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The Cost Effectiveness of Helicobacter pylori Population Screening - Economic Evaluation alongside a Randomised Controlled Trial with 13-year Follow-Up

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Summary  

Background Helicobacter Pylori eradication improves dyspeptic symptoms in 8-10%, prevents peptic ulcer and may reduce the risk of gastric cancer. Availability of a high quality diagnostic test
and an effective treatment makes population screening and eradication of Helicobacter pylori an attractive option.

**Aims** To evaluate the cost effectiveness of Helicobacter pylori population screening and eradication.

**Methods** Cost effectiveness analysis and cost utility analysis alongside randomised controlled trial with 13-years follow-up. The evaluation has a societal perspective.

A random general population sample of 20,011 individuals aged 40–65 were randomised and invited in 1998–99; 12,530 were enrolled and of these 8,658 individuals have been successfully followed up at 1, 5, and 13 years after intervention. Questionnaires included the quality of life instrument SF-36. From SF-36 responses an SF-6D score was derived and used for calculation of quality adjusted life years. Register data on costs, use of health care resources and medication were obtained for all randomised individuals. The intervention was an invitation to Helicobacter pylori screening by in-office blood test; positive tests were validated by $^{13}$C-Urea Breath test. Those who tested positive were offered eradication therapy. Main outcome measures were Incremental cost per quality adjusted life year and life-years gained.

**Results** Helicobacter pylori population screening and eradication with 13-years follow-up was not effective in regards to quality of life and the cost per screened person was higher than not screening (mean difference 11,269 DKK (95% CI: 3,175–19, 362)). The probability of being cost-effective was 80% at a threshold of 400,000 DKK of willingness-to-pay per life-year gained.

**Conclusion** Helicobacter pylori population screening and eradication with 13-years follow-up was not effective in regards to quality of life and the cost of screening was higher than not screening.

ClinicalTrials.gov identifier: NCT02001727

**Keywords** Helicobacter pylori, population screening, cost effectiveness, Quality adjusted life years, Life-years.

**Background** Helicobacter pylori (H. pylori) is a Gram-negative motile pathogen bacteria that colonizes gastric mucosae. H. pylori prevalence varies widely with geographical area, age, race, and socioeconomic status. Denmark, Sweden, Norway, United Kingdom, and Germany are low prevalence areas. Most H. pylori infections are asymptomatic but 15% of those infected with H. pylori will eventually experience dyspepsia or peptic ulcer. Dyspepsia is a common condition reported by up to 40% of
the population\(^3\) and \(H.\ pylori\) eradication improves dyspeptic symptoms in 8-10\(^\%\)\(^4,5\). \(H.\ pylori\) eradication prevents peptic ulcer disease and recurrence of peptic ulcer disease\(^6,7\) and may reduce the risk of gastric cancer\(^8\).

\(H.\ pylori\) screening and eradication meets the main criteria of antecedent systematic screening set by WHO in 1968 as well a the Danish national criteria\(^9,10\). \(H.\ pylori\) infection is acquired during childhood\(^11,12\). Recurrence or new infection in adulthood is rare\(^13,14\). Screening is a one-time-intervention per birth cohort. \(H.\ pylori\) Urea breath test is accurate, inexpensive, and noninvasive and the one-week eradication therapy is 80%-90% effective\(^15,16\). The most common side effects to \(H.\ pylori\) eradication therapy are short-term side effects: diarrhoea and altered taste.

Previous studies have found that \(H.\ pylori\) eradication therapy in \(H.\ pylori\) positive individuals was cost-effective compared to long-term acid suppression and led to lower rates of gastric and duodenal ulcer relapse\(^17\). \(H.\ pylori\) eradication therapy may be cost effective treatment for non-ulcer dyspepsia in \(H.\ pylori\) positive individuals\(^18\). Previous studies were mainly based on data from studies where only the \(H.\ pylori\) positive individuals were randomised to eradication therapy or placebo\(^19,20\). Most cost-effectiveness studies of \(H.\ pylori\) population screening are based on computer modelling e.g. Markov model rather than randomised controlled trials and have mainly evaluated the effect of \(H.\ pylori\) population screening on gastric cancer prevention\(^19\). These models contain numerous assumptions and probability estimates based on data extracted from different studies and populations\(^20\). Models can predict only potential effects not actual effects of implementation of screening. The randomised controlled trial analysed in this paper gives the actual effects and costs over a 13-year follow-up period.

