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Molecular Characteristics of Clarithromycin-Resistant *Helicobacter pylori* Strains in Russia: A Systematic Review and Meta-Analysis

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Aim: to analyze the prevalence of *Helicobacter pylori* (*H. pylori*) clarithromycin resistance mutations across the Russian Federation based on molecular genetic studies.
Materials and methods. A systematic literature review was conducted in accordance with PRISMA 2020 guidelines. Searches were performed in PubMed, Google Scholar, and the Russian Science Citation Index (RSCI) for studies published between 1985 and 2025. Analyses focused on point mutations in the 23S rRNA gene, including A2142G (referred as A2146G), A2143G (referred as A2147G), A2144G, T2182C, and T2717C.
Results. Nine eligible studies encompassing 639 *H. pylori* isolates (collected between 2009 and 2024) were included. The pooled prevalence of clarithromycin resistance based on molecular genetic studies was 25.1 % (95% confidence interval: 15.7–36.0). The most prevalent mutation was A2143G (78.2 %), followed by A2142G (15.7 %) and T2717C (13.6 %). Significant heterogeneity was observed among studies (I^2 = 88.6 %). No publication bias was detected via Begg's and Egger's tests.
Conclusion. This meta-analysis demonstrated that the pooled clarithromycin resistance rate of *H. pylori* strains in Russian studies conducted between 2009 and 2024 using molecular-genetic methods exceeds 25 %. Clarithromycin resistance among *H. pylori* strains in Russia is primarily driven by the A2143G mutation. These data are highly relevant for the design of local PCR diagnostic systems aimed at promptly identifying clarithromycin resistance in *H. pylori*, enabling clinicians to select personalized eradication regimens based on genetic profiles.
Keywords: *Helicobacter pylori*, Russia, antibiotic resistance, clarithromycin, meta-analysis, systematic review
Conflict of interest: the authors declare no conflict of interest.

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Характеристика кларитромицин-резистентных штаммов *Helicobacter pylori* в России: систематический обзор и метаанализ

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Цель: систематизировать данные о частоте мутаций, ассоциированных с резистентностью *Helicobacter pylori* к кларитромицину, на территории Российской Федерации по результатам молекулярно-генетических исследований.

Материалы и методы. В соответствии с рекомендациями PRISMA 2020 проведен систематический поиск публикаций в базах данных PubMed, Google Scholar и РИНЦ за период с 1985 по 2025 годы. В метаанализ включены девять оригинальных исследований, соответствующих критериям отбора, с общей выборкой 639 изолятов *H. pylori*. Основное внимание уделено распространенности мутаций в гене 23S рРНК, включая A2142G (aka A2146G), A2142C, A2143G (aka A2147G), A2143C, A2144G, T2182C, T2717C.

Результаты. Были включены девять подходящих исследований, охватывающих 639 изолятов *H. pylori* (собранных в период с 2009 по 2024 г.). Обобщенная частота резистентности *H. pylori* к кларитромицину составила 25,17 % (95% ДИ: 15,74–35,98). Наиболее распространенной мутацией оказалась A2143G (78,2 %), далее следовали A2142G (15,7 %) и T2717C (13,6 %). Выявлена высокая гетерогенность между исследованиями (I^2 = 88,61 %). Публикационное смещение исключено по результатам тестов Бегга и Эггера.

Выводы. Этот метаанализ показал, что общий уровень резистентности штаммов *H. pylori* к кларитромицину в российских исследованиях, проведенных в период с 2009 по 2024 г. с использованием молекулярно-генетических методов, превышает 25 %. Преобладание мутации A2143G соответствует тенденциям, наблюдаемым в странах Южной и Западной Европы, что подчеркивает необходимость регионального молекулярного мониторинга и обновления стратегий антихеликобактерной терапии.

Ключевые слова: *Helicobacter pylori*, Россия, устойчивость к антибиотикам, кларитромицин, метаанализ, систематический обзор

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Introduction

Helicobacter pylori (*H. pylori*) is an extremely widespread pathogen. Infection with this bacterium inevitably leads to the development of chronic gastritis, which can progress to severe complications such as peptic ulcer disease and gastric cancer [1–3]. Eradication therapy, which combines proton pump inhibitors with antibacterial agents, helps resolve gastric mucosa inflammation and prevents the development of precancerous conditions, including atrophic gastritis and intestinal metaplasia [4–6].

