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Review

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Abstract: Background: *Helicobacter pylori (H. pylori)* is a prevalent bacterial pathogen implicated in various gastroduodenal diseases, including chronic gastritis, peptic ulcer disease, and gastric cancer. The COVID-19 pandemic has significantly influenced antibiotic prescription practices, potentially exacerbating antibiotic resistance in *H. pylori*. **Objective:** This study aims to investigate antibiotic prescription during COVID-19 pandemic in Croatia and its possible impact on *H. pylori* antibiotic resistance, with a focus on Croatia. **Methods:** A comprehensive literature search was conducted to identify relevant studies from March 2020 to June 2024. The search strategy included terms related to COVID-19, antibiotic prescription, and Croatia. Studies were selected based on predefined eligibility criteria, focusing on observational research addressing antibiotic use during the pandemic. **Results:** The COVID-19 pandemic leads to significant fluctuations in community antibiotic consumption within the European Union/European Economic Area. In Croatia, antibiotic use in 2022 surpassed 2019 levels, driven by increased consumption of macrolides and other antibiotics. This surge, influenced by early pandemic treatment claims and penicillin shortages, contributed to rising antibiotic resistance in *H. pylori*. Resistance rates to clarithromycin and levofloxacin were notably high, driven by mutations in the 23S rRNA, gyrA, and gyrB genes. **Discussion:** The increased antibiotic use during the COVID-19 pandemic has highly likely complicated *H. pylori* eradication efforts, highlighting the necessity of judicious antibiotic use and robust antimicrobial stewardship. The pandemic underscored the need for new therapeutic strategies, optimized eradication regimens, and advanced diagnostic methods to manage bacterial infections effectively. **Conclusions:** The COVID-19 pandemic has significantly impacted antibiotic use and resistance patterns, posing new challenges for *H. pylori* eradication. Addressing these challenges requires a multifaceted approach, including the development of new drugs and advanced diagnostics, coupled with sustained efforts in antimicrobial stewardship to combat emerging resistance threats.

Keywords: *H. pylori*; COVID-19; antibiotic resistance; antimicrobial stewardship; antibiotic consumption; eradication therapy

1. Introduction

Helicobacter pylori (H. pylori) represents a ubiquitous bacterial pathogen, responsible for colonizing the gastric mucosa, and plays a pivotal role in the pathogenesis of various gastroduodenal diseases, including chronic gastritis, peptic ulcer disease, gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma. The global prevalence of *H. pylori* infection is substantial, affecting over half of the world's population, with marked variation between developed and developing regions due to differences in socioeconomic factors and hygiene standards [1,2].

Also, *H. pylori* infection has been recognized as the most common infection-related cause of death by cancer. International Agency for Research of Cancer and the World Health Organisation

have classified *H pylori* as a group I carcinogen since *H pylori* is the major aetiological factor for gastric cancer, which can be prevented by early eradication before metaplasia and atrophy occur. Moreover, *H pylori* eradication in high-risk areas reduces the risk of gastric cancer in asymptomatic individuals [3,4].

The eradication of *H. pylori* is complex, necessitating a combination antibiotic therapy alongside proton pump inhibitors to enhance bacterial eradication and facilitate gastric mucosal healing. The standard regimen typically comprises two antibiotics, selected from clarithromycin, amoxicillin, metronidazole, or tetracycline, to circumvent resistance development [2].

However, the rising global prevalence of antibiotic-resistant *H. pylori* strains has significantly challenged eradication efforts, leading to the recommendation of tailored therapy based on local resistance patterns or the use of quadruple therapy as first-line treatment in areas of high antibiotic resistance. The mechanism of resistance in *H. pylori* is multifactorial, involving chromosomal mutations that confer reduced susceptibility to antibiotics. Resistance rates exceed 15% for clarithromycin, range between 45% to 55% for metronidazole, and between 14% to 20% for levofloxacin [5]. Also, resistance to clarithromycin and levofloxacin primarily arises from point mutations in the bacterium's genetic material, which alter the antibiotics' target sites and interfere with drug activity [6].

