Helicobacter pylori antibiotic-resistance patterns and risk factors in adult dyspeptic patients from ethnically diverse populations in central and south London during 2000

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Surveillance of Helicobacter pylori antibiotic susceptibility from patients in London, the largest metropolitan area in the UK, is limited, despite resistance being a key factor in treatment failure. A two-centre survey was performed over 12 months (1999–2000) to determine antibiotic-resistance rates of isolates from dyspeptic patients attending endoscopy clinics serving two ethnically diverse central and south London communities. The in vitro antibiotic susceptibilities were determined from disc diffusion and epsilometer (E) tests on 101 H. pylori isolates. Overall resistance rates were 59 % for metronidazole and 11 % for clarithromycin, with 8 % resistance to both antibiotics. Corresponding primary resistance rates were 50 % and 7 %, respectively. High-level-resistance was a feature of 82 % of the metronidazole (MIC > 256 mg l⁻¹) -resistant and 55 % of the clarithromycin (MIC > 32 mg l⁻¹) -resistant strains. All isolates were susceptible to amoxicillin and tetracycline. No associations between resistance and either the gender or the age of the patients were detected. The main risk for resistance to metronidazole was non-UK birth as comparative rates were 68 % for non-UK vs. 40 % for UK-born individuals. Resistant isolates were genotypically diverse with respect to cagA/vacA type. Four 23S rDNA nucleotide polymorphisms were associated with clarithromycin resistance, mostly (9/11) at A2143G. In conclusion, the high overall metronidazole-resistance rate of 59 % for H. pylori from inner London was twice the rate found in other UK-based studies and was attributed to the higher risk of resistant strains infecting individuals born outside the UK. The need for continued resistance surveillance is indicated to monitor the effects of the ‘test and treat’ strategy for H. pylori eradication, particularly of isolates from at-risk individuals.

INTRODUCTION

Over the past two decades, the Gram-negative microaerobic bacterium Helicobacter pylori has been found infecting the gastric mucosa of humans worldwide, including an estimated 7.5 million people in England and Wales (Vyse et al., 2002). The organism induces a chronic gastritis and, although associated clinical disease presentations develop in less than 20 % of individuals, is recognized as a cause of peptic ulcer disease and associated with lymphoproliferative disorders as well as the development of gastric carcinoma (Suerbaum & Michetti, 2002). Some evidence also suggests infection with H. pylori as a possible trigger factor in the development of chronic cardiovascular disease (Aceti et al., 2004).

Eradication therapy is central to the treatment of H. pylori infection in duodenal ulcer and other at-risk patients, and a
'test and treat' policy is recommended by guidelines in the UK for the management of uncomplicated dyspepsia (NICE, 2003; SIGN, 2003). Commonly used therapies are based on administering combinations of two antibiotics (from clarithromycin, metronidazole, amoxycillin and tetracycline) with an acid suppressor, usually a proton-pump inhibitor. Treatment is successful in about 80% of cases (Harris & Misiewicz, 2001). However, pre-treatment resistance, in particular to clarithromycin, has a dramatic effect on clinical outcome (Mégraud, 2001). Failure to eradicate may be due to non-compliance in some cases, but antibiotic resistance is recognized as a significant problem, as indicated by a meta-analysis of various clinical trials (Dore et al., 2000) and the fact that post-treatment failures have a high rate of infection with resistant strains (Heep et al., 2000; Kist & Glocker, 2004).

Various surveillance studies have shown that 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 (Glupczynski et al., 2001). There is no systematic surveillance of primary antibiotic resistance in London, the largest ethnically diverse metropolitan area in the UK, although widely divergent rates depending on patient ethnic origin were reported in a single-centre study in east London (Banatvala et al., 1994). Resistance rates of 29–40% for metronidazole and 1–7% for clarithromycin have been reported for several regional populations in England, notably Ipswich (Cameron et al., 2004), Gloucester (Glupczynski et al., 2001), Sheffield (Parsons et al., 2001), Chelmsford (Teare et al., 1999) and north Wales (Elviss et al., 2004a).

