**Helicobacter pylori** antibiotic resistance patterns and genotypes in adult dyspeptic patients from a regional population in North Wales

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Received 19 February 2004; returned 21 April 2004; revised 27 May 2004; accepted 29 May 2004

**Objective**: Surveillance data on **Helicobacter pylori** antibiotic susceptibilities in Wales are limited, despite resistance being a key factor in treatment failure. A single-centre survey was undertaken over 3 years to determine local antibiotic resistance rates on isolates from dyspeptic patients in Bangor, Gwynedd (North Wales).

**Methods**: Susceptibilities were determined for 363 isolates by disc diffusion and the Etest. Isolates were also genotyped (cagA presence and vacA allelic types).

**Results**: Overall in vitro resistance rates were 24% for metronidazole and 7% for clarithromycin, with 4% resistant to both antibiotics. Resistant strains typically had high MICs of >256 mg/L. Tetracycline resistance was identified in only one isolate whereas no isolates showed resistance to amoxicillin. There was a two-fold increase in resistance over the study period. No gender and age associations with resistance were detected. Resistant and susceptible isolates were genotypically diverse with respect to cagA/vacA type but the vacA s1m2 form was a feature of all clarithromycin-resistant isolates compared with 56% of the susceptible isolates.

**Conclusion**: Although the overall antibiotic resistance rates of **H. pylori** from North Wales were low compared with many other regions in Europe, continued surveillance, particularly of high-level resistance (MIC >256 mg/L), is recommended to monitor the effects of the ‘test and treat’ strategy for **H. pylori** eradication.

**Keywords**: clarithromycin, metronidazole, dual resistance, surveillance

**Introduction**

**Helicobacter pylori** chronically infects an estimated 7.5 million persons in England and Wales. Typical clinical presentations include peptic ulcer disease and gastric cancer. Eradication therapy is used for duodenal ulcer and other at-risk patients, and a test and treat strategy is recommended in the management of uncomplicated dyspepsia. However, antibiotic resistance is recognized increasingly as a contributing factor in the 10–15% of patients who fail **H. pylori** eradication therapy. A meta-analysis on the effect of pre-treatment resistance found that efficacy was reduced by up to 38% for metronidazole and up to 55% for clarithromycin. pre-treatment resistance rates in **H. pylori** vary markedly between countries and between regions and, in Europe, mean rates of 27% for metronidazole and 10% for clarithromycin are typical. There is no systematic surveillance of primary antibiotic resistance rates in Wales, and widely divergent rates have been reported in England, depending on the local population, as reported in single-centre studies in East London, Sheffield and Chelmsford.

We undertook the present study to improve our understanding of UK regional variation of **H. pylori** antibiotic resistance rates in relation to gender and age, and to obtain evidence of any local temporal trend. The focus of this study was the predominantly white ethnic population in rural North Wales where previous exposure of individuals to metronidazole in treatment of other infections was likely to be low. We also examined the possibility of an association between high-level antibiotic resistance and **H. pylori** strain type and for that purpose used two established genotypic markers—presence of the cagA locus in the cag pathogenicity island, and allelic variants of the vacuolating cytotoxin...
gene (vacA). H. pylori strain type distribution is not known for the North Wales population, and was investigated in relation to antibiotic resistance as there is evidence from the Netherlands that cagA-negative/vacA s2 strains are associated with less severe inflammation but are more difficult to eradicate.

Materials and methods

Bacterial strains

We used routine isolates of H. pylori that were cultured from single gastric (antral) biopsies according to standard laboratory procedures as described previously. The patients were from consecutive endoscopy lists and were undergoing routine investigation at the Ysbyty Gwynedd Hospital, Bangor, for a variety of upper gastrointestinal tract symptoms. The hospital serves a rural region of North-west Wales (Anglesey, Conwy and Gwynedd) that has a predominantly (98.8%) white resident population of approximately 240 000 (http://neighbourhood.statistics.gov.uk (date last accessed 21 May 2004)).

