

## **Supplementary Appendix 2**

Table 1. The prevalence of clarithromycin resistance in countries of included RCTs (page 2-3)

Figure 1a, 1b. Network meta-analysis of regimens in countries with high- and low-clarithromycin resistance (page 4-5)

Figure 2a, 2b. Estimation of effect sizes in subgroup of high- and low-clarithromycin resistant countries (page 6)

Reference (page 7-9)

**Table 1. The prevalence of clarithromycin resistance in countries of included RCTs**

<b>Country</b>	<b>Rate %</b>	<b>Number of participant</b>
Chile[1]	9	240
China[2, 3]	21.5	17731
	86.7	15
Croatia[4]	21.2	345
Ecuador[1]	7.9	63
Finland[5, 6, 7]	8	505
	2	292
	6	50 – 100
France[7, 8]	26	530
	21.3	50 – 100
Greece[7, 9, 10]	40	106
	42	57
	24.7	50 – 100
Hong Kong[11]	32	41
India[12]	45	259
Iran[13]	16	50
Italy[7, 14, 15, 16]	21.3	178
	9.9	253
	16.9	255
	26.7	50 – 100
Japan[17]	28.8	1005
	55.6	153
Kenya[18]	0	70
Korea[19, 20]	7	71
	12.4	113
Kuwait[21]	0	63
Mexico[1]	13	676

Morocco[22]	28.2	78
Spain[7, 23]	35.6	118
	14	50 – 100
Saudi Arabia[24]	27.7	137
Singapore[25]	15.6	488
Taiwan[26, 27, 28]	10.6	180
	7.9	1395
	5.5	307
Thailand[29, 30]	11.3	151
	3.7	400
Turkey[31, 32, 33, 34]	36.7	98
	48.2	110
	40.5	37
	16.4	213
UK[7]	9	50 – 100
USA[35]	12.9	347

