THE FERRARA CONSENSUS REPORT: THIRD ITALIAN GUIDELINES ON DIAGNOSIS AND TREATMENT OF HELICOBACTER PYLORI INFECTION

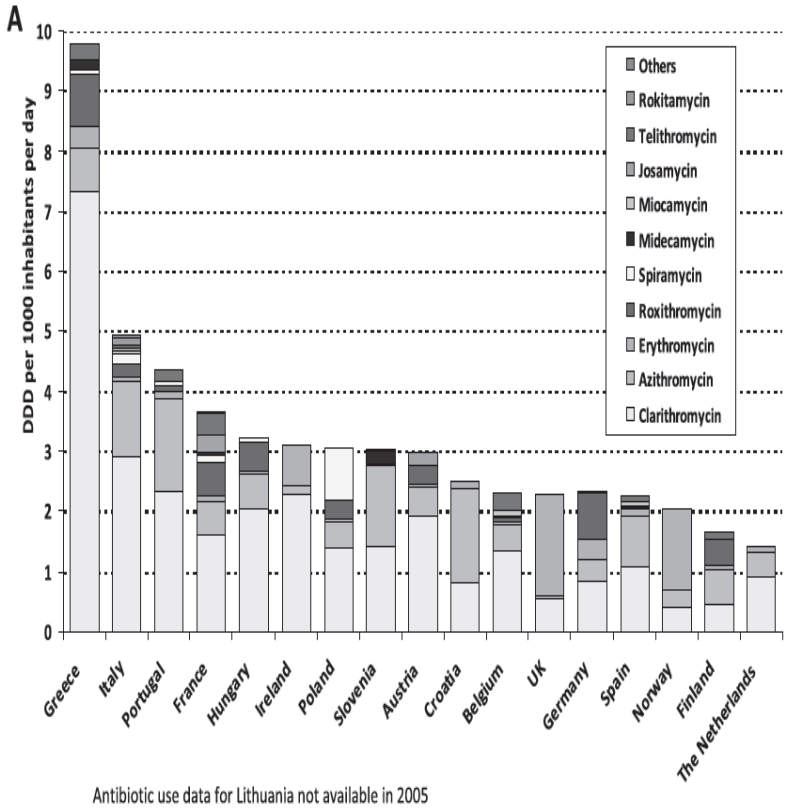
FERRARA 4-5 APRIL 2014

Terapia:

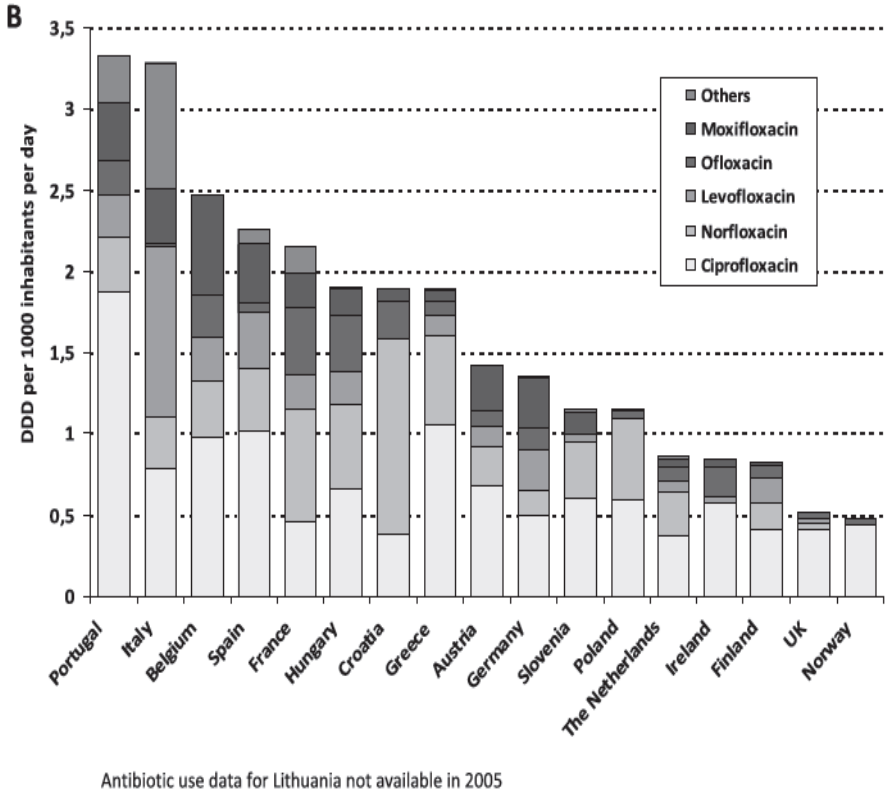
- **Problema delle resistenze batteriche dell' *H. pylori*.**
- Utilizzo dei probiotici nella terapia dell'H.p.: quali, quando, come.
- I PPI: ugualmente efficaci negli schemi di trattamento?

Outpatient use of macrolides and quinolones in 17 European countries in 2005.

Macrolides



Quinolones



Megraud F et al, Gut 2012

H. pylori antibiotic resistance after one course of antibiotic treatment

Antibiotic course	Antibiotic sensitivity tested	N. of patients(%resistant) Pre-therapy	After 1 course
Clarithromycin	Clarithromycin	103 (7%)	21 (19%)
Erythromicin	Clarithromycin	104 (8%)	15 (20%)
Metronidazolo	Metronidazole	114 (28%)	13 (38%)
Amoxicillin	Amoxicillin	57 (0%)	25 (4%)
Quinolone	Levofloxacin	114 (4%)	7 (14%)

McNulty et al, APT 2012

Which treatment should be used?

M1

First-line treatment:

7 days treatment with Proton Pump Inhibitor and:

- Clarithromycin plus Metronidazole
- Clarithromycin plus Amoxycillin

Quadruple therapy (omeprazole plus classic bismuth based triple therapy) can be used in case of failure of triple therapy

Maastricht **I - 1997**

Reduction of triple therapy efficacy due to resistance

	Nitroimidazole resistance % (95% CI)	Clarithromycin resistance % (95% CI)
Amoxicillin triple therapy (PCA)	-	**66,2** (58,2 – 74,2)
Nitroimidazole triple therapy (PCM)	**18,2** (13,1 - 23,3)	**35,4** (25,4 - 45,4)

Fischbach et al. APT 2007

Optimum duration of regimens for *Helicobacter pylori* eradication (Review)

Yuan Y, Ford AC, Khan KJ, Gisbert JP, Forman D, Leontiadis GI, Tse F, Calvet X, Fallone C, Fischbach L, Oderda G, Bazzoli F, Moayyedi P

THE COCHRANE COLLABORATION®

PPI triple therapy 14 days versus 7 days

overall eradication rate

(45 studies, 7722 patients)

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THE COCHRANE COLLABORATION®

Study or subgroup	Favours 14 days n/N	7 days n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 PPI + clarithromycin+ amoxicillin					
Subtotal (95% CI)	**2850**	**2951**	◆	**66.9 %**	**0.65 [0.57, 0.75]**

Increased duration of PPI triple therapy (from 7 to 14 days) significantly increased *H. pylori* eradication rate

72.9% versus 81.9%

Total (95% CI)	**3770**	**3952**	◆	**100.0 %**	**0.66 [0.60, 0.74]**

Total events: 683 (Favours 14 days), 1072 (7 days)

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 70.06$, df = 49 (P = 0.03); $I^2 = 30\%$

PPI triple therapy 14 days versus 7 days

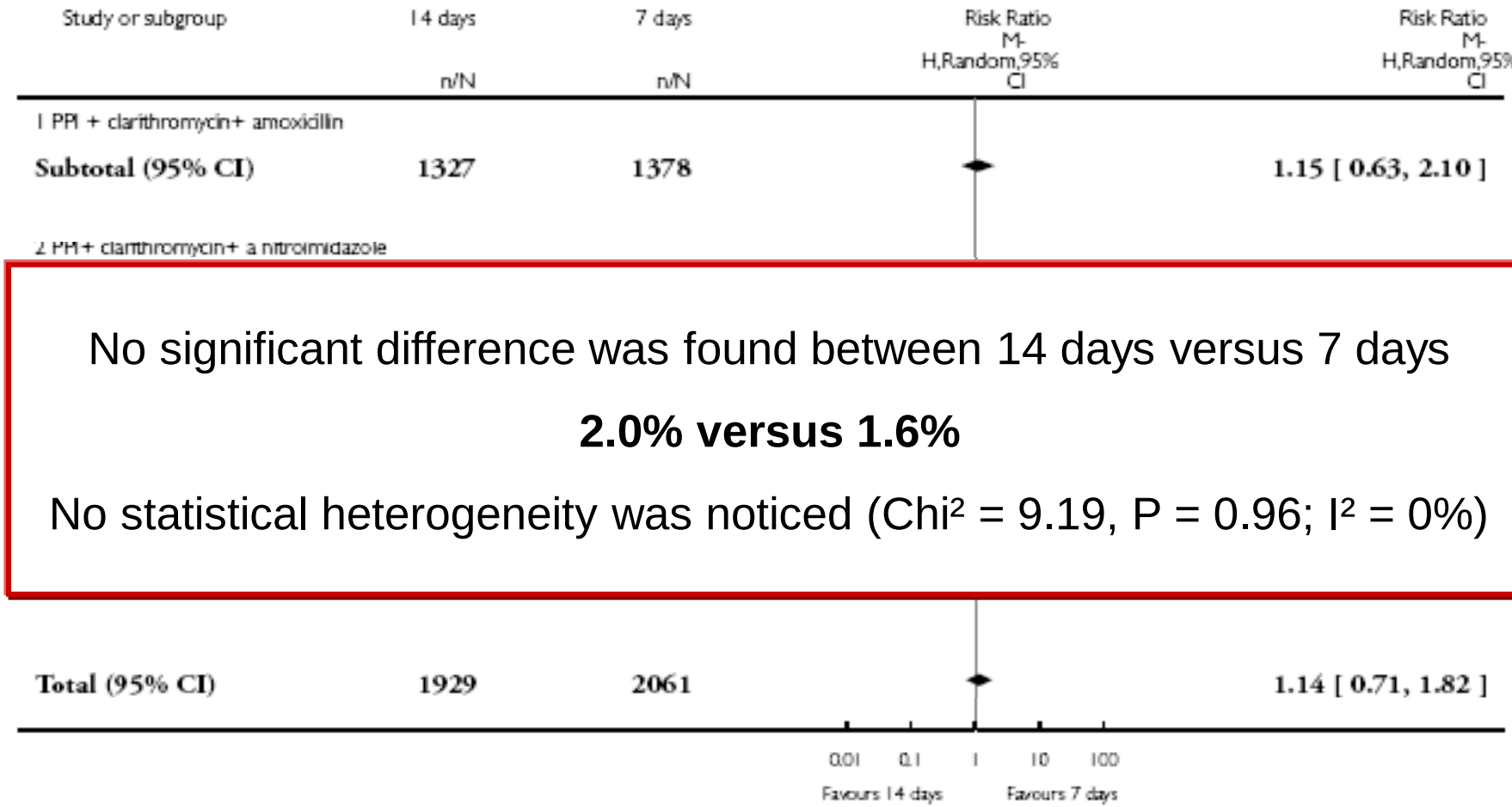
discontinued treatment due to adverse events