To further improve our understanding of variation in H. pylori antibiotic-resistance rates in different regions of the UK, we undertook the present study of isolates from patients attending two London hospitals (one central London and one south London). Populations in inner London are ethnically diverse and previous exposure to antibiotics particularly metronidazole, in treatment of other infections may be high, as indicated by previous data from patients in east London (Banatvala et al., 1994). Host factors (gender, age, ethnicity and gastric disease associations) and associations with two putative strain virulence markers – presence of the cagA locus in the cag pathogenicity island, and allelic variants of the vacuolating cytotoxin gene (vacA) (Suerbaum & Michetti, 2002) – were investigated in relation to H. pylori antibiotic resistance. Also mutations in the 23S rRNA gene associated with clarithromycin resistance (Owen, 2002) were investigated as additional epidemiological markers in relation to high-level-resistance in isolates from patients in London.

**METHODS**

**Bacterial strains.** A total of 402 routine diagnostic gastric (antral) biopsies were obtained from consecutive patients with a variety of upper gastrointestinal tract symptoms undergoing routine investigation over a 12-month period (December 1999 to December 2000) in endoscopy clinics at two hospitals serving inner London GP practices (Hospital 1, University College London Hospitals, WC1, 185 biopsies; and Hospital 2, St George’s Hospital, SW17, 217 biopsies). Hospital 1 serves two boroughs with a population of 373 000 people and hospital 2 serves three boroughs with a population of about 677 000 people. Black and ethnic minority groups constitute about 25% of the populations, the largest groups of which are Bangladeshi, Black African, Indian and Black Caribbean. Each specimen was accompanied by a special report form (40 variables) to record age, gender, demographic and clinical disease information including known history of previous H. pylori eradication therapy. Multiple biopsies from different sampling sites of the same patient were excluded.

All biopsies were transported for analysis at the reference laboratory in a medium comprising 3·7% (v/v) brain heart infusion broth (Oxoid), 2·5% yeast extract (Oxoid), 5% sterile horse serum (TCS Biosciences) and the Dent H. pylori selective antibiotic supplement containing vancomycin (10 mg l−1), cefsulodin (5 mg l−1), trimethoprim (5 mg l−1) and amphotericin B (5 mg l−1) (Oxoid). Primary culture of H. pylori was performed according to standard operating procedures on Columbia agar base with 10% (v/v) defibrinated horse blood (10% CBA) and on Dents selective agar at 37°C under microaerobic conditions (4% O2, 5% H2, 5% CO2 and 86% N2) in a MACS-VAS500 Microaerophilic Workstation (Don Whitley Scientific). Identity as H. pylori was confirmed by Gram stain and by tests for urease, catalase and oxidase activity.

**Antibiotic-susceptibility testing.** There are no approved standardized methods for testing H. pylori antimicrobial susceptibilities and the protocols used in this study were based on previously published guidelines provided by the British Society for Antimicrobial Chemotherapy (Andrews, 2003), the USA National Committee for Clinical Laboratory Standards (NCCLS, 1999), the European H. pylori Study Group (Glupczynski et al., 2001) and the PHLS Helicobacter Working Group (McNulty et al., 2002). Briefly, exponential growth from a 48 h culture was suspended in maximum recovery diluent (Oxoid) to a density equivalent to a McFarland number 4 standard (approximately 12·108 cfu ml−1) (Remel). A pre-dried 10% CBA plate was inoculated with the culture suspension and either an Etest strip (AB Biodisk) or an antibiotic disc (Oxoid) was placed on the surface of the medium. Tests for in vitro susceptibility to metronidazole, clarithromycin, amoxycillin and tetracycline were performed as described previously (Elviss et al., 2004a). Reference strains NCTC 13206 (CCUG 38770) and NCTC 13207 (CCUG 38772) were included as quality controls (Glupczynski et al., 2001).

