Is it cost effective to screen against Helicobacter pylori in Sweden?

- A contribution to the evaluation of a potential screening program against Helicobacter pylori.

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Abstract

Title: Is it cost effective to screen against Helicobacter pylori in Sweden? A contribution to the evaluation of a potential screening program against H. Pylori.
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Problem: Would it be cost effective in Sweden on a societal level to implement a population wide screening program against Helicobacter pylori bacterium?

Purpose: Gastric cancer and peptic ulcer are associated with H. pylori infection and are diseases with severe consequences for the Swedish population. The aim of the study is to through a cost-effectiveness analysis contribute to an evaluation of a screening program against Helicobacter pylori from the perspective of guidelines provided by WHO.

Methodology: The problem is evaluated through a comparison of the discounted costs and life years saved. The comparison is made between a scenario where a screening program against the bacterium is implemented and a scenario where no screening program is implemented. These scenarios are evaluated through a decision analytic model using an individual sampling technique. A combined qualitative and quantitative approach, including interviews and literature studies, are used to build the model and to populate the model with data. Finally, a sensitivity analysis of the model is carried out.

Conclusions: According to this study, an implementation of a screening program against H. pylori would be profitable with a net present value of approximately 864 MSEK. It would also save lives and decrease suffering. The evaluation of the model quality and the principles regarding how assumptions have been made makes it likely that this observation is accurate.

Keywords: screening, health care, economic evaluation, Helicobacter pylori, gastric cancer, peptic ulcer, Sweden

Preface

We would like to thank our supervisors Gudbjörg Erlingsdottir and Carl-Hampus Lyttkens for their support. You have inspired us.

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Lund, May 8th, 2012
Anton Öberg and Sara Lindblom

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1. Background

This chapter introduces the background to the issue of study. An overview of the current health care situation is presented, screening programs are explained and the bacterium Helicobacter Pylori is introduced. Further follows a motivation of the bacterium as a screening candidate and a motivation why it is relevant to evaluate the cost effectiveness of a potential screening program against the bacterium. Finally the problem, purpose of the study and focus area is presented.

1.1 Introduction

The health-care sectors faces new times. Health care systems globally and in Sweden are in crisis and meet a challenging future. There are many positive indications such as competent health-care professionals, generics medicine and information-based medicine. Despite this, negative indications are even more present and threatening. Costs of health care are increasing and quality is not following the same increase. Problems are arising due to new circumstances driven by demographic changes, consumerism and larger burden of disease. Expensive investments in new technology are expected to force fundamental change in health care in coming years. Health care systems that cannot adapt to these changes of prerequisites will not be successful (OECD, 2006).

A dilemma in health care is that innovations and new technology seldom results in decreased costs. New innovations and new technology instead often gives the opportunity to treat more conditions and to further increase people's lives, which instead often are associated with additional costs. This is hard to avoid because informed patients demands the latest and most effective technology (IBM, 2006).

To be prepared for the future in health care a change of mindset for stakeholders is needed. Health care providers have to expand focus from symptomatic treatment to preventive care. They should approach the management of chronic diseases as well as life-long prediction and prevention of illness. Payers should help patients to get as cost effective care as possible and assist care delivery organizations to provide high value health care. Suppliers of health care are responsible to work collaboratively with care providers and patients to produce products that improve output or provide equivalent outcomes for less cost. Governments should address the instability through supporting the other stakeholders by developing stable solutions. In the future, they have to understand that health care expenditure is not limitless why high value has to be the only outcome, both for individuals as for governments. Cost efficient health care with high value is the only way for the future (IBM, 2006).

In the beginning of the 20th century, the majority of the widely spread diseases were infectious diseases and these were the major causes of death. In year 1928, penicillin was discovered and this together with improved hygiene and nutrition, changed the way we perceived diseases and die from diseases (Ligon, 2004). Today, cancer is the second largest cause of death in EU and is responsible for approximately 30% of all death causes. As we do not have an effective medication for cancer, prevention and early detection are important weapons in the battle against our national disease (Cancerfonden, 2009). For some cancers the five-years survivability can be as high as 95 % when detected in a very early stage and as low as 5 % when detected in a very late stage (Agabegi, 2008). To identify a cancer in an early stage there is usually a need to detect the cancer before any symptoms are present. This is the basic idea behind screening programs. Under the right circumstances a screening program can be cost efficient and a preventive approach to health care that fits into the picture of the health care of the future.

1.2 Screening

Screening is a term used in many different circumstances and can in general be described as a process where a large number of subjects are investigated to find a proportion that is relevant in some aspect. In the context of health care screening is by WHO defined as: *"the presumptive identification of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly. Screening tests sort out apparently well persons who probably 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."* The aim of screening is to find persons who have a disease without symptoms and treat these patients in an early stage (Jungner, Principle and practise of screening for disease, 1968).

Screening can either be on the initiative of specific individuals, which is called spontaneous screening, or can be carried out through screening programs. These programs target a subset of a population characterized by for example age, gender or family history. How the target group is defined depends on characteristics of the disease, treatments and resources available. One example is mammography where females in a specific age-span are examined with the purpose of identifying early stage tumors in their breasts.

There are several potential benefits of a screening program. Benefits include a more efficient use of resources, the possibility to reduce deaths and increased life quality for the population (Birbeck, 2000). Screening programs have in some cases been very successful and for example are the major cause behind the 13 per cent decrease in cancer mortality in the US between 1990 and 2004 (Drummond, 2005).

In Sweden there are currently two active screening programs, against breast cancer and cervical cancer. Since around 1960, health controls have been made with cell tests, testing for cervix cancer, and 1976 it was implemented in all county councils in the country. A recent study in Sweden shows that early detection cures up to 92% of detected cervical cancer (Andrae, 2012). Mammography started 1986 in Sweden. According to many studies, risk reduction of breast cancer through screening is from many perspectives a well functioning screening program (Andersson, 1998).

A general screening program in Sweden works in general as follows: Firstly, the persons in the chosen age group to be screened get an invitation to attend a test session. Invited individuals who want to participate goes to the closest medical care center that is involved in the screening program. Usually a nurse sees the patient and tests the patient. In most cases it takes a while before the patient receives the result of the test. If the result is positive, the patient gets a new time for more a detailed examination with further tests with aim to diagnose the patient. Depending on outcome it can be necessary to proceed with surgery and/or medications. If the test is negative, nothing more happens as the patient is considered healthy (Svedelius, 2012).

In practice, there are challenges with screening programs and there is an ongoing discussion regarding which screening programs should be implemented (Holland, 2006). The success of a screening program depends on a number of factors. To initiate a screening program, a lot of resources are needed. The preventive effect of a screening program results in that people are saved from diseases in the future, sometimes as far as 20 years ahead. Reduced costs and other earnings for society and the health care system, associated with the disease, are also positive outcomes evident in a long-term perspective. The direct costs of the screening programs are instead immediate. This often results in a long payback time. The politicians are, in Sweden, the final decision makers when screening programs are to be implemented. The tenure of four years results in an investment horizon often far shorter than the payback time of a screening program. The long payback time (related to the tenure time) can make politicians unwilling to invest. In Sweden, different parts of the health system carry different costs. For a screening program, it is complicated for the politicians to in forehand estimate which parts of the health care system that will carry the costs of the program. It is also difficult to estimate which part of the system that can enjoy reduced costs in the future due to lighter burden of treatment against the specific disease. This makes it complex to predict and measure the result and total costs of a program and can turn into an obstacle when a potential screening program is evaluated. Even if it is likely to be very cost effective (Baratt, 2002).

To decide if a specific screening program should be implemented or not a range of different aspects needs to be taken into consideration. Some related to medical aspects of the disease, available tests and treatments and others to aspects related

to costs and cost effectiveness. As support in the evaluation process, specific policies and guidelines exist. In the European Union that Sweden is a part of, the policies that determine if a specific screening program should be implemented are built on four principles: 1) that the condition should be an important health problem, 2) there should exist suitable diagnostic tests, 3) there should be an accepted and established treatment and 4) costs should be economically balanced (Jungner, Principle and practise of screening for disease, 1968). The European Commission supports three cancer-screening programs for breast, cervical and colorectal cancer (European Commission, 2008).

The two authors Wilson and Jungner published for WHO 1968 ten criterion to evaluate a screening program. Sweden uses an extended version of these criterions specified by Danish Council of Ethics. A screening program should fulfill all of the criterions stated below if it is to be implemented. Socialstyrelsen (2012) describes the Swedish criterion for a screening program as following:

1. The condition should be an important health problem.
2. There should be a treatment for the condition
3. Facilities for diagnosis and treatment should be available.
4. There should be a latent stage of the disease.
5. There should be a test or examination for the condition.
6. The test should be acceptable to the population.
7. Screening is acceptable for the population.
8. The natural history of the disease should be adequately understood.
9. There should be an agreed policy on whom to treat.
10. The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole.
11. The treatment can be offered long-term and influence the prognoses for the treated patients.
12. The organization of the screening has been explained in detail.
13. The test and treatment costs for the screening have been described.
14. The cost effectiveness of the screening has been estimated.

There is currently a discussion in Sweden if additional screening programs should be initiated. One candidate is a program against prostate cancer. Year 2013, a large study will start that will involve 200 000 men with age between 50 and 69. The purpose of this study is to improve the precision of the diagnosis to a level that makes it feasible to initiate a nation wide screening program against prostate cancer. Stockholm started 2008 and Gotland area 2009, to implement a test program for colorectal cancer screening and if shown successful screening against colorectal cancer is a candidate (Socialstyrelsen, 2012). Another potential candidate is screening against the bacterium Helicobacter Pylori.

1.3 Helicobacter pylori

1.3.1 H. pylori

H. pylori is a bacterium responsible for 60-90 % of all cases of gastric cancer, for 85% of gastric ulcers and for 95% of duodenal ulcers worldwide (Kusters, 2006). In Sweden this translates into 670 deaths in peptic ulcer and 530 deaths in gastric cancer during 2010 as an effect of the H. pylori bacterium (Cancerfonden, 2012) (Lundstedt, 2012).

The relationship between the bacterium and diseases was found 1983 by the Australian scientists Barry Marshall and Robin Warren, for which they 2005 received the Nobel Prize in Medicine. The bacterium lives in around half of all humans' stomach in the world. In some developing countries more than 80% of the population are H. pylori positive while the occurrence in some developed countries is less than 40% (Kusters, 2006). A bacterium infection is possible to detect with a simple blood test or breath urea test (Karnon, 2007). It is possible to eradicate the bacterium with a non-costly three-part antibiotics cure, which cure over 90 % of treated individuals who gets rid of the bacterium within 2 weeks (Roderick, 2003).

The bacterium is gram-negative and is two to four micrometers in length and 0.5 to 1 micrometer in width. Most of the time its spiral-shaped but can sometime appear as a rod and after antibiotic treatments be shaped as a coccid (Kusters, 2006). See figure 1.

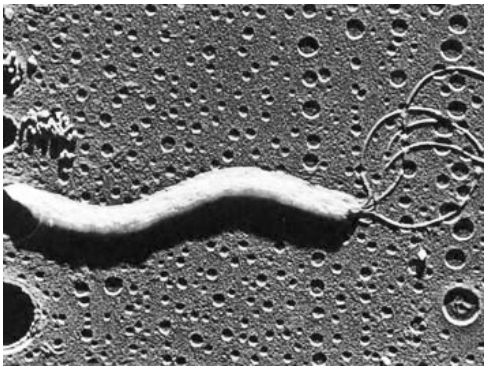

Figure 1. Picture of Helicobacter pylori taken with electronic microscope. Source: (Dave, 2011)

Diseases directly associated with H. pylori infection are: chronic gastritis, peptic ulcer disease, non-ulcer dyspepsia, gastric cancer and MALT-lymphoma (Kusters, 2006). There are also a number of non-gastric conditions associated with Helicobacter Pylori infections (Nilsson, 2005).

1.3.2 Chronic gastritis

Colonization of H. pylori practically always leads to chronic inflammation in the stomach that is called a chronic gastritis. The chronic gastritis by it self is in most cases not a dangerous conditions but the development of other H. pylori-related diseases likely depends on the severity of the gastritis and the location of colonization (Shiotani, 2002). If there are symptoms present they can be pain, water brash, vomiting, weight loss, fecal occult blood and blood vomiting (Gremse, 1996).

1.3.3 Peptic duodenal and gastric ulcer

Gastric or duodenal ulcer are mucosal erosions equal or larger than 0,5 mm, penetrating the muscularis mucosa (holes in the stomach or duodenal wall). Gastric ulcer occurs in the stomach, while duodenal ulcer is located in the duodenal part, which is the first part in the small intestine after the stomach. Duodenal ulcer is four times more usual than gastric ulcer in Western countries, while the ulcers are equally common in other parts of the world. Symptoms are pain, vomiting, weight loss or loss in appetite, blood and black stools, nausea and hematemesis (blood vomiting) (Stevens, 2001). Bleeding ulcer is a state when the ulcer penetrates a blood vessel. The bleeding ulcer is in more than 80 percent of the cases not dangerous, as it heals itself. When it does not heal itself, it is acute and life threatening. Symptoms are, except the same symptoms as for non-bleeding gastritis, also black or blood in stool, pain, vomiting blood (Laine, 1994).

In 2012 in Sweden a total of 9.805 cases of bleeding ulcers were recorded resulting in 670 deaths with causes directly related to bleeding ulcer (Lundstedt, 2012). Around 85% of gastric ulcers and 95% of duodenal is caused by H. pylori (Kusters, 2006).

1.3.4 Gastric cancer

The name gastric cancer refers to all cancers affecting the stomach (Cancerfonden, 2012). Gastric cancer is like other cancers a process in which cells' cell division mechanisms are disturbed in a way that results in uncontrolled cell growth. The process of disturbance of cell division mechanisms in the case of stomach cancer is a complex matter that is not fully understood (Cancerfonden, 2011).

Approximately 1000 individuals are diagnosed with gastric cancer in Sweden every year. The majority of those, about 75%, are above 65 years when they are diagnosed. Of the 1000 diagnosed individuals, 70% dies from causes directly related to the cancer (Cancerfonden, 2011).

Around 1-2 % of individuals infected with H. Pylori develop gastric cancer (Kusters, 2006) and epidemiological evidence suggests that 60-90 % of gastric cancers are attributed to H. pylori (Nilsson, 2005) H. pylori were 1994 classified as a Group 1

human carcinogen by International Agency for Research on Cancer, which is the highest grade on the scale (Svedelius, 2012).

1.4 H. pylori as a screening candidate

Mammography, screening against cervical cancer, colorectal cancer and prostate cancer are traditional screening programs in the sense that the purpose is to find the dangerous disease in an early stage. Another approach is to screen against something that later develops into a dangerous diseases and instead of treating this disease in an early stage minimize the risk of developing it in the first place. Screening against the bacteria Helicobacter Pylori would work this way.

The suffering and costs associated with diseases caused by H. pylori combined with the fact that there do exist effective methods to find and eradicate the bacteria have led to discussions and studies evaluating the feasibility of performing mass screening against the bacterium.

Below follows an evaluation of the H. pylori as a screening candidate using the extended guidelines from WHO.

1. The condition should be an important health problem:
Worldwide, gastric cancer is the fourth largest cancer disease and year 2007 over 1 million gastric cancer cases were diagnosed. Gastric cancer is after lung cancer the second largest cause of cancer-related cases (IARC, 1994). Gastric cancer hits approximately 1000 new patients every year in Sweden and the cancer form is highly aggressive. During year 2010, 662 persons died in this cancer form in Sweden (compared to 139 who died from cervical cancer) (Cancerfonden, 2012). Further 9.805 cases of bleeding ulcers were recorded resulting in 670 deaths with causes directly related to bleeding ulcer (Lundstedt, 2012). The bacterium is responsible for the majority of these cases of cancer and ulcer.

2. There should be a treatment for the condition:
Treatment for the condition is a non-costly three-part antibiotics cure. Over 90% of treated individuals get rid of the bacterium after 2 weeks (Roderick, 2003).

3. Facilities for diagnosis and treatment should be available:
Facilities are available as Sweden has a developed health care structure and implemented screening programs for other diseases (Svedelius, 2012).

4. There should be a latent stage of the disease:
The majority of individuals infected with the bacterium acquirer it childhood but the related diseases usually happens in the later stages of the infected individuals lives. This can be translated to a latent stage spanning over 1 - 80 years (Agréus, 2012).

5. There should be a test or examination for the condition:
There are different tests available, where urea breath test is simple to use and gives the result direct.

6. The test should be acceptable to the population:
As the tests are less unpleasant than other screening methods, they should be acceptable.

7. Screening is acceptable for the population:
As there are no cultural oppositions against screening in Sweden, screening is acceptable and there exists active screening programs in Sweden.

8. The natural history of the disease should be adequately understood:
Since the Nobel price were given to Barry Marshall and Robin Warren H. pylori have been a hot topic to study and the history of disease have been described and understood.

9. There should be an agreed policy on whom to treat:
It is not yet a determined policy regarding whom to treat but since the bacterium are widely spread in the whole Swedish population and there are no known methods to identify groups of individuals with higher risks the whole population is an option..

10. The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole:
To evaluate this a study of screening cost in relation to benefits needs to be performed. This have been done outside Sweden and shows in general that it is economically balanced.

11. The treatment can be offered long-term and influence the prognoses for the treated patients:
An identified case of cancer will need to be treated with more or less complicated methods including surgery or chemotherapy. When a H. pylori infection is identified its possible to eradicate the bacteria and after this elimination there is no need for further long term treatment and the prognosis for the treated patient is improved.

12. The organization of the screening have been explained in detail:
An implementation of screening program against H. pylori is not in the stage where this has been done.

13. The test and treatment costs for the screening have been described:
This has been done for both the different available tests and the eradication treatments

14. The cost effectiveness of the screening have been estimated:
No cost effectiveness studies have been done in Sweden.

When evaluating screening against H. Pylori using the extended WHO guidelines 10 of the 14 criteria are met, no criteria disqualifies the bacterium and four are still to be evaluated. Of the four still to be evaluated are two related to costs and cost effectiveness of the screening program.

If screening against H. pylori is likely to be cost effective for any specific group criterion 10 and 14 will be met. Specific groups that are shown to be cost effective can be a start point of a discussion regarding whom to treat. After this the technical details regarding how the screening program should be organized can be specified. In this situation the screening program will be evaluated against all of the extended WHO guidelines.

If all criteria are fulfilled a screening program against H. pylori can be a part of a more preventive approach in health care and save lives in a cost effective way.

1.5 Issue of study

Would it be cost effective in Sweden, on a societal level, to implement a screening program against Helicobacter pylori bacterium for a part of the population?

1.6 Purpose

The aim of the study is to contribute to an evaluation of a screening program against H. pylori from the perspective of the extended WHO guidelines. Our contribution to the research area is to evaluate these criterions specific for Sweden.

