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Artigo Original

Prophylaxis Against Covid-19: Analysis Of The Supply of Hydroxychloroquine, Ivermectin And Azithromycin and Covid-19 Cases and Deaths

Prevenção Contra Covid-19: Análise Do Fornecimento De Hidroxicloroquina, Ivermectina e Azitromicina e Casos e Óbitos por Covid-19

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Maiara Cristina De Cesaro[1] ORCID https://orcid.org/0000-0002-6256-0535, Andressa de Souza[1] ORCID https://orcid.org/0000-0002-6608-4695, Rafael Fernandes Zanin[1]* ORCID https://orcid.org/0000-0003-3146-0221, Douglas Nunes Stahnke[2] ORCID https://orcid.org/0000-0002-6871-4355, Fernanda Rabaioli da Silva[1] ORCID https://orcid.org/0000-0001-9130-7435, Liciane Fernandes Medeiros[1] ORCID https://orcid.org/0000-0002-6842-7241

ABSTRACT

Introduction: The evidence suggesting the possible use of Hydroxychloroquine, Ivermectin and Azithromycin in the management of COVID-19 is still inconclusive. **Objective**: This is an interrupted time series ecological study where a temporal analysis of the consumption of hydroxychloroquine, ivermectin and azithromycin in the pre-pandemic and pandemic periods in the São Lourenço do Oeste/ Santa Catarina, was performed, a Brazilian city. **Material and Methods**: Data were collected monthly from January 2018 to March 2021 directly from pharmacies/drug stores for medications, and from April 2020 to March 2021 for COVID-19. The temporal analysis was performed using the Prain-Winsten test. Associations between variables (drugs and COVID-19 data) were made by Spearman's correlation test. **Results**: The supply of ivermectin (coefficient, 7.71 p=0.005) and hydroxychloroquine increased (coefficient 26.84, p=0.021) in the pandemic; and azithromycin remained stable (p≥ 0.05). There was a positive correlation between new cases of COVID-19 and the supply of azithromycin, hydroxychloroquine and ivermectin (Spearman rho 0.857, 0.760 and 0.741 p<0.01, respectively) and a positive correlation between deaths with azithromycin (Spearman rho 0.690, p<0.01) and hydroxychloroquine (Spearman rho 0.617, p<0.05). **Conclusions**: According to our data, it is possible to infer that the increased supply of ivermectin, azithromycin or hydroxychloroquine was not able to reduce new cases or deaths by COVID-19, showing no effectiveness as prophylaxis of this disease.

Keywords: Hydroxychloroquine; Ivermectine; Azithromycin; COVID-19 pandemic; Mortality; Number of cases.

1 Programa de Pós-Graduação em Saúde e Desenvolvimento Humano, Universidade La Salle, Canoas, RS, Brasil

2 Programa de Pós-Graduação em Saúde Coletiva, Universidade do Vale do Rio dos Sinos, São Leopoldo, RS, Brasil

***Autor correspondente:** Avenida Victor Barreto, 2288. Centro, Canoas/RS, Brasil. E-mail: rafaelzaninn@gmail.com

RESUMO

Indrodução: A prevenção da COVID-19 ainda permanece inconclusiva quanto à ação da ivermectina, hidroxicloroquina e azitromicina. **Objetivo**: Trata-se de um estudo ecológico de série temporal interrompida onde foi realizada uma análise temporal do consumo de hidroxicloroquina, ivermectina e azitromicina nos períodos pré-pandemia e pandemia em São Lourenço do Oeste/Santa Catarina, uma cidade brasileira. **Materiais e M**étodos: Os dados foram coletados mensalmente de janeiro de 2018 a março de 2021 diretamente de farmácias/drogarias para medicamentos, e de abril de 2020 a março de 2021 para COVID-19. A análise temporal foi realizada por meio do teste de Prain Winsten. As associações entre as variáveis (medicamentos e dados COVID-19) foram feitas pelo teste de correlação de Spearman. **Resultados**: O fornecimento de ivermectina (coeficiente 7,71 p=0,005) e hidroxicloroquina aumentou (coeficiente 26,84, p=0,021) na pandemia; e a azitromicina permaneceu estável (p≥ 0,05). Houve correlação positiva entre casos novos de COVID-19 e a distribuição de azitromicina, hidroxicloroquina e ivermectina (Spearman rho 0,857, 0,760 e 0,741 p<0,01, respectivamente) e correlação positiva entre óbitos com azitromicina (Spearman rho 0,690, p< 0,01) e hidroxicloroquina (Spearman rho 0,617, p<0,05). **Conclusões**: De acordo com nossos dados, é possível inferir que o aumento da oferta de ivermectina, azitromicina ou hidroxicloroquina não foi capaz de reduzir novos casos ou óbitos por COVID-19, não apresentando eficácia como profilaxia dessa doença.