(28 studies, 3990 patients)

Optimum duration of regimens for *Helicobacter pylori* eradication (Review)

Yuan Y, Ford AC, Khan KJ, Gisbert JP, Forman D, Leontiadis GI, Tse F, Calvet X, Fallone C, Fischbach L, Odeda G, Bazzoli F, Moayyedi P

THE COCHRANE COLLABORATION®



No significant difference was found between 14 days versus 7 days

2.0% versus 1.6%

No statistical heterogeneity was noticed ($Chi^2 = 9.19$, $P = 0.96$; $I^2 = 0\%$)

Use a PPI plus all three antibiotics

Standard triple therapies

PPI
Clarithromycin
Metronidazole

PPI
Clarithromycin
Amoxicillin

Both sequential and concomitant treatment are designed to overcome increasing clarithromycin resistance

Concomitant

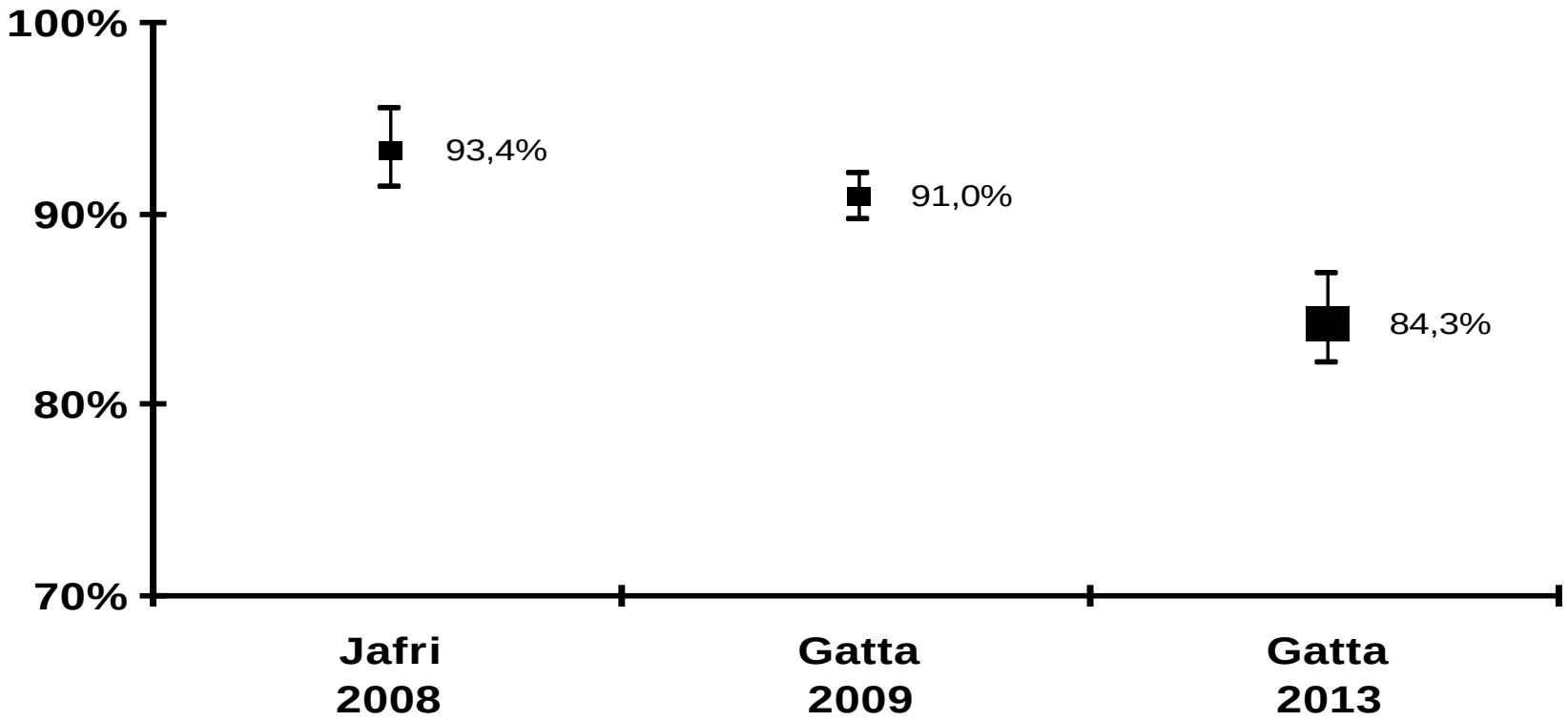
PPI
Clarithromycin
Metronidazole
Amoxicillin

Sequential

PPI
Amoxicillin
+
PPI
Clarithromycin
Metronidazole

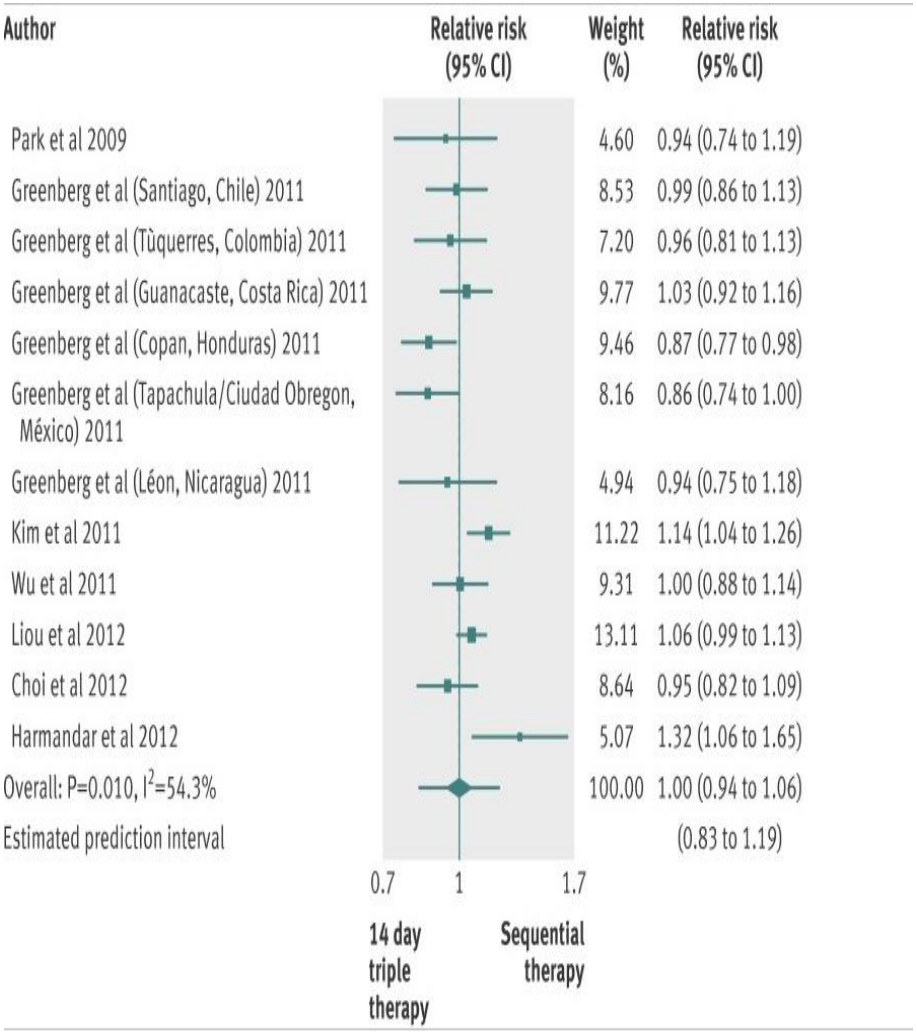
Overall eradication rate of sequential therapy

Data from meta-analysis of RCTs



Jafri NS et al, Ann Intern Med 2008
Gatta L. et al, Am J Gastroenterol 2009
Gatta L et al, BMJ 2013

