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Helicobacter pylori Eradication Has the Potential to Prevent Gastric Cancer: A State-of-the-Art Critique

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Helicobacter pylori **infection continues to play a key role in gastric diseases. Colonization of the gastric mucosa with the bacterium invariably results in the development of chronic gastritis and subsets of patients have a progression of the chronic gastritis to either ulcer or cancer. Epidemiological evidence indicates that the proportion of all gastric cancers attributable to *H. pylori* infection, and hence potentially preventable upon elimination of this risk factor, is somewhere in the range of 60% to 90%. This portends significant benefit in terms of morbidity and mortality, not least in populations with high prevalence of *H. pylori* infection coupled with high incidence of gastric cancer. The effect of prophylactic *H. pylori* eradication on gastric cancer incidence in humans remains unknown, however. Results from randomized trials are eagerly awaited, but availability of strong conclusive results may take many years. A growing number of studies show considerable variation in risk for gastric cancer development, depending on *H. pylori* strain type and the genetic predisposition of the host. There is also a remote possibility that elimination of the infection may have adverse health implications (*e.g.*, antibiotic resistance), and therefore "simple" risk stratification and targeted chemoprevention is required. Based on "in depth" evidence presented at this workshop, the majority of the scientific task force favored a search-and-treat strategy in first-degree relatives of gastric cancer patients and an overwhelming majority felt that a more general screen-and-treat strategy should be focused in the first instance on a population with a high incidence of *H. pylori*-associated diseases.**

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INTRODUCTION

It is now more than 10 yr since *Helicobacter pylori* was cited as a gastric carcinogen (1). In the latest available epidemiological studies, based on the most accurate methodology, the presence of *H. pylori* infection combined with CagA antibody status increases the risk of gastric cancer 20-fold, compared with controls. One estimate attributed 70% of distal gastric cancers to *H. pylori* (2), while the highest estimate claimed that *H. pylori* is a condition *sine qua non* for gastric cancer development (3).

There is, however, no conclusive evidence that *H. pylori* eradication prevents gastric cancer. Supportive data could, theoretically, be obtained from prospective trials of eradication, but, in practice, such trials do not exist and may be impossible to conduct for reasons of duration, ethics, etc. Consequently, decisions may be based on the biological plausibility, and on indirect evidence which shows a beneficial effect of eradication on conditions and lesions of the stomach mucosa that precede overt gastric cancer. There is no doubt that the pathogenesis of gastric cancer is associated with a variety of environmental factors, of which *H. pylori* infection appears to be the most prominent and with genetic predisposition, a variety of gene errors and abnormal gene expression. Changes in biology, growth, and death of the cancer cells have been observed in conjunction with *H. pylori* infection. It is also a known fact that these same genomic and cellular lesions also occur in the benign gastric epithelium long before the appearance of an overt cancer, and that these lesions predispose to the development of cancer. It is conceivable, therefore, and highly probable, that any beneficial effects of eradication

For a list of the Contributors to the Lejondal *H. pylori*–Gastric Cancer Tast Force, see Appendix.

therapy on these precancerous conditions, lesions, or cellular and genomic changes (*i.e.*, reversal) should also prevent gastric cancer.

This review represents a state-of-the-art critique of evidence obtained from many experimental investigations conducted in animal models as well as in human tissues and cells. In order to assess what preclinical and clinical evidence is currently available, a number of statements were formulated and discussed at a workshop with experts in the field of *H. pylori* research, held in Lejondal, near Stockholm. The evidence for each suggested statement was presented by one of the experts in that particular field and a vote was taken concerning the validity of the statement and the level of supportive documentary evidence. In view of the depth of information required for each statement, two parallel workshops took place, one dealing with experimental and microbiological evidence and the other with clinical evidence. These were followed by a joint plenary session with all experts present, at which they were invited to vote on all statements under discussion and to agree/disagree with the suggested level of the evidence. The methods used for voting and for assessing documentary evidence are summarized in Table 1.

The document is based largely on information available at the time of the workshop, but has also been updated with more recent relevant literature. In view of the magnitude of the gastric cancer problem in China and Japan, provision was also made for additional comments from the perspective of specialists practicing in these geographical areas (Professors Xiao and Sugano).

GASTRIC CANCER PREVENTION: THE EVIDENCE

Experimental and Microbiological Evidence

The statements voted upon for this section are presented in Table 2.

EVIDENCE FOR THE ROLE OF BACTERIAL VIRULENCE. There is some evidence that bacterial strain variation may affect disease outcome in *H. pylori*-infected individuals, as only a subset of colonized individuals develops serious *H. pylori*-related disease (4). Microbial and host factors that are thought to contribute to pathogenesis have been described and these factors, together with the environment, seem to determine which groups of individuals are predisposed to develop disease (5). The microbial virulence factors such as the pathogenicity island (PAI) are found in bacteria infecting all types of patients, and thus cannot be used to explain these differences. *H. pylori* strains are highly diverse and over a period of years, the populations colonizing an individual host are changing (6). This variation has not yet been well defined. However, *H. pylori* have a plastic genome that presumably allows the organism to adapt and persist in the human stomach throughout the life of the colonized individual (7). Unrelated individuals are rarely, if ever, colonized by strains with the same genetic fingerprint. Individuals are normally colonized with one single strain of *H. pylori*, but multiple strain infections occur (8, 9). Genetic variation is accomplished by recombination, point mutations, and horizontal transfer of genetic elements as mentioned above (10). *H. pylori* have been shown to exhibit free recombination, *i.e.*, recombination is so frequent that alleles at independent loci are rarely co-inherited for long time periods (linkage equilibrium) (11). In addition, the median mutation frequency in *H. pylori* is very high (12, 13). This feature might influence diversity and adaptation, with a correlation to biological fitness, compared with other competing strains. It may replace regulatory elements for regulation of gene expression of nonessential genes through, *e.g.*, phase variation (14). The focal distribution of this infection can allow genetic variation to create subpopulations of clones or subspecies with differing genotypic and phenotypic features. In these microniches, the different clones can evolve in different directions, but still affect the macroniche of the entire stomach. The subclones can vary their virulence potential, for example, by excising the PAI or switching the Lewis epitopes expressed on the LPS.

