

Risks of gastric cancer

Although *H. pylori* infection is associated with an increased risk of gastric cancer (see appendix 3), the extent to which it is implicated is not known, nor how successful *H. pylori* eradication is in delaying or preventing the onset of gastric cancer. The simulation assumes that an individual's risk of developing gastric cancer is dependent on their age, gender, year of birth and *H. pylori* status, based on age–period–cohort modelling.

It can be seen in *Figure 3* that gastric cancer mortality declines by birth cohort for men. Mortality in women is lower but shows a similar

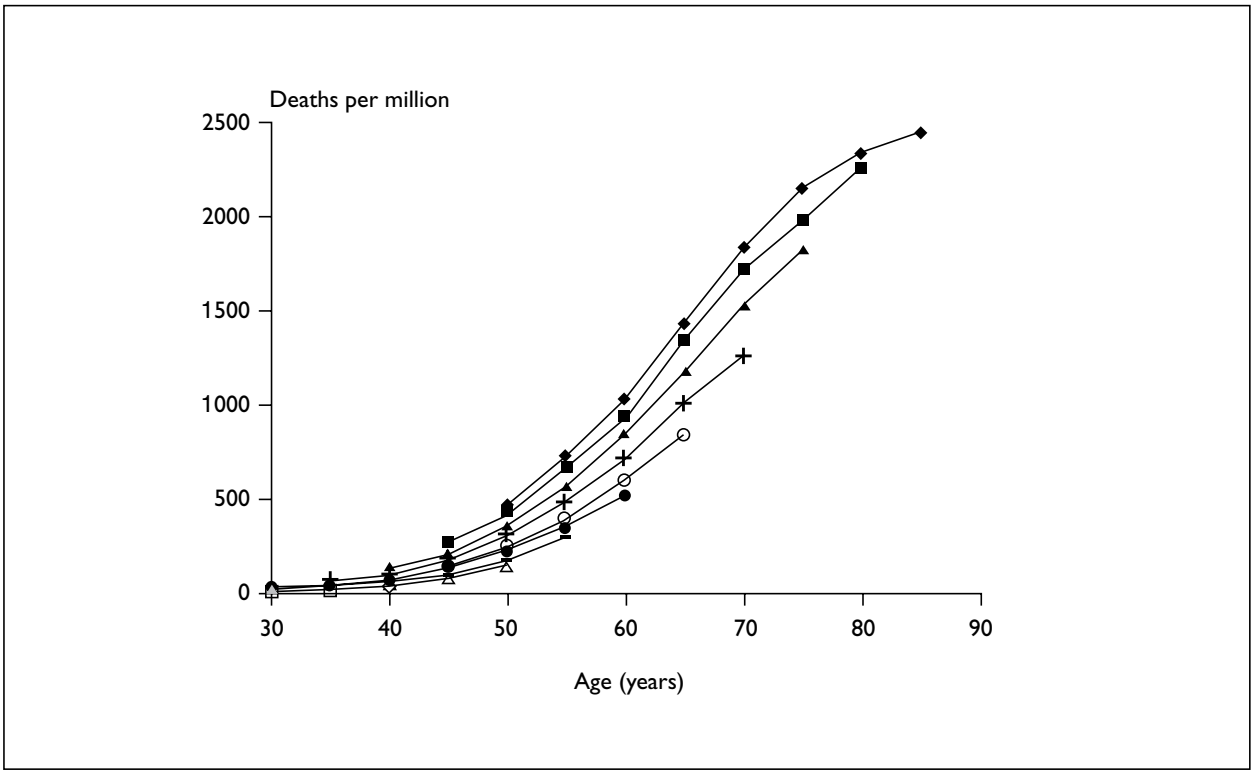

FIGURE 3 *Gastric cancer mortality by birth cohort for men (◆, 1900; ■, 1905; ▲, 1910; +, 1915; ○, 1920; ●, 1925; −, 1930; △, 1935; —, 1940; ◇, 1945; □, 1950; ▲, 1960). Reproduced from Davies* et al. Health Care Man Sci *2002;**5**:249–58, by permission of Kluwer Academic Publishers*

decline. We undertook additional analyses to determine age, period and cohort effects (see appendix 4). We used gastric cancer mortality data from 1950 onwards for birth cohorts from 1860 onwards, using a 1999 dataset from the Office of National Statistics. Poisson regression models provided estimates of age, period and birth cohort effects.[49] Separate models for males and females were fitted using PROC GENMOD in SAS 6.12.[50] It was found that an age and cohort model fitted the observed data better than a model containing age alone. The models described gastric cancer mortality well for most age groups, although the fit was less good for the over-70s. The model produced estimates of cohort effects, standardised to a reference population based on the 1910–19 age cohort. These are estimates of the factor by which an age-specific death rate from the reference population needs to be multiplied in order to forecast the death rate for that age group in a different cohort. For a younger cohort, the multiplier is less than one, and for an older cohort it is greater than one (see *Table 2*). For more recent cohorts, it is estimated to be between about one-tenth and one-quarter, and we have assumed that it remains the same after the 1960–69 birth cohort. This can be justified because the values for the more recent cohorts were close together and there were relatively little data for these cohorts. *Table 2* shows the reference population cancer mortality rates based on the 1910–19 birth cohort.

As gastric cancer is usually fatal within a few years, the incidence rate is only a little higher than the death rate. The mortality rate is multiplied by constants based on 5-year survival data[51] shown in *Table 3*.

The post 1960–69 birth cohort multiplier, together with its upper and lower limits, are shown in *Table 4*. There is uncertainty about the extent to which the risk of gastric cancer can be reversed by *H. pylori* eradication. In the simulation, we assume that the risk can be reduced, providing we are not within a certain interval of the time when the individual is due to get cancer. In order to model this, after the eradication of *H. pylori*, an individual's risk of cancer is maintained at the *H. pylori*-positive level for a period of the interval, referred to as the 'lag'. After the lag, the individual's relative risk is changed to the *H. pylori*-negative level and the time to cancer is increased. *Figure 4* shows the relationship between the lag and the efficacy of eradication with regard to gastric cancer risk, up to

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TABLE 2 *Cancer cohort multipiers and reference gastric cancer mortality rates (deaths per million), predicted from the 1910–19 birth cohort. Reproduced from Davies* et al. Health Care Man Sci *2002;**5**:249–58, by permission of Kluwer Academic Publishers*

Cohort	Cohort effect standardised on 1910–19		Age group	Modelled rate for 1990–94		Period relating to the 1910–19 cohort for this age group	Predicted rate for this age group and period	
	Men	Women		Men	Women		Men (column 5/ column 2)	Women (column 6/ column 3)
1955–64	0.18	0.21	30–34	4.5	4.8	1945–49	25.0	22.7
1950–59	0.19	0.22	35–39	10.0	7.6	1950–54	52.5	34.7
1945–54	0.23	0.24	40–44	23.3	13.2	1955–59	101.1	54.8
1940–49	0.29	0.28	45–49	52.1	22.6	1960–64	179.5	80.7
1935–44	0.37	0.34	50–54	111.6	40.7	1965–69	301.6	119.6
1930–39	0.45	0.46	55–59	216.0	79.4	1970–74	480.0	172.6
1925–34	0.58	0.57	60–64	408.0	140.6	1975–79	703.4	246.7
1920–29	0.72	0.73	65–69	708.5	252.8	1980–84	984.0	346.3
1915–24	0.82	0.81	70–74	1028.5	387.0	1985–89	1254.3	477.8
1910–19	1.00	1.00	75–79	1484.2	619.3	1990–94	1484.2	619.3
1905–14	1.19	1.24	80–84	1863.5	920.0	1995–99	1566.0	741.9
1900–09	1.37	1.47	85–89	2098.0	1183.9	2000–04	1531.4	805.4

TABLE 3 *Percentage 5-year gastric cancer survival. Reproduced from Davies* et al. Health Care Man Sci *2002;**5**:249–58, by permission of Kluwer Academic Publishers*

Age group	Men	Women
20–44	17.0	10.3
45–54	16.0	19.3
55–64	12.6	13.6
65–74	6.7	10.7
75+	4.8	5.3

the age of 75 years, for people screened at different ages. The efficacy was defined as the percentage of cancer prevented (risk reduction), compared with the no-screening scenario, for *H. pylori*-positive individuals who do not get peptic ulcers.

Acquisition of *H. pylori*

Over the duration of the simulation, *H. pylori*-negative individuals would be at risk of acquiring *H. pylori*. The acquisition rate is the percentage per year, of *H. pylori*-negative individuals who acquire *H. pylori* during adulthood (i.e. older than 20 years). This may be either as a first occurrence of *H. pylori* or a recurrence of *H. pylori* following eradication. (See appendix 5 for further details.)

Following *H. pylori* acquisition, new times to duodenal ulcer, gastric ulcer and gastric cancer are determined, that reflect the change in the patient's *H. pylori* status and consequently a change in their risk for the diseases. The risks for peptic ulcers are changed to the *H. pylori*-positive risk immediately, with no lag.

We assumed no spontaneous eradication of *H. pylori*.

Simulation input and output

Input

Simulations are often required to answer 'What if?' questions, which involve changing the input to the simulation. The *H. pylori* simulation was designed so that it was easy to record and reload the input of completed runs and to enable easy implementation of factorial design run sets. The model was constructed to allow batch runs to be programmed with varying input values for the most commonly changed variables. *Table 1* shows how the events are sampled and scheduled.

The input and output for the simulation program is described in more detail in appendix 6.

Output

Output variables were selected in order to provide discounted or undiscounted information on costs, morbidity (here represented by hospitalisation for complicated ulcer), deaths prevented and years of life saved. Additional output was produced to aid verification and validation. It was possible to collect variance data from each replication of each run in order to estimate the confidence intervals of the output for different input scenarios.

TABLE 4 *Parameter estimates used in the model*

Variable	Specification	Base case value	Sensitivity analysis
H. pylori prevalence rates	UK studies[31,52]	**Age** **Men (%)** **Women (%)** 20–24 17 12 25–29 20 15 30–34 24 19 35–39 28 23 40–44 32 27 45–49 37 32	Low*: –7.5 + 0.53Age High*: 17.8 + 0.95Age
Peptic ulcer relative risk	Observational studies[46]	3	Low: reduce risk of *H. pylori*-positive ulcers having complications to half that of *H. pylori*-negative ulcers; relative risk of 1.5 Low: 2* High: 8*
Gastric cancer relative risk	Observational studies[7,53]	3	Low: 2* High: 8* Age-specific risks, after Huang[54]
Lag time (a proxy for reduction in risk of future gastric cancer)	Time for *H. pylori*-positive individuals to reduce gastric cancer risk to *H. pylori*-negative levels after eradication	10 years	Low: 5 years* High: 15 years*, 20 years
Cancer cohort multiplier	Relative to 1910–19 cohort	Men 0.19 Women 0.2	Low: 0.05/0.1* High: 0.26*
Screening method	Serology[55,56]	Sensitivity 95% Specificity 90%	High: UBT – Sensitivity 98% – Specificity 96% Low: serology – Sensitivity 85% – Specificity 78%
Treatment method	PCM 250[57]	Efficacy 90%	Low PAM 75.8%
Net acquisition Reinfection	Infection after age 20 Reinfection after eradication	0% 0%	0.3% 0.3%
Compliance	Screening[58,59] Treatment	70% 80% (screened) 100% (opportunistic)	50% in 20-year-olds; high 90%; low 50%

* *In factorial sensitivity analysis*

The costs and benefits could be related to events occurring in the simulation to patients of all age groups or only to those occurring to patients below a certain age. The user could specify up to four age limits and the output could then be collected that related to the simulated events occurring below those ages. The default ages were 75, 80, 85, and 100 years.

In order to assess the benefits of *H. pylori* screening and eradication programmes, the output was the difference between runs with screening and runs with identical input conditions but without a screening and eradication programme. The simulation output was copied into spreadsheet templates.

The output, which included cost data, provided the following range of information, for various age limits and discount rates:

- those invited for screening
- those attending screening
- those tested opportunistically
- false-negative results
- treatments for *H. pylori* eradication as a result of screening

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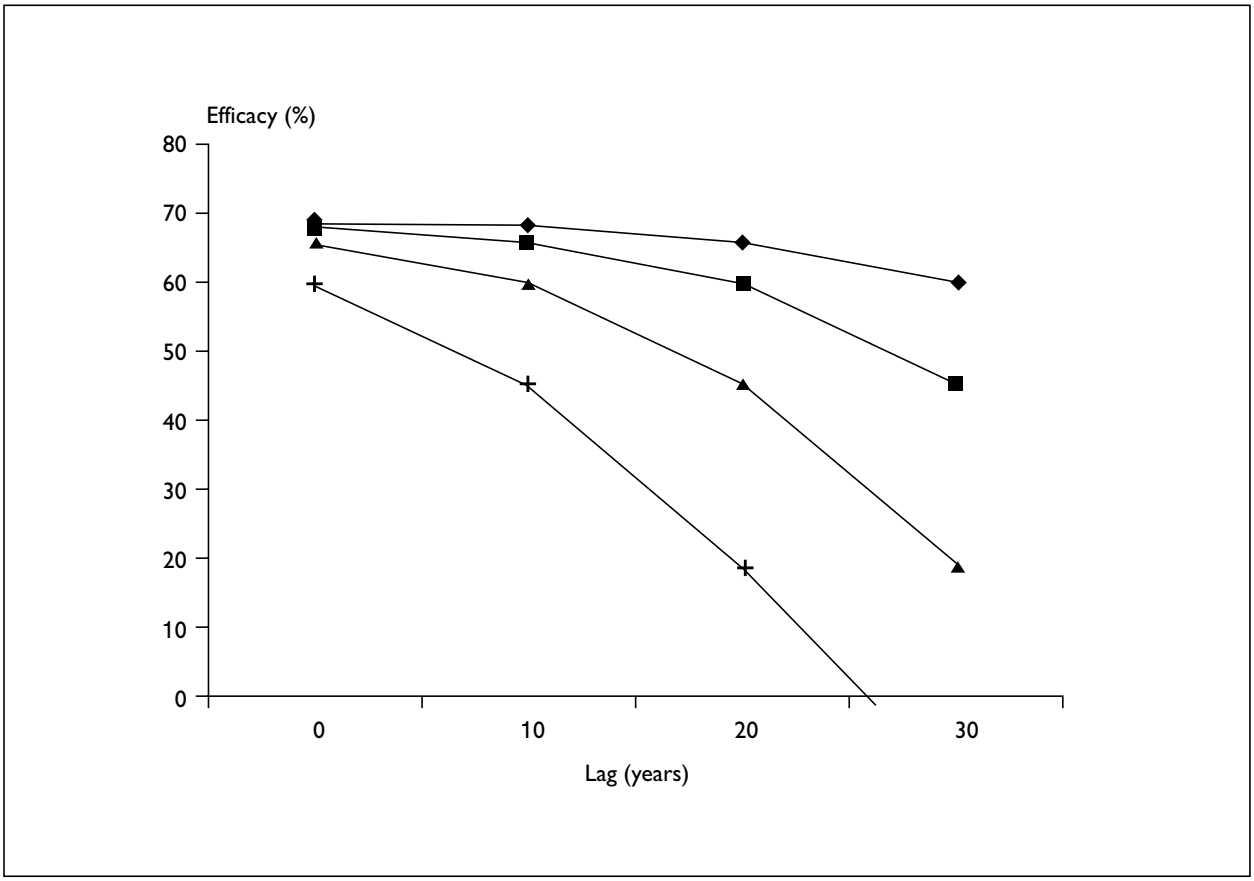

FIGURE 4 *Relationship between the length of the lag and the efficacy of* H. pylori *eradication, up to the age of 75 years, in determining the incidence of gastric cancer (age of screening: ◆, 20; ■, 30; ▲, 40; +, 50). Reproduced from Davies* et al. Health Care Man Sci *2002;**5**:249–58, by permission of Kluwer Academic Publishers*

- total treatments for *H. pylori* eradication
- ulcers prevented
- gastric cancers prevented
- ulcer perforations and haemorrhages prevented (measured as hospitalisations)
- ulcer deaths prevented
- total deaths prevented
- years of life saved
- gastric cancer deaths prevented
- cost of screening programme
- cost of treatment programme
- saved costs
- additional costs
- total costs
- cost per LYS
- cost per death prevented (ulcer and cancer).

Variance reduction

The simulation samples random numbers to imitate the variability in 'real life'. However, when simulation results are derived, average values are of principal interest. In this model, the values of main interest, such as the number of cancer deaths prevented and the years of life saved, are small in relation to the total population and so the results are likely to be very variable.

One way to address this problem is to increase the population size. However, the results from running a simulation n times with different random numbers for a population p, are the same, on average, as running the simulation once with population P, where $P = np$. Above a fixed time, the computer time used by the simulation increases exponentially with the size of population. Thus, when acquiring results for a population of size P, the size of p must be optimised, together with the appropriate value of n, to minimise the simulation running time.