1.7 Expected result

Based on an initial overview of the study issue, expected result is that a screening program against H. pylori in Sweden is cost effective over a long-term period. A hypothesis is that the net present value, of an implementation of a screening program, is positive. Simplifications and assumptions will be made in directions that decrease the probability of the hypothesis being true.

1.8 Delimitations

The issue of study will be examined using a mathematical model and in the process of creating a model a large number of delimitations will be used. The delimitations described below should be perceived as a start or frame.

When evaluating the cost effectiveness of the study the will primarily focus will be on monetary aspects of a potential screening program. Consequences in terms of health outcomes will be evaluated in terms of life years saved. Gastric cancer, peptic duodenal and gastric ulcer will be the only diseases modeled. This even though it is known that H. pylori increase the risk of other conditions. Negative effects of increased antibiotics used, such as resistance, will not be considered.

2. Work process

This chapter describes the work process used during the study. The work process can be divided into two parts. An initial part is where the background was set, the issue specified and a suitable model framework determined. In the second part the model framework was used to develop a model. Input data for the model was gathered and different scenarios were simulated. Finally the results were interpreted and discussed.

The overall work process used can be described by figure 2.

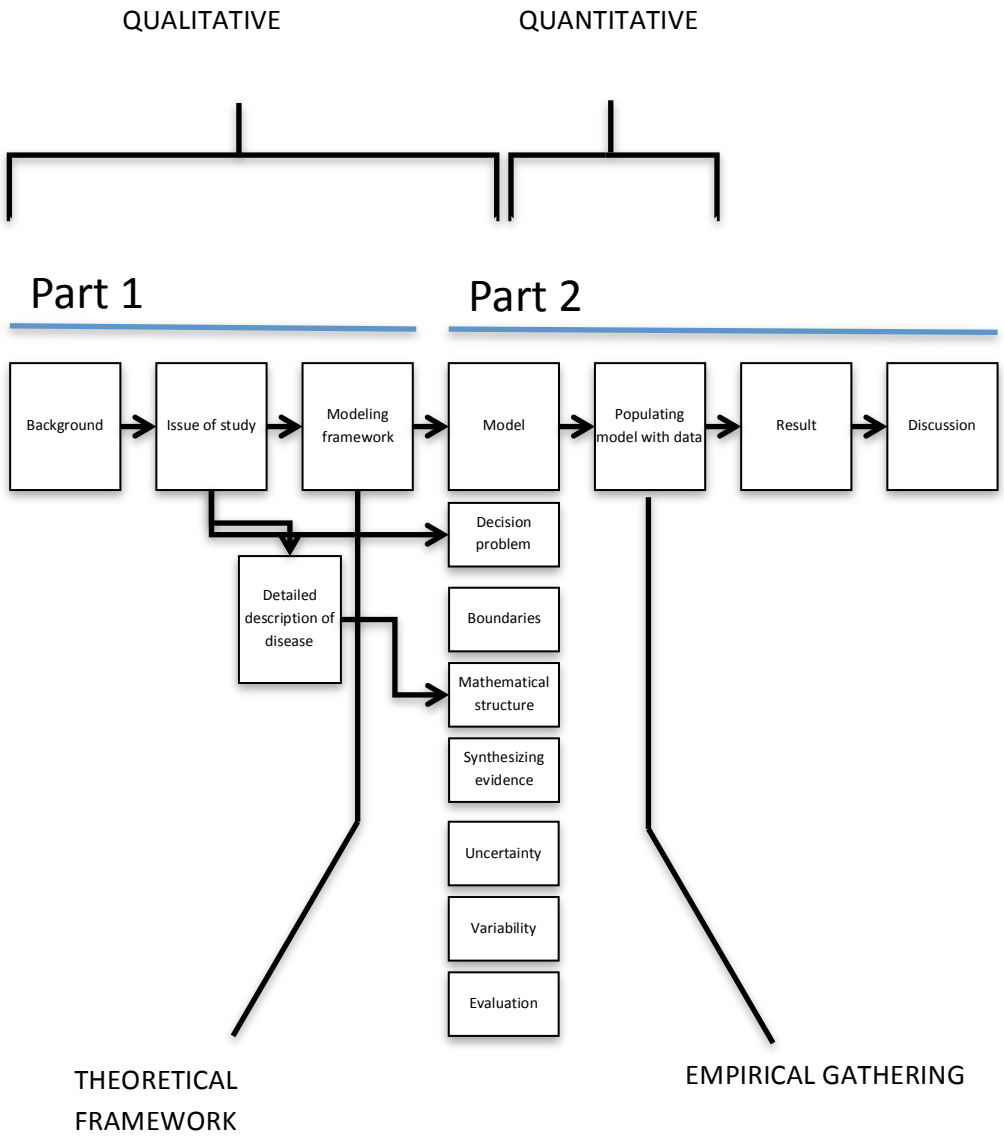

Figure 2. Overview work process.

2.1 Part one

Firstly, an initial issue was set. This issue was investigated with a qualitative research strategy.

Qualitative method

A qualitative research strategy is inductive and interpretive. There are several different ways of performing a qualitative study, where observations, interviews,

focus groups and gathering of documents are some of them. There are predetermined steps when performing a qualitative study. Initially, the aim of the study is to be determined. After that, a choice of relevant sources and research persons is made and after that the gathering of data takes place. Then follows interpretation of gathered data. The last step is to re-work the problem and eventual gathering of additional data (Bryman & Bell, 2005).

This process was followed and experts with knowledge related to the issue were interviewed and literature studies performed. This initial qualitative study resulted in a solid background that made it possible to further specify the issue of the thesis. This thesis was the same as the final issue: *Would it be cost effective in Sweden, on a societal level, to implement a screening program against Helicobacter pylori bacterium for a part of the population?*

After the finial issue was specified, the next step was to determine a suitable theoretical framework.

2.2 Choice of theory

A theoretical framework is theory used to present a preferred approach to an idea. The theoretical framework determines the things to measure and what relationships to look for. The main theoretical framework is taken from Drummond's "Method for economic evaluation of health care programs" (2005). He uses a seven-step process that starts broadly with defining the problem, narrowing it down to the last step where a detailed decision of how to build the model is taken. Drummond's evaluation is chosen because it covers all the important areas for an economic evaluation in health care and delimitations can be made to look deeper into relevant parts for this study (Drummond, 2005). Used is also theory from several relevant articles with which we have added and angled Drummond's framework to suit our study properly.

2.3 Part two

In the second part, the theoretical framework determined in the first part was used to build a model. The result was a model built in the programming language MATLAB. When the model was finished, model input were gathered. This was primarily done through a quantitative research strategy approach.

Quantitative method

A quantitative research strategy is built upon gathering of data, which consists of numerical data. This data is often easy to measure and compare. The problem is often set as a hypothesis. Quantitative method is suitable when knowledge is relatively high and when the issue of study is set. Before gathering numerical data, there is a need to categorize that is easier to do when the problem is set. The quantitative method is appropriate to use when to describe the frequency or extent

of a phenomenon, which is well suited with our study (Jacobsen, 2002). It is important to secure reliability and validity of the data when performing a quantitative analysis. In this study, numerical data is gathered from national data registers and from other relevant studies made mainly outside Sweden. We have also used data from Swedish institutions. Extra important when working with secondary quantitative data is to control the studies from where we take data. Important is also that the studies measure the same things that we want to measure (Bryman & Bell, 2005).

2.4 Empirical gathering

To get the initial picture of screening against H. pylori, we have deliberately searched for persons with different views of the area. The interviews have been performed mainly semi-structured, where we have prepared basic questions before the interview but been open to follow the interview objects path (Bryman & Bell, 2005). For the document study, the database of Lund University, Summon, have been used to find reports from studies and articles. If this kind of study were performed through gathering primary data, the study would preferably be followed-up every five years. Since the time is limited, all the data collected for the simulations are secondary data. Used is data gathered by other researchers and institutions that has access to long-term studies and resources to make studies with large number of persons. With this data, a longitude study over years is made. The quality of the data is questioned in the part “Model data”. As we have not had control over the studies where data is taken from, a critical approach of the sources are even more important (Bryman & Bell, 2005) (Jacobsen, 2002).

2.5 Deductive and inductive approach

According to the science of research methods, there are different ways of acquiring knowledge. A deductive approach predicts a certain relationship from a fixed understanding frame. An inductive approach is based on the thought that all knowledge is series of separate cases, from where conclusions can be drawn after observations are done (Andersen, 1994). The approach for the thesis has been deductive; as we have worked thesis-driven from the theory ground we had when the study started. The starting point was that since there are studies indicating on positive results for cost-effectiveness studies in other parts of the world, a study on the Swedish market with an addition of indirect costs should also have a positive outcome. Studies that this study is based on are done both inside and outside Sweden. They are performed with the same test as in this study, urea breath test. They have tested different asymptomatic age groups. This study has been based on the thesis that is economical defensible to implement a screening program for H. pylori. After data gathering and result was found, the theory was revised after our results (Bryman & Bell, 2005).

3. Disease

In this chapter diseases related to H. pylori will be described in detail. Natural history of disease for H. pylori, treatment and management for respective H. pylori-related diseases will be explained. Further Ethical aspects of screening against H. pylori are presented.

3.1 Disease process

The exact route of H. pylori transmission is not known but oral-oral or fecal-oral routes are most likely. When swallowed the H. pylori bacterium infects a human by colonizing the mucosa close to the stomachs epithelial cells, see figure 2. The epithelial cell layer is the outermost cell layer of the wall towards the stomach cavity. Mucus (phlegm) is covering the epithelial cells and is constantly segregated from mucus-segregating cells located among the epithelial cells. This creates a barrier that protects the epithelial cells from the acidic stomach juice.
The bacteria use its arms to swim through the mucus, away from the stomach cavity, closer to the epithelial cells (Kusters, 2006), see figure 3.

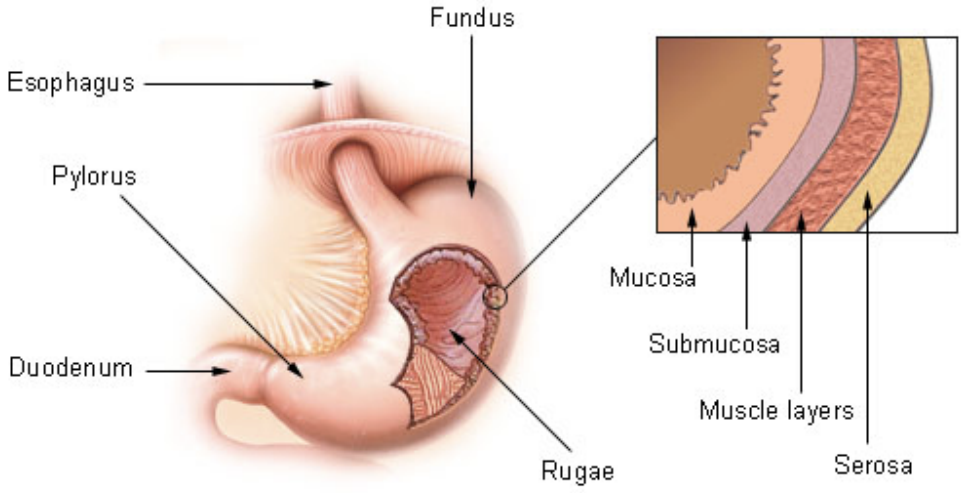

Figure 3. Illustration of human stomach Source: (Helicobacter Test, 2010)

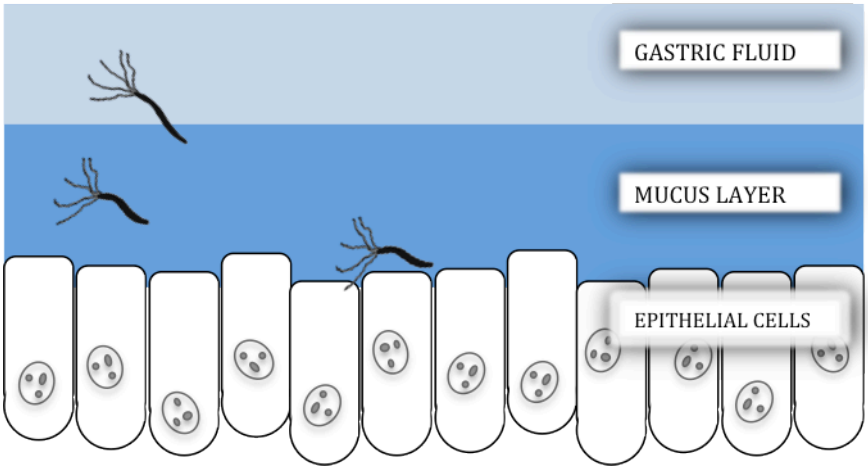

Figure 4. H. pylori invasion part one. Source: (Helicobacter Test, 2010)

Chronic gastritis

The bacteria can anchor itself to the epithelial cells by using a protein that bind to membrane-associated carbohydrates and lipids of epithelial cells. The pH-level in the body of the stomach is very low and the environment is not attractive for the bacteria that prefer the more neutral pH - level closer to the epithelial cells (Schreiber, 2004).

H. pylori affect its environment in many ways. One central part is the large production of the enzyme urease that breaks down urea located in the stomach to ammonia and carbon dioxide. Ammonia neutralizes the gastric acid by accepting a proton and forming ammonium. The neutralization of the gastric acid close to the bacteria adjusts the pH-level towards a neutral level, which is vital for the survival of the bacteria (Dixon, 2000). See Figure 4.

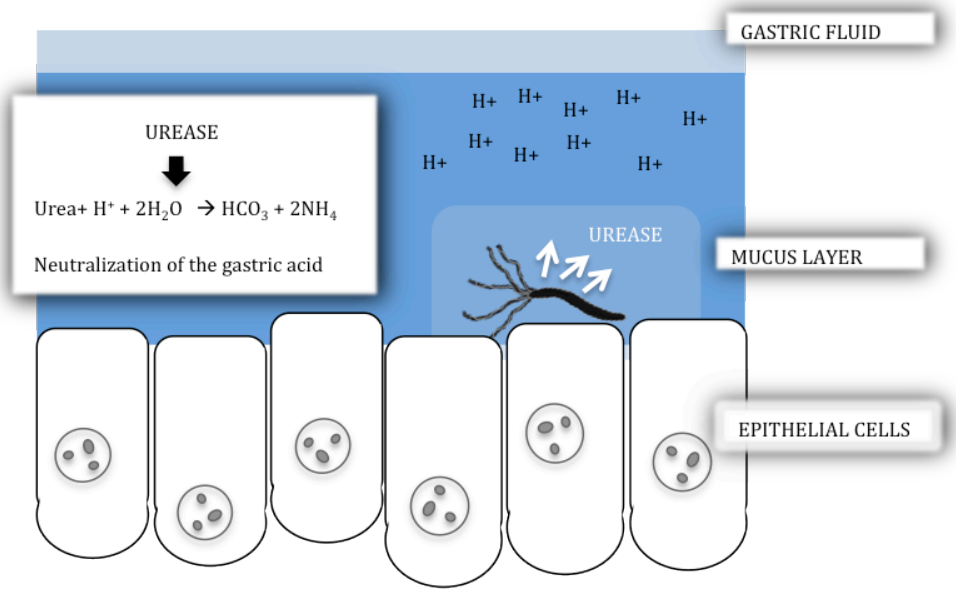

Figure 5. H. pylori invasion part two. Source: (Helicobacter Test, 2010)

The more beneficial environment allows the bacteria to reproduce and colonize. The produced ammonia is toxic to the epithelial cells. This is one of many mechanisms that damage the epithelial cells and results in an inflammation of the stomach lining, which is called chronic gastritis (Smoot, 1997), see figure 5.

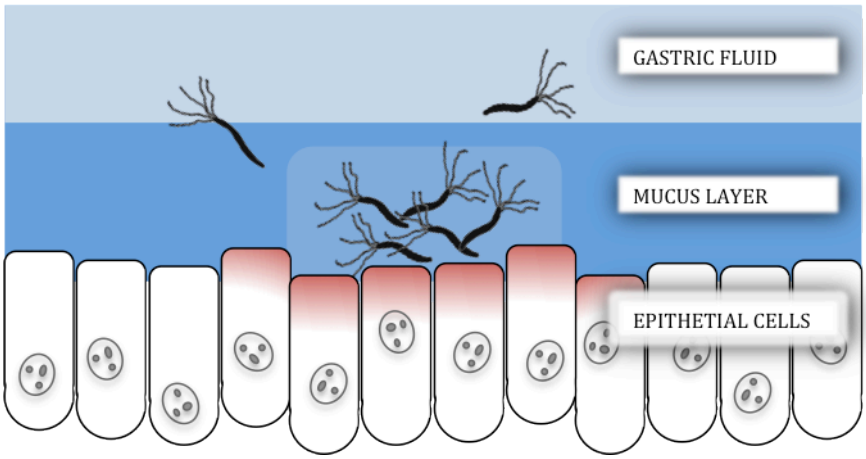

Figure 6. H. pylori invasion part three. Source: (Helicobacter Test, 2010)

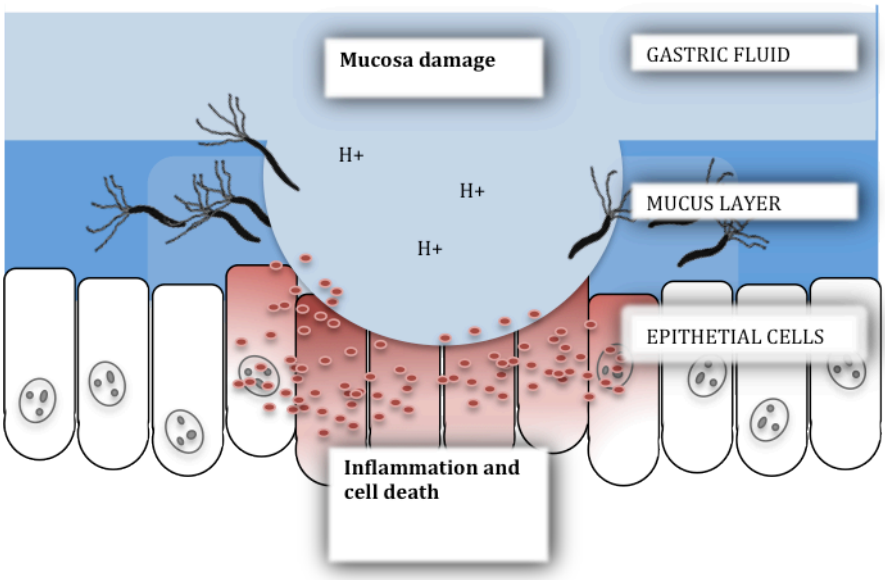

Figure 7. H. pylori invasion part four. Source: (Helicobacter Test, 2010)

Peptic ulcer
A severe chronic gastritis can erode the mucosa and leave a hole in the mucosa, which is called a peptic or gastric ulcer depending on location.

