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REVIEW

Primary Antibiotic Resistance of *Helicobacter pylori* in China

Yi Hu[1] · Yin Zhu[1] · Nong-hua Lu[1]

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Abstract
Background and Aims Antibiotic resistance is the most important factor leading to the failure of eradication regimens; thus, it is important to obtain regional antibiotic resistance information. This review focuses on the prevalence of *Helicobacter pylori* primary resistance to clarithromycin, metronidazole, amoxicillin, levofloxacin, tetracycline, and furazolidone in China.
Methods We searched the PubMed, EMBASE, the China National Knowledge Infrastructure, and Chinese Biomedical databases from the earliest date of each database to October 2016. The search terms included the following: *H. pylori*, antibiotic (including clarithromycin, metronidazole, amoxicillin, levofloxacin, tetracycline, and furazolidone) resistance with or without China or different regions of China. The data analysis was performed using MedCalc 15.2.2. Each article was weighted according to the number of isolated *H. pylori* strains. A pooled proportion analysis was performed.
Results Twenty-three studies (14 studies in English and 9 in Chinese) were included in this review. A total of 6274, 6418, 3921, 5468, 2802, and 275 *H. pylori* strains were included in this review to evaluate the prevalence of *H. pylori* primary resistance to clarithromycin, metronidazole, levofloxacin, amoxicillin, tetracycline, and furazolidone, respectively. Overall, the primary resistance rates of clarithromycin, metronidazole, levofloxacin, amoxicillin, tetracycline, and furazolidone were 28.9, 63.8, 28.0, 3.1, 3.9, and 1.7%, respectively.
Conclusions In China, the prevalence of *H. pylori* primary resistance to clarithromycin, metronidazole, and levofloxacin was high and increased over time, whereas the resistance rates to amoxicillin, tetracycline, and furazolidone were low and stable over time.

Keywords *Helicobacter pylori* · Clarithromycin · Metronidazole · Levofloxacin · Resistance · China

Introduction

Helicobacter pylori (*H. pylori*), a gram-negative, spiral-shaped microaerophilic bacterium, is an important pathogen in gastrointestinal diseases because *H. pylori* infection may lead to asymptomatic chronic gastritis in 70% of the infected population, gastric ulcers in 15–20% of the infected population, dyspepsia in 10% of the infected population, and gastric cancer in 1% of the infected population [1–3]. In addition, numerous studies have implicated the role of *H. pylori* in extragastric diseases, e.g., idiopathic thrombocytopenic purpura, sideropenic anemia, and vitamin B12 deficiency [4]. The World Health Organization classified *H. pylori* as a type-1 carcinogen in 1994 [5]. The Kyoto Global Consensus reported that *H. pylori* gastritis should be defined as an infectious disease [2]. The transmission mode of *H. pylori* includes oral-oral (unhygienic feed, saliva, etc.), fecal-oral (water or food contaminated by feces), and gastro-oral (water or food contaminated by vomitus) [6]. Currently, the prevalence of *H. pylori* remains high in some areas (up to 90% in some developing countries) despite the decreasing trend of *H.*

✉ Yin Zhu
zhuyin27@sina.com.cn

✉ Nong-hua Lu
lunonghua@ncu.edu.cn

[1] Department of Gastroenterology, The First Affiliated Hospital of Nanchang University, 17 YongWaizheng Street, Donghu District, Nanchang 330006, Jiangxi Province, China

pylori prevalence observed over time [7]. Unhygienic conditions, low socioeconomic status, and improper living habits are risk factors for *H. pylori* infection [8].

China is a country with a high prevalence of *H. pylori* infection; in fact, the mean prevalence of *H. pylori* infection was 55% during the period 1983–2013 [9]. Moreover, in China, gastric cancer remained the second and third most commonly diagnosed cancers among men and women, respectively. The year 2015 presented a total of 679,100 estimated new gastric cancer cases. Moreover, gastric cancer remains the second leading cause of cancer-related death in both men and women, and the year 2015 presented a total of 498,000 estimated new gastric cancer cases [10]. Recently, Pan et al. [11] conducted a large community-based intervention trial in Linqu County. This study enrolled 184,786 residents aged 25–54 years, and the overall prevalence of *H. pylori* was 57.6%. A prospective, cross-sectional, population-based study was conducted in three cities of China to evaluate the prevalence of *H. pylori* infection in children. Among 3491 children (0–18 years), 237 (6.8%) were diagnosed as *H. pylori* positive. Additionally, an increasing rate of *H. pylori* infection with age was observed in this study [12]. Considering the poor sanitation and low socioeconomic status, *H. pylori* infection remains a serious problem in China.