This study presents an economic evaluation performed alongside the HEP-FYN study - results have been published elsewhere\(^21\). The HEP-FYN study is a randomised controlled study of population \(H.\ pylori\) screening and eradication with 13-years follow-up, where randomisation was done prior to invitation. Therefore the study mimics the actual screening programme setting and shows the effect of screening on population scale\(^21\). The HEP-FYN study was not powered to detect effect on gastric cancer as Denmark is a low prevalence area\(^22\).

The hypothesis was that screening for \(H.\ pylori\) reduces the prevalence of dyspepsia and the incidence of peptic ulcer disease, resulting in improved quality of life. Furthermore our hypothesis was that the potential future savings resulting from reduced requirement to investigate and treat
peptic ulcer disease and dyspepsia would offset the costs of carrying out an *H. pylori* screening programme. If benefits accumulate over years, savings in health care costs could make *H. pylori* population screening cost effective.

Our aim was to evaluate the cost-effectiveness of *H. pylori* population screening from a societal perspective.

**Methods**

**Design and participants in HEP-FYN**

This study was designed as a cost effectiveness analysis and cost utility analysis from a societal perspective. It is based on the 13-year follow-up of the HEP-FYN study described in detail previously and results published elsewhere\(^2\). Briefly, in 1998 20,011 individuals aged 40–65 years, living in the county of Fyn (Denmark) were identified in the population register and randomised to the *H. pylori* screening and eradication treatment (screening group) or no screening (control group). Randomisation was done prior to invitation. Of these, 12,530 (63%) individuals were enrolled at baseline: 5,749 from the screening group and 6,781 from the control group. 9,641 individuals had participated in the 5-year follow-up and were still eligible at 13-year follow-up, in which a total of 8,658 (69%) individuals took part: 4,144 in the screening group and 4,514 in the control group\(^2\). Data were collected through questionnaires and National Register data at individual level via Statistics Denmark\(^2\). All national registers can be linked via the Danish Civil Registration Number assigned to all residents upon birth or immigration.

**Intervention**

At baseline those randomised to the *H. pylori* screening group were invited to *H. pylori* screening by in-office blood test; all positive in-office blood tests were validated by 13C-Urea Breath test\(^2\). In case of an *H. pylori* positive Urea breath test, triple eradication treatment was offered. The *H. pylori* prevalence was 17.5%.

**Health outcomes**
We used quality of life, quality-adjusted life years (QALY) and life-years in the study as health outcome measures. Life-years in the study were calculated in years from the index date to the date of the 13-year follow-up or to the date of death. Quality of life was measured with the validated quality of life questionnaire Short Form-36 (SF-36)\(^{25}\) at baseline, and at the 1, 5 and 13 year follow-up. In order to calculate QALYs, we converted the SF-36 scores at baseline, 1, 5 and 13 years to a single preference-based measure of health-related quality of life using the Short Form-6D (SF-6D) algorithm developed by Brazier and colleagues\(^{26-29}\). The algorithm was based on utility scores collected from a representative sample of the United Kingdom general population using the Standard Gamble technique\(^{26}\). The SF-6D utility scores ranges between 0, which represents death, and 1, which represents full health. We calculated QALYs by plotting utilities against time, calculating the area under the curve\(^{30}\).

The EQ-5D-5L questionnaire and the EQ-VAS (visual analogue scale) was included only in the final HEP-FYN follow-up\(^{31}\). Each health state was converted into a utility score from a representative sample of the Danish population as well as for a UK population. This allowed us to compare the utility score obtained with the two quality of life instruments. Further analysis comparing scores was beyond the scope of this study and EQ5D was only incorporated at the 13-year follow-up.

**Resource use**

Data on the consumption of ulcer drugs and *H. pylori* eradication therapy was obtained from The Danish National Prescription Register\(^{32}\) which covers use of prescription medicine outside hospitals. Drug utilization was analysed using the defined daily dose (DDD)\(^{32}\).