Peptic duodenal ulcer
One important factor that determines the localization site of the colonization of H. pylori is the acidity in the lumen. Cells producing stomach acid are located in the lumen or main body of the stomach. If an individual produce a large amount of acid, H. pylori will infect the astral part of the stomach (downstream), far away from these cells, to avoid the most acidic environment. When colonized in this part, the H. pylori infection will initiate the production of a hormone that will further increase the production of stomach acid. This up-regulation of acid levels results in a higher risk of developing ulcer in the duodenum. The increased risk of ulcer in the duodenum can be due to more stomach acid transported to the duodenum. The duodenum is normally an environment not suitable for the H. pylori bacteria, as the existence of bile acids that inhibits growth of the H. pylori bacterium. The stomach juice precipitates bile acids located in the duodenal bulb and a reduction of bile acids promote the growth of the bacteria. Existence of H. pylori bacteria in the duodenal increases toxic effects of epithelial cells, which together with high levels of stomach acids damages and erodes the epithelial cells. When a damaged area becomes sufficiently large, it will be classified as an ulcer (Kusters, 2006).

Peptic gastric ulcer
If the initial acid production in the individual is lower than normal, H. pylori can colonize the corpus of the lumen. Through affecting the mechanisms involved in producing the stomach juice the acidity in the stomach can further decrease. This results in a pH-level even more suitable for the H. pylori bacteria and increases the colonization and can lead to cell death and the development of ulcer in the stomach lumen (Kusters, 2006).

Bleeding peptic duodenal and gastric ulcer
Bleeding peptic and gastric ulcer occurs spontaneously when the ulcer spread to a blood vessel. In most of the cases, more than 80 percent, it heals itself, but in some cases it does not. This leads to acute bleeding ulcer. Acute bleeding ulcer is highly life threatening (Laine, 1994).

Gastric cancer
Colonization of the corpus is associated with an increased risk of developing gastric cancer. The exact mechanisms are not known, but it is proposed that increased production of free radicals or a local inflammation can be the cause. In contrast, a colonization of the more astral part (downstream) of the stomach is not associated with an increased risk of gastric cancer (Kusters, 2006).

Gastric cancer can be classified into five different medical stages depending on the progress of the cancer. The first stage is a very early stage of cancer where abnormal cells are found inside the lining of the mucosa of the stomach wall. The later stages depends on how the cancer has spread - which layers in the stomach walls that are invaded and in number of nearby lymph nodes cancer cells can be found. In later stages, cancer has spread to nearby organs and in the last stage to distal parts of the body (National Cancer Institute, 2012).

3.2 Treatments

For the different diseases caused by H. pylori, there are different treatments. Below are the most common treatments for each respective disease.

H. pylori
In Sweden there is currently no population screening against H. pylori. Spontaneous screening with patients without symptoms exists to some extent but is not common. Patients who seek medical care for dyspepsia, such as peptic ulcer, which often has a strong connection related to H. pylori infection, are tested for H. pylori (Svedelius, 2012). Unfortunately, not all persons seeking care for dyspepsia get tested for H. pylori even though it should be done according to national guidelines. Only approximately 43% of patients seeking care for dyspepsia get H. pylori tested (SBU, 2011).

To eradicate H. pylori a three-part therapy, containing two antibacterial agents with an anti-secretory agent, is used. The last part is a so-called proton pump inhibitor (PPI) or an H2 antagonist. The treatment duration is approximately one week and after the treatment duration the H. pylori infection is eradicated in 95%. Eradication is defined as "*absence of detectable organisms one month after cessation of treatment*" (Roderick, 2003). This combination has some drawbacks. When used in larger scale increased antibiotic resistance can be an issue.

Chronic gastritis

When the patient suspects gastritis, the patient goes for a medical examination at their house doctor or closest primary care center. If symptoms are diffuse, the patient might receive a letter of referral to a specialist in the gastric area where the patient is examined with gastroscopy or blood test. The treatment when the patient gets the diagnosis gastritis is a PPI treatment as described above under "H. pylori" (Svedelius, 2012).

Peptic duodenal and gastric ulcer

Firstly, the patient visits his house doctor or the closest primary care central. To diagnose ulcer, secondly a letter of referral is given to the patient for a medical examination at the gastrologist, including gastroscopy and blood test. Treatment of ulcer is made mainly through medicine (the same as for gastritis). If the ulcer is bleeding, the patient will have acute surgery as this condition is life-threatening (Svedelius, 2012).

Gastric cancer

The first step for a person with suspected gastric cancer is to visit the house doctor or the primary care center, which is generally done when symptoms are present. Here, the doctor will make a basic medical examination in order to understand the often-diffuse symptoms. The house doctor will, if he/she suspects gastric cancer, send a letter of referral to a specialist in the gastric area. The patient will be sent to a gastrolog. Here, matrix tests (biopsy) will be taken that are sent for analysis to a pathologist. Also, gastroscopy will be performed. Gastroscopy is an examination that allows the doctor to see through a small video camera that is sent down through the intestine to look at the gastric area. Additional x-ray treatment is performed (Svedelius, 2012).

If the gastrolog confirms the diagnosis gastric cancer, the pathologist defines which type of cancer the person has through the biopsy test. The cancer stadium will be confirmed, and based on which stadium the cancer is in, there are different treatments. If the cancer is in stage three or higher, cytostatic will be set in for the patient directly. The cancer might then have spread to the lymphatic glands. Often in this case, the treatment is mainly regarding facilitation of the last period in the patient's life, as this condition is very severe. If the cancer is in stage one or two, and the patient has a normal condition (is not to old, weak or sick in other diseases),

surgery will be the next step. The size of the surgery depends on the condition of the patient and the stage of the cancer. Removal of lymphatic glands can be a necessary (Svedelius, 2012).

If the outcome of the surgery is positive, without complications and the patient recovers the patient will attend a medical examination at a minimum of once per year, likely more often. After five years of no cancer cells growing, the patient is considered as fully recovered. If the outcome of the surgery is negative or if it has severe complications, the outcome is highly related to the specific case. For those where the surgery cannot save the patient, it is a matter of home care for the last time alive (Svedelius, 2012).

Treatment course for gastric cancer in Sweden:

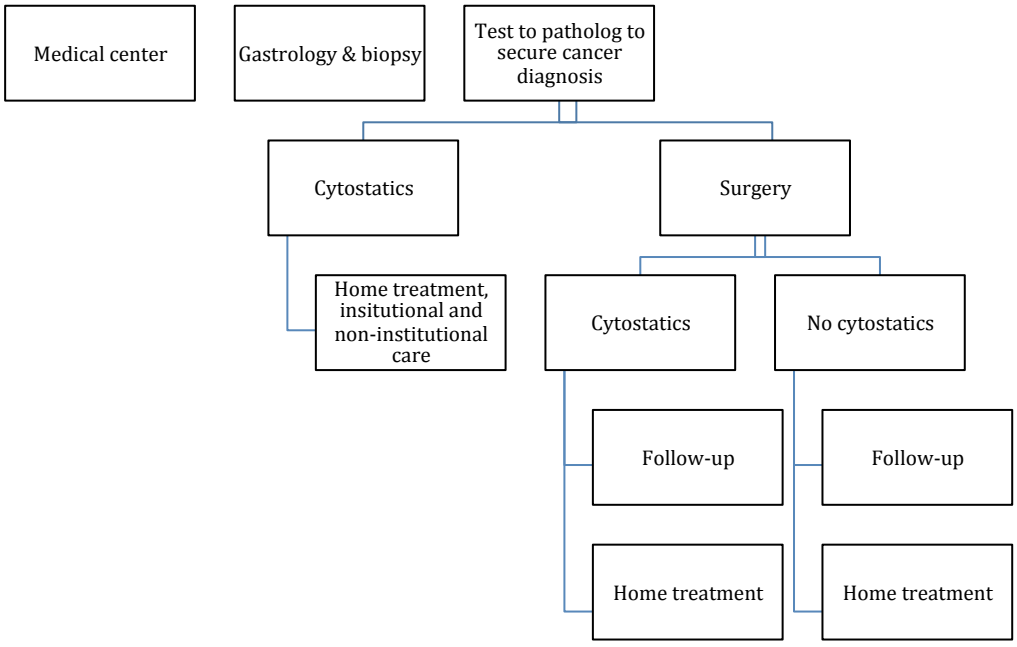

Figure 8. Source: (Svedelius, 2012)

4. Modeling framework

In this chapter a modeling framework is presented. The modeling framework provides a structure and a process to be used when performing an economic evaluation of a screening program. The modeling framework consists of different parts in which different techniques or approaches are possible. These will be reviewed and their benefits and drawbacks will be presented. Theories regarding how to handle costs and outcomes for the screening program will be presented.

4.1 Economic evaluation of screening programs

Economic evaluation of screening programs belongs to the discipline economic evaluations in health care. Economic evaluation in health care have since the birth of the discipline in the 1960's continuously increased in maturity. Today the discipline involves well-developed methodical procedures and frameworks (Arrow, 1963).

The health care systems today are large and complex, why it can be difficult for decision makers to evaluate effects of specific decisions or investments. An important purpose of economic evaluation in health care is to support policymakers and decision makers regarding which health care program to implement and which medical devices to invest in (Philips, 2006). The discipline have today gained acknowledgement as an important tool in decision making in health care (Drummond, 2005).

The gains of using a structured economic evaluation increases with the complexity of the issue associated with a decision. The issue whether a particular screening program should be implemented is very complex. Usually it involves a detailed description of a specific disease, costs and health indicators related do the disease, the disease prevalence in a population and the interaction between the screening program and previous named aspects. Due to this complexity, a structured economic evaluation can provide a better understanding of the issue compared to a more ad hoc approach (Drummond, 2005).

Drummond (2005) defines economic evaluation in health care as "*the comparative analysis of alternative courses of action in terms of both their costs and consequences*". An evaluation only considering costs or only considering consequences is not according to this definition an economic evaluation, but belongs to the broader category of health care evaluation. In economic evaluations, costs represent different costs arising from health care practices, and in some cases costs for other parts of the society that for example can be an effect of productivity losses. Consequences include many measurements depending on the specific issue.

It ranges from time in hospital to difference in quality-adjusted life years (QALY) (Drummond, 2005).

4.1.1 Types of economic evaluation

Drummond (2005) distinguishes between three different kinds of economic evaluations; cost-effectiveness analysis, cost-utility analysis and cost benefit analysis. They can all be used as economic evaluations of a screening program and the difference between the analyses are which consequence that is related to the costs. A cost effectiveness analysis compares costs related to a single effect or consequence of a health care program. A common used unit of consequence is saved life years. Cost utility analyses are similar to cost effectiveness analysis, with the difference that cost utility analysis includes how different consequences are perceived by health care receivers. It is common to use the unit of quality-adjusted life years saved (QALY). In cost benefit analysis, money is used as only measurement. Consequences like QALY need to be translated into monetary benefits. This can be useful when there is no maximum budget involved (Drummond, 2005).

4.1.2 Costs

Which costs to consider in an economic evaluation in health care depends on the specific case. Nevertheless, there are different approaches to choose between. One way is to map out all the events from a macro perspective, which are the sources to related costs. These sources are given values, and the result is a total cost per year. Another way is to trace costs for a perspective of individual patients, where the resources that the patients uses during a period of interest are studied. This approach gives the cost related to the incidence or to the number of caused cases. It also gives the average costs per fallen ill person, from the disease is diagnosed, until the patient dies (Brown, 1996).

Drummond (2005) states that costs associated with health care studies can be divided into four different parts; health sector, other sectors, patient and family costs and productivity losses. *Health sector* includes costs such as hospitalization, physician visits, diagnostics, treatment, and medicaments et cetera. It includes not only the initial care, such as surgery, but also the following costs such as treatments and check ups after the disease is cured. Resources used in *other sectors* include all costs from other sectors than health sector. These costs are very individual and depend on the specific case an example can be costs related to homemaker service. *Patient and family costs* include “out-of-the-pocket costs”, mainly costs for travels, expenditure in the home such as new equipment. The most important cost here is time - time that could be spent on for example work or leisure time. The time can be spent on seeking and receiving care or getting information regarding the disease and treatment. Also, a lot of time is spent on worrying. The cost with the largest impact is *loss in productivity* (Drummond, 2005). Productivity can be measured in two ways.

For both methods, valid is that only time until retirement age is counted, as retirement not is a societal cost and does not matter for an economic evaluation. One method, the *human capital method*, follows one individual and measures all the time that an individual cannot work properly due to the disease. This is based on estimation of changes in productivity for the person. Typically estimated are gross earnings of those in employment, and included is the use of average wages. The other method is *friction cost method*. In this method the amount of production loss is calculated only for the friction time between one sick person is leaving the job until the next person takes its position. Friction cost method is more complex to calculate since all employments are different. The friction time is likely to differ between industry, location, firm and category of employed persons (Drummond, 2005).

Also other classifications occur, such as direct and indirect costs. Direct costs are costs such as prevention, diagnostics, medicine, care, other treatments and terminal care. Direct costs also include travel expenses for the patients, costs for home care and closely related care. Indirect costs include costs for the time that relates to the care for the patient and the closely related and production loss for the patient. Psychosocial costs are also important, though very difficult to measure. These costs are costs for a decreased life quality for the time during and after the cancer. Examples are unwanted changes home or at work, social changes, pain, psycho-related difficulties (Brown, 1996).

4.1.3 Consequence

Consequences can be measured in different units. What unit that is appropriate depends on the specific issue and which evaluation is made; cost-effectiveness analysis, cost-utility analysis or cost benefit analysis.

The consequence of a cost-effectiveness analysis can for example be years of life saved, premature births averted or lives gained.

The consequence of cost-utility analysis is similar to consequences used in cost-effectiveness analysis. The important difference is that cost-utility adds the preference individuals or different societies may have on the health outcome outcomes. A unit of consequence that includes this addition is QALY, earlier described. Life years saved with the treatment is also measured. The advantages of QALY as a measure of health outcome is that it can capture gains from reduced morbidity (quality gains) as well as reduced mortality (quantity gains) and combine these in one measure while at the same time taking individuals preferences into consideration. The measurement method is a relative measurement that is used when comparing two scenarios (Drummond, 2005).

The consequence of a cost benefit analysis is always monetary; as for example saved years will be to be translated into money.

4.1.4 Approach to economic evaluation

Regardless if it is a cost-effectiveness analysis, cost-utility analysis or cost benefit analysis the process of performing an economic evaluation of a screening program share many components. One important component is the gathering of evidence from various primary studies with information including the natural history of disease, impact of treatments and costs of treatments. The other part is the use of an analytic framework to merge evidence and produce output in terms of the costs and consequences (Philips, 2006). One structured approach or framework that includes both these parts is decision-analytic modeling (Philips, 2006) (Drummond, 2005).

Decision-analytical modeling is particular good to use when the primary receivers are policy-makers. It is suitable to use when extrapolation of primary data is needed, as the evaluation time is longer than the time of study. Further, it is specifically good to use when making a comparison between two outfalls where no primary data study is performed for the exact two alternatives at the same time. In the development of new public programs where primary data is scarce, decision analytical modeling is a good tool to use for decision-makers. A well functioning model should act as aid for the decision-makers, which decision-analytical modeling does. An economic evaluation based on decision-analytical modeling adds value when taking investment decisions. It also structures the existing data and prioritizing data in a helpful way (Buxton, 1998).

4.2 Decision-analytic modeling

The use of decision-analytic modeling in health care is getting more and more common. According to Philips (2006) "*decision-analytic models represent an explicit way to synthesize evidence currently available on the outcomes and costs of alternative (mutually exclusive) health care interventions*" (Philips, 2006). Drummond describes a general process of creating a decision model under the following seven headlines:

4.2.1 Defining the decision problem

The decision problem is the specific question that is to be answered. There is a need to define the recipient group and the relevant scenarios to be compared. These scenarios need to be explicit defined and well explained. In an evaluation of a screening program the different scenarios can be classified into two groups of different scenarios. One group with scenarios related to a situation without a screening program and the other group with scenarios representing variations of a screening program. Also, the output in terms of costs and consequences needs to be defined including which costs to include and how the consequences is measured (Drummond, 2005). In this process it will be determined what type of economic

evaluation that will be used, for example cost-effectiveness, cost-benefit or cost-utility.

4.2.2 Defining the boundaries of the model

The boundaries of the model should include larger initial simplifications. All models are simplifications of the reality and simplifications are necessary. Using more simplifications or narrower boundaries reduces the complexity but can make the result less accurate. Extending boundaries increases the complexity but can as a potential gain increase the accuracy of the result. Available data and quality of available data is one aspect that effect outer limits of the model boundaries. An ambition should be to set the boundaries in a way that makes extending them unlikely to impact the result in a significant way. If there exist similar studies, it is a strength if the boundaries can be set in a similar way to increase credibility and comparability. Example of boundaries includes: time frame under which the scenarios are compared, unit of time used and which complications related to the involved disease that are studied (Drummond, 2005)

4.2.3 Structuring of a decision model and choosing mathematical structure

The purpose of structuring a decision model and choosing mathematical structure is what many would refer to as building the model: to determine how the different scenarios will be evaluated and transferred into the specified output within the specified boundaries of the model. The creation of such a model would involve many steps. The first involves figuring out what the input would be and how that input will connect do the desired output. In the later stages the main activity would be building the model in a suitable programming language.

A decision model can be described using three different dimensions or levels: general structure, mathematical technique and detailed model, ranging from a higher to lower abstraction. The general structure would result in the big picture, explaining the relations between different important aspects on a fairly abstract level. The mathematical technique would describe the mathematical structures to use. The detailed model would be a detailed description of how the inputs and outputs are connected with help from the mathematical techniques.

The creation of a model is most often an iterative process involving studying existing screening models structures, literature describing natural history of diseases and communication with analysts and experts. In earlier iteration of the modeling, a complex model structure should be used. In an iterative process the complexity of the model can be reduced by using adequate assumptions (Karnon, 2007).

4.2.3.1 General structure

According to (Milton 2003), general structure *"should be consistent both with a coherent theory of the health condition being modeled and with available evidence*

regarding causal linkages between variables" and *"[t]he structure of the model should be as simple as possible, while capturing underlying essentials of the disease process and interventions*". This general structure should explain how the reality is interpreted in the model. The boundaries of the model described above would set the outer boundaries for the model structure (Karnon, 2007).

The preferred general modeling approach within screening is to model the natural history of diseases, which describes diseases from the time they can be detected until a potential death. Also, the relationship between the natural history of disease and specified output in terms of costs and consequences should be defined. When these relations are specified, base scenarios could be built by using the current health care policies and practices (Karnon, 2007). When describing the general structure, different states together with relations between states could be used. This is a general approach not limiting the possibility of using different mathematical techniques. When describing disease states, parameters that influence treatment choice and effectiveness should be used.