At any given time, there may be a varying ratio of PAI-positive (virulent) to PAI-negative (less virulent) subclones. The net virulence of the total population as well as the virulence of a single clone might affect the outcome of infection. The evolution and divergence of these subclones can affect the outcome of infection for both host and microbe by skewing the balance of minimal inflammation (that provides nutrients for the micro-organism) toward pathology that is unfavorable for *H. pylori* (such as atrophy and intestinal metaplasia). In addition, these divergent subclones can increase diversity, and potentially virulence, by recombination. Challenges in *H. pylori* gastric cancer research will be to identify genetic or functional markers in the micro-organism that predict the development of gastric cancer, as well as constitutional factors in the host or environmental factors that affect/modify the *H. pylori*-gastric cancer relationship.

In Western populations, the carriage of cagA+ strains is associated with an increased risk of development of peptic ulcer disease and adenocarcinoma of the distal stomach, as well as its precursor lesions. In Asian countries such as China, Japan, and India, most *H. pylori*-positive persons carry cagA+ strains (95%) (15) and the associations with disease are not readily apparent (16, 17). Therefore, is there perhaps a difference of PAI between the *H. pylori* strains isolated from patients with distal gastric cancer, peptic ulcer, and nonulcer dyspepsia in these Asian countries (18)?

Several studies have shown that gastric cancer development is influenced by certain virulence characteristics of the bacterium such as cagA (19–22). In addition to the widely recognized association of gastric cancer with the cagA+ geno- and phenotype of *H. pylori*, vacA s1, and vacA m1 genotypes have also been implicated as markers of a particularly strong association (23, 24). In this context it is also important to quote the new discovery of Lehours *et al*. (25) regarding the role of other virulence patterns (*e.g.*, HopZ) in the development of gastric B-cell lymphoma.

Table 1. Methods Used for Voting and for Assessing Documentary Evidence

Method of Voting

Each proposition considered by the workshop was evaluated for:

- Strength of recommendation
- Level (quality of evidence)

The strength of recommendation was voted on formally in the plenary sessions by all workshop participants, using electronic voting. The level (quality of evidence) was considered in detail within the workshops and graded according to the criteria given below. The consensus of workshops on level of evidence was reported to the plenary sessions, but was not voted on within these sessions.

Strength of recommendation

Participants chose one of the following options:

1 Strongly agree
2 Agree with reservation
3 Disagree with reservation
4 Strongly disagree

Grading level of evidence

The quality of the evidence was categorized into five levels A–E. These levels are summarized below, and involved judgement on study design and execution, consistency of the findings, and the directness of the evidence.

Level of Evidence	Study Design	Study Execution	Consistency	Directness of Evidence
A	Meta-analysis of RCTs (for interventions) RCTs (for interventions) Nonrandomized studies (for diagnosis and prognosis)	No important flaws	Consistent	Direct or strong indirect
B	Meta-analysis of RCTs or RCTs (for interventions)	Important flaw < OR >	Inconsistent < OR >	Weak indirect
	Nonrandomized studies (for diagnosis or prognosis)	Important flaw < OR >	Inconsistent < OR >	Weak indirect
	Nonrandomized controlled studies (for interventions)	No important flaws	Consistent	Direct or strong indirect
C	Nonrandomized controlled studies (for interventions)	Important flaw < OR >	Inconsistent < OR >	Weak indirect
	Meta-analyses or RCTs with a combination of important flaws AND inconsistency AND/OR indirect evidence			
D	Other evidence (not expert opinion)			
E	Expert opinion			

Exceptions that can alter the quality of grading.

Sparse data (few events); use of data not in its initial randomization or apparent publication bias can lower the quality; a very strong association can raise the quality.

Coding notes

Important flaws occur when the highest standards of research that could be achieved by a study are not applied.

Consistency occurs at two levels—design: consistent methods, patients, outcomes; and, statistical: a test of homogeneity of a summary estimate when the level of design consistency is acceptable and meta-analysis appropriate.

Directness. Direct evidence: relevant patient benefits and harms are measured in studies; strong indirect: the surrogate endpoint is strongly related to desirable endpoints, or that direct evidence is available for a sufficiently related patient group; weak indirect: the relationship between the study outcomes and patient benefits or harms is insufficient.

Table 2. Preclinical Evidence, Clinical Evidence, and Risks

Statement	Evidence Level	Plenary Voting 1	2	3	4
Experimental and microbiological evidence					
1. Certain H. pylori characteristics are associated with an increased risk of gastric cancer, but currently genotyping cannot predict individual risk of disease.	*B	17	5	0	0
2. Host genetic factors contribute to an increased risk of gastric cancer	B	20	2	0	0
3. There is strong cell biological evidence to implicate H. pylori in gastric carcinogenesis	*A	17	5	0	0
4. Experimental studies with animal models provide evidence that eradication of H. pylori at an early time point can prevent gastric cancer development	*A	18	4	0	0
5. There is correlation between effects of eradication and expression of molecular markers linked to gastric carcinogenesis	C	9	9	3	1
Clinical evidence					
6a. H. pylori eradication heals chronic activation of atrophic gastritis and halts the progression to preneoplastic conditions (atrophic gastritis and intestinal metaplasia)	A	14	5	2	1
6b. In a subset of patients, regression of preneoplastic conditions (atrophic gastritis & intestinal metaplasia) may occur.	B	15	3	4	0
7. H. pylori eradication can reduce the risk of developing gastric cancer	C	16	5	1	0
Risks					
8. The use of antimicrobials for H. pylori is a moderate risk for antimicrobial resistance in H. pylori and other bacteria	C	15	4	1	0
9. There is an inverse association between H. pylori infection and GERD	nr	10	2	5	2
10. H. pylori eradication in the short term does not lead to GERD symptoms and/or erosive esophagitis	nr	8	11	0	0
11. There is an inverse association between H. pylori infection and esophageal adenocarcinoma.	nr	8	3	6	2

*These studies are not related to clinical trials.

nr = not recorded.