The following actions were taken to reduce the variance of the results:

- The simulation used random number streams such that each distribution had its own random number stream. Thus, when comparing a screening scenario to a no-screening scenario, providing each individual accessed the distributions in the same order

in each scenario, the same random numbers were used for the same individuals in the same situations. For example, the same individuals would be *H. pylori*-positive at the beginning of the simulation and, unless screened, would get their first ulcers at the same point in time. This reduced the variance of the results and hence the number of runs needed.
- Each individual was assigned a sampled time-to-cancer on entry to the simulation, though for most this time was greater than their predicted lifespan. This time was increased (in relation to the decrease in relative risk and taking account of the lag) when *H. pylori* was eradicated and reduced when it was acquired. This approach avoided the further sampling of random numbers, which would have increased the variance of the results.
- When an individual had had a duodenal or gastric ulcer, the time to the next one was re-sampled with a new random number. However, even when common random numbers were in use, the random numbers used for an individual's second or subsequent ulcer were not the same between different scenarios. In order to reduce the variance still further, each individual was allocated a set of random numbers at the beginning of a simulation run which could be used for sampling ulcer times. These changed for each iteration but the numbers remained the same between sets of comparative runs. This further reduced the variance which arose from the common random number streams.
- All individuals starting the simulation aged over the highest age of screening that was to be considered (aged 49) were eliminated. These individuals were not going to be screened and would therefore not influence the comparative results between the screening and no-screening scenarios. The lower numbers reduced the time taken to run the simulation.

The confidence limits of the simulation results were estimated, and consequently the number of runs needed to maintain the principal results at or within 10% of the actual mean was determined, with 95% confidence. The results were totalled from 2500 replications of runs with approximately 2,900,000 people, aged 20 to 49 years old in the prevalent population and 100,000 in the incident population of 20-year-olds in each year for 20 years. This corresponds to all people under the age of 50 years in the year 2000 and is roughly 4.9 million in total. In order to round this up to the expected total population in England and Wales under the age of 50 years in the year 2000, the results were multiplied by 7.44. Results were collected on all individuals in the simulation until they died, or the simulation had been run for 80 years.

Verification and validation of the model

The verification and validation strategies are outlined in appendix 7.

Derivation of parameters

The flow diagram in *Figure 1* shows the structure of the screening imposed on the natural history of *H. pylori* infection. The following parameters were required for the model:

- the prevalence of *H. pylori* pylori infection
- the risk of gastric cancer and *H. pylori* infection
- the risk of peptic ulcer and *H. pylori* infection
- trends in gastric cancer and age cohort effects
- gastric cancer survival
- peptic ulcer occurrence – in primary care, hospital admissions and mortality
- effects of screening and eradication on relative risk of gastric cancer and peptic ulcer disease
- screening
- uptake
- accuracy of testing methods – serological, UBT
- compliance with eradication treatment
- efficacy of *H. pylori* eradication in reducing risk of gastric cancer
- side-effects of eradication
- reinfection and acquisition rates for *H. pylori*
- costs of screening, and eradication
- costs of opportunistic testing and eradication
- costs of treating peptic ulcer disease and gastric cancer.

Given the scope and breadth of the parameters required we could not undertake formal systematic reviews of each parameter. A variety of sources was used pragmatically:

- the Cochrane database of reviews and of clinical trials
- MEDLINE and EMBASE
- bibliographies of retrieved articles
- communication with relevant experts
- search of recent abstracts from gastro-enterology meetings.

The inclusion or exclusion criteria depended on the parameter of interest. UK studies were used where possible.

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Routine mortality and morbidity data were used, from the following sources:

- the Office of National Statistics – data about national (England) all-cause mortality for 1997 and gastric cancer mortality 1950–94, and peptic ulcer mortality 1994–96
- Department of Health – HES for peptic ulcer 1994–95, 1995–96, 1996–97
- GP Morbidity Survey 1991–92 – peptic ulcer incidence in primary care.[45]

The baseline case

A set of baseline parameters with which all other scenarios could be compared is presented in *Tables 4* and *5*. These show our best estimates and a range of low and high values for use in sensitivity analysis, to take account of uncertainty in the estimates and to explore different scenarios.

Prevalence of H. pylori

The age- and sex-specific prevalence of *H. pylori* infection was derived from recent *H. pylori* population-based UK studies (Harvey R, Frenchay Hospital, Bristol: personal communication, 1999).[31,52] The base case used Eurogast data. We assumed that the prevalence of new incident cases would be that of current 20–24-year-olds (see appendix 8). We also assumed that *H. pylori* prevalence would be the same in different ethnic groups and therefore screened the total population. This was supported by data from a general practice-based study in Leicester in which found similar *H. pylori* prevalence amongst Indo-Asians and whites.[63]

Risks of peptic ulcer and gastric cancer

The relative risks of gastric cancer and peptic ulcer associated with *H. pylori* infection were derived from observational studies.[7,46,53] (See appendices 1 and 3.)

Our base case relative risk of 3 for gastric cancer associated with *H. pylori* was applied to all gastric cancers, therefore, including cardia cancer for which no association with *H. pylori* has been found but which is relatively rare in the UK. This might be conservative as a recent systematic review has suggested that the risk might be as high as 6 for non-cardia cancers.[53]

Effect of eradication on future risk of gastric cancer

In the simulation, eradication of *H. pylori* reduced gastric cancer risk to *H. pylori*-negative levels after

TABLE 5 *Cost estimates used in the model*

Variable	Specification	Base case value	Sensitivity analysis
Cost of screening and eradication	Invitation/administration[58]	£2.0	High: £5 Low: £5.0
	Cost of test (serology and nurse time)[58]	£10.1	High: £12 High: £1
	Cost of sending result	£0.5	
	Nurse time[60]	£7.76	Low: £15
	Triple therapy[61]	PCM250 £28.63	High: 30 PAM £21.27
Cost of opportunistic *H. pylori* testing and eradication	UBT[61]	£21.01	Low: £15 High: £21.01
	Cost of sending result[58]	£0.5	High: £1
	Doctor time (opportunistic initial consultation)[60]	£16.38	
	Nurse time (receive treatment in both screening and opportunistic testing)[60]	£7.76	
	Triple therapy[61]	PCM250 £28.63	Low: £15 High: £30 PAM £21.27
Gastric cancer treatment	1-year observational study	£6,355	Low: £6,355 High: £10,000
Peptic ulcer complications	Hospitalisations[62]	£1,315	Low: £921 High: £1,710
Discount rate		6% benefit, 6% cost	1.5% benefit, 6% cost

a certain interval, referred to as the lag, with those scheduled to get gastric cancer within this time period being unaffected by eradication.[64] This allowed the efficacy of eradication to vary with age. The size of the lag was inversely related to efficacy (defined as the proportion of *H. pylori*-positive individuals under the age of 75 who were prevented from getting cancer). For example a lag of 10 years was equivalent to an efficacy of 45% when screening at age 50, and of 60% when screening at age 40; extending the lag to 20 years at age 40 reduced the efficacy to 45% (*Figure 4*). The base case used a lag time of 10 years.

Future risk of gastric cancer

We used the cohort estimate for the 1960–69 birth cohort to investigate different future gastric cancer incidence. These were applied to all new cohorts joining the model at age 20.

Risks of non-gastric cancer and non-peptic ulcer death

These were based on national mortality data for 1997, by age and gender.

Screening method

Our base case used serological testing whose accuracy (sensitivity and specificity) were taken from diagnostic assessment studies where two of three gold standard methods had been applied.[55,56] (See appendix 9.)

Eradication and efficacy

Eradication therapy could occur both opportunistically, after patients presented with dyspepsia, and after screening. Data for the efficacy of *H. pylori* eradication were taken from randomised trials which used an intention-to-treat analysis. The base case assumed the use of a proton pump inhibitor, metranidazole and clarithromycin at 250 mg twice daily (PCM 250).[57] (See appendix 10.)

Compliance

Levels of screening uptake and compliance were set higher than those given in recent primary care studies of *H. pylori* screening,[58,59] on the basis that these studies were not set up to prevent gastric cancer or peptic ulcer.

Acquisition as adults and reinfection after eradication

The base case assumed this did not occur. We did reduce the efficacy of eradication by 1% to allow for recrudesence of infection due to incomplete eradication.

Opportunistic testing

Patients tested opportunistically had the UBT[65] and were assumed to have higher treatment compliance (100%) The triple-therapy regime was assumed to be the same as that used after population screening. The base case assumed eradication only in patients with diagnosed ulcers.

Side-effects

Serious side-effects of eradication therapy are rare, and were not included in the model.[66]

Cost estimates

Screening costs were taken from a recent primary care-based study.[58] The averted costs of treating gastric cancer and ulcers causing hospitalisation were taken from an *ad hoc* costing study (Bachmann M, Department of Social Medicine, University of Bristol: personal communication, 1999) and NHS Trust reference costs, respectively.[62] For the costs of time expended by health professionals we used the report of Netten and Dennett.[60] Drug costs were obtained from the *British National Formulary*.[61] All costs were adjusted to year 2000 prices.

The discount rate

The default discount rate was taken conservatively as 6% for costs and 6% for benefits.

The scenarios considered in the sensitivity analysis

The baseline values and ranges of low and high values are shown in *Tables 4* and *5*.

H. pylori *prevalence*

Low and high values for *H. pylori* prevalence were derived from recent surveys in southern England (Harvey R, Frenchay Hospital, Bristol: personal communication, 1999) and Northern Ireland,[52] and regression lines were fitted to derive age-specific prevalence.

Peptic ulcer risk associated with H. pylori

The risk of complicated ulcer was halved from a base of 3 to a lower estimate of 1.5 to take account of uncertainty about the effect of *H. pylori* on complicated ulcer, as discussed above, particularly in the light of NSAID use. In factorial analysis, ulcer risk was varied from 2 to 8.

Gastric ulcer risk associated with H. pylori

Gastric cancer risk was similarly varied from 2 to 8. We also evaluated the age-specific risks found by Huang and colleagues.[54] We tested the sensitivity

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of using the following age-specific risks, taken from Huang and colleagues: age 20–29, 9.29; age 30–39, 7.27; age 40–49, 3.65; age 50–59, 1.86; age 60–69, 1.46, and age 70+, 1.05.[54]

Effect of eradication on risk of gastric cancer

Given the uncertainty about the effect of eradication on the pathological process, we varied the lag by up to 20 years.

Future gastric cancer rates

We used the 95% confidence limits on the estimate of the cohort effect for the 1960–69 birth cohort, and also halved the lower confidence limit to allow for an even larger decline in future cancer incidence.

Variation of screening method

We replaced the serological test with the UBT. Salivary screening is less accurate than serological testing (sensitivity 0.85, specificity 0.78)[36] but equally costly, so we did not consider it in the model but we present the effectiveness data to reflect the effect of a less accurate serological test.

Eradication of H. pylori

We used a less efficacious triple-therapy regimen combining a proton pump inhibitor with amoxicillin and metronidazole (PAM), with a lower cost.[66]

Compliance

Compliance was reduced to as low as 50%[58] and raised to 90%. A primary care screening study by Stone and colleagues[58] indicated that compliance in 20-year-olds was at least 20% less than in other age groups; this was also modelled.

Acquisition and reinfection

We used an estimate of 0.3%[67,68] for the acquisition rate in *H. pylori*-negative individuals over the age of 20. This was included as a scenario either as a first occurrence of *H. pylori* or as a recurrence following eradication. When the simulated patients were reinfected, their times to gastric cancer and peptic ulcer were reduced.

Opportunistic testing

To investigate the impact of opportunistic testing, we increased testing levels by a factor of five-fold, from only testing patients with diagnosed peptic ulcers (using GP morbidity study incident data) to include some of those patients presenting to primary care with dyspepsia and non-ulcer dyspepsia.

Other sensitivity analyses

We modelled the benefits and cost-effectiveness ratios for *H. pylori* screening on peptic ulcer and gastric cancer separately, assuming no benefit for the other outcome. We modelled a high opportunistic eradication level and a high lag time together.

Cost estimates

The costs of screening were increased, per person, to allow for higher administration charges.

The cost of testing was reduced to take account of increased demand if screening was introduced, which would lead to reduction in cost of the test. The cost of screening was increased to take account of higher administration and quality assurance costs.

The cost of triple therapy (PCM) was increased to allow for antibiotic resistance of *H. pylori* which would necessitate the addition of newer, more expensive drugs, and was reduced to allow for the ending of drug patents.

The cost of gastric cancer was increased as the base estimate was based on 1 year's treatment. The costs of peptic ulcer hospitalisation were arbitrarily increased and decreased by 30%.

We used the high value for costs of administration, screening and eradication along with the low value for costs averted for treatment of peptic ulcer and gastric cancer, and vice versa, to produce limits to the net costs of screening and averted costs.

Discount rate

We tested a lower discount rate for benefits of 1.5%, as recommended by the Department of Health.[69]

Sensitivity analysis

We varied some parameters in a univariate analysis, i.e. screening tests and triple-therapy regimens, compliance with screening in younger age groups, age-specific cancer relative risk, and reinfection/acquisition rate. A complete factorial design, in which results were obtained for a combination of high and low values for screening of individuals aged 40 to 49 from the prevalent population and individuals aged 40 from the incident population, was undertaken. The key parameters were the time lag, *H. pylori* prevalence, cancer and ulcer relative risk, future cancer risk, and screening compliance.

In order to reduce the number of combinations it was assumed that men and women, over all age groups, would incur high and low values together. Furthermore the high and low values for relative risk for cancer and ulcer were taken together. Hence there were five sets of baseline parameters to vary, and 32 simulation runs and sets of output.

The discount rates were 6% for both costs and benefits, and 'costs' included all the different types.

We used an acquisition and reinfection rate of 0.3%, which is why the best estimate differs from the base run.

Running the simulation

The population structure used was that of the population of England in the 1991 Census. The population was scaled to the total population of England and Wales. To test the effect of age, four scenarios were used with the prevalent population as at the year 2000; the model was run for 80 years to allow sufficient time for benefits regarding gastric cancer to accrue. The scenarios were as follows:

- screen the prevalent population aged 20 to 49 years, and screen all new 20-year-olds for 20 years
- screen the prevalent population aged 30 to 49 years, and screen all new 30-year-olds for 30 years
- screen the prevalent population aged 40 to 49 years, and screen all new 40-year-olds for 40 years
- screen all new 50-year-olds for 50 years.

The number of runs of the model was set to maintain the main results within 10% of the actual mean with 95% confidence.

The duration of running of the model was varied from 20 to 80 years to examine how long it takes for screening to become cost-effective (if at all) and to what extent this is sensitive to the discount rate.

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Chapter 3
Results

Effectiveness and cost-effectiveness of *H. pylori* screening

Base case: varying age at screening

In *Table 6* it is shown that the total number of individuals screened in each scenario is approximately 25 million, with over 5 million people treated in response to population screening. With a prevalent round for 20–49-year-olds as in the first scenario, approximately 60% of those screened would occur in the prevalent round; this falls to 40% in the prevalent round for 30–49-year-olds, to 20% for 40–49-year-olds and to none for 50-year-olds. After the initial prevalent population screening round, the number of screens per year is approximately 500,000.

The number of deaths prevented (undiscounted) falls as the age at screening increases, particularly for gastric cancer between screening ages 40 and 50. The present value of costs also falls as the age of screening increases because there is less prevalent screening and costs are deferred. The number of people needed to treat per death prevented by screening can be estimated; for example at age 40 it is 333.

Effect of varying key parameters

It can also be seen in *Figure 5* that the total number of deaths prevented falls as age at screening increases. Reinfection and acquisition of *H. pylori* after age 20 has a small impact on the effect of screening, especially for the younger age groups. Extending the lag from 10 to 20 years, thereby lowering the risk reduction for gastric cancer after eradication, has a large impact particularly when screening older age groups. A higher level of opportunistic testing and eradication reduces the benefits of screening as does an age-related gastric cancer risk.

The cost-effectiveness ratios for these scenarios are shown in *Figure 6* as cost/LYS. In the base case, the ratio falls with age and it is under £10,000/LYS for all age groups over an 80-year follow-up. It is most cost-effective to screen at age 50, though with less absolute benefit. Lowering the discount rate for benefits significantly reduces the ratio to under £2000 in all groups and has most effect on younger age groups. Increasing the time lag for risk reversion to 20 years or increasing the level of opportunistic eradication will reduce the impact of lowering the discount rate.

