

From the Department of Molecular Medicine and Surgery
Karolinska Institutet, Stockholm, Sweden

HELICOBACTER PYLORI ERADICATION TREATMENT AND THE RISK OF GASTRIC AND OESOPHAGEAL CANCER

Eva Doorackers



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Helicobacter pylori eradication treatment and the risk of
gastric and oesophageal cancer
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Eva Doorackers

Principal Supervisor:

Associate Professor Nele Brusselaers
Karolinska Institutet
Department of Microbiology, Tumor and Cell
Biology
Centre for Translational Microbiome Research

Co-supervisors:

Professor Jesper Lagergren
Karolinska Institutet
Department of Molecular Medicine and Surgery
Upper Gastrointestinal Surgery

Professor Lars Engstrand
Karolinska Institutet
Department of Microbiology, Tumor and Cell
Biology
Centre for Translational Microbiome Research

Opponent:

Professor Ernst Kuipers
Erasmus University Medical Center
Department of Gastroenterology and Hepatology

Examination Board:

Professor Kamila Czene
Karolinska Institutet
Department of Medical Epidemiology and
Biostatistics

Associate Professor Hans Törnblom
University of Gothenburg
Institute of Medicine
Department of Internal Medicine and Clinical
Nutrition

Associate Professor Jakob Hedberg
Uppsala University
Department of Surgical Sciences

ABSTRACT

Helicobacter pylori is a strong and well-established risk factor for gastric cancer, but seems to decrease the risk of oesophageal adenocarcinoma. Thus, eradication treatment for *Helicobacter pylori* may decrease the risk of gastric cancer, and increase the risk of oesophageal adenocarcinoma. The aim of this thesis was to examine how eradication treatment influences the risk of these tumours in various settings and different study designs.

Study I assessed the risk of gastric cancer after *Helicobacter pylori* eradication treatment in a systematic review and meta-analysis. Relevant literature was collected from PubMed, Web of Science, Embase and the Cochrane Library. The results of eight eligible cohort studies in predominantly Asian populations showed a risk decrease of more than 50% after eradication treatment for *Helicobacter pylori* (risk ratio (RR) 0.46, 95% confidence interval (CI) 0.32-0.66).

Study II described prescription patterns of *Helicobacter pylori* eradication treatment in the Swedish population based on nationwide data from the Prescribed Drug Registry. From 2005 to 2014 there were 140,391 individuals (1.5% of the Swedish population) receiving eradication treatment, with a decreasing use during the study period. Nearly all eradications (95.4%) used the standard triple therapy with a proton pump inhibitor and the antibiotics clarithromycin and amoxicillin, also for repeated eradication episodes (92.7%).

Studies III and IV were Swedish nationwide, population-based cohort studies based on the Prescribed Drug Registry, Cancer Registry, Causes of Death Registry and the Patient Registry. The risks of gastric adenocarcinoma (Study III), as well as oesophageal adenocarcinoma, oesophageal squamous cell carcinoma and the premalignant condition Barrett's oesophagus (Study IV) in the cohort of individuals who received *Helicobacter pylori* eradication treatment were compared to the risks in the corresponding Swedish general population. Study III showed a nearly 70% decrease in gastric adenocarcinoma risk from five years after eradication treatment (Standardised Incidence Ratio (SIR) 0.31, 95% CI 0.11-0.67), indicating that this treatment is effective also in a Western population. Study IV showed a decreased risk of oesophageal adenocarcinoma (SIR 0.17, 95% CI 0.00-0.92) and Barrett's oesophagus (SIR 0.71, 95% CI 0.45-1.05) five years after eradication treatment, which was in contrast to the hypothesis. A decreasing trend was suggested also for oesophageal squamous cell carcinoma.

In conclusion, this thesis has indicated that eradication treatment for *Helicobacter pylori* prevents gastric cancer development both in Asian populations and in the Swedish population. There was no evidence that eradication treatment increases the risk of oesophageal adenocarcinoma, Barrett's oesophagus or oesophageal squamous cell carcinoma.

LIST OF SCIENTIFIC PAPERS

- I. Doorakkers E, Lagergren J, Engstrand L, Brusselsaers N.
Eradication of *Helicobacter pylori* and gastric cancer: a systematic review and meta-analysis of cohort studies.
Journal of the National Cancer Institute. 2016 Jul;108(9):djw132.
- II. Doorakkers E, Lagergren J, Gajulapuri VK, Callens S, Engstrand L, Brusselsaers N.
***Helicobacter pylori* eradication in the Swedish population.**
Scandinavian Journal of Gastroenterology. 2017 Jun-Jul;52(6-7):678-685.
- III. Doorakkers E, Lagergren J, Engstrand L, Brusselsaers N.
***Helicobacter pylori* eradication treatment and the risk of gastric adenocarcinoma in a Western population.**
Gut. 2018 Dec;67(12):2092-2096.
- IV. Doorakkers E, Lagergren J, Engstrand L, Brusselsaers N.
***Helicobacter pylori* eradication treatment and the risk of Barrett's esophagus, esophageal adenocarcinoma and esophageal squamous cell carcinoma.**
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LIST OF ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical
CagA	Cytotoxin-associated gene A
CI	Confidence Interval
DDD	Defined Daily Dose
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
IRR	Incidence Rate Ratio
MALT	Mucosa-Associated Lymphoid Tissue
PPI	Proton Pump Inhibitor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised Controlled Trial
RR	Risk Ratio
SIR	Standardised Incidence Ratio
VacA	Vacuolating cytotoxin

1 INTRODUCTION

Gastric cancer is the fifth most common malignancy and the third most common cause of cancer death worldwide. The strongest risk factor for developing gastric cancer is infection with the bacterium *Helicobacter pylori*, with 89% of all non-cardia gastric cancers being attributable to this bacterium.(1) However, *Helicobacter pylori* has been associated with a decreased risk of oesophageal adenocarcinoma, a highly lethal cancer with an increasing incidence over the past decades. This can probably be explained by a decrease in gastro-oesophageal reflux as a result of gastric atrophy caused by *Helicobacter pylori*, decreasing gastric acid production. In Sweden (and many other Western countries) the incidence of oesophageal adenocarcinoma is currently higher than that of oesophageal squamous cell carcinoma. The latter histological type of oesophageal cancer accounts for 87% of oesophageal cancer cases worldwide and is not associated with *Helicobacter pylori*.(2)

Helicobacter pylori is estimated to be present in the gastric tissue of around half of the human population. The prevalence in Sweden is lower at approximately 16% according to recent estimates.(3) The largest part of individuals with *Helicobacter pylori* will not show any symptoms from the infection.

The recommended treatment for *Helicobacter pylori* is a 7 to 14 day eradication treatment, most often consisting of a proton pump inhibitor and two to three antibiotics. Some data indicate that eradication treatment may decrease the risk of gastric cancer by 30-50%,(4, 5) but this needs to be evaluated in further research. The risk of oesophageal adenocarcinoma after *Helicobacter pylori* eradication treatment has not been studied before.

The aims of this thesis were to clarify the risk of gastric and oesophageal cancer after eradication treatment for *Helicobacter pylori*.

2 BACKGROUND

2.1 HELICOBACTER PYLORI

2.1.1 History

The bacterium *Helicobacter pylori* was discovered in 1982 by Barry Marshall and Robin Warren, when they were the first to link its presence in the gastric tissue of patients with gastritis and peptic ulcers to these conditions.(6) They published their findings in *The Lancet* in 1984, and in 2005 they received the Nobel Prize in Physiology or Medicine for their discovery. The bacterium was previously noticed by other researchers, but thus far no one had made the connection between this infection and peptic ulcer disease. At the time of discovery, the bacterium was first named *Campylobacter pyloridis*. In 1987, the name became *Campylobacter pylori*, until in 1989 it was discovered by genome sequencing that the bacterium was not supposed to be a part of the *Campylobacter* genus and it finally was named *Helicobacter pylori*. Not long after its discovery, it became clear that *Helicobacter pylori* is an important causative agent for gastric cancer and it was classified as a definite class I carcinogen by the International Agency for Research on Cancer (IARC) in 1994.(7)

2.1.2 Epidemiology

Helicobacter pylori is estimated to be present in the stomach of more than 50% of the human population.(8) A systematic review and meta-analysis published in 2017 aimed at mapping worldwide *Helicobacter pylori* prevalence contains data published between 1970 and 2016.(9) Globally, the highest prevalence is found in Central Asia (79.5%) and Africa (79.1%), while the lowest prevalence is found in Oceania (24.4%), Western Europe (34.3%) and North America (37.1%).(9) The countries with the highest described prevalence are Nigeria (87.7%), Portugal (86.4%) and Estonia (82.5%). Countries with the lowest prevalence are Switzerland (18.9%), Denmark (22.1%), and New Zealand (24.0%).(9) *Helicobacter pylori* prevalence in Sweden was 26.2% with a 95% confidence interval (CI) of 18.3-34.1% as reported from a random effects meta-analysis on 6 different studies with data from 1991-2001.(9) Another Swedish study that included data from 2012 reported an overall prevalence of *Helicobacter pylori* of 15.8%.(3) This study also indicated that over the last two decades, the prevalence had decreased by more than 20% in Sweden.(3) A similar decrease in prevalence was also seen in Europe overall, North America and Oceania, but not in Asia and Latin America.(9) In general, *Helicobacter pylori* prevalence is higher in older adults compared to young adults.(10)

2.1.3 Aetiology

Helicobacter pylori is usually acquired early in life, before the age of 10, by person-to-person transmission.(11) It is believed that transmission occurs orally via saliva, for example by using the same kitchen utensils or eating from the same pot, or via faeces or vomit, for example from a faeces contaminated water source. Transmission is more likely to occur in individuals that grow up in an environment with low socioeconomic status,(12) crowded

living conditions and lack of access to running water.(13) Apart from these environmental factors, twin research has also shown a role for genetics in acquiring *Helicobacter pylori*.(14)

2.1.4 Microbiology

Helicobacter pylori is a gram-negative, spiral shaped bacterium with flagella (Figure 1). It is able to survive in the stomach due to the bacterial enzyme urease that breaks down urea in the stomach into ammonia and carbon dioxide. These basic substances neutralise gastric acid and form a protection around the bacterium. It can then enter the gastric mucosa and move through this layer with the help of its flagella. There the bacterium is able to attach to the gastric epithelium.(15) Strains with different levels of virulence have been found, depending on the expression of proteins like vacuolating cytotoxin (VacA) and the oncoprotein cytotoxin-associated gene A (CagA). These highly virulent strains have been associated with an increased risk of gastric cancer and peptic ulcer disease.(16, 17)

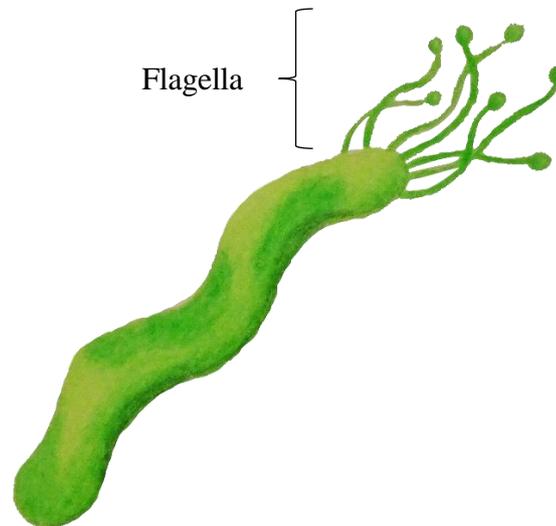


Figure 1. *Helicobacter pylori*. Drawing by the author ©.

