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Effect of Covid-19 pandemic on azithromycin, chloroquine/hydroxychloroquine and ivermectin outpatient consumption in Brazil: a joinpoint regression analysis

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Abstract

Background The endorsement of unproven COVID-19 treatment marked the political bias in Brazil's pandemic response. This study aimed to analyze the trends in the consumption of azithromycin (AZI), chloroquine/hydroxychloroquine (CQ/HCQ), and ivermectin (IVM) considering COVID-19 cases and key political events.

Methods A retrospective cohort study was conducted to analyze the weekly outpatient dispensing records of AZI, CQ/HCQ, and IVM from the National Database of Actions and Services of Pharmaceutical Services in SUS (BNAFAR) and the COVID-19 incidence rates from January 2019 to December 2021. A joinpoint regression analysis was employed to assess shifts in COVID-19 incidence rates and AZI, CQ/HCQ, and IVM consumption in outpatients, expressed as Defined Daily Dose per 1,000 inhabitants per day (DID), in Brazil and its five geographical regions taking into consideration the timing of three political events.

Results There was a significant increase in AZI, CQ/HCQ, and IVM consumption during the COVID-19 pandemic in Brazil of 62.8%, 504.6%, and 525.7%, respectively. Adults and women had higher DID; however, a higher proportional rise was observed among men, especially for CQ/HCQ. A notable increase in the consumption of CQ/HCQ during the first COVID-19 wave, IVM in the second, and AZI in both waves was more pronounced in the South, Midwest, and North of Brazil. This pattern coincided closely with the timeline of COVID-19 incidence rates and showed an upward trend in all three medicines after key political events that endorsed their use, particularly in these three regions. No corresponding downward trend in COVID-19 cases was observed despite the increased use of these medicines. A significant reduction in consumption nationwide was observed after an increase in vaccination coverage, resulting in a DID near pre-pandemic levels.

Conclusion The study provides substantial evidence on the relationship between COVID-19 incidence, political events, and the consumption of AZI, CQ/HCQ, and IVM during the pandemic in Brazil. The findings suggest that consumption trends were aligned with regional political affiliations and the COVID-19 incidence rates. These highlight

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the importance of political determinants of inappropriate medicine utilization that wastes scarce resources and increases the risk of adverse health outcomes and antimicrobial resistance.

Keywords COVID-19, Drug utilization, Health policy, Azithromycin, Chloroquine, Hydroxychloroquine, Ivermectin, Brazil

Introduction

The coronavirus disease 2019 (COVID-19) pandemic posed new challenges to healthcare systems globally. At the onset of the pandemic, initial studies showed a potential off-label use of medicines such as ivermectin (IVM), and chloroquine/hydroxychloroquine (CQ/HCQ) among others repurposing available drugs to treat COVID-19 [1, 2]. In March 2020, early studies indicated that COVID-19 patients were at risk of bacterial co-infection or secondary infection, particularly associated with *Mycoplasma*, for which the antibiotic azithromycin (AZI) is the primary treatment [1, 3]. Shortly after, in April 2020, a study argued for an antiviral activity of IVM against the SARS-CoV-2 virus in vitro [2].

In the early pandemic, this discussion quickly became part of political debates where individuals in positions of power gave CQ/HCQ the silver bullet status [4, 5]. Influential figures' advocacy for unproven medicines during the pandemic has intensified public interest in these therapies with extensive promotion on social media across the globe, notably in Brazil and the U.S [6, 7]. The scientific knowledge and evidence became a subject of political polarization.

Several national guidelines, particularly in Latin America, recommended the use of AZI, CQ/HCQ, and IVM use for COVID-19 treatment or prevention, despite the lack of good-quality scientific evidence [8]. In Brazil and Latin America, the promotion and distribution of medicines for "early treatment" of COVID-19, commonly referred to as the 'Covid Kit' [9] was observed. Endorsing unproven medications to prevent the spread of the virus instead of non-pharmacological preventive measures symbolized political bias in Brazil's pandemic response [10], implying a significant financial cost of approximately $16 million [11].

In Brazil, physicians were encouraged to prescribe COVID-19 kit medicines under medical autonomy by a decision from the Brazilian Federal Board of Medicine (FBM-Br) in April 2020 advocating for CQ/HCQ use in COVID-19 patients [12]. Additionally, physicians were also guided by a national protocol– "Early Treatment of Patients with COVID-19"– from the Ministry of Health (MoH) in May 2020 [13]. The protocol, in effect from May 2020 to May 2021, recommended using CQ/HCQ alone or in combination with AZI for patients at any stage of the disease, including in ambulatory settings.

Bolsonaro, a far-right populist, ascended to power in 2018 [14]. His presidency was characterized by pro-market policies and the strategic use of disinformation and anti-scientific rhetoric to undermine democratic institutions that opposed his political agenda [15].

