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Helicobacter pylori eradication in the Swedish population

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Running title: *Helicobacter pylori* eradication in Sweden

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Objectives: *Helicobacter pylori (H. pylori)* is associated with peptic ulcers and gastric cancer and its eradication aims to prevent these conditions. The recommended eradication regimen is triple therapy, consisting of a proton pump inhibitor in combination with clarithromycin and amoxicillin or metronidazole for 7 days. Yet, other antibiotic regimens are sometimes prescribed. We aimed to assess the use of eradication therapy for *H. pylori* in the Swedish population during the last decade.

Materials and Methods: This population-based study used data from the Swedish Prescribed Drug Register. From July 2005 until December 2014, all regimens that can eradicate *H. pylori* were identified and evaluated according to patients' age and sex and calendar year of eradication.

Results: We identified 157,915 eradication episodes in 140,391 individuals (53.8% women, 42.6% older than 60 years), who correspond to 1.5% of the Swedish population. The absolute number and incidence of eradications decreased over the study period. Overall, 91.0% had 1 eradication and 0.1% had more than 3. Of all eradications, 95.4% followed the recommended regimen, while 4.7% did not. The latter group was overrepresented among individuals aged ≥80 years (7.8%). Amoxicillin and clarithromycin were most frequently prescribed, while metronidazole was rarely used (0.01%). Other prescribed antibiotics were ciprofloxacin (2.4%), doxycycline (1.4%), nitrofurantoin (0.7%), norfloxacin (0.5%) and erythromycin (0.3%).

Conclusions: During the last decade in Sweden *H. pylori* eradication has been frequently prescribed, but the incidence of eradication has slowly declined. Most eradications followed the recommended regimen, including those occurring after a previous eradication.

Keywords: Helicobacter pylori, eradication, population-based, epidemiology, Sweden, antibiotics.

Introduction

Helicobacter pylori (*H. pylori*) is a bacterium associated with an increased risk of peptic ulcers and gastric cancer.[1] Once detected, *H. pylori* is usually eradicated, mainly to prevent the recurrence of ulcers. In parts of Asia, where the prevalence of *H. pylori* is high, the bacterium is also eradicated to prevent gastric cancer, sometimes even in asymptomatic individuals.[2] In Sweden, where the prevalence of *H. pylori* is lower (11%),[3, 4] there is no population screening for *H. pylori*, so eradication is usually restricted to symptomatic patients. However, recent consensus states that all individuals with documented *H. pylori* infection should receive eradication.[5] Eradication therapy usually consists of a combination of 2 antibiotics with a gastric acid inhibitor (most often a proton-pump inhibitor (PPI)), sometimes in combination with bismuth compounds. The recommended eradication regimen in Northern Europe is triple therapy with a PPI in combination with clarithromycin and amoxicillin or metronidazole for 7 days.[5] A treatment alternative with comparable efficacy is bismuth-containing quadruple therapy, since the addition of bismuth can lead to a 30-40% increase in eradication success in areas with high antibiotic resistance.[6] However, bismuth is rarely used in Sweden, and many other combinations of antibiotics can also be prescribed.[5] The most important reasons to prescribe an alternative regimen are antibiotic resistance and unsuccessful previous eradication. Globally, the antibiotic resistance of *H. pylori* ranges from 10 to 80% for metronidazole, 1 to 25% for clarithromycin, and less than 1% for amoxicillin.[7] In Sweden, antibiotic resistance for *H. pylori* is lower than average, with an estimated 16% for metronidazole, 2% for clarithromycin and 0% for amoxicillin.[8]. These numbers are based on studies performed more than a decade ago in Sweden and no recent data on antibiotic resistance in *H. pylori* is available. Although the Swedish guidelines are based on the European recommendation for triple therapy, it is unclear to what extent these guidelines are followed, in particular after failure of a previous eradication attempt. Therefore,

the aim of this study was to explore patterns and trends for *H. pylori* eradication in the entire Swedish population.

Materials and methods

Design

This was a descriptive study of *H. pylori* eradication therapy within the Swedish population from 1st July 2005 to 31st December 2014. Data were derived from the Swedish Prescribed Drug Register, which started on 1st July 2005 and contains information about all prescribed and dispensed medications in Sweden. Drugs used only during in-hospitalizations are not recorded. The register contains information about the name and code from the Anatomical Therapeutic Chemical (ATC) Classification System of the medication, dates of prescription and dispensing, patient characteristics, the practice issuing the prescription, the prescriber's profession, and costs. The National Corporation of Swedish Pharmacies directs the data collection and each month sends all information to the National Board of Health and Welfare, which holds and manages the Swedish Prescribed Drug Register. We used information on patients' age and sex, ATC codes for antibiotics and drugs for peptic ulcers and gastroesophageal reflux disease, dates of dispensing, and defined daily dose (DDD) per package. The exact prescribed daily dosage and duration was not available and indications for prescriptions were not recorded. The register is complete for the whole Swedish population (patient identification data are missing in <0.3% of all items).[9] Availability of individual information about study participants is enabled by the personal identity numbers given to each Swedish resident upon birth or immigration, and used throughout life. The study was approved by the Regional Ethical Review Board in Stockholm (2014/1291-31/4), which waived informed consent.