2.1.5 Diagnosis

Indications for testing for the presence of *Helicobacter pylori* are peptic ulcer disease, early gastric cancer or mucosa-associated lymphoid tissue (MALT) lymphoma. Some guidelines also advise testing in dyspeptic individuals less than 60 years old without alarm symptoms like weight loss. Testing with non-invasive methods may be initiated immediately in individuals below 50 years of age without alarm symptoms who present with dyspepsia. This ‘test-and-treat’ strategy is recommended over prescribing a proton pump inhibitor (PPI) or endoscopy in this patient group.(18, 19)

Both invasive and non-invasive methods can be used to detect the presence of *Helicobacter pylori*. The non-invasive test that has the highest sensitivity and specificity is the urea breath test.(20) This test is based on the knowledge that *Helicobacter pylori* possesses the enzyme urease, which allows it to break down urea into ammonia and carbon dioxide. During the test, a patient is given urea orally, after which the amount of labelled carbon dioxide is measured in the exhaled breath. Another non-invasive test with high sensitivity and specificity when using ELISA, is the monoclonal stool antigen test. Here the presence of *Helicobacter pylori* is tested for using a stool sample. For both these tests, the use of a PPI has to be discontinued two weeks in advance in order to prevent false-negative results. Serology is an often used method to detect *Helicobacter pylori* because it is readily available and in contrast to most other test, the results remain reliable in patients with atrophic gastritis, gastrointestinal bleeding, gastric MALT lymphoma and gastric cancer. However, the sensitivity and specificity vary locally and therefore serology has to be validated in each setting. Rapid serological test are not yet approved for diagnostic use.

Endoscopy with biopsies is an invasive method to detect *Helicobacter pylori*. This has the advantage that it allows for assessment of the histology of the gastric mucosa at the same time. The biopsies can also be used for culture and the rapid urease test. This test can be performed during the endoscopy, giving immediate results. It is based on the same concept as the urea breath test, where the breakdown of urea by *Helicobacter pylori* will increase the pH of the test medium. Thus, any use of a PPI also has to be discontinued two weeks before the endoscopy.

The success of eradication should be proven in all individuals with a test at least 4 weeks after finishing the antibiotic treatment. Recommended tests in this context are the urea breath test, the stool antigen test or endoscopy with biopsies.

2.1.6 Treatment

Treatment for *Helicobacter pylori*, called eradication, is initiated after a positive test result. Therefore it is important that the indications for testing are followed. Standard eradication treatment is triple therapy using a PPI in combination with two antibiotics; clarithromycin, and amoxicillin or metronidazole in case of penicillin allergy.(18) However, this treatment has become less effective in most parts of the world because of the increasing clarithromycin resistance, except for in Northern Europe (including Sweden) where clarithromycin resistance is still low.(18, 21) The latest available resistance rates for *Helicobacter pylori* in Sweden are 2% for clarithromycin, 16% for metronidazole and 0% for amoxicillin.(21) International guidelines advice against the use of clarithromycin-based triple therapy in areas with high clarithromycin resistance, defined as more than 15%.(18, 22) Global resistance rates for *Helicobacter pylori* are 1-25% for clarithromycin, 10-80% for metronidazole and less than 1% for amoxicillin.(23) In case of high clarithromycin resistance, the first step is to consider the metronidazole resistance in the area. If this is low, triple therapy can be given using the antibiotics amoxicillin and metronidazole.(18) In case of high antibiotic resistance for both clarithromycin and metronidazole, eradication treatment can be given as quadruple

therapy with a PPI, two antibiotics and bismuth, or without bismuth using a PPI and three antibiotics.(18, 22) Another recommended second line option is levofloxacin-based treatment.(22) Sometimes sequential therapy is given, where the antibiotics are administered one after the other, but superior efficacy has not been shown.(18) Recommended antibiotics in case of high resistance are tetracycline, levofloxacin, rifabutin, and furazolidone.(18) If eradication fails with standard triple therapy, one of the above-mentioned treatments can be prescribed. Repeating the same regimen is not meaningful.(24) If the second line treatment also fails, resistance testing should be performed to guide further treatment.(18)

Eradication treatment in Sweden is currently given for a duration of 7 days as recommended by local guidelines.(25, 26) However, several meta-analyses have shown that 10 and 14 day treatments achieved higher eradication rates than 7 day treatment, with the highest success rates found after 14 days of treatment.(18, 27-29)

2.1.7 Association with gastric and oesophageal cancer and related health conditions

In all individuals infected with *Helicobacter pylori*, the bacterium will cause chronic gastritis, which can later develop into associated conditions like atrophic gastritis, peptic ulcer disease, gastric cancer and MALT lymphoma.(18) Since the majority of individuals with *Helicobacter pylori* will not develop any symptoms, the bacterium is sometimes considered to be non-pathogenic, and thus not considered an infection.(30)

Soon after its discovery it became clear that *Helicobacter pylori* was a causal factor for the development of peptic ulcer disease.(31, 32) *Helicobacter pylori* is associated with approximately 95% of duodenal ulcers and 70% of gastric ulcers.(33) Around 10% of all individuals with *Helicobacter pylori* develop peptic ulcer disease.(34)

Helicobacter pylori infection has been shown to be a risk factor for gastric cancer in a number of studies.(35, 36) Meta-analyses yielded an effect size of around 2 for developing gastric cancer in individuals with *Helicobacter pylori*.(37, 38) The mechanism by which the bacterium causes cancer is not completely clear. Most likely there are different factors that play a role, for example bacterial characteristics like the virulence of the strain,(39) genetic factors of the infected individual that determine immune responses, and environmental factors like dietary differences.(40-42) A report from IARC found that 89% of all non-cardia gastric cancers were attributable to *Helicobacter pylori*.(1) No association between cardia cancers and the bacterium has been shown (Figure 2).(8) Despite this evidence supporting a causal role of *Helicobacter pylori* in the development of gastric cancer, only an estimated 3% of all infected individuals develop this cancer.(34) This indicates a contributing role for bacterial, genetic and environmental factors presented above. Eradication treatment may decrease the risk of developing gastric cancer by 30-50%,(4, 5) but this needs to be evaluated in further research.

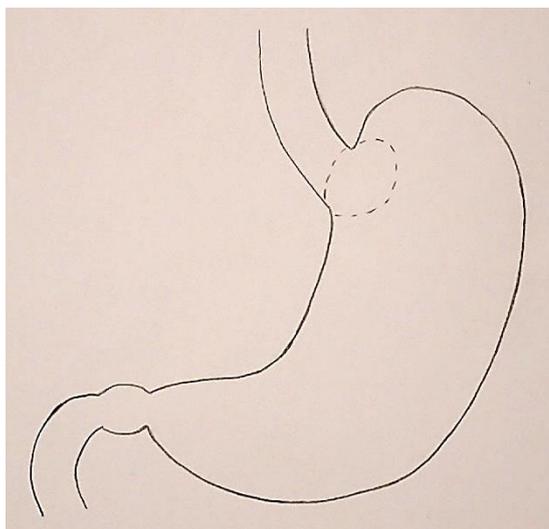


Figure 2. The stomach with the gastric cardia indicated between the dotted lines. Drawing by the author ©.

Another gastric malignancy that has been shown to have a causal relation with *Helicobacter pylori* is MALT lymphoma.(43, 44) Multiple studies have shown regression of this malignancy after eradication treatment for *Helicobacter pylori*.(45-47)

An inverse association has been shown with the risk of oesophageal adenocarcinoma. Meta-analyses have reported an approximately 40% decreased risk of this cancer type in individuals with *Helicobacter pylori*.(48, 49) The explanation for this decreased risk is thought to be a decrease in gastro-oesophageal reflux, due to gastric atrophy caused by *Helicobacter pylori* which leads to a decrease in gastric acid production.(50) Also the risk of Barrett's oesophagus, the precursor lesion of oesophageal adenocarcinoma, has been shown to be decreased by 30-60% in individuals with *Helicobacter pylori*.(51, 52) No association has been found between *Helicobacter pylori* and oesophageal squamous cell carcinoma, a cancer that is not associated with gastro-oesophageal reflux.(48, 49)

2.2 GASTRIC CANCER

With over 1,000,000 new cases and nearly 800,000 deaths in 2018, gastric cancer is the fifth most common malignancy and the third most common cause of cancer death globally.(53) The highest incidence rates are found in Eastern Asia, while the incidence is lower in Northern America, Northern Europe and Africa.(53) The incidence is about two times higher in men, compared to women.(53) The overall 5-year survival is less than 30%.(54) Of all gastric cancers, over 95% are histologically classified as adenocarcinoma, which is further divided into intestinal or diffuse type carcinoma, both of which are associated with *Helicobacter pylori* infection.(39, 55) The development of the diffuse type is not clear, but the intestinal type has been shown to develop according to a specific pathway, the Correa pathway; from chronic gastritis, gastric atrophy, intestinal metaplasia, and dysplasia to invasive adenocarcinoma (Figure 3).(56)

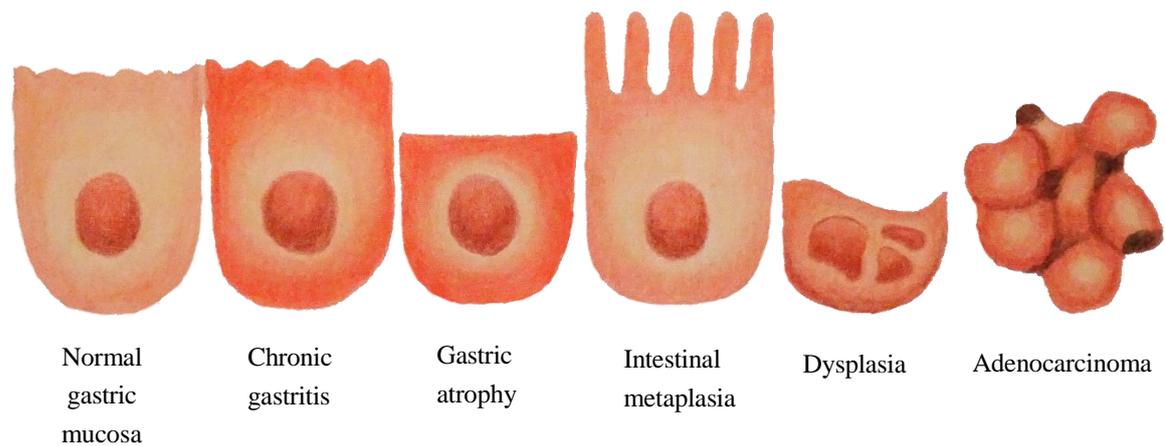


Figure 3. Development of the intestinal type of gastric adenocarcinoma according to the Correa pathway. Drawing by the author ©.

Helicobacter pylori is the strongest risk factor for gastric cancer. Among other risk factors it has been found that a diet high in fruits and vegetables protects against gastric cancer, while a diet high in salt can increase the risk.(57-59) Tobacco smoking has also been found to be a moderately strong risk factor for gastric cancer.(60) There is a possible acceleration of the cancer risk in individuals who smoke and also have a more virulent strain of *Helicobacter pylori*.(61) Low socioeconomic status is also associated with an increased risk of gastric cancer.(62)

2.3 OESOPHAGEAL CANCER

Oesophageal cancer was diagnosed in nearly 600,000 individuals and a little over 500,000 deaths occurred worldwide in 2018, making oesophageal cancer the seventh most common cancer and the sixth most common cause of cancer death.(53) Oesophageal cancer has a poor prognosis with less than 20% surviving 5 years after the diagnosis,(63) and a 5-year survival of 30-40% after treatment with curative intent.(64)

The two main types of oesophageal cancer, adenocarcinoma and squamous cell carcinoma, have different aetiologies. Adenocarcinoma usually arises from Barrett's oesophagus, a condition with metaplasia of the cells in the lower part of the oesophagus.(63) The main risk factors are gastro-oesophageal reflux and obesity. Chronic reflux can lead to inflammation and erosions of the oesophageal mucosa (oesophagitis) and from there Barrett's oesophagus can develop, which is a precancerous condition. Obesity increases the risk of reflux, but is also a risk factor for adenocarcinoma by itself.(65) The incidence of oesophageal adenocarcinoma has increased during recent decades, particularly in white men in Western populations like Western and Northern Europe, Northern America and Oceania.(2) Men are around 3-9 times more likely to develop this cancer type than women.(63)

The main risk factors for oesophageal squamous cell carcinoma are smoking and heavy alcohol consumption.(66) Globally this histological type represents 87% of all oesophageal cancer cases.(2) Most cases occur in Eastern and South-East Asia, and oesophageal squamous cell carcinoma is three times more common in men than in women.(2) The incidence has been fairly stable over the last decades, but declined in some Western populations.(66)

3 AIMS

The overall aim of the thesis was to assess the risk of gastric and oesophageal cancer after eradication treatment for *Helicobacter pylori*.