While AZI, CQ/HCQ, and IVM consumption trends have been extensively studied in North America, Europe, and Australia, evidence from South America is still lacking. Furthermore, it is unclear how the political discourse, guidelines, and the COVID-19 incidence rate possibly influence medicine consumption trends.

This study aims to fill this knowledge gap by studying the consumption trends of azithromycin (AZI), chloroquine/ hydroxychloroquine (CQ/HCQ), and ivermectin (IVM) in the Brazilian universal public health system, called Unified Health System (SUS, from the Portuguese "Sistema Único de Saúde), between January 2019 and December 2021, considering COVID-19 incidence rates and key political events.

Methods

Study design and setting

This is a retrospect cohort study that uses a joinpoint regression analysis to assess changes in trend in the incidence of COVID-19 and the consumption of AZI, CQ/HCQ, and IVM in outpatients treated at public ambulatory health facilities in Brazil, from January 2020 to December 2021 (EW 1/2020 to 52/2021).

The political events during the COVID-19 pandemic management in Brazil considered in the analysis were: (a) the publication of a Technical Report by the FBM-Br advocating the use of CQ/HCQ in COVID-19 patients on April 16, 2020 [12] (Flag 1); (b) the launch by the MoH of 'TrateCov' application in Manaus (capital of Amazonas state) on January 11, 2021[16] (Flag 2); and (c) the achievement of more than 60% of COVID-19 vaccination coverage for the first dose [17], which varied according to the geographical region (Flag 3).

Data source and inclusion criteria

We used the National Database of Actions and Services of Pharmaceutical Services in SUS (BNAFAR). BNAFAR contains medicine dispensing records from SUS's health facilities at the outpatient level. Created in 2013, it is under the responsibility of the MoH and consolidates the national data on Pharmaceutical Services in the Brazilian public health system, known as the Unified Health System (SUS) [18].

Primary health care (PHC) data reporting to BNAFAR is mandatory only for municipalities that receive

subsidies from the federal government to improve the infrastructure of pharmaceutical services [19, 20], accounting for 63% of all municipalities until 2023 [21]. Therefore, BNAFAR is still in implementation, not all municipalities report their data Approximately 32% of SUS PHC facilities that dispense medicines to users [22] had records of antimicrobials dispensing in BNAFAR between 2019 and 2021. BNAFAR's coverage across geographical regions is Southeast (52.5%) and South (51.9%), followed by Midwest (39.3%), North (25.5%), and Northeast (17.1%). Patients have to show a prescription to obtain AZI, CQ/HCQ, and IVM, as well as any other medicines dispensed through the SUS.

We used individualized and anonymized data from AZI, CQ/HCQ, and IVM dispensing records from January 2019 to December 2021. Our primary outcome was changes in medicine consumption trends during the COVID-19 pandemic and the exposure of interest. The consumption was analyzed weekly and expressed as a Defined Daily Dose (DDD) per 1,000 inhabitants per day (DID) [23]. DDD is the average daily dose of a medication used for adults and its primary intended use, as standardized by a World Health Organization (WHO) collaborating center [23].

To minimize the risk of bias, we excluded facilities that did not record at least one dispensation of any antimicrobial each year and those that registered all dispensations under a single user identification as well as patients with more than 30 dispensing records throughout the period.

Our secondary outcome was the incidence of COVID-19, aiming to compare trends in disease incidence in Brazil and its five geographical regions with the evolution of AZI, CQ/HCQ, and IVM consumption. This data was collected from the Coronavirus Brazil website [24]. We calculated the incidence rates by dividing the number of new cases in each epidemiological week (EW) by the population of Brazil and each region.

Statistical analysis

We conducted descriptive bivariate analysis illustrating the distribution of consumption by medicine, patient sex, age group, and geographical region over time. We performed an ANOVA test to analyze the difference between the means of DID in the years for each variable, considering a 95% confidence interval. We also calculated the percentage difference from 2019 (pre-pandemic year) to 2020 and 2021 (pandemic years).

To analyze medicine consumption trends and COVID-19 incidence, we performed a joinpoint regression analysis [25]. Joinpoint regression is a statistical method that identifies points where a significant change in trend occurs in a data series. It models the data by fitting linear segments, and at each "joinpoint" (the point where two segments meet), a statistically significant change in the trend is identified. The model estimates variation using Poisson regression and significance tests for trend change using the Monte Carlo permutation method. In the final model, each joinpoint represents a statistically significant shift in the trend (increase or decrease), and each of the segments is described by a coefficient (slope), which indicates the rate of change within that segment [25, 26]. Each inflection point highlights significant changes even if the slope of a particular segment may not be statistically significant (p-value < 5%). Using the software Joinpoint Regression Program, version 4.6.0.0, we analyzed the data under the assumption of constant variance (homoscedasticity) and first-order autocorrelation.