Definition of eradication regimens

An eradication episode of *H. pylori* was a priori defined as a combination of prescriptions for at least 2 different systemic antibiotics (dispensed on the same date) and a PPI within a time window of 60 days before or 5 days after antibiotic prescription. The 60-day limit was used to capture individuals already using PPIs, e.g. before any *H. pylori* test results are known, and the 5-day limit takes potential temporary non-availability in the pharmacy into account. The construction of the cohort is visualised in Figure 1. The prescriptions (with ATC codes) were grouped according to the antibiotics prescribed:

1) "Recommended eradication regimen" consisted of 1 PPI and 2 antibiotics (amoxicillin (J01CA04) and/or clarithromycin (J01FA09) and/or metronidazole (J01XD01)), either prescribed separately at the same occasion or in a combination package designed specifically for *H. pylori* eradication (A02BD06: esomeprazole, amoxicillin and clarithromycin).

2) "Alternative eradication regimens" included prescription of a PPI in combination with 2 or more different antibiotics of which at least 1 was from the following groups (excluding the antibiotics used for recommended eradication): macrolides (J01FA), imidazole derivatives (J01XD), tetracyclines (J01AA), fluoroquinolones (J01MA), nitrofuran derivatives (J01XE) or rifabutin (J04AB04), possibly in combination with bismuth subcitrate (A02BX05).[5, 10, 11] To exclude antibiotic combination treatment for indications other than *H. pylori* eradication, we excluded prescription episodes including antibiotics with a dosage for >21 days (based on the defined daily dosage (DDD) per package) and individuals who received ≥50 prescriptions for antibiotics during the study period, since these were unlikely to be prescribed for *H. pylori* eradication.

Statistical analyses

Absolute and relative frequencies of the different eradication regimens and different antibiotics were calculated, and stratified by age group (10-year intervals), sex and calendar year. The first eradication treatment during the study period for each individual and subsequent eradication episodes were analyzed separately. If an individual received ≥4 eradication episodes during the study period, only the first 3 were evaluated to assure validity, since with increasing number of eradication episodes the likelihood of compliance and proper use of therapy decreases. Additionally, prescription trends over time were assessed by calculating the incidence proportion for each calendar year from 2006 onwards, by dividing all prescriptions in 1 year by number of inhabitants in Sweden for the same year. All analyses were performed using the statistical software STATA (Stata Corp v 13.0).

Results

Overall eradication cohort

During the study period (2005-2014), 157,915 prescriptions for *H. pylori* eradication were dispensed to 140,391 individuals. This corresponds to 1.5% of the Swedish population. Of these individuals, 53.8% were female, and 42.6% were older than 60 years. A female predominance was present in all age groups, but was smaller in the age groups 60 to 79 years (Figure 2). Overall, 127,810 individuals (91.0%) received 1 eradication, 9,900 (7.1%) received 2 eradications, 1,669 (1.2%) received 3 eradications, and 1,012 (0.1%) received ≥4 eradications. A second or third eradication was more often seen in individuals aged 40-49 (18.9%) or 50-59 (20.9%), and less often in individuals aged ≥80 years (6.0%) compared to first eradications (15.4%, 17.2%, and 9.3%, respectively) (Appendix 1 and 2). In 95.3% of all eradications a PPI was prescribed on the same day as the antibiotics. The mean and median time between first and second eradication was 19 months and 10 months (range 0-110 months), respectively. The total number of eradications decreased slightly over the study period (Table 1). Of all *H. pylori* eradications, 95.4% were prescribed according to the recommended regimen, while 4.7% followed an alternative regimen (Table 1). This distribution remained stable throughout the study period, and was similar for both sexes and most age groups (Table 1).

Recommended eradication regimen

The age, sex and calendar year of eradication in individuals who were prescribed the recommended regimen followed that of the overall cohort. The combination package was used most often, but in children (≤19 years) and elderly (≥80 years) larger proportions, 35.5% and 12.8%, respectively, had this regimen prescribed using separate medications (Table 1). This was likely due to reductions in doses for children and the elderly. A slight increase of the

prescription of a combination package was seen over the study period. The incidence of recommended *H. pylori* eradication decreased during the study period, from 193 eradications per 100,000 inhabitants in 2006 to 148 eradications per 100,000 inhabitants in 2014 (Figure 3).

