SHORT COMMUNICATION

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Public interest in "early treatments" for coronavirus disease 2019 in Brazil: insights from Google Trends

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INTRODUCTION

The first case of coronavirus disease 2019 (COVID-19) in Brazil was reported on February 26, 2020, in the city of São Paulo, and the outbreak spread rapidly to other cities. At the time of this writing (November 4, 2021), 21,835,785 reported cases and 608,235 associated deaths had been confirmed in the country. The COVID-19 outbreak in Brazil has been characterized by sensationalism, fear, and misinformation[1]. Social media has been extensively used to support the false usefulness of the "early treatments" intended to prevent COVID-19 and cast doubt on the methods capable of mitigating the pandemic, such as the use of masks and social distancing[2]. These "early treatments" include the use of drugs with no proven efficacy for COVID-19, such as ivermectin, chloroquine, hydroxychloroquine (HCQ), and azithromycin. Ivermectin is a widely used drug for the treatment and control of many parasitic diseases[3]. Chloroquine is used to prevent and treat malaria and has efficacy as an anti-inflammatory agent for treating some inflammatory diseases such as rheumatoid arthritis and lupus erythematosus. Azithromycin is a broad-spectrum macrolide antibiotic used widely in the treatment and prevention of certain bacterial infections[4]. Although HCQ, chloroquine, and azithromycin have been used to treat patients with COVID-19 during the early pandemic period[4], recent systematic review and meta-analysis studies have not been able to support evidence for the efficacy of these drugs in the treatment and prevention of COVID-19[3,5-7]. Moreover, the irrational use of ineffective "early treatments" to prevent the disease can lead to bacterial resistance and adverse reactions[8].

In the present communication, we analyzed the public interest in ivermectin, chloroquine, HCQ, and azithromycin as early treatments during the COVID-19 pandemic. These drugs have been proposed as possible therapies for COVID-19, and even without proven efficacy for the treatment and prevention of the disease, they have been cited among the most commonly known drugs among the Brazilian population[9].

METHODS

Public interest was measured using Google Trends, a popular tool that provides information on frequencies of Internet queries from users on the Google search engine[10]. Data on COVID-19 were obtained from Cota[11], based on official sources from the Brazilian Ministry of Health. Statistical analysis of data was carried out using R version 4.1.1.

We performed a Google Trends search on November 8, 2021, to observe trends in the Internet searches in Brazil for Portuguese language versions of the terms "ivermectin," "chloroquine," "hydroxychloroquine," and "azithromycin" from January 6, 2019 until November 6, 2021. This period corresponds to the epidemiological week (EW) 2–52 in 2019, 1–53 in 2020, and 1–44 in 2021 (by convention, an EW is counted from Sunday to Saturday). Google Trends measures the public interest of a particular search query in relative search volume (RSV). RSV of a search term in a given week is measured on a scale of 0–100 based on its popularity compared to its peak search volume over a specified period. For example, the RSV for the search query "ivermectin" is 100 in the EW 28 of 2020 and 62 in the EW 29 of 2020. This means that in the EW 29 of 2020, this search term was 62% as popular as it was in the most popular week (EW 28 of 2020).

Generalized additive models (GAMs) were used to assess the association between the RSV for each drug and the weekly reported cases of COVID-19 infection. In this case, correlation coefficients are inappropriate due to the nonlinear relation between these series, and GAM provides more flexibility

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in the shape of the relationships between the variables compared to traditional models[12]. The mathematical formulation of the GAM model is given by $y_t=a+s(\log x_t)+e_t$. The variable y_t corresponds to the number of COVID-19 cases reported at the week t, x_t is the RSV for a given drug at the week t, a is a constant parameter, s is a smooth function, and e_t are independent and identically distributed error terms. The variable x_t was log-transformed to avoid the effect of outliers. In our analysis, GAMs were fitted using the "mgcv" package of R software. The model adequacy was assessed by plotting residuals versus fitted values and QQ plots, and the model fit was evaluated by the proportion of the null deviance explained (D).