Limitations of evidence: At present, no definite predictive diagnosis can be made as to who will suffer from the infection and who will live unaffected by it. Genetic or functional markers in the micro-organism and constitutional factors in the host that predict or lead to development of gastric cancer remain yet to be identified.

EVIDENCE FOR THE ROLE OF HOST GENETIC FACTORS. Host genetic factors contribute significantly to the clinical outcome of *H. pylori* infection. There is emerging evidence of important host genetic factors that control both the host's innate immune response and its inflammatory response against *H. pylori* infection. There is an important interaction between these host genetic factors and *H. pylori* virulence factors which contribute to the mucosal damage and physiological abnormalities that increase the risk of cancer and its precursors. In the host, there are functional polymorphisms in the *interleukin-1* (*IL-1*) gene cluster (26, 27) and tumor necrosis factor alpha genes (*TNF-A-308*) (28) that increase the risk of noncardia gastric cancer (but not other upper GI malignancies) (29), and the risk seems to be significantly increased in the presence of pro-inflammatory genotypes of *IL-1* and of *H. pylori* virulent strains (23) in some geographical areas. The risk applies to both intestinal and diffuse types of gastric adenocarcinoma (30).

Limitations of evidence: Most of the evidence relating to host genetic factors and their influence on disease outcome has been obtained from studies in Caucasian populations. A study of *Interleukin 1B* polymorphism and *H. pylori* infection in regions with a high incidence (Shanxi) and low incidence (Guangdong) of gastric cancer in China showed that *IL-1B-511T/T* genotypes are also associated with gastric cancer. (31). There is now some evidence emerging that there are similar associations in Asians, but the studies so far have been underpowered and have given mixed conclusions (32). Consequently, more work is required in other ethnic groups in order to consolidate the data obtained thus far and to confirm that they are universal in application. There is currently no convincing evidence of a role for specific host genetic factors in peptic ulcer disease, but this may be because most of the studies have been underpowered and patient phenotypes have not been adequately characterized.

EVIDENCE FROM EXPERIMENTAL CELL BIOLOGY. There is considerable evidence that *H. pylori* takes direct command of gastric epithelial cell signaling and triggers hyperproliferative processes. *H. pylori* regulates the activity of growth factor receptors, *i.e.*, the EGF receptor (33), the EGFR-related receptor (Her2/Neu), and the c-Met receptor (34), thus promoting epithelial cell growth and cell survival, as well as cell dissociation and cell motility. The translocated *H. pylori* effector protein, CagA, targets the c-Met receptor (intracellularly) and enhances the cell motility (34). Promotion of cell motility through direct physical interaction between CagA and the adaptor protein Grb2 (35), the tyrosine phosphatase SHP-2 (36), or phospholipase C gamma (34) has also been described. Thus, CagA directly interacts with signal transducing proteins and may play a role as an adaptor protein in *H. pylori*-induced growth factor receptor signaling. For the evasion of apoptosis *H. pylori* activates nuclear hormone receptor peroxisome proliferator activated receptor δ (PPARδ) (37), which involves *H. pylori*-induced cyclo-oxygenase-2 (COX-2) activity (38). Moreover, *H. pylori* induce VegfA (39) and drive putatively the angiogenesis process. Decreased cell-cell contacts are common in gastric cancers and may be related to the tendency to develop metastasis. In polarized epithelial cells, *H. pylori* affects the scaffolding protein ZO-1 and the tight junctional adhesion protein (JAM), and disrupt the junction-mediated epithelial barrier functions in a CagA-dependent manner (40). Furthermore, the *H. pylori* effector protein VacA binds to the tyrosine phosphatase receptor PTP-ζ and the induced signaling leads to the phosphorylation of the G protein-coupled receptor kinase-interactor 1 (Git1) and induces ulcerogenesis in mice (41). In summary, *H. pylori* interfere with cell biological phenomena that are linked with gastric carcinogenesis. Consequently, *H. pylori* infection induces alterations in cell physiology which could collectively contribute to malignant growth, namely: (i) activation of growth factor receptors; (ii) evasion of apoptosis; (iii) unlimited replicative potential; (iv) sustained angiogenesis; and (v) cell dissociation and tissue invasion.

Limitations of evidence: Although the data are very strong, most have been generated under *in vitro* conditions. However, an understanding of which pathways are involved, in regulation or dysregulation of these cellular processes, should enable us to examine whether *H. pylori* eradication reverses them.

EVIDENCE FROM EXPERIMENTAL ANIMAL MODELS. In early studies it was noticed that aged ferrets who were infected with *Helicobacter mustelae* developed spontaneous gastric adenocarcinomas (42). A number of animal models have now been developed to examine gastric carcinogenesis in animals, the most widely used being ferrets, mice, and Mongolian gerbils. A few studies in the Mongolian gerbil have provided, for the first time, evidence that *H. pylori* is indeed a complete carcinogen and can, by itself, induce well-differentiated adenocarcinomas (43–45). More consistently it has been shown that *H. pylori* is a weak carcinogen on its own, but in the presence of nitrosamine it leads to a high rate of cancer 1-yr postinfection (46–49). The standard model to study *Helicobacter* infection is the mouse model and some mouse strains develop a vigorous TH_1 response to *H. pylori or Helicobacter felis*, while others have a predominant TH_2 immune response and are relatively resistant to mucosal changes (50). Those with the vigorous TH_1 response (the C57BL/6 strain) go on to develop atrophy, metaplasia, and invasive gastric cancer in *H. felis* infection. The majority of male mice infected with *H. felis* for more than 14 months show the development of gastric cancer (51). These studies

have suggested that progression to gastric cancer is determined by the host immune response, being influenced to a lesser extent by dietary factors (*e.g.*, high-salt diet), or bacterial virulence factors. Studies in gerbils (52–54), and more recently in mice (55) have provided important evidence of beneficial effects from *H. pylori* eradication, where atrophy and metaplasia have been reversed, in some cases completely.