Alternative eradication regimen

The lowest proportions of alternative eradication treatment were seen in individuals aged between 20-29 years (1.7%) and 30-39 years (2.1%). In individuals younger than 20 years, 3.7% received an alternative eradication. In older adults (≥60 years) more than 6.0% of the eradications were according to an alternative regimen (up to 7.8% among individuals aged ≥80 years) (Table 1). The distribution of alternative regimens per sex and calendar year followed that of the overall cohort (Table 1). The incidence of alternative *H. pylori* eradication remained between 7 and 9 eradications per 100,000 inhabitants throughout the study period (Figure 3).

Antibiotics used during first eradication

Recommended eradication regimen

For the first eradication, the combination package for eradication was prescribed in 84.9% of the cases. The separate antibiotics most often prescribed were amoxicillin plus clarithromycin (10.9%) (Table 2). Metronidazole was used in only 8 cases (0.006%) for the first eradication.

Alternative eradication regimen

In total, 15 different antibiotics and 74 different antibiotic combinations were identified (including bismuth). The most frequently used antibiotics for an alternative regimen during the first eradication episode were ciprofloxacin (2.4%), doxycycline (1.4%), nitrofurantoin

(0.7%), norfloxacin (0.5%), and erythromycin (0.3%). Combinations of 2 antibiotics that were used 100 times or more in total (16 out of 74) are listed in Table 2. Overall, the most common alternative antibiotic combinations were amoxicillin and ciprofloxacin, amoxicillin and doxycycline, and doxycycline and ciprofloxacin. Bismuth was rarely used (only in 1 first eradication episode) (Table 2).

Antibiotics used during repeated eradications

Recommended eradication regimen

The recommended eradication regimen was used in 92.7% of all second and third eradications. Of these, 85.3% received a combination package, which was similar to the proportion in first eradications. The proportion of separately prescribed amoxicillin and clarithromycin (7.5%) was lower than in first eradications. Metronidazole was used only 2 times (0.01%) for a second or third eradication (Table 2).

Alternative eradication regimen

In total, 12 different antibiotics and 51 different antibiotic combinations were identified for repeated eradication therapy. The alternative antibiotics used were similar to those for first eradications, adding azithromycin (0.5%) to the often used antibiotics. For most separate alternative antibiotics and alternative antibiotic combinations the proportions increased for second and third eradications, compared to first eradications (Table 2).

Discussion

This study shows that eradication therapy for *H. pylori* was common in 2005-2014, although the incidence of eradication slowly declined over the same time period. The recommended regimen dominated, and only fewer than 5% of all prescriptions consisted of alternative combinations of antibiotics, which were especially prescribed among older age groups.

Strengths of this study include the large sample size, population-based design, long study period, and the high validity and nationwide completeness of the Prescribed Drug Register.[9] Since the exposure information was based on the Prescribed Drug Register, there is no risk of recall bias. However, because the register started in 2005 it is not possible to collect information on previous eradication episodes in the included individuals, which could have led to an incorrect definition of a first eradication episode and a possible underestimation of repeated eradication episodes. Another possible limitation is our definition of an eradication episode, established a priori in discussions with clinical experts. Unfortunately, no information on the indication of treatment was available in the Prescribed Drug Register, so we could not verify the validity of our definition. However, the combination package is licensed only for *H. pylori* eradication, so we can be confident about treatment indication for these prescriptions. The alternative antibiotic regimens may have been prescribed for other bacterial infections, but such error should be limited by the restriction to combined prescription of antibiotics and concomitant prescription of a PPI, as well as the restrictions regarding dosage and duration of antibiotic use. Combining different types of antibiotics in an outpatient setting is rarely indicated. Yet, even if other indications have been misclassified as *H. pylori* eradication, it is likely that this treatment also eradicated *H. pylori,* especially since it was combined with PPIs.[12] Yet, by using these rather strict inclusion criteria (aiming for

high specificity), we may also have missed some eradication episodes (i.e. decreasing sensitivity).

Unfortunately, no information was available for failure of the *H. pylori* eradication. It may also be questionable if the efficacy of treatment is tested in all individuals receiving *H. pylori* eradication, even if this is recommended.

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Borttagen: Finally, we have no information on eradications before the start date of the study, which could have led to an incorrect definition of a first eradication episode and a possible underestimation of repeated eradication episodes.

One previous study has characterized *H. pylori* eradication in the general population. In that Danish population, 28,784 individuals received eradication in 1994-1996 (86% had only 1 episode compared to 91% in our study).[13] Eradication was defined as a prescription of ulcer drugs combined with antibiotics on the same day. There was no separate description of recommended or alternative regimens. In our study, most commonly the combination package was prescribed to eradicate *H. pylori*. Reasons not to prescribe the combination package can include antibiotic resistance, patient intolerance or allergy to one of the antibiotics or unsuitable dosage (e.g. for children, elderly and patients with renal insufficiency).

