

HELICOBACTER PYLORI

Helicobacter pylori was considered by a previous IARC Working Group in 1994 ([IARC, 1994](#)). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

Helicobacter pylori is a highly heterogenous bacterium with a large genomic diversity. In addition, humans may sometimes harbour multiple strains, and *H. pylori* can change genotypically and phenotypically during colonization in a single host ([Suerbaum & Josenhans, 2007](#)).

1.1 Taxonomy, structure, and biology

1.1.1 Taxonomy

The presence of spiral-shaped bacteria on human gastric mucosa was first recognized nearly one hundred years ago ([Pel, 1913](#)). These bacteria were originally named *Campylobacter pylori* (*C. pylori*) ([Warren, 1983](#)).

In 1989, a new genus, *Helicobacter*, was proposed, and *C. pylori* was renamed *Helicobacter pylori* ([Goodwin et al., 1989](#)). Recently ([Garrity et al., 2005](#)), the genus *Helicobacter* has been included with the genus *Wolinella* in the family *Helicobacteraceae* which, with the family *Campylobacteraceae*, constitutes the *Epsilonproteobacteria*.

Over the past 20 years, 23 *Helicobacter* species have been validated, and two candidates

and several strains are awaiting official classification ([Table 1.1](#)).

According to the usual site of colonization, *Helicobacter* species can be divided into gastric and enteric or enterohepatic *Helicobacter* types.

Some gastric *Helicobacter* species from animals can infect humans: *H. bizzozeroni*, *H. salomonis*, *H. felis*, *H. candidates*, *H. suis*. Because they are extremely difficult to grow in cultures, the exact speciation is usually not done, and they are known as “*Gastrospirillum hominis*” or “*H. heilmannii*” ([De Groote et al., 2005](#)).

1.1.2 Structure of the bacterium

H. pylori is a spiral or slightly curved Gram-negative rod with 2–6 characteristic unipolar flagella. The bacterium has bluntly rounded ends and measures 2.5–4.0 µm in length and 0.5–1.0 µm in width. The cell wall is smooth and may be coated with a prominent glycocalyx with a thickness of up to 40 nm ([Goodwin et al., 1989](#)); it is covered with ring-like subunits with a diameter of 12–15 nm. Occasionally, the bacterium may contain bacteriophages. The flagella measure 2.5 µm in length and around 30 nm in thickness, and have a distinctive terminal bulb ([Goodwin & Worsley, 1993](#)). The bacterium

Table 1.1 Validated species of the genus *Helicobacter*

Species
<i>Helicobacter pylori</i>
<i>Helicobacter acinonychis</i>
<i>Helicobacter aurati</i>
<i>Helicobacter bilis</i>
<i>Helicobacter bizzozeronii</i>
<i>Helicobacter canadensis</i>
<i>Helicobacter canis</i>
<i>Helicobacter chrolecystus</i>
<i>Helicobacter cinaedi</i>
<i>Helicobacter felis</i>
<i>Helicobacter fennelliae</i>
<i>Helicobacter ganmani</i>
<i>Helicobacter hepaticus</i>
<i>Helicobacter mesocricetorum</i>
<i>Helicobacter muridarum</i>
<i>Helicobacter mustelae</i>
<i>Helicobacter nemestrinae</i>
<i>Helicobacter pametensis</i>
<i>Helicobacter pullorum</i>
<i>Helicobacter rodentium</i>
<i>Helicobacter salomonis</i>
<i>Helicobacter trogontum</i>
<i>Helicobacter typhoniis</i>
<i>Candidatus Helicobacter bovis</i>
<i>Candidatus Helicobacter suis</i>

displays remarkable motility in viscous solutions, and the flagella play a central role in this motility ([Hazell et al., 1986](#); [Suerbaum et al., 1993](#)).

In certain circumstances, *H. pylori* can evolve from this typical helical form to a coccoidal form. Some studies suggested that they are live organisms ([Sisto et al., 2000](#); [Willén et al., 2000](#)), but others concluded that they are degenerating organisms ([Kusters et al., 1997](#)).

1.1.3 Structure of the genome

The genome of three *H. pylori* strains has now been fully sequenced: strain 26695 from a patient with gastritis, strain J99 from a duodenal ulcer patient, and strain HPAG1 from a patient with

chronic atrophic gastritis ([Tomb et al., 1997](#); [Alm et al., 1999](#); [Oh et al., 2006](#)).

Strains 26695, J99 and HPAG1 have a circular chromosome of 1667867 base pairs (bp), 1643831 bp and 1596366 bp, respectively. HPAG1 also has a single 9369 bp plasmid, pHPAG1.

The percentage of genome-coding sequences of strains 26695, J99 and HPAG1 is around 92%, and they contain 1552 ([Alm et al., 1999](#); [Boneca et al., 2003](#)), 1495 ([Tomb et al., 1997](#); [Alm et al., 1999](#)), and 1536 ([Oh et al., 2006](#)) predicted protein-coding genes, respectively. In these three small genomes, 1379 open reading frames (ORFs) are common to all three strains and about 10% of the genes are strain-specific ([Alm et al., 1999](#)); 117 and 89 genes present in strains 26695 and J99, respectively, are absent in the other strain ([Alm et al., 1999](#)); in contrast, 43 of the HPAG1 genes are either not detectable at all or incompletely represented in the 26695 and J99 genomes ([Oh et al., 2006](#)).

A comparison of the three genomic sequences revealed that the genetic organization was similar in all three strains. However, it confirmed the panmictic structure of *H. pylori*, which is the result of a high mutation rate (microdiversity, i.e. high polymorphism among orthologous genes), and free recombinations ([Falush et al., 2003](#)). A significant macrodiversity (presence or absence of the genes) was also observed ([Raymond et al., 2004](#)). A comparative genomic analysis of isolates from 15 Caucasians ([Salama et al., 2000](#)) allowed to extend the pool of strain-specific genes from 6–7% (as determined from the comparison of the first two sequenced genomes) to 18–22%. More recently, a large study was conducted on 56 *H. pylori* strains and four *H. acinonychis* strains, with whole genome microarrays. They concluded that the core genome present in all *H. pylori* isolates contains 1111 genes, with a weighted average of 27% of the genome variably present in different isolates ([Gressmann et al., 2005](#)).

Besides the *cag* pathogenicity island, which is known to be a variable region, half of the

strain-specific genes are clustered in a hypervariable region, known as the 'plasticity zone' (Salama *et al.*, 2000). The group of genes containing the most variability are those that comprise genes of unknown function (44%), genes associated with DNA metabolism (most of them are restriction-modification systems 54%), outer-membrane proteins (22%), cellular processes/cagPAI (40%) and others (100%, including transposases) (Gressmann *et al.*, 2005).

The genomic analyses suggest that *H. pylori* strains have essentially identical metabolic potential (Table 1.2).

1.1.4 Host range

H. pylori is the *Helicobacter* species of humans. *H. pylori* isolation from several other animal species (monkey, pig, cat, dog) has been reported, but these reports were anecdotal, and these bacteria were most likely acquired from humans.

1.1.5 Target cells and tissues

The target cell of *H. pylori* is the gastric mucus-secreting cells. A low acid output leads *H. pylori* to also infect the corpus (Louw *et al.*, 1993). *H. pylori* lives mainly in the surface mucus layer and within the pits, and can adhere to mucus-secreting cells especially close to intercellular junctions (Hazell *et al.*, 1986). It is not found on intestinal-type cells in the case of intestinal metaplasia. In contrast, it has the ability to colonize metaplastic gastric cells present in the duodenum and elsewhere, for example, in the oesophagus, in Meckel's diverticulum, and in the rectum (Hill & Rode, 1998).

The main cell receptor for this adherence is the blood group antigen A, and the corresponding adhesin is named BabA. In a low proportion of the cells, *H. pylori* may be intracellular, a situation which contributes to its persistence (Dubois & Borén, 2007).

H. pylori can be present transiently in the mouth when regurgitated, and may also be found in the faeces, but it cannot survive with competing organisms (Parsonnet *et al.*, 1999).

1.1.6 Function of gene products

(a) Colonizing factors

Colonization by *H. pylori* involves an interaction between a large family of *Helicobacter* outer membrane proteins (Hop) and the gastric epithelial cells of the host. Several genes involved in determining the composition of the outer membrane are differentially regulated by a phase variation called slipped-strand repair. This phenomenon is possible due to the presence of repeated intragenic sequences, allowing replicative shifts and mismatches, leading to changes in the status of a gene ("on/off") (Salaün *et al.*, 2004). Such proteins are the blood group antigen binding adhesion (BabA), sialic acid binding adhesion (SabA), adherence-associated lipoprotein (AlpA and AlpB), and HopZ.

Lipopolysaccharides play an important role in the interaction between Gram-negative bacteria and their host. They are potential stimulators of the immune system (Moran *et al.*, 1996). The *H. pylori* lipopolysaccharides, however, have remarkably low activity, and their synthesis may involve over 20 genes, scattered throughout the genome, unlike other bacteria in which they are grouped into a single cluster.

The expression of fucosyltransferase, an enzyme essential for the lipopolysaccharide biosynthesis pathway, is also subject to phase change, and is a key enzyme allowing *H. pylori* to mimic human Lewis antigens, which allows it to escape the host immune response (Lozniewski *et al.*, 2003).

It has been suggested that this differential regulation and the strain-specific outer-membrane-related genes may play a role in the severity of *H. pylori*-related disease, and the

Table 1.2 Classification of the genes of two *Helicobacter pylori* strains sequenced

Annotation category	No. of genes in:	
	<i>H. pylori</i> J99	<i>H. pylori</i> 26695
Functionally classified	877	898
Aminoacid biosynthesis	44	44
Biosynthesis of cofactors etc.	60	59
Cell envelope	160	164
Cellular processes	96	113
DNA replication	23	23
DNA restriction-modification, etc.	66	68
Energy metabolism	104	104
Fatty acid and phospholipid metabolism	28	29
Purine and pyrimidine biosynthesis	34	34
Regulatory functions	32	32
Transcription	13	13
Translation	128	128
Transport and binding proteins	88	87
Conserved with no known function	275	290
<i>Helicobacter pylori</i> specific	343	364
Total	1495	1552

From [Doig et al. \(1999\)](#)

ability of *H. pylori* to persist chronically in its host ([Mahdavi et al., 2002](#)).

(i) *BabA*

The blood group antigen Lewis b was identified as a receptor for *H. pylori* in 1993 ([Borén et al., 1993](#)). This is the dominant antigen in the gastric mucosa of secretor-positive individuals. The adhesion-recognizing Lewis b was characterized as an *H. pylori* outer-membrane protein, namely BabA ([Ilver et al., 1998](#)). Another protein with almost identical amino terminal and identical carboxy terminal domains but divergent central domains, BabB, does not bind to Lewis b antigen ([Aspholm-Hurtig et al., 2004](#)).

A *babA* allele and a *babB* allele are both present in each of the three sequenced strains, but in different locations. In the strain from which *bab* genes were initially cloned, there were two *babA* genes but only one of them (*babA2*) has Lewis b binding activity. According to two studies, the *babA* gene is present in approximately 70% of

H. pylori strains, and the *babB* gene is present in almost them all ([Colbeck et al., 2006](#); [Hennig et al., 2006](#)).

Several mechanisms have been elucidated for the regulation of BabA expression including chimera formation ([Pride & Blaser, 2002](#)) between *babA* and *babB*, and phase variation of *babA* through slipped-strain mispairing ([Solnick et al., 2004](#)).

To date, BabA-Lewis b is the adhesin-receptor interaction in *H. pylori* that is best characterized, and probably one of the most important ([Yamaoka, 2008](#)).

(ii) *SabA*

Another outer-membrane protein conferring adherence to host sialyl Lewis x was identified as sialic acid-binding adhesin (SabA) ([Mahdavi et al., 2002](#)). The sialyl-Lewis x expression is induced in the gastric epithelium during persistent *H. pylori* infection, suggesting that the bacterium can trigger the host tissue to modify

the mucosal glycosylation patterns for enhanced adherence. The event could occur via induction of 3GnT5, a GlcNAc transferase essential for the biosynthesis of Lewis antigens ([Marcos et al., 2008](#)). SabA could in this way contribute to the chronicity of *H. pylori* infection. SabA can also bind specifically to granulocytes and induce an oxidative burst ([Unemo et al., 2005](#)).

(iii) *AlpA and AlpB*

A genetic locus involved in *H. pylori* adherence to Kato cells was identified in 1999 ([Odenbreit, 2005](#)). It was named *alpAB* (adherence-associated lipoprotein A and B), and encodes two outer-membrane proteins. However, because no receptor has been identified for these proteins, their role as adhesins is unclear.

(iv) *HopZ*

HopZ has been described as an adhesin ([Peck et al., 1999](#)) but no receptor has yet been identified for this putative adhesin.

(b) Pathogenicity factors

(i) *cag* Pathogenicity island

In many parts of the world, including Asia and most of Africa, almost all *H. pylori* strains contain an intact *cag* pathogenicity island, whereas about 30% of strains from Europe and North America lack the entire island, and are considered “*cag*-negative”. However, both *cag*-positive and *cag*-negative strains can exist together in the same stomach, and the *cag* pathogenicity island can be partially deleted with the loss of type 4 secretory function ([Suerbaum & Josenhans, 2007](#)), therefore, the simple designation of *cag* status as positive or negative may not be absolute. The CagA protein encoded by the *cagA* gene within the *cag* pathogenicity island is a highly immunogenic protein that elicits serum antibody responses allowing for the detection of *cag*-positive strains by enzyme-linked immunosorbent assay (ELISA)

or Western blot analysis in serum samples for epidemiological studies.

The *cag* pathogenicity island of *H. pylori* is a DNA fragment of approximately 40 kbp which exhibits the characteristics of pathogenicity islands in general: i) a G+C% different from the rest of the chromosome (35% vs 39%), ii) two direct repeat sequences at its ends, iii) several genes linked to virulence, iv) a secretion system, and v) an insertion sequence ([Censini et al., 1996](#)).

This pathogenicity island is always located between the same two genes: HP519, a gene of unknown function, and *murI*, the glutamate racemase gene. It is integrated at the 3' end of the glutamate racemase gene and flanked by two repeated 31 bp sequences probably derived from the duplication of the 3' end of this gene ([Akopyants et al., 1998](#)). Because this island appears to be acquired *in toto*, it may then be separated into two regions, namely *cagI* and *cagII*, by an insertion sequence (IS605) coding for two transposases (*tnpA* and *tnpB*) ([Censini et al., 1996](#)). There are 27 potential coding sequences in the *cag* pathogenicity island ([Censini et al., 1996](#)).

Not all *H. pylori* strains possess the *cag* pathogenicity island. In addition, it can be lost or gained via recombination ([Kersulyte et al., 1999](#)). In addition, partial deletions have been described. Among the *cag* pathogenicity island genes, six show sequence similarity with genes coding for a secretion system in other bacteria. This is a type IV secretion system, a multi-protein complex that allows the bacterium to inject specific molecules into an eukaryotic cell ([Krause et al., 2000](#)). Among such translocated molecules is the product of one of the *cag* pathogenicity island genes, CagA. This immunodominant protein of 120–145 kDa was the first *H. pylori* protein to be linked to more severe disease ([Crabtree et al., 1991](#)). Phosphorylated CagA was also detected inside epithelial cells infected with *H. pylori* ([Yamazaki et al., 2003](#); [Higashi et al., 2005](#)).

