

**Screening for *Helicobacter pylori*:
studies in two population samples
from central England**

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Publications

The following work relating to the content of this thesis has been published or has been accepted for publication.

Original Articles:

Stone MA, Mayberry JF, Wicks ACB, Livsey SA, Stevens M, Swann RA, Robinson RJ. Near patient testing for *Helicobacter pylori*: a detailed evaluation of the Cortecs Helisal Rapid Blood test. *Eur J Gastroenterol Hepatol* 1997; 9: 257-260

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Stone MA, Patel H, Panja KK, Barnett DB, Mayberry JF. Reasons for non-compliance with screening for infection with *Helicobacter pylori*, in a multi-ethnic community in Leicester, UK. *Public Health* 1998; 112: 153-156

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Review articles:

Stone MA. Non-invasive testing for *Helicobacter pylori*. *Postgrad Med J* (in press)

Stone MA. Transmission of *Helicobacter pylori*. *Postgrad Med J* (in press)

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Letter:

Robinson RJ, Stone MA, Mayberry JF. Validation of a rapid whole blood test for diagnosing *Helicobacter pylori* infection. Assessment lacked certain considerations (letter). *BMJ* 1997; 314: 1689

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Margaret A Stone. Screening for *Helicobacter pylori*: studies in two population samples from central England

Abstract

If it is clearly demonstrated that eradicating *Helicobacter pylori* (*H pylori*) in asymptomatic subjects would lead to a reduction in morbidity and mortality, population screening may become justified. It must also, however, be shown that prevalence of infection can be effectively reduced; these studies addressed the hypothesis that this can be achieved through community screening and eradication.

A serological screening test for infection with *H pylori* was offered in two community programmes in Market Harborough and Belgrave. Those testing positive were offered a prescription for eradication therapy and successful eradication was assessed by urea breath testing. Consideration was given to compliance at each stage, also to the association between dyspepsia and *H pylori* and to risk factors for infection. For possible long-term follow-up regarding health benefits, subjects in Market Harborough were randomised to be offered screening or to a matched control group not invited.

The feasibility of community screening and eradication was demonstrated. Compliance with medication (100% in Market Harborough, 95% in Belgrave) and eradication rates (95%, 92%) were good in those who accepted therapy. Uptake of screening (39%, 26%) and therapy (79%, 81%) were however limited, with men and younger people less likely to attend. In Belgrave, low uptake was influenced by the inaccuracy of the mailing list, but attendance was similar in Asians and non-Asians and was not improved by the use of Asian language materials.

No correlation was found between infection with *H pylori* and overall symptoms of dyspepsia ($P=0.626$ after adjustments). Using logistic regression, the association between the infection and childhood living conditions was confirmed. Intrafamilial transmission was suggested by an association between *H pylori* status of self and spouse in married couples (odds ratio 2.65 after adjustments). Asian ethnicity was not a risk factor for infection in Belgrave ($\chi^2=0.31$, $P=0.611$).

Introduction and Guide to the Thesis

Prevention of morbidity and mortality through screening is dependent not just on the ability of the intervention to reduce disease, but also on the effectiveness of the process of intervention. The studies described in this thesis were designed with the primary aim of investigating the process of screening. The vehicles for study were two programmes of screening for infection with *Helicobacter pylori* (*H pylori*), followed by eradication of the bacterium in those found to be infected. These programmes would be carried out in very different communities, one in the market town of Market Harborough, Leicestershire and the other in the Belgrave area of the city of Leicester. Without compromising the primary aim, the main study in Market Harborough was designed to include secondary aims concerned with risk factors for infection, the association between *H pylori* and dyspeptic symptoms and follow-up for health benefits of screening. Risk factors would also be considered in the Belgrave study. Aims and justification for the studies carried out are described more fully in the course of the thesis, but briefly the aims were -

- to test the hypothesis that if health benefits of eradicating *H pylori* in asymptomatic subjects can be demonstrated, such benefits could be realised in the general population through community screening and eradication in collaboration with general practitioners
- to identify key areas of good and poor compliance which would be likely to affect the efficacy of *H pylori* screening and eradication in the community. Good compliance would be important for effective trials investigating potential health

benefits of *H pylori* screening and for routine screening if recommended

- to determine whether specific problems of non-compliance would apply in a multi-ethnic inner-city population
- to establish a cohort of subjects in two groups offered or not offered screening, for possible follow-up in terms of health benefits. It was considered that the value and nature of long-term follow-up would be dependent on the results of our own study and other ongoing and future research
- to investigate the relationship between infection with *H pylori* and symptoms of dyspepsia in the community
- to investigate risk factors for infection with *H pylori* in 2 general population samples

The first chapter of the thesis offers an introduction to the concept and practice of screening and is followed by a general overview of *H pylori* as a topic in Chapter 2. In Chapters 3 to 5, the two screening programmes are described and discussed in terms of effectiveness and compliance. Dyspepsia and risk factors are dealt with in Chapters 6 and 7 and the thesis is completed by a brief summary of conclusions drawn.

Chapter 1

The concept of screening

- i. Introduction**
- ii. What is screening?**
- iii. Validity of screening**
- iv. Advantages and disadvantages of screening**

i. Introduction

Although reference is made to various types of screening, this chapter is not intended as a comprehensive review of current screening programmes or those which have existed in the past or may be introduced in the future. The aim is to consider issues surrounding the practice of screening. Key texts on the principles of screening are cited and quotations given where these are considered to be particularly apt.

ii. What is screening?

Prevention has been defined by the Commission on Chronic Illness [1] in the narrowest sense as “*averting the development of a pathological state*” and more broadly to include also “*all the measures which halt progression of disease to disability or death*”. Preventive measures may be directed either at the promotion of better overall health or at the prevention of specific diseases. Two further definitions were adopted by the Commission [1] to distinguish between primary prevention meaning “*averting the occurrence of disease*” and secondary prevention concerned with “*halting the progression of a disease from its early unrecognised stage to a more severe one and preventing complications or sequelae of disease*”.

Public health interventions such as health education and immunisation fall within the

definition of primary prevention, whereas screening generally has aims associated with secondary prevention. Wilson and Junger [2] for the World Health Organisation (WHO) adopted the definition of screening proposed by the Commission on Chronic Illness [1] as *“the presumptive identification of unrecognised disease or defects by the application of tests, examinations or other procedures which can be rapidly applied. Screening tests sort out apparently well persons who have a disease from those who probably do not. A screening test is not intended to be diagnostic. Persons with positive or suspicious findings must be referred to their physicians for diagnosis and necessary treatment”*. Cuckle and Wald [3] defined screening in much the same way, as *“the identification, among healthy individuals, of those who are sufficiently at risk of a specific disorder to justify a subsequent diagnostic test or procedure, or in certain circumstances, direct preventive action”*.

Morrison [4] defined screening for disease control as *“the examination of asymptomatic people in order to classify them as likely, or unlikely, to have the disease that is the object of screening. People who appear likely to have the disease are investigated further to arrive at a final diagnosis. Those people who are then found to have the disease are treated”*. He also draws attention to other uses of the term ‘screening’ in medicine and epidemiology. In clinical practice, for example, the term is sometimes used refer to tests applied to a symptomatic patient in order to establish a diagnosis. Screening procedures may also be used to obtain epidemiological information about disease prevalence. Although the ultimate aims in the latter case are likely to be associated with prevention of the disease in question, there may be no such immediate objectives in relation to the subjects being screened. Wilson and Junger [2]

refer to studies of this type as 'population or epidemiological surveys', but point out that 'case-finding' (the identification of subjects for appropriate follow-up) may be a by-product of screening which is primarily directed toward epidemiological findings.

Screening may have as its aim the identification of early markers or manifestations of the disease in question, for example in screening for cervical cancer where a smear test is directed at identifying cellular changes, or the use of a faecal occult blood test to identify persons who may need further investigation in colorectal cancer screening programmes. In this type of screening the aim is to detect and treat disease at an earlier stage than would be the case following clinical presentation with symptoms. Alternatively, screening may be directed towards finding people with risk factors for the disease in question, for example identification of smokers in order to encourage discontinuation of smoking, with the aim of reducing the likelihood of lung cancer and heart disease. Here the aim is to identify risk factors and remove them before the onset of changes which could lead to disease. The distinction between screening for disease and screening for risk factors may however not always be clear-cut. Morrison [4] cites the example of hypertension which could be regarded as either a risk factor or an early manifestation of cardiovascular disease.

Where a disease is communicable, the primary objective of screening may be associated with public health in terms of disease control, rather than with prolonging the health or life of the individual, which would be an important but secondary aim. Wilson and Junger [2] noted that prioritisation of objectives may change over time, for example in the early days of chest radiography for detection of pulmonary tuberculosis, health

benefits to the individual were secondary to the primary aim of controlling the spread of disease. It is only when prevalence of communicable disease has been minimised that prolonged health and life for the individual are likely to become the main aim of early disease detection. Screening for the benefit of the person screened is sometimes known as ‘prescriptive screening’, described by Holland and Stewart [5] as screening which has “*as its main aim a direct contribution to the health of individuals*”.

Screening may be carried out in a variety of ways. The Commission on Chronic Illness [1] defined ‘mass screening’ as “*the application of screening tests rapidly and economically to large population groups, to identify persons who probably have abnormalities so they can be referred for diagnosis and, if indicated, for medical care.*” Wilson and Junger [2] distinguish between ‘mass screening’ meaning “*the large-scale screening of whole population groups....where no selection of population groups is made*” and ‘selective screening’ referring to “*screening of selected high-risk groups in the population. It may still be large-scale, and can be considered as one form of population screening*”. Where selection is applied, the degree of selection will vary. Screening may be targeted widely at an age/sex group as in breast and cervical cancer screening or to a more specific group known to be at highest risk of the disease, for example in genetic disorders such as haemophilia in the unborn child, where screening for factor VIII can be limited to pregnant women with an affected male relative, or screening for bladder cancer in high risk occupational groups in the dye manufacturing and rubber industries.

The Commission on Chronic Illness [1] defines the distinction between ‘single-test

screening' and 'multiple screening', the former being "*the application of a simple laboratory or related test to groups of people in an effort to detect a particular unrecognised disease*", whilst the latter refers to "*the application of two or more screening tests in combination to large groups of people. Applying a battery of laboratory and related procedures simultaneously to presumably well population groups ...*". In this country, multiple screening is sometimes carried out opportunistically by general practitioners, but is more commonly the province of workplace medical care and private health care, where there is a consumer-led demand for this type of package.

A further distinction, between screening and 'surveillance', is highlighted by Wilson and Junger [2]. Although the two may be similar, a person screened has generally not complained of the disease in question, whereas surveillance normally applies to patients who have already sought medical help. Surveillance implies keeping under observation and requires repeated examination or testing. Wilson and Junger have described it as "*routine examination of patients in particular high risk groups for certain conditions*". Examples of surveillance are periodic endoscopic review of patients with Barrett's oesophagus for early indications of oesophageal cancer and review of sufferers from ulcerative colitis for early colorectal cancer detection.

iii. Validity of screening

The concept of screening is an attractive one in that it aims to prevent the development of serious and often fatal chronic disease. The fact that much latent, undetected disease exists in the population was highlighted many years ago by a study in Peckham, London. Following an initial exploratory phase which began in 1926, the Pioneer Health Centre set up a field experiment in 1935, to investigate the health of a defined population [6-8]. Although this population was specifically selected as likely to represent the most healthy section of populace, only 10% of those who underwent a health review were found to be free from any clinically discoverable disorder. Some 65-70% had some pathological disorder of which they were unaware, or which they ignored. In 1963, using epidemiological methods, Last [9] described an attempt to quantify the 'iceberg of disease', much of which lies submerged. In diabetes and pulmonary tuberculosis, for example, he proposed that at that time "*the figures support the dictum that for every known case there is another undiscovered.*"

Although it is evident that much latent disease exists, enthusiasm for the concept of early disease detection should not override proper evaluation. Commenting in 1985 on the results of a trial of screening for scoliosis in American school children, Berwick [10] suggested that these results should "*fuel skepticism about the widespread adoption of mass scoliosis screening*". The study in question [11] suggested that screening for scoliosis in schools, using the bending test, produced large numbers of false positive cases and a fair number of true positives with a non-progressive condition who might never need treatment. In addition, unnecessary exposure to X-

rays and poor cost-effectiveness were highlighted. Berwick proposed that the study in question “reminds us again that the ‘search and destroy’ reflex belongs in war movies, not in public policy”. Before the introduction of any new screening programme its validity or effectiveness should be fully considered. Moreover, it should not be assumed that existing screening programmes are effective simply because they are well established.

Limiting the use of the term screening to case-finding, Wilson and Junger [2] presented a list of 10 ‘principles of early disease detection’ adopted by the WHO. These are often referred to in assessing the validity of particular screening programmes and are quoted in full in Table 1.1. Holland and Stewart [5] suggested that these 10 principles can be usefully grouped into 4 categories, namely those associated with the condition sought by screening (principles 1, 4 and 7); with diagnosis (principles 3, 5, 6, 8 and 10); treatment (principles 2 and 3) and cost (principle 9). Further consideration of the WHO principles grouped in this way is given below.

The Condition:

In considering whether a disease is an ‘important problem’ (principle 1), account must be taken not only of prevalence but of gravity. Screening for uncommon diseases may be justified only where a high risk group can be selected for screening, as is the case with genetic disorders. In such cases, the disease can be considered as an important problem for the group to be screened even if not for the population as a whole. However, even where selection is not possible, screening for an uncommon condition may still be justified on account of its seriousness, as in the case of phenylketonuria.

Table 1.1. Principles of early disease detection (World Health Organisation)

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognised disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognisable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a “once and for all” project.

From: Wilson and Junger. World Health Organisation Public Health Papers no 34. [2]

On the other hand, high prevalence of a condition is not on its own a justification for screening if other criteria for validity are not met.

Screening aims to detect signs of disease in people who are without symptoms of the condition under consideration, or who are at least sufficiently asymptomatic not to have sought medical help. It therefore follows that screening must be able to identify people at risk of the disease at a latent or early symptomatic stage (principle 4). If such a stage does not exist or has not yet been shown to be detectable, then it is possible to diagnose only and not to screen for that disease.

The length of time between detection of disease by means of screening and by normal routine diagnosis is known as 'lead time', described by Morrison [4] as the "*interval from detection to the time at which diagnosis would have been made without that screening*". Lead time will vary between individual cases, but a good understanding of the natural history of the disease (principle 7) may assist with identification of the point at which optimum lead time can be gained by screening. Lead time may be difficult to determine from the results of trials and may be affected by increased awareness of early symptoms in the community after screening is introduced, resulting in earlier presentation for routine medical help. Where survival is compared between groups with screen detected disease and those in whom disease has been routinely diagnosed, there may be 'lead time bias', since diagnosis through screening is likely to have been made at an earlier stage of disease. Survival time will therefore be longer even if the actual timing of death remains unaltered. Prognostic selection or 'length-biased selection' may also apply, if asymptomatic cases detected through screening are likely

to have a more favourable clinical course than symptomatic cases presenting routinely. In describing length-biased sampling, Morrison [4] draws attention to the possibility that *“screening itself preferentially identifies disease with a long preclinical phase ... Presumably patients with such disease also would have a long clinical phase, that is favourable survival.”*

Diagnosis:

Practicality is rightly included in the WHO principles of screening, with attention drawn to consideration of the availability of facilities (principle 3). Facilities for testing must provide not only for carrying out the test itself but also for administering the screening programme, including identifying and achieving good compliance in the target population. The value of proving through research that screening can affect the course of disease is seriously limited if the screening proposed is impractical. These considerations will apply particularly in less developed countries where facilities will be most limited, but the developed world is not immune. Although it is easier to be wise with hindsight, enthusiasm to begin screening may lead to proper consideration of practicalities being left until such time as it has been shown that effectiveness is not being achieved. This was very much the case in the early days of cervical cancer screening, where problems such as inaccuracy in age-sex registers led to low uptake by appropriate women [12].

The suitability of the test used for screening (principle 5) will depend firstly on its ability to accurately select those persons most likely to have the disease at which

screening is directed. The accuracy with which a test predicts those with disease is known as sensitivity. It is usually expressed as a percentage and calculated thus -

$$\frac{\text{Number of persons identified as positive by the test}}{\text{Number of persons who are truly positive}}$$

Sensitivity is probably the most important consideration in a screening test, in order that positive cases should not be missed. However, the importance of correctly excluding those who are not at risk of disease should not be underestimated. To correctly exclude these people, the test must have high specificity, calculated from -

$$\frac{\text{Number of persons identified as negative by the test}}{\text{Number of persons who are truly negative}}$$

Sensitivity and specificity of 100% are unlikely in any test. By raising or lowering the cut-off point for a positive result it is possible to adjust sensitivity and specificity, but raising one will lower the other. In deciding on an optimum balance between sensitivity and specificity, consideration must be given to the consequences of false positive and false negative results with reference to the disease and screening process in question.

Absolute numbers of persons for whom false negative and false positive results will be obtained will be dependent not only upon the sensitivity and specificity of the test, but on two other considerations. The size of the target population must obviously be considered; even where sensitivity and specificity fall only a little below 100%, there will be a high absolute number of false results when a large population is tested. In addition, the prevalence of the condition under consideration should be considered,

since the positive and negative predictive values (PPV and NPV) of the test will be partly dependent on this prevalence. PPV is calculated from -

$$\frac{\text{Number of persons who are truly positive}}{\text{Number of persons identified as positive by the test}}$$

and NPV from -

$$\frac{\text{Number of persons who are truly negative}}{\text{Number of persons identified as negative by the test}}$$

With higher prevalence of disease, the absolute number of false negative results will rise and the absolute number of false positive results will fall, with the converse applying for lower prevalence. Thus, if there is a very low prevalence of disease, even a test with very high specificity may lead to a high proportion of false positive results, with large numbers of people consequently being wrongly selected for further testing or treatment.

As well as good sensitivity and specificity, a screening test should have good reliability, with the ability to perform consistently with repeated application. If there is a subjective element to the reading of results, as with blood pressure measurement, there should be minimal inter- and intra-observer error. Furthermore, in considering the suitability of a screening test, practical considerations such as the speed and ease with which it can be administered need to be taken into account, as well as the grade of personnel required to administer the test and analyse samples. Where large numbers are being targeted for screening, a test should ideally be capable of being carried out quickly and easily by a nurse or technician, with doctors' time being reserved for follow-up.

The acceptability of testing (principle 6) is an important consideration, as no screening programme can be effective without good compliance. In a trial of screening for colorectal cancer, the unpleasantness of the stool collection procedure was identified as the most common reason for non-compliance in those who returned unused faecal occult blood test kits [13]. Account should also be taken of the acceptability of the time and place at which screening is offered. In workplace screening for hypertension in the USA, for example, on-site screening led to better compliance than testing at a hall located away from the workplace [14].

Agreement on who should be treated (principle 8) on the basis of screening results should be based on understanding of the natural history of the disease in question. In particular, an evidence-based decision on further management of those with borderline results or questionable abnormalities is needed. In cervical cancer screening, for example, Hirschowitz [15] has pointed out that a borderline smear may show minor nuclear abnormalities only, which could reflect either the effects of inflammation or the potential for neoplastic growth. In a long term follow-up study she showed that women with borderline smear test results of this type had a significantly increased risk of developing high grade dyskaryosis, particularly in cases of borderline changes where there were no cytological features of human papillomavirus infection. She concluded that careful follow-up of women with borderline results was indicated [15].

Screening should be a continuing process (principle 10), except where the need no longer exists, for example after elimination of an infectious disease or advances in treatment of symptomatic cases obviating the need for early detection. In some

instances, there is a need to screen individuals repeatedly, for example for cervical cancer where disease can occur at different ages. Trials will generally be needed in order to determine the optimum interval between screens. In breast screening, for example, Woodman *et al* [16] found that the incidence of interval cancers in the third year after screening approached that which would have been expected in the absence of screening, suggesting that a three year interval between screens for breast cancer is too long. Screening for some conditions may need to be carried out only once for each individual, as is the case with neonatal screening for phenylketonuria, but the overall screening process must still be continuous, with each new eligible case being targeted.

Treatment:

The early detection of disease is of no benefit to the individual if treatment is unavailable, either because no recognised effective treatment exists (principle 2) or because adequate resources and facilities for carrying out such treatment are lacking in the community where screening is offered (principle 3). The latter consideration may apply particularly in developing nations, but the availability of resources should not be overlooked even in more prosperous settings.

For some diseases, no early treatment has been demonstrated to be effective in reducing mortality, for example in lung cancer, where the prognosis is poor in both screen detected cases and general practitioner referrals [17]. If effective treatment is unavailable, screening may in fact be harmful, by adding to the length of time when an individual is aware of being diseased. Labelling people as diseased has been shown to be detrimental to well-being, for example in a study [18] where absenteeism from work

increased in patients after they were labelled as hypertensive, compared with those who were unaware of their hypertension. Another study of hypertension showed loss of well-being because of disease labelling, even though the patients had in fact been mislabelled [19].

A further consideration in assessing whether suitable treatment is available is acceptability. In antenatal screening, for example, termination of pregnancy is the only 'treatment' available for conditions such as Down's syndrome and thalassaemia. This form of 'treatment' may be unacceptable to some couples and no purpose would be served by screening a person for a disorder if they would refuse treatment following a positive screen. In a study looking at perceived and actual risks in those who underwent or declined amniocentesis, it was found that those who did not have the test were significantly more likely to have a negative attitude towards termination of pregnancy following evidence of an affected foetus [20]. The current practice of self-selection for screening, involving an informed choice by the individual, may be appropriate in the case of tests such as amniocentesis.

Cost:

Financial resources available for healthcare are finite even in the developed world and careful consideration must be given to the most appropriate use of those resources. The results of a controlled trial of multiphasic screening in a middle-aged population in London, presented in 1977 [22], showed no significant differences between subsequent morbidity in screened and unscreened groups. The authors estimated the cost of a similar multiphasic screening programme for the entire middle-aged population of the

UK to be £142 million at 1976 prices. In this instance it was easy for the authors to conclude that multiphasic screening in the middle aged is unjustified in economic terms, as no benefit had been demonstrated. However, the economic validity of screening (principle 9) is not always easy to measure, both in relation to actual monetary expenditure and more particularly considering the difficulties that exist in 'valuing' human life and health. Teeling-Smith [21] has pointed out that economic justification for a particular screening programme "*does not mean that 'it will pay off in financial terms'....An 'economic' justification for a particular treatment implies that the benefit to the population from having it available is greater than if the treatment were abandoned and the resources so released were used to provide alternative forms of medical care.*"

iv. Advantages and disadvantages of screening

Finally, some of the positive and negative aspects of screening will be considered. In many types of screening, the evaluation of benefit may require determination of the degree to which lead time improves the effectiveness of intervention. In a paper drawing attention to the limited validity of some types of screening, Chamberlain [23] has postulated that although screening is sometimes termed secondary prevention, as a strategy for disease control "*it comes a rather poor third after primary prevention - the winner - and effective treatment of established disease - in second place. This is because of the considerable effort, cost and possible morbidity it entails for society at*

large and for screened individuals in particular, only a tiny minority of whom will achieve through it improved prognosis.” The implication is that if effective treatment could ensure good outcome after presentation of symptoms in all diseases, screening, which is not without disadvantages, would be unnecessary.

