Pharmacoepidemiology and Drug Safety

WILEY

BRIEF REPORT OPEN ACCESS

Use of Azithromycin Attributable to Acute SARS-CoV-2 Infection

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Received: 31 October 2023 | **Revised:** 13 March 2024 | **Accepted:** 5 June 2024

Funding: The authors received no specific funding for this work.

Keywords: attributable use | azithromycin | defined daily dose | ORCHESTRA project | population-based cohort | SARS-CoV-2 infection

ABSTRACT

Purpose: In the early stages of the COVID-19 pandemic, preliminary results that later proved to be incorrect suggested the possible efficacy of anti-infective drugs such as azithromycin for the treatment of SARS-CoV-2 infection. These preliminary data may have influenced the prescription of azithromycin. However, no individual-level data linking the use of this antibiotic to acute SARS-CoV-2 infection are available. The present analysis aims to fill this gap.

Methods: A retrospective population-based cohort design was used including patients diagnosed with SARS-CoV-2 infection in the period ranging from February 2020 to February 2022. The data source for antibiotic consumption was the drug database of outpatient prescriptions of Emilia-Romagna Region (Italy). Antibiotics were classified according to the Anatomical Therapeutic Chemical (ATC) classification system. Consumption rates and percentages of azithromycin DDDs (defined daily doses) during the acute phase of the infection were compared with a previous control period and with the post-acute phase. Analyses were stratified by four groups according to the prevalent virus variant at time of diagnosis.

Results: Comparing the previous control period with the acute phase of infections, the rates of azithromycin consumption (DDD per 1000 individuals per day) increased from 1.17 to 23.11, from 0.80 to 33.03, from 0.81 to 21.01, and from 1.02 to 9.76, in the pre-Alpha, Alpha, Delta, and Omicron periods, respectively. Similarly, the percentages of individuals receiving azithromycin, and the azithromycin DDDs percentages over total systemic antibiotics DDDs increased in acute phases of infection compared with control periods. The consumption rates and percentages returned to preinfection levels in the post-acute phase. In the study period, 12.9% of the use of azithromycin in the entire adult population of Emilia-Romagna was attributable to acute SARS-CoV-2 infection.

Conclusions: Considering the low likelihood of bacterial coinfections, the increased azithromycin consumption in the acute phase of SARS-CoV-2 infection suggests inappropriate prescribing of this antibiotic.

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Summary

- An overuse of azithromycin during the COVID-19 pandemic has been suggested.
- There are no individual-level data linking azithromycin use to acute SARS-CoV-2 infection.
- This article fills the gap through appropriate study design.
- Study results show a notable increase of azithromycin prescription during the acute phase of SARS-CoV-2 infection.
- The increase was particularly evident in the February–June 2021 period.

1 | Introduction

During the COVID-19 pandemic, a reduction in community consumption of antibiotics was observed in many countries, due to the implementation of preventive measures, which also impacted the circulation of microorganisms other than SARS-CoV-2 [1]. In the early stages of the pandemic, a study reported about the possible efficacy of anti-infective drugs such as azithromycin for the treatment of COVID-19 [2]. The postulated efficacy of azithromycin later proved to be incorrect [3, 4]. However, the possible efficacy reported in an early pandemic stage influenced the prescription of azithromycin in Italy which, unlike other antibiotics, remained at pre-pandemic levels in 2020–2022 and even increased in some months [5].

This happened despite the recommendations of the Italian Medicines Agency (AIFA), which promptly reported the ineffectiveness of azithromycin for the treatment of COVID-19 [6]. In the Emilia-Romagna (E-R) region (in northern Italy) a specific pattern of use of azithromycin was observed compared with other antibiotics: the overall consumption of systemic antibiotics in the period from March to May 2020 had in fact dramatically reduced while for azithromycin, consumption increased in March 2020, remained unchanged in April 2020 and decreased in May 2020, compared with the same months in previous years [7]. The present analysis aims to evaluate whether the use of azithromycin at an individual level was influenced by the diagnosis of SARS-CoV-2 infection and what percentage of the systemic antibiotics used in the acute phase of the infection is represented by azithromycin compared with the preceding and following periods.