Data on all hospital contacts were obtained from the Danish National Patient Register for all randomised individuals\(^{33}\). The diagnostic coding was used to extract information on the resource use relevant for dyspepsia and peptic ulcer disease. Diagnoses were recorded according to the 8th and 10th revision of the WHO International Classification of Diseases (ICD)\(^{34,35}\). Incident peptic ulcer disease was defined as the first hospital contact with a peptic ulcer diagnoses (ICD8: 531-4; ICD-10: K25-8) verified by upper endoscopy or surgery occurring during the 13-year follow-up. In-patient and outpatient care and surgical procedures are almost exclusively performed under national healthcare services therefore the data can be regarded as complete. Furthermore, the
diagnostic coding is used as basis for payment of public and private hospitals and giving an economic incentive for complete recording.

Data on the use of services from General practitioners were obtained from the National Health Insurance Service Register. The register includes information on the date of the service provided, type of service, and the fee paid to the provider. It is based on reimbursement claims of the health professionals contracted by the public health system and is therefore considered complete. We included all resources used in general practice regardless of whether the resource was directly associated with the intervention.

**Costs**

Costs were converted into year 2014 prices using the Danish EU-standardised consumer price index. Costs were reported in Danish kroner (DKK) (1 € = 7.44 DKK). Costs were estimated both undiscouted and as present value using an annual discount rate of 4% according to recommendations of the Danish Ministry of Finance.

The hospital care services are valued by the Diagnostic Related Group charges and Diagnostic Outpatient Related Group charges. These charges reflect the average hospital cost of treating and examining patients with similar conditions in a Danish hospital and were considered to approximate public health sector opportunity costs. Register data allowed for inclusion of all health contact costs incurred during follow-up at individual level.

The costs of General practitioners services were based on the fee for service charges and the per capita fee. The market prices of peptic ulcer drugs, drugs for *H. pylori* eradication therapy, and other drugs redeemed during follow-up were included in the data from the Danish National Prescription Register. The use of over-the-counter drugs was only available for the participants successfully followed for 13 years and setting a fixed unit prize was not possible thus the costs were not included.

From a societal perspective, the costs of participant work absence and transport for participation in the screening programme was included. The transport cost was calculated based on distance from each participant’s residence (postal number) to Odense University Hospital and unit cost per kilometre in 2014 (2.10 DKK/km travelled) set by the Danish Tax Assessment Council. The mean
disposable income (total income minus taxes and interest paid) at baseline was obtained from the Register of Income Statistics \textsuperscript{42} and used for calculating the cost of 2 working hours.

**Intervention costs**

Calculation of base case intervention costs were based on detailed recordings of the actual resource use in the HEP-FYN study, which include equipment, time used on planning and rescheduling appointments, testing and preparation for testing, analysing tests, and documentation, and notifying of test results. Furthermore, we applied the observed participation rates (57% of the 10,007 invited persons), and the proportion of reminders (40%) for the cost estimation.

Costs of establishment of an outpatient clinic using hospital facilities were calculated including overhead i.e. rent, electricity, heating and water. Costs for the purchase and maintenance of an isotope ratio mass spectrometer for Urea breath test analysis with a conservative estimated lifetime of 10 years were estimated. Costs of sundry equipment for testing included glass tubes, straws, plastic cups, stir-pins, printing paper, labels were calculated from the 2013 market prices. The cost of printing and posting invitations and information were based on the prices paid for sending questionnaires at the 13-year follow-up.

We estimated the staff cost: one full time social and health service assistant (SOSU) for performing 58 tests per day; one SOSU 12 hours/week for analysing tests and weighing urea and citric acid; one secretary 24 hours/week for administration of invitations, reminders, and rescheduling appointments. One young MDs 12 hours/week for staff supervision, interpretation of tests, information of patients and writing prescriptions for \textit{H. pylori} eradication. The actual yearly wage paid in 2013 for each of these staff members was obtained from the finance department of Odense University Hospital.

The mean cost per person screened is calculated.

**Statistical analysis**

Sociodemographic data and comorbidity index were compared for the randomisation groups at baseline. No significant differences were found \textsuperscript{24}. 

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Both intention-to-treat (ITT) and per protocol (PP) analyses were possible for the outcome life-years because event detection and cost data were based on register data. QALY analysis was based on questionnaire data and was only possible for those who answered questionnaires.

In case of a missing item score in SF-36, the mean of the questions completed by the patient within the dimension was used, provided that >50% of the questions within the dimension had been answered by the participant. These imputations were made prior to deriving the SF-6D index score.

We used the students t-test to compare cost differences, expressed as a mean costs difference with 95% confidence interval (CI).