In Croatia, a rise in primary resistance to these antibiotics in *H. pylori* has been noted, with mutations identified in the 23S rRNA, gyrA, and gyrB genes affecting clarithromycin and levofloxacin resistance by modifying target sites or protein structures, thereby diminishing treatment efficacy. Also, molecular docking analyses have shown that *H. pylori* strains harboring resistance-related mutations exhibit reduced susceptibility to clarithromycin and levofloxacin compared to wild-type strains, due to altered non-covalent interactions that weaken antibiotic-protein binding, leading to antibiotic resistance [7].

The coronavirus disease 2019 (COVID-19) pandemic is a global outbreak caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first cases of this novel coronavirus (nCoV) were detected in China in December 2019, with the virus rapidly spreading worldwide. In response, the World Health Organization (WHO) declared a Public Health Emergency of International Concern (PHEIC) on 30 January 2020 and subsequently characterized the outbreak as a pandemic on 11 March 2020. More than three years into the pandemic, on 5 May 2023, the WHO Emergency Committee on COVID-19 recommended to the Director-General that the disease, now well established and ongoing, no longer met the criteria for a PHEIC. This recommendation was accepted, signifying that the global emergency phase of the pandemic was over. However, it is important to note that this does not indicate the end of the pandemic itself, but rather the conclusion of its status as a global emergency [8].

The interrelation between COVID-19 management, particularly the use of antibiotics, and increased resistance in *H. pylori* has emerged as a notable concern. Research indicates that antibiotic regimens utilized in COVID-19 treatment may inadvertently foster antibiotic resistance in *H. pylori*, complicating subsequent eradication efforts [9].

This development underscores the necessity of judicious antibiotic use and highlights the broader implications of antimicrobial resistance in the context of a global pandemic. The scientific investigation into the relationship between COVID-19 infection and antibiotic resistance in *H. pylori* reveals intricate dynamics that are of significant concern to the medical community. Investigation has shown us that antibiotic treatments for *H. pylori* infections have shown lower-than-accepted eradication rates in patients previously treated for COVID-19, suggesting a link between the pandemic and increased antibiotic resistance in *H. pylori* infections [10].

The increased resistance rates to commonly used antibiotics in *H. pylori* eradication regimens call for a reevaluation of current treatment strategies and highlight the need for new drugs, eradication regimens, and diagnostic methods such as next-generation sequencing to improve the control of *H. pylori* infections. The impact of COVID-19 on antibiotic resistance in *H. pylori* also emphasizes the importance of cautious antibiotic use during and beyond the pandemic to mitigate the risk of exacerbating resistance issues [10,11].

The aim of this review article was to determine the prescription of antibiotics during the COVID-19 pandemic in Croatia, as it may have an impact on the effectiveness of *H. pylori* eradication.

2. Materials and Methods

2.1. Information Source and Search Strategies

A literature search was performed in July 2024 to collate relevant studies addressing the review questions. For the period from pandemic's inception on 11 March 2020 to 30 June 2024, Medline electronic database (https://www.ncbi.nlm.nih.gov/pubmed) was searched comprehensively to identify relevant articles by using both free text terms and appropriate indexing terms. The basic search strategy employed was as follows: "COVID-19 AND ANTIBIOTIC AND PRESCRIPTION AND CROATIA". The selection of studies was refined independently by two authors according to the predefined eligibility criteria. The articles retrieved from the electronic database used were initially screened for inclusion based on the title of the article and the abstract. Thereafter, the full texts of potentially relevant studies were obtained and assessed by the same two authors.

2.2. Eligibilty Criteria

The studies included in this systematic review adhered to the following inclusion criteria: (1) original observational research, and (2) studies assessing antibiotic prescription practices during the COVID-19 pandemic for patients infected with SARS-CoV-2, as well as for other infectious diseases during the COVID-19 pandemic period from March 2022 to May 2023. Specific inclusion criteria were: studies involving human subjects only, encompassing an adult or young study population (without age restrictions), inclusive of both male and female participants, and addressing the diagnosis of acute COVID-19 infection or other infectious diseases during the pandemic. Exclusion criteria for this review were delineated as follows: (1) studies with primary endpoints not aligned with the scope of this review, (2) case reports, case series, narrative reviews, or commentaries, (3) animal or in vitro research, (4) research published in languages other than English, (5) articles lacking full-text availability, and (6) duplicate research publications.