After primary isolation, isolates were transported for further testing at the reference laboratory in a medium that comprised 3.7% (v/v) brain heart infusion broth (Oxoid, Basingstoke, UK), 2.5% (w/v) yeast extract (Oxoid), 5% (v/v) sterile horse serum (TCS Biosciences Ltd, Heywood, UK) and H. pylori selective antibiotic supplement containing vancomycin (10 mg/L), cefsulodin (5 mg/L), trimethoprim (5 mg/L) and amphotericin B (5 mg/L) (Oxoid). Isolates were then subcultured on Columbia agar base containing 10% (v/v) brain heart infusion broth (Oxoid, Basingstoke, UK), 2.5% (v/v) glycerol at /C0 under microaerobic conditions (4% O2, 5% H2, 5% CO2 and 86% N2) in a MACS-VA500 microaerophilic workstation (Don Whitley Scientific Ltd, Lenexa, KS, USA). A pre-dried 10% CBA plate was inoculated with defibrinated horse blood (10% CBA) at 37°C under microaerobic conditions (4% O2, 5% H2, 5% CO2 and 86% N2) in a MACS-VA500 microaerophilic workstation (Don Whitley Scientific Ltd, Shipley, UK). Identity as H. pylori was confirmed by Gram’s stain, and by tests for urease, catalase and oxidase activity. Cultures were preserved on glass beads in nutrient broth (Oxoid) containing 10% (v/v) glycerol at −80°C.

Antibiotic susceptibility testing

The reference laboratory standard operating procedures developed from previously published guidelines were followed as there are no generally agreed national/international standardized methods and interpretive criteria for testing H. pylori in vitro susceptibility to metronidazole, clarithromycin, amoxicillin and tetracycline. Briefly, exponential growth from a 48 h culture was suspended in maximum recovery diluent (Oxoid) to a density equivalent to a McFarland 0.5 standard (≈12 × 108 colony forming units) (Remel, Lenexa, KS, USA). A pre-dried 10% CBA plate was inoculated with the culture suspension recovered and recultured after transportation.

Susceptibilities were determined by the Etest strip (AB Biodisk, Solna, Sweden) and antibiotic disc (Oxoid) diffusion methods. Reference strains NCTC 13206 (CCUG 38770) and NCTC 13207 (CCUG 38772) were included as controls. Susceptibility results were recorded as resistant according to the following interpretive criteria. For disc tests, growth inhibition zones of ≤20 mm (5 μg disc) and no zone of growth inhibition (2 μg disc) were used for metronidazole and clarithromycin, respectively. For Etests, MIC breakpoints of ≥2 mg/L and ≥8 mg/L were used for metronidazole and clarithromycin, respectively. Intermediate susceptibility (MIC >2 to <8 mg/L) was also recorded for metronidazole. High-level resistance to both of these antibiotics was defined as MIC >256 mg/L. The breakpoint MICs used for amoxicillin and tetracycline were ≥2 mg/L and ≥4 mg/L, respectively; disc tests were not performed for these antibiotics.

Genotyping

Genomic DNA was extracted from sweep cultures prepared from isolate stocks stored at −80°C, and the primers and PCR conditions for the assay for cagA (a marker for the 3’ end of the cag pathogenicity island and for the cagl region) using the D008/R008 primer set were as described previously. Vacuolating cytotoxin (vacA) genotyping based on signal (s) and mid (m)-region alleles was performed using a multiplex assay.

Statistical analysis

Fisher’s exact test and P values were determined. A P value of <0.05 was considered significant.

Results

Individual antibiotic susceptibilities

Over the 36 months of the study period from February 2000 to January 2003, a total of 363 isolates of H. pylori was obtained from patients comprising 167 men aged between 22 and 90 years (median age of 60.8 years) and 196 women aged between 16 and 92 years (median age of 65.1 years). Most patients (275/363, 76%) were aged >51, 23% (83/363) were aged between 21 and 50 years, and five patients (all female) were aged <20 years. Overall primary resistance rates were: 7% (27/363) for clarithromycin with 67% (18/27) showing high-level resistance (MICs >256 mg/L); and 24% (86/363) for metronidazole with 85% (73/86) showing high-level resistance. Tetracycline resistance (MIC 4 mg/L) was identified in only one isolate, whereas no isolate showed resistance to amoxicillin.