Cost-effectiveness was evaluated by relating differences in total costs per screened person to differences in life-years across treatment groups. The incremental cost-effectiveness ratio (ICER) is the ratio between the difference in mean total costs (ΔC) and the difference in health effect (ΔE) of two groups: ICER = ΔC/ΔE. ICER was calculated for each health outcome measure. We estimated the uncertainty of the ICERs using bootstrapping, generating 1,000 replications of each ratio. These ΔC/ΔE pairs were depicted in a cost effectiveness plane to evaluate the simultaneous dispersion of cost and health effects and to infer the likelihood of *H. pylori* screening and eradication being cost effective. The replicated ICERs were used to produce cost-effectiveness-acceptability-curves. The cost-effectiveness-acceptability-curves was estimated as the probability that *H. pylori* population screening was cost effective compared with no screening, for a range of monetary values that a decision-maker might be willing to pay for a unit increase in health outcome measure.

**Sensitivity analysis**

One-way sensitivity analyses or scenarios analysis were performed to test the robustness of the results. The main uncertainties were in the intervention cost assumptions (of the outpatient clinic) in the cost analysis and the inclusion of all health contact costs incurred.

The intervention cost for a 20% lower participation rate was calculated and included in a sensitivity analysis. Furthermore analysis including only peptic ulcer disease related health care costs was performed. Peptic ulcer disease related cost were defined as the total cost of hospital
contacts with a peptic ulcer disease diagnosis validated by endoscopy in the same contact, an endoscopy, gastric cancer, ulcer medication, and cost of intervention as described above.

In the analysis of QALY we explored the implications of enhancing data by adding those who died during follow-up. SF-6D indices for follow-up points were included and the quality of life score was given the value 0 for all missing observations after time of death. Lastly we explored the implications of providing values for missing data. Substitutes for missing values of SF-6D index scores were calculated using multiple imputation technique in STATA. QALY was calculated for these imputed scores with and without including those who died during follow-up.

**Ethical considerations**

The Regional Medical Ethics Committee of the Region of Southern Denmark approved the protocol (project-ID: S-VF-19970262). The participants gave their informed consent.

Data were handled according to the laws regulating private research registers and authorized by the Danish Data Protection Agency. The study was registered at ClinicalTrials.gov (identifier: NCT02001727).

**Results**

**Effectiveness outcome**

The mean SF-6D index scores at each follow-up point are displayed in Table 1. For individuals who participated at all follow-up points (8,658) complete index scores were obtained for 8,232 (95%), 8,150 (94%), 7,918 (91%), and 7,734 (89%) individuals for baseline, 1-, 5-, and the 13-year follow-up, respectively. Missing scores were equally distributed between groups.

There were no significant differences in mean SF-6D index scores between the screening group and the control group neither with nor without dead or imputed index scores. The SF-6D index scores declined similarly in both groups during follow-up. However, the mean quality of life score is high and the decline small despite participants ageing 13 years during the study. The decline was unsurprisingly a little steeper when including those who had died.

EQ5D-5L scores were calculated for 96% of responders at the 13-year follow-up. There was no difference in mean index scores between groups (0.824 (s.d. 0.18) in the screening group vs. 0.826 (s.d. 0.17) in the control group) (Table 1).
The EQ5D-VAS score was obtained for 95.6% of responders at the 13-year follow-up (5.1% missing in the screening group vs. 4.0% in controls). There was no difference in mean EQ5D-VAS scores between groups (0.795 (s.d. 0.18) in the screening group vs. 0.801 (s.d. 0.17) in the control group). These scores are relatively high, reflecting a high quality of life in both groups at the 13-year follow-up point.

QALY
A total of 6,733 (54%) individuals enrolled at baseline had SF-6D index scores for all follow-up points meaning QALY could be calculated. By adding those who had died during follow-up QALY calculation was possible for 7,179 (57%). By imputing missing index scores QALY calculation was possible for 8,627 (69%) and 9,270 (74%) of those enrolled at baseline, respectively without and with including those who had died. However, there was no significant difference in mean QALY between groups with or without enhancing data by imputation or including dead (Table 2).

