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TITLE PAGE

Title: *Helicobacter pylori* Eradication Therapy to Prevent Gastric Cancer: Systematic Review and Meta-analysis.

Short running head: *H. pylori* Eradication Therapy to Prevent Gastric Cancer.

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Abbreviations:

ACR	assumed control risk
b.i.d.	twice-daily
CI	confidence interval
DALYS	disability-adjusted life-years
H. pylori	*Helicobacter pylori*
IARC	International Agency for Research on Cancer
NNT	number needed to treat
o.d.	once-daily
RCT	randomised controlled trial

RR	relative risk
t.i.d.	three times daily

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ABSTRACT

Objectives: Gastric cancer is strongly associated with *Helicobacter pylori* (*H. pylori*). We conducted a previous systematic review and meta-analysis that suggested eradication therapy reduced future incidence of gastric cancer, but effect size was uncertain, and there was no reduction in gastric cancer-related mortality. We updated this meta-analysis, as more data has accumulated. We also evaluated impact of eradication therapy on future risk of gastric cancer in patients having endoscopic mucosal resection for gastric neoplasia.

Design: We searched the medical literature through February 2020 to identify randomised controlled trials (RCTs) examining effect of eradication therapy on subsequent occurrence of gastric cancer in healthy *H. pylori*-positive adults, and in *H. pylori*-positive patients with gastric neoplasia undergoing endoscopic mucosal resection. The control arm received placebo or no treatment. Follow-up was for ≥2 years. We estimated the relative risk (RR) number needed to treat (NNT), and evaluated the disability-adjusted life-years (DALYs) gained from screening from the meta-analysis.

Results: We identified 10 RCTs, seven recruited 8323 healthy individuals, and three randomised 1841 patients with gastric neoplasia. In healthy individuals, eradication therapy reduced incidence of gastric cancer (RR = 0.54; 95% CI 0.40-0.72, NNT = 72), and reduced mortality from gastric cancer (RR = 0.61; 95% CI 0.40-0.92, NNT = 135), but did not affect all-cause mortality. These data suggest that 8,743,815 DALYs (95% CI 11,847,456-5,646,173) would be gained if population screening and treatment was implemented globally. In patients with gastric neoplasia, eradication therapy also reduced incidence of future gastric cancer (RR = 0.49; 95% CI 0.34-0.70, NNT = 21). Adverse events were incompletely reported.

Conclusion: There is moderate evidence to suggest that *H. pylori* eradication therapy reduces the incidence of gastric cancer in healthy individuals and patients with gastric neoplasia in East Asian countries. There also appears to be a reduction in gastric cancer-related mortality.

What is already known about this subject?

Gastric cancer is the third commonest cause of cancer death worldwide and is causally related to *Helicobacter pylori* (*H. pylori*).

A previous systematic review and meta-analysis demonstrated that eradicating *H. pylori* in healthy infected individuals reduced the incidence of gastric cancer, but the efficacy was relatively modest, and there did not appear to be any effect on mortality.

What are the new findings?

In terms of trials conducted among healthy individuals, we identified one new trial, containing 1826 individuals, and one existing trial completed follow-up out to 22 years.

The number needed to treat (NNT) to prevent one gastric cancer decreased, from 124 overall in our previous meta-analysis, to 72.

The effect was even stronger in individuals with gastric neoplasia; the NNT with eradication therapy to prevent one future gastric cancer was only 21.

In addition, eradication therapy was associated with a significant reduction in gastric-cancer related mortality in healthy individuals; the NNT to prevent one gastric-cancer related death was 135.

Over 8.7 million disability-adjusted life-years would be gained by instituting *H. pylori* screening and treatment globally.

How might it impact on clinical practice in the near future?

This meta-analysis provides contemporaneous estimates of the impact of eradication of *H. pylori* on both incidence of, and mortality from, gastric cancer, which can be used to inform future public health decisions.

INTRODUCTION

Despite a declining incidence in the developing world, [1] gastric cancer is the third commonest cause of cancer death worldwide. [2] In 2017 there were over 850,000 deaths attributable to gastric cancer, and it is estimated that one in 33 men, and one in 78 women will develop the disease during their lifetime. [2] Global mortality from gastric cancer is likely to further increase due to improving life expectancy in developing countries, and recent observations of an increased risk in younger generations. [1]

Helicobacter pylori (*H. pylori*) colonises the stomach of approximately 50% of the world's population. [3] Infection with the bacterium causes chronic gastritis. [4] In a minority of susceptible individuals, [5] this can lead to a stepwise progression through gastric atrophy, intestinal metaplasia, and dysplasia, to the development of carcinoma. [6] As a result, *H. pylori* is classified as a human carcinogen by the International Agency for Research on Cancer (IARC). [7] Eradication of the infection in populations at high risk of gastric cancer could therefore lead to a reduction in incidence of, and mortality from, gastric cancer, [8] and in 2014 an IARC working group report recommended that countries explore the possibility of introducing population-based *H. pylori* screening and treatment programmes. [9] Gastric cancer is a major cause of morbidity and mortality worldwide; it is estimated that over 19 million disability-adjusted life-years (DALYs) are currently lost due to the disease. [10]

