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ABBREVIATIONS: *Helicobacter pylori* (*H. pylori*); intention-to-treat (ITT); modified intention-to-treat (mITT); per-protocol (PP); proton pump inhibitor (PPI).

KEY WORDS: *Helicobacter pylori*, treatment, bismuth, amoxicillin, clarithromycin, tetracycline, metronidazole, single-capsule, registry.

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SUMMARY

Objective: The best approach for *Helicobacter pylori* management remains unclear. An audit process is essential to ensure clinical practice is aligned with best standards of care.

Design: International multicentre prospective non-interventional registry starting in 2013 aimed to evaluate the decisions and outcomes in *H. pylori* management by European gastroenterologists. Patients were registered in an e-CRF by AEG-REDCap. *Variables included*: demographics, previous eradication attempts, prescribed treatment, adverse events, and outcomes. Data monitoring was performed to ensure data quality. Time-trends and geographical analyses were performed.

Results: 30,394 patients from 27 European countries were evaluated and 21,533 (78%) first-line empirical *H. pylori* treatments were included for analysis. Pre-treatment resistance rates were: 23% to clarithromycin, 32% to metronidazole, and 13% to both. Triple therapy with amoxicillin and clarithromycin was most commonly prescribed (39%), achieving 81.5% modified intention-to-treat eradication rate. Over 90% eradication was obtained only with 10-day bismuth quadruple or 14-day concomitant treatments. Longer treatment duration, higher acid inhibition and compliance were associated with higher eradication rates. Time trend analysis showed a region-dependent shift in prescriptions including abandoning triple therapies, using higher acid-inhibition and longer treatments, which was associated with an overall effectiveness increase (84% to 90%).

Conclusion: Management of *H. pylori* infection by European gastroenterologists is heterogeneous, suboptimal, and discrepant with current recommendations. Only quadruple therapies lasting at least ten days are able to achieve over 90% eradication rates. European recommendations are being slowly and heterogeneously incorporated into routine clinical practice, which was associated with a corresponding increase in effectiveness.

Significance of this study

1. What is already known on this subject? ➢ *H. pylori* affects billions of people worldwide and is the main cause of chronic gastritis, peptic ulcer disease and gastric cancer. ➢ The ideal regimen to treat the infection remains unclear after more than 30 years of experience.
2. What are the new findings? ➢ Triple therapy prescriptions (reporting cure rates of approximately 80%) have decreased, especially in those regions with high-clarithromycin resistance. ➢ Over 90% eradication was only obtained with 10-day bismuth quadruple therapies or 14-day concomitant treatment. ➢ From 2013 to 2018, the observed shift to longer treatment duration, higher acid inhibition and compliance provided an increase in the effectiveness.
3. How might it impact on clinical practice in the foreseeable future? ➢ The results of this study indicate that the management of *H. pylori* infection by European gastroenterologists is heterogeneous, frequently suboptimal, and discrepant with current recommendations. Consensus guideline improvements are being slowly incorporated into the daily clinical practice, which emphasises the importance of regular medical education and the need of surveillance.

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a bacterial pathogen with a 50% worldwide prevalence, being the main cause of chronic gastritis, peptic ulcer disease and gastric cancer. However, the ideal strategy to manage *H. pylori* infection remains unclear. The diagnostic method, the use of culture and antibiotic susceptibility testing, the treatment to prescribe and the test to confirm eradication are debatable, and recommendations have changed over time.[1-5] Currently, most treatments are prescribed on an empiric basis, unaware of the bacterial antibiotic resistance profile. Noteworthy, recommendations have changed over time, with a shift from triple to quadruple therapies in the last consensus conferences.[5, 6] Therefore, a continuous evaluation of practice outcomes using the different management options is required in order to achieve high quality “evidence based medicine”.

It is now accepted that chronic colonization by *H. pylori* is an infectious disease and should be managed as such.[7] For this reason, an optimal anti-*H. pylori* regimen is currently defined as one that reliably offers a cure rate of at least 90%, accepted as an arbitrary threshold.[8, 9] Triple therapies, using clarithromycin and amoxicillin, are still the most commonly used first-line therapies in spite of their failure in ≥ 20-30% of patients. Resistance to clarithromycin has been identified as one of the major factors affecting *H. pylori* eradication success, and the rate of resistance to this antibiotic is steadily increasing in many geographic areas.[10] For this reason, non-bismuth quadruple regimen, comprising a proton pump inhibitor (PPI), amoxicillin, clarithromycin and a nitroimidazole, has more recently been used as first-line treatment,[5, 6, 11, 12] and has improved the efficacy of triple therapy,[13] although its efficacy is impaired when dual metronidazole-clarithromycin resistance is present.

Bismuth has a strong bacteriostatic effect unaffected by resistance and displays a

beneficial synergy when combined with several antibiotics, allowing to overcome bacterial resistance.[14, 15] Thus, combinations containing bismuth may be promising options in settings where there are high, unknown or increasing *H. pylori* antibiotic resistance rates. Traditionally, bismuth has been prescribed in a quadruple regimen containing a PPI with tetracycline and metronidazole. However, the treatment schemes are complex, and bismuth salts and tetracycline are not available in many parts of the world; therefore, these drawbacks have caused a tendency to restrict its use to patients with penicillin allergy, or those who require rescue treatments after failure of a clarithromycin-containing first-line treatment.[16, 17] The latest approach to *H. pylori* eradication has been the addition of bismuth to the standard triple therapy containing clarithromycin and amoxicillin, and this has also achieved encouraging results.[18]

Considering these treatment combinations, and all of the possible optimizations that can be added (length of treatment,[19] dose of PPI,[20] among others), it is hard to decide which treatment will provide good results (≥90% cure rates) aligned with current recommendations and standards. Evidence from clinical trials will always be equivocal because it is impossible to perform a single randomised trial to evaluate all existing treatments. Network meta-analyses however may provide an acceptable pooled approach enabling analysis of combinations of data from several treatment trials. However, evidence derived from clinical trials may not be extrapolated to clinical practice, in which there are no restrictive inclusion criteria, and where available care-time per patient and patient follow-up are more limited.[21]

Finally, there is a general delay from publication of recommendations to their implementation in routine clinical practice,[22, 23] in which sometimes they reach full penetration after being outdated.[24] Therefore, scientists recommend long-term studies evaluating practice and outcome trends, and tools able to provide real time

data from real practice (local, regional and global).[25]

The European Registry on *Helicobacter pylori* management (Hp-EuReg) brings together information on the real clinical practice of a majority of European countries, including thousands of patients with different bacterial resistance patterns and treatment accessibility. For these reasons, our aim was to establish a large-scale long-term prospective clinical practice study providing an overview of the current situation regarding *H. pylori* management. The study would allow not only continuous assessment on the integration of clinical recommendations agreed on medical consensus, but also monitoring of the temporal trends of management options and outcomes. These evaluations were aimed to decide on the best possible treatment strategies for improvement (globally and locally) ensuring that routine clinical practice is aligned with best standards of care.

METHODS

European Registry on *H. pylori* Management

The “European Registry on *H. pylori* Management” (Hp-EuReg) is an international multicentre prospective non-interventional registry recording information of *H. pylori* infection management since May 2013. Detailed information can be found in the published protocol,[26] and is summarised in supplementary file 2.

Statistical analyses

Continuous variables are presented as mean and standard deviation (SD). Qualitative variables are presented as absolute and relative frequencies with percentages (%). Graphical representations are used to show temporal trends in prescriptions. In the multivariate analysis, the effect was evaluated by calculating odds ratios (OR) and 95% confidence intervals (CI). Statistical significance was considered at $p < 0.05$.

Effectiveness analysis

The main outcome, which is treatment eradication rate, was studied in three sets of patients as follows: Intention-to-treat (ITT) analysis included all patients registered up to December 2017, to allow at least a 6-month follow-up, and lost to follow-up cases were considered treatment failures. Per-protocol (PP) analysis included all cases that finished follow-up and had taken at least 90% of the treatment drugs, as defined in the protocol. A modified ITT (mITT) was designed aiming to reach the closest result to those obtained in clinical practice. This mITT included for analyses all cases that had completed follow up (that is, a confirmatory test —success or failure— was available after eradication treatment). Overall (ITT, mITT and PP)

analyses were performed jointly for patients treated empirically. Additional PP effectiveness analyses were performed separately in those patients with a result of *in vitro* susceptibility testing.