Palavras-chave: Hidroxicloroquina; Ivermectina; Azitromicina; Pandemia do COVID-19; Mortalidade; Número de casos.

INTRODUCTION

COVID-19 is an infectious disease caused by the new coronavirus (SARS-CoV-2) and its main symptoms are fever, tiredness and dry cough. Most people (80%) recover without needing hospital treatment[1]. However, 20% develop the moderate and severe form of the disease, which need hospital-based interventions. Since the beginning of the COVID-19 pandemic, a lot of drugs have been associated to reduce the risk of SARS-CoV-2 infection.

Hydroxychloroquine, azithromycin and ivermectin were widely promoted to treat COVID-19 following early in vitro antiviral effects against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Today, there is enough evidence showing the ineffectiveness of these drugs for this purpose[2-7]. A study by HORBY et al[8] showed that hospitalized patients treated with hydroxychloroquine were less likely to be discharged alive within 28 days. In addition, azithromycin administered to hospitalized patients did not reduce mortality and length of hospital stay[3], while azithromycin associated with hydroxychloroquine in high and low-risk outpatients did not accelerate symptom resolution and was associated with gastrointestinal side effects[4]. Finally, ivermectin did not anticipate time to resolution of symptoms in 21 days, 82% in the ivermectin group and 79% in the placebo group had solved symptoms on the 21st day[9].

In Brazil, sales of chloroquine and hydroxychloroquine rose from 55 million in 2019 to 91.6 million in 2020, while those of ivermectin jumped from 44.4 million to 409 million[10]. Regarding azithromycin, a study carried out in a Spanish hospital noted an increase in hospital consumption of antibiotics in the pandemic period compared to the pre-pandemic period, with an increase in azithromycin in March 2020[11]. In India, the sale of azithromycin from 2018 to 2020 increased from 40 million to 90 million, while that of hydroxychloroquine from 20 million rose to 35 million during the first wave of COVID-19[12].

Considering this scenario, our study aimed to conduct a temporal analysis of hydroxychloroquine, ivermectin and azithromycin supply in the pre-pandemic and pandemic period in the city of São Lourenço do Oeste (SLO), Santa Catarina (SC).

MATERIALS AND METHODS

Study design

Interrupted time series ecological study where a temporal analysis of the consumption of medications in the pre-pandemic and pandemic periods in the SLO city was performed.

Study site

SLO is located at the northwest of SC state, Brazil, with a territorial area of 356,193km², 895 meters above sea level. The estimated population according to the Brazilian Institute of Geography and Statistics (IBGE) in 2010 was 21.792 people, concentrated between 10 and 49 years of age. In 2019, the average monthly salary was 2.4 minimum wages. The proportion of employed people in relation to the total population was 47.9% (11,544 people). In comparison with other municipalities in the state, it occupied positions 55 out of 295 and 10 out of 295, respectively. Other sociodemographic data can be seen in the Table 1.

Table 1: Other sociodemographic data of SLO residents.