The ‘yield’ from screening is described by Wilson and Junger [2] as “*the measure of previously unrecognised disease (whether overt or latent), diagnosed as a result of screening and brought to treatment*”, with the possible inclusion also of persons with previously recognised disease returned to medical care after a period of lapsed treatment. However, in addition to this group (the true positives), screening will also yield groups with true negative, false negative and false positive results. Consideration of the beneficial and harmful effects of screening must include these groups. Chamberlain [23] has usefully summarised the benefits and disadvantages of screening, as shown in Table 1.2.

Positive or negative results from screening, whether true or false, may carry disadvantages for some people:

- People with true positive results cannot be assumed to have benefited from screening, since prognosis may not be altered in all cases by early intervention. In some cases, apparently true positive results may have identified borderline abnormalities, possibly leading to overtreatment of disease which would not have progressed.
- Those with true negative screening results may have benefited from reassurance, but in some instances such reassurance can be harmful. An editorial by Stewart-

**Table 1.2. Benefits and disadvantages of screening as summarised by
J M Chamberlain**

Benefits:

Improved prognosis for some cases detected by screening

Less radical treatment which cures some early cases

Resource savings

Reassurance for those with negative test results

Disadvantage:

Longer morbidity for cases whose prognosis is unaltered

Overtreatment of questionable abnormalities

Resource costs

False reassurance for those with false negative results

Anxiety and sometimes morbidity for those with false positive results

Hazard of screening test

From: Jocelyn M Chamberlain (1984). Which prescriptive screening programmes are worthwhile? [18]

Brown and Farmer [24], emphasising the need to consider social and psychological costs of screening, has drawn attention to the possibility that people reassured by a negative result may be more resistant to lifestyle advice. Those shown to have low serum cholesterol, for example, may feel that they have a licence to continue with an unhealthy diet.

- Those with false positive results may have been subjected to unnecessary anxiety, further testing and possibly treatment.
- Those with false negative results will have been falsely reassured, in some cases possibly leading to delay in seeking medical help if symptoms develop.

The editorial cited above [24] points to the fact that in screening programmes the number of people who achieve direct health gains is usually far outweighed by those who do not. *“A small adverse effect of screening on quality of life, health promoting behaviour, or individuals’ capacity to care for themselves could have an impact on the public health which outweighs any health gains to be achieved by screening.”*

People with all categories of result may have been disadvantaged not only by risks associated with the screening test but also by anxiety generated by screening. Reduction in well-being after hypertension labelling has already been mentioned and a study by Stoate published in 1989 [25] showed an increase in psychological distress in healthy adults who had attended by invitation a general practice screening clinic for coronary heart disease, when compared to an unscreened control group.

Simple quantification of the beneficial and harmful aspects of screening is not possible, in order to determine whether advantages outweigh disadvantages. However, both

sides of the coin must be carefully considered in evaluating the benefits of screening for specific conditions. As Berwick [10] has aptly pointed out, *“The disease is evil; the hunters, good; the clarion sounds. What could be simpler? But it is not simple. Screening carries its own forms of harm ...The disease has many faces, and the hunt is not benign”*.

Chapter 2

Helicobacter pylori: an overview

- i. Introduction**
- ii. Discovery and characteristics**
- iii. Epidemiology**
- iv. Disease associations**
- v. Methods of diagnosis**
- vi. Treatment**
- vii. Screening**

i. Introduction

The discovery of the bacterium *Helicobacter pylori* (*H pylori*) and its role in gastroduodenal disease can lay claim to being the most important development in gastroenterology in recent times. An exhaustive review of all the literature concerning *H pylori* would be beyond the scope of this chapter; a Medline literature search carried out in January 1998, using the topic '*Helicobacter pylori*' selected 1143 documents for the year 1996 and 812 for 1997. An overview of the topic will be presented here, with more detailed discussion of some aspects reserved for later chapters.

ii. Discovery and characteristics

Although Bottcher [26] described spiral organisms seen in the human stomach as early as 1874, discovery of the bacterium eventually named *Helicobacter pylori* is generally credited to workers at the Royal Perth Hospital, Western Australia, where the bacteria were first successfully cultured in 1982 [27]. In that year, a young doctor, Barry Marshall, and a microbiologist, Robin Warren, reviewed a series of patients in whom large numbers of gastric spiral bacteria were found. They initially failed to culture these spiral organisms found in biopsy specimens, but one specimen was left incubating for 5 days over the Easter holiday and after this longer incubation period colonies had become visible [28]. In 1984, in an attempt to fulfil Koch's postulates with regard to the bacterium, Barry Marshall famously carried out a self-experiment in which he voluntarily ingested a test isolate obtained from a 66-year old man with non-ulcer

dyspepsia who had undergone endoscopy. The volunteer developed a condition which he described as 'acute pyloric campylobacter gastritis' and proposed that this condition might lead to a chronic infection predisposing to peptic ulceration [29]. Originally named *Campylobacter pyloridis* and subsequently the more grammatically correct *Campylobacter pylori*, the spiral bacterium was later recognised to be a new genus and re-named *Helicobacter pylori* [30].

H pylori is a spiral Gram-negative rod with flagellae. The bacteria most commonly colonize the stomach, living closely attached to gastric epithelial cells, beneath a protective layer of mucus. There have also been reports of the organism found in association with metaplastic or heterotopic gastric-type epithelium in the duodenum [31], oesophagus [32,33], rectum [34] and Meckel's diverticulum [35]. *H pylori* is unusual in its ability to survive in an acidic environment. It possesses potent urease activity and the production of ammonia raises the pH in its immediate vicinity; this may explain the ability of bacteria to survive between being ingested and reaching their destination beneath the gastric mucus, where pH is virtually neutral [36].

iii. Epidemiology

Prevalence and incidence of infection, and reinfection:

Studies investigating the prevalence of infection with *H pylori* have in general been

limited by the age range tested and by being based on samples such as blood donors and clinic attenders who may not be truly representative of the general population. Even where volunteers have been recruited from the general population, they may differ from those who do not come forward. Nevertheless, a high prevalence of infection has been shown, particularly in developing countries. Table 2.1 gives examples of data from studies in different communities [37-48]. In the Eurogast study [42], prevalence ranged from 15% or less in populations aged 25-34 from Oxford (UK) and centres in the United States and Denmark, to over 80% in those aged 55-64 in Poland and two Japanese centres.

Without intervention, infection with *H pylori* normally persists throughout life once acquired, although gastric atrophy may lead to loss of infection. Prevalence is therefore highly dependent upon the incidence of infection. Incidence rates are difficult to determine, since the infection is generally acquired without reporting of acute symptoms and data on individuals at different points in time are difficult to collect. Estimates based on epidemiological studies are however available. In industrialised countries, incidence of *H pylori* infection is falling, with an estimated 0.5% infection rate per year in the susceptible population, but in the developing world incidence continues to be much higher [49]. Infection probably occurs mainly in childhood [38,43] and increased prevalence with age [37-48], combined with falling incidence, suggest a cohort effect for infection [50], particularly in industrialised countries where living conditions have undergone marked improvement. Rates of reinfection after eradication are not easy to establish, as apparent eradication may in fact be due to recrudescence of non-eradicated organisms [51-54], but in the developed world it is

Table 2.1. *H pylori* prevalence data from studies in different communities

Geographical Location	Sample size	Age range in years	Sample selection	Overall prevalence	Prevalence range by (age-group in years)	Main author	Reference
Houston, USA	485	15- 80	Healthy volunteers	52%	-**	Graham	37
London, UK	215	18- 82	Health screening clinic attenders	33%	9% (<30); 67% (≥70)	Mendall	38
California, USA	113	18-91	Healthy volunteers	32%	10% (18-29); 47% (60-69)	Dooley	39
Northern Ireland	4742	12-64	Random population (recruited to other studies)	50.5%	23.4% (12-14); 72.7% (60-64)	Murray	40
South Wales, UK	749	30-75	Random male population (stored blood from other studies)	56.9	29.8% (30-34); 59% (>45)	Sitas	41
Combined populations from Europe, North America, North Africa & Japan	3194	23-55 & 55-64	Random population volunteers	48.9%	34.9% (25-34); 62.4% (55-64)	Eurogast Study Group	42
Stoke on Trent, UK	471	18-65	Workplace male volunteers, including some blood donors	37%	29.7% (<30); 63% (55-65)	Webb	43
Manchester, UK	607	6-80+	Healthy subjects including health screening clinic attenders	21%	5% (6-9); 49% (61-80)	Jones	44
Combined populations from France, Vietnam, Ivory Coast & Algeria	2215	0 to 9- >60	Health check or outpatient dept attenders, or blood donors, or recruited to other study.	46.7%	34.9% (25-34); 62.4% (55-64)	Mégraud	45
Africans living in Natal/Kwazulu, South Africa	398	<1-60	Hospital attenders, healthy volunteers, or blood donors	76%	41% (0-1); 94% (21-30)	Sather	46
Japan	426	0-80	Health screening centre attenders or recruited to other studies	-*	10% (0-9); >80% (60-79)	Asaka	47
Lima, Peru	407	<1-12	Recruited through local health posts, schools, churches or social organisations	48%	-**	Klein	48

* Overall prevalence unavailable from results presented

** Age related prevalence indicated in study results, but details not presented

likely that true reinfection seldom occurs [53,55]. In developing countries, reinfection after eradication of *H pylori* may be more common [56].

Risk factors and transmission:

In addition to year of birth, factors associated with lower social class and deprived living conditions in childhood are likely to raise the risk of infection [33,38,40-43,48]. Some occupational groups [57], such as endoscopists [58,59], may also be at increased risk, suggesting that although infection is most commonly acquired in childhood, adults may also become infected. Conclusive evidence about the mode or modes of transmission of the bacterium remains elusive, but person-to-person transmission is suggested by epidemiological data [43] and studies showing intrafamilial clustering of infection [60-62]. Transmission by both faecal-oral and oral-oral routes are strong possibilities [63] and a convincing argument has been put forward for transmission by the gastro-oral route, via vomitus [64,65]. However, transmission by these routes remains unproven, as does the suggestion of water-borne infection as a possible mode of transmission [48].

iv. Disease associations

Gastritis, peptic ulceration and dyspepsia:

Infection with *H pylori* is not a disease in itself; a high proportion of those infected may experience no associated symptoms [66]; it has been suggested that fewer than

20% of all infected people will develop any clinical consequences [67]. Infection may however predispose the host to disease. Pathogenic properties of the bacterium are known to be associated with chronic gastritis [27,29,39,68] and *H pylori* is recognised to be a major aetiological factor in the development of peptic ulceration [69]. Although some gastric ulcers are caused by use of non-steroidal anti-inflammatory drugs, the majority of peptic ulcers are associated with *H pylori* infection. It has been shown that eradication of *H pylori* not only leads to healing, but also prevents or reduces recurrence of duodenal [70] and gastric [71] ulcers. Conflicting results have been obtained in clinical trials of *H pylori* eradication in dyspeptic patients without peptic ulcer; the association between *H pylori* and non-ulcer dyspepsia therefore remains unresolved and in need of further investigation [72,73].

Gastric cancer:

The association between infection with *H pylori* and gastric cancer has been suggested by epidemiological studies, notably the Eurogast study [74] which demonstrated a positive correlation between the prevalences of gastric cancer and *H pylori* in 17 populations. A nested case-control study by Parsonnet *et al* [75] showed an association between infection with the bacterium and gastric adenocarcinoma, excluding tumors of the gastro-oesophageal junction. Tumors in the cardia were not found to be statistically associated with *H pylori* infection. Gastric cancer is a disease with multifactorial causality, but it has been suggested that up to 73% of gastric cancers in developed countries and 87% in developing countries may be attributable to infection with *H pylori* [76]. It has been proposed that gastric cancer develops

through a progression from gastritis to gastric atrophy, to metaplasia, then dysplasia and finally cancer [77,78]. If gastritis is caused by *H pylori* then the bacterium is the trigger that starts the progression. The latest point in the chain at which intervention by eradication of *H pylori* can effectively halt the progression from gastritis to cancer has yet to be demonstrated. Only in low grade primary B-cell gastric mucosa-associated lymphoid tissue (MALT) lymphoma has eradication of *H pylori* been shown to lead to regression of established neoplasia [79].

Heart Disease:

A possible association between coronary heart disease and infection with *H pylori* has been suggested [80,81]. If proven, this would be extremely important on account of the high rates of mortality from ischaemic heart disease in some populations. An independent association between ischaemic heart disease and *H pylori* seropositivity was shown by Patel *et al* after adjustment for possible confounding factors [81], with a possible explanation being the effect of the infection on plasma fibrinogen concentration and other inflammatory markers. Results showing a lack of association between *H pylori* and heart disease have however also been reported [82,83] and a meta-analysis of results from 18 relevant studies was also unresponsive [84]. This possible link therefore remains controversial.

Virulence factors:

There has been much recent interest in the possibility of identifying certain toxigenic strains of the bacterium *H pylori* which predispose the host to disease. In particular, interest has focused on genotypes of *vacA* (the gene encoding the vaculating cytotoxin)

and on Cag (cytotoxin associated gene) status [85]. It has been speculated that there may be benign and even beneficial strains of the bacterium as well as those that cause harm and that particular combinations of host characteristics and bacterial strain may lead to disease [67]. A study [86] using samples from the earlier Eurogast gastric cancer study showed a significant association between the prevalence of individuals with *CagA* seropositivity in each population and the mortality rate from gastric cancer, but as yet no simple pattern of benign and harmful bacteria has emerged. Further advances in identifying ulcerogenic and carcinogenic strains of *H pylori* may be important in determining clinical management strategies.

v. Methods of diagnosis

Invasive Methods:

The evaluation of tests for diagnosing *H pylori* infection is limited by the lack of a gold standard reference test with perfect sensitivity and specificity, but biopsy based tests performed on patients undergoing endoscopy are generally regarded as having good accuracy. Biopsy based diagnosis by rapid urease test, histology or culture does however have limitations. The sensitivity of these methods may be limited by the possibility of sampling error, since *H pylori* is often patchily distributed, although this limitation can be reduced by taking more than one biopsy. Recent treatment with some therapies may render *H pylori* difficult to detect at endoscopy and should therefore ideally be discontinued at least one month prior to biopsy testing for infection. The

bacterial load is likely to be reduced after treatment with antibiotics, or with bismuth (which is antibacterial to *H pylori*) [87] and proton pump inhibitors (PPIs) may suppress infection by creating an unfavourably neutral environment. Treatment with PPIs may also cause migration of *H pylori* from the antrum to the corpus [88], making multiple biopsies from different sites appropriate.

The biopsy urease test is based on the potent urease activity of *H pylori*. The enzyme digests urea, producing carbon dioxide and ammonium ions and hence alkali. A positive result is indicated when alkali is thus produced, changing the colour of the pH indicator phenol red. There are a number of versions of the biopsy urease test, the most commonly used being the CLO test[®], first developed by Barry Marshall [89]. Histology has the advantage that it can provide diagnostic information in addition to its use in determining *H pylori* status, but there is a subjective element to the reading of results. Bacteria can be identified after staining, for example with modified Giemsa stain [90]. Culture is highly specific, but requires a high level of technical accuracy if good sensitivity is to be obtained [91,92]. Unlike other test methods, culture can provide information about antibiotic resistance, which may be useful for selecting the eradication regimen to be used, particularly where a subsequent course of therapy is being considered after failed treatment.

Non-invasive methods:

H pylori is capable of eliciting both local and systemic antibody response in infected persons [93]. A number of serological tests are now available for diagnosing *H pylori*

infection, generally based on detection of Immunoglobulin G (IgG) antibodies to the bacterium. The accuracy of these enzyme-linked immunosorbent assays (ELISAs) varies considerably [94-96]. As these tests are based on antibody detection, past infection may lead to false positive results even where *H pylori* is no longer present. For this reason, these tests are unsuitable for determining success of eradication after treatment. The advantages of serology are convenience and cost, but attention must be paid to selecting an ELISA which will perform well in the population to be tested. A number of 'near patient' or 'office' tests based on serology are also available. Whilst these tests are highly convenient, particularly for single use, accuracy varies and may be limited [97-100].

The Urea Breath Test (UBT), like the biopsy urease test, depends on *H pylori*'s urease activity. Two versions, the ^{13}C [101] and ^{14}C [102] have been developed. The patient drinks a solution of urea containing a labelled carbon atom and in an infected patient, labelled carbon dioxide can subsequently be detected in expired air. Breath testing is more costly and time consuming and less convenient than serology, but direct comparison suggests that it is more accurate [103,104]. The ^{14}C version can be carried out more economically than the ^{13}C test, but has the disadvantage of involving a very small but measurable dose of radiation. Breath testing has the advantage of being free from sampling error, since the whole stomach is involved. Unlike serology, it detects current infection only and is particularly appropriate as a non-invasive test to check for successful eradication of *H pylori* after treatment. This should however be delayed for at least four weeks after completion of therapy, to avoid misleading results [105].

vi. Treatment

Treatment regimens for *H pylori* eradication are manifold [106]. One, 2 or 3 antibiotics are prescribed in combination with a bismuth preparation, an H₂-receptor antagonist, a PPI or more recently ranitidine bismuth citrate. In these treatments, the suppression of acid leads to more effective antibacterial activity. A one week course of triple therapy involving the use of a PPI in combination with two antibiotics selected from clarithromycin, amoxicillin and a nitroimidazole (metronidazole or tinidazole) is now widely regarded as the treatment of choice [107]. These regimens are likely to be associated with better compliance than bismuth based therapy and it has been shown that eradication rates of over 90% can be achieved [108,109]. Eradication rates of 79% to 96% were achieved using regimens of this type in an international trial of patients in different treatment groups [110]. Quadruple therapy has been recommended for re-treatment after failed eradication [107]. Compliance is an important consideration in choice of therapy and may be affected by side effects, number of tablets and duration of treatment. The effectiveness of the regimen will also be limited if bacteria are resistant to the antibiotic selected [111-113].

vii. Screening for *H pylori* infection

It has been proposed that younger dyspeptic patients could be screened non-invasively for infection with *H pylori* in order to reduce numbers referred for endoscopy [114-117]. Gastric cancer is rarely found in the younger age group (below 40 or 45 years).

Serious pathology would therefore be rare in a young *H pylori*-negative patient, since absence of infection would virtually exclude peptic ulceration, except where an association with NSAIDs was suspected. In this situation, the term 'screening' is not used in its most usual sense associated with preventive medicine and the detection of disease in asymptomatic subjects. Patients are being 'screened' in order to decide whether further investigation for peptic ulcer disease is warranted.

It has been suggested the *H pylori* infection represents a serious public health problem [107,118,119]. Screening for infection with *H pylori* in the general population has consequently been proposed as a possibility, although the report of a consensus group concluded that such screening should at the present time be restricted to trials [107]. It has also been suggested that at present screening for the infection should perhaps be limited to opportunistic testing of patients being investigated for symptoms of dyspepsia [120]. It is with the proposed strategy of screening for *H pylori* in the general population that the current thesis is mainly concerned. In the first chapter principles of screening were considered and current knowledge of the bacterium *H pylori* has been briefly reviewed above. To conclude the present chapter, consideration will be given to the extent to which proposed population screening for *H pylori* currently fulfils the requirements of good practice in screening as suggested by Wilson and Junger for the WHO (Table 1.1). As in Chapter one, these principles will be considered in relation to the condition sought, diagnosis, treatment and cost. In examining the validity of screening for *H pylori*, attention will be drawn to issues which are addressed in the current thesis. Some possible disadvantages of population screening for *H pylori* will also be considered.

The condition:

The strongest arguments for population screening for *H pylori* are related to the bacterium's association with gastric carcinoma. Convincing evidence that *H pylori* is a risk factor for this cancer has led to the bacterium being classified as a Class I carcinogen by the WHO [121]. A comparison of figures for 1975 and 1980 suggested an annual rate of decline in the crude incidence rate of gastric cancer of 2.2 % [122]. In spite of this decline, however, mortality figures for 1985 indicated 620,000 deaths throughout the world from stomach cancer [123]. Worldwide, in 1985, gastric cancer was the second most frequent cause of death from any cancer in each sex. Only breast cancer in women and lung cancer in men and the two sexes combined accounted for higher cancer mortality [123]. Clearly gastric cancer can be regarded as an important health problem (Principle 1). In addition, it has been suggested in a recent editorial that 65% of 4,000 deaths per year from peptic ulcer bleeds in England and Wales may be attributable to the infection [119]. Combining estimates relating to gastric cancer and peptic ulcer disease, the authors of this editorial estimated that in England and Wales over 8,000 deaths per year may be caused by the infection and argued that eradication of *H pylori* in endoscopy patients without peptic ulceration is justified by the association between the bacterium and these diseases [119]. The same argument could be used in support of population screening for *H pylori*. Additionally, if it can be demonstrated that screening for *H pylori* could reduce the number of deaths from heart disease and lower the prevalence of dyspepsia in the community, then the association with two further important health problems would support the case for screening.

In population screening for *H pylori*, the screening test would be used not to detect an

early stage of disease (Principle 4) but to identify subjects with a risk factor for disease, with the aim of eliminating that risk factor. If removing a risk factor can be shown to reduce morbidity and mortality, the justification for screening would be similar to that associated with early disease detection.

Understanding of the relationship between *H pylori* infection and the natural history of gastric carcinoma (Principle 7) is incomplete. The progression from *H pylori* induced gastritis to gastric carcinoma has been recognised, but only a small proportion of those with the infection develop gastric cancer. High prevalence of *H pylori* infection is not necessarily associated with high incidence of gastric cancer, a difficulty highlighted by results in African populations [124]. Current understanding of the importance of varying strains of *H pylori* and other risk factors for gastric cancer is limited. Incomplete understanding of the relationship between *H pylori* and the aetiology of gastric cancer provides an argument for regarding population screening as premature. In particular, it has yet to be demonstrated whether and at what stage eradication of established *H pylori* infection would prevent gastric cancer. Conclusive evidence for a reduction in mortality from gastric cancer as a result of eradicating *H pylori* may be hard to obtain in the near future, but as each new piece of evidence emerges, the arguments for and against screening must be weighed in the balance to determine whether screening may be justified even in the absence of full knowledge.

If studies primarily addressing the question of potential health benefits of *H pylori* screening are to be carried out effectively, the design of such studies should take account of expected levels of compliance and methods of obtaining optimum

compliance. In this thesis, compliance with screening and therapy are considered in detail. In addition, establishing a cohort of subjects in groups offered and not offered screening, for possible long-term follow-up in terms of health benefits, is included in the aims of the Market Harborough study.

Diagnosis:

The practicality (Principle 3) and acceptability (Principle 6) of testing are important considerations. Inferences can be drawn from experience of *H pylori* testing in symptomatic patients, from epidemiological studies that have involved population samples and from screening programmes for other conditions. Direct evidence concerning the logistics and acceptability of population screening for *H pylori* is however desirable and will be presented in the current thesis.

Non-invasive tests for diagnosing *H pylori* infection are available (Principle 5). Serology is both cheaper and less time consuming than urea breath testing and would therefore appear to be the test of choice for screening. Sensitivity and specificity, though limited, may be improved through careful choice of ELISA and setting of a local cut-off point for determining positive results (Principle 8). The use of urea breath testing in the case of borderline results may warrant evaluation. Near patient serology has advantages in terms of convenience, particularly since no laboratory facilities are required for carrying out these tests. The accuracy and acceptability of a near patient serological test is considered in the present thesis.

In developed countries, the risk of reinfection is low [53, 55], so each person would

probably need a single screen only, but a continuing process (Principle 10) would be needed for screening new eligible cases until such time as the infection has been eliminated in the population. Higher rates of reinfection in developing countries [56] might make repeat screenings for individuals advisable.