A sensitivity test is recommended after failed eradication,[5, 14] which apparently is rarely performed in practice since this study revealed a substantial rate of additional eradication episodes and yet a low proportion of alternative regimens (<5%). Re-infection with *H. pylori* does not seem to be a sufficient explanation for the high number of repeated eradication episodes, since re-infection rates in adults are less than 1% in developed countries.[5, 15] Suitable antibiotics for second line therapy, or first line in the case of resistance, are tetracycline, doxycycline, levofloxacin, tinidazole, rifabutin, and moxifloxacin, possibly in combination with bismuth.[5, 16-22] Of these, 4 have been used in our study, predominantly doxycycline. Metronidazole was used very rarely, possibly because it has the highest proportion of antibiotic resistance for *H. pylori* in Sweden.[8]

These findings raise some concerns about the management of *H. pylori* in Sweden, because they suggest that either no formal diagnosis of *H. pylori* is confirmed before eradication or that an antibiogram is not made in Sweden after a failed eradication, since the same combination of antibiotics is used in 92.7% of secondary eradications. An antibiogram should guide treatment after initial eradication failure in order to achieve effective eradication and prevent (long-term) side effects of systemic antibiotics, e.g. change in microbiome, especially since no recent information on antibiotic resistance in Sweden is available. This is important for individual patient treatment, and also to prevent antibiotic resistance in the population. Thus, there seems to be an urgent need to raise clinical awareness about antibiotic resistance in *H. pylori* and optimize the treatment after eradication failure.

To conclude, over 140,000 individuals (1.5% of the population) have been treated with a combination of antibiotics and a PPI that could eradicate *H. pylori* during the last decade in Sweden, although the eradication incidence declined over this period. Eradication mostly followed a recommended regimen, including after the first eradication attempt, which indicates there may be a need for better awareness about *H. pylori* antibiotic resistance and eradication therapy in Sweden.

Disclosures

Competing interests: the authors have no competing interests.

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Table 1. Number of *Helicobacter pylori* eradications in Sweden (2005-2014) by age, sex and calendar year for each different prescribed regimen.

	Combination package	Recommended regimen	Alternative regimen	Total
	Number (%)	**Number (%)**	**Number (%)**	**Number (%)**
Total	134,079 **(84.9)**	16,499 **(10.5)**	7,337 **(4.7)**	157,915 **(100)**
Age (years)				
0-19	3,942 **(60.8)**(2.9)*	2,302 **(35.5)**(14.0)	241 **(3.7)**(3.3)	6,485 (4.1)
20-29	10,916 **(89.6)**(8.1)	1,068 **(8.8)**(6.5)	201 **(1.7)**(2.7)	12,185 (7.7)
30-39	17,137 **(89.5)**(12.8)	1,621 **(8.5)**(9.8)	395 **(2.1)**(5.4)	19,153 (12.1)
40-49	21,930 **(88.1)**(16.4)	2,149 **(8.6)**(13.0)	801 **(3.2)**(10.9)	24,880 (15.8)
50-59	24,207 **(86.5)**(18.1)	2,425 **(8.7)**(14.7)	1,361 **(4.9)**(18.6)	27,993 (17.7)
60-69	25,494 **(84.6)**(19.0)	2,767 **(9.2)**(16.8)	1,864 **(6.2)**(25.4)	30,125 (19.1)
70-79	19,245 **(83.8)**(14.4)	2,359 **(10.3)**(14.3)	1,375 **(6.0)**(18.7)	22,979 (14.6)
≥ 80	11,208 **(79.4)**(8.4)	1,808 **(12.8)**(11.0)	1,099 **(7.8)**(15.0)	14,115 (8.9)
Sex				
Male	61,608 **(84.4)**(46.0)	8,004 **(11.0)**(48.5)	3,384 **(4.6)**(46.1)	72,996 (46.2)
Female	72,471 **(85.3)**(54.1)	8,495 **(10.0)**(51.5)	3,953 **(4.7)**(53.9)	84,919 (53.8)
Year				
2005	6,657 **(79.0)**(5.0)	1,230 **(14.6)**(7.5)	536 **(6.4)**(7.3)	8,423 (5.3)
2006	15,264 **(83.1)**(11.4)	2,288 **(12.5)**(13.9)	822 **(4.5)**(11.2)	18,374 (11.6)
2007	15,019 **(84.1)**(11.2)	2,071 **(11.6)**(12.6)	767 **(4.3)**(10.5)	17,857 (11.3)
2008	14,552 **(84.2)**(10.9)	1,938 **(11.2)**(11.8)	795 **(4.6)**(10.8)	17,285 (11.0)
2009	13,834 **(84.5)**(10.3)	1,823 **(11.1)**(11.1)	724 **(4.4)**(9.9)	16,381 (10.4)
2010	13,871 **(86.2)**(10.4)	1,511 **(9.4)**(9.2)	709 **(4.4)**(9.7)	16,091 (10.2)
2011	14,218 **(86.1)**(10.6)	1,524 **(9.2)**(9.2)	770 **(4.7)**(10.5)	16,512 (10.5)
2012	13,864 **(86.0)**(10.3)	1,492 **(9.3)**(9.0)	765 **(4.8)**(10.4)	16,121 (10.2)
2013	13,580 **(86.4))**(10.1)	1,370 **(8.7)**(8.3)	760 **(4.8)**(10.4)	15,710 (10.0)
2014	13,220 **(87.2)**(9.9)	1,252 **(8.3)**(7.6)	689 **(4.5)**(9.4)	15,161 (9.6)
First eradication	119,152 **(84.9)**	15,350 **(10.9)**	5889 **(4.2)**	140,391 **(100)**
Second/third eradication	13,022 **(85.3)**	1145 **(7.5)**	1095 **(7.2)**	15,262 **(100)**