(ii) VacA cytotoxin

A cytotoxic activity was first reported in broth culture filtrates of *H. pylori* incubated with mammalian cells *in vitro* ([Leunk et al., 1988](#)). The protein responsible for the observed effect of large intracellular vacuoles was designated vacuolating cytotoxin VacA ([Cover & Blaser, 1992](#)). It is a high-molecular weight multimeric pore-forming protein encoded by the chromosomal gene *vacA* ([Cover et al., 1994](#); [Schmitt & Haas, 1994](#); [Telford et al., 1994](#)).

As with *cagA*, no close homologues of *vacA* exist in other *Helicobacter* species nor in other bacteria or eukaryotic cells. Mature 88 kDa VacA toxin molecules are secreted as soluble proteins into the extracellular space, but can also remain localized on the surface of *H. pylori* ([Ilver et al., 2004](#)). The secreted toxin can assemble into oligomeric structures ([Cover et al., 1997](#); [Adrian et al., 2002](#)) for insertion into planar lipid bilayers to form anion-selective membrane channels allowing anions and urea to exit ([Iwamoto et al., 1999](#); [Tombola et al., 1999](#)). The microscopic analysis of VacA oligomeric complexes has shown their dissociation into monomeric components with low vacuolating potential that can be activated by pH changes.

The secreted mature 88 kDa toxin can be cleaved in two fragments: p33 and p55 ([Nguyen et al., 2001](#)). The p55 domain has a role in the binding of VacA to host cells, and the p33 domain, together with 100 amino acids of the p55 domain, is sufficient to induce intracellular vacuolation ([de Bernard et al., 1998](#)).

Unlike *cagA*, *vacA* is conserved among all *H. pylori* strains, but exhibits a high level of genetic diversity. Several *vacA* alleles can be distinguished on the basis of diversity in the 5' region, namely in the signal region, (s region) s1 and s2, and in the mid-region (m region) m1 and m2 ([Atherton et al., 1995](#)). Among the different combinations, the s1m1 type produces the most active vacuolating activity in different

cell lines, s1m2 produces detectable vacuolation in a limited range of cell types, s2m2 is inactive, and s2m1 does not appear to exist.

More recently, a third group of alleles has been described in the intermediary region (i) – i1 and i2 ([Rhead et al., 2007](#)).

A strong association between *vacA* s1 and *cag* pathogenicity island has been described ([Van Doorn et al., 1999](#)).

1.2 Epidemiology of infection

1.2.1 Prevalence, geographic distribution

The most common test used to determine the prevalence of infection in healthy populations is serology for *H. pylori* IgG by ELISA ([Vaira et al., 2002](#); [Mueller et al., 2006](#)). Serological testing for CagA antibody is more sensitive for individuals who are infected with CagA⁺ *H. pylori*, but *H. pylori* IgG ELISA is most often used in screening. Other diagnostic tests for *H. pylori* are available but less often used in large epidemiological studies or to estimate population prevalence ([Mégraud & Lehours, 2007](#)).

H. pylori infection is common, with a global prevalence of over 50%, but with substantial country-to-country variations ([Parsonnet, 1998](#); [Suerbaum & Michetti, 2002](#)). Prevalence rates differ by age, race/ethnicity, and socioeconomic characteristics. As a rule, rates are higher in developing countries than in developed ones; however, in several eastern European countries the prevalence of infection is high.

The prevalence of infection is highest in the older age groups ([The EUROGAST Study Group, 1993](#)). The rate of *H. pylori* infection has been shown to have decreased in successive birth cohorts over the past several decades in developed countries ([Roosendaal et al., 1997](#)). [Banatvala et al. \(1993\)](#) screened a total of 631 serum samples collected from adults and children in 1969, 1979, and 1989, and the cohort effect on *H. pylori* positivity was estimated by Western blot based

on year of birth. The seropositivity declined by 26% (8–41%) per decade ($P < 0.008$). [Eslick \(2003\)](#) reported on 451 pregnant women screened for *H. pylori* infection in Australia, and found that infection rates declined from 44% in the birth cohort of 1951–60, to 29% in the birth cohort of 1961–70, to 20% in the birth cohort of 1971–80, to 9% in the birth cohort of 1981–90.

[Rothenbacher et al. \(1998\)](#) used ^{13}C -urea breath tests for population screening of approximately 1000 preschool children as part of a physician-administered school fitness test. This demonstrated its utility for determining current infection status in a relatively large population of healthy subjects.

Because of the substantial differences in the prevalence of infection over time by age group and race/ethnicity within a country, international comparisons of the overall prevalence of *H. pylori* where the populations were tested during different time periods, and different age composition or race/ethnicity or type of test performed are crude comparisons at best, and likely to be misleading (for a review, see [Everhart, 2000](#)).

The results of the EUROGAST Study Group ([The EUROGAST Study Group, 1993](#)) illustrate the importance of age-specific prevalence estimates. In Japan, the population prevalence was 61% in the 25–34 years age group, and 89% in the 55–64 years age group; in Poland the prevalence was 69% in the 25–34 years age group, and 89% in the 55–64 years age group; in Denmark the prevalence was 15% in the 25–34 years age group, and 30% in the 55–64 years age group; in the United States of America, the prevalence rate was 15% in the 25–34 years age group, and 34% in the 55–64 years age group.

Similar variations are seen within the USA between racial and ethnic groups. [Hyams et al. \(1995\)](#) conducted serological testing of 1000 military personnel aged 17–50 years. The overall prevalence of infection in the group was 25%, ranging from 18% in Caucasians to 45% in Hispanics and 46% in Blacks, with other races at 29%. More

recently [Everhart et al. \(2000\)](#) conducted a larger seroprevalence survey in the USA in which 7465 adults were tested for *H. pylori* by IgG ELISA. The overall seroprevalence was 32.5%. It was substantially higher among non-Hispanic blacks (52.7%) and Mexican-Americans (61.6%) than among non-Hispanic Caucasians (26.2%).

1.2.2 Transmission

(a) Person-to-person route

Humans are the only known significant reservoir of *H. pylori* ([Oderda, 1999](#)). Person-to-person contact is believed to be the primary route of transmission in developed countries, and is also important in developing countries. Close personal contact, particularly within the family including mother/parents to child, sibling to sibling and spouse to spouse, has been consistently demonstrated as a risk factor for transmission of infection ([Dominici et al., 1999](#); [Escobar & Kawakami, 2004](#)).

[Brenner et al. \(2006\)](#) determined current *H. pylori* infection in 670 spousal pairs by ^{13}C -Urea breath test and monoclonal antigen immunoassay for *H. pylori* in stool. The prevalence of infection was significantly greater in women with infected partners, compared to women whose partner was not infected (34.9% vs 14.5%).

Person-to-person transmission can occur in several ways. [Parsonnet et al. \(1999\)](#) conducted a controlled clinical experimental study to determine how humans shed *H. pylori* into the environment. A total of 16 asymptomatic individuals positive for *H. pylori* were administered a cathartic and an emetic and 1/10 participating *H. pylori*-negative individuals was given an emetic. Stool and vomitus samples were collected. All vomitus specimens from *H. pylori* positive individuals grew *H. pylori* (confirmed by polymerase chain reaction (PCR)). Air was sampled during vomiting and *H. pylori* were grown from 6 of 16 samples (37.5%). Small quantities of *H. pylori* were grown in three (18.8%) and nine (56.3%)

saliva samples obtained from subjects before and after emesis, respectively. Cultures from 7/14 (50%) positive subjects had at least one positive culture and 22/101 cathartic stools (21.8%) grew *H. pylori*. Samples from negative subjects did not grow the organism on culture.

Transmission of *H. pylori* was also examined by [Perry et al. \(2006\)](#) who tested 2752 household members for *H. pylori* in serum or stool at baseline and then again 3 months later. A total of 30 new infections occurred among 1752 persons uninfected at baseline. Exposure to a household member with gastroenteritis was associated with a relative risk of 4.8 (95%CI: 1.4–17.1) for definite or probable new infection. Risk of infection was greater for exposure to vomiting (odds ratio (OR), 6.3) than to diarrhoea (OR, 3.0).

Significantly higher than expected prevalence rates of *H. pylori* infection have been observed in institutionalized adults and children ([Malaty et al., 1996](#); [Böhmer et al., 1997](#)).

(b) Oral-oral route

H. pylori DNA has been detected in the saliva of *H. pylori*-positive subjects by PCR ([Namavar et al., 1995](#); [Madinier et al., 1997](#)). *H. pylori* organisms have also been successfully detected from the dental plaque of infected persons ([Nguyen et al., 1993](#)). In general, isolation has not been uniformly successful, however, perhaps as a result of the transient presence of *H. pylori* in the oral cavity or poor detection capability resulting from the co-occurrence of many other bacteria in the oral cavity.

(c) Faecal-oral route

H. pylori has been detected in faeces by culture and its DNA by PCR ([Kelly et al., 1994](#); [Namavar et al., 1995](#)), although other investigators have failed to replicate this ([van Zwet et al., 1994](#)). One study found detectable DNA in the faeces of 73% of known infected subjects ([Gramley et al., 1999](#)). These data, together with those from [Parsonnet](#)

[et al. \(1999\)](#), document the possible role of faecal shedding of *H. pylori* into the environment.

(d) Waterborne transmission

Studies in the People's Republic of China and in Latin America found that the source of water used for consumption, bathing or swimming could possibly be associated with *H. pylori* infection ([Goodman et al., 1996](#); [Zhang et al., 1996](#)). Contamination of drinking-water and sewage water has been demonstrated. [Hegarty et al. \(1999\)](#) found *H. pylori* in 60% of the samples of surface water, and 65% of the shallow ground water collected in several states in the USA. A Japanese study also reported *H. pylori* contamination of water from rivers and ponds ([Sasaki et al., 1999](#)).

(e) Iatrogenic transmission

Endoscopes used routinely in upper gastrointestinal procedures may be the source of iatrogenic infection as a result of improper disinfection between procedures ([Langenberg et al., 1990](#); [Tytgat, 1995](#)).

1.2.3 Risk factors for infection

The best established risk factor for *H. pylori* infection is low socioeconomic status, particularly during childhood when initial infection generally occurs ([Malaty & Graham, 1994](#)). Both education and income as components of socioeconomic status are inversely related to risk of infection ([Replogle et al., 1995](#)). Factors closely linked to socioeconomic status that appear to contribute to this inverse relation between poverty and risk of infection include hygienic conditions, household density/crowding, and the number of young children in the household ([Goodman et al., 1996](#); [Ford et al., 2007](#)).

Neither smoking nor alcohol were found to be associated with the prevalence of *H. pylori* seropositivity in the large EUROGAST study of 17 asymptomatic populations ([The EUROGAST](#)

[Study Group, 1993](#)). Because the literature is inconsistent, the most recent studies also report no significant association between *H. pylori* infection and tobacco use ([Brown, 2000](#)). Alcohol, particularly wine consumption, was found to have an inverse association with *H. pylori* infection in several studies ([Brenner et al., 1997, 1999a, b](#)). Other studies have also found modest reductions in risk that were not statistically significant ([Fontham et al., 1995](#); [Peach et al., 1997](#)).

1.2.4 Persistence, latency, and natural history of infection

Acquisition of *H. pylori* infection typically occurs in childhood ([Malaty & Graham, 1994](#); [Goodman et al., 1996](#); [Brown, 2000](#)). Once infection is established, it usually lasts for life, unless treated. At present there is no vaccine available, and the treatment of infection is generally a 2-week course of triple therapy consisting of an antisecretory agent, and two antibiotics.

H. pylori antibody titre has been shown to decline over the progression of premalignant lesions, and impacts the validity of serology, particularly in retrospective studies. [Kokkola et al. \(2003\)](#) followed 47 men with advanced *H. pylori*-positive atrophic corpus gastritis by endoscopy over a 6-year period, and by serum levels of pepsinogen I and antibodies to *H. pylori* over a 10-year period. None was treated for *H. pylori* infection during the study. The mean *H. pylori* antibody titres (IgG and IgA) declined during the course of follow-up, and 11 (23%) men converted to a seronegative status, and no significant changes were observed in the grade of atrophy or intestinal metaplasia in the antrum, or in the grade of intestinal metaplasia in the corpus. Using material from a population-based case-control study, [Ekström et al. \(2001\)](#) re-evaluated the association between *H. pylori* and gastric cancer by comparing ELISA assay against *H. pylori* IgG with immunoblot against CagA antibodies to detect evidence of past *H. pylori*

infection. Among cases, the seroprevalence of *H. pylori* was around 70% by ELISA and around 90% by immunoblot; among controls, the seroprevalence was similar by the two methods (55% positive). The odds ratios relating *H. pylori* exposure to gastric cancer substantially increased when CagA antibody positivity rather than *H. pylori* IgG ELISA was used to classify past exposure.

[Yoo et al. \(2007\)](#) examined the positivity of several currently available diagnostic tests for *H. pylori* when atrophic gastritis and/or intestinal metaplasia, and presumably more advanced lesions as well, are present. The CLO test (based on urease activity), has lower sensitivity in cases of both atrophy or intestinal metaplasia. Histological identification of *H. pylori* with Giemsa stain was markedly reduced as the degree of intestinal metaplasia increased ($P < 0.01$), but was not affected in cases of atrophy only. The culture test was not affected except at the highest grade of atrophy or intestinal metaplasia, with 0% positivity.

2. Cancer in Humans

2.1 Cancer of the stomach

The previous *IARC Monograph* ([IARC, 1994](#)) reviewed results from four cohort and nine case-control studies that considered gastric carcinoma. Since its publication, results from several further cohort studies have been published. Some of these, together with the cohort studies presented in the earlier *Monograph*, were included in a pooled reanalysis ([Helicobacter and Cancer Collaborative Group, 2001](#)).

In analysing the relationship between gastric carcinoma and *H. pylori*, there is a specific bias in retrospective determination of *H. pylori* status in that precancerous subjects may undergo a loss of infection, thus producing an underestimate of prevalence in cases but not in controls ([Kokkola et al., 2003](#); [Yoo et al., 2007](#)). For this

reason, relatively little weight is given to case-control studies in the assessment of the relationship between gastric carcinoma and *H. pylori*, although some are cited below as they provide specific evidence.

Since the previous *IARC Monograph*, it has also been reported that *H. pylori* appears to have a different relationship with gastric carcinoma arising in the region of the stomach distal to the cardia (non-cardia gastric carcinoma) compared with the cardia region located adjacent to the oesophageal sphincter. As a consequence, the following presentation of results, where possible, distinguishes non-cardia from cardia gastric carcinoma.

2.1.1 Non-cardia gastric carcinoma

Results are available from 17 prospective cohort studies with nested case-control designs and six further full cohort studies. Whereas the nested case-control comparisons all specify cases defined as non-cardia gastric carcinoma, for the full cohort studies, incident cancers are generally defined as gastric carcinoma without further subsite specification. [The Working Group noted that in the main, these can be assumed to be of the non-cardia.]

