

Helicobacter pylori: the size of the problem

J Parsonnet

Introduction

My task is to describe the magnitude of the problem *Helicobacter pylori* poses worldwide. This is a daunting assignment for, while it would be relatively simple to summarise the prevalence of *H pylori*, to characterise those at risk for infection, and to delineate incidence trends, it is far more difficult to quantify the actual disease that *H pylori* causes. Certainly, *H pylori* is an extraordinarily common infection. Its mere commonness, however, is not in itself a problem. Rather, it is the propensity *H pylori* has for causing illness that determines its public health significance. Unfortunately, for several reasons, the total extent of disease worldwide is far more difficult to quantify than the amount of infection. Firstly, *H pylori* related diseases (for example, ulcer disease) are often treated empirically without resorting to diagnostic testing. There are, therefore, very incomplete data on the incidence and corresponding morbidity for these processes. Secondly, because some very common diseases or syndromes (for example, atherosclerosis, dyspepsia, and diarrhoea) are as yet only equivocally linked to infection, the true magnitude of *H pylori*'s consequences are not known. Finally, it is possible, although as yet unproved, that *H pylori* has some beneficial effects to counterbalance its detrimental effects.¹

The epidemiology of *H pylori*—how many people are infected?

H pylori infection is extremely common worldwide. By some estimates, over one half of the world is infected with this organism.² Prevalence can vary widely, however, between and within population groups. In some developing countries, most children are infected by 10 years of age and infection is almost universal by mid-life.³ In industrialised countries, however, prevalence of infection is considerably lower. This is not meant to imply that infection is rare in these countries, however, as even in the United States, Europe and Oceania, at least one third of the population is likely to be infected.

Prevalence of infection increases with advancing age. In some populations, a disproportionately high prevalence of *H pylori* infection is observed in those over 40. This seems to reflect a birth cohort effect—that is, transmission of this chronic infection was more common years ago than it is today.⁴⁻⁶ In other populations, however, the elderly (those older than 60 or 70) seem to have a lower rate of infection than would have been anticipated. While this, too, may represent a birth cohort or period effect, a more likely explanation is that infection is lost as *H pylori*'s niche in the normal gastric architecture is destroyed by progressive inflammatory damage

Overall, *H pylori* incidence has been decreasing in industrialised countries over recent generations. According to Banatvala *et al*, the rate of decline may be as high as 26% per decade.⁵ Seroconversion studies from the 1990's indicate that only 0.4% of uninfected adults acquire *H pylori* each year.⁷ In children, however, the incidence may be higher. Thus, many now consider *H pylori* a predominantly childhood infection that persists throughout life. Yet, even in children, the likelihood of infection seems to be diminishing as the century draws to a close.

Other demographic factors have also been linked to infection. Several large epidemiological studies indicate a 5–20% higher prevalence of infection in males than in females.⁸⁻¹⁰ Although this has not been uniformly reported, it could partially explain observed sex differences in propensity to duodenal ulcer and gastric cancer. Virtually all studies to date have shown an inverse relation between *H pylori* infection and socioeconomic status.¹¹⁻¹² Socioeconomic status during childhood serves as a particularly good gauge of *H pylori* risk.¹³ In the United States, African-Americans and Hispanics exhibit higher rates of infection than do non-Hispanic whites.^{8, 12, 14} Racial/ethnic variations in *H pylori* prevalence have also been observed outside the United States.^{15, 16} The reasons for racial/ethnic differences are not understood. Socioeconomic conditions during childhood, as measured by household crowding and parental income, are thought to play an important role. A genetic component to infection is also possible.⁸ A comparison of *H pylori* concordance in monozygotic and dizygotic twins suggested that heritability may explain 57% of infection prevalence.¹⁷

The consequences of *H pylori* infection—how much sickness?

An increasingly large number of diseases have been ascribed to infection with *H pylori*. Some are well documented, others less well so. Prevalently accepted are roles for *H pylori* in duodenal ulcer, gastric ulcer, gastric adenocarcinoma, and gastric lymphoma. Less well accepted are its role in non-ulcer dyspepsia and its more indirect influences on coronary artery disease, rosacea, diarrhoeal diseases in children in developing countries, and hepatic encephalopathy.¹⁸⁻²³ These latter conditions have all been epidemiologically linked to infection but a causal role for the organism has not been proved. Yet, if *H pylori* is confirmed as even a weak causal factor in dyspepsia, heart disease, diarrhoea and/or encephalopathy, the overall importance of the organism will rise dramatically as these conditions engender high worldwide morbidity and considerable medical expenditure.