Standard triple therapy consists of a proton pump inhibitor and two antibiotics, which achieved up to a 90% success rate in the early 1990s. Currently, this therapy is unacceptable as a first-line treatment for *H. pylori* because of the increasing trend of antibiotic resistance in most parts of the world [13]. Therefore, bismuth quadruple or non-bismuth quadruple concomitant therapies are recommended in high (>15%) clarithromycin resistance areas [14]. In addition, achieving the information of local primary antibiotic resistance of *H. pylori* is of great importance to guide the treatment of *H. pylori*.

This review discusses the prevalence of *H. pylori* primary resistance to antibiotics (clarithromycin, metronidazole, levofloxacin, amoxicillin, tetracycline, and furazolidone) in different regions of China and the trends of antibiotic resistance over time in two cities: Beijing (North China) and Shanghai (East China).

Materials and Methods

Data Sources

We searched the PubMed, EMBASE, the China National Knowledge Infrastructure (CNKI), and the Chinese Biomedical (CBM) databases from the earliest date of each database to October 2016. The search terms included the following: *H. pylori*, antibiotic (including clarithromycin, metronidazole, amoxicillin, levofloxacin, tetracycline, and furazolidone) resistance with or without China or different regions of China. The articles included in this review met the following inclusion criteria: (1) a study population composed of individuals who had not received treatment for eradication of *H. pylori*; (2) *H. pylori* diagnosed by the Epsilometer test, Agar dilution, Kirby–Bauer, or PCR; (3) older than 18 years; and (4) inclusion of mainland Chinese residents.

Statistical Analysis

The data analysis was performed using MedCalc 15.2.2. Each article was weighted according to the number of isolated *H. pylori* strains. The overall prevalence of antibiotic resistance was presented with 95% confidence intervals (CIs). Heterogeneity was evaluated using the χ^2 statistic (with a P value <0.10 considered significant) and the I^2 test (25, 50, and 75% represents low, moderate, and high heterogeneity, respectively). The random effects model was used to combine the effect sizes of the included studies when heterogeneity existed ($P < 0.1$ or $I^2 > 50\%$). If no heterogeneity existed, a fixed effect model was used to pool the data.

Results

Among the 23 studies included in this review, seven studies were conducted in North China, eight studies in East China, three studies in South China, two studies in Southwest China, and three studies were multicenter studies. In addition, three studies focused on the primary antibiotic resistance of *H. pylori* and on the trends of *H. pylori* resistance over time. Interestingly, one study compared the prevalence of *H. pylori* resistance to antibiotics in two populations (fishermen and urban residents). Moreover, one study focused on the difference of resistance rates in three nationalities (Han, Bai, and Naxi). A total of 6274, 6418, 3921, 5468, 2802, and 275 *H. pylori* strains were included in this study to evaluate the prevalence of *H. pylori* primary resistance to clarithromycin, metronidazole, levofloxacin, amoxicillin, tetracycline, and furazolidone, respectively. All *H. pylori* strains were derived from patients diagnosed as *H. pylori* positive, including dyspepsia and peptic ulcer patients. Overall, the primary resistance rates of clarithromycin, metronidazole, levofloxacin, amoxicillin, tetracycline, and furazolidone were 28.9 (95% CI: 23.4–34.8), 63.8 (95% CI: 57.7–69.6), 28.0 (95% CI: 17.7–39.8), 3.1 (95% CI: 1.8–4.9), 3.9 (95% CI: 2.0–6.4), and 1.7 (95% CI: 0.6–4.1), respectively (Table 1). The Epsilometer test (15/23, 65.2%) was the most commonly used method for detecting *H. pylori* primary

Table 1 Primary antibiotic resistance of *H. pylori* in different regions of China