(a) Nested case-control analyses within cohort studies

These are summarized in Table 2.1 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.1.pdf>). The pooled reanalysis ([Helicobacter and Cancer Collaborative Group, 2001](#)) presented results based on 762 cases of non-cardia gastric carcinoma and 2250 control subjects derived from 12 independent prospective cohort studies in nine countries (China, Finland, Iceland, Japan, Norway, Sweden, Taiwan (China), the United Kingdom, and USA). The overall matched odds ratio for the risk of non-cardia gastric carcinoma was 2.97 (95%CI: 2.34–3.77), and odds ratios for

individual studies varied from 1.52–11.1. There were no substantive differences in the odds ratios between men and women or between gastric carcinoma with intestinal or diffuse histological type. Younger cases at diagnosis had a higher odds ratio than older cases (OR, 7.10; 95%CI: 2.93–17.2, for those aged < 50 years at diagnosis).

Six of the individual studies included in the pooled reanalysis accrued more cases, and updated results have since been published ([Nomura et al., 2002a](#); [Kamangar et al., 2006a, 2007](#); [Knekt et al., 2006](#); [Hansen et al., 2007](#); [Simán et al., 2007](#)). Using ELISA for *H. pylori* IgG to determine *H. pylori* infection status, odds ratios in these studies varied from 1.6–7.9, and all were statistically significant. One study ([Simán et al., 2007](#)) used immunoblot against *H. pylori* or CagA to determine infection status, and reported an increase in the odds ratios from 11.1 using ELISA ([Simán et al., 1997](#)) to 16.8 or 17.8 respectively, using immunoblot.

New results have been reported from four further prospective studies with nested case-control designs ([Shin et al., 2005](#); [Sasazuki et al., 2006](#); [Palli et al., 2007](#); [Mitchell et al., 2008](#)). Using ELISA for IgG to determine *H. pylori* infection status, odds ratios for non-cardia gastric carcinoma varied from 1.07–5.10, and two were statistically significant ([Sasazuki et al., 2006](#); [Palli et al., 2007](#)). One study ([Mitchell et al., 2008](#)) also used immunoblot to determine infection status, and reported an increase in the odds ratio from 2.3 using ELISA to 10.6 using immunoblot.

[The Working Group noted that some of the variations between study results may result from variation in the sensitivity and specificity of the original ELISA assays used ([Feldman et al., 1995](#)). The Working Group noted the substantial increase in estimated odds ratios in recent studies using immunoblot assays ([Simán et al., 2007](#); [Mitchell et al., 2008](#)).]

In the pooled reanalysis ([Helicobacter and Cancer Collaborative Group, 2001](#)), when the results were stratified by period of follow-up, the

odds ratio for non-cardia gastric carcinoma with cases diagnosed less than 10 years after recruitment was 2.39 (95%CI: 1.82–3.12), and for those with cases diagnosed 10 or more years after recruitment, 5.93 (95%CI: 3.41–10.3). A similar relationship in the magnitude of the odds ratio with period of follow-up was reported in two of the updated studies ([Nomura et al., 2002a](#); [Knekt et al., 2006](#)), but not in two others ([Kamangar et al., 2006a, 2007](#)). A study from Iceland, of which preliminary results were included in the pooled reanalysis, has been reanalysed taking into account quantitative changes in antibody titre between the time of initial blood sample and the diagnosis of gastric carcinoma ([Tulinus et al., 2001](#)). Repeat blood samples were available from 23/41 of the original gastric carcinoma cases, and 128 controls matched for sex, age, time, and number of repeat samples. The odds ratio for gastric carcinoma (predominantly non-cardia) was 1.16 (95%CI: 1.05–1.28) for those showing a decline in antibody titre compared with those with constant or rising levels.

(b) Cohort studies

These studies are summarized in Table 2.2 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.2.pdf>). Three studies, two in Japan ([Yamagata et al., 2000](#); [Yanaoka et al., 2008](#)) and one in China ([You et al., 2000](#)) followed adult subjects undergoing health checks or general screening examinations in relation to *H. pylori* infection status. All three showed a statistically significant increased relative risk of gastric carcinoma associated with infection (in [Yamagata et al., 2000](#) only in men), with relative risks varying from 1.8–3.48.

Three further studies, two in Japan ([Uemura et al., 2001](#); [Watabe et al., 2005](#)) and one in Taiwan, China ([Hsu et al., 2007](#)) followed adult patients undergoing endoscopy procedures for non-malignant conditions, and found statistically significant higher rates of gastric carcinoma in *H. pylori*-positive subjects, with relative

risks [estimated by the Working Group] of 3.6 in one study ([Watabe et al., 2005](#)), and infinity (no *H. pylori*-negative subjects) in the other two. None of these studies was adjusted for potential confounders.

(c) Case-control studies

In a retrospective case-control study of 234 non-cardia gastric carcinoma cases and 238 population controls in Sweden ([Ekström et al., 2001](#)), the reported odds ratio when using conventional IgG ELISA to assess *H. pylori* infection status was 2.2 (95%CI: 1.4–3.6). The odds ratio increased to 21.0 (95%CI: 8.3–53.4) after exclusion from the reference group of all subjects who were ELISA-negative and CagA-positive by immunoblot [The Working Group noted that the immunoblot used was reported to be specific for CagA-positive strains of *H. pylori*.]

In a retrospective case-control study of 57 non-cardia gastric carcinoma cases and 360 controls (with colorectal cancer) in Germany ([Brenner et al., 2004](#)), the reported odds ratio using an IgG ELISA to assess *H. pylori* infection status was 3.7 (95%CI: 1.7–7.9). The odds ratio increased to 18.3 (95%CI: 2.4–136.7) after exclusion from the analysis of defined groups of subjects who might have been susceptible to a misclassified serological result.

(d) Meta-analyses

Four meta-analyses of the association between gastric carcinoma and *H. pylori* infection have been published. [Huang et al. \(1998\)](#) identified 19 studies, both retrospective and prospective, including data from 2491 cases and 3959 controls. For non-cardia gastric carcinoma, the summary odds ratio was 3.08 (95%CI: 1.78–5.31) over all study designs, with evidence of significant heterogeneity. An inverse monotonic association was observed between age at diagnosis and the magnitude of the odds ratio, for non-cardia and cardia gastric carcinoma combined,

from 9.29 (95%CI: 3.43–34.04) at 20–29 years to 1.05 (95%CI: 0.73–1.52) at 70 years or older.

[Danesh \(1999\)](#) identified 34 retrospective and 10 nested prospective case–control studies, which included data from 3300 and 800 cases, respectively. Because of concerns about the validity of the controls, no summary estimate of the odds ratio was calculated for the retrospective studies. For the nested case–control studies, the summary odds ratio for gastric carcinoma was 2.5 (95%CI: 1.9–3.4), with no evidence of significant heterogeneity [The Working Group noted that no distinction was made between non-cardia and cardia gastric carcinoma.]

[Eslick et al. \(1999\)](#) identified 42 studies: eight cohort and 34 case–control designs [The Working Group noted that, unlike other meta-analyses, this included studies where the assessment of *H. pylori* status included non-serological methods.] The summary odds ratio was 2.04 (95%CI: 1.69–2.45). Cancer subsite (non-cardia vs cardia) was not a significant effect modifier. There was statistically significant heterogeneity between studies, but no evidence of publication bias.

A more recent meta-analysis focused on 16 seroprevalence studies of CagA and gastric cancer, which included a total of 2284 cases and 2770 controls from diverse geographic populations ([Huang et al., 2003](#)). Overall, ten studies provided results stratified by subsite of the tumour. Evidence of *H. pylori* infection was associated with a 2.71-fold risk of developing non-cardia gastric cancer. Because antibodies against CagA may persist longer than antibodies against other *H. pylori* components normally detectable by *H. pylori* status serology, the risk of cancer in patients who were CagA-positive but *H. pylori*-negative was also evaluated. Compared with controls who were both *H. pylori*-negative and CagA-negative, the summary odds ratio of gastric cancer (non-cardia and cardia combined) was 2.89.

(e) *Impact of H. pylori CagA status*

Many of the nested case–control studies identified above reported odds ratios for the risk of gastric carcinoma associated with infection with CagA-positive strains of *H. pylori* to see if disease was exclusively or predominantly associated with this genotype. In the meta-analysis by [Huang et al. \(2003\)](#), the analysis confined to *H. pylori*-positive cases and controls showed an additional risk of 2.01 (95%CI: 1.21–3.32) associated with CagA-positive strains.

Eight of the nested case–control studies have reported separately on results relating to CagA status ([Parsonnet et al., 1997](#); [Nomura et al., 2002a, 2005](#); [Gwack et al., 2006](#); [Kamangar et al., 2006a, 2007](#); [Sasazuki et al., 2006](#); [Palli et al., 2007](#); [Simán et al., 2007](#)). Five of these studies compared adjusted odds ratios for non-cardia gastric carcinoma in subjects with both CagA-positive and -negative infection status against a baseline of *H. pylori*-negative subjects. The reported odds ratios were, respectively, 5.8 vs 2.2 ([Parsonnet et al., 1997](#)), 8.93 vs 6.55 ([Kamangar et al., 2006a](#)), 6.5 vs 1.6 ([Palli et al., 2007](#)), 12.5 vs 9.5 ([Sasazuki et al., 2006](#)), and 1.58 vs 1.62 ([Kamangar et al., 2007](#)). Thus, in 4/5 studies, the odds ratio associated with CagA-positive infection was substantively greater than that for CagA-negative infection. One other study ([Gwack et al., 2006](#)), in an analysis restricted to *H. pylori*-infected individuals, reported a statistically significant increased odds ratio in relation to CagA-positive status of 3.74 (95%CI: 1.10–12.73) compared with CagA-negative status, even though the risk associated with *H. pylori* *per se* was not significant ([Shin et al., 2005](#)). In the other two nested case–control studies reporting on CagA-positive status ([Nomura et al., 2002a](#); [Simán et al., 2007](#)), odds ratios were decreased in comparison with those for *H. pylori* infection alone.

(f) *Impact of H. pylori eradication*

Results are available from six randomized intervention studies in which the subsequent risk of gastric carcinoma or gastric precancerous lesions has been evaluated in *H. pylori*-infected adult subjects who were randomized to receive *H. pylori* eradication therapy or placebo/no treatment (see Table 2.3 available at <http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.3.pdf>). Only one study (Wong *et al.*, 2004) was specifically designed to analyse gastric carcinoma outcomes. A total of 1630 *H. pylori* positive subjects undergoing endoscopy were followed up for a mean of 7.5 years after being randomized to eradication therapy ($n = 817$) or placebo ($n = 813$). The therapy was successful in eradicating the infection in 84% of subjects in the intervention arm. There were 7 (0.86%) and 11 (1.35%) incident cases of gastric carcinoma diagnosed in the intervention and placebo arms respectively, a non-significant difference ($P = 0.33$). A *post-hoc* subgroup analysis of subjects with no precancerous lesions at recruitment showed 0 (0.0%) and 6 (1.2%) incident cases in the intervention and placebo arms ($P = 0.02$) [The Working Group viewed the design of this study to be underpowered to assess adequately the relationship between eradication and gastric carcinoma outcomes.]

Three studies (Leung *et al.*, 2004; Mera *et al.*, 2005; You *et al.*, 2006) were designed to analyse changes in precancerous histological pathology as the primary end-point but also reported results for gastric carcinoma outcomes. These studies respectively randomized 587, 795 and 2258 *H. pylori*-positive subjects to receive eradication therapy or placebo. In the intervention and placebo arms of the three studies, during follow-up, there were four and six, three and two, and 19 and 27 incident cases of gastric carcinoma diagnosed, respectively. None of these associations was statistically significant. In terms of progression or regression of precancerous pathology

compared with baseline, all three studies showed a statistically significant benefit in the intervention arms as did a further intervention study (Ley *et al.*, 2004) of 248 subjects which did not specifically report on gastric carcinoma as an outcome.

Fukase *et al.* (2008) reported a study of 544 *H. pylori*-positive patients who were all diagnosed with early gastric carcinoma, and underwent endoscopic mucosal resection and were followed up for a mean of three years after being randomized to eradication therapy ($n = 272$) or standard care ($n = 272$). There were 9 (3.3%) and 24 (8.8%) incident metachronous cases of gastric carcinoma diagnosed in the intervention and placebo arms respectively, a statistically significant difference (hazard ratio [HR], 0.35; 95%CI: 0.16–0.78). In an earlier non-randomized study (Uemura *et al.*, 1997), 132 *H. pylori* positive patients, 44–85 years of age, diagnosed with early gastric carcinoma and treated with endoscopic mucosal resection, were followed up for two years after 65 patients received eradication therapy, and 67 did not. There were no gastric carcinomas in the intervention group and six (9%) in the control group. [The Working Group viewed these two latter studies as not applicable to populations outside Japan.]

(g) *Synthesis*

Since the previous *Monograph*, a substantial number of prospective observational studies, both nested case-control and cohort, had provided results supportive of an association between *H. pylori* infection and non-cardia gastric carcinoma. The magnitude of the risk is increased when more sensitive assay procedures are used and there appears to be a stronger association with CagA-positive strains of *H. pylori*. Results from randomized studies have not had sufficient power to evaluate the effect of the impact of *H. pylori* eradication on gastric carcinoma risk.

2.1.2 Cardia gastric carcinoma

Results are available from ten prospective cohort studies with nested case–control designs. These are summarized in Table 2.4 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.4.pdf>).

(a) Nested case–control analyses within cohort studies

The pooled reanalysis ([Helicobacter and Cancer Collaborative Group, 2001](#)) presented results based on 274 cases of cardia gastric carcinoma and 827 control subjects derived from 12 independent prospective cohort studies in nine countries (the United Kingdom, Finland, Sweden, Norway, Iceland, USA, Taiwan (China), and Japan) analysed using a nested design. Cases were matched to controls on the basis of study, sex, age and date of blood sample collection but no further adjustment in the analysis was possible. In all studies, *H. pylori* infection status was determined by a conventional ELISA for IgG antibodies against *H. pylori*. The overall matched odds ratio for the risk of cardia gastric carcinoma was 0.99 (95%CI: 0.72–1.35). Odds ratios for individual studies varied from 0.40–1.77.

Five of the individual studies included in the pooled reanalysis accrued more cases, and updated results have since been published ([Kamangar et al., 2006a, 2007](#); [Knekt et al., 2006](#); [Hansen et al., 2007](#); [Simán et al., 2007](#)). Odd ratios showed a statistically significant reduced risk (0.27 and 0.31) in two studies, no significant difference from unity in two further studies (0.82 and 1.5), and a significantly increased risk in one study (1.64).

New results were reported from four further prospective studies with nested case–control designs ([Shin et al., 2005](#); [Sasazuki et al., 2006](#); [Palli et al., 2007](#); [Mitchell et al., 2008](#)). Using ELISA for IgG status to determine *H. pylori* infection status, odds ratios for cardia gastric

carcinoma varied from 0.8–3.7 but none was statistically significant.

In the pooled reanalysis ([Helicobacter and Cancer Collaborative Group, 2001](#)) when the results were stratified by period of follow-up, the odds ratio for gastric carcinoma with cases diagnosed less than 10 years after recruitment was 1.23 (95%CI: 0.86–1.75), and for those with cases diagnosed 10 or more years after recruitment, 0.46 (95%CI: 0.23–0.90). A similar relationship in the magnitude of the odds ratio with period of follow-up was reported in one of the updated studies ([Kamangar et al., 2006a](#)), but not in another ([Kamangar et al., 2007](#)).