As secondary data available online were used, the research was not submitted to an Ethics Committee on Human Research.

RESULTS

Figure 1 describes the weekly RSV for these four drugs. The dashed vertical line in the figure indicates the week when the World Health Organization (WHO) declared COVID-19 a global pandemic (March 11, 2020). We can note that the RSV for "ivermectin," "chloroquine," and "hydroxychloroquine" are close to zero before the dashed line, but weekly Google searches for "chloroquine" and "hydroxychloroquine" increased substantially just after that point. The peak of searches of the term "ivermectin" was reached when the public interest in chloroquine and HCQ decreased. Public interest in azithromycin was already substantial before the pandemic period, but it is observed that the number of searches for this term also increased after the WHO declaration.

Figure 2 compares the weekly RSV for the four drugs from February 23, 2020, until November 6, 2021 (EWs 9–53 in 2020 and EWs 1–44 in 2021, upper panel) and the time series of the weekly reported cases of COVID-19 in Brazil (lower panel). In Figure 2, we can note that the highest search volumes for ivermectin, HCQ, and azithromycin in the year 2021 occurred around EWs 11 and 12 (in mid-March). These peaks coincide with a period with a large number of notifications of COVID-19 (Figure 2B).

Figure 3 shows smoothed plots for the weekly Google searches for each drug versus the number of reported cases of COVID-19 infection in Brazil. All graphs in Figure 3 show a significant association between these variables so that the weeks in which there were more Internet searches for information on these drugs tended to be those with the highest number of COVID-19 notifications. In this analysis, we disregard the pandemic's exponential phase so that the time series used in the model started at EW 30 of 2020 (see Figure 2). Thus, in the model formulation, we consider t=1, …, 68. We highlight that these models are used only to describe the shape of the association between these variables without establishing cause-and-effect relationships.

DISCUSSION AND LIMITATIONS

Although ivermectin, HCQ, chloroquine, and azithromycin have no proven beneficial effect for treating COVID-19[3,5-7]