Despite this, most countries at high risk of gastric cancer have not considered this policy seriously, although in 2013 Japan approved reimbursement of the use of eradication therapy as a treatment for *H. pylori*-induced gastritis, [11] and in China a trial of population screening and treatment, recruiting over 180,000 individuals, is ongoing. [12] However, there is already some evidence from both observational and controlled studies that eradication of *H. pylori* reduces future incidence of gastric cancer. In 2004 Matsu Island, a region of Taiwan with an annual death rate for gastric cancer three-fold that of the rest of the country,

introduced a population-based eradication programme for *H. pylori*. During the 4 years prior to the screening programme commencing, the incidence of gastric cancer was 40.3 per 100,000 person-years, compared with 30.4 for the years 2004 to 2008; a 25% reduction in incidence. [13] A previous Cochrane Collaboration systematic review and meta-analysis of six randomised controlled trials (RCTs) of eradication therapy, compared with placebo or no treatment, demonstrated a 34% reduction in the relative risk (RR) of an incident gastric cancer, and a number needed to treat (NNT) of 124. [14, 15]

This effect is relatively modest, based on the NNT, and there was no significant impact of eradication therapy on mortality from gastric cancer. [14, 15] The impact may be more dramatic in higher risk groups, such as those with gastric neoplasia, including dysplasia or early gastric cancer. Given that it is 6 years since the publication of this meta-analysis, the possibility that there may now be more published trials, as well as longer duration of follow-up in the existing trials, led us to re-examine this issue. In addition, we evaluated how population screening and treatment may impact on DALYs in the population. Our hypothesis was that as a result of longer follow-up in existing trials, as well as studies published subsequent to our previous systematic review, the effect of eradication therapy, in terms of reducing future gastric cancer incidence, would become stronger, and that there may now be a significant effect on gastric cancer-related mortality, which may translate into a significant gain in DALYs. We also aimed to study the effect of eradication of *H. pylori* on the incidence of future gastric cancer in patients with gastric neoplasia.

METHODS

Search Strategy and Study Selection

We updated our previous systematic review and meta-analysis examining this issue. [14, 15] We searched MEDLINE (1947 to February 2020), EMBASE and EMBASE Classic (1947 to February 2020), and the Cochrane central register of controlled trials to identify potential studies. In addition, we searched clinicaltrials.gov for unpublished trials, or supplementary data for potentially eligible studies. In order to identify studies published only in abstract form, we hand searched conference proceedings (Digestive Diseases Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week) between 2001 and 2019. We contacted authors of trial reports published only as abstracts and asked them to contribute full datasets or completed papers. Finally, we performed a recursive search, using the bibliographies of all obtained articles.

Eligible RCTs examined the effect of at least 7 days of eradication therapy on subsequent occurrence of gastric cancer in *H. pylori*-positive adult subjects (≥18 years) who were otherwise healthy (Supplementary Table 1), or in *H. pylori*-positive adult subjects with gastric neoplasia, including dysplasia or early gastric cancer, undergoing endoscopic mucosal resection. A minimum follow-up duration of 2 years was required, and at least two gastric cancers had to occur during follow-up. We extracted all endpoints at the last point of follow-up that they were reported, using the most contemporaneous publication from each trial.

Two investigators (YY and ACF) conducted the literature search, independently from each other. The search terms used are detailed in the supplementary materials. Two investigators (YY and ACF) evaluated all abstracts identified by the search for eligibility, again independently from each other. We obtained all potentially relevant papers and evaluated them in more detail, using pre-designed forms, in order to assess eligibility

independently, according to the pre-defined criteria. We resolved disagreements between investigators by discussion. There were no language restrictions. We translated foreign language papers, where required.

For fully published studies that did not report data concerning subsequent occurrence of gastric cancer, we contacted the first or senior author in order to maximise our chances of identifying eligible studies. We also contacted authors of all eligible studies that did report subsequent occurrence of gastric cancer, in order to obtain data at the most recent point of follow-up. Finally, where multiple articles for a single study were found, we contacted the first or senior author in order to ensure that only data from the latest publication from each eligible study were extracted.

Outcome Assessment

Our primary outcome was the effect of *H. pylori* eradication therapy, compared with placebo or no treatment, on the subsequent occurrence of gastric cancer. Secondary outcomes included the effect of eradication therapy on gastric cancer-related mortality, effect on all-cause mortality, and adverse events arising from eradication therapy.