Treatment:

Eradication of *H pylori* can be achieved through a simple course of medication (Principle 2) which can be prescribed through general practitioners (Principle 3). With good compliance, a one week course of triple therapy comprising a PPI and two antibiotics is effective in most cases. This thesis addresses the question of whether good rates of eradication that have been achieved in symptomatic patients [108-110] can be matched in the general population where there may be less motivation to comply with therapy.

Cost:

A cost-effectiveness analysis (Principle 9) based on United States populations has suggested that screening for *H pylori* infection to prevent gastric cancer may be justified, particularly in high risk groups [125]. It has also been proposed that in the UK expenditure on screening for *H pylori* would be partially offset by a reduction in the high cost of treating dyspepsia in the community and that a screening strategy could be cost-beneficial [126]. Cost-benefit would however be dependent on confirmation of reduced morbidity and mortality as a result of screening and the authors of both proposals [125,126] have emphasised the urgent need for prospective randomised trials to investigate potential health benefits. Cost-effectiveness of

screening is by no means universally acknowledged and it has been argued that eradication of *H pylori* can be justified financially and clinically in patients with proven or suspected ulcer disease only [127]. In order to assess the relationship between expenditure and benefit, good estimates of the cost of screening are needed and levels of compliance with screening and treatment must be taken into account in arriving at these estimates. In the current thesis, the cost of running two *H pylori* screening and eradication programmes in different communities is considered.

Proposed disadvantages:

It has been argued that widespread treatment of *H pylori* infection with antimicrobials could exacerbate problems with antibiotic-resistant strains of *H pylori* and other pathogens [67]. For this reason, vaccination against *H pylori* [128,129] may be the strategy of choice for eliminating the infection. However, in spite of encouraging early results in a mouse model [130], the development of a vaccine capable of effectively preventing *H pylori* in humans does not appear likely in the near future. A single course of eradication therapy prescribed for those infected might in any event have a low impact on the development of resistant bacterial strains of *H pylori* and other pathogens, since antibiotics are already prescribed frequently for other conditions. Statistics for 1994 indicate that 45.8 million prescriptions for antibacterial drugs were issued in that year in England [131]. In those with resistant strains of *H pylori*, treatment with eradication therapy is not necessarily ineffective and the clinical relevance of metronidazole resistance may be limited when the newer triple therapies are used [111,132]. It has been shown, for example, that a combination of omeprazole

with low dose clarithromycin and a nitroimidazole can work well even in patients with metronidazole resistant strains of *H pylori* [133].

The issue of anxiety generated by screening [18,19,25] has been raised in Chapter one and is considered in relation to screening for *H pylori* in this thesis. It has also been suggested that there may be some benefits associated with the bacterium and that widespread elimination of *H pylori* would be premature before this possibility has been fully investigated [67,127]. In particular, concern has been raised by the possibility that the infection may protect against gastro-oesophageal reflux [134,135]. In an analysis presented in Chapter 6 of this thesis, the association between *H pylori* infection and symptoms of reflux in a general population sample is investigated.

Chapter 3

The Market Harborough screening programme: design of the study, including results from pilot and related studies

- i. Introduction**
- ii. Rationale**
- iii. Feasibility study**
- iv. Overall design of the study**
- v. Choice of screening test**
- vi. Screening in a small branch surgery using dual therapy**

i. Introduction

In this chapter, the justification for carrying out the main screening study is presented, together with the overall design. A feasibility study carried out prior to the main study is described, together with brief details from pilot and related studies where they contributed to the details of the study design.

ii. Rationale

Clinical trials are necessary to answer the question of whether and to what extent eradication of *H pylori* can reduce morbidity and mortality. To justify the introduction of routine population screening for the bacterium, these health benefits must be demonstrated to outweigh possible disadvantages. A reduction in mortality from gastric cancer and bleeding peptic ulcers would weigh heavily in the pro-screening side of the balance, but even if benefits can be shown, the effectiveness of population screening would also be dependent on an efficient screening process and levels of compliance achieved. To state the case simply, if only a proportion of the target population accept screening, health benefits that have been demonstrated will be reduced in the community targeted, although those attending would still achieve full individual benefit. If non-attenders are likely to be more at risk than those who accept screening, then health benefits will be further diluted. In one study of cervical cancer screening, for example, only 30% of women aged 56-65 years in an inner-city area attended, compared to 52% of those aged 32-41, although most deaths from cervical

cancer occur in women over 50 years of age [12]. If some of those with positive tests fail to comply with treatment, overall benefits in the community would again be reduced. If screening for *H pylori* infection is considered not just in terms of benefit to the individual but also as a public health intervention, then overall success of screening in the community must be regarded as important. Compliance rates suggested by clinical trials may not be representative of routine practice and it cannot be assumed that they would be matched in actual screening programmes.

The primary aims of the study were to look at the process of screening for *H pylori* in the UK in collaboration with general practitioners. Interventions to achieve compliance would be limited to ones considered to be appropriate to a non trial setting and areas of good and poor compliance would be identified and considered. Although research-based, the programme would be conducted as a prescriptive or ‘case-finding’ exercise. Where additional areas of epidemiological study concerning disease association and risk factors for infection could be carried out opportunistically without compromising the primary aims, these would be included as secondary aims. Although the study would be based on screening for *H pylori*, it was considered that the exercise would be relevant more generally to the process of screening, particularly with regard to compliance.

iii. Feasibility study

There has been considerable media coverage of *H pylori*, including *Ulcer Wars*, an edition of the BBC television documentary series *Horizon* devoted entirely to the

subject, which was transmitted on four occasions during 1994. Before embarking on the main screening study, a small feasibility exercise was carried out during June 1995, in the proposed study community. The aims were to establish whether people in this community had any knowledge of *H pylori* from the media or elsewhere and whether they thought they would wish to be screened if offered such an opportunity. The effectiveness of the information offered as a tool for recruiting people for screening would also be considered, prior to finalising the wording of an information leaflet to be used in the definitive study.

Methods:

A market research style questionnaire was designed, to be used in a street setting. A street interview was selected in preference to a postal questionnaire, where some people might have been tempted to find out about *H pylori* before answering. It was also considered that a response could be obtained from a better cross-section of the community using the method selected. Each interview took about 5 minutes, with interviewees being asked between 5 and 13 questions, depending on whether certain questions were 'skipped' following a negative answer. Answers were mostly recorded as Yes, No or Unsure, with longer answers occasionally invited and flash cards used in some instances, for example pictures of an endoscope and a patient undergoing endoscopy. For consistency, questions were asked and link passages were read verbatim from the questionnaire and all interviews were conducted by the same interviewer (the author). The interview began with questions about previous knowledge of *H pylori* and interviewees were then read a short passage giving some information about the bacterium. The text of this passage was very similar to that

contained in an information leaflet designed for use in the screening study (see Appendix A). Readability and simplicity were important considerations in the preparation of this leaflet and a very good level of readability was indicated by a Flesch reading ease score [136] of 72.1, obtained using the Readability Plus computer programme [137]. The inconclusive state of current research and differing medical opinion on the appropriateness of eradicating *H pylori* in those without symptoms were included in the information presented. After being read the information, interviewees were asked some questions about whether they felt that they would accept an offer of screening.

A target of 100 interviews was set. Whilst acknowledging that the sample size was fairly small and not based on power calculations, it was felt this number would be a realistic target for one interviewer and would provide a sufficient indication of levels of awareness and interest for the purpose of a feasibility study. A quota was set as follows:

- Age: 25 subjects from each of the following groups - 21-35; 36-55; >55; the remaining 25 to be taken from any group.
- Social class: 25 subjects from each of the following groups - A/B (professional or managerial); C1/C2 (clerical or skilled manual); D/E (semi-skilled, unskilled or unwaged); plus 25 from any group.
- Sex: 50 male, 50 female.

In setting this quota, the intention was not to accurately reflect the population profile in Market Harborough, but rather to obtain a good representation from different ages and socio-economic groups. During the final session, people were interviewed only if

they were in a category needed to complete the quota.

Results:

When asked at the beginning of the interview whether they had heard of *H pylori*, having also been shown the name printed on a card, only 4 people out of the 100 interviewed remembered hearing the name and were able to give some appropriate information. This indicated a 4% minimum figure for prior awareness, including only those people who had definitely heard of the bacterium without prompting. Two more people said that they recognised the name, but were unable to give any information about the bacterium and a further 3 who claimed to have heard of it gave inappropriate information: one thought she had read about it in an article about food poisoning; one said it was something to do with the eyes and the other thought it was a helicopter that transported patients to hospital. After being read the passage about *H pylori*, a further 8 people said they had definitely or possibly read or seen something about it in the press or on television, giving a maximum of 14/100 (14%) who had previously come across some reference to *H pylori*.

After being read the passage, subjects were asked whether they thought they would want to be tested if offered screening for *H pylori* infection. Sixty people answered affirmatively, 13 were unsure or felt that it would depend on the type of test and the remaining 27 said they would not want to be tested. The most commonly stated reasons for not wanting to be tested were lack of symptoms and a belief that one should 'leave well alone' and not 'tempt fate'.

Discussion:

The street survey was intended to provide a general indication of public interest in being screened for *H pylori*, prior to initiating a research based screening programme. Although what people say is not necessarily a reflection of what they will do in practice, the exercise nevertheless established that in spite of extremely limited prior awareness, there was a strong interest in being screened for the bacterium. This may have indicated a general interest in health rather than a specific interest in the particular screening intervention under consideration. It is also possible that people had misconceptions about the value of screening for *H pylori*, a consideration which applies to screening in general. In 1985, in an article on breast screening, Skrabanek proposed that *“evidence that breast cancer is incurable is overwhelming. The philosophy of breast cancer screening is based on wishful thinking... it would appear that no woman needs to die of breast cancer if she reads and heeds the leaflets of the cancer societies and has her breasts examined regularly”* [138]. Even where benefits of screening have been established, it is likely that some people who come forward for testing may not fully understand the limitations in terms of missed diagnoses, false positive results and possible risks associated with some screening tests.

It was considered that the feasibility study had established that limited prior knowledge and the inconclusive state of current research would probably not be major limiting factors in compliance with screening. The information to be included in the leaflet to be sent with screening invitations appeared to be sufficient to stimulate interest in screening for an infection about which most people had no prior knowledge.

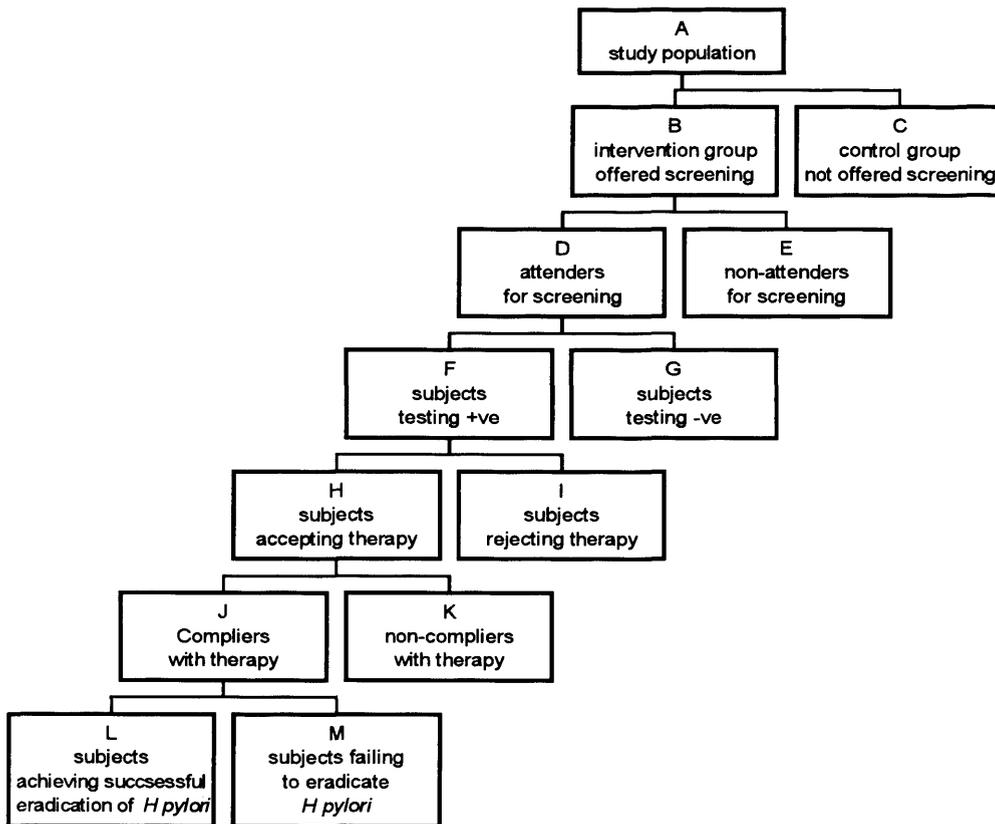
iv. Overall design of the study

On the basis of the feasibility study, it was considered that a research based community screening programme for infection with *H pylori* would be a realistic area of study. An age range of 21-55 was selected on the grounds of being the group most likely to benefit from screening. Bearing in mind the primary aims, an overall design for the study was drawn up as shown in Figure 3.1. Randomisation of subjects to intervention or control status would provide groups for possible long term follow-up to compare health benefits in those offered or not offered screening. Similar comparisons of screening/not screening have been made in the Nottingham study of screening for colorectal cancer using faecal occult blood testing [139] and in the Edinburgh breast cancer screening trial [140].

Additional randomisation of subjects later in the study design would have compromised the main aims associated with the measurement of compliance. Useful information about the effect of eradication on symptoms of dyspepsia could have been obtained by randomisation of group F (those testing positive) to receive an offer or no offer of medication, or by randomisation of group H (those opting to take eradication therapy) to receive medication or placebo. These strategies could however have influenced rates of uptake for screening and therapy and were therefore rejected as part of the design. Although subjects would be aware of the research basis of the programme, it was considered important that they should be made an offer of screening carrying guaranteed access to treatment for those testing positive. In addition, placebo controlled trials with effect on symptoms of dyspepsia as a primary

Figure 3.1. Flow chart showing groups to be studied in the Market

Harborough *H pylori* screening study



end point are being conducted by other research groups. Randomisation of group B to two groups to be offered different screening tests, to compare uptake, was considered, but it was decided that this should be confined to pilot studies in order to avoid over-complicating the study and reducing numbers in each arm. The main overall outcome measures would be:

- Numbers achieving successful eradication (group L) expressed as a proportion of those offered screening (group B)
- Numbers achieving successful eradication (group L) expressed as a proportion of the number of those offered screening (group B) estimated to be positive (on the basis of the prevalence of infection, estimated from results in groups F and G).

Compliance rates at various intermediate stages of the programme would also be identified, namely acceptance of screening (self selection of those in group B to groups D and E); acceptance of therapy (self selection of those in group F to groups H and I) and compliance with therapy (self selection of those in group H to groups J and K).

Without compromising the primary aims, it was considered that information could be collected from those attending for screening in order to look at risk factors for infection, plus prevalence of dyspepsia and its possible association with *H pylori*. Information about dyspepsia collected from the control group could also be used in assessing the prevalence of dyspepsia in the study community.

v. Choice of screening test

Urea breath testing was rejected as an option for the study primarily on the grounds of cost, both in terms of kit required and the time needed to carry out each test. Although cheaper to carry out than the ^{13}C test, no on site facilities were available for ^{14}C testing, which was also considered to be inappropriate for use in asymptomatic subjects on account of exposure to a small but measurable dose of radiation.

The other non-invasive option for testing was serology and both conventional testing by laboratory ELISA and near patient testing were considered. Greater acceptability than conventional serology was considered to be a possible advantage of using a near patient test requiring a finger prick blood sample only. Two pilot studies for the screening programme, carried out primarily to test the methodology proposed for the main project, did not however suggest this to be the case. In the first of these studies, a screening test for *H pylori* was offered to 50 people aged 21-55, selected from those registered at a small branch surgery in Market Harborough. In order to compare the acceptability of the two test methods being considered, 25 people were offered a conventional blood test and 25 the Cortecs Helisal[®] Rapid Blood near patient test requiring a finger prick blood sample only and providing an on-site result in about 10 minutes. Randomisation to receive the two types of test was carried out using case-control pairs matched for age group and sex. Invitation letters were identical apart from details describing the test and availability of results. The comparison was subsequently repeated using the same numbers in a second pilot study. Combining results from the two pilot studies, 28 out of 50 (56%) accepted conventional

venepuncture, with only 13 out of 50 (26%) accepting the near patient test. The significantly lower acceptance rate for the near patient test (Yates corrected $\chi^2 = 8.10$, $P = 0.004$) suggested that near patient testing might in fact be less acceptable as a screening test, possibly because this type of test is less familiar than conventional venepuncture.

In a separate study, the accuracy of the Cortecs Helisal[®] near patient test was assessed in a symptomatic population attending for upper GI endoscopy. Four reference tests were used, namely rapid urease CLOtest[®], culture, histology and serology (Meridian Diagnostics Premier ELISA). Where two reference tests were positive this was regarded as a gold standard positive; cases where no reference test was positive were taken to be a gold standard negative and one positive reference result was regarded as equivocal. Sixty-three patients were deemed to be *H pylori* positive and 93 negative, with 15 equivocal cases. It was considered that omitting the equivocal cases might have distorted results; performance figures were therefore calculated twice, treating patients with equivocal status as either positive or negative. Results are shown in table 3.1. Over all patients, sensitivity was acceptable (91-92%, 95% confidence interval 82-97%), but specificity was poor (56-62%, 95% confidence interval 45-72%). In patients aged over 45 and those of South Asian origin specificity was particularly low (Table 3.1).

There has been wide variation in results obtained in evaluations of the Helisal[®] test [141]. Although good results for both sensitivity (88%) and specificity (91%) have been presented [142], results similar to our own have also been obtained elsewhere

Table 3.1. Analysis of the performance of the Helisal[®] rapid blood test, overall, by age and by ethnic origin, in 171 patients attending for upper GI endoscopy, using 4 reference tests.

	Overall n = 171	Under 45 n = 54	45 or over n = 117	S. Asian n = 26	European n = 143
Sensitivity	91-92%	85-88%	93-93%	79-81%	93-96%
Specificity	56-62%	78-82%	44-51%	42-50%	57-64%
PPV	55-67%	65-74%	52-65%	61-72%	52-65%
NPV	89-92%	90-94%	88-91%	63-63%	93-96%
Accuracy	69-75%	81-83%	63-72%	62-69%	70-76%

PPV = positive predictive value; NPV = negative predictive value

Ranges shown indicate the different results which would be obtained when treating 15 patients deemed to have equivocal *H pylori* status as either positive or negative

[98] and it is considered that this test lacks the ability to perform consistently with an accuracy suitable for population screening.

The decision to use laboratory serology as the screening test left the choice between a large number of commercial ELISAs. The Meridian Diagnostics Premier kit, distributed in the UK by Launch Diagnostics, was selected on the grounds that it has been shown to compare well with other ELISAs in studies carried out in local and other populations [95,96,143]. Patients included in the Helisal[®] evaluation described above were among those recruited to the large Medical Devices Agency (MDA) series of evaluations [96] carried out locally. Results for sensitivity and specificity of the Premier ELISA, from the MDA series and two smaller studies, are shown in Table 3.2. In one study [95] sensitivity and specificity of the test were both 100%. Although sensitivity and specificity were lower in the local study than elsewhere, this was true in general for the various kits tested. In the Leicester study [96,144], the Premier kit was generally considered easy to use, having the advantages of coloured sample diluent, a small number of control wells and a short time (1 hour 35 minutes) for testing one plate. The kit was also rated highly for ease of use by other evaluators [95,143] and it was felt that practical considerations should not be ignored when selecting a test.

v. Screening in a small branch surgery using dual therapy

Prior to beginning the main study and after selecting the test to be used, a small run-in study was carried out in the branch surgery used for the pilot studies. This branch

Table 3.2. Performance of the Meridian Diagnostics Premier ELISA: results from three evaluations

No of patients	Age in years	Recruitment	Reference tests	Sensitivity	Specificity	Main author	Reference
82	≥18	Patients referred for endoscopy	Histology Culture Rapid urease test	97%	85%	Nair	143
84	22-79	Patients referred for endoscopy	Histology (all) Urea breath test (60 patients only)	100%	100%	Wilcox	95
588	15-87	Patients referred for endoscopy	Histology Culture Rapid urease test	85%	80%	Stevens	96, 144

surgery covers subjects living in Market Harborough not registered at the Medical Centre, where the main study was to be based. This small study was run according to the main study design, with the exception that a dual therapy regimen (14 days omeprazole 20 mg bd and clarithromycin 500 mg tds) was prescribed for treating those found to have *H pylori* infection, rather than the triple therapy regimen proposed for the main project.

Results from screening in the run-in study were as follows:

- The screening test was accepted by 133/256 (52%) subjects
- There were 21/133 (16%) positive tests
- A prescription for eradication therapy was accepted by 16/21 (76%) of those who tested positive
- The course of medication was completed by 14/16 (88%) of those who elected to take therapy
- Eradication of *H pylori* was confirmed by UBT in 11/14 (79%) cases
- Overall, 11/256 (4%) of those offered screening achieved successful eradication
- Estimating that 41 (16%) of those offered screening were positive, the prevalence of *H pylori* infection in those offered screening was reduced by 27% (11/41).

It had been considered possible that a regimen involving 2 types of medication rather than 3 might have an advantage in terms of compliance. However, 2 of the 14 patients who accepted the therapy failed to complete the course of tablets, in one case because

of sickness and dizziness, with the other subject reporting that the tablets had caused his teeth to ache. It therefore seemed unlikely that lower eradication rates typically achieved with dual rather than triple therapy [106] would be balanced by better compliance in the general population.

Chapter 4

Screening and eradication in Market Harborough: a community programme

- i. Methods**
- ii. Results**
- iii. Discussion**

i. Methods

Ethical Approval and Study Sample:

Approval for a research based programme of *H pylori* screening and eradication was sought and obtained from the local ethics committee. The study was to be carried out in collaboration with the Market Harborough Medical Centre. This large general practice covers most of the residents living in Market Harborough, a small town in Leicestershire with a population generally of relatively high socio-economic status. The practice provided a list of patients aged 21 to 55 years at the start of the study. Those living in the outlying villages were not included in the study, but there was no selection according to history of symptoms or consultation. The practice was asked to nominate any subjects suffering from terminal illness whose inclusion in the study was considered inappropriate, but there were no other selection criteria at this stage. A total of 8030 subjects were included in the study.

Randomisation:

In randomising the study population in equal numbers to intervention and control groups, it was considered that -

- each individual should have an equal chance of being assigned to a particular group
- the two groups should be matched for age and sex
- for practical and ethical reasons it was also felt that eligible persons in each household should all be assigned to the same group.

Straightforward stratified randomisation would not have been satisfactory given the last requirement. Randomisation was carried out in batches of 1,000 persons, using the following stages -

1. Eligible persons were listed by address and Lotus 123 software was used to computer-code each individual to one of six categories: AM (males aged 21-34); BM (males aged 35-45); CM (males aged 46-55); AF (females aged 21-34); BF (females aged 35-45) and CF (females aged 46-55).
2. Households or groups of households were matched by hand according to age/sex categories of those living in the household(s). One group in each pair was coded as 'A' and the other as 'B'.
3. A list of case-control pairs was generated using Arcus Pro-Stat software (© Ian Buchan 1990) and household groups were allocated to the intervention or control group according to whether 'A' or 'B' emerged as the 'case' (intervention group).