Sociodemographic data	Results
Territorial area	356,193 km² [2021]
Estimated population	21.792 inhabitants [2010]
Demographic density	60,45 inhabitants/km² [2010]
Schooling rate from 6 to 14 years old	99% [2010]
Municipal Human Development Index (IDHM)	0,749 [2010]
Child mortality	21,21 deaths per thousand live births [2020]
Realized recipes	75.054,92 R$ (×1000) [2017]
Committed expenses	65.088,35 R$ (×1000) [2017]
Gross Domestic Product per capita	46.216,41 R$ [2019]

Source: https://cidades.ibge.gov.br/brasil/sc/sao-lourenco-do-oeste/panorama

Data collection

Data were collected from drug sales reports from SLO pharmacies. The municipality has 23 pharmacies and data from 10 pharmacies were included in this study. The selection of pharmacies was made through an electronic invitation to all pharmacies present in the municipality of SLO. All those who committed in providing the necessary data to carry out this study and signed the Term of Authorization and Commitment for the use of the Data were included.

Time period collection

The consumption data for these drugs were separated month by month from January 2018 to March 2021. It was characterized as the pre-pandemic period from January 2018 to March 2020 and the pandemic period from April 2020 to March 2021.

COVID-19 data collection

In order to assess the progress of the pandemic and make comparisons, data were collected

on the number of new and accumulated cases of COVID-19 and the number of new and accumulated deaths of coronavirus in the municipality of SLO, in the state of SC and in Brazil, using the Coronavirus Panel: https://covid.saude.gov.br/

Variables

a. Temporal analysis of the consumption of ivermectin, hydroxychloroquine and azithromycin from January 2018 to March 2021.

b. Consumption (per 1000 population) of azithromycin, ivermectin and hydroxychloroquine related to the number of new cases and deaths from COVID-19 during the pandemic (April 2020 to March 2021) in SLO.

Drug classification

In order to separate only the drugs of interest from the total drugs that made up the reports, drugs were grouped by pharmacological classes following the National Health Surveillance Agency (ANVISA) electronic bulletin: https://consultas.anvisa.gov.br/#/bulario/

The class of antimalarials is hydroxychloroquine, of systemic antibiotics azithromycin and of antiparasitic ivermectin.

Data presentation

Ivermectin, hydroxychloroquine, and azithromycin were dispensed by pharmacies. The basic health units reports contained the amount of medication dispensed per pill, while the commercial pharmacies reports per box. In order to establish a unit of measure, all medicines dispensed per box were converted into tablets as indicated in the product description. The dependent variable then was the total number of pills per 1000 inhabitants and the independent variable for each three months.

To make a correlation between the supply of azithromycin, ivermectin and hydroxychloroquine with the number of confirmed cases and deaths of COVID-19 in SLO, we normalized the data using the following formula: Total number of pills per month/total number of inhabitants in SLO*1000. The total number of inhabitants used for the calculation was estimated by IBGE (2021): https://www.estadosecidades.com.br/sc/sao-lourenco-do-oeste-sc.html

The dependent variable then was the total number of pills per 1000 inhabitants and the independent variable the month.

Ethics

Data was provided only upon consent and signature of a Term of Authorization and Commitment for the use of the Data, issued in two copies, one with the researcher and the other with the person responsible for the establishment. As it does not involve human beings and other personal data, there was no need for this research to be approved by the Research Ethics Committee.

Statistical analysis

Data was tabulated in Microsoft Excel and later transferred to the statistical program. Continuous variables with normal distribution were described using mean and standard deviation, while those with non-normal distribution were described using median and interquartile range. Categorical variables were described using frequencies and percentages. Temporal analysis was made using the Prain

Winsten regression with the STATA software, version 11. Associations between variables (drugs *vs* COVID-19 data) included non-parametric Spearman correlation test from SPSS 26.0. For all analyses, the level of statistical significance for the established alpha error was P < 0.05 two-tailed.

RESULTS

Increased supply of ivermectin and hydroxychloroquine in the pandemic period

The Figure 1 shows the number of pills supplied by pharmacies. In relation to hydroxychloroquine and ivermectin, it is possible to observe an increase in the supply from the third quarter of 2020. The trend analysis (Table 2) showed an increased over time in the supply of hydroxychloroquine (coefficient 26.84, p=0.021) and ivermectin (coefficient, 7.71 p=0.005), whereas azithromycin was stable (p≥ 0.05).