Overall, within a few months of inoculation, *H. pylori* infection in animal models can lead to the disintegration of the gastric mucus by the release of endotoxins and *H. pylori*-produced enzymes (56). The host inflammatory response is associated with the production of free radicals, including reactive oxygen species, and inducible nitric oxide synthase (iNOS) (57, 58). Interestingly, transgenic mice with moderate hypergastrinemia, who have increased parietal cell numbers and acid secretion, show an increased expression of TGF-family growth factors and a progression toward gastric cancer (59). Within the cascade to the initiation of precancerous lesions, the attracted neutrophils enhance the generation of oxygen-reactive species in the tissue. The consequence is oxidative DNA damage that leads to genotoxic effects on the gastric mucosa (60).

Limitations of evidence: Whether we can use data from animal models in humans is still questionable.

EVIDENCE FOR THE REVERSIBILITY OF MOLECULAR CHANGES. Various molecular and genetic changes have been identified in gastric cancer cells obtained from established tumors (61). A reduction of cellular adhesion due to mutations in E-cadherin (50% of diffuse cancers), α-catenin (60%), and β-catenin (25%), the presence of microsatellite instability (25–40%) and increased telomerase activity has been described in nearly all gastric cancers (61). The most common abnormalities are inactivation of tumor suppressor genes such as p53 (occurs in 60–70%), which occur in *H. pylori*-associated gastritis even before metaplasia (62, 63), but the effect of eradication on p53 expression/mutation has not been well studied. In an early study, eradication of *H. pylori* infection resulted in a significant reduction in iNOS and nitrotyrosine, and a marginally significant reduction in apoptosis. Studies about inflammatory mediators have shown that *H. pylori* eradication was associated with a reduction in cyclooxygenase-2 and ornithine decarboxylase expression in atrophic in premalignant and malignant lesions (64, 65). *H. pylori* infection induces upregulation of growth factors (EGF, HB-EGF, amphiregulin, TGFα) along with their receptors (EGFR, Her2/Neu) (61). *H. pylori* eradication led to a reduction in the levels of EGF and EGFR from gastric antral biopsies (66). Furthermore, eradication of *H. pylori* from patients was associated with an improvement in metaplasia and a disappearance of markers of genomic instability. Increased expression of the oncogene c-Myc correlated with abnormal DNA content and the presence of atrophy (67). Alterations in cell cycle control, *e.g.*, overexpression of cyclins D1/D2 and E were detected in *H. pylori*-associated chronic gastritis and intestinal metaplasia. Cyclin D2 was reduced after eradication of the organism (68). In addition, decreased p27 expression was seen in gastric cancer and intestinal metaplasia; in the latter, p27 expression was restored 1 yr after eradication (68). Activation of oncogenes such as c-Met and Her2/Neu is relatively frequent, while K-ras mutations appear to be less common ($<$10%) (69). It must be stressed that none of these changes is specific for gastric cancer. The most frequently reported changes in the gastric mucosa are changes in proliferation and apoptosis.

Limitations of evidence: As yet, the precise sequence of molecular events leading to gastric cancer has not been elucidated. None of the indicated changes is specific for gastric cancer.

Clinical Evidence

EVIDENCE FOR REGRESSION OF ATROPHIC GASTRITIS/INTESTINAL METAPLASIA AFTER *H. PYLORI* ERADICATION. The overwhelming majority of subjects with atrophic gastritis (defined as the presence of significant areas of atrophy in the gastric mucosa) have metaplastic atrophy, *i.e.*, intestinal metaplasia is seen in the biopsy in association with classic atrophy, where there is loss of normal cells. Pure "nonmetaplastic" atrophy may exist focally, but it is quite rare, thus these two inextricably related conditions should not be calculated separately (70, 71). There is consistent evidence that eradication of *H. pylori* cures gastritis, but the question remains as to whether this intervention can not only halt the progression to atrophic gastritis and metaplasia, but also reverse these lesions. Review of the literature indicates that, in studies with a control group who remain *H. pylori* positive, there is either no change or else progression of atrophy and metaplasia in those patients. In contrast, atrophy and metaplasia do not progress in patients who have had *H. pylori* eradicated (72–90). *H. pylori* eradication is associated with reduced cell turnover, elimination of DNA damage by reactive oxygen species, increased gastric acid secretory capacity, and an increase in ascorbic acid secretion into the gastric juice (91–96). These data are most important with respect to the issue of gastric cancer prevention. The majority of data support the proposition that a regression of atrophic gastritis can occur in a subset of patients, although many of the available studies have significant limitations in their design, including inability to blind pathologists to the presence of *H. pylori*. The recent randomized prospective study by Wong *et al.* (97) does, however, suggest that *H. pylori* eradication reduces the incidence of gastric cancer only in patients without preexistent atrophy or intestinal metaplasia. However, the majority of data, with all its limitations, support the proposition that regression of atrophic gastritis and, to a lesser extent, intestinal metaplasia, can occur in a subset of patients with long-term follow-up (98, 99). Even though regression of lesions may occur in some patients at the present stage we have no markers to tell us whether this may happen or not in the individual patient. Therefore eradication at the earliest stage in the disease seems reasonable, when the

probability of progression to neoplasia is likely to be at its lowest (100).

Limitations of evidence: Baseline scores for atrophy and metaplasia are very low and most studies had significant limitations in their design (nonrandomized, not controlled, small numbers of patients, short follow up periods).