3. Results

The literature search identified four (4) relevant titles and abstracts from the Medline database search. A total of four studies met the full inclusion criteria for this review were retrieved and fully reviewed [12–15].

Bogdanic et al. conducted a retrospective observational study and investigated azithromycin consumption in Croatia in 2020 and compared this to the period 2017 to 2019. Authors analyzed data on azithromycin distribution for the period from 1st January 2017 to 31st December 2020. Azithromycin consumption was measured as days of therapy (DOT) which represents a ratio of the total dose of azithromycin in one package divided by the defined daily dose unit of 0.3 gr. The data on azithromycin distribution to hospital and non-hospital pharmacies in Croatia served as a proxy to consumption. According to results of this study, in the period from 2017 to 2020, total azithromycin DOT distribution per calendar year increased in 2017, 2018, 2019, and 2020 (1.76, 1.91, 1.91, and 2.01/1000 inhabitant-days, respectively). This was a 5.2% increase from 2019 to 2020 and an 8.1% increase from the average of 2017–2019 to 2020. This 8.1% increase corresponds to a total of 37224 5-day courses of azithromycin prescriptions. Azithromycin was distributed to non-hospital pharmacies in 93.2% to 95.6% of total DOT, with an increasing trend of distribution to hospital pharmacies from 2017–2020 (4.4, 4.5, 5.1, and 6.8% of total DOT, respectively). The total annual amount of azithromycin DOT units distributed was lowest in 2017 (2.670 million units) and highest in 2020 (2.976 million units), whereas the population adjusted distribution was 642.85/1000 inhabitants in 2017 and 733.43/1000 inhabitants in 2020. The monthly pattern of azithromycin distribution was quite different in 2020 compared to the previous three years. Azithromycin distribution to both hospital and non-hospital pharmacies in 2020 was highest in March, followed by November and December. Even though an increase of 8.1% of total azithromycin DOT from the average of 2017–2019 compared to 2020 seems modest, we should highlight the fact that Croatia is already one of the countries with highest percentage of macrolide resistant isolates among EU/EEA countries [12,16].

Papst et al. conducted a multicentre point-prevalence survey in seven tertiary university hospitals (in medical wards and intensive care units (ICUs)) in Croatia, Italy, Serbia and Slovenia from 11 February 2021 to 15 April 2021. Of 988 COVID-19 patients, 521 were receiving antibiotics and/or antifungals (52.7%; range across hospitals: 32.9–85.6%) on the day of the study. Differences

between hospitals were statistically significant (χ^2 (6, N = 988) = 192.57, p < 0.001). The majority of patients received antibiotics and/or antifungals within 48 h of admission (323/521, 62%; range across hospitals: 17.4–100%), their most common use was empirical (79.4% of prescriptions), and pneumonia was the main indication for starting the treatment (three-quarters of prescriptions). The majority of antibiotics prescribed (69.9%) belonged to the "Watch" group of the World Health Organization (WHO) AWaRe classification: cephalosporins (2nd–4th generation), antipseudomonal beta-lactams with beta-lactamase inhibitors, carbapenems, fluoroquinolones, macrolides and vancomycin. In ICUs, antifungals and antibiotics from the "Reserve" group of the AWaRe classification (5th generation cephalosporins, polymyxins, glycylcyclins, oxazolidinones, lipopeptides, etc.) were prescribed more frequently than in medical wards; antifungals accounted for 11.6% and antibiotics from the "Reserve" group for 19.3% of antimicrobial prescriptions in ICUs. The pattern of antimicrobial use varied across hospitals. In some hospitals, antibiotics from the "Access" group (penicillins, beta-lactams with beta-lactamase inhibitors, tetracyclines, trimethoprim with sulfametoxazole, aminoglycosides, metronidazole, etc.) accounted for approximately one-third of prescriptions (including in ICUs), whereas in other hospitals their use was rare. Authors concluded the vast majority of prescriptions was empirical (79.4%), especially early in the hospitalisation. Targeted treatment was more common in ICUs, probably due to the sampling of the lower respiratory tract [13] .