Susceptibility results were recorded as resistant according to the following interpretive criteria: for clarithromycin, no zone of growth inhibition (2 μg disc) and breakpoint MIC ≥ 2 μg ml−1 (high-level-resistance was defined as MIC ≥ 32 μg ml−1), and for metronidazole, a growth inhibition zone <16 mm (5 μg disc) and breakpoint MIC ≥ 8 μg ml−1 (high-level-resistance was defined as MIC ≥ 256 μg ml−1). Intermediate susceptibilities (MIC ≥ 2 to <8 μg ml−1 or 16–21 mm zone of growth inhibition) were also recorded for metronidazole. Breakpoint MICs used for amoxycillin and tetracycline were ≥0·5 μg ml−1 (Glupczynski et al., 2001) and ≥4 μg ml−1, respectively; disc tests were not performed for these antibiotics.

**Strain genotyping.** Genomic DNA was extracted from sweep cultures of H. pylori, 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 cagI region), using the D008/R008 primer set, were as described previously (Owen et al., 2002). Vacuolating cytotoxin (vacA) genotyping based on signal (s)- and mid (m)-region alleles was performed using a multiplex assay (Chisholm et al., 2002).

**Detection of clarithromycin-resistance-associated mutations.** The 3′-mismatched reverse primer PCR was used according to
previously described protocols to detect clarithromycin-resistance-associated mutations in 23S rRNA genes for all isolates with in vitro resistance (Elviss et al., 2004b).

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

RESULTS

Individual antibiotic susceptibilities

Over the 12-month study period from December 1999 to December 2000, a total of 101 isolates of *H. pylori* were cultured from the 402 gastric biopsies received (representing an isolation rate of 25%). Overall single-antibiotic-resistance rates (Etest results) for isolates from both hospitals were 11% (11/101) for clarithromycin (six isolates from men vs. five from women) and 59% (60/101) for metronidazole (30 isolates from men vs. 27 from women, plus three patients with gender unspecified). One culture from a female patient (Hospital 1) interpreted as intermediate to metronidazole, was recorded as susceptible in the overall analysis. The results (Hospital 1) interpreted as intermediate to metronidazole, had an Etest MIC of ≤1 mg l⁻¹ (susceptible). Five were susceptible by Etest (MIC results all ≤1 mg l⁻¹) but had a resistant disc diffusion zone of <16 mm, and one was intermediate by Etest (MIC 6 mg l⁻¹) but was resistant (zone 0 mm) by disc diffusion.

Combined antibiotic susceptibilities

Each isolate of *H. pylori* was characterized by the assignment of a susceptibility pattern based on its combined susceptibilities to metronidazole and clarithromycin (Table 1). The frequencies of patterns in each hospital showed no marked differences in the two patient populations. Overall, 38% of strains were fully sensitive (MtzS-ClaS) or intermediate (MtzI-ClaS), whereas 52% were resistant only to metronidazole (MtzR-ClaS). Eight strains (8%) were resistant to both antibiotics (MtzR-ClaR), with high-level-resistance to both being a feature of two isolates. Three isolates (3%) were resistant just to clarithromycin (MtzS-ClaR) and two of these (H1531 and H1696) had high-level-resistance.

Host factors and resistance – variation by gender

The patients studied comprised 54 men aged between 22 and 90 years (median 60±8 years) and 44 women aged between 16 and 92 years (median 65±1 years). Analysis of *H. pylori* antibiotic resistance in relation to gender using the pooled data available on 98 patients for the two centres (Table 1) showed that males and females were infected in similar proportions by metronidazole-resistant isolates, with a rate of 56% (29/54) for men vs. 59% (27/44) for women.

