Original research

Empirical rescue treatment of *Helicobacter pylori* infection in third and subsequent lines: 8-year experience in 2144 patients from the European Registry on *H. pylori* management (Hp-EuReg)

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ABSTRACT

Objective To evaluate the use, effectiveness and safety of *Helicobacter pylori* empirical rescue therapy in third and subsequent treatment lines in Europe.

Design International, prospective, non-interventional registry of the clinical practice of European gastroenterologists. Data were collected and quality reviewed until October 2021 at Asociación Española de Gastroenterología-Research Electronic Data Capture. All cases with three or more empirical eradication attempts were assessed for effectiveness by modified intention-to-treat and per-protocol analysis.

Results Overall, 2144 treatments were included: 1519, 439, 145 and 41 cases from third, fourth, fifth and sixth treatment lines, respectively. Sixty different therapies were used; the 15 most frequently prescribed encompassed >90% of cases. Overall effectiveness remained <90% in all therapies. Optimised treatments achieved a higher eradication rate than non-optimised (78% vs 67%, p<0.0001). From 2017 to 2021, only 44% of treatments other than 10-day single-capsule therapy used high proton-pump inhibitor doses and lasted ≥14 days. Quadruple therapy containing metronidazole, tetracycline and bismuth achieved optimal eradication rates only when prescribed as third-line treatment, either as 10-day single-capsule therapy (87%) or as 14-day traditional therapy with tetracycline hydrochloride (95%). Triple amoxicillin-levofloxacin therapy achieved 90% effectiveness in Eastern Europe only or when optimised. The overall incidence of adverse events was 31%.

Conclusion Empirical rescue treatment in third and subsequent lines achieved suboptimal effectiveness in most European regions. Only quadruple bismuth-metronidazole-tetracycline (10-day single-capsule or 14-day traditional scheme) and triple amoxicillin-levofloxacin therapies reached acceptable outcomes in some settings. Compliance with empirical therapy optimisation principles is still poor 5 years after clinical practice guidelines update.

Trial registration number NCT02328131.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ *Helicobacter pylori* infection treatment effectiveness decreases as eradication failures accumulate.

⇒ Most patients requiring a third or subsequent eradication treatment for the infection are treated empirically.

INTRODUCTION

Helicobacter pylori infection affects 50% of the world's population[1], generating a significant

WHAT THIS STUDY ADDS

⇒ While single-capsule bismuth quadruple therapy has become the most commonly prescribed rescue regimen, a wide variety of empirical third-line to sixth-line therapies are used in Europe.

⇒ Although these infections are most likely caused by multiresistant strains, the rescue therapies prescribed are often not optimised and antibiotics that have already failed are frequently prescribed in subsequent lines.

⇒ Only 10-day single-capsule bismuth quadruple therapy, 14-day traditional bismuth quadruple therapy and optimised levofloxacin triple therapy achieve 90% effectiveness in some settings.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ European gastroenterologists should improve compliance with evidence-based recommendations in the management of *H. pylori* infection, especially when facing cases in which two or more treatments have already failed.

⇒ Suboptimal eradication rates of quinolone-based therapies make it desirable to closely monitor their effectiveness outcomes and to update local antibiotic resistance rates in the coming years.

healthcare and economic burden. Although the bacterium was officially discovered in 1982,[2 3] it is still the main aetiology of peptic ulcer and gastric cancer, as well as the only cause of dyspepsia that can be eliminated. It is well established that treatment should be offered to any patient diagnosed with the infection,[4] but the ideal eradication strategy has not yet been defined. This is particularly evident after one or more failed eradication attempt.

Due to the continuous increase in antibiotic resistance worldwide,[5–7] it has been essential to optimise empirical therapies to achieve >90% effectiveness in both first-line and second-line treatment.[8–12] Using potent acid inhibition (between 54 and 128 mg omeprazole equivalents given two times per day)[13 14] and lengthening treatments up to 14 days increase eradication rates in most therapies and are generally recommended. Triple therapies can also be efficiently improved by the addition of bismuth salts, turning them into quadruple therapies.[15] Additionally, levofloxacin and clarithromycin should not be prescribed if the patient has already been exposed to them. These cornerstones of *H. pylori* treatment were established in the most relevant clinical practice guidelines and consensus reports of 2016–2017.[16–19] If they were rigorously followed in daily practice, it would be anecdotal to find patients with a medical history of two or more failed eradication attempts. However, it is not exceptional nowadays to face cases requiring a third-line treatment. This is partially explained by the fact that many of the empirical treatments prescribed during the last decade were not optimised, yielding a reported effectiveness of the most commonly used first-line, second-line and third-line therapies of 88%,[20 21] 80%[22] and 70%,[23] respectively. On the other hand, recent evidence has exhibited poor adherence to consensus documents in first-line treatment throughout Europe,[20 24] which suggests that this is also true for subsequent treatment lines.

In clinical practice, the effectiveness of treatment decreases as eradication failures accumulate over time.[25 26] However, although an isolated eradication rate below 90% is considered unacceptable for an infectious disease, the cumulative eradication rate after two consecutive suboptimal treatments may exceed 95%.[25] This implies that the number of third-line cases is tiny compared with the first and second lines. Hence if quality data are to be available to generate robust conclusions on treatments beyond the second line, a large number of patients need to be treated. Some studies have reported significant figures, but as they are single centre and/or have been conducted in reference hospitals, they probably do not reflect the clinical practice of larger geographical regions.[25] Accumulating infrequent cases to generate knowledge is one of the fundamentals of multicentre registries such as the 'European Registry on *H. pylori* management' (Hp-EuReg). Therefore, the aim of the present study was to obtain a large-scale, up-to-date overview of the empirical prescription patterns and their effectiveness in the most difficult-to-treat *H. pylori* infections, that is, in those for which at least two lines of treatment have already failed.

METHODS

European Registry on *H. pylori* infection management

This is a substudy of the Hp-EuReg, an international (28 countries), multicentre (up to 200 investigators), prospective, non-interventional registry promoted by the European *Helicobacter* and Microbiota Study Group (www.helicobacter.org), which started in 2013. The study was prospectively registered at ClinicalTrials.gov (NCT02328131) (online supplemental file 2). Participating investigators were gastroenterologists who routinely manage patients in whom *H. pylori* eradication treatment is indicated. For further details regarding the methodology of Hp-EuReg, refer to the published protocol.[27]

Study aim

The aim of the current analysis was to evaluate the frequency of use, effectiveness and safety of empirical third and subsequent lines of treatment for *H. pylori* infection in Europe. The secondary objective was to assess the evolution in the prescription patterns of empirical rescue therapies.

Selection criteria, data collection and data quality review

As most of the rescue treatments were prescribed empirically in all countries, the few cases for which antibiotic susceptibility testing was available (2%) were heterogeneously distributed across Europe. Therefore, in the absence of a representative sample of this subpopulation in all European regions, the analysis was limited solely to empirically treated cases. All patients registered in the Hp-EuReg until October 2021 who had received an empirical third-line, fourth-line, fifth-line or sixth-line therapy were included for analysis.

At least 10% of the records included in each country and each hospital were monitored using the Research Electronic Data Capture tool. The latter has been developed at Vanderbilt University's Institute for Clinical and Translational Research and is a web-based system, which facilitates collection, storage, security, management and retrieval/reusage of research data.[28] The review process evaluated mainly whether the study selection criteria had been met and whether information had been correctly registered and ultimately aimed to ensure the study was conducted according to the highest scientific and ethical standards. Data discordances were resolved by querying the investigators and through group emailing. Additionally, after extracting the data and prior to the statistical analysis, the database was reviewed for inconsistencies and subsequent data cleaning was performed.

Data management

All countries were clustered in five main regions based both on their geographical location and on the 2019 gross domestic product (GDP) per capita: South-West and/or medium GDP (Spain and Portugal), Centre and/or medium-high GDP (Italy and France), South-East and/or low-medium GDP (Slovenia, Lithuania, Greece, Latvia, Croatia, Hungary, Poland and Israel—Israel is the only Asian country participating in the registry and has a high GDP; it is included in the South-East cluster for geographical reasons), North and/or high GDP (the UK, Norway, Ireland, Denmark, Germany, Belgium, Switzerland, the Netherlands and Finland) and East and/or low GDP (Russia, Serbia, Romania and Ukraine). For more detailed information, see online supplemental table 1.

The variable duration of treatment was assessed using four categories corresponding to the most frequently prescribed treatment durations: 7, 10, 12 and 14 days.

The variable proton-pump inhibitor (PPI) dose was grouped into three categories as reported by Graham *et al*[13] and Kirchheiner *et al*[14]: low dose, when the potency of acid inhibition was between 4.5 and 27 mg omeprazole equivalents given twice a day; standard dose, between 32 and 40 mg omeprazole equivalents given twice a day; and high dose, between 54 and 128 mg omeprazole equivalents given twice a day.

Prescribing high-dose PPI and extending the treatment duration up to 14 days are the only optimisation strategies applicable to any regimen. Adding bismuth salts implies turning a triple therapy into a quadruple therapy and, consequently, changing the treatment regimen.[15] Thus, adding bismuth was not considered as an optimisation strategy for overall analysis purposes. An optimised treatment was defined as one lasting 14 days or more and using high-dose PPI. Therapies that did not meet either of these two criteria were considered as non-optimised.

Three-in-one single capsule is only marketed in a 10-day format and therefore its duration cannot be extended (unless two full treatment cycles are prescribed and the patient bears their cost). Moreover, increasing the PPI dose has not proven to improve the results of this regimen.[11 29 30] Therefore, it was considered that the traditional optimisation rules[15] do not apply to PPI-single-capsule therapy and the analyses of global prescription and effectiveness trends were performed both including and excluding it.

Subanalyses of prescription and effectiveness trends were performed according to the geographical region, treatment duration, PPI dose and regimen type (quadruple, sequential, triple, dual). Additionally, two periods were established (before and since the year 2017) to assess the impact and/or adherence to the consensus guidelines published in late 2016 and early 2017[16–19] on empirical rescue treatment prescriptions by European gastroenterologists.

Graphs were used to summarise the results. For the graphical representation of the different therapies, six categories were established according to the key antibiotic prescribed: (1) therapies containing metronidazole, tetracycline and bismuth; (2) quinolone-based therapies; (3) rifabutin-based therapies; (4) clarithromycin-containing therapies; (5) other common therapies; (6) marginal therapies (see online supplemental table 2).

Effectiveness and safety analysis

Effectiveness as the treatment eradication rate was studied in three sets of patients as follows: (1) the intention-to-treat (ITT) analysis included all patients registered up to October 2021, to allow at least a 6-month follow-up, where cases lost to follow-up were considered treatment failures; (2) a modified intention-to-treat (mITT) analysis was designed with the aim of achieving the results closest to those obtained in clinical practice. It included all patients with completed follow-up (ie, a confirmatory test—success or failure—was available after the eradication treatment), regardless of compliance; (3) the per-protocol (PP) analysis included all patients with completed follow-up who had taken at least 90% of the treatment drugs as defined in the protocol.

Adverse events (AEs) and treatment compliance were evaluated through patient interrogation using both open-ended questions and a predefined questionnaire conducted by face-to-face interview. Adequate treatment compliance was defined as having taken at least 90% of the prescribed drugs.

Statistical analysis

Continuous variables were presented as the arithmetic mean and SD. Qualitative variables were presented as absolute and relative frequencies with percentages (%). Differences between groups were analysed with the χ^2 test. Statistical significance was considered at $p<0.05$ (two-tailed).

To evaluate the different factors that may influence the effectiveness of third-line treatment, a multivariate analysis was performed using a logistic regression model where mITT eradication (treatment success) was the dependent variable. The independent factors assessed were: age, gender (female (reference category) vs male), treatment indication (dyspepsia and other (reference category) vs peptic ulcer), duration of treatment (7 (reference category), 10, 12 or 14 days), PPI dose (low (reference category), standard or high), compliance (no: <90% drug intake (reference category) vs yes: ≥90%), prior use of metronidazole (yes (reference category) vs no), prior use of quinolones (yes (reference category) vs no) and the prescribed third-line treatment.This last-mentioned variable was categorised into five groups, which were established according to the most frequently prescribed treatments: (1) triple therapy with PPI, amoxicillin and rifabutin (PPI-A+R) (reference category), (2) 'other therapies', (3) quadruple therapy with PPI, amoxicillin, levofloxacin and bismuth (PPI-A+L+B), (4) triple therapy with PPI, amoxicillin and levofloxacin (PPI-A+L) and (5) the quadruple therapy of a PPI together with metronidazole, tetracycline hydrochloride and bismuth (PPI-M+Tc+B)—either as single-capsule therapy or as traditional therapy (the same drugs given separately). The group 'other therapies' contained all third-line treatment regimens other than PPI-single-capsule, PPI-M+Tc+B, PPI-A+L, PPI-A+L+B and PPI-A+R. Triple therapy with PPI-A+R was established as the reference category as it was the treatment group with the lowest effectiveness in the bivariate analysis. Multivariate analysis was not performed for fourth-line, fifth-line and sixth-line treatment due to the limited sample size in these subgroups. ORs and 95% CIs were provided.

Data were analysed using IBM SPSS Statistics V.25.0 (IBM, Armonk, New York, USA).

RESULTS

From May 2013 to October 2021, a total of 2516 cases were registered in Hp-EuReg as having received three or more empirical treatments for *H. pylori* infection. Of these, 2144 from 25 countries met the quality inclusion criteria and were eligible for the current analysis.

Baseline characteristics

Mean (SD) age of patients was 52 (14) years, 69% were women, 6% were allergic to at least one key antibiotic and peptic ulcer

was the indication for eradication in 14%. Further demographic details by geographical regions are presented in table 1. Peptic ulcer was the indication for investigation of *H. pylori* infection in 39% of cases in Eastern Europe, whereas in the remaining regions this cause was less common (<16%).

Diagnosis of *H. pylori* infection

Previous eradication failure was confirmed by a non-invasive test in the majority of cases (64%), with ^{13}C-urea breath test being the most commonly used method (59%). A confirmatory eradication test was performed in 96% of cases after a rescue treatment; the ^{13}C-urea breath test was again the most frequently used technique (78%).

Prescriptions in rescue therapy

There were 1519 (71%), 439 (21%), 145 (7%) and 41 (2%) cases from third, fourth, fifth and sixth treatment lines, respectively. The 2144 empirical rescue therapies were distributed in five geographical regions as follows: South-West 1164 (54%), Centre 443 (21%), South-East 326 (15%), North 142 (7%) and East 69 (3%). The detailed distribution of cases per geographical region, per line of treatment and per year is shown in table 1. Distribution of cases by country is illustrated in online supplemental table 1.

Sixty different rescue treatment schemes were identified (online supplemental table 3), although the 16 most commonly prescribed accounted for 92% (1961) of the cases. Of these, the quadruple regimen of a PPI along with M+Tc+B, either as three-in-one single-capsule or as traditional therapy, was the most prescribed overall (33%). In particular, PPI-single-capsule was the most widely used therapy, both globally (25%) and as third-line treatment (26%), followed by triple PPI-L+A therapy (15% overall, 17% as third line). Triple PPI-R+A therapy was the most commonly used fourth-line treatment in Europe (28%).

Overall, 18% of the patients treated with quinolone-containing therapies had already received levofloxacin as part of a previous treatment and 69% of those with clarithromycin-containing regimens had been exposed to clarithromycin previously. The re-exposure rate to levofloxacin decreased from 2017 to 2021 (22% vs 11%), whereas that of clarithromycin increased over the same time period (64% vs 79%, online supplemental table 4). Figure 1 shows third-line cases distributed according to the failed empirical therapies that were prescribed as first and second lines. It illustrates part of the re-exposure to clarithromycin and to levofloxacin.

Triple therapies were preferred in South-Eastern (65%) and Central Europe (55%), whereas quadruple therapies were mostly prescribed in the South-West (76%), East (52%) and North (52%). The use of different treatment schemes also varied by region: therapies based on the combination of M, a tetracycline (Tc or doxycycline (D)) and B (either as single-capsule or as traditional formats PPI-M+Tc+B or PPI-M+D+B) were most frequently prescribed in South-Western (50%) and Northern Europe (37%); quinolone-based therapies were preferred in the South-East (PPI-A+L and PPI-A+L+B accounted for 50% of the treatments); rifabutin-based therapies were prescribed more often in Central Europe (PPI-R+A: 37%) and clarithromycin-containing therapies were mostly prescribed in Eastern Europe (33% as PPI-C+A, PPI-C+A+M or PPI-C+A+B) (table 1).

Duration of treatment was also region specific: 7-day therapy was used almost exclusively in the North (29%) and 10-day prescriptions were most usual in Central (58%) and South-Western Europe (57%, table 1). Excluding 10-day single-capsule therapy from the analysis, a duration of 10 days for all the other therapies was most frequent in Central (46%) and Northern Europe (40%), whereas 14-day therapy was preferred in the South-East, South-West and East (68%, 63% and 56%, respectively, online supplemental table 5). More than 95% of the 12-day treatment registered in the current study came from a single Italian hospital and accounted for 32% of all rescue therapies in Central Europe.

Trends in the use of rescue therapy

Figure 2 depicts the prescription trends for each rescue therapy over the years 2013–2021. Globally, the use of quadruple therapies increased from 40% in 2013–2014 to 70% in 2016, and specifically the use of bismuth-containing quadruple regimens increased from 33%–35% in 2013–2014 to 64%–75% in 2018–2021. However, this prescription shift varied regionally: while triple therapies practically disappeared in South-Western Europe, they remained frequent in the other regions. Particularly in Central Europe, quadruple therapies (with or without bismuth) other than the single-capsule were barely used. Central Europe was also the single region where sequential therapy presented a relevant number of prescriptions (10%–16% in 2013–2014).

The average duration of treatments increased over the years in the South-East (from 10.6 days in 2014 to 12.9 days in 2018–2019) and East (from 9.0 days in 2014 to 13.2 days in 2018), decreased in the South-West (from 12.2 days in 2013–2014 to 11.0 days in 2018–2019) and remained stable in Central Europe (around 11%).

In terms of potency of gastric acid inhibition, the mean daily dose of PPI increased in all regions except Central and Eastern Europe, where it started to decrease in 2015–2016.

Overall use of rescue therapies (type of therapy, duration of treatment, PPI dose and optimisation rate) prior to and since publication of the 2016–2017 clinical guidelines is shown in table 2.

The prescription trends (type of regimen, duration of treatment and PPI dose) excluding PPI-single-capsule therapy are shown in figure 3.

Overall effectiveness

Overall mITT effectiveness exceeded 80% in Eastern (86%) and South-Eastern Europe (81%). Central and South-Western Europe had an overall effectiveness of 74%, whereas in the North it was significantly lower, with a reported cure rate of 59%. The highest overall eradication rates were achieved in the third line in all regions (the highest effectiveness being 86% in the South-East) and progressively decreased with each new eradication attempt. Table 3 shows overall eradication rates by treatment line in each region.

In the time-trend analysis, overall (third-line to sixth-line) effectiveness increased from 70% in 2013 to 83% in 2021, mainly attributable to third-line treatments, as the overall eradication rate of the latter rose from 73% to 85%. For fourth-line and fifth-line treatments, an improvement was observed in 2020–2021, whereas for sixth-line treatments no significant change in eradication rate was seen over the entire period (figure 4). When evaluated by region, an upward trend in the overall eradication rate was observed only in the South-West, with an increase from 61%–69% in 2013–2015 to 77%–83% in 2019–2021 (online supplemental table 6).