It was considered that this method met all the criteria set for allocating individuals to the two groups, providing two well matched groups (see results), with all eligible members of each household in the same group.

The screening invitation and control group survey:

Subjects in the intervention group were sent a screening invitation letter (Appendix B) on general practice headed paper, together with an information leaflet (Appendix A)

and a questionnaire (Appendix C). An appointment time was given for a day or evening screening session to be held at the local hospital, situated almost opposite the local practice. The letter explained that the test was being offered as part of a research study and that all those with positive tests would be entitled to request a prescription for eradication therapy. Those deciding to attend were asked to complete the questionnaire and bring it to the screening session.

Subjects allocated to the control group were sent a letter on general practice headed paper asking them to participate in a 'health survey' and were asked to complete and return their questionnaire in a reply paid envelope. This questionnaire was very similar to that sent to the intervention group, but the final page included a statement of consent to information being stored on a computer and to possible future follow-up.

The screening tests:

Those attending for screening were asked to sign a form giving consent to being tested, to information being used for research and to possible follow-up. Venous blood samples were collected at the screening sessions, frozen and subsequently analysed at the local Public Health Laboratory, using the Meridian Diagnostics Premier ELISA. All the assays were performed by the same person. In previous evaluations of this ELISA [95,96,143,144] qualitative (positive/negative) results were used by the investigators; for the present study, quantitative results were obtained in accordance with the manufacture's instructions, with the aim of increasing the accuracy of the test offered by identifying borderline results. Pre-setting an optimum positive/negative cut-off point for a local asymptomatic population using a useful number of subjects would

have involved high expenditure on urea breath testing; it was therefore decided that during the study subjects with borderline serology would be offered a ^{13}C -UBT to check their result. Breath testing was performed at the local hospital where screening sessions were held. The tests were carried out fasting, with a test meal of orange juice, which has been shown to be acceptable in addition to giving good results [145]. Breath samples were analysed at the Manchester Medical Mass Spectrometry Centre.

Notification of results and therapy prescribed:

All subjects were notified of their test results and those found to be positive were given the opportunity to obtain a prescription for eradication therapy from their general practitioner, with the additional option of requesting a referral for upper GI endoscopy where there was a history of dyspeptic symptoms, a family history of gastric cancer or anxiety about the test result. Subjects were however also advised that they could decide not to take any action following a positive test result. Prescriptions were supplied on the usual basis, with prescription charges payable except by those eligible for exemption. Subjects were asked to notify their decision about whether or not they wished to take eradication therapy and any who failed to make contact were sent a reminder with a reply slip and a pre-paid envelope. Subjects were asked to retain any tablets not taken and to return them when attending for their follow-up UBT. Those who failed to send back their diary were sent a reminder and a reply slip to return in a reply-paid envelope.

In evaluations of eradication regimens involving a PPI, omeprazole has most frequently been used. Lansoprazole has however been shown to have selective activity against *H pylori* [146] and in a large multicentre trial 90% eradication was achieved using this PPI in combination with metronidazole and low dose clarithromycin for one week [147]. For consistency, the same eradication regimen was generally prescribed for all subjects, namely lansoprazole 30mgs, clarithromycin 250 mgs and metronidazole 400 mgs, all twice daily for 7 days. There were five exceptions where an alternative triple therapy was considered more suitable, in 4 cases because of possible interactions with other medication, plus one person already taking omeprazole who continued with this in place of lansoprazole.

All those who decided to take eradication therapy received an information pack (Appendix D). This was produced in-house and included an information leaflet, a medication diary to be completed daily and returned in a reply-paid envelope, plus two A5 size notices to display as memory aids if required.

Follow-up of compliers and non-compliers:

To determine the success of eradication, a fasting ^{13}C -UBT, using orange juice as the test meal, was carried out at least one month following completion of the course of eradication therapy, as indicated in returned diaries or on reply slips. A Delta ^{13}C excess cut off of 3.5 [148] was used to determine positive or negative status, but to increase accuracy it was also considered that a repeat test should be offered in any cases of results between 2.5 and 5.0. When attending for breath tests, subjects were questioned about compliance, strategies used to remember to take the medication and

side effects of the treatment. Replies were recorded on a standardised form. Further management of cases of failed eradication was considered outside of the study on an individual patient basis.

Screening sessions commenced in June 1996 and UBTs were completed in October 1997. When the study was nearing completion any subjects who had made no telephone contact and had also failed to return reply slips were sent a final letter giving the last dates for arranging prescriptions or breath tests as part of the study. They were advised that if they should decide that they would like to take eradication therapy after completion of the study, they would need to contact their general practitioner to discuss this.

Estimation of cost:

The cost of obtaining successful eradication of *H pylori* in one person was estimated using results obtained in the study in combination with a possible model for conducting this type of screening programme in general practice. The cost of UBTs to check borderline serology results and success of eradication was not included, as it was considered that these would probably not be used in an actual screening programme. Personnel costs were based on the grade of staff considered likely to carry out the tasks in routine practice. Prescription charges paid were not deducted from the cost of medication as it was not known how many people paid this charge; the cost of medication was therefore simply based on the net cost given in the British National Formulary [149]. Overheads were built in to the costing of practice nurse and general practitioner time [150], but incidental overheads and other expenses were not included.

One-year follow-up:

A sample of those who had attended for screening was invited to complete a follow-up questionnaire. This exercise was not intended as a definitive study and the small sample size was determined by the time scale of the present project rather than by a power calculation. The limited aim was to consider whether two areas of study (anxiety generated by screening and outcome relating to dyspepsia) might warrant more detailed investigation in the future, in our own or other study populations.

The follow-up survey sought information about perceived levels of anxiety generated by the screening process and the effect that this experience might have on future participation in screening. Additional questions relating to dyspepsia are discussed in chapter 6. Questionnaires were sent to the first 50 subjects who had completed therapy 12 months previously and had also been breath tested, including 3 people who had failed to eradicate the infection. Slightly modified questionnaires were sent to 50 consecutive subjects whose result had been negative after a test 13 months previously, a time lapse between receiving the test result and the follow-up questionnaire estimated to be similar to that in the positive group.

Respondents were asked to describe anxiety at various stages by selecting one of five options (not at all worried; a little worried; worried; very worried or extremely worried). Those with negative tests were asked to describe the relief felt on receiving their negative result by choosing one of five similar options for levels of relief and an additional response available for this question was worded 'I was disappointed as I had some symptoms which I thought might have been caused by *Helicobacter pylori*

infection'. Those in both groups were asked if they thought they would accept 'a similar screening test for another health problem' in the future, with 5 possible replies ranging from 'yes, definitely' to 'definitely not'.

ii. Results

Uptake of screening:

Randomisation of the study population provided two well matched groups each of 4015 subjects (male 2048, female 1967 in each group). The mean age was 38.1 years for the intervention group and 38.0 years for the control group. Excluding 7 people who attended but who reported previous treatment with eradication therapy, 1566 (39%, 95% Confidence Interval (CI) 37% to 41%) of the 4015 subjects invited for screening accepted the offer. Table 4.1 shows acceptance rates in the different age/sex groups previously used in carrying out the randomisation to intervention and control groups. Women in the 46-55 year old age group were the most likely to attend (54%), with lowest attendance rates in younger men aged 21-34 years (24%). There was a statistically significant difference between acceptance rates of 44% in all women invited and 34% in all men invited (Yates' corrected $\chi^2 = 40.48$, $p = < 0.001$). Combining figures for men and women, older people were more likely than younger subjects to attend (χ^2 for linear trend = 137.36, $p = < 0.001$).

Analysis of questionnaire data showed that 50% of those screened were in the higher socio-economic groups according to non-manual rather than manual occupation of the head of household (see Chapter 7, Table 7.1). Similar data were unavailable for those

Table 4.1. Acceptance rates in age/sex groups for a serological test for *H pylori* infection, offered as part of a population programme of screening and eradication.

Sex/Age group	Number offered screening	Number accepting screening	Acceptance rate (%)
Men aged 21-34 yrs	860	206	24
Men aged 35-45 yrs	671	267	40
Men aged 46-55 yrs	517	227	44
All Men	2048	700	34
Women aged 21-34 yrs	835	269	32
Women aged 35-45 yrs	619	321	52
Women aged 46-55 yrs	513	276	54
All women	1967	866	44
All subjects	4015	1566	39

who did not come forward for screening, so it was not possible to make an accurate comparison of attenders and non-attenders in terms of social class. However, an estimation from 1991 census data [151] indicated that at that time 53% of economically active households in Market Harborough were classified in the higher (non-manual) social classes. It cannot be assumed that this figure would be exactly applicable to a sample aged 21-55 derived more recently from those registered at the Market Harborough Medical Centre, but there was nevertheless some indication that those who attended for screening were reasonably representative of those who were invited in terms of social class.

Results of screening:

Eight people with borderline serology declined a breath test and were therefore considered to have equivocal *H pylori* status. In the remaining 1558 attenders, there were 235 (15%, 95% CI 13% to 17%) positive tests and 1323 negatives. For 36 people who had UBTs following borderline serology, there were 30 negative and 6 positive results, whilst the remaining results were based on serology alone.

Any subjects with positive tests who failed to make contact either after notification of their result or following a reminder letter were assumed to have decided against taking eradication therapy. Those who initially expressed an interest in taking eradication therapy, but who failed to return a diary and also made no contact by telephone or reply slip following a reminder letter, were assumed to have changed their minds about taking the medication. One subject with a history of dyspepsia was referred for endoscopy by their general practitioner following a positive test result, but was

admitted to hospital with haematemesis prior to the endoscopy appointment and was therefore at this point excluded from the study. A total of 186 (79%, 95% CI 74% to 84%) of the remaining 234 people with positive tests decided to take eradication therapy as part of the study, with 21 of these also requesting a referral for endoscopy. There were 8 essentially normal endoscopies and a range of minor pathologies in the remaining cases, as shown in Table 4.2. There were 2 patients in whom there was evidence of present or past ulceration, one with a healing and also a healed gastric ulcer and scarring in the pylorus and one with evidence of a small healed duodenal ulcer. It was noted that neither of these patients had experienced symptoms; referral for endoscopy had been requested in the one case because of a family history of gastric cancer and in the other for reassurance following their positive test result.

Treatment with eradication therapy:

Successful eradication was confirmed in 170 (95%, 95% CI 91% to 98%) of the 179 subjects who attended for a breath test, with 9 people remaining positive. There were no UBT results with a Delta ^{13}C excess between 2.5 and 5.0, so no repeat tests were indicated. Seven patients who returned diaries or reply slips indicating completion of the course of therapy did not have a UBT; these included one taking maintenance omeprazole for reflux, in whom the test would not have given a reliable result and one who had moved from the area.

In reply to an open question about side effects of treatment, 77/179 (43%) subjects said they had experienced no side effects and a further 46 (26%) reported mild or very mild side effects only (usually slight nausea, diarrhoea or headaches). The remaining 56

Table 4.2. Findings in 21 subjects who elected to undergo upper GI endoscopy following a positive screening test for infection with *H pylori* during a population screening programme.

Findings	Number of cases
Essentially normal endoscopy	8
Gastritis only	4
Mild gastritis and hiatus hernia	2
Gastritis and evidence of healed duodenal ulcer	1
Bile reflux	1
Reflux oesophagitis and hiatus hernia	1
Duodenitis only	1
Duodenitis, gastritis and hiatus hernia	1
Duodenitis and gastritis with chronic erosions	1
Healing and healed gastric ulcer and scarring in pylorus	1

(31%) subjects between them described more significant side effects as shown in Table 4.3. There were no cases of hospitalisation or failure to complete the course of therapy because of side effects.

No tablets were returned. Compliance with taking medication as assessed by this method and also by verbal questioning and completed diaries or reply slips was considered to be 100% (179/179) in those who attended for UBTs. Minor deviations in timing and an occasional missed dose taken at the end of the course were not considered as non-compliance. When asked an open question about whether they had used the reminder notices or any other methods of remembering to take the medication, 59/179 (33%) said they had used the notices, although 3 of these thought they would have remembered without them. Two in addition had made their own notices. Thirty-three people said that the diary had helped, 25 left the tablets in a prominent position, 34 mentioned that keeping to a routine had been helpful and 22 had been reminded by other members of the household (usually wives) or work colleagues. Three people had set alarms, 3 mentioned that they had chosen a 'good' week when they thought compliance would be easiest and 2 said that high prescription charges motivated them to comply.

Overall results:

Overall, successful eradication of *H pylori* within the duration of the study and after a single course of eradication therapy was confirmed in 170 (4%, 95% CI 4% to 5%) of the 4015 people invited for screening. Assuming successful eradication in the 7 subjects who completed the therapy but did not have a UBT, this percentage would

Table 4.3. Side effects described by 56 of 179 subjects who had a Urea Breath Test after taking a course of eradication therapy (generally 1 week lansoprazole, clarithromycin and metronidazole). Side effects specifically reported as mild or very mild are excluded.

Side effect	Number of subjects reporting side effect
Taste disturbance/ dry or sore mouth, tongue or throat	17
Thrush	12
Headaches	12
Diarrhoea or loose motions	10
Nausea	8
Dizziness or light-headedness	4
Abdominal pain	2
Lethargy	2
Other side effects each reported by one person (including one prescribed an alternative regimen) *	11

* rash; constipation; confusion; hot sweats; depression; bloating; wind; rectal bleeding; itching on body and arms; anal pruritis; tingling in fingers and legs leading to panic attack

have remained as 4% (177/4015). If a 15% overall prevalence of *H pylori* infection applied to the 4015 subjects offered a screening test, it can be estimated that there would have been 602 positives in the intervention group. Assuming successful eradication in the 7 subjects who did not have a breath test, it could be estimated that 177/602 (29%, 95% CI 26% to 33%) *H pylori* positives in the intervention group had achieved successful eradication as part of the study.

Estimation of cost:

Using results for compliance and detected infection, combined with a possible model for routine serological screening and eradication through general practitioners, an estimated cost of £138 (to the nearest pound) per subject achieving successful eradication of *H pylori* was obtained, as shown in Table 4.4.

One-year follow-up:

Follow-up questionnaires were returned by 41/50 (82%) people who had tested positive and 37/50 (74%) negatives, a 78% overall response rate. Responses relating to anxiety are shown in Table 4.5. Fourteen (8 positive, 6 negative, $P = 0.934$, ns) subjects recalled being worried, very worried or extremely worried on receiving the screening invitation and/or while waiting for their result. A further 7 people with positive results reported being significantly worried at later stages, giving a total of 21 (27%) people who recalled anxiety at one or more stages. Of those with negative tests, 15/37 (41%) recalled feeling relieved, very relieved or extremely relieved on receiving their result, with 4 (11%) subjects reporting disappointment because of symptoms which they had thought might be related to *H pylori*, suggesting a further negative

Table 4.4. Estimated cost of obtaining successful eradication of *H pylori* in one subject, based on a model for possible clinical practice combined with results obtained in a population screening study conducted in Market Harborough.

Item costed	Basis for estimated cost	Estimated cost per person £	No of subjects	Total cost per item £
Mailed screening invitation	Clerical time plus 2nd class postage and stationery	0.50	4015	2007.50
Screening test using serology	One visit to practice nurse, plus kit, plus laboratory time	9.30	1566	14563.80
Mailed results	Clerical time plus 2nd class postage and stationery	0.50	1566	783.00
Consultation (subjects with positive tests wishing to take eradication therapy)	Five minute GP consultation	8.60	186	1599.60
Cost of medication	One week lansoprazole, metronidazole (Flagyl) and clarithromycin (British National Formulary prices)	29.12	186	5416.32
Total cost				24370.22

Cost per subject achieving successful eradication of *H pylori* (n = 177, including 7 cases not confirmed by UBT) = £24370.22 / 177 = £137.68

Table 4.5. Proportion of subjects who recalled being significantly worried at various stages of the screening process, as identified by responses to a questionnaire mailed approximately 13 months after they accepted a screening test for infection with *H pylori*

Stage of screening/ eradication process	n =	No (%) who reported being worried, very worried or extremely worried
Receiving screening invitation	78	9 (12)
Awaiting test result	78	12 (15)
Receiving positive result*	41	15 (37)
Awaiting breath test result*	41	12 (29)

*Subjects who had tested positive for *H pylori* infection

aspect of the screening experience for some people.

Thirty-nine (50%) respondents said they would definitely accept 'a similar screening test for another health problem' in the future; 31 (40%) would probably accept and 5 (6%) were unsure. These responses were given by similar numbers with positive and negative results. Three (4%) people, all of whom had tested positive, felt they would probably not participate in the future, but no-one said they would definitely not accept. The 3 questionnaires sent to subjects who had failed to eradicate *H pylori* were all returned; 2 of these people said they would probably accept again, with the other being one of the 3 who probably would not. Subjects who reported feeling worried, very worried or extremely worried during the screening process were less likely to think that they would definitely participate in screening in the future (7/21, 33%) than those who reported that they had not been worried at all or only marginally worried (32/57, 56%). This difference was not however found to be significant ($P = 0.126$, ns).

iii. Discussion

Assessment of the effectiveness and economic validity of any type of population screening must take account not just of health benefits but also of the levels of compliance which can be expected. The benefits of eradicating *H pylori* infection in asymptomatic populations have yet to be established and conclusive evidence may not be available in the near future. In particular, answers regarding the possibility of reduced mortality from gastric cancer will be obtained only from large or pooled

studies of long duration. Against this background, however, the present study has shown that good compliance with medication and a good *H pylori* eradication rate (95% in this study) can be achieved in a general population sample. The study achieved an acceptance rate of 39% for the screening test and led to an estimated 29% reduction in the prevalence of *H pylori* in the population invited for screening. In a climate where benefits of screening are unconfirmed, it was considered inappropriate to apply pressure on subjects either to attend for screening or to take medication. Failure to attend for screening and to a lesser extent failure to accept therapy were however identified as problems of compliance which would need to be further addressed if health benefits should be demonstrated and population screening were to become a real possibility prior to the development of a successful vaccine. Men would need to be particularly targeted for increased uptake of screening, as would younger people if the age range for screening was similar to that used in the present study.

Some issues concerning the choice of screening test were beyond the scope of the present study. For practical and economic reasons, serology was selected for the screening programme. It is however acknowledged that serology has limitations in terms of accuracy [96] and that those limitations would need further assessment in asymptomatic populations if serology were to be considered for routine population screening for *H pylori* infection. The commercial ELISA selected was chosen on the basis of good performance in evaluations carried out using patients attending for endoscopy; determination of sensitivity and specificity in an asymptomatic local population was not included in the current study, where the primary interest was compliance. A further area which may merit full investigation is the logistics of

population screening for *H pylori* using urea breath testing, including a comparison of fasting and non-fasting tests. Good performance has been demonstrated using a non-fasting version of the ¹³C-UBT [152] a consideration which could be important in terms both of practicality and compliance. In the present study, the use of UBTs to check the *H pylori* status of those with borderline serological tests was considered to be for the benefit of the individuals concerned, since a positive/negative cut off had not previously been set. The aim was not to assess increased accuracy obtained using this approach in place of serology alone and the number of people who had UBTs was too small to be useful for setting an optimum cut off point. It is considered that further investigation of the advantages of using breath tests to check cases of borderline serology, in terms of increased sensitivity and specificity, would however be of value.

The effectiveness of the programme in terms of the proportion of those offered screening who achieved successful eradication was determined partly by a low (15%) prevalence of infection in a study population characterised by relatively high socio-economic status. Limited uptake of screening by those invited and of therapy by those who tested positive also reduced effectiveness. In selecting the screening invitation procedure, consideration had been given to strategies for encouraging good uptake. Screening invitations were sent on general practice headed paper and were signed by the senior partner at the practice. In colorectal cancer screening using faecal occult blood testing, in Nottingham, compliance was improved by direct invitation from the general practitioner rather than from the department of community health [153] and a study of compliance with breast screening found that a letter from the general practitioner was as effective as a home visit from a nurse [154]. Appointment times

were allocated to those invited for *H pylori* screening in Market Harborough, a strategy which a study of compliance with breast screening found to be more effective than an open invitation to make an appointment [155]. In cervical cytology screening, giving appointment times has also been shown to be associated with better compliance [156].

Information leaflets were effective in encouraging acceptance of screening in some but not all groups in colorectal cancer screening [157]. In the feasibility study (Chapter 3) the information proposed for the leaflet about *H pylori* was effective in creating an expressed interest in screening. In order to achieve the best possible compliance, all subjects invited for screening were sent the information leaflet, so it was not possible to quantify the leaflet's usefulness in the present study. Using this intervention and a single mailed screening invitation, the acceptance rate for the screening test was 39%, a level of uptake very similar to that obtained (38%) when colorectal screening was offered to an older age group in the same population [158]. Further interventions in terms of publicity and increased encouragement to attend would become appropriate if health benefits of screening for the bacterium can be demonstrated in clinical trials.

Another potential limiting factor is failure to complete the course of medication correctly, although in our study this was not a problem. Compliance with medication is extremely difficult to measure [159,160], but it is considered that our use of a request to return tablets, combined with verbal questioning and medication diaries, provided a good assessment. Our 100% compliance rate is probably confirmed as reasonably accurate by the very good (95%) eradication rate achieved. As with uptake of

screening, and in accordance with the primary aims of the study, our intention was to achieve optimum compliance with medication. All subjects taking eradication therapy therefore received the information pack and it is acknowledged that, in the absence of randomisation, quantifying the effectiveness of the intervention used was again not possible. However, those attending for breath tests commented favourably on the pack's usefulness and it is likely that this intervention played a part in the good rates of compliance and eradication achieved. It could be argued that good compliance was achieved in this study because likely non-compliers had deselected themselves at previous stages, either by not attending for screening or by failing to opt for eradication therapy, but results were nevertheless encouraging.

The effectiveness of the therapy used will affect the success of treatment-based interventions to reduce the prevalence of infection. We found the triple therapy used in the present study to be very effective in the population studied, with eradication in 95% subjects who opted for treatment (both per protocol and intention to treat, as there were no non-compliers). No-one failed to complete the course of eradication therapy because of side effects. We had only 9 (5%) cases of failed eradication, which we can speculate to have been due to resistant bacteria. Selection of resistant strains as a result of failed eradication is a potential problem which should not be disregarded, although it is likely that most resistance is produced by use of antibiotics for conditions other than *H pylori* infection [132]. In the group who attended for screening in Market Harborough, 490 (31%) people indicated on their questionnaire that they had been prescribed antibiotics in the previous year. It is acknowledged that this figure is based on self-reporting, which is unlikely to be entirely accurate, but a high level of antibiotic

use in this population was nevertheless suggested.

Our estimated cost of £138 per subject in whom successful eradication of *H pylori* was achieved was based on results in our study population and it acknowledged that this figure is a crude estimate only which cannot be generalised to screening in all populations. The intention was to provide a general indication of costs involved and the estimate is probably conservative. The cost of setting up a database was not included, as the general practice involved held computerised records of registered patients, but this could be a potential additional cost of initiating a screening programme.

It is acknowledged that the follow-up exercise was not a controlled study and that the sample size was small. A measurable amount of anxiety generated by various stages of the screening process was however identified, with 27% people reporting significant worry. Serological testing for *H pylori* does not have perfect sensitivity and specificity and is therefore unlikely to provide accurate results in all cases; in considering the findings of the follow-up study, account must therefore be taken not just of overall psychological effects, but also of the fact that some of the worry experienced following positive tests and the relief felt by some of those whose tests were negative, may have been generated by an incorrect result. Also of considerable concern was the suggestion that the screening experience might have an adverse effect on future uptake of screening in a small number of cases. Our results suggested that this might be partly attributable to anxiety experienced, but we were unable to confirm this in the small sample studied. Enthusiasm for demonstrating health benefits of screening may lead to

underestimation of the importance of disadvantages; although a certain amount of anxiety may be necessary for obtaining good uptake of screening, it is considered that the follow-up exercise highlighted the need to consider negative as well as positive aspects of screening.