* Numbers in bold are row percentages and numbers in light font are column percentages.

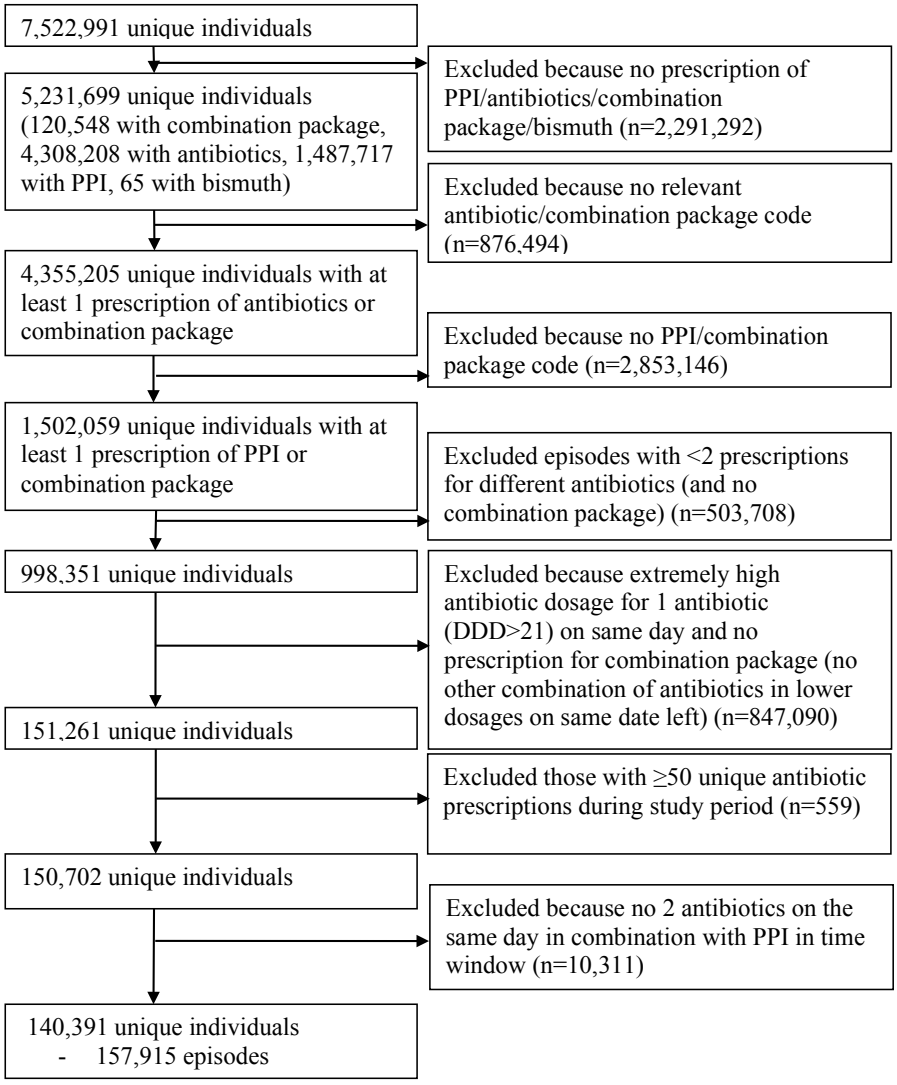
Table 2. Use of the most often prescribed combinations of antibiotics and individual antibiotics for *Helicobacter pylori* eradication.