Data Extraction

We extracted all data independently. This was done by two investigators (YY and ACF) as dichotomous outcomes (presence or absence of gastric cancer). In addition, we extracted the following data for each trial: geographical location, country of origin, number of centres, method used to confirm *H. pylori* infection, type of *H. pylori* eradication regimen used (including dose and schedule of individual drugs within it), duration of treatment, eradication rate, duration of follow-up, mortality from gastric cancer, mortality from other causes, and total number of adverse events reported.

We extracted data using a modified intention-to-treat analysis. In this, we excluded from the analysis individuals found to be ineligible after randomisation (e.g. heathy individuals in whom a gastric cancer was detected at baseline, patients with gastric neoplasia who underwent surgery rather than endoscopic mucosal resection, or any trial participants who were found to be *H. pylori*-negative), and those who did not receive the intervention to which they were assigned and, due to the relatively rare nature of the outcome of interest, we assumed that all subjects lost to follow-up had not developed gastric cancer, but kept them in the denominator for the study. This was particularly important, given that the shortest duration of follow-up in the studies we identified was ≥3 years, and therefore drop-out rates were relatively high. We also performed a complete case analysis, as a sensitivity analysis, where all participants for whom data were missing or unavailable were excluded from the analysis altogether. [16]

Quality Assessment and Risk of Bias

We performed this at the study level. Risk of bias was assessed by two investigators independently (YY and ACF), using the Cochrane risk of bias tool. [17] We resolved disagreements by discussion. We recorded the method used to generate the randomisation schedule and conceal treatment allocation, as well as whether blinding was implemented for participants, personnel, and outcomes assessment, whether there was evidence of incomplete outcomes data, and whether there was evidence of selective reporting of outcomes.

Data Synthesis and Statistical Analysis

We pooled data using a random effects model, [18] to give a more conservative estimate of the effect of *H. pylori* eradication therapy on the subsequent occurrence of gastric cancer, allowing for any heterogeneity between studies. We expressed the impact of

eradication therapy, compared with placebo or no treatment, as a RR of occurrence of gastric cancer with 95% confidence intervals (CIs). We planned to summarise adverse events data with RRs. We calculated the NNT, with a 95% CI, using the formula NNT = 1 / (assumed control risk (ACR) x (1 – RR)).

We also modelled the impact that *H. pylori* screening and treatment would have on DALYs, using estimates of DALYs lost due to gastric cancer in various populations, [10] using previously described data sources and methodology. [2] DALYs gained were estimated by applying the RR with 95% CIs derived from the meta-analysis to DALYs lost due to gastric cancer (with 95% CIs), [2] using Monte Carlo simulation with 10,000 runs. Both DALYs and RR were assumed to follow a normal distribution and, in these analyses, we assumed that any benefit of eradication therapy persisted beyond the duration of follow-up of RCTs.

We assessed heterogeneity between studies using both the I^2 statistic with a cut off of ≥ 50%, and the chi-squared test with a P value <0.10, to define a significant degree of heterogeneity. [19] We used Review Manager version 5.3.5 (RevMan for Windows 2014, the Nordic Cochrane Centre, Copenhagen, Denmark) to generate Forest plots of pooled RRs for primary and secondary outcomes with 95% CIs, as well as funnel plots. We assessed the latter for evidence of asymmetry, and therefore possible publication bias or other small study effects, using the Egger test, [20] if there were ≥10 eligible studies included in the meta-analysis, in line with previous recommendations. [21] We used Excel (Microsoft Excel for Mac, version 16.33) to conduct the Monte Carlo simulations.

RESULTS

The search strategy identified 2115 citations. We reviewed the titles and abstracts, and retrieved and evaluated 37 articles that appeared potentially eligible for inclusion (Supplementary Figure 1). Of these, 10 articles, [22, 23, 24, 25, 26, 27, 28, 29, 30, 31] reporting relevant data from seven separate RCTs, compared *H. pylori* eradication therapy with placebo or no treatment in 8323 healthy individuals, and provided data on subsequent occurrence of gastric cancer. All these trials recruited healthy people from the community, with the exception of one Korean RCT, which recruited healthy first-degree relatives of gastric cancer patients. [29] Another three trials compared *H. pylori* eradication therapy with placebo or no treatment in 1841 patients with gastric neoplasia undergoing endoscopic mucosal resection, and provided data on the occurrence of future gastric cancer. [32, 33, 34]

