

SUPPLEMENTARY MATERIAL

Supplementary file 1. Hp-EuReg investigators.

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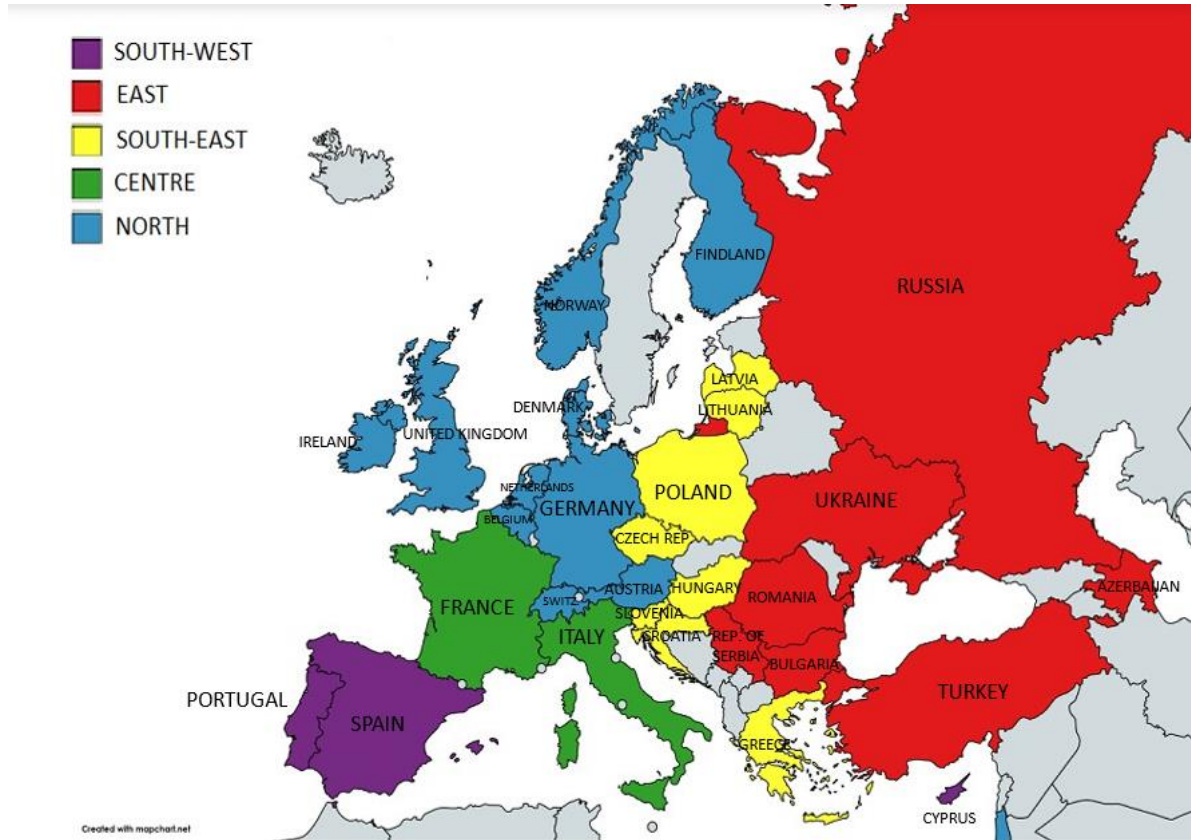
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Supplementary file 2. Participating Hp-EuReg countries by European region.



SOUTH-WEST: Portugal, Spain, Cyprus; EAST: Ukraine, Serbia, Bulgaria, Turkey, Russia, Romania. Azerbaijan; SOUTH-EAST: Croatia, Poland, Hungary, Latvia, Lithuania, Greece, Slovenia, Czech Republic CENTRE: Italy, France; NORTH: United Kingdom, Belgium, Germany, Finland, The Netherlands, Ireland, Israel, Norway, Switzerland, Austria, Denmark.

Supplementary file 3. Regional clusters of the participating Hp-EuReg countries.

1. **East.** Low gross domestic product per capita (GDP) (€ 2.5K to 11K): Ukraine, Serbia, Bulgaria, Turkey, Russia, Romania. Azerbaijan.

2. **South-east.** Low-medium GDP (€ 13K to 24K): Croatia, Poland, Hungary, Latvia, Lithuania, Greece, Slovenia, Czech Republic.