Figure 1. Distribution of hydroxychloroquine, ivermectin and azithromycin per 1.000 inhabitants in SLO from the 1st quarter of 2018 to the 1st quarter of 2021 by unit (pill).

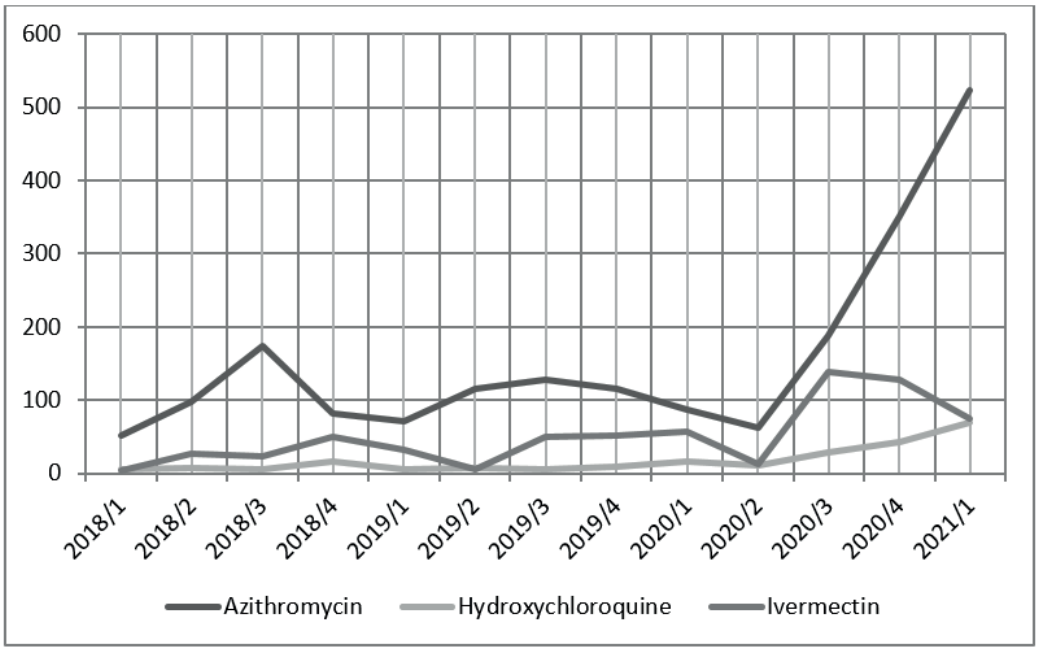

Table 2. Trend of total medicines distribution coefficients per 1.000 inhabitants in SLO from the 1st quarter of 2018 to the 1st quarter of 2021.

	Coefficient	95%CI		p-value	Trend
Azithromycin	190.17	-19.11	399.45	0.070*	Stable
Hydroxychloroquine	26.84	5.03	48.64	**0.021***	Ascending
Ivermectin	7.71	2.93	12.49	**0.005***	Ascending

*Prais-Winsten with Cochrane-Orcutt transformation.

Ascending trend: positive coefficient and p-value < 0.05.

Decreasing trend: negative coefficient and p-value < 0.05.

Stable trend: p-value ≥ 0.05.

COVID-19 cases and deaths

Regarding the number of confirmed cases and deaths by COVID-19, the results are in Figure 2. The first wave in Brazil was July 2020, followed by the second wave in January 2021 and the third starting in March 2021 (Figure 2, Panel A). The first wave in SC achieved its plateau in August 2020, the second wave in December 2020 and the third one starting in March 2021 (Figure 2, Panel B). The municipality of SLO had waves in the same months as the state of SC (Figure 2, Panel C).