Regions	Year	Method	CLA *n* (%)	MTZ *n* (%)	LEV *n* (%)	AMO *n* (%)	TET *n* (%)	FUR *n* (%)	Authors
North China									
Beijing	2000	ET	47 (12.8)	47 (34)	–	47 (2.1)	–	–	Gao et al. [22]
	2001		63 (12.7)	63 (31.7)	–	63 (0)	–	–	
	2002–2003		22 (9.1)	22 (54.5)	–	22 (0)	–	–	
	2004–2005		24 (20.8)	24 (70.8)	–	24 (0)	–	–	
	2006–2007		71 (38)	71 (80.3)	40 (25)	71 (0)	41 (0)	–	
	2008		39 (38.5)	39 (66.7)	39 (46.2)	39 (0)	39 (0)	–	
	2009		24 (25)	24 (66.7)	24 (41.7)	24 (0)	24 (4.2)	–	
Beijing	2009–2010	ET	371 (39.9)	371 (66.8)	371 (34.5)	371 (6.7)	371 (4.9)	–	Zhang et al. [23]
	2013–2014		950 (52.6)	950 (63.4)	950 (54.8)	950 (4.4)	950 (7.3)	–	
Beijing	2012–2013	PCR	130 (37.7)	–	–	–	–	–	Liu et al. [24]
Beijing	2013	ET	37 (25.7)	80 (55.6)	–	–	–	–	Bai et al. [25]
Beijing	2013–2014	ET	700 (50.1)	700 (63.9)	700 (54.4)	700 (3.7)	700 (7.3)	–	Zhang et al. [26]
Beijing	2014–2015	ET	200 (44.9)	200 (67.3)	–	200 (2.0)	–	–	Song et al. [27]
Hebei	2014–2015	KB	155 (21.3)	155 (94.2)	155 (5.8)	155 (2.6)	–	155 (1.9)	Meng et al. [28]
East China									
Shanghai	2005–2006	ET	36 (8.3)	36 (44.4)	–	36 (2.8)	–	–	Gu et al. [29]
Shanghai	2008–2009	AD	77 (20.8)	77 (41.6)	–	77 (0)	77 (0)	–	Zheng et al. [30]
Shanghai	2009–2010	KB	120 (36.7)	120 (82.5)	120 (41.7)	120 (22.5)	–	120 (0.8)	Tan et al. [31]
Shanghai	2012	AD	112 (18.7)	–	112 (30.3)		–	–	Liao et al. [32]
Shanghai	2014–2015	ET	129 (19.8)	129 (57)	129 (29.1)	129 (0)	–	–	Zhang et al. [33]
Shanghai	2014	AD	53 (26.4)	91 (45.1)	–	–	–	–	Zhang et al. [34]
Shanghai	–	AD	133 (18)	133 (42.1)	–	133 (0)	–	–	Sun et al. [35]
Jiangxi	2014	ET	374 (13.9)	374 (58.3)	374 (12.6)	–	–	–	Hong et al. [36]
South China									
Guangdong	2011–2013	ET	230 (25.7)	230 (70.9)	230 (6.1)	230 (6.5)	–	–	Lu et al. [37]
Fujian	2012–2013	ET	44 (25)	–	–	–	–	–	Hu et al. [38]
Fujian	2001	ET	47 (10.6)	47 (34)	–	47 (0)	–	–	Ruan et al. [39]
	2004		89 (18)	89 (38)	–	89 (0)	–	–	
	2006		102 (29.4)	102 (47.1)	–	102 (2.0)	–	–	
Southwest China									
Chongqing	2015	AD	65 (20)	305 (94.4)	77 (24.7)	–	–	–	Han et al. [40]
Yunnan	2000–2001	ET	–	109 (67.9)	–	–	–	–	Hu et al. [48]
Multiple center									
Beijing, Shanghai Wuhan, Guangzhou	2008–2010	ET	280 (40)	280 (66.8)	–	280 (4.6)	–	–	Zhou et al. [41]
Beijing, Shanghai Wuhan, Guangzhou	2008–2012	ET	600 (37.5)	600 (67.2)	600 (33.5)	600 (6.8)	600 (3.5)	–	Song et al. [42]
Beijing, Zhejiang Shandong	2013–2014	ET	950 (48.8)	950 (65.7)	–	959 (2.0)	–	–	Zhou et al. [43]
Overall			6274 (28.9)	6418 (63.8)	3921 (28.0)	5468 (3.1)	2802 (3.9)	275 (1.7)	