4.2.3.2 Mathematical techniques

From a given general structure there are several different mathematical techniques that can be used. Which one that is the most appropriate depends on the general structure. The different modeling techniques can be categorized by three important properties, which are called simulation taxonomy. The dimensions are:
Presence of time - static or dynamic time. A dynamic model takes into consideration if the model needs to handle events that are separated with time, while a static does not.
Basis of value - discrete or continuous. A discrete model handles data in chunks as separable pieces while a continuous model represents continuous data. Models working with continuous data usually involve differential equations.
Behavior **-** deterministic or probabilistic. A deterministic model produces the same output every time, given a specific set of parameters. A probabilistic or stochastic model involves randomness from parameters in the form of probability distributions or through introducing randomness in model propagation. (Sulistio, 2004).
Level of analysis – individual or aggregated. A model an individual level of analysis allows individual subjects to propagate through the model and aggregates the result after the simulation. When the level of analysis is aggregated a population of subjects propagates through the model resulting in an aggregated output. This can also be viewed as a micro or macro perspective.

In the history of health care evaluations a number of different modeling techniques, with different simulation taxonomy, have been used. Some of the techniques commonly used are described below with a description of strengths and weaknesses:

A. Decision tree analysis

Decision tree is a common structure in health care evaluation (Drummond, 2005). A decision tree is a structured way to evaluate outcomes or alternatives that can be structured in a tree hierarchy with one parent node and one or more child nodes in each level. This structure results in a number of separate pathways that are the result of different turns in each node. The output of a decision tree analysis can be expected value of costs and benefits associated with each pathway. One advantage with tree analysis is that it makes it possible to separate a complex problem into parts. One drawback is that it is hard to evaluate alternative pathways separated in time (Barton, 2004). Using the simulation taxonomy explained above decision tree analysis is a static, discrete and deterministic approach and it can either be individual or aggregated (Sulistio, 2004).

B. Markov Models

Markov models are getting more and more common in health care evaluation as this model represents stochastic processes, which is random processes that evolves over time. This, together with the fact that Markov models can handle costs and outcomes, separated in time, in a simple and powerful way makes it suitable for economic evaluation in health care. The basic idea behind Markov models is that a process is described as transitions between a number of states, which occurs at fixed intervals. From each state it is possible to stay in the same state or to move into one or more other states (Drummond, 2005). This is determined by probabilities that are specific for each state transition and only depend on the current state. This can be interpreted as that the Markov model has no memory and this is called the Markov property (Sulistio, 2004). Mathematically this can be expressed as follows:

$$\Pr(X_{n+1} = x | X_1 = x_1, X_2 = x_2, \ldots, X_n = x_n) = \Pr(X_{n+1} = x | X_n = x_n).$$

Markov models are convenient when recurring events are to be evaluated. If a process has probabilities that vary with time it can be inconvenient to use a Markov model. It is possible but can result in a very large amount of states, which will add complexity (Barton, 2004) (Drummond, 2005). Markov model is a dynamic, discrete or continuous and deterministic approach (Sulistio, 2004).

C. Individual sampling

Individual sampling models are a collection of models where an individual is tracked individually. In some literature this is also called discrete-event simulation or state-transition model. This technique gives the benefit of greater flexibility but makes the data population of the model more complex (Drummond, 2005). This structure can follow the principle of Markov models with a number of states each individual can move between in fixed intervals. As an addition to Markov model, this technique has the flexibility to lose the Markov property and can have transition probabilities that depend on time and history (Barton, 2004).

In 1985 the ‘‘Micro simulation Screening Analysis” (MISCAN) model was introduced to evaluate the impact of cancer screening (Rutter, 2011). MISCAN has later been used to evaluate screening against cervical, breast, colorectal and prostate cancer. Micro-simulation is an example of natural history modeling, which lately has been described as the preferred general modeling approach to evaluate screening by Karnon (Karnon, 2007). Individual sampling models are dynamic, discrete and probabilistic (Sulistio, 2004).

D. Discrete event simulation

Discrete event simulation is a term used by Robinson (2004) to describe models that in many ways are similar to individual sampling but allows the modulation of interaction between individuals. This adds one more layer of complexity to the model calculations, which can result in computational challenges during for example sensitivity analysis (Barton, 2004). Discrete event simulation models are dynamic, discrete and probabilistic (Sulistio, 2004).

5. System dynamic model

System dynamic models represent a group of models that takes interaction between individuals into consideration but works on an aggregated level and not simulate individuals (Sulistio, 2004).

Choice of mathematical technique

Each mathematic technique described above has its own strengths and benefits. The most appropriate one depends on the general structure (Karnon, 2007). Robinson (2004) created a framework to decide which mathematical technique to use depending on key aspects in the modeling structure.

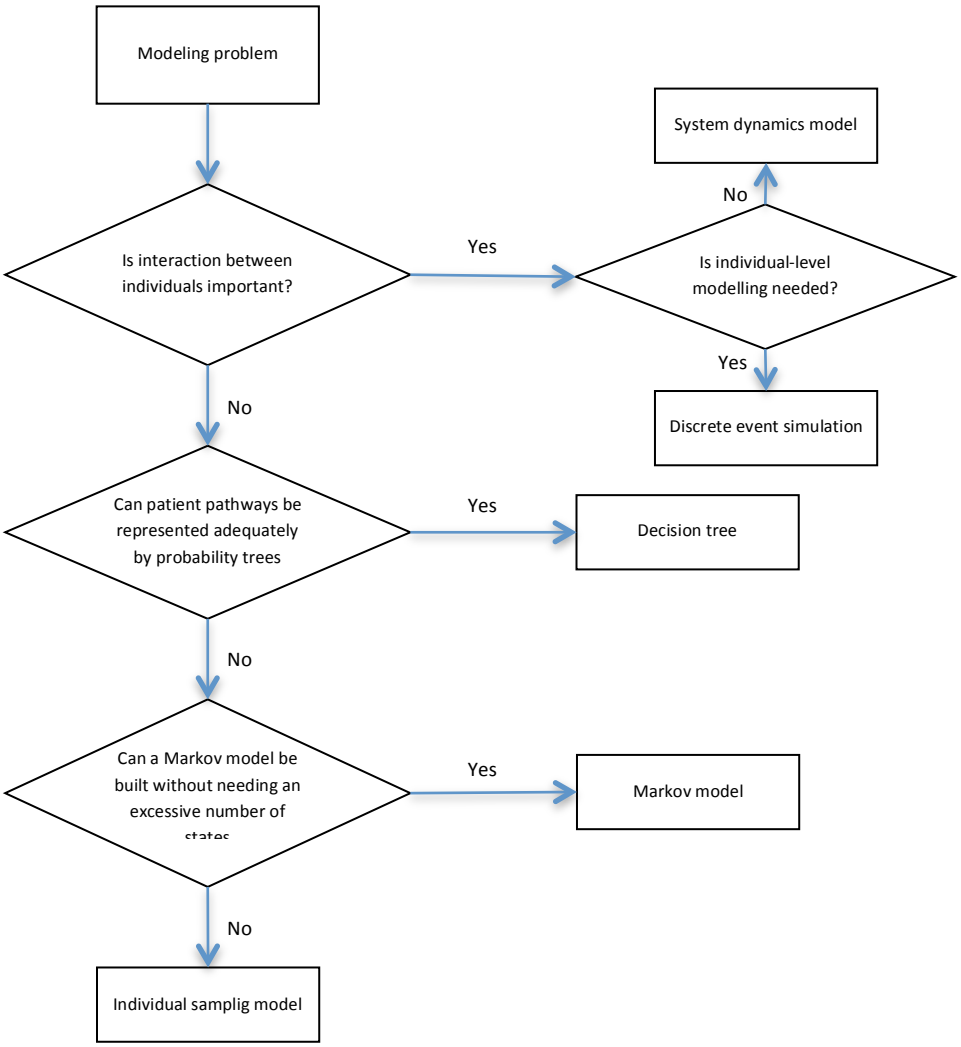

Figure 9. Choice of mathematical technique. Source: (Barton, 2004)

4.2.3.3 Detailed model description

A detailed model description explains how the mathematical technique is used to deliver results. The described relationships between the input parameters are described as the general structure. This detailed model description can be explained in code, in pseudo code or in a more abstract fashion.

4.2.4 Identifying and synthesizing evidence

When the structure of the model is established, it is necessary to identify available data to populate the model. The data should not be identified selectively, but systematically. As one parameter input can be the result of several sources, evidence synthesis is important in a decision-analytics model. This can include how to use observational data in estimating treatment effects, how to estimate effectiveness when trials have not been compared 'head-to-head' and how to estimate treatments when different follow-up periods have been used (Drummond, 2005).

4.2.5 Dealing with uncertainty

Uncertainty exists in all models and it is vital to handle this uncertainty. There are different kinds of uncertainty in decision analytical modeling.
Parameter uncertainty reflects the uncertainty within input data. All data should be estimated as precise as possible, as a certain amount of uncertainty in every parameter can give a large uncertainty in the result. Also, it is important to use all data available, as a sample of data that is used may not represent the whole properly. In order to handle issues with parameter uncertainty, a sensitivity analysis on how it impacts the result should be made. It can be made through standard sensitivity analysis, where the parameters are tested in a range to see how much impact they have on the final result. Another sensitivity analysis is probabilistic sensitivity analysis, which is more complex and the uncertainty is estimated in different stages of the model (Drummond, 2005).

Structural uncertainty is the uncertainty that comes with the simplification of the reality. In all models, simplification has to be done by assumptions. The assumptions are preceded by judgments made regarding the structure of the model. This structure can therefor induce uncertainty. An analysis should be performed that determines to which extent every assumption has impact on the final result. This can be made through making other assumptions than the chosen, place weights on the different assumptions and test and observe the outfall. This is called 'modeling averaging'. A less complex way is to test with different assumptions and run the model to see how it affects the output. In some complex models, for example comparing cost and effectiveness with micro simulation in cohorts, this is not straight forward applicable because there are many assumptions made. It would probably result in two different models. In this case, a Markov model can be built in order to test the structural uncertainty (Drummond, 2005).

4.2.6 Dealing with variability

Variability concerns that input data might be collected in a context that differs from the context of the study. For example if data is collected from a group of individuals that differs from the group of individuals to be evaluated in the study. Data can also vary between studies as they have used different follow-up time, test age groups etc. The appropriate way of dealing with variability is to run the model and present the data for every subgroup. The decision model is an allowing model to work with regarding variability, as its assumptions rely on heterogeneity. Nevertheless, it is for every specific case a need to deal with parameter variability suited for every subgroup (Drummond, 2005).

4.2.7 Evaluation of the decision model

Even though decision analytic modeling have been used frequently in health care several different best practices have emerged. In a review from 2006, Philips and her team merged different best practices into a decision analytic model evaluation framework. This framework can provide support during model development and to ensure quality of the developed model (Philips, 2006).

The framework is divided into three parts: structure, data and consistency, with a number of guidelines associated with each part. Structure concerns the models general structure, mathematical technique and detailed model description. Data includes identification of data and also the process of pre-model data analysis. Consistency is concerned with the overall quality of the model (Philips, 2006). The full list of guidelines is presented in Appendix 1.

5. Model

This chapter will present the model for the economic evaluation. The model is built upon the theoretical framework presented in "Model framework".

5.1 Defining the decision problem

The decision problem is to evaluate if there is a screening scenario against H. pylori that is cost effective on a societal level for Sweden. The recipients are the state of Sweden. To evaluate this problem, two distinct scenarios are compared. The first scenario reflects the current practice regarding treatment and management of the H. pylori infection and related diseases. The second includes an implementation of a screening program. The two different scenarios are described in more detail below.

5.1.1 Scenario one

The first scenario describes the current situation regarding management and treatment of H. pylori and the diseases that are associated with the bacterium.

5.1.2 Scenario two

Scenario two describes a group of scenarios simulating the result of different screening programs against H. pylori. The difference between the different scenarios will be which part of the population in terms of age groups that are to be invited for screening. The screening programs will be added to the current H. pylori management and treatment direction and practices.

The version of the screening program will be constructed as follows: an individual who belongs to the screening target group gets an invitation to attend a test session. Some of the invited individuals attend a screening session at a medical care center where they will be tested against H. pylori with urea breath testing. With this test, the result is shown direct and if the result is positive the individual is offered a three-part therapy to eradicate the H. pylori infection.

5.1.3 Cost and consequences considered

The two scenarios will be evaluated through a comparison of the discounted costs associated with the two scenarios and difference in life years saved.

5.1.3.1 Costs

Costs considered will be 1) costs associated with diagnosis of the diseases related to the H. pylori infection. The main costs are divided into health-sector costs and productivity losses per disease diagnosis, 2) costs associated with implementation

and running of a screening program. These costs are also divided into health care and productivity losses.

5.1.3.2 Consequences

The consequence considered will be measured as the difference in life years saved. QALY will not be used. This is measurement that has some benefits compared to measurement of life years saved. However the hypothesis of this study is that an implementation of screening program would be associated with a net present value above zero. If this is the case and the difference in life years saved favor the screening program adding complexity by calculating QALYs would not change the implications of the result.

5.1.4 Evaluation time

The two different scenarios will be compared during a time of 100 years. The time limit of 100 years is a balance between accuracy and computation time. Costs (and benefits) are meant to discount, in order to provide a net present value. When performing net present value calculations of an investment all costs, revenues and benefits associated with the investment should ideally be included (Valuation). In practice it is usually not possible to include all future costs, revenues and benefits and also costs, events in a distant future is unlikely to affect the result in a significant way due to the effect of discounting. According to Drummond (2005), the evaluation time should be “long enough to capture the major health and economic consequences”. A time shorter time period would result in missing some important aspects. The prevalence of the H. pylori infection amongst newborns is much lower compared to older age cohorts. The effect of the newborns would not be observable if the time length would be shorter than the age when these individuals are likely to develop ulcers and gastric cancers, which is as high as 80 years old. A longer time period would add computation time and with a discount rate of 3 %, costs in 100 years will be discounted with a factor below 0.05 and have an insignificant impact on result. See “Model data” for details.

5.2 Defining the boundaries of the model

Time unit used is year. Left out is patient and family costs as well as retirement costs. Also, time-consuming activities that decrease quality of life such as worrying costs are not considered. We are only looking at the impact of H. pylori on the diseases described in the study, gastric cancer and peptic ulcer. Unit for cases is number of diagnosed cases. The fact that the H. pylori infection increases the risk of developing other diseases is not included. Costs of diagnosis and treatments are treated as constant. All costs are considered constant during the time; as for example technical innovations disrupting the industry is not taken into account.

5.3 Structuring of a decision model, choosing mathematical technique and mathematical structure

In this part the decision problem will be developed into a mathematical structure that with the right input will be able to deliver a solution to the problem. Initially the general characteristics and specifications of the model will be outlined. Followed is a description of the interpretation of the disease process from a societal perspective. This will make it possible to decide upon which mathematical technique that is suitable. Finally the final model will be described.

To deliver the output the model needs to estimate the difference between the non-screening and the screening scenario in terms of: number of diagnosed cases of gastric cancer, peptic duodenal and gastric ulcer. From this, the model needs to estimate health care costs and costs for society as well as the difference in the total number of years all individual, dying in gastric cancer and peptic ulcer, are losing compared to if the individuals would have died from other causes instead. Number of people attending screening and eradication sessions during the considered time period needs to be translated into costs.

To estimate the difference between the two scenarios, the first non-screening scenario will be created first. The screening scenario will be created as an extension of the non-screening scenario.

In the first scenario the future effects of the current H. pylori practice and management should be simulated and estimated. To achieve this, a model of how individuals acquire H. pylori, get ulcer and cancer and die from these diseases is needed. This model of the natural history of disease should be build upon knowledge of H. pylori infection and heath care practices. It is important that this model has the right level of detail and balancing accuracy and complexity.

On top on this first scenario, a model of a screening program should be applied, which during the simulation time will result in different prevalence of H. pylori. This would in turn affect the number of cancers and ulcer diagnosis and also increase costs from the screening practice.

The model of the natural history of disease for the H. pylori infection and related diseases can for one individual be described by a number of states and a number of state transition probabilities. Initially, there are many different states. For the ambitious reader these are presented in Appendix 2. The number of states is then reduced to decrease the complexity. The ambitious reader can find this explained in detail in Appendix 3.

Interpretation of the natural history of disease state description
An individual without an H. pylori infection can acquire the bacteria at any age. An infected individual can get rid of the bacteria or get a H. pylori infection induced peptic ulcer and/or gastric cancer diagnosis. An individual with a prior H. pylori infection can also develop a H. pylori infection induced peptic ulcer and/or gastric cancer diagnosis.

An individual with a H. pylori infection induced peptic ulcer diagnosis receives a treatment that results in costs and an outcome as either treated from the ulcer or dead. The H. pylori infection is either treated or not treated.

An individual with a H. pylori infection induced gastric cancer diagnosis receives a treatment that results in costs and an outcome as either treated from the ulcer or dead. The H. pylori infection will either be treated or not treated.

The states are described in Figure 10 below.

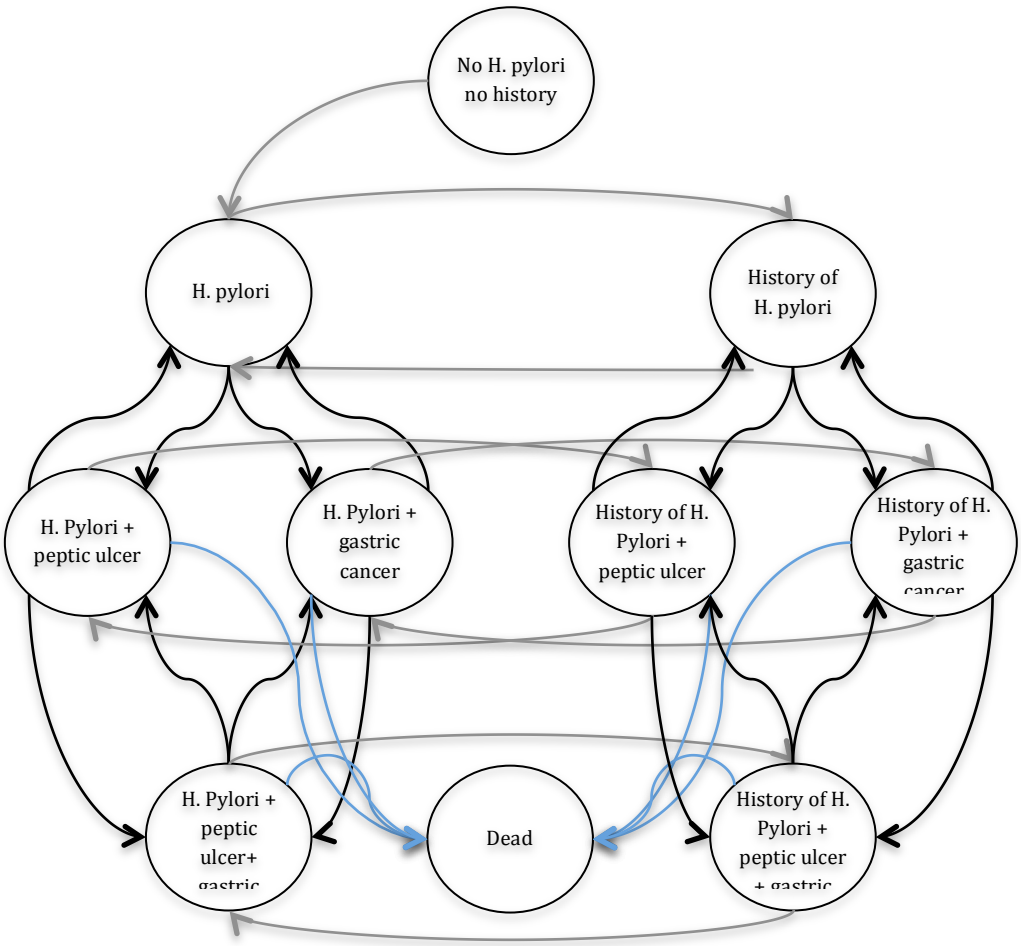

Figure 10. Final state description used in model.