EVIDENCE THAT ERADICATION OF *H. PYLORI* CAN REDUCE THE RISK OF DEVELOPING GASTRIC CANCER. The progression from normal gastric mucosa to gastric cancer is associated with *H. pylori* infection. Attempts to evaluate the magnitude of risk associated with the infection have been made in many studies and in several meta-analyses and an important analysis is provided by the *Helicobacter* and Cancer Collaborative Group (101) as this analysis combined data from all (and only) case-control studies nested within prospective cohorts, to assess more reliably the relative risk of gastric cancer. *H. pylori* infection was associated with noncardia gastric cancer (OR 3.0; 95% CI 2.3–3.8) and the association was stronger when blood samples for *H. pylori* serology were obtained 10 yr or more before cancer diagnosis (5.9; 3.4–10.3). Thus, although *H. pylori* infection has been demonstrated to be a significant risk factor for the development of gastric cancer in case–control epidemiological studies, data to suggest that eradication of the infection can prevent the progression from normal gastric mucosa to gastric cancer are still few.

The only way to determine the effect of *H pylori* eradication is to perform a prospective randomized clinical trial. Unfortunately, attempts to do this have met with problems. The reason for this is that once a patient has been tested for *H. pylori* and the nature of the trial has been explained, few are prepared to enter the placebo arm. Recruitment, therefore, has been a major drawback for some studies (102, 103) and some have been abandoned or are progressing only slowly. If cancer is taken as the endpoint, large numbers have to be recruited—at least 100,000—and follow-up should be over one to two decades (104). Alternatively, smaller studies are ongoing where patients are randomized to treatment or nontreatment and are then followed up endoscopically. In these, a primary endpoint such as atrophy or intestinal metaplasia may be a surrogate marker for cancer.

Since the efficacy of eradication in cancer prevention is unknown, Parsonnet *et al.* (105) assumed estimates of prevention varying from 30% to 5%. Results of this decision analytical model suggested that screening and treatment for *H. pylori* is potentially cost-effective in the prevention of gastric cancer, particularly in high-risk populations. The possibility to look at atrophy and intestinal metaplasia as intermediate markers of gastric cancer risk and to evaluate their reversibility after eradication has been considered in many studies. Existing data (*e.g.*, Ito *et al.* 2002) (76) suggest that precancerous gastric lesions (atrophy and intestinal metaplasia) do not progress as much, and may even regress, after successful eradication of *H. pylori*. On the other hand, the definition of a point (lesion) of "no return" remains difficult to determine and other changes in the gastric mucosa that follow eradication may be more important to arrest the progression to cancer than the regression of atrophy and intestinal metaplasia (106). From this viewpoint, there are few interventional studies that have examined the effect of *H. pylori* eradication on cancer incidence. Uemura *et al*. (107) conducted a nonrandomized *H. pylori* eradication trial in patients whose gastric cancer was removed by endoscopic resection; after 3-yr follow-up, 6 of 67 metachronous cancers developed in those not treated, compared with 0 of 65 in those who received anti-*H. pylori* therapy. Furthermore, in a prospective observational study, the same group were able to show that gastric cancer develops in persons infected with *H. pylori*, but not in uninfected persons (108). Although this was not planned as an interventional study, no gastric cancer developed after eradication of *H. pylori* in 253 infected patients. A 7-yr prospective-randomized, placebo-controlled study to assess the long-term effect of *H. pylori* eradication on the incidence of gastric cancer has recently been published (97). Although no difference in gastric cancer incidence was observed between treated and placebo groups, *H. pylori* eradication was shown to reduce the incidence of gastric cancer significantly in the subgroup of those without atrophy/intestinal metaplasia at baseline, suggesting that eradication may be beneficial in arresting the progression to gastric cancer only if applied before the appearance of preneoplastic lesions.

Limitations of evidence: Data from randomized control studies are few and long-term follow-up would be required to confirm the benefit of treatment. Further, data on prevention of gastric cancer recurrence are even more scant and it is difficult to draw any conclusion at this moment. There are still few data to confirm that eradication of the infection can prevent the progression from normal gastric mucosa to gastric cancer. Only a few interventional studies have examined the effect of *H. pylori* eradication on cancer incidence. The role of eradication in preventing cancer, though suggestive, remains to be confirmed.

Risks

The statements voted upon for this section are presented in Table 2.

THE POSSIBLE RISKS OF POPULATION *H. PYLORI* TESTING AND TREATMENT. (a) *The induction of antimicrobial resistance*. An association has been found between the consumption level of antibiotics and the rate of bacterial resistance to antimicrobials. The association between level of antibiotic consumption and resistance development is strong only in closed environments such as special departments in hospitals (109–111)—it is weaker in the community (112–115). In Europe, a trend toward a higher resistance of *H. pylori* to macrolides can be noted in countries with the highest consumption of these drugs (116–124). An association is more likely to be causal if there is a temporal relationship, there is a dose–response effect, the association is

biologically plausible, and intervention has an impact on the disorder.

A temporal relationship indeed exists, since resistance is usually nonexistent when antibiotics are first employed. A dose–response effect has also been observed with most antibacterial-antibiotic combinations, but only in some hospitals (125–127). There is a biological plausibility based on the selective pressure of antibiotics, but it is important to differentiate between the cases where resistance is due to mutations leading to vertical transmission (the case of *H. pylori*) and those where it is done by gene acquisition, *i.e.*, plasmids, leading to horizontal transmission which may evolve as outbreaks. The effect of an intervention is the strongest argument for causality (128, 129). However, few data exist in the community (130–135). The best example may be the limitation of macrolide use in Finland, which was followed by a decreased resistance of *Streptococcus pyogenes* to this drug, but only after a lag time of 5 yr (131). No similar data are available for *H. pylori*.