Sequential therapy *vs* 14-day triple therapy



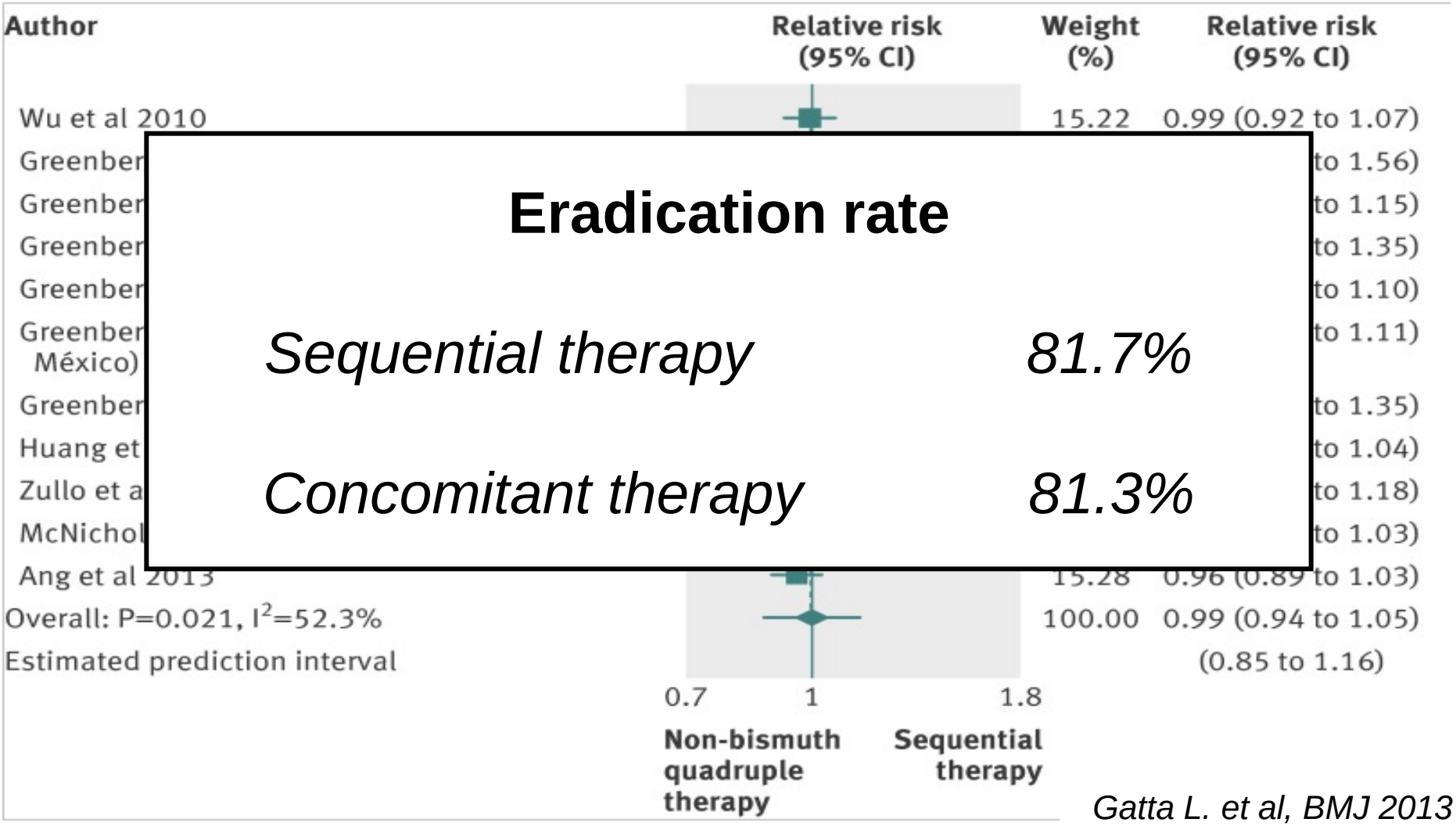
Eradication rate

Sequential therapy *80.8%*

14-day triple therapy *81.3%*

Gatta L. et al, BMJ 2013

Sequential therapy *vs* concomitant therapy



Eradication rate

Sequential therapy	*81.7%*
Concomitant therapy	*81.3%*

Gatta L. et al, BMJ 2013

Pool eradication rates of sequential, concomitant and triple therapies in patients with **clarithromycin resistance**

***H. pylori* strains resistant to clarithromycin**		
Studies	Sequential therapy (n=33)	Triple therapy-7 days (n= 34)
Zullo et al 2003 *Gatta et al 2011*	87.8%	38.2%
	Sequential therapy (n=17)	Triple therapy-10 days (n= 30)
Vaira et al 2007 *Chung et al 2012*	76.4%	26.6%
	Sequential therapy (n=17)	Triple therapy-14 days (n= 20)
Liou et al 2012	58.8%	55%
	Sequential therapy (n=12)	Concomitant therapy (n=7)
Wou et al 2010 *Huang et al 2012*	58.3%	85.7%

Gatta L et al BMJ 2013

Pool eradication rates of sequential,concomitant and triple therapies in patients with **both clarithromycin and metronidazole resistance**

H. pylori strains resistant to clarithromycin and metronidazole		
Studies	Sequential therapy (n=10)	Triple therapy-7 days (n= 5)
Zullo et al 2003	87.8%	38.2%
	Sequential therapy (n=7)	Triple therapy-10 days (n= 13)
Vaira et al 2007 *Chung et al 2012*	14.2%	15.3%
	Sequential therapy (n=7)	Triple therapy-14 days (n= 4)
Liou et al 2012	42.8%	50%
	Sequential therapy (n=7)	Concomitant therapy (n=6)
Wou et al 2010 *Huang et al 2012*	42.8%	83.3%

Gatta L et al BMJ 2013

Pool eradication rates of sequential, concomitant and triple therapies in patients with **metronidazole resistance**

***H. pylori* strains resistant to metronidazole**		
Studies	Sequential therapy (n=36)	Triple therapy-7 days (n= 37)
Zullo et al 2003	94.4%	70.2%
	Sequential therapy (n=50)	Triple therapy-10 days (n= 44)
Vaira et al 2007 *Chung et al 2012*	92%	75%
	Sequential therapy (n=44)	Triple therapy-14 days (n= 46)
Liou et al 2012	72.7%	89.1%
	Sequential therapy (n=48)	Concomitant therapy (n=42)
Wou et al 2010 *Huang et al 2012*	85.4%	95.2%

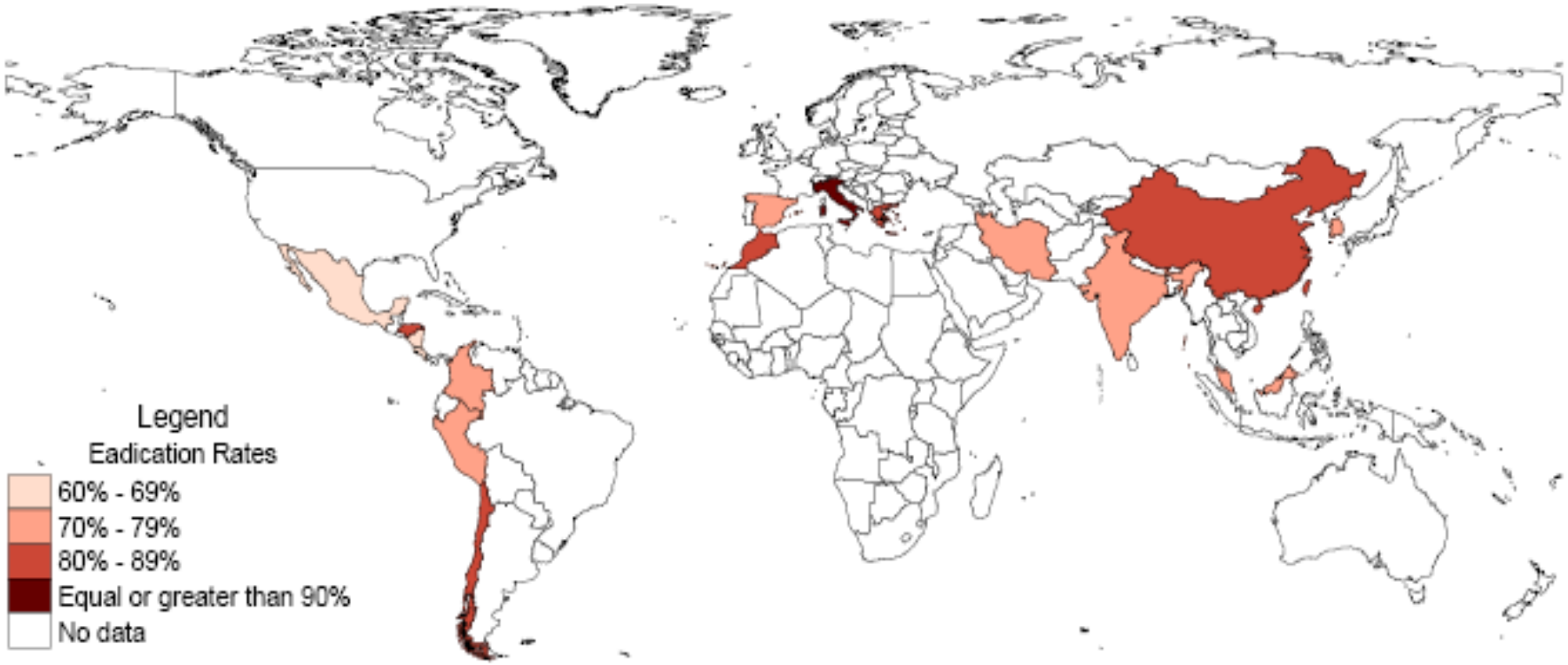
Gatta L et al BMJ 2013

Eradication rates in strains with primary resistance to antibiotics: RCT

	10 days triple therapy		Sequential therapy	
	Eradication n (%)	*p value*	Eradication n (%)	*p value*
Clarithromycin resistance				
Yes	26 (49.1)	<0.001	26 (52.0)	<0.001
No	67 (89.3)		75 (91.5)	
Metronidazole resistance				
Yes	60 (72.3)	0.899	61 (67.8)	0.001
No	33 (73.3)		40 (95.2)	

Zhou L et al, Am J Gastroenterol 2014

Overall eradication rates of sequential therapy of RCTs according to the country of origin