Table 1 Baseline characteristics of third and subsequent empirical treatment lines for *Helicobacter pylori* infection

Variable	Europe	South-West	Centre	South-East	North	East
Number of cases, n (%)						
Per line						
Third line	1519 (70.8)	861 (74.0)	291 (65.7)	238 (73.0)	74 (52.1)	55 (79.7)
Fourth line	439 (20.5)	214 (18.4)	105 (23.7)	71 (21.8)	40 (28.2)	9 (13.0)
Fifth line	145 (6.8)	74 (6.4)	34 (7.7)	13 (4.0)	19 (13.4)	5 (7.2)
Sixth line	41 (1.9)	15 (1.3)	13 (2.9)	4 (1.2)	9 (6.3)	0 (0.0)
Per year						
2013 (May–December)	250 (11.7)	119 (10.2)	69 (15.6)	30 (9.2)	28 (19.7)	4 (5.8)
2014	371 (17.3)	176 (15.1)	101 (22.8)	37 (11.3)	54 (38.0)	3 (4.3)
2015	292 (13.6)	190 (16.3)	47 (10.6)	35 (10.7)	14 (9.9)	6 (8.7)
2016	366 (17.1)	272 (23.4)	18 (4.1)	52 (16.0)	12 (8.5)	12 (17.4)
2017	254 (11.8)	164 (14.1)	36 (8.1)	35 (10.7)	6 (4.2)	13 (18.8)
2018	208 (9.7)	76 (6.5)	91 (20.5)	34 (10.4)	2 (1.4)	5 (7.2)
2019	124 (5.8)	62 (5.3)	31 (7.0)	25 (7.7)	5 (3.5)	1 (1.4)
2020	171 (8.0)	64 (5.5)	25 (5.6)	63 (19.3)	13 (9.2)	6 (8.7)
2021 (January–September)	108 (5.0)	41 (3.5)	25 (5.6)	15 (4.6)	8 (5.6)	19 (27.5)
Female, n (%)	1478 (68.9)	780 (67.0)	339 (76.5)	229 (70.2)	89 (62.7)	41 (59.4)
Age, mean (SD)	51.5 (13.6)	51.9 (13.7)	53.1 (12.9)	50.8 (13.7)	46.4 (12.5)	51.7 (14.8)
Race, n (%)						
White/Caucasian	1923 (89.7)	1087 (93.4)	398 (89.8)	316 (96.9)	64 (48.6)	53 (76.8)
Not available	103 (4.8)	51 (4.4)	2 (0.5)	1 (0.3)	47 (33.1)	2 (2.9)
Others	69 (3.2)	14 (1.2)	25 (5.6)	5 (1.5)	12 (8.5)	13 (18.8)
Black	26 (1.2)	6 (0.5)	13 (2.9)	3 (0.9)	4 (2.8)	0 (0.0)
Asian	23 (1.1)	5 (1.1)	5 (1.1)	1 (0.3)	10 (7.0)	1 (1.4)
Drug allergies, n (%)						
No	2012 (93.8)	1101 (94.6)	419 (94.6)	302 (92.6)	123 (86.6)	67 (97.1)
Penicillin	102 (4.8)	52 (4.5)	18 (4.1)	16 (4.9)	15 (10.6)	1 (1.4)
Fluorquinolones	13 (0.6)	6 (0.5)	3 (0.7)	2 (0.6)	2 (1.4)	0 (0.0)
Macrolides	11 (0.5)	3 (0.3)	2 (0.5)	4 (1.2)	2 (1.4)	0 (0.0)
Tetracyclines	6 (0.3)	4 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)	1 (1.4)
Indication for investigation of infection, n (%)						
Dyspepsia	1298 (60.5)	760 (65.3)	203 (45.8)	208 (63.8)	100 (70.4)	27 (39.1)
Ulcer	291 (13.6)	185 (15.9)	23 (5.2)	36 (11.0)	20 (14.1)	27 (39.1)
Others	555 (25.9)	219 (18.8)	217 (49.0)	82 (25.2)	22 (15.5)	15 (21.7)
Treatment regimen, n (%)						
Quadruple	1259 (58.7)	887 (76.2)	160 (36.1)	102 (31.3)	74 (52.1)	36 (52.2)
Triple	796 (37.1)	248 (21.3)	243 (54.9)	210 (64.4)	65 (45.8)	30 (43.5)
Sequential	49 (2.3)	6 (0.5)	38 (8.6)	2 (0.6)	2 (1.4)	1 (1.4)
Dual	40 (1.9)	23 (2.0)	2 (0.5)	12 (3.7)	1 (0.7)	2 (2.9)
Bismuth-containing therapies, n (%)	1106 (51.6)	790 (67.9)	132 (29.8)	94 (28.8)	57 (40.1)	33 (47.8)
Duration of treatment, n (%)						
7 days	61 (2.8)	5 (0.4)	0 (0.0)	13 (4.0)	41 (28.9)	2 (2.9)
10 days	1113 (51.9)	658 (56.5)	258 (58.2)	105 (32.2)	57 (40.1)	35 (50.7)
12 days	151 (7.0)	2 (0.2)	144 (32.5)	4 (1.2)	0 (0.0)	1 (1.4)
14 days	815 (40.0)	498 (42.8)	41 (9.3)	203 (62.3)	42 (29.6)	31 (44.9)
Unknown	4 (0.2)	1 (0.1)	0 (0.0)	1 (0.3)	2 (1.4)	0 (0.0)
Duration of treatment in days, mean (SD)	11.6 (2.0)	11.7 (2.0)	11.0 (1.3)	12.4 (2.2)	10.3 (2.7)	11.7 (2.1)
PPI dose, n (%)*						
Low	739 (34.5)	365 (31.4)	214 (48.3)	46 (14.1)	94 (66.2)	20 (29.0)
Standard	337 (15.7)	248 (21.3)	19 (4.3)	28 (8.6)	17 (12.0)	25 (36.2)
High	1041 (48.6)	537 (46.1)	199 (44.9)	252 (77.3)	29 (20.4)	24 (34.8)
Unknown	27 (1.3)	14 (1.2)	11 (2.5)	0 (0.0)	2 (1.4)	0 (0.0)
Compliance, n (%)						
No (<90% drug intake)	85 (4.0)	41 (3.5)	17 (3.8)	12 (3.7)	7 (4.9)	8 (11.6)
Yes (≥90% drug intake)	1797 (83.8)	1068 (91.8)	354 (79.9)	190 (58.3)	127 (89.4)	58 (84.1)
Unknown	262 (12.2)	55 (4.7)	72 (16.3)	124 (38.0)	8 (5.6)	3 (4.3)

Continued

Table 1 Continued

Variable	Europe	South-West	Centre	South-East	North	East
Most frequent treatments, n (%)						
PPI-single-capsule†	530 (24.7)	380 (32.6)	107 (24.2)	25 (7.7)	4 (2.8)	14 (20.3)
PPI-A+L	322 (15.0)	78 (6.7)	63 (14.2)	145 (44.5)	19 (13.4)	17 (24.6)
PPI-A+R	279 (13.0)	80 (6.9)	165 (37.2)	31 (9.5)	3 (2.1)	0 (0.0)
PPI-M+Tc+B	178 (8.3)	92 (7.9)	24 (5.4)	9 (2.8)	48 (33.8)	5 (7.2)
PPI-A+L+B	139 (6.5)	118 (10.1)	0 (0.0)	18 (5.5)	0 (0.0)	3 (4.3)
PPI-M+D+B	115 (5.4)	114 (9.8)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
PPI-C+A+M	84 (3.9)	74 (6.4)	1 (0.2)	3 (0.9)	3 (2.1)	3 (4.3)
PPI-A+M	57 (2.7)	34 (2.9)	1 (0.2)	13 (4.0)	9 (6.3)	0 (0.0)
PPI-C+A	49 (2.3)	6 (0.5)	4 (0.9)	7 (2.1)	21 (14.8)	11 (15.9)
PPI-A	39 (1.8)	23 (2.0)	2 (0.5)	11 (3.4)	1 (0.7)	2 (2.9)
PPI-C+A+B	37 (1.7)	19 (1.6)	0 (0.0)	8 (2.5)	1 (0.7)	9 (13.0)
Sequential PPI-C+A+T	30 (1.4)	2 (0.2)	27 (6.1)	1 (0.3)	0 (0.0)	0 (0.0)
PPI-A+Mx	27 (1.3)	27 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PPI-A+R+B	27 (1.3)	27 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PPI-C+A+T	24 (1.1)	0 (0.0)	23 (5.2)	0 (0.0)	1 (0.7)	0 (0.0)
PPI-A+M+B	24 (1.1)	16 (1.4)	0 (0.0)	6 (1.8)	2 (1.4)	0 (0.0)
Marginal therapies‡	183 (8.5)	74 (6.4)	26 (5.9)	48 (14.7)	30 (21.1)	5 (7.2)
Overall	2144 (100)	1164 (100)	443 (100)	326 (100)	142 (100)	69 (100)

*Low-dose PPI: 4.5–27 mg omeprazole equivalents, two times per day (eg, 20 mg omeprazole equivalents, two times per day). Standard-dose PPI: 32–40 mg omeprazole equivalents, two times per day (eg, 40 mg omeprazole equivalents, two times per day). High-dose PPI: 54–128 mg omeprazole equivalents, two times per day (eg, 60 mg omeprazole equivalents, two times per day).
†Three-in-one single-capsule containing bismuth, tetracycline and metronidazole.
‡Marginal therapies were considered to be those with 20 or fewer cases. There were 44 different regimens, with a total of 183 cases across Europe (see table 1 and online supplemental table 3).
A, amoxicillin; B, bismuth; C, clarithromycin; D, doxycycline; L, levofloxacin; M, metronidazole; Mx, moxifloxacin; PPI, proton-pump inhibitor; R, rifabutin; T, tinidazole; Tc, tetracycline hydrochloride.

Effectiveness by therapy and optimisation

Table 4 shows mITT eradication rates by therapy, treatment line and region (online supplemental table 7 shows PP eradication rates). Figure 5 shows the eradication rates of the most commonly prescribed therapies based on their optimisation. Online supplemental table 8 shows the eradication rates of optimised therapies and online supplemental table 9 includes the country of origin of those prescriptions.

Triple PPI-A+L was the most widely used therapy in the South-East, North and East of Europe (table 1). Its third-line effectiveness—irrespective of optimisation—was close to 90% in Northern and Eastern Europe and to 80% in the remaining regions (table 4). Optimised versions of PPI-A+L were mostly used in the South-East and achieved an eradication rate of 90% (online supplemental tables 8 and 9). Quadruple PPI-A+L+B therapy was mainly used in the South-West, where no significant difference in third-line eradication rate was reported compared with triple PPI-L+A (79.6% vs 74.6%, respectively, p=0.3545).

In those regions where it was available, single-capsule bismuth quadruple therapy achieved the best overall results, approaching 90% effectiveness as third-line treatment (table 4). Non-single-capsule variants of the traditional bismuth quadruple therapy performed worse (PPI-M+Tc+B: 73%, PPI-M+D+B: 63%); however, when subanalysing optimised therapies, quadruple PPI-M+Tc+B therapy achieved a 95% mITT overall eradication rate (online supplemental table 10).

Rifabutin-based triple therapy (PPI-R+A) was mainly prescribed in South-Western and Central Europe, with different dosages in each of these regions and better overall results in the latter (51% vs 77%, online supplemental table 11). Quadruple PPI-A+R+B therapy was used in the South-West and no differences were reported in the overall mITT eradication rate compared with triple PPI-A-R (60% vs 51%, respectively, p>0.05, table 4). The use of high-dose PPI and ≥14-day treatment durations did not improve the outcomes of rifabutin-based therapy (online supplemental table 8).

Figure 1 shows mITT eradication rates of therapies that were prescribed following 2016–2017 consensus guidelines' algorithms. The eradication rate of quadruple PPI-M+Tc+B regimen after a clarithromycin-based and a quinolone-based regimen was 86% for the single-capsule format and 74% for the traditional format. The eradication rate of triple PPI-A+L therapy after a clarithromycin-based and a M+Tc+B-based regimen was 78%. The mITT eradication rate of quadruple PPI-A+L+B therapy after a clarithromycin-based and a M+Tc+B-based regimen was 73%.

Overall, optimised treatments achieved a higher eradication rate than non-optimised treatments (78% vs 67%, p<0.0001, figure 5).

Multivariate analysis

The use of quadruple PPI-M+Tc+B therapy (either as single-capsule or as traditional therapy; OR 5.2, 95% CI 1.7 to 15.7) or triple therapy PPI-A+L (OR 3.16, 95% CI 1.0 to 9.9) was significantly associated with mITT eradication success. Good compliance (OR 3.3, 95% CI 1.7 to 6.4), higher gastric acid inhibition (high PPI dose OR 2.1, 95% CI 1.6 to 2.9) and longer treatment durations (12 days OR 8.6, 95% CI 2.0 to 36.4; 14 days OR 2.6, 95% CI 1.1 to 6.0) were also independent factors associated with eradication success (table 5).

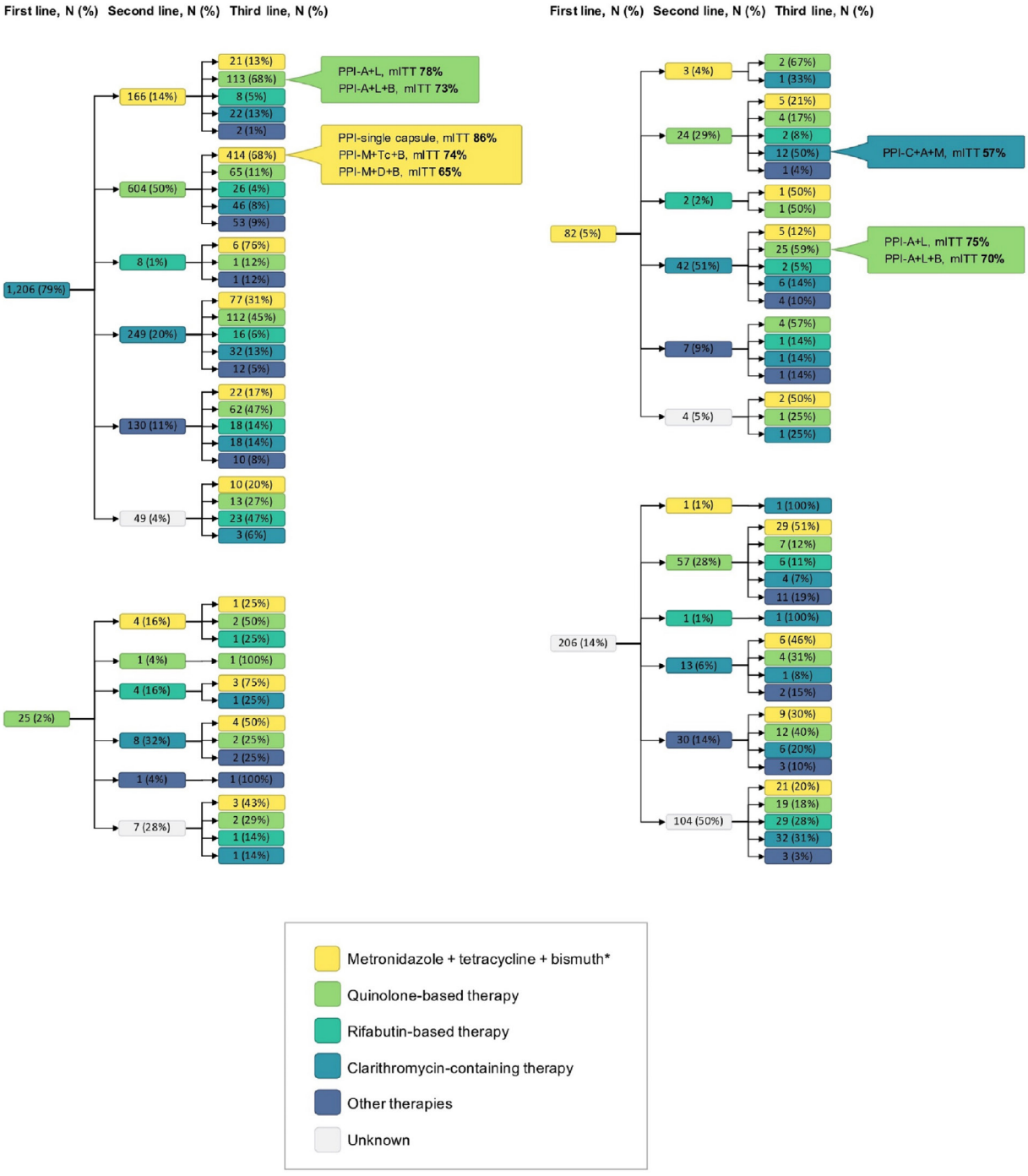

Figure 1 Third-line cases (N=1519) distributed according to the empirical treatment categories that were prescribed as the first and second treatment lines. Absolute number of cases (N) and relative number with respect to the total number of cases per line (%) are shown. Modified intention-to-treat eradication rates are shown only for therapies that were prescribed following the 2016-2017 consensus guideline algorithms.[16–19] Note that these are third-line treatment effectiveness with no sub-analysis by optimisation or region. *A tetracycline, either tetracycline hydrochloride or doxycycline. A, amoxicillin; B, bismuth; C, clarithromycin; D, doxycycline; L, levofloxacin; M, metronidazole; mITT, modified intention-to-treat; R, rifabutin; Tc, tetracycline.

Safety and compliance

The overall incidence of at least one AE was 31% (95% CI 29% to 33%), most of them being of mild (49%) or moderate (43%) intensity and of short duration (mean 7.6 days, SD 4.4). There were five (0.4%) serious AEs, none of them lethal and each related to a different therapy: two patients developed diarrhoea with *Clostridioides difficile* isolation (one was prescribed PPI-M+Tc+B therapy and the other, PPI-A+M+B), one developed a severe rash (PPI-tinidazole+D+B), one required care for severe vomiting (PPI-C+A B) and one experienced severe cytopenias with fever (PPI-A+R). Treatment had to be interrupted in 8% of the patients who experienced an AE, independently of the type, duration and intensity of the AE (online supplemental table 12).