Specific aims of the included studies were:

- To evaluate the risk of gastric cancer after *Helicobacter pylori* eradication treatment in a systematic review and meta-analysis.
- To describe the prescription patterns and the antibiotic regimens used for *Helicobacter pylori* eradication in Sweden.
- To assess the risk of gastric adenocarcinoma after *Helicobacter pylori* eradication treatment in the Swedish population.
- To determine the risk of oesophageal adenocarcinoma, oesophageal squamous cell carcinoma and Barrett's oesophagus after *Helicobacter pylori* eradication treatment.

4 MATERIALS AND METHODS

Table 1. Overview of materials and methods used in the studies.

	Study I	Study II	Study III	Study IV
Design	Systematic review and meta-analysis	Descriptive study	Population-based cohort studies	
Data sources	Existing literature	Swedish Prescribed Drug Registry	Swedish Prescribed Drug Registry, Cancer Registry, Patient Registry, and Causes of Death Registry	
Participants	Individuals receiving <i>Helicobacter pylori</i> eradication treatment	Swedish residents aged ≥ 18 years receiving <i>Helicobacter pylori</i> eradication treatment		
Study period	Until 10 November 2015	1 July 2005 – 31 December 2014	1 July 2005 – 31 December 2012	
Exposure	<i>Helicobacter pylori</i> eradication treatment			
Outcome	Gastric and oesophageal cancer, MALT lymphoma	Not applicable	Gastric adenocarcinoma	Oesophageal adenocarcinoma, oesophageal squamous cell carcinoma, and Barrett's oesophagus
Confounders	As assessed in included studies	Not applicable	Age, sex, calendar period, and place of residence	
Statistical analysis	Random effects meta-analysis	Frequency calculations	Standardised incidence ratios	

4.1 DATA SOURCES

4.1.1 Published literature

The data source in Study I was published literature available from PubMed, Embase, Web of Science or the Cochrane Library.

4.1.2 The Swedish Prescribed Drug Registry

This registry started on 1 July 2005 and contains information on almost all prescribed and dispensed drugs for Swedish residents. The registry contains information on some patient characteristics, i.e. age, sex, and place of residence; the medication itself including name, Anatomical Therapeutic Chemical (ATC) code, dosage, and drug package size; the prescriptions including the prescribed amount, dates of prescription and dispensing; the costs; and information about the practice issuing the prescription including the prescribers' profession and medical specialty. Prescriptions given only during in-hospitalisations and over-the-counter medications are not recorded. Indications for prescriptions as well as the exact prescribed daily dose and duration are not available. Instead dosages and durations are available as defined daily dose (DDD) per package. A company that provides nationwide pharmaceutical services, the National Corporation of Swedish Pharmacies, transfers information on all dispensed prescriptions to the Swedish National Board of Health and Welfare once per month. The latter is responsible for the holding and management of the registry. The registry is virtually complete for the whole Swedish population with patient identifying data missing in less than 0.3% of all records.(67) This registry was linked to other registries using the personal identity number that is given to each Swedish resident upon birth or immigration and used throughout life. Personal identity numbers are replaced with code numbers by the National Board of Health and Welfare before data is sent out, to ensure anonymity of the patients.

4.1.3 The Swedish Cancer Registry

This registry was established in 1958 and contains information on malignant cancers for all Swedish residents. Recorded information includes the patients' personal identity number, sex, place of residence at diagnosis, reporting hospital and department, date of diagnosis, clinical and histological cancer type, and tumour stage at diagnosis. The registry has an at least 96% complete registration of the type and date of diagnosis of all cancers in Sweden since 1961. The completeness of the recording is 98% for non-cardia gastric adenocarcinoma as well as for oesophageal cancer.(68, 69)

4.1.4 The Swedish Patient Registry

This registry is comprised of three separate registries. The Swedish Inpatient Registry, which is nationwide complete since 1987 and contains information on in-hospital stays; the Swedish Day Surgery Registry which was added in 1997; and the Swedish Outpatient Registry, which contains information on patients visiting an outpatient clinic from 2001. The registry does not hold information on primary health care and visits where no medical doctor was involved.

Recorded information includes the patients' age, diagnoses recorded according to the International Classification of Diseases (ICD), date of visit or admission to hospital, discharge date, operation codes and dates, and information on the clinic.

4.1.5 The Swedish Causes of Death Registry

This registry contains data on all deaths in Sweden since 1961. Until 2011 only deaths among Swedish residents, occurring both in Sweden and abroad, were recorded. From 2012 the registry also includes deaths that occurred in Sweden among non-Swedish residents. Registration of death dates is essentially 100% complete. The cause of death is recorded according to the international version of the ICD. Around 0.5% of deaths do not have a recorded cause of death.

4.2 STUDY I

4.2.1 Design

This was a systematic review and meta-analysis following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The study aimed to assess the risk of gastric cancer, oesophageal cancer and MALT lymphoma after eradication treatment for *Helicobacter pylori*.

The exposure was eradication treatment for *Helicobacter pylori* using any antibiotic regimen with the intention of eradicating this bacterium. The risk of the outcomes gastric cancer, oesophageal cancer or MALT lymphoma had to be compared to either non-eradicated or unsuccessfully eradicated individuals.

The literature was searched in PubMed, Embase, Web of Science and the Cochrane Library until November 2015, using four search blocks. The first block consisted of the term "*Helicobacter pylori*" and synonyms. The second block covered "eradication" and included generic medication names for antibiotics and proton pump inhibitors. A third block consisted of either "gastric" or "oesophageal" and synonyms. The fourth block included "cancer" and synonyms as well as the histological cancer types. Searches for gastric and oesophageal were conducted separately from each other. There were no specific restrictions regarding the search. Backwards and forwards citation tracking was applied to the included articles to identify other possible relevant studies.

The retrieved articles were first evaluated based on titles by the author, after which the selection based on abstracts and full text was performed by both the author and the principal supervisor independently. Any disagreement was solved by consensus. Exclusion criteria were animal studies, studies without original data, meeting abstracts, case reports and case-control studies. Authors of articles were contacted in an attempt to retrieve the number of cancer cases found in comparison groups. For studies based on the same study population, the most recent article with the longest follow-up time was included.

Extracted data from the studies included cancer cases in the treatment and control groups, adjusted relative risks (if reported), geographical location, method to detect *Helicobacter pylori*, *Helicobacter pylori* eradication regimen, success of eradication, age (mean and range), sex ratio, follow-up time, and the histological type of the cancer. The quality of the studies was assessed using the Newcastle Ottawa scale.(70) This tool includes items on the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of the exposure, demonstration that the outcome of interest was not present at the onset of the study, comparability of study cohorts on the basis of the design or analysis, assessment of outcome, length and adequacy of the follow-up of the cohorts. From a maximum of 9 points, studies that scored below 4 were deemed to be of low quality, 4 and 5 of moderate quality, and above 5 of high quality. The data extraction and quality assessment were performed independently by the author and the principal supervisor.

4.2.2 Statistical analysis

A random effects model was used for the meta-analysis, to take heterogeneity between studies into account. To assess the risk of cancer development, the cancer risk in individuals receiving *Helicobacter pylori* eradication treatment was compared to the risk in those with no eradication or unsuccessful eradication and expressed as unadjusted risk ratios (RRs) with 95% CIs. A second analysis included the studies reporting adjusted relative risks and their 95% CIs, grouped by Cox or Poisson models, taking follow-up time into account. Subgroup analyses were performed for baseline gastric histology (atrophic gastritis or intestinal metaplasia versus not reported), and type of control group (eradicated versus non-eradicated, or successful versus unsuccessful eradication). Heterogeneity was assessed using the I^2 statistic, defining an I^2 of greater than 50% as a substantial degree of heterogeneity.(71) Cochran's Q test was used to assess the statistical significance of heterogeneity, with values smaller than 0.10 representing substantial heterogeneity. Publication bias was assessed using a funnel plot and Egger's test, where a P-value of >0.05 indicated no evidence for this bias. All statistical tests were two-sided.

4.3 STUDY II

4.3.1 Design

This descriptive study presents the use of *Helicobacter pylori* eradication treatment in Sweden from 1 July 2005 until 31 December 2014. The Swedish Prescribed Drug Registry was used for information on patients' age and sex, ATC codes for antibiotics and drugs for peptic ulcers and gastro-oesophageal reflux disease, DDD per package, and dates of dispensing. An eradication episode for *Helicobacter pylori* was a priori defined as a combination of prescriptions of at least two different antibiotics dispensed on the same date. A PPI had to be prescribed from 60 days before to 5 days after the antibiotics. This time window was used to include individuals already using PPIs, as well as to take temporary non-availability in the pharmacy into account. Prescription episodes including antibiotics with a dosage for >21 days (according to the DDD), and individuals who received ≥ 50 prescriptions

for antibiotics during the study period were excluded to avoid including treatment indications other than *Helicobacter pylori* eradication. Three different prescription combinations were included as eradication regimens: 1) The recommended eradication regimen in Sweden using a combination package (A02BD06) containing esomeprazole, amoxicillin and clarithromycin; 2) the recommended eradication regimen prescribed as separate drugs (at least two antibiotics) consisting of amoxicillin (J01CA04) and/or clarithromycin (J01FA09) and/or metronidazole (J01XD01) in combination with a PPI (A02BC). To be considered a recommended regimen, no other antibiotics were to be prescribed at the same time; 3) alternative eradication regimens consisting of a PPI in combination with two or more antibiotics of which at least one was from the following groups (excluding the above mentioned recommended antibiotics): macrolides (J01FA), imidazole derivatives (J01XD), tetracyclines (J01AA), fluoroquinolones (J01MA), nitrofurans derivatives (J01XE) or rifabutin (J04AB04), possibly in combination with bismuth subcitrate (A02BX05).

4.3.2 Statistical analysis

Absolute and relative frequencies of the different eradication regimens and individual antibiotics were calculated and stratified by age group (10-year intervals), sex, and calendar year. The first eradication treatment in each individual during the study period was analysed separately from second and third eradication episodes. Fourth or any subsequent eradication episodes in one individual were not included in this study to assure validity, e.g. that the treatment was administered as intended. Prescription trends over time were assessed by dividing all prescriptions in one year by number of inhabitants in Sweden for the same year, thus calculating the incidence proportion for each calendar year from 2006 onwards.