Gatta et al, BMJ 2013

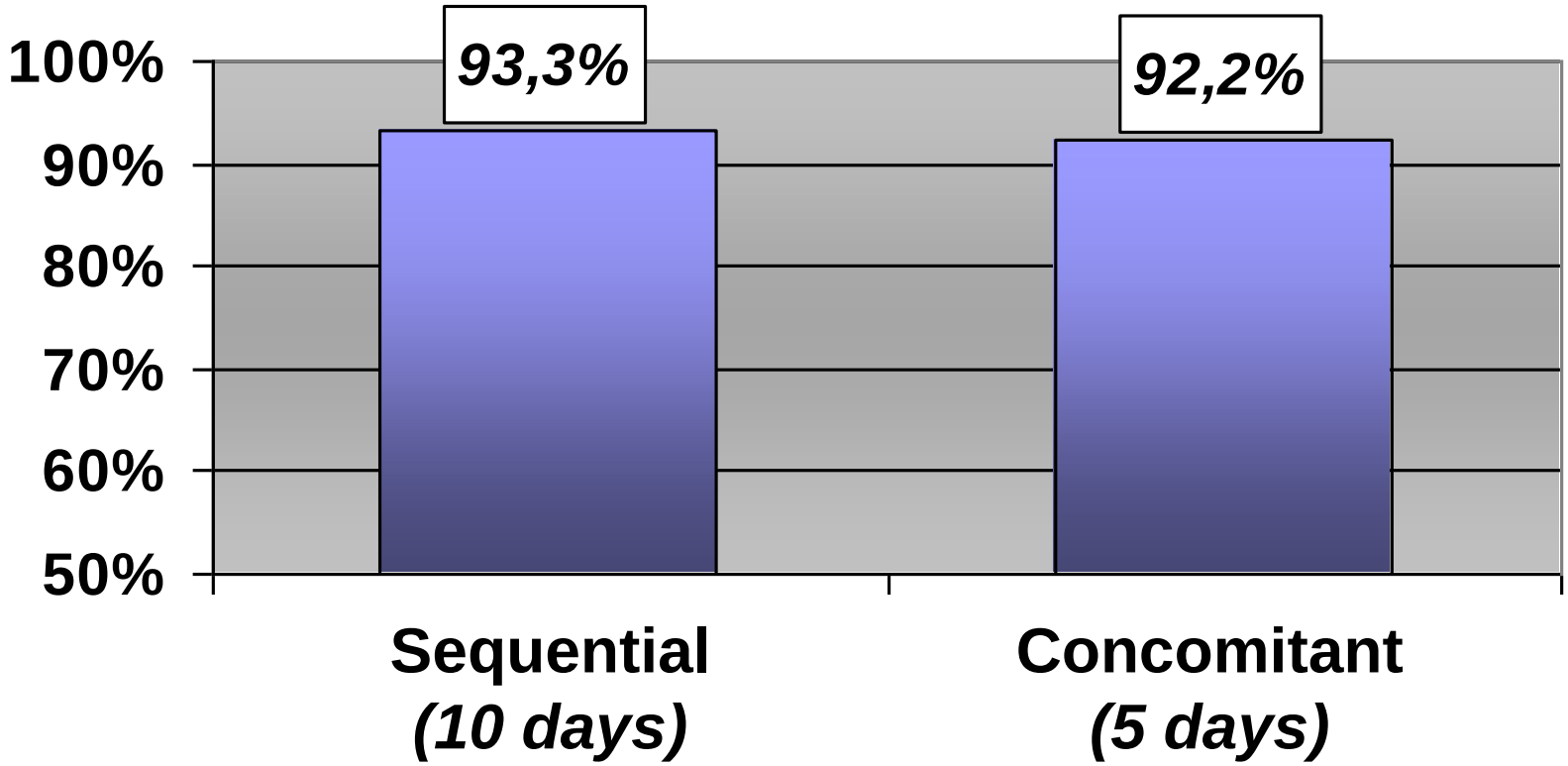
Outcome of sequential therapy vs 7-10 days triple therapies stratified by the use of metronidazole or tinidazole:

A pool analysis

	Sequential therapy using Metronidazole = n. 6 studies OR (95%CI)	Sequential therapy using Tinidazole = n.3 studies OR (95%CI)
ITT analysis	1.4 (0.67 - 2.88)	**1.43 (1.02 -2.0)**
PP analysis	**2.17 (1.67- 2.82)**	1.7 (0.95-3.07)

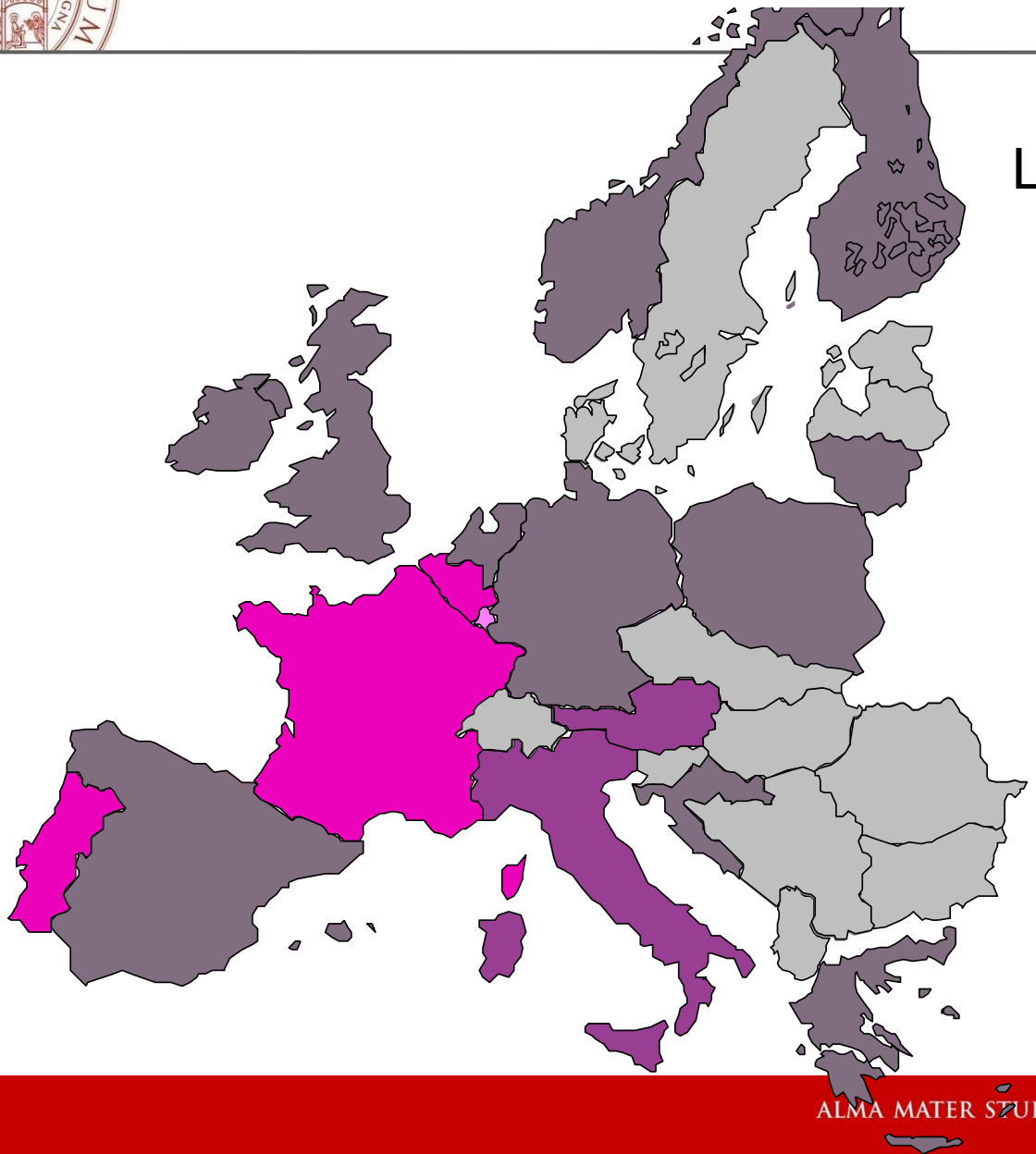
Kim JS et al. Clin and Res in Hepatol and Gastroenterol 2014

Levoxacin-containing Sequential and Concomitant therapies for *H.pylori* eradication



Federico et al. Gastroenterology 2012

Rising rates of levofloxacin resistance should be taken into account

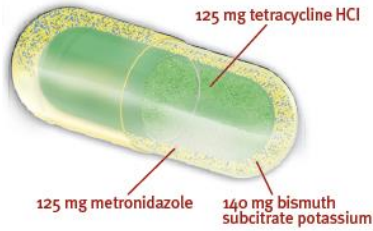


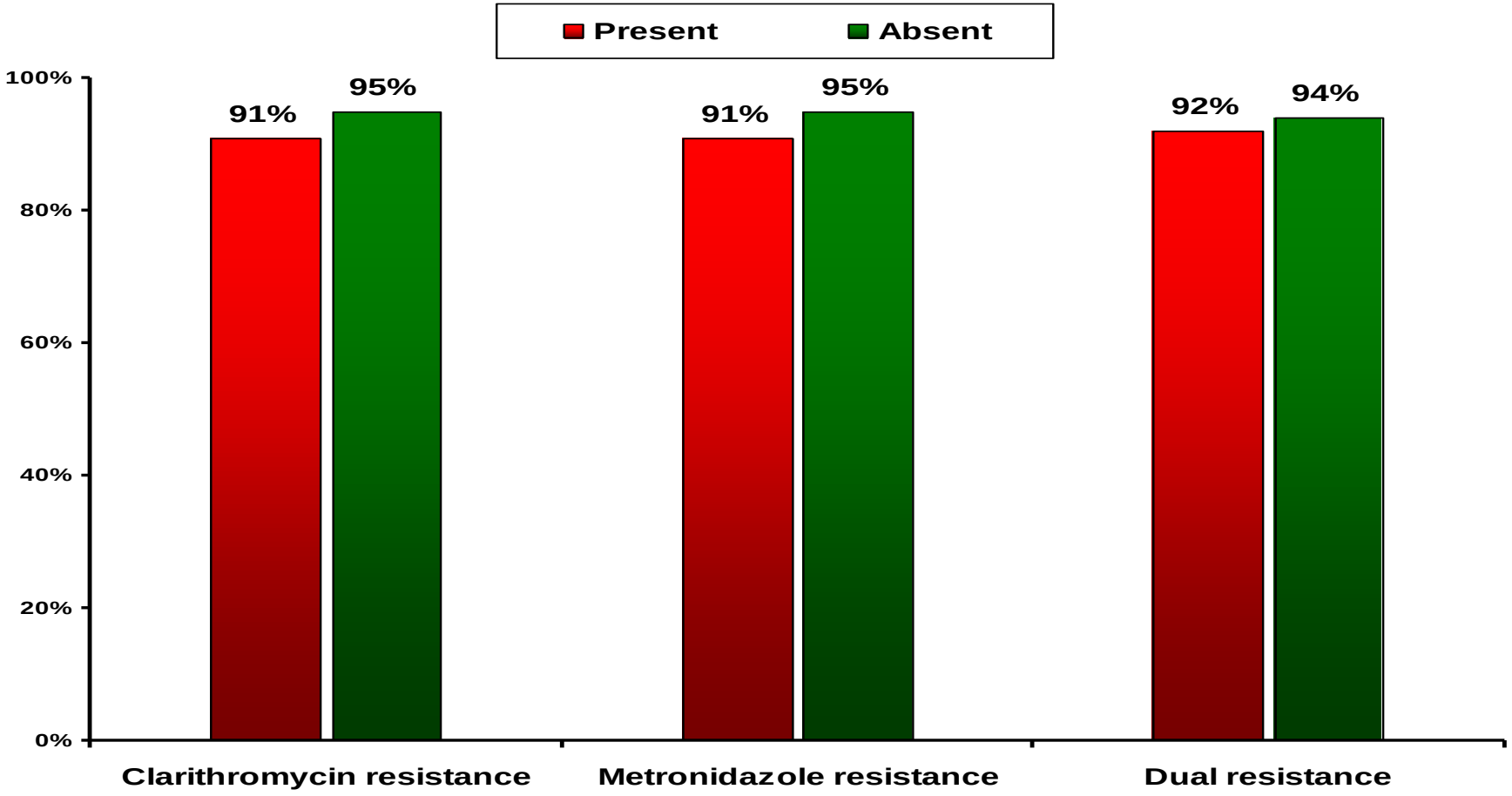
Levofloxacin resistance of H. pylori in adults (n:1860)