Characteristics of eligible and included studies are provided in Tables 1 and 2. Three of the trials, reported in five separate publications, were of factorial design with some participants also randomised to receive vitamins, anti-oxidants, or celecoxib. [22, 23, 26, 27, 28] All trials were conducted in East Asia, except one study that was conducted among a population at high risk of gastric cancer in Colombia. [22, 23] The longest duration of follow-up in the studies we identified was 22 years, [27] and the shortest duration was ≥3 years. [32] Risk of bias assessment of all included RCTs is provided in Supplementary Table 2. We classed four trials as being at low risk of bias, [25, 26, 27, 28, 29] two trials were at unclear risk, [24, 34] and four trials were at high risk of bias. [22, 23, 30, 31, 32, 33] Three were high risk of bias due to the fact that no placebo comparator was used for the active eradication therapy regimen and therefore this part of the trial was unblinded. [22, 23, 32, 33] The other was considered high risk due to inconsistencies in data reporting at various points of follow-up. [30, 31]

Table 1. Characteristics of Randomised Controlled Trials of *H. pylori* Eradication Therapy Versus Placebo or No Treatment in the Prevention of Gastric Cancer in Healthy Individuals.

Study	Location	Method used to confirm presence of *H. pylori*	Sample size (No. receiving *H. pylori* eradication therapy)	Characteristics of participants	Proportion with pre-neoplastic lesions* at baseline	*H. pylori* eradication therapy regimen used	Eradication rate†	Last point of follow-up	Method of ascertainment of gastric cancer cases
Correa 2000 [22] and Correa 2001 [23]	Two communities in Narino Province, Colombia.	Histological examination of gastric biopsies obtained at upper gastrointestinal endoscopy.	852 (437)	Mean age 51.1 years (range 29-69 years), 46.1% male.	100%	Bismuth subsalicylate 262mg, amoxicillin 500mg, and metronidazole 375mg t.i.d± for 2 weeks.	58.0%	6 years.	Histological examination of gastric biopsies obtained at upper gastrointestinal endoscopy at 6 years.

Leung 2004 [31] and Zhou 2014 [30]	11 villages in Yantai County, Shandong Province, China.	Histological examination of, and rapid urease testing using, gastric biopsies obtained at upper gastrointestinal endoscopy.	587 (295) Leung 2004 552 (276) Zhou 2008	Mean age 52.0 years (range 35-75 years), 47.8% male.	33.7%	Omeprazole 20mg, amoxicillin 1g, and clarithromycin 500mg b.i.d‡ for 1 week.	55.6%	5 years in Leung, 10 years in Zhou.	Histological examination of gastric biopsies obtained at upper gastrointestinal endoscopy at 2, 5, 8, and 10 years.

Wong 2004 [25]	Seven villages in Changle County, Fujian Province, China.	Histological examination of, and rapid urease testing using, gastric biopsies obtained at upper gastrointestinal endoscopy.	1630 (817)	Mean age 42.2 years (range 35-65 years), 54.0% male.	37.7%	Omeprazole 20mg, co-amoxiclav 750mg, and metronidazole 400mg b.i.d for 2 weeks.	83.7%	7.5 years.	Histological examination of gastric biopsies obtained at upper gastrointestinal endoscopy at 7.5 years or, if diagnosed before 7.5 years, review of clinical records and pathology specimens by three blinded clinicians.

Saito 2005 [24]	145 centres in Japan.	Not reported.	692 (379)	Mean age not reported (range 20-59 years), proportion male not reported.	Not reported.	Lansoprazole 30mg, amoxicillin 1.5g, and clarithromycin 400mg o.d§ for 1 week.	74.4%	≥4 years.	Histological examination of gastric biopsies obtained at upper gastrointestinal endoscopy at ≥4 years.
Ma 2012 [28] and Li 2019 [27]	13 villages in Linqu County, Shandong Province, China.	Serological testing.	2258 (1130)	Mean age 46.8 years (range 35-64 years), 50.0% male.	64.0%	Omeprazole 20mg and amoxicillin 1g b.i.d for 2 weeks.	73.2%	22.3 years.	Histological examination of gastric biopsies obtained at upper gastrointestinal endoscopy, or from clinical, laboratory, or pathological data.

Wong 2012 [26]	12 villages in Linqu County, Shandong Province, China.	^{13}Carbon-urea breath testing.	513 (255)	Mean age 53.0 years (range 35-64 years), 46.4% male.	100%	Omeprazole 20mg, amoxicillin 1g, and clarithromycin 500mg b.i.d for 1 week.	63.5%	5 years.	Histological examination of gastric biopsies obtained at upper gastrointestinal endoscopy at 5 years.
Choi 2020 [29]	One hospital in Goyang, South Korea.	Histological examination of, and rapid urease testing using, gastric biopsies obtained at upper gastrointestinal endoscopy.	1826 (912)	Mean age 48.8 years (range 40-65 years), 49.5% male.	Not reported.	Lansoprazole 30mg, amoxicillin 1g, and clarithromycin 500mg b.i.d. for 1 week	60.4%	9.2 years.	Access to the Korean National Cancer Incidence Database to confirm all cases of gastric cancer diagnosed by endoscopic surveillance during the trial.

