Characterization of rifampicin-resistant clinical *Helicobacter pylori* isolates from Germany

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Received 31 October 2006; returned 14 December 2006; revised 25 January 2007; accepted 29 January 2007

Objectives: The aim of this study was to assess the rate of rifampicin resistance in *Helicobacter pylori* isolated from patients in Germany, to detect rifampicin resistance-associated mutations and to identify non-resistance-associated genetic variants in the *rpoB* gene.

Methods: Susceptibility to rifampicin in a total of 1585 clinical isolates obtained between January 2003 and July 2006 was tested by disc diffusion and/or by the Etest method. The *rpoB* genes of a selection of both resistant (*n* = 17) and susceptible (*n* = 100) clinical isolates were sequenced in order to distinguish between resistance- and non-resistance-associated genetic alterations. *In vitro* mutagenesis experiments such as site-directed mutagenesis were carried out to demonstrate the pivotal role of *rpoB* mutations in rifampicin resistance.

Results: From 1585 clinical isolates examined, 22 (1.4%) showed phenotypic resistance to rifampicin (MIC >4 mg/L). The majority of the resistant strains harboured point mutations in their *rpoB* genes at codons 530, 540 and 545 and showed cross-resistance to rifabutin. Four clinical isolates with moderate rifampicin resistance (8 mg/L) showed a rifabutin-susceptible phenotype and did not harbour any mutation in the sequenced *rpoB* fragments. Sequence analysis of 100 rifampicin-susceptible isolates revealed numerous novel silent mutations in the *rpoB* genes resulting in amino acid exchanges, but not in resistance.

Conclusions: Resistance to rifampicin/rifabutin in *H. pylori* strains isolated in Germany is still low and is associated with mutations in the *rpoB* gene. Further surveillance studies analysing the use of rifabutin in *H. pylori* eradication and its association with the occurrence of rifabutin-resistant strains are required.

Keywords: antibiotic resistance, mutations, RpoB, rifabutin

Introduction

*Helicobacter pylori* colonizes worldwide more than half of the human population, causes chronic gastritis in all infected individuals and is associated with complications such as peptic ulcer diseases, mucosa-associated lymphoid tissue (MALT) lymphoma or gastric cancer.¹,² In Germany, eradication is recommended using a standard regimen consisting of clarithromycin and amoxicillin or metronidazole in combination with a proton pump inhibitor.³

More recently, drug-resistant *H. pylori* strains have become an increasing clinical problem and pose a challenge for gastroenterologists. Rifabutin-based rescue strategies including amoxicillin and a proton pump inhibitor are useful alternatives, frequently recommended and well tolerated.⁴–⁶ Rifabutin, structurally related to rifampicin, inhibits the β-subunit of the DNA-directed RNA polymerase, abrogates both the RNA and the protein synthesis of bacteria and is more active against *H. pylori* than rifampicin.⁷,⁸ Most knowledge about rifabutin resistance in *H. pylori*, caused by point mutations affecting the *rpoB* gene, is...
due to in vitro generation of rpoB mutants.\textsuperscript{8–11} In vivo, rifabutin resistance is rarely seen, and only one natural resistant clinical isolate that developed resistance during therapy by acquiring a rpoB gene mutation has been described in Germany.\textsuperscript{9}

Since data on rifampicin/rifabutin resistance are poorly documented and comprehensive studies are not yet available, we examined 1585 diagnostic \textit{H. pylori} isolates for their susceptibility to rifampicin. We show that a select number of rpoB mutations play a critical role in rifampicin and/or rifabutin resistance and further demonstrate that other mutations in this gene are not necessarily associated with resistance to rifabutin.