- ≥ 20%
- 15-20%
- <15 %
- No Data

Megraud et al. GUT 2012

Quadruple Therapy Using a 3-in-1 Capsule of Bismuth Subcitrate Potassium, Metronidazole, and Tetracycline (Pylera®)





Malfertheiner et al, Lancet 2012

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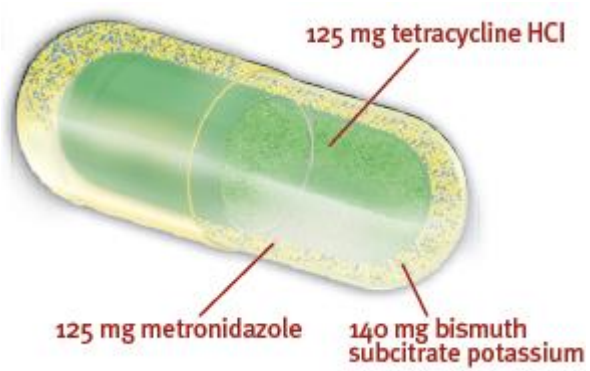


10 day therapy

PPI x 2 / day

Pylera® : 3 capsules x 4 / day

2 large multicentre randomized controlled studies

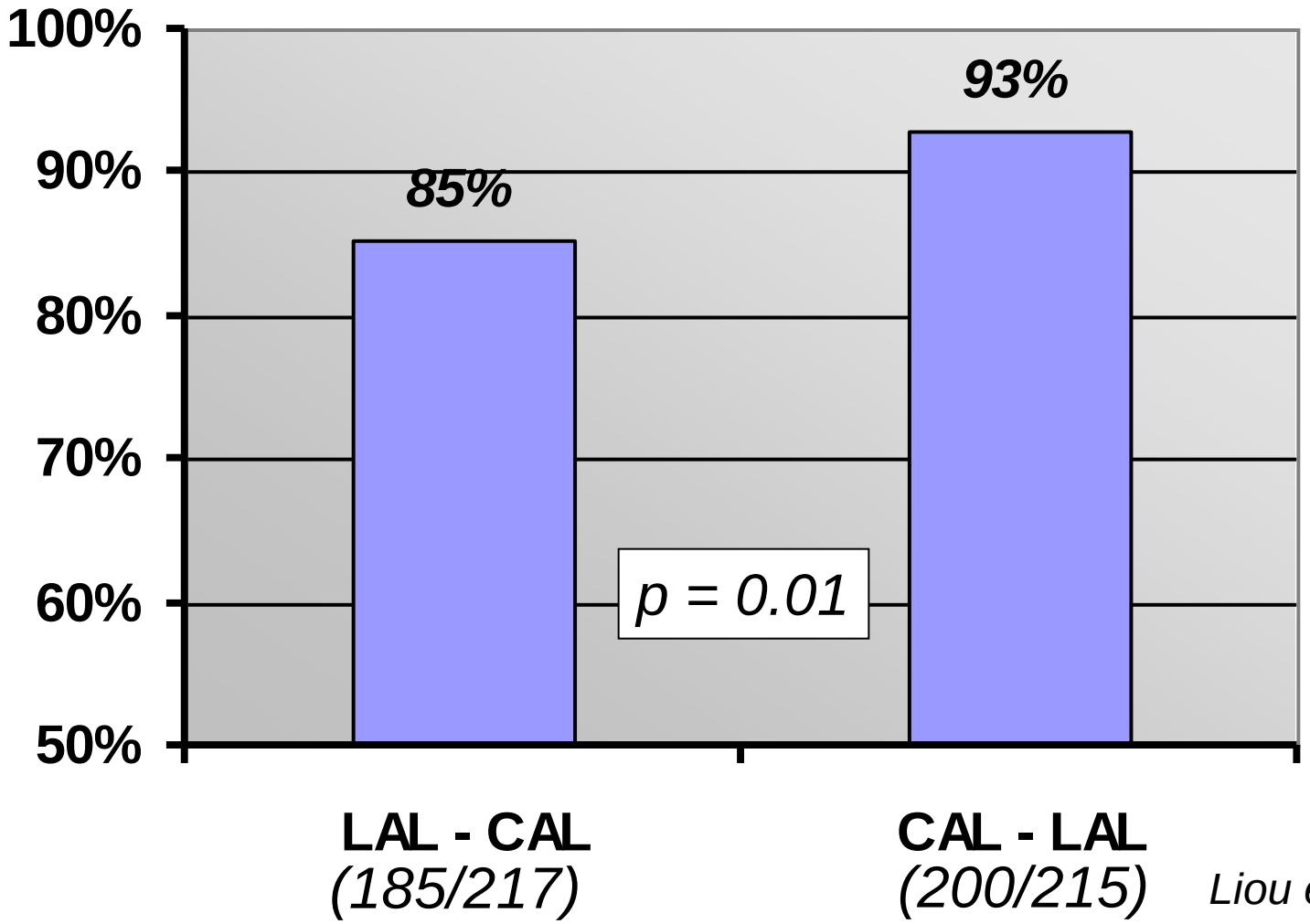
in USA and Europe, for first line treatment

Pylera ® : Registration in Europe granted on July, 6, 2011.
Local translations of the Marketing Authorizations are pending.
In combination with omeprazole, Pylera ® is indicated for the eradication of *Helicobacter pylori* and prevention of relapse of peptic ulcers in patients with active or a history of *H. pylori* associated ulcers.

Laine et al. AJG 2003, Malfertheiner et al. Lancet 2011

Levofloxacin (LAL) and Clarithromycin (CAL) triple therapies as first- and second-line treatments