However, the increasing *H. pylori* antibiotic resistance, observed globally, is recognized as a major challenge now limiting the effectiveness of most of established eradication regimens [7, 8]. Clarithromycin, a macrolide antibiotic and erythromycin derivative, has been one of the first-line agents of *H. pylori* eradication therapy for more than two decades [9].

The Maastricht VI Consensus (2022) recommends selecting specific eradication regimens based on the regional level of *H. pylori* resistance to clarithromycin, with a threshold of 15 % [1, 10]. Today, global clarithromycin resistance may exceed 27 % [11]. Resistance is strongly associated with failure of clarithromycin-based regimens (OR = 6.97; 95% CI: 5.23–9.28; $p < 0.001$) [12]. In 2018, the World Health Organization classified clarithromycin-resistant *H. pylori* among high-priority pathogens requiring the development of new antimicrobial strategies [13].

H. pylori resistance to clarithromycin is primarily caused by point mutations in the region encoding the peptidyl transferase center (the main macrolide target) within domain V of the 23S rRNA gene [9, 14, 15]. These molecular changes lead to structural alterations in the ribosome, reducing clarithromycin binding affinity and ultimately resulting in antibiotic resistance (Fig. 1) [9, 16].

The most common mutations are A2142G (also referred to as A2146G) and A2143G (also referred to as A2147G) [9, 16, 17]. Other mutations have also been described — including A2142C, A2115G, G2141A, C2147G, T2190C, T2182C, T2717C, C2195T, A2223G, and C2694A — although their clinical significance regarding *H. pylori* resistance to clarithromycin remains uncertain [9, 15, 18].

Earlier meta-analyses of Russian studies published up to 2020 reported that the prevalence of *H. pylori* resistance to clarithromycin in the Russian Federation did not exceed 15 % [19, 20]. However, these findings require updating and clarification, particularly regarding the mutation profile responsible for resistance in this region.

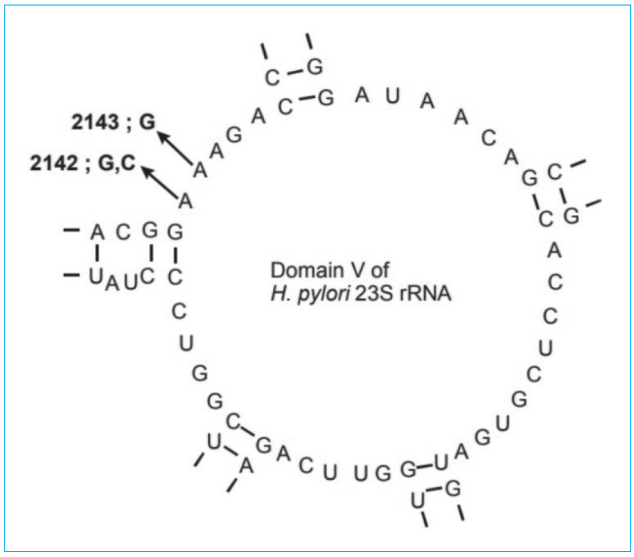

Figure 1. Major point mutations in domain V of *H. pylori* 23S rRNA associated with clarithromycin resistance. Reproduced by license Creative Commons Attribution Non-Commercial License from [Yeon-Ji Kim, Woo Chul Chung. Eradication Therapy for *Helicobacter pylori* with Diagnostic Test for Clarithromycin Resistance. Korean J Helicobacter Up Gastrointest Res. 2019;19(4):225-230. https://doi.org/10.7704/kjhugr.2019.0019]

Рисунок 1. Основные точечные мутации в домене V 23S рРНК *H. pylori*, связанные с устойчивостью к кларитромицину. Воспроизведено по лицензии Creative Commons Attribution Non-Commercial License из [Yeon-Ji Kim, Woo Chul Chung. Eradication Therapy for *Helicobacter pylori* with Diagnostic Test for Clarithromycin Resistance. Korean J Helicobacter Up Gastrointest Res. 2019;19(4):225-230. https://doi.org/10.7704/kjhugr.2019.0019]

The aim of this systematic review and meta-analysis is to analyze the prevalence of *H. pylori* clarithromycin resistance mutations across the Russian Federation based on molecular genetic studies.