TABLE 6 *Benefits and costs of programme at different screening ages. Reproduced from Davies* et al. Health Care Man Sci *2002;**5**:249–58, by permission of Kluwer Academic Publishers*

	Prevalent 20–49 Incident 20	Prevalent 30–49 Incident 30	Prevalent 40–49 Incident 40	Prevalent 50 Incident 50
Number screened	25,392,282	25,313,923	25,140,100	24,635,891
Number extra treated	5,447,060	5,436,012	5,413,595	5,315,650
Ulcer deaths prevented	6,891	6,929	6,891	6,593
Gastric cancer deaths prevented	10,549	10,207	9,372	6,563
Total deaths prevented	17,440	17,360	16,263	13,156
Prevalent round, ulcer complications prevented	142,235	10,4039	55,458	0
Incident round, ulcer complications prevented	67,675	98,228	127,827	149,216
Total ulcer complications prevented	209,910	202,267	183,285	149,216
Costs incurred in first year (£ millions)	374.66	256.13	138.24	11.03
Present value of costs incurred in screening and treatment at 6% (£ millions)	464.43	380.02	281.40	171.50
Present value costs and benefits at 6% (£ millions)	354.99	279.23	197.66	117.34

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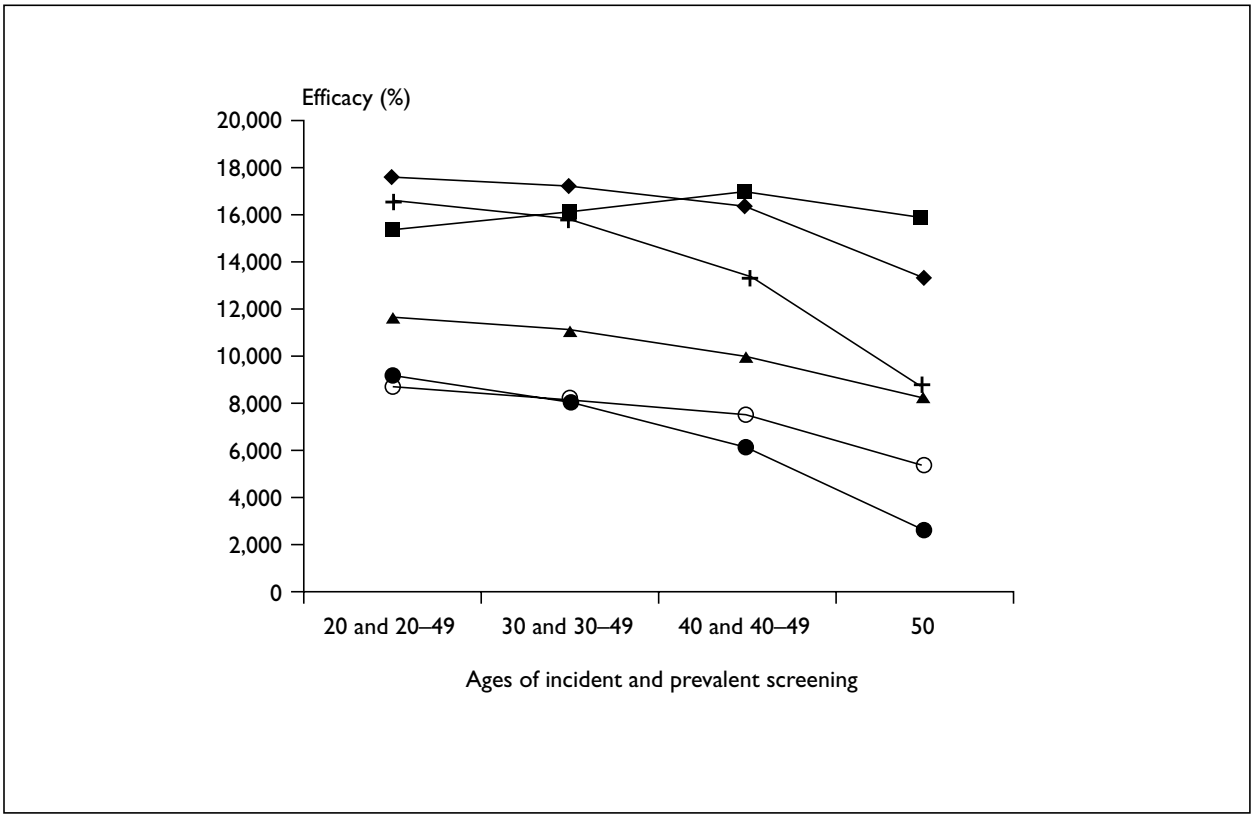

FIGURE 5 *Total deaths to age 75 prevented under the different scenarios (◆, base run; ▲, age-related cancer risk; ■, reinfection rate 0.3%; ○, high opportunistic* H. pylori *eradication; +, base run, high lag 20 years; ●, high* H. pylori *eradication, high lag 20 years)*

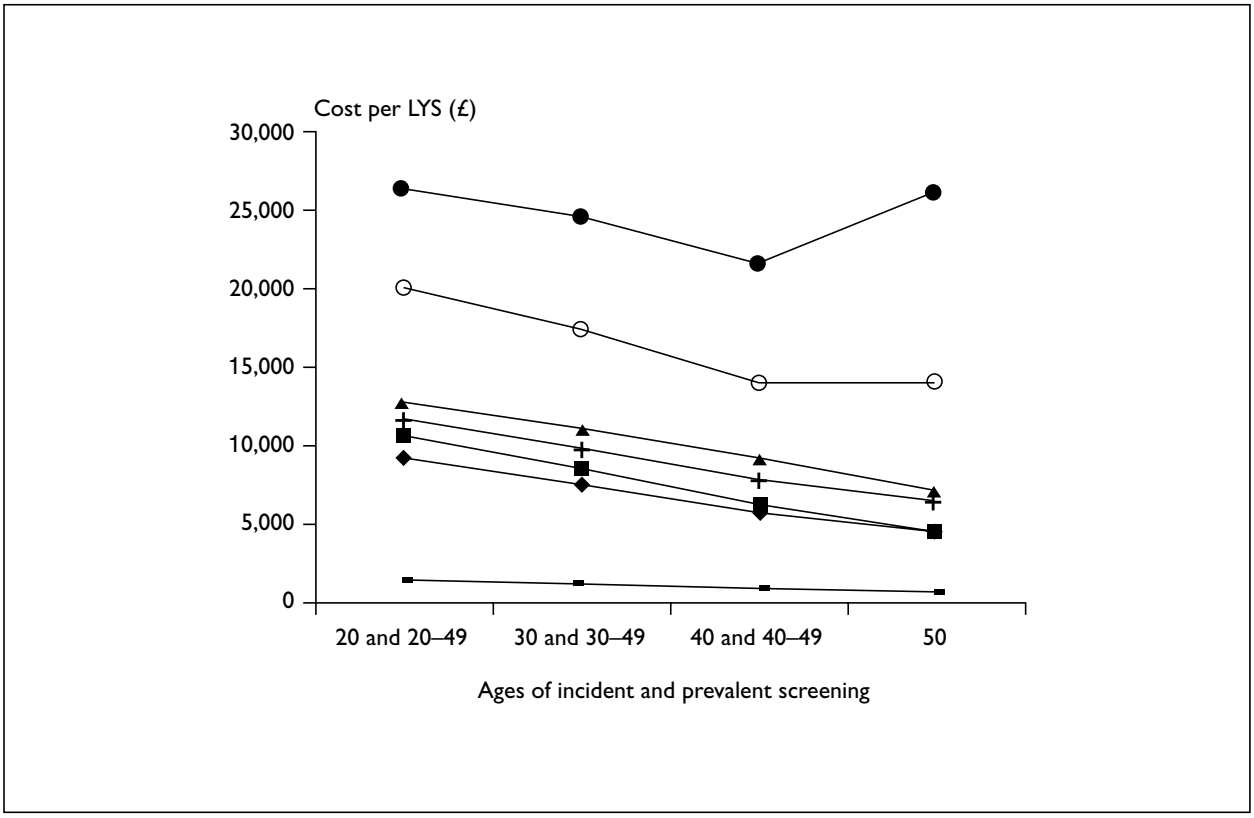

FIGURE 6 *Cost/LYS; for all costs for all ages discount rates 6% unless stated (◆, base run; ▲, age-related cancer risk; ■, reinfection rate 0.3%; ○, high opportunistic* H. pylori *eradication; +, base run, high lag 20 years; −, base run, discount 6% and 1.5%; ●, high* H. pylori *eradication, high lag 20 years)*

These data suggest that screening at age 40 with a prevalent round for the 40–49 age group might be the most pragmatic policy, balancing cost-effectiveness and the feasibility of screening. The cost/LYS for the base run at this age is £5866, falling to £1027 if the benefit is discounted at 1.5%.

Output for screening at age 40

With regard to the scenario of a prevalent round for the 40–49-year-old group and an incident round for 40-year-olds, the output of the simulation for screening at this age is shown in *Table 7*. The total numbers screened and treated have small confidence limits whereas, despite the efforts made to reduce the variance, the number of deaths prevented, particularly ulcer deaths, is still quite variable. The ranges of costs are based on the upper and lower limits of the unit costs rather than the variability in the simulation output, which is very small for the screening and treatment activities.

The cost/LYS and total deaths prevented by screening, with both low- and high-cost scenarios for screening at age 40 are shown in *Table 8*.

TABLE 7 *The mean and confidence limits of the output where screening takes place at 40 years with a prevalent screening round of ages 40 to 49 years. Reproduced from Davies* et al. Health Care Man Sci *2002;**5**:249–58, by permission of Kluwer Academic Publishers*

Variable	Mean	Confidence limits (±)	% difference of total
Screening numbers	25,140,100	14,788	0.06
Number extra treated	5,413,595	11,443.82	0.21
Cancer deaths prevented to age 75	9,372	513	5.79
Ulcer deaths prevented to age 75	6,891	638	10.20
Total deaths prevented to age 75	16,263	811	5.25
Total deaths prevented	34,456	1,278	3.85
Life-years saved	368,045	15,359	4.01
Costs (£ millions)	**Mean**	**Lower limit**	**Upper limit**
Costs incurred in first year	138.24	86.08	175.81
Present value of costs incurred in screening and treatment at 6%	281.40	175.19	363.62
Present value: costs and benefits at 6%	197.66	72.83	296.56

TABLE 8 *Deaths prevented to age 75 years and cost per LYS for different scenarios when screening at age 40 (prevalent population 40–49)*. Reproduced from Davies* et al. Health Care Man Sci *2002;**5**:249–58, by permission of Kluwer Academic Publishers*

Scenario	Deaths prevented	Cost/LYS (£s)	Low–high cost/LYS (£s)
Base	16,263	5,866	1,858–9,023
Less accurate test	14,617	8,652	3,122–11,369
More accurate test (UBT)	16,763	8,930	4,889–11,324
Less efficacious eradication (PAM)	14,252	6,411	2,364–10,226
Cancer outcome only	10,288	16,377	9,345–21,511
Peptic ulcer outcome only	6,921	12,563	5,007–18,887
Higher *H. pylori* prevalence and cohort risk	26,909	4,385	901–6,884
Lower *H. pylori* prevalence and cohort risk	5,014	14,558	7,007–21,560
Higher opportunistic eradication and lag (20 years)	6,042	21,704	11,569–30,317
Lower future cancer risk	10,460	8,413	3,050–12,777
Lower risk ulcer complications	12,948	8,844	4,061–12,350

* *Discount rates: 6% costs, 6% benefits; 80-year run*

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The base estimate is a cost-effectiveness ratio of £5866/LYS. Serological screening is more cost-effective than the UBT. A less accurate serological test does impact on cost-effectiveness. Using the less efficacious but cheaper eradication regimen (PAM) was as cost-effective but with fewer deaths prevented. If the benefits of reducing peptic ulcer disease are disregarded, the cost-effectiveness ratio is £16,377/LYS. For peptic ulcer disease alone, assuming no benefit from reducing gastric cancer, it is £12,563/LYS.

The cost-effectiveness ratio varies depending on *H. pylori* prevalence and the future incidence of gastric cancer. The ratio exceeds £20,000 if there is a high level of opportunistic eradication and lower efficacy. If the cohort risk of gastric cancer is dropped even further, to half the lower confidence limit, it is £8413/LYS. If the risk of complicated ulcer is dropped to half its base value, the cost/LYS rises to £8844. However, in all the scenarios shown the discount rate for benefits is conservative at 6%, and there is scope for reducing the costs of a screening programme, both of which would make the cost-effectiveness ratio more favourable.

Many of the scenarios and the life-years saved and cost for different scenarios are summarised in *Figure 7*. It shows for example how switching from PCM to PAM is less costly but at the expense of future deaths prevented. The most cost-effective scenario is when there is high *H. pylori* prevalence and a higher gastric cancer incidence. Opportunistic eradication is more costly because of the assumed widespread use of the UBT and high compliance.

However, *Figure 8* shows how the payback from screening would continue over time. The base case has allowed the model to run for 80 years; for shorter times the cost/LYS is very high, only falling below £10,000/LYS at 40 years after starting screening.

Sensitivity analysis

The 2500 iterations for each run were divided into 10 independent sets of 250 iterations for analysis. The numbers in the example discussed below in this section have been multiplied by 10 to be comparable to the results in *Table 7*. The low values in each of the categories shown in *Table 4* are represented in the factorial design by –1 and the high values by +1.

The results for the factorial design for the numbers of deaths prevented to the age of 75, under each scenario, are shown in *Table 9*, including interactions. The *t* test indicates that all the parameters and pairs of parameters have a significant impact on the results. The most important parameters are *H. pylori* prevalence and the relative risk of peptic ulcer or gastric cancer associated with *H. pylori*.

In *Table 9*, the 'Effect' column shows what happens when a single variable is moved from its lowest to its highest point, assuming independence from all other variables. The effect of two variables in combination shows the additional effect of combining them, again assuming that all of the others are independent. For example, the effect of increasing *H. pylori* prevalence by itself from its lowest range to its highest, if there were no effect from other variables, would increase by 11,333 (1133.3 × 10) the number of deaths prevented before age 75. The combined effect of increasing both *H. pylori* prevalence and the cancer cohort multiplier from the lowest to the highest values, assuming independence from all other parameters, is 11,333 plus 4851 plus 2351, i.e. an increase of 18,535 in deaths prevented.

The factorial analysis (*Table 10*) shows that even when all the parameters are unfavourable with regard to screening, the cost/LYS is less than £30,000.

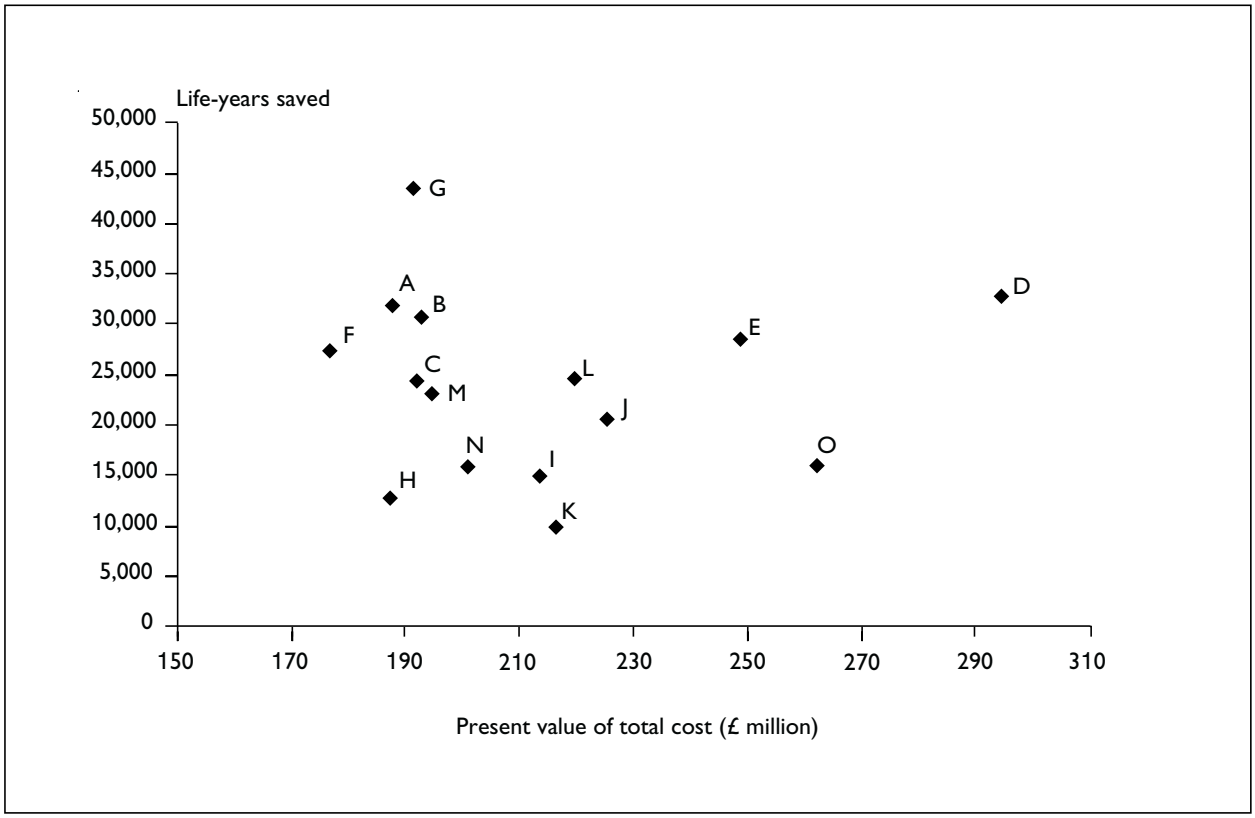

FIGURE 7 *Comparison of incremental benefits (life-years saved) and costs for different scenarios. All costs are based on a prevalent screening round of those aged 40 to 49 and an incident round of those reaching the age of 40, at a 6% discount for costs and benefits*