Table 1. Numbers of isolates of H. pylori from gastric biopsies in North Wales resistant to each antibiotic (2000–2003)

<table>
<thead>
<tr>
<th></th>
<th>2000 (38 isolates)</th>
<th>2001 (155 isolates)</th>
<th>2002 (170 isolates)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(%) M/F</td>
<td>(%) M/F</td>
<td>(%) M/F</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>4/1 (13)</td>
<td>13/23 (23)</td>
<td>23/22 (27)</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>1/1 (5)</td>
<td>3/4 (5)</td>
<td>6/12 (11)</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>0/0</td>
<td>0/0</td>
<td>1/0 (0.6)</td>
</tr>
</tbody>
</table>

M. male; F. female.
Table 1 shows the annual rates for metronidazole resistance (13% in 2000, 23% in 2001 and 27% in 2002) \((P=0.095)\). For clarithromycin, the comparable annual rates were 5%, 5% and 11% \((P=0.54)\). Although the overall rates of resistance doubled for both antibiotics over the 3 year period of the study, a larger sample would be needed to determine statistically significant year-on-year trends; for instance with a resistance rate of 10%, 316 patients would be needed to detect a change of 5% in the population.

Analysis of \(H.\ pylori\) antibiotic resistance in relation to the sex of the patient using pooled data for the 3 years (Table 1) showed that males and females were infected in identical proportions by metronidazole-resistant isolates with a rate of 23% \((39/167\) for males and \(47/196\) for females). Likewise, analysis of clarithromycin results showed similar proportions of resistant isolates infecting males \((6\%,\ 10/167)\) and females \((9\%,\ 17/196)\).

The variation between \(H.\ pylori\) strains in levels of antibiotic resistance was examined and Figure 1(a) shows the distribution of MICs of metronidazole. Isolates with MICs of \(<8\ mg/L\), which were interpreted as susceptible and intermediate, had diverse values whereas 85% of isolates interpreted as resistant had MICs of \(>256\ mg/L\). The four isolates \((1\%)\) that had intermediate metronidazole susceptibility were recorded as susceptible in the overall analysis. In contrast, the range of MICs of clarithromycin (Figure 1b) was less diverse with most susceptible strains having MICs of \(\leq 0.032\ mg/L\), and 11/18 of resistant strains having high-level resistance MICs of \(>256\ mg/L\).

### Combined antibiotic susceptibilities

Each isolate of \(H.\ pylori\) was characterized by the assignment of a susceptibility pattern based on combined susceptibilities to metronidazole and clarithromycin (Table 2). Amoxicillin and tetracycline results were excluded from this analysis as all isolates were fully susceptible to amoxicillin, and all except one isolate were also susceptible to tetracycline—that isolate was also resistant to metronidazole. Most strains \((72\%)\) were fully susceptible (MtzS/ClaS) or intermediate (MtzI/ClaI), whereas 20% were resistant only to metronidazole (MtzR/ClaR). A subset of 15 isolates of the latter type, although interpreted as metronidazole resistant, appeared to contain a combination of metronidazole-susceptible and -resistant subpopulations on plate cultures. Thirteen strains \((4\%)\) were resistant to both antibiotics (MtzR/ClaR). Finally, 14 isolates \((4\%)\) were resistant only to clarithromycin (MtzS/ClaR).

The results for \(H.\ pylori\) isolates with different antibiotic susceptibility patterns analysed according to age and sex of patient are shown in Table 2. For the two main age groups, the relative combined (male and female) rates for susceptibility to metronidazole and clarithromycin were 59\% \((21–50\ years)\) versus 75\% \((\geq 51\ years)\). For metronidazole only, the comparative resistance rates were 34\% versus 21\%, and for clarithromycin the comparative resistance rates were 9.1\% versus 6.9\%.

The relative susceptibility rates to both antibiotics by patient sex (all ages) were 74\% \((males)\) versus 69\% \((females)\). For metronidazole, the comparative resistance rates were 23\% \((males)\) versus 23\% \((females)\), while for clarithromycin, the rates were 6\% \((males)\) versus 8.9\% \((females)\). Within the \(\geq 51\ years\) age group, there was also a gender difference for clarithromycin with 8.6\% \((13/151)\) of female isolates being resistant compared with 4.8\% \((6/124)\) of male isolates; the difference was not significant \((P=1)\). The results also highlighted the fact that the two main age groups (21 and over) contained a small proportion \((3–6\%)\) of dually resistant (MtzR/ClaR) isolates.