4.4 STUDY III AND IV

4.4.1 Design

These population-based, nationwide, Swedish cohort studies included all individuals who received at least one prescription and dispensing of *Helicobacter pylori* eradication treatment with a recommended regimen during 1 July 2005 to 31 December 2012, as assessed in Study II. The cancer outcomes were obtained from the Swedish Cancer Registry, and these were gastric adenocarcinoma, non-cardia gastric adenocarcinoma and cardia adenocarcinoma in Study III, and oesophageal adenocarcinoma and squamous cell carcinoma in Study IV. Study IV also included Barrett's oesophagus, assessed from the Swedish Patient Registry. The outcomes had to be the first in each individual and only primary cancers were included. Similarly, patients with Barrett's oesophagus were eligible only if they had no history of cancer. Diagnoses occurring within one year of the eradication treatment were excluded to avoid detection bias. The included codes from the ICD version 7 (ICD7) were 151 (gastric cancer), 151.0 (non-cardia gastric cancer), 151.1 (cardia cancer), 151.8 (multifocal gastric cancer), and 151.9 (gastric cancer, not further specified) for gastric cancer; 150 (oesophageal cancer), 150.0 (oesophageal cancer, all parts), 150.8 (multifocal oesophageal cancer), and 150.9 (oesophageal cancer, not further specified) for oesophageal cancer; and K22.7 for

Barrett's oesophagus from the ICD10. The histological code 096 from the C24 WHO classification of histology defined adenocarcinoma, and the code 146 defined squamous cell carcinoma. The possible confounders adjusted for by standardisation were age (categorised into age groups 18-59, 60-69 or ≥ 70 years), sex (men or women) and calendar period (2005-2006, 2007-2009 or 2010-2012). Confounding by place of residence (urban or rural) was assessed from the Swedish Prescribed Drug Registry because of its correlation with socioeconomic and lifestyle factors.(72)

4.4.2 Statistical analysis

Standardised incidence ratios (SIRs) with 95% CIs were calculated by dividing the observed number of cases in the eradication cohort by the expected number of cases derived from the Swedish general population of the same sex, age and calendar period with the categorisation presented above. To calculate the exact number of person-years of follow-up in each stratum, Clayton's algorithm was used, where follow-up started from the date of the first dispensed prescription for eradication of *Helicobacter pylori*.(73) An additional analysis was performed which started from the last dispensed prescription of eradication treatment. Follow-up continued until the occurrence of any cancer, death, or the end of the study period (31 December 2012), whichever came first. For Barrett's oesophagus follow-up ended at the first date of a Barrett's diagnosis, in addition to the criteria listed above. Subgroup analyses were performed for time after eradication (grouped into 1-2, 3-4 or 5-7.5 years) and number of dispensed eradication treatments (1, 2 or >2). Multiple eradication treatments indicated that an individual was infected with *Helicobacter pylori* for a prolonged amount of time. In Study III additional subgroup analyses evaluated the risk of cancer in individuals with peptic ulcer (gastric or duodenal), and gastritis (chronic or atrophic). Poisson regression was used to analyse the influence of length of follow-up and potential confounding by place of residence (urban or rural), yielding incidence rate ratios (IRRs) with 95% CIs.

5 RESULTS

5.1 STUDY I

Of the 3629 articles identified in the systematic database searches, eight cohort studies assessing the risk of gastric cancer after *Helicobacter pylori* eradication were included in the systematic review and meta-analysis (Figure 4). There was only one study assessing the risk of oesophageal cancer, and no study assessed the risk of MALT lymphoma. Randomised controlled trials (RCTs) were excluded because a previously published meta-analysis included all identified RCTs.(4)

Of the included studies, seven were conducted in Japan and one in Finland. Two of the Japanese studies included 98% and 89% men.(74, 75) The largest study had 3650 individuals receiving eradication treatment and 11,628 individuals as control group. The same study also had the longest follow-up time of all included studies with a maximum of 20 years.(76)

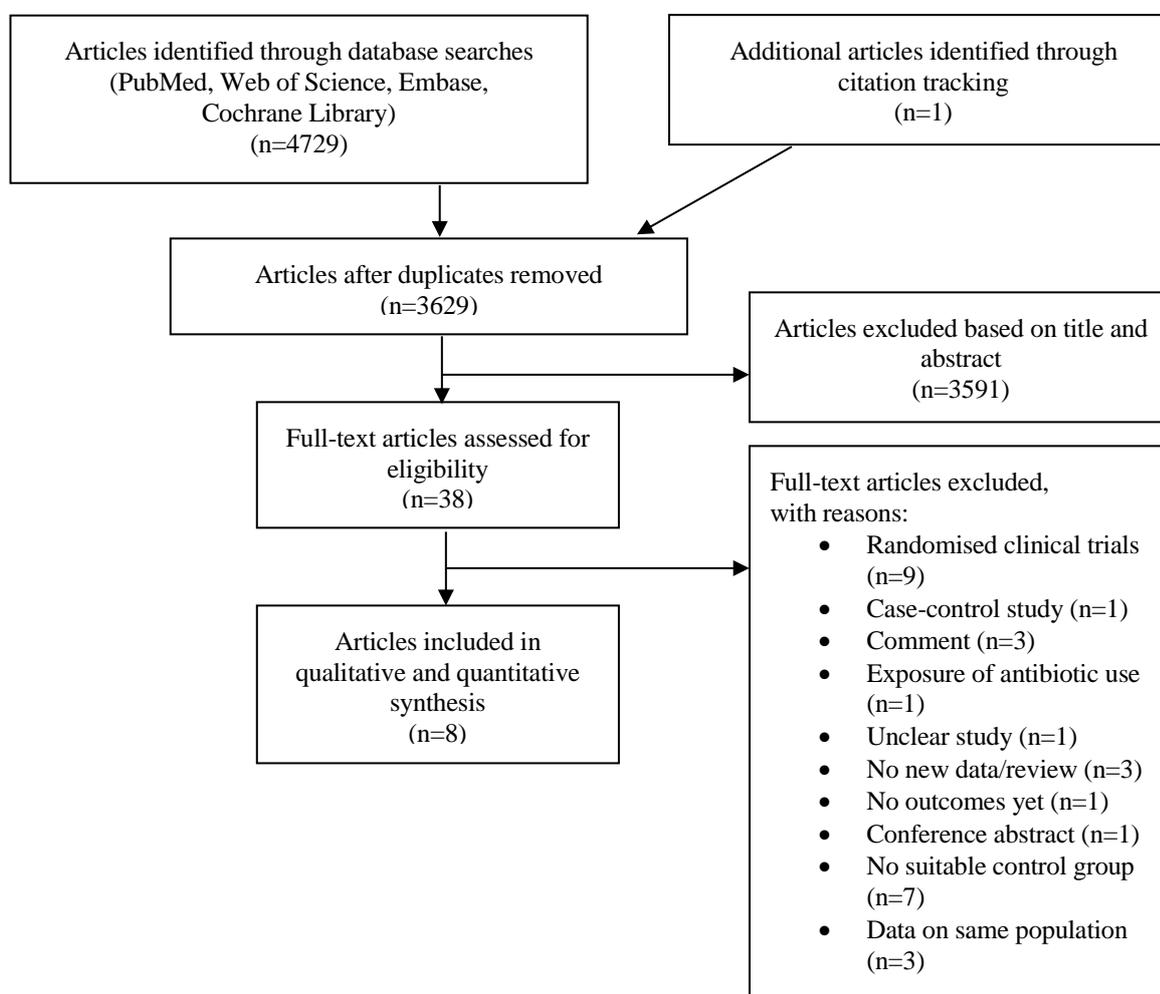


Figure 4. Study selection for a systematic review and meta-analysis of studies assessing gastric cancer risk after *Helicobacter pylori* eradication.

Gastric cancer developed in 119 (0.9%) out of 12,899 patients receiving eradication treatment, and in 208 out of 18,654 (1.1%) unsuccessfully treated or non-eradicated patients. Meta-analysis of the eight included studies yielded a RR of 0.46 (95% CI 0.32-0.66) favouring eradication treatment (Figure 5). Analysis of the five studies comparing successful to unsuccessful eradication provided a RR of 0.47 (95% CI 0.31-0.71), while the three studies comparing eradicated to non-eradicated individuals provided a RR of 0.39 (95% CI 0.14-1.08) (Figure 5).

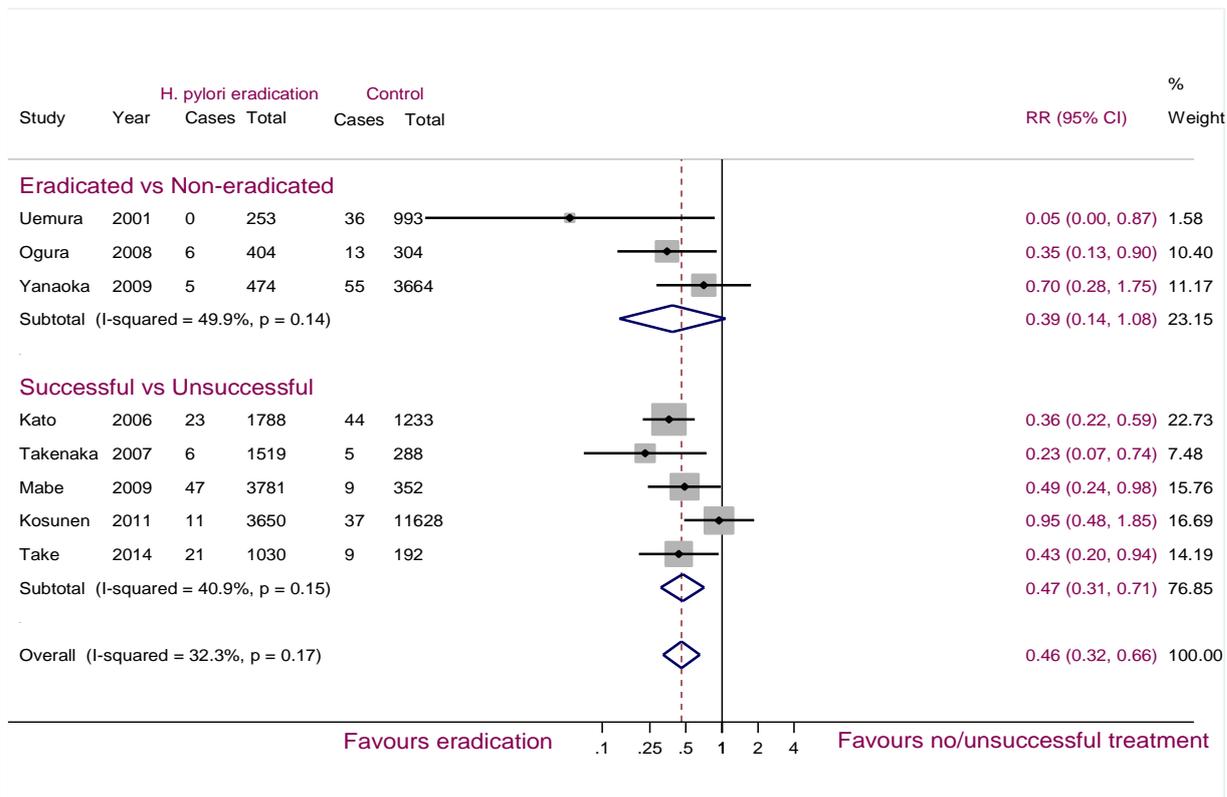


Figure 5. Forest plot of studies assessing gastric cancer risk after *Helicobacter pylori* eradication comparing eradicated to non-eradicated individuals, and successful to unsuccessful eradication.

In a Chinese RCT assessing oesophageal cancer risk, two out of 817 (0.2%) eradicated individuals developed oesophageal squamous cell carcinoma, while one out of 813 (0.1%) individuals receiving placebo developed this cancer type.

5.2 STUDY II

In Sweden, a total of 157,915 prescriptions for *Helicobacter pylori* eradication were dispensed to 140,391 individuals (1.5% of the Swedish population) during July 2005 to December 2014. The largest part (127,810 individuals, 91.0%) received one eradication, 9900 (7.1%) received two eradications, 1669 (1.2%) received three eradications, and 1012 (0.1%) received four or more eradications. In most cases (95.3%) a PPI was prescribed on the same day as the antibiotics. The recommended regimen was prescribed in 95.4% of all eradications. From 2006 to 2014 the dispensed prescriptions of the recommended eradication regimen decreased from 193 to 148 per 100,000 residents (Figure 6). Even during second and third eradications, the recommended regimen was used in 92.7% of eradications (this was 95.8% during first eradications) (Table 2). Although used in few cases, the most common combinations for an alternative eradication regimen were amoxicillin and ciprofloxacin (1.3%), and amoxicillin and doxycycline (0.5%) (Table 2).