	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 + erythromycin	100 (0.07)	17 (0.1)	125 (0.08)
Amoxicillin + azithromycin	84 (0.06)	16 (0.1)	102 (0.06)
Amoxicillin + ciprofloxacin	1739 (1.2)	286 (1.9)	2118 (1.3)
Amoxicillin + norfloxacin	164 (0.1)	23 (0.2)	191 (0.1)
Amoxicillin + nitrofurantoin	184 (0.1)	7 (0.05)	193 (0.1)
Clarithromycin + ciprofloxacin	119 (0.08)	11 (0.07)	131 (0.08)
Doxycycline + erythromycin	122 (0.09)	20 (0.1)	148 (0.09)
Doxycycline + ciprofloxacin	538 (0.4)	97 (0.6)	654 (0.4)
Doxycycline + norfloxacin	214 (0.2)	40 (0.3)	263 (0.2)
Doxycycline + nitrofurantoin	152 (0.1)	17 (0.1)	172 (0.1)
Erythromycin + ciprofloxacin	99 (0.07)	12 (0.08)	117 (0.07)
Azithromycin + ciprofloxacin	119 (0.08)	32 (0.2)	162 (0.1)
Ciprofloxacin + norfloxacin	124 (0.09)	19 (0.1)	148 (0.09)
Ciprofloxacin + nitrofurantoin	412 (0.3)	41 (0.3)	454 (0.3)
Individual antibiotics*^			
Amoxicillin	18,322 (13.1)	1726 (11.3)	20,269 (12.8)
Clarithromycin	15,571 (11.1)	1181 (7.7)	16,828 (10.7)
Metronidazole	8 (0.006)	2 (0.01)	10 (0.006)
Tetracyclines			
Doxycycline	1912 (1.4)	413 (2.7)	2418 (1.5)
Lymecycline	62 (0.04)	28 (0.2)	96 (0.06)
Oxytetracycline	1 (0.0007)	0 (0.0)	1 (0.0006)
Tetracycline	65 (0.05)	39 (0.3)	117 (0.07)
Tigecycline	1 (0.0007)	0 (0.0)	1 (0.0006)
Macrolides			
Erythromycin	444 (0.3)	70 (0.5)	548 (0.3)
Roxithromycin	73 (0.05)	28 (0.2)	104 (0.07)
Azithromycin	303 (0.2)	71 (0.5)	393 (0.2)
Fluoroquinolones			
Ofloxacin	13 (0.009)	2 (0.01)	15 (0.009)
Ciprofloxacin	3411 (2.4)	543 (3.6)	4099 (2.6)
Norfloxacin	739 (0.5)	115 (0.8)	881 (0.6)
Levofloxacin	93 (0.07)	47 (0.3)	153 (0.1)
Moxifloxacin	92 (0.07)	20 (0.1)	116 (0.07)
Nitrofuran derivates			
Nitrofurantoin	942 (0.7)	86 (0.6)	1041 (0.7)
Bismuth subcitrate	1 (0.0007)	0 (0.0)	1 (0.0006)

* Percentages for individual antibiotics do not add up to 100 because the combination package is excluded

^ All individual antibiotics were part of a combination of at least 2 antibiotics dispensed on the same date, including a PPI within a time window of 60 days before or 5 days after antibiotics prescription.

Figure 1: Flowchart of the construction of the cohort being prescribed eradication for *Helicobacter pylori*



PPI: proton pump inhibitor, DDD: defined daily dose

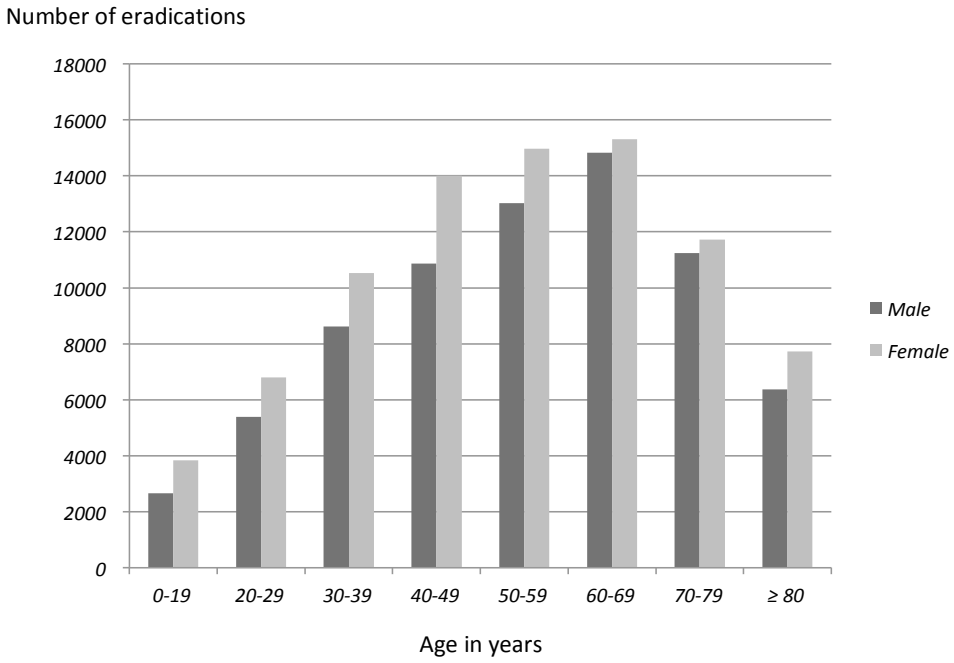


Figure 2. Number of *Helicobacter pylori* eradications in relation to sex and age.