3. **South-west.** Medium GDP (€ 21K to 30K): Portugal, Spain, Cyprus.

4. **Centre.** Medium-high GDP (€ 30K to 40K): Italy, France.

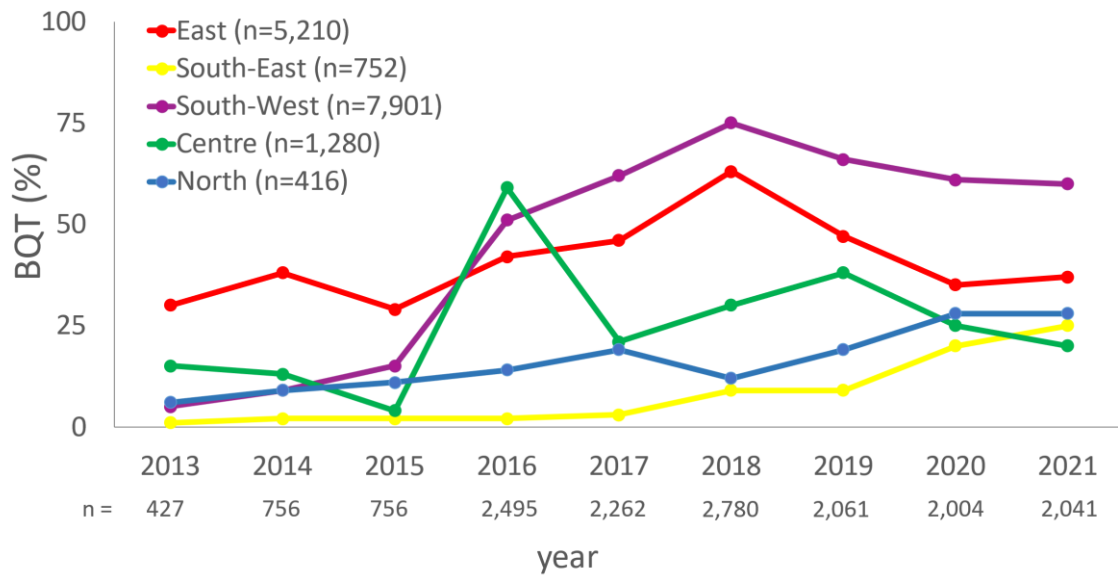
5. **North.** High GDP (€ 40K to 80K): United Kingdom, Belgium, Germany, Finland, The Netherlands, Ireland, Israel, Norway, Switzerland, Austria, Denmark.

Supplementary file 4. Most frequent bismuth quadruple treatments schemes by country.

Schemes	Country																											Total		
	BE	BG	HR	DK	FI	FR	DE	GR	HU	IE	IL	IT	LV	LT	NO	PL	PT	RO	RU	RS	SI	ES	CH	NL	GB	UA	CZ		TR	AZ
PPI+ScBQT																														
n	2	-	-	-	-	31	108	2	-	-	1	1,095	6	1	-	28	160	-	7	20	43	5,133	28	-	-	-	14	-	-	6,679
PPI+CAB																														
n	-	-	1	-	-	-	-	-	-	-	9	-	2	119	2	1	-	-	2,810	12	-	1,259	-	-	1	448	-	-	267	4,931
PPI+LAB																														
n	-	-	1	-	-	-	-	-	5	2	5	-	-	172	8	-	-	-	122	12	16	765	-	-	1	2	-	-	1	1,112
PPI+MTB																														
n	1	3	3	23	-	104	3	4	3	26	1	53	21	-	83	53	-	-	260	6	10	190	1	-	40	7	1	2	-	898
PPI+JAB																														
n	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	531	-	-	-	-	-	-	1	-	-	-	532
PPI+MAB																														
n	-	5	6	-	-	-	-	-	35	3	-	-	-	46	-	10	-	-	194	1	40	22	-	-	3	-	1	-	1	367
PPI+MDB																														
n	-	-	-	-	-	-	-	-	6	-	3	-	2	1	-	-	-	-	-	-	-	205	-	-	-	-	-	-	-	217
PPI+TAB																														
n	-	-	-	-	-	-	-	-	17	-	-	1	12	-	1	-	-	-	6	-	-	2	-	1	1	1	-	77	-	119
Total																														
n	3	8	11	23	0	135	111	6	66	31	19	1,149	43	339	94	92	160	0	3,930	51	109	7,576	29	1	46	459	16	79	269	14,855