Materials and methods

Literature search

The literature search was conducted in accordance with PRISMA 2020 recommendations [21]. Publications from January 1, 1985, to April 20, 2025, were retrieved through systematic searches in MEDLINE/PubMed, Google Scholar, and the Russian Science Citation Index (RSCI). Titles and abstracts were screened using keyword combinations such as *Helicobacter pylori*, mutation A2142G OR A2143G OR A2146G OR A2147G OR T2717C OR T2182C, resistance, Russia. Both Russian and English keywords were used across all databases.

Inclusion and exclusion criteria

Studies were eligible for inclusion if they met the following criteria: 1) peer-reviewed articles published in English or Russian; 2) availability of descriptive statistics suitable for meta-analysis; 3) adult patient populations; and 4) use of molecular genetic methods for identifying *H. pylori* resistance. Exclusion criteria: experimental laboratory studies; systematic reviews; registries; narrative reviews; non-English/Russian language papers; animal studies; case series with fewer than 10 subjects; missing statistical data. In cases of duplicate reporting, only one version was included.

Data extraction

Two independent reviewers (K.A.R. and A.D.N.) extracted data using standardized forms. Extracted variables included publication year, location, total number of isolates, prevalence of clarithromycin resistance, and frequencies of specific mutations. Conflicts were resolved by discussion. The Rayyan web application facilitated data screening and extraction. Methodological quality was assessed using the Newcastle-Ottawa Scale (NOS).

Statistical analysis

Statistical analysis was conducted using MedCalc 23.2.1 (MedCalc Software, Belgium) on Microsoft Windows 11 (Microsoft Corp., USA). Pooled resistance rates and 95 % confidence intervals (95% CI) were calculated using a random-effects model due to observed heterogeneity. Heterogeneity was assessed with Cochran's Q test and the I^2 statistic, with significance set at $p < 0.05$ and $I^2 > 50$ % indicating substantial heterogeneity. Publication bias was assessed using funnel plots along with Begg — Mazumdar and Egger's tests.

Results

Study selection

A total of 314 articles were initially identified. After screening, 294 studies were excluded due to irrelevance ($n = 187$), duplication ($n = 47$), being laboratory studies ($n = 46$) or reviews ($n = 14$). Of the remaining 20 articles, 11 were excluded following full-text evaluation, leaving 9 studies for meta-analysis (Fig. 2, Table 1) [22–30].

Characteristics of included studies

The included studies ($n = 9$) encompassed a total of 639 *H. pylori* isolates collected between 2009 and 2024 from six Russian cities: Moscow ($n = 2$), St. Petersburg ($n = 2$), Kazan ($n = 2$), and one each from Novosibirsk, Kursk, and Chita. The most assessed mutations were

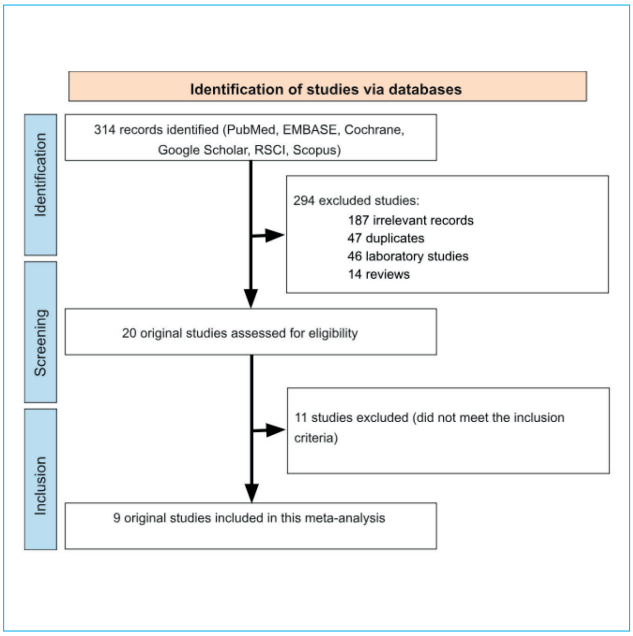

Figure 2. Diagram detailing the study selection strategy

Рисунок 2. Диаграмма, детализирующая стратегию отбора исследований

A2143G (also referred to A2147G, $n = 9$) and A2142G (also referred to A2146G, $n = 8$).

H. pylori resistance to clarithromycin according to molecular genetic studies

The pooled prevalence of clarithromycin resistance based on molecular genetic studies was 25.17 % (95 % CI: 15.74–35.98) (Fig. 3).