AEs were significantly more frequent in quadruple than in triple therapies (38% vs 21%, p<0.0001). The highest AE rates were reported with bismuth-containing quadruple

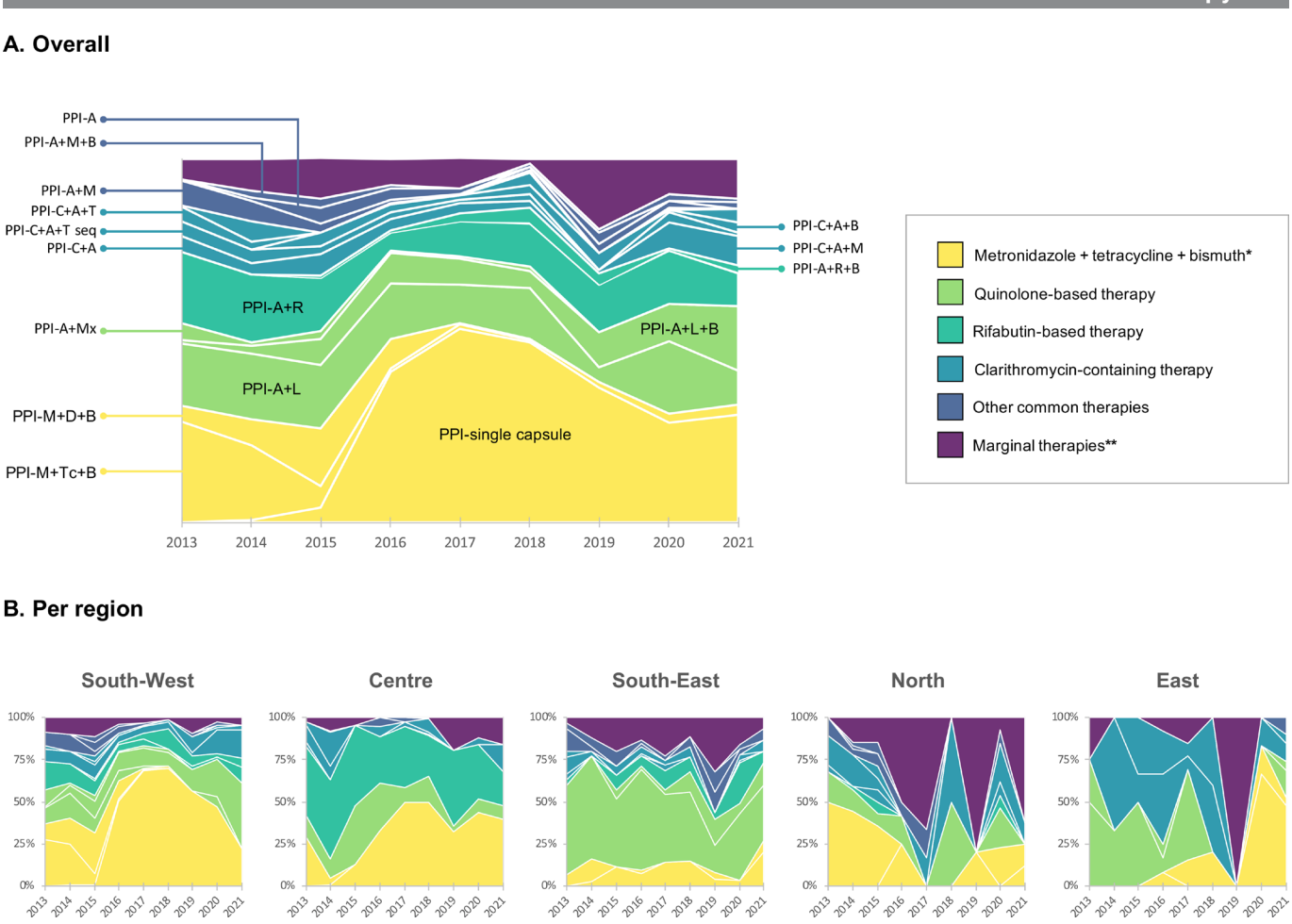

Figure 2 Empirical rescue treatment prescription trends (2013-2021) in third-line to sixth-line treatments, (A) overall in Europe and (B) by European region. *A tetracycline, either tetracycline hydrochloride or doxycycline. **Marginal therapies were considered to be those with 20 or fewer cases. There were 44 different marginal therapies, with a total of 183 cases (see table 1 and online supplemental table 3). A, amoxicillin; B, bismuth; C, clarithromycin; D, doxycycline; L, levofloxacin; M, metronidazole; Mx, moxifloxacin; PPI, proton-pump inhibitor; R, rifabutin; Seq, sequential; T, tinidazole, Tc, tetracycline hydrochloride.

therapies (PPI-A+R+B: 52%; PPI-C+A+B: 47%; PPI-single-capsule:41%; traditional PPI-M+Tc+B: 40%). Quinolone-based triple therapies had the lowest incidence of AEs (PPI-A+L: 16%; PPI-A+Mx: 8%).

Overall, 96% of patients complied with treatment. Treatment compliance could not be evaluated in 199 patients (11%) and the confirmatory test could not be performed in 84 (4%); the most common reasons were that the patient did not return to the clinic or that the physician did not set a follow-up visit date. AEs and compliance with the most frequently prescribed therapies are summarised in table 6.

DISCUSSION

This study showed that the management of persistent *H. pylori* infection is highly variable and frequently discrepant with current recommendations throughout Europe. It also highlighted the suboptimal performance of quinolone-based and rifabutin-based therapies (even quadruple ones), the increasing prominence of single-capsule bismuth quadruple therapy as rescue treatment, and the need to enhance medical education on clinical guideline statements in the coming years.

Antibiotic bacterial resistance represents, together with treatment compliance, the most important determinant of treatment success in any infection.[31] In the current context of increasing antibiotic resistance worldwide, several regions have reported a high prevalence of *H. pylori* infection resistant to clarithromycin, metronidazole and even levofloxacin.[6 32 33] As treatment failures accumulate, the prevalence of multiresistant strains increases and, consequently, the eradication rate drops.[25 26] Therefore, if achieving optimal effectiveness is not an easy task in second-line treatment, it is even more challenging when a third treatment has to be prescribed. In the present study, the overall third-line eradication rate was far from 90% for the most commonly prescribed regimens except for PPI-single-capsule therapy.

Several optimisation strategies have been shown to improve empirical rescue treatment outcomes. Thus, 12-day to 14-day durations and high-dose PPIs are recommended for most regimens.[16–18] It is also well established that standard triple therapies should be avoided (unless proven locally effective), as should re-exposure to clarithromycin and levofloxacin.[24] Despite this, from the publication of the three main consensus guidelines in 2016–2017 to the end of 2021, only 67% of third-line to sixth-line treatments were quadruple therapies, and among all treatments other than PPI-single-capsule therapy, only 63% lasted 14 days, only 52% used high-dose PPIs and only 44% were prescribed both for 14 days and with high-dose PPIs. Additionally, the re-exposure cumulative rate to clarithromycin was 79%,

Table 2 Overall prescriptions and effectiveness by modified intention-to-treat of rescue therapies prior to and since publication of the 2016–2017 clinical guidelines

	Before 2017 (n=1275)			Since 2017 (n=865)		
	Use, N (%)	mITT N	ER, % (95% CI)	Use, N (%)	mITT N	ER, % (95% CI)
Regimen						
Quadruple (including single-capsule)	675 (52.9)	619	72.4 (69 to 76)	581 (67.2)	485	82.7 (79 to 86)
Quadruple (excluding single-capsule)	508 (40.1)	471	69.2 (65 to 73)	218 (25.2)	167	76.6 (70 to 82)
Sequential	33 (2.6)	29	62.1 (44 to 77)	15 (1.7)	13	53.9 (29 to 77)
Triple	537 (42.1)	454	71.6 (67 to 76)	259 (29.9)	177	66.1 (59 to 73)
Dual	30 (2.4)	26	57.7 (39 to 75)	10 (1.2)	6	33.3 (10 to 70)
Duration						
7 days	41 (3.2)	32	56.3 (39 to 72)	20 (2.3)	17	23.5 (10 to 47)
10 days (including single-capsule)	645 (50.7)	577	68.5 (65 to 72)	467 (54.1)	405	81.2 (77 to 85)
10 days (excluding single-capsule)	483 (43.4)	433	64.0 (59 to 68)	113 (13.1)	95	67.4 (57 to 76)
12 days*	97 (7.6)	83	90.4 (82 to 95)	54 (6.3)	51	58.8 (45 to 71)
14 days	490 (38.5)	435	73.1 (69 to 77)	323 (37.4)	205	78.5 (72 to 84)
Unknown	2 (0.2)	1	0.0 (0 to 79)	1 (0.1)	1	0.0 (0 to 79)
PPI dose (all treatments)						
Low	391 (30.7)	350	63.7 (59 to 69)	346 (40.0)	307	70.0 (65 to 75)
Standard	231 (18.1)	212	70.8 (64 to 76)	106 (12.3)	75	88.0 (79 to 94)
High	631 (49.5)	546	77.8(74 to 81)	408 (47.2)	294	83.3 (79 to 87)
Unknown	22 (1.7)	20	40.0 (22 to 61)	5 (0.6)	5	20.0 (4 to 62)
PPI dose (excluding single-capsule)						
Low	341 (30.8)	304	61.5 (56 to 67)	173 (34.5)	157	57.3 (50 to 65)
Standard	192 (17.3)	175	66.3 (59 to 73)	62 (12.4)	39	89.7 (76 to 96)
High	554 (50.0)	481	77.5 (74 to 81)	262 (52.2)	162	79.0 (72 to 85)
Unknown	21 (1.9)	20	40.0 (22 to 61)	5 (1.0)	5	20.0 (4 to 62)
Treatment optimisation†						
Non-optimised (excluding single-capsule)	796 (62.4)	708	68.8 (65 to 72)	278 (32.1)	231	64.5 (58 to 70)
Optimised (excluding single-capsule)	290 (22.7)	251	75.3 (70 to 80)	219 (25.3)	127	81.9 (74 to 88)
Single-capsule	167 (13.1)	148	82.4 (76 to 88)	363 (42.0)	318	85.9 (82 to 89)
Missing	22 (1.7)	21	38.1 (21 to 59)	5 (0.6)	5	20.0 (4 to 62)

*12-day treatments were prescribed only in one Italian centre.
†Optimised therapies: high-dose PPI and duration ≥14 days. Low-dose PPI: 4.5–27 mg omeprazole equivalents, two times per day (eg, 20 mg omeprazole equivalents, two times per day). Standard-dose PPI: 32–40 mg omeprazole equivalents, two times per day (eg, 40 mg omeprazole equivalents, two times per day). High-dose PPI: 54–128 mg omeprazole equivalents, two times per day (eg, 60 mg omeprazole equivalents, two times per day).
ER, eradication rate; mITT, modified intention-to-treat; N, number of cases; PPI, proton-pump inhibitor.

and to levofloxacin 11%. These findings are concerning and underscore the need for further medical education in the management of *H. pylori* infection.

Despite the great heterogeneity in prescriptions, some regional distinctiveness was identified. The use of quadruple therapies was more established in the South-West: this was the region where PPI-single-capsule therapy was most commonly prescribed, and the only region where bismuth salts were added to quinolone-based or rifabutin-based regimens in a relevant number of cases. Central Europe was at the opposite end of the spectrum, with the highest triple therapy use rate. The number of rifabutin-based prescriptions did not decrease with the commercialisation of single-capsule therapy, and the Centre remained the region where PPI-A+R therapy was used the most (and where it performed the best). Northern Europe stood out as the only region where 7-day treatments persisted. This, together with the facts that centres did not have access to single-capsule therapy and that a quarter of treatments contained clarithromycin, resulted in a lower overall eradication rate. Prescriptions in the South-East were dominated by triple PPI-L+A therapy, which only achieved acceptable eradication rates when optimised. Finally, Eastern data should be interpreted with caution due to the small sample size. This was the only region where peptic ulcer was the main reason for investigation of the infection, and also the one with the highest relative use of clarithromycin. Of note was the excellent performance of triple PPI-L+A therapy regardless of optimisation.

Quinolone-based therapies

From 2013 to the last quarter of 2021, one in four rescue treatments were quinolone based and triple PPI-A+L therapy was the second most frequently prescribed regimen globally. This contrasts with the fact that its effectiveness beyond the second line was around 80% in most regions, reaching the 90% threshold only in Eastern and Northern Europe and in cases where high-dose PPIs and 14-day duration were applied. Several studies have previously demonstrated that optimisation of triple PPI-A+L therapy can achieve adequate results, which supports the recommendation to use 14-day regimens.[34 35] The arrival of quadruple PPI-A+L+B therapy in 2014 did not detract from the prominence of triple PPI-A+L, with use of quadruple therapy largely limited to South-Western Europe (85% of cases coming

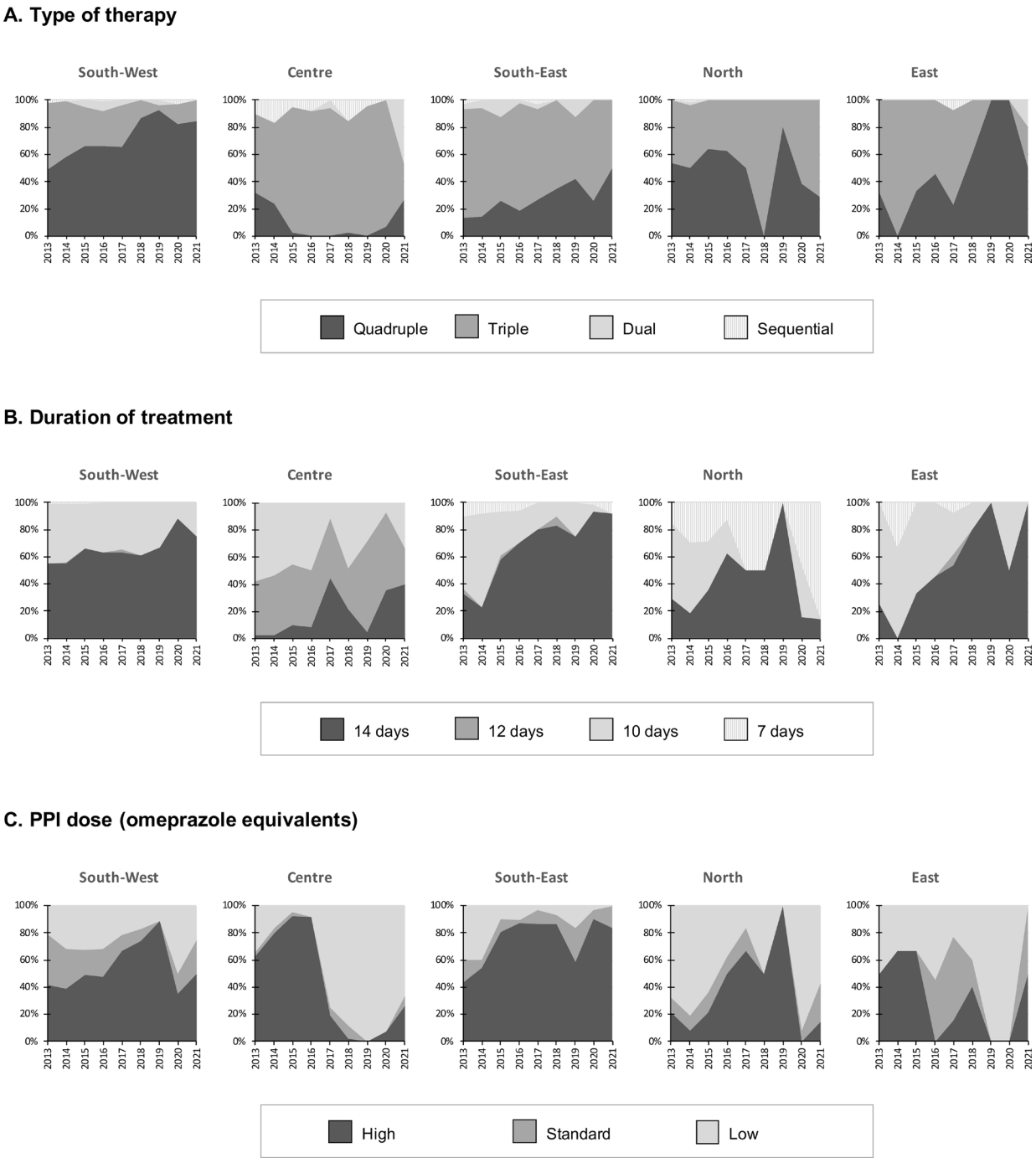

Figure 3 Trends (2013-2021) in (A) type of therapy, (B) duration of treatment and (C) dose of proton pump inhibitors in non-single capsule therapies in third-line to sixth-line treatments, by European region. Low-dose PPI: 4.5-27 mg omeprazole equivalents, two times per day (e.g. 20 mg omeprazole equivalents, two times per day). Standard-dose PPI: 32-40 mg omeprazole equivalents, two times per day (e.g. 40 mg omeprazole equivalents, two times per day). High-dose PPI: 54-128 mg omeprazole equivalents, two times per day (e.g. 60 mg omeprazole equivalents, two times per day). PPI, proton-pump inhibitor.

from Spain). The satisfactory results of this regimen as an empirical second-line approach led to its inclusion in the 2016 European Consensus Guidelines as an optimised rescue treatment alternative.[10 16] However, its effectiveness as third-line treatment in the present study was inferior to that reported when using it as second-line regimen,[10 23 36] with cure rates below 82% in the 'best-case scenario' and no improvement compared with triple PPI-L+A therapy. On the other hand, in 27% of cases where quadruple PPI-A+L+B therapy was prescribed, levofloxacin had already been used as part of a previous eradication attempt. Although still concerning, this would not explain the suboptimal performance of this therapy, as the eradication rate was not significantly higher in those cases with no re-exposure to quinolones (75% vs 78%, p>0.05). It has been reported that quadruple PPI-A+L+B therapy can achieve over 90% effectiveness as long as the local bacterial levofloxacin resistance rate remains below 26%.[37] In a recent systematic review, the prevalence of secondary levofloxacin resistance in Europe was reported to be 19%.[6] Given the findings of the current study, it appears urgent to update the local antibiotic resistance rates and

Table 3 Overall effectiveness by treatment line and European region, all therapies included

			Overall	Third line	Fourth line	Fifth line	Sixth line
Europe	PP	N	1751	1240	352	121	38
		% (95% CI)	74.6 (73 to 77)	79.3 (77 to 81)	66.8 (62 to 71)	58.7 (50 to 67)	47.4 (32 to 63)
	mITT	N	1809	1283	363	123	40
		% (95% CI)	73.7 (72 to 76)	78.4 (76 to 81)	65.3 (60 to 70)	57.7 (49 to 66)	47.5 (33 to 63)
	ITT	N	1958	1394	396	130	38
		% (95% CI)	64.9 (63 to 67)	68.9 (66 to 71)	57.3 (52 to 62)	52.3 (44 to 61)	42.1 (28 to 58)
South-West	PP	N	1061	788	192	66	15
		% (95% CI)	74.4 (72 to 77)	78.3 (75 to 81)	64.1 (57 to 71)	62.1 (50 to 73)	53.3 (30 to 75)
	mITT	N	1090	811	198	66	15
		% (95% CI)	73.6 (71 to 76)	77.6 (75 to 80)	62.6 (56 to 69)	62.1 (50 to 73)	53.3 (30 to 75)
	ITT	N	1099	817	202	67	13
		% (95% CI)	69.2 (66 to 72)	73.3 (70 to 76)	57.4 (51 to 64)	58.2 (46 to 69)	46.2 (23 to 71)
Centre	PP	N	350	225	85	29	11
		% (95% CI)	75.1 (70 to 79)	80.0 (74 to 85)	70.6 (60 to 79)	55.2 (38 to 72)	63.7 (35 to 85)
	mITT	N	363	235	86	30	12
		% (95% CI)	73.6 (69 to 78)	77.9 (72 to 83)	70.9 (61 to 79)	53.4 (36 to 70)	58.4 (32 to 81)
	ITT	N	413	274	95	31	13
		% (95% CI)	62.7 (58 to 67)	65.0 (59 to 70)	62.1 (52 to 71)	48.4 (32 to 65)	53.9 (29 to 77)
South-East	PP	N	166	122	34	6	4
		% (95% CI)	81.9 (75 to 87)	86.1 (79 to 91)	76.5 (60 to 88)	50.0 (19 to 81)	50.0 (15 to 85)
	mITT	N	170	124	35	7	4
		% (95% CI)	81.2 (75 to 86)	86.3 (79 to 91)	74.3 (58 to 86)	42.9 (16 to 75)	50.0 (15 to 85)
	ITT	N	254	188	52	11	3
		% (95% CI)	51.2 (45 to 57)	53.2 (46 to 60)	50.0 (37 to 63)	27.3 (10 to 57)	33.3 (6 to 79)
North	PP	N	119	62	33	16	8
		% (95% CI)	58.8 (50 to 67)	71.0 (59 to 81)	54.6 (38 to 70)	43.8 (23 to 67)	12.5 (2 to 47)
	mITT	N	124	64	35	16	9
		% (95% CI)	58.9 (50 to 67)	71.9 (60 to 81)	51.4 (36 to 67)	43.8 (23 to 67)	22.2 (6 to 55)
	ITT	N	129	66	38	16	9
		% (95% CI)	55.8 (47 to 64)	68.2 (56 to 78)	47.4 (32 to 63)	43.8 (23 to 67)	22.2 (6 to 55)
East	PP	N	55	43	8	4	0
		% (95% CI)	89.1 (78 to 95)	86.1 (73 to 93)	100 (68 to 100)	100 (51 to 100)	NA
	mITT	N	62	49	9	4	0
		% (95% CI)	85.5 (75 to 92)	83.7 (71 to 91)	88.9 (57 to 98)	100 (51 to 100)	NA
	ITT	N	63	49	9	5	0
		% (95% CI)	79.4 (68 to 88)	77.6 (64 to 87)	88.9 (57 to 98)	80.0 (38 to 96)	NA

ITT, intention-to-treat; mITT, modified intention-to-treat; N, number of cases; NA, not available; PP, per protocol.

to closely monitor the effectiveness outcomes of levofloxacin-based therapies in the coming years.