All 27 countries were clustered in five main regions based both on their geographical situation and the 2017 gross domestic product (GDP) per capita (supplementary file 3).

More than 100 different treatment schemes were used as first-line treatment. They were pooled in 13 categories (supplementary file 4).

Similarly, PPI data were standardised using the PPI acid inhibition potency as defined by Kirchheiner[27] and Graham,[28, 29] classified as low, standard, and high dose PPI (supplementary file 5).

The relation between eradication rate and age, gender, diagnosis, treatment length, PPI dose and compliance was studied in the mITT population considering six treatment categories (supplementary file 6).

Mixed logistic regression models were used in a three-step strategy: the null model, the global mixed model with interaction between compliance and treatment and the mixed effects logistic regression for each treatment (supplementary file 7).

RESULTS

From May 2013 to June 2018, 30,394 cases were registered in the Hp-EuReg from 27 countries (distribution of patients per country is shown in supplementary Table 1). From those, 21,533 (91%) were first-line therapies included in current analysis (Figure 1). Most of them were empirically treated; however, in 11% of the cases bacterial antibiotic resistance data was available and were evaluated separately...

Geographical analysis

The 21,533 naïve patients were distributed in the following five geographical regions: east (3,679), south-east (4,299), south-west (10,118), centre (1,985), and north (1,452). The baseline characteristics are shown in Table 1. A preliminary inspection showed high heterogeneity of practice and outcomes between European regions. For instance, seven-day treatment prescription was marginal in south-western Europe (1.7%) while it was mostly prescribed in south-eastern (60.0%) and northern (53.9%) regions. Most common treatments were also region specific: triple therapies were favoured in most of Europe (82-88% in south-eastern and northern Europe, 67% in the east and 34% in south-west) whereas quadruple therapies were preferred in south-western and central Europe (63-82%). Results of an additional cluster comparison performed between regions and the highest recruiting countries are presented in supplementary Table 2.

Baseline characteristics

Overall baseline characteristics, regional demographics and concomitant drug use

are presented in Table 1.

Diagnosis

Methods used for diagnosis of the infection and confirmation of eradication are detailed in supplementary file 8.

Temporal trend analysis

Figure 2A shows the prescription trends in Europe, where prescription shifts were region dependent: triple therapies did nearly disappear in south-western and central Europe, while they remained in the east, south-east and north. Triple therapies decreased from over 50% of prescription in 2013/15 to less than 32% in 2017/18. Sequential therapies were prescribed in 8% in 2013 but yearly prescriptions were reduced up to 0.5% in 2018, and concomitant therapy from 21% in 2013/14 to 11% in 2018. Use of bismuth quadruple therapies increased from 0-2% in 2013/14 to 20% in 2018.

Figure 2B depicts the trends on treatment duration, showing an increase in mean duration of treatments from 9.6 days in 2013, to 9.7 in 2014, 10.0 in 2015, 11.0 in 2016, 11.8 in 2017 and 11.8 days in 2018; with regional differences. A major change that appeared to consistently occur throughout Europe was the discontinuation of 7-day therapies, especially in south-eastern and northern Europe, where it was still the most common therapy duration; however, 7-day therapies were scarcely used in other regions (supplementary Table 3).

Figure 3A shows the trends in daily PPI dose (mg of omeprazole equivalent) by region and year, whereas Figure 3B shows the temporal trends in mean daily PPI dose. The potency of acid inhibition increased from a dose equivalent of 58 mg of

omeprazole in 2013 to 75 mg in 2018, showing differences between regions. Mean daily dose of PPI increased in all regions except in central Europe where it decreased in 2017-2018. High doses of PPI were mainly used in south-eastern, south-western and northern Europe (supplementary Table 3).

Treatment use and overall effectiveness

Overall eradication rate increased from 2013 to 2018 independently of the population analysed:

- ITT: 70.1% (2013), 72.6% (2014), 74.5% (2015), 76.7% (2016), 75.2% (2017), 77.3% (2018).
- PP: 84.5% (2013), 85.1% (2014), 85.7% (2015), 87.4% (2016), 88.6% (2017), 88.1% (2018).
- mITT: 83.9% (2013), 84.5% (2014), 85.2% (2015), 86.8% (2016), 88.3% (2017), 87.8% (2018).

The effectiveness trends were region-specific (Figure 4): east-europe reported eradication rates lower than 70% in 2013 and 2014, but achieved 80% mITT in the following years. The remaining regions reported an overall treatment effectiveness higher than 80% in 2013. These rates increased in south-eastern and south-western countries, but remained constant in the centre and north.

The effectiveness trends also appeared to be treatment-dependent in each region (Table 2).

Triple therapy with clarithromycin and amoxicillin was the most frequent treatment in all regions but its eradication rate remained below 86.6% by mITT. None of the 12 treatments considered, except the concomitant therapy with clarithromycin,

amoxicillin and tinidazole in the south-east, reached 90% effectiveness by mITT, whereas quadruple treatments achieved nearly 90% eradication rate. In general, single capsule bismuth quadruple treatment was the most successful, achieving approximately 90% mITT eradication in those regions where it was prescribed.

The effectiveness was likewise modified depending on the duration of treatment. Table 3 shows the impact of treatment duration (7, 10 or 14 days). Overall, effectiveness increased with longer treatment duration; and this was mostly marked with specific treatments, such as the triple therapy with clarithromycin and amoxicillin or when bismuth was added to this triple regimen.

An additional univariate sub-analysis was performed to evaluate the effect of standard (recommended) or high doses PPI in those 14-day treatments not reaching 90% effectiveness (Table 3).

Resistance rates

Data on susceptibility tailored prescription of antibiotics is presented in Table 1 and supplementary file 9.

The effect of resistance on eradication rate in the most frequent first-line treatments is reported in supplementary Table 4.

Mixed effects logistic regression

Null model

A null model without explanatory variables was developed to assess the proportion of variance of the outcome explained by grouping the cases in a second level "centre". There were 163 centres with an average of 89 cases per group. The variance of the intercept at centre level was 0.556 (SE 0.110) on the logit scale, and intra-class correlation coefficient (ICC) was 0.145; meaning the 14.5% of the

variance of mITT effectiveness was explained by the differences between centres.

Global mixed effects model with interaction between compliance and treatment

The global mixed effects model showed a significant effect of compliance, with an OR of 6.8 (4.1–11.3), as well as an effect of treatment on mITT effectiveness. Using quadruple therapies with a PPI-clarithromycin-amoxicillin-bismuth as the reference category, ORs (95% CI) were as follows: triple with clarithromycin-amoxicillin 0.494 (0.39—0.622), triple with clarithromycin-metronidazole 0.220 (0.156—0.311), sequential with clarithromycin-amoxicillin-metronidazole/tinidazole 0.452 (0.305—0.669), concomitant with clarithromycin-amoxicillin-metronidazole/tinidazole 1.130 (0.879—1.453), and the single capsule bismuth quadruple 1.766 (1.240—2.516); showing significantly higher mITT eradication rates in quadruple therapies compared to triple or sequential therapies. The interaction between compliance and treatment was significant (p=0.02) showing that the difference in eradication rate between compliant and non-compliant patients changed from treatment to treatment. The interaction between compliance and treatments in terms of effectiveness is plotted in Figure 5, which shows that independently of the treatment considered, in compliant patients, the rate of eradication (ranging between 80-95%) was always higher compared to non-compliant patients. The effect of non-compliance on the mITT eradication rate was lower in concomitant therapy with clarithromycin-amoxicillin-metronidazole/tinidazole and quadruple therapy with a PPI-clarithromycin-amoxicillin-bismuth than in the remaining treatments.

Mixed effects logistic regression by treatment

The final mixed effects logistic regression models were different for each treatment considered. To compare treatments easily, a tabular summary was built detailing: the first level independent variables, the random variance component and ICCs for each model (Table 4), whereas the final models are described in supplementary file 10.