* Defined as gastric atrophy, intestinal metaplasia, or dysplasia

† True intention-to-treat analysis, with all drop-outs assumed to have failed eradication therapy

± t.i.d; three times daily

‡ b.i.d; twice daily

§ o.d; once daily

Table 2. Characteristics of Randomised Controlled Trials of *H. pylori* Eradication Therapy Versus Placebo or No Treatment in the Prevention of Future Gastric Cancer in Individuals with Gastric Neoplasia Undergoing Endoscopic Mucosal Resection.

Study	**Location**	**Method used to confirm presence of *H. pylori***	**Sample size (No. receiving *H. pylori* eradication therapy)**	**Characteristics of participants**	***H. pylori* eradication therapy regimen used**	**Eradication rate†**	**Last point of follow-up**	**Method of ascertainment of gastric cancer cases**
Fukase 2008 [32]	51 hospitals in Japan	Histological examination of, and rapid urease testing using, gastric biopsies obtained at upper gastrointestinal endoscopy.	544 (272)	Median age 68.5 years (range 20-79 years), 76.4% male.	Lansoprazole 30mg, amoxicillin 750mg, and clarithromycin 200mg b.i.d for 1 week.	74.9%	3 years.	Histological examination of gastric biopsies obtained at upper gastrointestinal endoscopy at ≥3 years.

Choi 2018a [33]	One hospital in Seoul, South Korea.	Histological examination of, and rapid urease testing using, gastric biopsies obtained at upper gastrointestinal endoscopy.	901 (444)	Mean age 60.4 years (range 20-75 years), 67.7% male.	Omeprazole 20mg, amoxicillin 1g, and clarithromycin 500mg b.i.d for 1 week.	81.3%	6 years.	Histological examination of gastric biopsies obtained at upper gastrointestinal endoscopy.
Choi 2018b [34]	One hospital in Goyang, South Korea.	Histological examination of, and rapid urease testing using, gastric biopsies obtained at upper gastrointestinal endoscopy.	396 (194)	Mean age 59.8 years (range 18-75 years), 75.3% male.	Rabeprazole 10mg, amoxicillin 1g, and clarithromycin 500mg b.i.d for 1 week.	80.4%	5.9 years.	Histological examination of gastric biopsies obtained at upper gastrointestinal endoscopy at 3 months and 3 years.

Effect of *H. pylori* Eradication Therapy in Healthy Individuals

When we pooled data from the seven RCTs at the last point of follow-up in our primary analysis, [22, 23, 24, 25, 26, 27, 28, 29, 30, 31] there were 68 (1.6%) gastric cancers occurring among 4206 healthy infected subjects who received *H. pylori* eradication therapy, compared with 125 (3.0%) in 4117 individuals allocated to placebo or no treatment. There was only one case of gastric MALT lymphoma reported in the six studies, [24] but this was not included in the analyses. The RR of subsequent occurrence of gastric cancer with eradication therapy versus placebo or no treatment was 0.54 (95% CI 0.40 to 0.72) (Figure 1), with no heterogeneity between studies (I^2 = 0%, P = 0.61). We could not assess for funnel plot asymmetry, as there were insufficient RCTs. The NNT, using data from the meta-analysis with an ACR of 3.0%, was 72 (95% CI 56 to 119).

We modelled these data to estimate the impact of population screening and treatment of *H. pylori* on DALYs gained. We estimated that this programme would result in a gain of over 8.8 million DALYs (95% CI 5.7 to 11.9) globally (Table 3). 5.65 million (95% CI 3.7 to 7.6 million) DALYs were gained in men and 3.2 million (95% CI 2.0 to 4.3 million) DALYs were gained in women. The impact was highest in East Asia (3.75 million DALYs gained) and lowest in Australasia (18,000 DALYs gained) (Table 3).

We conducted a sensitivity analysis pooling data from these seven trials using a complete case analysis. There were 67 (1.7%) gastric cancers among 3894 people assigned to eradication therapy, compared with 125 (3.3%) among 3804 people allocated to placebo or no treatment (RR = 0.53; 95% CI 0.40 to 0.71), with no heterogeneity between studies (I^2 = 0%, P = 0.61). The NNT was 64 (95% CI 51 to 104). We also assessed the impact of excluding the trial with the longest duration of follow-up and the most events of interest, which contributed 63.6% weight to the analysis. [27, 28] There was still a significant effect of eradication therapy, compared with placebo or no treatment, in preventing subsequent

Table 3. Estimate of Disability-adjusted Life-years Gained by *H. pylori* Screening and Treatment in Different Populations*.