The risk of antimicrobial resistance for bacteria other than *H. pylori* is also interesting to consider, but the data are scarce. The influence of triple therapy was studied on the quantitative modification of the normal flora from saliva, stomach, and intestine, as well as on the qualitative changes concerning resistance to antibiotics after administration of PPI-amoxycillin-metronidazole or PPI-clarithromycin-metronidazole (136). Amoxycillin MICs against *Streptococcus* species and *Enterococcus* species increased when this drug was administered, as did the ratio of resistance to susceptible strains. The same occurred for clarithromycin in those receiving this drug for *Streptococcus* species, *Enterococcus* species, *Enterobacteriaceae*, and *Bacteroides* species. The total anaerobic microflora was suppressed in both treatment groups, but the effect was more pronounced with PPI-clarithromycin-metronidazole. However, these changes were not observed for more than 35 days after the end of the treatment.

In another study focused on intestinal *Enterococcus* species, specimens were obtained 1 and 3 yr after treatment. High-level clarithromycin resistant *Enterococci* were selected in stools of five patients receiving clarithromycin-based eradication treatment, and these persisted for 1–3 yr in three cases (137). It can also be inferred from the study in Finland by Seppala (131) that macrolide resistance would increase in *Streptococcus pyogenes*, *Streptococcus preumoniae*, and other gram-positive bacteria if clarithromycin was widely used, as would be the case for systematic *H. pylori* treatment.

In conclusion, the use of antimicrobials constitutes a risk for antimicrobial resistance. However, for *H. pylori*: (1) the resistance mechanism is mutation, (2) the spread of the bacteria is limited in our Western societies, and (3) the type of prescription is essentially with more than one antibiotic, theoretically avoiding the possibility of resistance development. Consequently, this risk is likely to be moderate. We can also foresee that resistance will increase for other bacteria but the magnitude of resistance is difficult to estimate because of a lack of data.

(b) *The development of gastroesophageal disease*. A systematic review of case–control studies suggested that *H. pylori* infection was less common in patients with GERD compared to controls (138), particularly in studies conducted in Eastern countries. Evidence supporting the proposition that *H. pylori* eradication leads to GERD symptoms and/or erosive esophagitis is conflicting, however. While one study (139) showed an increase in the prevalence of GERD after *H. pylori* eradication, during the first year following eradication another study (140) showed an increase in new reflux esophagitis only in patients who carried the predisposition of hiatus hernia and in whom atrophic gastritis was reversed following *H. pylori* eradication. A *post hoc* meta analysis of eight double blind studies of *H. pylori* eradication (141) and a large *post hoc* analysis of the peptic ulcer trials, GU MACH, and DU MACH (142, 143) revealed no indication that *H. pylori* eradication for ulcer disease led to development of erosive esophagitis or new symptomatic GERD or that there was worsening of symptoms in patients with preexisting GERD. The results were similar for studies conducted in patients with preexisting GERD (144–146), or in the general population (147, 148). Overall, therefore, there is little randomized controlled trial evidence to suggest that *H. pylori* eradication leads to *de novo* GERD development (149).

(c) *Risk of Barrett's esophagus and esophageal adenocarcinoma*. There appears to be an inverse association between *H. pylori* infection (CagA type) and GERD or Barrett's esophagus (150–152). Epidemiological studies have also demonstrated that *H. pylori* CagA seropositivity is inversely and strongly associated with risk of esophageal adenocarcinoma (153, 154), although this has not been a universal observation (155). The uncertainty in the data is reflected in the voting of the panel, but overall it was felt that there was moderate evidence of an inverse association between *H. pylori* and esophageal adenocarcinoma. Whether this association is causal is not clear and as long as the incidence of gastric cancer is much higher than that of esophageal adenocarcinoma (which seems to be the case in all populations, although the latter cancer is coming close to the former in some parts of Western Europe), a 6- to 20-fold increased risk of gastric adenocarcinoma associated with *H. pylori* infection outweighs any theoretical benefit in terms of protection from esophageal adenocarcinoma (70–80% reduction according to available epidemiological data).

TREATMENT RECOMMENDATIONS AND PREVENTION STRATEGIES

The statements voted upon for this section are presented in Table 3.

Treatment Strategies

(a) *Test and Treat (i.e., patients with dyspeptic symptoms tested for H. pylori and treated accordingly)*. A number of studies have indicated that the test and treat approach for *H. pylori* is as effective and safe as endoscopy in uncomplicated

Table 3. Treatment Recommendations and Prevention Strategies

Statement	Plenary Voting 1	2	3	4
1a. *H. pylori* eradication resolves symptoms in a small proportion of NUD patients, but the efficacy is similar to the alternative treatments.	13	5	3	0
1b. *H. pylori* eradication is the treatment of choice in uninvestigated dyspepsia.	14	6	1	0
1c. *H. pylori* test and treat is more appropriate than endoscopy in uncomplicated dyspepsia.	12	5	4	0
2. Search for *H. pylori* and a treatment strategy should be offered to first-degree relatives of gastric cancer patients.	10	8	1	2
3a. Screen and treat will reduce *H. pylori*-associated death by about 15%.	12	6	1	1
3b. A screen and treat strategy should be evaluated in a population with a high incidence of *H. pylori*-associated diseases.	19	1	0	1

dyspepsia (156–160), the main benefit being due to treatment of undiagnosed peptic ulcer disease (161), although there may also be some benefit in non ulcer dyspepsia (162).

Although patients who seek health care for dyspeptic symptoms do not constitute a high-risk group that should be targeted specifically in an attempt to reduce the incidence of gastric cancer, this opens a window of opportunity not only for curing *H. pylori* infection with the aim of resolving dyspeptic symptoms (*i.e.*, patients with peptic ulcer disease and subsets of patients with functional dyspepsia) but also for minimizing the risk of gastric cancer development.