Mathematical technique: individual sampling

To transfer the model interpretation into a detailed model that will be able to deliver output, a choice regarding which mathematical technique to use needs to be made. To choose an appropriate mathematical model the framework suggested by Robinson (2004) has been used. See Figure 11.

The first question addresses whether individuals can be viewed as independent or if interaction between individuals needs to be taken into consideration. Even though there might be interaction between individuals, concerning for example the process in which the H. pylori bacteria is acquired, the individuals will be viewed as independent. In literature this is the common way of viewing interaction between individuals when evaluating screening programs. The two different decision alternatives will be evaluated during a period of 100 years. This time factor makes it inappropriate to use a decision tree to compare pathways. The model described above in Figure 10 includes 10 different states when not taking time dependent transition probabilities into account. When this is taken into account this number would grow to be far to large to represent in a Markov model, which leads to individual sampling as a appropriate model candidate. It has been used in many screening program evaluations including models evaluating screening program against H. pylori and will therefore be the modeling technique of choice.

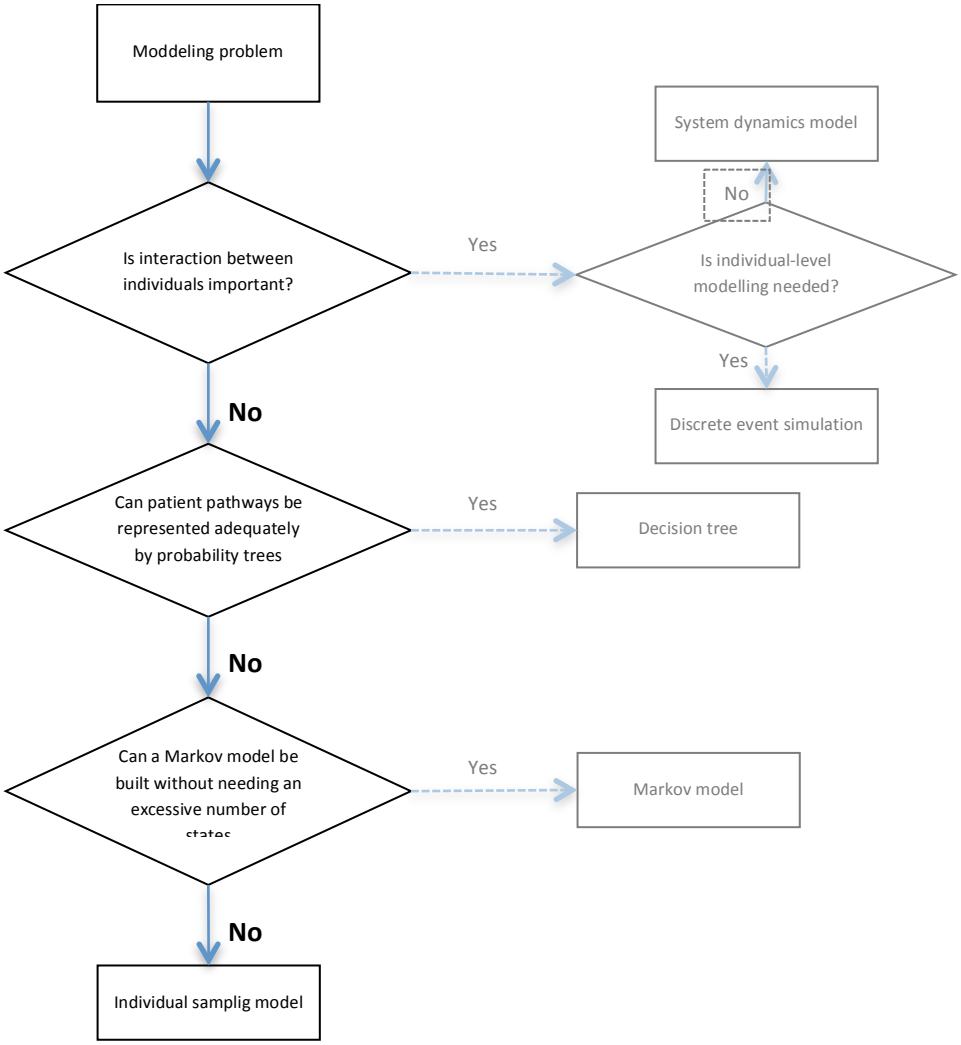

Figure 11. Figure explaining which modeling technique to use. Robinson (2004)

Description final model

To compare the two scenarios with an individual sampling model, a number of individuals corresponding to the Swedish population will be modeled individually during the evaluation time. Each year of the simulation individuals will age. A minority will develop diseases related to H. pylori and the majority will not. Some individuals will die from causes related to H. pylori. New individuals will be born. During this time, costs related to diagnosed cases will be aggregated. In one of the scenarios a screening program will be modeled which will add costs and change prevalence of H. pylori and related diseases.

The individual in the model will be described by the following parameters: age, if the person has H. pylori, if the person has ulcer, if the person has cancer and the total

time the individual have been infected with H. pylori. These parameters covers the different states described above in figure 10.

The model can be viewed as a four-phase process with the phases:
1. Creating population representing the population in Sweden today
2. Simulating the effect of progress during 100 years
3. Structuring of output
4. Comparison of scenarios and visualizing output.

The model is displayed in Figure 12:

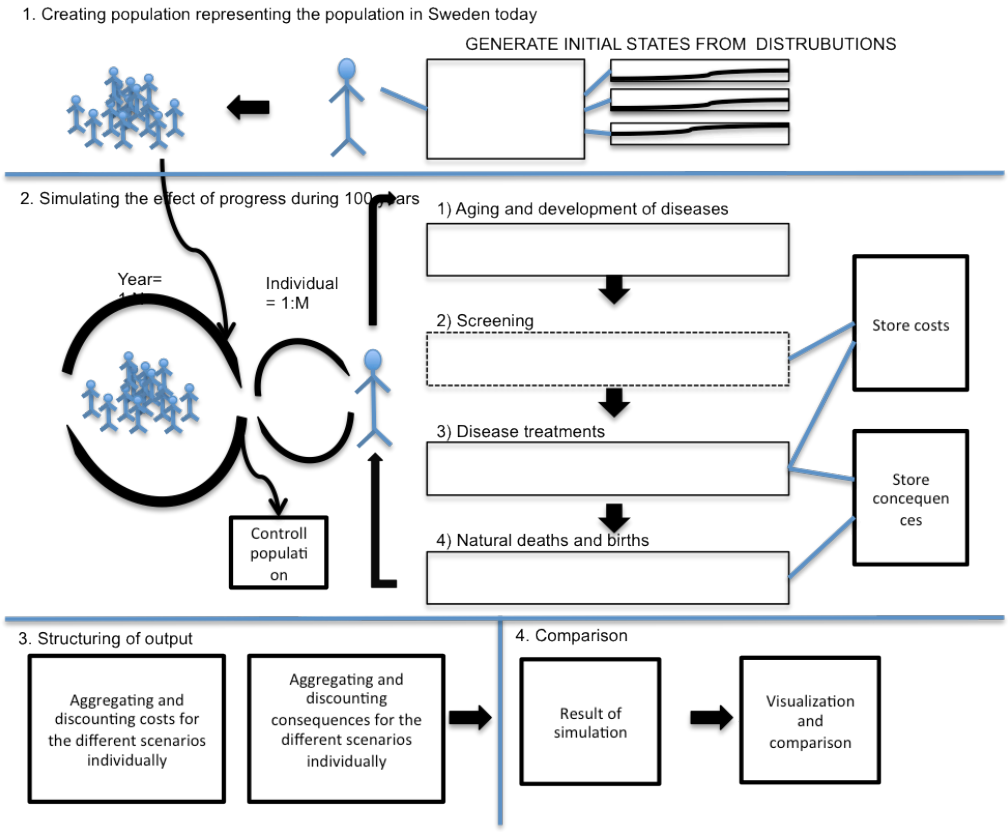

Figure 12. Economic evaluation model. Source: (Drummond, 2005)

Phase 1,2 and 3 will be created for each respective scenario, i.e. first for scenario one and thereafter for scenario two. In phase 4, a comparison of the simulated scenarios will be performed.

Phase 1) Creating population representing the population today

In phase one a number of individuals that corresponds to individuals in Sweden are created. Values of the parameters described above are assigned for each individual with values drawn from distributions representing the situation in Sweden today. The age of the individual is drawn from the distribution dAge. If the individual are infected by H. pylori, has peptic ulcer or gastric cancer, this is drawn from the distributions dH. pylori, dUlcer and dCancer.

Phase 2) Simulating the effect of progress of 100 years
In phase two, each individual is simulated separately in yearly cycles. Each year each individual goes through four steps and the individual's parameters are updated. The steps are:

1) Aging and development of diseases: During this step the age of the individual is increased. After that, it is evaluated if the individual acquires a H. pylori infection (probability: pAquireH) or enjoys natural eradication of a H. pylori infection (probability: pNaturalEradicationH). It is further evaluated if the individual are diagnosed with gastric cancer (probability: pDevelopCancer) and/or are diagnosed with peptic ulcer (probability: pDevelopUlcer).

2) Screening: Screening will only occur in the screening scenario.
In the screening scenario, some individuals are invited to a screening session. Who is invited is determined by scenario specific rules. For each individual there is a probability that the individual attends the screening program (probability: pAttendScreening). This attendance is associated with a cost (cScreening). Depending on if the individual has a H. pylori infection or not, there is a chance that the individual receives a true positive test result (probability: pTestPositive) or a false positive test result (probability: pTestFalsePositive) and will be invited to eradication. There is a probability that the invited person attends the eradication (probability: pAttendEradication), which will result in a treatment protocol that will add a cost (cEradication). If the individual has the bacteria, there is a probability that the eradication is successful (probability: pSuccessfullEradication)).

3) Disease treatments
If an individual are diagnosed with ulcer, costs associated with the ulcer treatment (cUlcerHealthCare) will be added. After that, the individual either is considered treated (probability: pUlcerTreatmentSuccessful) or dies.

If an individual are diagnosed with gastric cancer, costs associated with the cancer treatment (cCancerHealthCare) will be added. Either the individual is considered treated (probability: pCancerTreatmentSuccessfull) or dies.

4) Natural deaths and births

In this step, natural deaths and births are simulated. Each year there is a probability that an individual dies a natural death (pDieNatural). A number of individuals are born, which is determined by a draw from a distribution (dNumberBirths).

Phase 3) Structuring of output
In this phase, the output from each simulation is restructured and costs are discounted to today's value. The output life years saved is summarized.

Phase 4) Comparison
During the final phase output from the different scenarios are compared and various aspects of the model visualized and later interpreted.

5.4 Identifying and synthesizing evidence

Data is needed to populate the model. Evidence used in the model have been identified and research in a systematical way through document studies. The process has sometimes been selectively as input from experts regarding high quality studies has had influence on the research. When searching for specific parameters, evidence synthesis is made by comparing studies in order to get the most appropriate data. Chosen parameter data is taken from studies that are as alike as possible to this theoretical study. Data on costs are taken mainly from experts, hospitals and statistics data bases in Sweden.

5.5 Dealing with uncertainty

To handle uncertainty, the framework proposed by Philips (2004) will be used.

Structural uncertainty
To minimize negative impact of structural simplifications, assumptions have been made in directions that adjust the result in a way that does not support the hypothesis. It is a complex matter to evaluate structural uncertainty and a more detailed analysis of this is outside the scope of this thesis.

Parameter uncertainty
The majority of the in-data used in this study: probabilities, population distributions and costs, are estimated from sample data. The quality of the in-data varies depending of source. To evaluate how the uncertainty of different parameters affects the result a two-way sensitivity analysis have been carried out and the result of this sensitivity analysis is presented in “Sensitivity analysis” below. Uncertainty related to specific parameters is discussed below in “Model data”.

5.6 Dealing with variability

Main variability issues in this study are that certain parameters, for example the prevalence of H. pylori, varies systematically between different groups in Sweden and that information regarding these differences are not available. To deal with this issue assumptions have been in a direction that increases the likeliness of falsifying the hypotheses. Issues related to specific parameters are discussed below under the data section.

5.7 Evaluation of the decision model

Evaluation of the model is performed in accordance with the framework for evaluations by Philips et al. (2004). Evaluation steps are found in Appendix 4.

6. Model data

In this chapter, in data for the model is presented. The data is presented as the parameters used in the model under headlines corresponding to the four different phases of the model. It consists of costs associated with diseases and treatments, probabilities for different states of the diseases and population distribution characteristics in Sweden.

6.1 Model data notation

Parameters describing costs are denoted with a prefix lower-case c, parameters describing probabilities are denoted with a prefix lower-case p and parameters describing distributions are denoted with a prefix lower-case d.

6.2 Creation of population

dAge

dAge is representing the current age distribution in Sweden. The distribution is derived from data from SCB that contains information regarding the current age distribution in Sweden (SCB, 2012). See figure 13.

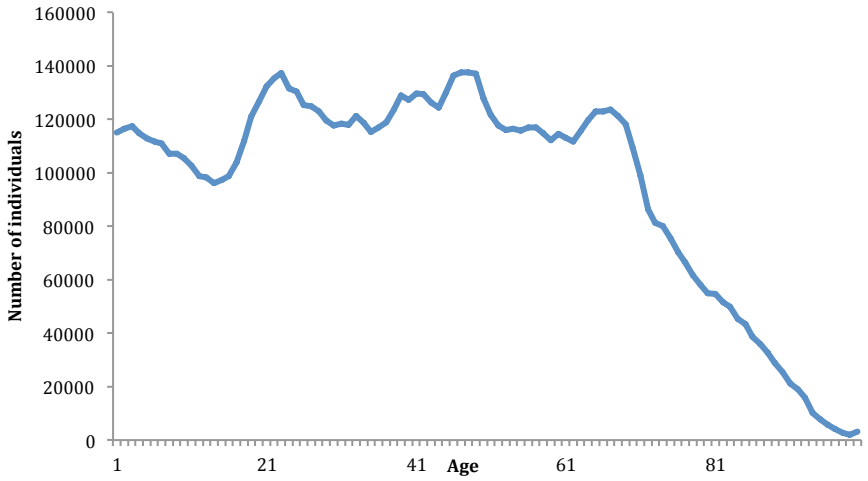

Figure 13. Age distribution in Sweden 2010. Source: (SCB, 2012)

dH. pylori

dH. pylori describes the current prevalence distribution of H. pylori infections in Sweden today. H. pylori prevalence has been studied in many Western countries and some studies have examined the prevalence in the Swedish population. According to Lars Agréus, expert in the H. pylori field, the best current description can be found in a study by Storskrubb (2005). In this study, individuals living in Kalix, Sweden, have been examined. The results in terms of H. pylori infection prevalence are displayed for 4 different age groups: 20 - 34, 39 - 49, 50 - 64 and 65 - 81. From the prevalence in these different age groups, prevalence in each age group between one and 100, separated with one year, are estimated with linear interpolation. The endpoints one and 100 are estimated with help from expert Lars Agréus (Storskrubb, 2005) (Agréus, 2012).

There are some issues related to variability in this distribution. The absolute majority of individuals studied in the Kalix study are native Swedish. In the sense of origin, this group does not represent the heterogeneity of the Swedish population. It is well known that the prevalence of H. pylori is higher in many groups of individuals that have immigrated from developing countries. Not taking this into consideration has the effect that the modeled prevalence is lower than the actual. This reduces the likeliness that the screening program is shown to be effective. See figure 14.

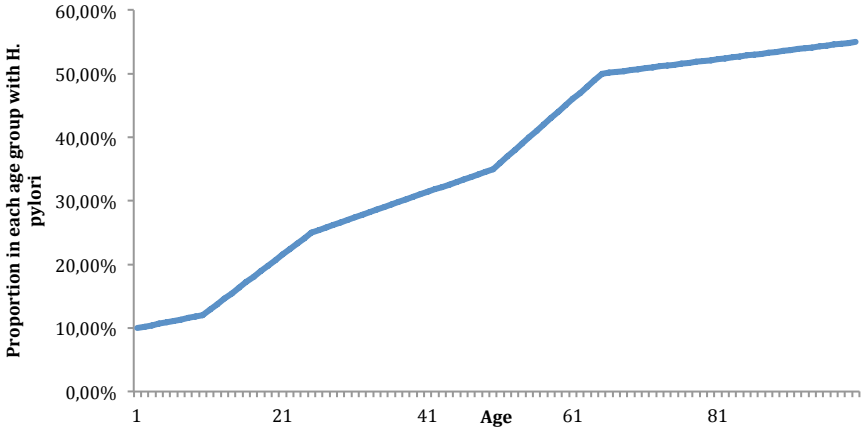

Figure 14. Prevalence of H. pylori in age. Source: (Storskrubb, 2005)

dUlcer

In the model, new diagnosed cases of Ulcer are the unit associated with costs. Ulcer diagnosis set earlier will be identical between the two scenarios and will not have any impact on the result.

(b1-c1– c12) – (b2-c2-c12) = (b1-c1) – (b2-c2)

Therefor the current distribution, or distribution at simulation start, is not relevant and will be set to 0 for all age groups. However information regarding current distributions will be used to calculate the risk of getting ulcer in the future.

dCancer
In the model, new diagnosed cases of cancer are the unit associated with costs. Therefor the current distribution is not relevant and will be set to 0 for all age groups. Compare with dUlcer.

Table of ulcer and cancer

Parameter	***Data***
dUlcer	*0*
dCancer	*0*

6.2.1 Aging

pAquireH
pAquireH denotes the probability of acquiring the infection for a individual that are not infected and that have left early childhood.