![Fig. 1. Distribution of antibiotic susceptibilities (MICs) estimated by Etest for *H. pylori* from gastric biopsies of dyspeptic patients over 1 year in inner London (1999–2000). MIC results for metronidazole are shown in hatched and grey, representing hospitals 1 and 2, respectively. MIC results for clarithromycin are shown in black and white, representing hospitals 1 and 2, respectively. Cla, clarithromycin; Mtz, metronidazole; I, intermediate; R, resistant; S, susceptible.](http://jmm.sgmjournals.org)
Likewise, analysis of clarithromycin results showed similar proportions of resistant isolates infecting men (11%, 6/54) and women (14%, 5/44). The results also highlighted the fact that both male and female patients contained a small proportion (8–9%) of dual-resistant (MtzR-ClaR) isolates and that the gender distribution of high-level-resistance was identical, but possibly attributable to the small sample size.

**Host factors and resistance – variation by age**

The distribution of antibiotic-susceptibility patterns in relation to age is shown in Table 2. Most patients (51/98, 52%) were in the 21–50 years age cohort, whereas 33 were aged between 51 and 70 years. Only one patient was aged <20 years, and the *H. pylori* strain associated with this patient had high-level-resistance to metronidazole but was susceptible to clarithromycin. Resistance to antibiotics was widely distributed amongst strains irrespective of patient age and no gender associations were evident in the age groups.

**Host factors and resistance – variation by place of birth**

Demographic details (place of birth) were available for 83 patients, these indicated diverse origins, with 36% (30/83) from the UK. The non-UK born patients originated (in order of frequency) from Asia (22%, 18/83), north and south America (17%, 14/83), Africa (13%, 11/83) and continental Europe (12%, 10/83). Overall, 68% (36/53) of strains from non-UK patients were metronidazole resistant compared to 40% (12/30) of those from UK patients – a difference that was statistically significant ($P = 0.02$, or $0.315$, 95% CI $0.12–0.8$). By contrast, clarithromycin resistance showed no association with the place of birth of the patient. However, the numbers were small as details were available for only seven of the patients infected with a clarithromycin-resistant strain, and four of those were UK-born. Likewise, for the 89 patients recorded as UK-born irrespective of ethnicity, 40% (14/35) were resistant to metronidazole, compared to 69% (37/54) of those born outside the UK, a difference that was also statistically significant ($P = 0.009$, or $0.306$, 95% CI $0.126$ to $0.744$).

**Table 1. Distribution of *H. pylori* by patterns of strain antibiotic susceptibility and gender of patients from two hospitals in London (1999–2000)**

M, male patients; F, female patients; Mtz, metronidazole; Cla, clarithromycin; S, susceptible; I, intermediate susceptibility; R, resistant.

| Susceptibility pattern | No. of isolates | Hospital 1 | | Hospital 2 | | Both hospitals |
|------------------------|----------------|-----------|-----------|-----------|-----------|
|                        | M/F Total*     | M/F Total* | M/F Total* |
| MtzS-ClaS              | 13/8 (39)      | 9/8 (36)   | 22/16 (38) |
| MtzS-ClaR              | 1/0 (2)        | 1/1 (4)    | 2/1 (3)    |
| MtzR-ClaS              | 14/9 (48)†     | 12/14 (55)| 26/23 (52)|
| MtzR-ClaR              | 3/3 (11)       | 2/4 (4)    | 4/4 (8)    |
| All patterns           | 54             | 47         | 101        |

*Data represented as no. (%).
†Three additional isolates were from patients whose gender was not recorded.