DISCUSSION

In the present manuscript we analysed the changes in *H. pylori* treatment outcomes throughout a period of 5 years (2013 to 2018) across Europe. We found gastroenterologists' management of *H. pylori* in Europe is extremely heterogeneous (over 100 different first-line schemes), but a set of standard treatment schemes are most widely used: two thirds as triple therapies and a quarter as quadruple therapies, and both generally prescribed as 10—day regimens. Moreover, our data show that there are strong regional differences in practice among European Gastroenterologists. In this sense, our study shows that the generally un-recommended triple therapies have been abandoned in southern Europe, and are disappearing in eastern regions; however, their use is still widespread in central and northern Europe. This finding evidences an incomplete penetration or implementation of the last consensus conferences, which recommended switching from triple to quadruple therapies.[4-6] This lack of update in clinical practice causes a high rate of failures (>20% in those patients), far from the current arbitrary threshold for acceptance of a proposed treatment (≥90% eradication rate).[6, 8, 9]

However, our trend analyses of first-line prescriptions showed that European gastroenterologists are at last adapting their practice to recommendations: some regions have dropped or are abandoning triple therapies, causing an overall drop of prescriptions from 50% to less than 20%. Furthermore, central, northern and south-western Europe are increasing PPI dose and lengthening treatment duration (seven day therapies have decreased from 1/3 of prescriptions to less than 1%, being currently marginal in all regions). As expected, this improvement in adherence to guidelines and recommendations has correlated with an improvement in efficacy rates, reaching in 2018 almost the proposed minimum 90% cure rate by ITT.

This manuscript focused on the most relevant first-line treatments used according to either their popularity or their success rate. The most commonly prescribed treatment was standard triple therapy with a PPI, clarithromycin and amoxicillin, achieving lower than 90% eradication rate even when given for 14-days, as previously described in the literature.[30, 31] Moreover, in our study this treatment was greatly affected by clarithromycin resistance, reducing the effectiveness to below 50% in patients harbouring resistant strains. In this respect, pre-treatment clarithromycin resistance in our study was 23%, quite higher than the 15% resistance threshold generally considered (although the number of patients with susceptibility testing in the Hp-EuReg was very limited). However, triple therapy could be still used in those areas with low clarithromycin resistance and proven high effectiveness.

One of the proposed options chosen to improve triple therapy has been to combine PPI, amoxicillin, clarithromycin and metronidazole in one single scheme, the so called “non-bismuth quadruple treatment”, given as either a sequential or concomitant regimen. Non-bismuth quadruple sequential treatment comprises PPI with amoxicillin combined during a first phase, and a second phase with a PPI, clarithromycin and metronidazole, respectively, each phase lasting for at least 5 days. Although it was successfully proposed and implemented in the early 2000s,[32] it has been falling into disuse and it accounted for less than 10% of first-line treatments in our study. The eradication rate of the sequential therapy in our study (86%) was superior to that of triple therapies but still below 90%. Furthermore, sequential therapy is affected by single and, especially, by dual resistance to clarithromycin and metronidazole,[13] scoring below 80% and 75% in single and dual resistances, respectively.

Non-bismuth quadruple concomitant therapy includes the same drugs as sequential therapy but they are all taken together, with benefits in terms of simplicity,

for both patients and physicians. The literature is clear regarding its superiority to triple therapies and, although more debatable, it is better than the quadruple sequential therapy as well.[12, 33-35] Our study showed that concomitant regimen during 10 days with standard acid inhibition was still unable to reach the 90% cure rate arbitrary threshold, but optimised regimens lasting 14 days and/or using high dose PPIs did achieve over 90% eradication even in clarithromycin resistant strains.

Another treatment that has resurfaced recently in light of increased resistance rates is bismuth quadruple therapy, which contains a PPI, bismuth salts, tetracycline and metronidazole.[34, 36] This combination has been available as a rather complicated multi-prescription regimen scheme for many years, but recently, a three-in-one single, combination treatment has emerged.[37] In the literature, both the traditional and the single capsule bismuth quadruple regimens achieve eradication rates near or superior to 90% irrespective of clarithromycin resistance, and even overcoming metronidazole resistance.[37-39] In our study, they both achieved this threshold in 10-day treatments, even though the treated population was biased towards a higher prevalence of penicillin allergy, which has been proposed to be a risk factor for treatment failure.[40] As in previous literature,[37] metronidazole resistance did not significantly affect these bismuth quadruple regimens in our study.

Finally, bismuth may also be combined with clarithromycin and amoxicillin to improve the efficacy of standard triple therapy. This approach has not been widely used in the literature, but a few studies have been published recently with encouraging results and have promoted a change in practice.[41, 42] Our results with this treatment were also promising when prescribed for 14 days, scoring over 90% eradication by mITT.

In our mixed multilevel analysis, several factors were found to be independently associated with treatment effectiveness, especially adherence to treatment, with a

global OR of approximately 7. Remarkably, compliance was excellent (97%) and was indeed the factor which was mostly associated with higher eradication rate in all treatment categories evaluated, with an OR ranging from 4 (concomitant treatment) to 50 (quadruple therapy with clarithromycin, amoxicillin and bismuth). Additionally, use of the recommended dose of PPI improved cure rates in all treatment categories, although when high instead of standard doses where used, no additional benefit was found as shown in Table 4.

Findings from the present study should be interpreted with caution on account of a number of limitations. First of all, this study is not a randomised controlled clinical trial; therefore, comparisons of treatments must be taken with care, due to unidentified allocation biases that may affect effectiveness. These include different local resistance rates, the age of treatment groups, treatment and care costs for patients and providers, and the use of the mITT analysis versus the traditional ITT (which could overestimate eradication) among others. However, these limitations are inherent to studies focused on clinical practice, which are necessary to elucidate the outcomes in routine practice.

Another drawback is that inclusion rates and numbers varied between centres, regions and countries according to the number of *H. pylori* infections managed in each outpatient clinic. For example, standard clinics in regions with low infection prevalence may obviously attend a lower number of *H. pylori*-infected patients, thus affecting their inclusion rates. Although results may not be fully representative of the general population, it is important to mention that in those highest recruiting countries such as Spain, there was a wide variety of centre types (large hospitals versus small outpatients clinics) and therefore this could balance the distribution and the representativeness of the population. In any case, in our sensitivity analysis, we did not identify any significant bias derived from high vs. low inclusion countries. In

addition, even if we may think heterogeneity was inevitably present, it is important to highlight that the standard triple therapy did not reach an optimal effectiveness in any of the regions; and, by contrast, in all the regions all quadruple regimens (concomitant, single capsule bismuth quadruple and bismuth-amoxicillin-clarithromycin quadruple therapies) achieved ≈90% eradication rates, which confers consistency to the cluster-by-cluster analysis of the data.

Finally, our intention to study clinical practice forced us to register as many open management options as possible; this increases heterogeneity and sometimes limits the amount of data obtainable from each case. For example, individual antibacterial resistance was available in a relatively low proportion of cases, translating what happens in day-to-day clinical practice in Europe. In the future, PCR testing could ease bacterial antibiotic susceptibility evaluation if such method is shown to be reliable in faecal samples, which would avoid invasive testing such as endoscopy.

In contrast to these limitations, we believe that this type of study has a number of strengths that compensate the weaker areas. The open inclusion criteria ensure that our data represents the real clinical practice of the participant centres, and it allows the evaluation of the widest range of therapeutic options and patient contexts. Although data are heterogeneous, the analyses showed that the measure of the effect is consistent throughout Europe. Moreover, the large number of recruiters and countries has provided, to our knowledge, the largest international prospective series on *H. pylori* treatment under a common research protocol. This has enabled us to perform multivariate analyses to control for confounding variables, data bias and heterogeneity, to develop regional and time-trend approaches. The inclusion of centres with different levels of experience in *H. pylori* gave us a wide view of real practice. Finally, a high quality method has been used to register, store, manage and monitor the data by the use of Online Platform for Collaborative Research AEG-

REDCap, which provides stability and coherence to the data with programmed and real-time quality controls, queries, reports and statistics.