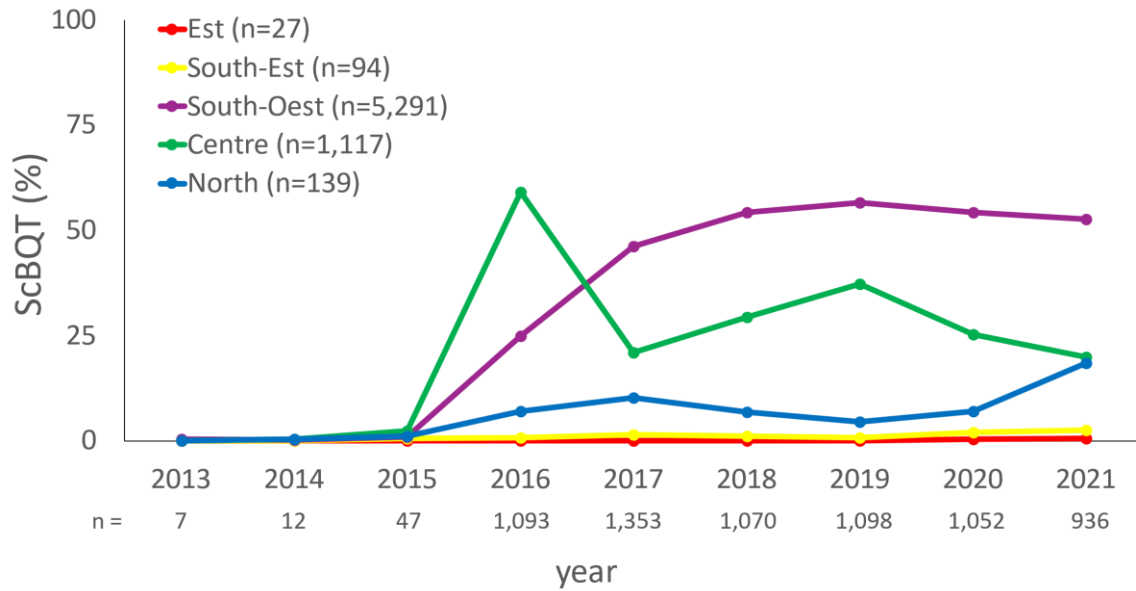
BE, Belgium; BG, Bulgaria; HR, Croatia; DK, Denmark; FI, Finland; FR, France; DE, Germany; GR, Greece; HU, Hungary; IE, Ireland; I, Israel; IT, Italy; LV, Latvia; LT, Lithuania; NO, Norway; PL, Poland; PT, Portugal; RO, Romania; RU, Russia; RS, Serbia; SI, Slovenia; ES, Spain; CH, Switzerland; NL, The Netherlands; GB, United Kingdom; UA, Ukraine; CZ, Czech Republic; TR, Turkey; AZ, Azerbaijan; PPI, proton pump inhibitor; ScBQT, three-in-one single capsule containing bismuth, tetracycline and metronidazole; A, amoxicillin; B, bismuth salts; C, clarithromycin; D, doxycycline; J, josamycin; L, levofloxacin; M, metronidazole; T, tetracycline.

Supplementary file 5. Proportion (%) of bismuth-containing quadruple therapy (excluding the single capsule) by European region between 2013 and 2021.



BQT: bismuth quadruple therapy; East: Ukraine, Serbia, Bulgaria, Turkey, Russia, Romania, Azerbaijan; South-East: Croatia, Poland, Hungary, Latvia, Lithuania, Greece, Slovenia, Czech Republic; South-West: Portugal, Spain, Cyprus. Centre: Italy, France; North: United Kingdom, Belgium, Germany, Finland, The Netherlands, Ireland, Israel, Norway, Switzerland, Austria, Denmark.

Supplementary file 6. Proportion (%) of single capsule bismuth quadruple therapy prescription by European region between 2013 and 2021.