Key to Figure 7 *scenarios, showing any change from base case*

		Present value of cost at 6% discount	**LYS at 6% discount**
A	Base run	£187,610,327	31,982
B	Reinfection rate 3%	£192,883,331	30,843
C	Base run, high lag time = 20 years	£192,221,023	24,375
D	UBT, not serology	£294,504,592	32,978
E	Less accurate serology	£248,475,767	28,718
F	Less effective eradication, PAM triple therapy	£176,552,121	27,539
G	High *H. pylori* prevalence, higher future gastric cancer incidence	£191,187,938	43,596
H	Low *H. pylori* prevalence, lower future gastric cancer incidence	£187,339,107	12,869
I	High *H. pylori* opportunistic eradication	£213,319,608	15,154
J	High *H. pylori* opportunistic eradication, high *H. pylori* prevalence	£225,153,528	20,640
K	High *H. pylori* opportunistic eradication, high lag time = 20 years	£215,984,286	9,951
L	Lower risk of ulcer complications	£219,329,592	24,800
M	Very low future gastric cancer incidence	£194,684,219	23,141
N	Peptic ulcer-only outcome	£200,642,307	15,971
O	Gastric cancer-only outcome	£262,047,907	16,001

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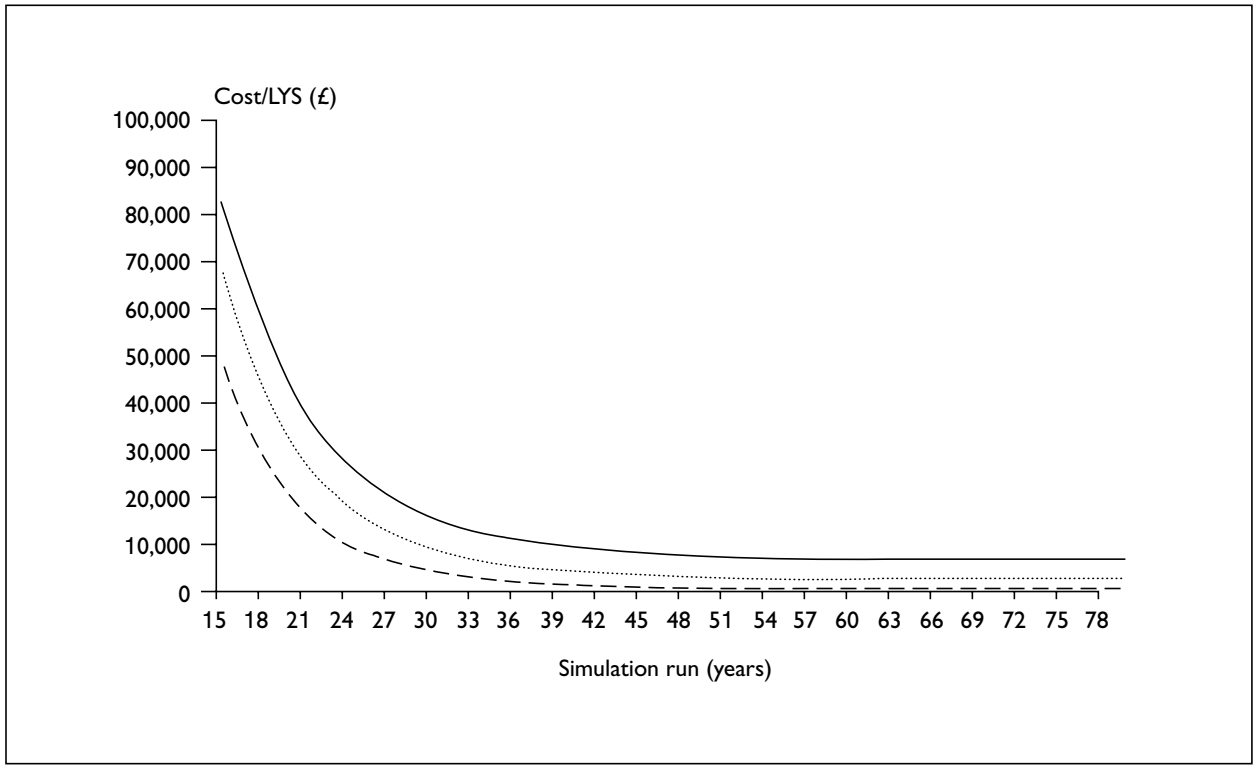

FIGURE 8 *The cost-effectiveness ratio, by duration of run of simulation model and discount rates for costs and benefits (discounted rates, costs/benefits: ——, 6% 6%; ·····, 3% 3%; – – –, 6% 1.5%)*

TABLE 9 *Factorial analysis of effects on deaths prevented (including 0.3% acquisition and reinfection)*

Term	Effect	Coefficient	*t* test values	Probability that effect is not significant
Constant	–	1235.3	206.1	0.000
Lag	–138.2	–69.1	11.5	0.000
Relative risk	967.7	483.9	80.7	0.000
Compliance	731.2	365.6	61.0	0.000
Cancer cohort risk	485.1	242.6	40.5	0.000
H. pylori prevalence	1133.3	566.6	94.5	0.000
Lag * Relative risk	–48.1	–24.1	–4.0	0.000
Lag * Compliance	–41.2	–20.6	–3.4	0.001
Lag * Cancer cohort risk	–41.2	–20.6	–3.4	0.001
Lag * *H. pylori* prevalence	–79.2	–39.6	–6.6	0.000
Relative risk * Compliance	290.0	145.0	24.2	0.000
Relative risk * Cancer cohort risk	204.0	102.0	17.0	0.000
Relative risk * *H. pylori* prevalence	308.1	154.1	25.7	0.000
Compliance * Cancer cohort risk	144.0	72.0	12.0	0.000
Compliance * *H. pylori* prevalence	324.1	162.1	27.0	0.000
Cancer cohort risk * *H. pylori* prevalence	235.1	117.6	19.6	0.000

TABLE 10 *Results from the factorial design runs, screening at 40 years, with a prevalent screen of 40–49 years, scaled to the population of England and Wales. A value of 1 indicates the high value and –1 indicates the low value. Results from the base run were: 16,844 for deaths prevented; 135,955 life-years saved to age 75, and £6554 cost per LYS*

Lag	Relative risk	Compliance	Cancer cohort multiplier	*H. pylori* prevalence	Deaths prevented to age 75	Life-years saved to age 75	Cost per LYS (£)
–1	–1	–1	–1	–1	2,101	19,318	23,892
1	–1	–1	–1	–1	1,900	15,854	28,316
–1	1	–1	–1	–1	5,796	54,229	8,594
1	1	–1	–1	–1	5,282	42,353	10,553
–1	–1	1	–1	–1	3,770	32,810	22,315
1	–1	1	–1	–1	3,405	26,187	26,717
–1	1	1	–1	–1	11,033	101,521	7,641
1	1	1	–1	–1	10,207	79,864	9,327
–1	–1	–1	1	–1	2,891	27,319	17,544
1	–1	–1	1	–1	2,645	19,936	22,438
–1	1	–1	1	–1	8,620	82,345	6,073
1	1	–1	1	–1	7,979	60,382	7,908
–1	–1	1	1	–1	5,476	48,686	16,188
1	–1	1	1	–1	4,924	35,112	20,953
–1	1	1	1	–1	16,167	155,042	5,395
1	1	1	1	–1	14,796	112,733	7,008
–1	–1	–1	–1	1	6,958	59,600	11,981
1	–1	–1	–1	1	6,437	48,283	14,374
–1	1	–1	–1	1	14,423	123,007	5,774
1	1	–1	–1	1	13,038	98,482	6,963
–1	–1	1	–1	1	12,456	107,116	11,459
1	–1	1	–1	1	11,376	86,092	13,753
–1	1	1	–1	1	26,291	223,001	5,528
1	1	1	–1	1	23,900	176,587	6,693
–1	–1	–1	1	1	10,482	92,455	8,462
1	–1	–1	1	1	9,059	66,722	11,020
–1	1	–1	1	1	22,186	196,807	4,007
1	1	–1	1	1	19,363	139,501	5,300
–1	–1	1	1	1	19,117	165,375	8,065
1	–1	1	1	1	16,770	119,245	10,504
–1	1	1	1	1	40,468	355,142	3,825
1	1	1	1	1	35,522	252,220	5,040

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Chapter 4
Discussion

In this study a discrete-event simulation was developed to evaluate the benefits and costs of screening for *H. pylori* in the general population of England. It is the first to evaluate the impact of screening on both gastric cancer and peptic ulcer disease and to incorporate the effect of opportunistic eradication. Population screening is likely to be cost-effective with cost per LYS being under £10,000 with the base assumptions, which compares favourably with other screening programmes,[70] although this is over an 80-year follow-up. Once-only screening at age 40 with an initial prevalent round of those aged 40–49 appears to be the most pragmatic policy. Screening at younger ages could prevent more deaths but is likely to have lower compliance, and is more sensitive to the discount rate for benefits. Moreover, the logistics of screening a large prevalent round of 20–49-year-olds would be considerable. However if a variable age-specific relative risk for gastric cancer or a longer lag (less reduction in gastric cancer risk) is assumed, it is more cost-effective to screen at an earlier age. The initial cost of a screening programme is likely to be around £138 million, but might be considerably lower at £86 million if the costs of pathology tests and drugs were to fall.

One major uncertainty is the efficacy of eradication of *H. pylori* with regard to gastric cancer risk. Gastric cancer is thought to be the end-stage of a gradual progression from chronic inflammation through atrophy, intestinal metaplasia and dysplasia.[14] The literature is not clear regarding whether this process can be arrested or reversed and at what stage this would occur. It is unlikely that an all-or-none phenomenon exists, and more probable that despite eradication of infection a proportion of individuals will still progress to cancer. Current prospective studies may answer this question but data will not be available for another decade.[71] Theoretically, screening at earlier ages might be most efficacious because the prevalence of later stages in the pathological process would be lower. The model suggested that age 40 is not too late even when the lag was extended to 20 years. Our method of using a constant lag time, which has the effect of reducing efficacy with age, is more realistic than assuming a fixed efficacy. Sensitivity to this lag, which represents the time between which gastric cancer is irreversible and symptoms are detected, appears relatively small unless the lag is large. For example, if screening were to take place at the age of 50 and the lag was assumed to be 25 years, then no cancer deaths would be prevented at all in individuals in under 75 years old.

The overall cost-effectiveness was sensitive to the relative risk of cancer and ulcer, falling when it was reduced to 2. For gastric cancer this seems very conservative given the available epidemiological evidence. Our base case risk of gastric cancer associated with *H. pylori* was conservative at 3, partly because we assumed this association was found for all cancer types (despite evidence of no association for cardia cancer). We made this assumption because the observational studies do not consistently distinguish type nor do routine gastric cancer mortality data in the UK provide information about type of cancer. This might be conservative as a recent systematic review has suggested that the risk might be as high as 6 for non-cardia cancers.[53]

We tried to take account of the declining incidence and mortality from gastric cancer by fitting an age–cohort model and using the age–cohort estimates. There is uncertainty over whether the trend of a declining rate will continue in the most recent birth cohorts, as there are too few data. We assumed a levelling off with the1960–69 cohort (i.e. the 30 to 39 age group in the model). We did investigate a lower risk for all subsequent groups by taking the lower limit of the confidence interval and even halving this. The cost-effectiveness ratio was still favourable in these circumstances.

Whilst cost-effectiveness decreased when we modelled lower *H. pylori* prevalence populations it remained reasonable, and it would be difficult to establish any national programme in selective geographical areas The converse is that *H. pylori* screening may be more cost-effective in populations with high *H. pylori* prevalence and high gastric cancer risk. Monitoring of gastric cancer trends in the UK over the next decade would generate more precise estimates of the cohort effects in recent generations eligible for screening.

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We included peptic ulcer disease as an important outcome. Despite some concerns about the accuracy of the data used, such as finished consultant episode (FCE) inflation and re-admission data being subsumed in HES data and under-ascertainment of peptic ulcer in mortality data, this has allowed us to include opportunistic eradication and prevention of death from ulcers. A significant component of the benefit of *H. pylori* screening was the prevention of peptic ulcer disease. There remains uncertainty about the effect of *H. pylori* eradication on complicated ulcer. A recent meta-analysis found that the risk associated with *H. pylori* infection and complicated peptic ulcer (i.e. bleeding) varied with the type of *H. pylori* test (there are false negatives when invasive methods are used), and the presence of NSAIDs.[20] There was variation in the control groups which may have affected estimates of risk (e.g. some control groups had uncomplicated ulcer, some included hospital controls). Compared to such data we might have overestimated life-years saved from peptic ulcer disease though we did include a lower risk of complicated ulcer and a no-ulcer scenario. We also excluded the burden of peptic ulcer morbidity which would be high if the risk of uncomplicated peptic ulcer is raised 18-fold in *H. pylori*-positive individuals and is 3.5 times higher due to *H. pylori* in those already on NSAIDs.[20] The inclusion of peptic ulcer disease allowed us to include opportunistic eradication and the prevention of complications and deaths from ulcers.

The extent of opportunistic testing of individuals presenting with dyspepsia, which will vary depending on local practice, influenced cost-effectiveness. Our base run used an estimate of the incidence of peptic ulcer disease diagnosed in primary care before widespread *H. pylori* testing. This is probably a conservative estimate of the current degree of *H. pylori* testing (though the incident data may have overestimated definite peptic ulcer disease). Our opportunistic scenario would lie between a policy of routine endoscopy with *H. pylori* testing of those found to have peptic ulcer disease, and a policy of testing all patients presenting with dyspepsia and eradication in all found to be *H. pylori*-positive (test and treat) which may be most effective in terms of peptic ulcer disease management.[72–74] Further research is needed to determine the cost-effectiveness of *H. pylori* screening in relation to the changing management of dyspepsia.

It appeared cost-effective to use a more expensive triple-therapy regime and serological testing. The UBT's expense overrode its accuracy in saving more lives (fewer false-negative results) and reducing the number of patients with false-positive results, which in turn make up almost half of those treated under the other scenarios. The practicalities of screening (with regard to time and resources) with the UBT would be complex. We did not model the use of a confirmatory UBT; Fendrick and colleagues have shown that this would not be cost-effective.[75] Cost-effectiveness would be better with the falls in the costs of tests and triple therapy that might occur if there was a national screening programme and when drug patents expire.

We assumed that compliance in a national screening programme would achieve higher levels than in primary care-based research programmes which did not mention gastric cancer prevention.[58,59] Lower compliance did not affect overall cost-effectiveness, though absolute gains fall because screening is a 'one-off' event and compliance is likely to have a simple linear relationship with the number of deaths prevented. Those who fail to turn up for screening and treatment give rise to few costs. We envisaged that the screening programme would be implemented in primary care and so built our cost estimates on a study of primary care screening. General practices would be best placed to institute an age-related programme, using their age–sex registers. There would be a central administration cost for monitoring compliance with the programme and for laboratory quality control.

Reinfection and adult acquisition of *H. pylori* did reduce the cost-effectiveness especially in younger ages. However any acquisition is likely to be balanced by spontaneous eradication (e.g. because of antibiotic use for other reasons) and would fall if an *H. pylori* screening and eradication programme was initiated, and thus the assumption of zero acquisition is probably more realistic.

The cost-effectiveness ratio of screening was very sensitive to the discount rate. We used a conservative discount rate of 6% for benefits; even here screening was favourable. Reducing this to 1.5%, as recommended recently by the NICE, improved the cost-effectiveness dramatically.[69]

There were several factors that may increase cost-effectiveness of which we did not take account. We used life-years saved as our main outcome. We ignored the considerable morbidity of patients with peptic ulcer disease and the averted costs of managing peptic ulcer disease in primary care.

Moreover a recent Cochrane Review has shown that *H. pylori* eradication may have a small but significant effect in reducing non-ulcer dyspepsia symptoms.[76] We did not consider the morbidity associated with gastric cancer. To take account of the effect of *H. pylori* eradication with regard to non-fatal problems would have required derivation of costs per quality-adjusted life-year, which was beyond the scope of this research.

We did not investigate whether eradication could be confined to groups at higher risk of gastric cancer, such as smokers, though the model could be used to do this. The additional costs of identifying such patients would need to be considered as well as the absolute losses in disease prevented in non-smokers. More specifically, the CagA strain of *H. pylori* is associated with higher risks of gastric cancer and peptic ulcer. Restricting eradication to individuals who are CagA-positive is not much more cost-effective than including all *H. pylori* individuals in preventing gastric cancer, and there is a considerable absolute loss.[77] Such a policy would not prevent peptic ulcer disease in CagA-negative individuals.

There were factors that would reduce cost-effectiveness. Any screening programme would entail widespread use of antibiotics leading to antibiotic resistance, both for *H. pylori* specifically and more generally. The impact on wider antibiotic resistance is hard to quantify. Side-effects of triple therapy were not modelled but would reduce cost-effectiveness. Serious side-effects, however, are rare; less severe side-effects such as diarrhoea would affect quality of life and would partly offset the gains from preventing the morbidity of non-fatal peptic ulcer disease. The question of whether *H. pylori* eradication can increase the incidence of oesophagitis has been debated,[78] but recent randomised controlled trials (RCTs) of *H. pylori* eradication have not demonstrated any increase in such symptoms.[59] Nevertheless, the impact of widespread eradication of infection on the efficacy of PPIs in gastro-oesophageal reflux disease is unknown. Furthermore there are no good data to support the suggestion of an increase in incidence of oesophageal cancer after eradication of *H. pylori*. We assumed that the risk of gastric cancer was independent of peptic ulcer occurrence. There is some evidence that patients who have a duodenal ulcer have a reduced risk of gastric cancer compared with the general population whereas those with gastric ulcer have a higher risk.[48] We may therefore have overestimated the effect of *H. pylori* eradication on future gastric cancer risk in patients with duodenal ulcers. The likely effect is to make opportunistic eradication rather than population screening less effective. However there are few persistent duodenal ulcers in the no-screening arm as there is widespread opportunistic eradication in patients who are *H. pylori*-positive and who have a diagnosed peptic ulcer. Another issue is the effect of *H. pylori* separately on first and recurrent ulcers. This is complex, particularly as our only sources of data on the incidence of peptic ulcer were routine data which do not distinguish these groups. However as we eradicate *H. pylori* in most of the patients presenting with ulcers in the no-screening scenario, we assume that there will be little recurrence of *H. pylori*-related ulcer disease.