Quadruple therapies with metronidazole, tetracycline and bismuth salts

The combination of metronidazole, a tetracycline (either tetracycline hydrochloride or doxycycline) and bismuth salts has re-emerged as a rescue regimen since the three-in-one single-capsule was marketed. In this regard, until 2015 only 27% of the rescue treatments were M+Tc/D+B, whereas in the period 2016–2018 this figure exceeded 50%. While in 2019–2021 the use of this regimen seemed to have plateaued at around 30%, PPI-single-capsule has become the most commonly prescribed empirical rescue therapy. Prior to the single-capsule era, traditional bismuth quadruple therapy achieved eradication rates above 90% only when prescribed with tetracycline hydrochloride and for ≥14 days. Regarding metronidazole, a trend towards better results was identified when it was prescribed at higher doses, but the large variability in dosage (mg/24 hours) between centres did not allow statistical significance to be reached. These results reinforce the fact that obtaining good results in the presence of multidrug-resistant strains requires therapies of longer duration, the use of high doses of metronidazole and avoidance of substitution of tetracycline hydrochloride by doxycycline.[29 38 39]

Concerning PPI-single-capsule therapy, excellent results have been reported when using it in the first two lines of treatment,[11 20 30 36] but the evidence on its performance beyond the second-line is variable: the most relevant meta-analysis of this therapy showed a third-line eradication rate of 82%,[11] whereas the Hp-EuReg clinical practice experience evidenced a grouped third-line to sixth-line effectiveness of 92%.[30] The outcomes of the present study fall in between the two aforementioned data, with a third-line eradication rate of 87%–92% and a fourth-line to sixth-line eradication rate below 80%. Furthermore, the only factors associated with higher treatment success in the bivariate analysis were treatment compliance and administration of the treatment in third-line (86.8% in third line vs 75.8% in fourth to sixth lines). Additionally, as in other recent studies,[11 29 30] no

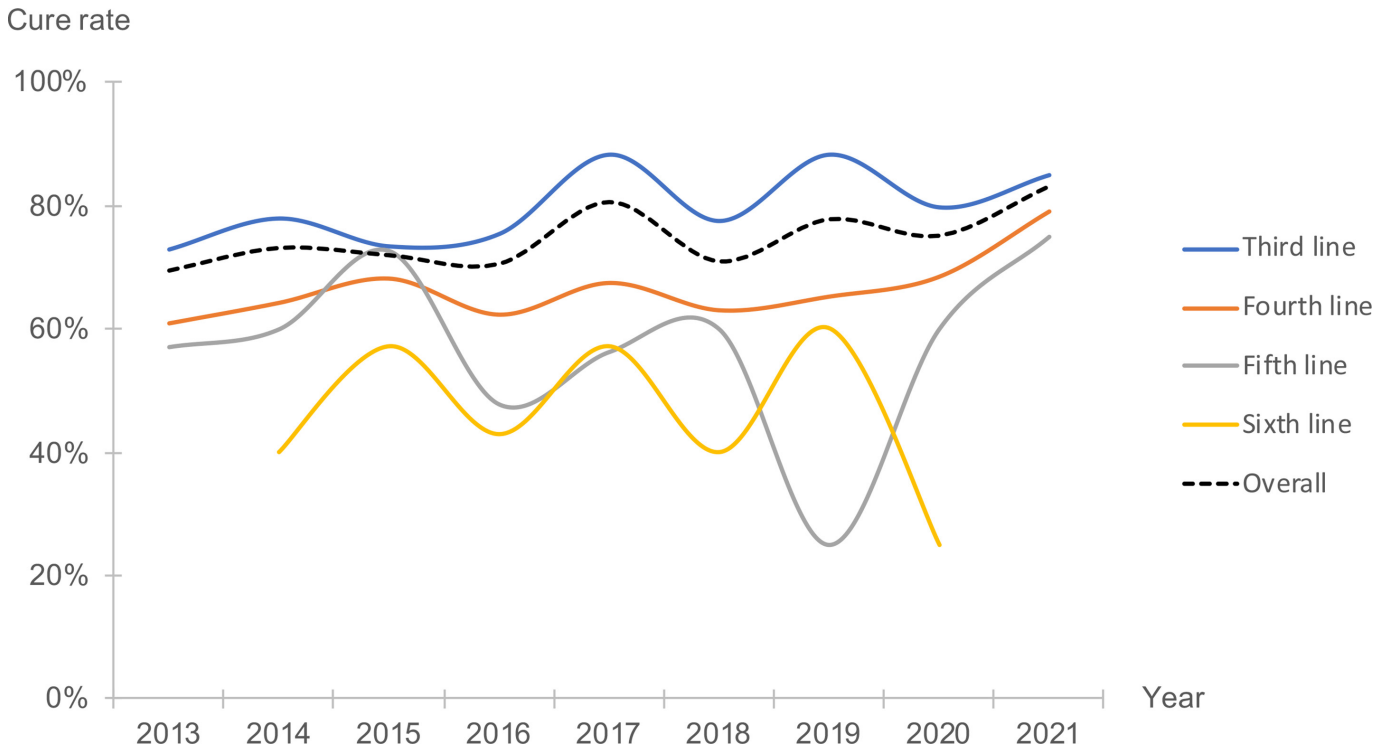

Figure 4 Trends of effectiveness (by modified intention to treat) of empirical third-line, fourth-line, fifth-line and sixth-line treatments in Europe. The total number of cases (third-line to sixth-line) per year was 250 (2013), 371 (2014), 292 (2015), 366 (2016), 254 (2017), 208 (2018), 124 (2019), 171 (2020) and 108 (2021).

significant differences by type or dose of PPI were identified. While the use of high-dose PPIs ameliorates eradication rates in triple therapies, there is no solid evidence regarding quadruple PPI-B+Tc+M regimen (either as single-capsule or as traditional therapy).[40 41] The findings of this study indicate that the benefit of gastric acid inhibition in this regimen has a ceiling that can be reached with standard-dose PPIs, a fact that is relevant from a cost-effectiveness point of view.

Ultimately, single-capsule bismuth quadruple therapy is the most widely used and the best performing rescue therapy in those regions where it is available, but there is growing evidence that its results worsen as eradication failures accumulate (ie, as the prevalence of metronidazole-resistant strains increases). In this scenario, there is probably room for improvement by applying what has been learnt from decades of experience with traditional bismuth quadruple PPI-B+Tc+M therapy, that is, the value of extending treatment to 14 days, keeping the daily dose of metronidazole above 1500–1600 mg and ensuring treatment compliance.

Rifabutin-based therapies

Rifabutin is usually reserved for fourth-line treatment in the therapeutic algorithm for *H. pylori* infection, being used once clarithromycin-containing, levofloxacin-containing and metronidazole-containing therapies have already failed. However, rifabutin could also be used as third-line or even second-line treatment if multiple antibiotic resistance has been demonstrated (or is highly suspected) and/or when bismuth salts are not available. Current evidence establishes the rate of rifabutin resistance to be 0.13%,[42] so it can be assumed that if a rifabutin-based therapy fails, it is probably due to other variables of the treatment and not to drug resistance per se.

In Europe, rifabutin-based therapies were used almost exclusively in the Centre and South-West, in different ways: while in Central Europe triple PPI-A+R therapy was mainly prescribed as third line, with a rifabutin dose of 150 mg/24 hours, high-dose PPIs and a duration of 12 days, in the South-West it was more often used as fourth line, with rifabutin doses of 300 mg/24 hours, lower PPI doses and for 10 days. These variations in the use of each component of the treatment probably explain the widely discrepant regional performances, as in Central Europe the third-line and fourth-line eradication rates were 84% and 73%, respectively, while in the South-West they were 14% and 52%. In line with this, the most recent systematic review and meta-analysis of rifabutin-containing treatments identified the following factors to be associated with greater therapeutic success: third-line prescription,[42] use of rifabutin doses of 300 mg/24 hours,[43] frequent administration of a high-dose amoxicillin (total daily dose ≥3000 mg)[44] and potent acid inhibition.[45–47] The optimal duration of treatment remains controversial, as extending treatment from 10–12 days to 14 days does not appear to provide a clear eradication benefit and may increase the incidence of AEs.[42]

The addition of bismuth to triple PPI-A+R therapy showed encouraging results in recent publications,[48 49] but these were not replicated in the current study, where the use of quadruple PPI-A+R+B therapy offered only marginal benefit, with an eradication rate of 60% and twice as many AEs. The same finding has recently been reported in a further Hp-EuReg study specifically focused on the use and effectiveness of rifabutin,[50] calling into question the clinical benefit of adding bismuth to rifabutin-based therapies.

Safety and adverse events

One-third of patients (31%) reported at least one AE and, in general, triple therapies were better tolerated than quadruple

Table 4 Effectiveness (by mITT) of the most commonly prescribed therapies by treatment line and by European region (16 different therapies, 1961 patients, 91.5% of the total number of cases)

		Europe		South-West		Centre		South-East		North		East	
Rescue therapy	Use, N	mITT, N	% (95% CI)	mITT, N	% (95% CI)	mITT, N	% (95% CI)	mITT, N	% (95% CI)	mITT, N	% (95% CI)	mITT, N	% (95% CI)
PPI-single-capsule*													
Overall	530	466	84.8 (81 to 88)	351	83.5 (79 to 87)	78	85.9 (76 to 92)	20	95.0 (77 to 99)	3	66.7 (21 to 94)	14	100 (78 to 100)
Third-line	398	353	87.0 (83 to 90)	283	85.9 (81 to 89)	42	90.5 (78 to 96)	17	94.1 (73 to 99)	2	50.0 (9 to 91)	9	100 (70 to 100)
Fourth-line	85	69	79.7 (69 to 88)	41	73.2 (58 to 84)	21	85.7 (65 to 95)	2	100 (34 to 100)	1	100 (21 to 100)	4	100 (51 to 100)
Fifth-line	36	34	73.5 (57 to 85)	22	72.7 (52 to 87)	10	70.0 (40 to 89)	1	100 (21 to 100)	0	NA	1	100 (21 to 100)
Sixth-line	11	10	80.0 (49 to 94)	5	80.0 (38 to 96)	5	80.0 (38 to 96)	0	NA	0	NA	0	NA
PPI-A+L													
Overall	322	234	77.8 (72 to 83)	69	76.8 (66 to 85)	56	73.2 (60 to 83)	76	81.6 (71 to 89)	16	62.5 (39 to 82)	17	94.1 (73 to 99)
Third-line	262	189	80.4 (74 to 85)	63	74.6 (63 to 84)	45	80.0 (66 to 89)	58	82.8 (71 to 90)	8	87.5 (53 to 98)	15	93.3 (70 to 99)
Fourth-line	41	29	69.0 (51 to 83)	2	100 (34 to 100)	6	66.7 (30 to 90)	15	80.0 (55 to 93)	5	20.0 (4 to 62)	1	100 (21 to 100)
Fifth-line	15	12	75.0 (47 to 91)	3	100 (44 to 100)	4	25.0 (5 to 70)	2	100 (34 to 100)	2	100 (34 to 100)	1	100 (21 to 100)
Sixth-line	4	4	25.0 (5 to 70)	1	100 (21 to 100)	1	0 (0 to 79)	1	0.0 (0 to 79)	1	0.0 (0 to 79)	0	NA
PPI-A+R													
Overall	279	237	66.7 (60 to 72)	78	51.3 (40 to 62)	145	76.6 (69 to 83)	11	54.6 (28 to 79)	3	33.3 (6 to 79)	0	NA
Third-line	126	105	78.1 (69 to 85)	8	25.0 (7 to 59)	94	81.9 (73 to 88)	3	100 (44 to 100)	0	NA	0	NA
Fourth-line	126	106	61.3 (52 to 70)	66	54.6 (43 to 66)	34	76.5 (60 to 88)	5	40.0 (12 to 77)	1	100 (21 to 100)	0	NA
Fifth-line	21	20	40.0 (22 to 61)	4	50.0 (15 to 85)	13	46.2 (23 to 71)	2	0.0 (0 to 66)	1	0.0 (0 to 79)	0	NA
Sixth-line	6	6	50.0 (19 to 82)	0	NA	4	50.0 (15 to 85)	1	100 (21 to 100)	1	0.0 (0 to 79)	0	NA
PPI-M+Tc+B													
Overall	178	167	73.1 (66 to 79)	91	75.8 (66 to 83)	19	57.9 (36 to 77)	7	100 (65 to 100)	46	69.6 (55 to 81)	4	75.0 (30 to 95)
Third-line	138	130	73.8 (66 to 81)	84	76.2 (66 to 84)	14	50.0 (27 to 73)	6	100 (61 to 100)	22	72.7 (52 to 87)	4	75.0 (30 to 95)
Fourth-line	28	27	70.4 (52 to 84)	7	71.4 (36 to 92)	4	75.0 (30 to 95)	1	100 (21 to 100)	15	66.7 (42.85)	0	NA
Fifth-line	8	6	83.3 (44 to 97)	0	NA	1	100 (21 to 100)	0	NA	5	80.0 (38 to 97)	0	NA
Sixth-line	4	4	50 (15 to 85)	0	NA	0	NA	0	NA	4	50.0 (15 to 85)	0	NA
PPI-A+L+B													
Overall	139	119	77.3 (69 to 84)	110	76.4 (68 to 83)	0	NA	7	100 (65 to 100)	0	NA	2	50.0 (9 to 91)
Third-line	117	98	79.6 (71 to 86)	93	79.6 (70 to 87)	0	NA	3	100 (44 to 100)	0	NA	2	50.0 (9 to 91)
Fourth-line	19	18	72.2 (49 to 88)	14	64.3 (39 to 84)	0	NA	4	100 (51 to 100)	0	NA	0	NA
Fifth-line	2	2	50.0 (9 to 91)	2	50.0 (9 to 91)	0	NA	0	NA	0	NA	0	NA
Sixth-line	1	1	0.0 (0 to 79)	1	0.0 (0 to 79)	0	NA	0	NA	0	NA	0	NA
PPI-M+D+B													
Overall	115	109	63.3 (54 to 72)	108	63.9 (55 to 72)	0	NA	1	0 (0 to 79)	0	NA	0	NA
Third-line	95	90	65.6 (55 to 75)	90	65.6 (55 to 75)	0	NA	0	NA	0	NA	0	NA
Fourth-line	14	14	50.0 (27 to 63)	13	53.9 (29 to 77)	0	NA	1	0 (0 to 79)	0	NA	0	NA
Fifth-line	5	4	50.0 (15 to 85)	4	50.0 (15 to 85)	0	NA	0	NA	0	NA	0	NA
Sixth-line	1	1	100 (21 to 100)	1	(21 to 100)	0	NA	0	NA	0	NA	0	NA
PPI-C+A+M													
Overall	84	79	65.8 (55 to 75)	70	67.1 (56 to 77)	1	0.0 (0 to 79)	3	66.7 (21 to 94)	2	0.0 (0 to 66)	3	100 (44 to 100)
Third-line	64	60	71.7 (59 to 81)	54	70.4 (57 to 81)	1	0.0 (0 to 79)	2	100 (34 to 100)	0	NA	3	100 (44 to 100)