AMO amoxicillin, *CLA* clarithromycin, *MTZ* metronidazole, *LEV* levofloxacin, *TET* tetracycline, *FUR* furazolidone. *ET E* test, *AD* agar dilution, *KB* Kirby–Bauer. *CI* confidence interval *with 95% CI: CLA: 28.9 (95% CI: 23.4–34.8), *MTZ* 63.8 (95% CI: 57.7–69.6), *LEV* 28.0 (95% CI: 17.7–39.8), *AMO* 3.1 (95% CI: 1.8–4.9), *TET* 3.9 (95% CI: 2.0–6.4), *FUR* 1.7 (95% CI: 0.6–4.1)

resistance to antibiotics, followed by the Agar dilution (5/23, 21.7%), Kirby–Bauer (2/23, 8.7%), and real-time PCR (1/23, 4.3%) methods.

Primary Clarithromycin Resistance to *H. pylori*

Clarithromycin is an important antibiotic used in regimens for eradicating *H. pylori*; its resistance undermines the efficacy of triple and sequential therapy [14]. The role of clarithromycin in inhibiting bacteria depends on its interaction with the peptidyl transferase loop of the V domain of the 23S ribosomal RNA molecule, leading to the inhibition of bacterial protein synthesis. The point mutations of the 23S rRNA gene may restrict the interactions between clarithromycin and the 23S ribosomal RNA, which contributes to clarithromycin resistance [15]. Common mutations of the 23S ribosomal RNA gene are A2143G, A2142G, and A2142C, which account for 80–90% of clarithromycin resistance [16]. Moreover, numerous researchers have implicated the importance of A2115G, G2141A, G2172T, T2182C, T2190C, C2195T, A2223G, G2224A, G2245T, G2254T, T2289C, and C2611A mutations in the primary or secondary clarithromycin resistance [17–20]. In addition, alterations of the outer membrane protein profile may be a novel mechanism involved in clarithromycin resistance to *H. pylori* [21].

Gao et al. [22] evaluated the evolution of *H. pylori* antibiotic resistance in Beijing city (North China) during the period 2000–2009. A total of 374 *H. pylori* strains were collected and analyzed for antibiotic susceptibility using the Epsilometer test. The prevalence of primary clarithromycin resistance was 12.8, 12.7, and 9.1% in 2000, 2001, and 2002–2003, respectively. During the period 2004–2009, the primary resistance rate of clarithromycin increased and was greater than 20%. The same trend was also observed in this region during the periods of 2009–2010 and 2013–2014, with primary clarithromycin resistance rates of *H. pylori* of 39.9 and 52.6%, respectively [23]. Liu et al. [24] recruited 385 patients diagnosed with functional dyspepsia in 2012–2013, and 130 patients were examined by real-time PCR for antibiotic susceptibility; the overall resistance rate to clarithromycin was 37.7%. During the same period, another study reported the resistance rate to be 25.7% [25]. However, only 37 *H. pylori* strains were isolated in this study for clarithromycin susceptibility. Out of a total of 700 *H. pylori* strains isolated from patients with dyspepsia during 2013–2014, 351 (50.1%) were resistant to clarithromycin [26]. Recently, Song et al. [27] conducted a prospective study to evaluate the efficacy of hybrid therapy as a first-line regimen for *H. pylori*; in this study, 90 *H. pylori* strains (90/200, 44.9%) were resistant to clarithromycin. In the only other study conducted in the rest of North China, 155 *H. pylori* strains were successfully cultured and tested for antibiotic susceptibility using the Kirby–Bauer method, which showed that the primary resistance of clarithromycin was 21.3% in the Hebei province [28].