In relation to coronavirus deaths, the first COVID-19 wave in Brazil started in July 2020, the second wave in February 2021 and the third wave in March 2021 (Figure 2, Panel D). In SC, the first wave plateaued in August 2020, the second wave in December 2020 and the beginning of the third in March (Figure 2, Panel E). The municipality of SLO had COVID-19 waves in the months of June, September, December 2020 and February/March 2021 (Figure 2, Panel F).

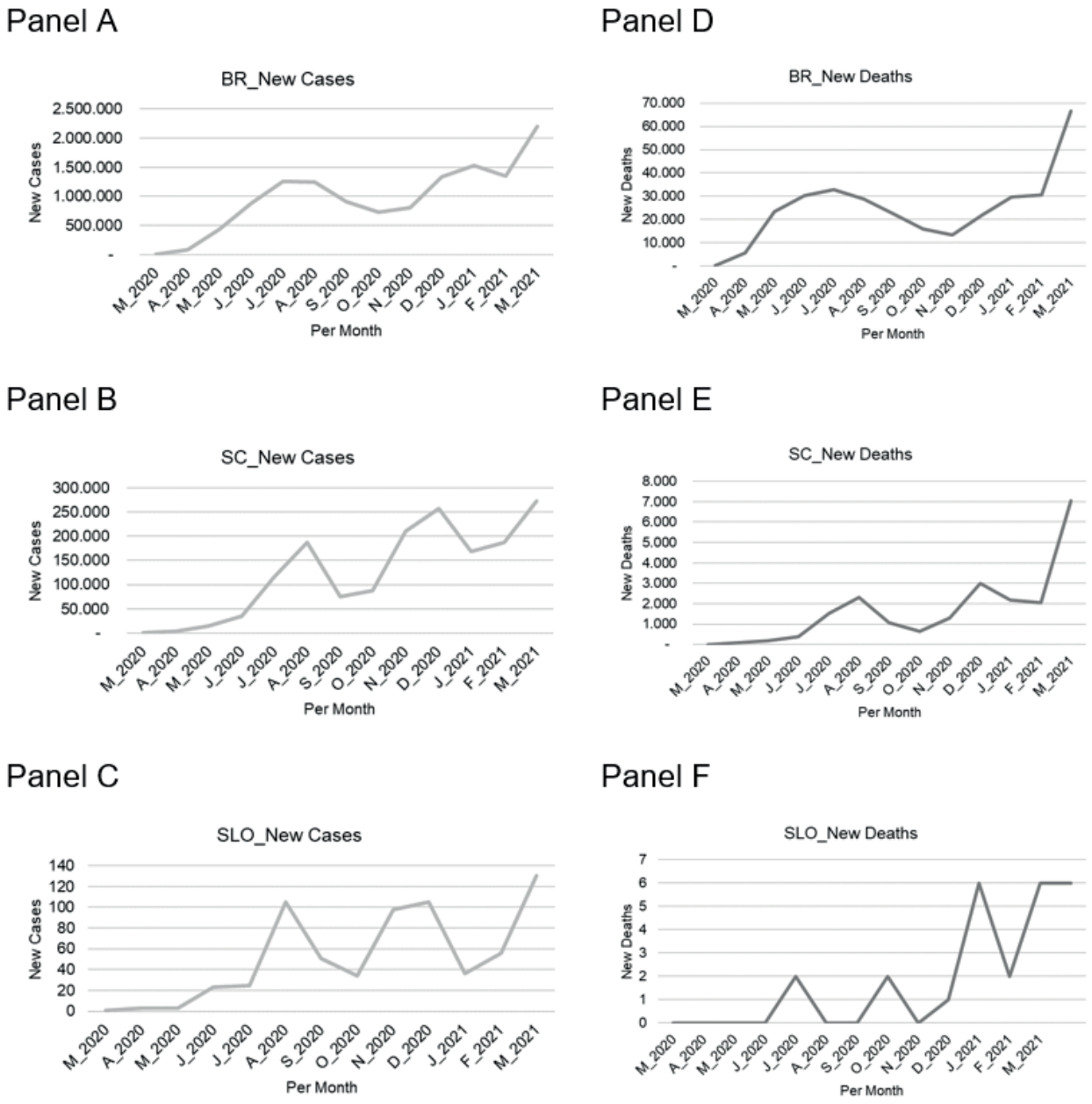

Figure 2. The Panel A, B and C represent the new cases of COVID-19 March 2020 to March 2021 in Brazil, SC and SLO, respectively. The Panel D, E and F represent the new deaths of COVID-19 March 2020 to March 2021 in Brazil, SC and SLO, respectively. The y axis of the graphs represents time in months. Starting with M for March, A for April, M for May, J for June, J for July, A for August, S for September, O for October, N for November, D for December, J for January, F for February and M for March.

Positive correlation between drugs and COVID-19 new cases or deaths

The correlation between COVID-19 new cases and the azithromycin, hydroxychloroquine and ivermectin supply showed a statistically positive correlation (Spearman rho 0.857, 0.760 and 0.741, $p<0.01$, respectively). In Figure 3, it is possible to observe a positive linear association between COVID-19 new cases and the azithromycin (Figure 3, Panel A), hydroxychloroquine (Figure 3, Panel B) and ivermectin distribution (Figure 3, Panel C) in SLO.

Regarding COVID-19 deaths, there was a statistically positive correlation when compared to azithromycin (Spearman rho 0.690, $p<0.01$) and hydroxychloroquine supply (Spearman rho 0.617, $p<0.05$). There was no statistically significant correlation compared with the consumption of ivermectin (Spearman rho 0.363, $p>0.05$) (Figure 3, Panel F). Regarding the number of deaths from COVID-19 in SLO, Figure 3 shows a positive association only between the use of azithromycin (Figure 3, Panel D) and hydroxychloroquine (Figure 3, Panel E).