2 | Methods

This study was conceived and carried out in E-R, a northern Italian region of 4.5 million inhabitants, within the context of the EU's Horizon 2020 research project called ORCHESTRA (Connecting European Cohorts to increase common and effective response to SARS-CoV-2 pandemic; www.orchestra-cohort.eu). The study has a retrospective population-based cohort design including all consecutive adult (≥18 years) residents tested positive for SARS-CoV-2 infection with molecular or antigen test in the period ranging from February 2020 to February 2022. The aim is to investigate the use of azithromycin and of other systemic antibacterials before, during, and after the SARS-CoV-2 infection. Data were extracted from the region healthcare administrative databases, which include comprehensive information about healthcare provision by the regional healthcare systems. The data sources for antibiotic consumption were the regional databases of outpatient drug prescriptions reimbursed by the Regional Health Service whereas the data source for infections was the registry of official SARS-CoV-2 notifications. Secure record-linkage procedures were carried out at the individual level to merge pseudonymized data collected in administrative databases. Antibiotics were classified according to the Anatomical Therapeutic Chemical (ATC) classification system and their consumption was measured in defined daily dose (DDD) units [8]. Consumption of azithromycin (ATC J01FA10) and other antibacterials for systemic use (ATC J01 other than J01FA10) in the general cohort population was reported in three ways: (1) the consumption rate, calculated as the number of DDD per 1000 individuals per day at risk of receiving community antibiotic prescriptions; (2) the percentage of individuals with at least one drug prescription; (3) the percentage of azithromycin DDDs over the total DDDs of antibacterials for systemic use (ATC J01). The consumption rate was calculated excluding days of in-hospital stay from the person-time at risk of receiving prescriptions. Consumption rates in five different time periods were considered: control period (from Days 360 to 31 before testing), acute phase (from Days 0 to 29 after testing), post-acute phase month 1 (from Days 30 to 59 after testing), post-acute phase month 2 (from Days 60 to 89 after testing) and post-acute phase month 3 (from Days 90 to 119 after testing); the 30 days preceding the execution of the test were not considered as the date of onset of the symptoms is not known and it was therefore not possible to discriminate which prescriptions were made before and which after that date. The person-time of individuals who died, who moved residence outside the E-R, or who had a reinfection was censored at the time of the first of these events. Analyses were stratified by four groups according to the prevalent virus variant at the time of diagnosis: pre-Alpha from February 2020 to January 2021; Alpha from February to June 2021; Delta from July to December 2021; Omicron from January to February 2022. The proportion of individuals with azithromycin prescriptions in the acute phase in the four periods was compared using a chi-square test. R statistics software was used for data analysis.

3 | Results

A total of 745 356 subjects positive for SARS-CoV-2 were included in the data analysis, 170 547 in the pre-Alpha period, 123 565 in the Alpha period, 139 787 in the Delta period, and 311 457 in the Omicron period. Consumption rates of azithromycin in the control periods were 1.17, 0.80, 0.81, and 1.02 DDDs per 1000 individuals per day, in the pre-Alpha, Alpha, Delta and Omicron periods, respectively (Figure 1A). In the acute phase, consumption rates increased sharply to 23.11, 33.03, 21.01, and 9.76 DDDs per 1000 individuals per day, respectively (Figure 1A). Considering the entire observation period of the cohort, the DDDs of azithromycin prescribed to subjects with SARS-CoV-2 infection in the acute phase (within