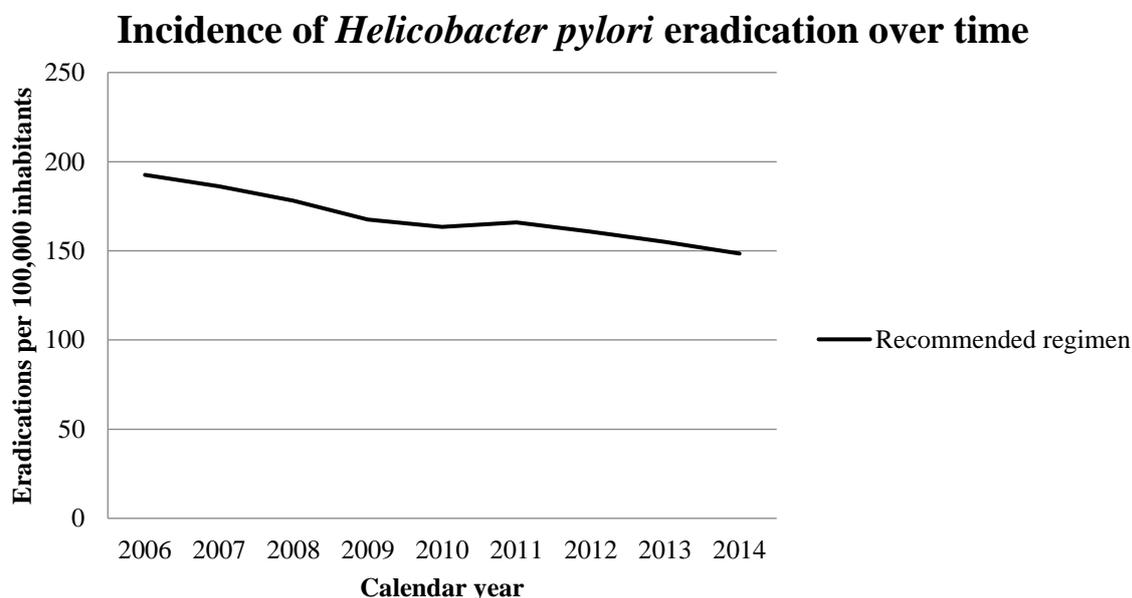


Figure 6. Incidence of *Helicobacter pylori* eradication over time in Sweden per 100,000 residents.

Table 2. Use of the most often prescribed combinations of antibiotics and individual antibiotics for *Helicobacter pylori* eradication.

	First eradication	Second/third eradication	Total (n, %)
Total	140,391 (100)	15,262 (100)	157,915 (100)
Combinations			
Combination package	119,152 (84.9)	13,022 (85.3)	134,079 (84.9)
Amoxicillin + clarithromycin	15,342 (10.9)	1143 (7.5)	16,553 (10.5)
Amoxicillin + doxycycline	643 (0.5)	160 (1.0)	834 (0.5)
Amoxicillin + ciprofloxacin	1739 (1.2)	286 (1.9)	2118 (1.3)

5.3 STUDY III AND IV

Participants

The study cohort included 95,176 individuals receiving at least one prescription for *Helicobacter pylori* eradication treatment during the study period 2005-2012. Slightly more than half of the participants were women (53.7%) and the largest part resided in urban areas (74.6%) (Table 3). During 351,018 person-years of follow-up, with a mean of 3.7 and a maximum of 7.5 years, 75 (0.08%) individuals developed gastric adenocarcinoma. Of these, 69 (0.07%) were non-cardia adenocarcinomas, and 6 (0.01%) were cardia adenocarcinomas. Gastric adenocarcinoma developed in 3 out of 732 (0.4%) individuals with gastric ulcer, while none of the 1235 individuals with duodenal ulcer was diagnosed with this cancer type. Gastric adenocarcinoma developed in 2 out of 1898 (0.1%) individuals with chronic or atrophic gastritis. Oesophageal adenocarcinoma developed in 11 (0.01%) individuals, and oesophageal squamous cell carcinoma in 10 (0.01%) individuals. Barrett's oesophagus developed in 178 out of 95,013 individuals (0.19%) during a follow-up time of 349,759 person-years (Table 3). This cohort included fewer individuals because those diagnosed with Barrett's oesophagus before a first eradication treatment were excluded.

Table 3. Descriptive characteristics of study participants receiving eradication treatment for *Helicobacter pylori* in Sweden during 2005-2012.

Characteristic	Participants Number (%)
Total	95,176 (100.0)
Sex	
<i>Men</i>	44,028 (46.3)
<i>Women</i>	51,148 (53.7)
Age (years)	
<i>18-59</i>	57,214 (60.1)
<i>60-69</i>	17,808 (18.7)
<i>≥70</i>	20,154 (21.2)
Calendar period at entry	
<i>2005-2006</i>	21,218 (22.3)
<i>2007-2009</i>	38,573 (40.5)
<i>2010-2012</i>	35,385 (37.2)
Place of residence	
<i>Rural</i>	23,686 (24.9)
<i>Urban</i>	71,032 (74.6)
<i>Missing</i>	458 (0.5)
Gastric cancer	
<i>All gastric adenocarcinoma</i>	75 (0.08)
<i>Non-cardia gastric adenocarcinoma</i>	69 (0.07)
<i>Cardia adenocarcinoma</i>	6 (0.01)
Oesophageal cancer	
<i>Oesophageal adenocarcinoma</i>	11 (0.01)
<i>Oesophageal squamous cell carcinoma</i>	10 (0.01)
Follow-up (years) for cancer	
<i>Total</i>	351,018
<i>Mean</i>	3.7
Barrett's oesophagus (out of 95,013 individuals)	178 (0.19)
Follow-up (years) for Barrett's oesophagus	
<i>Total</i>	349,759
<i>Mean</i>	3.7

Gastric adenocarcinoma

The overall risk of gastric adenocarcinoma decreased over time after eradication treatment, with SIRs of 8.65 (95% CI 6.37-11.46) 1-2 years, 2.02 (95% CI 1.25-3.09) 3-4 years, and 0.31 (95% CI 0.11-0.67) 5-7.5 years after eradication treatment (Table 4). Analysis starting from the last eradication treatment showed a similar trend. The risk of gastric adenocarcinoma was increased for those with a higher number of eradication treatments. The SIR was 1.88 (95% CI 1.44-2.41) in individuals with one eradication treatment, and 7.44 (95% CI 2.72-16.19) in those with more than 2 eradication treatments. There was no difference in gastric adenocarcinoma risk between individuals residing in rural or urban areas (IRR 0.98, 95% CI 0.59-1.61) (Table 4).

The risk of non-cardia gastric adenocarcinoma also decreased over time after eradication, and the risk increased by number of eradication treatments. The trends were similar to those for all gastric adenocarcinoma, but with wider CIs (Table 4).

For cardia adenocarcinoma there were too few cases to allow analysis over time after eradication and by number of eradications, but the overall SIR was 0.60 (95% CI 0.22-1.30) (Table 4).

Oesophageal cancer

The risk of oesophageal adenocarcinoma decreased over time after eradication treatment, from SIR 3.31 (95% CI 1.21-7.20) 1-2 years to 0.17 (95% CI 0.00-0.92) 5-7.5 years after eradication treatment (Table 4). Ten of the 11 cases were found in individuals receiving one eradication treatment, thus a risk assessment by number of eradications was not possible. Place of residence did not influence the risk (IRR 4.43, 95% CI 0.57-34.70).

For oesophageal squamous cell carcinoma, five cases were detected during 1-2 years after eradication, another five cases 3-4 years after eradication, and no cases 5-7.5 years after eradication (Table 4). The SIR showed a decreasing trend, which was confirmed by Poisson regression yielding an IRR of 0.07 (95% CI 0.02-0.28) for 3-4 years after eradication, compared to 1-2 years after eradication. Nine of the 10 cases occurred in individuals receiving one eradication treatment, and there was no influence of place of residence on the outcome (IRR 0.94, 95% CI 0.24-3.66) (Table 4).

The SIRs of Barrett's oesophagus also decreased over time after eradication treatment, from 10.96 (95% CI 8.95-13.28) at 1-2 years, to 2.72 (95% CI 2.02-3.59) 3-4 years, and 0.71 (95% CI 0.45-1.05) at 5-7.5 years after eradication (Table 4), although Poisson regression was non-significant with an IRR of 1.00 (95% CI 0.40-2.49) 5-7.5 years after eradication treatment. An increased risk was seen in individuals with 2 and more than 2 eradication treatments with SIRs of 2.50 (95% CI 2.10-2.95) in individuals with 1 eradication treatment, 5.83 (95% CI 3.93-8.33) in those with 2 eradication treatments, and 4.51 (95% CI 1.81-9.29) in those with more than 2 eradication treatments. There appeared to be a trend towards a risk decrease for individuals residing in urban areas (IRR 0.75, 95% CI 0.54-1.02).

Table 4. The risk of gastric and oesophageal cancer and Barrett's oesophagus after eradication treatment for *Helicobacter pylori*.

Gastric tumours						
	Gastric adenocarcinoma		Non-cardia gastric adenocarcinoma		Cardia adenocarcinoma	
	<i>Number of cases</i>	<i>SIR (95% CI)</i>	<i>Number of cases</i>	<i>SIR (95% CI)</i>	<i>Number of cases</i>	<i>SIR (95% CI)</i>
Total	75	2.08 (1.63-2.60)	69	2.64 (2.06-3.35)	6	0.60 (0.22-1.30)
Follow-up time, years						
1-2	48	8.65 (6.37-11.46)	43	10.74 (7.77-14.46)	5	3.23 (1.04-7.54)
3-4	21	2.02 (1.25-3.09)	20	2.67 (1.63-4.13)	1	0.35 (0.01-1.93)
5-7.5	6	0.31 (0.11-0.67)	6	0.43 (0.16-0.93)	0	NA
Number of eradications						
1	61	1.88 (1.44-2.41)	56	2.38 (1.80-3.10)	5	0.56 (0.18-1.30)
2	8	2.84 (1.22-5.59)	7	3.45 (1.38-7.11)	1	1.26 (0.02-7.02)
>2	6	7.44 (2.72-16.19)	6	10.47 (3.82-22.78)	0	NA
Oesophageal tumours						
	Barrett's oesophagus		Oesophageal adenocarcinoma		Oesophageal squamous cell carcinoma	
	<i>Number of cases</i>	<i>SIR (95% CI)</i>	<i>Number of cases</i>	<i>SIR (95% CI)</i>	<i>Number of cases</i>	<i>SIR (95% CI)</i>
Total	178	2.82 (2.42-3.26)	11	0.96 (0.48-1.72)	10	1.24 (0.59-2.28)
Follow-up time, years						
1-2	104	10.96 (8.95-13.28)	6	3.31 (1.21-7.20)	5	4.08 (1.32-9.53)
3-4	50	2.72 (2.02-3.59)	4	1.20 (0.32-3.08)	5	2.17 (0.70-5.06)
5-7.5	24	0.71 (0.45-1.05)	1	0.17 (0.00-0.92)	0	NA
Number of eradications						
1	141	2.50 (2.10-2.95)	10	0.97 (0.47-1.79)	9	1.24 (0.57-2.36)
2	30	5.83 (3.93-8.33)	1	1.12 (0.02-6.25)	0	NA
>2	6	4.51 (1.81-9.29)	0	NA	1	5.34 (0.07-29.71)

SIR, standardised incidence ratio. CI, confidence interval. NA, not applicable.

6 METHODOLOGICAL CONSIDERATIONS

6.1 STUDY DESIGN

The study designs in this thesis include a systematic review and meta-analysis (Study I), a descriptive study (Study II) and two cohort studies (Study III and IV).