**Figure 1. Network meta-analysis of regimens in countries with high clarithromycin resistance (>15%)**

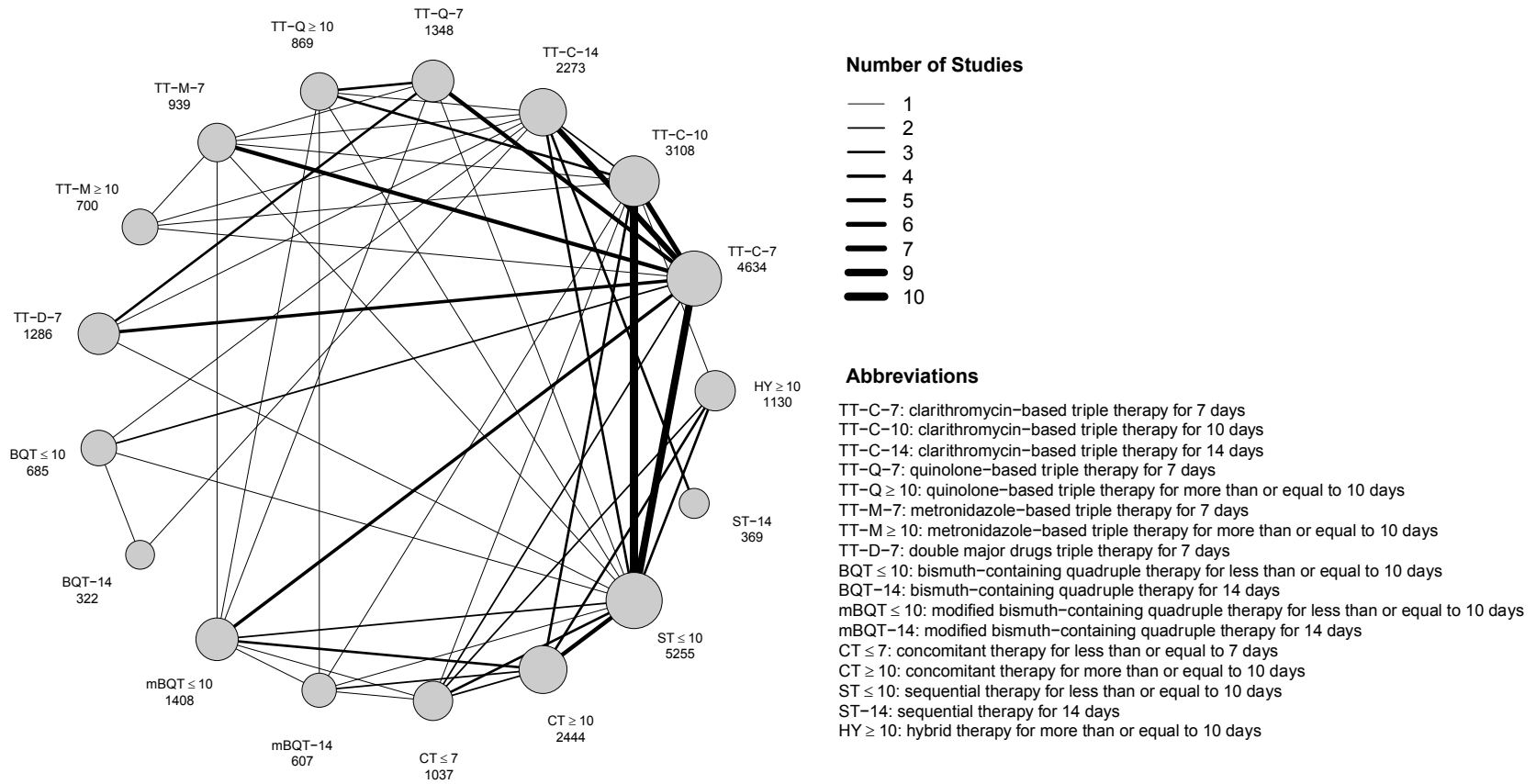
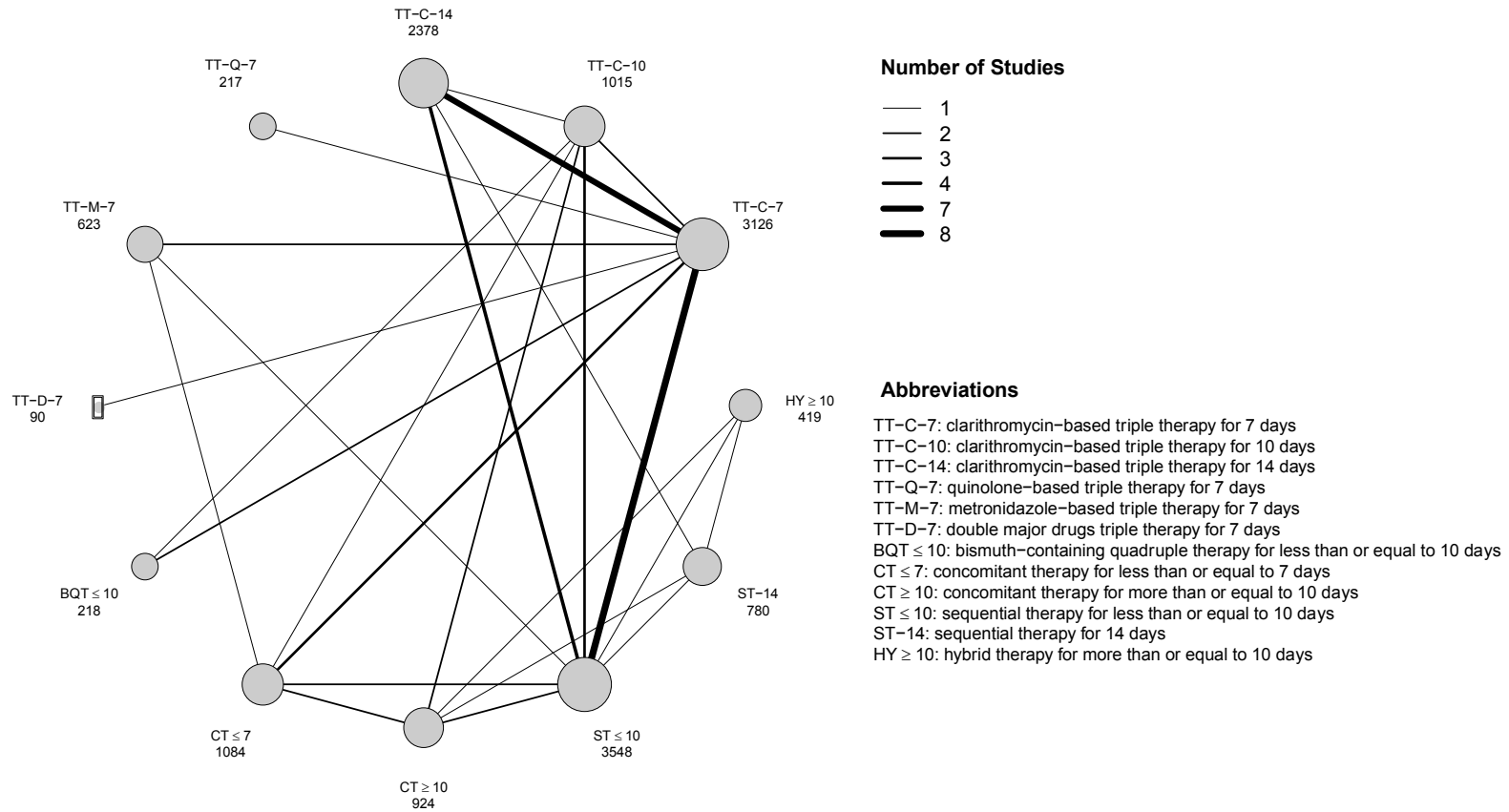
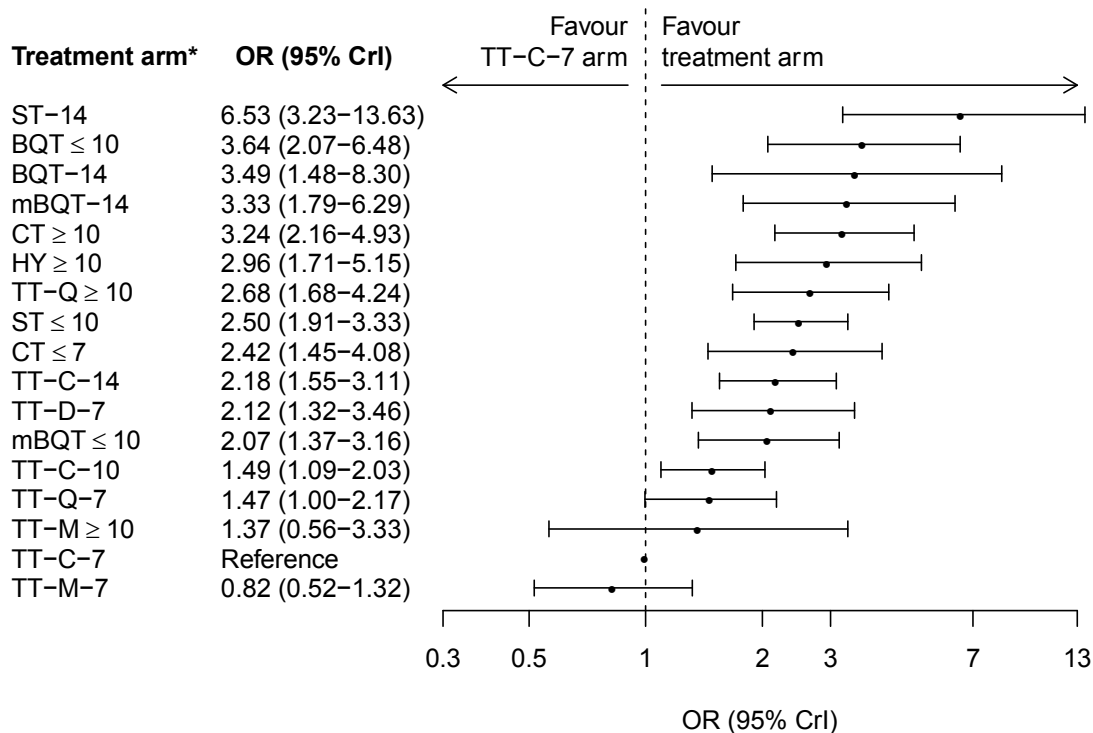