In the pooled reanalysis ([Helicobacter and Cancer Collaborative Group, 2001](#)), no substantive difference in the odds ratios between men (0.98; 95%CI: 0.68–1.40) and women (1.03; 95%CI: 0.55–1.92) was observed. There was, however, a difference between gastric carcinoma with intestinal (0.42; 95%CI: 0.24–0.75) and diffuse (0.93; 95%CI: 0.21–4.10) histological types. [The Working Group noted that this difference was unexplained.]

(b) Meta-analysis

Only one meta-analysis has reported specifically on the risk of cardia gastric carcinoma ([Huang et al., 1998](#)). Based on the results from six studies with several study designs, the summary odds ratio was 0.93 (95%CI: 0.62–1.38), with no significant heterogeneity.

(c) Impact of *H. pylori* CagA status

A meta-analysis ([Huang et al., 2003](#)) including results from both retrospective and prospective studies identified 16 eligible studies, ten of which provided results stratified by cardia subsite location of the tumour. The odds ratio associated with *H. pylori* infection (determined by *H. pylori* seroprevalence) was 1.13 (95%CI: 0.75–1.70); a further analysis, confined to *H. pylori*-positive cases and controls, showed a risk associated with CagA positivity of 0.70 (95%CI: 0.44–1.10).

Three nested case-control studies have reported results in which the risk of cardia gastric carcinoma in relation to CagA-positive and -negative status can be compared. Respectively, these odds ratios were 0.43 and 0.21 ([Kamangar et al., 2006a](#)), 0.8 and 0.8 ([Palli et al., 2007](#)), and 1.75 and 1.35 ([Kamangar et al., 2007](#)). In the other nested case-control study reporting on CagA-positive status ([Simán et al., 2007](#)), an increased odds ratio of 2.3 in comparison with that for *H. pylori* infection alone (OR, 1.3) was reported.

[The Working Group noted that there are substantial difficulties in the reliability of classification of cardia gastric carcinoma. Some studies may be more inclusive of distal non-cardia gastric carcinoma and other studies may be more inclusive of lower oesophageal adenocarcinoma cases, which may lead to variability of outcome between studies.]

2.2 Gastric mucosa-associated lymphoid tissue (MALT) lymphoma

Results are available from one prospective cohort study with a nested case-control design and one retrospective case-control study. These are summarized in Table 2.5 available at <http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.5.pdf> and Table 2.6 available at <http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.6.pdf>.

2.2.1 Nested case-control analysis within a cohort study

[Parsonnet et al. \(1994\)](#) analysed a database of 33 cases of gastric non-Hodgkin lymphoma and 132 matched controls. *H. pylori* infection status was determined by ELISA for IgG antibodies and the odds ratio for risk of gastric non-Hodgkin lymphoma was 6.3 (95%CI: 2.0–19.9).

For low-grade MALT lymphoma, the odds ratio was 2.8 (95%CI: 0.2–28.5).

2.2.2 Case-control study

A study from Spain ([de Sanjosé et al., 2004](#)) compared ten cases of gastric lymphoma (four gastric MALT) with matched hospital controls. *H. pylori* infection status was determined by ELISA for IgG antibodies, the odds ratio for the risk of both gastric lymphoma and gastric MALT was infinity (all cases infected).

2.2.3 Impact of *H. pylori* eradication

A total of 16 uncontrolled studies ([Wotherspoon et al., 1993](#); [Stolte et al., 1994](#); [Bayerdörffer et al., 1995](#); [Neubauer et al., 1997](#); [Pinotti et al., 1997](#); [Savio et al., 2000](#); [Chen et al., 2001, 2005](#); [Fischbach et al., 2004](#); [Nakamura et al., 2005, 2008](#); [Wündisch et al., 2005](#); [Hong et al., 2006](#); [El-Zahabi et al., 2007](#); [Terai et al., 2008](#); [Stathis et al., 2009](#)) reported on the effect of *H. pylori* eradication therapy on B-cell MALT gastric lymphoma regression (see Table 2.7 available at <http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.7.pdf>). In all studies, the eradication rates were very high (in general over 94%), and were accompanied by high rates of complete remission of the MALT lymphoma (62–100%). Where assessed, remission was more strongly associated with the successfully treated patients. Subsequent relapse rates, where reported, were in the order of 10% over the 1–3 year follow-up periods. [The Working Group recognized that these results made it unlikely that ethics committees would approve randomized intervention studies on the effect of *H. pylori* eradication on MALT regression.]

2.2.4 Synthesis

Despite the small number of observational studies of B-cell lymphoma in relation to *H. pylori* infection, evidence from the eradication studies

is critically important. Treatment of patients to eradicate *H. pylori* is strongly associated with remission of low-grade lymphomas. Therefore, infection with *H. pylori* causes low-grade B-cell MALT gastric lymphoma in humans.

2.3 Cancer of the oesophagus

2.3.1 Oesophageal adenocarcinoma

Results are available from two prospective cohort studies with nested case-control designs, 15 retrospective case-control studies, and three meta-analyses.

(a) Cohort studies

Two studies ([de Martel et al., 2005](#); [Simán et al., 2007](#)) analysed a database of 51 and 12 cases of oesophageal adenocarcinoma, respectively, and reported adjusted odds ratios of 0.37 (95%CI: 0.16–0.88) and 0.46 (95%CI: 0.07–2.6) respectively (see Table 2.8 available at <http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.8.pdf>). Analysis for CagA-positive infection status did not substantially modify these results. Both studies adjusted for smoking but only the former adjusted for body mass index [The Working Group noted that this is a potential confounder for this type of cancer.]

(b) Case-control studies

Among the available studies, four were population-based ([El-Omar et al., 2003](#); [Wu et al., 2003](#); [Ye et al., 2004](#); [Anderson et al., 2008](#)). Two studies ([Ye et al., 2004](#); [Anderson et al., 2008](#)) reported significantly reduced odds ratios of 0.3 and 0.38, respectively. The other two studies ([El-Omar et al., 2003](#); [Wu et al., 2003](#)) reported odds ratios that were not significantly different from unity; however, the odds ratios associated with CagA positivity decreased to 0.82 and 0.33, respectively, with the latter being statistically significant.

Three studies ([Wu et al., 2003](#); [Ye et al., 2004](#); [Anderson et al., 2008](#)) adjusted for body mass index, and all of them adjusted for other potential confounders. One further hospital-based study ([Früh et al., 2008](#)) that used friends and spouses as controls reported an odds ratio of 0.71 (0.95%CI: 0.4–1.0) for *H. pylori* infection, with borderline statistical significance after adjustment for confounders including body mass index.

Nine other case-control studies were based on comparisons within clinical patient groups and all reported odds ratios that were either significantly reduced or not significantly different from unity (see Table 2.9 available at <http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.9.pdf>).

(c) Meta-analyses

A meta-analysis ([Islami & Kamangar, 2008](#)) reviewed the results from 13 studies (2 prospective and 11 retrospective case-control studies) of oesophageal adenocarcinoma. A comparison of 840 cases with 2890 controls and an assessment of *H. pylori* infection status mainly by ELISA resulted in a summary odds ratio of 0.56 (95%CI: 0.46–0.68). There was no statistically significant heterogeneity between studies, and no evidence of publication bias. Sensitivity analyses to include only large studies or only population-based studies or similar methods for assessment of infection did not substantially modify the odds ratio. Five studies included comparisons of CagA-positive and -negative strain status against *H. pylori*-negative subjects, and for these, the summary odds ratios were 0.41 (95%CI: 0.28–0.62) and 1.08 (95%CI: 0.76–1.53), respectively.

Two further meta-analyses ([Rokkas et al., 2007](#); [Zhuo et al., 2008](#)), which included fewer studies, also reported a significant decrease in risk with both *H. pylori* and CagA positivity (see Table 2.10 available at <http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.10.pdf>).

(d) Synthesis

The observational epidemiological studies are all consistent in showing a lack of association between *H. pylori* infection and an increased risk of oesophageal adenocarcinoma. Several of these studies as well as the meta-analyses show a statistically significant reduced risk of oesophageal cancer.

2.3.2 Oesophageal squamous cell carcinoma

Results are available from two prospective cohort studies with nested case–control designs, five retrospective case–control studies, and three meta-analyses.

(a) Cohort studies

Two studies ([Kamangar et al., 2007](#); [Simán et al., 2007](#)) analysed a database of 300 and 37 cases of oesophageal squamous cell carcinoma respectively. The adjusted odds ratios for *H. pylori* infection were 1.17 (95%CI: 0.88–1.57) and 0.56 (95%CI: 0.24–1.3), respectively. CagA infection status did not substantially modify these results (see Table 2.11 available at <http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.11.pdf>).

(b) Case–control studies

Four studies were population-based ([El-Omar et al., 2003](#); [Wang et al., 2003a](#); [Ye et al., 2004](#); [Wu et al., 2005](#)). One of these (El Omar et al., 2003) included 53 cases and reported a statistically significant increased odds ratio of 2.11; another study ([Wu et al., 2005](#)) included 127 cases and reported a significantly reduced odds ratio of 0.51. The other two studies ([Wang et al., 2003a](#); [Ye et al., 2004](#)) included 63 and 85 cases, respectively, and reported odds ratios not significantly different from unity. The studies all adjusted for age and sex but differed in the extent of adjustment for other confounding factors. Only one study ([Wu et al., 2005](#)) adjusted for alcohol consumption. One hospital-based study ([Iijima](#)

[et al., 2007](#)) reported a non-significantly increased odds ratio of 1.40 (95%CI: 0.62–3.15 [calculated by the Working Group]) (see Table 2.12 available at <http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.12.pdf>).

(c) Meta-analyses

One meta-analysis ([Islami & Kamangar, 2008](#)) reviewed results from nine studies (two prospective and seven retrospective case–control studies) of oesophageal squamous cell carcinoma. A comparison of 921 cases of oesophageal squamous cell carcinoma with 2743 controls and an assessment of *H. pylori* infection status mainly by ELISA resulted in a summary odds ratio of 1.10 (95%CI: 0.78–1.55). There was statistically significant heterogeneity between studies, but no evidence of publication bias. Sensitivity analyses to include only large studies or only population-based studies or similar methods for assessment of infection did not substantially modify the risk. Four studies included comparisons of CagA-positive and -negative strain status against *H. pylori*-negative subjects: the meta-relative risks were 1.01 (95%CI: 0.80–1.27) and 1.41 (95%CI: 1.00–1.97), respectively. Two further meta-analyses ([Rokkas et al., 2007](#); [Zhuo et al., 2008](#)), which included fewer studies, reported similar results (see Table 2.13 available at <http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.13.pdf>).

(d) Synthesis

The Working Group concluded that there was little evidence of an association between *H. pylori* infection and the risk of oesophageal squamous cell carcinoma.

2.4 Other cancers

2.4.1 Cancer of the liver

(a) Hepatocellular carcinoma

Results are available from 17 retrospective case–control studies, and a meta-analysis.

Two studies, based on 46 and 11 cases and using ELISA to detect IgG antibodies to *H. pylori*, showed odds ratios [calculated by the Working Group] that were significantly increased in one study (OR, 3.02; 95%CI: 1.12–8.34) (Leone *et al.*, 2003), but not in the other (OR, 2.3; 95%CI: 0.15–15.1) (Dore *et al.*, 2002) (see Table 2.14 available at <http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.14.pdf>). No adjustment was carried out for potential confounders. All the other studies used PCR assays of liver biopsy samples from cases and controls to detect the presence of *Helicobacter* species (see Table 2.15 available at <http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.15.pdf>). The primers used for the PCR assays (16S rDNA primers) were for genes associated with the *Helicobacter* genus but were not specific for *H. pylori*. In some of the studies, DNA from a subsample of positive samples was sequenced, and found to be specific for *H. pylori*. A higher proportion of positive results in 13/15 studies were observed among cases when compared to controls. Cases numbers were small in all studies, the largest having 48 cases, and studies varied in the extent to which they adjusted for potential confounding factors.

[The Working Group noted the small size of these studies, the potential problems of specificity associated with PCR assays, the use of opportunistic control series selected from patient groups, and the lack of adjustment for potential confounders.]

A meta-analysis (Xuan *et al.*, 2008) reviewed results from ten studies (nine case–control and one cross-sectional) (see Table 2.16 available at <http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.16.pdf>). A comparison of 242 cases of hepatocellular carcinoma with 280 hospital controls and an assessment of *H. pylori* infection status by PCR on liver biopsy samples resulted in a summary odds ratio of 13.63 (95%CI: 7.90–23.49). [The Working Group were concerned about the comparability of studies within this

meta-analysis as a wide variety of control groups and methodologies were employed.]

(b) *Cholangiocarcinoma*

A review (de Martel *et al.*, 2009) summarized results from eight studies in which PCR was used to detect the presence of *Helicobacter* species in bile or tissue biopsies from patients with biliary tract cancers and controls usually with benign biliary tract diseases (see Table 2.17 available at <http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.17.pdf>). The primers used for the PCR assays were not specific for *H. pylori*. In 2/8 studies, none of the cases was reported as positive but the other six studies all showed a higher proportion of positive results in cases compared to controls. None of these studies included more than 20 cases.

[The Working Group noted the small size of these studies, the potential problems of specificity associated with PCR assays, the use of opportunistic control series selected from patient groups, and the lack of adjustment for potential confounders.]

2.4.2 *Cancer of the colorectum*

Results are available from two prospective cohort studies with a nested case–control design, 12 retrospective case–control studies, and one meta-analysis.

(a) *Nested case–control analyses with cohort studies*

Two studies (Thorburn *et al.*, 1998; Limburg *et al.*, 2002) were based on 233 and 118 cases of colorectal cancer associated with *H. pylori* infection, and reported non-significant adjusted odds ratios of 0.9 (95%CI: 0.5–1.5) and 1.05 (95%CI: 0.63–1.74), respectively, associated with *H. pylori* infection (see Table 2.18 available at <http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.18.pdf>). CagA-positive infection status

did not influence the latter result, and was not tested for in the former study.

(b) Case-control studies

Out of 11 studies, three ([Hartwich et al., 2001](#); [Machida-Montani et al., 2007](#); [Zumkeller et al., 2007](#)) were population-based (see Table 2.19 available at <http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.19.pdf>). Two of these ([Hartwich et al., 2001](#); [Zumkeller et al., 2007](#)), based on 80 and 384 cases, respectively, reported statistically significant odds ratios of 3.78 and 1.41, respectively, for colorectal cancer associated with *H. pylori* infection. The third study ([Machida-Montani et al., 2007](#)) included 121 cases, and reported no significant risk. CagA-positive status did not affect the observed risk. Three studies ([Moss et al., 1995](#); [Fireman et al., 2000](#); [Siddheshwar et al., 2001](#)) were based within colonoscopy clinics, and included 41, 51 and 189 cases, respectively, with adjusted odds ratios for colorectal cancer associated with *H. pylori* infection reported to be between 0.74–2.43, none of which statistically significant. One other colonoscopy clinic study ([Fujimori et al., 2005](#)) included 154 cases of adenocarcinomas, and reported a statistically significant odds ratio of 1.8.