The prevalence of primary clarithromycin resistance was reported as 8.3% in Shanghai city (East China) during 2005–2006, which was relatively low [29]. However, the primary clarithromycin resistance rate showed a slight increase in this region during the period 2008–2015. Zheng et al. [30] isolated 77 *H. pylori* strains and examined their primary resistance rates to antibiotics by the agar dilution method; this research showed that a total of 16 *H. pylori* strains (16/77, 20.8%) were resistant to clarithromycin during 2008–2009. Other studies [31–34] reported that the primary clarithromycin resistance to *H. pylori* in this region was 36.7, 18.7, and 19.8% during three periods (2009–2010, 2012, and 2014–2015, respectively). In addition, a similar result was also observed in another study conducted in Shanghai, which reported a resistance rate of 18.0% [35]. However, a lower primary clarithromycin resistance rate (13.9%) was reported in Jiangxi province (East China) during 2014–2015 [36].

There were three studies performed in South China regarding primary antibiotic resistance to *H. pylori*. Two provinces (Guangdong and Fujian) reported similar resistance rates of clarithromycin between 2011 and 2013: 25.7 [37] and 25% [38], respectively. Interestingly, Ruan et al. [39] recruited two populations (fishermen and urban residents) for antibiotic susceptibility determination during the period 2001–2006, and the results showed that the prevalence of primary clarithromycin resistance was 5.7% in the subpopulation of fishermen in 2004, and the primary resistance rate of clarithromycin was 10.6, 26, and 29.4% in the subpopulation of urban residents during the time periods of 2001, 2004, and 2006, respectively. For the Southwest region of China, only one study was performed [40], and this study reported that the primary antibiotic resistance to *H. pylori* was 20.1 and 19.8% in rural and urban patients, respectively.

Zhou et al. [41] conducted a national multicenter trial between 2008 and 2010 that included four cities: Beijing, Shanghai, Wuhan (Central China), and Guangzhou (South China). A total of 280 *H. pylori* strains were isolated from patients with dyspepsia, and the prevalence of primary clarithromycin resistance to *H. pylori* was relatively high (40%). Similar results (37.5%) were observed in a prospective multi-region study (including North, East, Central, and South regions) with 600 patients [42]. Another national multicenter trial was conducted between September 2013 and April 2014 in three cities: Beijing, Hanzhou (East China), and Jinan (East China). Nine hundred and fifty *H. pylori* strains were isolated and examined, and 464 *H. pylori* strains (464/950, 48.8%) were resistant to

clarithromycin [43]. This high resistance rate of clarithromycin may be attributed to the widespread and indiscriminate use of antibiotics in China.

Primary Metronidazole Resistance to *H. pylori*

Metronidazole resistance is a serious problem in most parts of the world, which undermines the efficacy of sequential therapy [13, 14]. The mutations of *rdxA*, a gene that encodes an oxygen-insensitive NADPH nitroreductase, were the main cause of *H. pylori* resistance to metronidazole [44]. Additionally, the inactivation of *frxA* (encoding the NADPH flavin oxidoreductase) and *fdxB* (encoding the ferredoxin-like protein) was also involved in the mechanisms of metronidazole resistance [45, 46]. Moreover, Mehrabadi et al. [47] indicated that the resistance nodulation cell division family of efflux pumps may play a role in the metronidazole resistance of *H. pylori*.

The prevalence of primary metronidazole resistance was relatively high in North China (Beijing and Hebei). All of the studies in this region reported a high resistance rate (above 30%) [22, 23, 25–28], particularly up to 80.3% in Beijing during the period 2006–2007 [22] and 94.2% in Hebei between 2014 and 2015 [28]. Similarly, a high metronidazole resistance rate was also observed in East China (Shanghai and Jiangxi) [29–31, 33–36]. The highest resistance rate of metronidazole in this region was reported as 82.5% during the period 2014–2015 [33]. In rural populations from Southeast China, 213 *H. pylori* strains were isolated and 212 *H. pylori* strains (212/213, 99.5%) were identified to be resistant to metronidazole using the agar dilution method [40]. The lowest prevalence of metronidazole resistance (11.4%) was shown in the fishermen population from South China [39]. Interestingly, Hu et al. [48] investigated the prevalence of metronidazole resistance in three different nationalities (Han, Bai, and Naxi); the results indicated that the resistance rate was 63.6, 74.2, and 66.7% in Han, Bai, and Naxi nationalities, respectively. No significant differences were observed among different nationalities. Considering the wide use of metronidazole in the treatment of anaerobic infection (applied in the oral cavity, gastrointestinal tract, etc.), its resistance was also a serious problem in China. However, metronidazole resistance can be overcome when metronidazole is administered at a high dose (1500 or 1600 mg per day) in traditional bismuth-containing quadruple therapies [34].