Continued

Table 4 Continued

Rescue therapy	Use, N	Europe		South-West		Centre		South-East		North		East	
		mITT, N	% (95% CI)	mITT, N	% (95% CI)	mITT, N	% (95% CI)	mITT, N	% (95% CI)	mITT, N	% (95% CI)	mITT, N	% (95% CI)
Fourth-line	10	9	44.4 (19 to 73)	7	57.1 (25 to 84)	0	NA	1	0 (0 to 79)	1	0.0 (0 to 79)	0	NA
Fifth-line	6	6	66.7 (30 to 90)	6	66.7 (30 to 90)	0	NA	0	NA	0	NA	0	NA
Sixth-line	4	4	25.0 (5 to 70)	3	33.3 (6 to 79)	0	NA	0	NA	1	0.0 (0 to 79)	0	NA
PPI-A+M													
Overall	57	50	68.0 (54 to 79)	32	68.8 (51 to 82)	1	0.0 (0 to 79)	9	100 (70 to 100)	8	37.5 (14 to 69)	0	NA
Third-line	46	42	76.2 (61 to 87)	30	70.0 (52 to 83)	0	NA	9	100 (70 to 100)	3	66.7 (21 to 94)	0	NA
Fourth-line	7	4	50.0 (15 to 85)	2	50.0 (9 to 91)	0	NA	0	NA	2	50.0 (9 to 91)	0	NA
Fifth-line	3	3	0.0 (0 to 56)	0	NA	0	NA	0	NA	3	0.0 (0 to 56)	0	NA
Sixth-line	1	1	0.0 (0 to 79)	0	NA	1	0.0 (0 to 79)	0	NA	0	NA	0	NA
PPI-C+A													
Overall	49	37	62.2 (46 to 76)	6	66.7 (30 to 90)	1	100 (21 to 100)	5	80.0 (38 to 96)	18	50.0 (29 to 71)	7	71.4 (36 to 92)
Third-line	37	28	75.0 (57 to 87)	5	80.0 (38 to 96)	1	100 (21 to 100)	5	80.0 (38 to 96)	13	69.2 (42 to 87)	4	75.0 (30 to 95)
Fourth-line	5	4	25.0 (5 to 70)	1	0.0 (0 to 79)	0	NA	0	NA	1	0.0 (0 to 79)	2	50.0 (95 to 91)
Fifth-line	5	3	33.3 (6 to 79)	0	NA	0	NA	0	NA	2	0.0 (0 to 66)	1	100 (21 to 100)
Sixth-line	2	2	0.0 (0 to 66)	0	NA	0	NA	0	NA	2	0.0 (0 to 66)	0	NA
PPI-A													
Overall	39	31	51.6 (35 to 68)	22	54.5 (27 to 65)	1	100 (21 to 100)	5	60.0 (23 to 88)	1	100 (21 to 100)	2	50.0 (9 to 91)
Third-line	13	8	62.5 (31 to 86)	2	50.0 (9 to 91)	0	NA	3	66.7 (21 to 94)	1	100 (21 to 100)	2	50.0 (95 to 91)
Fourth-line	4	3	66.7 (21 to 94)	2	50.0 (9 to 91)	1	100 (21 to 100)	0	NA	0	NA	0	NA
Fifth-line	17	15	53.3 (30 to 75)	15	53.3 (30 to 75)	0	NA	0	NA	0	NA	0	NA
Sixth-line	5	5	20.0 (4 to 62)	3	0.0 (0 to 56)	0	NA	2	50.0 (9 to 91)	0	NA	0	NA
PPI-C+A+B													
Overall	37	31	74.2 (57 to 86)	17	76.5 (53 to 90)	0	NA	4	100 (51 to 100)	1	0.0 (0 to 79)	9	66.7 (35 to 88)
Third-line	29	25	72.0 (52 to 86)	15	73.3 (48 to 89)	0	NA	3	100 (44 to 100)	0	NA	7	57.1 (25 to 84)
Fourth-line	5	4	75.0 (30 to 95)	1	100 (21 to 100)	0	NA	1	100 (21 to 100)	1	0.0 (0 to 79)	1	100 (21 to 100)
Fifth-line	3	2	100 (34 to 100)	1	100 (21 to 100)	0	NA	0	NA	0	NA	1	100 (21 to 100)
Sixth-line	0	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
Sequential PPI-C+A+T													
Overall	30	27	55.6 (37 to 72)	2	100 (34 to 100)	25	52.0 (34 to 70)	0	NA	0	NA	0	NA
Third-line	22	17	64.7 (41 to 83)	2	100 (34 to 100)	17	47.1 (26 to 69)	0	NA	0	NA	0	NA
Fourth-line	8	8	50.0 (22 to 78)	0	NA	8	50.0 (22 to 78)	0	NA	0	NA	0	NA
Fifth-line	0	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
Sixth-line	0	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
PPI-A+Mx													
Overall	27	26	69.2 (50 to 84)	26	69.2 (50 to 84)	0	NA	0	NA	0	NA	0	NA
Third-line	20	20	65.0 (43 to 82)	20	65.0 (43 to 82)	0	NA	0	NA	0	NA	0	NA
Fourth-line	4	3	100 (44 to 100)	3	100 (44 to 100)	0	NA	0	NA	0	NA	0	NA
Fifth-line	3	3	66.7 (21 to 94)	3	66.7 (21 to 94)	0	NA	0	NA	0	NA	0	NA

Continued

Table 4 Continued

Rescue therapy	Use, N	Europe		South-West		Centre		South-East		North		East	
		mITT, N	% (95% CI)	mITT, N	% (95% CI)	mITT, N	% (95% CI)	mITT, N	% (95% CI)	mITT, N	% (95% CI)	mITT, N	% (95% CI)
Sixth-line	0	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
PPI-A+R+B													
Overall	27	25	60.0 (41 to 77)	25	60.0 (41 to 77)	0	NA	0	NA	0	NA	0	NA
Third-line	3	3	100 (44 to 100)	3	100 (44 to 100)	0	NA	0	NA	0	NA	0	NA
Fourth-line	16	16	56.3 (33 to 77)	16	56.3 (33 to 77)	0	NA	0	NA	0	NA	0	NA
Fifth-line	7	5	40.0 (12 to 77)	5	40.0 (12 to 77)	0	NA	0	NA	0	NA	0	NA
Sixth-line	1	1	100 (21 to 100)	1	100 (21 to 100)	0	NA	0	NA	0	NA	0	NA
PPI-C+A+T													
Overall	24	22	54.5 (35 to 73)	0	NA	21	52.4 (32 to 72)	0	NA	1	100 (21 to 100)	0	NA
Third-line	15	14	54.3 (39 to 84)	0	NA	14	64.3 (39 to 84)	0	NA	0	NA	0	NA
Fourth-line	9	8	37.5 (14 to 69)	0	NA	7	28.6 (82 to 64)	0	NA	1	100 (21 to 100)	0	NA
Fifth-line	0	NA	NA	0	NA	0	NA	0	NA	0	NA	0	NA
Sixth-line	0	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
PPI-A+M+B													
Overall	24	18	88.9 (67 to 97)	16	87.5 (64 to 97)	0	NA	1	100 (21 to 100)	1	100 (21 to 100)	0	NA
Third-line	16	12	91.7 (65 to 99)	11	90.9 (62 to 98)	0	NA	0	NA	1	100 (21 to 100)	0	NA
Fourth-line	7	6	83.3 (44 to 97)	5	80.0 (38 to 96)	0	NA	1	100 (21 to 100)	0	NA	0	NA
Fifth-line	1	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
Sixth-line	0	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA

*Three-in-one single-capsule containing bismuth, tetracycline hydrochloride and metronidazole.
A, amoxicillin; B, bismuth; C, clarithromycin; D, doxycycline; L, levofloxacin; M, metronidazole; mITT, modified intention-to-treat; Mx, moxifloxacin; NA, not available; PP, per protocol; PPI, proton-pump inhibitor; R, rifabutin; T, tinidazole; Tc, tetracycline hydrochloride.

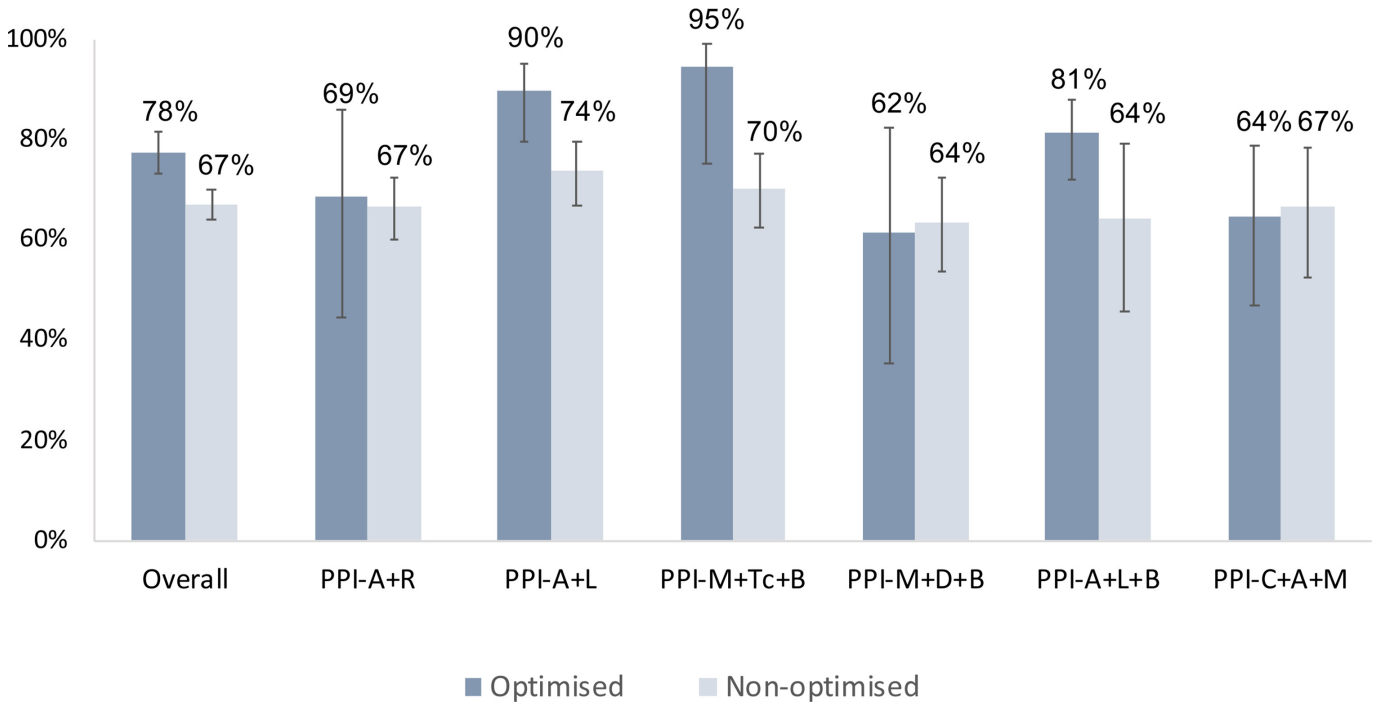

Figure 5 Effectiveness (by modified intention-to-treat) and 95% confidence intervals of the most commonly prescribed therapies based on their optimisation and excluding the three-in-one single-capsule therapy. An optimised treatment was defined as one lasting 14 days or more and using high-dose PPI. Only therapies with a representative number (N>20) of optimised and non-optimised cases are shown. "Overall" includes all therapies except PPI-single-capsule therapy (59 therapies, N=1614). High-dose PPI: 54-128 mg omeprazole equivalents, two times per day (e.g. 60 mg omeprazole equivalents, two times per day). A,amoxicillin; B,bismuth; C,clarithromycin; D,doxycycline; L, levofloxacin; M, metronidazole; PPI, proton-pump inhibitor; R, rifabutin; Tc, tetracycline hydrochloride.

Table 5 Multivariate analysis of third-line treatments

Independent variables	OR (95% CI)	P value
Third-line treatment group (ref. PPI-A+R)		
Other therapies*	2.08 (0.70 to 6.19)	0.191
PPI-A+L+B	2.18 (0.67 to 7.14)	0.198
PPI-A+L	3.16 (1.01 to 9.89)	0.048
PPI-single-capsule or PPI-M+Tc+B	5.15 (1.69 to 15.69)	0.004
PPI dose† (ref. low dose)		
Standard	1.47 (0.98 to 2.21)	0.064
High	2.13 (1.55 to 2.94)	0.000
Duration of treatment (ref. 7 days)		
10 days	2.07 (0.92 to 4.66)	0.080
12 days	8.57 (2.02 to 36.38)	0.004
14 days	2.59 (1.12 to 5.98)	0.026
Compliance (ref. <90% drug intake)	3.29 (1.70 to 6.35)	0.000

Treatment success was defined as mITT eradicaction.
Dependent variable: mITT. Independent variables: treatment group ((1) PPI-A+R, (2) other therapies, (3) PPI-A+L+B, (4) PPI-A+L or (5) PPI-single-capsule or traditional PPI-M+Tc+B), duration of treatment (7, 10, 12 or 14 days), PPI dose (low, standard or high), compliance (≥90% vs <90% drug intake), prior use of metronidazole, prior use of quinolones, age, gender and treatment indication (dyspepsia vs peptic ulcer).
*The group 'other therapies' contains all treatment regimens other than PPI-single-capsule, PPI-M+Tc+B, PPI-A+L, PPI-A+L+B and PPI-A+R.
†Low-dose PPI: 4.5–27 mg omeprazole equivalents, two times per day (eg, 20 mg omeprazole equivalents, two times per day). Standard-dose PPI: 32–40 mg omeprazole equivalents, two times per day (eg, 40 mg omeprazole equivalents, two times per day). High-dose PPI: 54–128 mg omeprazole equivalents, two times per day (eg, 60 mg omeprazole equivalents, two times per day).
A, amoxicillin; B, bismuth; C, clarithromycin; D, doxycycline; L, levofloxacin; M, metronidazole; mITT, modified intention-to-treat; PPI, proton-pump inhibitor; R, rifabutin; Tc, tetracycline hydrochloride.

ones. Among the most commonly prescribed therapies, the worst tolerated were those combining M+Tc+B (either as single-capsule therapy or in the traditional format). As for rifabutin, cytopenias were reported in 1% of patients receiving this drug and only one case (0.4%) was serious. Overall, the safety of the therapies was comparable to that reported in a recently published Hp-EuReg study on the safety of *H. pylori* infection treatments, with over 22 000 patients analysed.[51]

Limitations and strengths

The main drawback of the current study is one inherent to any observational non-interventional registry, namely, that the number of included cases depends on the number of patients attending the participating centres and on the commitment of the recruiting investigators. This results in marked differences in case numbers among countries, and, therefore, not all regions are equally represented. Countries such as Spain, Italy, Israel and Slovenia are considered to be well profiled, whereas other regions lack included cases beyond the second line (occasionally, entire countries are represented by just a few treatments with high eradication rates). Under these circumstances, cautious interpretation of findings is warranted, since it could be wrongly deduced that countries with scarce data perform better than others including hundreds of patients. The same consideration applies to further aspects such as duration of treatment or PPI dose (eg, one of the main recruitment centres in Italy prescribed 12-day therapies and low-dose PPI, which could lead to the misinterpretation that most of Central Europe uses these regimens on a regular basis).

In addition, the lack of antibiotic resistance testing in the Hp-EuReg could be considered a drawback. Nevertheless, it should be borne in mind that the aim of Hp-EuReg was always

Table 6 Safety and compliance of most frequently empirically prescribed third to sixth treatment lines

	Adverse events		Compliance ≥90%	
Rescue treatment	**n/N**	**% (95% CI)**	**n/N**	**% (95% CI)**
PPI-single-capsule*	193/474	40.7 (36 to 45)	456/475	96.0 (94 to 97)
PPI-A+L	41/264	15.5 (12 to 20)	245/253	96.8 (94 to 98)
PPI-A+R	63/259	24.3 (20 to 30)	236/249	94.8 (91 to 97)
PPI-M+Tc+B	69/174	39.7 (33 to 47)	164/169	97.0 (93 to 99)
PPI-A+L+B	38/120	31.7 (24 to 40)	116/121	95.9 (91 to 98)
PPI-M+D+B	33/112	29.5 (22 to 39)	106/112	94.6 (89 to 98)
PPI-C+A+M	19/81	23.5 (16 to 34)	77/80	96.3 (90 to 99)
PPI-A+M	19/55	34.6 (23 to 48)	51/55	92.7 (83 to 97)
PPI-C+A	13/47	27.7 (17 to 42)	39/43	90.7 (78 to 96)
PPI-A	13/34	38.2 (24 to 55)	33/34	97.1 (85 to 100)
PPI-C+A+B	16/34	47.1 (32 to 63)	29/32	90.6 (76 to 97)
Sequential PPI-C+A+T	7/28	25.0 (13 to 43)	26/28	92.9 (77 to 98)
PPI-A+Mx	2/26	7.7 (2 to 24)	26/27	96.3 (82 to 99)
PPI-A+R+B	13/25	52.0 (34 to 70)	24/25	96.0 (81 to 99)
PPI-C+A+T	10/23	43.5 (26 to 63)	22/24	91.7 (74 to 98)
PPI-A+M+B	9/20	43.5 (26 to 63)	17/18	94.4 (74 to 99)

*Three-in-one single-capsule containing bismuth, tetracycline hydrochloride and metronidazole.
A, amoxicillin; B, bismuth; C, clarithromycin; D, doxycycline; L, levofloxacin; M, metronidazole; Mx, moxifloxacin; PPI, proton-pump inhibitor; R, rifabutin; Tc, tetracycline hydrochloride.

to capture the clinical practice: if hardly any cases with antibiotic susceptibility assessment are included in the database, it is probably because *H. pylori* culture is scarcely performed in Europe.[52]

Despite the above-mentioned concerns, it has to be acknowledged that multicentre collaboration with high-quality projects such as Hp-EuReg is the only secure way to collect a critical mass of difficult-to-treat cases, which ultimately will allow powerful statistical analysis and yield meaningful results. In this respect, the current study is the largest cohort of third and subsequent lines of rescue treatments for *H. pylori* infection published to date worldwide.

CONCLUSION

In summary, a wide variety of empirical treatments are used in Europe beyond the second line, although single-capsule bismuth quadruple has become the most prescribed rescue therapy. Only 10-day single-capsule bismuth quadruple therapy, 14-day traditional bismuth quadruple therapy and 14-day levofloxacin triple therapy achieve the 90% effectiveness threshold in some settings. There is poor adherence to the principles of optimisation (ie, use of quadruple therapies, longer durations, high-dose PPIs and avoidance of re-exposure to clarithromycin or levofloxacin) despite dealing with infections in which multiple antibiotic resistance is assumed. European gastroenterologists should critically evaluate empirical regimens and continue improving adherence to evidence-based recommendations.

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Contributors DB-S: Spanish recruiter. Reviewed the quality of the database, performed the statistical analysis, synthesised the data, interpreted the data, wrote the manuscript drafts and approved the submitted manuscript. OPN: Scientific Director and member of the Scientific Committee. Planned and coordinated the study, designed and programmed the electronic case report form, performed the data extraction, the monitoring and the dataset quality check, supervised the statistical analysis and reviewed the data interpretation, critically reviewed the manuscript drafts and approved the submitted manuscript. AG, DB, PP, JK, BT, RM-P, VM, TR, ML, AT, DSB, VL, LGC, DD, OG, MD, FL, GMB, SS, MV and WM: acted as national coordinators for their country and as recruiters. Selected national recruiters, collected and helped interpret data, critically reviewed the manuscript drafts and approved the submitted manuscript. IP: Scientific Director and member of the project's Scientific Committee. Critically reviewed the manuscript drafts and approved the submitted manuscript. FM: member of the Scientific Committee. Designed the protocol, critically reviewed the manuscript drafts and approved the submitted manuscript. CO'M: member of the Scientific Committee. Designed the protocol, collected the data, critically reviewed the manuscript drafts and approved the submitted manuscript. JPG: Principal Investigator, member of the Scientific Committee and guarantor of the study. Directed the project, obtained funding, designed the protocol, planned the study, acted as Spanish National Coordinator, recruited patients, interpreted the data, critically reviewed the manuscript drafts and approved the final submitted manuscript.

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Competing interests OPN has received research funding from Mayoly and Allergan. JPG has served as speaker, consultant and advisory member for or has received research funding from Mayoly, Allergan, Diasorin, Gebro Pharma and Richen. MC-F has received retribution from Allergan for formative actions. AP-A has received retribution from Allergan and Mylan for formative actions. Laimas Jonaitis has served as speaker for KRKA. AL has served as a consultant to Bayer.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study was conducted according to the guidelines of the 1975 Declaration of Helsinki, was in compliance with the Guidelines of Good Clinical Practice, was classified by the Spanish Drug and Health Product Agency and was approved in 2012 by the Ethics Committee of La Princesa University Hospital (Madrid, Spain), which acted as reference Institutional Review Board. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. All data relevant to the study are included in the article or uploaded as supplementary information. The data supporting the conclusions of this study are not publicly available, as their content may compromise the privacy of research participants. However, previously published data from the Hp-EuReg study, or de-identified raw data referring to the current study, as well as further information on the methods used to explore the data, may be shared, with no particular time constraint. Individual participant data will not be shared.