**Table 2. Antibiotic-susceptibility patterns of *H. pylori* by age group and gender of infected patients**

Gender details were not available for three patients with the MtzR-ClaS resistotype.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>No. of isolates (from male/female patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total ($n = 98$)</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>1/0</td>
</tr>
<tr>
<td>21–50</td>
<td>31/20</td>
</tr>
<tr>
<td>51–70</td>
<td>17/16</td>
</tr>
<tr>
<td>&gt;71</td>
<td>7/3</td>
</tr>
</tbody>
</table>
Host factors and resistance – variation by disease presentation

Data for disease presentation were available for 85 patients, and these were categorized into three groups: isolates from patients with endoscopically defined peptic ulcer disease (28 strains), non-ulcer dyspeptics with endoscopic evidence of gastritis and other inflammatory diseases (22 strains) and non-ulcer dyspeptics with normal endoscopy (35 strains). Metronidazole-resistance rates in each of these groups were 50% (14/28), 59% (13/22) and 57% (20/35), respectively. The corresponding clarithromycin-resistance rates were 4% (1/28), 14% (3/22) and 14% (5/35), respectively.

Host factors and resistance – previous therapy

For the 82 patients on whom information about previous anti-

H. pylori therapy was documented, 89% (73/82) were reported as not having received eradication therapy. The overall primary resistance rates for this untreated group were 50% for metronidazole and 7% for clarithromycin. The resistotypes of strains from those patients who had received therapy were MtzS-ClaS (four strains), MtzR-ClaS (four strains) and MtzR-ClaR (one strain). Details of the previously prescribed therapy were only available for three of these patients. All three were prescribed with a combination therapy of lansoprazole, amoxycillin and clarithromycin, two patients had a MtzR-ClaS strain and the other had a MtzS-ClaS strain.

Strain genotype and resistance

Genotypes (cagA status and vacA allelic form) were determined for 100 isolates of H. pylori. The numbers of strains grouped by antibiotic-susceptibility pattern, combined genotype and geographic origin are shown in Table 3. Most isolates were cagA-positive (81%) and these were either vacA type s1m1 (48%) or s1m2 (30%), with three isolates that were s2m2. For the cagA-negative isolates, the vacA m2 form was a feature of most (18/19) isolates, of which 11 (58%) were vacA s1m2. The two predominant susceptibility patterns (MtzS-ClaS and MtzR-ClaS), which represented 86% of isolates, were genotypically diverse.

High-level-resistance to either metronidazole or clarithromycin was not associated with a particular vacA genotype as most strains irrespective of resistotype had the vacA s1 allele. The distribution of the mid-region alleles was more variable. Overall, 61% (31/51) of the m2 isolates and 57% (28/49) of the m1 isolates were resistant to metronidazole.

We also performed mismatched PCR analyses to determine the specific mutations associated with resistance in the 11 clarithromycin-resistant isolates of H. pylori (Table 4). The most frequent mutation, present in nine strains, was A2143G, and five of these were specifically associated with high-level-resistance to clarithromycin. One strain (H1531) had polymorphisms at positions A2142G and A2143G and their presence was confirmed by single colony analysis.

DISCUSSION

We report on a survey over 12 months, during 1999–2000, of H. pylori antimicrobial-susceptibility levels from patients undergoing routine endoscopy at centres in central and south London. The overall mean metronidazole-resistance rate for H. pylori of 59% in these locations was markedly higher than the mean European primary resistance rate of 33% derived from a multicentre study performed in 1998 (Głupczynski et al., 2001). Our rate had the highest similarity to the 62% rate recorded in Helsinki, Finland (Głupczynski et al., 2001). Previous single-centre studies in England reported lower metronidazole-resistance rates of 29% for Gloucester (Głupczynski et al., 2001), 32% for Bangor (Elviss et al., 2004a) and Ipswich (Cameron et al., 2004), 36% for Chelmsford (Teare et al., 1999) and 40% for Sheffield.
(Parsons et al., 2001). It is important to note, however, when comparing different sets of data that the significance of variations between rates in the order of 5% cannot be precisely assessed, because of the possible effects of inter-laboratory reproducibility caused by the lack of standardized testing protocols, particularly for metronidazole (Glupczynski et al., 2002). Even so, the underlying primary metronidazole-resistance rate determined in the present study was 50%, which is still markedly higher than the rates of 29–40% reported at the other UK locations.