Life-years in the study
During follow-up 1,238 individuals enrolled had died (546 screening group vs. 692 control group). Mean life-years in the study were 12.49 (s.d. 1.93) vs. 12.43 (s.d. 2.07) for the screening group and the control group, respectively; the mean difference was 0.059 years (95%CI -0.011−0.130) (Table 3). The mean difference in life-years in the study between groups were not significant neither for all randomised, enrolled nor for those who had died.

Resource use
Table 4 shows the use of health care resources for the 13 years following intervention. Per protocol (PP) analysis showed that the proportion of users and mean DDD/user of ulcer drugs was higher in the control group: with a relative risk (RR) at 1.06 (95%CI 1.01–1.10) and RR 1.11 (95%CI 1.00–1.22), for proton pump inhibitors and H2-antagonists, respectively. The mean number of in- and outpatient visits to hospital for peptic ulcer disease was higher in the control group; however, the difference was not significant. The use of upper endoscopies and General practitioners contacts were higher in the control group, the difference was not significant.
Costs

Costs were calculated based on the HEP-FYN study inviting 20,011 for *H. pylori* screening and based on the observed participation rate (57%), rate of reminders (40%), equipment use, assuming 240 working days/year, and facilities capable of testing 58 persons/day resulting in a total of 13,920 individuals screened/year.

The total estimated intervention cost per year was 2,372,940 DKK or 170 DKK/year/per screened person. With a 4% discount rate the cost is 209 DKK/year/per screened person. The detailed estimated intervention costs are shown in Supplementary Table 1.

The differences in costs between groups are shown in Table 5. Over 13 years the mean total cost of HEP-FYN intervention was 134,534 DKK/person (s.d. 262,513 DKK/person), while the mean total cost of current clinical practice is 123,265 DKK/person (s.d. 198,952 DKK/person) at a 4% discount rate. The difference was 11,269 DKK/person (95%CI: 3,175–19,362). The differences in cost were mostly due to difference in cost for peptic ulcer disease admissions.

Sensitivity analysis including only peptic ulcer disease related costs reduced the difference to 1,688 DKK/person (95%CI: -570–3,946 DKK/person) at a 4% discount rate. Thus we found no significant difference in peptic ulcer disease (and dyspepsia) related costs between the screening group and the control group.

Sensitivity analyses were performed to explore the impact of the changing the cost assumptions made for outpatient clinics in the cost analysis to 20% less participation, this did however not change results.

Cost-effectiveness analysis

No significant difference in mean QALY between groups was observed and therefore we did not go forward with the cost-utility analysis.

Figure 1 shows ICER based on 1,000 bootstrap replicates of cost utility pairs, discounted 4% for those enrolled and all randomised, respectively. Most were located in the upper right quadrant of the cost-effectiveness plane, meaning the intervention (screening programme) caused higher costs and increased life-years in the screening group.
For all randomized the cost-effectiveness acceptability curve shows that the probability that screening was cost-effective relative to no screening was approximately 0.4 or 0.8, at a threshold of 100,000 DKK or 400,000 DKK per life-year gained (Figure 2).

A sensitivity analysis was performed including only peptic ulcer disease related costs and with a 20% lower participation rate, separately. The analyses were performed both for those enrolled and those randomised.

When including only the peptic ulcer disease related costs and only those enrolled in the study at baseline the cost-effectiveness acceptability curve shows that the probability that screening was cost-effective relative to no screening was 0.8, at a threshold of 100,000 DKK per life-years gained (Figure 3 and 4). The same were observed for all randomised. A 20% lower participation rate did not change results regarding cost-effectiveness. The same were observed for all randomised. A 20% lower participation rate did not change results regarding cost-effectiveness.

Discussion

This economic evaluation based on data from a randomised controlled study of population Helicobacter pylori screening and eradication with 13-years follow-up showed that H. pylori population screening was not effective in regards to quality of life and the cost of screening was higher than not screening. Higher cost in the intervention group was not only related to intervention costs but also due to higher cost for General practitioner visits and use of medication. This may reflect the higher baseline prevalence of dyspepsia and reflux in the screening group (24.8% vs. 21.0%, OR 1.26 (95%CI 1.16−1.37))

There was no significant difference in index scores and in mean QALY between groups with or without enhancing data by imputation or including participants who had died. Analysis of Quality of life of SF-36 scores on full questionnaire data also showed no difference between groups.