A random-effects model was used due to high heterogeneity ($I^2 = 88.61$ %; $p < 0.0001$). Funnel plot analysis (Fig. 4) showed no significant asymmetry, and publication bias was ruled out using Begg's ($p = 0.8301$) and Egger's tests ($p = 0.7210$).

To characterize mutation frequency, only mutations reported in at least three studies were analyzed. The most frequent mutation was A2143G (78.19 %; 95% CI: 66.76–87.77), followed by A2142G (15.75 %; 95% CI: 10.41–21.95), and T2717C (13.61 %; 95% CI: 7.00–23.04) (Table 2).

Discussion

Clarithromycin-resistant *H. pylori* strains are currently designated by the WHO as high-priority pathogens requiring novel therapeutic approaches [13]. A prior meta-analysis of 120 studies found that clarithromycin resistance significantly reduced eradication therapy effectiveness (OR = 0.682; 95% CI: 0.636–0.731), more so than metronidazole resistance (OR = 0.843; 95% CI: 0.810–0.877) [31]. The molecular basis of resistance is based on point chromosomal mutations in the region encoding peptidyl transferase in domain V of 23S rRNA [14, 16].

The present meta-analysis demonstrated that the pooled rate of clarithromycin resistance in the pool of studies (2009–2024) analyzed using molecular genetic methods was 25.17 % (95% CI: 15.74–35.98). This rate is approximately 10 % higher than previously published meta-analytic studies that summarized the results of studies conducted up to 2020 using both phenotypic and genotypic resistance assessment methods [19, 20]. The findings are similar to those of the recently published Hp-EuReg study, which showed that in Europe the incidence of *H. pylori* resistance to clarithromycin is 22 % [32].

The predominant resistance-associated mutations in Russian *H. pylori* strains were A2143G (78.2 %), A2142G (15.7 %), and T2717C (13.6 %). It is extremely difficult to objectify the frequency of other mutations (A2142C, A2143C, A2144G and T2182C) in the Russian population of strains, since these variations were studied in isolated studies. It is worth noting that in the literature there are virtually no such studies, data on the frequency of mutations that determine the resistance of *H. pylori* to clarithromycin in specific populations and countries.

In Turkey, the most frequently detected mutation was A2143G (41.3 %), while A2142G was found in 15.2 % of cases [33]. However, in Spain, the predominant mutation was A2143G (85.3 %), while the A2142G variation was found in only a small percentage of cases (8.8 %) [34]. In a large study conducted in Italy over 15 years, the prevalence of A2143G was noted (71 %), while A2142G was detected in 15.7 % of cases [35]. However, a meta-analysis conducted in Iran showed that this country has an approximately equivalent percentage of the frequency of A2142G mutation (17.8 %) and a slightly lower frequency of A2143G mutation (59.1 %) [36]. In African countries, according to the latest systematic review (2025), on the contrary, the A2142G variant is somewhat more common among clarithromycin-resistant strains (34 %) [37].

Current clinical guidelines, including the Maastricht VI Consensus (2022), recommend a differentiated approach to selecting *H. pylori* eradication regimens based on regional antimicrobial resistance rates — especially to clarithromycin — and local effectiveness data [1]. A recent meta-analysis has demonstrated

Table 1. Characteristics of included studies
Таблица 1. Характеристика включенных исследований

Research, year ***Исследование, год***	**City** ***Город***	**Number of isolates, *n*** ***Количество изолятов, n***	**Number of strains resistant to clarithromycin, *n*** ***Количество резистентных штаммов к кларитромицину, n***	**Method for detecting mutations** ***Метод выявления мутаций***	**Mutations under study** ***Исследуемые мутации***	**NOS**
Baryshnikova N.V. et al., 2009 [22]	Saint Petersburg *Санкт-Петербург*	150	60	PCR *ПЦР*	A2142G (A2146G), A2143G (A2147G), T2717C	6
Lazebnik L.B. et al., 2012 [23]	Moscow *Москва*	62	9	PCR *ПЦР*	A2143G (A2147G), A2143C, A2144G	6
Osipenko M.F. et al., 2012 [24]	Novosibirsk *Новосибирск*	50	3	PCR *ПЦР*	A2142G (A2146G), A2143G (A2147G)	6
Abdulkhakov R.A. et al., 2012 [25]	Kazan *Казань*	62	8	PCR *ПЦР*	A2142G (A2146G), A2143G (A2147G), T2717C	7
Kalugin A.A. et al., 2016 [26]	Kursk *Курск*	29	7	PCR *ПЦР*	A2142G (A2146G), A2143G (A2147G), T2182C	4
Luzina E.V. et al., 2020 [27]	Chita *Чита*	27	10	PCR *ПЦР*	A2142G (A2146G), A2143G (A2147G)	5
Bodunova N. et al., 2024 [28]	Moscow *Москва*	112	27	Sanger sequencing *Секвенирование по Сэнгеру*	A2142G (A2146G), A2143G (A2147G)	7
Starkova D.A., 2024 [29]	Saint Petersburg *Санкт-Петербург*	50	30	Sanger sequencing *Секвенирование по Сэнгеру*	A2142G (A2146G), A2143G (A2147G)	7
Kupriyanova E.A. et al., 2024 [30]	Kazan *Казань*	97	17	PCR *ПЦР*	A2143G (A2147G)	7