**Materials and methods**

\textit{Gastric specimen, bacterial strains, culture conditions and antimicrobial susceptibility testing}

Between January 2003 and July 2006, a total of 1585 \textit{H. pylori} strains were isolated from gastric tissue samples sent to our diagnostic laboratory by gastroenterologists from all parts of Germany. Isolates were derived from patients suffering from gastritis (n = 789), peptic ulcer disease (n = 203) or malignant diseases such as gastric cancer or MALT lymphoma (n = 11). In 582 cases, data concerning an underlying disease were not available. All isolates investigated in this study were grown on Columbia-agar-based culture medium containing 10% (v/v) washed human erythrocytes and 10% (v/v) heat-inactivated horse serum (HHPlates) under microaerophilic conditions at 37°C for 72 h. Grown bacteria were identified as \textit{H. pylori} by typical morphology, biochemical reactions, Gram-staining and PCR.\textsuperscript{12,13}

Information on antimicrobial pre-treatment was missing for 607 patients, but given for 978 patients. For 88% (n = 859) of these latter patients, prior eradication treatments were reported; 12% (n = 119) were not treated before. Pre-treatments included predominantly amoxicillin/clarithromycin, amoxicillin/metronidazole, metronidazole/clarithromycin or amoxicillin/clarithromycin/metronidazole. In 38 patients, the application of rifabutin due to multiple treatment failures was documented.

Antimicrobial susceptibility to metronidazole, clarithromycin, ciprofloxacin, tetracycline and amoxicillin was tested by the Etest\textsuperscript{6} method (AB Biodisk, Solna, Sweden) as previously described applying the following resistance breakpoints: metronidazole, 8 mg/L; clarithromycin, 1 mg/L; ciprofloxacin, 1 mg/L; amoxicillin, 1 mg/L and tetracycline, 1 mg/L.\textsuperscript{14} Since there is no rifabutin Etest\textsuperscript{6} available, we alternatively tested for susceptibility to rifampicin by using 5 μg rifampicin discs (RA5; Becton-Dickinson, Germany) and the rifampicin Etest\textsuperscript{6} as recommended previously.\textsuperscript{11} Strains with inhibition zone diameters of ≥21 mm were classified as susceptible to rifampicin/rifabutin, and strains exhibiting inhibition zones <21 mm were further tested by rifampicin Etests.\textsuperscript{6} Isolates with MICs >4 mg/L were classified as resistant, and strains with MICs ≤4 mg/L were classified as susceptible to rifampicin.\textsuperscript{11,15}

MICs of rifabutin were determined by serial 2-fold agar dilution according to a modified protocol described previously.\textsuperscript{15} In brief, \textit{H. pylori} were grown for 2 days and suspended in \textit{Brucella} broth supplemented with 5% newborn calf serum (NCS; Invitrogen, Germany). Suspended cells (10\textsuperscript{7} cfu/10 μL) were spotted on Iso-Sensitest culture medium (Oxoid, Germany) containing different rifabutin concentrations ranging from 0.032 up to 64 mg/L. MICs were defined as the lowest concentration that allowed no visible growth or growth of ≤10 cfu after 48 h of incubation at 37°C.

**DNA extraction from culture, amplification of rpoB gene fragments and sequencing**

After culturing \textit{H. pylori} and testing for antimicrobial susceptibility, DNA of a random selection of 100 rifampicin-susceptible and DNA of 17 rifampicin-resistant isolates was isolated using the QIAmp DNA mini kit (Qiagen, Germany). Amplification of a 499 bp PCR product of the rpoB gene (GenBank accession no. AE000625) covering codons 457–622 was performed by using the primers 1369fw (5' - AGGGCACCTTGGAATTGATGAG-3') and 1867rv (5'-TAGCGGTCAAATGAATCGTCAC-3'), amplification of a 1542 bp fragment covering codons 80–593 was performed by using the primers 239Fw (5'-CACCCTAGA GAAGCGATGAGAG-3') and rpoB-1780Rv (Table 1), and amplification of a 947 bp fragment covering the beginning of the rpoB gene (codons 1–248) and the upstream flanking region was carried out by using the primers minus202Fw (5'-GCTTTTTGTGCTTTTTCTGCTC-3') and 744Rv (5'-TGCGTCTAATTGAGC3-3'), respectively (all primers were from Hermann GmbH, Germany). The following PCR conditions were used: 35 cycles including 30 s of denaturation at 94°C, 30 s of annealing at 53°C and 45 s of extension at 72°C.