### Variation by genotype

One hundred and eighty-three of the \(H.\ pylori\) isolated during years 2000 and 2001 were genotyped \((cagA\ status\ and\ vacA\ allele)\), and the numbers of isolates grouped by combined genotype according to each susceptibility pattern are shown in Table 3. Most isolates were \(cagA\ positive\ (76\%)\) and of those, most were either \(vacA\ type\ s1m1\ (41\%)\) or \(vacA\ s1m2\ (53\%),\ with 7 isolates that were \(s2m2\). For the \(cagA\-negative\ isolates,\ the\ \(vacA\ m2\ form\ was\ a\ feature\ of\ 84\%,\ and\ 79\%\ of\ those\ were\ \(vacA\ s1m2\).

Analysis of the genotypes in relation to resistance showed that the two predominant susceptibility patterns (MtzS/ClaS and MtzR/ClaR), which represented 91\% of isolates of \(H.\ pylori\), were genotypically diverse. Overall, susceptible isolates were strongly associated with the \(vacA\ s1m2\ genotype\ \(P=0.005)\). Even so, that genotype was a feature of all nine clarithromycin-resistant isolates. There was no evidence that high-level resistance (MIC >256 mg/L) to either metronidazole or clarithromycin was associated with a particular \(vacA\ genotype as most of those strains had the \(vacA\ s1\ allele. The distribution of the mid region alleles was more variable, and for the \(m1\ allele, the proportions

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**Figure 1.** Distribution of MICs of metronidazole (a) and of clarithromycin (b) for \(H.\ pylori\) from gastric biopsies of dyspeptic patients in North Wales (2000–2003).
were 40% of susceptible isolates versus 18% of resistant isolates, and for the m2 allele, the proportions were 59% of susceptible isolates versus 83% of resistant isolates.

**Discussion**

We describe the first single-centre study in North Wales of *H. pylori* antimicrobial resistance over time in patients undergoing routine endoscopy. The mean metronidazole resistance rate of 24% for *H. pylori* in this area was lower than the mean European primary resistance rate of 33% derived from a multicentre study performed in 1998.8 Our rate was similar to the rates of 23–26% recorded at several centres in central and eastern European regions, notably Bordeaux (France), Freiburg (Germany), Hoogeveen (Netherlands) and Yvoir (France).8 Previous single-centre studies in England reported metronidazole resistance rates of 29% for Gloucester,9 36% for Chelmsford11 and 40% for Sheffield.10 However, in an East London subpopulation, resistance rates varied according to ethnic origins: 37% for UK-born, 67% for non-UK born and 90% for patients from the Bangladeshi community.9 The European study showed likewise that ethnic origin (non-Caucasian versus Caucasian) was significantly associated with resistance to metronidazole.8 Our rate was consistent, therefore, with the low ethnic diversity of the local population and indicates low previous use of metronidazole. It is important to note, however, when comparing different sets of data that variations in rates may arise because of the effects of interlaboratory reproducibility caused by the lack of standardized testing protocols, particularly for metronidazole.8 Regional differences in rates of *H. pylori* metronidazole resistance are not fully understood but have been attributed to variations in prescribing practice; for instance in some countries policies on macrolide use are lax, and such antibiotics are used widely for parasitic infections, and for vaginal and dental infections.20

We detected a two-fold increase in the metronidazole resistance rate over the 3 year period of the survey—however, this difference was not significant and was consistent with the findings from Chelmsford, also over 3 years,11 and from Sheffield over 5 years.10 Although the numbers of resistant isolates reported annually in those studies were too small for rigorous

**Table 2.** Patterns of primary antibiotic susceptibility of *H. pylori* from gastric biopsies in North Wales (2000–2003) according to gender and age group