Factors that determines who get the H. pylori infection and when the individual get the infection include environmental and genetic factors. There is a strong relationship between age and H. pylori infection as well as origin and infection. Older individuals are in general more likely to be infected and individuals from developing countries are much more likely to have the infection compared to individuals born and living in developed countries. A view described in many studies is that birth environment is the most important influence regarding who will get the bacteria. The absolute majority of infections are happening during early childhood. The increased prevalence by age is likely due to different environmental conditions for different birth cohorts and not due to infection after childhood, which is very rare. This makes it suitable to treat the probability of acquiring the bacteria as zero after childhood (Agréus, 2012).

pBornH
pBornH is the probability of acquiring the infection in early years. There have been a declining trend of H. pylori prevalence amongst children and it's unlikely that this trend will change as it is related to hygiene and social standard, which probably will not decline in Sweden. There is no forecast made for the H. pylori prevalence in Sweden and a constant value based upon data from Storskrubb (2005) will be used.

Regarding the reliability; the probability that an individual is born with H. pylori is, as with the initial H. pylori distribution, not taking immigration into consideration.

pNaturalEradicationH
Natural eradication of the bacteria is a process where an individual with an infection gets rid of the infection without the use of medicines. This seems too rare and will be considered not existing (Agréus, 2012).

Table of different H. pylori states

Parameter	Data	Source
pAquireH	0%	(Agréus, 2012)
pBornH	10%	(Storskrubb, 2005)
pNaturalEradicationH	0%	(Agréus, 2012)

pDevelopUlcer
pDevelopUlcer is the probability for an individual with current H. pylori infection to develop peptic ulcer. The probability of developing peptic ulcer depends on various environmental and genetic factors where age and time infected with H. pylori are central. To determine the probability of developing peptic ulcer, as the result of an H. pylori infection, the following processes are used. First is determined the number of diagnosed peptic ulcer cases that are caused by the H. pylori infection. From population age distributions (SCB, 2012) and estimated H. pylori prevalence by age, the number of individuals in each age group with H. pylori infections is calculated. These individuals are considered to have acquired their infection at childhood. From this distribution and a distribution of number of peptic ulcer diagnosis and age (Roderick, 2003), the probability that an individual with a H. pylori infection and no peptic ulcer diagnosis year n, gets a peptic ulcer diagnosis year n + 1, is calculated. Then this distribution is normed using the total number of annual new cases of peptic ulcer diagnosis in Sweden (Lundstedt, 2012).

This is the risk of getting peptic ulcer if you have had an H. pylori infection during your entire life. If you get rid of the H. pylori infection it is likely that you will return to the same risk level as if you never have had an infection (Lundstedt, 2012). See figure 15.

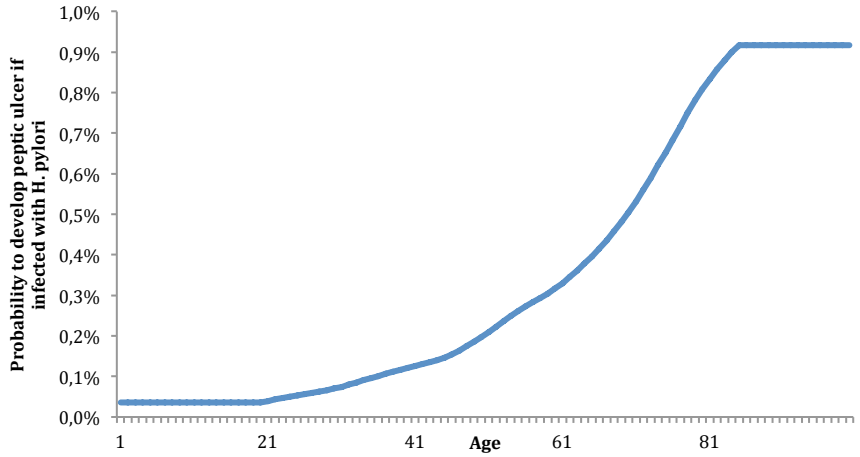

Figure 15. Probability to develop peptic ulcer. Source: (Lundstedt, 2012)

pDevelopCancer

pDevelopCancer is the probability for an individual with current or previous H. pylori infection to develop gastric cancer. The probability of developing cancer depends on a various environmental and genetic factors where age and time infected with H. pylorus is central. To determine the probability of developing gastric cancer as the result of an H. pylori infection, following process are used. First determine the number of diagnosed cancer cases that are caused by the H. pylori infection. From population age distributions (SCB, 2012) and estimated H. pylori prevalence by age calculate the number of individuals in each age group with H. pylori infections. These individuals are considered to have acquired their infection at childhood. From this distribution and a distribution of number of gastric cancer diagnosis and age (Roderick, 2003), the probability that an individual with a H. pylori infection and no gastric cancer diagnosis year n, gets a gastric cancer diagnosis year n + 1, is calculated. Then this distribution is normed using the total number of annual new cases of gastric cancer diagnosis in Sweden (Lundstedt, 2012). This is the risk of getting cancer if you have had an H. pylori infection during your entire life. If you get rid of the H. pylori infection it is unlikely that you will return to the same risk level as if you never have had an infection. The risk of getting a gastric cancer diagnosis for an individual with no current infection but with a history of H. infection will be treated the same as the probability of the last year the individual had the infection (Cancerfonden, 2012). See figure 16:

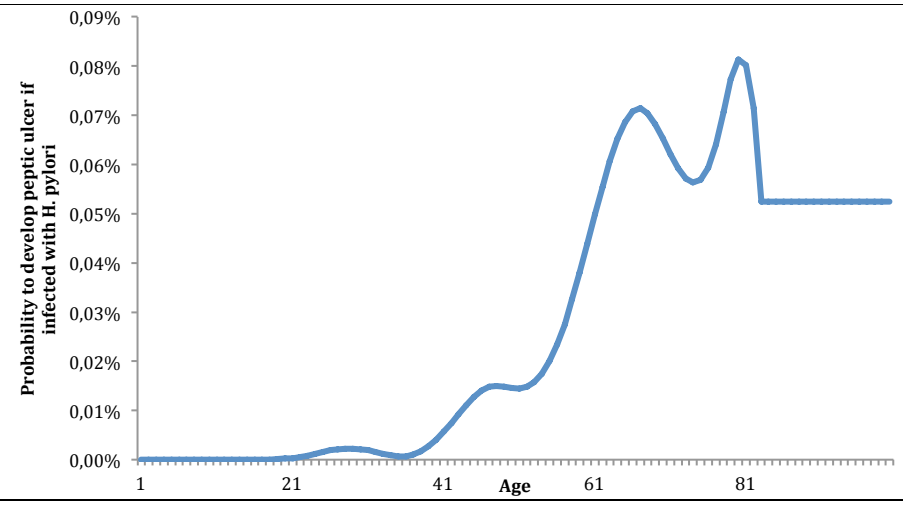

Figure 16. Probability to develop peptic ulcer when H. pylori infected. Source: (Lundstedt, 2012)

6.2.2 Screening

pAttendScreening
pAttendScreening reflects how many persons that attends a screening program after they have received an invitation. The data is taken from a breast cancer screening in Sweden from 2007, where 29 mammography-screening centers and 35 breast centers take part.

Comment variability: The percentage can vary between social groups, where high social groups tend to attend screening more than lower social groups (BRO, 2007).

cScreening
Cost for screening is the sum of different costs per patient. The first cost that occurs is cost for invitation to persons in the actual age groups. This cost is taken from an aneurysm screening study in UK from 2002, with 67800 men were invited in age group between 65-74. The study was made over four years. This cost is exchanged to Swedish currency and adjusted to today's price level (Buxton M. J., 2002).

Next partial cost for screening is cost for personnel. An estimation of time used for taking care of the patient, taking the breath test, get the result and eventually write a recipe of the eradication medicines is 15 minutes. This is made by a nurse, as a doctor most likely has written the recipe in advance (Ezmaeilzadeh, 2012). From Vårdförbundet, statistical data over mean nurse salary is taken (Vårdförbundet, 2011). Social charges are taken from Skatteverket (Skatteverket, 2011).

Cost for test is taken from one supplier in Sweden. The cost is representative for this kind of urea breath test, which is a cost-effective and accurate test. (Ibewuike, 2012).

pTestPositive ,
pTestPositive is the probability that a test against H. pylori displays a positive result when an individual is infected. This probability is derived from various evaluations of H. pylori test methods (Heliprobe, 2012).

pTestFalsePositive
pTestFalsePositive is the probability that a test against H. pylori displays a positive result when an individual is not infected. This probability is derived from various evaluations of H. pylori test methods (Heliprobe, 2012).

pAttendEradication
This is the probability that an individual receiving a positive result from H. pylori test initiates an eradication program. This statistics are derived from studies of other screening programs that are comparable in terms of suffering for the patient in different stages (Stone, 1998).

cEradication
Cost for eradication contains of the triple part therapy, containing two antibacterial agents with an anti secretory agent. Costs for medications are regulated in Sweden and are taken from the state-owned organization The Dental and Pharmaceutical Benefits Agency's statistics database (TLV, 2012).

pSuccessfullEradication
pSuccessfullEradication is the probability that the eradication treatment are successful. This probability is taken from statistics regarding eradication treatment results (Stone, 1998).

Table of different attending rates and costs

Parameter	Data	Source	Comment
pAttendScreening	82%	(BRO, 2007)	
cHScreening	354 SEK		Sum of cost personnel and H. pylori test
• Cost personnel	54,2 SEK	Time: (Ezmaeilzadeh, 2012) Average salary nurse: (Vårdförbundet, 2011) Social charges: (Skatteverket, 2011)	Time: 15 min Average salary nurse (2011): 26384 SEK Social charges (2011): 31,42%
• H. pylori test	280 SEK	(Ibewuike, 2012)	

cAScreening	355 SEK	Time: (Ezmaeilzadeh, 2012) averageYearlySalary (see below)	Time lost productivity: 2 hours
pTestPositive	95%	(Heliprobe, 2012)	
pTestFalsePositive	3.9%	(Osaki, 2007)	
pAttendEradication	79%	(Stone, 1998)	
cHEradication	1774 SEK	(Stone, 1998)	
pSuccessfullEradication	95%	(Stone, 1998)	

Disease treatment

cUlcerHealthCare
Cost for ulcer treatment is associated with each diagnosed case of ulcer. Cost is mean cost for institutional and non-institutional care of ulcer patient in Sweden during 2010. According to the source, the cost post is explained as " Other medical visit with diseases in organs for digestion and "Endoscopy of upper gastrointestinal canal, non-institutional care"". It is taken from statistics from Swedish Association of Local Authorities and Regions (SKL, 2012) (Lundstedt, 2012).

pUlcerTreatmentSuccessful
This is the probability that an individual do not die as an effect of the ulcer disease. This probability is derived from number of diagnosed cases of ulcer in Sweden (SKL, 2012) and the number of deaths associated with these cases as a function of age (Roderick, 2003) (SCB, 2012). See figure 17.

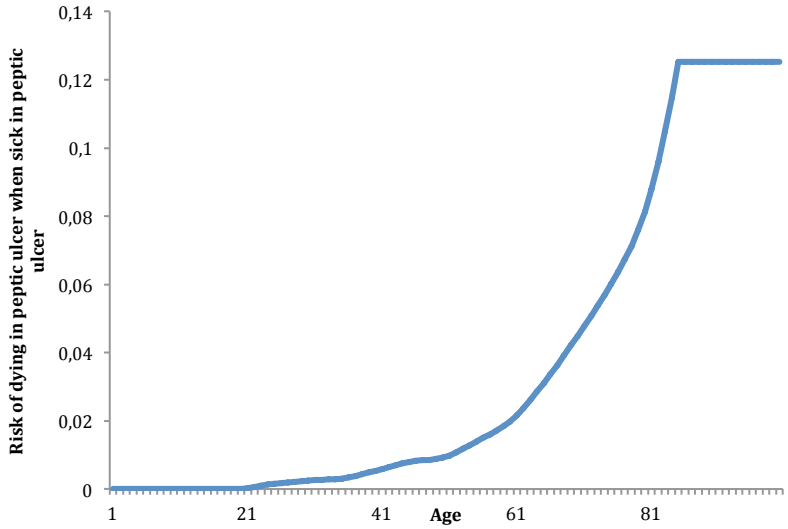

Figure 17. Risk of dying in peptic ulcer when sick in peptic ulcer. Source: (SKL, 2012)(SCB, 2012)

pUlcerTreatmentEradicationH
This parameter means how many persons with ulcer who seeks care that gets tested and if positive, treated, for H. pylori. (SBU, 2011).

cCancerHealthCare
Cost for treatment of cancer is the cost associated with each diagnosed case of gastric cancer. This cost follows the medical process of cancer cases. It includes cost for general medical examination, where cost data is gathered from SKL. Further, it includes costs for gastroscopy, biopsy with test result from pathology, datortomography and X-ray treatment for lungs. These costs are taken from a private clinic that has the same costs for the tests as medical instances driven by the county council (Danielsson, 2012). Cost for surgery of gastric cancer is also included. This cost includes the institutional care of surgery for malign melanoma in stomach, a mean cost for all cases in Sweden in 2010. There were 1189 cases (SKL, 2012). Assumptions regarding follow-up are made in accordance with Cancerfonden, which consists of costs for medical examinations (Cancerfonden, 2012).

pCancerTreatmentSuccessfull
This is the probability that an individual do not die as an effect of the gastric cancer disease. This probability is derived from a number of diagnosed cases of cancer in Sweden and the number of deaths associated with these cases (SKL, 2012).

pCancerTreatmentEradicationH. pylori
This number represents how many patients with gastric cancer that gets an eradication of H. pylori when seeking care. This is in Sweden estimated to be 100%,

as everybody who gets gastric cancer gets an eradication of the bacterium (Agréus, 2012).

pCancerTreatmentSuccessful
This probability represents the risk of dying in gastric cancer when diagnosed with cancer and is derived from the number of yearly gastric cancer diagnosis and the yearly number of gastric cancer deaths (Cancerfonden, 2012).

Table of different costs and probabilities

Parameter	Data	Source	Comment
cUlcerHealthcare	34284 SEK	(SKL, 2012)	Average cost per case, Sweden 2010
pUlcerTreatmentEradicationH. pylori	40%	(SBU, 2011)	
cCancerHealthcare	134000 SEK		Sum of row below.
• Malign tumor in stomach • Medical examination • Biopsy • Datortomography • Lung x-ray • Follow up	99 688 SEK 2642 SEK 10665 SEK 3047 SEK 1090 SEK 1700 SEK	(SKL, 2012) (SKL, 2012) (Danielsson, 2012) (Danielsson, 2012) (Danielsson, 2012) (Svedelius, 2012)	Malign tumor in stomach: average cost per case, Sweden 2010. All data is per examination.
pCancerTreatmentEradicationH. pylori	100%	(Agréus, 2012)	
pCancerTreatmentSuccessful	56%	(Cancerfonden, 2012)	

Society

nDaysYear, nWorkDaysYear
Number of days per year are 365 and number of working days are 20 per month.

averageYearlySalary
Average salary in Sweden for both genders is 28400 SEK (SCB, 2012).

treatmentWorkAbsenseUlcerYear
The absence from work caused by ulcer is considered to be negligible. This number is probably higher but as it is hard to separate general dyspepsia symptoms from ulcer symptoms and therefor estimate work absence only caused by ulcer, ulcer is here estimated to 0 (Agréus, 2012)

cancerTreatmentWorkAbsenseMonth
Average absence from work for a cancer sick patient is 5 days per month (Chang, 2004).

averageTreatmentTimeCancerYears
Average treated years for stomach cancer is five years (Svedelius, 2012).

cProductionLossLostLifeYear
Costs for production loss are calculated until the person reaches age retirement age, which in Sweden is 65 years. This is done in accordance with production loss cost theory and human capital method. The fact that an individual is sick only leads to production loss up to retirement age, and is therefor only a cost until then. Whether the individual is sick or not during the retirement does not matter for the economic evaluation. Retirement expenses are no societal cost, why these are not considered.

pensionAge
Retirement age in Sweden is 65 years (Stråfors, 2012).
Table of time

Parameter	Data	Source	Comment
nDaysYear	365		
nWorkDaysYear	20*12		
averageYearlySalary	28400*12	(SCB, 2012)	Average salary, all sectors, all genders, Sweden 2011
treatmentWorkAbsenseUlcerYear	0	(Agréus, 2012)	
cancerTreatmentWorkAbsenseMonth	5 days	(Chang, 2004)	
averageTreatmentTimeCancerYears	5 years	(Svedelius, 2012)	
pensionAge	65 years	(Stråfors, 2012)	Public retirement age in Sweden

6.2.3 Natural deaths and births

pDieNatural
The probability to die a natural death is determined using predictions of population age distributions from SCB (SCB, 2012). See figure 18.

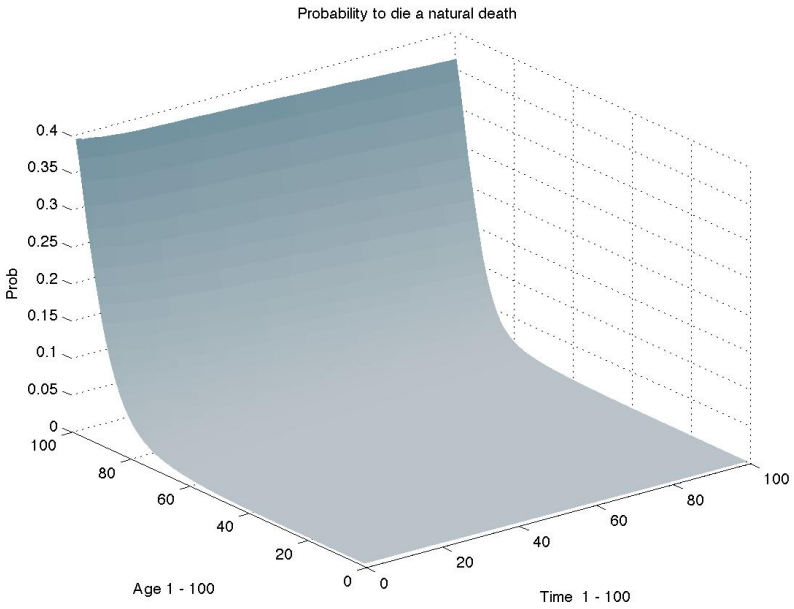

Figure 18. Probability to die a natural death. Source: (SCB, 2012)

dNumberBirths

The number of births is estimated from SCB data (SCB, 2012). See figure 19.