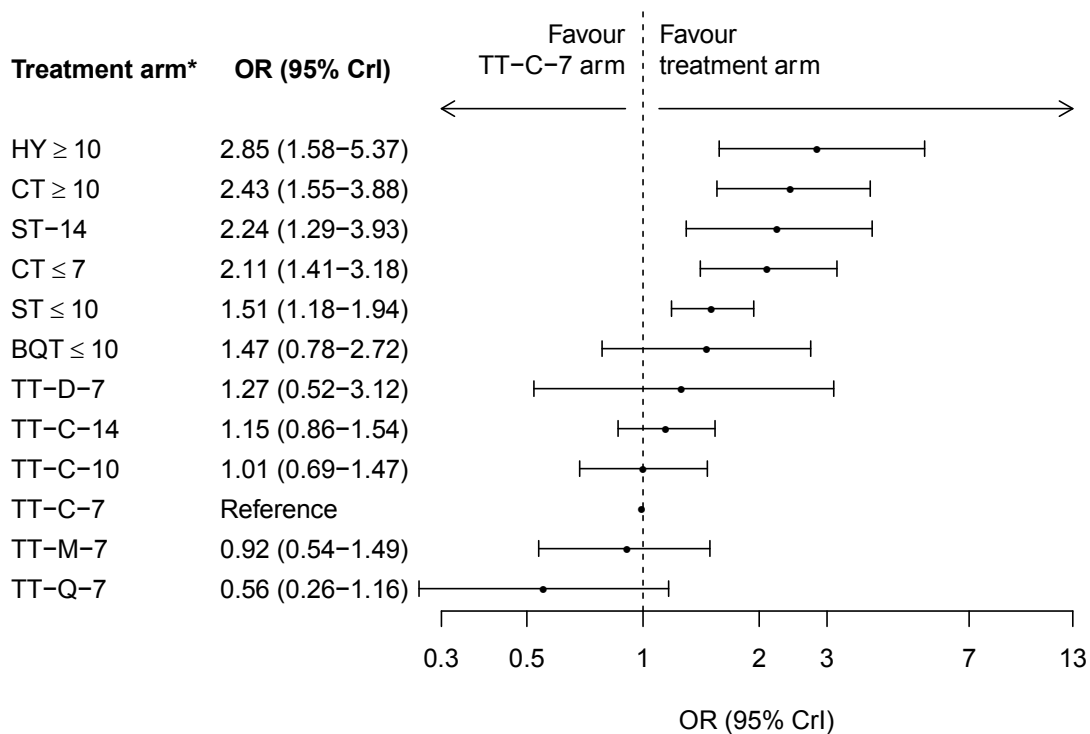
Figure 1b. Network meta-analysis of regimens in countries with low clarithromycin resistance (<15%)