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age (years)</th>
<th>MtzS/ClaS</th>
<th>MtzI/ClaS</th>
<th>MtzR/ClaS</th>
<th>MtzR/ClaR</th>
<th>MtzS/ClaR</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>≤20</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>21–50</td>
<td>28</td>
<td>0</td>
<td>11</td>
<td>1</td>
<td>3</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>≥51</td>
<td>96</td>
<td>1</td>
<td>21</td>
<td>6</td>
<td>0</td>
<td>124</td>
</tr>
<tr>
<td></td>
<td>total (%)</td>
<td>124 (74.3)</td>
<td>1 (0.5)</td>
<td>32 (19.2)</td>
<td>7 (4.2)</td>
<td>3 (1.8)</td>
<td>167</td>
</tr>
<tr>
<td>Female</td>
<td>≤20</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>21–50</td>
<td>21</td>
<td>1</td>
<td>14</td>
<td>2</td>
<td>2</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>≥51</td>
<td>109</td>
<td>2</td>
<td>27</td>
<td>4</td>
<td>9</td>
<td>151</td>
</tr>
<tr>
<td></td>
<td>total (%)</td>
<td>135 (68.9)</td>
<td>3 (1.5)</td>
<td>41 (20.9)</td>
<td>6 (3.1)</td>
<td>11 (5.6)</td>
<td>196</td>
</tr>
<tr>
<td></td>
<td>Total (%)</td>
<td>259 (71.3)</td>
<td>4 (1.1)</td>
<td>73 (20.1)</td>
<td>13 (3.6)</td>
<td>14 (3.9)</td>
<td>363</td>
</tr>
</tbody>
</table>

Mtz, metronidazole; Cla, clarithromycin; S, susceptible; I, intermediate susceptibility; R, resistant.

**Table 3.** Distribution of *H. pylori* by genotype and antibiotic susceptibility pattern

<table>
<thead>
<tr>
<th>Genotype</th>
<th>MtzS/ClaS (n = 141)</th>
<th>MtzI/ClaS (n = 2)</th>
<th>MtzR/ClaS (n = 31)</th>
<th>MtzR/ClaR (n = 6)</th>
<th>MtzS/ClaR (n = 3)</th>
<th>Total (n = 183)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cagA+/vacA s1m1</td>
<td>50</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>56 (30.6)</td>
</tr>
<tr>
<td>cagA+/vacA s1m2</td>
<td>49</td>
<td>1</td>
<td>17</td>
<td>5</td>
<td>1</td>
<td>73 (39.9)</td>
</tr>
<tr>
<td>cagA+/vacA s2m2</td>
<td>6</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>7 (3.8)</td>
</tr>
<tr>
<td>cagA+/vacA s1+s2m2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>cagA+/vacA s1m1+m2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>cagA−/vacA s1m1</td>
<td>6</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>7 (3.8)</td>
</tr>
<tr>
<td>cagA−/vacA s1m2</td>
<td>22</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>30 (16.4)</td>
</tr>
<tr>
<td>cagA−/vacA s2m2</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8 (4.4)</td>
</tr>
</tbody>
</table>
Antibiotic resistance of *H. pylori* in North Wales

analysis, there was no indication that metronidazole resistance rates, while remaining relatively high (>36%), had changed significantly, which would suggest that metronidazole use in the local populations had remained relatively stable. An interesting finding of the European study was that metronidazole resistance was significantly higher in females than in males, and a similar effect was also observed in Sheffield but that ended at 60 years of age. In contrast, we found no sex differences in the North Wales patient population; for instance in the ≥51 age group the female to male ratios were similar (21% versus 22%), and that was in agreement with a survey performed on patients in the rural northern part of the Netherlands. The reasons for gender differences in metronidazole resistance remain unclear but it has been suggested that they could be accounted for by its use in treating gynecological infections in some regions. For Bangor, the lack of a gender difference may be attributable to the high proportion of female patients aged ≥51 years in the study population and the low ethnic diversity of the local population, so that there were fewer females who might have acquired resistant isolates as a result of previous treatment than in other countries.