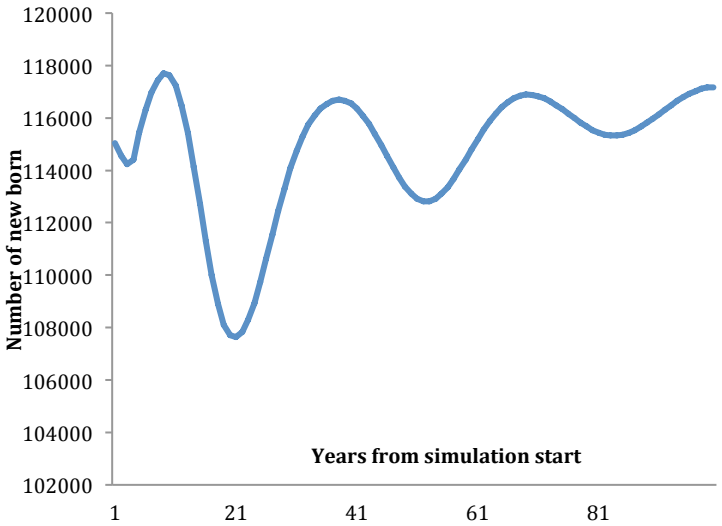

Figure 19. Number of newborns. Source: (SCB, 2012)

6.3 General

Discount rate

Discount rate is set after considering the recommendations from National Institute for Clinical Excellence (2004) and the World Health Organization Guide to cost effective analysis recommends the chosen discount rate (Drummond, 2005).

Table of discount rate used

Parameter	Data	Source
discountRate	3%	(Drummond, 2005)

Evaluation time

The time limit of 100 years is a balance between accuracy and computation time. With a discount rate over 3 %, costs in 100 years will be discounted with a factor below 0.05 and have an insignificant impact on result.

A shorter time-length could have been chosen but then some important aspects would have been missed. The prevalence of the H. pylori infection amongst newborns is much lower compared to older age cohorts. The effect of the newborns would not be observable if the time length would be shorter then the age when these individuals are likely to develop ulcers and gastric cancers, which is as high as 80 years old.

6.4 Age group test

To evaluate the most suitable age group to be screened, the model was run for different age groups. Estimated age group for screening was between 25 and 55 years. The program was run for these age groups with a 5-year interval. For every age, two programs were run to get a mean value. The mean value that gave the highest positive net present value was chosen, which after test were made showed to be the age of 40.

7. Result

This chapter will present the result from the economic evaluation with the comparison between the two scenarios.

A scenario where all individuals at the age of 40 annually are invited to participate in a screening program, compared to a scenario where no organized screening is implemented, is cost effective, has a positive net present value and a positive number of life years saved.

7.1 Comparison of costs

The mean difference in net present value between the screening scenario and the non-screening scenario are 864 825 008 SEK in favor of the screening program. The screening scenario is initially more costly and can be viewed as a large initial investment. The high initial investment and the time lag to the received benefits results in a mean payback time of 25 years. As an investment, an implementation of a screening program for individuals at the age of 40 would be profitable. The average discounted yearly cost is 51 MSEK during the first 13 years. After this the screening program generates positive cash flow.

This mean difference is the result of 20 simulations where the two scenarios are compared. The estimated standard deviation of the simulations are 162 000 000 SEK.

Difference in costs over time

The graph below shows the difference in discounted costs of the different scenarios for the 20 simulations. See figure 20.

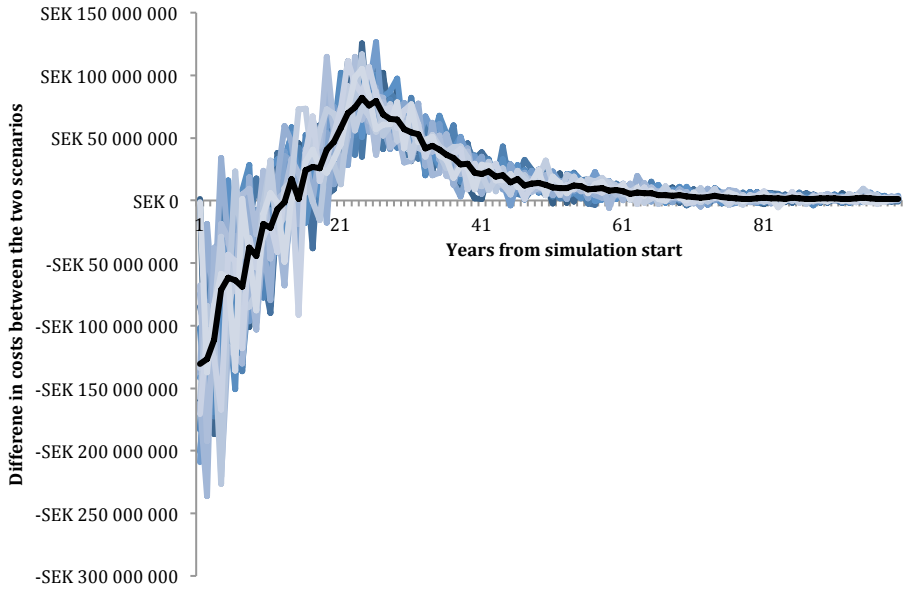

Figure 20. Difference in costs between two scenarios.

Cost distributions

Scenario one: In scenario one, productivity loss costs for cancer is more than 50% of total costs. Health-care costs for cancer is also a large part. See figure 21.

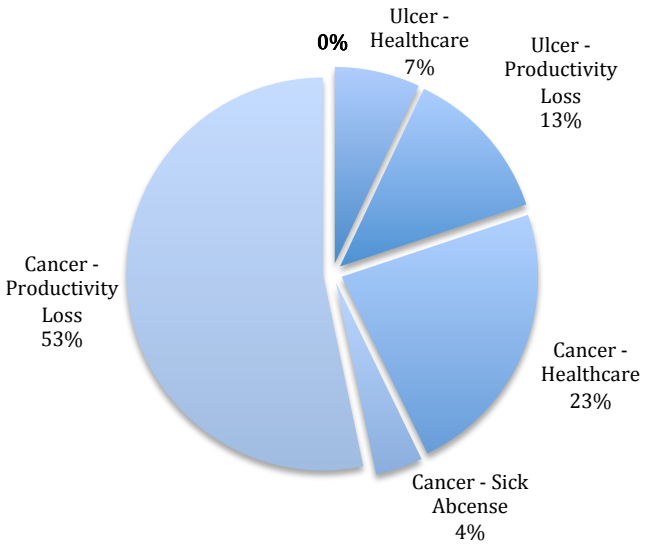

Figure 21. Costs for scenario one.

Scenario two: In scenario two, there are more different costs associated with the program. This leads to the fact that productivity and health-care costs for cancer gets a smaller part. Costs that is not a part of scenario one is health care costs for screening, work absence for screening, health care costs for eradication and work absence for eradication. See figure 22.

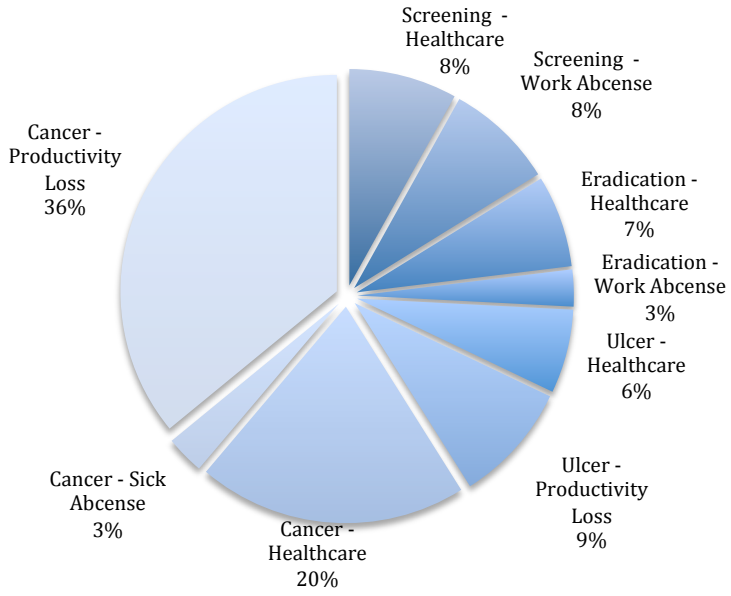

Figure 22. Costs for scenario two.

7.2 Comparison of consequences

Bellow follows a comparison of consequences between the two scenarios.

Figure 23 shows the difference in number of saved lives annually when the screening scenario is compared to the non-screening scenario.

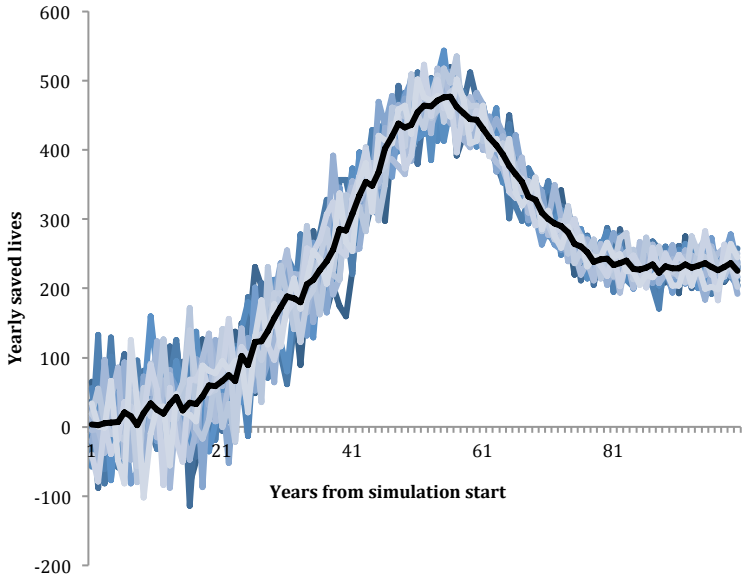

Figure 23. Yearly saved lives.

Figure 24 shows the difference in number of saved life years annually when the screening scenario is compared to the non-screening scenario.

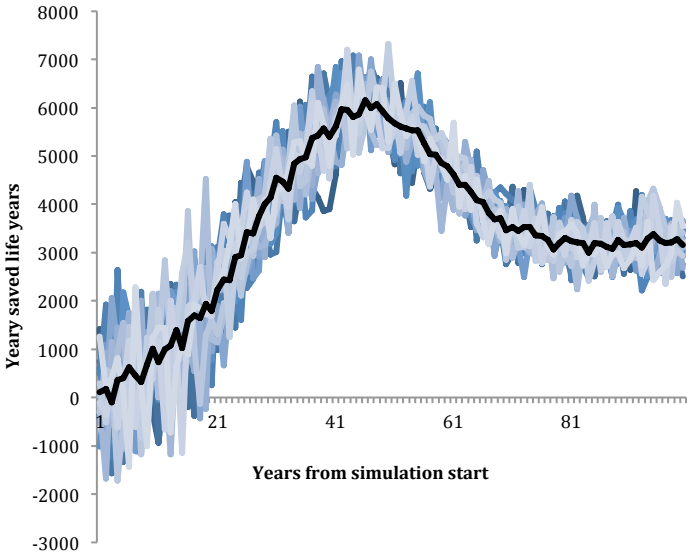

Figure 24. Yearly saved life years.

Figure 25 shows the difference in number of diagnosed cases of cancer between the two scenarios. The graph presents the number of less diagnosed cases in the screening scenario compared to the non-screening scenario.

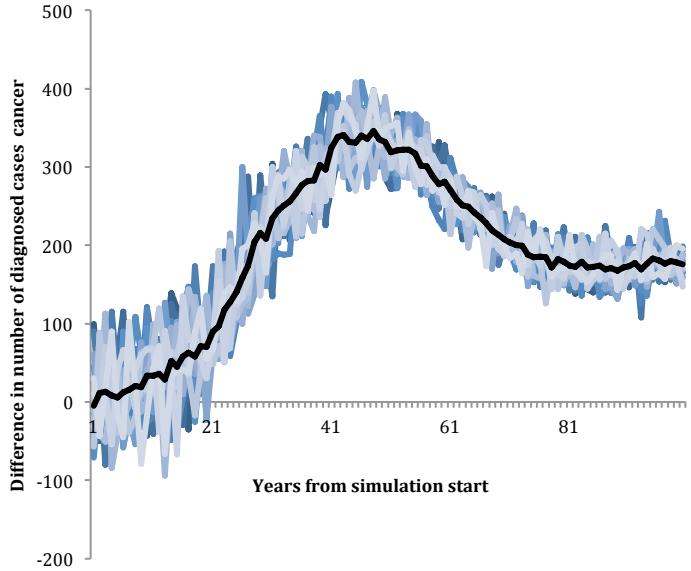

Figure 25. Difference in number of diagnosed cases of cancer.

Figure 26 shows the difference in number of diagnosed cases of peptic ulcer between the two scenarios. The graph presents the number of less diagnosed cases in the screening scenario compared to the non-screening scenario.

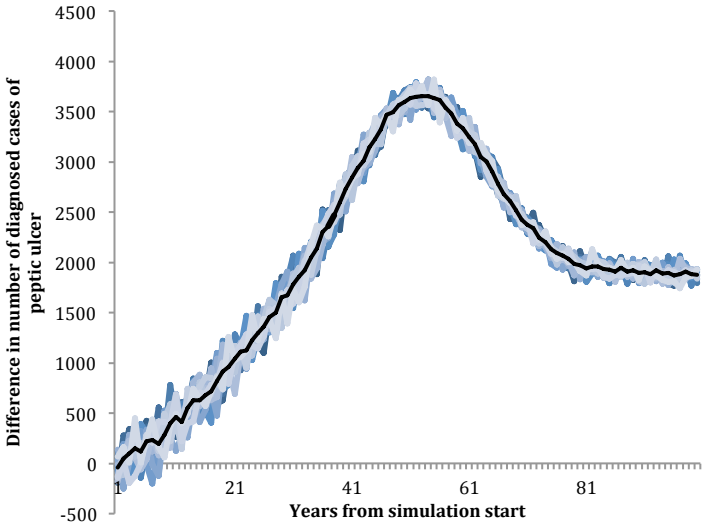

Figure 26. Difference in number of diagnosed cases of peptic ulcer.

Figure 27 shows the total number of individuals with a H. pylori infection in the different scenarios.

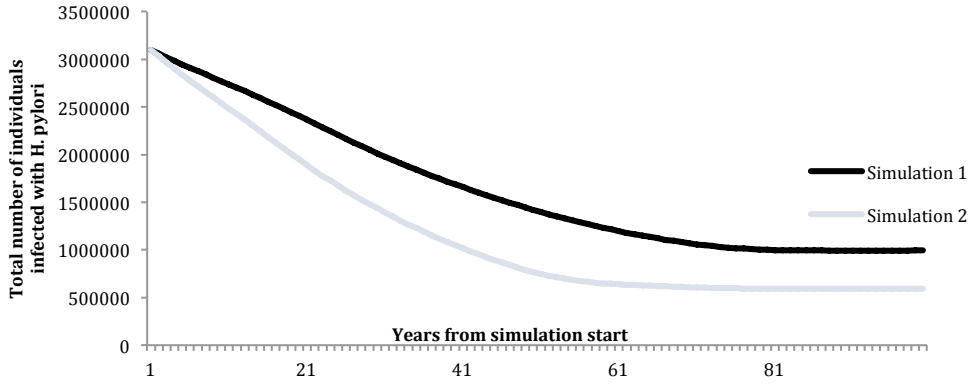

Figure 27. Total number of individuals infected.

7.3 Age group

To evaluate the most suitable age group to be screened, the model was run for different age groups. Age groups between 25 and 55 years were tested. The program was run for these age groups with a 5-year interval. For every age, two programs were run to get a mean value. The mean value that gave the highest

positive net present value was chosen, which after test were made showed to be the age of 40.

7.4 Sensitivity analysis

A sensitivity analysis is done for delimited input parameters. The standard analysis is done through standard sensitivity analysis, where the parameters are tested in a range to see how much impact they have on the final result. When performing the sensitivity analysis, a choice was made to look further into most uncertain parameters. A further investigation regarding what difference they would make on the result if the values were changed was made. Every parameter was first reduced with 10%. After that, net present value was calculated again in the model. This analysis was made 20 times and then a mean value was calculated. The mean value was compared to the base value (which is the net present value in the scenario with parameters in the final case used). After this, the same thing was made with all parameters when the parameter value was increased with 10%. The outcome from the sensitivity analysis is shown in Appendix 2.

The parameter with the largest impact on the result is the retirement age. If retirement age is increased with 10%, which means 6,5 years, NPV would be 4076 MSEK, which is an increase of 371%. The large increase is due to the costs for productivity losses that increase, why a screening program for H. pylori gets more cost effective. A decrease of retirement age with 10% would create a result of -800 MSEK, which is a difference with -191%.

The other parameters that have a large impact on the result are changes in probability of successful eradication of H. pylori in the screening program (pEradicationSuccessful) and discount rate. pEradicationSuccessful results when decreasing the numbers with 10% is a difference in NPV of -43%. When increasing with 10%, a difference of 35% will occur. Change of discount rate results in a difference of approximately 38% respective -33%.

7.5 Key findings

- To implement a screening program in Sweden against H. pylori is not only cost effective. It is profitable, as there are savings of approximately 864 825 008 SEK in current value with implementing the screening program. Payback time is relatively long, 25 years.
- Retirement age matters. If the society would prolong productive years and forward retirement age, cost effectiveness of a screening program would increase dramatically.
- Costs derived from loss of productivity are larger then health care costs.
- Variance between outfalls in the model exists, which is in accordance with the reality as the cases of persons fallen ill and death cases vary in reality. This involves a risk with the model.
- The prevalence of gastric cancer and peptic ulcer will decrease in the future, as newborn and child Swedes does not have as high infection as adults.
- The prevalence of gastric cancer and peptic ulcer will decrease in the future.

8. Discussion

This chapter will discuss the model, the result and the sensitivity analysis.

According to this study, a screening program against H. pylori would be cost effective, save lives and decrease suffering. The evaluation of the model quality and the principles regarding how assumptions have been made makes it likely that this observation is accurate. Delimitations are, as well as the assumptions, constructed to decrease complexity without increasing the likeliness of the hypothesis being true. This makes it reasonable to assume that an actual implementation of a screening program against H. pylori would be cost effective on a societal level.

Even though the program is likely to be cost effective using a net present value evaluation, the payback time of 25 years is a long time. This might be a problem in Sweden, as all final decisions regarding investment in health care are taken by politicians and their investment horizon are often shorter due to four year long tenures. It should be mentioned that the magnitude of the investment is relative small compared to the budget of the Swedish health care sector. The average discounted yearly cost is 51 MSEK during the first 13 years, which is no large sum, as the health care sector in Sweden has a budget of 60 billions SEK for 2012 (Vårdförbundet, 2011). Compared to other screening programmes, screening against H. pylori is unique in the sense that it is likely to be profitable. For example, screening against breast cancer is estimated to cost $21 400 per life year saved resulting in an infinity pay back time (Salzmann, 1997).