(b) *Search and Treat (i.e., screening of asymptomatic individuals who carry a risk for gastric cancer and treatment of H. pylori-infected individuals).* It is important to identify groups that may benefit from prophylactic *H. pylori* eradication, for example, those with a family history of gastric cancer and those who live in high-risk geographical areas, if they have gastritis. First-degree relatives of patients with gastric cancer are at greater risk, although there are few true "gastric families" with defined genetic mutations (163, 164). It appears that the risk among offspring is only moderate (about 50% excess), but higher among siblings (about threefold), most of the concordance being attributed to shared environment, where *H. pylori* no doubt plays a most important role (165). The risk is enhanced by the presence of *H. pylori* infection, particularly virulent strains. The Maastricht II guidelines strongly recommend screening of first-degree relatives of gastric cancer patients. The increased risk of gastric cancer in this group, combined with their heightened concern that they will develop the disease, makes the risk benefit more in favor of search and treat.

(c) *Screen and treat strategy for the global population*. Evidence suggests that *H. pylori* infection is the single most important etiological cause of gastric cancer, but the real question is whether infection with the organism is a necessary prerequisite for the disease or whether other risk factors such as diet and bile reflux could cause the disease in the absence of *H. pylori*. In certain cases *H. pylori* infection is not a necessary prerequisite. Cardia gastric cancer, for example, is not associated with the infection. The etiology of this particular cancer, which affects a small vulnerable area of the gastric mucosa and accounts for up to 20% of gastric cancer in some countries (166), is probably different from other gastric cancers. Similarly, certain hereditary gastric cancers appear to arise irrespective of *H. pylori* infection. In others, the disease results from autoimmune gastritis where infection with *H. pylori* is uncommon. Nevertheless, the major burden of gastric cancer is that associated with *H. pylori* infection together with other risk factors, which on their own would probably not lead to the development of this disease.

There is uncertainty as to how long *H. pylori* has to be present before eradication will no longer prevent the development of gastric cancer.

H. pylori infection occurs in early childhood (167, 168). However, there is little benefit in treating individuals who are at high risk of re-infection. It seems reasonable to assume, however, that if the progression to a corpus predominant gastritis with atrophy and intestinal metaplasia could be prevented, this would provide the greatest opportunity of preventing cancer.

Histological "diffuse" type cancer may respond differently to "intestinal" type. Diffuse cancer may be the product of direct inflammation, while intestinal type cancer probably follows mutation in intestinal metaplasia (169). If that were the case, *H. pylori* eradication would have a greater, immediate effect upon diffuse cancer because of the rapid elimination of the inflammatory reaction, while cancers arising from intestinal metaplasia would be less amenable to *H. pylori* eradication, because intestinal metaplasia reverses slowly, if at all (170).

In spite of these limitations, one would expect *H. pylori* treatment to have some benefit, even if given at a late stage. The reason for this is that once the infection is eradicated, the acute inflammatory response disappears almost immediately. In a proportion of individuals, gastric acid secretion recovers to some extent and may reduce colonization by other microorganisms. This, in turn, may reduce the amount of damage to the mucosa. Intestinal metaplasia does not seem to progress once treatment has been given compared with placebo. In those stomachs that are less severely damaged, not only will acid secretion improve, but the level of ascorbic acid in the gastric lumen will increase, cell turnover will decline and the production of reactive oxygen metabolites by inflammatory cells will fall.

(d) *Health economics of a screening program*. One of the Wilson and Jungner criteria (171) for an acceptable screening program is that it should be an efficient use of Health Services resources. *H. pylori* screening and treatment is likely to be cost-effective if it does have an effect in reducing gastric cancer mortality, as it involves a "once in a life time" inexpensive noninvasive test and a course of effective eradication therapy, although it must be borne in mind that cost-effectiveness diminishes as the age of treatment gets younger. This compares favorably with other screening programs, where the expensive tests need to be repeated at regular intervals. There is, however, no direct evidence that population *H. pylori* screening and treatment is cost-effective, as there are currently no trial data showing that it reduces mortality. Thus, data have to be extrapolated using health economic models in order to infer whether the strategy is cost-effective. A MEDLINE search revealed six papers modeling *H. pylori* screening and treatment to prevent gastric cancer and all concluded that the strategy is cost-effective (172–177). Four U.S. models (173, 174, 176, 177) suggested that *H. pylori* screening and treatment would cost between €6,300 to €25,000 per life year saved, whereas two U.K. models suggested that the strategy would at the most cost €8,500 per life year saved and under some assumptions the program could even save the health service money (172, 175). The model suggesting that *H. pylori* test and treat was cost saving also assessed the possibility that the strategy would reduce the dyspepsia burden in the community (175).