Chapter 5

Screening for *H pylori* in Belgrave: a comparative study in a multi-ethnic inner-city community

- i. Rationale and aims**
- ii. Methods**
- iii. Results**
- iv. Discussion**

i. Rationale and aims

The Market Harborough study looked at *H pylori* screening and eradication in a single defined community. Compliance with screening is likely to vary in different populations. In breast screening, for example, results for 1991-92 showed that although uptake across the UK was 71%, meeting the 70% target, in different large regions acceptance varied from 58% to 82% [161]. Within regions, uptake of screening is also likely to show considerable variation. In a study of women aged 50-64 years living in Manchester, breast screening was offered with or without an advance invitation for cervical screening. In this trial, overall uptake of breast screening in 10 single general practices and one group of practices varied from 33% to 72% [162]. The aims in the Belgrave study were to look at the effectiveness of a programme of *H pylori* screening and eradication in a population differing from that of Market Harborough. The population selected for this comparative study represents a multi-ethnic inner-city community. Comparative data for the two areas from which these study populations were derived are given in Table 5.1, using information from the 1991 census [163].

A high prevalence of both *H pylori* infection and peptic ulcer disease has been found in South Asians in India [164], but there may be particular problems of compliance with screening in ethnic minority communities. In the breast screening study cited above [162], there was a significant difference between uptake of 33% in Asian women and 56% in non-Asians. In a questionnaire survey involving Asian women living in Leicester, only 35% of 309 at risk (currently or previously married) Asian women

Table 5.1. Comparative data for Market Harborough and Belgrave, from the 1991 census [163]

	Market Harborough*	Belgrave**
Non-white population	0.8%	51.3%
Unemployed	5.1%	15.3%
Households in owner occupation	79.7%	56.1%
Overcrowded households	0.8%	6.2%
Households with no car	28.3%	49.8%
Households with no central heating	9.3%	24.3%
Rooms per household	5.7	4.9

* Data for Belgrave ward, Leicester city

** Combined data for the following wards from Harborough district: Market Harborough Bowden, Market Harborough North, Market Harborough South and Market Harborough West

claimed to have had a cervical smear in the previous 5 years [165]. A study from Australia found that women born in Asian and other non-English speaking countries were significantly less likely to undergo prenatal diagnostic testing for Down's syndrome [166] and significantly lower uptake of amniocentesis was also found in Asian women compared to those of European origin living in the UK [167].

The Belgrave study was designed to include a detailed investigation of reasons for non-compliance with screening in both Asian and non-Asian subjects living in a multi-ethnic inner-city community and also an assessment of the effectiveness of Asian language materials in increasing compliance. Possible long term follow-up for health benefits of screening was not included in the aims of this small study. The study design in this instance therefore excluded a control group of subjects not offered screening.

ii. Methods

Ethical approval was sought and obtained for a collaborative screening study involving a single general practice in the Belgrave area of Leicester. South Asians predominate in this area, with Gujarati being the most commonly spoken Asian language, but the practice was also known to have a number of patients of UK, other European and Afro-Caribbean origin. A research assistant, Mrs Hemlata Patel, fluent in Gujarati and Hindi languages was recruited to assist with the study under the author's supervision, in particular to conduct interviews and to translate written materials for use in the

study.

An age range of 21-55 was selected, as for the Market Harborough study. Since no computerised records were held at the general practice involved, a list of appropriate patients was obtained from the local health authority headquarters. Asian and non-Asian subjects were identified according to name, a method previously found to have a good accuracy [168]. Afro-Caribbeans are difficult to identify by name and are not strongly represented in the study population; it was therefore decided that the second group should consist of non-Asian rather than specifically European subjects. Each non-Asian household was assigned a number and 200 subjects were selected using a random number list generated by the Arcus Pro-Stat computer programme. Numbers were also allocated to Asian households and a second random number list was used to select a group of 200 subjects matched to the non-Asians for sex and age group.

Both groups were invited through their general practitioner to take part in a screening programme for infection with *H pylori*. The invitation letter was similar to that used in the Market Harborough study and was accompanied by the same information leaflet. A similar questionnaire was also enclosed, but for this study the questions about childhood living conditions were replaced by a request for details about ethnic origin and place of birth.

A record was kept of mail returned where the addressee had moved and of reply slips sent back by those who did not wish to accept the test. A list of those who had not attended was shown to the general practice manager, who indicated any patients

known to have moved from the address given by the health authority. The remaining non-attenders were identified for follow-up to assess reasons for non acceptance of the offer of screening. Semi-structured interviews were designed to be carried out either in person at the subject's home or by telephone and the research assistant with Asian language skills was trained to conduct these interviews. In order to avoid 'suggesting' reasons, interviewees were initially asked an open question, but a list of possible reasons was also available for use during the interview. Where the person offered the test was unavailable, an interview with a family member was accepted if it was considered that they could confidently give reasons on behalf of their relative, for example where the person invited had been on holiday at the time of screening. Those interviewed were assured that the purpose of the survey was to identify reasons for non-attendance and not to persuade the interviewee to accept the screening test.

For the second phase of the study, a further matched group of 200 Asians was selected using the original random number list. Screening invitations were sent out as before, but the information leaflet was sent in both English and Gujarati versions and a brief information slip in Gujarati explaining the contents of the letter was also included. Non-attenders in this group were not interviewed, but house to house enquiries were made to identify those who had changed address.

The methodology for the screening programme itself was very similar to that used in Market Harborough (Chapter 4). Variations from the Market Harborough design were as follows: screening sessions were held at the general practice itself; results were sent to Asian patients with an explanatory note in Gujarati and Hindi ; eradication therapy

information packs were made available in either English or Gujarati and the eradication therapy prescribed was ranitidine bismuth citrate (RBC) 400mg bd and clarithromycin 500 mg bd, concurrently for 14 days. It is acknowledged that the use of a different eradication regimen precluded direct comparison between eradication rates in Market Harborough and Belgrave. The choice of therapy for each study was dictated partly by the sponsorship available, but in justification for the choice in the Belgrave study, it was considered that the efficacy of the lansoprazole, clarithromycin and metronidazole regimen used in Market Harborough might be limited by the prevalence of metronidazole resistant strains of *H pylori*, which has been shown to be high in migrants to the UK. A study in London found metronidazole resistance in 90% of those born in Bangladesh, 37% of those born in the UK and 67% of those born elsewhere. The authors of the study speculated that this might be attributable to frequent use of nitroimidazoles before migration [169]. In addition to this consideration, simpler regimens should be welcomed provided that good efficacy is maintained. In a multicentre study, dual therapy using RBC was significantly more effective than omeprazole and clarithromycin for eradicating *H pylori* infection [170]. It was considered that the new RBC/clarithromycin regimen could usefully be evaluated in terms of compliance and efficacy in a multi-ethnic population. It was speculated that making the eradication regimen as simple as possible might have a positive influence on compliance; we therefore used clarithromycin 500 mg bd rather than 250 mg qds or 500 mg tds.

Where it was considered appropriate, the chi-squared test with Yates' correction for continuity, Fisher's exact test, or an independent sample t-test were used for statistical

analysis of results.

iii. Results

Uptake of screening:

Those randomly selected for the first phase comprised 116 men and 84 women in each group. The age range in each group was 21-55 (mean 38 years). Numbers who attended and were interviewed are included in the analysis shown in Table 5.2. Five subjects with European sounding first and last names were found to be of Asian origin (3 Goan, 2 exact origin not identified), either when they attended for screening or were interviewed. These five were excluded from the analysis and 42 (22%) of the remaining 195 attended for screening. Of the 200 Asians offered the screening test, none were identified to be non-Asian and 59 (30%) accepted the test. This difference in uptake was not significant ($\chi^2 = 2.88$, $P = 0.090$). In each group, two people telephoned to ask for an appointment after the screening sessions had been completed. Although they were offered a test during the second phase of screening, they were not included as attenders in the first part of the analysis where attendance rates were compared, since the option of a later appointment would not be available to those offered screening in the second phase.

Those non-attenders who had moved, as identified by returned mail, by the general practice manager or during house to house visits by the interviewer, comprised 81 non-Asians and 65 Asians. An attempt to determine whether the letter had been forwarded

Table 5.2. Numbers (percentages) of attenders and non-attenders at screening sessions for *H pylori* infection in Belgrave, with sub-categorisation of non-attenders.

	Non-Asians (n=195*)	Phase 1 Asians (n=200)	Phase 2 Asians (n=200)
Attended original screening sessions	42 (22)	59 (30)	51 (26)
Later appointment	2 (1)	2 (1)	n/a
Returned mail	30 (15)	12 (6)	18 (9)
Identified moved	51 (26)	53 (27)	50 (25)
Reply slip comment	8 (4)	3 (2)	n/a
Unable to interview	9 (5)	4 (2)	n/a
Interviewed	53 (27)	67 (34)	n/a
Non-attenders (phase 2)	n/a	n/a	81 (41)
Total	195*	200	200

*5 subjects excluded from sample

The screening invitation was sent in English to non-Asians and Asians in the first phase of the study. In the second phase, Asians also received information in Gujarati.

to those who had moved was not considered to be practical, but excluding those non-attenders who had definitely moved house, 42/114 (37%) non-Asians and 59/135 (44%) Asians attended the screening sessions. The difference was again not significant ($\chi^2 = 0.94, P = 0.332$). It was additionally noted that of those who attended, 10 Asians and 6 non-Asians were no longer at the address to which the letter had been sent. Including these subjects, we found that 162/395 (41%) invitations had been sent to an incorrect address.

Reasons for non-attendance:

Reply-slips giving reasons for non acceptance of the test were returned by 8 non-Asians and 3 Asians. Nine non-Asians and 4 Asians were unavailable for interview, but reasons for non-attendance were obtained from the remainder of non-attenders, either by personal interview (Asians 57, non-Asians 39) or telephone (Asians 10, non-Asians 14). Reasons for non-attendance were thus obtained, either by reply slip or interview, from 131/144 (91%) of those targeted. All those interviewed were able to give at least one reason for non attendance before being shown the list of possible reasons. Where more than one reason was given, interviewees were asked to nominate the main reason and an analysis of these primary reasons is shown in Table 5.3. In both Asians and non-Asians, other commitments appeared to be an the most important factor discouraging attendance. Other commitments (pressure of work, family commitments, inconvenient appointment times and holidays) together accounted for 59/131 (45%) of reasons given by those in the combined groups (Table 5.3). Significant differences between reasons given by the two groups were found in the case of two reasons only. Family commitments were cited by 10 Asians but by only one non-Asian ($\chi^2 = 5.23, p =$

Table 5.3. Primary reasons given by Asians and non-Asians for non-acceptance of an offer of serological screening for *H pylori*.

	Non-Asians (n=61)	Phase 1 Asians (n=70)
Too busy (work commitments)	10	18
Family commitments	1	10
Appointment time inconvenient	5	4
On holiday / away from home	10	1
No recall of receiving letter	12	7
Letter not read or not fully read/ understood	6	9
No symptoms	2	4
Not interested	4	5
Forgot appointment	5	6
Other illness / disability	2	1
Other	4	5
Total	61	70

0.022) and non-Asians were more likely to have been on holiday or away from home ($\chi^2 = 7.64$, $p = 0.006$). In both groups, a number of those interviewed admitted to incomplete reading or understanding of the letter, to having forgotten about the appointment, or to having no recall of receiving the letter. In the 'other' category in the Asian group were one who received the letter late after it was wrongly delivered; one who was worried about further tests; a couple who were both deterred by the husband's previous bad experience of hospitals and one lady who was pregnant and was advised by her midwife not to accept the test. Non-Asians who gave 'other' reasons comprised one who disliked blood tests; one who did not wish to be involved in research; one who did not like the plain language used in the questionnaire and one who said they would 'rather not know' their *H pylori* status.

In the Asian group, 21 of those interviewed who had given reasons relating to other commitments were asked whether they realised that they could have rearranged their appointment. Only 6 responded positively and similar results were obtained in the non-Asian group, where 1 person out of a possible 7 realised that the appointment given could be changed ($P = 0.639$, n.s.).

All those interviewed had access to an English reader to translate for them if they were unable to read English themselves. Asians who were interviewed were asked whether they would have taken more notice of the information sent if it had been in an Asian language. Thirteen people said they would have taken more notice of information in an Asian language (10 in Gujarati, 2 in Punjabi and 1 in Hindi), but of these only 5 (4 Gujarati, 1 Punjabi) felt that this would have made a difference to whether they

attended.

Although a further appointment was not suggested by the interviewer, 17 Asians and 11 non-Asians asked at the time of the interview whether they could now have the test. This request was accommodated where practical, but in the analysis only those who accepted the test in response to the mailed invitation were counted as attenders.

Use of Asian language materials:

In the second phase of the study, 116 men and 84 women aged 21-55 (mean 38 years) were randomly selected to be sent a screening invitation including Asian language materials. Of these, 51 (26%), attended the screening sessions and a further 68 were identified as having moved address. The difference in attendance rates between Asians in the first and second phases was not significant either including ($\chi^2 = 0.61$, $P = 0.433$) or excluding ($\chi^2 = 0.51$, $P = 0.474$) non-attenders who had moved.

Additional results from the screening programme:

For analysing the further stages of the study, the four people from the first phase of screening who requested a later appointment in response to the screening invitation letter were included as attenders. The overall acceptance rate for the screening test, combining the 3 groups, was 156/595 (26%, 95% CI 23% to 30%) of those to whom a screening invitation letter was sent. In this community, as in Market Harborough, the proportion of those invited who attended in response to the screening invitation letter was higher in women and older age groups. This observation applied to both Asians and non-Asians. In the two Asian groups 62/168 (37%) women and 50/232 (22%) men

attended ($\chi^2 = 10.64$, $P = 0.001$), and in non-Asians uptake was 19/113 (17%) in men compared with 25/82 (30%) in women ($\chi^2 = 4.33$, $P = 0.037$). The mean age of those who attended (40 years in the Asian group, 43 years in non-Asians) was higher than the mean age of those offered the test (38 years). The difference in age between attenders and non-attenders was significant both in Asians ($t = 2.41$, $P = 0.016$) and non-Asians ($t = 3.81$, $P = < 0.001$).

A breath test was offered to 4 people with borderline results from serology. One non-Asian who failed to accept was regarded as having equivocal *H pylori* status and there were 2 negative and one positive UBT results in the other 3 cases. The remaining 152 results (78 positive, 74 negative) were based on serology alone, giving an overall positive test rate of 79/155 (51%, 95% Confidence Interval (CI) 43% to 59%). *H pylori* prevalence was 59/112 (53%) in Asians and 20/43 (47%) in non-Asians. This difference was not significant ($\chi^2 = 0.26$, $P = 0.611$).

Of the 79 people with positive tests, 64 (81%, 95% CI 71% to 89%) accepted a prescription for eradication therapy. Fourteen of these (12 Asian, 2 non-Asian) also asked for a referral for endoscopy. Small duodenal ulcers were found in 2 patients and one patient had a gastric polyp, histology of which showed mild dysplasia. Endoscopy findings are summarised in Table 5.4.

Two people who returned a diary or reply slip to indicate that they had completed the course of medication failed to attend for a UBT to confirm successful eradication. In addition, one subject notified the research team that she had discontinued the

Table 5.4. Findings from upper gastrointestinal endoscopies undergone electively by 14 people who were seropositive for *H pylori* in a screening programme in Belgrave.

Findings	Number of cases
Normal appearance; histological gastritis	4
Gastritis only	3
Gastritis and small DU(s)	2
Gastritis and oesophagitis	1
Gastritis, oesophagitis and hiatus hernia	1
Gastritis, oesophagitis and bile reflux	1
Duodenal erosions, bile reflux and hiatus hernia	1
Gastritis, Barrett's oesophagitis and gastric polyp (mild dysplasia on histology)	1

eradication therapy after 2 days of severe stomach pains and diarrhoea; she declined a UBT but failed eradication was assumed in the analysis of results. A UBT was accepted by the remaining 61 subjects, one of whom had notified the research team that she had stopped taking the medication after 10 days because of nausea, swelling of the neck and ear-ache. Successful eradication was nevertheless confirmed by UBT in this case. One subject returned 8 (14%) tablets when attending for his breath test, having forgotten to take occasional doses. This man's UBT indicated failed eradication. One person had a UBT result of 4.3 ^{13}C excess, with a pre-urea Delta ^{13}C value of -28.7 (prior values obtained were in most cases between -24 and -27). He was offered and accepted a repeat test, which gave a negative result of 0.7 ^{13}C excess. The man concerned said that he had fasted overnight prior to both tests. Although there was an element of doubt attached to this subject's post eradication therapy *H pylori* status, it was considered that this should be regarded as negative, since the mean result from the two tests (2.5) was below 3.5. The remaining 60 breath tests indicated that *H pylori* infection had been eradicated in 56 people, with 4 remaining positive. Overall, this gave an intention to treat eradication rate of 57/62 (92%, 95% CI 82% to 97%) in those who elected to take eradication therapy. Excluding the 3 people who did not fully comply, the per protocol eradication rate was 95% (56/59).

Compliance with therapy, as estimated from diaries, tablet return and direct questioning, was indicated in 59/62 (95%, 95% CI 87% to 99%) cases. Side effects of the eradication therapy as reported at the time of breath testing or by telephone are summarised in Table 5.5. Including the woman who telephoned to report side effects but who did not have a UBT, 62 people were questioned about side effects. Of these,

Table 5.5. Side effects described by 40 of 65 people who took a course of eradication therapy (ranitidine bismuth citrate and clarithromycin) following a positive screening test for *H pylori* infection.

	No of subjects reporting side effect	Additional cases specifically reported as mild or slight
Taste disturbance	16	1
Loose bowels/diarrhoea	6	4
Nausea	6	2
Thirst/dry mouth or lips	5	-
Drowsiness/tiredness/weakness	3	1
Sleep disturbance	3	-
Loss of appetite	2	1
Bad breath	2	1
Dizziness	2	-
Constipation	2	-
Headaches	1	1
Stomach pains	1	-
Cold sweats	1	-
Neck swelling/earache	1	-
Itching	1	-
Acid indigestion	1	-
Wind	-	2
Urinary discomfort	-	1

24 (39%) reported no side effects, although 3 of these had noticed darkening of their stools. Nine people (15%) reported side effects which they specifically described as mild or slight only, with a further 29 (47%) having experienced more significant side effects. Taste disturbance, diarrhoea or loose bowels and nausea were the most commonly reported side effects and two people failed to complete the therapy because of side effects, as described above. One subject reported breathing problems, but after discussion with her general practitioner it was considered that these were unlikely to be associated with the medication.

Assuming successful eradication in the two people who notified us that they had completed the medication but did not attend for a UBT, *H pylori* was successfully eradicated after a single course of eradication therapy in 59/595 (10%, 95% CI 8% to 13%) people to whom a screening invitation was sent and who attended in response to the screening invitation letter. Assuming a 51% prevalence of infection, it was estimated that 303 of those to whom screening invitations were sent were positive for *H pylori* infection and that prevalence of infection had been reduced by 19% (59/303) as a result of the screening programme. Using the same model for possible routine practice used to estimate costs in Market Harborough, the cost of achieving successful eradication in one person in the Belgrave was estimated (Table 5.6) and found to be £117 (to the nearest pound).

A comparison of the main results in Market Harborough and Belgrave is summarised in Table 5.7. Two additional comparisons made but not included in the table were mail returned by the post office and numbers reporting side effects in each study. In Market

Table 5.6. Estimated cost of obtaining successful eradication of *H pylori* in one subject, based on a model for possible clinical practice combined with results obtained in a population screening study conducted in Belgrave.

	Basis for estimated cost	Estimated cost per person £	No of subjects	Total cost per item £
Mailed screening invitation	Clerical time plus 2nd class postage and stationery	0.50	595	297.50
Screening test using serology	One visit to practice nurse, plus kit, plus laboratory time	9.30	156	1450.80
Mailed results	Clerical time plus 2nd class postage	0.50	156	78.00
Consultation (subjects with positive tests wishing to take eradication therapy)	Five minute GP consultation	8.60	64	550.40
Cost of medication	Two weeks ranitidine bismuth citrate and clarithromycin (British National Formulary)	70.98	64	4542.72
Total cost				6919.42

Cost per subject achieving successful eradication of *H pylori* (n = 59, including 2 cases not confirmed by UBT) = £6919.42 / 59 = £117.28

Table 5.7 Comparison of results obtained in two community programmes of *H pylori* screening and eradication in Market Harborough and Belgrave

	Market Harborough Proportion (%)	Belgrave Proportion (%)	P-value*	Comments
Numbers accepting screening/invitations mailed	1566/4015 (39)	156/595 (26)	<0.001	Mailing lists from different sources
Positive tests/all tests (excluding equivocal results)	235/1558 (15)	79/155 (51)	<0.001	Equivocal results excluded
Numbers accepting therapy/numbers with positive tests	186/234 (79)	64/79 (81)	N.S.	One M. Harborough patient excluded for clinical reasons
Numbers complying with therapy/numbers accepting therapy	179/179 (100)	59/62 (95)	0.016	Excluding those in whom compliance was not assessed. Different regimens used
Numbers with confirmed eradication/ numbers in whom eradication was assessed	170/179 (95)	57/62 (92)	N.S.	Different eradication regimens
Numbers with successful eradication/ number of screening invitations mailed	177/4015 (4)	59/595 (10)	<0.001	Assuming eradication in those who did not have a UBT
Number with successful eradication/ number estimated to be positive in target population**	177/602 (29)	59/303 (19)	0.002	Assuming eradication in those who did not have a UBT

* from Yates' corrected χ^2 or Fisher's Exact Test

** based on the assumption that the prevalence of infection in all those to whom invitations were mailed was the same as in those tested.

Harborough, 363 (4.5%) of the 8030 intervention and control group letters were returned, compared to 60/595 (10.1%) returned mail in the Belgrave study ($\chi^2 = 35.58, P = <0.001$). Excluding those specifically described as mild, side effects were reported by 56/179 (31%) of those who took triple therapy in Market Harborough and by 30/65 (46%) of those who took the RBC/clarithromycin dual therapy in Belgrave ($\chi^2 = 3.99, P = 0.046$).

iv. Discussion

The Belgrave study confirmed findings from Market Harborough. In both populations, using an educational intervention, those who elected to take eradication therapy complied well, but uptake of screening and acceptance of therapy were limited.

The study highlighted the inadequacy of local health authority records, particularly in areas where the population is known to be mobile. As has been previously noted [171,172], Family Practitioner Committee/ Family Health Services Authority records may be notably out of date and in Belgrave the low proportion of those sent a screening invitation who actually attended was strongly influenced by the fact that so many people were no longer at the address to which the letter was sent. In two cases, the interviewer went to addresses where the house had in fact been demolished. The extent to which records are outdated would have serious economic implications in actual screening programmes, with much wastage of administrative resources. A study which looked at reasons for low uptake of breast screening in an inner-city area found

that 35% women did not receive invitations because of inaccuracies in addresses, with the authors suggesting that *“the single largest contribution to increasing response rates may clearly be made by more accurate data”* [173].