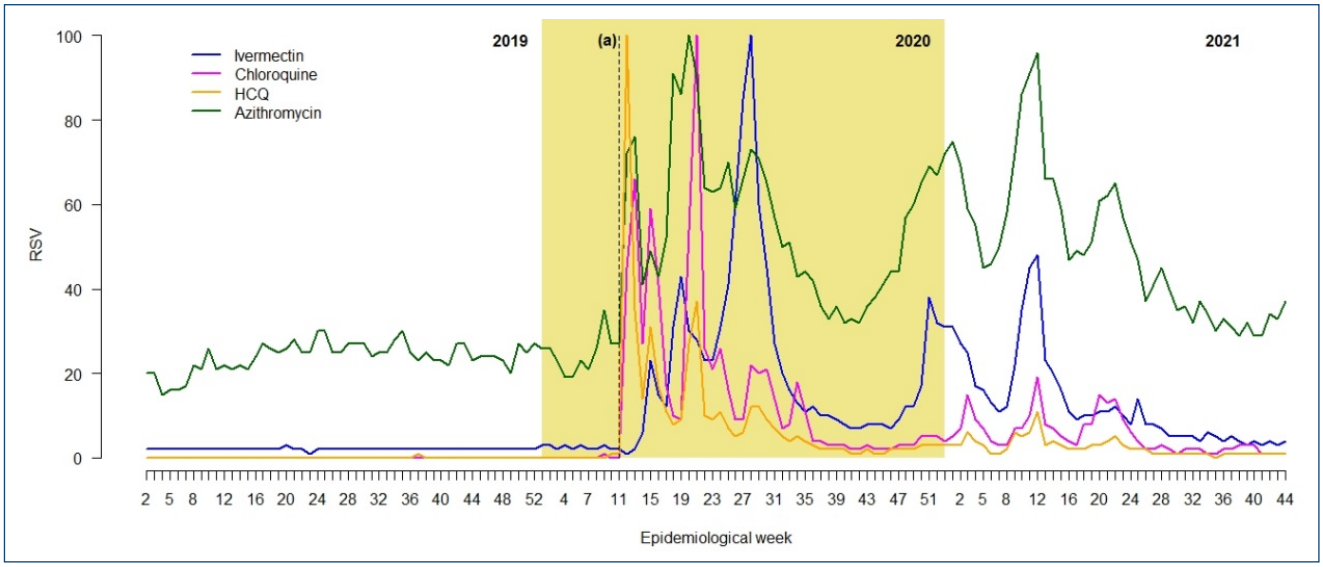

Figure 1. Weekly Google searches in Brazil for "ivermectin," "chloroquine," "hydroxychloroquine", and "azithromycin." The dashed vertical line labeled with an (a) indicates the week when the World Health Organization declared coronavirus disease 2019 a global pandemic (March 11, 2020).

their use as an "early treatment" for the disease has unfortunately been encouraged in Brazil by many politicians and religious leaders[13,14]. For example, Manaus, the capital of the state of Amazonas, bought US$71,000 in ivermectin for the treatment of COVID-19 and did not require a bidding process to reduce costs[13]. In April 2021, the Brazilian Senate created a Parliamentary Commission of Enquiry (CPI-Pandemia, acronym in Portuguese) to investigate actions and omissions of the federal government in tackling the pandemic, the collapse of healthcare in the state of Amazonas earlier this year, and irregularities in the use of public resources by states and municipalities. At the request of Senator Omar Aziz, President of the CPI-Pandemia, the Brazilian Federal Pharmacy Council produced a report on the sale of medicines associated with the treatment of COVID-19[15]. This report showed an 857% increase in ivermectin sales in the 12 months following the first recorded case of the disease in Brazil (March 2020). In this same period, the report showed a 126% increase in HCQ sales and a 71% increase in azithromycin sales. The report did not provide sales data for chloroquine, as this drug is distributed by the public health system and is not marketed to consumers by the private health sector. Despite this, the findings presented by the Brazilian Federal Pharmacy Council are consistent with those shown in Figure 1, which show that the public interest in "early treatments" for COVID-19 through Google search activity grew dramatically as soon as the WHO declared COVID-19 a global pandemic.

The increasing interest in ivermectin in the early months of the pandemic was largely motivated by the online publication of an article about its *in vitro* effect against the severe acute respiratory syndrome – associated coronavirus on April 3, 2020 (EW 14, 2020)[16] and by the subsequent media dissemination of the results of this research, which presented this drug as a promising treatment for the disease despite the lack of high-quality evidence. After the exponential phase of the pandemic (EWs 9–29, 2020), the public interest in "early treatment" is most intense in the periods with the highest notifications of COVID-19 cases (Figure 3).

The differences between officially reported cases of COVID-19 and the number of actual infections in the Brazilian population can be substantial, which could be viewed as a potential limitation of this study. This occurs due to many factors, including the underreporting of asymptomatic and mild cases, especially those that do not present for medical care, the insufficient