We did not include the costs of healthcare of patients who were prevented from dying from gastric cancer or ulcer complications. This would make the cost-effectiveness value less favourable but is not a generally used method for economic evaluation.[79] Newer cancer treatments might be developed for gastric cancer which improve survival. Likewise, better management of peptic ulcer might reduce ulcer complications. Both factors would reduce the cost-effectiveness of screening.

On comparing our results with those of the model of Parsonnet and colleagues,[42] we have shown that once-only screening in populations is likely to be cost-effective, although those authors suggested that screening at age 50 was more effective because of a higher prevalence and the effect of discounting. Two factors might support screening at an earlier age: taking peptic ulcer disease into account, and the uncertainty about the efficacy of eradication in reducing gastric cancer risk. Efficacy is likely to fall with age and so screening at 50 may be less beneficial.

Discrete-event simulation proved to be a powerful and flexible technique for analysing the benefits of screening. It was able to take account of the characteristics of individuals, for example, their age and *H. pylori* status, and to respond to changes in these as the simulation progressed. It described the progress of individuals and their relevant histories from entry to the population until death. The use of simulation made it possible to investigate the impact of complex and interrelated activities. We evaluated here the effect of screening on a system that involved more than one disease, affected overlapping groups of people and in which opportunistic screening was already taking place.

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Although the number of individuals in the simulation was large, the outcomes compared between two sets of runs were relatively small. Thus, despite the use of a range of variance reduction techniques, a large number of iterations was needed to produce sufficiently accurate results. The time taken to run a set of simulations is, however, declining significantly, as each generation of computers becomes faster and more powerful.

Using simulation, it was possible to evaluate a wide range of scenarios. These could be further extended to consider specific risk groups, screening by gender, different screening methods and different types of population. Simulation can readily be linked to cost information to provide discounted costs and benefits. A complete factorial design provided analysis of the sensitivity to key parameters.

The cost-effectiveness estimates compare favourably with those for other screening programmes in the UK. For example, for the breast cancer screening programme a cost per LYS of £2552 is estimated,[70] which becomes £2709 if the interval is shortened to 2 years. Colorectal cancer screening, which is being piloted in the UK, has an estimated cost per LYS (undiscounted) of £6300–£6700.[80]

What are the implications of these findings for research and policy?

Whilst population screening might be cost-effective this will not happen for at least 20–30 years, during which patterns of disease and treatment may change. Given the uncertainty about the efficacy of eradication of *H. pylori* with regard to cancer risk, the growth of opportunistic testing, and the problems of the time horizon and of antibiotic resistance, more evidence is needed before it can be recommended in England and Wales.

Research priorities

Key issues that could be addressed by research include the following.

1. The association of *H. pylori*, NSAIDs and complicated peptic ulcer disease could be investigated to derive the independent relative risk of complicated ulcer in *H. pylori*-positive individuals compared with those with negative *H. pylori* status. Case–control studies are needed; these could be undertaken relatively quickly.
2. The efficacy of eradication of *H. pylori* with regard to precancerous pathological changes could be studied; the results of current trials in gastric metaplasia are awaited.
3. The cost-effectiveness of 'test and treat' could be investigated (a trial funded by the Medical Research Council is currently underway), and the resulting impact of opportunistic screening.
4. The model could be used to re-evaluate the cost-effectiveness of *H. pylori* screening in the light of updated data on gastric cancer incidence and *H. pylori* prevalence and further information on the parameters mentioned above. If appropriate, a pilot *H. pylori* screening programme could be evaluated, which would probably screen all 40–49-year-olds as a prevalent round, then all 40-year-olds. This would provide information on compliance, eradication and reinfection (in a sample); on the impact on peptic ulcer disease and gastric pathology, and on the impact of opportunistic testing in the no-screening group.

Finally the model can be used to evaluate the effects of screening in other populations.

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Appendix 1

Studies of *H. pylori* infection and the risk of peptic ulcer disease

A MEDLINE search was conducted for studies from 1985 onwards of *H. pylori* and peptic ulcer disease (and duodenal and gastric ulcers), using the search terms Helicobacter pylori, peptic ulcer, duodenal ulcer, gastric ulcer.

Nine studies were identified, six of which were included in a meta-analysis by Kurata and Nogawa,[46] who calculated an overall relative risk for peptic ulcer associated with *H. pylori* of 3.3.[81—89] Not all of the studies considered the relative risks of duodenal ulcer and gastric ulcer separately, but in those that did so, the relative risk was found to be higher for duodenal ulcer. Details of the studies are shown in *Table 11*.

Previous uncontrolled studies have shown a high prevalence of *H. pylori* in those with ulcers, which was higher for duodenal than for gastric ulcers.[90] Eradication of *H. pylori* substantially reduces the risk of recurrence to low levels.[91,92]

Complications of peptic ulcer, are common with up to 20% of patients having bleeding and 5% perforation.[93] There is insufficient and conflicting evidence on *H. pylori* as a cause of complicated ulcer disease. Most studies were small case series and poorly designed case–control studies.

Concerning perforation, Reinbach and colleagues[94] investigated whether there was any link between *H. pylori* infection and perforated duodenal ulcer (gastric ulcer patients were excluded) in seven hospitals in Glasgow over a 1-year period. Of 111 patients identified, 31 were excluded due to early postoperative death or mental confusion; thus 80 patients were enrolled, and matched to 80 hospital controls. No association was found. In contrast, in a case series of patients with perforations, 24/29 were *H. pylori*-positive.[95]

Some case series of ulcer-related haemorrhage showed low levels of *H. pylori* infection,[96,97] but not all.[98] Cullen and colleagues showed that both *H. pylori* and NSAIDs increased the risks of bleeding in the elderly, without interaction.[99] The risk associated with *H. pylori* was 2.8 (1.1–7.2). Re-bleeding after complicated peptic ulcer can be reduced by *H. pylori* eradication.[100,101]

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TABLE 11 *Studies of the association between* H. pylori *infection and peptic ulcer disease*

Authors	Design	Details	Results	Comments
Nomura *et al.*, 1994[81]	Nested case–control study In cohort	Japanese-American men born between 1900 and 1919, followed-up over a 20-year period Serum for *H. pylori* testing obtained from study participants prior to diagnosis of *H. pylori* Mean time (months) between taking blood sample and hospitalisation: gastric ulcer, 67.5; duodenal ulcer, 64.5; both, 63.5	Duodenal ulcer 4.0 (CI, 1.1 to14.2) Gastric ulcer 3.2 (CI, 1.6 to 6.5)	60/65 (92%) with duodenal ulcer were *H. pylori*-positive 139/150 (93%) men with gastric ulcer were *H. pylori*-positive
Sipponen *et al.*, 1990[82]	Cohort study	10-year series of 454 consecutive patients (204 men, 250 women) who had endoscopy in 1979 and had no prior peptic ulcer Outpatient study	Peptic ulcer 13.8 (CI, 6.2 to 21.3)	Study widely cited in the literature. Development of ulcers observed in 34/321 (30 duodenal ulcer, 4 gastric ulcer) (11%) of patients with histological evidence of chronic gastritis, compared with 1/133 (0.8%) of patients without gastritis Mean time interval between endoscopy and development of ulcer, 41 months
Cullen *et al.*, 1993[83]	Cohort study	Population cohort, mean follow-up 18 years, Western Australia Baseline *H. pylori* serology	Peptic ulcer 5.5 (CI, 2.4 to 12.4)	Development of peptic ulcers (endoscopically or radiologically verified) in 24/157 (15%) *H. pylori*-positive patients and 7/250 (3%) *H. pylori*-negative patients Study remains unpublished in full
Leoci *et al.,* 1995[84]	Nested case–control study	265 men and 261 women; subgroup of 82 men and 96 women had gastric biopsies during baseline endoscopies for *H. pylori* testing	6/7 duodenal ulcer cases *H. pylori*-positive 8/14 controls *H. pylori*-negative Relative risk 5 (CI, 0.6 to 45)	27 participants lost to follow-up (11 had died) Small numbers in study give wide CIs
Schubert *et al.*, 1993[85]	Case–control study	Study evaluated influence of *H. pylori* and NSAIDs on risk of ulcers All patients referred for endoscopy between Dec 1988 and Nov 1991 (total 1088 patients)	112 patients with duodenal ulcer; 79% *H. pylori*-positive; relative risk 4.2 (CI, 2.6 to 7.0) 102 patients with gastric ulcer; 57.8% *H. pylori*-positive); relative risk 1.8 (CI, 1.1 to 2.9)	Age and sex not broken down Patients from various ethnic groups: 49 whites, 553 blacks, 20 Middle Easterners, 14 Asians and 10 hispanics Relative risk NSAIDs and gastric ulcer, 1.9 (CI, 1.2 to 3.2) Relative risk NSAIDs and duodenal ulcer, no association
Blaser *et al.*, 1995[86]	Nested case–control study	Japanese-American men; matched for age to one control from study cohort	147 gastric ulcer cases 64 duodenal ulcer cases Relative risk (calculated by Kurata) 4.5	Purpose of study was essentially to analyse sibship size and birth order data as risk factors for the development of gastric cancer and peptic ulcer disease
Graham *et al.*, 1988[87]	Case–control study	Assessed prevalence of *H. pylori*, using breath test Age range 20–84	24/54 asymptomatic US citizens *H. pylori*-positive; 9/15 asymptomatic Chinese citizens *H. pylori*-positive 77/85 patients with duodenal ulcer were *H. pylori*-positive 16/20 patients with gastric ulcer were *H. pylori*-positive Relative risk (calculated by Kurata) 7.9	75% of NSAID users were positive for *H. pylori*, 83% of non-users of NSAIDs

continued

***TABLE 11* contd** *Studies of the association between* H. pylori *infection and peptic ulcer disease*

Authors	Design	Details	Results	Comments
Martin *et al.*, 1989[88]	Case–control study	107 patients presenting for endoscopy, tested for *H. pylori* using serology Age range 18–83; 46 women and 61 men	Relative risk of having either duodenal ulcer or gastric ulcer was 4.5	14/107 patients had duodenal ulcer (all *H. pylori*-positive) 16/107 patients had gastric ulcer
Taha *et al.*, 1995[89]	Cohort study	Patients with chronic arthritis treated with NSAIDs recruited to examine predisposition to ulceration and relation to *H. pylori*; ulcer negative at start *H. pylori* identified by culture and histology	50 patients recruited Divided into 2 groups: 23 had erosions present (5 men, 18 women; aged 43–59) 27 erosions absent (6 men, 21 women; aged 43–61) Relative risk (calculated in Kurata's meta-analysis), 2.5	30/50 patients *H. pylori*-positive Duodenal erosions had a stronger association with subsequent ulceration than gastric erosions
Kurata & Nogawa, 1997[46]	Meta-analysis of risk factors for peptic ulcer	Six studies used to compute overall risk for peptic ulcer associated with *H. pylori*	Risk ratios varied from 2.4 to 7.9; overall relative risk summarised from the 6 studies is 3.3 (CI, 2.6 to 44)	Calculated risk ratios from the original data for the Blaser *et al.*, Graham *et al.*, Taha *et al.* studies

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Appendix 2

H. pylori-related peptic ulcer: incidence in primary care, hospital admissions, and mortality

Three sources of data were used:

- a GP morbidity survey study in 1991–92, to derive the incidence of peptic ulcer disease
- HES data for 1994–97 for hospitalisation
- mortality data from the Office for National Statistics for 1994–96.

Data were categorised by gender, 5-year age band and ulcer type (see *Table 12*). To generate duodenal and gastric ulcer rates, events coded as peptic ulcer in any age-sex group were reallocated to duodenal and gastric in proportion to those coded as duodenal or gastric. Haemorrhage and perforation could not be modelled separately, as in a significant proportion of cases these details were not specified.

To use the data to schedule future ulcer events, some assumptions and calculations were necessary. First, the GP presentation rates were divided into rates for *H. pylori*-negative and *H. pylori*-positive people, using *H. pylori* prevalence data and relative risk figures that relate ulcers to *H. pylori*, where:

$$\text{H. pylori-negative rate} = \frac{\text{Rate of everyone}}{(\text{Relative risk} \times \textit{H. pylori} \text{ prevalence}) + (1 - \textit{H. pylori} \text{ prevalence})}$$

$$\text{H. pylori-positive rate} = \text{Relative risk} \times \text{Negative rate}$$

It was assumed in the simulation that the *H. pylori*-negative and *H. pylori*-positive GP presentation rates would remain constant in the future. It was also assumed that all people dying from an ulcer complication had had a prior hospital admission for the ulcer and that all people admitted to the hospital had previously presented to a GP.

Furthermore, it was assumed that the percentage of patients presenting to the GP who developed an ulcer complication would remain constant in the future and that this percentage was independent of the patient's *H. pylori* status. The same assumption was made for the percentage of patients with ulcer complications who would die from their complication.

Under these assumptions it was essential that, for each gender, ulcer type and age group, the hospital admission rates were less than or equal to the GP presentation rates, and that the death rates were less than or equal to the hospital presentation rates. Any rates that did not satisfy this criteria were increased accordingly.

Finally, it was also assumed that only the first presentation to a GP for an ulcer could result in a hospital admission for a complicated ulcer. This was necessary to ensure that in the simulation, the rates for hospital presentation and for death from ulcer complications, were the same as the rates in the original data.

Thus, at the beginning of the simulation, the following were calculated:

- GP presentation rates dependent on *H. pylori* status
- the probability of developing a complication from a diagnosed ulcer
- the probability of dying from a complicated ulcer.

Ulcers were then scheduled in the simulation according to the GP presentation rates. On first presentation to a GP, the likelihood of ulcer complication was determined, and on admission to the hospital, the likelihood of death from the complication was accordingly determined.

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TABLE 12 *Estimated present annual peptic ulcer disease incidence and mortality rates per 100,000*

	Age (years)														
	15–19	**20–24**	**25–29**	**30–34**	**35–39**	**40–44**	**45–49**	**50–54**	**55–59**	**60–64**	**65–69**	**70–74**	**75–79**	**80–84**	**85+**
Duodenal ulcer rates/100,000															
Women															
GP presentation	70.0	70.0	199.3	199.3	199.3	199.3	344.8	344.8	344.8	344.8	301.4	301.4	279.1	279.1	294.1
Hospitalisation	2.6	5.8	10.6	15.9	22.1	29.5	35.1	42.7	51.9	63.2	76.3	95.0	134.0	182.3	209.9
Deaths	0.0	0.0	0.0	0.0	0.1	0.2	0.7	0.7	1.8	3.6	7.2	12.5	22.3	39.2	71.9
Men															
GP presentation	184.6	184.6	450.3	450.3	450.3	450.3	623.7	623.7	623.7	623.7	577.4	577.4	544.1	544.1	360.0
Hospitalisation	9.3	25.5	39.2	47.0	60.8	70.1	75.3	94.3	123.3	143.1	166.9	216.4	265.9	334.8	426.5
Deaths	0.0	0.0	0.1	0.2	0.3	0.6	1.2	1.9	3.5	6.0	11.9	21.9	39.0	64.2	105.6
Gastric ulcer rates/100,000															
Women															
GP presentation	0.0	0.0	30.7	30.7	30.7	30.7	55.2	55.2	55.2	55.2	78.6	78.6	190.9	190.9.1	205.9
Hospitalisation	2.7	5.8	7.5	10.0	16.3	24.8	36.4	50.6	68.2	83.1	114.5	147.4	195.2	243.8	242.1
Deaths	0.0	0.0	0.0	0.1	0.2	0.2	0.3	0.4	1.3	2.0	3.7	8.2	13.1	24.7	46.0
Men															
GP presentation	15.4	15.4	39.7	39.7	39.7	39.7	66.3	66.3	66.3	66.3	102.6	102.6	205.9	205.9	
Hospitalisation	4.1	8.6	12.3	17.5	25.1	32.4	42.4	67.6	94.8	119.7	153.9	194.5	247.6	284.3	308.0
Deaths	0.0	0.0	0.1	0.1	0.1	0.5	0.5	1.2	1.9	3.0	5.8	10.2	16.9	24.9	43.9

Appendix 3

H. pylori infection and the risk of gastric cancer

We searched MEDLINE for studies from 1990 onwards of the association between gastric cancer and *H. pylori*, using the search terms Helicobacter pylori, gastric cancer. We focused on nested case–control studies within cohorts, as giving the strongest evidence, and gave most consideration to studies in western populations. *Table 13* shows details of studies investigating the risk of gastric cancer associated with *H. pylori* infection.