Strengths
One strength of the present study is that it is based on data from a randomised controlled trial designed to show the effect of *H. pylori* population screening with a long follow-up period and with a participation profile similar to other national screening programmes. Therefore the economic evaluation gives a close approximation of reality for policy makers.

Another strength is the detailed estimation of intervention costs and the completeness of cost data from national registers under Statistics Denmark, which are known to be of high quality. The total costs based on register information on incurred charges for hospital care and prescription medication during follow-up were also included. Previous studies all used unit costs. By including all costs any possible savings resulting from reduced requirement to investigate and treat peptic ulcer disease and dyspepsia are included. Summed costs of health care services do not reflect exact estimates of the true opportunity costs. However, both the hospital care services valued by the Diagnostic Related Group charges and Diagnostic Out-patient Related Group charges as well as and General practitioner tariffs are used as the basis for reimbursement by national healthcare authorities, and in- and out-patient health care is almost exclusively under national health care services, and the population coverage can therefore be regarded as complete and is therefore a good approximation actual costs.

Costs of two hours work and transportation cost for participants rendered *H. pylori* population screening are included in intervention costs. Including these costs are important since the perspective is that of the society.

Weaknesses

The analyses of long-term health effects showed no difference in point prevalence of self-reported dyspepsia (adjusted OR 0.93 (0.82-1.04)) and no significant difference in incident peptic ulcer disease (adjusted OR 0.88 (0.70-1.11)) between the screening group and the control group. The results of ITT and PP analyses were similar. As discussed in the publication of the main long-term results of HEP-FYN these results could be due to bias introduced by nonparticipation and Denmark being an *H. pylori* low prevalence area. Analysis of register data on all randomised individuals showed that risk of not participating was higher in those who were male, retired, single, and had a lower level of education. These are risk
factors of peptic ulcer disease and of a higher *H. pylori* prevalence. There was a higher observed incident peptic ulcer disease rate in nonparticipant vs. enrolled. The population group with assumed highest risk tends to participate less in screening programmes. The motivation to participate and adherence may also be stronger when less effort is required and when symptoms are present. The inequality in participation may have introduced a selection bias that could weaken the external validity of the results. However, the description of non-responders in the HEP-FYN study is similar to the description of non-responders from other screening programs. It is realistic that the same self-selection would happen if a national population *Hp* screening program was implemented.

The *H. pylori* prevalence was 17.5% at inclusion. The study was carried out in an unselected population sample in a low prevalence area, which dilutes the effects of *H. pylori* eradication. However, the study answers the question of the effect of population screening in a low prevalence area.

It has been debated that the prevalence of *H. pylori* was declining as part of a cohort effect but has stabilised. A decline in the prevalence of *H. pylori* infection could reduce the effect of the intervention over time and undermine the power. This could reduce the health effects resulting from the intervention over time.

A higher probability of cost-effectiveness could be expected in countries with a higher *H. pylori* prevalence and gastric cancer incidence, since *H. pylori* eradication may prevent incident gastric cancer in those with no premalignant lesions.

*SF-36* is not a disease specific instrument and the results may be explained by the lack of precision of the instrument in measuring dyspepsia related quality of life changes. However, sensitivity of *SF-36* has been validated in dyspepsia and peptic ulcer disease and was also confirmed in HEP-FYN. The finding that perceived health seems unaffected by the intervention recent meta-analysis of seven RCTs evaluating the effect of *H. pylori* eradication in patients with functional dyspepsia. It seems rational since quality of life is multifactorial and in a population of this age is subject to more severe factors such as immobility, comorbidities and death of relatives and friends. Perception of quality of life and valuation of health states is influenced by many factors including previous experience of illness.
The mean SF-6D index score at 13-year follow-up was similar to the mean EQ5D-VAS score and lower than EQ5D-5L (UK) scores. Most studies comparing these instruments only compare EQ5D-3L derived estimates (e.g. group mean) but these have shown that the estimates are not interchangeable. The instruments differ in their concepts of health, their descriptive systems, and their evaluation techniques. Since EQ5D based quality of life scores were only available for the last follow-up further comparison was not performed. Preference indices for the UK population were used to calculate QALY, since no Danish preference values are available for SF-6D. This is considered reasonable since there are many parallels between Danish and British ethnicity, culture and lifestyle. However, there may be national differences in health preferences related to cultural factors that may include e.g. interpretation of health concepts, acceptance of disability, or pain states. If different subgroups differ in their health state preferences, then a lack of complete representation could bias the study results.