In light of these results we may conclude that in order to obtain over 90% eradication rates consistently, to avoid re-treatment and to prevent patient drop-out, physicians should be encouraged to use quadruple therapies, because these are the only regimens that consistently achieve eradication rates ≥ 90%. Those treatments were: 14-day non-bismuth quadruple concomitant therapy (PPI, amoxicillin, clarithromycin and metronidazole), 14-day standard triple plus bismuth (PPI, bismuth, amoxicillin and clarithromycin), and 10-day bismuth quadruple therapy (PPI, bismuth, tetracycline and metronidazole). If antibiotic resistance rates are high in the local geographical area, and especially if dual resistance to clarithromycin and metronidazole is greater than 15%, bismuth quadruple therapy may be the most reliable choice.

Prescribing physicians must also take into consideration that regardless of the treatment chosen or the clinical context, compliance with treatment was the most relevant factor for achieving successful eradication, so treatment, procedures and expectations must be carefully explained to the patient.

Although overall *H. pylori* cure rates in the European Registry are relatively disappointing, different regions of Europe are slowly and heterogeneously incorporating recommended practices such as prescribing quadruple therapies for two-weeks with an increased dose of acid inhibition. The observed ongoing adaptation of real clinical practice to recommendations gives room for hope, especially considering the parallel improvement (up to 10% in some regions) in overall efficacy in Europe in only 5 years.

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Author's contribution:

Olga P Nyssen: Scientific Director and member of the project's Scientific Committee, planned and coordinated the study, designed and programmed the electronic case report form, analysed the data, wrote the manuscript drafts, and approved the submitted manuscript.

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Competing interests:

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The rest of authors declare no conflict of interest.

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Table 1. Baseline characteristics of *H. pylori* first-line empirical treatments by region

Variable	Overall	East	South-east	South-west	Centre	North
Number of patients	21,533	3,679	4,299	10,118	1,985	1,452
Female, N (%)	12,743 (59.2)	2,180 (59.0)	2,492 (58.0)	6,147 (60.8)	1,192 (60.0)	732 (50.0)
Age, mean (SD)	50.4 (18.0)	46.4 (15.0)	52.2 (15.0)	50.5 (15.0)	52.2 (15.0)	52.7 (18.0)
Penicillin allergy, N (%)	670 (3.1)	57 (1.5)	126 (2.9)	414 (4.1)	13 (0.7)	60 (4.1)
Indication						
Dyspepsia	17,800 (82.7)	2,679 (7.8)	3,507 (81.6)	8,595 (84.9)	1,896 (95.5)	1,123 (77.3)
Ulcer disease	3,733 (17.3)	1,000 (27.2)	792 (18.4)	1,523 (15.1)	89 (4.5)	329 (2.7)
Culture, N (%)	2,396 (11.1)	67 (1.8)	219 (5.1)	365 (3.6)	1,397 (70.4)	348 (24.0)
No resistance	1,087 (45.4)	20 (29.7)	143 (65.3)	211 (57.8)	552 (39.5)	209 (60.1)
C	543 (22.7)	22 (32.4)	27 (12.1)	54 (14.9)	401 (28.7)	36 (10.2)
M	766 (32.0)	25 (37.8)	49 (22.2)	100 (27.5)	444 (31.8)	103 (29.7)
Dual C + M	321 (13.4)	2 (2.7)	15 (7.1)	18 (5.0)	233 (16.7)	19 (5.6)
Treatment length, N (%)						
7 days	4,109 (19.6)	568 (16.2)	2,548 (60.0)	165 (1.7)	68 (3.8)	760 (53.9)
10 days	11,461 (54.8)	2,080 (59.2)	981 (23.1)	6,220 (62.5)	1,691 (94.0)	489 (34.7)
14 days	5361 (25.6)	867 (24.7)	719 (16.9)	3574 (35.9)	39 (2.2)	162 (11.5)
PPI dose, N (%)						
Low	10,090 (48.9)	1,813 (56.6)	2,556 (60.6)	3.920 (39.1)	718 (40.3)	1,083 (76.9)
Standard	4,211 (20.4)	1,135 (35.6)	306 (7.3)	2,572 (25.7)	75 (4.2)	123 (8.7)
High	6,325 (30.7)	253 (7.9)	1,357 (32.2)	3,525 (35.2)	987 (55.4)	203 (14.4)
Compliance, N (%)						
No (<90% drug intake)	592 (3.0)	97 (2.7)	120 (3.0)	287 (3.0)	63 (4.3)	25 (1.8)
Yes (≥ 90% drug intake)	18,821 (97.0)	3,447 (97.3)	3,239 (96.4)	9,370 (97.0)	1,410 (95.7)	1,355 (98.2)
Unknown	2,119 (9.8)	134 (3.6)	940 (24.5)	461 (4.4)	512 (26)	72 (5.0)
Most frequent treatments, N (%)						
PPI-C+A	8,478 (39.4)	1,775 (48.2)	2,571 (59.3)	3,160 (31.2)	132 (6.6)	840 (57.9)
PPI-C+M	1,046 (4.9)	28 (0.8)	816 (19.0)	127 (1.3)	4 (0.2)	71 (4.9)

PPI-A+M	561 (2.6)	56 (1.5)	92 (2.1)	51 (0.5)	3 (0.2)	359 (24.7)
PPI-A+L	405 (1.9)	227 (6.2)	28 (0.7)	132 (1.3)	6 (0.3)	12 (0.8)
PPI-C+A+T seq	1,228 (5.7)	9 (0.2)	68 (1.6)	4 (0.0)	1,128 (56.8)	19 (1.3)
PPI-C+A+M seq	620 (2.9)	25 (0.7)	175 (4.1)	281 (38.6)	92 (4.6)	47 (3.2)
PPI-C+A+T conc	190 (0.9)	1 (0.0)	51 (1.2)	0 (0.0)	121 (6.1)	17 (1.2)
PPI-C+A+M conc	4,176 (19.4)	14 (0.4)	250 (5.8)	3,910 (38.6)	1 (0.1)	1 (0.1)
PPI-C+A+B	1,756 (8.2)	800 (21.7)	0 (0.0)	956 (9.4)	0 (0.0)	0 (0.0)
PPI-M+Tc+B	192 (0.9)	30 (0.8)	7 (0.2)	41 (0.4)	99 (5.0)	15 (1.0)
PPI-M+D+B	59 (0.3)	0 (0.0)	2 (0.0)	56 (0.6)	0 (0.0)	1 (0.1)
PPI+single capsule*	1,351 (6.3)	0 (0.0)	1 (0.0)	1,144 (11.3)	189 (9.5)	17 (1.2)
Other	1,471 (6.8)	714 (19.4)	238 (5.5)	256 (2.5)	210 (10.6)	53 (3.7)

PPI – proton pump inhibitor, Seq – sequential, Conc – concomitant, C – clarithromycin, L – levofloxacin, M – metronidazole, T – tinidazole, A – amoxicillin, D – doxycycline, B – bismuth salts, Tc – tetracycline, Low dose PPI: 4.5 to 27 mg omeprazole equivalents, b.i.d. (i.e. 20 mg omeprazole equivalents, b.i.d.), Standard dose PPI: 32 to 40 mg omeprazole equivalents, b.i.d. (i.e. 40 mg omeprazole equivalents, b.i.d.), High dose PPI: 54 to 128 mg omeprazole equivalents, b.i.d. (i.e. 60 mg omeprazole equivalents, b.i.d.), *three-in-one single capsule containing bismuth, tetracycline and metronidazole.