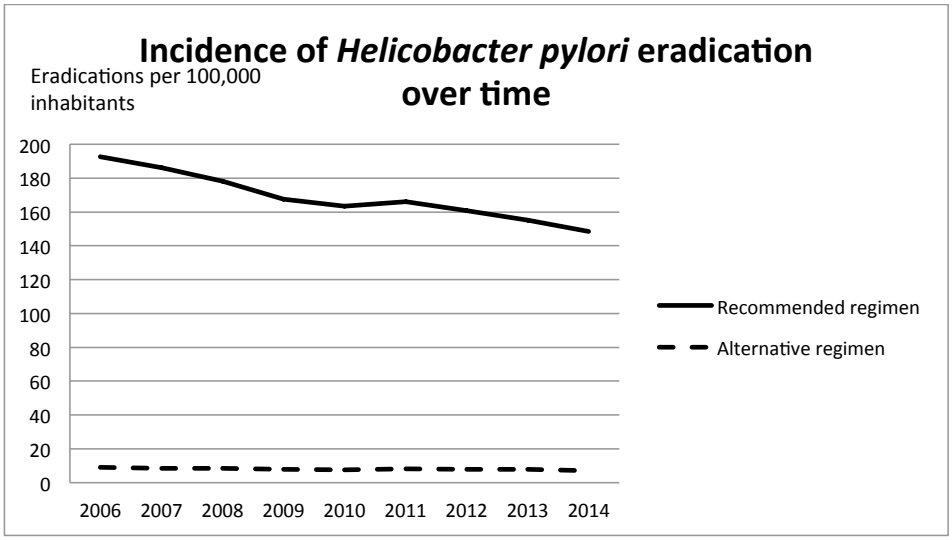


Figure 3. The incidence of *Helicobacter pylori* eradication over time in Sweden per 100,000 inhabitants.

Figure 1: Flowchart of the construction of the cohort being prescribed eradication for *Helicobacter pylori*

Figure 2. Number of *Helicobacter pylori* eradications in relation to sex and age.

Figure 3. The incidence of *Helicobacter pylori* eradication over time in Sweden per 100,000 inhabitants.

Appendix 1. Number of *Helicobacter pylori* eradications in Sweden (2005-2014) by age, sex and calendar year for each different prescribed regimen for first eradications.

	Combination package	Recommended regimen	Alternative regimen	Total
	Number (%)	**Number (%)**	**Number (%)**	**Number (%)**
Total	119,152 **(84.9)**	15,297 **(10.9)**	5,942 **(4.2)**	140,391 **(100)**
Age (years)				
0-19	3,657 **(61.4)**(3.1)*	2,116 **(35.5)**(13.8)	184 **(3.1)**(3.1)	5,957 (4.2)
20-29	10,009 **(89.5)**(8.4)	998 **(8.9)**(6.5)	171 **(1.5)**(2.9)	11,178 (8.0)
30-39	15,279 **(89.5)**(12.8)	1,482 **(8.7)**(9.7)	313 **(1.8)**(5.3)	17,074 (12.2)
40-49	18,985 **(88.1)**(15.9)	1,948 **(9.0)**(12.7)	623 **(2.9)**(10.5)	21,556 (15.4)
50-59	20,892 **(86.5)**(17.5)	2,213 **(9.2)**(14.5)	1,051 **(4.4)**(17.7)	24,156 (17.2)
60-69	22,482 **(84.7)**(18.9)	2,563 **(9.7)**(16.8)	1,489 **(5.6)**(25.1)	26,534 (18.9)
70-79	17,440 **(83.7)**(14.6)	2,245 **(10.8)**(14.7)	1,157 **(5.6)**(19.5)	20,842 (14.9)
≥ 80	10,408 **(79.5)**(8.7)	1,732 **(13.2)**(11.3)	954 **(7.3)**(16.1)	13,094 (9.3)
Sex				
Male	55,105 **(84.4)**(46.3)	7,432 **(11.4)**(48.6)	2,737 **(4.2)**(46.1)	65,274 (46.5)
Female	64,047 **(85.3)**(53.8)	7,865 **(10.5)**(51.4)	3,205 **(4.3)**(53.9)	75,117 (53.5)
Year				
2005	6,504 **(79.1)**(5.5)	1,211 **(14.7)**(7.9)	511 **(6.2)**(8.6)	8,226 (5.9)
2006	14,225 **(83.2)**(11.9)	2,180 **(12.8)**(14.3)	699 **(4.1)**(11.8)	17,104 (12.2)
2007	13,504 **(84.3)**(11.3)	1,920 **(12.0)**(12.6)	600 **(3.7)**(10.1)	16,024 (11.4)
2008	12,945 **(84.2)**(10.9)	1,777 **(11.6)**(11.6)	645 **(4.2)**(10.9)	15,367 (11.0)
2009	12,267 **(84.4)**(10.3)	1,693 **(11.7)**(11.1)	578 **(4.0)**(9.7)	14,538 (10.4)
2010	12,214 **(86.3)**(10.3)	1,366 **(9.7)**(8.9)	566 **(4.0)**(9.5)	14,146 (10.1)
2011	12,324 **(86.1)**(10.3)	1,369 **(9.6)**(9.0)	628 **(4.4)**(10.6)	14,321 (10.2)
2012	11,982 **(85.9)**(10.1)	1,359 **(9.7)**(8.9)	607 **(4.4)**(10.2)	13,948 (9.9)
2013	11,779 **(86.4))**(9.9)	1,257 **(9.2)**(8.2)	594 **(4.4)**(10.0)	13,630 (9.7)
2014	11,408 **(87.2)**(9.6)	1,165 **(8.9)**(7.6)	514 **(3.9)**(8.7)	13,087 (9.3)