Four studies were hospital-based ([Penman et al., 1994](#); [Meucci et al., 1997](#); [Shmueli et al., 2001](#); [D'Onghia et al., 2007](#)), and did not adjust for any potential confounders.

(c) Meta-analysis

A meta-analysis ([Zumkeller et al., 2006](#)) reviewed results from 11 studies (two prospective and nine retrospective case-control studies) (see Table 2.20 available at <http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.20.pdf>). A total of 899 cases of colorectal cancer were compared with 1476 controls; *H. pylori* infection status was assessed by ELISA in ten studies and by urea breath test in one study. The resulting meta-relative risk was 1.4 (95%CI: 1.1–1.8). The

meta-relative risk for the 2 prospective studies was 1.0 (95%CI: 0.8–1.4).

2.4.3 Cancer of the pancreas

[Nilsson et al. \(2002\)](#) analysed pancreatic biopsy specimens from patients undergoing surgery for possible pancreatic cancer to detect the presence of *Helicobacter* species and *H. pylori* by bacterial culture, PCR, and DNA sequencing. Five of six pancreatic ductal carcinomas and one malignant neuroendocrine cancer were positive for *Helicobacter* species by PCR with genus-specific primers; however, none of the five was positive for *H. pylori* by PCR with genus-specific primers. Two of the 16S rDNA PCR fragments were sequenced and compared with the GenBank database by a BLAST search (www.ncbi.nlm.nih.gov). One of those was 98% similar to the 16S rDNA of *Helicobacter* species liver 3, clustering to a phylogenetic group that includes *H. pylori*. The other was 99% similar to *H. pullorum*, and clustered to a phylogenetic group that also contains *H. bilis*.

Results are available from three informative prospective cohort studies with nested case-control designs, and one retrospective case-control study.

Two of the three prospective cohort studies ([de Martel et al., 2008](#); [Lindkvist et al., 2008](#)) based on 104 and 87 cases, respectively, of pancreatic cancer associated with *H. pylori* infection reported non-significant odds ratios of 0.85 (95%CI: 0.49–1.48) and 1.25 (95%CI: 0.75–2.09), respectively. The third study ([Stolzenberg-Solomon et al., 2001](#)) reported an odds ratio of 1.87 (95%CI: 1.05–3.34) for *H. pylori* seropositivity. CagA-positive infection status did not influence any of these results. All studies adjusted for age, sex, and smoking (see Table 2.21 available at <http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.21.pdf>).

The retrospective case-control study ([Raderer et al., 1998](#)) included 92 cases of pancreatic

cancer. The odds ratio for the risk of pancreatic cancer associated with *H. pylori* infection was 2.1 (95%CI: 1.1–4.1) (see Table 2.22 available at <http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.22.pdf>).

2.4.4 Cancer of the lung

Results are available from four retrospective case–control studies (see Table 2.23 available at <http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.23.pdf>).

Two retrospective case–control studies (Gocyk *et al.*, 2000; Ece *et al.*, 2005) included 50 and 43 cases of lung cancer, respectively, and showed statistically significant associations with *H. pylori* infection with odds ratios [estimated by the Working Group] of 5.06 and 13.33, respectively. The first study was not adjusted for smoking, and the second included only smokers. Two other studies (Philippou *et al.*, 2004; Najafizadeh *et al.*, 2007) included 72 and 40 cases of lung cancer, respectively, and neither showed a statistically significant association with *H. pylori* infection. [The Working Group noted that none of these four studies was adequately adjusted for smoking.]

2.4.5 Cancer of the head and neck

Results are available from four retrospective case–control studies (see Table 2.24 available at <http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.24.pdf>). The studies varied slightly in their case definitions. One (Grandis *et al.*, 1997) included 21 cases of squamous cell carcinomas of the head and neck and the odds ratio for *H. pylori* infection was 0.82 (95%CI: 0.24–2.76). A second study among smokers (Aygenç *et al.*, 2001) included 26 cases of squamous cell laryngeal cancers and the odds ratio for *H. pylori* infection [estimated by the Working Group] was 3.97 (95%CI: 1.32–11.89). A third study (Rubin *et al.*, 2003) included 55 cases

of squamous cell cancer of the upper aerodigestive tract (excluding oesophagus) and six cases of laryngeal severe dysplasia, and the odds ratio for *H. pylori* infection [estimated by the Working Group] for the risk of cancer/severe dysplasia was 1.86 (95%CI: 1.03–3.35). The final study (Nurgalieva *et al.*, 2005) included 119 cases of squamous cell carcinoma of the laryngopharynx, and the adjusted odds ratio for *H. pylori* infection was 1.27 (95%CI: 0.70–2.29).

2.4.6 Childhood leukaemia

One prospective cohort study (Lehtinen *et al.*, 2005) with a nested case–control design compared 341 children with acute lymphocytic leukaemia and 61 with other leukaemias with 1212 matched controls (see Table 2.25 available at <http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.25.pdf>). *H. pylori* infection status was determined on maternal serum samples (first trimester) by ELISA for IgG and IgM antibodies. The adjusted odds ratio for risk of all leukaemias combined was 1.0 (95%CI: 0.8–1.2) for IgG antibodies. Results for IgM antibodies or specifically for acute lymphoblastic leukaemia did not differ substantially.

2.5 Cofactors

Two studies have found an effect modification between smoking, *H. pylori* infection, and gastric carcinoma (Zaridze *et al.*, 2000; Brenner *et al.*, 2002). Zaridze *et al.* (2000) reported on the relative risk of gastric cancer associated with smoking by *H. pylori* status. Among men, the odds ratio for ever smoking compared to never smoking among *H. pylori* negatives was 1.0 (95%CI: 0.5–2.1), and ever smoking compared to never smoking among *H. pylori* positives was 2.3 (95%CI: 1.1–4.7), with a $P = 0.07$ for the effect modification between smoking and *H. pylori*.

Brenner *et al.* (2002) evaluated the individual and joint association of smoking and *H. pylori*

infection as well as CagA-positive *H. pylori* infection. The adjusted relative risk of gastric cancer was 2.6 (95%CI: 1.2–5.7) for CagA-positive *H. pylori* infection in non-smokers compared to uninfected non-smokers, and CagA-positive *H. pylori*-infected smokers had a relative risk of 7.2 (95%CI: 2.2–23.6). When analyses were restricted to non-cardia gastric cancer, the corresponding estimates of relative risk were 6.1 (95%CI: 2.3–16.5) for CagA-positive non-smokers and 16.6 (95%CI: 4.3–67.2) for CagA-positive smokers. Not all studies found this effect. [Machida-Montani et al. \(2004\)](#) found gastric cancer risk associated with smoking and dietary factors to be independent of risk associated with *H. pylori* infection.

Plasma levels of vitamin C are inversely associated with gastric cancer risk for both cardia and non-cardia, diffuse, and intestinal subsites. Vitamin C plasma levels showed no effect modification with *H. pylori* infection ([Jenab et al., 2006](#)). [Ekström et al. \(2000\)](#), however, found an effect modification on non-cardia gastric carcinoma risk by dietary intake of ascorbic acid, β -carotene, and α -tocopherol by *H. pylori* infection status. There was little or no association of these antioxidants in *H. pylori*-negative subjects, but 30–70% reductions in the relative risk of non-cardia gastric carcinoma in *H. pylori*-positive subjects were observed with dietary intake increments of 50 mg/day of ascorbic acid, 3.0 mg/day β -carotene or 8.0 mg/day of α -tocopherol.

A significant effect modification between *H. pylori* infection and salted, smoked foods and processed meat has been observed ([Phukan et al., 2006](#); [Shikata et al., 2006](#); [Epplein et al., 2008](#)). Two studies from East Asia have correlated dietary salt intake with an increased risk of non-cardia gastric cancer over and above that attributable to *H. pylori* alone ([Lee et al., 2003](#); [Shikata et al., 2006](#)).

In two recent studies, diets rich in fresh vegetables [and therefore high in antioxidants] intake were shown to be specially beneficial in reducing non-cardia gastric cancer risk among

those who are *H. pylori* infected ([Ekström et al., 2000](#); [Epplein et al., 2008](#)).

[Ekström et al. \(1999\)](#) found that risk of gastric cancer associated with *H. pylori* infection was independent of risk associated with specific occupational exposures.

3. Cancer in Experimental Animals

3.1 Mongolian gerbil

The first report of gastric cancer induced by *H. pylori* in an animal model was published by [Watanabe et al. \(1998\)](#). The authors infected Mongolian gerbils (*Meriones unguiculatus*) with *H. pylori* strain TN2GF4, and observed the gastric lesions after 62 weeks. Gastric adenocarcinomas were detected in 10/27 infected animals vs 0/30 controls.

The Mongolian gerbil model infected with *H. pylori* has been cited in seven other publications ([Honda et al., 1998](#); [Hirayama et al., 1999](#); [Zheng et al., 2004](#); [Elfvin et al., 2005](#); [Franco et al., 2005, 2008](#); [Romero-Gallo et al., 2008](#)), and all except one ([Elfvin et al., 2005](#)) reported gastric adenocarcinoma developments. They developed late in the animals' lives (62–90 weeks) except in three studies ([Franco et al., 2005, 2008](#); [Romero-Gallo et al., 2008](#)) where the development was extremely rapid (8–12 weeks).

It is noteworthy that in other experiments using chemical carcinogens in Mongolian gerbils and where *H. pylori*-infected animals were used as controls, none of the controls developed gastric cancer ([Sugiyama et al., 1998](#); [Tokieda et al., 1999](#); [Shimizu et al., 1999](#); [Nozaki et al., 2002](#); [Kato et al., 2006](#)) with a follow-up of 40–53 weeks, or in the study of [Cao et al. \(2007\)](#) despite a follow-up of 70 weeks.

These results indicate that the Mongolian gerbil is not the most reliable model for the development of gastric adenocarcinomas even after a long follow-up. The reason could be linked to the animal strain used. Mongolian gerbils were first bred in Japan, then exported to the USA,

and later to Europe. The genetic background of the animals may have evolved differently among the different colonies. The *H. pylori* strain used may also be the cause of these discrepant results. Two strains were essentially used (ATCC 43 504 and TN2GF4) but when [Franco et al. \(2005\)](#) used a Mongolian gerbil adapted strain (7.13) derived from the parent strain B128, they observed gastric adenocarcinomas in 59% of the animals. The high susceptibility of this strain was confirmed in two further studies by [Franco et al. \(2008\)](#) and [Romero-Gallo et al. \(2008\)](#). Another variable is the criteria used for grading the observed pathology. This point was raised by [Elfvin et al. \(2005\)](#) who published a negative result. Furthermore, in the Mongolian gerbil model, no metastasis was reported nor did any gerbil die of gastric carcinoma.

The limitation of this model led to test the impact of *H. pylori* infection in Mongolian gerbils receiving well known chemical carcinogens, e.g. *N*-methyl-*N*-Nitrosourea or *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine at different concentrations. Eight studies used such a design and in all of them, there was a synergistic effect of *H. pylori* infection on the incidence of gastric carcinomas compared to the incidence observed after treatment with the carcinogen alone.

In some studies gerbils were infected with *H. pylori* and then treated also with a chemical carcinogen to test the action of pharmacological agents such as a cyclooxygenase 2 inhibitor (etodolac) ([Magari et al., 2005](#)), and an antioxidative and anti-inflammatory compound (canolol) ([Cao et al., 2008](#)), both of which have a protective effect. The impact of a salty diet was also tested in two studies ([Nozaki et al., 2002](#); [Kato et al., 2006](#)), and a synergy between *H. pylori* infection and a high-salt diet was observed. [Romero-Gallo et al. \(2008\)](#) and [Nozaki et al. \(2003\)](#) showed the benefit of an early eradication using clarithromycin-based triple therapy, which decreased the gastric cancer incidence.

See [Table 3.1](#).

3.2 Mouse

3.2.1 Inbred mouse

The progression of the gastric lesions after *H. pylori* infection has also been observed in inbred mice, C57BL/6 and BALB/c. Despite a long follow-up of 80 and 100 weeks by [Kim et al. \(2003\)](#) and [Wang et al. \(2003b\)](#), respectively, no gastric adenocarcinoma occurred, only gastric lymphoma in the latter. When C57BL/6 mice crossed with 12996/SvEv mice were infected by *H. pylori* and submitted to a high-salt diet, high-grade dysplasia occurred but not adenocarcinoma ([Rogers et al., 2005](#)).

In a study where C57BL/6 mice infected with *H. felis* received an eradication treatment after different time periods, [Cai et al. \(2005\)](#) observed adenocarcinomas in all untreated infected animals after 24 months, no adenocarcinomas if the treatment was given after 2 or 6 months of infection, and a decrease in the incidence of adenocarcinomas if the treatment was delayed to the 12th month.

3.2.2 Transgenic mouse

The first model (of five transgenic models) used transgenic mice deficient for TGF- β infected with *H. pylori*. Gastric adenocarcinoma or dysplasia developed in 85.7% of the mice after 36 weeks ([Hahm et al., 2002](#)).