Table 2. Effectiveness of most common first-line empirical treatments per region

		Non-evaluable		Failure	Success	Eradication rate		
	N	n	%	n	n	ITT	PP	mITT
				East				
PPI-C+A	1,775	26	1.5%	739	1,010	57.7%	82.3%	81.5%
PPI-C+M	28	0	0.0%	11	17	60.7%	68.0%	68.0%
PPI-A+M	56	0	0.0%	22	34	60.7%	75.6%	75.6%
PPI-A+L	227	0	0.0%	191	36	15.9%	17.1%	16.7%
PPI-C+A+T seq	9	0	0.0%	9	0	0.0%		
PPI-C+A+M seq	25	0	0.0%	10	15	60.0%	68.2%	68.2%
PPI-C+A+T conc	1	0	0.0%	1	0	0.0%		
PPI-C+A+M conc	14	0	0.0%	5	9	64.3%	90.0%	90.0%
PPI-C+A+B	800	3	0.4%	191	606	76.0%	89.6%	89.2%
PPI-M+Tc+B	30	0	0.0%	6	24	80.0%	92.3%	92.3%
PPI-M+D+B	0	0						
PPI+single capsule*	0	0						
Other	714	6	0.8%	281	427	60.3%	72.6%	71.9%
Total in the region	3,679			1,466	2,178	59.8%	77.0%	76.3%
				South-east				
PPI-C+A	2,571	113	4.4%	1,013	1,445	58.8%	86.7%	86.6%
PPI-C+M	816	7	0.9%	217	592	73.2%	85.4%	85.3%
PPI-A+M	92	0	0.0%	64	28	30.4%	80.0%	80.0%
PPI-A+L	28	0	0.0%	6	22	78.6%	84.0%	84.6%
PPI-C+A+T seq	68	0	0.0%	9	59	86.8%	86.8%	86.8%
PPI-C+A+M seq	175	0	0.0%	37	138	78.9%	84.7%	81.2%
PPI-C+A+T conc	51	0	0.0%	4	47	92.2%	94.0%	92.2%
PPI-C+A+M conc	250	0	0.0%	28	222	88.8%	91.7%	91.4%
PPI-C+A+B	0	0						
PPI-M+Tc+B	7	0	0.0%	1	6	85.7%	100.0%	100.0%
PPI-M+D+B	2	0	0.0%	1	1	50.0%	50.0%	50.0%
PPI+single capsule*	1	0	0.0%	0	1	100.0%	100.0%	100.0%
Other	238	9	3.8%	73	156	68.1%	83.3%	83.0%
Total in the region	4,299			1,453	2,717	65.2%	86.5%	86.2%
				South-west				
PPI-C+A	3,160	1	0.0%	682	2,477	78.4%	84.3%	83.7%
PPI-C+M	127	0	0.0%	55	72	56.7%	63.7%	63.2%
PPI-A+M	51	0	0.0%	13	38	74.5%	79.2%	77.6%

PPI-A+L	132	1	0.8%	24	107	81.7%	85.2%	84.9%
PPI-C+A+T seq	4	0	0.0%	1	3	75.0%	100.0%	100.0%
PPI-C+A+M seq	281	0	0.0%	65	216	76.9%	84.2%	81.8%
PPI-C+A+T conc	0	0						
PPI-C+A+M conc	3,910	12	0.3%	540	3,358	86.1%	90.3%	89.8%
PPI-C+A+B	956	10	1.0%	108	838	88.6%	91.7%	91.6%
PPI-M+Tc+B	41	0	0.0%	8	33	80.5%	84.6%	82.5%
PPI-M+D+B	56	0	0.0%	11	45	80.4%	82.4%	81.8%
PPI+single capsule*	1,144	43	3.8%	151	950	86.3%	95.2%	94.6%
Other	256	5	2.0%	82	169	67.3%	78.3%	76.8%
Total in the region	10,118			1,740	8,306	82.7%	88.1%	87.5%
				Centre				
PPI-C+A	132	0	0.0%	56	76	57.6%	85.7%	85.4%
PPI-C+M	4	0	0.0%	1	3	75.0%	100.0%	75.0%
PPI-A+M	3	0	0.0%	0	3	100.0%	100.0%	100.0%
PPI-A+L	6	0	0.0%	3	3	50.0%	75.0%	60.0%
PPI-C+A+T seq	1,128	70	6.2%	243	815	77.0%	92.4%	91.7%
PPI-C+A+M seq	92	0	0.0%	35	57	62.0%	87.5%	86.4%
PPI-C+A+T conc	121	3	2.5%	14	104	88.1%	96.3%	93.7%
PPI-C+A+M conc	1	0	0.0%	1	0	0.0%		
PPI-C+A+B	0	0						
PPI-M+Tc+B	99	0	0.0%	28	71	71.7%	95.9%	95.9%
PPI-M+D+B	0	0						
PPI+single capsule*	189	8	4.2%	82	99	54.7%	98.0%	95.2%
Other	210	2	1.0%	164	44	21.2%	84.6%	83.0%
Total in the region	1,985			627	1,275	67.0%	92.3%	91.2%
				North				
PPI-C+A	840	1	0.1%	178	661	78.8%	84.8%	84.3%
PPI-C+M	71	0	0.0%	21	50	70.4%	76.6%	75.8%
PPI-A+M	359	0	0.0%	72	287	79.9%	86.5%	86.7%
PPI-A+L	12	0	0.0%	3	9	75.0%	90.0%	90.0%
PPI-C+A+T seq	19	0	0.0%	10	9	47.4%	100.0%	100.0%
PPI-C+A+M seq	47	0	0.0%	13	34	72.3%	71.1%	72.3%
PPI-C+A+T conc	17	0	0.0%	12	5	29.4%	100.0%	100.0%
PPI-C+A+M conc	1	0	0.0%	1	0	0.0%		
PPI-C+A+B	0	0						

PPI-M+Tc+B	15	0	0.0%	3	12	80.0%	91.7%	92.3%
PPI-M+D+B	1	0	0.0%	0	1	100.0 %	100.0%	100.0%
PPI+single capsule*	17	0	0.0%	4	13	76.5%	92.9%	86.7%
Other	53	0	0.0%	20	33	62.3%	84.2%	84.6%
Total in the region	1,452			337	1,114	76.8%	84.7%	84.4%
				All regions				
PPI-C+A	8,478	141	1.7%	2,668	5,669	68.0%	84.6%	84.1%
PPI-C+M	1,046	7	0.7%	305	734	70.6%	81.6%	81.3%
PPI-A+M	561	0	0.0%	171	390	69.5%	84.3%	84.2%
PPI-A+L	405	1	0.2%	227	177	43.8%	46.6%	46.3%
PPI-C+A+T seq	1,228	70	5.7%	272	886	76.5%	92.1%	91.4%
PPI-C+A+M seq	620	0	0.0%	160	460	74.2%	83.0%	80.8%
PPI-C+A+T conc	190	3	1.6%	31	156	83.4%	95.7%	93.4%
PPI-C+A+M conc	4,176	12	0.3%	575	3,589	86.2%	90.4%	89.9%
PPI-C+A+B	1,756	13	0.7%	299	1,444	82.8%	90.8%	90.6%
PPI-M+Tc+B	192	0	0.0%	46	146	76.0%	92.4%	91.8%
PPI-M+D+B	59	0	0.0%	12	47	79.7%	81.5%	81.0%
PPI+single capsule*	1,351	51	3.8%	237	1,063	81.8%	95.5%	94.6%
Other	1,471	22	1.5%	620	829	57.2%	76.6%	75.8%
Total in all regions	21,533	320	1.5%	5,623	15,590	73.5%	86.2%	85.6%

PPI – proton pump inhibitor, Conc – concomitant, Seq – sequential, C – clarithromycin, M – metronidazole, A – amoxicillin, L – levofloxacin, B – bismuth salts, Tc – tetracycline, D – doxycycline. mITT – modified intention-to-treat, ITT – intention-to-treat, PP – per protocol, *three-in-one single capsule containing bismuth, tetracycline and metronidazole.

Table 3. Effectiveness of first-line empirical treatments according to duration.