We identified one meta-analysis of observational studies by Huang and colleagues.[54] They identified 19 investigations, 14 case–control and five cohort studies, and calculated an overall risk estimate of 1.9. Using individual patient data they showed that this risk varied by age from 9.3 (95% confidence interval, 3.4 to 34.0) in 20–29-year-olds to 1.05 (0.7 to 1.5) in people over 70.

There was no risk associated with cardia cancer, and no difference in the *H. pylori* risk for intestinal and diffuse gastric cancers.

Reversibility studies

To evaluate whether *H. pylori* eradication was likely to reduce the risk of gastric cancer, we looked at whether eradication reversed the pathological changes of atrophic gastritis and intestinal metaplasia, which are thought to be part of the pathological progression to gastric cancer.[14] We searched MEDLINE and EMBASE 1985–98 for studies of *H. pylori* and atrophic gastritis/intestinal metaplasia. We included studies in which dual or triple therapy had been used to eradicate *H. pylori* and for which follow-up exceeded 6 months. These are shown in *Table 14*.

The evidence is conflicting but there is some, particularly with longer duration of follow-up, suggesting that *H. pylori* eradication does reduce the severity of gastritis, and it may reverse atrophic and metaplastic changes. There are problems in studying reversibility as these pathological changes are focal and hence evaluation is prone to sampling error. Moreover there is the problem of the lack of a precise definition of atrophic gastritis. If it is defined as glandular loss without defining what replaces it then reversibility is possible; however, if it is defined as glandular loss with replacement by fibrosis and metaplastic epithelium then it might be difficult to demonstrate reversibility. The majority of the studies did not mention the definition of atrophic gastritis that had been used.

Comments on reversibility studies

1. Van der Hulst *et al.*, 1997[107]

This study was mainly aimed at investigating the effect of *H. pylori* eradication on gastritis in relation to CagA. Atrophic gastritis was defined as loss of glands with replacement by intestinal epithelium. The dual regimen used had poor efficacy. The degree of atrophic gastritis and intestinal metaplasia was more severe in the antrum compared with the corpus. The severity of these lesions essentially remained unchanged: there was no regression but there was no progression either.

2. El-Omar *et al.*, 1997[108]

The primary aim of this study was to look at the effect of *H. pylori* infection and gastric hyposecretion. A highly selected group of 16 patients was identified after screening 250 patients and asymptomatic volunteers. There was no atrophic gastritis or intestinal metaplasia in the antrum of any of these pts but 13/16 had atrophy in the corpus and 7/16 had intestinal metaplasia in the corpus.

In this study atrophic gastritis was defined as loss of glands irrespective of their replacement. The results showed that there was significant improvement in acid secretion in 12/15 patients but no improvement in 3/15 patients. Histologically there was no improvement in atrophic gastritis and intestinal metaplasia (over 6 months), which are supposed to be responsible for hypochlorhydria, thus showing that there was functional improvement without any morphological improvement. This might mean that morphological improvement takes much longer to become visible compared with functional improvement.

3. Uemura *et al.*, 1996[109]

This study showed reversal of intestinal metaplasia in patients who had progressed as far as early

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TABLE 13 *Associations between* H. pylori *infection and gastric cancer*

Authors, country	Study design	Years between *H. pylori* diagnosis and cancer diagnosis	Numbers	Age range and sex	Odds ratio (CI)	Comment on type of cancer	Other comments
Forman *et al.*, 1991[4] UK	Nested case–control	Mean 6 years (4 months–13 years)	29 (23 + 6) cases 116 controls	35–59 men	2.77 (1.04 to 7.97)	Lack of detailed clinical or histopathological information precluded analysis by site	Healthy volunteers taking part in a medical examination at BUPA, London, and from Caerphilly heart disease study
Parsonnet *et al.*, 1991[6] US	Nested case–control	Mean 14.2 years (1–24 years)	109 cases 109 controls	Mean age at enrolment 53.7 Men and women	3.6 (1.8 to 7.3)	Gastric adenocarninomas classified as intestinal or diffuse Site specified: antrum or pylorus, body or fundus and cardia (n = 4)	*H. pylori* a particularly strong risk factor in women (n = 64)
Nomura *et al.*, 1991[5] US: Japanese-Americans in Hawaii	Nested case–control	Mean 13 years	109 cases 109 controls	Mean age at enrolment 59 Men	6.0 (2.1 to 17.3)	Histological type of carcinoma described 104 patients with cancer in antrum or body of stomach; 5 with cardia cancer	Japanese-Americans living in Hawaii Risk higher for longer duration from initial serological test to diagnosis
Hansen *et al.*, 1994[102] Norway	Nested case–control	Not known	201 cases 402 controls		1.8 (1.2 to 2.6)		
Aromaa et al., 1996[103] Finland	Nested case–control	Mean 9.5 years	84 cases 146 controls	Cases: mean 62.0 Controls: mean 60.9	2.5 (1.1 to 5.6) if IgA; 1.5 (0.7 to 3.2) for IgG	Tumour sites are not specified, 9/84 cardia	Odds ratio increased with follow-up duration
Siman *et al.*, 1997[104] Sweden	Nested case–control	Mean 5.7 years	56 cases 224 controls	Not stated in abstract	5.0 (2.2 to 11.5)	Site of tumours specified Tumours of fundus, corpus and antrum significantly associated with *H. pylori*; tumours of cardia not associated with *H. pylori* Numbers of patients in each group (site of tumour) not specified in abstract	
Webb, 1996[105] China	Nested case–control	Not known	87 cases 261 controls		1.17	Risk higher for non-cardia cancer	Risk higher for younger age, longer follow-up
Lin *et al.*, 1995[106] Taiwan	Nested case–control	Short follow-up between *H. pylori* diagnosis and cancer diagnosis	29 cases 220 controls		1.6 (0.7 to 2.6)		As above
Forman *et al.*, 1994[7]	Meta-analysis of first three studies				3.8 (2.3 to 6.2)		Longer duration of follow-up shows higher risk, e.g. 15+ years then risk 8.7

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TABLE 14 *Effect of* H. pylori *eradication on atrophic gastritis and intestinal metaplasia*

Authors	Study population	Treatment	Follow–up	Biopsy site	Atrophic gastritis reversal	Intestinal metaplasia reversal	Comments
1 Van der Hulst *et al.*, 1997[107]	Dutch; 101 dyspeptic patients with *H. pylori* Mean age 50	Omeprazole + amoxicillin; dual regimen with 68% efficacy	1 year	Antrum and corpus	No	No	80% of patients were CagA positive; reversal was unrelated to CagA Inflammation was reduced by eradication
2 El-Omar *et al.*, 1997[108]	Scottish; 16 hypochlorhydric patients Mean age 55	Triple	6 months	Antrum and corpus	No	No	Hypochlorhydric population with short follow-up
3 Uemura *et al.*, 1996[109]	Japanese; early gastric cancer (intestinal type) patients having endoscopic resection Non-randomised; 65 had triple therapy, 67 had no eradication	Triple	2 years (6, 48 months)	Antrum and corpus	–	Yes ($p < 0.05$)	Severity reduced Recurrence of cancer was also suppressed Inflammation reduced
4 Forbes *et al.*, 1996[110]	Australian; 54 patients, with duodenal ulcer at endoscopy, 1985–86 Eradication in 32, not in 22	Not efficacious as only 32 patients had *H. pylori* clearance	7.1 years	Antrum	No	No	On follow-up there was no change in atrophic gastritis and intestinal metaplasia Inflammation reduced
5 Cayla et al., 1995[111]	French; 28 patients with duodenal ulcer Mean age 54 All had atrophic gastritis/intestinal metaplasia but no dysplasia	Not specified	26 months (12–60 months)	Antrum	Yes	Yes	Changes greater with longer follow-up
6 Wyatt, 1995[112]	English; duodenal ulcer (a) 227 (b) 64	Dual (poor regimen)	(a) 6 months (b) 12 month	Antrum	–	Not statistically significant	Trend toward regression
7 Di Napoli *et al.*, 1992[113]	Italian; 50 non-ulcer dyspepsia	Triple (poor regimen)	6 months	Antrum	No	–	Inflammation reduced but not atrophy
8 Haruma *et al.*, 1997[114]	Japanese; 20 severe atrophic gastritis	Triple	6 months	Antrum and corpus	NS ? yes	Yes	Small numbers and short follow-up
9 Griffiths *et al.*, 1997[115]	English; endoscopically diagnosed *H. pylori*-positive patients 53 had eradication, 47 remained *H. pylori*-positive	Not specified	3.4 years	Not specified	Yes	Yes	Retrospective study Biopsies 2 years apart Greater changes with longer duration of eradication
10 Borody *et al.*, 1993[15]	Not specified	Triple	6 months	Antrum and corpus	Yes	–	Histology, culture and CLO were negative, only serology positive

gastric cancer. None of the 65 patients who received eradication treatment had recurrence of cancer after endoscopic resection, whereas 6/67 who did not receive eradication treatment had recurrence of cancer at different sites.

4. Forbes *et al.*, 1996[110]
These data relate to the changes in the antral mucosa of patients with duodenal ulcers. Although there was no regression, neither was there any progression in 7.1 years of follow-up.

5. Cayla *et al.*, 1995[111]
At 1 year, atrophic gastritis and intestinal metaplasia had regressed only partially but those who were followed for over 5 years showed a significant reversal, implying that the full effect of *H. pylori* eradication might take a few years to appear.

6. Wyatt *et al.*, 1995[112]
An extremely poor eradication regimen was used.

7. Di Napoli *et al.*, 1992[113]
Only 33 patients had *H. pylori* eradication treatment and the follow-up was short. Atrophic gastritis was not defined.

8. Haruma *et al.*, 1997[114]
Very small numbers were involved, but methylene blue staining identified regression in 70% (14/20), no change in 30% (6/20) and progression in 0%.

9. Griffiths *et al.*, 1997[115]
Hypochlorhydria improved, but not atrophy.

10. Borody *et al.*, 1993[15]
This retrospective study found that 74% of patients who had eradication of *H. pylori* showed reversal whereas only 47% of those who remained infected showed reversal. Thus it was shown that reversal can occur even with ongoing *H. pylori* infection, but eradication of *H. pylori* can increase the overall reversal rate. The study also demonstrated that a long follow-up is required to see these effects.

Appendix 4

Trends in gastric cancer incidence and mortality: age–period–cohort modelling

General considerations

The IARC has shown that trends in gastric cancer mortality for both sexes in all countries in Europe have reduced significantly between 1970 and 1985 (by approximately 15%).

Mortality rates are reducing with each birth cohort. Simple projected rates give a very optimistic picture, though it is not known whether in reality rates will continue to decline as dramatically as they have in the past.

There are factors other than declining *H. pylori* prevalence (e.g. dietary and smoking changes) which influence gastric cancer rates.

However, 5-year survival rates have shown little change in recent years.

Modelling gastric cancer trends

An age–period–cohort analysis was performed. To schedule the occurrence of gastric cancer in the simulation, the gastric cancer mortality cohort model was used as a basis for determining the incidence of gastric cancer, by the method described below.

Data were available by sex, age and year (in 5-year intervals) for the number of deaths from gastric cancer and the associated death rates per million of the population from 1950 to 1994. A number of Poisson regression models for ages 20 and over were considered, and fitted using PROC GENMOD in SAS (*Table 15*).

In both sexes, the Age + Cohort model fits much better than the model with Age alone, as measured by comparing the change in deviance with its associated χ^2 distribution. The models are still a poor fit, however, as a well-fitting model should have a deviance which follows a χ^2 distribution with its associated degrees of freedom. This manifests itself in the actual death rates for the over-70s being outside the confidence interval for the predicted rates. The Age + Period + Cohort model is slightly better than the Age + Cohort model, but the latter was chosen for ease of forecasting, as the full model is unidentifiable.

The cohort effects are shown in *Tables 16–19*.

The age- and gender-specific rates predicted by the model are shown in *Table 20*. In forecasting future cancer trends in *H. pylori*-positive individuals, the *H. pylori* prevalence in the future

TABLE 15 *Modelling gastric cancer trends*

	Scaled deviance	df	Change in scaled deviance	Change in df
Males				
Age	27,961	112		
Age + Cohort	196	91	27,765	21
Age + Cohort + Period	153	84	43	7
(Age + Period)	3,592	104	24,369	8
Females				
Age	32,858	112		
Age + Cohort	194	91	32,664	21
Age + Cohort + Period	145	84	49	7
(Age + Period)	1,245	104	31,613	8

df, degrees of freedom

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TABLE 16 *Cohort effects in gastric cancer modelling; male Age + Cohort model: age-specific rates estimated from the model*

Age group	Cohort	Period	Deaths per million			
			Actual	Predicted	Lower limit	Upper limit
85–	1900–09	1990–94	2,169	2,121	2,080	2,163
80–	1905–14	1990–94	1,904	1,918	1,889	1,948
75–	R1910–19*	1990–94	1,451	1,484	1,462	1,506
70–	1915–24	1990–94	995	1,027	1,011	1,044
65–	1920–29	1990–94	708	709	695	722
60–	1925–34	1990–94	412	411	401	421
55–	1930–39	1990–94	212	216	208	223
50–	1935–44	1990–94	103	113	107	118
45–	1940–49	1990–94	53	52	48	55
40–	1945–54	1990–94	24	23	21	26
35–	1950–59	1990–94	10	10	9	12
30–	1955–64	1990–94	4	4	4	6
25–	1960–69	1990–94	1	1	1	2
20–	1965–74	1990–94	1	1	0	2

* *Reference cohort*

TABLE 17 *Cohort effects in gastric cancer modelling; male Age + Cohort model: standardised estimates of cohort effects with 95% confidence intervals*

Cohort	Lower limit	Estimate	Upper limit
1860–69	156	167	179
1865–74	182	189	196
1870–79	192	197	202
1875–84	188	192	195
1880–89	177	180	183
1885–94	167	170	173
1890–99	156	158	161
1895–04	145	147	149
1900–09	135	137	139
1905–14	118	119	121
1910–19*		100	
1915–24	80	82	83
1920–29	71	72	74
1925–34	57	58	60
1930–39	43	45	47
1935–44	36	37	39
1940–49	27	29	31
1945–54	21	23	25
1950–59	16	19	23
1955–64	14	18	23
1960–69	8	13	19
1965–74	8	17	32

* *Reference cohort*

TABLE 18 *Cohort effects in gastric cancer modelling; female Age + Cohort model: age-specific rates estimated from the model*

Age group	Cohort	Period	Deaths per million			
			Actual	Predicted	Lower limit	Upper limit
85–	1900–09	1990–94	1,204	1,184	1,164	1,204
80–	1905–14	1990–94	892	920	904	936
75–	R1910–19*	1990–94	589	619	607	631
70–	1915–24	1990–94	374	389	380	398
65–	1920–29	1990–94	245	254	247	261
60–	1925–34	1990–94	137	141	136	147
55–	1930–39	1990–94	76	79	75	84
50–	1935–44	1990–94	40	41	38	44
45–	1940–49	1990–94	22	23	21	25
40–	1945–54	1990–94	14	13	11	15
35–	1950–59	1990–94	9	8	6	9
30–	1955–64	1990–94	5	4	4	6
25–	1960–69	1990–94	2	2	1	2
20–	1965–74	1990–94	1	1	0	1

* *Reference cohort*

TABLE 19 *Cohort effects in gastric cancer modelling; female Age + Cohort model: standardised estimates of cohort effects with 95% confidence intervals*

Cohort	Lower limit	Estimate	Upper limit
1860–69	295	310	326
1865–74	324	334	345
1870–79	315	323	331
1875–84	289	295	302
1880–89	252	258	264
1885–94	223	228	232
1890–99	198	202	206
1895–04	170	174	177
1900–09	144	147	150
1905–14	121	124	127
1910–19*		100	
1915–24	79	81	84
1920–29	71	73	76
1925–34	55	57	60
1930–39	44	46	48
1935–44	32	34	37
1940–49	25	28	31
1945–54	21	24	27
1950–59	19	22	26
1955–64	17	21	27
1960–69	8	12	19
1965–74	4	13	28

* *Reference cohort*

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TABLE 20 *Age effects from the model; rates per million population*

Age (years)	Male	Female
20–24	11	12
25–29	11	12
30–34	24	21
35–39	54	35
40–44	101	56
45–49	178	81
50–54	295	119
55–59	475	174
60–64	701	251
65–69	981	348
70–74	1248	482
75–79	1481	625
80–84	1601	752
85–89	1524	816

had to be estimated for ages 20–99 from 2000 to 2079. An assumption of the model was that *H. pylori* prevalence levels had levelled off in the younger age groups, and consequently, cancer mortality rates had levelled off also. The forecast *H. pylori* prevalence was thus solely dependent on the current prevalence of *H. pylori* and the rate of *H. pylori* acquisition in future years.

The future *H. pylori*-positive gastric cancer rates could then be calculated, given the age and birth cohort rates shown above, the *H. pylori* prevalence and the assumption of relative risk of cancer. Some smoothing was done to ensure that any birth cohort had decreasing rates over time and, for any age group, that predicted rates did not increase over time.