Note: *NOS — Newcastle — Ottawa Scale, a tool for assessing the quality of non-randomized studies used in meta-analyses; PCR — polymerase chain reaction.*
Примечание: *NOS — Шкала Ньюкасл — Оттава (Newcastle — Ottawa Scale), инструмент для оценки качества нерандомизированных исследований, используемый в метаанализах; ПЦР — полимеразная цепная реакция.*

that clarithromycin resistance in *H. pylori* exceeds the 15 % threshold established by Maastricht VI now, which limits the use of classical triple eradication therapy in the Russian population [38]. This aligns with the latest national clinical recommendations by the Russian Gastroenterological Association and the Scientific Society for the Study of the Human Microbiome (2022), which suggest several 14-day first-line regimens for patients testing positive for *H. pylori*: standard triple therapy enhanced with bismuth potassium dicitrate; classic bismuth-based quadruple therapy; and non-bismuth-based quadruple therapy [39]. These regimens may also be optimized by the addition of rebamipide [39]. Two independent meta-analyses have shown that including rebamipide significantly increases the effectiveness of eradication therapy (OR = 1.74; 95% CI: 1.19–2.53; and OR = 1.75; 95% CI:

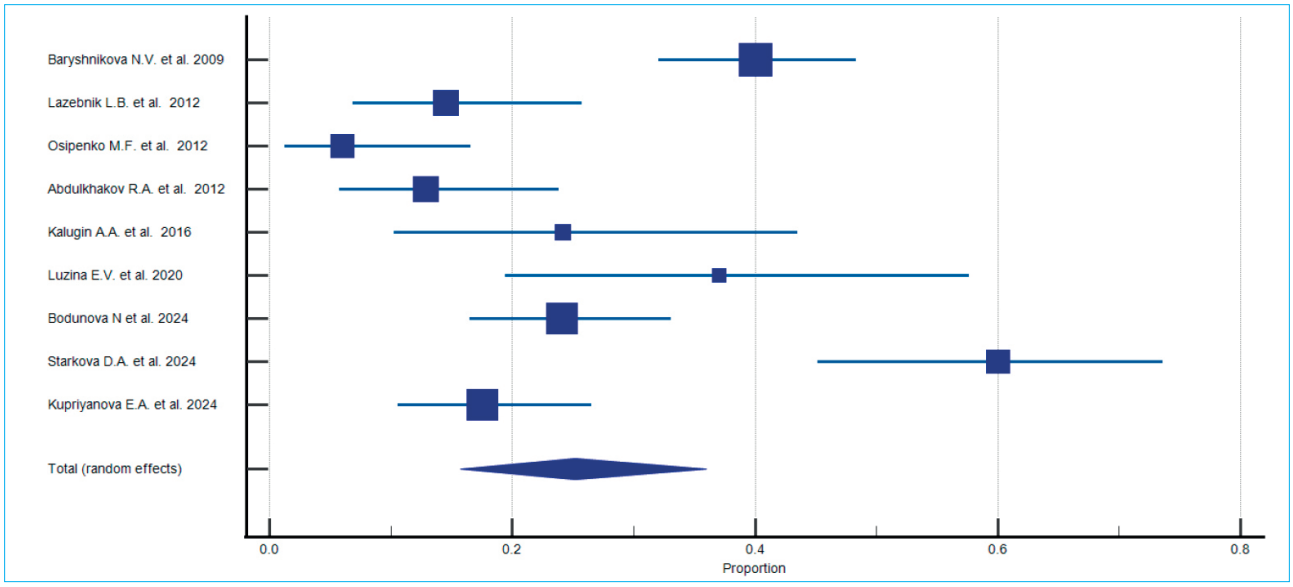

Figure 3. Generalized frequency of clarithromycin-resistant *H. pylori* isolates according to molecular genetic studies