	ITT eradication rate				PP eradication rate				mITT eradication rate			
		Treatment duration				Treatment duration				Treatment duration		
	N	7 days	10 days	14 days	N	7 days	10 days	14 days	N	7 days	10 days	14 days
PPI-C+A*	8,337	60.4%	71.5%	73.2%	6,647	83.0%	84.8%	86.7%	6,743	82.7%	84.2%	86.2%
PPI-C+M*	1,039	74.0%	57.4%	54.3%	898	84.8%	67.3%	67.9%	903	84.4%	66.7%	67.9%
PPI-A+M	561	69.3%	77.4%	25.0%	458	80.7%	85.9%	80.0%	463	80.8%	85.7%	80.0%
PPI-A+L	404	8.6%	78.0%	74.2%	371	8.9%	86.8%	85.2%	382	8.8%	85.4%	85.2%
PPI-C+A+T seq	1,158	NA	77.5%	NA	957	NA	92.1%	NA	969	NA	91.5%	NA
PPI-C+A+M seq*	620	NA	74.4%	NA	528	NA	82.9%	NA	569	NA	80.8%	NA
PPI-C+A+T conc	187	NA	85.4%	89.5%	162	NA	95.5%	100.0%	167	NA	92.8%	100.0%
PPI-C+A+M conc	4,164	NA	84.8%	88.2%	3,891	95.0%	88.9%	92.2%	3,992	90.9%	88.3%	92.1%
PPI-C+A+B	1,743	50.0%	74.6%	86.6%	1,577	76.9%	86.6%	92.6%	1,594	76.9%	86.2%	92.4%
PPI-M+Tc+B	192	NA	75.3%	83.3%	157	NA	93.8%	88.2%	159	NA	93.1%	88.2%
PPI-M+D+B	59	NA	93.8%	78.0%	54	NA	93.3%	81.1%	58	NA	93.8%	80.0%
PPI+single capsule**	1,300	NA	82.1%	NA	1,102	NA	95.4%	NA	1,124	NA	94.5%	NA
Other	1,449	62.1%	73.4%	54.5%	1,073	73.7%	85.0%	60.4%	1,094	73.7%	84.4%	59.7%
Total	21,213	61.1%	76.9%	79.6%	17,875	78.5%	87.8%	88.3%	18,217	78.2%	87.0%	88.0%

PPI – proton pump inhibitor, Conc – concomitant, Seq – sequential, C – clarithromycin, M – metronidazole, A – amoxicillin, L – levofloxacin, B – bismuth salts, Tc – tetracycline, mITT – modified-intention-to treat, ITT – intention-to-treat, PP – per protocol, NA – Not applicable, *An effectiveness univariate analysis was performed accounting 10/14-day treatments prescribed together with high doses PPI only, and following therapies reached over 90% mITT eradication rate: 14-day PPI-C+A (89.6%), 10-day PPI-C+A+M seq (91.6%), 10/14-day PPI-C+A+M conc (both 92.7 and 92.8%), 10-day PPI-C+A+B (95.5%), 10-day PPI-M+Tc+B (95.2%). A Chi^2 test was also performed and significant comparisons (10 vs 14 days with high dose PPIs) were reported in the table (*). Additional pair-wise comparison (by means of Chi^2 test and Fisher exact test) were performed between following treatments: 10-day sequential, 14-day concomitant and 10-day bismuth quadruple: statistically significant differences ($p < 0.001$) were found in all comparisons in favour the 14-day concomitant and 10-day bismuth quadruple therapies; **three-in-one single capsule containing bismuth, tetracycline and metronidazole.

Table 4. Mixed effects logistic models for each first-line empirical treatment category.

	Triple –C+A				Triple –C+M				Sequential –C+A+T/M			
		95%CI				95%CI				95%CI		
Fixed effects	OR	Lower	Upper	p	OR	Lower	Upper	p	OR	Lower	Upper	p
Age-centred	1.005	1.001	1.010	0.045	0.992	0.980	1.005	0.245	1.013	1.001	1.026	0.049
Sex	1.156	0.993	1.351	0.061	1.187	0.788	1.789	0.413	1.977	1.292	3.026	0.002
Diagnosis	1.354	1.093	1.677	0.006	1.730	0.935	3.199	0.081	1.389	0.557	3.466	0.481
Length												
7 days	1				1							
10 days	1.452	11.125	1.875	0.002	0.564	0.249	1.281	0.172	1			
14 days	1.547	1.109	2.159	0.010	0.665	0.255	1.737	0.406				
PPI dose OE**												
Low	1				1				1			
Standard	1.449	1.168	1.788	0.001	3.680	1.352	10.020	0.011	3.193	0.831	12.729	0.091
High	1.634	1.251	2.135	<0.001	1.806	1.080	3.019	0.024	1.832	1.113	3.014	0.017
Compliance	7.576	4.497	12.765	<0.001	41.479	2.022	850.79	0.016	22.241	7.310	67.670	<0.001
Constant	0.546	0.306	0.976	0.041	0.066	0.003	1.240	0.077	0.186	0.056	0.612	0.006
Random effects	Estim.	SE			Estim.	SE			Estim.	SE		
Variance	0.788	0.189		<0.001	1.541	0.852		<0.001	0.633	0.362		<0.001
ICC	0.193				0.312				0.161			

Table 4. (continued).

	Concomitant –C+A+T/M				Single capsule bismuth quadruple*				Quadruple –C+A+B			
		95%CI				95%CI				95%CI		
Fixed effects	OR	Lower	Upper	p	OR	Lower	Upper	p	OR	Lower	Upper	p
Age-centred	0.994	0.988	0.999	0.039	1.001	0.987	1.017	0.825	0.996	0.984	1.008	0.502
Sex	1.365	1.075	1.735	0.011	0.609	0.358	1.036	0.055	1.005	0.694	1.457	0.977
Diagnosis	1.500	1.037	2.161	0.031	1.706	0.678	4.294	0.212	1.546	0.893	2.676	0.120
Length												
7 days	1											
10 days	0.460	0.055	3.831	0.473	1				1			
14 days	0.536	0.064	4.499	0.566					1.913	0.999	3.661	0.051
PPI dose OE**												
Low	1				1				1			
Standard	1.662	1.127	2.452	0.010	1.191	0.563	2.517	0.648	2.151	1.077	4.294	0.027
High	1.699	1.192	2.421	0.003	1.132	0.565	2.268	0.726	1.377	0.677	2.803	0.296
Compliance	4.586	2.640	7.964	<0.001	24.919	9.742	63.744	<0.001	48.873	1.514	15.505	0.007
Constant	3.549	0.406	31.003	0.252	1.016	0.381	2.709	0.975	1.058	0.304	3.675	0.929
Random effects	Estim.	SE			Estim.	SE			Estim.	SE		
Variance	0.312	0.138		<0.001	0.370	0.298		0.015	0.328	0.219		<0.002
ICC	0.087				0.101				0.091			

95%CI – 95% Confidence interval; ICC – intraclass correlation coefficient. OR – odds ratio. Estim. – Estimate. SE – Standard error. PPI – proton pump inhibitor. OE – omeprazole equivalent. C – clarithromycin. M – metronidazole. A – amoxicillin. L – levofloxacin. B – bismuth salts. Tc – tetracycline. mITT – modified intention-to-treat. ITT – intention-to-treat. PP – per protocol. NA – Not applicable, *three-in-one single capsule containing bismuth, tetracycline and metronidazole. **Comparison between standard PPI dose [reference] and high PPI dose were performed and no statistically significant differences were found in any of the treatment categories.