Randomised comparative trial with crossover design

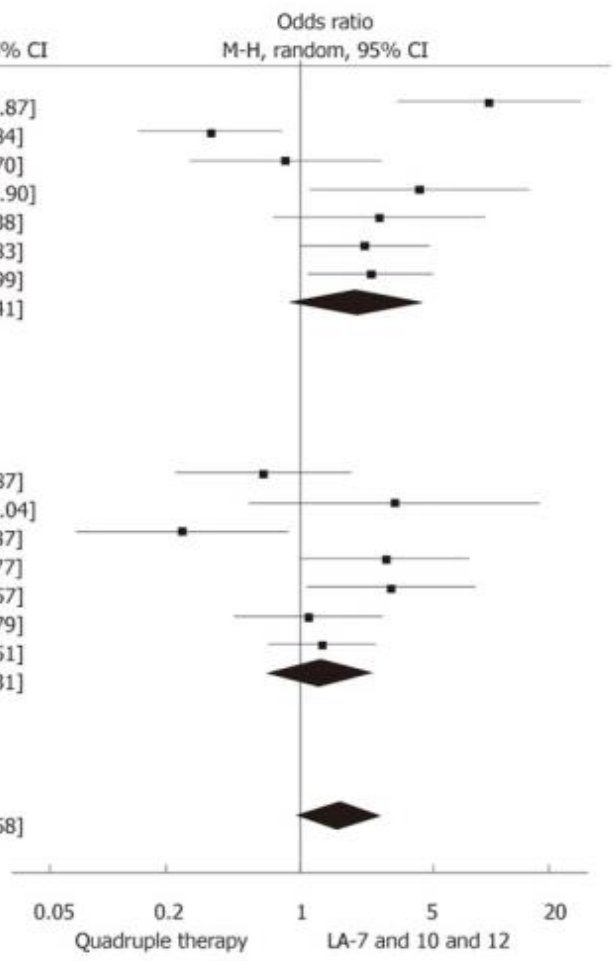


Liou et al, GUT 2010

Second-line therapy

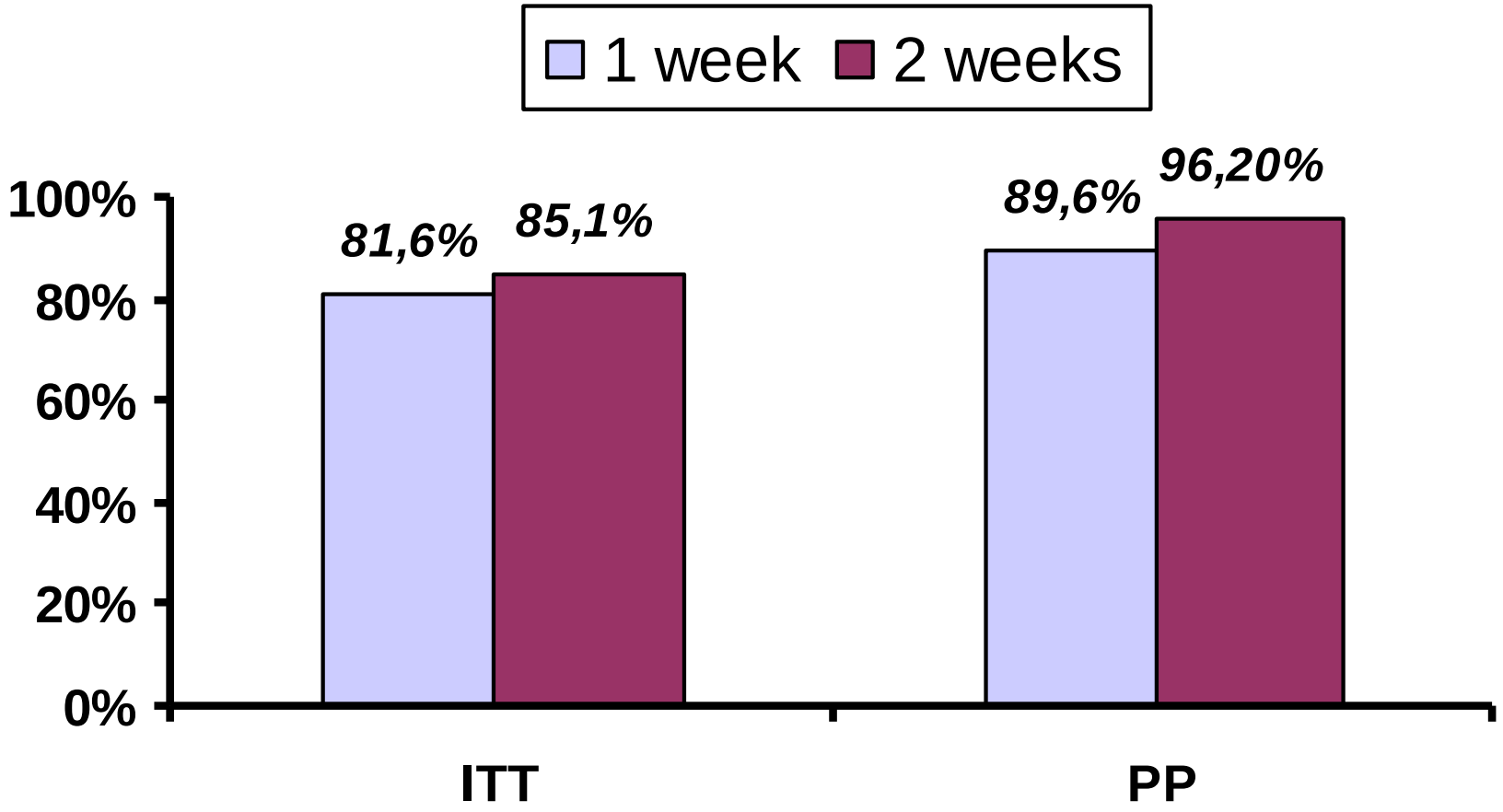
Bismuth quadruple *vs* Levofloxacin triple therapy

Study or subgroup	LA 7 and 10 and 12 Events	Total	Quadruple therapy Events	Total	Weight	Odds ratio M-H, random, 95% CI
1.4.1 Caucasian						
Nista *et al*[21]	66	70	44	70	6.9%	9.75 [3.18, 29.87]
Perri *et al*[29]	37	58	46	55	8.0%	0.34 [0.14, 0.84]
Orsi *et al*[38]	43	50	44	50	6.7%	0.84 [0.26, 2.70]
Bilardi *et al*[39]	16	23	6	17	6.0%	4.19 [1.10, 15.90]
Nista *et al*[35]	26	30	25	35	6.2%	2.60 [0.72, 9.38]
Nista *et al*[36]	79	96	34	50	8.4%	2.19 [0.99, 4.83]
Gisbert *et al*[28]	83	112	21	38	8.6%	2.32 [1.08, 4.99]
Subtotal (95% CI)		439		315	50.7%	1.99 [0.90, 4.41]
Total events	350		220			
Heterogeneity: $Tau^2 = 0.87$; $\chi^2 = 26.07$, df = 6 ($P = 0.0002$); $I^2 = 77\%$						
Test for overall effect: $Z = 1.69$ ($P = 0.09$)						
1.4.2 Asian						
Wong *et al*[44]	21	33	22	30	7.1%	0.64 [0.22, 1.87]
Lee *et al*[80]	5	9	4	14	4.5%	3.13 [0.54, 18.04]
Wong *et al*[19]	19	31	26	30	6.2%	0.24 [0.07, 0.87]
Zhang *et al*[43]	42	49	30	44	7.3%	2.80 [1.01, 7.77]
Zhang *et al*[37]	42	48	33	47	7.2%	2.97 [1.03, 8.57]
Jung *et al*[42]	16	31	22	45	7.8%	1.12 [0.45, 2.79]
Kuo *et al*[41]	58	83	53	83	9.1%	1.31 [0.69, 2.51]
Subtotal (95% CI)		284		293	49.3%	1.27 [0.70, 2.31]
Total events	203		190			
Heterogeneity: $Tau^2 = 0.35$; $\chi^2 = 13.88$, df = 6 ($P = 0.03$); $I^2 = 57\%$						
Test for overall effect: $Z = 0.79$ ($P = 0.43$)						
Total (95% CI)		723		608	100.0%	1.59 [0.98, 2.58]
Total events	553		410			
Heterogeneity: $Tau^2 = 0.57$; $\chi^2 = 41.66$, df = 13 ($P < 0.0001$); $I^2 = 69\%$						
Test for overall effect: $Z = 1.86$ ($P = 0.06$)						
Test for subgroup differences: $\chi^2 = 0.77$, df = 1 ($P = 0.38$); $I^2 = 0\%$						