PCR amplicons were examined by applying 10 μL on a 1.2% agarose gel (Peqlab, Germany) and then purified using the QiAquick PCR purification kit (Qiagen, Germany). Purified PCR products were sequenced with the ABI PRISM BigDye Terminator cycle sequencing ready reaction kit (Applied Biosystems, UK) using the PCR primers as sequencing primers. Three additional primers, 1357Fw (5'-TTGCGCTGATGTTTGGGATAT-3'), 237Fw (5'-TACACCGTTAGAAGCGCATGAG-3') and 350Rv (5'-GATGCCGTCTTGGCCACCTC-3'), were used for sequencing the interior parts of the 947 bp and the 1542 bp PCR products. Sequencing was accomplished with an ABI 310 DNA Sequencer (Applied Biosystems, UK).

**Site-directed mutagenesis and natural transformation**

Site-directed mutagenesis at nucleotides 1588–1590 of the rpoB gene was carried out with a three-step PCR approach by using mutagenesis primers listed in Table 1 (all primers were from Hermann GmbH, Germany), resulting in 429 bp PCR products harbouring the various mutations.\textsuperscript{10} The rifampicin-susceptible \textit{H. pylori} strain 26695 (10\textsuperscript{5} bacteria/mL) was naturally transformed with either 200 ng of these different 429 bp PCR products or with 200 ng of 499 bp rpoB gene fragments from various resistant clinical isolates according to a modified protocol previously described.\textsuperscript{17,18} Transformants were selected on HHP plates containing 16 mg/L of rifabutin. Individual bacterial colonies were picked, suspended in NCS-supplemented \textit{Brucella} broth and subcultured for 72 h on culture medium containing rifabutin (16 mg/L). As a control, \textit{H. pylori} 26695 was incubated with 429 and 499 bp rpoB fragments of a rifampicin-susceptible isolate and water, respectively, which yielded no resistant mutants (data not shown).
Successful transformation was confirmed by PCR and sequencing. All in vitro mutants (ATT 1588–1590, TAT 1588–1590, GTT 1588–1590, GGT 1588–1590, CTT 1588–1590, TTC 1588–1590) harboured the desired single, double or triple base pair mutations at codon 530.

Generation of spontaneous rifampicin-resistant H. pylori mutants

The rifampicin-susceptible H. pylori strain 26695 (~10^9 bacteria/mL) was grown for 72 h in the presence of RA5 discs. Three single clones growing inside the inhibition zone were randomly picked, suspended in Brucella broth (supplemented with 10% NCS), subcultured on rifabutin-containing (16 mg/L) culture medium or on culture medium without antibiotic addition and subsequently sequenced for rpoB mutations. MICs of rifampicin and rifabutin for the selected mutants were determined by Etest and agar dilution, respectively.

In order to examine the stability of the in vitro generated mutants, the resistant clinical isolates and the spontaneous mutants, these strains were subcultured for 10 passages on solid culture medium with and without the presence of rifabutin (16 mg/L). Afterwards, the MICs of rifampicin were again determined by the Etest® method and the genotypes were confirmed by PCR and sequencing.

Results

Proportion of rifampicin-resistant isolates

In a total of 1585 H. pylori routine isolates examined between January 2003 and June 2006, we identified 22 that were rifampicin-resistant (1.4%), with inhibition zones ≤21 mm in the disc diffusion test and MICs >4 mg/L when tested by Etest®.

During the whole period of observation, there was no evidence of an increasing trend in rifampicin resistance (data not shown).

The majority of rifampicin-resistant strains were isolated from patients already pre-treated, these mostly showed additional resistances to metronidazole, clarithromycin and/or quinolones and were susceptible to amoxicillin and tetracycline. In eight patients, we were able to detect H. pylori characterized by quadruple resistance (resistance to metronidazole, clarithromycin, ciprofloxacin and rifabutin; Table 2); in five patients, prior eradication attempts with treatments including rifabutin were documented (Table 2).

Resistance- and non-resistance-associated rpoB mutations

Nine of 17 sequenced rifampicin-resistant isolates showed mutations at codon 530. Five isolates revealed a G1588A transition (D530N), one isolate a G1588T transversion (D530Y) and an additional isolate an A1589G transition (D530G). In two isolates, we detected a novel T1590A transversion (D530E).