Figure 1. **Study flow chart**

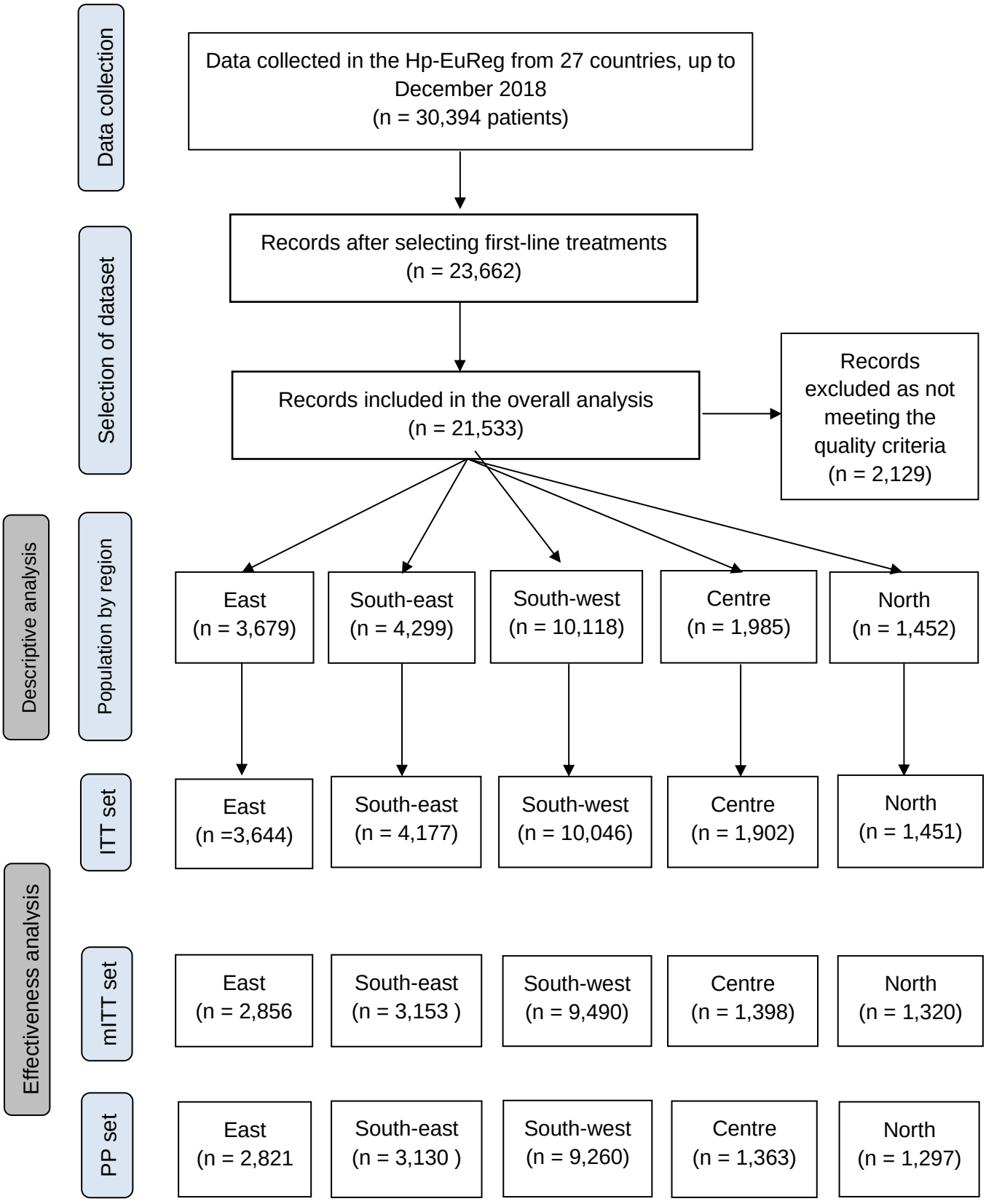


Figure 2. Treatment trends (2013-2018) in Europe per region

Figure 2A. Trends in the prescription of treatments

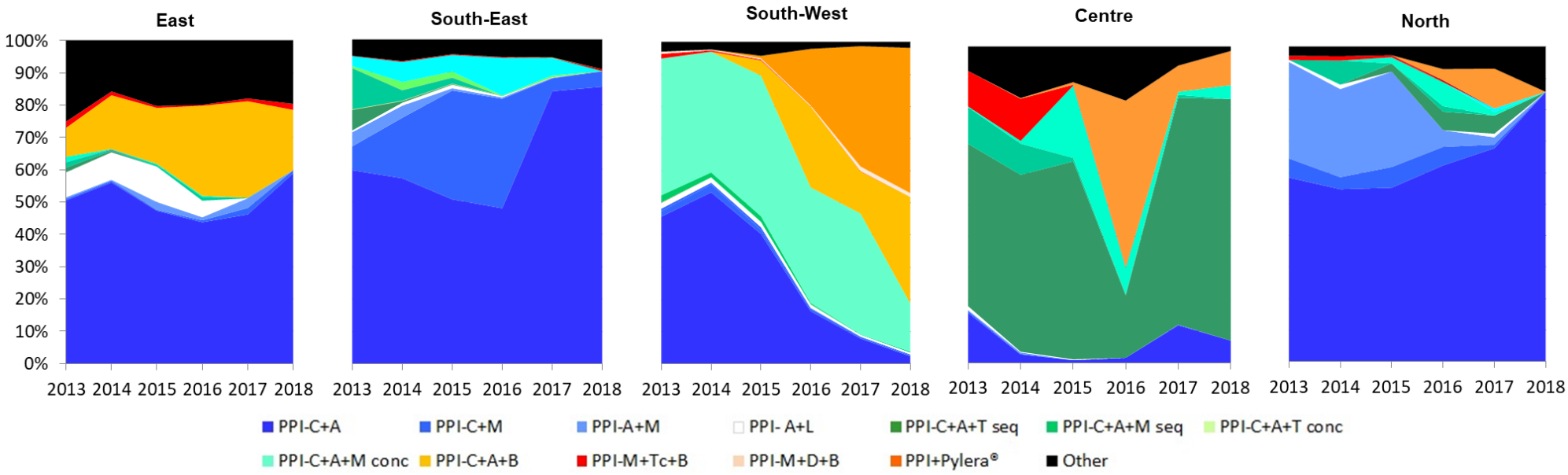
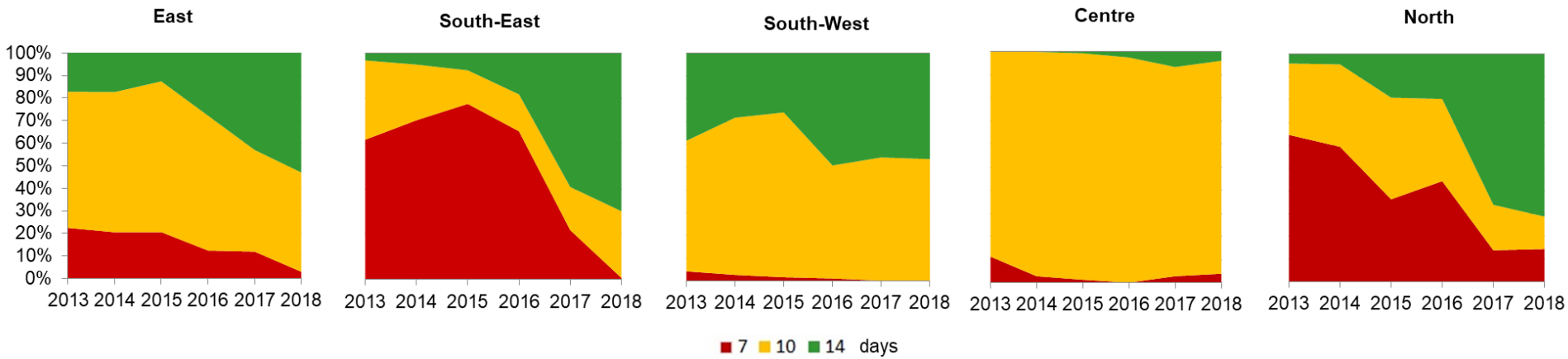


Figure 2B. Trends in the duration of treatments



C – clarithromycin. M – metronidazole. T – tinidazole. A – amoxicillin. L – levofloxacin. B – bismuth salts. Tc – tetracycline. D – doxycycline. Conc – concomitant. Seq – sequential.