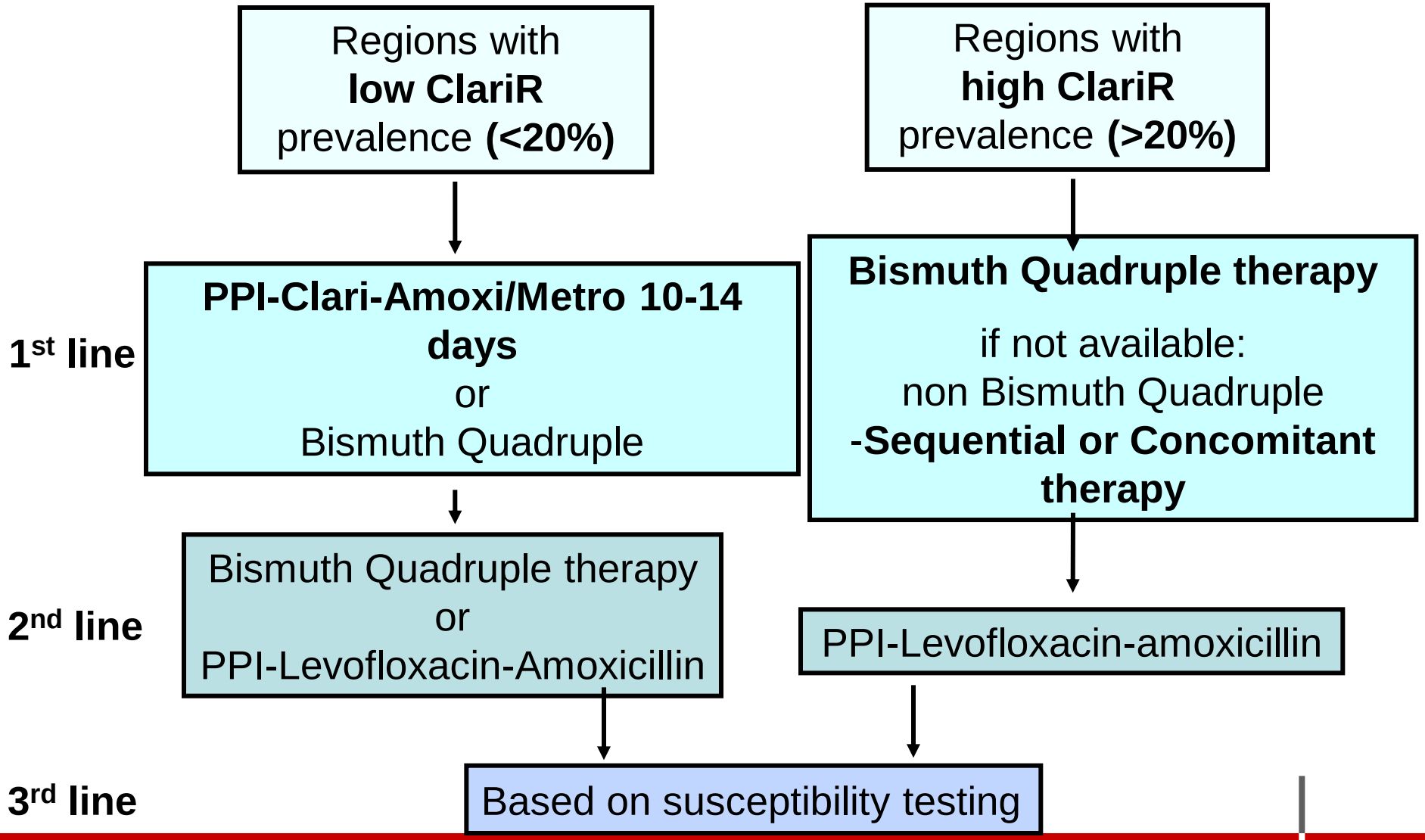
Di Caro S et al,WJG 2013

Second-line therapy
Duration of Bismuth quadruple therapy

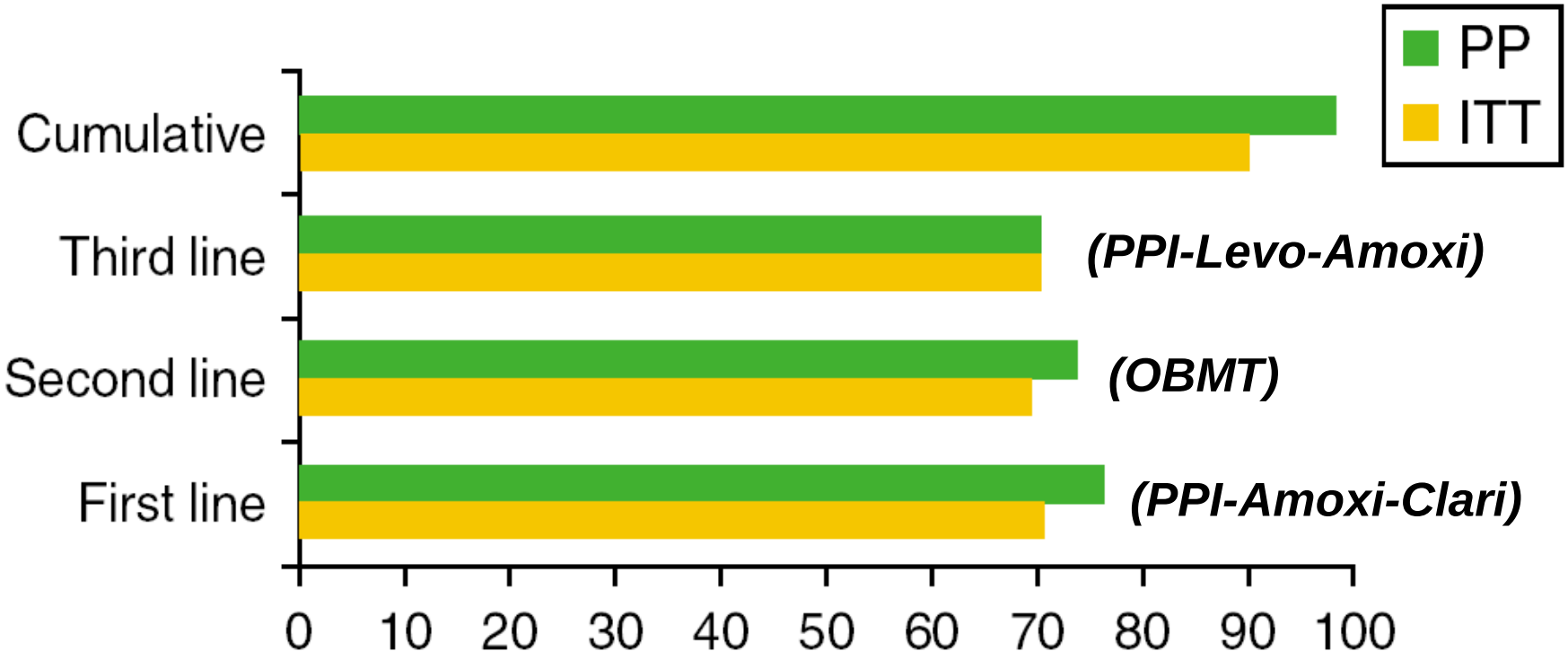


Chung et al. Helicobacter 2011

Maastricht/Florence IV: Treatment of *Helicobacter pylori* infection



Cumulative *H.pylori* Eradication Rates in Clinical Practice by Adopting an Empirical Third-Line Regimen



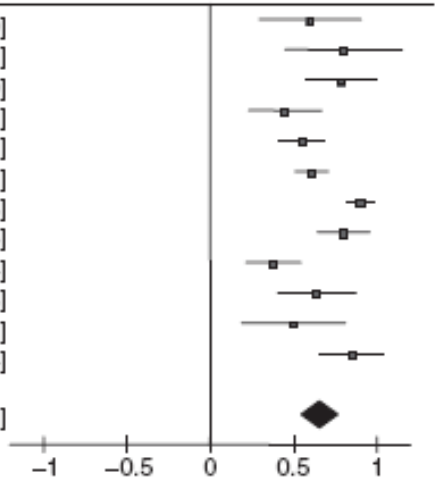
Rokkas et al. AJG 2009

Rifabutin in the treatment of refractory *H.pylori* infection

Third-line

Study or subgroup	Eradication rate	SE	Weight (%)	IV, Random, 95% CI
Beales 2001 2tx	0.6	0.15491933	6.3	0.60 [0.30, 0.90]
Bock 2000 2tx	0.8	0.17888544	5.5	0.80 [0.45, 1.15]
Gisbert 2003 2tx	0.79	0.10885771	8.1	0.79 [0.58, 1.00]
Gisbert 2006 2tx	0.45	0.11124298	8.0	0.45 [0.23, 0.67]
Gisbert 2008 2tx	0.55	0.06966305	9.8	0.55 [0.41, 0.69]
Gonzalez-Carro 2007 2tx	0.61	0.05085145	10.5	0.61 [0.51, 0.71]
Miehlke 2008 2tx	0.9	0.04160251	10.8	0.90 [0.82, 0.98]
Perri 2000 2tx	0.8	0.08	9.4	0.80 [0.64, 0.96]
Qasim 2005 2tx	0.38	0.08324309	9.2	0.38 [0.22, 0.54]
Van der Poorten 2007 2tx	0.64	0.12	7.7	0.64 [0.40, 0.88]
Van Zanten 2010 2tx	0.5	0.15811388	6.2	0.50 [0.19, 0.81]
Zullo 2010 2tx	0.85	0.09903379	8.6	0.85 [0.66, 1.04]
Total (95% CI)			100.0	0.66 [0.55, 0.77]

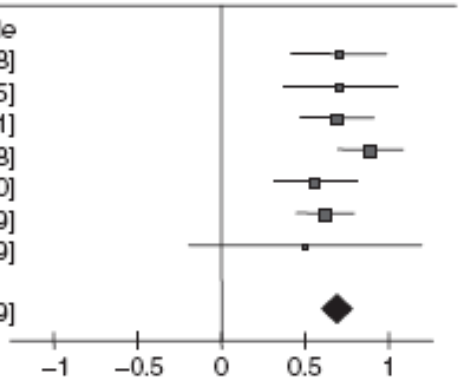
Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 57.79$, df = 11 ($P < 0.00001$); $I^2 = 81\%$
Test for overall effect: $Z = 11.42$ ($P < 0.00001$)



Fourth- or fifth-line

Study or subgroup	Eradication rate	SE	Weight (%)	IV, Fixed, 95% CI
Bock 2000 3tx	1	0		Not estimable
Canducci 2001 ≥3tx	0.7	0.14491377	10.2	0.70 [0.42, 0.98]
Gisbert 2008 3tx	0.71	0.17150593	7.3	0.71 [0.37, 1.05]
Miehlke 2008 3tx	0.69	0.11217109	17.0	0.69 [0.47, 0.91]
Miehlke 2008 ≥4tx	0.89	0.09894443	21.8	0.89 [0.70, 1.08]
Perri 2000 ≥3tx	0.56	0.12409674	13.9	0.56 [0.32, 0.80]
Van der Poorten 2007 ≥3tx	0.62	0.08717798	28.1	0.62 [0.45, 0.79]
Van Zanten 2010 3tx	0.5	0.35355339	1.7	0.50 [−0.19, 1.19]
Total (95% CI)			100.0	0.70 [0.60, 0.79]

Heterogeneity: $\chi^2 = 6.12$, df = 6 ($P = 0.41$); $I^2 = 2\%$
Test for overall effect: $Z = 15.03$ ($P < 0.00001$)



Gisbert and Calvet, APT 2012

Rifabutin as forth-line therapy for refractory *H.pylori* infection

- ✓ Cure rate: 60-70%
- ✓ Mean rate of adverse effects 22% (19-25%)
- ✓ Severe leucopenia and thrombocytopenia have been reported
- ✓ Increasing multiresistant strains of *M.tuberculosis*
- ✓ Mean *H.pylori* rifabutin resistance rate 1.3% (95%CI = 0.9-1.7%)

Rifabutin in the treatment of refractory *H.pylori* infection

- ✓ Very expensive
- ✓ Mean rate of ad (19-25%)
- ✓ Severe leucop ytopenia have been reporte
- ✓ Increasing r of *M.tuberculosis*
- ✓ Mean *H.pylori* nce rate 1.3% (95%CI = 0.9-1.7%)

Conclusions

- ✓ **Two weeks triple therapy, sequential therapy and concomitant therapy** can all be effective first-line regimens in Italy.
- ✓ However, a future increase of antibiotic resistance is likely to affect all these regimens.
- ✓ **Levofloxacin-based therapies** can be reliably used as **second-line therapy**, but also as first line. However rising rates of resistance should be taken into account
- ✓ Bismuth quadruple therapy when available may be consistently effective treatment for second line treatment.