The second model involves transgenic mice overexpressing gastrin (INS-GAS mice). A first study showed that infection of INS-GAS male mice with *H. pylori* strain SS1 could induce gastric adenocarcinoma in 4/6 male animals within 30 weeks ([Fox et al., 2003a](#)). This finding was repeated in another study (3/7 gastric adenocarcinoma within 28 weeks), and the protective effect of estradiol was shown ([Ohtani et al., 2007](#)). In a study designed to determine the impact of *H. pylori* eradication therapy ([Lee et al., 2008](#)), gastric carcinogenesis was inhibited. In another study where an H2-receptor antagonist

Table 3.1 Studies of gastric cancer in Mongolian gerbils infected by *H. pylori* by gavage with or without modifying agents

Duration Reference	Dosing regimen, strain Gender Animals/group at start	Incidence of tumours	Significance	Comments
62 wk Watanabe et al. (1998)	10 ⁷ CFU <i>H. pylori</i> , TN2GF4 (M) 55, 30 (controls)	Adenocarcinoma: 10/27 cases 0/30 controls	[P=0.0002]	Well differentiated intestinal type cancer of the pyloric region
18 mo Honda et al. (1998)	10 ⁹ CFU <i>H. pylori</i> , ATCC 43 504 (M) 15, 15 (controls)	Adenocarcinoma: 2/5 cases 0/5 controls	[NS]	
23 mo (average) Hirayama et al. (1999)	<i>H. pylori</i> , ATCC 43 504 (M) 56 (total), 3 (controls)	Adenocarcinoma; Carcinoids 12–18 mo: 1/16; 4/16 18–24 mo: 0/14; 3/14 >24 mo: 0/24; 11/26 Controls 0/3; 0/3	[NS]	Carcinoids were found in the fundus region of the stomach
84 wk Zheng et al. (2004)	<i>H. pylori</i> , ATCC 43 504 or <i>H. pylori</i> 161 (M, F) 1: <i>H. pylori</i> ATCC 43 504: n=18 2: <i>H. pylori</i> 161: n=18 3: Controls: n=10	Adenocarcinoma: 1: 1/6 (16.6%) 2: 2/11 (18.2%) 3: 0/10	[NS], Group 1 and 2 vs 3	
18 mo Elfvín et al. (2005)	1: <i>H. pylori</i> , TN2GF4: n=23 2: <i>H. pylori</i> , SS1: n=20 3: Controls: n=18 (M) Interim sacrifices at 3, 6 and 12 mo Group size: 3–10 animals	No adenocarcinoma observed in all 12 groups		[Age of the animals at start is described as 'sixty-seven-week-old', which could be a typo.] Discussion on the interpretation of the pathological findings to conclude adenocarcinoma: the authors conclude that, so far, adenocarcinomas have not yet been shown convincingly to develop in infected gerbils
4 wk, 8 wk or 16 wk Franco et al. (2005)	(M) Experiment 1 A. <i>H. pylori</i> B128: n=16 B. <i>H. pylori</i> 7.13: n=16 Experiment 2 C. <i>H. pylori</i> 7.13: n=116 D. Controls: n=42	Adenocarcinoma: A: 0/16 (8 wk) B: 4 wk: 2/8 (25%), 8 wk: 6/8 (75%) C: 4 wk: 17% [incidence NS], 8 wk: 59% [incidence NS], 16 wk: 59% [incidence NS] D: 0/42	[P<0.0001]; Group B (8 wk) vs D	<i>H. pylori</i> strains 7.13 is gerbil adapted, derived from parent strain B128 (human gastric ulcer strain). Experiment 2 is very likely to be positive at Weeks 8 and 16

Table 3.1 (continued)

Duration Reference	Dosing regimen, strain Gender Animals/group at start	Incidence of tumours	Significance	Comments
14–18 wk Romero-Gallo et al. (2008)	5 × 10 ⁹ CFU <i>H. pylori</i> strain 7.13 1. Eradication therapy at 4 wk post infection with lansoprazole, amoxicillin and clarithromycin, orally, for 2 wk (daily). Sacrifice 8 wk after end of treatment 2. Controls infected for 14 wk 3. Eradication therapy at 8 wk post infection with lansoprazole, amoxicillin and clarithromycin, orally, for 2 wk (daily). Sacrifice 8 wk after end of treatment 4. Controls infected for 18 wk	Adenocarcinoma: 0/8 6/20 (33%) 1/14 (7%) 5/10 (50%)	<i>P</i> =0.01 Group 1 vs 2 <i>P</i> =0.027 Group 3 vs 4	Eradication treatment decreased the carcinoma incidence
12–52 wk Franco et al. (2008)	(M) 1. <i>H. pylori</i> 7.13 (12–16 wk, <i>n</i> =18; 24–30 wk, <i>n</i> =19; 40–52 wk, <i>n</i> =9) 2. <i>H. pylori</i> 7.13 <i>cagA</i> - (12–16 wk, <i>n</i> =18; 24–30 wk, <i>n</i> =20; 40–52 wk, <i>n</i> =17) 3. <i>H. pylori</i> 7.13 <i>vacA</i> - (12–16 wk, <i>n</i> =13; 24–30 wk, <i>n</i> =9; 40–52 wk, <i>n</i> =17) 4. Controls (12–16 wk, <i>n</i> =19; 24–30 wk, <i>n</i> =5; 40–52 wk, <i>n</i> =13)	Adenocarcinoma: 53% [9/17], 50% [9/18], 55% (5/9) 0% (0/18), 0% (0/20), 0% (0/17) 16% (2/13), 37% [3/8], 47.5% (8/17) 0% (0/19), 0% (0/5), 0% (0/13)	[<i>p</i> =0.0003], [NS], [<i>p</i> =0.005] [NS], [NS], [NS], [NS], [NS], [<i>p</i> <0.005]	<i>cagA</i> , cytotoxin-associated gene <i>vacA</i> , vacuolating cytotoxin gene
MNNG (in the drinking-water)				
52 wk Tokieda et al. (1999)	10 ⁹ CFU <i>H. pylori</i> , ATCC 43 504 (M) 1. Controls: <i>n</i> =30 2. <i>H. pylori</i> : <i>n</i> =25 3. MNNG 50 ppm orally (20 wk): <i>n</i> =27 4. MNNG 50 ppm orally (20 wk) + <i>H. pylori</i> : <i>n</i> =25	Adenocarcinoma: 1: 0/20 2: 0/14 3: 3/17 (17.6%) 4: 4/6 (66.7%)	<i>P</i> <0.05, Group 4 vs 3	Group 3: poorly differentiated GC Group 4: well differentiated GC

Table 3.1 (continued)

Duration Reference	Dosing regimen, strain Gender Animals/group at start	Incidence of tumours	Significance	Comments
50 wk Shimizu et al. (1999)	10 ⁸ CFU <i>H. pylori</i> , ATCC 43 504 (M)	Adenocarcinoma:		
	1: MNNG 300 ppm (10 wk) followed by <i>H. pylori</i>	1: 12/27 (44%)	<i>P</i> <0.01, Group 1 vs 2	
	2: MNNG 300 ppm (10 wk) alone	2: 1/19 (5.3%)		
	3: MNNG 60 ppm (10 wk) followed by <i>H. pylori</i>	3: 6/27 (24%)	<i>P</i> <0.05, Group 3 vs 4	
	4: MNNG 60 ppm (10 wk) alone	4: 0/20		
	5: <i>H. pylori</i> followed by MNNG 100 ppm (30 wk)	5: 4/27 (14.8%)		
	6: MNNG 100 ppm (30 wk) alone	6: 3/18 (16.7%)		
	7: <i>H. pylori</i> followed by MNNG 20 ppm (30 wk)	7: 15/25 (60%)	<i>P</i> <0.001, Group 7 vs 8	
	8: MNNG 20 ppm (30 wk) alone	8: 1/19 (5%)		
	9: <i>H. pylori</i> alone	9: 0/20		
	10: Controls	10: 0/20		
MNU (in the drinking water)				
40 wk Sugiyama et al. (1998)	10 ⁹ CFU <i>H. pylori</i> , ATCC 43 504 (M)	Adenocarcinoma:		
	Experiment 1 (18–20/group)			
	A. <i>H. pylori</i> followed by MNU 10 ppm (20 wk)	A: 7/19 (36.8%)	<i>P</i> <0.01, Group A vs B	
	B. MNU 10 ppm (20 wk) alone	B: 0/18		
	C. <i>H. pylori</i> followed by MNU 3 ppm (20 wk)	C: 1/20 (5%)		
	D. MNU 3 ppm (20 wk) alone	D: 0/18		
	Experiment 2			
	E. MNU 30 ppm (6 wk) followed by <i>H. pylori</i>	E: 6/18 (33.3%)	<i>P</i> <0.05, Group E vs F	
	F. MNU 30 ppm (6 wk) alone	F: 0/18		
	G. MNU 10 ppm (10 wk) followed by <i>H. pylori</i>	G: 1/19 (5.3%)	<i>P</i> <0.005, Group 1 vs 3	
	H. MNU 10 ppm (10 wk) alone	H: 0/20	NS; Group 2 vs 4	
	I. Control: <i>H. pylori</i>	I: 0/17		

Table 3.1 (continued)

Duration Reference	Dosing regimen, strain Gender Animals/group at start	Incidence of tumours	Significance	Comments
50 wk Nozaki et al. (2002)	10 ⁸ CFU <i>H. pylori</i> , ATCC 43 504 (M) - Groups 1,2,3 & 4 MNU (20 ppm) orally alternate wk for a total of 5 wk - Groups 5,6,7 & 8 Controls <i>H. pylori</i> infection at Week 11 in Groups 1 & 2, 5 & 6 and vehicle in groups 3 & 4, 7 & 8. High salt diet at Week 12 in Groups 1 & 3, 5 & 7 and control diet in Groups 2 & 4, 6 & 8	Carcinoma: 1: 9/28 (32.1%) 2: 2/17 (11.8%) 3: 0/27 4: 0/20 5: 0/11 6: 0/6 7: 0/4 8: 0/4		Synergy between <i>H. pylori</i> infection & high salt diet to promote GC
75 wk Nozaki et al. (2002)	10 ⁸ CFU <i>H. pylori</i> , ATCC 43 504 (M) - Groups A, B, C, D, E MNU (30 ppm) orally alternate wks for a total of 5 wk - Groups A, B, C, D, F <i>H. pylori</i> infection at Week 10 - Groups A, B, C Eradication therapy at Week 5, 25 and 45 post infection with lansoprazole, amoxicillin and clarithromycin, orally - Group G not infected	Carcinoma: A: 1/15 B: 3/11 C: 13/34 D: 9/16 E: 1/16 F: 0/8 G: 0/9	<i>P</i> <0.05 vs C, <i>P</i> <0.005 vs D <i>P</i> <0.05 vs E <i>P</i> <0.005 vs E and G	<i>H. pylori</i> eradication can reduce cancer incidence when given relatively early
53 wk Magari et al. (2005)	3x10 ⁸ CFU <i>H. pylori</i> , ATCC 43 504; MNU: 10 ppm for 24 wk (M) A. <i>H. pylori</i> + MNU B. <i>H. pylori</i> + MNU + etodolac diet (5 mg/kg/d) C. <i>H. pylori</i> + MNU + etodolac diet (10 mg/kg/d) D. <i>H. pylori</i> + MNU + etodolac diet (30 mg/kg/d) E. Control (not infected)	Adenocarcinoma: A: 4/27 (14.8%) B: 8/34 (23.5%) C: 3/34 (8.8%) D: 0/39 E: 0/16	<i>p</i> <0.05, group A and B vs D	Etodolac is a selective cyclooxygenase 2 inhibitor preventing GC induction

Table 3.1 (continued)

Duration Reference	Dosing regimen, strain Gender Animals/group at start	Incidence of tumours	Significance	Comments
50 wk Kato et al. (2006)	<i>H. pylori</i> , ATCC 43 504 (M) 20 groups G1–10: MNU (30 ppm) G11–20: no MNU G1–5 & G11–15: + <i>H. pylori</i> at Week 10 + increasing NaCl concentrations (0%, 2.5%, 5%, 10% in food or a gavage with diet with a saturated salt solution)	Adenocarcinoma: G1: 6/40 (15%) G2: 8/24 (33%) G3: 9/25 (36%) G4: 19/30 (63%) G5: 5/21 (24%) G8: 1/25 (4%) G6, G7, G9, G10–20: 0% (<i>n</i> =7–27)	<i>P</i> for trend <0.01 (Groups G1→G4) <i>p</i> <0.01 (Group G4 vs G1)	
70 wk Cao et al. (2007)	10 ⁸ CFU <i>H. pylori</i> , ATCC 43 504 (M) 8 groups A to H A & E: inoculated at Week 0 B & F: inoculated at Week 12 C & G: inoculated at Week 18 D & H: Controls A, B, C & D received oral MNU (10 ppm) at Week 20 during 20 wk	Adenocarcinoma: A: 13/20 (65%) B: 2/10 (20%) C: 3/13 (23%) D: 0/16 E, F, G, H: 0/6	<i>P</i> <0.01; Group A vs D	
18 wk Cao et al. (2008)	10 ⁸ CFU <i>H. pylori</i> strain ATCC 43 504; (M); MNU: 10 ppm; BHT: used at 0.5 ppm in the diet; Canolol: 0.1% in the diet - Experiment 1: A: <i>H. pylori</i> + Canolol + BHT B: <i>H. pylori</i> + BHT C: <i>H. pylori</i> D: Canolol + BHT E: BHT F: Control - Experiment 2: G: <i>H. pylori</i> + MNU + Canolol + BHT H: <i>H. pylori</i> + MNU + BHT I: <i>H. pylori</i> + MNU + Control diet J: Control + Canolol + BHT	Adenocarcinoma: A to F: 0/58 G: 6/40 (15%) H: 13/33 (39.4%) I: 15/36 (41.7%) J: 0/5	<i>P</i> =0.031 (Group G vs H) <i>P</i> =0.011 (Group G vs I)	Canolol, an antioxidative and anti inflammatory compound, prevents GC induction. BHT is an antioxidant additive No MNU-only treated group

ATCC, American type culture collection; BHT, butylated hydroxytoluene; CFU, colony forming units; d, day or days; F, female; GC, gastric cancer; *H. pylori*, *Helicobacter pylori*; M, male; MNNG, *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine; MNU, *N*-methyl-*N*-nitrosourea; mo, month or months; NS, not significant; vs, versus; wk, week or weeks

(loxitidine) and a CCK-2-receptor antagonist were given for 6 months ([Takaishi et al., 2005](#)), gastric carcinogenesis was also inhibited in *H. felis*-infected animals. [The Working Group noted that no tumour incidences were provided.] Again, in the [Lee et al. \(2008\)](#) study, an early eradication (8 weeks) almost prevented gastric cancer development.

The third model used transgenic p27 deficient mice infected with *H. pylori* strain SS1. Infection and p27-deficiency were synergistic in gastric cancer development ([Kuzushita et al., 2005](#)).

The fourth model used Trefoil factor family 2 (TFF2)-deficient mice, with a B6129Sv strain background, infected with *H. pylori* strain SS1. Gastric adenocarcinomas were observed 19 months after infection ([Fox et al., 2007](#)).

The fifth model used transgenic mice over-expressing IL-1 β . The two lines of mice built infected with *H. felis* developed gastric adenocarcinomas but at a low incidence ([Tu et al., 2008](#)).

3.2.3 Mouse models of gastric MALT lymphoma

Mouse models have been used as models of gastric MALT lymphomas. Gastric lymphomas histologically similar to the low-grade lymphoma observed in humans have been observed in mice infected for about 2 years with *Helicobacter* species, including *H. pylori* and *H. felis*. [Enno et al. \(1995\)](#) infected BALB/c mice with *H. felis*, and observed lymphoepithelial lesions (gastric lymphomas) in 25% of the mice after 22–26 months. Such lesions were observed in both BALB/c and C57BL/6 mice infected with *H. pylori* in the study by [Wang et al. \(2003b\)](#) (see above), and in BALB/c mice infected with *H. felis* ([Sutton et al., 2004](#)). However, the best model corresponds to neonatal thymectomized mice because all animals infected by *H. pylori* developed these lesions within 12 months ([Fukui et al., 2004](#)).

See [Table 3.2](#).

4. Other Relevant Data

It had been well established much before the discovery of *Helicobacter pylori* in 1983 that gastric cancers usually arose in a chronically inflamed stomach. Since the recognition of the role of *H. pylori* infection as the dominant cause of chronic gastritis, affecting approximately half of the world's population, considerable evidence has accumulated that the nature of the chronic inflammatory process driven by *H. pylori* is of critical importance in gastric carcinogenesis.

H. pylori-related gastric carcinogenesis is a slow process, typically developing over 4–6 decades, and accompanied by specific histological changes ([Correa et al., 1975](#)). The 'intestinal' subtype of gastric adenocarcinoma develops through a preneoplastic sequence from chronic superficial gastritis through atrophic gastritis, intestinal metaplasia, and dysplasia. The 'diffuse' subtype is also usually preceded by many years of chronic *H. pylori*-associated gastritis, although the molecular pathways and histological changes involved in progression to cancer are less fully characterized ([Peek & Blaser, 2002](#)).