Primary Levofloxacin Resistance to *H. pylori*

Fluoroquinolone-containing triple therapy may be considered a rescue regimen after the failure of bismuth-containing quadruple therapy [14]. In China, levofloxacin-containing triple therapy (levofloxacin 500 mg qd, amoxicillin 1000 mg bid, and lansoprazole 30 mg bid for 7 days) was not superior to standard triple therapy (amoxicillin 1000 mg bid, clarithromycin 500 mg bid, and lansoprazole 30 mg bid for 7 days) as a first-line treatment for *H. pylori* [49]. In addition, 14-day levofloxacin plus bismuth quadruple therapy also reported undesirable eradication rates (below 90%) [32]. The role of fluoroquinolone in inhibiting bacteria depends on its interactions with DNA gyrase (encoded by *gyrA* and *gyrB*); the point mutations in *gyrA* may restrain this interaction, leading to the occurrence of fluoroquinolone resistance [50]. In addition, a recent study indicated that mutations in *gyrB* were also involved in fluoroquinolone resistance [51].

A high prevalence of primary levofloxacin resistance to *H. pylori* was reported in Beijing city, and a slightly increasing trend was observed between 2007 and 2014 [22, 23, 26]. However, a low primary levofloxacin resistance rate (5.8%) was reported in North China (Hebei province) [28], and a similar result was also shown in Guangdong (South China), which indicated that the primary levofloxacin resistance rate was 6.1% [37]. In the regions of East China and Southwest China, numerous studies reported a relatively high rate of levofloxacin resistance (above 20%) [31–33, 40] except one study conducted in Jiangxi [36].

Primary Amoxicillin, Tetracycline, and Furazolidone Resistance to *H. pylori*

Amoxicillin interacted with penicillin binding proteins (PBPS) tightly and inhibited the synthesis of the cell wall, resulting in the dissolution of bacteria. Currently, studies have reported that PBPS were expressed in *H. pylori*. The mutations of *pbp 1A* were the common mechanisms of moderate or low-level *H. pylori* resistance to amoxicillin [52, 53]. In addition, the mutations of *pbp 2*, *pbp 3*, *hefC*, *hopC*, and *hofH* were also related to *H. pylori* resistance to amoxicillin [54, 55]. Moreover, the production of beta-lactamase was associated with high-level amoxicillin resistance [53]. The primary amoxicillin resistance rates remained low and stable in Beijing during the period 2000–2015 [22, 23, 26, 27], which was consistent with a study conducted in Hebei [28]. Similarly, a low amoxicillin resistance rate was also reported in the two regions of South China [37, 39]. However, a relatively high primary amoxicillin resistance (22.5%) was reported in Shanghai during 2009–2010 [31]. This result may be explained by the wide use or improper use of amoxicillin in local populations.

Tetracycline is a bactericidal antibiotic that binds to the 30S subunit of ribosomes, leading to the inhibition of protein synthesis. The resistance of tetracycline was mainly