When evaluating the distributions of costs, it is clear that costs associated with production losses are very high. Many other studies evaluating the cost effectiveness of H. pylori screening do not include these costs. In Sweden, the health care system is primary financed by the state, which makes it reasonable to have the decision-makers on state level as recipient for the study.

Some important structural assumptions that could have resulted in an even more favorable outcome for the screening program are worth to be mentioned. Some categories of costs and items related to costs are not included in the simulation. If these costs had been taken into account that could have changed the result. These areas are subvention of medicine from the state, time consumed for worry for patients and their family and other family time spent such as production loss. Travels, medicine and other personal costs paid from the patient's pocket are not considered. When estimating population cohort, immigration is not taken into account. Due to the higher prevalence in many immigrant group a modeling of these groups would also have increased the cost effectiveness of the screening program.

There are other aspects that have not been taken into consideration. Some of these aspects could have decreased the likeliness of the program being cost effective, and would have added risk to the investment. 100 years into the future is a long time and it is hard to predict technical innovations that might change important parameters in the model. For example, would a general cure for cancer potentially drastically reduce the profitability of a screening program? Even without a general cure for cancer it is likely that costs for certain treatments or medicines will change over 100 years. Though, this kind of risk always occurs when performing long-term economic evaluations and there is an agreed policy regarding not to model this. One way to avoid this could have been to decrease the evaluation time, but a shorter evaluation time would have resulted in that some important aspects would have been missed.

The sensitivity analysis indicates that changes in input parameters affects the result in a leveraged way. The relative change in output is in general larger than the relative change in the input. The retirement age is the parameter that has the largest impact. The reason for this is that many of the cancer cases are diagnosed at ages close to 65, which is the current retirement age. An adjustment of this value in any direction would result in a relative large change in lost working years in each cancer case. If the retirement age would increase to the age of 71,5 years, net present value would increase with 371%. There are currently discussions regarding an extension of the retirement age in Sweden (DN, 2012). If the retirement age would be prolonged, which is very likely in the future, production loss would increase even more and cost effectiveness of a screening program increase.

Change in probability of successful eradication of H. pylori in the screening program and change of discount rate would also have a large impact on the results, as seen in the sensitivity analysis. Eradication numbers would have to be tested in a study to get a correct probability.

The discount rate has a large impact of result in this economic evaluation, as in all economic evaluations with a long payback time. 3% discount rate that is used in this model is taken from recommendations for economic evaluations in health care.

It is a large variance between the simulations, which probably reflects the reality. Number of diagnosed cases of cancer is a large driver of costs. The long evaluation time decreases this variance. However, the variance gets weighted as the earlier years of the simulation have large impact compared to later years.

The decrease in prevalence of cancer and stomach ulcer is probably due to a diminishing prevalence of H. pylori. In spite of this, the prevalence distributions of H. pylori for children does not impact the result very much, as it takes many years until they might be affected by cancer or peptic ulcer caused by the bacteria. The discount rate and time effect therefore makes this influence small.

After tests were made with the model regarding test age, the age of 40 was the age with the highest cost effective result. This means that persons at the age of 40 years will be screened. Comparing the results with an economic evaluation for H. pylori made in UK, their results are that the age of 40 was the most cost effective age to screen. This means that our result is the same as the result of an economic evaluation in the area for UK (Roderick, 2003).

WHO extended screening criteria

In this study a potential screening program have been evaluated for the criterion 10 and 14 of the extended screening evaluation criterion of WHO. The criterion number 14 states that "*The cost effectiveness of the screening program have been estimated",* which has been the purpose of the study. Criterion number 10 states, "*The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole",* which is the result of the study.

This leaves all but two of the 14 criterions evaluated and fulfilled. The criteria that demands that the organization of the screening should be explained in detail, is a criteria that should not be a problem for the Swedish health care as there are organizations in place for other screening programs. The final criteria to evaluate are the policies regarding whom to treat. This group can be defined in many ways. In this study the most profitable group to screen were 40-year-old individuals. It is possible that there are existing groups, separated by other dimensions than age, that are even more cost effective to screen, as immigrants or high-risk individuals.

Concluding remarks

Gastric cancer and peptic ulcer are diseases with severe consequences for the Swedish population and a screening program against H. pylori is an opportunity to combat an aggressive form of cancer in a cost effective way, as well as decreasing deaths in peptic ulcer. As the health care system in Sweden is experiencing problems with rising costs and increased burden of disease, investments that are shown to deliver good returns in a cost effective way should be prioritized. Sweden should consider implementing a screening program against H. pylori in order to make health care more cost efficient and to increase life quality for the Swedish population.

9. Further research

The remaining two guidelines from WHO should be evaluated to further prove that H. Pylori is a cost-effective screening candidate. A more detailed economic evaluation should also be made in order to recognize more specific subgroups to screen, as there could be more cost-effective subgroups than 40-year old persons, such as high-risk groups.

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Appendix

Appendix 1. Quality checklist for decision analytic models

A suggested checklist for assessing quality in decision analytic models (from Philips et al. 2004)

Structure

S1. Statement of decision problem/objective
S2. Statement of scope/perspective
S3. Rationale for structure
S4. Structural assumptions
S5. Strategies/comparators
S6. Model type
S7. Time horizon
S8. Disease states/pathways
S9. Cycle length

Data

D1. Data identification
D2. Data modeling
D2a. Baseline data
D2b. Treatment effects
D2c. Costs
D2d. Quality of life weights (utilities)
D3. Data incorporation
D4. Assessment of uncertainty
D4a. Methodological
D4b. Structural
D4c. Heterogeneity
D4d. Parameter

Consistensy

C1. Internal consistency
C2. External consistency

Appendix 2. States of natural disease state model

States of the natural disease state model

In this part, a state model of the H. pylori infection will be presented. The complexity will initially be expanded by including a large number of states. This to ensure that there is a sufficient level of detail.

To describe the H. pylori infection, a person can be in three states; he can be without a H. pylori infection, can have a H. pylori infection and be in a state with no current infection but with a previous one. An individual with the H. pylori infection is considered having a chronic gastritis. A chronic gastritis and H. pylori infection are viewed as interchangeable and the term H. pylori infection will be used. When including the diseases related to H. pylori, a person in any of the three states described above can seek medical help and get a peptic duodenal or gastric ulcer diagnosis. When considering potential outcomes of the diseases, an additional state, dead, should be included.

A combination of gastric peptic ulcer and a H. pylori infection should initially be treated as another state, compared to an individual with a gastric peptic ulcer but without a H. pylori infection. This give rise to additional sub states coding for a combination of the states representing the H. pylori infection and the related diseases. A combination between gastric peptic ulcer, duodenal peptic ulcer and gastric cancer will result in in following 22 possible states:

State number	State name
1	No H. pylori infection and no history of H. pylori infection.
2	Current H. pylori infection.
3	No current H. pylori infection but a history of H. pylori infection.
4.1	No H. pylori infection and no history of H. pylori infection and gastric peptic ulcer diagnosis caused by other factor.
4.2	Current H. pylori infection and gastric peptic ulcer diagnosis.
4.3	No current H. pylori infection but a history of H. pylori infection and gastric peptic ulcer diagnosis.
5.1	No H. pylori infection and no history of H. pylori infection and duodenal peptic ulcer diagnosis.

5.2	Current H. pylori infection and duodenal peptic ulcer diagnosis.
5.3	No current H. pylori infection but a history of H. pylori infection. Duodenal peptic ulcer diagnosis.
6.1	No H. pylori infection and no history of H. pylori infection. Gastric cancer diagnosis.
6.2	Current H. pylori infection and gastric cancer diagnosis.
6.3	No current H. pylori infection but a history of H. pylori infection. Gastric cancer diagnosis.
4.5.1	No H. pylori infection, no history of H. pylori infection. Gastric peptic ulcer diagnosis and duodenal peptic ulcer diagnosis.
4.5.2	Current H. pylori infection. Gastric peptic ulcer diagnosis and duodenal peptic ulcer diagnosis.
4.5.3	No current H. pylori infection but a history of H. pylori infection. Gastric peptic ulcer diagnosis and duodenal peptic ulcer diagnosis.
4.6.1	No H. pylori infection and no history of H. pylori infection. Gastric peptic ulcer diagnosis and gastric cancer diagnosis.
4.6.2	Current H. pylori infection. Gastric peptic ulcer diagnosis and gastric cancer diagnosis.
4.6.3	No current H. pylori infection but a history of H. pylori infection. Gastric peptic ulcer diagnosis and gastric cancer diagnosis.
5.6.1	No H. pylori infection and no history of H. pylori infection. Duodenal peptic ulcer diagnosis and gastric cancer diagnosis.
5.6.2	Current H. pylori infection. Duodenal peptic ulcer diagnosis and gastric cancer diagnosis.
5.6.3	No current H. pylori infection but a history of H. pylori infection. Duodenal peptic ulcer diagnosis and gastric cancer diagnosis.
7	Dead

Each disease could further be divided into additional states representing different stages in the disease. The cost associated with each case of diagnosis, compared to costs related to the screening program, is to be considered. It is thereby not

necessary to evaluate the impact of a screening program. An implication of this is that each state above includes various levels of progress for each disease.

Appendix 3. Reduction of states and complexity

Since many of the states above are not likely to happen or very similar each other, these states can be removed to simplify the reality. These simplifications are necessary when structuring the model. An explanation of which reductions and why they are made are as follows:

Remove states 4.1, 5.1 and 6.1, 4.5.1, 4.6.1, 5.6.1
The purpose of the model is to evaluate the difference between the two scenarios. The cases of ulcer and cancer not associated with the H. pylori infection will not be affected by the screening program. Therefore states 1, 4.1, 5.1 and 6.1, 4.5.1, 4.6.1, 5.6.1 can be removed.

Combine states 4.2 and 5.2, 4.3 and 5.3
Depending on the location of the H. pylori infection and the natural production of gastric juice in an individual, there are different risks to develop peptic gastric ulcer, peptic duodenal ulcer and gastric cancer. Compared with an individual without a H. pylori infection a low production of gastric juice is associated with a higher risk of developing gastric ulcer and gastric cancer. A high production of gastric juice is associated with a higher risk of developing duodenal ulcer and a lower risk of developing gastric cancer. If information regarding the production of gastric juice in individuals infected with the bacteria were available, a model could benefit from including this as a state. However, this information is not available and hence it is not plausible to include. Without this state the state preceding gastric and duodenal ulcer will be the same. This together with the fact that the treatments of these two diseases are similar makes it suitable to treat gastric and duodenal ulcer as one state. The drawback with this simplification is that the model will not reflect the different probabilities of developing gastric cancer for individuals with peptic gastric ulcer and peptic duodenal ulcer. This limitation will not affect the result in a significant way. This makes it possible to treat peptic duodenal ulcer and peptic gastric ulcer as one state and the state transition probability leading to this state independent of state transition probabilities leading to gastric cancer.

This leaves the following states with updated notations:

State number	State name
1	No H. pylori infection and no history of H. pylori infection
2	Current H. pylori infection
3	No current H. pylori infection but a history of H. pylori infection

4.2	Current H. pylori infection. Peptic ulcer diagnosis.
4.3	No current H. pylori infection but a history of H. pylori infection. Peptic ulcer diagnosis.
5.2	Current H. pylori infection. Gastric cancer diagnosis.
5.3	No current H. pylori infection but a history of H. pylori infection. Gastric cancer diagnosis.
4.5.2	Current H. pylori infection. Peptic ulcer diagnosis and gastric cancer diagnosis.
4.5.3	No current H. pylori infection but a history of H. pylori infection. Peptic ulcer diagnosis and gastric cancer diagnosis.
7	Dead

Appendix 4. Evaluation of decision model

Evaluation of the model is performed in accordance with the framework for evaluations by Philips (2004). Evaluation steps are found in Appendix 1.

Structure
The evaluation of the decision model starts with structure, where the first point (S1) is statement of decision problem. The objective of the evaluation is clearly specified and consistent with the decision problem. The decision problem defines the disease and relevant conditions under evaluation. The decision maker or recipient is stated. The time frame is stated.

The second point (S2) is statement of scope/ perspective. The perspective for this study is from the society's point of view. The model's inputs in terms of costs and probabilities are all estimated from the society's perspective, as well as the outcome.

S3 is rationale for structure. According to the natural history of the disease, the structure of the model is chosen to fit the scope. Sources of data are chosen after the model was selected, and are evaluated through articles and expert opinions to become as correct as possible for the specific case.

Structural assumptions (S4) are clearly stated and transparent. The amount and grade of assumptions are always evaluated with regards to the overall importance in the model, and tested with the sensitivity analysis.

The two options in the study have been evaluated and are practicable for the society (S5). For S6, the chosen model individual sampling is chosen in order to follow one individual over time. This is made, as the condition of the study will be most appropriate with individual sampling.

The time cycle (S7) 100 years is chosen because we have seen in preliminary tests that a longer forecast period have such small impact on the result that it is not worth the extra counting time. This is due to the discount rate. Chosen time horizon also reflects important differences between the two alternatives, as a screening program might influence one person's life before he dies. The time horizon is also chosen because it is approximately the expected life length for newborns, and thereby we can follow one individual over the life length. The time horizon of the model is 100 years and the duration of treatment is approximately one week. Duration of treatment effect is almost the rest of the person's life (there is a recurrence of 0,5% but in this study this is simplified to zero).

Disease states (S8) of H. pylori caused diseases reflects the underlying biological process as we have initially stated out natural history of disease and thereafter built the model around that process.

The cycle length (S9) is one year. The diseases in the study develop over long time why we have chosen one year.

Data
Data identification methods are transparent. Mainly, data have been taken from studies from other countries than Sweden. Important have been to certify number of persons involved in the study (the more persons the better validity) and follow-up time after tests have been done, as the diseases take time to develop. After performing the sensitivity analysis, the most influencing parameters have been re-considered to as appropriate data as possible. The three parameters with largest influence on total net present value are retirement age, probability of successful eradication of H. pylori and discount rate (see "Sensitivity analysis"). Sources to these parameters have been looked over again. The quality of the data is assessed appropriately. Where expert opinions are used, interview questions are not enclosed, as the interviews have been open. Where problems to get data have been identified, it is explained in the study which simplifications that have been made. To a certain extent, the availability of data is a limitation to the study. In particular, the number of patients with peptic ulcer caused by H. pylori has been hard to identify. This is because the disease has diffuse symptoms and many patients do not seek medical care, as they do not get registered.

Data modeling consists of baseline data, treatment effects, costs and quality of life weights. Baseline data is gathered from observational studies that are evaluated to become the most appropriate for this study. Transition probabilities are most often taken from studies. In those cases where we have calculated them ourselves, the calculations are made correctly.

Treatment effects are gathered from studies where they have used the same test method as in this study (urea breath test). Short-term results that are translated into final result are not used in this model, as all data used is taken from long-term studies in order to get an appropriate result. For data that was missing in studies, we have consulted the person that is seen as the best expert in the area in Sweden, Lars Agréus.

Costs incorporated in the model are justified. They are gathered from Swedish statistics divisions and as the government regulates them, a belief is that they are correct. Costs are also judged to be reasonable by comparing them with costs in other countries and by consulting experts. Sources for costs are described thoroughly in the empirical part. Discount rates have been described and justified given the target decision-maker. Also, utilities used are described and referenced to.

Data incorporation is to the most extent described and referenced to. Where different data is incorporated in the two alternatives, this is carefully described, as

these differences are important in the analysis. Assumptions and choices of this inconsistent data are described.

In the assessment of uncertainty, the four types have been considered. Regarding the methodological uncertainties, running the model and testing different times have not fully addressed them. This is due to that we saw no other methodological alternatives than the ones we did, available during the time frame for this study. Structural uncertainties have been addressed by testing the model with different cycles and different simplifications that were assumed in different ways. Heterogeneity has been dealt with while testing the specific age of screening. This is when we tested to screen different age groups, and thereby got an understanding of the heterogeneity within sub-groups in the test population. For the parameter uncertainty, a sensitivity analysis is made.

Consistency
The internal consistency is judged as proven and certified, as many economical evaluations uses individual sampling. The mathematical logic of the model has been tested through discussions with experts in the field and is evaluated to be approved. The external consistency is considered as suitable, as we believe the result is easy to understand and easy to transform into some kind of decision for the target receivers. The conclusions are valid given the data presented. All relevant data for the case found is incorporated in the model. Results of this model have been compared with similar economical evaluations in other countries to be reliable.

Appendix 5. Sensitivity analysis

Parameter	Value difference	Mean net present value	Difference from base scenario
discountRate	-10%	1 194 085 150 SEK	38%
discountRate	+10%	578 248 365 SEK	-33%
dStartHelicobacter	-10%	567 395 159 SEK	-34%
dStartHelicobacter	+10%	1 038 160 771 SEK	20%
pBornHelicobacter	-10%	838 662 027 SEK	-3%
pBornHelicobacter	+10%	883 525 597 SEK	2%
propUlcerHelico	-10%	1 045 480 049 SEK	21%
propUlcerHelico	+10%	868 439 356 SEK	0%
nDeadCasesCancer	-10%	612 499 245 SEK	-29%
nDeadCasesCancer	+10%	1 030 391 391 SEK	19%
propCancerHelicobacter	-10%	613 194 720 SEK	-29%
propCancerHelicobacter	+10%	1 141 455 754 SEK	32%
pAttendScreening	-10%	626 319 027 SEK	-28%
pAttendScreening	+10%	909 190 788 SEK	5%
pEradicationSuccessful	-10%	490 421 027 SEK	-43%
pEradicationSuccessful	+10%	1 168 737 777 SEK	35%
pensionAge	-10%	- 790 384 276 SEK	-191%

pensionAge	+10%	4 075 889 753 SEK	371%
Base scenario	**0**	**864 825 008 SEK**	0%

Appendix 6. Model analogy

To make the distinctions between the different terms used above easier for a reader not familiar with mathematic modeling an analogy from the real world could be appropriate.

An analogy from construction could help to grasp the different concepts. The general structure could in a house construction project be viewed as the sketches provided by the architect. When looking at these sketches one would get a feeling of what the house would look like - how many rooms and what kind of family that could live in the house and so on. The mathematical technique could in this house example be translated into which building technique the builders would use. Would they use wood and if so what building standards would be used. The detailed model would be a detailed blueprint describing where different pieces of wood will be placed and the distance between walls on so forth.

This analogy works in many ways. For example is it true in the model and in the housing example the more detailed level with lower abstraction is dependent on the levels above.

Depending on the sketches provided by the architect different building techniques would be appropriate. One would not build a 20 floor building in wood. The same is true for the detailed description. Depending on building techniques the actual blueprint would be very different. No need for screws in the same places if a house is built in concrete compared to in wood.

If a general structure describes a situation where timing of different events are not affecting the result, it would not be wise to use a mathematical technique like Markov modeling which has handling time dependency as core strength.