Epidemiological studies are commonly divided in experimental and observational studies. Well-designed experimental studies like RCTs are usually seen as having the strongest level of evidence, since the design of the study minimises the risk of bias if the sample size is sufficient and the study is well conducted. In these experimental studies, the researchers appoint the exposure to study participants. However, many research questions do not allow for an experimental study, because this can be unethical or infeasible. The studies in this thesis (Study III and IV) are conducted with an observational design, since at least in Sweden an experimental design would be unethical. Individuals are tested for *Helicobacter pylori* in case of peptic ulcer disease, early gastric cancer, MALT lymphoma or when experiencing dyspepsia without any alarm symptoms. In these cases, a diagnosis of *Helicobacter pylori* requires treatment, and it would be unethical to be left untreated. Furthermore, the availability of large, nationwide datasets in Sweden makes an observational design more feasible.

Observational studies are often also more representative of actual clinical practice and the findings are more generalisable, because there are no strict inclusion criteria like in RCTs, making the study population more similar to the population seen in everyday clinical practice. The researchers observe individuals with different exposures and evaluate if they develop the outcome of interest or not. The main types of observational studies are cohort studies, case-control studies, and cross-sectional studies which assess associations on an individual level, and ecologic studies where associations are assessed on group level. Cohort studies are usually preferred over case-control studies, because they have a lower risk of recall bias and selection bias, and can use the entire source population. Cohort studies can become very expensive and time-consuming when all the data have yet to be collected. However, with the availability of the Swedish health care registries this problem can be solved.

In cohort studies the study participants are grouped by exposure status and followed over time to observe if they develop the outcome of interest. In Study III and IV the cohort was assembled from individuals exposed to *Helicobacter pylori* eradication. The unexposed group was the general population of Sweden, and it was assumed they (at least the vast majority) did not receive eradication treatment. This cannot be ascertained completely, since the Swedish Prescribed Drug Registry did not start until July 2005. In the cohort studies the exposure data were recorded in the registries before the outcome occurred, which counteracts bias. The outcome was already known at the start date of the studies (making the studies in some sense “retrospective”, although the data collection itself was prospective), but this could not have affected the exposure classification because this was already recorded. However, different definitions are in use to define prospective and retrospective studies, and a more

present-day definition would recommend the term “prospective” when the outcome could not have influenced exposure information.

A descriptive study (Study II) was conducted in order to better understand the current clinical practice in Sweden regarding eradication treatment for *Helicobacter pylori* and analyse the trend over a recent decade. This study was based on the entire Swedish population and could thus provide unselected information representative of the Swedish population.

A systematic review and meta-analysis (Study I) is supposed to present the current knowledge in an unbiased manner by systematically searching several databases. Meta-analysis provides the opportunity to quantify the effect size based on several relevant studies and could give a more robust estimate than each individual study by increasing the sample size. By putting together all relevant existing information, this study was also used to highlight a knowledge gap, leading on to Studies III and IV.

6.2 INTERNAL VALIDITY

There are three main types of systematic errors that threaten the internal validity of epidemiologic studies; selection bias, information bias and confounding.

6.2.1 Selection bias

This type of bias arises when study participants are not representative of the population that was intended to be studied. This could happen for example if study participants choose to consult a clinician because someone in their family has gastric cancer, and therefore are more likely to be tested for *Helicobacter pylori*, and consequently receive eradication. The participants would then have a higher risk of developing gastric cancer compared to the general population, possibly due to genetic factors, and they might also be more likely to receive *Helicobacter pylori* eradication treatment (exposure) even with mild symptoms, since infection with the bacterium mostly occurs within families.⁽⁷⁷⁾ The main issue with selection bias is that the relation between exposure and outcome cannot be studied the way it was intended, and the results of the study will not depict the true causal effect. Studies II-IV were based on nationwide registries with procedural registration of the information, including the exposure and outcomes (for Study III and IV) of these studies. The comparison group was the Swedish general population. This way of selecting study participants has minimised the risk of selection bias.

6.2.2 Information bias

This bias arises when the exposure or outcome is not measured correctly, and thus is not classified in the right category. In Studies III and IV there is a possibility of misclassification of the exposure. Individuals could have received the combination of drugs for another indication than *Helicobacter pylori* eradication. However, this misclassification was limited by only including the recommended eradication regimen as exposure, which in around 85% of cases was prescribed using the *Helicobacter pylori* eradication package as described in Study II. If individuals did receive the drugs for another indication, the treatment will most

likely still have eradicated the bacterium, if present. The Swedish general population (unexposed group) did contain the participants who received eradication treatment. This is unlikely to have had major influence on the results, since the studied cohort only represents only 1.3% of the population. Any influence would have diluted the associations towards the null. Cancer outcomes could have been misclassified in the Cancer Registry, especially oesophageal adenocarcinomas and cardia adenocarcinomas, because the distinction between these two is not always clear.(69) This misclassification occurs independent of the exposure status and other variables in the study, and is therefore non-differential with possible bias towards the null. Another misclassification of cancer could have occurred if the diagnosis was not reported to the Cancer Registry. However, this registry has a 98% completeness for both gastric and oesophageal cancer, and thus the risk of misclassification was small.(68, 69) Detection bias could have occurred if the cancer is diagnosed earlier in individuals that received eradication treatment, because they are under surveillance or they more readily contact a doctor given their medical history. This would have been a differential misclassification, however it is unlikely to have influence the results since the exposed individuals were also part of the general population, and the majority of the general population in Sweden was never infected with *Helicobacter pylori* and thus does not carry an increased risk of gastric cancer.

6.2.3 Confounding

A confounder is a variable that influences both the exposure and the outcome and does not lie on the causal pathway. Studies III and IV adjusted for some potential confounders like age, sex and calendar period. Another possible confounder is socioeconomic status, which influence was assessed by a proxy variable place of residence. Because of the design, there is always a possibility of residual confounding in observational studies, here for example by dietary factors, genetic factors, smoking or obesity. These possible confounders could not be assessed from the registries since they are not collected regularly on a nationwide level.

6.3 PRECISION

Precision can be seen as the opposite of random error, meaning that with a large precision and increasing power, there is less random error in a study. An approach to random error is needed to examine if the results of a study can be explained by chance alone. This can be done by hypothesis testing, which estimates the likelihood that the null hypothesis is true. The null hypothesis is the hypothesis that there is no association between the exposure and outcome under study. This can be estimated by 95% CIs and P-values. The level of the P-value is usually set at 0.05, which means that if P is smaller than this value there is a less than 5% chance that the null hypothesis is true. This is known as a statistically significant association. However, the P-value does not give much information on the precision of this association. Therefore 95% CIs were used in Studies I, III and IV, where it is possible to test if the association was significant (if the CI did not include 1) and at the same time the precision can be estimated from how wide the CI is. The precision can be increased by increasing the sample size of the study. In Study I the 95% CI was narrow, since the sample

size was large by adding multiple studies together in a meta-analysis. In Studies III and IV some of the 95% CIs from the subgroup analyses are relatively wide. However, the 95% CIs were narrow for the overall analyses per cancer type and the subgroup with the longest follow-up on account of the large number of person-years included in the analyses, indicating sufficient precision.

6.4 EXTERNAL VALIDITY

The external validity of a study is also called generalisability, which concerns whether the results of a study are applicable to other populations than the one that was studied. Generalisability should only be assessed if the internal validity of the study is good. In Study I all of the included studies were conducted in Japan, except for one study from Finland.⁽⁷⁶⁾ It was therefore decided that the results of this study were not generalisable to the Swedish population, which identified the need for further studies on this topic, leading to Study III. The results of Studies III and IV are at least generalisable to the whole Swedish population, because they were based on nationwide registries. It can be argued that these results are even applicable in populations with a similar low prevalence of *Helicobacter pylori* and low prevalence of antibiotic resistance, and similar incidences of gastric and oesophageal adenocarcinomas, for example other Scandinavian countries. Study II was conducted to visualise the use of *Helicobacter pylori* eradication treatment in Sweden and can therefore not be generalised to other populations. However, the findings may be generalisable to populations with similar characteristics to that of the Swedish population and similar treatment regimens for *Helicobacter pylori* eradication.

6.5 SYSTEMATIC REVIEWS AND META-ANALYSES

Meta-analyses are conducted to quantify the results of multiple earlier studies, and provide a more robust estimate by increasing the sample size. A meta-analysis cannot be conducted without a systematic review; a qualitative overview of the existing literature that is unbiased as to which studies are included, as opposed to narrative reviews. If these included studies are considered to be sufficiently homogeneous, a meta-analysis may be conducted. One of the biggest challenges with meta-analyses is though that there are possible sources of bias in each individual included study that cannot be entirely accounted for.

When conducting a meta-analysis the search is the first step after completion of the study protocol. The search needs to be done in such a way that the risk of missing important articles is small, but that at the same time does not generate too many studies for feasibility. For this reason it is important to use multiple databases, and use several synonyms for the keywords in the search. Not all relevant studies may be found in these databases, and this issue is referred to as publication bias. Publication bias arises when not all studies in the field are published, most often due to negative results that did not show any association. Publication bias is sometimes also referred to as small study effects, because smaller studies more often lead to statistically non-significant results and will not be published. A way to assess publication bias is to construct a funnel plot, a scatterplot that shows the distribution of

studies according to their measured effect and size (indicated by the standard error). Visual inspection of this funnel plot will show publication bias if the studies are distributed unequally (asymmetrically) in the plot. Another way to assess publication bias is to use Egger's test, a statistical test to assess the asymmetry of the funnel plot. However, this test has low power when less than ten studies are included.(71)

Another issue that needs to be addressed in meta-analyses is heterogeneity. Analysis of heterogeneity describes the variability between the included studies. Heterogeneity may for example stem from differences in study design, study participants, or the way exposures and outcomes were assessed. In Study I a certain amount of heterogeneity was expected, since studies were conducted in different settings, and different regimens were used for *Helicobacter pylori* eradication. The analysis was therefore conducted using a random effects model. Heterogeneity can be measured with the I^2 statistic, where a value of 0 to 40% represents low heterogeneity, 30 to 60% moderate heterogeneity, 50 to 90% substantial heterogeneity, and 75 to 100% represents considerable heterogeneity.(71) The statistical significance of heterogeneity may be assessed by Cochran's Q test. However, this test has a low power when a low number of studies is included in the meta-analysis and the sample size in the studies is small.(71) Therefore a statistical significance level of 0.10 was chosen to determine heterogeneity in Study I. Another approach to heterogeneity is sensitivity analysis, where studies that are in some way different from the others are excluded to test the robustness of the results. In Study I several sensitivity analyses were conducted; one excluding the studies that did not adjust for confounding or follow-up time, one excluding the study that included individuals with intestinal metaplasia at baseline, and one excluding the study from Finland. All these sensitivity analyses yielded low to moderate heterogeneity. Heterogeneity may also be assessed using meta-regression, but this approach requires at least 10 studies in the meta-analysis and was therefore not used in Study I.

7 GENERAL DISCUSSION

7.1 STUDY I

This systematic review and meta-analysis supports the hypothesis that *Helicobacter pylori* eradication treatment prevents gastric cancer.

The meta-analysis was based on an a priori study protocol and was conducted according to the PRISMA guidelines. An inclusive search was performed in four databases, and there was no evidence of publication bias. The heterogeneity was low to moderate, which could partially be due to the inclusion of only cohort studies. Furthermore, these cohort studies better reflect the actual clinical situation, compared with RCTs. Although these studies carry a higher risk of bias, the study quality that was assessed using a recommended tool was found to be good in seven out of eight studies, while none of the studies was of low quality. A concern was the generalisability of the results to other populations, because almost all studies were conducted in Japan, a region with high prevalence of *Helicobacter pylori* and a high incidence of gastric cancer.

A previous meta-analysis based on RCTs and a simultaneously published meta-analysis on both RCTs and cohort studies also showed a reduced risk of around 50% for gastric cancer after *Helicobacter pylori* eradication treatment,(4, 5) indicating consistency of the findings. The cohort studies included in the most recent study were largely the same as in the present meta-analysis, making these studies comparable regarding the characteristics of the included studies. In contrast, that similar meta-analysis analysed gastric cancer risk by different levels of baseline gastric cancer risk, concluding that the preventive effect of *Helicobacter pylori* eradication treatment is larger in populations with a higher baseline gastric cancer risk, which possibly contradicts the existence of a point-of-no-return in gastric cancer development according to the Correa pathway.(5, 78)

In conclusion, this systematic review and meta-analysis suggests that *Helicobacter pylori* eradication treatment prevents the development of gastric cancer. There were not enough studies (only one) assessing the risk of oesophageal cancer after *Helicobacter pylori* eradication treatment to allow any evaluation of this risk in a meta-analysis.