Population	Mean DALYs gained	95% confidence interval
Global	8,814,649	5,742,067 to 11,887,230
Men	5,650,560	3,672,479 to 7,628,640
Women	3,165,033	2,049,244 to 4,280,822
East Asia	3,754,826	2,459,850 to 5,049,802
South Asia	1,211,289	786,289 to 1,636,290
North Africa and the Middle East	395,681	254,071 to 537,291
Eastern Europe	468,015	304,225 to 631,804
Western Europe	470,721	303,803 to 637,640
High income North America	192,702	124,729 to 260,675
Central Latin America	224,425	144,883 to 303,966
Southern Latin America	93,391	59,901 to 126,881
Australasia	18,286	11,638 to 24,933

* These analyses relate to all of the impact of *H. pylori* testing and eradication in the population described, and the DALYs gained is what would be achieved hypothetically over the lifetime of the population being screened at a given time point.

occurrence of gastric cancer (RR = 0.56; 95% CI 0.35 to 0.92), with no heterogeneity between studies (I^2 = 0%, P = 0.49), and a NNT of 144 (95% CI 98 to 795).

There were four studies, containing 6301 subjects, which provided data on mortality from gastric cancer. [25, 27, 29, 31] Follow-up in these three trials ranged from 5 years to 22.3 years. Overall, there were 36 deaths (1.1%) from gastric cancer among 3154 healthy infected individuals randomised to eradication therapy, compared with 59 (1.9%) deaths in 3147 participants allocated to placebo. The RR of death from gastric cancer with eradication therapy compared with placebo was 0.61 (95% CI 0.40 to 0.92) (Figure 2), with no heterogeneity between studies (I^2 = 0%, P = 0.95). The NNT, using an ACR of 1.9%, was 135 (95% CI 88 to 658).

There were five studies that reported all-cause mortality among 7079 recruited individuals according to treatment allocation. [22, 25, 26, 28, 29] Follow-up in these five RCTs ranged from 6 years to 14.7 years. In total, 315 (8.9%) of 3551 healthy infected subjects receiving eradication therapy were dead at last point of follow-up, compared with 323 (9.2%) of 3528 individuals receiving placebo or no treatment. The RR of death from any cause at last point of follow-up with eradication therapy compared with placebo or no treatment was 0.97 (95% CI 0.85 to 1.12) (Figure 3), with no heterogeneity between studies (I^2 = 0%, P = 0.50).

Effect of *H. pylori* Eradication Therapy in Individuals with Gastric Neoplasia Undergoing Endoscopic Mucosal Resection

When we pooled data from the three RCTs at the last point of follow-up in our primary analysis, [32, 33, 34] there were 41 (4.5%) future gastric cancers occurring in 910 patients randomised to eradication therapy, compared with 87 (9.3%) in 931 patients receiving placebo or no treatment. The RR of a future gastric cancer with eradication

therapy versus placebo or no treatment was 0.49 (95% CI 0.34 to 0.70) (Figure 1), with no heterogeneity between studies (I^2 = 0%, P = 0.73). Again, with only three trials we could not assess for funnel plot asymmetry. The NNT, using data from the meta-analysis with an ACR of 9.3%, was 21 (95% CI 16 to 36). When we used a complete case analysis in these three trials in a sensitivity analysis, there were 41 (4.6%) gastric cancers among 886 patients assigned to eradication therapy, compared with 87 (9.8%) among 892 patients allocated to placebo or no treatment (RR = 0.48; 95% CI 0.33 to 0.69), with no heterogeneity between studies (I^2 = 0%, P = 0.72). The NNT was 20 (95% CI 15 to 33). Mortality data were only reported by two of these RCTs. [32, 34] In the first trial, there was one death from extra-gastric disease in each treatment arm, [32] and in the second RCT there were 11 deaths (one from gastric cancer) in the eradication therapy arm, and six (one from gastric cancer) in the placebo arm (P = 0.19). [34]

Adverse Events

Adverse events data were incompletely reported by the majority of trials. One RCT conducted in healthy individuals reported these in a separate paper; [35] there was no statistically significant difference in adverse event rates, with the exception of skin rash which occurred in 3.1% of those receiving eradication therapy compared with 0.1% of those allocated placebo. Another trial in healthy individuals reported that drug-related adverse events were significantly more common with eradication therapy (53.0% vs. 19.1%, P<0.001), but that the majority were mild. [29] The Colombian study reported that side effects were monitored closely, and none of any clinical importance were detected. [22] Among trials conducted in patients with gastric neoplasia, soft stools and diarrhoea were reported as occurring in 12% and 7%, respectively, of those receiving eradication therapy in one RCT, [32] and in the placebo-controlled trial from Korea, mild drug-related

adverse events were significantly more common with eradication therapy (42.0% vs. 10.2%, P<0.001). [34]