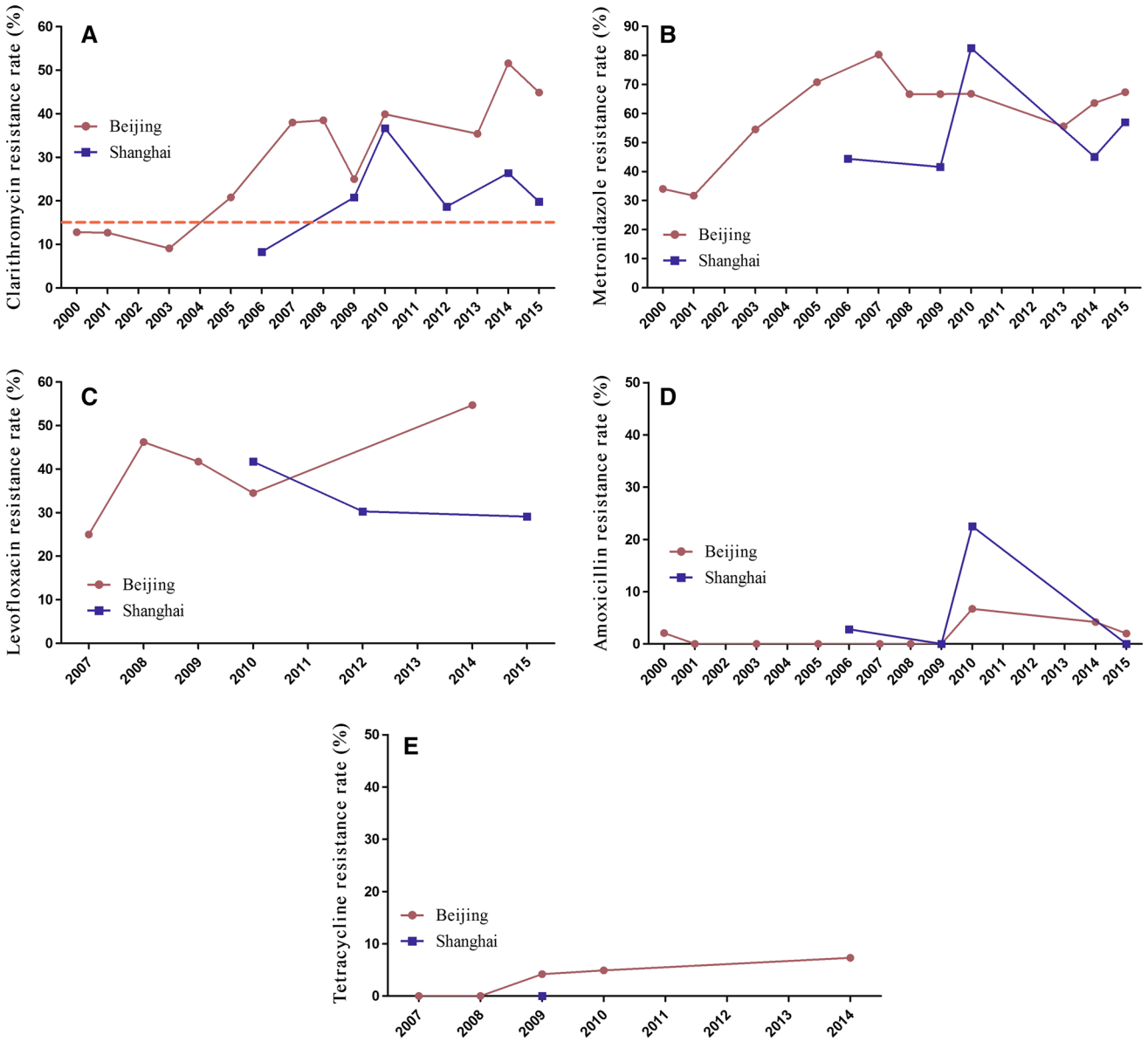

Fig. 1 **a** Primary clarithromycin resistance of *H. pylori* in Beijing and Shanghai cities over time (2000–2015) [22–27, 29–34]; the *red dotted line* represents the resistance rate (15%). **b** The primary metronidazole resistance of *H. pylori* in Beijing and Shanghai cities over time (2000–2015) [22, 23, 25–27, 29–31, 33, 34]. **c** The primary levofloxacin resistance of *H. pylori* in Beijing and Shanghai cities over time (2007–2015) [22, 23, 26, 31–33]. **d** The primary amoxicillin resistance of *H. pylori* in Beijing and Shanghai cities over time (2000–2015) [22, 23, 26, 27, 29–31, 33]. **e** The primary tetracycline resistance of *H. pylori* in Beijing and Shanghai cities over time (2007–2014) [22, 23, 26, 30]

caused by the point mutations of *tet-1* in 16S rRNA [56]. Additionally, proton motive force-dependent efflux appeared to be important in the resistance of *H. pylori* to tetracycline [57]. A total of five studies were conducted in China regarding the prevalence of primary tetracycline resistance. A low resistance rate (below 10%) was reported in the five studies [22, 23, 26, 30, 42].

Mutations in *H. pylori porD* and *oorD* genes were associated with furazolidone resistance [58]. Only two studies (one in Hebei and another in Shanghai) reported a low primary furazolidone resistance rate (below 2%) [28, 31].