7.2 STUDY II

This descriptive study based on the whole Swedish population showed that more than 95% of eradication treatments consisted of a recommended or standard eradication regimen. The incidence of *Helicobacter pylori* eradication treatment decreased during 2006-2014.

This register-based study found that 91% of individuals ever receiving *Helicobacter pylori* eradication treatment only received one eradication episode. This number could be overestimated because no information was available before the start of the registry in July 2005. Although the registry did not provide information on indications for treatment, it is likely that the recorded eradication episodes were given for *Helicobacter pylori* eradication,

since in nearly 85% of eradications the combination package was used, and a PPI was prescribed on the same day as the antibiotics in more than 95% of all eradication episodes. Some eradication episodes may still have been missed, among others because the ATC code used for metronidazole was the code for intravenous use (J01XD) and the code for oral use (P01AB01) was not available, since this was not classified as a systemic antibiotic (J01) but as an antiprotozoal (P01). Given that separate prescriptions of antibiotics for eradication were not very common, and that metronidazole is only recommended in case of penicillin allergy or clarithromycin resistance, this should only have had limited influence on the results. However, this does explain why almost no eradication episodes were found using metronidazole. There was no information about any eradication episodes taking place during hospitalisations, since the Drug Registry only records prescriptions picked up at a pharmacy, but this number should be very limited. In nearly 93% of second and third eradication episodes the recommended regimen was used again. This indicates that a sensitivity test for antibiotic resistance is rarely performed in clinical practice. Awareness is required regarding management of *Helicobacter pylori* eradication in Sweden, since repetition of the same regimen might not cure the patient and it could lead to increased antibiotic resistance in the population.

During 1994-1996 a study described *Helicobacter pylori* eradication in a Danish population.(79) That study defined an eradication episode as a prescription of ulcer drugs (PPI or H₂-receptor antagonist) in combination with one, two or three antibiotics on the same day. In that study, 86% of individuals had only one eradication episode. The incidence of eradication treatment was 220 per 100,000 inhabitants per year, compared to less than 200 eradications per 100,000 inhabitants per year in the present study.(79) In contrast to Study II, the Danish study did not provide any description of recommended versus alternative eradication regimens.

In conclusion, from July 2005 until December 2014 more than 140,000 individuals received *Helicobacter pylori* eradication treatment in Sweden. Eradication was mostly prescribed using a recommended regimen, also for secondary eradication episodes. Awareness needs to be raised regarding correct use of *Helicobacter pylori* eradication treatment in Sweden to prevent increase of antibiotic resistance and assure appropriate clinical treatment for individual patients.

7.3 STUDY III

This nationwide Swedish cohort study showed a decrease in risk of gastric adenocarcinoma from five years after *Helicobacter pylori* eradication treatment compared to the risk in the Swedish general population.

This study is one of the first studies exploring the risk of gastric adenocarcinoma after *Helicobacter pylori* eradication treatment in a population with a low incidence of gastric cancer and low prevalence of *Helicobacter pylori*. Separate analyses were conducted for non-cardia gastric adenocarcinoma which gives a more specific estimate of the studied

association, since *Helicobacter pylori* is not associated with an increased risk of cardia adenocarcinoma, but only of non-cardia gastric adenocarcinoma.(8) The follow-up of 7.5 years was relatively short for cancer outcomes, but robust analyses were still possible due to the large sample size. Unfortunately, the registries do not contain information on success of the eradication treatment, which could mean that *Helicobacter pylori* was still present after treatment in some individuals, leading to a misclassification with probable dilution of effects when studying the per protocol treatment effect. The main results in this study were measured simulating an intention to treat protocol to emulate an RCT.(80) This was done to avoid unknown confounding because individuals who receive multiple eradications might have different characteristics than those who receive only one eradication.

The decreased risk of gastric adenocarcinoma found in this study is in line with the only other cohort study assessing the association between *Helicobacter pylori* eradication and gastric cancer in a Western population, which was conducted in Finland.(76) That study also found a strong decrease in gastric cancer risk five years after eradication treatment in individuals who were successfully treated (SIR 0.14, 95% CI 0.00-0.75) and in those who lacked information on successful treatment (SIR 0.13, 95% CI 0.02-1.00), compared to *Helicobacter pylori* negative individuals. The results of the present study are also in line with the meta-analyses on RCTs and cohort studies, and with the meta-analysis in Study I, that all found a significant decrease in gastric cancer risk after eradication treatment for *Helicobacter pylori*.(4, 5)

In conclusion, this study provides support for the hypothesis that eradication treatment for *Helicobacter pylori* prevents gastric adenocarcinoma also in countries with a low incidence of gastric cancer. This information can guide clinical decision-making for health care providers in these regions. This does not mean that widespread screening and eradication programs should be implemented, but it is instead recommended to follow the guidelines for indications to test for *Helicobacter pylori* and eradicate only when the test result is positive.

7.4 STUDY IV

This nationwide Swedish cohort study found a decreasing risk of oesophageal adenocarcinoma, Barrett's oesophagus, and oesophageal squamous cell carcinoma over time after eradication treatment for *Helicobacter pylori*.

During the study period, only 11 individuals were diagnosed with oesophageal adenocarcinoma, which makes it difficult to draw inferences because of the small number of cases. However, there were 178 cases of the premalignant condition Barrett's oesophagus, and both the SIRs for oesophageal adenocarcinoma and Barrett's oesophagus showed a decreasing risk over time after eradication treatment, which strengthens the study results.

Based on previously published research that showed a decreased risk of oesophageal adenocarcinoma and Barrett's oesophagus in individuals with *Helicobacter pylori*, the hypothesis for this study was that the risks of these conditions would instead increase after eradication treatment.(48, 49, 51, 52) However, in order for the risk of oesophageal adenocarcinoma to increase after eradication treatment the gastric atrophy caused by

Helicobacter pylori would need to be reversed. It is a possibility that gastric atrophy is not reversible, or that it would take many years to do so, explaining why no increased risk of oesophageal adenocarcinoma or Barrett's oesophagus was found in the present study.

The results of this study can counteract some of the concerns that eradication treatment for *Helicobacter pylori* would increase the risk of oesophageal adenocarcinoma, which could be a point of discussion especially in patients with risk factors for this cancer type, i.e. gastro-oesophageal reflux and obesity. Therefore the recommendations for eradication treatment for *Helicobacter pylori* remain the same as in Study III; to eradicate after a positive test result based on a valid test indication.

In conclusion, this was the first study assessing the risk of oesophageal adenocarcinoma and Barrett's oesophagus after *Helicobacter pylori* eradication treatment. The results indicated a decreased risk of these conditions from five years and later after eradication treatment, which contradicted the hypothesis of an increased risk. This indicates that *Helicobacter pylori* eradication treatment should not be withheld in patients with a valid treatment indication.

8 CONCLUSIONS

- *Helicobacter pylori* eradication treatment seems to prevent the development of gastric adenocarcinoma, both in settings with a low and high prevalence of *Helicobacter pylori* and low and high incidence of gastric cancer.
- The risk of oesophageal adenocarcinoma and Barrett's oesophagus does not seem to increase after eradication treatment for *Helicobacter pylori*, but may rather decrease.
- *Helicobacter pylori* eradication treatment in Sweden mostly consists of the standard triple therapy regimen, even after a failed first eradication attempt.

9 FUTURE RESEARCH

Although it might now seem clear that *Helicobacter pylori* eradication treatment decreases the risk of gastric adenocarcinoma, more research is needed to determine if there is a stage in the developmental pathway to gastric cancer, a so-called point of no return, where eradication treatment can no longer prevent gastric adenocarcinoma. This would require a large cohort study with gastric biopsies in different stages of development on the Correa pathway with a long follow-up duration.

It is also still insufficiently clear why some people with *Helicobacter pylori* develop gastric cancer and the majority does not. Future research should focus on identifying individuals at an increased risk of developing gastric cancer, which can be for example targeted at bacterial characteristics or other aetiological factors that could enhance cancer development in combination with *Helicobacter pylori*.

More and larger studies that examine the risk of oesophageal adenocarcinoma after *Helicobacter pylori* eradication are needed to validate our findings, and should be conducted in both regions with low and high incidence of oesophageal adenocarcinoma.

Research should also aim at clarifying other potential harmful effects of *Helicobacter pylori* eradication treatment, for example increased antibiotic resistance due to unnecessary eradications and possible long-term changes in the human microbiome, especially in the stomach and gut, which pose a risk for a range of other conditions such as obesity and inflammatory diseases.

Recent research has also highlighted that long-term use of PPIs could lead to an increased risk of gastric cancer. This is especially important in individuals with *Helicobacter pylori*, because they are already more prone to develop gastric atrophy. More research concerning the continued use of PPIs after *Helicobacter pylori* eradication is needed.

Helicobacter pylori is possibly also associated with an increased risk of other gastrointestinal cancers, e.g. colorectal cancer, pancreatic cancer, and biliary tract cancer. More research is needed to confirm these associations and to examine the effect of eradication treatment on these outcomes.

10 POPULAR SCIENCE SUMMARY

***Helicobacter pylori*: to treat or not to treat – that is the question**

Stomach cancer is included in the top 5 of most common cancers worldwide, and only a minority of people with this disease will survive more than 5 years after the diagnosis. The most important risk factor for stomach cancer is infection with the stomach bacterium *Helicobacter pylori*. Around half of all the people in the world have this bacterium. In Sweden, this rate is lower at about 20% of the population. Most often people get infected with the bacterium during childhood. *Helicobacter pylori* is transferred by people, probably partly due to sharing food and unhygienic living conditions. Because of the improvement in living circumstances in Sweden, the bacterium has become less common during recent decades. *Helicobacter pylori* can also cause stomach ulcers. Symptoms from ulcers commonly lead to detection and treatment of the bacterium. Treatment is called eradication and is given using a medicine that decreases acid production in the stomach (proton pump inhibitor) in combination with at least 2 antibiotics. However, only a small amount of people with *Helicobacter pylori* will get any disease from it, so it is not meaningful to test for the bacterium in all individuals and treat them. Treatment can however be an important approach to prevent stomach cancer. But more recently studies have shown that *Helicobacter pylori* infection can instead decrease the risk of oesophageal cancer, indicating a possibility that treatment can increase the risk of this cancer type. Oesophageal cancer has become more common during recent decades and is hard to cure. Therefore, the studies in this thesis try to answer the questions whether treatment of *Helicobacter pylori* actually reduces the risk of stomach cancer, and if it elevates the risk of oesophageal cancer. The aim was to provide scientific evidence to answer part of the question if *Helicobacter pylori* should be treated or not.

Study I was based on a systematic review of published studies examining if treatment of *Helicobacter pylori* reduces the risk of stomach cancer. These studies were selected in a systematic way to ensure that all relevant studies were found. By putting together the results of several studies, the number of participants and cancer cases becomes larger, which makes the results more reliable. The 8 included studies, of which 7 were from Japan and 1 from Finland, showed that the risk of stomach cancer was around 50% lower after treatment of *Helicobacter pylori*.

Study II was based on a nationwide Swedish health data registry (Prescribed Drug Registry) that collects information every time someone receives a doctor's prescription for a medicine and picks it up at a pharmacy. The study described how the treatment for *Helicobacter pylori* is given in Sweden. In the period from July 2005 to December 2014 more than 140,000 people had received eradication treatment, which equals 1.5% of the Swedish population. Most of these people (91%) got treated only once. The majority (95%) of treatments used the standard antibiotics that are recommended for this treatment. These standard antibiotics were also used in most second or third treatments.