TABLE 21 *Turning mortality into incidence*

Age (years)	Male	Female
20–24	17.0	19.3
25–29	17.0	19.3
30–34	17.0	19.3
35–39	17.0	19.3
40–44	17.0	19.3
45–49	16.0	19.3
50–54	16.0	19.3
55–59	12.6	13.6
60–64	12.6	13.6
65–69	6.7	10.7
70–74	6.7	10.7
75–79	4.8	5.3
80–84	4.8	5.3
85–89	4.8	5.3
90–94	4.8	5.3

$$\text{H. pylori-negative rate} = \frac{\text{Total gastric cancer rate}}{(\text{Relative risk} \times \text{H. pylori prevalence}) + (1 - \text{H. pylori prevalence})}$$

$$\text{H. pylori-positive rate} = \text{Relative risk} \times \text{Negative rate}$$

The 5-year survival figures for stomach cancer, 1989 registrations in England and Wales, were taken from *Monitor – Population and Health* supplied by the Office for National Statistics. The gastric cancer mortality rates, supplied by the cohort model, were adjusted in relation to the 5-year survival figures to provide crude cancer incidence rates (*Table 21*).

Appendix 5

Reinfection and acquisition of *H. pylori* infection

Reinfection

A MEDLINE search for studies from 1990 onwards of reinfection after eradication of *H. pylori*, using the search terms Helicobacter pylori, reinfection, produced the studies shown in *Table 22*.

The UK study of Bell and colleagues was the most robust, with large numbers (more than 1000) and showing reinfection rates broken down by time periods.[68] In the study of Van der Hulst and colleagues reinfection rates were not broken down into time periods.[117] Outdated eradication treatments were used in the investigations of Berstad and Xia and their co-workers,[118,119] but limited DNA analysis of the *H. pylori* strains did suggest that *H. pylori* infection after eradication was more likely to be recrudesence of the original *H. pylori* infection, due to inadequate eradication, rather than new infection, although reinfection from the same strain could not be excluded

Bell's study supported this. First, most reinfection occurred within the first 6 months,[68] and secondly, reinfection was highest in those patients who despite a negative breath test at 1 month post treatment had received a less efficacious drug combination. In patients receiving treatment with an overall success rate of greater than 60%, 23 out of 34 'reinfections' (67.6%) occurred by 6 months, seven (20.6%) by 1 year and four (11.8%) after 1 year. After 1 year the chances of reinfection were less than 1%.

Acquisition of infection in *H. pylori*-negative individuals with no previous infection

MEDLINE and EMBASE were searched for studies from 1985 to 1998 on the incidence of *H. pylori*. We only included studies in adults and with follow-up of more than 1 year.

Studies of acquisition are shown in *Table 23*. In all of these serological status over time was evaluated. No UK studies were found.

Net seroconversion is a balance of conversion and reversion. The former arises from continued exposure to *H. pylori* infection during adult life; sero-reversion can occur due to exposure to antibiotics not given specifically for eradication or due to gastric atrophy.

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TABLE 22 *Studies of* H. pylori *reinfection after eradication*

Authors, country, study period	Type of study	No. of patients	Test used	*H. pylori* reinfection rate	Comments
Miehlke *et al.*, 1996[116] Germany Study period not stated	Follow-up study 1.5–5 years (mean 24 months) following antibacterial treatment for peptic ulcer disease, resulting in histologically documented cure Various regimens used but not specified	217	Pre-test: 'endoscopically proven' Post-test: histology (2 antral and 2 corpus biopsies taken)	8/217 patients, i.e. 0.8% per patient-year in first 2 years	
Van der Hulst *et al.*, 1997[117] Holland Study period 1984–94	Follow-up study Cohort (dyspeptic patients) followed since 1984 (mean 3.5 years; range 1.0–9.2 years) Various treatment regimens used: bismuth dual and triple, and PPI dual; PPI triple therapy not used	173	Pre- and post-treatment: histology, 2 antrum biopsies for culture and 2 for histopathology Corpus biopsies added to follow-up procedure after PPIs became part of therapy 4 weeks post-treatment assessment	7/171 patients, i.e. 1.2% per patient-year Reappearing infection diagnosed after a mean H. pylori-n-negative period of 14.6 months (range 3–32 months)	2 patients excluded from analysis, because iatrogenically infected via endoscopy, pre-1988 DNA profiling confirmed recrudescence, rather than reinfection
Berstad *et al.*, 1995[118] Norway Study period 1990–93	Follow-up study at 1 month and 1 year	242		1.7% (4 cases at 1 year)	Assessed at 4 weeks Efficacy of treatment regimens was low, bismuth included
Berstad *et al.*, 1995[118] Norway	Follow-up study	306	1 year post-eradication (3 regimens)	4/242 H. pylori-negative at 4 weeks after eradication were H. pylori-positive at 1 year Reinfection rate 1.7%	Eradication rates for 2 regimens under 90% at 4 weeks
Xia *et al.*, 1995[119] Ireland	Follow-up study Treatment: bismuth, metronidazole and tetracycline	320	4 weeks post-treatment: CLO, histology, Gram staining and culture Endoscopy 1 year after apparent eradication	0% reinfection rate 9.1% recrudescence (29/320 patients)	Fingerprinting carried out on 5 patients only Unclear whether any loss to follow-up
Bell *et al.*, 1996[68] Study period 10/86–3/95	Follow-up study	1182	Pretreatment: histological and bacteriological examination of endoscopically obtained biopsy, and/or a positive UBT Breath test 1 month post-treatment	57/1182 patients Annual reinfection of 3.7% per year 45 detected at 6 months 8 detected at 1 year 4 at 2 years	Repeat UBTs at regular intervals for up to 8 years following apparently successful initial eradication Most reinfections occurred in the first 6 months post-treatment: 1 year after therapy subsequent chance of reinfection was less than 1% per year Study shows that reinfection was dependent on the efficacy of the treatment used Most reinfections were late recrudescences

TABLE 23 *Acquisition of* H. pylori*: studies of seroconversion*

Population studied, authors	Number	Follow-up (years)	New infections in initially negative individuals	Incidence per annum (%)
Dutch endoscopy patients Kuipers *et al.*, 1993[67]	115	11.5	2/59*	0.3 (0.04 to 1.8)
Australian adults Cullen *et al.*, 1993[120]	141	21.0	6/86	0.33 (0.08 to 0.59)
US epidemiologists Parsonnet *et al.*, 1992[2]	341	8.5	11/278	0.5
US heart transplants Dummer *et al.*, 1992[121]	100	3.4	1/65†	0.5
Canadian cohort Veldhuyzen van Zanten *et al.*, 1994[122]	316	1.5	3/112‡	1.0 (0.3 to 4.3)

* *Also, 6/59* H. pylori*-positive individuals reverted to negative state despite not receiving eradication therapy; in three this was due to stomach resection*

† H. pylori *reversion in 14/35*

‡ *Reversion in three cases, in older individuals (42, 70 and 71 years old)*

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Appendix 6

Input and output for the simulation program

Input

The categories of input to the simulation derived from epidemiological sources are shown in *Table 24*. Other simulation input is shown in *Table 25*.

Output

All annual events

These are results totalled over all replications, given by simulation year and by upper age group. They are used for calculating the main simulation output. The data collected are as follows:

- number invited for prevalent population screening
- number invited for screening through an ongoing screening programme
- number of prevalent screens
- number of screens in ongoing screening programme
- number of false-positive screening tests
- number of false-negative screening tests
- number of *H. pylori* eradication treatments
- number of people who have had cancer
- number of infections
- number of reinfections
- number of new people entering the simulation
- number of people alive in the simulation at end of year
- number of people who did not arrive for screening
- number of people who have died
- number of people who have ever had *H. pylori*

TABLE 24 *Simulation input derived from epidemiological sources*

Input	Subdivision categories
Population	
Baseline	Gender/5-year age groups
Age distribution	Gender/Age
Prevalence	
H. pylori	Gender/5-year age groups
Disease	Gender/10-year age groups
Acquisition	Gender
Relative risk	
Ulcer and *H. pylori*	Gender
Cancer and *H. pylori*	Gender/10-year age groups
Presentation rates	
Ulcer at GP	Gender/5-year age groups/ulcer type
Ulcer complications	Gender/5-year age groups/ulcer type
Cancer	
Cohort effect	Gender/Overlapping 10-year birth cohorts starting every 5 years
Cohort mortality	Gender/5-year age groups
Screening methods	Name, sensitivity and specificity
Treatment methods	Name and efficacy of eradication of *H. pylori*
Compliance	Gender/10-year age groups/Reason for invitation
Mortality	
Baseline	Gender/Age (assumed all die by age 100)
Complications	
Ulcer	Gender/5-year age groups/ulcer type
Cancer	Gender/5-year age groups

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TABLE 25 *Other simulation input*

Input	Description
Lag	Variable to control the efficacy of *H. pylori* eradication in preventing gastric cancer
Number of iterations	Defines the number of replications to be performed of one scenario Multiple replications reduce the variance of the results
Screening programme	Defines whether to include an initial screening round and if so what age range to screen Also defines whether to include an ongoing screening programme, and if so, at what age to call people for screening and how long to run the programme for
Simulation duration	Maximum duration of 80 years
New arrivals	Defines whether new patients enter the simulation each year (at age 20), and if so, the number of years that they enter for

- number attending GP for duodenal ulcers
- number of complications from duodenal ulcers
- number attending GP for gastric ulcers
- number of complications from gastric ulcers
- number of deaths from cancer
- number of deaths from duodenal ulcer complications
- number of deaths from gastric ulcer complications
- number of deaths from causes other than duodenal and gastric ulcer complications
- number of *H. pylori* eradication treatments resulting from either screening programme
- number of *H. pylori* eradication treatments resulting from presentation with an ulcer to GP.

Record of input data

This output documents the data which is input to each run in a batch, to enable them to be used again.

Individual replication events

This output provides results separated by replication and upper age group but not separated by simulation year. This is used for calculating confidence intervals.

Data for graphs

This output collects the data required to display the graphs for model validation. The graphs are shown by year, over the duration of the simulation, or by patient age, as appropriate. They are as follows:

- cancers per person
- ulcers per person
- gastric ulcers per person
- duodenal ulcers per person
- all ulcers per person
- repeat ulcers per person
- infections per person
- reinfections per person
- percentage of ulcers that become complicated
- percentage of complications that result in death
- time since last ulcer if repeat ulcer
- cancer life expectancy
- age of death.

Time spent in the natural history states

These results give the total time spent in each natural history state, summed over all replications of a simulation run.

Appendix 7

Verification and validation

For the purpose of simulation verification the following checks were completed.

- Patients remained in the simulation until they died.
- The simulation routines that calculated future cancer incidence rates, from the simulation input data of cancer presentation rates, produced the same results as those calculated on a spreadsheet.
- Patients remained dead after dying.
- *H. pylori*-negative patients remained *H. pylori*-negative.
- Different input values were tested to ensure that the simulation worked in a consistent manner in accordance to the input. For example, the following were checked:
  - the relative risk of *H. pylori* prevalence on cancer and ulcer incidence
  - the lag in the effect of *H. pylori* elimination on cancer incidence
  - treatment efficacy
  - screening sensitivity and specificity
  - compliance figures for screening and treatment
  - acquisition rates of ulcers and cancers
  - presentation rates of ulcer and cancer.

For the purpose of simulation validation, the following values were checked to see that they were the same as those input, or values predicted from the input.

- overall mortality
- *H. pylori* prevalence by year in simulation
- cancer mortality rates by year – no *H. pylori* treatment
- cancer mortality rates by year – *H. pylori* treatment for presenting ulcer but no screening
- ulcer mortality rates by year – no *H. pylori* treatment
- ulcer mortality rates by year – *H. pylori* treatment for presenting ulcer but no screening
- ulcer incidence rate over time – no *H. pylori* treatment.

In addition, all variables were set at their current best estimate and run without a screening programme to check that all factors remained stable or within expected trends.

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Appendix 8

The prevalence of *H. pylori*

MEDLINE and EMBASE were searched for population-based studies, from 1985 onwards, of the prevalence of *H. pylori* in the UK, using the search terms Helicobacter pylori, prevalence. The abstracts from 1995 to 1998 of the British Society of Gastroenterologists and the American Gastroenterology Association were searched. We excluded studies in selected populations (e.g. blood donors, occupational groups) and in children. Six studies, all using random sampling from population in the UK were considered (see *Tables 26* and *27*).

The Eurogast study was chosen as the most appropriate study for the prevalence of *H. pylori* in England.[8] People were sampled randomly from registers in general practices in Stoke-on-Trent and Oxford. A lower prevalence estimate came from a population-based study from south-west England (Harvey R, Frenchay Hospital, Bristol: personal communication, 1998), and a higher estimate from a study from Northern Ireland.[52]

Prevalence was considered to increase with age, with an overall value of 29%. We were obliged to assume a linear age gradient. Predicted values are shown in *Table 27*.

TABLE 26 *Prevalence of* H. pylori

Source	Population	Year	Test used	Overall prevalence (%)
Murray *et al.*[52]	Northern Ireland, *n* = 4742 Population base for Monica coronary heart disease study Age 12–64	1986–7	Serology	51
Sitas *et al.*[28]	South Wales, *n* = 749 Population base: men 30–75 for Caerphilly coronary heart disease study	1979–83	Serology	57
McDonagh *et al.*[123]	Glasgow, *n* = 1428 Population base for Monica coronary heart disease study Age 25–74	Year?	Serology	66
Eurogast Oxford[8]	Oxford, *n* = 158 Population from GP Age 25–34, 55–64	1991–2	Serology	Male 29 Female 25
Eurogast Stoke[8]	Stoke, *n* = 200 Population (GP) Age 25–34,55–64	1991–2	Serology	Male 38 Female 26
Harvey (personal communication)	Bristol, *n* = 10,000 invited Population from GP	1997–	Serology	15%
Stone *et al.*[58]	Northamptonshire, *n* = 4,015 invited Population from GP	1997	Serology	15%

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TABLE 27 H. pylori *prevalence by age group in six studies and predicted values*

	Age												
	12–14	**15–19**	**20–24**	**25–29**	**30–34**	**35–39**	**40–44**	**45–49**	**50–54**	**55–59**	**60–64**	**65–69**	**70–75**
***Murray* et al.**[52]													
Total	23.4%	24.1%	39.7%	37.6%	44.0%	51.6%	56.8%	63.3%	68.8%	68.2%	72.7%		
n	337	531	423	423	366	440	488	498	423	444	429		
***Sitas* et al.**[28]													
Male					29.8%	40.7%	49.4%	72.6%	66.7%	64.7%	69.1%	60.3%	75/0%
n					106	81	87	62	84	68	42	131	88
Predicted from Eurogast[8]													
Male		14%	17%	20%	24%	28%	32%	37%	42%	47%	53%	59%	> 60%
Female		9%	12%	15%	19%	23%	27%	32%	37%	42%	48%	54%	> 55%
Eurogast Oxford[8]				**(age 25–34)**						**(age 55–64)**			
Male				8% (*n* not given)						49%			
Female				8%						42%			
Total				8%						45.5%			
Eurogast Stoke[8]													
Male				27%						49%			
Female				10%						41%			
Total				18.5%						45%			
Harvey (personal communication)			**(age 20–29)**		**(age 30–39)**		**(age 40–49)**		**(age 50–59)**				
Total			3.4%		9%		15%		22%				
***McDonagh* et al.**[123]													
Male				56%		59%		65%		81%		80%	
n				57		77		93		136		129	
Female				50%		54%		61%		70%		69%	
n				52		79		97		105		116	
***Stone* et al.**[58]			**(age 21–55)**										
Total			15%										

Appendix 9

Accuracy of serological testing

MEDLINE was searched, using the search terms Helicobacter pylori, serology, for studies from 1990 employing enzyme-linked immunosorbent assay (ELISA) serology.

We included studies which used gold standard reference tests (two out of three of histology, UBT and culture) (*Table 28*).

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TABLE 28 *Accuracy of serological testing*

Author	Population	Assessment	Kit used	Sensitivity	Specificity	Comments
Wilcox *et al.*, 1996[55]	84 new dyspeptic patients in primary care Mean age 45.9	Histology and breath test Blinded	Biorad Bio Whitaker Genesis Kenstar Launch Orion Porton Sigma	97 100 97 97 100 97 97 90	84 96 91 76 100 93 95 98	8 different kits tested Patients excluded if they had recently been on any drugs which may have had anti-*H. pylori* activity
Feldman *et al.*, 1995[56]	59 patients from endoscopy clinics Age range 19–79	Histology and culture 19/40 with positive cultures also breath-tested Blinded	Amrad (no. of labs 17) Biorad (17) Orion (17) Biolab (15) Porton (17) Radim (13) Roche (17) Whitaker (16)	89.4 94.9 95.8 79.9 92.3 81.6 99.3 92.9	93.3 91.3 95.5 98.6 87.1 90.7 86.5 89.4	Multi-lab comparisions Patients from Ireland, Belguim, Holland, Italy, and Switzerland Grey zones considered negative Results from 4 labs excluded due to reported difficulties in using Radim kit Wide age range
Crabtree *et al.*, 1991[124]	242 patients referred for endocopy Mean age 56.7 (range 19–95)	Histology only Blinding unclear	Biorad	Total population 93.5 Age < 61 97.5	 79.0 85.5	Wide range of ages in study Accuracy greater in younger ages
Reilly et al., 1994[125]	303 dyspeptic patients > 50 years attending for endoscopy Median age 63	Histology and CLO test Gold standard positives defined as those with at least 2 positive tests among slide urease, breath test or histology; gold standard negatives as those with all these (or 2 when the breath test was done) Blind unclear	Helico G Helisal serum	94 95	67 70	Sensitivity lower when grey zone area considered positive (87 and 90 respectively) No exclusion criteria When patients recently or currently receiving treatment were excluded (n = 39), sensitivity remained the same, but specificity increased for both kits Elderly population
Tham *et al.*, 1994[126]	129 dyspeptic patients for endoscopy Mean age 50 (range 15–80)	Histology and culture Blinded	Helico G	88	72	Subgroup of 52 patients with mean age 35 was analysed separately; sensitivity and specificity for this group not separately reported

Appendix 10

Efficacy of *H. pylori* eradication therapy

MEDLINE, Cochrane and DARE databases were searched, using the search terms Helicobacter pylori, eradication, triple therapy, from 1993 for RCTs and reviews of triple therapy. We excluded studies using dual therapy and earlier combinations such as those including bismuth. Studies were considered if they included pre- and post-treatment testing, ideally with more than one type of test (e.g. breath test, histological investigation), and patients were tested at least 4 weeks following treatment (*Table 29*). It was agreed that RCTs were more robust than non-systematic reviews. No systematic reviews were identified.