The likelihood that the Belgrave mailing list was less accurate must be borne in mind when comparing uptake of screening with that obtained in Market Harborough, where the population is less mobile and where a mailing list was obtained from the general practice. A study comparing Family Practitioner Committee and general practice records found 30.6% disagreement for patients' addresses. General practice records were more likely to be correct: including a small number incorrect on both lists, 29.3% addresses were incorrect on Family Practitioner Committee lists, compared with only 2.3% on general practice records [171]. Door to door enquiries to establish numbers of people who had moved were considered impractical in the larger Market Harborough study, so no accurate figures were available for numbers of incorrectly addressed invitations. We were therefore unable to measure the extent to which lower uptake in Belgrave was the result of greater inaccuracy of the mailing list used. The significantly higher proportion of mail returned from Belgrave addresses would however suggest a much lower rate of mail received by those to whom it was sent in this study.

Difficulty with language was not the most important factor affecting compliance with screening in this study. Asian communities tend to be close-knit and an English reader is generally available to assist with translating English mail. Where non-English speakers attended for screening there was usually a family member to interpret. These observations are consistent with the findings of a survey commissioned by the Health

Education Authority [174]. This showed that of those of Indian origin living in England, 86% are able to speak and 76% able to read English. Men were identified as being more likely than women to be able to read English, particularly young men in the 16-29 year old age group, of whom 96% were English readers. Although only 34% of older women aged 50-74 could read English, the Health Education Authority findings would suggest that in a high proportion of households there would be at least one person able to read the language.

Although the difference was not significant, it was noted that failure to fully read or understand the letter was more frequently reported by Asians than non-Asians (Table 5.3). However, less than half of those who said they would have taken more notice of information in an Asian language also said that it would actually have made a difference to whether they attended. This was borne out by the failure to increase uptake in the second phase of the study when Asian language materials were used. The ineffectiveness of written Asian language materials in increasing compliance has also been shown in cervical smear testing [175] and diabetic education [176]. The Health Education Authority survey [174] showed that 50% of those of Indian origin living in England are able to speak Gujarati. Rather less, 34%, are able to read Gujarati, with young people particularly unlikely to be able to read the language. It seems probable that there would be relatively few households or family groups with a reader of Gujarati but no-one able to read English.

The high proportion of Asians who cited family commitments as their main reason for non-attendance may reflect the importance of family life in this ethnic group. In both

the Asian and non-Asian groups, however, other commitments connected either with family or work apparently took priority over interest in health screening. People appeared insufficiently interested to have read the information fully themselves or to have asked for help, as was apparent from the small number who realised that the appointment could be changed.

Lack of symptoms was rarely given as the main reason for non-attendance, which may reflect the high prevalence of dyspeptic symptoms in the general population [177]. Forgetting appointments has been previously noted as an important reason for non attendance at outpatient clinics [178] and a number of those interviewed in both groups had simply forgotten about the screening test. Personal visits have previously been shown to increase compliance with screening in ethnic minority communities [175], but we found that this applied also in a similar population of mainly UK origin, with 6 people from the non-Asian group admitting to not having read or fully understood the information and 11 from this group expressing an interest in being screened after speaking to the interviewer. For economic reasons personal visits may however be impractical without specific targeting.

Results obtained in Belgrave suggested that it should not be assumed that poor compliance with screening in ethnic minority populations is related mainly to language difficulties. Although there were some differences between primary reasons for non-compliance given by Asians and non-Asians, these reasons were dominated in both groups by an unwillingness to prioritise health screening above other demands on their time. Maximum flexibility in appointment times offered might help to overcome some

of these difficulties, but it appeared that a more important issue is the continuing need for educational interventions to promote the value of preventive medicine.

Although 100% compliance with medication was not suggested in Belgrave as it was in Market Harborough, 95% compliance was nevertheless considered to be good and was achieved in spite of more frequent reporting of side effects. We found the RBC/clarithromycin dual therapy to be an effective regimen in the population studied, with no significant difference between eradication rates achieved in the 2 studies. The cost of the eradication regimen used in Belgrave was, however, high at over £70 per person treated, compared with approximately £29 for the triple therapy used in Market Harborough.

Higher prevalence of infection in Belgrave compared to Market Harborough led to a significantly higher proportion of those invited for screening achieving successful eradication of *H pylori*, but lower uptake of screening in Belgrave than in Market Harborough resulted in a significantly lower estimated reduction in the prevalence of infection as a result of the screening programme (Table 5.7).

The cost of achieving eradication of *H pylori* in one person was lower in the Belgrave study at £117 compared with £138 in Market Harborough (Tables 5.6 and 4.4), in spite of the use of a much more costly eradication regimen. If the cheaper therapy had been used with equal efficacy, the cost per person in Belgrave would have been considerably less at approximately £72. These findings confirm that greater cost-benefit would be achieved in populations with a high prevalence of *H pylori* infection,

provided that good compliance with medication and consequent good eradication rates are obtained.

Chapter 6

Dyspepsia and infection with *H pylori* in the community

- i. Introduction**
- ii. Methods**
- iii. Results**
- iv. Discussion**

i. Introduction

Arguments in favour of population screening for *H pylori* are likely to centre around the association between the bacterium and gastric cancer. Further benefits could be a reduction in mortality from bleeding peptic ulcers and from heart disease if the link can be proven. In addition, however, eliminating *H pylori* in the community could lead to a reduction in symptoms of dyspepsia. Results from a postal survey of a general population sample in Hampshire, in which a 77% response rate was obtained, found a 38% six month prevalence of dyspepsia, with one in 4 people with these symptoms having consulted their general practitioner in this period [177]. Similar results have been obtained in other centres, suggesting a prevalence of dyspepsia of 41% in England and Scotland [179].

Evidence concerning the benefit of eradicating *H pylori* in dyspeptic patients without proven peptic ulcer disease (PUD) is currently inconclusive. Positive results have been obtained in some studies, for example where symptom improvement was found to be associated with clearance of *H pylori* infection in a double blind randomised trial testing the benefit of treating non-ulcer dyspepsia (NUD) patients with colloidal bismuth subcitrate [180]. By contrast, in a trial in which infected and uninfected NUD patients were treated with eradication therapy, long term follow-up (at mean 40 months) gave similar results in terms of symptoms in both infected and control (uninfected) groups [181]. Papers reviewing other work [72,73,182-186] have emphasised the fact that in many trials methodology has been flawed. These reviews have also underlined the conflict between results obtained in different studies, although

the authors of one paper concluded that combined results suggested positive benefits of eradicating *H pylori* in patients with non-ulcer dyspepsia [184]. The aims of the present analyses were to look at the prevalence of dyspepsia in the main (Market Harborough) study community and to determine whether there was any correlation between infection with *H pylori* and overall symptoms of dyspepsia in this population sample. An additional aim was to determine whether those attending for screening were more likely to suffer from dyspepsia than those who did not accept the test. Large-scale follow-up was not within the scope of study for the present thesis, but changes relating to dyspepsia were considered in one year follow-up of two samples.

ii. Methods

The dyspepsia questions:

In order to avoid deterring people from taking part in the study, relative brevity and simplicity were considered to be important in designing the questionnaire (Appendix C). The self-completion dyspepsia survey incorporated into our questionnaire was chosen on the grounds that it was concise, simply worded and had been previously validated by its authors for use in identifying the prevalence of dyspepsia in a general population sample [187]. Questions were asked about ‘pain and discomfort’ and ‘excessive wind or fullness’ in the upper abdomen. Also included were questions about heartburn, acid regurgitation, nausea, vomiting and ‘difficulty swallowing (food sticking in the throat)’. Where symptoms were reported, there were additional

questions about frequency (6 or more occasions in the previous year) and medical consultation.

In order to limit the length of the overall questionnaire, the questions on dyspepsia were restricted to those included in the questionnaire previously validated by its authors as a tool for assessing community prevalence of dyspepsia. Classification of symptoms by severity or exact frequency was therefore not invited. Because of some doubts about the validity of symptoms of nausea and vomiting as indicators of dyspepsia in the absence of other symptoms, an additional question was included on our full questionnaire, asking subjects who reported nausea and vomiting for their opinion on the cause of these particular symptoms. Reasons given in answer to this question included pregnancy, vertigo, migraine, 'tummy bugs' and specific instances of excess alcohol intake. In view of these answers, it was decided that subjects reporting nausea and/or vomiting in the absence of other symptoms of frequent dyspepsia would not be included in the category of sufferers from frequent dyspepsia. Whilst acknowledging that the validated version of the questionnaire had included the questions on nausea and vomiting, for the purpose of the current analysis frequent dyspepsia was therefore defined as any symptoms, excluding nausea and vomiting, reported as having occurred on 6 or more occasions in the past year. Details of smoking history, alcohol consumption and days lost from work because of indigestion were also requested.

Follow-up of non compliers:

The full questionnaire also included a single question designed by the author to give a

self-assessment of the effect of indigestion on quality of life (see Appendix C). Six statements about dyspepsia ranged in severity from 'I don't suffer from indigestion at all' to 'Indigestion rules my life and makes it a misery'. Those completing the questionnaire were asked to tick the statement considered most appropriate. As previously stated, restricting the length of the questionnaire was considered to be important; a single question was therefore selected rather than a more detailed quality of life survey, but the lack of previous validation for the question used is acknowledged. In order to gauge whether attenders were more likely to suffer from dyspepsia than non-attenders, 100 people who had returned a reply slip indicating that they did not wish to accept the screening test were sent a very short questionnaire comprising the quality of life question only. This strategy of a very brief reply slip was adopted in order to encourage a good return rate and for the same reason subjects were invited to return their reply slips anonymously in the reply-paid envelope provided.

To determine whether people suffering from dyspepsia were over-represented in those who completed control group questionnaires, 100 people in the control group who had not returned their questionnaires were also invited to complete and return an identically worded reply slip. Different coloured paper was used in order to distinguish between anonymous replies received from the 2 groups. In order to validate the use of the quality of life question to identify differences in prevalence of dyspepsia between compliers and non-compliers, correlation was sought between those who self-reported symptoms of frequent dyspepsia and those who reported that their quality of life was affected by indigestion, that is those who ticked boxes 3,4,5 or 6 in answering the

quality of life question.

One-year follow-up of subjects who attended for screening:

After one year, a follow-up survey was sent to 50 people who had tested negative for *H pylori* and 50 people who had been treated with eradication therapy, as described in Chapter 4. In addition to the previously described questions concerning anxiety, this questionnaire included some questions relating to dyspepsia. An open question asking about any symptom changes was followed by the dyspepsia and quality of life questions included on the original study questionnaire (see Appendix C). Results from the original and follow-up questionnaires were compared in those subjects who returned their follow-up survey. Three questionnaires returned by people in whom treatment with eradication therapy had been unsuccessful and one questionnaire returned anonymously by a subject who had tested negative, were excluded from the analysis of results relating to dyspepsia.

Analysis of results:

The chi-squared test with Yates' correction for continuity was used to determine whether there was any significant correlation between answers to the dyspepsia and quality of life questions and between infection with *H pylori* and the following: frequent dyspepsia, frequent upper abdominal pain and frequent reflux-like symptoms. To investigate the effect of possible confounding factors, the chi-squared test, unpaired *t*-test and logistic regression were used. McNemar's test was used to compare results obtained after one year with those derived from the original questionnaires.

iii. Results

Prevalence of dyspepsia:

Frequent dyspepsia according to our interpretation of questionnaire replies was reported in 604 (39%) of the 1557 questionnaires returned by those attending for screening with the questions about dyspepsia fully completed. Of those who completed questionnaires, 175 (11%) reported that they had consulted a doctor about symptoms of dyspepsia during the preceding year. Twenty-eight people between them reported 207.5 days lost from work because of indigestion in the previous year (0.13 days per person per year in those who completed a questionnaire). There were 1528 intervention group questionnaires on which the dyspepsia questions and the quality of life questions had been fully completed. Seventy-seven (13%) of 594 sufferers from frequent dyspepsia reported quality of life to be affected, whereas quality of life was affected in only 27/934 (3%) of those who did not report frequent dyspepsia. This difference was highly significant ($\chi^2 = 56.49$, $P = <0.001$); it was therefore considered that using the quality of life question to determine whether non compliers were less likely to suffer from dyspepsia than compliers was valid.

Non-attenders in the intervention group returned a total of 81/100 (81%) replies to the follow-up mailing. Whereas 297/1528 (19%) of attenders reported that quality of life was affected by indigestion, the same was reported by only 2/81 (2%) of those who had notified that they did not wish to attend ($\chi^2 = 13.54$, $P = <0.001$). This suggested that those with less dyspeptic symptoms were more likely to decide not to attend for screening and also that the 39% prevalence of dyspepsia reported by attenders might

be an overestimate for the study population as a whole.

Subjects in the control group returned 1475 questionnaires and the dyspepsia questions had been fully completed on 1466 of these (37% of the total 4015 sent out). Frequent symptoms of dyspepsia were reported in 562 (38%) cases. Of the 100 brief reply slips sent to subjects in the control group who failed to return the original questionnaire, 39 (39%) were returned. Five (15%) of these responders reported their quality of life to be affected by indigestion, compared to 256/1449 (18%) of those who returned the original questionnaire with the quality of life question correctly completed. This difference was not significant ($\chi^2 = 0.33$, $P = 0.567$, n.s.) and although it was based on a small number of returned follow-up reply slips, it was considered that there was some indication that 38% prevalence of dyspepsia in the study population might not be an overestimate.

Correlation between dyspepsia and infection with H pylori:

Figure 6.1 illustrates the process by which the final sample for determining possible correlation between dyspepsia and infection with *H pylori* was derived from the study population. Excluding subjects with equivocal test results, there were 1524 eligible cases where answers to the questions about dyspepsia, smoking and alcohol consumption had been fully completed. This group comprised 684 men and 840 women, age range 21-55 years (mean 40 years) at the start of the study. Analysis of results showed no correlation between infection with *H pylori* and frequent symptoms of dyspepsia, upper abdominal pain or reflux, as shown in Table 6.1.

Figure 6.1. Flow chart showing how the sample of 1524 cases for analysis of results relating to dyspepsia and *H pylori* was derived from the study population in Market Harborough.

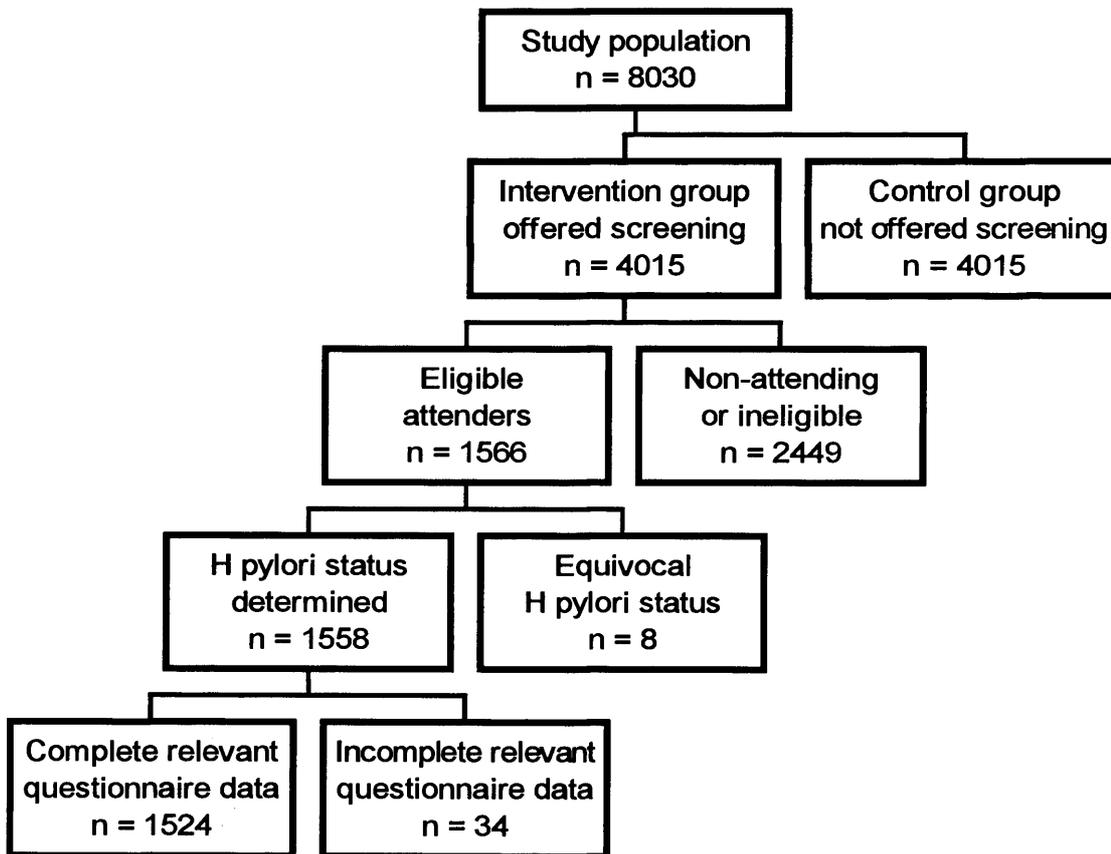


Table 6.1. Table showing lack of correlation between frequent dyspeptic symptoms and infection with *H pylori* in a general population sample from Market Harborough

Symptoms	Number (%) reporting symptoms		χ^2	P - value
	<i>H pylori</i> +ve (n = 228)	<i>H pylori</i> -ve (n = 1296)		
Frequent dyspepsia	90 (40)	502 (39)	0.02	0.891
Frequent upper abdominal pain	52 (23)	276 (21)	0.18	0.671
Frequent reflux-like symptoms	52 (24)	324 (25)	0.04	0.842

In the sample analysed, the average age of those reporting frequent dyspepsia was 39.29 years (\pm 8.93 years), whilst the mean age of those who did not report these symptoms was 40.31 years (\pm 9.23 years), suggesting a significant inverse association between age and frequent dyspepsia in this group ($t = 2.13$, $P = 0.034$). Frequent dyspepsia was reported by 307/684 (45%) men and 285/840 (34%) women, a highly significant difference ($\chi^2 = 18.59$, $P = <0.001$). Although more current smokers (139/319, 44%) than non-smokers (453/1205, 38%) reported frequent dyspepsia, the difference just failed to reach significance ($\chi^2 = 3.55$, $P = 0.060$). Of the 653 subjects who recorded an average weekly alcohol intake of 11 units (88g) or more, 281 (43%) reported frequent dyspepsia, compared to 311/871 (36%) who drank an average of 10 units (80g) or less, a significant difference ($\chi^2 = 8.13$, $P = 0.004$). In a logistic regression model, adjustments for age (in years), male gender, status as a current smoker and status as a higher consumer of alcohol did not reverse the lack of association between symptoms of dyspepsia and infection with *H pylori* ($P = 0.626$, odds ratio (OR) = 1.08). In this multivariate analysis, the only factors found to be independently associated with dyspepsia in our population sample were age (inverse association, $P = 0.028$, OR = 0.99 per year) and male gender ($P = < 0.001$, OR = 1.51).

Follow-up after one year:

In 38 people who had successfully eradicated *H pylori* and who returned the follow-up survey, frequent dyspepsia was reported in 10 cases on both the original and follow-up questionnaire and in 11 cases on neither (Table 6.2). There were eleven cases where frequent dyspepsia was reported on the original questionnaire but not at follow-up,

Table 6.2. One-year follow up: frequent dyspepsia and quality of life affected by dyspepsia, as reported by subjects who had tested positive for *H pylori* and subsequently eradicated the infection and by subjects who had tested negative.

	<i>H pylori</i> eradicated n = 38		<i>H pylori</i> negative n = 36	
	Original questionnaire no (%)	Follow-up questionnaire no (%)	Original questionnaire no (%)	Follow-up questionnaire no (%)
Frequent dyspepsia	21 (55)	16 (42)	14 (39)	14 (39)
Quality of life affected by dyspepsia	8 (21)*	1 (3)*	6 (17)	8 (22)

* Significant change ($P = 0.016$)

Follow-up questionnaires were sent one year after completion of eradication therapy in those who tested positive and 13 months after testing in the *H pylori* negative group

with converse findings in 6 cases. Overall, prevalence of dyspepsia in this sample had decreased from 55% (21/38) to 42% (16/38), but the difference was not significant ($P = 0.332$). In 36 people with negative tests who returned their follow-up survey, there were 10 cases where frequent dyspepsia was reported on both questionnaires and 18 cases where it was reported on neither. Four people had changed from reporting to not reporting frequent dyspepsia, with the converse indicated in an equal number of cases. In this group, overall prevalence of frequent dyspepsia therefore remained unchanged at 39% (14/36).

In those who had eradicated *H pylori*, quality of life affected by dyspepsia (option 3,4,5 or 6 ticked) was indicated in one case on both questionnaires and in 30 cases on neither. In the remaining 7 cases, quality of life had changed from being affected to unaffected, with no cases of change in the other direction. The change from 21% to 3% people who considered their quality of life to be affected by dyspepsia was found to be significant ($P = 0.016$). In the 36 people who had tested negative, quality of life affected by dyspepsia was indicated on both questionnaires in 3 cases and on neither questionnaire in 25 cases. In 3 cases there was a change from quality of life being affected to unaffected, with a change from unaffected to affected in 5 cases. The increase from 17% to 22% affected was not significant ($P = 0.727$).

iv. Discussion

In this study, the difficulty of obtaining an accurate estimate of the community

prevalence of dyspepsia was underlined. In the absence of a 100% response rate, results based on questionnaire replies may not be representative of the total population under consideration. Even where non-responders are followed up, there are likely to be non-responders at this second stage, particularly where those receiving a follow-up survey are unselected, as in the case of our control group. When those for follow-up are selected, a better response may be obtained, but those questioned may be unrepresentative of all non-responders. Those in our intervention group to whom follow-up questionnaires were sent had made a conscious decision not to attend for screening as suggested by the fact that they had returned a reply slip in response to the screening invitation. Those not suffering from dyspepsia may have been over-represented in this group, as other non-attenders may not have made a conscious decision to reject screening and may not even have read the invitation.

Whilst acknowledging these limitations, it is considered that there was an indication from follow-up of non-attenders that the prevalence of dyspepsia indicated by questionnaire replies from those attending for screening was overstated. Because of these limitations, however, it was felt that any attempt to assess the extent of the overestimate would be unreliable. These results suggest, however, that those with less symptoms of dyspepsia might need additional encouragement to attend for *H pylori* screening.

Dyspepsia is not a discrete disease entity and the term encompasses a wide range and combination of symptoms. The problem of definition will be a limiting factor in any study involving the identification of people with dyspepsia and this limitation is

acknowledged in the present analyses. An international working party [188] included in its broad definition of dyspepsia all “*symptoms referable to the proximal alimentary tract*”. The difficulty of subdividing such symptoms of dyspepsia has been emphasised in a paper by Talley *et al* [189], in which considerable overlap between subgroups of dyspeptic symptoms was demonstrated.