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Supplementary file 2. Approval of the Ethics Committee of La Princesa University Hospital (Madrid, Spain), which acted as reference Institutional Review Board

Hospital Universitario de La Princesa
SaludMadrid

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INFORME DEL COMITÉ ÉTICO DE INVESTIGACIÓN CLÍNICA

Dña. Mª del Mar Ortega Gómez, secretaria del Comité Ético de Investigación Clínica del Hospital Universitario de la Princesa

Certifica

Que este Comité ha evaluado la propuesta del promotor e investigador principal **Dr. Javier P. Gisbert (Servicio de Digestivo)** para que se realice el estudio observacional prospectivo, con código de protocolo **Hp-EuReg,** titulado**: Registro Europeo de manejo de la infección por *Helicobacter pylori;* versión 1: 04-12-12)**, y considera que:

Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto.

La capacidad del investigador y los medios disponibles son apropiados para llevar a cabo el estudio.

Son adecuados tanto el procedimiento previsto para obtener el consentimiento informado del paciente como la compensación prevista para los sujetos por daños que pudieran derivarse de su participación en el ensayo.

El alcance de las compensaciones económicas previstas no interfiere con el respeto a los postulados éticos.

Y que este Comité acepta que dicho estudio observacional prospectivo sea realizado por el **Dr. Javier P. Gisbert (Servicio de Digestivo)** como investigador principal en el Hospital Universitario de La Princesa.

Lo que firmo en **Madrid** a **20** de **diciembre** de **2012**

Hospital Universitario de la Princesa Madrid
COMITÉ ÉTICO DE INVESTIGACIÓN CLÍNICA

Fdo: Dra. Mª del Mar Ortega Gómez
SECRETARIA DEL C.E.I.C.

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COMITÉ ÉTICO DE INVESTIGACIÓN CLÍNICA

Dña. Mª del Mar Ortega Gómez, secretaria del Comité Ético de Investigación Clínica del Hospital Universitario de la Princesa

Certifica

Que el estudio observacional prospectivo, cuyo promotor e investigador principal es el **Dr. Javier P. Gisbert (Servicio de Digestivo)**, Hospital universitario de La Princesa, con código de protocolo **Hp-EuReg**, titulado: **Registro Europeo de manejo de la infección por *Helicobacter pylori;* versión 1: 04-12-12):**

Que en la fecha de aprobación de dicho estudio la composición del CEIC era la siguiente:

Presidente:	Francisco Abad Santos (Servicio de Farmacología Clínica)
Vicepresidente:	Rosario Ortiz de Urbina Barba (no perteneciente a profesiones sanitarias, Directora de la Fundación para la Investigación Biomédica).
Secretario:	Mª del Mar Ortega Gómez (Especialista en Inmunología Clínica)
Vocales:	Dolores Ochoa Mazarro (Especialista en Farmacología Clínica, Servicio de Farmacología Clínica)
	Carmen del Arco Galán (Servicio de Urgencias)
	Rafael Fernández Alonso (Fundación para la Investigación Biomédica)
	Jesús González Cajal (Servicio de Psiquiatría; miembro del Comité Asistencial de Ética)
	Andrés López Romero (Médico de Atención Primaria, Subdirector Médico de la Gerencia de Atención Primaria del Área 2)
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Que durante la evaluación de este estudio existía quorum suficiente para tomar decisiones de acuerdo a nuestros Procedimientos Normalizados de Trabajo.

Que este CEIC ha sido acreditado por el Servicio de Control Farmacéutico y Productos Sanitarios de la Dirección General de Farmacia y Productos Sanitarios de la Consejería de Sanidad de la Comunidad de Madrid (resolución de renovación de acreditación de fecha 19-07-10).

Lo que firmo en Madrid a 20 de diciembre de 2012

Fdo: Dra. Mª del Mar Ortega Gómez
SECRETARIA DEL C.E.I.C.

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Supplementary Table 1. Regional clusters of the participating Hp-EuReg countries and cases included per country and per treatment line

Region and/or GDP per capita 2019	Country	N (%)	Third line, N	Fourth line, N	Fifth line, N	Sixth line, N
South-West and/or medium GDP	Spain	1,124 (52.4)	828	207	74	15
	Portugal	40 (1.9))	33	7	0	0
	Total	1,164 (54.3)	861	214	74	15
Centre and/or medium-high GDP	Italy	395 (18.4)	258	96	31	10
	France	48 (2.2)	33	9	3	3
	Total	443 (20.6)	291	105	34	13
South-East and/or low-medium GDP	Israel*	135 (6.3)	84	44	6	1
	Slovenia	88 (4.1)	76	10	1	1
	Lithuania	45 (2.1)	38	5	2	0
	Greece	17 (0.8)	11	2	2	2
	Latvia	14 (0.7)	8	4	2	0
	Croatia	12 (0.6)	10	2	0	0
	Hungary	11 (0.5)	7	4	0	0
	Poland	3 (0.1)	3	0	0	0
	Total	326 (15.2)	238	71	13	4
North and/or high GDP	UK	65 (3.0)	25	20	12	8
	Norway	28 (1.3)	21	5	1	1
	Ireland	17 (0.8)	10	5	2	0
	Denmark	9 (0.4)	4	5	0	0
	Germany	6 (0.3)	4	1	1	0
	Belgium	6 (0.3)	3	2	1	0
	Switzerland	6 (0.3)	4	1	1	0
	the Netherlands	4 (0.2)	3	1	0	0
	Finland	2 (0.1)	1	0	1	0
	Total	142 (6.7)	74	40	19	9
East and/or low GDP	Russia	39 (1.8)	34	5	0	0
	Serbia	24 (1.1)	18	4	2	0
	Romania	3 (0.1)	3	0	0	0
	Ukraine	3 (0.1)	0	0	3	0
	Total	69 (3.1)	55	9	5	0
Europe		2,144 (100)	1,519	439	145	41

GDP: gross domestic product. High GDP € 40K-80K, medium-high € 30K-40K, medium GDP € 21K-30K, low-medium GDP € 13K-24K, low GDP € 2.5K-11K.
*Israel is the only Asian country participating in the registry and has a high GDP. It was included in the South-East cluster for geographical reasons.

Supplementary Table 2. Categories of empirical treatments prescribed in third and subsequent lines.

Treatment group	Colour	Therapies
Therapies containing metronidazole, tetracycline (tetracycline hydrochloride or doxycycline) and bismuth salts.		PPI-single-capsule PPI-M+Tc+B PPI-M+D+B
Quinolone-based therapies		PPI-A+L PPI-A+L+B PPI-A+Mx
Rifabutin-based therapy		PPI-A+R PPI-A+R+B
Clarithromycin-containing rescue therapy		PPI-C+A+M PPI-C+A PPI-C+A+B Sequential PPI-C+A+T PPI-C+A+T
Other common therapies		PPI-A+M PPI-A PPI-A+M+B
Marginal therapies		PPI-A+D PPI-C+L PPI-A+Mx+B PPI-A+M+L PPI-A+D+B Sequential PPI-C+A+M PPI-A+T+L PPI-M+L PPI-A+Rx PPI-T+D+B PPI-A+M+Tc PPI-A+Tc+B PPI-C+M Sequential PPI-A+T+L Sequential PPI-A+M+L PPI-M+L+Tc PPI-M+R PPI-L+D+B PPI-A+M+D PPI-M+D PPI-L+D PPI-A+Tc PPI-A+Ciprofloxacin Sequential PPI-C+A+L PPI-Mx+Tc+B PPI-M+L+B PPI-C+A+D PPI-T+L PPI-R+Tc PPI-M+Tc PPI-M+Mx Sequential PPI-C+M+L PPI-T+Tc+B PPI-Mx+D+B PPI-M+Tc+Cefuroxime PPI-L+Tc+B PPI-C+M+L PPI-C+L+B PPI-C+B+Nitrofurantoin PPI-C+A+L PPI-A+T+Tc PPI-A+T+D PPI-A+M+Mx PPI-L

A,amoxicillin; B,bismuth; C,clarithromycin; D,doxycycline; L, levofloxacin; M, metronidazole; Mx, moxifloxacin; PPI, proton-pump inhibitor; R, rifabutin; Rx, rifaximin; T, tinidazole, Tc, tetracycline hydrochloride.

*Three-in-one single-capsule containing bismuth, tetracycline and metronidazole.

Supplementary Table 3. Empirical rescue treatment prescriptions in third- and subsequent lines in Europe

Therapy	Overall, N (%)	Third line, N (%)	Fourth line, N (%)	Fifth line, N (%)	Sixth line, N (%)
PPI-single-capsule	530 (24.7)	398 (26.2)	85 (19.4)	36 (24.8)	11 (26.8)
PPI-A+L	322 (15)	262 (17.2)	41 (9.3)	15 (10.3)	4 (9.8)
PPI-A+R	279 (13)	126 (8.3)	126 (28.7)	21 (14.5)	6 (14.6)
PPI-M+Tc+B	178 (8.3)	138 (9.1)	28 (6.4)	8 (5.5)	4 (9.8)
PPI-A+L+B	139 (6.5)	117 (7.7)	19 (4.3)	2 (1.4)	1 (2.4)
PPI-M+D+B	115 (5.4)	95 (6.3)	14 (3.2)	5 (3.4)	1 (2.4)
PPI-C+A+M	84 (3.9)	64 (4.2)	10 (2.3)	6 (4.1)	4 (9.8)
PPI-A+M	57 (2.7)	46 (3)	7 (1.6)	3 (2.1)	1 (2.4)
PPI-C+A	49 (2.3)	37 (2.4)	5 (1.1)	5 (3.4)	2 (4.9)
Dual-A	39 (1.8)	13 (0.9)	4 (0.9)	17 (11.7)	5 (12.2)
PPI-C+A+B	37 (1.7)	29 (1.9)	5 (1.1)	3 (2.1)	0 (0.0)
Sequential-C+A+T	30 (1.4)	22 (1.4)	8 (1.8)	0 (0.0)	0 (0.0)
PPI-A+Mx	27 (1.3)	20 (1.3)	4 (0.9)	3 (2.1)	0 (0.0)
PPI-A+R+B	27 (1.3)	3 (0.2)	16 (3.6)	7 (4.8)	1 (2.4)
PPI-C+A+T	24 (1.1)	15 (1)	9 (2.1)	0 (0.0)	0 (0.0)
PPI-A+M+B	24 (1.1)	16 (1.1)	7 (1.6)	1 (0.7)	0 (0.0)
PPI-C+L	13 (0.6)	12 (0.8)	0 (0.0)	1 (0.7)	0 (0.0)
PPI-A+D	13 (0.6)	7 (0.5)	4 (0.9)	1 (0.7)	1 (2.4)
PPI-A+T+L	11 (0.5)	7 (0.5)	4 (0.9)	0 (0.0)	0 (0.0)
PPI-A+Mx+B	11 (0.5)	7 (0.5)	3 (0.7)	1 (0.7)	0 (0.0)
PPI-A+M+L	11 (0.5)	10 (0.7)	0 (0.0)	1 (0.7)	0 (0.0)
PPI-A+D+B	10 (0.5)	7 (0.5)	1 (0.2)	2 (1.4)	0 (0.0)
PPI-T+Tc+B	9 (0.4)	4 (0.3)	4 (0.9)	1 (0.7)	0 (0.0)
Sequential-C+A+M	8 (0.4)	7 (0.5)	1 (0.2)	0 (0.0)	0 (0.0)
PPI-M+L	6 (0.3)	6 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
PPI-C+M	6 (0.3)	2 (0.1)	4 (0.9)	0 (0.0)	0 (0.0)
PPI-A+Rx	6 (0.3)	2 (0.1)	4 (0.9)	0 (0.0)	0 (0.0)
PPI-T+D+B	6 (0.3)	4 (0.3)	2 (0.5)	0 (0.0)	0 (0.0)
PPI-A+Tc+B	6 (0.3)	6 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
PPI-A+M+Tc	6 (0.3)	0 (0.0)	5 (1.1)	1 (0.7)	0 (0.0)
PPI-A+Tc	4 (0.2)	1 (0.1)	2 (0.5)	1 (0.7)	0 (0.0)
Sequential-A+T+L	4 (0.2)	2 (0.1)	1 (0.2)	1 (0.7)	0 (0.0)
Sequential-A+M+L	4 (0.2)	4 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
PPI-M+L+Tc	4 (0.2)	2 (0.1)	2 (0.5)	0 (0.0)	0 (0.0)
PPI-M+R	3 (0.1)	1 (0.1)	2 (0.5)	0 (0.0)	0 (0.0)
PPI-L+D+B	3 (0.1)	2 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)
PPI-C+L+B	3 (0.1)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
PPI-C+A+L	3 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
PPI-A+M+D	3 (0.1)	2 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)
PPI-R+Tc	2 (0.1)	1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)
PPI-M+D	2 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
PPI-L+D	2 (0.1)	1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)
PPI-A+other	2 (0.1)	0 (0.0)	1 (0.2)	1 (0.7)	0 (0.0)
Sequential-C+A+L	2 (0.1)	2 (0.1)	1 (0.2)	1 (0.7)	0 (0.0)
PPI-Mx+Tc+B	2 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
PPI-M+L+B	2 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
PPI-L+Tc+B	2 (0.1)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)
PPI-C+A+D	2 (0.1)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)
PPI-T+L	1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
PPI-M+Tc	1 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
PPI-M+Mx	1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Sequential-C+M+L	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
PPI-Mx+D+B	1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
PPI-M+Tc+	1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
PPI-C+M+L	1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
PPI-C+B+	1 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
PPI-A+T+Tc	1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
PPI-A+T+D	1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
PPI-A+M+Mx	1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Dual-L	1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Total	2,144 (100)	1,519 (100)	439 (100)	145 (100)	41 (100)

A,amoxicillin; B,bismuth; C,clarithromycin; D,doxycycline; L, levofloxacin; M, metronidazole; Mx, moxifloxacin; PPI, proton-pump inhibitor; R, rifabutin; Rx, rifaximin; T, tinidazole, Tc, tetracycline hydrochloride.
*Three-in-one single-capsule containing bismuth, tetracycline and metronidazole.

Supplementary Table 4. Re-exposure rates to clarithromycin and quinolones in third- to sixth-line treatments, overall, prior to and since publication of the 2016-2017 clinical guidelines

	Overall	Before 2017	Since 2017
Clarithromycin-containing therapies, N (%)	264 (12.3)	172 (13.4)	92 (10.6)
Re-exposure to clarithromycin, N (%)	183 (69.3)	110 (64.0)	73 (79.3)
Quinolone-containing therapies, N (%)	557 (26.0)	347 (27.1)	210 (24.3)
Re-exposure to quinolone, N (%)	100 (18.0)	77 (22.2)	23 (11.0)

N, number of cases

Supplementary Table 5. Frequency of use of type of regimen, duration of treatment and proton pump inhibitor dose in therapies other than single-capsule therapy in third- to sixth-line in Europe (2013-2021)

	Europe	South-West	Centre	South-East	North	East
Number of cases, N	1,614	719	310	231	118	43
Regimen, N (%)						
Quadruple	729 (45.2)	507 (64.7)	53 (15.8)	77 (25.6)	70 (50.7)	22 (40.0)
Triple	796 (49.3)	248 (31.6)	243 (72.3)	210 (69.8)	65 (47.1)	30 (54.5)
Sequential	49 (3.0)	6 (0.8)	38 (11.3)	2 (0.7)	2 (1.4)	1 (1.8)
Dual	40 (2.5)	23 (2.9)	2 (0.6)	12 (4.0)	1 (0.7)	2 (3.6)
Duration of treatment, N (%)						
7 days	59 (3.7)	3 (0.4)	0 (0.0)	13 (4.3)	41 (30.1)	2 (3.6)
10 days	596 (37.0)	287 (36.7)	153 (45.5)	80 (26.7)	55 (40.4)	21 (38.2)
12 days	149 (9.3)	2 (0.3)	142 (42.3)	4 (1.3)	0 (0.0)	1 (1.8)
14 days	806 (50.1)	491 (62.7)	41 (12.2)	203 (67.7)	40 (29.4)	31 (56.4)
Unknown	4 (0.2)	1 (0.1)	0 (0.0)	1 (0.3)	2 (1.4)	0 (0.0)
PPI dose, N (%)*						
Low	516 (32.0)	224 (28.6)	137 (40.8)	44 (14.6)	92 (66.7)	19 (34.5)
Standard	254 (15.7)	175 (22.3)	12 (3.6)	28 (9.3)	16 (11.6)	23 (41.8)
High	818 (50.7)	371 (47.3)	177 (52.7)	229 (76.1)	28 (20.3)	13 (23.6)
Unknown	26 (1.6)	14 (1.8)	10 (3.0)	0 (0.0)	2 (1.4)	0 (0.0)

*Low-dose PPI: 4.5-27 mg omeprazole equivalents, two times per day (e.g. 20 mg omeprazole equivalents, two times per day). Standard-dose PPI: 32-40 mg omeprazole equivalents, two times per day (e.g. 40 mg omeprazole equivalents, two times per day).
High-dose PPI: 54-128 mg omeprazole equivalents, two times per day (e.g. 60 mg omeprazole equivalents, two times per day

Supplementary Table 6. Overall effectiveness by European region and by year

		2013	2014	2015	2016	2017	2018	2019	2020	2021	Overall
Europe	**PP, N (%)**	214 (70.1)	322 (74.2)	243 (73.7)	309 (71.5)	213 (81.2)	156 (73.1)	95 (77.9)	116 (75.0)	83 (84.3)	1,751 (74.6)
	mITT, N (%)	223 (69.5)	328 (73.2)	257 (72.0)	320 (70.6)	223 (80.7)	162 (71.0)	95 (77.9)	117 (75.2)	84 (83.3)	**1,809 (73.7)**
	ITT, N (%)	250 (62.0)	369 (65.0)	291 (63.6)	365 (61.9)	254 (70.9)	208 (55.3)	63 (81.0)	116 (69.8)	42 (90.5)	1,958 (64.9)
South-West	**PP, N (%)**	110 (61.8)	166 (77.1)	173 (69.9)	240 (70.8)	148 (82.4)	67 (83.6)	56 (76.8)	62 (77.4)	39 (84.6)	1,061 (74.4)
	mITT, N (%)	113 (61.1)	169 (75.7)	180 (69.4)	249 (70.3)	150 (82.7)	71 (80.3)	56 (76.8)	62 (77.4)	40 (82.5)	**1,090 (73.6)**
	ITT, N (%)	119 (58.0)	175 (73.1)	190 (65.8)	272 (64.3)	164 (75.6)	76 (75.0)	37 (81.1)	57 (77.2)	9 (88.9)	1,099 (69.2)
Centre	**PP, N (%)**	55 (76.4)	80 (78.8)	33 (81.8)	18 (83.3)	31 (77.4)	69 (62.3)	28 (71.4)	19 (78.9)	17 (82.4)	350 (75.1)
	mITT, N (%)	59 (74.6)	82 (76.8)	36 (77.8)	18 (83.3)	33 (75.8)	71 (60.6)	28 (71.4)	19 (78.9)	17 (82.4)	**363 (73.6)**
	ITT, N (%)	69 (63.8)	101 (62.4)	46 (60.9)	18 (83.3)	36 (69.4)	91 (47.3)	20 (75.0)	18 (77.8)	14 (85.7)	413 (62.7)
South-East	**PP, N (%)**	22 (86.4)	24 (83.3)	22 (77.3)	31 (67.7)	20 (80.0)	15 (86.7)	9 (100)	17 (88.2)	6 (100)	166 (81.9)
	mITT, N (%)	22 (86.4)	25 (84.0)	23 (73.9)	31 (67.7)	21 (76.2)	15 (86.7)	9 (100)	18 (88.9)	6 (100)	**170 (81.2)**
	ITT, N (%)	30 (63.3)	36 (58.3)	35 (48.6)	52 (40.4)	35 (45.7)	34 (38.2)	4 (100)	23 (60.9)	5 (100)	254 (51.2)
North	**PP, N (%)**	23 (73.9)	50 (52.0)	9 (100)	11 (72.7)	6 (50.0)	2 (50.0)	2 (50.0)	12 (25.0)	4 (25.0)	119 (58.8)
	mITT, N (%)	25 (76.0)	50 (52.0)	12 (83.3)	11 (72.7)	6 (50.0)	2 (50.0)	2 (100)	12 (25.0)	4 (25.0)	124 (58.9)
	ITT, N (%)	28 (67.9)	54 (48.1)	14 (71.4)	11 (72.7)	6 (50.0)	2 (50.0)	2 (100)	12 (25.0)	0 (NA)	129 (55.8)
East	**PP, N (%)**	4 (100)	2 (100)	6 (83.3)	9 (77.8)	8 (100)	3 (33.3)	0 (NA)	6 (100)	17 (94.1)	55 (89.1)
	mITT, N (%)	4 (100)	2 (100)	6 (83.3)	11 (63.6)	13 (92.3)	3 (33.3)	0 (NA)	6 (100)	17 (89.5)	**62 (85.5)**
	ITT, N (%)	4 (100)	3 (66.7)	6 (83.3)	12 (58.3)	13 (92.3)	5 (20.0)	0 (NA)	6 (100)	14 (92.9)	63 (79.4)