DISCUSSION

This updated systematic review and meta-analysis demonstrates that eradication of *H. pylori*, in both healthy individuals and patients with gastric neoplasia undergoing endoscopic mucosal resection, significantly reduces the future incidence of gastric cancer. The effect was strongest in those with gastric neoplasia, with a NNT of 21. However, among healthy individuals, due to increased follow-up in one of the existing trials, and a new trial conducted in 1826 people, the NNT to prevent one gastric cancer dropped considerably, from our estimate of 124 in the previous version of this meta-analysis, [14, 15] to 72. In addition, in populations at higher risk of gastric cancer we estimate that *H. pylori* screening and treatment could result in 3.7 million DALYs gained in East Asia, where the majority of these trials were conducted. Finally, we observed a significant impact of eradication of *H. pylori* on gastric cancer-related mortality, with a NNT to prevent one death from gastric cancer of 135.

We updated our previous systematic review and meta-analysis using a contemporaneous and exhaustive search strategy. This allowed us to identify one existing trial with longer follow-up and one new trial recruiting over 1800 individuals, meaning that we were able to pool data from over 8000 subjects in our primary analysis conducted in healthy individuals. We also contacted authors of some included studies, in order to obtain data from the last point of follow-up, as well as to ensure we had not missed potentially eligible RCTs, or included data from the same study at two different points of follow-up. Finally, we used a random effects model and a modified intention-to-treat analysis, in order to minimise the possibility that the effect of eradication therapy on the future incidence of gastric cancer, and gastric cancer-related mortality, has been overestimated.

Limitations of this study include the fact that only one of the trials was conducted outside East Asia, [22, 23] meaning that it is not possible to assess the effect of eradicating

H. pylori on gastric cancer incidence in other populations. In terms of the quality assessment of the RCTs we identified, only four were at low risk of bias. [25, 26, 27, 28, 29] All of these recruited healthy individuals, and when the analysis was restricted to only these trials eradication therapy still led to a significant reduction in the incidence of gastric cancer (RR = 0.54; 95% CI 0.39 to 0.73). One of the trials, with 22.3 years of follow-up, [27, 28] contributed the most weight to the analyses. Excluding this study from the analysis of the effect of eradication therapy on subsequent occurrence of gastric cancer did not change the statistical significance of our results, but the magnitude of the effect was reduced. If this trial were to be excluded from the analysis of the effect on mortality from gastric cancer, there would be no significant impact of eradication therapy on this endpoint. Due to the factorial design of some of the trials, it is difficult to determine whether the reduction in RR of subsequent gastric cancer was only due to eradication therapy, although when the analysis was limited to the four trials that used eradication therapy alone, [24, 25, 29, 30, 31] there was still a benefit (RR = 0.48; 95% CI 0.28 to 0.80). The eradication regimens used varied considerably between the individual trials, and some, such as PPI dual therapy, would now be considered "historical". However, if anything, lower eradication rates with these older regimens is likely to have led to an underestimate of the effect of eradication therapy in preventing future gastric cancer. Finally, individual adverse events data were not reported by many of the RCTs we identified, meaning that balancing the benefits and harms of eradicating *H. pylori*, particularly in healthy individuals, might be difficult.

Nevertheless, our findings support screening for, and treatment of, *H. pylori* in both healthy individuals and patients with gastric neoplasia, as a means of reducing future incidence of gastric cancer. Once *H. pylori* has been eradicated successfully it is unlikely to be acquired again, [36] so unlike other cancer prevention programmes, it is likely that

screening would only need to occur once during an individual's life. However, ideally, any cancer screening programme should also be cost-effective. The earliest economic model to examine this issue, which was based on screening and treating people at the age of 50 years, reported a cost-effectiveness of $25,000 per year of life saved. [8] Numerous subsequent, and similar studies, modelling various populations and methods of screening, have all demonstrated cost-effectiveness using a cut-off of $50,000 per life-year saved. [37, 38, 39, 40, 41, 42, 43] Although this is unlikely to be relevant in Western countries, where gastric cancer incidence is declining, [1] there may be other benefits from eradicating *H. pylori* in these populations, such as a reduction in the prevalence of peptic ulcer disease or the incidence of dyspepsia in the community, [13, 44, 45] and the costs associated with managing these conditions. [46, 47, 48] Furthermore, our data suggest there could be approximately 0.5 million DALYs gained in relatively affluent populations, such as Western Europe, so population screening and treatment may even be appropriate in some continents that are considered "low risk".