Sokota et al. reviewed the medical records of pediatric patients visiting emergency departments of four tertiary medical centers in Croatia (Dr Fran Mihaljević University Hospital for Infectious Diseases Zagreb (UHID), Children's Hospital Zagreb (CHZ), University Hospital Center Split (UHC Split), and Clinical Hospital Center Rijeka (CHC Rijeka)) between February 25 and April 25, 2018 and 2019, and between February 25 and April 24, 2020. Antimicrobial prescription was analyzed as well. In 2020, the number of visits significantly decreased in the majority of diagnosis categories, especially in the category of infectious diseases.

The most frequently prescribed oral antibiotic was amoxicillin (n = 1160; 22.3%), followed by amoxicillin/clavulanate (n = 903, 17.3%), oral cephalosporins (n = 885, 17%), and azithromycin (n = 426, 8.2%). The structure of antibiotic prescribing remained unchanged during all the observed periods. The hospital with the greatest number of antibiotic prescriptions was UHID (n = 2073, 39.8%), followed by UHC Split (n = 1174, 22.5%), CHZ (n = 1042, 20%), and CHC Rijeka (n = 923, 17.7%). Azithromycin prescription was 3.4% in UHID, 7.1% in CHZ, 14.8% in UHC Split, and 11.6% in CHC Rijeka [14] .

Sutej et al. conducted retrospective observational study about the impact of the COVID-19 pandemic on prescribing trends in dental medicine in Croatia. Data on dental prescriptions and medications dispensed were obtained from the Croatian Health Insurance Fund (CHIF), a central government medical insurance agency. The basis for this analysis was all dental prescriptions funded by CHIF. Intervals of 2 years, from 2014/2015 to 2020/2021, were compared. Antibacterial agents (J01 and P01) were by far the most frequently prescribed drugs, accounting for an average of 80% of all dental prescriptions. The first choice, as the most commonly prescribed antibiotic, was amoxicillin with clavulanic acid (co-amoxiclav), which accounted for an average of 64% of all prescriptions and 49% of all prescriptions. The total number of antibiotics prescribed by dentists increased by 7.744 (2.4%) in the first pandemic year (2020) and 6.222 (1.7%) compared with 2019. The major increase was recorded for azithromycin in the first (39%) and second (9%) pandemic years, but the change was not statistically significant (p = 0.055). A statistically significant increase in utilization during the pandemic period was observed for co-amoxiclav (p = 0.002) for both pandemic years and clindamycin for the first pandemic year (p = 0.043). For cephalexin, a statistically significant decrease was observed during the pandemic period (p = 0.044) [15]. See Table 1.

Table 1. Antibiotic prescription during COVID-19 pandemic in Croatia.

Authors and year of publication	Analyzed period	Antibiotic/group	Results
Bogdanic et al. /2022	2017-2019 and 2020	Azithromycin	A 5.2% increase from 2019 to 2020 and an 8.1% increase

			from the average of 2017–2019 to 2020
Papst et al. /2022	2021	cephalosporins (2nd–4th generation), antpseudomonal beta-lactams with beta-lactamase inhibitors, carbapenems, fluoroquinolones, macrolides and vancomycin.	most prescriptions were empirical (79.4%)
Sokota et al./ 2021	2018,2019, 2020	Amoxicillin amoxicillin/clavulanate oral cephalosporins azithromycin	The most frequently prescribed was amoxicillin (22.3%), followed by amoxicillin/clavulanate (17.3%), cephalosporins (17%), and azithromycin (8.2%).
Sutej et al. 2023	2014/2015, 2020/2021	amox. + clavulanic acid amoxicilin clindamycin metronidazole cephalexin azithromycin	the most prescribed was amoxicillin with clavulanic acid (64% of all prescriptions in 2020 and 49% of all prescriptions in 2021); The major increase was recorded for azithromycin in the first (39%) and second (9%) pandemic years

4. Discussion

The COVID-19 pandemic has had a profound impact on healthcare systems globally, including significant shifts in antibiotic prescription practices. Notably, the observed patterns in community antibiotic consumption within the European Union/European Economic Area (EU/EEA) reflect these changes.