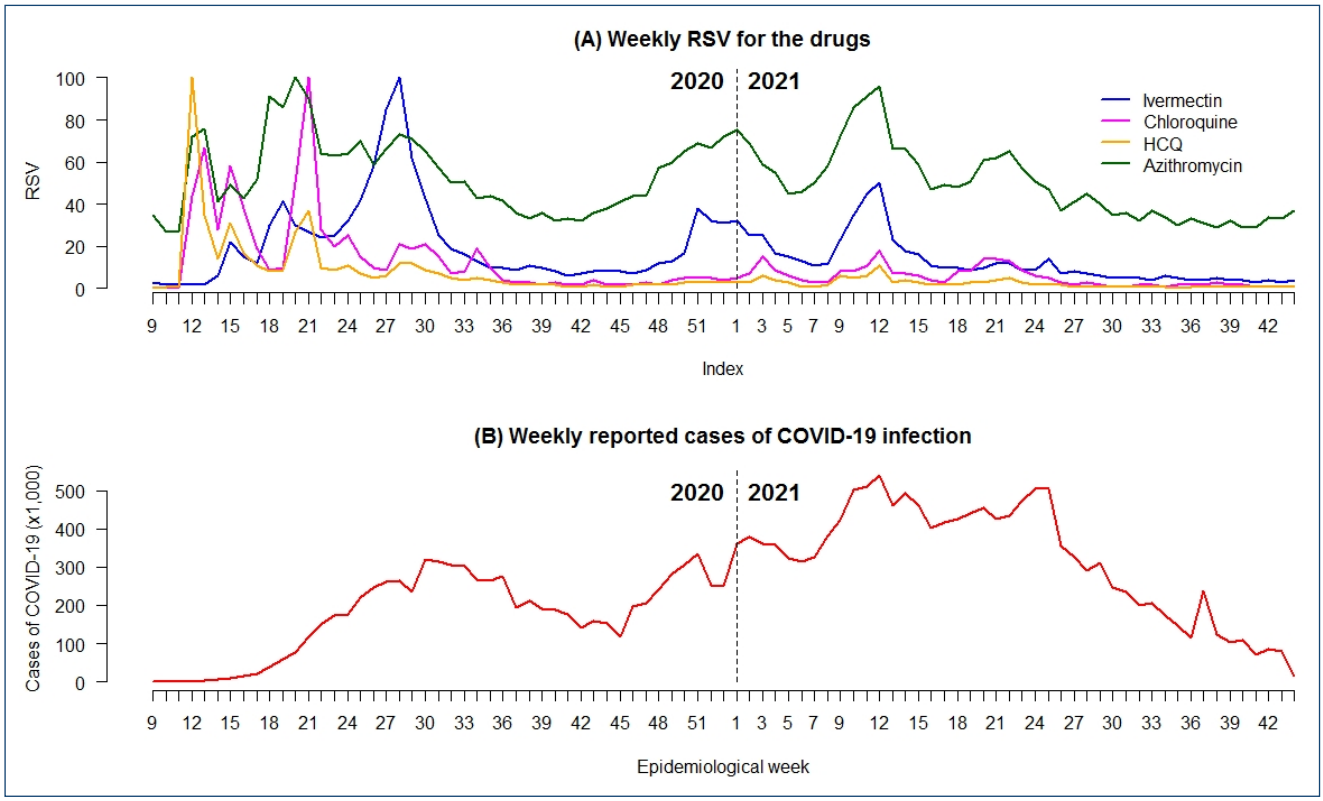

Figure 2. Panel (A) shows the weekly Google searches in Brazil for "ivermectin," "chloroquine," "hydroxychloroquine", and "azithromycin" from February 23, 2020 until November 6, 2021. Searches are presented as relative search volumes from 0 (least) to 100 (the highest number of searches). Panel (B) shows the weekly reported cases of coronavirus disease 2019 infection in Brazil in the same period of time.