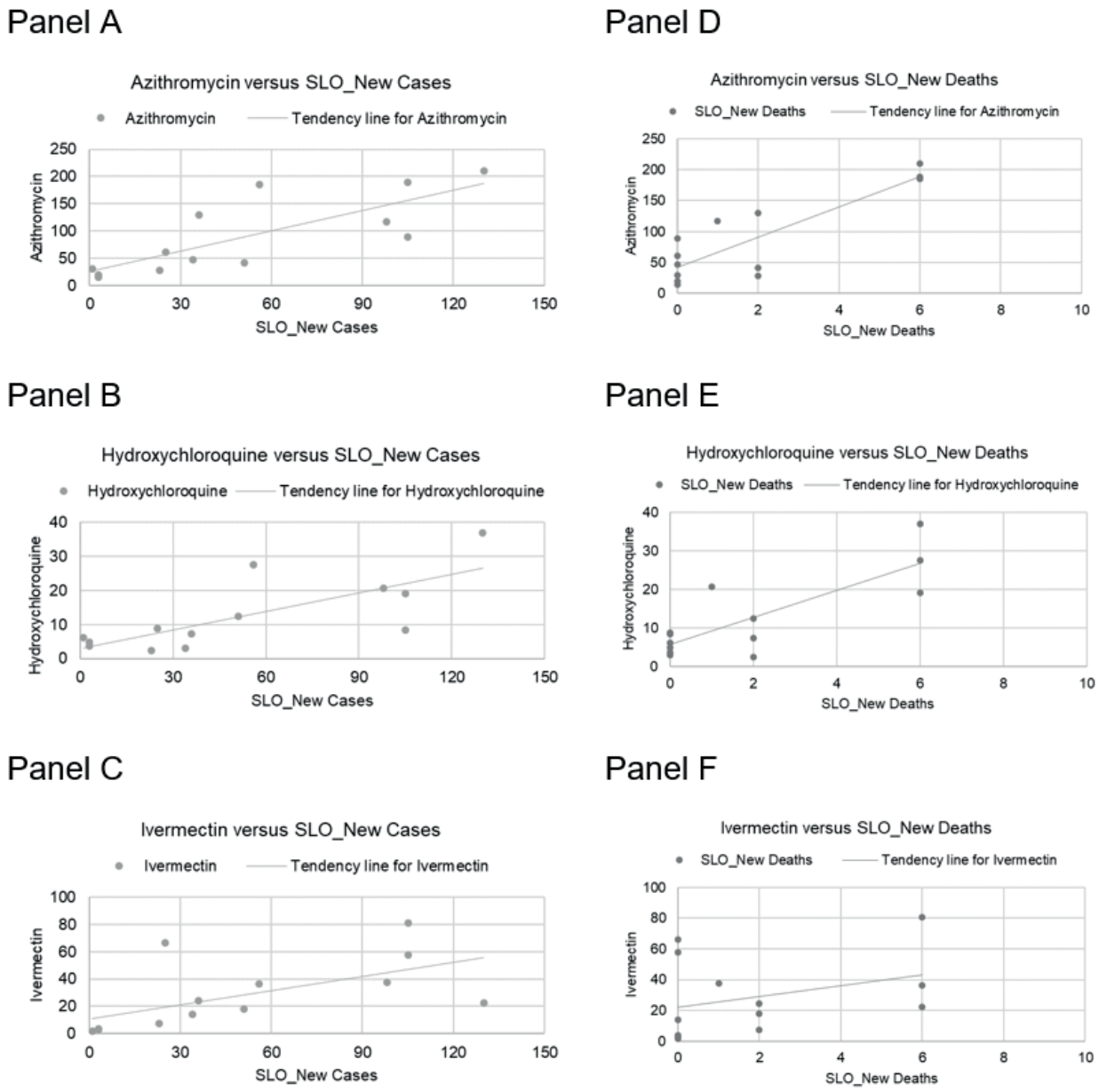

Figure 3. The Panel A, B and C represent the correlation between azithromycin, hydroxychloroquine and ivermectin (per 1000 habitants) and new cases of COVID-19 in SLO from March 2020 to March 2021, respectively. The Panel D, E and F represent the correlation between azithromycin, hydroxychloroquine and ivermectin (per 1000 habitants) and new deaths of COVID-19 in SLO from March 2020 to March 2021, respectively.

DISCUSSION

Temporal analysis results indicate that ivermectin and hydroxychloroquine consumption increased during the pandemic when compared to pre-pandemic time in SLO. Furthermore, we observed a positive correlation among new cases of COVID-19 and the prophylactics drugs (hydroxychloroquine, ivermectin and azithromycin). In relation to COVID-19 deaths, the outcomes showed positive correlation with azithromycin and hydroxychloroquine.

The temporal analysis revealed an increased supply of hydroxychloroquine in the pandemic compared to the pre-pandemic period. Around the world, it is possible to observe a similar phenomenon. A study conducted in India showed cumulative sales of hydroxychloroquine increased by 35.4% from 2019 to 2020[12]. In some hospitals in Spain and Italy, more than 60% of patients received hydroxychloroquine during hospitalization[13-14]. Also, in community pharmacies in Portugal, two months after the first confirmed cases of COVID-19, the pharmaceutical market continued to suffer from a shortage of hydroxychloroquine, where pharmacies still had difficulties to fulfill orders[15]. Hydroxychloroquine consumption increased significantly in March 2020 and remained high through September, with an estimated variation of +11.1 million doses (95% CI: 9.2 to 13.0 million; P <0.001) in March[12]. When compared to the number of COVID-19 cases per 100,000 population, the plateau of COVID-19 cases in India was seen in September 2020; after that peak, hydroxychloroquine sales and the number of cases started to decrease[12].

Although the scientific literature now corroborates our findings, we can bring to the light two important aspects for this increase in hydroxychloroquine use at the beginning of the pandemic: 1) an huge number of clinical studies of hydroxychloroquine for COVID-19 were launched from March to April (first months of the pandemic), and that a significant proportion of them remained active until November 2020[16-21]; and 2) the health professions appear to have responded very quickly to political interest in hydroxychloroquine, while responding much more slowly to the evolving medical evidence of its lack of efficacy. In this sense, our data showed a positive and significant linear correlation between hydroxychloroquine consumption during the pandemic with new cases and deaths of COVID-19, suggesting that the use of this drug did not reduce new cases or deaths by COVID-19.