All mutations were associated with high-level resistance to rifampicin (>32 mg/L) and conferred cross-resistance or reduced susceptibility to rifabutin, as shown by agar dilution (Table 2).

In contrast, four isolates with rifampicin MICs of 8 mg/L did not harbour any known mutation in the examined rpoB region and were susceptible to rifabutin (MICs ≤0.032 mg/L) (Table 2).

The transformation of the rifampicin-resistant H. pylori strain 26695 with the 499 bp rpoB PCR products of the resistant isolates carrying codon 530, 540 or 545 mutations supported the critical role of rpoB mutations for rifampicin resistance in H. pylori. The resulting transformants showed a rifampicin-resistant phenotype as reflected by MICs >32 mg/L and harboured genotypes of the respective donor strains (data not shown).
Since the resistance-conferring rpoB mutations mostly affected triplet 530, we created a panel of six mutants representing different codon 530 genotypes. All mutants had rifampicin MICs \(< 32\) mg/L, were cross-resistant to rifabutin and showed, with the exception of the TAT 1588–1590 mutant, a non-restricted bacterial growth when cultured on solid growth medium or in liquid medium (data not shown).

When growing the \(H.\) pylori strain 26695 in the presence of RA5 discs, spontaneous rifampicin-resistant mutants were obtained after a single selection step. These mutants exhibited high MICs \((>32\) mg/L), cross-resistance to rifabutin and a non-restricted bacterial growth when cultured on solid growth medium or in liquid medium in the presence of rifabutin (data not shown). Resistant mutants revealed an A1580G (Q527R), an A1589T (D530V) and a C1618T (H540Y) mutation, respectively (Table 3).

Sequencing and phenotypic susceptibility testing by Etest\(^\text{w}\) showed that all resistance-conferring mutations were stable after 10 passages when culturing the strains on solid culture medium with or without 16 mg/L of rifabutin (data not shown).

In order to distinguish resistance-associated rpoB mutations from genetic variants, we compared a random selection of 100 rifampicin-susceptible clinical isolates (MICs \(< 4\) mg/L) with rifampicin-resistant in vitro mutants obtained by culturing rifampicin-susceptible strain 26695 in the presence of RA5 discs.

### Table 2. MICs of rifampicin and rifabutin for rifampicin-resistant \(H.\) pylori isolates, susceptibility to antimicrobials used in pre-treatments and rpoB mutations

<table>
<thead>
<tr>
<th>Isolate</th>
<th>MIC(^\text{a}) of RIF (mg/L)</th>
<th>MIC(^\text{b}) of RFB (mg/L)</th>
<th>Susceptibility(^\text{a})</th>
<th>Antimicrobials used in prior treatments</th>
<th>Mutation(^\text{c})</th>
</tr>
</thead>
<tbody>
<tr>
<td>HP-Rif-1</td>
<td>(&gt;32)</td>
<td>32</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>HP-Rif-2</td>
<td>(&gt;32)</td>
<td>ND</td>
<td>R</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>HP-Rif-3</td>
<td>24</td>
<td>ND</td>
<td>R</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>HP-Rif-4</td>
<td>(&gt;32)</td>
<td>32</td>
<td>R</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>HP-Rif-5</td>
<td>(&gt;32)</td>
<td>ND</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>HP-Rif-6</td>
<td>(&gt;32)</td>
<td>ND</td>
<td>S</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>HP-Rif-7</td>
<td>(&gt;32)</td>
<td>16</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>HP-Rif-8</td>
<td>(&gt;32)</td>
<td>64</td>
<td>R</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>HP-Rif-9</td>
<td>(&gt;32)</td>
<td>8</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>HP-Rif-10</td>
<td>(&gt;32)</td>
<td>ND</td>
<td>S</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>HP-Rif-11</td>
<td>(&gt;32)</td>
<td>64</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>HP-Rif-12</td>
<td>8</td>
<td>0.032</td>
<td>R</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>HP-Rif-13</td>
<td>(&gt;32)</td>
<td>64</td>
<td>S</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>HP-Rif-14</td>
<td>(&gt;32)</td>
<td>(&gt;64)</td>
<td>R</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>HP-Rif-15</td>
<td>(&gt;32)</td>
<td>16</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>HP-Rif-16</td>
<td>8</td>
<td>&lt;0.032</td>
<td>R</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>HP-Rif-17</td>
<td>(&gt;32)</td>
<td>16</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>HP-Rif-18</td>
<td>(&gt;32)</td>
<td>16</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>HP-Rif-19</td>
<td>8</td>
<td>&lt;0.032</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>HP-Rif-20</td>
<td>8</td>
<td>&lt;0.032</td>
<td>R</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>HP-Rif-21</td>
<td>(&gt;32)</td>
<td>16</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>HP-Rif-22</td>
<td>(&gt;32)</td>
<td>8</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
</tbody>
</table>