Table 1 Proportion of disease worldwide attributable to *Helicobacter pylori* infection, adjusted for sensitivity and specificity of diagnostic tests

	Estimated new cases annually	Per cent distal stomach	Number potentially linked to <i>H pylori</i>	<i>H pylori</i> prevalence (%)	RRs as reported in meta-analyses	Sensitivity and specificity of <i>H pylori</i> tests (%)	Adjusted RR	Adjusted PAR (%)
Gastric adenocarcinoma*								
Developing countries	559 000	90	503 100	75	1.5	85	5.1	68
Industrialised countries	340 000	60	204 000	35	3.0	90	5.1	35
Duodenal ulcer disease†								
All countries	6 000 000	NA	6 000 000	60	3.3	90	6.3	76

Adapted from *Pisani and colleagues² and †Kurata and Nogawa.³⁰
PAR, population attributable risk per cent; RR, relative risk.

If one considers only the diseases most strongly linked to *H pylori*, gastric adenocarcinoma and duodenal ulcer disease, it is still evident that *H pylori* infection imposes a heavy toll on world health. Gastric adenocarcinoma is the second leading cause of death from cancer worldwide. According to the International Agency for Research on Cancer, gastric cancer afflicts 900 000 people annually, most of whom will die of their disease.² Data on duodenal ulcer disease are fewer but indicate that between 0.1 and 0.2% will develop an ulcer annually and roughly 2–5% will have an ulcer at some time in their life. If these rates are extrapolated to the world population, then at least 6 000 000 duodenal ulcers occur annually and at least 120 000 000 people suffer from the disease at some point; up to 200 000 will die each year from perforation or bleeding.²⁴

Yet, not all gastric cancers or duodenal ulcers can be ascribed to *H pylori*. Moreover, the proportion of disease caused by infection varies from population to population. For example, a group in Rochester recently reported finding *H pylori* in only 30% of duodenal ulcers.²⁵ Similarly, investigators from Johns Hopkins found *H pylori* in only 50% of patients with duodenal ulcer (in 25% of whites) and, in a prospective study, investigators from Harvard reported *H pylori* in only 60% of physicians who developed duodenal ulcer.^{26–27} These studies contrast with the 90% *H pylori* prevalence previously presumed in duodenal ulcer patients. To complicate the issue further, Laine *et al* reported 20% recurrence of duodenal ulcer in subjects whose initial *H pylori* infection had been successfully eradicated.²⁸ Thus, even in subjects infected with *H pylori*, a considerable proportion of ulcers seems to be due to other causes. Heterogeneous results have similarly been reported for the *H pylori*–gastric cancer association.

There are two primary reasons why disease is so variably attributed to *H pylori*. Firstly, the imperfect sensitivity and specificity of diagnostic tests for *H pylori* result in an inaccurate measure of the relative risk (RR) for disease in infected people. For example, let us suppose that investigators are studying peptic ulcer disease (PUD) in a population with 40% *H pylori* prevalence and, in conducting their study, use a diagnostic test for *H pylori* with 90% sensitivity and specificity. If these hypothetical investigators observe a RR for PUD of 2.2 in infected subjects, they will have underestimated the true RR (3.3) by 33% (for details on methods, see Kleinbaum and colleagues²⁹). If the diagnosis of the disease also is subject to some misclassi-

fication (that is, there may be some subjects with undiagnosed PUD), the RR could be further affected.

The second reason disease is so variably attributed to *H pylori* is that the prevalence of *H pylori* varies from population to population. This causes different estimations of the portion of disease attributable to infection (the population attributable risk (PAR)). PAR is dependent on both RR for disease and on the prevalence of infection:

$$(\text{PAR} = [p(\text{RR} - 1)]/[p(\text{RR} - 1) + 1])$$

where *p* is the prevalence of *H pylori* in the populations).²⁹ Thus, assuming the relative risk for disease is the same from population to population, then the prevalence of *H pylori* will determine how much disease is related to infection in a given population. For example, in many communities worldwide, the prevalence of *H pylori* is as high as 50%. In wealthy communities in the United States, however, prevalence of *H pylori* may be as low as 20%. This difference in *H pylori* prevalence would translate into a considerable difference in the PAR. Assuming a RR of 3.3 in both settings, the proportion of PUD caused by *H pylori* would be 53% in the high prevalence community compared with only 32% in the low prevalence community.