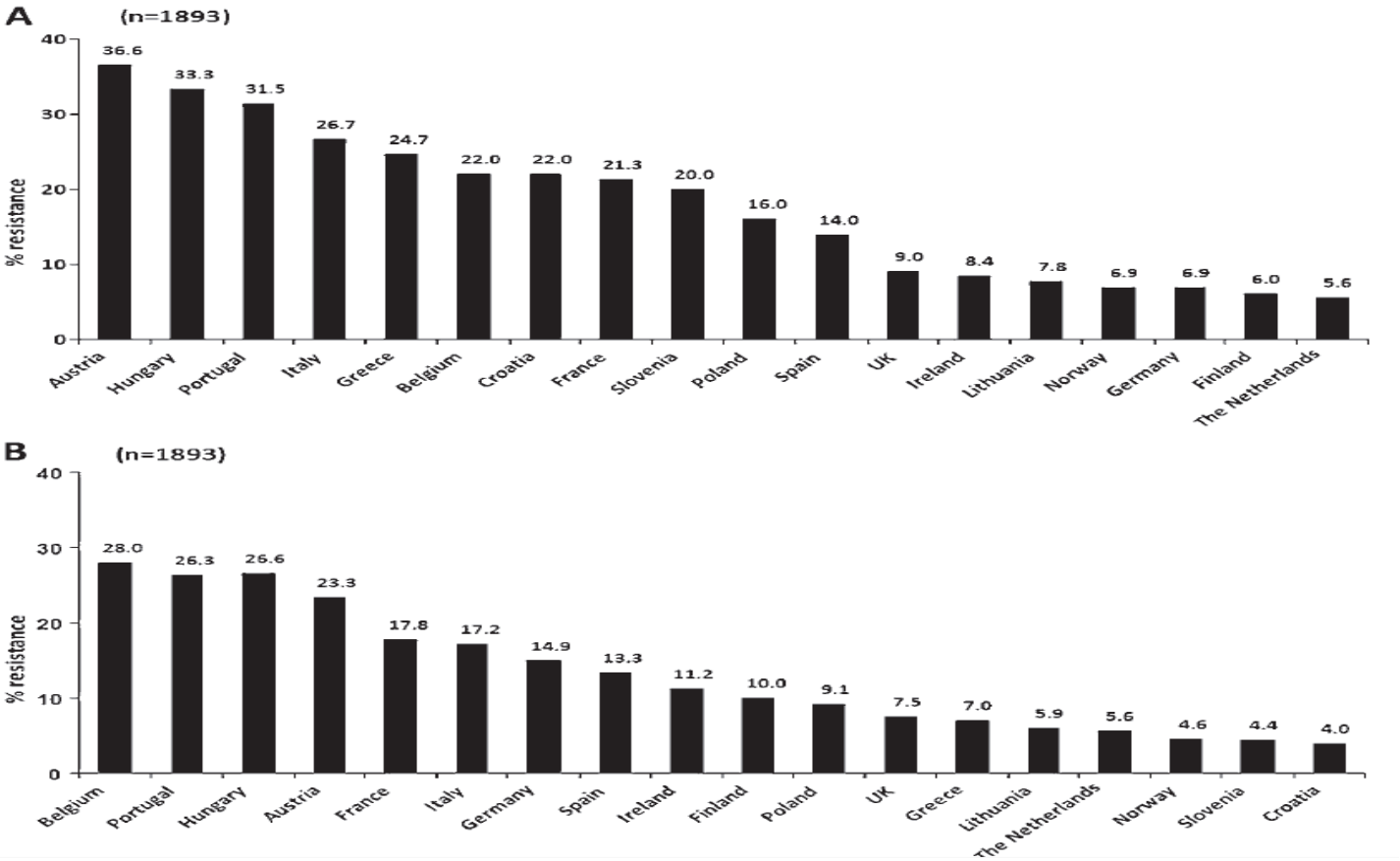
H. pylori clarithromycin resistance in Italy

	No of patients	Sex (Male/Female)	Age (Mean ± SD)	Disease (NUD/PUD)*	Resistance N (%)
Northern Italy					
Lombardia	22	8/14	58.9±16.4	14/8	3 (13.6%)
Liguria	15	7/8	56.5±13.5	14/1	1 (6.7%)
Veneto	16	7/9	48.5±15.1	16/0	1 (6.3%)
Emilia Romagna	10	4/6	47.5±16.0	8/2	0 (0.0%)
Central Italy					
Toscana	20	8/12	57.9±14.7	19/1	3 (15%)
Abruzzo	28	10/18	48.9±12.1	24/4	2 (7.1%)
Lazio	21	11/10	55.2±11.9	14/7	2 (9.5%)
Southern Italy					
Calabria	20	10/10	48.8±15.4	14/6	2 (10.0%)
Campania	19	10/9	54.4±19.0	19/0	2 (10.5%)
Basilicata	20	11/9	49.0±15.1	16/4	0 (0.0%)
Puglia	21	6/15	52.8±15.4	19/2	4 (19.1%)
Sardinia	21	11/10	46.1±15.2	15/6	0 (0.0%)
Sicily	20	11/9	44.6±18.7	17/3	5 (25.0%)
Overall	253	114/139	51.5±15.6	209/44	25 (9.9%)

*NUD: non-ulcer dyspepsia; PUD: peptic ulcer

De Francesco V, Dig Liver Dis 2011

H. pylori resistance to clarithromycin (A) and levofloxacin (B) in Italy: data from an european survey including a total of 1893 patients in 2008-2009



Several of the larger countries (**Italy**, Germany,UK and Poland) recruited fewer patients than expected

Megraud F. et al, Gut 2013

Primary *H.pylori* antibiotic resistance in 145 dispeptic patients in Bologna

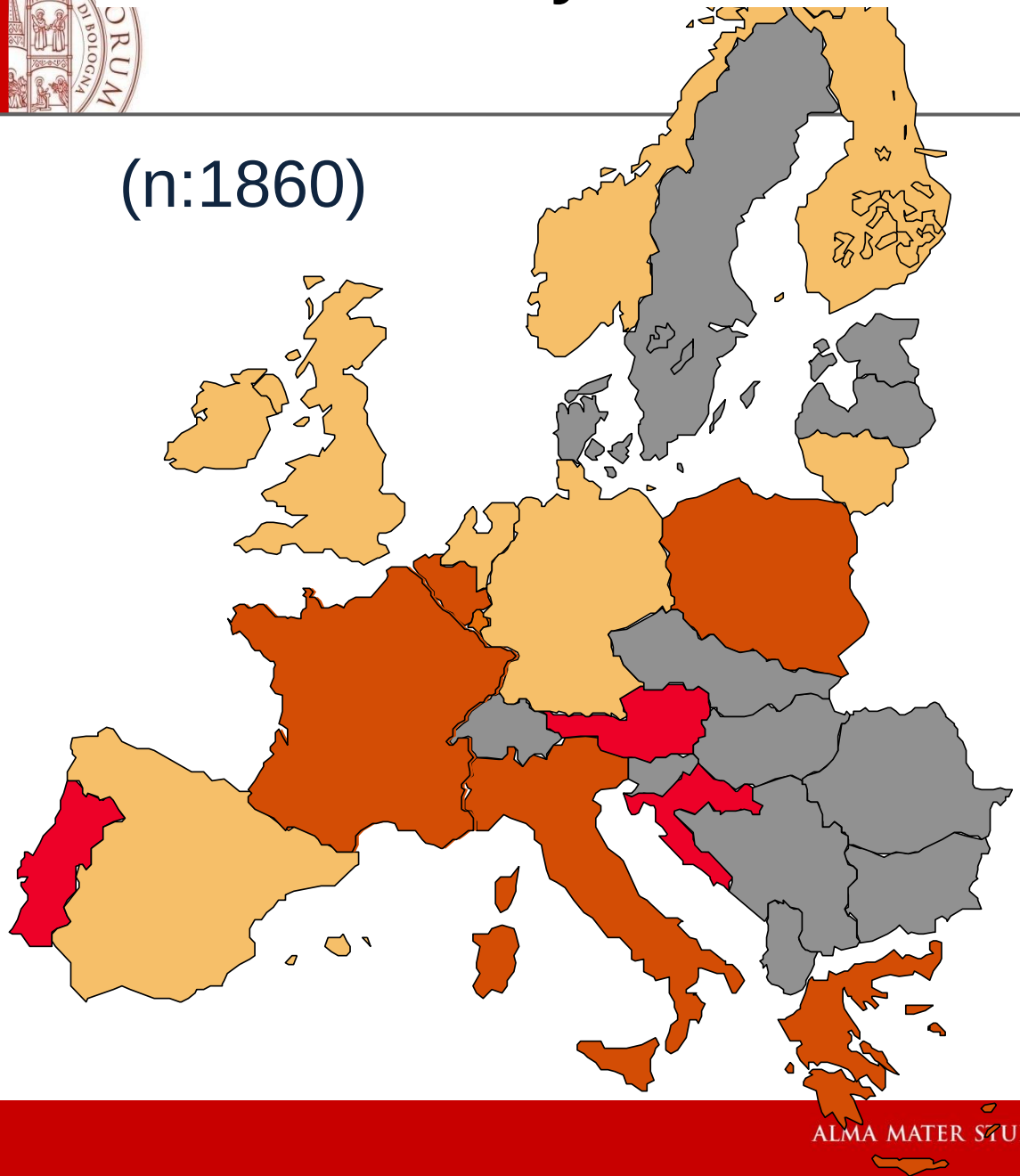
Antibiotic	Resistent Strains n (%)
Metronidazole	86 (59.3%)
Clarithromycin	51 (35.2%)
Levofloxacin	32 (22.1%)

Antibiotic	Resistant strains; N (%)
Clarithromycin	11 (7.6)
Metronidazole	41 (28.3)
Levofloxacin	8 (5.5)
Clarithromycin plus metronidazole	27 (18.6)
Clarithromycin plus levofloxacin	6 (4.1)
Clarithromycin plus metronidazole plus levofloxacin	7 (4.8)
Metronidazole plus levofloxacin	11 (7.6)

Saracino et al. J Gastrointestin Liv Dis 2012

Clarithromycin resistance in Europe

(n:1860)



≥ 30%

10%-30%

<10 %

No Data

F. Megraud et al. GUT 2013

H. pylori resistance to antibiotics according to country of residence in Europe

European region	No. of resistant strains/No. tested	% Resistance	95% CI
Clarithromycin			
Northern	31/401	7.7	5.4 to 10.7
Western/Central	136/725	18.7	16.1 to 21.7
Southern	165/767	21.5	19.9 to 25.5
Levofloxacin			
Northern	31/401	7.7	5.4 to 10.7
Western/Central	135/725	18.6	15.9 to 21.6
Southern	101/767	13.1	11.0 to 15.8
Metronidazole			
Northern	115/401	28.6	24.3 to 33.1
Western/Central	318/725	43.8	40.2 to 47.3
Southern	228/767	29.7	26.5 to 32.9

Northern Europe: Finland, Ireland, Lithuania, Norway, The Netherlands, UK.
Western/Central Europe: Austria, Belgium, France, Germany, Hungary, Poland.
Southern Europe: Croatia, Greece, Italy, Portugal, Slovenia, Spain.

Megraud F, Gut 2013

Maastricht/Florence IV: Treatment of *Helicobacter pylori* infection

	Regions with **low ClariR** prevalence **(<20%)**	Regions with **high ClariR** prevalence **(>20%)**
1st line	PPI-Clari-Amoxi/Metro 10-14 days or Bismuth Quadruple therapy	Bismuth Quadruple therapy if not available: non Bismuth Quadruple (either Sequential or Concomitant therapy)
2nd line		
3rd line		

Malfertheiner et al, GUT 2012