As the vast majority of *H. pylori* infection is acquired in childhood, [49] probably between the ages of 6 and 15, [50, 51] the most logical point to perform screening would be either in adolescence or young adulthood. This may also give the greatest chance of interrupting progression of the pre-cancerous cascade towards gastric cancer. Preliminary screening programmes in these types of populations are now under way in some regions of Japan, [52, 53] although it will be many years until their effects are known. One concern of adopting such strategies may be that prescribing eradication therapy in younger people will promote antibiotic resistance or lead to substantial alterations of the microbiome, [54] although recent evidence suggests that the gastric microbial dysbiosis seen with *H. pylori* infection is reversed by eradication, and there also appear to be beneficial effects on the intestinal microbiota. [55] However, our data demonstrate that even among patients having

endoscopic mucosal resection for gastric neoplasia, eradication therapy at this late stage can have an impact on gastric cancer incidence, suggesting that eradication of *H. pylori* at any age may still have a beneficial effect.

A previous systematic review and meta-analysis, which pooled data from both RCTs and observational studies, demonstrated a reduction in the future incidence of gastric cancer with eradication therapy, and also reported that the benefit varied according to baseline risk of gastric cancer. [56] Due to the identification of two new RCTs since the publication of this meta-analysis, [29, 34] as well as longer follow up in one of the previously identified trials, [27] our study has been able to provide a more contemporaneous estimate of the magnitude of the effect of *H. pylori* eradication therapy on future occurrence of gastric cancer, and has also been able to demonstrate a reduction in disease-specific mortality.

According to the latest estimates from the Global Burden of Disease Study for 2017, there were 1.2 million incident cases of gastric cancer, and 865,000 deaths worldwide. [2] Incidence rates increased by 25% between 2007 and 2017, due to changes in the population age structure and population expansion. [2] This suggests that the total number of deaths from gastric cancer may well continue to rise for the foreseeable future, partly due to an increase in the average age of the world's population. [57] Migration of people from high to low prevalence regions, due to a combination of economic and environmental reasons, is also likely to ensure it remains a major public health concern worldwide. [58] Despite this, and recommendations from the IARC, [9] no country has adopted a national screening and treatment programme for *H. pylori.* However, even if population screening and treatment were to be adopted by high risk countries, there may be barriers to implementation of mass screening, such as prioritisation versus other public health challenges, lack of infrastructure to provide an efficient and organised service, and

low adherence to eradication therapy among infected individuals, due to the perceived risks versus the proposed benefits.

Our updated systematic review and meta-analysis provides moderate quality evidence that searching for and eradicating *H. pylori* can reduce the incidence of gastric cancer in healthy infected individuals, and in patients with gastric neoplasia. The NNT in these two groups were 72 and 21, respectively, but these should not be extrapolated to populations outside East Asia. Our confidence in the estimate has improved, the magnitude of the effect has increased, and there is now a reduction in gastric cancer-related mortality, although not in all-cause mortality. Over 8 million DALYS would be gained globally if population screening and treatment for *H. pylori* were to be introduced. However, reporting of the potential harms of *H. pylori* eradication therapy in these situations is still limited. Despite this, due to the reduction in the NNT, it is likely that any benefit of *H. pylori* eradication therapy will outweigh the potential harms, especially in countries with a high risk of gastric cancer. Other RCTs are ongoing, and we will continue to update this work as more evidence becomes available in the future.

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CONTRIBUTOR AND GUARANTOR INFORMATION

Guarantor: ACF is guarantor. He accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Specific author contributions: ACF, YY, and PM conceived and drafted the study. ACF, YY, and PM collected all data. ACF, YY, and PM analysed and interpreted the data. ACF, YY, and PM drafted the manuscript. All authors commented on drafts of the paper. All authors have approved the final draft of the manuscript.

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COMPETING INTERESTS DECLARATION

Potential competing interests: Alexander C. Ford: none. Yuhong Yuan: none. Paul Moayyedi: has received honoraria from Allergan and Salix, and research funding from Allergan.

ROLE OF THE FUNDING SOURCE

None.

PATIENT AND PUBLIC INVOLVEMENT STATEMENT

We did not involve patients or the public in this work. We will disseminate our findings in lay terms via the national charity for people living with digestive diseases, “Guts UK”, and the national charity for people living with IBS, the IBS Network.

DATA SHARING

No additional data available.

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FIGURE LEGENDS

Figure 1. Forest Plot of Randomised Controlled Trials of *H. pylori* Eradication Therapy: Effect on Subsequent Occurrence of Gastric Cancer (Modified Intention-to-treat Analysis).

Figure 2. Forest Plot of Randomised Controlled Trials of *H. pylori* Eradication Therapy: Effect on Subsequent Mortality from Gastric Cancer.

Figure 3. Forest Plot of Randomised Controlled Trials of *H. pylori* eradication therapy: Effect on Subsequent All-cause Mortality.