* Numbers in bold are row percentages and numbers in light font are column percentages.

Appendix 2. Number of *Helicobacter pylori* eradications in Sweden (2005-2014) by age, sex and calendar year for each different prescribed regimen for second and third eradications.

	Combination package	Recommended regimen	Alternative regimen	Total
	Number (%)	**Number (%)**	**Number (%)**	**Number (%)**
Total	13,022 **(85.3)**	1,135 **(7.4)**	1,105 **(7.2)**	15,262 **(100)**
Age (years)				
0-19	277 **(55.3)**(2.1)*	178 **(35.5)**(15.7)	46 **(9.2)**(4.2)	501 (3.3)
20-29	857 **(90.2)**(6.6)	68 **(7.2)**(6.0)	25 **(2.6)**(2.3)	950 (6.2)
30-39	1,703 **(89.3)**(13.1)	132 **(6.9)**(11.6)	73 **(3.8)**(6.6)	1,908 (12.5)
40-49	2,555 **(88.8)**(19.6)	183 **(6.4)**(16.1)	140 **(4.9)**(12.7)	2,878 (18.9)
50-59	2,745 **(86.0)**(21.1)	198 **(6.2)**(17.4)	249 **(7.8)**(22.5)	3,192 (20.9)
60-69	2,550 **(83.7)**(19.6)	192 **(6.3)**(16.9)	305 **(10.0)**(27.6)	3,047 (20.0)
70-79	1,602 **(85.5)**(12.3)	110 **(5.9)**(9.7)	162 **(8.6)**(14.7)	1,874 (12.3)
≥ 80	733 **(80.4)**(5.6)	74 **(8.1)**(6.5)	105 **(11.5)**(9.5)	912 (6.0)
Sex				
Male	5,689 **(84.5)**(43.7)	542 **(8.1)**(47.8)	501 **(7.4)**(45.3)	6,732 (44.1)
Female	7,333 **(86.0)**(56.3)	593 **(7.0)**(52.3)	604 **(7.1)**(54.7)	8,530 (55.9)
Year				
2005	152 **(79.6)**(1.2)	19 **(10.0)**(1.7)	20 **(10.5)**(1.8)	191 (1.3)
2006	983 **(82.0)**(7.6)	108 **(9.0)**(9.5)	108 **(9.0)**(9.8)	1,199 (7.9)
2007	1,399 **(83.6)**(10.7)	147 **(8.8)**(13.0)	127 **(7.6)**(11.5)	1,673 (11.0)
2008	1,421 **(83.6)**(10.9)	153 **(9.0)**(13.5)	125 **(7.4)**(11.3)	1,699 (11.1)
2009	1,389 **(85.4)**(10.7)	121 **(7.4)**(10.7)	116 **(7.1)**(10.5)	1,626 (10.7)
2010	1,435 **(85.8)**(11.0)	136 **(8.1)**(12.0)	101 **(6.0)**(9.1)	1,672 (11.0)
2011	1,627 **(86.1)**(12.5)	141 **(7.5)**(12.4)	121 **(6.4)**(11.0)	1,889 (12.4)
2012	1,580 **(86.2)**(12.1)	127 **(6.9)**(11.2)	127 **(6.9)**(11.5)	1,834 (12.0)
2013	1,513 **(86.8))**(11.6)	104 **(6.0)**(9.2)	126 **(7.2)**(11.4)	1,743 (11.4)
2014	1,523 **(87.7)**(11.7)	79 **(4.6)**(7.0)	134 **(7.7)**(12.1)	1,736 (11.4)

* Numbers in bold are row percentages and numbers in light font are column percentages.