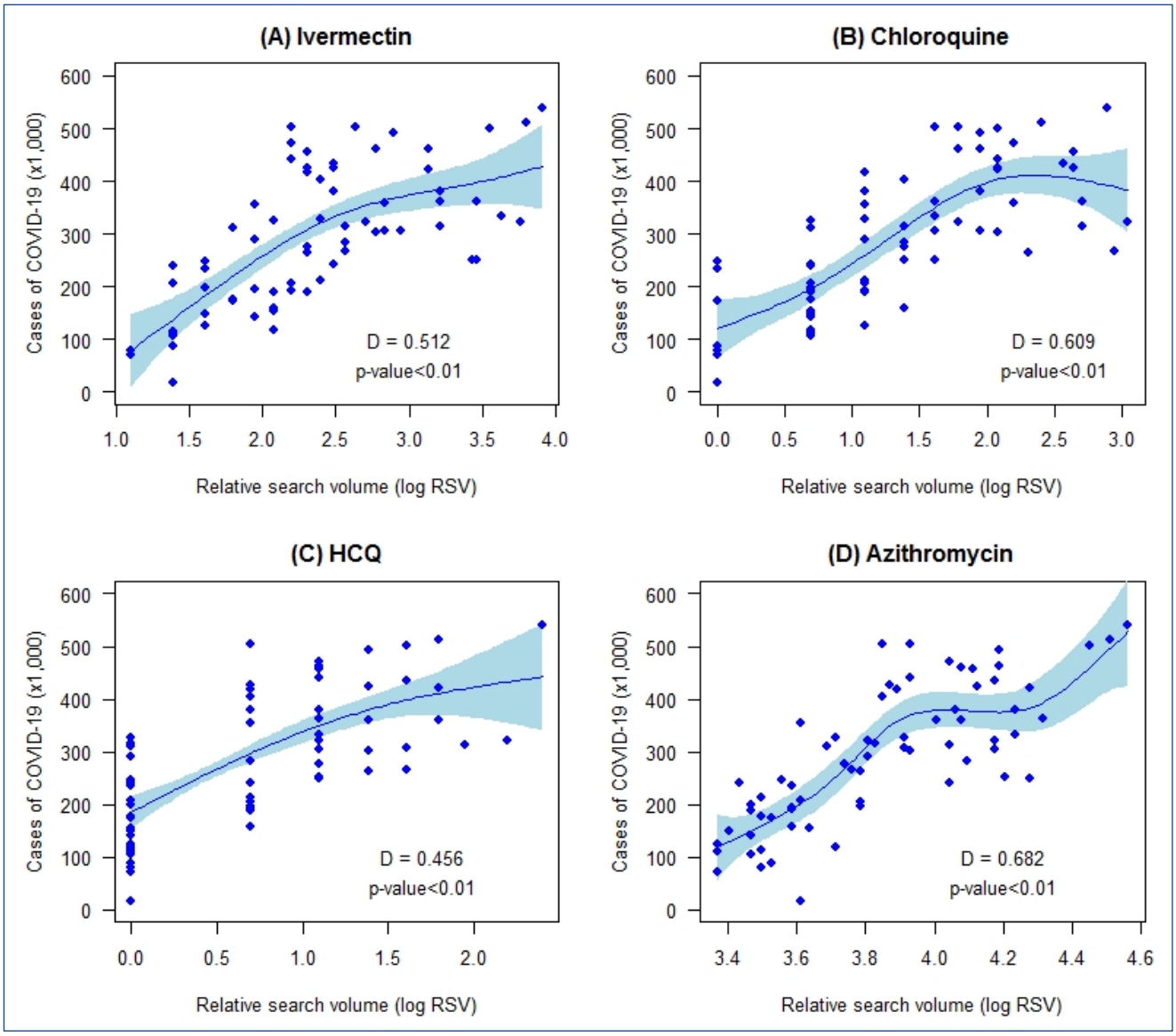

Figure 3. Generalized additive model analysis of the weekly reported cases of coronavirus disease 2019 infection in Brazil as a function of the weekly Google searches (in log scale) for (A) "ivermectin," (B) "chloroquine," (C) "hydroxychloroquine", and (D) "azithromycin" from July 19, 2020 until November 6, 2021. The shaded areas are error bands, panel (D) denotes the proportion of the null deviance explained by each model, and the p-values correspond to the approximate significance of smooth terms.

number of screening tests, false negative laboratory test results, and delays in reporting cases, among others.

CONCLUSIONS

Despite the limitations discussed previously, our findings suggest that Google Trends may be a useful tool for the continuous surveillance of the population's interest in inappropriate treatments for COVID-19 and, in an indirect manner, the consequent off-label use of medicines for this disease. The insights into the population's behavior provided by Google Trends can help create healthcare policies and information sources.

AUTHORS' CONTRIBUTIONS

EZM: Conceptualization, Formal Analysis, Writing – original draft, Writing – review & editing. **DCA**: Writing – original draft, Writing – review & editing. **MLZ**: Writing – original draft, Writing – review & editing.

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