Study III and IV included people from Study II who received eradication treatment. More information about these individuals was retrieved from other nationwide health data registries that collect information about cancers (Swedish Cancer Registry), other diseases and hospital stays (Swedish Patient Registry) and deaths (Swedish Causes of Death Registry). The risk of stomach cancer was higher in people who received eradication treatment compared to the stomach cancer risk in the rest of the comparable Swedish population. However, the risk went down over time and was around 70% lower from 5 years after the eradication treatment. For oesophageal cancer there were few cases, making the results less reliable. That is why the risk of Barrett's oesophagus, a condition where the cells in the oesophagus change which may develop to oesophageal cancer, was also measured. Both the risk of oesophageal cancer and Barrett's oesophagus seemed to decrease over time. The risk of Barrett's oesophagus seemed to be lower than that of the general Swedish population from 5 years after eradication treatment.

The conclusions that can be drawn from this thesis are that the treatment of *Helicobacter pylori* reduces the risk of stomach cancer. This was the case in both Asia and Sweden, although people from these parts of the world grow up and live in different circumstances. The risk of oesophageal cancer did not seem to be elevated after *Helicobacter pylori* eradication treatment. This means that *Helicobacter pylori* should probably be treated in all people that qualify for this treatment. There is a reason to believe that treatment can be improved in Sweden, by using different antibiotics if the treatment does not work the first time.

11 POPULÄRVETENSKAPLIG SAMMANFATTNING

***Helicobacter pylori*: att behandla eller inte behandla – det är frågan**

Magsäckscancer är bland de 5 mest vanligaste cancersjukdomar i världen, och det är många människor med sjukdomen som avlider inom 5 år efter att den har upptäckts. Den viktigaste riskfaktorn för magsäckscancer är infektion med magsäcksbakterien *Helicobacter pylori*. Ungefär hälften av alla människor i världen är infekterade med den här bakterien. I Sverige är det färre, ungefär 20 % av alla människor. Infektion med bakterien uppstår oftast i barndomen. *Helicobacter pylori* får man av andra människor, troligen när man delar mat och lever under ohygieniska levnadsvillkor. På grund av den förbättrade levnadsstandarden i Sverige har bakterien blivit mindre vanlig under de senaste decennierna. *Helicobacter pylori* kan även orsaka magsår. Besvär av magsår leder ofta till att bakterien blir upptäckt och behandlad. Behandlingen kallas för eradikering och genomförs med ett läkemedel som minskar syreproduktion i magen (protonpumpshämmare) i kombination med minst 2 antibiotika. Det är dock få personer med *Helicobacter pylori* som får besvär av denna infektion, varför det inte är meningsfullt att göra en utredning av alla människor och behandla. Behandlingen kan dock vara viktig för att minska risken för magsäckscancer hos vissa individer. På senare tid har studier visat att infektion med *Helicobacter pylori* kan minska risken för matstrupscancer, varför behandling av *Helicobacter pylori* skulle kunna öka risken för denna cancertyp. Matstrupscancer har blivit vanligare och är svår att bota. Studierna i den här avhandlingen försöker besvara frågor om behandling av *Helicobacter pylori* verkligen minskar risken för magsäckscancer, och om behandlingen ökar risken för matstrupscancer. Syftet med avhandlingen är att ge vetenskapligt underlag till och delvis besvara fråga om *Helicobacter pylori* ska behandlas eller inte.

Studie I byggde på tidigare publicerade studier som undersökte om behandling av *Helicobacter pylori* minskar risken för magsäckscancer. Dessa studier valdes ut på ett systematiskt sätt för att säkerställa att alla relevanta studier hittades. Genom att sammansätta resultaten av flera studier ökas antalet deltagarna och antalet cancerfall, vilket gör resultaten mer pålitliga. De 8 inkluderade studierna, varav 7 från Japan och 1 från Finland, visade att risken för magsäckscancer minskades med ungefär 50 % efter behandling av *Helicobacter pylori*.

Studie II byggde på ett nationellt Svensk hälsodataregister (Läkemedelsregistret) vilket samlar in information för varje gång en person erhåller ett recept för ett läkemedel och hämtar ut det från apoteket. Den här studien beskriver hur behandling av *Helicobacter pylori* används i Sverige. Under perioden juli 2005 till december 2014 fick mer än 140 000 personer eradikering av *Helicobacter pylori*, vilket motsvarar 1,5 % av svenska befolkningen. De flesta människor (91 %) fick bara en behandling. I majoriteten (95 %) av behandlingarna användes standardantibiotika, som är rekommenderade för den här behandlingen. Samma standardantibiotika har också använts i andra eller tredje behandlingen.

Studie III och IV inkluderade personer som enligt Studie II hade fått eradikeringsbehandling. Ytterligare information om de här personerna inhämtades från andra nationella hälsodataregister som samlar in information om cancer (Cancerregistret), andra sjukdomar samt sjukhusvistelser (Patientregistret) och dödsfall (Dödsorsaksregistret). Risken för magsäckscancer var högre bland personer som fick eradikeringsbehandling jämfört med risken för magsäckscancer i resten av svenska befolkningen. Risken minskade dock med tiden och var omkring 70 % lägre från 5 år efter eradikeringsbehandling. Det fanns ganska få fall av matstrupscancer, vilket gjorde att resultaten inte var helt pålitliga. Därför studerade vi även risken för Barretts esofagus, ett förstadium till matstrupscancer som är betydligt vanligare än canceren. Både risken för matstrupscancer och Barretts esofagus minskade med tiden. Risken för Barretts esofagus verkade vara lägre än risken i svenska befolkningen från 5 år efter eradikeringsbehandling.

Slutsatser från den här avhandlingen är att behandling av *Helicobacter pylori* minskar risken för magsäckscancer. Det gäller både i Sverige och Asien, där människor växer upp och lever under olika levnadsförhållanden. Risken för matstrupscancer verkade inte vara förhöjd efter eradikeringsbehandling för *Helicobacter pylori*. Det betyder att *Helicobacter pylori* antagligen bör fortsätta behandlas hos de människor som behöver behandlingen. Det finns anledning att tro att behandling kan förbättras i Sverige, genom att använda andra antibiotika än de som användes när behandlingen inte fungerade första gången.

12 POPULAIR WETENSCHAPPELIJKE SAMENVATTING

Helicobacter pylori: te behandelen of niet behandelen – dat is de vraag

Maagkanker is een van de 5 meest voorkomende kankers ter wereld, en de meeste patiënten sterven gedurende de eerste 5 jaar na de diagnose. De belangrijkste risicofactor voor maagkanker is infectie met de bacterie *Helicobacter pylori*. Ongeveer de helft van de wereldbevolking draagt deze bacterie met zich mee. In Zweden is dat ongeveer 20% van de bevolking en in Nederland ongeveer 30%. De bacterie wordt vaak overgedragen op zeer jonge leeftijd. Overdracht van *Helicobacter pylori* gaat via menselijk contact, waarschijnlijk door het delen van eten en onhygiënische levensomstandigheden. Dankzij de verbetering in deze levensomstandigheden in Zweden komt de bacterie steeds minder voor, met een duidelijke daling tijdens de laatste decennia. *Helicobacter pylori* is ook verantwoordelijk voor het ontstaan van maagzweren. Het zijn de klachten van deze maagzweren die er vaak voor zorgen dat de bacterie gevonden en vervolgens behandeld wordt. Deze behandeling heet ook wel eradicatie en bestaat uit een maagzuurremmer in combinatie met ten minste 2 verschillende soorten antibiotica. Het is echter maar een klein deel van de mensen met *Helicobacter pylori* die daadwerkelijk ziek wordt, en dus is het niet zinvol om iedereen op deze bacterie te testen en te behandelen. De behandeling kan echter wel van belang zijn om maagkanker te voorkomen. Maar sinds kort is het ook duidelijk geworden dat *Helicobacter pylori* het risico op slokdarmkanker juist lijkt te verminderen. Het idee is dus dat behandeling het risico op deze kankervorm kan verhogen maar dit werd nog niet eerder onderzocht. Slokdarmkanker komt de laatste jaren meer voor en is moeilijk te genezen, en heeft dus een nog slechtere prognose dan maagkanker. De studies in dit proefschrift proberen een antwoord te vinden op de vraag of behandeling van *Helicobacter pylori* het risico op maagkanker kan verkleinen, en of dit tegelijkertijd het risico op slokdarmkanker vergroot. Het doel was om door middel van wetenschappelijke studies dichterbij een antwoord op de vraag te komen of *Helicobacter pylori* behandeld moet worden of niet.

Studie I is een overzichtsstudie gebaseerd op reeds gepubliceerde artikelen die onderzoeken of behandeling van *Helicobacter pylori* het risico op maagkanker verkleint. Deze artikelen zijn op een systematische manier geselecteerd om ervoor te zorgen dat alle relevante studies werden gevonden. Door de resultaten van meerdere studies samen te nemen wordt het aantal deelnemers en het aantal patiënten met kanker groter, waardoor de resultaten betrouwbaarder zijn. De 8 artikelen in deze studie, waarvan 7 afkomstig uit Japan en 1 uit Finland, lieten zien dat het risico op maagkanker ongeveer 50% lager was na het behandelen van *Helicobacter pylori*.

Studie II is gebaseerd op een nationaal Zweeds zorgregister (het Zweedse geneesmiddelenregister) waarin informatie wordt ingezameld voor elke keer dat iemand een geneesmiddel op recept bij de apotheek ophaalt. De studie beschrijft hoe de behandeling van *Helicobacter pylori* wordt gegeven in Zweden. In de periode van juli 2005 tot en met december 2014 werden er meer dan 140 000 mensen behandeld met eradicatie, wat overeenkomt met 1,5% van de Zweedse bevolking. De meeste mensen (91%) werden slechts

één keer behandeld. In het grootste deel (95%) van de behandelingen werden de standaardantibiotica, die worden aanbevolen voor deze behandeling, gebruikt. Dezelfde antibiotica werden echter ook gebruikt voor tweede en derde behandelingen.

Studie III en IV zijn gebaseerd op dezelfde groep mensen uit studie II die werden behandeld met eradicatie. Verdere informatie over deze personen kwam van andere nationale zorgregisters die informatie verzamelen over kanker (het Zweedse kankerregister), andere ziekten en opnames in het ziekenhuis (het Zweedse patiëntenregister) en sterfgevallen (het Zweedse doodsoorzakenregister). Het totale risico op maagkanker was verhoogd bij mensen die behandeld werden met eradicatie in vergelijking met de rest van de Zweedse bevolking. In de loop van de tijd werd het risico echter lager en vanaf 5 jaar na de eradicatie was het risico ongeveer 70% lager dan in de rest van de Zweedse bevolking. Het aantal gevallen van slokdarmkanker was laag, wat ervoor zorgde dat de resultaten niet geheel betrouwbaar waren. Daarom werd ook het risico op een Barrett slokdarm geëvalueerd, een aandoening waarbij de cellen in de slokdarm veranderen en wat zich kan ontwikkelen tot slokdarmkanker. Voor zowel slokdarmkanker als Barrett slokdarm werd het risico lager in de loop van de tijd. Het risico op Barrett slokdarm leek lager te zijn dan in de rest van de Zweedse bevolking vanaf 5 jaar na de eradicatiebehandeling.

De conclusies van dit proefschrift zijn dat behandeling van *Helicobacter pylori* het risico op maagkanker verkleint. Dit was het geval zowel in Zweden als in Azië, gebieden waar mensen in verschillende omstandigheden opgroeien en leven. Het risico op slokdarmkanker leek niet verhoogd te zijn na de behandeling van *Helicobacter pylori*. Dit betekent dat alle mensen met *Helicobacter pylori* die in aanmerking komen voor de behandeling ook behandeld moeten worden. Er is waarschijnlijk ruimte voor verbetering van de behandeling in Zweden, door andere antibiotica te gebruiken wanneer de behandeling de eerste keer niet slaagt.

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