Studies by Lind and colleagues, published in 1996,[57] and Misiewicz and colleagues, published in 1997,[66] provided the best evidence for parameter estimates on efficacy as they were recent RCTs including UK centres and patients.

Analyses were on the basis of intention to treat, not on treatment.

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TABLE 29 *Efficacy of eradication*

Authors	Study design	Patients	Analysis	Regimen	Results	Comments
Lind *et al.*, 1996[57] (Mach Study)	International multicentre RCT: Canada, Germany, Ireland, Sweden and UK	787 patients, duodenal ulcer proven Note: 103 patients excluded: 48 *H. pylori*-negative and 16 UBT test failures at entry; 12 adverse event discontinuations and 27 miscellaneous	Intention-to-treat analysis; all patients treated analysis and per protocol analysis carried out	7 days b.d. PPI 20 mg omeprazole, metronidazole 400 mg, amoxicillin 1000 mg; compared with PPI and placebo	*Intention-to-treat* PAC 250 79.5% (92/117) PAC 500 90.6% (106/117) PCM 250 89.7% (105/117) PCM 500 85.5% (107/124) PAM 75.8% (94/124)	Pre- and post-treatment breath tests (post-treatment at least 4 weeks) Intention-to-treat analysis takes into account those not having UBT at follow-up, who were then assumed to have a treatment failure. If these cases were excluded, efficacy or rose by 3–5% Side-effects associated with antibiotics 2.5% discontinued Diarrhoea 12–31% in 5 treatment arms; taste alteration 8–27%
Misiewicz *et al.*, 1997[66]	Study period Nov 1994–May 1995 Multicentre comparative UK study. Single-blind prospectively randomised (computer) parallel group; 55 hospitals	496 patients with duodenal ulcer/gastritis/both Age range 18–80; mean 48 443/496 completed study 53 patients excluded due to having breath test < 28 days post-treatment or had not attended for visit 3 (day 28)	Intention-to-treat and per protocol	7 days b.d. Metronidazole 400 mg b.d. Clarithromycin 250 mg b.d. Amoxicillin 1 g b.d. PAM (20 mg) PAM (30 mg) PCA PCM	*n* = 131 (66.4%) *n* = 126 (74.6%) *n* = 121 (86.0%) *n* = 118 (87.3%)	Pre-treatment testing: CLO test and breath test. Endoscopy carried out on patients with positive breath test at 28 days for *H. pylori* culture and sensitivity 1.4% (7) discontinued due to side-effects Most common symptoms: diarrhoea, taste disturbance, headache 1 case pseudomembranous colitis

continued

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TABLE 29 contd *Efficacy of eradication*

Authors	Study design	Patients	Analysis	Regimen	Results	Comments
Other studies						
Unge *et al.*, 1996[127] Studies to 1995	Non-systematic review		Intention-to-treat analysis	Treatment 7–14 days		Testing 4 weeks minimum post-treatment; all methods except serology
	22 studies	1726 patients		PAM	1450/1726 eradication (84%)	Studies have been categorised as to whether RCT, >50 patients, blind. etc.
	17 studies	902 patients		PCA	769/902 eradication (85%)	The worst-case approach used in this analysis may be too conservative:
	20 studies	824 patients		PCM	714/824 eradication (87%)	could be the reason for one of the therapies reaching a 90% success level in analysis
						Importance of resistance to antibiotics, but cites the Mach study where PPI triples have shown a high efficacy in countries with 30–40% metronidazole resistance prevalence
Van der Hulst *et al.*, 1996[128] Studies up to 1995	Review		Not stated whether per protocol analysis or intention-to-treat	Treatment 7–14 days	Mean eradication:	Comments on problem of resistance to metronidazole; multicentre European study found 27.5% of
		21 treatment arms pooled 1119 patients;		PCM	88.7%	*H. pylori* strains were resistant
		14 treatment arms 651 patients;		PCA	88.0%	Test for eradication at least 4 weeks post-treatment
		14 treatment arms 621 patients;		PAM	79.7%	
		8 treatment arms 412 patients		(quad: recommended as second-line therapy)	96.4%	
Axon, 1996[129] Studies up to 1995	Review		Intention-to-treat not specified			Method of pre-/post-treatment *H. pylori* testing not specified
	8 studies	406 patients		PCM (7–14 days)	374/406 eradication (92%)	
	7 studies	492 patients		PAM (7–28 days)	428/492 eradication (87%)	

continued

***TABLE 29* contd** *Efficacy of eradication*

Authors	Study design	Patients	Analysis	Regimen	Results	Comments
O'Connor *et al.*, 1996[130] Ireland	Prospective study, non-randomised	100 patients (2 lost to follow-up) Mean age 50	Intention-to-treat included in analysis	7 days b.d. PCM PPI: 20 mg Clarithromycin 500 mg Metronidazole 400 mg	94/98 eradication 94% intention-to-treat 96% per protocol	Histology and CLO test pre- and 4 weeks post-treatment
Cottrill *et al.*, 1997[131] UK and Ireland	Multicentre (32 GP practices), double-blind, randomised, parallel group comparison of triple vs dual treatment	183 patients	30 patients lost to follow–up; intention-to-treat included in analysis			Breath test pre- and post-treatment
		98 triple therapy		PPI 40 mg 1 per day Amoxicillin 1 g b.d. for 2 weeks Metronidazole 400 mg t.d.s. for 1st week (PAM)	79/83 eradication (95%) Intention-to-treat 79/98 (80%)	
		85 dual therapy		PPI 40 mg 1 per day Amoxycillin 1 g b.d. for 2 weeks and placebo during 1st week (PPI + A)	33/70 eradication (53%) Intention-to-treat: 37/85 (44%)	

Appendix 11

National Screening Committee criteria and the simulation of screening for *H. pylori* to prevent gastric cancer

The condition

1. *The condition should be an important health problem.*
   Gastric cancer remains one of the most common causes of cancer. In 2000 it was the seventh most frequent cause of cancer deaths in the UK with 6610 deaths. Survival is poor at 10–15% at 5 years.

2. *The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, or disease marker and a latent period or early symptomatic stage.*
   The natural history of gastric cancer is understood. There is a progression through various pathological stages to cancer, namely atrophic gastritis, gastric atrophy, dysplasia, metaplasia and cancer.

   H. pylori is an established cause, according to the IARC. However *H. pylori* prevalence is falling in developed countries as it is strongly associated with socioeconomic conditions. Gastric cancer trends in England also are downward due to changes in *H. pylori* prevalence and other risk factor changes (such as diet, and smoking).

3. *All the cost-effective primary prevention interventions should have been implemented as far as practicable.*
   Health promotion activity on diet change and smoking reduction, given a boost by the Coronary Heart Disease National Service Framework, will reduce future risk of gastric cancer.

   H. pylori prevalence will fall as socio-economic conditions improve. Policies to improve housing conditions and childhood poverty are crucial.

The test

4. *There should be a simple, safe, precise and validated screening test.*
   A blood test for serological investigation is a simple, safe and accurate test to detect *H. pylori*.

5. *The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.*
   This is not an issue.

6. *The test should be acceptable to the population.*
   Yes, a serological blood test is required.

7. *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.*
   Individuals with a positive screening result do not need further investigation, as the model has shown that it is not cost-effective to confirm true-positive results by the more accurate UBT.

   Triple-therapy treatment would be given to individuals with a positive test result.

The treatment

8. *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.*
   Whilst there is strong evidence of the effectiveness of triple therapy (a combination of a proton pump inhibitor and two antibiotics) in eradicating *H. pylori*, there are no randomised trial data to show that *H. pylori* eradication will alter the natural progression and prevent gastric cancer. Modelling can only indicate the likely cost-effectiveness of screening using various assumptions. The model has incorporated uncertainty about the reversibility of progression after *H. pylori* eradication. It shows that screening might be cost-effective, given a major assumption about reversibility (with efficacy in the range of 45–60%), and taking into account the benefits

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of eradication with regard to peptic ulcer disease. However there would be a long period of two to three decades before the programme would be cost-effective, largely due to the delay before patients screened between the ages of 20 to 50 years would have developed gastric cancer.

9. *There should be agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.*
   The modelling suggested that one-off screening at age 40 including a prevalent round for those aged 40–49 would be most cost-effective. This was partly pragmatic balancing the effect of age on compliance, *H. pylori* prevalence, reinfection and reversibility of progression.

10. *Clinical management of the condition and patient outcomes should be optimised by all health care providers prior to participation in a screening programme.*
    We have only considered the impact of wider use of opportunistic assessment of *H. pylori* status in the management of dyspepsia.

The screening programme

11. *There must be evidence from high quality RCTs that the screening programme is effective in reducing mortality or morbidity.*
    Not available; there are ongoing trials of eradication in patients with gastric metaplasia.

    Where screening is aimed solely at providing information to allow the person being screened to make an 'informed choice' (e.g. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.
    Not applicable.

12. *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.*
    There is no obvious reason why the programme might not be acceptable; there have been *ad hoc* primary care-based screening studies. The main obstacle would be achieving high uptake/compliance.

13. *The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).*
    This is unclear. The major benefit is a reduction in mortality from gastric cancer (and peptic ulcer disease). The modelling has shown that with regard to these outcomes screening might be effective. Not included were other benefits in reducing non-fatal peptic ulcer disease, which could be substantial, and to a lesser degree an effect on the incidence of non-ulcer dyspepsia.

    However widespread use of antibiotics may lead to side-effects, and to antibiotic resistance in *H. pylori* and other organisms normally sensitive to the antibiotics, such as amoxicillin and metronidazole, which are used.

14. *The opportunity cost of the screening programme (including testing, diagnosis, treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money).*
    This is hard to judge. The cost-effectiveness maybe favourable in the long term but in the short term little benefit will be obtained and, given other priorities in the NHS budget, it may not be appropriate to invest in screening.

15. *There must be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.*
    Screening would be based in primary care. A system to monitor uptake, compliance, and side-effects would be required but could build on primary care computerised information systems. Gastric cancer incidence would be monitored by cancer registries, and mortality data and better data on the incidence of peptic ulcer disease in primary and secondary care would be needed.

16. *Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be made available prior to the commencement of the screening programme.*
    Primary care staff would be required to counsel patients, take blood for serological testing and to prescribe the triple therapy.

17. *All other options for managing the condition should have been considered (e.g. improving treatment, providing other services), to ensure that no more cost-effective intervention could be introduced or*

current interventions increased within the resources available.
Not considered.

18. *Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.*
The evidence base for screening is only from modelling. There are significant uncertainties, which include the efficacy of eradication with regard to gastric cancer risk, the impact of opportunistic testing for *H. pylori* in dyspeptic patients, antibiotic resistance and further declines in *H. pylori* prevalence in England.

19. *Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.*
Not applicable.

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Appendix 12

National Screening Committee criteria and the simulation of screening for *H. pylori* to prevent peptic ulcer disease

The condition

1. *The condition should be an important health problem.*
   Peptic ulcer disease is an important public health problem. The incidence is high which leads to a burden on primary care for diagnosis and treatment, and on secondary care for endoscopy and management of complicated ulcers There is significant mortality, some of which is premature, deemed avoidable, or both.

2. *The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, or disease marker and a latent period or early symptomatic stage.*
   The natural history of peptic ulcer disease in relation to *H. pylori* is not fully understood. There is no doubt that *H. pylori* infection predisposes to increased incidence of both duodenal and gastric ulcers and that eradication reduces the recurrence rate and complication rate substantially. However the interaction between *H. pylori* and the use of NSDAIDs with regard to complicated peptic ulcers (i.e. those requiring hospitalisation for haemorrhage and perforation, and which are potentially fatal) is less clear; although several studies have been done, there have been problems in their design. There is uncertainty about the extent to which *H. pylori* infection *per se* is associated with such ulcers and therefore about the impact of eradication.

   H. pylori prevalence is falling in developed countries as it is strongly associated with socioeconomic conditions. Peptic ulcer disease trends are also downward, due to changes in *H. pylori* prevalence and other risk factor changes (e.g. smoking). Widespread NSAID use is counterbalancing these trends in certain groups, such as older women.

3. *All the cost-effective primary prevention interventions should have been implemented as far as practicable.*
   Health promotion activity on smoking reduction, given a boost by the Coronary Heart Disease National Service Framework, will reduce the future risk of peptic ulcer disease.

   H. pylori prevalence will fall as socio-economic conditions improve; policies to improve housing conditions and childhood poverty are crucial.

The test

4. *There should be a simple, safe, precise and validated screening test.*
   A blood test for serological investigation is a simple, safe and accurate test to detect *H. pylori.*

5. *The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.*
   This is not an issue.

6. *The test should be acceptable to the population.*
   Serological blood testing is required.

7. *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.*
   Individuals with a positive screening result do not need further investigation, as the model has shown that it is not cost-effective to confirm true-positive results by the more accurate UBT.

   Triple-therapy treatment would be given to individuals with a positive test result.

The treatment

8. *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.*

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There is strong evidence of the effectiveness of triple therapy (a combination of a proton pump inhibitor and two antibiotics) in eradicating *H. pylori*, and in reducing recurrence and complications. A test-and-treat strategy for managing new dyspepsia is currently under trial, whereby all individuals newly presenting with dyspepsia are tested for *H. pylori*, and those with positive screen results are given eradication therapy. The impact of such widespread testing on the effectiveness and costs of a screening programme is unclear.

9. *There should be agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.*
   The modelling suggested that one-off screening at age 40 including a prevalent round for those aged 40–49 years would be most cost-effective. This was largely driven by consideration of the impact on gastric cancer based on the effect of age on compliance, *H. pylori* prevalence, reinfection and reversibility of progression to cancer. For peptic ulcer disease alone, screening at an earlier age may be more cost-effective.

10. *Clinical management of the condition and patient outcomes should be optimised by all health care providers prior to participation in a screening programme.*
    We have only considered the impact of wider use of opportunistic assessment of *H. pylori* status in the management of dyspepsia.

The screening programme

11. *There must be evidence from high quality RCTs that the screening programme is effective in reducing mortality or morbidity.*
    This is not available.

    Where screening is aimed solely at providing information to allow the person being screened to make an 'informed choice' (e.g. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.
    Not applicable.

12. *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.*
    There is no obvious reason why the programme should not be acceptable; there have been *ad hoc* primary care-based screening studies. The main obstacle would be achieving high uptake/compliance.

13. *The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).*
    This is unclear. The major benefit considered in the model is a reduction in mortality from peptic ulcer disease and gastric cancer; with these outcomes screening might be effective. Not included were other benefits from reducing non-fatal peptic ulcer disease, which could be substantial, and to a lesser degree an effect on the incidence of non-ulcer dyspepsia.

    However widespread use of antibiotics may lead to side-effects, and to antibiotic resistance in *H. pylori* and other organisms normally sensitive to the antibiotics used, such as amoxicillin and metronidazole.

14. *The opportunity cost of the screening programme (including testing, diagnosis, treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money).*
    This is hard to judge. The cost-effectiveness maybe favourable in the long term but in the short term little benefit will be obtained and, given other priorities in the NHS budget, it may not be appropriate to invest in screening.

    Much opportunistic testing and eradication is already taking place which reduces the potential benefits of screening.

15. *There must be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.*
    Screening would be based in primary care. A system to monitor uptake, compliance and side-effects would be required, but could build on primary care computerised information systems. Gastric cancer incidence would be monitored by cancer registries and mortality data; better data on the incidence of peptic ulcer disease in primary and secondary care would be needed.

16. *Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be made available prior to the commencement of the screening programme.*

Primary care staff would be needed to counsel patients, take blood for serological testing and to prescribe triple therapy.

17. *All other options for managing the condition should have been considered (e.g. improving treatment, providing other services), to ensure that no more cost-effective intervention could be introduced or current interventions increased within the resources available.*
Not considered.

18. *Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.*
The evidence base for screening is only from modelling. There are significant uncertainties, which include the efficacy of eradication with regard to gastric cancer risk, the impact of opportunistic testing for *H. pylori* in dyspeptic patients, antibiotic resistance and further declines in *H. pylori* prevalence in England.

19. *Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.*
Not applicable.

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We look forward to hearing from you.

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