AMX, amoxicillin; MTZ, metronidazole; CLA, clarithromycin; TET, tetracycline; CIP, ciprofloxacin; RIF, rifampicin; RFB, rifabutin; ND, not determined.

\(^\text{a}\)Susceptibility determined by Etest\(^w\).

\(^\text{b}\)Susceptibility determined by agar dilution.

\(^\text{c}\)Amino acid exchanges relative to \(H.\) pylori strain 26695.

### Table 3. MICs of rifampicin/rifabutin and rpoB mutations of rifampicin/rifabutin-resistant in vitro mutants

<table>
<thead>
<tr>
<th>Isolate or mutant</th>
<th>MIC(^\text{a}) of RIF (mg/L)</th>
<th>MIC(^\text{b}) of RFB (mg/L)</th>
<th>rpoB mutation(^\text{c})</th>
</tr>
</thead>
<tbody>
<tr>
<td>GGT(^d)</td>
<td>(&gt;32)</td>
<td>32</td>
<td>D530G</td>
</tr>
<tr>
<td>GTT(^d)</td>
<td>(&gt;32)</td>
<td>32</td>
<td>D530V</td>
</tr>
<tr>
<td>ATT(^d)</td>
<td>(&gt;32)</td>
<td>32</td>
<td>D530I</td>
</tr>
<tr>
<td>TAT(^d)</td>
<td>(&gt;32)</td>
<td>64</td>
<td>D530Y</td>
</tr>
<tr>
<td>CTT(^d)</td>
<td>(&gt;32)</td>
<td>64</td>
<td>D530L</td>
</tr>
<tr>
<td>TTC(^d)</td>
<td>(&gt;32)</td>
<td>32</td>
<td>D530F</td>
</tr>
<tr>
<td>RIF-Mut1(^e)</td>
<td>(&gt;32)</td>
<td>32</td>
<td>Q527R</td>
</tr>
<tr>
<td>RIF-Mut2(^e)</td>
<td>(&gt;32)</td>
<td>32</td>
<td>D530V</td>
</tr>
<tr>
<td>RIF-Mut3(^e)</td>
<td>(&gt;32)</td>
<td>32</td>
<td>H540Y</td>
</tr>
</tbody>
</table>

\(^\text{d}\)Susceptibility determined by Etest\(^w\).

\(^\text{e}\)Susceptibility determined by agar dilution.

\(^\text{f}\)Amino acid exchanges relative to \(H.\) pylori strain 26695.

\(^\text{g}\)Codon 530 mutants created by site-directed mutagenesis.

\(^\text{h}\)In vitro mutants obtained by culturing rifampicin-susceptible strain 26696 in the presence of RA5 discs.
Rifampicin is normally used in the treatment of mycobacterial infections and in severe bone and prosthetic joint infections due to Staphylococcus aureus or life-threatening infections such as Legionnaires’ disease. The structurally related rifabutin, originally reserved for the treatment of mycobacterial infections, has been shown to possess high efficacy against H. pylori and is therefore increasingly recommended in drug-resistant H. pylori infections.5,6 Our data show that rifampicin resistance in H. pylori is still uncommon in Germany, because it occurred in only 1.4% (n = 22) of the examined isolates, without any significant evidence of an increasing trend.