Research into the association between *H pylori* and NUD has produced conflicting results [72,73,182-186] and the difficulty of practising evidence based medicine where current research is inconclusive has been emphasised by the results of a postal survey of gastroenterologists [190]. This study by Milne *et al* identified considerable confusion between opinion and practice in the whole area of *H pylori* eradication, and in the context of the present study it was particularly noted that whereas 75% of Milne’s responders did not regard *H pylori* as a cause of NUD, 69% reported that they used eradication therapy to treat patients with these symptoms. Placebo controlled trials are needed to investigate the benefit of *H pylori* eradication in patients with NUD, although such studies may be limited by the difficulty of dividing dyspepsia into the two categories of PUD and NUD. In particular, given the episodic nature of PUD, there is the problem of whether those without active ulceration at the time of investigation can truly be categorised as sufferers from NUD. Subjects taking part in the screening programme had not generally undergone investigation for PUD and the current study therefore looked at overall symptoms of dyspepsia, comprising NUD and possible cases of PUD. In order to obtain a representative population sample, subjects were not excluded on the basis of previous investigations for dyspepsia, except where eradication therapy had already been taken. The phrase ‘overall symptoms of

dyspepsia' was therefore considered to be more appropriate than 'uninvestigated dyspepsia'.

The inverse association between age and symptoms of dyspepsia and the correlation between male gender and dyspepsia found in the Market Harborough sample are not necessarily representative of the population from which the sample was drawn, as these findings may be the result of younger people and men being less likely to attend for the screening test offered in the absence of symptoms of dyspepsia. In those who attended for screening, no correlation was found between overall symptoms of dyspepsia and infection with *H pylori*. It may be that symptoms associated with acid reflux should be regarded as separate from dyspepsia and the inclusion of excessive wind or fullness and food sticking in the throat in the symptom questionnaire could also be seen as controversial. However, the exclusion of any of these symptoms would not alter overall findings in the Market Harborough study population; when the analysis was restricted to those subjects reporting upper abdominal pain, correlation between dyspepsia and infection was still lacking (Table 6.1). It is acknowledged that those reporting upper abdominal pain could have included some sufferers from Irritable Bowel Syndrome, a condition which has however been shown to commonly overlap with dyspepsia [189].

Results from those who attended for screening in Market Harborough suggest a lack of strong association between infection with *H pylori* and dyspeptic symptoms in the majority of sufferers from NUD. Although one or more subgroups of sufferers from dyspepsia without active ulceration may benefit from eradication of *H pylori*, subjects

in this category may be difficult to identify. *H pylori*-positive males, especially those who smoke heavily and/or have a family history of peptic ulcer disease have however been identified as being at risk of having underlying PUD [191]. It may be that patients with these risk factors would benefit symptomatically from empirical treatment for eradication of *H pylori* in the absence of current peptic ulceration.

An increase in symptoms of acid reflux following eradication of *H pylori* infection in sufferers from duodenal ulcer has been previously reported and possibly explained by the loss of acid-neutralising substances in the oesophagus following cure of *H pylori* infection in this group [134,135]. A potential cause for concern has been raised by this observation, with widespread eradication of the bacterium possibly leading to an overall increase in symptoms of reflux in the community. In the current study, however, no correlation between frequent symptoms of reflux and infection with *H pylori* was found. An exceptional subgroup can again not be excluded, but our findings suggest that *H pylori* does not provide an important protective value in preventing acid reflux in most subjects without duodenal ulceration.

The limitations of the follow-up exercise relating to dyspepsia are acknowledged. Placebo controlled trials with primary aims relating to dyspepsia will provide the most convincing answers concerning reduction in symptoms. In our studies, outcome measures relating to dyspepsia were secondary to measurement of the effectiveness of the screening process. For logistic reasons relating to the timescale of the study, the samples followed up in Market Harborough were fairly small and questions relating to dyspepsia and quality of life had not previously been validated for detecting change.

Nevertheless, it was noted with interest that although we found no overall correlation between *H pylori* infection and dyspepsia in the population screened, in those who had successfully eradicated *H pylori*, a statistically significant improvement in perceived quality of life relating to dyspepsia was suggested by follow-up at one year. Perception of increased well-being may in itself be considered an important factor in the health of the individual, but there was also some indication of symptom improvement in those successfully treated with eradication therapy. It is possible that failure to reach statistical significance for this finding was due to the small size of the sample followed up at one year and that a subgroup of people with dyspepsia may have benefited from eradication of *H pylori*. Failure to find any correlation between *H pylori* infection and dyspepsia in those screened suggested that follow-up relating to dyspepsia might not be useful in the Market Harborough study population. It was considered, however, that results from the small follow-up survey left open the possibility that further investigation might be of value in the future.

Chapter 7

Infection with *H pylori*: observations on risk factors and transmission

- i. Introduction**
- ii. Methods**
- iii. Results**
- iv. Discussion**

i. Introduction

Some may consider that effective public health interventions to reduce the incidence of infection with *H pylori* should be favoured over the introduction of general population screening. Such interventions are however dependent on a good understanding of the sources and routes of transmission of *H pylori* and conclusive evidence in these areas remains elusive. Identification of risk factors can lead to a better understanding of acquisition and transmission of infection and would also be important if selective screening of high risk groups were to be considered.

Evidence has been presented which shows that infection with *H pylori* occurs mainly in early childhood. The annual incidence of infection was calculated to be only 0.3% in a group of Finnish children followed up for seroconversion between ages 3 to 12 years, suggesting that infection is generally acquired before 3 years of age in this population [192]. Children under 5 years of age were suggested to be most at risk of infection and reinfection in a follow-up study of Irish children with confirmed eradication of *H pylori*, in whom reinfection was common (59.25% per child per year) before age 5, but rare in those over this age [193]. However, higher than average rates of infection in some occupational groups [57] suggest that infection may occur in some adults. Gastroenterologists, for example, have been shown to be significantly more likely to be infected than age-matched controls, suggesting transmission from patients to doctors performing endoscopy [58,59]. In general, however, new infection is thought to occur infrequently in adults in developed countries, with studies suggesting annual seroconversion rates of only 0.5% [194] and 0.3% [195] per person.

The association between *H pylori* infection and factors such as social class and living conditions in childhood is well documented [37,38,40-43], confirming childhood as the most likely time for infection to occur. Lower prevalence in younger age groups is probably due to improvements in living conditions; a birth cohort study from Japan, for example, showed that infection was most prevalent in those born in the 1940s and 1950s, a time of post-war deprivation [196].

The method by which *H pylori* infection is acquired remains unclear. Transfer of bacteria from stomach to stomach has been shown to occur via inadequately disinfected endoscopy equipment [197], but this is clearly not the normal route. Three vehicles of transfer of the organism from its reservoir in the human stomach of an infected subject to the stomach of a previously uninfected person have been suggested: faeces, saliva and vomitus [63,65,198].

Evidence that transmission occurs mainly in early childhood concurs with the suggested faecal-oral pathway, but arguments for this mode of transfer are far from conclusive. Although polymerase chain reaction (PCR) has been used to show *H pylori* DNA in faeces [199], the viability of these bacteria has not been proven and culture of *H pylori* from stools, though reported [200], has proved difficult. Hepatitis A is transmitted by the faecal-oral route and if the same route characterises the spread of *H pylori* then similarities in patterns of prevalence would be expected. Evidence of this type is unclear; although similar sero-prevalence curves have been found in Thailand [201] and South Africa [46], results from the UK were not supportive [202].

The oral cavity as a possible reservoir of *H pylori* has been suggested, but attempts to demonstrate the presence of *H pylori* in saliva and dental plaque have yielded inconsistent results in much the same way as attempts to isolate the bacteria in faeces. In one study, the bacteria were found in dental plaque from only one of 29 patients with positive stomach biopsies, with negative results in all saliva samples [203], whilst another group failed to isolate *H pylori* from any samples of saliva or plaque [204]. Use of chopsticks as a risk factor for infection has been used to argue the case for oral-oral transmission [205] and contrasting results in two animal studies have been used in support of the dominance of this route over the faecal-oral pathway. A study in beagles showed transmission of *H felis* from infected to uninfected puppies and it was noted that these animals had a tendency to lick one another extensively. By contrast, rats and mice, who are coprophagic but have little oral-oral contact, did not transmit the infection [206]. Other evidence has however failed to support the predominance of the oral-oral route, for example the lack of increased risk of infection found in dentists [207,208] and those with higher numbers of sexual partners [209].

It has been suggested that transmission may occur more directly from stomach to mouth, via vomitus, without the need for an oral reservoir [64,65]. The animal studies mentioned above have also been used in support of the gastro-oral route [64], since rats and mice do not vomit. In suggesting this route of transmission, it has also been argued that vomiting caused by acute *H pylori* infection may be the bacterium's mechanism for promoting survival, by providing a vehicle for transmission to new hosts [64,65]. For this route to be feasible, *H pylori* would need to be able to survive in vomitus, but survival of the bacteria in an acidic environment without the presence

of urea is limited [36]. To counter this argument, it has been suggested that the period of hypochlorhydria which may accompany acute infection [210] may aid survival of the bacterium outside the stomach by creating an environment in which vomitus lacking in acid is produced [64,65].

Through whichever vehicle it occurs, it appears likely that transmission of *H pylori* is most commonly from person-to-person, as suggested by intrafamilial clustering shown in some studies [60-62,134,211-213]. A common external source of infection cannot however be ruled out. *H pylori* has been identified in drinking water using PCR amplification [214] and transmission through contamination of water supply has also been suggested by epidemiological evidence linking the municipal water supply to infection in Peru [48]. Transmission via food such as uncooked vegetables treated with sewage has been proposed [215] and the possibility of zoonotic transmission has been raised by the finding of *Helicobacter* infection in domestic cats [216]. From the evidence to date, it seems probable that the transmission of *H pylori* may occur through multiple pathways, both from person-to-person and via external sources, with the dominant route perhaps varying between different populations.

In the present analyses, data from the Market Harborough study concerning possible risk factors for infection were considered in detail, with the aim of confirming or refuting findings from previous studies. Ethnic origin and place of birth as possible risk factors were considered in looking at results from the study in Belgrave.

ii. Methods

To investigate possible correlations between infection and potential risk factors in the Market Harborough study population, results of screening tests were analysed in conjunction with information obtained from the questionnaires completed by those who attended for screening (Appendix C). As with details of dyspepsia status, information sought in relation to risk factors was limited to the minimum considered to be useful, in order to avoid deterring people from attending and thus compromising the primary aims of the study. Information requested on the questionnaire included age, current occupation, occupation of spouse or partner, occupation of father in childhood and number of siblings. Subjects were asked to give the number of rooms, excluding bathrooms and lavatories, in the childhood home (at around 10 years of age) and the number of persons living in the childhood home. Also of relevance to the present analyses, the questionnaire asked whether a bedroom and also a bed had been shared in childhood; about the availability of hot and cold running water in the childhood home; plus history of smoking. Categorisation by social class was based on the occupation of the head of household (male where present), either non-manual (socio-economic groups I,II and IIINM) or manual (groups IIIM, IV and V). A value for crowding in the childhood home was obtained by dividing the number of persons by the number of rooms. Ex-smokers and current smokers were categorised together for comparison with non-smokers.

For the whole sample, the apparent effects of single risk factors were assessed using the chi-squared test with Yates' correction for continuity (gender, current and

childhood social class, shared bedroom and bed, water supply and smoking), unpaired *t*-test (age) or Mann-Whitney U-test (crowding, siblings). To determine whether risk factors remained independently significant in a multivariate analysis, logistic regression was used.

Randomisation to intervention and control groups had been carried out by household, and it was noted retrospectively that a useful number of currently married couples had attended for screening. It was considered that analysis of results in this subset of currently married couples might be of value and results were initially analysed using the corrected chi-squared test. Results in men and women were similar and for the purpose of this analysis women were used as the index partners. To determine whether status of spouse remained as an independent risk after adjustment for possible confounding factors, data for married couples were analysed using logistic regression, including those factors for which significance or near significance had been found in the overall population sample.

Test results from the Belgrave study, together with questionnaire data including ethnic origin and place of birth, were analysed to assess possible correlations, using the corrected chi-squared test and unpaired *t*-test as appropriate. Social class and ethnicity as risk factors for infection were considered in comparing results from Belgrave and Market Harborough.

iii. Results

Overall results from Market Harborough:

Unequivocal test results and complete relevant questionnaire data from the Market Harborough study population were obtained in 1431 cases (36% of those offered screening). The sample was obtained in a similar manner to that used for analysis of results concerning dyspepsia, as illustrated in Figure 6.1, although in this instance there were more cases (127 as opposed to 34) excluded on account of incomplete questionnaire data. The most common reason for excluding cases was missing data concerning occupation of father in childhood. This information may have been omitted on the self-completion questionnaire because the father had not been present in the childhood home or because of inability to recall his occupation, a limitation which had not been anticipated when designing the questionnaire. The sample analysed was nevertheless substantial and comprised 636 men and 795 women, with a mean age of 40 years (range 21-55 years) at the start of the screening programme. Two hundred and ten (14.7%) subjects in this sample were found to be seropositive for *H pylori* infection.

Univariate analysis of possible risk factors (Table 7.1) showed a significant correlation between *H pylori* infection and increased age, lower current social class (based on manual/non-manual occupation), lower childhood social class, higher degree of crowding in the childhood home (persons per room), greater number of siblings, shared bedroom in childhood, shared bed in childhood and lack of hot and cold water supply in childhood. There was a steady rise in the rate of infection with increased age

Table 7.1. Univariate analysis of potential risk factors for *H pylori* infection in a general population sample aged 21-55, from Market Harborough.

Potential risk factor	H pylori +ve (n = 210)	H pylori -ve (n=1221)	P-value
Age (in years)	42.6 (8.8)*	39.3 (9.2)*	<0.001
Male gender	100 (48) [†]	536 (44) [†]	0.354
Current social class (manual: non-manual)	129 (61) [†]	584 (48) [†]	<0.001
Childhood social class (manual:non-manual)	169 (80) [†]	827 (68) [†]	<0.001
Childhood crowding (persons per room)	1.0 (0.5) [‡]	0.8 (0.3) [‡]	<0.001
Number of siblings	2.0 (3.0) [‡]	2.0 (2.0) [‡]	<0.001
Shared bedroom in childhood	137(65) [†]	518 (42) [†]	<0.001
Shared bed in childhood	59(28) [†]	163 (13) [†]	<0.001
Lack of H &C water supply in childhood	29 (14) [†]	80 (7) [†]	<0.001
History of smoking	93 (44) [†]	483 (40) [†]	0.225

* Mean (standard deviation)

[†] Number (%) with risk factor present

[‡]Median (interquartile range)

(Tables 7.1 and 7.2), but correlation was not found in this sample between *H pylori* infection and male gender or history of smoking.

Using a logistic regression model, including those factors found to be significant as above, age, crowding in the childhood home and childhood social class remained clearly significant as independent risk factors for infection (Table 7.3). Significance was borderline for number of siblings ($P = 0.054$), sharing a bedroom just failed to remain significant ($P = 0.057$) and current social class was not far from significance ($P = 0.087$). Absence of hot and cold running water in childhood was not found to be an independent risk factor in this analysis, nor was sharing a bed in childhood, which became negatively associated with *H pylori* infection, though not significantly so ($P = 0.510$).

Results in married couples living in Market Harborough:

Complete relevant data were obtained for 389 married couples who both attended for screening. In 19 couples, both were positive, 287 were both negative, 44 had the husband positive and wife negative and 39 had the wife positive and husband negative. The individual positive test rate was 15.5% in this subset. Taking women as the index cases, there was a highly significant association between *H pylori* status of spouse and status of subject ($\chi^2 = 13.78$, $P = < 0.001$). Whereas under the assumption of no association there would be an expected value of 9 for both partners being positive, there were in fact 19 couples in this category. The OR for infection in those with a positive spouse compared to those with a negative spouse was 3.18 (95% CI 1.69 to 5.99). After adjustment for age, childhood social class, current social class, childhood

Table 7.2. Analysis of results of *H pylori* screening in Market Harborough by age group

Age group	No. positive	% positive
21-29 (n=237)	20	8
30-39 (n=422)	55	13
40-49 (n=525)	80	15
50-55 (n=247)	55	22
Total (n=1431)	210	15

Table 7.3. Multivariate analysis of risk factors for *H pylori* in a general population sample from Market Harborough.

Potential risk factor	<i>P</i> -value	OR (95% CI)
Age (in years)	<0.001	1.04(1.02 to 1.06)
Current social class (manual: non-manual)	0.087	1.33 (0.96 to 1.83)
Childhood social class (manual:non-manual)	0.039	1.51 (1.02 to 2.22)
Childhood crowding (persons per room)	0.003	2.08 (1.28 to 3.38)
Number of siblings	0.054	1.11 (1.00 to 1.23)
Shared bedroom in childhood	0.057	1.46 (0.99 to 2.16)
Shared bed in childhood*	0.510	0.86 (0.56 to 1.34)
Lack of H &C water supply in childhood	0.958	1.01 (0.59 to 1.73)

* Negative association

crowding, number of siblings and shared bedroom in childhood (Table 7.4), only status of spouse remained clearly significant as an independent risk factor for infection ($P = 0.005$, OR 2.65, 95% CI 1.34 to 5.25), with age just failing to remain significant ($P = 0.051$).

Results from Belgrave:

Excluding one person who failed to return their questionnaire after saying that they would post it, the sample of 111 Asians for analysis of risk factors comprised 51 men and 60 women. The majority (91) were of Gujarati origin, with 18 of Punjabi origin, one Bengali and one person of Asian origin whose family had lived in Fiji for many years but who did not know his exact ethnic origin. In this group there were 59 (53%) positive tests and analysis of risk factors for infection is summarised in Table 7.5. The positive test rate in women and men was very similar but age was significantly associated with infection ($P = 0.005$). Only 16 people in the sample had been born in this country. Although birth outside the UK was more common in those who tested positive than those who were negative, the difference was not significant and those born in this country were significantly younger (mean 25.75 years compared to 42.65 years, $t = 12.18$, $p = <0.001$) and thus less likely to be infected on the basis of age. Positive test rates in Asians born in India and in East Africa were similar. The validity of paternal occupation as an indicator of childhood social class in those whose childhood was spent outside the UK was uncertain, so social class in childhood was not considered in this group. Current social class based on manual/non-manual occupation of the head of household was however found to be a significant risk factor in spite of very small numbers classified in the non-manual group. Comparison of

Table 7.4. Multivariate analysis of risk factors for *H pylori* in a subset of 389 married couples from a general population sample, taking women as the index partners.

Potential risk factor	<i>P</i> -value	OR (95% CI)
Age (in years)	0.051	1.04 (1.00 to 1.09)
Current social class (manual: non-manual)	0.442	1.27 (0.69 to 2.37)
Childhood social class (manual:non-manual)	0.270	1.51 (0.73 to 3.14)
Childhood crowding (persons per room)	0.206	2.13 (0.66 to 6.87)
Number of siblings	0.068	1.21 (0.99 to 1.50)
Shared bedroom in childhood	0.936	1.03 (0.49 to 2.17)
Spouse <i>H pylori</i> positive	0.005	2.65 (1.34 to 5.25)

Table 7.5. Univariate analysis of potential risk factors for *H pylori* infection in a general population sample of 111 Asians aged 21-55 living in the Belgrave area of Leicester.

Potential risk factor	<i>H pylori</i> +ve (n = 59)	<i>H pylori</i> -ve (n = 52)	P-value
Age (in years)	42.7 (8.9) *	37.4 (10.8)*	0.005
Male gender	27 (46) †	24 (46) †	1.000
Current social class (manual: non-manual)	54 (92) †	38 (73) †	0.020
Birth outside UK	54 (92) †	41 (79) †	0.104
Country of birth (India: East Africa, excluding those born elsewhere)	26 (49) †	22 (54) †	0.815

* Mean (standard deviation)

† Number (%) with risk factor present

positive results in those whose ethnic origin was Gujarati (45/91, 49%) or Punjabi (12/18, 67%) is not included in Table 7.5, as numbers in the latter category were small. Statistical significance was not found for the comparison ($\chi^2 = 1.16$, $P = 0.281$).

Excluding one person with equivocal *H pylori* status, results for 43 non-Asians were analysed in relation to risk factors. This sample comprised 19 men and 25 women, 38 of whom were of British or Irish origin, plus 2 Greek Cypriots, 2 Afro-Caribbeans, one person of Polish origin and one of mixed Afro-Caribbean/British origin. Two had been born in Cyprus, 2 in Ireland, one in the West Indies and the remainder (38) in mainland Britain. In this group, there were 20 (47%) positive tests. The sample of non-Asians was small and within this group infection with *H pylori* was not found to be significantly associated with age, gender, social class or country of birth.

Using the samples analysed for risk factors, the difference between positive test rates in Asians (59/111) and non-Asians (20/43) was not significant ($\chi^2 = 0.31$, $p = 0.611$), but there was a significant difference ($\chi^2 = 29.76$, $p = <0.001$) between seropositivity in non-Asians in Belgrave (20/43, 47%) and in the predominantly Caucasian population sample in the same age range from Market Harborough (210/1431, 15%). It was noted that the proportion of people in the higher socio-economic groups according to non-manual/manual occupation was much greater in the Market Harborough sample (718/1431 50%, Table 7.1) than in the sample from Belgrave, where only 4/43 (9%) people were found to be in the non-manual category.

iv. Discussion:

The sample for analysis from the Market Harborough population represented 36% of those to whom screening was offered. Selection bias is always a possibility where there is a response rate below 100%. It is possible that the overall positive test rate may have been affected by under-representation of particular groups, for example lower uptake by younger people (Table 4.1), but there was no specific reason to assume that under-representation of any groups would be likely to distort the analysis of risk factors in the sample available for analysis. The low prevalence of infection found in those tested is likely to be related to the relatively high socio-economic status of those living in Market Harborough (Table 5.1) and in Chapter 4 it has been shown that there was some indication that those who attended for screening were reasonably representative of those invited in terms of socio-economic status.

Classification by socio-economic status or social class can be difficult and at times arbitrary, with various possible measures available, such as occupation, housing tenure and educational attainment. In analysing results from Market Harborough, occupation of the head of household was used, but the limitations of any single measure are acknowledged. Current social class failed to remain significant after adjustments ($P = 0.087$), confirming childhood as the most likely time for acquisition of infection. Close links between factors associated with living conditions make it difficult to determine which of these markers is most directly related to acquisition of infection.

Male gender has been shown to be correlated with infection in some studies [40,217].

In common with other studies [37,42], however, analysis of results in Market Harborough indicated no such association, suggesting a possible variation between populations. In common with the same studies [37,42], lack of correlation was also found between history of smoking and infection. Although Murray's finding of a such an association [40] is convincing in terms of his significant result after adjustments, it would seem unlikely that an infection which probably occurs mainly in early childhood is related independently to smoking.

Transmission of *H pylori* infection between spouses has previously been suggested [62,134,212,213]. Although a common source of infection cannot be ruled out, results in our subset of married couples living in Market Harborough suggested intrafamilial person-to-person transmission. It is acknowledged that the analysis of results in married couples was carried out retrospectively using data collected prospectively for the overall sample. In spite of this limitation, however, it was found that, in the study population, being married to a subject who is positive for *H pylori* infection was an independent risk factor for infection. The OR for infection where the spouse was infected was reduced only slightly from 3.18 to 2.65 after adjustment for other variables. A previous study [218] found that having a spouse who is positive for *H pylori* infection did not remain as a risk factor for infection after adjustment for age and national origin. This study was however based on subjects attending a fertility clinic, who would be atypical of married couples in terms of the presence or absence of children in the household. Transmission between spouses by way of a child or children has been suggested by epidemiological evidence [43] and more directly by a case history suggestive of transmission within a family via an infant [219]. Transmission via

children would appear a strong possibility in couples, given the absence of evidence for sexual transmission of *H pylori* [209] and would explain the difference between our results and those obtained in infertile couples [218].