Analysis of the demographic data indicated that place of birth was a key determinant for an increased risk of infection with a metronidazole-resistant strain, with a rate of 69% for non-UK birth compared to 40% for UK birth. These findings were consistent with the findings of the European study that ethnic origin (non-Caucasian vs. Caucasian) was significantly associated with resistance to metronidazole (Glupczynski et al., 2001). Ethnicity was not investigated in the other UK studies except for Banatvala et al. (1994), who reported marked local differences in an east London patient population according to ethnic origins, with resistance rates varying from 37% for UK born, to 67% for non-UK born and to 90% for patients from the local Bangladeshi community. The isolates from 18 Asian patients in our study group also had a high resistance rate (83%) to metronidazole, which possibly reflected local rates in the country of origin. In India, for example, resistance rates of 78% to metronidazole, 45% to clarithromycin and 33% to amoxicillin have been reported (Thyagarajan et al., 2003). These rates probably result from indiscriminate use of such antibiotics for treatment of parasitic and other infections, although the reason why high rates for clarithromycin and amoxicillin resistance are not more common in isolates from our non-UK born individuals is unclear. Amoxicillin resistance can be unstable in *H. pylori*, but clarithromycin resistance associated with mutations in the 23S rDNA is stable under *in vitro* conditions (Owen, 2002). A prospective multicentre program monitoring *H. pylori* resistance in the USA also found on multivariate analysis that black race was the only significant risk factor for infection with a resistant strain (Duck et al., 2004). Likewise, a US national meta-analysis using data from 20 clinical trials of *H. pylori* eradication showed that white persons had a relatively low incidence of metronidazole resistance compared with persons of other ethnicities, while Asian persons had the highest incidence – the reason for this was unclear (Meyer et al., 2002).

A notable finding of the European study was that metronidazole resistance was more common in females than males (Glupczynski et al., 2001), and a similar association was observed in Sheffield in patients less than 60 years old (Parsons et al., 2001) and in Suffolk, where resistance was also common in younger persons (Cameron et al., 2004). By contrast we found no marked gender differences in resistance rates for the two inner London patient populations, which was similar to our findings for north Wales (Elviss et al., 2004a). These regional resistance rate variations with gender remain unexplained in the UK.

Strains are genomically diverse and there are no particular *cagA* or *vacA* forms specifically associated with metronidazole resistance. The mechanisms for metronidazole resistance in so far as they are understood may be partly due to mutations in nitroreductase genes, but these do not provide reliable epidemiological markers (Chisholm & Owen, 2003).

In the case of clarithromycin, the second of the most commonly used antibiotics in *H. pylori* eradication therapy, our resistance rate of 11% in London was most similar to the

### Table 4. Genomic characteristics of clarithromycin-resistant isolates of *H. pylori* and demographic details of infected patients from two London hospitals