About ivermectin supply, our current data showed a statistically significant increase in distribution during the pandemic when compared to the pre-epidemic period, with a positive and significant linear correlation only between the number of new cases COVID-19 in SLO. Ivermectin had already become known through a preprint publication (April 2020), where an observational case-control study evaluated the clinical efficacy of ivermectin and concluded that it was able to reduce mortality in patients. However, the result was not confirmed and a retraction was necessary[22]. This increase in ivermectin consumption may be related to mass disclosures of the benefits of ivermectin consumption to treat COVID-19, in a study that ivermectin showed 93% inhibition of coronavirus in cell cultures within 24h, published in June 2020[23]. In July 2021, a recent study evaluated the efficacy and safety of ivermectin for the treatment and prophylaxis of COVID-19, however it was retracted after ethical problems identified[24]. On the other hand, studies with robust methodological quality have investigated the effects of ivermectin for preventing hospitalization[7] or treatment[9]; and both studies concluded that there was no benefit compared to the placebo group.

Regarding azithromycin, no statistical changes were observed a long time, despite the absolute value increased along the years. Also, a significant linear correlation between this drug and COVID-19 new cases and deaths. In India, the proportion of antibiotic sales increased by 5.93% from 2019 to 2020, with a monthly increase in the azithromycin sales trend after lockdown period (+9.5 million doses)[12]. In Spain, in the intensive care unit the consumption of antibacterial, in 2020 increased by 23.42%, compared to 2019 (508.12 vs. 627.21), especially macrolides (azithromycin 275.09%)[25]. The azithromycin consumption in COVID-19 patients in hospitals in August and September 2020 vs 2019 increased from 11.5 DDDs per 100 occupied bed-days in 2019 to 17.0 DDDs per 100 occupied bed-days in 2020[26]. According to our results, the correlation showed that azithromycin also did not reduce new cases or death by COVID-19. Scientific literature concludes that this drug is not effective to treat

or prevent COVID-19 and it should not be recommended in treatment guidelines for hospitalized COVID-19 patients, taking as an example the German national treatment[27].

This current study has some limitations. First, the sample size of our study represents 10 of the 23 pharmacies/drugstores in the city of SLO. Second, our study was based on secondary data, then we did not collect population data, for example, age, sex, presence of comorbidities, vaccinated or not, if they took any medication to prevent COVID-19 without a confirmed diagnosis of the disease, if they contracted COVID-19. Third, we established the pandemic period of only 1 year including the first and second waves, being able to draw conclusions from the findings only between the analyzed period. Fourth, ecological studies cannot be used to determine the cause of something. Future studies can collect data about individuals and investigate the causality of the number of cases and deaths per COVID-19 related consumption of medications.

CONCLUSION

In conclusion, our findings showed according to other data in the literature that consumption of ivermectin and hydroxychloroquine increased over the pandemic time and as hydroxychloroquine as ivermectin prophylaxis probably do not reduce the risk of SARS-CoV-2 infection or deaths due to COVID-19 in SLO.

Authors contribution

MCC: contributed substantially to the conception and design of the research, data collection, analysis, interpretation of data, and drafted the manuscript with an important intellectual contribution.

AS: contributed substantially to the conception and design of the research, data collection, analysis, interpretation of data, and drafted the manuscript with an important intellectual contribution.

RFZ: contributed substantially to the conception and design of the research, data collection, analysis, interpretation of data, and drafted the manuscript with an important intellectual contribution.

DNS: contributed substantially to the analysis, interpretation of data, and drafted the manuscript with an important intellectual contribution.

FRS: contributed substantially to the analysis, interpretation of data, and drafted the manuscript with an important intellectual contribution.

LFM: contributed substantially to the conception and design of the research, data collection, analysis, interpretation of data, and drafted the manuscript with an important intellectual contribution.

Conflict of interest

Authors declare no conflict of interest.

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