So what proportion of disease really is caused by *H pylori*? Recently, Pisani *et al* calculated that 55% of gastric cancers worldwide were due to *H pylori* infection.² In a similar meta-analysis, Kurata *et al* calculated that between 48 and 64% of peptic ulcers were caused by *H pylori*.³⁰ These calculations are likely to underestimate risk as use of imperfect diagnostic tests in the analysed studies would tend to negatively bias findings.²⁹ The paper by Kurata *et al* may also inaccurately reflect global risk for PUD by evaluating only United States populations; these populations may differ significantly from others worldwide in the prevalence of potentially confounding PUD risk factors such as cigarette smoking and use of non-steroidal anti-inflammatory agents. The problem of risk measurement is even more complicated in the case of gastric cancer because misclassification of antecedent infection may be more pronounced in cancer cases than in the population at large. Conversely, Pisani *et al*'s calculations would also tend to overestimate the proportion of cancers attributable to infection because they considered all gastric adenocarcinomas to be similarly related to infection. It is now thought that cancers in the proximal stomach, which account for up to 50% of cancers in industrialised countries, are

not linked to *H pylori*. Thus, these tumours should not be considered in overall calculations of PAR.

In table 1, I extrapolate on Pisani *et al*'s and Kurata *et al*'s work, taking into account the likely underestimation of RR caused by using imperfect diagnostic tests³⁰ and including only distal cancers in the calculations. It is assumed that diagnostic tests for *H pylori* are 90% sensitive and specific for infection in the industrialised countries where the tests were developed and are somewhat less sensitive and specific in developing countries (85% sensitivity and specificity). It is also assumed that 10% of ulcers may remain undiagnosed either due to empirical treatment without diagnostic testing or to lack of symptoms. In industrialised countries, I assumed that 60% of cancers occurred in the distal stomach compared with 90% in developing countries. Based on these assumptions, it can be seen that the RRs for cancer and for ulcer disease rise substantially (from 1.5/3.0 to 5.1 for cancer and from 3.3 to 6.3 for ulcer disease). The PAR also rises correspondingly with 56% of cancers and 76% of ulcers due to *H pylori*. It should be noted, however, that these figures will vary widely from population to population based on infection prevalence. Thus, only one third of gastric cancers in industrialised nations are due to infection compared with two thirds in the developing world.

Using these adjusted RRs, one can also calculate the proportion of disease in infected people that is due to infection [attributable risk in the exposed = (RR - 1)/RR]. This is particularly important for patients with duodenal ulcer disease as the attributable risk in the exposed can predict the failure rate of duodenal ulcer treatment in patients in whom infection is successfully eradicated. Using the adjusted RR in table 1 one would expect *H pylori* eradication to cure 80% of duodenal ulcers leaving 20% to relapse despite successful eradication therapy. This is remarkably similar to the actual findings reported by Laine *et al*.²⁸

Thus, based on adjusted calculations of PAR, it seems that, worldwide, at least 5 000 000 new cases of gastric cancer and duodenal ulcer disease due to *H pylori* occur each year. If one further considers that *H pylori* causes gastric ulcers and may lead to other diseases and syndromes as well, the magnitude of sickness due to this single organism reaches truly frightening proportions.

***H pylori*—stamp it out or “live and let die”?**

H pylori infection is decreasing in frequency worldwide. By some reports, infection in children is almost non-existent. Moreover, the diseases associated with *H pylori* are either rare (gastric lymphoma) or decreasing in incidence despite lack of *H pylori* directed intervention (gastric cancer and duodenal ulcer disease). Data from the International Agency for Research on Cancer indicate that gastric cancer incidence has decreased almost in parallel worldwide at rates ranging between 10% and 19% per decade.³¹ This occurred despite the

increase in non-*H pylori* related tumours of the proximal stomach. The rates of decline for duodenal ulcer disease are more difficult to determine but certainly, the incidence of serious morbidity (major bleeding) and/or mortality have declined considerably in industrialised nations.^{32 33} Even with these favourable trends, however, the magnitude of morbidity and mortality engendered by *H pylori* continues to be sizable. Unfortunately, the regions where *H pylori* is most prevalent and where benefits are most likely to be realised, are often those with the least resources for large eradication programmes. Yet, the time has come to test the effects of *H pylori* eradication on morbidity and mortality in large populations. It is only by knowing how *H pylori* eradication contributes to not only cancer and ulcer disease, but also to overall mortality and morbidity, that we rationally determine the magnitude of disease and formulate public health strategies to combat this formidable organism.

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