**Figure 2a. Estimation of effect sizes in subgroup of high clarithromycin resistance (>15%)**



**Figure 2b. Estimation of effect sizes in subgroup of low clarithromycin resistance (<15%)**



## Reference

- 1 Camargo MC, Garcia A, Riquelme A, Otero W, Camargo CA, Hernandez-Garcia T, *et al.* The problem of *Helicobacter pylori* resistance to antibiotics: a systematic review in Latin America. *Am J Gastroenterol* 2014;**109**:485-95.
- 2 Su P, Li Y, Li H, Zhang J, Lin L, Wang Q, *et al.* Antibiotic resistance of *Helicobacter pylori* isolated in the Southeast Coastal Region of China. *Helicobacter* 2013;**18**:274-9.
- 3 Zhen-Hua Z, De-Qiang H, Yong X, Lin-Lin L, Nong-Hua L. Characterization of 23S rRNA gene mutation in primary and secondary clarithromycin-resistant *Helicobacter pylori* strains from East China. *Turk J Gastroenterol* 2013;**24**:5-9.
- 4 Tonkic A, Tonkic M, Brnic D, Novak A, Puljiz Z, Simunic M. Time trends of primary antibiotic resistance of *Helicobacter pylori* isolates in Southern Croatia. *J Chemother* 2012;**24**:182-4.
- 5 Kostamo P, Veijola L, Oksanen A, Sarna S, Rautelin H. Recent trends in primary antimicrobial resistance of *Helicobacter pylori* in Finland. *Int J Antimicrob Agents* 2011;**37**:22-5.
- 6 Koivisto TT, Rautelin HI, Voutilainen ME, Niemela SE, Heikkinen M, Sipponen PI, *et al.* Primary *Helicobacter pylori* resistance to metronidazole and clarithromycin in the Finnish population. *Aliment Pharmacol Ther* 2004;**19**:1009-17.
- 7 Megraud F, Coenen S, Versporten A, Kist M, Lopez-Brea M, Hirschl AM, *et al.* *Helicobacter pylori* resistance to antibiotics in Europe and its relationship to antibiotic consumption. *Gut* 2013;**62**:34-42.
- 8 Raymond J, Lamarque D, Kalach N, Chaussade S, Burucoa C. High level of antimicrobial resistance in French *Helicobacter pylori* isolates. *Helicobacter* 2010;**15**:21-7.
- 9 Georgopoulos SD, Xirouchakis E, Martinez-Gonzalez B, Sgouras DN, Spiliadi C, Mentis AF, *et al.* Clinical evaluation of a ten-day regimen with esomeprazole, metronidazole, amoxicillin, and clarithromycin for the eradication of *Helicobacter pylori* in a high clarithromycin resistance area. *Helicobacter* 2013;**18**:459-67.
- 10 Karamanolis GP, Daikos GL, Xouris D, Goukos D, Delladetsima I, Ladas SD. The evolution of *Helicobacter pylori* antibiotics resistance over 10 years in Greece. *Digestion* 2014;**90**:229-31.
- 11 Lee CC, Lee VW, Chan FK, Ling TK. Levofloxacin-resistant *Helicobacter pylori* in Hong Kong. *Chemotherapy* 2008;**54**:50-3.
- 12 Thyagarajan SP, Ray P, Das BK, Ayyagari A, Khan AA, Dharmalingam S, *et al.* Geographical difference in antimicrobial resistance pattern of *Helicobacter pylori*

- clinical isolates from Indian patients: Multicentric study. *J Gastroenterol Hepatol* 2003;**18**:1373-8.
- 13 Sadeghifard N, Seidnazari T, Ghafourian S, Soleimani M, Maleki A, Qomi MA, *et al.* Survey in Iran of clarithromycin resistance in *Helicobacter pylori* isolates by PCR-RFLP. *Southeast Asian J Trop Med Public Health* 2013;**44**:89-95.
- 14 De Francesco V, Margiotta M, Zullo A, Hassan C, Giorgio F, Burattini O, *et al.* Prevalence of primary clarithromycin resistance in *Helicobacter pylori* strains over a 15 year period in Italy. *J Antimicrob Chemother* 2007;**59**:783-5.
- 15 De Francesco V, Giorgio F, Ierardi E, Zotti M, Neri M, Milano A, *et al.* Primary clarithromycin resistance in *Helicobacter pylori*: the Multicentric Italian Clarithromycin Resistance Observational (MICRO) study. *J Gastrointest Liver Dis* 2011;**20**:235-9.
- 16 Zullo A, Perna F, Hassan C, Ricci C, Saracino I, Morini S, *et al.* Primary antibiotic resistance in *Helicobacter pylori* strains isolated in northern and central Italy. *Aliment Pharmacol Ther* 2007;**25**:1429-34.
- 17 Yamade M, Sugimoto M, Uotani T, Nishino M, Kodaira C, Furuta T. Resistance of *Helicobacter pylori* to quinolones and clarithromycin assessed by genetic testing in Japan. *J Gastroenterol Hepatol* 2011;**26**:1457-61.
- 18 Kimang'a AN, Revathi G, Kariuki S, Sayed S, Devani S. *Helicobacter pylori*: prevalence and antibiotic susceptibility among Kenyans. *S Afr Med J* 2010;**100**:53-7.
- 19 An B, Moon BS, Kim H, Lim HC, Lee YC, Lee G, *et al.* Antibiotic resistance in *Helicobacter pylori* strains and its effect on *H. pylori* eradication rates in a single center in Korea. *Ann Lab Med* 2013;**33**:415-9.
- 20 Kim N, Kim JM, Kim CH, Park YS, Lee DH, Kim JS, *et al.* Institutional difference of antibiotic resistance of *Helicobacter pylori* strains in Korea. *J Clin Gastroenterol* 2006;**40**:683-7.
- 21 John Albert M, Al-Mekhaizeem K, Neil L, Dhar R, Dhar PM, Al-Ali M, *et al.* High prevalence and level of resistance to metronidazole, but lack of resistance to other antimicrobials in *Helicobacter pylori*, isolated from a multiracial population in Kuwait. *Aliment Pharmacol Ther* 2006;**24**:1359-66.
- 22 Bouilhat N, Burucoa C, Benkirane A, El Idrissi-Lamghari A, Al Bouzidi A, El Feydi A, *et al.* High-level primary clarithromycin resistance of *Helicobacter pylori* in Morocco: a prospective multicenter molecular study. *Helicobacter* 2015;**20**:422-3.
- 23 Agudo S, Perez-Perez G, Alarcon T, Lopez-Brea M. Rapid detection of clarithromycin resistant *Helicobacter pylori* strains in Spanish patients by polymerase chain reaction-restriction fragment length polymorphism. *Rev Esp Quimioter* 2011;**24**:32-6.