An international survey among physicians involved in the treatment of COVID-19 patients on antibiotic prescribing practices conducted in April 2020 revealed that the decision on antibiotic use was mostly based on clinical presentation, with the need for coverage of atypical pathogens and more than half of the participants reported use of a combination of β-lactams and macrolides or fluoroquinolones [17].

The Council Recommendation adopted in June 2023 on stepping up EU actions against antimicrobial resistance in a One Health approach (2023/C 220/01) set an EU target of a 20% reduction in total antibiotic consumption (community and hospital sectors combined) by 2030, using 2019 as the baseline year (Council of the European Union. Council Recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach) [18]. Between 2019 and 2022, Ventura-Gabarró C. et al. observed a high variability in the European Union/ European Economic Area (EU/EEA) population-weighted mean community antibiotic consumption, in contrast to a continuously slow decrease observed between 2015 and 2019. Although there was an unprecedented 18.5% decrease in community consumption in 2020 compared with the 2019 baseline, this decrease appeared to be transient. Between 2021 and 2022, the EU/EEA mean community consumption increased by 18.8% and showed no significant difference from the pre-pandemic level in 2019. Moreover, in 13 of 27 countries, including Croatia, community antibiotic consumption was higher in 2022 than in 2019, with an average increase of 8.4% among these 13 countries. Increased consummation compared for baseline 2019 was recorded for Croatia in 2022 for antibacterials for systemic use, in 2022 for other beta-lactam antibacterials, in 2021 and 2022 for macrolides, lincosamides and streptogramins, and for other antibacterial groups in 2021 and 2022. At the EU/EEA level, the surge in consumption of 'macrolides, lincosamides and streptogramins' (ATC group J01F) in 2022 was largely driven by macrolide consumption and more particularly azithromycin (European Centre for Disease Prevention and Control (ECDC) [19,20].

Following claims in the media that azithromycin could be used to treat COVID-19, its consumption increased in some European countries, in particular during the first months of the COVID-19 pandemic [12,21,22].

It is also possible that macrolides were more frequently used during the shortages of penicillins reported during 2022, which could potentially also explain the increased consumption of 'other beta-lactam antibacterials' (J01D, which includes cephalosporins) in some countries in 2022 [23,24].

The retrospective observational study by Bogdanic et al. reveals significant insights into azithromycin consumption trends in Croatia during the COVID-19 pandemic. Notably, the study indicates an 8.1% increase in total azithromycin Days of Therapy (DOT) from the average of 2017-2019 to 2020. This rise, while modest, translates to a substantial 37,224 additional 5-day courses of azithromycin prescriptions. The pronounced increase in azithromycin distribution to hospital pharmacies (from 4.4% in 2017 to 6.8% in 2020) alongside a stable high distribution to non-hospital pharmacies suggests a shift possibly influenced by the pandemic's healthcare demands. The monthly distribution pattern in 2020, peaking in March, November, and December, likely reflects the waves of COVID-19 infections and the corresponding surge in antibiotic use [12]. Papst et al.'s multicentre point-prevalence survey underscores the widespread use of antibiotics among COVID-19 patients across several countries, including Croatia. The significant variability in antibiotic prescription rates among hospitals (32.9% to 85.6%) points to differences in clinical practice and possibly varying degrees of adherence to antimicrobial stewardship principles. The predominance of empirical antibiotic use (79.4%) early in hospitalization highlights the urgent need for rapid diagnostic tools to guide targeted therapy. The frequent use of "Watch" group antibiotics aligns with global concerns about antimicrobial resistance, stressing the importance of cautious prescribing practices [13]. Sutej et al.'s study on dental prescriptions highlights an interesting facet of antibiotic use during the pandemic. Despite a general increase in antibiotic prescriptions by dentists, the significant rise in azithromycin use (39% in the first pandemic year) aligns with the trends observed in general healthcare settings. However, the lack of statistical significance (p = 0.055) suggests that this increase might not be entirely attributed to changes in clinical practice due to the pandemic. The significant increase in co-amoxiclav utilization underscores the need for continued surveillance and stewardship efforts to mitigate antimicrobial resistance risks [15]. Collectively, these studies paint a comprehensive picture of antimicrobial use in Croatia during the COVID-19 pandemic. The observed trends in azithromycin consumption, particularly the increase in hospital distribution and the peaks corresponding to COVID-19 waves, reflect the pandemic's influence on prescribing practices. The high rates of empirical antibiotic use and the reliance on broad-spectrum agents underscore the challenges faced by healthcare providers in managing suspected bacterial infections amidst a viral pandemic. Given Croatia's already high rates of macrolide-resistant isolates, as noted by the European Centre for Disease Prevention and Control, the increased azithromycin use is particularly concerning. It underscores the critical need for robust antimicrobial stewardship programs to balance the immediate demands of the pandemic with the long-term goal of preserving antibiotic efficacy.