<table>
<thead>
<tr>
<th>Isolate number</th>
<th>Hospital</th>
<th>Cla MIC (mg l⁻¹)</th>
<th>23S rRNA mutation</th>
<th>Mtz MIC (mg l⁻¹)</th>
<th>Genotype</th>
<th>Patient</th>
</tr>
</thead>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H1531</td>
<td>2</td>
<td>&gt;32</td>
<td>A2142G &amp; A2143G</td>
<td>0-5</td>
<td>+</td>
<td>s1m1</td>
</tr>
<tr>
<td>H1579</td>
<td>1</td>
<td>&gt;32</td>
<td>A2143G</td>
<td>24</td>
<td>–</td>
<td>s2m2</td>
</tr>
<tr>
<td>H1616</td>
<td>1</td>
<td>&gt;32</td>
<td>A2143G</td>
<td>96</td>
<td>+</td>
<td>s1m1</td>
</tr>
<tr>
<td>H1696</td>
<td>1</td>
<td>&gt;32</td>
<td>A2142G</td>
<td>0-25</td>
<td>+</td>
<td>s1m1</td>
</tr>
<tr>
<td>H1830</td>
<td>1</td>
<td>&gt;32</td>
<td>A2142C</td>
<td>&gt;256</td>
<td>+</td>
<td>s1m1</td>
</tr>
<tr>
<td>H1908</td>
<td>1</td>
<td>&gt;32</td>
<td>A2143G</td>
<td>&gt;256</td>
<td>+</td>
<td>s1m1</td>
</tr>
<tr>
<td>H2149</td>
<td>2</td>
<td>8</td>
<td>A2143G</td>
<td>&gt;256</td>
<td>+</td>
<td>s1m2</td>
</tr>
<tr>
<td>H2157</td>
<td>2</td>
<td>8</td>
<td>A2143G</td>
<td>&gt;0-94</td>
<td>+</td>
<td>s1m2</td>
</tr>
<tr>
<td>H2162</td>
<td>2</td>
<td>12</td>
<td>A2143G</td>
<td>&gt;256</td>
<td>–</td>
<td>s1m1</td>
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<td>&gt;256</td>
<td>+</td>
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</tr>
<tr>
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<td>1</td>
<td>12</td>
<td>A2143G</td>
<td>&gt;256</td>
<td>+</td>
<td>s1m2</td>
</tr>
</tbody>
</table>

*Numbers in bold indicate isolates that were dual resistant to clarithromycin and metronidazole.*
Isolates of *H. pylori* with resistance to both metronidazole and clarithromycin are recognized as difficult to eradicate (Mégraud, 2001). Dual resistance to these antibiotics may compromise the effectiveness of current triple-therapy regimens, and was a feature of about 87% of the patients who failed therapy at two centres in Germany (Heep et al., 2000). A nationwide German sentinel study for surveillance of antimicrobial resistance in *H. pylori* concluded that repeated empirical treatment regimes were especially associated with post-treatment presence of strains exhibiting dual resistance to metronidazole and clarithromycin (Kist & Glover, 2004). Interestingly, our analysis of resistance patterns showed that isolates with dual resistance were relatively uncommon and only represented 8% of the isolates in the London study populations, and were a feature of both UK- and non-UK-born individuals.

Although the number of clarithromycin-resistant isolates is small, our rate was in line with the pre-treatment dual-resistance rate of 6% in Chelmsford (Teare et al., 1999). In the European study of pre-treatment isolates, dual resistance was observed in 14 centres and exceeded 5% in eight of them (Glupczynski et al., 2002). Dual antibiotic resistance in *H. pylori* was not sex- or age-related, nor a feature of any particular strain genotype, but six such isolates described in the present study had high-level MICs of $>256$ mg l$^{-1}$ to metronidazole and such isolates could be viewed as potentially difficult to eradicate. Our analysis also indicated that resistance to clarithromycin can arise in metronidazole-susceptible strains – the MtxZ-ClaR susceptibility type currently represents only 3% of isolates as previously observed in the Bangor survey (Elviss et al., 2004a). Such isolates do not have unique genotypes according to cagA, vacA and 23S rDNA markers. However, the epidemiology of strains with single resistance to clarithromycin needs to be monitored further as they could contribute significantly to treatment failure (Dore et al., 2000).

In summary, our 12-month study showed that antibiotic resistance, in particular metronidazole resistance, was a feature of *H. pylori* from over half of the gastric biopsies of dyspeptic patients from the two inner London population study groups, and that non-UK birth was a significant risk factor for being infected by such a strain. With the proposals for a ‘test and treat’ strategy for management of dyspeptic patients in the UK (NICE, 2003; SIGN, 2002), there is a risk of future increases in antibiotic resistance if empirical treatment is used. It is therefore important to continue monitoring antibiotic resistance to have accurate information on local rates, particularly for high-level-resistance within at-risk groups, to guide selection of the most specific and appropriate treatment regimens as recommended in the Maastricht Consensus guidelines (Malfertheiner et al., 2002).

**REFERENCES**