ScBQT: three-in-one single capsule containing bismuth, tetracycline and metronidazole; East: Ukraine, Serbia, Bulgaria, Turkey, Russia, Romania. Azerbaijan; South-East: Croatia, Poland, Hungary, Latvia, Lithuania, Greece, Slovenia, Czech Republic; South-West: Portugal, Spain, Cyprus. Centre: Italy, France; North: United Kingdom, Belgium, Germany, Finland, The Netherlands, Ireland, Israel, Norway, Switzerland, Austria, Denmark

Supplementary file 7. Overall effectiveness (by modified intention-to-treat) of the different bismuth quadruple therapies schemes by European region.

Treatments	European regions				
	East	South-East	South-West	Centre	North
PPI+ScBQT					
Cure rate (%)	92.6	93.3	91.4	93	95.8
n	27	75	5,025	1,003	118
95% CI	74-99	84-98	91-92	91-95	90-98
PPI+CAB					
Cure rate (%)	91.2	93.3	90.9	-	66.7
n	2,792	30	1212	0	9
95% CI	90-92	77-99	89-92	-	31-91
PPI+MTB					
Cure rate (%)	90.1	90.1	79	84,7	80.7
n	243	81	186	118	145
95% CI	86-93	81-95	72-85	77-90	73-87
PPI+MDB					
Cure rate (%)	-	55,6	69,5	-	100
n	0	9	200	0	2
95% CI	-	23-85	63-76	-	20-95
PPI+TAB					
Cure rate (%)	85.4	72.4	100	100	66.7
n	82	29	1	1	3
95% CI	76-92	53-87	6-89	6-89	13-98
PPI+LAB					
Cure rate (%)	87.2	98.3	84.9	-	87.5
n	117	58	727	0	16
95% CI	80-92	90-100	82-87	-	60-98
PPI+MAB					
Cure rate (%)	90.5	85.7	90.5	-	60
n	189	84	21	0	5
95% CI	85-94	76-92	68-98	-	17-93
PPI+JAB					
Cure rate (%)	86.6	-	-	-	-
n	509	0	0	0	0
95% CI	83-89	-	-	-	-
Total					
Cure rate (%)	90.3	89.1	89.8	92.2	86.2
n	3,959	366	7,372	1,122	298
95% CI	89-91	85-92	89-91	90-94	82-90

PPI, proton pump inhibitor; ScBQT, three-in-one single capsule containing bismuth, tetracycline and metronidazole; A, amoxicillin; B, bismuth salts; C, clarithromycin; D, doxycycline; J, josamycin; L, levofloxacin; M, metronidazole; T, tetracycline; CI, confidence interval. Treatment schemes with 90% or more effectiveness are marked in bold.

Supplementary file 8. Modified intention-to-treat effectiveness of bismuth quadruple therapy schemes in Europe between 2013 and 2021.

Scheme	Year of treatment									TOTAL
	2013	2014	2015	2016	2017	2018	2019	2020	2021	
PPI+ScBQT										
Cure rate (%)	100	80	91.7	92.2	92.2	92.3	91.7	88.6	93.7	91.8
n	7	10	36	1,010	1,268	1,022	1,047	983	831	6,238
95% CI	56-99	44-97	77-98	90-94	91-94	90-94	90-93	86-91	92-95	91-93
PPI+CAB										
Cure rate (%)	93.8	82.4	88.3	94	83.8	89.8	91.5	94.7	95.5	91.1
n	65	153	230	906	458	899	390	415	516	4,040
95 % CI	84-98	75-88	83-92	92-95	80-87	88-92	88-94	92-96	93-97	90-92
PPI+MTB										
Cure rate (%)	77.8	87.1	81	90.5	72.5	92	89.9	89	85.7	84.4
n	180	209	63	42	51	50	79	73	49	796
95% CI	71-84	82-91	69-89	77-97	58-84	80-97	81-95	79-95	72-94	82-87
PPI+MDB										
Cure rate (%)	66.7	68.4	72.9	60.9	79.3	60	50	100	66.7	69.2
n	21	38	59	46	29	10	2	3	3	211
CI 95%	43-85	51-82	60-83	45-75	60-91	27-86	3-97	0-75	13-98	62-75
PPI+TAB										
Cure rate (%)	100	78	100	-	50	83.3	80	-	69,2	81.9
n	24	59	1	0	2	12	5	0	13	116
95% CI	83-100	65-87	55-89	-	3-97	51-97	30-99	-	39-90	79-83
PPI+LAB										
Cure rate (%)	100	92.8	88.6	83.8	84.5	89.1	78.9	81.3	86.1	86.1
n	6	139	166	148	103	92	109	80	72	918
95% CI	52-99	87-96	83-93	81-84	81-85	85-90	76-80	77-82	81-87	86-86
PPI+MAB										
Cure rate (%)	33.3	77.8	73.3	85.7	80	92.6	90.4	90.3	91.4	88.6
n	3	9	15	7	10	27	73	62	93	299
95% CI	2-88	40-96	45-91	48-91	52-87	78-94	85-91	84-90.9	84-91	87-89
PPI+JAB										
Cure rate (%)	84.6	81.8	87	88.5	86.1	89.2	85.7	85.9	100	86.6
n	13	55	23	61	79	93	98	78	8	509
95% CI	54-97	69-91	65-97	77-95	76-93	81-94	77-92	76-92	60-99	83-89
Total										
Cure rate (%)	82.8	84.7	85.8	91.6	88.9	90.8	90.3	89.7	93.4	90
n	319	672	593	2,220	2,000	2,205	1,803	1,694	1,585	13,127
95% CI	78-87	82-83	83-89	90-93	87-90	90-92	89-92	88-91	92-95	90-91