Cost of medicine was based on the market price obtained from Danish National Prescription Register, which only records prescription medication and not the costs of over-the-counter drugs. Using market prices gives good estimate of the societal cost since it includes both the reimbursed amount and how much was paid by the citizen.

The intervention costs were calculated based on an outpatient hospital setting. Alternatively, a home-kit or a test at the General practitioners office could be considered. This would reduce the cost of staff and overheads but could introduce a possibility of more false negative tests due to inaccurate performance of tests. The options were not explored in this study.

Comparison with other studies

Two randomised controlled trials with long-term follow-up found that *H. pylori* population screening could be cost effective by reducing dyspepsia costs. We did not find evidence to support this. In the Leeds and Bristol study only the *H. Pylori* positive individuals were randomized to *H. pylori* eradication therapy or placebo. Their design allows for evaluating the effect of *H. pylori* screening and eradication in the *H. pylori* positive individual. In the HEP-FYN randomization was done prior to invitation and therefore it can evaluate the effect of screening on a population scale. In the Leeds study the population follow-up is 10 years. They found a reduction in dyspepsia-related costs of $117 per person over 10 years for those who were *H. pylori* positive; 40%
participated in the follow-up. The Bristol study found a significant decrease in general practitioner consultations but not in dyspepsia related drug consumption in the *H. pylori* -eradication group at 7-year follow-up.

In the Leeds study the *H. pylori* negatives were randomised to placebo triple therapy or informed of their negative *H. pylori* status. Those informed of their negative status incurred lower health care costs for dyspepsia in a two-year period than those unaware. This suggests that there might be additional cost savings in the screening group due to reduced use of health care resources in those aware of their negative status. We did however not observe this in the HEP-FYN long-term follow-up study with all incurred cost.

The data from the Leeds study 2-year follow-up have been used in a Markov model and this showed an insignificant cost difference in favour of *H. pylori* eradication in the *H. pylori* positive compared to placebo. Sub analysis by sex showed significant lower dyspepsia related costs in males. The cost per life year saved was 14,200 £ (=163,726 DKK in 2001) modelling the dyspepsia related cost savings set at the lowest of the 95% confidence interval and *H. pylori* eradication having 10% efficacy in preventing mortality from gastric cancer and peptic ulcer disease. Computer modelling gives the advantage of the possibility of incorporating several uncertainties at a time and extrapolating to lifetime effects. However they are all based on assumptions and often incorporate data from several studies which each have their weaknesses.

The finding is in line with our findings when including only peptic ulcer disease related costs.

Two reviews published in 2013 cost-effectiveness studies on *H. pylori* screening to prevent gastric cancer concluded that *H. pylori* screening was cost-effective with Urea breath test and more so with *H. pylori* serology-test. The studies were based on computer modelling e.g. Markov model. The only randomised controlled trial published on *H. pylori* screening vs. placebo shows that *H. pylori* screening can only prevent gastric cancer in those with no premalignant lesions. A cost effectiveness and cost-utility analysis using these data showed *H. pylori* screening to be cost effective in preventing gastric cancer. The HEP-FYN study was not powered to detect effect on gastric cancer. The HEP-FYN data could be used in computer modelling to extrapolate the lifetime effect of *H. pylori* screening and to model the effect given a higher *H. pylori* prevalence. A higher probability of cost-effectiveness could be expected in countries with a higher *H. pylori* prevalence and gastric cancer incidence. There is no current evidence of the optimal number of *H. pylori*
screening successions needed to reduce the \textit{H. pylori} prevalence in the population – \textit{H. pylori} screening being a one-time intervention in each birth cohort.

\textbf{Conclusion}

This randomized clinical trial with 13-years follow-up was designed to give evidence of the effect of Hp population screening from a societal perspective. The study showed no long-term effect of Hp population screening when compared to usual care – neither on health outcomes (dyspepsia prevalence, PUD incidence, and quality of life), nor on use of health care resources. However, the study showed that Hp population screening can be effectively run with a high participation rate and low intervention cost.

The implementation of population screening program has the potential to contribute to unequal distribution of health care resources due to inequality in participation. Allocation of large parts of the public health care budget for a screening program may be at the expense of management strategies for other diseases with potential more benefit - the concept of opportunity costs.

\textbf{References}