Рисунок 3. Обобщенная частота *H. pylori*-изолятов, резистентных к кларитромицину, по данным молекулярно-генетических исследований

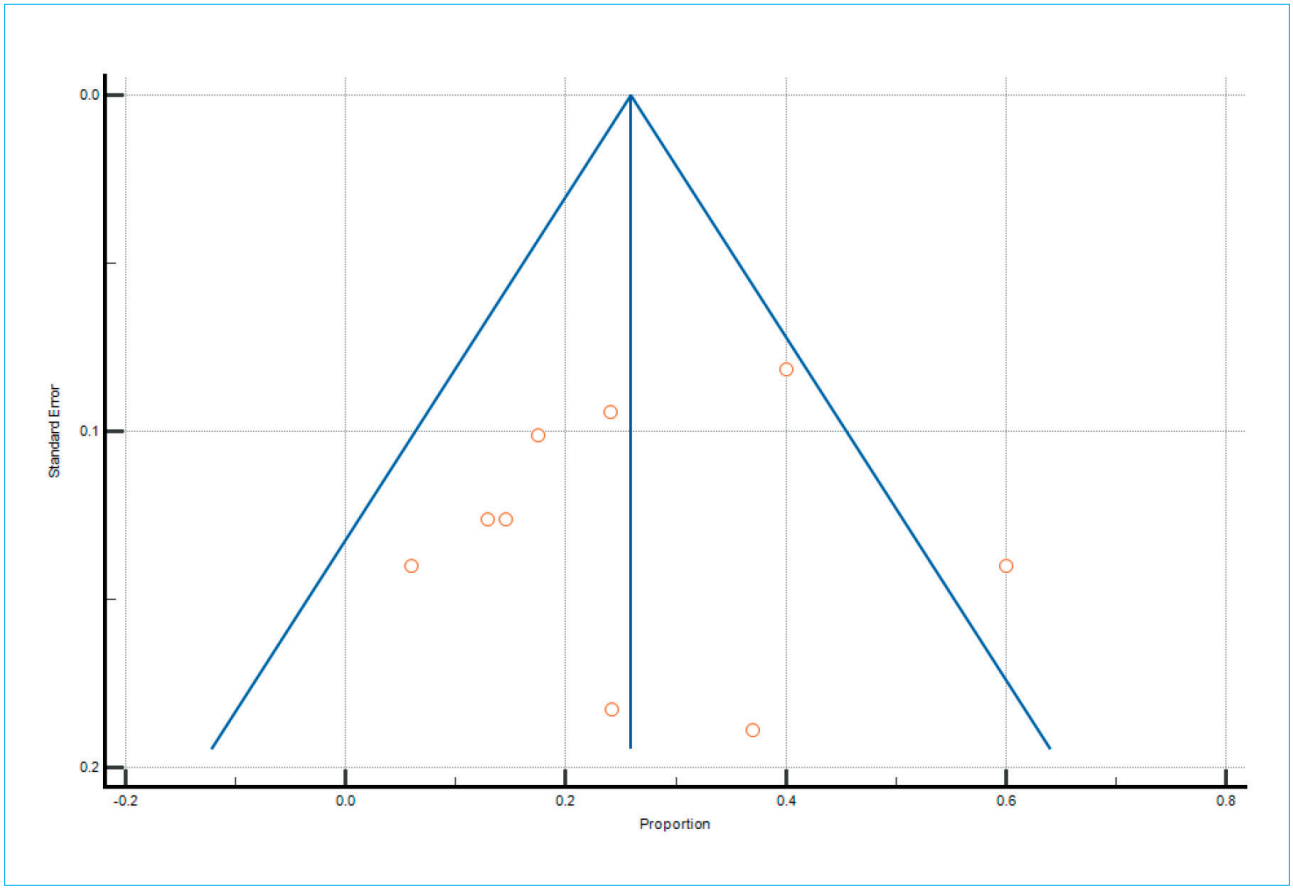

Figure 4. Funnel plot for assessing the likelihood of publication bias

Рисунок 4. Воронкообразная диаграмма рассеяния для оценки вероятности наличия публикационного смещения