Discussions and Conclusions

In the majority of the world, standard triple therapy was ineffective (eradication rate below 80%) and thus not recommended as a first-line treatment for *H. pylori* [59]. Multiple factors were associated with the failure of *H.*

pylori treatment, e.g., high gastric acidity, gene polymorphisms (IL-1B and CYP2C19), poor patient compliance, overloading bacteria in the stomach, internalizing bacteria, antimicrobial washout and dilution, biofilm formation, and, most importantly, resistance to antibiotics [60, 61]. Therefore, it is of great importance to obtain regional antibiotic resistance information to guide the choice of antibiotics in the treatment of *H. pylori*. We searched the PubMed, EMBASE, CNKI, and CBM databases regarding the primary resistance of antibiotics in different regions of China and included 23 studies (14 studies in English and 9 in Chinese) in this review.

Currently, the primary clarithromycin resistance to *H. pylori* remains a serious problem in most regions of the world. The efficacy of clarithromycin was "all-or-none," which cannot be improved by increasing dosage or frequency. As reported in other countries of Asia, such as Japan, Korea, and Singapore, the primary clarithromycin resistance rate was above 15% and increased over time [62–64]. A similar result was also observed in Europe [65]. Recently, a cross-sectional study was performed in the USA regarding the prevalence of clarithromycin resistance in the male veteran population: among 110 patients with no history of treatment for *H. pylori*, 16 (14.5%) were resistant to clarithromycin [66]. Here, we reported an overall primary prevalence of clarithromycin resistance of 28.9 (95% CI: 23.4–34.8), which was relatively high (above 15%). In addition, an increasing trend of primary clarithromycin resistance over time (2000–2015) was observed in Beijing and Shanghai city (Fig. 1a). Moreover, the highest resistance rate was reported as 52.6% in Beijing between 2013 and 2014 [23]. Consistent with clarithromycin, the overall primary metronidazole resistance rate was high [63.8% (95% CI: 57.7–69.6%)]. Additionally, there were no differences in three nationalities (Han, Bai, and Naxi) regarding the resistance rate. The increasing trend of primary metronidazole or levofloxacin resistance over time was observed in Beijing, and the resistance rate remained high and stable over time in Shanghai (Fig. 1b, c). Therefore, levofloxacin-containing triple therapy with or without bismuth would not achieve a desirable result in China. The primary resistance rate of amoxicillin and tetracycline was reported below 10% in China and remained stable over time in Beijing and Shanghai (Fig. 1d, e). In addition, the overall primary resistance rate of furazolidone was 1.7% (95% CI: 0.6–4.1). Therefore, 10-day quadruple furazolidone-based therapies achieved a desirable result (per-protocol >90%) in a multicenter study conducted in China [67].

Considering the current situation of antibiotic resistance and the availability of bismuth in China, the addition of bismuth in triple therapy improved the *H. pylori* eradication rate in subpopulations with resistant strains [68]. Numerous researchers confirmed that bismuth-containing quadruple therapies were effective in China [69]. Therefore, bismuth-containing quadruple therapies were recommended as a first-line treatment of *H. pylori* in China. In addition, antibiotics with low resistance rates (amoxicillin, tetracycline, or furazolidone) should be applied in bismuth-containing quadruple therapies [70]. Moreover, sequential therapy showed no superior to standard triple therapy in China [41], which was associated with antibiotic resistance. Hong et al. [36] conducted open-label, randomized, single-center clinical trials to evaluate the efficacy of concomitant therapy, and the results showed that 10-day concomitant therapy yielded an eradication rate of nearly 90%, which was acceptable. However, further study must be conducted regarding the efficacy of concomitant therapy in China.

There are still some limitations in this review. First, the major studies were conducted in North or East China, limited data were obtained from South and Southwest China, and no data were obtained from West, Central, or Northeast China. Second, the method of antibiotic susceptibility varied in different studies. Third, heterogeneity existed when combining and analyzing the data from different studies.

In conclusion, the prevalence of *H. pylori* primary resistance to clarithromycin, metronidazole, and levofloxacin was high and increased over time, whereas the resistance rates of amoxicillin, tetracycline, and furazolidone were low and stable over time in China.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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