PPI, proton pump inhibitor; ScBQT, three-in-one single capsule containing bismuth, tetracycline and metronidazole; A, amoxicillin; B, bismuth salts; C, clarithromycin; D, doxycycline; J, josamycin; L, levofloxacin; M, metronidazole; T, tetracycline.

Supplementary file 9. Adherence > 90% by bismuth quadruple therapy scheme in Europe.

Scheme	Adherence		
	%	n	95% CI
PPI+ScBQT	96.5	6,202	96-97
PPI+CAB	97.4	4,630	97-98
PPI+MTB	96.6	817	95-98
PPI+MDB	94.9	205	91-97
PPI+TAB	96.6	115	91-99
PPI+LAB	95.1	922	93-96
PPI+MAB	97.8	305	95-99
PPI+JAB	97	516	95-98
Total	96.7	13,712	96-97

CI, confidence interval; PPI, proton pump inhibitor; ScBQT, three-in-one single capsule containing bismuth, tetracycline and metronidazole; A, amoxicillin; B, bismuth salts; C, clarithromycin; D, doxycycline; J, josamycin; L, levofloxacin; M, metronidazole; T, tetracycline

Supplementary file 10. Adverse events by bismuth quadruple therapy scheme in Europe.

Scheme	Adverse events		
	%	n	95% CI
PPI+ScBQT			
Mild/Moderate	28.4	1,823	26-31
Severe	5.9	394	4-9
Serious	0.4	8	1-41
PPI+CAB			
Mild/Moderate	30.0	1,429	28-33
Severe	7.5	371	5-11
Serious	0.2	3	3-69
PPI+MTB			
Mild/Moderate	32.1	282	27-38
Severe	7.1	64	3-17
Serious	0.5	1	10-95
PPI+MDB			
Mild/Moderate	32.1	69	22-45
Severe	7.8	17	1-33
Serious	0	0	-
PPI+TAB			
Mild/Moderate	24.4	29	11-44
Severe	5.0	6	0-53
Serious	0	0	-
PPI+LAB			
Mild/Moderate	26.2	250	0-53
Severe	4.9	55	1-15
Serious	0	0	-
PPI+MAB			
Mild/Moderate	59.6	187	1-15
Severe	1.6	6	1-49
Serious	0.5	1	10-95
PPI+JAB			
Mild/Moderate	26.5	141	20-35
Severe	8.8	47	3-22
Serious	1.5	2	42-81

CI, confidence interval; PPI, proton pump inhibitor; ScBQT, three-in-one single capsule containing bismuth, tetracycline and metronidazole; A, amoxicillin; B, bismuth salts; C, clarithromycin; D, doxycycline; J, josamycin; L, levofloxacin; M, metronidazole; T, tetracycline. Adverse events: metallic taste, diarrhoea, nausea, abdominal pain, dyspepsia, asthenia, vomiting, anorexia, heartburn; Mild: not interfering with daily routine; Moderate: affecting daily routine; Severe: not allowing normal daily routine; Serious: causing death, hospitalization, disability, congenital anomaly, and/or requiring intervention to prevent permanent damage.