Being married, regardless of the *H pylori* status of the spouse, has been demonstrated as a risk factor for infection [211] and this could be explained by increased risk of infection because of greater contact with young children in those who are married. The analysis of results in married couples from the Market Harborough population was carried out retrospectively and data on numbers and *H pylori* status of children of these couples were not available. In considering results in Market Harborough couples, the significance of children in the transmission of infection between spouses can therefore be considered speculatively only, in the light of results from other studies. However, results from the present study, from a UK population with a low prevalence of *H pylori* infection, support clustering of infection in households and intrafamilial transmission in this type of community. In differing populations, the situation may however vary; results from a study in Bangladesh suggested that in that country, in a community with a high prevalence of *H pylori* infection, transmission was more likely to have occurred outside than within the home [220].

In a study from the United States, ethnic origin remained significantly associated with *H pylori* infection in an asymptomatic population, after adjustment for possible confounding factors [37], with prevalence of infection higher in blacks than whites. A study in couples found that persons born outside the United States had a significantly higher prevalence of infection than those born in the United States [218]. In

Melbourne, Australia, prevalence of *H pylori* infection was higher in Chinese and Japanese compared to Caucasians [205]. In the UK, however, a study in Southall found similar rates of infection in Indian (52%) and white (43%) patients attending for endoscopy [221], results which are very similar to those obtained in the Belgrave community. Both Southall and Belgrave are areas with a high proportion of Asian immigrants and in both communities ethnic origin appeared unimportant with regard to prevalence of *H pylori* infection. Results obtained in Belgrave and Market Harborough suggested that social class was of far greater importance in determining the *H pylori* status of both Asian and non-Asian subjects.

Most people in the Belgrave South Asian sample had been born outside the UK, which was also true of those of Indian origin living in Southall. It might be expected that if infection occurs mainly in early childhood then prevalence would be similar to that in the country of origin. A study in Hyderabad, India, found *H pylori* prevalence to be over 80% by age 20 [222] and in a Tibetan community in Karnakatan State 77% of those randomly selected were infected [164]. Seery *et al* [221] speculated that lower rates of infection in immigrants could be due to lower prevalence of *H pylori* infection in the Punjab than in other parts of India, but we obtained very similar results in the Belgrave South Asian population which is predominantly of Gujarati origin.

The authors of the Southall study [221] suggested that the lower than expected prevalence of infection in the Southall Indian population could be the result of breaking a cycle of infection and reinfection on immigration to the UK. Persistence of infection is however likely to be more common than spontaneous elimination and possible

differences between those who migrate and those who remain in their country of birth could alternatively explain lower rates of infection in South Asians in the UK. In addition, results from studies carried out in developing countries may provide prevalence data that are unrepresentative of the overall population of the country under consideration, leading to inaccurate expectations of prevalence in immigrants from that country. The study from Hyderabad [222], for example, was conducted in a population characterised by lower socioeconomic status and the Karnakatan sample was drawn from a community of male monks living in a monastic settlement [164]. It is possible that selection bias may have affected our own estimation of prevalence to some extent, but our comparison of results in Asians and non-Asians living in a UK community is unlikely to have been compromised, since samples were drawn from the same population and uptake was similar in the 2 ethnic groups.

Summary of Conclusions

The main conclusions drawn from the studies described in this thesis are presented below, with reference to the hypothesis and aims outlined in the Introduction and Guide to the Thesis. Possibilities for future study are also considered.

- These studies addressed primarily the hypothesis that if health benefits of eradicating *Helicobacter pylori* in asymptomatic subjects can be clearly demonstrated, then such benefits can be effectively achieved through community programmes of screening and eradication. In Market Harborough, it was demonstrated that such a programme can be carried out efficiently in collaboration with general practitioners. Compliance with therapy was not shown to be an important limiting factor and good eradication rates were achieved in a relatively asymptomatic general population sample. Uptake of screening and of therapy were however identified as areas of limited compliance which would need to be addressed if consideration is given to the introduction of routine screening.
- A similar screening programme also ran smoothly in an inner-city area and good compliance with therapy and a good eradication rate were again achieved. The importance of an accurate database of eligible patients was emphasised by this study, where poor uptake was strongly influenced by the inaccuracy of the patient list used. Reasons for failure to accept screening were found to be similar in Asians and non-Asians in this community and the use of Asian language materials did not increase uptake. Screening was found to be more cost-beneficial in a population

with a high prevalence of infection. The proportional reduction in prevalence of infection was however greater in Market Harborough, where uptake of screening was higher.

- Long term follow-up was not within the scope of study for this thesis. A cohort of subjects offered and not offered screening has however been established, for possible follow-up in terms of health benefits. Numbers from these studies alone would be insufficient for useful follow-up with reference to gastric cancer, but pooled studies are a possibility. The usefulness of follow-up with reference to heart disease will depend on future findings in relation to this possible disease association. The value of follow-up in terms of dyspepsia may be limited by the lack of placebo control, but comparison of relevant consultations, prescriptions and referrals in the groups offered/not offered screening would be a possibility.
- Overall symptoms of frequent dyspepsia were not found to be correlated with *H pylori* infection in the population samples studied, suggesting that a reduction in the prevalence of infection through screening might be of limited value in reducing symptoms of non-ulcer dyspepsia in the community. The question of benefit in relation to dyspepsia was however left open by results of follow-up in a small sample.
- Observations concerning risk factors supported person-to-person transmission, mainly in childhood. The likelihood of transmission between spouses suggested, however, that acquisition of infection also occurs in adults. Asian ethnic origin was

not identified as a risk factor for infection, with social class the more likely determinant of *H pylori* status. If selective screening is to be considered, those living in lower socio-economic communities should be considered to be most at risk of infection, regardless of Asian/Caucasian ethnic origin.

Appendix A

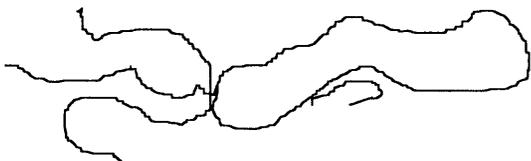
Information leaflet

(This *H pylori* information leaflet was sent with the screening invitation. The text was based on information presented in the feasibility study. In the second phase of the Belgrave study, a Gujarati version of this leaflet was also sent to those invited)

Helicobacter pylori

What is it?

Helicobacter pylori is a small bacterium or 'bug' that grows in the stomach of some people. It is often called just '*H pylori*'. The organisms are very tiny. They can be seen only under a microscope, but they look something like this -



Who has it?

Up to half the population of this country is probably infected. We think that most people who have *H pylori* have had it since they were children. People of all ages may have the infection but it is more common in older people than the young. We think this is because living conditions are better these days.

What does it do to you?

Most people who are infected don't get any symptoms at all. However, we do know that most people who have an ulcer are infected. There is some evidence that having the infection makes you a bit more likely to get stomach cancer and maybe heart disease. It is also possible that there is a link with indigestion. Having the infection does not mean that you will necessarily get an ulcer or cancer - most people don't get any ill effects at all.

How can you tell if you have *Helicobacter pylori*?

There are several ways of testing people to see if they have the infection. For some tests you have to have an endoscopy. This means swallowing a small tube with a camera on the end. The doctor can look inside your stomach and also take one or more tiny pieces of the stomach wall to test. Tests where you don't need an endoscopy include blood tests and breath tests.

Can you get rid of it?

Once you have the infection, it usually stays with you for the rest of your life unless you have some treatment. It is possible to get rid of it by taking a lot of tablets for one or two weeks.

Should you get rid of it?

At the moment, some doctors think you should get rid of the bug even if you don't have any symptoms. Other doctors think this isn't necessary. Most doctors agree that ulcer patients should definitely get rid of *H pylori*.

What other ways are there of making it less likely that you will get stomach cancer or heart disease?

Apart from getting rid of *H pylori*, you can also -

- * Give up smoking
- * Change your diet, for example
 - eat more fruit, vegetables and fibre
 - eat less salt
 - eat less fat
- * Take more exercise

Appendix B

Screening invitation letter

(This letter was sent on general practice headed notepaper)

Dear.....

**THIS LETTER IS OFFERING YOU A FREE HEALTH TEST
YOU CAN ALSO HELP WITH HEALTH RESEARCH**

We are doing some research jointly with the gastroenterology departments at Market Harborough Hospital and Leicester General Hospital. The research is about *Helicobacter pylori* (sometimes known as *H pylori*). This is a bacterium or 'bug' which can be found in many people's stomachs. It can cause inflammation in the stomach and sometimes ulcers. It may possibly also be linked to stomach cancer and heart disease. Many people have the infection without getting any symptoms. An information leaflet explaining more about *Helicobacter pylori* is enclosed.

We are writing to offer you a screening test to find out if you have *H pylori*. There are a number of tests for the infection, which doctors may recommend for people with specific symptoms. A screening test for the general population is not usually available on the National Health at the moment, although you can have it done privately. You are being offered a free test because this general practice has been chosen to try out a screening programme for *H pylori*.

For the test we shall just need a small blood sample from your arm. The result will be sent to you in the post. If your test was positive, you will be given the opportunity to discuss this and we will be able to prescribe tablets to get rid of the bacterium. If you would like to talk to someone before deciding whether you want to be tested, you can come along to the screening session to do this first, or you can telephone Margaret Stone at Leicester General Hospital, on 0116-2584439.

Screening sessions will be held at Market Harborough Hospital. An appointment has been made for you to attend at on in
Please complete and return the reply slip to Leicester General Hospital in the envelope provided, which does not need a stamp. It would be helpful if you could keep to the appointment given, but if it would be very difficult for you to come at this time, please telephone 0116-2584439 to sort out a different time. Daytime and evening appointments are available. If you do not wish to accept the screening test, it would be helpful if you could still return the reply slip to let us know this. If you are coming to be screened, it would help us if you could complete the enclosed questionnaire and bring it with you.

Yours sincerely

Dr A T Johnston and Partners

Appendix C

Questionnaire

(This questionnaire was sent with the screening invitation, to be self-completed by those attending for screening.)

HEALTH SURVEY QUESTIONNAIRE

Please answer the questions below by entering the correct information or ticking the boxes.

A. YOURSELF AND YOUR FAMILY:

FULL NAME: _____ DATE OF BIRTH: _____

TITLE (eg MR, MRS, MS) _____ SEX: Male [] Female []

ADDRESS: _____

POST CODE: _____ TELEPHONE NO: _____

Your NATIONAL HEALTH SERVICE NUMBER, if known. (You should be able to find this on your Medical Card) _____

It would be helpful if you could give us THE NAME AND ADDRESS OF RELATIVE OR CLOSE FRIEND (in case we have difficulty contacting you in the future): _____

WHAT IS/WAS YOUR OCCUPATION? _____

WHAT IS/WAS YOUR HUSBAND, WIFE OR PARTNER'S OCCUPATION? _____

WHAT WAS YOUR FATHER'S OCCUPATION WHEN YOU WERE A CHILD? _____

ARE YOU...? Employed full time [] Housewife [] Part-time []
Retired [] Unemployed [] Student []

HOW MANY BROTHERS AND/OR SISTERS DID/DO YOU HAVE? _____

Please think back to where you lived AS A CHILD, say around 10 years old.

a) HOW MANY ROOMS WERE THERE IN THE HOUSE? DO NOT INCLUDE BATHROOM(S) OR TOILET(S) _____

b) HOW MANY PEOPLE WERE LIVING IN THE HOUSE? _____

c) DID YOU SHARE A BEDROOM? YES [] NO [] Can't remember []

d) DID YOU SHARE A BED? YES [] NO [] Can't remember []

e) DID YOU HAVE HOT AND COLD RUNNING WATER? YES [] NO []
Can't remember []

PLEASE TURN TO PAGE 2

DO YOU SMOKE? YES [] NO [] EX-SMOKER []

If YES, about how many cigarettes a day do you smoke? _____

HOW MANY UNITS OF ALCOHOL do you drink on average in a WEEK? _____
(NB. ONE UNIT is half a pint of beer or lager, a glass of wine or sherry, or one measure of spirits)

B. HEALTH QUESTIONS:

Below you will find some questions about indigestion (dyspepsia). To answer these, please place a tick in the appropriate box. If you are not sure of the answer, please tick 'NO'.

Have you had any pain or discomfort in the place shown in the picture *in the last year*?

YES [] NO []

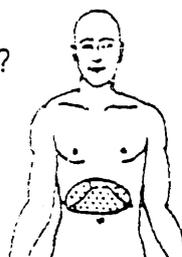
If **yes** to the last question then:

Have you had this pain on more than **six** occasions *in the last year*?

YES [] NO []

Did you see a doctor about it?

YES [] NO []



Have you had a feeling of excessive wind or fullness, in the place shown in the picture, after eating or drinking *in the last year*?

YES [] NO []

If **yes** to the last question then:

Have you had this feeling on more than **si** occasions *in the last year*?

YES [] NO []

Did you see a doctor about it?

YES [] NO []

Heartburn is a burning or ache behind the breast bone **in the chest**, that is not due to angina or heart trouble.

have you had heartburn *in the last year*?

YES [] NO []

If **yes** to the last question then:

Have you had this feeling on more than **six** occasions *in the last year*?

YES [] NO []

Did you see a doctor about it?

YES [] NO []

When lying in bed, have you had heartburn during *the last year*?

YES [] NO []

If **yes** then:

Has this happened on more than **six** occasions *in the last year*?

YES [] NO []

Do you get heartburn **only** when lying in bed?

YES [] NO []

Does this heartburn occur **only** while you are still awake?

YES [] NO []

Does this heartburn **waken** you from your sleep?

YES [] NO []

Did you see a doctor about it?

YES [] NO []

PLEASE TURN TO PAGE 3

TO ANSWER THE QUESTIONS TICK THE APPROPRIATE BOX. IF YOU ARE UNSURE TICK "NO"

Have you had a very sour or acid tasting fluid at the back of your throat *in the last year?* YES [] NO []

If yes then:

Has this happened on more than six occasions *in the last year?* YES [] NO []

Did you see a doctor about it? YES [] NO []

Have you had a feeling of wanting to throw up (nausea) *in the last year?* YES [] NO []

If yes then:

Has this happened on more than six occasions *in the last year?* YES [] NO []

Did you see a doctor about it? YES [] NO []

Have you **actually thrown up** (vomited) *in the last year?* YES [] NO []

If yes then:

Has this happened on more than six occasions *in the last year?* YES [] NO []

Did you see a doctor about it? YES [] NO []

Have you had **difficulty swallowing** (food sticking in your throat) *in the last year?* YES [] NO []

If yes then:

Has this happened on more than six occasions *in the last year?* YES [] NO []

Did you see a doctor about it? YES [] NO []

Have you **ever** been diagnosed as having a gastric (stomach) or duodenal **ulcer?** YES [] NO []

Have you ever had a **barium meal** examination? (you have to drink a white liquid while the X-rays are taken) YES [] NO []

Have you ever had an **endoscopy** or **gastroscopy?** (A tube with a light source is swallowed to look inside the stomach) YES [] NO []

KINDLY CHECK THAT ALL THE QUESTIONS ABOVE ARE ANSWERED, EVEN THE "NO" ONES.

If you answered **YES** to any of the questions about nausea or vomiting, please could you tell us briefly what you think caused you to feel or be sick

.....
.....

PLEASE TURN TO PAGE 4

In the last year, have you had any time off work because of illness?

YES [] NO [] CAN'T REMEMBER [] DON'T WORK []

If YES, about how many days did you have off work in the last year? (enter number of days or NONE) _____

How many of these days off work were because of indigestion? _____

If you DON'T WORK, on about how many days in the last year were you unable to go about your usual tasks because of illness? (enter number of days or NONE) _____

On how many of these days was indigestion the problem? _____

Below you will find some statements about indigestion. Please tick the one which is nearest to how you feel.

1. I don't suffer from indigestion at all []
2. I suffer a bit from indigestion but it doesn't really make a difference to the things I can do or how happy I feel []
3. I suffer from indigestion and it makes a little bit of difference to what I can do and the way I feel []
4. I suffer from indigestion and it makes quite a lot of difference to what I can do and the way I feel. []
5. Indigestion really makes a big difference to the things I can do and the way I feel. []
6. Indigestion rules my life and makes it a misery. []

Can you remember the doctor putting you on a course of ANTIBIOTICS over the last year?

YES [] NO [] Don't know/Can't remember []

If YES, enter the number of times you remember taking a course of antibiotics in the last year []

When was the last time? _____

Did/does anyone in your family have stomach cancer?

YES [] NO [] DON'T KNOW []

If YES, Who? _____

PLEASE TURN TO PAGE 5

Did/does anyone in your family have an ulcer?

YES [] NO [] DON'T KNOW []

If YES, Who? _____

Did/does anyone in your family have heart disease?

YES [] NO [] DON'T KNOW []

If YES, Who? _____

Is there anything which we have not asked about and which you think it would be important for us to know?

THANK YOU AGAIN FOR YOUR ASSISTANCE. KINDLY CHECK CAREFULLY THAT YOU HAVE ANSWERED **ALL** THE QUESTIONS. PLEASE BRING YOUR QUESTIONNAIRE WITH YOU TO THE SCREENING CLINIC.

Appendix D

Eradication therapy information pack

(Contents of an information pack sent to those who elected to take eradication therapy in Market Harborough. A similar pack was prepared for the eradication therapy used in Belgrave; this was also made available in Gujarati)

Eradication therapy information leaflet: page 1

YOUR ERADICATION THERAPY

You have been prescribed some tablets to get rid of your *Helicobacter pylori* infection. This is called eradication therapy. Please read the information in this leaflet carefully. Please also read any information that comes with your tablets before you start taking them.

Your prescription is for three different tablets. You must take all three twice every day for 7 days.

Two of the tablets are antibiotics, which work together to kill the *Helicobacter* bugs. It is best to take the antibiotics at a mealtime:

Klaricid is also called clarithromycin. It is a yellow tablet.



(not actual size)

You need to take ONE 250mg Klaricid tablet each time.

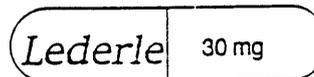
The other antibiotic is metronidazole. Not all metronidazole tablets look the same. You need to take 400mgs each time (either one 400mg tablet or two 200mg tablets). You must not drink alcohol while taking metronidazole and for 2 days after finishing the tablets.

The third tablet is Zoton, which is also called

Eradication therapy information leaflet: page 2

lansoprazole. It is a two-colour capsule, light and dark purple.

(not actual size)



Zoton helps to make your stomach less 'acid'. This lets the antibiotics work much better to kill the infection. You have to take **ONE** capsule each time. It is best not to take these tablets too near a mealtime.

IT IS VERY IMPORTANT THAT YOU TAKE ALL THE TABLETS. YOUR ERADICATION THERAPY IS NOT LIKELY TO WORK IF YOU JUST TAKE A FEW OF THEM. Also, if you only take some of the tablets, you can be left with some bugs that have been made even stronger. This is called antibiotic resistance and if this happens it is even more difficult to get rid of the *Helicobacter* if you try again. **THIS MEANS YOU REALLY NEED TO SUCCEED THE FIRST TIME.**

Are there any side effects?

Most people can take this therapy without any trouble. Some people do get side effects such as diarrhoea, a bad taste in the mouth, headaches and feeling sick. Usually these are not serious. If you have any mild side effects such as a slightly upset stomach, remember that you will only be on the tablets for one week and try to carry on taking them. **VERY RARELY**, more serious side effects can occur

- if you start getting problems such a skin rash or breathing difficulties, or if you are worried about any side effects you are getting, it is important that you get in touch with your doctor straight away.

How can I remember to take the tablets?

Most people find it difficult to remember to take their tablets every time, especially if they are not used to taking pills regularly. Here are a few suggestions -

* Leave the tablets somewhere you will notice them, unless there are young children in the house, in which case you must always put your tablets away safely.

*Set an alarm clock or watch to go off when you next need to take your tablets.

* You will find some 'reminder notices' in this pack. Pin or stick one or both of these somewhere you are sure to notice, such as on a door you go through a lot.

* Fill in the diary in this pack and leave it somewhere you will see it to remind you.

What if I DO forget to take my tablets?

The tablets need to be taken regularly, so try to take them all at the right time. However, if

you do forget to take any doses, here is some advice about what to do -

* If it is more than an hour before the time for your next dose, take the missed dose as soon as you remember.

* If it is less than an hour before the time for your next dose, take two doses together.

* DON'T take more than two doses at once.

* If you miss a whole day, DON'T take the doses for two whole days in one day. At the end of the week carry on with the tablets for an extra day (or days) until they are finished.

Does the therapy always work?

This eradication therapy will work for most people as long as they take all the tablets at the right time. There will however always be a few people for whom it doesn't work, for example because they already have antibiotic resistance before they take the therapy. If this happens, it may be necessary to try again using different antibiotics.

REMEMBER - YOU WILL ONLY HAVE TO TAKE THESE TABLETS FOR ONE WEEK TO GET RID OF YOUR *HELICOBACTER*. IT IS UP TO YOU TO TRY YOUR BEST TO TAKE THEM ALL AT THE RIGHT TIME.

Sample page from eradication therapy diary (other pages similar)

Eradication Therapy Diary

Please use this diary to keep a record of when you take your tablets.

NAME: _____

Please tick when you have taken each dose and if possible write in the approximate time that you took the tablets. If you miss any doses altogether, put a cross in the box and take the extra dose(s) at the end of the week.

DAY 1. (Date: _____)

ZOTON:

Dose 1 [] Time _____ Dose 2 [] Time _____

KLARICID:

Dose 1 [] Time _____ Dose 2 [] Time _____

METONIDAZOLE:

Dose 1 [] Time _____ Dose 2 [] Time _____

DAY 2. (Date: _____)

ZOTON:

Dose 1 [] Time _____ Dose 2 [] Time _____

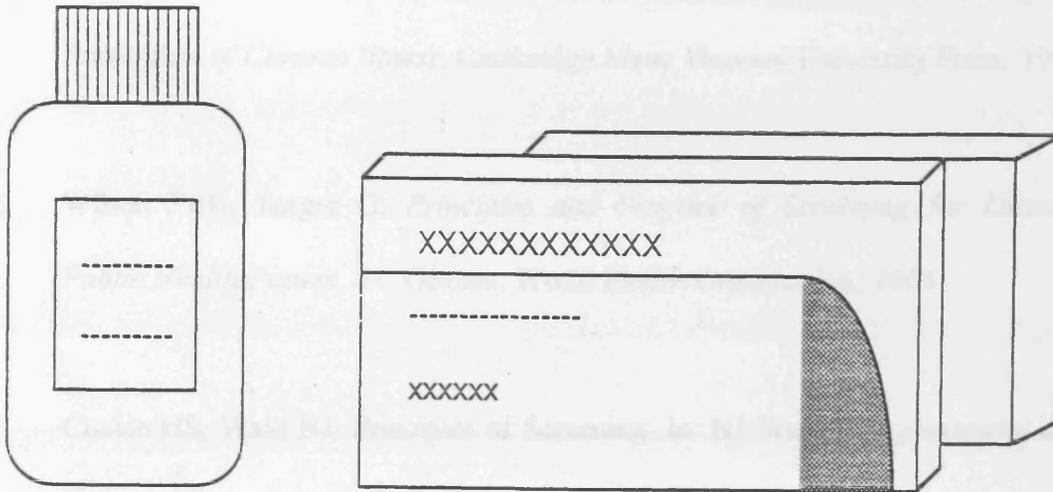
KLARICID:

Dose 1 [] Time _____ Dose 2 [] Time _____

METONIDAZOLE:

Dose 1 [] Time _____ Dose 2 [] Time _____

Reminder notices



REMEMBER

TO TAKE THE TABLETS!

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