Investigating the mechanisms responsible for gastric carcinogenesis through studies *in vivo* necessitates investigating simultaneously the effects of the bacterium together with the associated intense neutrophilic and mononuclear inflammatory response, which always accompanies *H. pylori* infection. In contrast, examining direct effects of the bacterium on gastric epithelial cells is only possible in co-culture experiments *in vitro* that are subject to numerous artefacts including the almost universal use of cancer-derived gastric epithelial lines, and the lack of the normal stroma, substrate and cell-cell interactions that exist *in vivo*.

Table 3.2 Studies of gastric cancer in mice infected by *H. pylori* by gavage

Strain Duration Reference	Dosing regimen, strain Gender Animals/group at start	Incidence of tumours	Significance	Comments
Inbred mice				
C57BL/6 80 wk Kim et al. (2003)	10 ⁶ CFU <i>H. pylori</i> , SS1 Gender NR <i>H. pylori</i> : n=25 Controls: n=35	No gastric tumours observed		
C57BL/6 & BALB/c 23 mo Wang et al. (2003b)	<i>H. pylori</i> , 119p <i>H. pylori</i> , G50 <i>H. pylori</i> , SS1 Gender NR C57BL/6 <i>H. pylori</i> : n=9 (total) Controls: n=4 BALB/c <i>H. pylori</i> : n=9 (total) Controls: n=4	Gastric lymphoma C57BL/6 <i>H. pylori</i> 119p: 3/4 <i>H. pylori</i> G50: 3/3 <i>H. pylori</i> SS1: 0/2 controls: 0/4 BALB/c <i>H. pylori</i> 119p : 2/4 <i>H. pylori</i> SS1 : 0/5 controls : 0/4		
C57BL/6 24 mo Cai et al. (2005)	10 ⁷ CFU <i>H. felis</i> (M) <i>H. felis</i> eradication therapy* after 2 , 6 & 12 mo * made of tetracycline, metronidazole & bismuth subsalicylate orally for 14 d Controls: no eradication Number of animals per group NR	Adenocarcinoma when eradication of infection after 2 mo: 0%; 6 mo: 0%; 12 mo: 30% Adenocarcinoma when no eradication: 100%		
C57BL/6 × 12 996/SvEv 15 mo Rogers et al. (2005)	10 ⁸ CFU <i>H. pylori</i> , SS1 (M, F) (gender distribution NR) 4 groups: 1. 0.25% salt diet 2. 7.5% salt diet 3. 0.25% salt diet + <i>H. pylori</i> 4. 7.5% salt diet + <i>H. pylori</i> Total n=62	Increased incidence of high-grade dysplasia (indefinite dysplasia or atypical hyperplasia) in Groups 3 & 4. No adenocarcinoma		High-salt diet switch Th1 to a Th2 immune response. Th1: <i>H. pylori</i> -specific IgG2c; Th2: <i>H. pylori</i> -specific IgG1.

Table 3.2 (continued)

Strain Duration Reference	Dosing regimen, strain Gender Animals/group at start	Incidence of tumours	Significance	Comments
TGF-β deficient mice				
pS2-dnRII derived from FVB/N strain (wild-type) 36 wk Hahm et al. (2002)	10 ⁹ CFU <i>H. pylori</i> , 43 504 (M, F) 1. TGF- β -deficient mice (infected): <i>n</i> =48 2. wild-type (infected): <i>n</i> =48 3. TGF- β -deficient mice (non infected): <i>n</i> =38	Dysplasia or carcinoma: 6/7 (85.7%) 0/6 No lesion		
INS-GAS mice				
7 mo Fox et al. (2003a)	10 ⁸ CFU <i>H. pylori</i> , SS1 (M/F) <i>n</i> =20 (total)	Carcinoma: 4/6 males; 0/6 females; 0/8 male and female controls		Only males developed gastric adenocarcinomas
28 wk Ohtani et al. (2007)	10 ⁸ CFU <i>H. pylori</i> strain SS1 (M, F) 1. Males: <i>n</i> =29 2. Ovariectomized females: <i>n</i> =35 3. Intact females: <i>n</i> =29 4. Estradiol-treated* ovariectomized females: <i>n</i> =16 Part of each group was infected or not. Sacrifice occurred at Weeks 16 & 28 post- infection *Subcutaneous placement of a time- release estradiol pellet 16 wk post- infection	Adenocarcinoma: A. 3/7 (42%) infected males B. 1/10 (10%) infected ovariectomized females C. 0/7 infected intact females D. 0/8 E ₂ treated ovariectomized females (infected) F. 0% non infected males and females		Protective effect of estradiol
28 wk Lee et al. (2008)	10 ⁹ CFU <i>H. pylori</i> , SS1 (M) 1. Infected and untreated 2. Eradication therapy* at 8 wk post- infection 3. Eradication therapy* at 12 wk post- infection 4. Eradication therapy* at 22 wk post- infection 5. Non infected * with omeprazole, metronidazole and clarithromycin in 0.2 mL orally, for 7 d	Adenocarcinoma: 1. 10/10 (100%) 2. 1/11 (9%) 3. 8/9 (89%) 4. 6/12 (50%) 5. 0/7	 [<i>P</i> <0.0001], Group 1 vs 5 [<i>P</i> <0.05], Group 1 vs 2 [<i>P</i> <0.05], Group 1 vs 4	Protective effect of eradication to the greatest extent when given early

Table 3.2 (continued)

Strain Duration Reference	Dosing regimen, strain Gender Animals/group at start	Incidence of tumours	Significance	Comments
p27-deficient mice				
17 mo Kuzushita et al. (2005) C57BL/6 (p27-deficient) C57BL/6 (wild-type)	10 ⁹ CFU <i>H. pylori</i> , SS1 (M, F) Sacrifice at 15, 30, 45, 60 and 75 wk post-inoculation 1. wild-type + <i>H. pylori</i>	Gastric carcinoma or dysplasia 0/40, carcinoma		Incidence for carcinoma (vs dysplasia) in Group 2 can not be ascertained from data provided
	2. p27 ^{-/-} + <i>H. pylori</i>	1/10 (30 wk), 1/6 (45 wk), 5/6 (60 wk), 2/6 (75 wk)	<i>P</i> <0.05 (60 wk vs Group 1), <i>P</i> <0.05 (75 wk vs Group 4)	
	3. Wild-type (controls)	0/9, carcinoma		
	4. p27 ^{-/-} (controls) 25–50 animals/group	0/10, carcinoma		
TFF2-deficient mice				
19 mo Fox et al. (2007) TFF2 ^{-/-} C57BL/6 X Sv129 C57BL/6 X Sv129 (wild-type)	10 ⁸ CFU <i>H. pylori</i> , SS1 (M, F) 1. TFF2-deficient (infected): 20 2. TFF2-deficient (not infected): 10 3. Wild-type (infected): 20 4. Wild-type (not infected): 10	Gastric intraepithelial neoplasia 2/10 (20%) 0% 1/20 (10%) 0%		
IL-1β transgenic mice				
12 mo Tu et al. (2008)	10 ⁸ CFU <i>H. felis</i> , ATCC 49179 (M) 1. Infected mice overexpressing human IL-1 β (line 19) 2. Infected mice overexpressing human IL-1 β (line 42) 3. Infected control mice 4. Uninfected line 42	Carcinomas: 1/12 (8.4%) 1/10 (10%) 0% 0%		

Table 3.2 (continued)

Strain Duration Reference	Dosing regimen, strain Gender Animals/group at start	Incidence of tumours	Significance	Comments
MALT lymphoma mice models				
26 mo Enno et al. (1995) BALB/c	10 ⁹ CFU <i>H. felis</i> , ATCC 49179 (F) 1. Infected a. Sacrifice 0–19 mo: 167 b. Sacrifice 22–26 mo: 80 2. Controls (uninfected) a. Sacrifice 0–19 mo: 95 b. Sacrifice 22–26 mo: 48	Lymphoepithelial lesions (gastric lymphoma) 1a: 0/167 1b: 20/80 (25%) [<i>P</i> <0.0001] 2a: 0/95 2b: 0/48		Lesions are B-cell lymphoid infiltrates
22 mo Sutton et al. (2004) BALB/c	10 ⁸ CFU <i>H. felis</i> , CS1 (F) A. Untreated (control): <i>n</i> =17 B. Infected: <i>n</i> =15 C. Immunised + infected. - <i>H. felis</i> positive: <i>n</i> =4 - <i>H. felis</i> negative: <i>n</i> =15	MALT lymphoma 1/17 13/15 4/4 5/15	[<i>P</i> <0.0001], Group B vs A [<i>P</i> <0.0001], Group C positive vs A [NS], Group C negative vs A	
12 mo Fukui et al. (2004) BALB/c	10 ⁸ CFU <i>H. pylori</i> , TN2GF4 (M, F) Sacrifice at 2, 4, 6 and 12 mo 1. Non-thymectomized mice uninfected (Control): 40 2. Non-thymectomized mice infected: 40 3. Neonatal thymectomized (3 d) mice (nTx) uninfected: 40 4. Neonatal thymectomized (3 d) mice (nTx) infected: 40	Lymphoepithelial lesions (gastric lymphoma) 0/40 0/40 0/40 2 mo: 6/10 4 mo: 8/10 6 mo: 9/10 12 mo: 10/10		

ATCC, American Type Culture Collection; CFU, colony forming units; d, day or days; F, female; GC, gastric cancer; *H. pylori*, *Helicobacter pylori*; IL-1 β , interleukin-1 β ; M, male; MALT, mucosa-associated lymphoid tissue; mo, month or months; TFF2, trefoilfactor family 2; vs, versus; wk, week or weeks

4.1 Data supporting the carcinogenicity of *H. pylori*

4.1.1 Genotoxicity linked to *H. pylori* infection

The intense gastric inflammatory infiltrate (gastritis) that accompanies gastric colonization by *H. pylori* in humans (or by related *Helicobacter* species in animal models) can generate potentially genotoxic reactive oxygen and nitrogen species from the inflammatory cells themselves, and from adjacent gastric epithelial cells ([Macarthur et al., 2004](#); [Ding et al., 2007](#)).

H. pylori is not directly genotoxic *in vitro*, and evidence for genotoxicity related to *H. pylori* and/or the associated inflammatory response *in vivo* is relatively limited. An increased frequency of micronuclei in the peripheral blood lymphocytes of *H. pylori*-infected patients ([Suárez et al., 2007](#)), more DNA strand breaks as shown by the comet assay ([Ladeira et al., 2004](#)), increased gastric mucosal DNA adduct (8-hydroxy-2'-deoxyguanosine) formation ([Farinati et al., 1998](#)), and an increased mutation frequency in the gastric mucosa of *H. pylori*- or *felis*-infected transgenic mutation reporter mice ([Touati et al., 2003](#); [Jenks et al., 2003](#)) have all been reported to occur relatively early during *Helicobacter* infection, before gastric cancer development.

Increased expression of activation-induced cytidine deaminase (AID), a DNA- and RNA-editing enzyme, was reported in *H. pylori*-infected human gastric biopsies, and was noted to decrease following *H. pylori* eradication. When human gastric adenocarcinoma epithelial cells were infected *in vitro* with *H. pylori*, the resulting AID overexpression occurred in parallel with the accumulation of mutations in *p53*, but much less frequently in *β-catenin* and *c-myc* genes; this supports a relatively specific role for AID in the generation of *p53* mutation by *H. pylori* ([Matsumoto et al., 2007](#)).

4.1.2 Changes in gene expression

Several reports have demonstrated that *H. pylori* alters the expression of specific oncogenes and tumour-suppressor genes implicated in gastric carcinogenesis. For example *H. pylori* infection promotes the nuclear translocation of β -catenin, thereby activating downstream β -catenin-responsive genes including cyclin D ([Franco et al., 2005](#)), upregulates the *p53* homologue *p73* in gastric cells to promote apoptosis ([Wei et al., 2008](#)), and decreases expression of the cell-cycle inhibitory protein *p27* ([Eguchi et al., 2003](#)) that is known to be lost in aggressive gastric cancers.

Hypermethylation of several genes has been found in *H. pylori*-associated chronic gastritis, including *E-cadherin* and *p14*, that are of potential importance mechanistically in gastric carcinogenesis. Methylation of the *E-cadherin* gene has been reported to reverse with the eradication of *H. pylori*. *In vitro*, *H. pylori* and the reactive oxygen species or nitric oxide released during the chronic inflammatory process may be responsible for gene methylation ([Hmadcha et al., 1999](#); [Tamura, 2004](#); [Chan et al., 2006](#); [Maekita et al., 2006](#); [Nardone et al., 2007](#); [Tahara et al., 2007](#)).

4.1.3 Altered cell turnover

It is well established that in human and experimental animal infections, *H. pylori* is associated with increased numbers of both apoptotic and proliferating gastric epithelial cells ([Shirin et al., 2001](#)). Increased cell turnover has long been linked to a risk of carcinogenesis, based on the increased chance of mutations arising under conditions of accelerated DNA replication ([Preston-Martin et al., 1990](#)). In contrast to the stimulation of apoptosis in association with *H. pylori* infection, some have reported that *H. pylori* may have anti-apoptotic effects ([Peek et al., 1997](#); [Mimuro et al., 2007](#)), which could directly promote aberrant tissue growth and perhaps gastric neoplasia.

The development of an acquired resistance to *H. pylori*-induced gastric epithelial apoptosis has been associated with decreased expression of p27 *in vitro* (Shirin *et al.*, 2000), and downregulation of Fas-mediated signalling pathways *in vivo* (Houghton *et al.*, 2000). However, there is no evidence that the balance between programmed cell death and cell proliferation is any different in subjects who are at higher risk for cancer compared with the *H. pylori*-infected population in general (Moss *et al.*, 1999). [The Working Group noted that most studies addressing postulated mechanisms of carcinogenicity *in vivo* have compared only *H. pylori*-infected patients with uninfected patients (or the same patients before and after *H. pylori* eradication), but have not compared the minority of subjects who develop gastric cancer with the majority who do not.]

4.1.4 Changes in gastric acid secretion

While some persons infected by *H. pylori* develop duodenal ulcers related to depletion of somatostatin secretion and increased gastrin and gastric acid secretion (Calam, 1995), in some others, there is a marked decrease of acid secretion from the loss of or damage to the acid-secreting parietal cells. This state of hypochlorhydria typically occurs in patients progressing towards the ‘intestinal’ type of gastric cancer, where the loss of acid secretion can promote intragastric colonization of non-*Helicobacter* bacteria, and the formation of luminal *N*-nitrosamines with some genotoxic potential (Sanduleanu *et al.*, 2001).

4.1.5 Inflammation and bone-marrow derived stem cells

An especially intense inflammatory response to *H. pylori* is thought to induce greater gastric epithelial cell damage, faster cell turnover, and the eventual emergence of gastric epithelial cells carrying cancer-prone mutations (Moss & Blaser, 2005). An alternative view of the detrimental

effects of the infiltrating inflammatory cells in the gastric mucosa is that of Houghton *et al.* (2004), who provided evidence in *H. felis*-infected mice that the bone-marrow-derived haematopoietic stem cells recruited to the gastric mucosa by *H. felis* can repopulate this mucosa, and progress through metaplasia and dysplasia to intraepithelial cancer. Whether this occurs during human gastric carcinogenesis remains untested thus far.