- 24 Aiman MMA, H. A. Prevalence and antibiotic resistance among helicobacter pylori clinical isolates from main hospitals in the western region of Saudi Arabia. *Pak J Med Sci* 2008;**24**:100-3.
- 25 Ang TL, Fock KM, Ang D, Kwek AB, Teo EK, Dhamodaran S. The Changing Profile of Helicobacter pylori Antibiotic Resistance in Singapore: A 15-Year Study. *Helicobacter* 2016.
- 26 Chang WL, Sheu BS, Cheng HC, Yang YJ, Yang HB, Wu JJ. Resistance to metronidazole, clarithromycin and levofloxacin of Helicobacter pylori before and after clarithromycin-based therapy in Taiwan. *J Gastroenterol Hepatol* 2009;**24**:1230-5.
- 27 Liou JM, Chang CY, Chen MJ, Chen CC, Fang YJ, Lee JY, *et al.* The Primary Resistance of Helicobacter pylori in Taiwan after the National Policy to Restrict Antibiotic Consumption and Its Relation to Virulence Factors-A Nationwide Study. *PLoS One* 2015;**10**:e0124199.
- 28 Hsu PI, Wu DC, Chen WC, Tseng HH, Yu HC, Wang HM, *et al.* Randomized controlled trial comparing 7-day triple, 10-day sequential, and 7-day concomitant therapies for Helicobacter pylori infection. *Antimicrob Agents Chemother* 2014;**58**:5936-42.
- 29 Mahachai V, Sirimontaporn N, Tumwasorn S, Thong-Ngam D, Vilaichone RK. Sequential therapy in clarithromycin-sensitive and -resistant Helicobacter pylori based on polymerase chain reaction molecular test. *J Gastroenterol Hepatol* 2011;**26**:825-8.
- 30 Vilaichone RK, Gumnarai P, Ratanachu-Ek T, Mahachai V. Nationwide survey of Helicobacter pylori antibiotic resistance in Thailand. *Diagn Microbiol Infect Dis* 2013;**77**:346-9.
- 31 Caliskan R, Tokman HB, Erzin Y, Saribas S, Yuksel P, Bolek BK, *et al.* Antimicrobial resistance of Helicobacter pylori strains to five antibiotics, including levofloxacin, in Northwestern Turkey. *Rev Soc Bras Med Trop* 2015;**48**:278-84.
- 32 Onder G, Aydin A, Akarca U, Tekin F, Ozutemiz O, Ilter T. High Helicobacter pylori resistance rate to clarithromycin in Turkey. *J Clin Gastroenterol* 2007;**41**:747-50.
- 33 Sezgin O, Aslan G, Altintas E, Tezcan S, Serin MS, Emekdas G. Detection of point mutations on 23S rRNA of Helicobacter pylori and resistance to clarithromycin with PCR-RFLP in gastric biopsy specimens in Mersin, Turkey. *Turk J Gastroenterol* 2008;**19**:163-7.
- 34 Tuzun Y, Bayan K, Yilmaz S, Dursun M, Ozekinci T. The prevalence of primary and secondary Helicobacter pylori resistance to clarithromycin and probable contributing cofactors: data from southeastern Anatolia. *Hepatogastroenterology* 2008;**55**:289-93.
- 35 Duck WM, Sobel J, Pruckler JM, Song Q, Swerdlow D, Friedman C, *et al.*

Antimicrobial resistance incidence and risk factors among *Helicobacter pylori*-infected persons, United States. *Emerg Infect Dis* 2004;**10**:1088-94.