So, in Croatia the patterns mirrored broader EU/EEA trends, with consumption of antibacterials for systemic use, including other beta-lactam antibacterials, macrolides, lincosamides, and streptogramins, as well as other antibacterial groups, significantly higher in 2022 compared to the 2019 baseline. This surge in antibiotic use, particularly macrolides like azithromycin, was influenced by early pandemic media claims suggesting azithromycin as a potential COVID-19 treatment. Additionally, reported penicillin shortages during the pandemic may have driven the increased consumption of other beta-lactam antibacterials, including cephalosporins. The increased use of antibiotics during the pandemic has important implications for antimicrobial resistance particularly concerning *H. pylori*. The rise in antibiotic-resistant *H. pylori* strains poses a significant challenge to eradication efforts. For example, the standard regimen for *H. pylori* eradication, typically comprising two antibiotics alongside proton pump inhibitors, can be complicated by increasing resistance. Resistance rates exceed 15% for clarithromycin, range between 45% to 55% for metronidazole, and between 14% to 20% for levofloxacin, driven by chromosomal mutations that reduce antibiotic susceptibility. In Croatia, primary resistance to these antibiotics in *H. pylori* has been rising, with mutations identified in the 23S rRNA, gyrA, and gyrB genes, affecting clarithromycin and levofloxacin resistance by modifying target sites or protein structures, diminishing treatment efficacy. Molecular docking analyses have shown that *H. pylori* strains harboring resistance-related mutations

exhibit reduced susceptibility to clarithromycin and levofloxacin compared to wild-type strains, due to altered non-covalent interactions that weaken antibiotic-protein binding, leading to antibiotic resistance [7]. The Council Recommendation adopted in June 2023 on stepping up EU actions against antimicrobial resistance in a One Health approach (2023/C 220/01) set an EU target of a 20% reduction in total antibiotic consumption (community and hospital sectors combined) by 2030, using 2019 as the baseline year [24]. The intersection of COVID-19 and *H. pylori* antibiotic resistance underscores the necessity of judicious antibiotic use. The pandemic has highlighted the broader implications of antimicrobial resistance, necessitating a reevaluation of current treatment strategies and the development of new drugs, eradication regimens, and diagnostic methods. The utilization of next-generation sequencing to identify resistance patterns and tailor antibiotic therapy is crucial in improving the control of *H. pylori* infections. Moreover, the COVID-19 pandemic's influence on antibiotic resistance extends beyond *H. pylori*. The increased prescription of antibiotics during the pandemic, often as a precautionary measure against secondary bacterial infections, has likely contributed to the rise in resistant strains of various pathogens [25]. This phenomenon emphasizes the importance of antimicrobial stewardship programs and the development of comprehensive strategies to mitigate the risk of exacerbating resistance issues.

5. Conclusions

The COVID-19 pandemic has significantly impacted antibiotic use and resistance patterns, posing new challenges for the eradication of *H. pylori.* Addressing these challenges requires a multifaceted approach that includes the development of new drugs, optimized eradication regimens, and advanced diagnostic methods. Ensuring effective management of bacterial infections in the post-pandemic era will depend on sustained efforts in antimicrobial stewardship and innovative research to combat emerging resistance threats.

6. Future Directions

Regarding the increase in antibiotic prescriptions during the COVID-19 pandemic, it is necessary to investigate the primary, secondary and tertiary resistance of *H. pylori* to antibiotics in Croatia and the world. Data on antibiotic resistance of *H. pylori* are needed in order to be as effective as possible in the eradication of *H. pylori* and thus prevent further antibiotic resistance, which is a global and important public health problem.

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