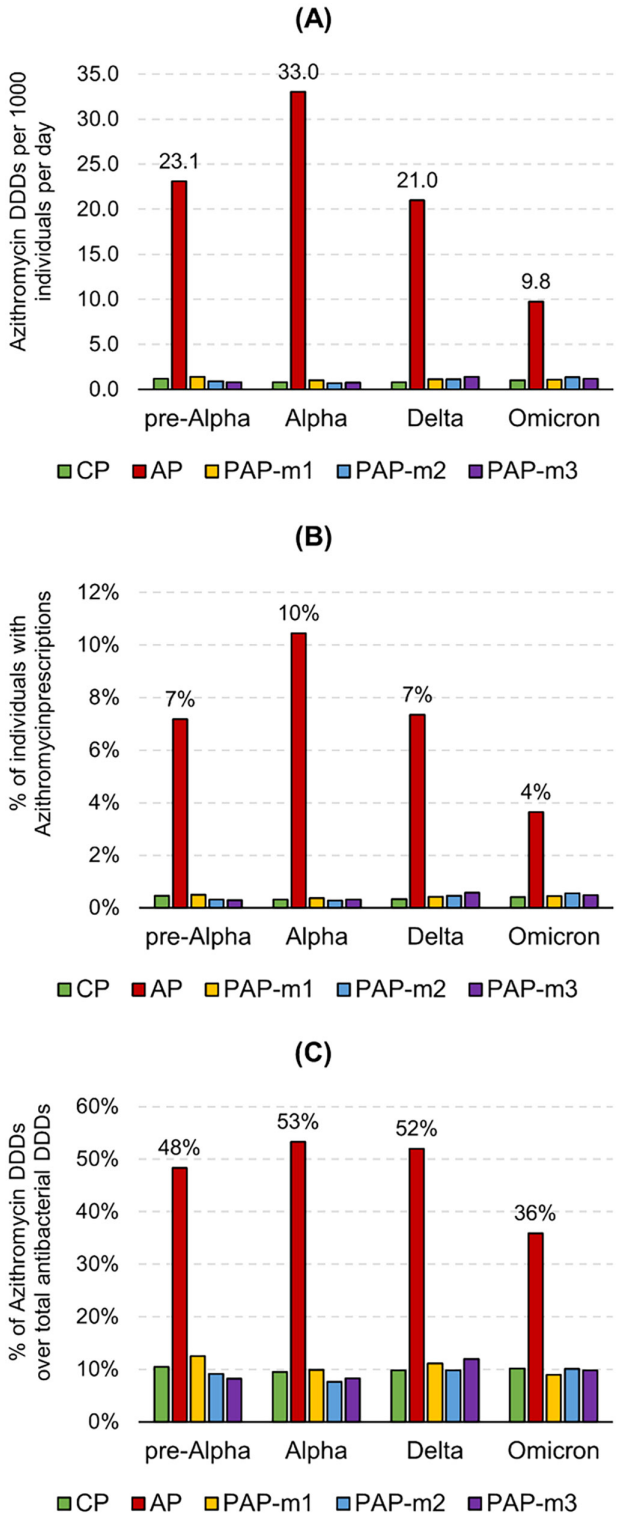

FIGURE 1 | Community consumption of azithromycin in Emilia-Romagna before and after SARS-CoV-2 infection. (A) Azithromycin consumption rate (DDDs per 1000 individuals per day). (B) The percentage of individuals with at least one azithromycin prescription. (C) The percentage of azithromycin DDDs over total antibacterial for systemic use DDDs. The pre-Alpha period ranges from February 2020 to January 2021. The Alpha period ranges from February to June 2021. The Delta period ranges from July to December 2021. The Omicron period ranges from January to February 2022. Green bars represent the control period (CP) before SARS-CoV-2 infection. Red bars represent the acute phase (AP) after SARS-CoV-2 infection. Yellow, blue, and purple bars represent the first (m1), second (m2), and third (m3) months of the post-acute phase (PAP) after SARS-CoV-2 infection, respectively.