In the case of clarithromycin, the second most widely used antibiotic in *H. pylori* eradication therapy, our resistance rate of 7% in Bangor was similar to the 9% rate for isolates originating from the central/eastern region of Europe. In contrast, the resistance rates for the northern and southern regions of Europe were 4% and 18%, respectively, while a rate of 4% was reported over 3 years (1995–1998) in Chelmsford. The number of isolates from Bangor was insufficient to establish any significant sex- or age-related differences in resistance rates, although it was notable for the ≥51 age group that the female resistance rate was slightly higher but not of significance (P = 1.0). The main finding of the multicentre European study in relation to clarithromycin was that resistance was significantly higher in children and teenagers, and also that there was a general north to south gradient of increasing resistance within Europe. That aspect could not be examined in the present study, as there were only five patients aged <20 years, and the isolates were fully susceptible.

Isolates of *H. pylori* with resistance to both metronidazole and clarithromycin have been recognized as difficult to eradicate. Dual resistance may compromise the effectiveness of current triple therapy regimens, and was a feature of ~87% of patients who failed therapy at two centres in Germany. Interestingly, our analysis of resistance patterns showed that isolates with dual resistance were relatively uncommon (4%) in the North Wales study population. When the small numbers of clarithromycin-resistant isolates are taken into account, our rate was in line with pretreatment dual resistance isolates of 6% in Chelmsford. In the European study, dual resistance was observed in 14 centres and exceeded 5% in eight of them. Although the dual antibiotic resistance profile of *H. pylori* was not gender- or age-related, all such isolates described in the present study had high-level MICs of ≥256 mg/L of both antibiotics and so could be viewed as potentially difficult to eradicate. The fact that 48% (13/27) of all the clarithromycin-resistant isolates were also resistant to metronidazole was suggestive of exposure to previous eradication therapy, as there is no genetic basis to explain a link between resistance to these two antibiotics. Clarithromycin resistance is determined mainly by mutations in the 23S ribosomal RNA gene, whereas the mechanisms for metronidazole resistance, in so far as they are understood, may be partly due to mutations in nitroreductase genes. Furthermore, our analysis indicated that resistance to clarithromycin and metronidazole can arise independently as 4% of isolates were resistant only to clarithromycin—a pattern not previously described.

*cagA* and *vacA* genotype markers are widely used to characterize *H. pylori* virulence in relation to disease severity although direct associations with peptic ulcer and gastric cancer have not been established. The development of severe histological changes in the gastric mucosa may depend on the synergic effect of bacterial and host factors. Our analysis of the epidemiology of such strain markers showed that the frequency of distribution of the various genotypes in North Wales was similar to that reported previously for isolates from dyspeptic patients in the Chelmsford area as most were *cagA* positive and had either the *vacA* s1m1 or the *vacA* s1m2 genotype. While isolates within the two main susceptibility groups were genotypically diverse, there was an indication that resistant isolates contained a higher proportion of m2 forms. As such isolates are thought to induce less inflammation in the host gastric epithelia, their presence may be a contributory factor in reducing antibiotic delivery and could hinder eradication of *H. pylori*. At the molecular level, there is no theoretical basis for predicting an association between antibiotic resistance and *cagA*/*vacA* genotype, as such loci appear to be neither physically nor functionally linked by genome organization. Similarly, a study of isolates in the Netherlands also failed to find any general association between such virulence markers and antibiotic resistance although it was noted that cure rates seemed to be higher for patients with *cagA*+/*vacA* s1 strains.

In summary, our study has shown that metronidazole resistance is a feature of *H. pylori* isolates from at least a quarter of all dyspeptic patients in the Bangor area whereas resistance to clarithromycin occurs at a lower rate (7%). For the resistant isolates, the MICs were frequently at a high level (≥256 mg/L). The proposal for a ‘test and treat’ strategy for management of dyspeptic patients in the UK increases the risk of future rises in resistance rates due to indiscriminate use of antibiotics. For instance, it is established in the mouse model that exposure to metronidazole readily induces resistance. It is therefore important to continue monitoring antibiotic resistance to obtain accurate information on local rates, particularly that of high-level resistance to clarithromycin and metronidazole. Such information should guide selection of the most effective treatment regimens, as recommended in the Maastricht Consensus guidelines, and can be used to establish the precise clinical impact of *in vitro* *H. pylori* antibiotic resistance on eradication.

**Acknowledgements**

The work was supported in part by a Public Health Laboratory Service Central Research and Development Fund Studentship (1999–2002) awarded to N.C.E.

**References**