A Global Policy for Prevention of Gastric Cancer

Deaths from gastric cancer still occur at the rate of about three quarters of a million per year. As the disease is not often curable at discovery, the eradication of *H. pylori* should lead to considerable health benefit, without significant danger to the population. The benefit is likely to be greater in those countries with a high incidence of gastric cancer, but often these are the ones where, at present, economic conditions are not conducive to large-scale investment in preventative measures. Nevertheless, the economy in Asia generally and Southeast Asia in particular is likely to grow within the foreseeable future. Furthermore, the political system in China is such that it would lend itself more readily to state sponsored preventative measures. In China, the government is now paying more attention to health care as a consequence of its rapid economic growth. Gastric cancer is one of the most common malignant diseases in the northern part of China, as well as in the provinces and cities along the seacoast. Ideally, the incidence of gastric cancer should decrease if the prevalence of *H. pylori* infection becomes lower. Other areas of high incidence such as Central and Southern America will represent more of a problem in the near future, while the incidence of gastric cancer in Africa and India are relatively low compared with other developing countries, despite the high prevalence of *H. pylori* infection—the "African Enigma" (178). It has been suggested that this is because the populations do not have the same life expectancy as western populations and therefore are less likely to reach their sixth or seventh decade, when gastric cancer more commonly develops. Additionally, it has been shown that co-infection with parasites changes the immune response of the gastric mucosa from TH1 to TH2 (179), which would be more protective against gastric cancer. Furthermore, in the countries of Africa, the ravages of the malaria and HIV infection will justifiably consume the major part of any health prevention budget. Within the developed world there is every reason to believe that a screen and treat policy would not only be effective in health terms, but cost effective as well. However, the greatest opportunity lies in the emerging countries of Eastern Europe, where the incidence of gastric cancer is high, and in the strong economies in Southeast Asia. Japan is one such country, where gastric cancer is the leading cause of death. Indeed, for the last 30 yr, the annual death rate from gastric cancer has been almost 50,000 and more than 100,000 cases of gastric cancer are newly diagnosed annually. Up until now, secondary preventative measures such as mass screening programs (including radiographic and endoscopic examination) for those above 40 yr have been extensively implemented and financially supported by local government in Japan to reduce gastric cancer mortality (180). Almost half of the gastric cancer patients in Japan are now diagnosed as early gastric cancer and many of them can be treated with minimally invasive measures such as endoscopic mucosal resection (EMR). Even when they require operation and/or chemotherapy their survival rates are much better than those of Western countries. However, for more effective disease prevention, primary prevention by interfering with the mechanisms of gastric carcinogenesis is necessary. Eradication of *H. pylori* as a primary preventative measure may be feasible in a country like Japan with a high incidence of gastric cancer and a strong economy. Japan would also seem to be a country best suited for demonstrating that medical intervention based on scientific rationale can successfully achieve a reduction in gastric cancer incidence. At present, the Japanese national health insurance system has not yet approved the use of eradication therapy for *H. pylori*-infected chronic gastritis, although it is recognized as a predisposing condition for gastric cancer. Hopefully, an alliance of international scientists such as a gastric cancer prevention task force will serve to implement a primary intervention program to prevent gastric cancer in Japan as well as in the rest of the world.

Whom to Target?

In the short term, the best approach may be to target a specific country or district with a high level of gastric cancer so as to demonstrate potential benefits. This could be done at the same time as increasing pressure on the developed countries themselves to introduce a screen and treat policy. What is needed is the introduction of public health measures aimed toward eradication of *H. pylori* in specific areas in order to demonstrate that a screen and treat policy is possible, that it is reasonably constrained in financial terms, that it does not produce significant disadvantage to the community and,

that after some 5 to 10 yr, there is a fall in the incidence of death from *H. pylori*-related disease compared with contiguous communities. In other words, what is required in the short term is proof of concept. If that can be done, it will stimulate health-care groups and governments to introduce similar measures where it is economically possible, while at the same time enabling the screen and treat protocol to be improved, generate more research in identifying more effective and less expensive measures for identifying infection and curing the disease. The introduction of community "screen and treat" will also stimulate further research aimed toward identifying the best age for intervention and possibly even the discovery of how the organism is transmitted.

In conclusion, for countries with a high risk of cancer, the greatest benefit would be gained by eradicating or preventing *Helicobacter* infection in early adulthood.

SUMMARY

Benefit of Broadening the Indication for Anti-H. Pylori Therapy

H. pylori infection continues to play a key role in acid-related disorders, with a general consensus that colonization with the bacterium invariably results in the outcome of chronic gastritis. Subsets of patients have a progression of the chronic gastritis to either ulcer or cancer. Several indications have proved beneficial over the years but are not as yet implemented on a large scale. Apart from the classical indications such as peptic ulcer (181), there are several other beneficial indications for *H. pylori* eradication and therapy strategies.

In patients with uninvestigated dyspepsia who are less than 45–50 yr of age with no alarm symptoms, the key variable in determining the appropriateness and cost-effectiveness of screening for *H. pylori* infection *versus* initiation of empiric proton pump inhibitor therapy is the prevalence of the infection and peptic ulcer disease in the local population. The test and treat approach is considered cost-effective if the prevalence of *H. pylori* in the population is 20% or greater, while empiric proton pump inhibitor therapy is favored when prevalence is less than 20%.

Epidemiological evidence indicates that the proportion of all gastric cancers attributable to *H. pylori* infection and hence potentially preventable upon elimination of this risk factor is somewhere in the range of 60–90%. This portends significant benefit in terms of morbidity and mortality, not least in populations with high prevalence of *H. pylori* infection coupled with high incidence of gastric cancer. While there is some discordance regarding who should undergo a search and treat strategy with the current available therapy, there is broad agreement that cure of the infection reduces the risk for gastric cancer development.

Whether the association between *H. pylori* infection and gastric cancer is causal or not is no longer an issue. Largely consistent results from epidemiological studies and animal experiments all support a carcinogenic role of the microorganism, and a web of plausible mechanisms is slowly emerging. Although the true strength of the association, and the proportion of all gastric cancers that can be attributed to *H. pylori*, is still under debate, it is becoming increasingly evident that the early studies may have underestimated the importance of the infection. The effect of prophylactic eradication on gastric cancer incidence in humans remains unknown, though. Results from ongoing randomized trials are eagerly awaited, but it will probably take many years before strong conclusive results from such studies will become available, if at all. Given the growing number of studies showing considerable variation in *H. pylori* strain type and genetic predisposition of the host, and the admittedly remote possibility that elimination of the infection might increase the risk for other adverse health outcomes, including an increase in the prevalence of antibiotic-resistant micro-organisms, there is a need for "simple" risk stratification and a targeted approach to chemoprevention. There is little scientific support for the notion that patients who seek health care for dyspeptic symptoms constitute a high-risk group that should be particularly targeted. This population will, in any case, have the opportunity for therapy with the dual aim of relieving their symptoms and preventing *H. pylori*-related complications. Presently, the critical question is whether it is justifiable to wait with chemoprevention for another decade or two, until the desired solid scientific data are at hand, or whether prophylactic eradication should be offered already now to some selected groups.

In conclusion, a majority of this scientific panel favored a test-and-treat strategy in first-degree relatives of gastric cancer patients. The overwhelming majority also felt that a more general screen-and-treat strategy should be focused in the first instance on a population with a high incidence of *H. pylori*-associated diseases.

APPENDIX

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