4.2 Host immune system and genetic susceptibility

Some of the genetic factors underpinning the pathophysiology of the loss of normal gastric secretory function and severe inflammation in gastric carcinogenesis have been uncovered in recent years. Based upon evidence that interleukin-1 β (IL-1 β) is both a potent gastric acid secretion inhibitor and a pro-inflammatory gastric cytokine, El-Omar *et al.* (2000, 2001) documented the association of pro-inflammatory single nucleotide polymorphisms (SNPs) in both the *IL-1 β* gene and the *IL-1RN* gene that encode the endogenous IL-1 receptor antagonist in association with hypochlorhydria and gastric atrophy in first-degree relatives of gastric cancer patients in a Scottish population. They also showed that pro-inflammatory *IL-1 β* and *IL-1RN* SNPs were associated with a 2–3-fold increase in gastric cancer risk in a case–control study from Poland. Figueiredo *et al.* (2002) evaluated simultaneously *H. pylori vacA* and *cagA* genotypes together with *IL-1 β* and the *IL-1RN* genotypes of a large group of Portuguese shipyard workers with chronic gastritis and gastric cancer patients. They obtained risk ratios for gastric cancer among *H. pylori*-infected patients that differed markedly, based upon a combination of these four genes.

Moderate associations between SNPs in other genes encoding cytokines or genes involved in the initiation and maintenance of inflammation

have also been reported that include genes that encode tumour necrosis factor α (TNF- α), IL-10, IL-8, and toll-like receptor 4 ([Amieva & El-Omar, 2008](#)). Furthermore, increased non-cardia gastric cancer risk in *H. pylori*-infected subjects has also been related to polymorphisms in IL-1 β , IL-1RN, TNF- α and IL-10 in subjects from a multicentre case-control study in the US population ([El-Omar et al., 2003](#)) but not, in that same study, to cardia gastric cancer or oesophageal adenocarcinoma risk. Thus, these SNPs appear to be relatively specific to increased distal gastric cancer risk following *H. pylori* infection.

There remains considerable debate regarding the reproducibility of many of these findings, reflecting perhaps differences in the populations studied, and the relationship of the cases to the controls in individual studies ([Perri et al., 2005](#); [Starzyńska et al., 2006](#)). Most studies are relatively small and evaluate only a few SNPs simultaneously, without adjustment for other potential confounding variables such as *H. pylori* genotype or other SNPs. Recent meta-analyses suggest that the influence of IL-1 β and IL-1RN SNPs on gastric cancer risk is relatively weak, and/or confined to Caucasians ([Camargo et al., 2006](#); [Kamangar et al., 2006b](#)), whereas the relationship between non-cardia gastric cancer and two specific TNF- α SNPs (especially the -308AA SNP) is more consistent, though again mainly in Western populations ([Gorouhi et al., 2008](#); [Zhang et al., 2008](#)). [The Working Group noted that larger and more extensive studies are necessary to determine the importance of individual SNPs in gastric cancer risk in different populations, and in understanding how they may modulate the risk of cancer following *H. pylori* infection.]

4.3 Factors associated with gastric carcinogenesis

4.3.1 *H. pylori* virulence factors

(a) *cag* Pathogenicity island

As reviewed in Section 2, although CagA-positive strains confer an increased risk of gastric carcinogenesis, CagA-positive infections are also associated with the development of duodenal ulcer disease, which is itself inversely related to gastric cancer risk ([Hansson et al., 1996](#); [Nomura et al., 2002b](#)). This suggests that factors other than just the presence or absence of CagA may be important in gastric carcinogenesis. In regions such as south-eastern Asia, where almost all strains are CagA-positive, structural variations in tyrosine phosphorylation sites in the C-terminal domain of the CagA protein have been identified. These variations within regions encoded by the five amino acids sequence Glu-Pro-Ile-Tyr-Ala (EPIYA) serve as sites of CagA phosphorylation by gastric epithelial Src kinases. Four types of EPIYA motifs have been described (A through D), but the number of repeats of the EPIYA-C sequence in particular correlates with increased CagA phosphorylation, and a more marked phenotypic effect on infected gastric epithelial cells *in vitro*. EPIYA sequences differ markedly between east Asian strains (where gastric cancer is most prevalent), and western European/North American strains ([Yamaoka et al., 1998](#); [Basso et al., 2008](#)). In a multivariate analysis of 203 Italian *H. pylori*-infected patients, 53 of whom had gastric cancer, the number of repeats of the EPIYA-C motif was associated with the prevalence of both gastric cancer and its histological precursor, intestinal metaplasia ([Basso et al., 2008](#)). Similar associations of EPIYA motifs with gastric cancer have been described in smaller studies from east Asia ([Yamaoka et al., 1998](#)).

(b) *Evidence of carcinogenic effect of cag genes in animal models*

CagA-positive strains of *H. pylori* are associated with more vigorous gastric inflammatory responses. Several genes within the *cag* pathogenicity island, though not *cagA*, may facilitate colonization (Marchetti & Rappuoli, 2002). Two studies have highlighted the importance of an intact *cag* pathogenicity island in the induction of gastric cancer in rodent species. In the gerbil model infected by *H. pylori* strain 7.13, an isogenic mutant lacking the *cagA* gene failed to produce gastric cancer whereas cancers were seen in over 50% of the gerbils infected by wild-type or *vacA*-negative strains. There was also much less inflammation with the *cagA* knockout strain (Franco *et al.*, 2008). Deletion of *cagE*, which is known to be important in the functionality of the type 4 secretory system, delayed, but did not prevent, gastric cancer in the INS-GAS mouse model (Fox *et al.*, 2003b).

The only direct evidence of oncogenicity of the CagA protein *in vivo* is in transgenic mice overexpressing a virulent form of the *cagA* gene (Ohnishi *et al.*, 2008). About 10% of such mice developed hyperplastic polyps and about 1% gastric or small intestinal cancer after 72 weeks, whether the CagA protein was targeted specifically to parietal cells in the stomach or expressed ubiquitously in all cells. Unexpectedly, transgenic CagA expression did not induce gastric inflammation, and leukaemias were also observed in some of the mice. The latter is consistent with the known effect of CagA on activating SHP-2 tyrosine phosphatase, an event that is also involved in leukaemogenesis.

In contrast to the paucity of data regarding the carcinogenic effects of *cag*-encoded proteins in animal models, there is a very extensive literature describing the cellular and molecular consequences of CagA translocation by the type 4 secretory system that is encoded by multiple genes within the *cag* pathogenicity island

(reviewed in Buret *et al.*, 2005; Backert & Selbach, 2008; Wen & Moss, 2009). Following adherence of *H. pylori* to gastric epithelial cells, the CagL protein on the *cag* pilus interacts with the $\alpha_5\beta_1$ host cell integrin to initiate CagA translocation. Translocated CagA is then phosphorylated by host cell Src kinases at EPIYA tyrosine phosphorylation sites to promote downstream signalling, resulting in reorganization of the actin cytoskeleton, and enhanced cellular motility (thus giving rise to the so-called “humming bird” phenotype in cultured cells). Activation of the transcription factor NF- κ B by CagA leads to mitogenic signalling through mitogen-activated protein (MAP) kinase pathways, and also to pro-inflammatory gene activation. Some other cellular events activated by CagA translocation are not dependent on CagA phosphorylation. These events include the disruption of tight and adherent junctions between adjacent gastric epithelial cells through interactions with occludin, zonulin-1, junctional adhesion molecules, claudins, E-cadherin, and β -catenin. β -Catenin translocation to the nucleus promotes further mitogenic gene expression. One of the hallmark epithelial consequences of *cag*-positive infections is secretion of the pro-inflammatory chemokine IL-8, but it is currently unclear whether this is dependent on CagA translocation or by some other *cag*-island dependent stimulus. The muramyl dipeptide component of *H. pylori*'s cell wall, peptidoglycan, is also translocated to gastric epithelial cells by type 4 secretion, where it can interact with the intracellular NOD1 protein, a component of the innate immune response to pathogen-associated molecular patterns of bacteria. NOD1-binding also stimulates NF- κ B-dependent signalling.

(c) *VacA*

In many studies in Western populations, peptic ulcer disease has been strongly associated with the *vacA* genotype (particularly s1m1), while in some of these studies the s1m1 genotype has been linked to gastric cancer (Miehlke *et al.*,

2000). East Asian strains are almost universally s1m1, and are not associated with any particular clinical outcome. The recent reports of *vacA* i region polymorphism where the i1 type was associated with gastric cancer in Iranian (Rhead *et al.*, 2007) and Italian (Basso *et al.*, 2008) populations are worthy of further corroboration by other groups. However, as for *cagA*, the *vacA* i region polymorphism may not correlate with gastric cancer risk in east Asia, where very few strains are of the i2 type (Ogiwara *et al.*, 2008).

(d) *Evidence of carcinogenic effect of vacA in animal models*

VacA deletion does not alter the inflammatory or carcinogenic effects of *H. pylori* in the gerbil model (Franco *et al.*, 2008). Multiple biological effects of VacA have been demonstrated *in vitro*, including the induction of apoptosis in epithelial cells, and the inhibition of T-cell activation and proliferation that may allow for *H. pylori* persistence, but the relevance of these observations to gastric carcinogenesis remains obscure (Takeshima *et al.*, 2009; Matsumoto *et al.*, 2011).

(e) *BabA and SabA*

Some studies have demonstrated an association between the *babA2* genotype and gastric cancer (Yu *et al.*, 2002) though this association may be confounded by the frequent co-association of *babA2* with *vacA* s1m1 and *cagA* positivity. Although the induction of *SabA* expression in *H. pylori* strains has been associated with gastric epithelial cell adhesion (Marcos *et al.*, 2008), no good evidence points to a more direct role of *SabA* in carcinogenesis.

4.3.2 Cofactors and co-infections

Effects of dietary salt on inflammation and proliferation have been observed in some animal studies, but the data from these is not consistent (Rogers *et al.*, 2005).

H. pylori induces a predominantly Th1 immune response which is more typical of intracellular bacteria rather than extracellular organisms that produce typically a Th2 response. Because gastric cancer is thought to result from a Th1 pro-inflammatory immune response, it has been postulated that concurrent parasitic infection (which is more likely to induce a Th2 immune response) may modify the gastric inflammation and carcinogenic effects of *H. pylori*. Such a hypothesis is supported by *H. felis*-induced gastric atrophy in mice with concurrent intestinal nematode infection (Fox *et al.*, 2000). Although gastric cancer was not evaluated in this model, this hypothesis may perhaps explain the low rate of *H. pylori*-associated cancer despite high *H. pylori* infection rate in areas of the world where parasitic infection is common (Whary *et al.*, 2005).

4.4 Mechanisms of lymphomagenesis

4.4.1 Host immune system and genetic susceptibility in humans

Several different host polymorphisms associated with gastric lymphoma have been reported. These include the 49 G/G polymorphism in *CTLA4*, coding for a receptor on CD4-positive T cells, which inhibits T-cell functioning on ligand binding. This polymorphism was associated with a 6-fold higher risk of developing MALT lymphoma after *H. pylori* infection in a study from Taiwan, China (Cheng *et al.*, 2006). Association of the R702W mutation in the *NOD2/CARD15* gene was demonstrated in a study in German/Austrian patients with a 2.4-fold risk of gastric lymphoma development (Rosenstiel *et al.*, 2006). Susceptible polymorphisms for gastric lymphoma have also been reported at certain human leukocyte antigen (HLA) loci in a small Japanese cohort (Kawahara *et al.*, 2005), and within the *TNF- α* gene (moderate effects at distinct loci, which were different for low- and

high-grade lymphoma) ([Hellmig et al., 2005a](#)), and in the toll-like receptor TLR4 in German/Austrian patients ([Hellmig et al., 2005b](#)). Each of these findings requires independent corroboration in other populations, and the understanding of additional factors that may predispose certain individuals or populations to gastric lymphoma following *H. pylori* exposure remains poor.

4.4.2 *H. pylori* virulence factors

Unlike the large literature regarding the importance of certain *H. pylori* factors in association with gastric cancer, the data for gastric lymphoma are inconsistent, and generally not supportive of any specific association.

4.4.3 Molecular mechanisms

The normal human gastric stomach contains few or no inflammatory cells. On infection by *H. pylori* or other *Helicobacter* species, such as *H. heilmanii*, an active infiltration of acute and chronic inflammatory cells (including B-cell lymphoid follicles) results. This so-called MALT lymphoma is the precursor of a low-grade lymphoma of B cells, gastric MALT lymphoma, originating in B cells of the marginal zone of the secondary follicles that are generated in the inflammatory response to *H. pylori* ([Du & Isaacson, 2002](#)). [Hussell et al. \(1993\)](#) demonstrated that in the early stages of MALT, lymphoma B-cell proliferation was dependent on both *H. pylori* antigens, and tumour-infiltrating T cells.

Most cases of MALT lymphoma are clonal, and will respond to *H. pylori* eradication. However, approximately 20% of MALT lymphomas are not responsive to eradication therapy, and it is thought that this is because they acquire further mutations, in particular the *API2-MALT1* fusion gene that results from a translocation of [t(11;18)(q21;q21)]. Three other relatively uncommon translocations [t(1;14)(p22;q32), t(14;18)(q32;q21), and t(3;14)(p13;q32)] are also associated with

gastric MALT lymphoma. Three of the four above translocations lead to the activation of NF- κ B, a transcription factor important in inhibiting programmed cell death ([Sagaert et al., 2007](#)). Other mutations in gastric MALT lymphoma include *TP53*, *c-MYC* (approximately 20% of cases each), and epigenetic events such as gene promoter hypermethylation of *p16* ([Isaacson, 1999](#); [Huang et al., 2004](#)).

[The Working Group noted that how *H. pylori* and/or the associated inflammatory response promote downstream mutations that result in subsequent *H. pylori*-independent growth and high-grade disease that may be refractory to removing the offending antigen has not been defined. Whether high-grade lymphomas that are refractory to *H. pylori* eradication arise through the same pathways that lead *H. pylori* to promote low-grade lymphomagenesis is also unclear and worthy of further investigation. Little is known of possible environmental cofactors in the predisposition to *H. pylori*-induced gastric lymphomagenesis.]

4.5 Synthesis

Multiple lines of evidence point to a central role for the chronic gastric inflammatory response and resulting oxidative stress in *H. pylori*-associated gastric carcinogenesis. This leads to altered cellular turnover accompanied by changes in gene expression, methylation, and mutation. The nature and extent of the inflammatory response, and the subsequent effects of the inflammatory environment on gastric epithelial cells are associated with three inter-related factors: 1) host-determined modulation of inflammatory responses, 2) specific *H. pylori* virulence factors, including CagA, and 3) altered gastric secretory function.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of chronic infection with *Helicobacter pylori*. Chronic infection with *Helicobacter pylori* causes non-cardia gastric carcinoma and low-grade B-cell MALT gastric lymphoma.

For oesophageal adenocarcinoma, there is *evidence suggesting lack of carcinogenicity* of chronic infection with *Helicobacter pylori* in humans.

There is *sufficient evidence* in experimental animals for the carcinogenicity of infection with *Helicobacter pylori*.

Chronic infection with *Helicobacter pylori* is *carcinogenic to humans (Group 1)*.

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