The majority of the rifampicin-resistant strains were isolated from patients after treatment failures, suggesting that previous, unsuccessful attempts of eradication seem to be an important risk factor for the development of rifabutin resistance and/or multiresistance.

In five of these patients, a previous therapy including rifabutin was administered. These patients underwent a single microbiological investigation only; thus it remains unclear whether resistance to rifabutin had developed during therapy.

As shown in the present study, resistance to rifampicin is due to single point mutations and in contrast to others, we readily obtained spontaneous rifampicin-resistant mutants exhibiting codon 527, 530 or 540 mutations after a single selection step when culturing the rifampicin-susceptible strain 26695 in the presence of RA5 discs.3 Thus, a direct impact of rifampicin on the emergence of rifampicin resistance in H. pylori can be assumed. Since 33 patients with documented rifabutin-based therapies harboured strains still susceptible to rifabutin; this hypothesis has to be confirmed by further studies.

All sequenced H. pylori clinical isolates with high resistance to rifampicin (MIC >32 mg/L) carried rpoB mutations, predominantly affecting codon 530, and were either cross-resistant to rifabutin or showed reduced susceptibility as verified by growth on rifabutin-containing (16 mg/L) culture medium or by agar dilution assays. With the exception of the D530E mutation, the presented resistant clinical isolates revealed point mutations as described in earlier in vitro studies.8,10,11

Natural transformation experiments and site-directed mutagenesis confirmed the pivotal role of the detected rpoB mutations in rifampicin resistance in H. pylori. Furthermore, we also identified numerous previously unknown genetic variants resulting in amino acid exchanges, but not in resistance to rifampicin, when compared with the published H. pylori 26695 sequence, thereby demonstrating that mutations in the rpoB gene do not generally confer resistance to rifampicin.

In four isolates characterized by a moderate level of rifampicin resistance (MIC = 8 mg/L), we could not detect a related rifabutin phenotype, because these strains were still susceptible to rifabutin (MIC ≤0.032 mg/L). This observation suggests currently unknown mechanisms of rifampicin resistance and/or additional mutations outside the sequenced rpoB gene fragments or in other genes. The impact of such a moderate level of rifampicin resistance or reduced susceptibility to rifabutin on therapy outcome is unclear and has to be examined in clinical studies.

The prescription of rifampicin and rifabutin as antimycobacterial drugs or reserve antibiotics in life-threatening infections is limited to inpatients, and thus data concerning the consumption of rifabutin due to usually ambulant-treated H. pylori infections are not yet available. To confirm an association between the use of rifabutin in H. pylori eradication regimens or in unrelated bacterial infections and the frequency of rifabutin resistance, in vivo studies are required.

Both in clinical isolates and in in vitro mutants, mutations affecting codons 527, 530, 540 and 545 in the rpoB gene played a critical role in rifampicin resistance and also mediated cross-resistance to rifabutin. Owing to the low number of rifampicin/rifabutin-resistant isolates, resistance screening by using the 5 μg rifampicin disc diffusion test followed by the rifampicin Etest is still a practicable strategy.11 However, in cases of rifampicin resistance, agar dilution should be performed to reliably identify rifabutin-resistant strains. Subsequent rpoB genotyping by PCR and sequencing might be a useful procedure to distinguish mutations mediating cross-resistance to rifabutin from genetic variations, thereby confirming rifabutin resistance and standardizing rifabutin susceptibility testing.20 Further investigations clarifying additional mechanisms of rifampicin resistance are equally necessary as studies analysing the impact of phenotypic moderate rifampicin resistance (up to 8 mg/L) and reduced susceptibility to rifabutin on therapy outcome. Finally, in order to maintain the potential of rifabutin as a rescue drug in H. pylori eradication regimens and also for the treatment of tuberculosis, it is indispensable to restrict its use and to perform continuous surveillance studies focusing on risk factors for rifabutin resistance.

Acknowledgements
We thank Christine Ganter, Beate Hobmaier, Christine Melzl and Marianne Vetter-Knoll for excellent technical assistance. This work was supported by the Robert-Koch-Institut by a grant to M. Kist (1369-239) of the German Ministry of Health.

Transparency declarations
None to declare.

References