30 days of diagnosis) make up 12.9% of all the DDDs of azithromycin prescribed in the entire adult population of the E-R region in the same period. The average monthly proportion of individuals with azithromycin prescriptions in the control periods were 0.5%, 0.3%, 0.3%, and 0.4% in the pre-Alpha, Alpha, Delta, and Omicron periods, respectively. In the acute phase, the proportion increased to 7.2%, 10.5%, 7.3%, and 3.6%, respectively (Figure 1B); the proportion of individuals with azithromycin prescription was not constant over the four periods ($p < 0.001$). Rates and percentages returned to control period levels in the post-acute phase (Figure 1B). Similarly, in the control periods, the percentage of azithromycin DDDs over total systemic antibiotics DDDs were 10.5%, 9.6%, 9.8%, and 10.2%, in the Pre-alpha, Alpha, Delta, and Omicron periods, respectively (Figure 1C). Such percentages increased in the acute phase to 48.4%, 53.3%, 52.0%, and 35.9%, respectively. Percentages returned to control period levels in the post-acute phase (Figure 1C).

Results did not change if considering only the individuals who had asymptomatic or mild acute COVID-19.

4 | Discussion

The results of the study show that in the E-R region the use of azithromycin increased significantly in subjects diagnosed with SARS-CoV-2 during the acute phase of the infection and that, in most cases, this drug was preferred to other systemic antibiotics. This occurred despite the recommendation given in Italy at the beginning of the pandemic, to use this antibiotic in subjects with COVID-19 only for bacterial coinfections, and after strong evidence was published demonstrating the ineffectiveness of azithromycin in the treatment of SARS-CoV-2 [3, 4, 6]. Concurrent with the overall decrease in community-level systemic antibiotic use during the pandemic, azithromycin use remained stable or even increased compared with the pre-pandemic period [5, 7]. Moreover, based on the study results, a significant part (12.9%) of the total azithromycin consumption during the pandemic is attributable to acute SARS-CoV-2 infection. Although individual azithromycin use increased significantly across all periods of the pandemic, the increase peaked during the Alpha period (February–June 2021) and tapered afterwards. This could be explained by the different attitudes in prescribing azithromycin in different periods of the pandemic rather than by a causal link with the prevailing variant. The peak was observed in a period when the inefficacy of azithromycin for SARS-CoV-2 was already reported, probably due to the lag between the availability of scientific evidence and its impact on clinical practice.

The present analysis has some limitations related to data sources that do not provide the cause of the antibiotic prescription nor the date of onset of COVID-19 symptoms. This study, on the other hand, thanks to its design and population-based approach,

makes it possible to evaluate the individual use of azithromycin attributable to the acute phase of SARS-CoV-2 infection and not simply the average consumption of the entire population. Another study providing individual data reported a high frequency of antibiotic use during SARS-CoV-2 although it did not include comparisons before and after the acute phase of the infection [9].

Available data show a low frequency of bacterial coinfection in patients with COVID-19, including hospitalized ones, ranging between 5.6% and 8.6% [10, 11]. These coinfection rates would likely be significantly lower if only outpatient patients were considered. The study findings highlight instead a frequent outpatient use of azithromycin in the acute phase of SARS-CoV-2 infection with a peak of 10.5% of subjects who received this antibiotic (representing 53.3% over total systemic antibiotics DDDs) in the period February–June 2021. Thus, based on the results of our study on community prescriptions, the overall use of antibiotics, and particularly of azithromycin in the acute phase of the SARS-CoV-2 infection was arguably inappropriate in many cases. This confirms the importance of maintaining antimicrobial stewardship activities especially in times of health crisis such as the COVID-19 pandemic [12].

Ethics Statement

This study was reviewed and approved by Comitato Etico Area Vasta Emilia Nord (on February 8, 2022), Comitato Etico Area Vasta Emilia Centro (on January 19, 2022), and Comitato Etico della Romagna (on February 18, 2022). In the protocol revised and accepted by the ethics committees, it was specified that the request for written informed consent was not planned as this study was considered an exception to the art. Fourteen of the General Data Protection Regulation (GDPR), due to the disproportionate effort in providing information to data subjects on the existence of the study processing operation and on the fact that the personal (health) data were processed for scientific purposes.

Conflicts of Interest

The authors declare no conflicts of interest.

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