Table 2. Generalized frequency of mutations determining resistance of *H. pylori* to clarithromycin in Russia

Таблица 2. Обобщенная частота мутаций, определяющих резистентность *H. pylori* к кларитромицину в России

23S* rRNA gene mutation** ***Мутация гена 23S рРНК	**Number of studies, *n*** ***Количество исследований, n***	**Pooled frequency, 95% CI** ***Обобщенная частота, 95% ДИ***	**Heterogeneity, I^2** ***Гетерогенность, I^2***
A2142G (aka A2146G)	8	15.75 (10.41–21.95)	6,23 %
A2142C	1	3.70 (0.09–18.97)	Not applicable *Неприменимо*
A2143G (aka A2147G)	9	78.192 (66.76–87.77)	60,53 %
A2143C	1	0	Not applicable *Неприменимо*
A2144G	1	0	Not applicable *Неприменимо*
T2182C	1	42.86 (9.90–81.60)	Not applicable *Неприменимо*
T2717C	3	13.61 (7.00–23.04)	60,12 %

Table 3. Generalized frequency of mutations determining resistance of *H. pylori* to clarithromycin in different countries

Таблица 3. Обобщенная частота мутаций, определяющих резистентность *H. pylori* к кларитромицину в разных странах

23S* rRNA gene mutation** ***Мутация гена 23S рРНК	**Region, type of research / *Регион, тип исследования***					
	Russia ***Россия***	**Turkey** ***Турция*** **[33]**	**Spain** ***Испания*** **[34]**	**Italy** ***Италия*** **[35]**	**Iran** ***Иран*** **[36]**	**Africa** ***Африка*** **[37]**
	Meta-analysis ***Метаанализ***	**Study of isolates** ***Исследование изолятов***	**Study of isolates** ***Исследование изолятов***	**Study of isolates** ***Исследование изолятов***	**Meta-analysis** ***Метаанализ***	**Meta-analysis** ***Метаанализ***
A2142G (aka A2146G)	15.7 %	15.2 %	8.8 %	15.7 %	17.8 %	34 %
A2143G (aka A2147G)	78.2 %	41.3 %	85.3 %	71 %	59.1 %	40 %
A2144G	no data *нет данных*	no data *нет данныха*	no data *нет данных*	no data *нет данных*	6.2 %	13 %
T2182C	13.6 %	4.3 %	5.9 %	no data *нет данных*	no data *нет данных*	44 %

1.31–2.34) [40, 41]. Moreover, a recent meta-analysis of six controlled studies conducted in Russia confirmed a significant improvement of the treatment success when rebamipide is added to eradication regimen (OR = 2.16; 95% CI: 1.27–3.68) [42]. Emerging data suggest that adding rebamipide as a fifth component — alongside standard triple therapy and bismuth — can further raise eradication rates to over 95 % [43, 44]. The relevant data were demonstrated in 2024 at the conference of the European Helicobacter and Microbiota Study Group in Porto (Portugal) [44] and the Expert Council on Gastritis in Moscow (Russia) [43].

This meta-analysis has some limitations, including a relatively small sample size compared to larger studies from Europe, North America, and Asia. Additionally, significant heterogeneity exists among the included studies, especially regarding the spectrum of mutations assessed. Nevertheless, this is the first meta-analysis of its kind to provide a detailed molecular-genetic profile of clarithromycin-resistant *H. pylori* strains in Russia. The findings are directly applicable to the development of localized PCR-based diagnostic kits capable of rapidly detecting clarithromycin resistance in biopsy samples, thus enabling personalized eradication strategies.

Conclusion

This meta-analysis demonstrated that the pooled clarithromycin resistance rate of *H. pylori* strains in Russian studies conducted between 2009 and 2024 using molecular-genetic methods exceeds 25 %. The most

prevalent resistance-associated mutations were A2143G (78.2 %), A2142G (15.7 %), and T2717C (13.6 %). While A2143G remains the dominant resistance mutation throughout the study period, improved detection methods have revealed a more complex mutation landscape that includes emerging patterns like T2717C. These studies have practical implications for the development of local genetic tests that enable rapid detection of clarithromycin resistance in biopsy samples, which facilitates the selection of individual treatment strategies.

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