ITT, intention-to-treat; mITT, modified intention-to-treat; N, number of cases; PP, per protocol

Supplementary Table 7. Effectiveness of the most commonly prescribed therapies by treatment line and by European region (16 different therapies, 1,961 patients, 91.5% of the total number of cases)

		Europe				South-West				Centre				South-East				North				East			
		PP		mITT		PP		mITT		PP		mITT		PP		mITT		PP		mITT		PP		mITT	
Rescue therapy	**Use, N**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
PPI-single-capsule*																									
Overall	530	452	85.8 (82-89)	466	84.8 (81-88)	338	84.6 (80-88)	351	83.5 (79-87)	77	87.0 (78-93)	78	85.9 (76-92)	20	95.0 (77-99)	20	95.0 (77-99)	3	66.7 (21-94)	3	66.7 (21-94)	14	100 (78-100)	14	100 (78-100)
Third line	398	342	87.7 (84-91)	353	87.0 (83-90)	272	86.7 (82-90)	283	85.9 (81-89)	42	90.5 (78-96)	42	90.5 (78-96)	17	94.1 (73-99)	17	94.1 (73-99)	2	50.0 (9-91)	2	50.0 (9-91)	9	100 (70-100)	9	100 (70-100)
Fourth line	85	67	82.1 (71-89)	69	79.7 (69-88)	39	76.9 (62-87)	41	73.2 (58-84)	21	85.7 (65-95)	21	85.7 (65-95)	2	100 (34-100)	2	100 (34-100)	1	100 (21-100)	1	100 (21-100)	4	100 (51-100)	4	100 (51-100)
Fifth line	36	33	75.8 (59-87)	34	73.5 (57-85)	22	72.7 (52-87)	22	72.7 (52-87)	9	77.8 (45-94)	10	70.0 (40-89)	1	100 (21-100)	1	100 (21-100)	0	NA	0	NA	1	100 (21-100)	1	100 (21-100)
Sixth line	11	10	80.0 (49-94)	10	80.0 (49-94)	5	80.0 (38-96)	5	80.0 (38-96)	5	80.0 (38-96)	5	80.0 (38-96)	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
PPI-A+L																									
Overall	322	227	78.0 (72-83)	234	77.8 (72-83)	68	76.5 (65-85)	69	76.8 (66-85)	52	75.0 (62-85)	56	73.2 (60-83)	76	81.6 (71-89)	76	81.6 (71-89)	16	62.5 (39-82)	16	62.5 (39-82)	15	93.3 (70-99)	17	94.1 (73-99)
Third line	262	183	80.9 (75-86)	189	80.4 (74-85)	62	74.2 (62-83)	63	74.6 (63-84)	42	83.3 (69-92)	45	80.0 (66-89)	58	82.8 (71-90)	58	82.8 (71-90)	8	87.5 (53-98)	8	87.5 (53-98)	13	92.3 (67-99)	15	93.3 (70-99)
Fourth line	41	28	67.9 (49-82)	29	69.0 (51-83)	2	100 (34-100)	2	100 (34-100)	5	60.0 (23-88)	6	66.7 (30-90)	15	80.0 (55-93)	15	80.0 (55-93)	5	20.0 (4-62)	5	20.0 (4-62)	1	100 (21-100)	1	100 (21-100)
Fifth line	15	12	75.0 (47-91)	12	75.0 (47-91)	3	100 (44-100)	3	100 (44-100)	4	25.0 (5-70)	4	25.0 (5-70)	2	100 (34-100)	2	100 (34-100)	2	100 (34-100)	2	100 (34-100)	1	100 (21-100)	1	100 (21-100)
Sixth line	4	4	25.0 (5-70)	4	25.0 (5-70)	1	100 (21-100)	1	100 (21-100)	1	0 (0-79)	1	0 (0-79)	1	0.0 (0-79)	1	0.0 (0-79)	1	0.0 (0-79)	1	0.0 (0-79)	0	NA	0	NA
PPI-A+R																									
Overall	279	230	67.8 (62-74)	237	66.7 (60-72)	75	53.3 (42-64)	78	51.3 (40-62)	142	76.8 (69-83)	145	76.6 (69-83)	10	60.0 (31-83)	11	54.6 (28-79)	3	33.3 (6-79)	3	33.3 (6-79)	0	NA	0	NA
Third line	126	102	78.4 (70-85)	105	78.1 (69-85)	7	28.6 (8-64)	8	25.0 (7-59)	92	81.6 (72-88)	94	81.9 (73-88)	3	100 (44-100)	3	100 (44-100)	0	NA	0	NA	0	NA	0	NA
Fourth line	126	103	63.1 (53-72)	106	61.3 (52-70)	64	56.3 (44-68)	66	54.6 (43-66)	34	76.5 (60-88)	34	76.5 (60-88)	4	50.0 (15-85)	5	40.0 (12-77)	1	100 (21-100)	1	100 (21-100)	0	NA	0	NA
Fifth line	21	20	40.0 (22-61)	20	40.0 (22-61)	4	50.0 (15-85)	4	50.0 (15-85)	13	46.2 (23-71)	13	46.2 (23-71)	2	0.0 (0-66)	2	0.0 (0-66)	1	0.0 (0-79)	1	0.0 (0-79)	0	NA	0	NA
Sixth line	6	5	60.0 (23-88)	6	50.0 (19-82)	0	NA	0	NA	3	66.7 (21-94)	4	50.0 (15-85)	1	100 (21-100)	1	100 (21-100)	1	0.0 (0-79)	1	0.0 (0-79)	0	NA	0	NA
PPI-M+Tc+B																									
Overall	178	162	73.5 (66-80)	167	73.1 (66-79)	89	76.4 (67-84)	91	75.8 (66-83)	18	61.1 (39-80)	19	57.9 (36-77)	6	100 (61-100)	7	100 (65-100)	45	68.9 (54-80)	46	69.6 (55-81)	4	75.0 (30-95)	4	75.0 (30-95)
Third line	138	126	74.6 (66-81)	130	73.8 (66-81)	82	76.8 (67-85)	84	76.2 (66-84)	13	53.9 (29-77)	14	50.0 (27-73)	5	100 (57-100)	6	100 (61-100)	22	72.7 (52-87)	22	72.7 (52-87)	4	75.0 (30-95)	4	75.0 (30-95)
Fourth line	28	27	70.4 (52-84)	27	70.4 (52-84)	7	71.4 (36-92)	7	71.4 (36-92)	4	75.0 (30-95)	4	75.0 (30-95)	1	100 (21-100)	1	100 (21-100)	15	66.7 (42.85)	15	66.7 (42.85)	0	NA	0	NA
Fifth line	8	6	83.3 (44-97)	6	83.3 (44-97)	0	NA	0	NA	1	100 (21-100)	1	100 (21-100)	0	NA	0	NA	5	80.0 (38-97)	5	80.0 (38-97)	0	NA	0	NA
Sixth line	4	3	33.3 (6-79)	4	50 (15-85)	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	3	33.3 (6-79)	4	50.0 (15-85)	0	NA	0	NA
PPI-A+L+B																									
Overall	139	116	78.4 (70-85)	119	77.3 (69-84)	109	77.1 (68-84)	110	76.4 (68-83)	0	NA	0	NA	6	100 (61-100)	7	100 (65-100)	0	NA	0	NA	1	100 (21-100)	2	50.0 (9-91)
Third-line	117	96	80.2 (71-87)	98	79.6 (71-86)	93	79.6 (70-87)	93	79.6 (70-87)	0	NA	0	NA	2	100 (34-100)	3	100 (44-100)	0	NA	0	NA	1	100 (21-100)	2	50.0 (9-91)
Fourth-line	19	17	76.5 (53-90)	18	72.2 (49-88)	13	69.2 (42-87)	14	64.3 (39-84)	0	NA	0	NA	4	100 (51-100)	4	100 (51-100)	0	NA	0	NA	0	NA	0	NA
Fifth-line	2	2	50.0 (9-91)	2	50.0 (9-91)	2	50.0 (9-91)	2	50.0 (9-91)	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
Sixth-line	1	1	0.0 (0-79)	1	0.0 (0-79)	1	(21-100)	1	0.0 (0-79)	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
PPI-M+D+B																									
Overall	115	105	63.8 (54-72)	109	63.3 (54-72)	104	64.4 (55-73)	108	63.9 (55-72)	0	NA	0	NA	1	0 (0-79)	1	0 (0-79)	0	NA	0	NA	0	NA	0	NA
Third-line	95	86	66.3 (56-75)	90	65.6 (55-75)	86	66.3 (56-75)	90	65.6 (55-75)	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
Fourth-line	14	14	50.0 (27-63)	14	50.0 (27-63)	13	53.9 (29-77)	13	53.9 (29-77)	0	NA	0	NA	1	0 (0-79)	1	0 (0-79)	0	NA	0	NA	0	NA	0	NA
Fifth-line	5	4	50.0 (15-85)	4	50.0 (15-85)	4	50.0 (15-85)	4	50.0 (15-85)	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
Sixth-line	1	1	100 (21-100)	1	100 (21-100)	1	(21-100)	1	(21-100)	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
PPI-C+A+M																									
Overall	84	76	67.1 (56-77)	79	65.8 (55-75)	69	66.7 (55-77)	70	67.1 (56-77)	0	NA	1	0.0 (0-79)	3	66.7 (21-94)	3	66.7 (21-94)	1	0.0 (0-79)	2	0.0 (0-66)	3	100 (44-100)	3	100 (44-100)
Third-line	64	58	72.4 (60-82)	60	71.7 (59-81)	53	69.9 (56-80)	54	70.4 (57-81)	0	NA	1	0.0 (0-79)	2	100 (34-100)	2	100 (34-100)	0	NA	0	NA	3	100 (44-100)	3	100 (44-100)
Fourth-line	10	8	50.0 (22-78)	9	44.4 (19-73)	7	57 (25-84)	7	57.1 (25-84)	0	NA	0	NA	1	0 (0-79)	1	0 (0-79)	0	NA	1	0.0 (0-79)	0	NA	0	NA
Fifth-line	6	6	66.7 (30-90)	6	66.7 (30-90)	6	66.7 (30-90)	6	66.7 (30-90)	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
Sixth-line	4	4	25.0 (5-70)	4	25.0 (5-70)	3	33.3 (6-79)	3	33.3 (6-79)	0	NA	0	NA	0	NA	0	NA	1	0.0 (0-79)	1	0.0 (0-79)	0	NA	0	NA
PPI-A+M																									
Overall	57	48	68.8 (55-80)	50	68.0 (54-79)	31	71.0 (53-84)	32	68.8 (51-82)	1	0.0 (0-79)	1	0.0 (0-79)	9	100 (70-100)	9	100 (70-100)	7	28.6 (8-64)	8	37.5 (14-69)	0	NA	0	NA
Third line	46	40	77.5 (63-88)	42	76.2 (61-87)	29	72.4 (54-85)	30	70.0 (52-83)	0	NA	0	NA	9	100 (70-100)	9	100 (70-100)	2	50.0 (9-91)	3	66.7 (21-94)	0	NA	0	NA
Fourth line	7	4	50.0 (15-85)	4	50.0 (15-85)	2	50.0 (9-91)	2	50.0 (9-91)	0	NA	0	NA	0	NA	0	NA	2	50.0 (9-91)	2	50.0 (9-91)	0	NA	0	NA
Fifth line	3	3	0.0 (0-56)	3	0.0 (0-56)	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	3	0.0 (0-56)	3	0.0 (0-56)	0	NA	0	NA
Sixth line	1	1	0.0 (0-79)	1	0.0 (0-79)	0	NA	0	NA	1	0.0 (0-79)	1	0.0 (0-79)	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
PPI-C+A																									
Overall	49	34	61.8 (45-76)	37	62.2 (46-76)	6	66.7 (30-90)	6	66.7 (30-90)	1	100 (21-100)	1	100 (21-100)	5	80.0 (38-96)	5	80.0 (38-96)	17	47.1 (26-69)	18	50.0 (29-71)	5	80.0 (38-96)	7	71.4 (36-92)
Third line	37	26	73.1 (54-86)	28	75.0 (57-87)	5	80.0 (38-96)	5	80.0 (38-96)	1	100 (21-100)	1	100 (21-100)	5	80.0 (38-96)	5	80.0 (38-96)	12	66.7 (39-86)	13	69.2 (42-87)	3	66.7 (21-94)	4	75.0 (30-95)
Fourth line	5	3	33.3 (6-79)	4	25.0 (5-70)	1	0.0 (0-79)	1	0.0 (0-79)	0	NA	0	NA	0	NA	0	NA	1	0.0 (0-79)	1	0.0 (0-79)	1	100 (21-100)	2	50.0 (95-91)
Fifth line	5	3	33.3 (6-79)	3	33.3 (6-79)	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	2	0.0 (0-66)	2	0.0 (0-66)	1	100 (21-100)	1	100 (21-100)
Sixth line	2	2	0.0 (0-66)	2	0.0 (0-66)	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	2	0.0 (0-66)	2	0.0 (0-66)	0	NA	0	NA
PPI-A																									
Overall	39	31	51.6 (35-68)	31	51.6 (35-68)	22	54.5 (27-65)	22	54.5 (27-65)	1	100 (21-100)	1	100 (21-100)	5	60.0 (23-88)	5	60.0 (23-88)	1	100 (21-100)	1	100 (21-100)	2	50.0 (9-91)	2	50.0 (9-91)
Third line	13	8	62.5 (31-86)	8	62.5 (31-86)	2	50.0 (9-91)	2	50.0 (9-91)	0	NA	0	NA	3	66.7 (21-94)	3	66.7 (21-94)	1	100 (21-100)	1	100 (21-100)	2	50.0 (95-91)	2	50.0 (95-91)
Fourth line	4	3	66.7 (21-94)	3	66.7 (21-94)	2	50.0 (9-91)	2	50.0 (9-91)	1	100 (21-100)	1	100 (21-100)	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
Fifth line	17	15	53.3 (30-75)	15	53.3 (30-75)	15	53.3 (30-75)	15	53.3 (30-75)	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
Sixth line	5	5	20.0 (4-62)	5	20.0 (4-62)	3	0.0 (0-56)	3	0.0 (0-56)	0	NA	0	NA	2	50.0 (9-91)	2	50.0 (9-91)	0	NA	0	NA	0	NA	0	NA
PPI-C+A+B																									
Overall	37	28	82.1 (64-92)	31	74.2 (57-86)	16	81.3 (57-93)	17	76.5 (53-90)	0	NA	0	NA	4	100 (51-100)	4	100 (51-100)	0	NA	1	0.0 (0-79)	8	75.0 (41-93)	9	66.7 (35-88)
Third-line	29	23	78.3 (58-90)	25	72.0 (52-86)	14	78.6 (52-92)	15	73.3 (48-89)	0	NA	0	NA	3	100 (44-100)	3	100 (44-100)	0	NA	0	NA	6	66.7 (30-90)	7	57.1 (25-84)
Fourth-line	5	5	60.0 (23-88)	4	75.0 (30-95)	1	100 (21-100)	1	100 (21-100)	0	NA	0	NA	1	100 (21-100)	1	100 (21-100)	0	NA	1	0.0 (0-79)	1	100 (21-100)	1	100 (21-100)
Fifth-line	3	2	100 (34-100)	2	100 (34-100)	1	100 (21-100)	1	100 (21-100)	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	1	100 (21-100)	1	100 (21-100)
Sixth-line	0	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
Sequential PPI-C+A+T																									
Overall	30	25	60.0 (41-77)	27	55.6 (37-72)	2	100 (34-100)	2	100 (34-100)	23	56.5 (37-74)	25	52.0 (34-70)	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
Third line	22	19	57.9 (36-77)	17	64.7 (41-83)	2	100 (34-100)	2	100 (34-100)	15	60.0 (36-80)	17	47.1 (26-69)	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
Fourth line	8	8	50.0 (22-78)	8	50.0 (22-78)	0	NA	0	NA	8	50.0 (22-78)	8	50.0 (22-78)	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
Fifth line	0	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
Sixth line	0	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA

PPI-A+Mx																					
Overall	27	26	69.2 (50-84)	26	69.2 (50-84)	26	69.2 (50-84)	26	69.2 (50-84)	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
Third line	20	20	65.0 (43-82)	20	65.0 (43-82)	20	65.0 (43-82)	20	65.0 (43-82)	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
Fourth line	4	3	100 (44-100)	3	100 (44-100)	3	100 (44-100)	3	100 (44-100)	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
Fifth line	3	3	66.7 (21-94)	3	66.7 (21-94)	3	66.7 (21-94)	3	66.7 (21-94)	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
Sixth line	0	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
PPI-A+R+B																					
Overall	27	24	58.3 (39-76)	25	60.0 (41-77)	24	58.3 (39-76)	25	60.0 (41-77)	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
Third line	3	3	100 (44-100)	3	100 (44-100)	3	100 (44-100)	3	100 (44-100)	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
Fourth line	16	15	53.3 (30-75)	16	56.3 (33-77)	15	53.3 (30-75)	16	56.3 (33-77)	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
Fifth line	7	5	40.0 (12-77)	5	40.0 (12-77)	5	40.0 (12-77)	5	40.0 (12-77)	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
Sixth line	1	1	100 (21-100)	1	100 (21-100)	1	100 (21-100)	1	100 (21-100)	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
PPI-C+A+T																					
Overall	24	22	54.5 (35-73)	22	54.5 (35-73)	0	NA	0	NA	21	52.4 (32-72)	21	52.4 (32-72)	0	NA	0	NA	1	100 (21-100)	1	100 (21-100)	0	NA	0	NA
Third line	15	14	54.3 (39-84)	14	54.3 (39-84)	0	NA	0	NA	14	64.3 (39-84)	14	64.3 (39-84)	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
Fourth line	9	8	37.5 (14-69)	8	37.5 (14-69)	0	NA	0	NA	7	28.6 (82-64)	7	28.6 (82-64)	0	NA	0	NA	1	100 (21-100)	1	100 (21-100)	0	NA	0	NA
Fifth line	0	NA	NA	NA	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
Sixth line	0	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
PPI-A+M+B																					
Overall	24	17	94.1 (73-99)	18	88.9 (67-97)	15	93.3 (70-99)	16	87.5 (64-97)	0	NA	0	NA	1	100 (21-100)	1	100 (21-100)	1	100 (21-100)	1	100 (21-100)	0	NA	0	NA
Third line	16	11	100 (74-100)	12	91.7 (65-99)	10	100 (72-100)	11	90.9 (62-98)	0	NA	0	NA	0	NA	0	NA	1	100 (21-100)	1	100 (21-100)	0	NA	0	NA
Fourth line	7	6	83.3 (44-97)	6	83.3 (44-97)	5	80.0 (38-96)	5	80.0 (38-96)	0	NA	0	NA	1	100 (21-100)	1	100 (21-100)	0	NA	0	NA	0	NA	0	NA
Fifth line	1	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
Sixth line	0	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA

A, amoxicillin; B, bismuth; CI, confidence interval; C, clarithromycin; D, doxycycline; L, levofloxacin; M, metronidazole; mITT, modified intention-to-treat; Mx, moxifloxacin; NA, not available; PP, per protocol; PPI, proton-pump inhibitor; R, rifabutin; T, tinidazole; Tc, tetracycline hydrochloride.
*Three-in-one single-capsule containing bismuth, tetracycline hydrochloride and metronidazol

Supplementary Table 8. Overall effectiveness in optimised therapies (high-dose PPI and ≥14 days)

		PP		mITT	
Rescue therapy	**Use, N (%)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**
PPI-A+L	107 (20.7)	57	89.5 (79-95)	59	89.8 (80-95)
PPI-A+L+B	100 (19.3)	90	82.2 (73-89)	91	81.3 (72-88)
PPI-A+R	36 (7.0)	15	73.3 (48-89)	16	68.8 (44-86)
PPI-C+A+M	34 (6.6)	31	64.5 (47-79)	31	64.5 (47-79)
PPI-A	30 (5.8)	26	53.8 (36-71)	26	53.8 (36-71)
PPI-A+M	27 (5.2)	24	62.5 (43-79)	25	60 (41-77)
PPI-C+A+B	25 (4.8)	20	85.0 (64-95)	20	85.0 (64-95)
PPI-A+Mx	21 (4.1)	20	65.0 (43-82)	20	65.0 (43-82)
PPI-M+Tc+B	21 (4.1)	17	94.1 (73-99)	19	94.7 (75-99)
PPI-A+M+B	19 (3.7)	14	100 (79-100)	14	100 (79-100)
PPI-M+D+B	14 (2.7)	13	61.5 (36-82)	13	61.5 (36-82)
PPI-A+T+L	10 (1.9)	5	100 (57-100)	5	100 (57-100)
PPI-T+Tc+B	7 (1.4)	0	NA	0	NA
PPI-A+M+L	7 (1.4)	7	100 (65-100)	7	100 (65-100)
PPI-T+D+B	6 (1.2)	1	100 (21-100)	1	100 (21-100)
PPI-A+D+B	6 (1.2)	4	50.0 (51-100)	4	50.0 (51-100)
PPI-single-capsule*	6 (1.2)	4	100 (51-100)	5	100 (57-100)
PPI-C+A	4 (0.8)	2	50.0 (10-91)	2	50.0 (10-91)
PPI-A+Rx	4 (0.8)	0	NA	0	NA
PPI-M+L+Tc	4 (0.8)	3	100 (44-100)	3	100 (44-100)
PPI-C+A+L	3 (0.6)	2	50.0 (10-91)	2	50.0 (10-91)
PPI-A+Tc+B	3 (0.6)	3	67 (21-94)	3	6.7 (21-94)
PPI-A+D	2 (0.4)	1	100 (21-100)	1	100 (21-100)
PPI-L+D+B	2 (0.4)	1	100 (21-100)	1	100 (21-100)
PPI-C+L+B	2 (0.4)	2	100 (34-100)	2	100 (34-100)
PPI-C+A+T	2 (0.4)	1	100 (21-100)	1	100 (21-100)
PPI-A+R+B	2 (0.4)	1	0.0 (0-79)	1	0 (0-79)
PPI-R+Tc	1 (0.2)	1	100 (21-100)	1	100 (21-100)
PPI-M+R	1 (0.2)	1	100 (21-100)	1	100 (21-100)
PPI-M+L	1 (0.2)	1	100 (21-100)	1	100 (21-100)
PPI-M+D	1 (0.2)	1	100 (21-100)	1	100 (21-100)
PPI-A+Cefuroxime	1 (0.2)	0	NA	1	0 (0-79)
Sequential PPI-A+T+L	1 (0.2)	1	100 (21-100)	1	100 (21-100)
PPI-M+Tc+Cefuroxime	1 (0.2)	1	100 (21-100)	1	100 (21-100)
PPI-M+L+B	1 (0.2)	1	100 (21-100)	1	100 (21-100)
PPI-L+Tc+B	1 (0.2)	0	NA	0	NA
PPI-C+A+D	1 (0.2)	1	0 (0-79)	1	0 (0-79)
PPI-A+M+Tc	1 (0.2)	0	NA	0	NA
PPI-A+M+Mx	1 (0.2)	1	100 (21-100)	1	100 (21-100)
PPI-A+M+D	1 (0.2)	1	100 (21-100)	1	100 (21-100)
Total	517 (100)	374	78.3 (74-82)	383	77.8 (73-82)

A, amoxicillin; B, bismuth; CI, confidence interval; C, clarithromycin; D, doxycycline; L, levofloxacin; mITT, modified intention-to-treat; M, metronidazole; Mx, moxifloxacin; N, number of cases; NA, not available; PP, per protocol; PPI, proton-pump inhibitor; R, rifabutin; Rx, rifaximin; T, tinidazole, Tc, tetracycline hydrochloride. High-dose PPI: 54-128 mg omeprazole equivalents, two times per day (e.g. 60 mg omeprazole equivalents, two times per day).
*Three-in-one single-capsule containing bismuth, tetracycline and metronidazole.

Supplementary Table 9. Optimised therapies (high dose PPI and ≥14 days of treatment) by country

Optimised rescue therapy	Country	N (%)
PPI-A+L	Israel	57 (53,3)
	Slovenia	20 (18,7)
	Spain	10 (9,3)
	Latvia	7 (6,5)
	Croatia	4 (3,7)
	Serbia	3 (2,8)
	France	2 (1,9)
	Ireland	1 (0,9)
	Lithuania	1 (0,9)
	Poland	1 (0,9)
	Russia	1 (0,9)
	Total	107 (100)
PPI-A+L+B	Spain	91 (91)
	Lithuania	4 (4)
	Israel	4 (4)
	Slovenia	1 (1)
	Total	100 (100)
PPI-A+R	Israel	29 (80,6)
	Spain	4 (11,1)
	Italy	2 (5,6)
	Ireland	1 (2,8)
	Total	36 (100)
PPI-C+A+M	Spain	26 (76,5)
	Portugal	4 (11,8)
	Greece	2 (5,9)
	Serbia	1 (2,9)
	Israel	1 (2,9)
	Total	34 (100)
Dual-A	Spain	22 (73,3)
	Greece	3 (10)
	Israel	2 (6,7)
	Slovenia	1 (3,3)
	Ireland	1 (3,3)
	Lithuania	1 (3,3)
	Total	30 (100)
PPI-A+M	Spain	21 (77,8)
	Portugal	2 (7,4)
	Croatia	1 (3,7)
	France	1 (3,7)
	Greece	1 (3,7)
	Switzerland	1 (3,7)
	Total	27 (100)
PPI-C+A+B	Spain	17 (68)
	Israel	7 (28)
	Russia	1 (4)
	Total	25 (100)
PPI-A+Mx	Spain	21 (100)
PPI-M+Tc+B	Spain	17 (81)
	Ireland	1 (4,8)
	Latvia	1 (4,8)
	UK	1 (4,8)
	Russia	1 (4,8)
	Total	21 (100)
PPI-A+M+B	Spain	13 (68,4)
	Lithuania	3 (15,8)
	Croatia	1 (5,3)
	Slovenia	1 (5,3)
	Ireland	1 (5,3)
	Total	19 (100)
PPI-M+D+B	Spain	14 (100)
PPI-A+T+L	UK	5 (50)
	Italy	4 (40)
	Israel	1 (10)

	Total	10 (100)
PPI-T+Tc+B	Israel	7 (100)
PPI-A+M+L	Spain	6 (85,7)
	UK	1 (14,3)
	Total	7 (100)
PPI-T+D+B	Israel	6 (100)
PPI-A+D+B	Spain	4 (66,7)
	Israel	2 (33,3)
	Total	6 (100)
PPI-single-capsule*	Spain	5 (83,3)
	Switzerland	1 (16,7)
	Total	6 (100)
PPI-C+A	Slovenia	1 (25)
	Spain	1 (25)
	France	1 (25)
	Italy	1 (25)
	Total	4 (100)
PPI-A+Rx	Israel	3 (75)
	Ireland	1 (25)
	Total	4 (100)
PPI-M+L+Tc	Ireland	3 (75)
	Spain	1 (25)
	Total	4 (100)
PPI-C+A+L	Spain	2 (66,7)
	UK	1 (33,3)
	Total	3 (100)
PPI-A+Tc+B	Croatia	1 (33,3)
	Hungary	1 (33,3)
	Lithuania	1 (33,3)
	Total	3 (100)
PPI-A+D	Slovenia	1 (50)
	Spain	1 (50)
	Total	2 (100)
PPI-L+D+B	Spain	1 (50)
	Israel	1 (50)
	Total	2 (100)
PPI-M+L+B	Spain	1 (100)
PPI-C+L+B	Spain	2 (100)
PPI-C+A+T	Italy	2 (100)
PPI-A+R+B	Spain	2 (100)
PPI-R+Tc	Israel	1 (100)
PPI-M+R	Spain	1 (100)
PPI-M+L	Spain	1 (100)
PPI-M+D	Spain	1 (100)
PPI-A+Cefuroxime	Israel	1 (100)
Sequential PPI-A+T+L	Italy	1 (100)
PPI-M+Tc+Cefuroxime	Hungary	1 (100)
PPI-L+Tc+B	Israel	1 (100)
PPI-C+A+D	Spain	1 (100)
PPI-A+M+Tc	Spain	1 (100)
PPI-A+M+Mx	Spain	1 (100)
PPI-A+M+D	Spain	1 (100)

A, amoxicillin; B, bismuth; C, clarithromycin; D, doxycycline; L, levofloxacin; M, metronidazole; Mx, moxifloxacin; PPI, proton-pump inhibitor; R, rifabutin; Rx, rifaximin; T, tinidazole, Tc, tetracycline hydrochloride. High-dose PPI: 54-128 mg omeprazole equivalents, two times per day (e.g. 60 mg omeprazole equivalents, two times per day). *Three-in-one single-capsule containing bismuth, tetracycline and metronidazole.

Supplementary Table 10. Modified intention-to-treat effectiveness of traditional bismuth quadruple therapy by type of tetracycline and dose of metronidazole used

		Non-optimised			Optimised*		
		N	**mITT, % (95% CI)**	***P* value**	**N**	**mITT, % (95% CI)**	***P* value**
Type of tetracycline	Tetracycline HCl	148	70.3 (63-77)	0.2684	19	94.7 (75-99)	0.0201
	Doxycycline	96	63.5 (54-72)		13	61.5 (36-82)	
Metronidazole dose	500 mg	4	100 (51-100)		0	NA	
	750 mg	5	40 (12-77)		0	NA	
	800 mg	4	25 (5-70)		0	NA	
	1,000 mg	74	75.7 (65-84)		9	66.7 (35-88)	
	1,200 mg	21	71.4 (50-86)		1	100 (21-100)	
	1,500 mg	117	61.5 (52-70)		6	50 (19-81)	
	1,600 mg	9	100 (70-100)		0	NA	
	2,000 mg	10	60 (31-83)		16	100 (81-100)	
	<1,500 mg	108	72.2 (63-80)	0.1748	10	70.0 (40-89)	0.2780
	≥1,500 mg	136	64.0 (56-72)		22	86.4 (67-95)	

CI, confidence interval; HCl, hydrochloride; mITT, modified intention-to-treat; N, number of cases; NA, not applicable. *Optimised therapy: high-dose PPI and duration ≥14 days. High-dose PPI: 54-128 mg omeprazole equivalents, two times per day (e.g. 60 mg omeprazole equivalents, two times per day)

Supplementary Table 11. Use of triple therapy with proton-pump inhibitor, rifabutin and amoxicillin, by region

	South-West	Centre	South-East	North
Treatment-line, N (%)				
Third line	9 (11.3)	108 (65.5)	9 (29.0)	1 (33.3)
Fourth line	67 (83.8)	39 (23.6)	19 (61.3)	1 (33.3)
Fifth line	4 (5.0)	14 (8.5)	2 (6.5)	1 (33.3)
Sixth line	0 (0.0)	4 (2.4)	1 (3.2)	0 (0%)
Overall	80 (100)	165 (100)	31 (100)	3 (100)
Duration of treatment, N (%)				
10 days	63 (78.8)	9 (5.5)	0 (0.0)	2 (66.7)
12 days	1 (1.3)	140 (84.8)	2 (6.5)	0 (0.0)
14 days	16 (20.0)	16 (9.7)	29 (93.5)	1 (33.3)
Total dose of rifabutin (mg/24h), N (%)				
150 mg	0 (0.0)	72 (43.6)	0 (0.0)	0 (0.0)
250 mg	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)
300 mg	56 (70.0)	25 (15.2)	30 (96.8)	2 (66.7)
1,000 mg	1 (1.3)	1 (0.6)	0 (0.0)	0 (0.0)
Missing	23 (28.7)	65 (39.4)	1 (3.2)	1 (33.3)
Total dose of amoxicillin (mg/24h), N (%)				
2,000 mg	57 (71.3)	98 (59.4)	27 (87.1)	2 (66.7)
3,000 mg	0 (0.0)	2 (1.2)	3 (9.7)	0 (0.0)
Missing	23 (28.7)	65 (39.4)	1 (3.2)	1 (33.3)
PPI dose, N (%)*				
Low	28 (35.0)	57 (34.5)	1 (3.2)	1 (33.3)
Standard	23 (28.7)	3 (1.8)	1 (3.2)	0 (0.0)
High	15 (18.8)	96 (58.2)	29 (93.5)	1 (33.3)
Missing	14 (17.5)	9 (5.5)	0 (0.0)	1 (33.3)
Overall mITT effectiveness, % (CI 95%)	51.3 (40-62)	76.6 (69-83)	54.5 (28-79)	33.3 (6-79)
Missing, N (%)	2 (2.5)	20 (12.1)	20 (64.5)	0(0.0)

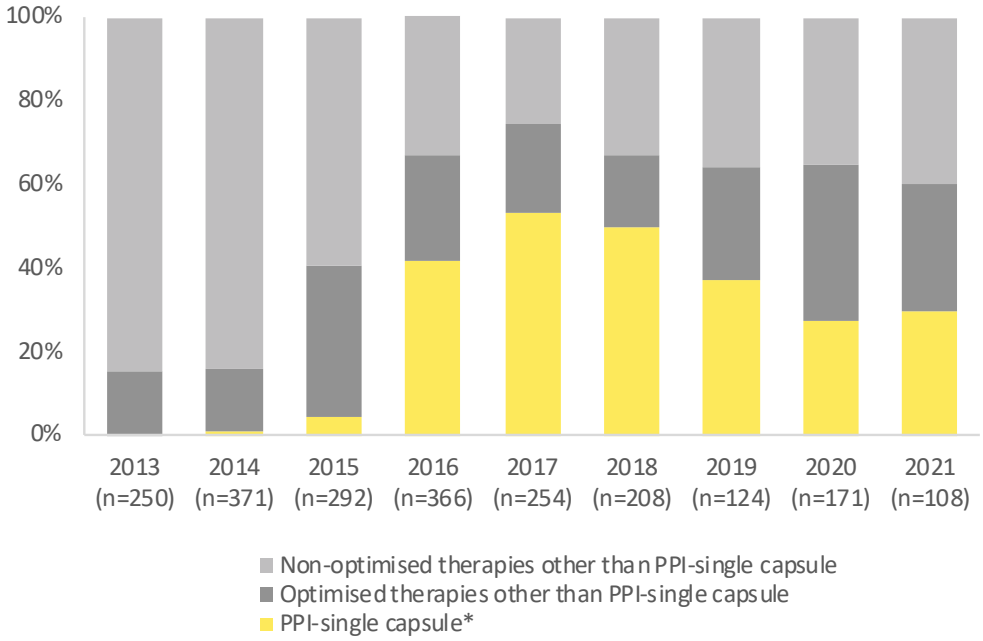
CI, confidence interval; m-ITT, modified intention-to-treat.
*Low-dose PPI: 4.5-27 mg omeprazole equivalents, two times per day (e.g. 20 mg omeprazole equivalents, two times per day). Standard-dose PPI: 32-40 mg omeprazole equivalents, two times per day (e.g. 40 mg omeprazole equivalents, two times per day). High-dose PPI: 54-128 mg omeprazole equivalents, two times per day (e.g. 60 mg omeprazole equivalents, two times per day).

Supplementary Table 12. Incidence of adverse events

	n/N	% (95% CI)
At least one adverse event	601/1,924	31.2 (29-33)
Serious adverse events	5/1,251	0.4 (0-1)
Adverse events leading to discontinuation of medication	49/601	8.2 (6-11)
Adverse event by treatment regimen		
• Quadruple	430/1,141	37.7 (35-41)
• Triple	147/701	21.0 (18-24)
• Sequential	11/47	23.4 (14-37)
• Dual	13/35	37.1 (23-54)
Type of adverse event (n, %)		
• Nausea	243	19.4
• Diarrhoea	218	17.4
• Metallic taste	130	10.4
• Asthenia	122	9.8
• Vomiting	98	7.8
• Dyspepsia	100	8.0
• Abdominal pain	103	8.23
• Anorexia	77	6.16
• Heartburn	30	2.40
• Others	130	10.39
• All adverse events	1,251	100.0

CI, confidence interval; N, number of total cases; n, number of cases.

Supplementary figure 1: Prescribing trends (% of use) in optimised treatments, non-optimised treatments and single-capsule bismuth quadruple therapy in Europe



An optimised treatment was defined as one lasting 14 days or more and using high-dose PPI.
Low-dose PPI: 4.5-27 mg omeprazole equivalents, two times per day (e.g. 20 mg omeprazole equivalents, two times per day). Standard-dose PPI: 32-40 mg omeprazole equivalents, two times per day (e.g. 40 mg omeprazole equivalents, two times per day). High-dose PPI: 54-128 mg omeprazole equivalents, two times per day (e.g. 60 mg omeprazole equivalents, two times per day).
*PPI-single-capsule therapy was analysed separately because it is only marketed in a 10-day format and because increasing the PPI dose has not proven to improve its effectiveness outcomes.