Figure 3. Trends (2013-2018) in the use of proton pump inhibitors (PPI) in Europe per region

Figure 3A. Trends in the daily dose (low, standard and high) of PPI

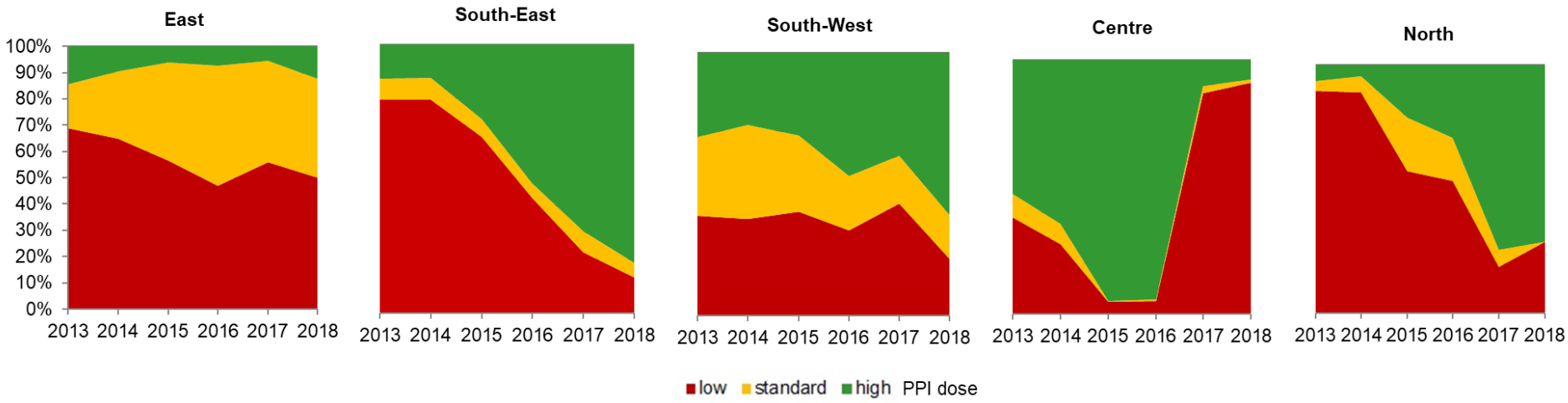
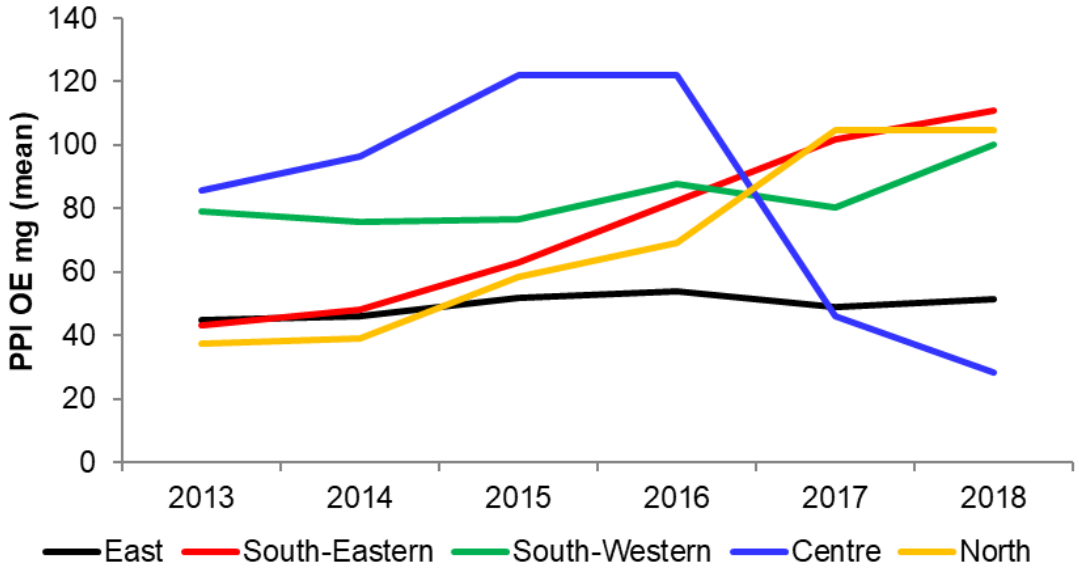


Figure 3B. Trends in the mean daily dose of PPI



OE: omeprazole equivalent

Figure 4. Trends in the eradication rate (modified intention-to-treat) by region

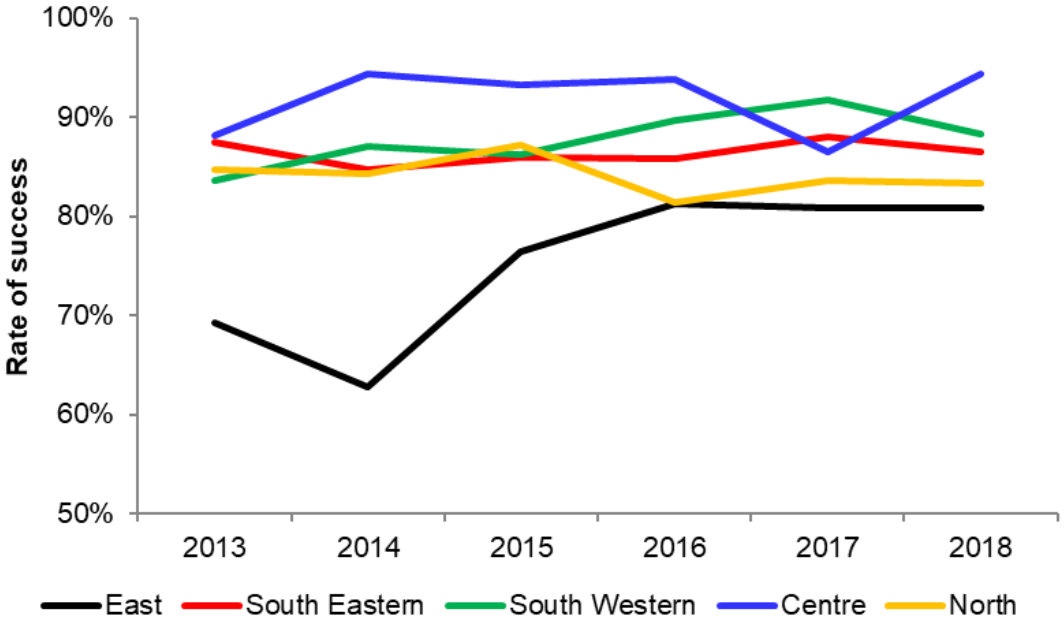
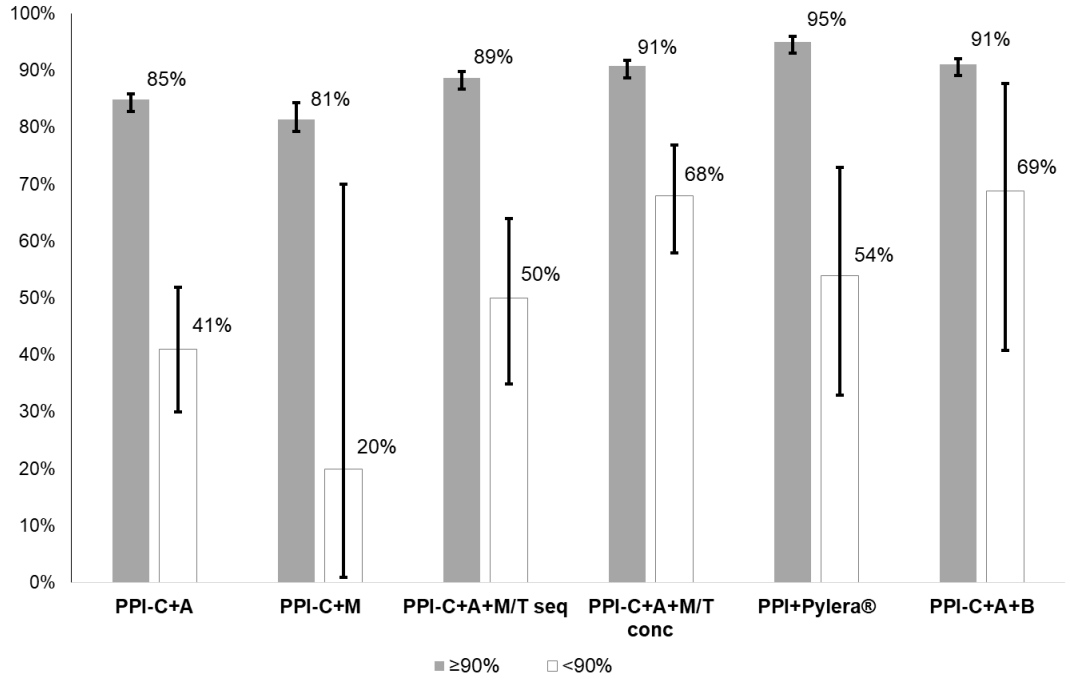


Figure 5. Eradication rate (and 95% confidence interval) by treatment according to compliance



C – clarithromycin. M – metronidazole. T – tinidazole. A – amoxicillin. B – bismuth salts. conc – concomitant. seq – sequential.