We chose joinpoint analysis instead of interrupted times series (ITS) due to the difficulty of controlling many time-varying confounders in a dynamic event like the COVID-19 pandemic. Therefore, the series was not a candidate for the ITS approach, which presupposes the non-existence of concomitant policies/events affecting the outcome and the time itself [27]. Joinpoint is a data-driven analysis that is better suited for this scenario since where it is unclear which event determined changes in trend [28].

Results

This study analyzed 7,217,313 AZI, CQ/HCQ, and IVM dispensing records in SUS public outpatient pharmacies from January 2019 to December 2021, accounting for 17.3% of all public antimicrobial records during this period. The data covered 48.7% of health facilities at this level of care, which dispensed at least one antimicrobial in this period.

There was an increase in consumption of all these drugs during the COVID-19 pandemic. IVM and CQ/HQC exhibited a step up of over 500% in their consumption from 2019 to 2021, and AZI 62.8%. Adults and females were the biggest consumers. However, men had a higher proportional increase in 2020 and 2021 compared to 2019, especially for CQ/HCQ (1,697.2% and 1,724.2%, respectively).

Consumption was higher in the South, Midwest, and North. The percentage difference between the post and pre-pandemic years was higher in the Midwest (305.3%) and Northern (260.4%) regions (Table 1). Most health facilities included in this study were in the Southeast (33.49%), Northeast (27.28%), and South (25.78%).

The trends in AZI, CQ/HCQ, and IVM consumption during the pandemic period and in COVID-19 incidence were similar (Table 2; Figs. 1 and 2, and 3). The AZI and IVM time series inflection points, which represent the changes in their consumption trends, coincided with those of the COVID-19 incidence series, mainly in the Southern, Midwest, and Northern regions. The same happened with CQ/HCQ, but in contrast, it only

Table 1 Azithromycin, chloroquine/ hydroxychloroquine, and ivermectin consumption in a defined daily dose per 1,000 inhabitants per day. Brazil, January 20,219 to December 2021

Variables		Consumption (DID)					
		2019	2020	2021	Total	Dif%* 2019–2020	Dif%* 2019–2021
Total		0.2176	0.4068	0.5257	0.1500	86.9%	141.6%
Drugs	Azithromycin	0.1805	0.2530	0.2939	0.7275	40.1%	62.8%
	Chloroquine/ Hydroxychloroquine	0.0002	0.0011	0.0011	0.0024	**479.0%**	**504.6%**
	Ivermectin	0.0369	0.1526	0.2307	0.4202	**314.0%**	**525.7%**
Sex	Female	0.1090	0.2088	0.2477	0.5655	91.5%	127.1%
	Azithromycin	0.0909	0.1309	0.1382	0.3600	44.1%	52.2%
	Chloroquine/ Hydroxychloroquine	0.0001	0.0006	0.0007	0.0015	**336.8%**	**387.0%**
	Ivermectin	0.0180	0.0773	0.1087	0.2040	**328.4%**	**502.6%**
	Male	0.0662	0.1406	0.1797	0.3865	112.5%	171.6%
	Azithromycin	0.0544	0.0848	0.0964	0.2356	56.1%	77.3%
	Chloroquine/ Hydroxychloroquine	0.0000	0.0004	0.0004	0.0007	**1697.2%**	**1724.2%**
	Ivermectin	0.0118	0.0554	0.0829	0.1501	**370.5%**	**604.2%**
Age groups	Children (0–12 years)	0.0084	0.0068	0.0083	0.0235	-20.0%	-1.8%
	Adolescents (13–17 years)	0.0042	0.0056	0.0075	0.0173	31.2%	77.3%
	Adults (18–64 years)	0.0434	0.1017	0.1258	0.2710	**134.2%**	**189.7%**
	Older adults (> = 65 years)	0.0078	0.0134	0.0143	0.0355	72.3%	84.0%
Regions	North	0.0784	0.1998	0.2826	0.5608	**154.8%**	**260.4%**
	Northeast	0.0398	0.0804	0.0608	0.1811	101.9%	52.6%
	Southeast	0.0641	0.0981	0.1341	0.2963	53.0%	109.2%
	South	0.1971	0.3298	0.4686	0.9954	67.3%	137.7%
	Midwest	0.0859	0.2670	0.3480	0.7009	**210.9%**	**305.3%**

p-value < 5% for each row in the ANOVA test by years

*Dif% = difference percentage

happened in the first peak of incidence, especially in the Northern region. A significant reduction in AZI, CQ/HCQ, and IVM usage was observed after the vaccination coverage increase around EW 13/2021. Flag 3 (> 60% vaccination coverage) occurred from EW 34–37/2021, with a delay in the North until EW 45/2021.

The consumption trends of AZI, CQ/HCQ, and IVM exhibited some relevant differences among themselves and across regions. Regarding AZI, the consumption trends are very similar to the COVID-19 case rates in the Midwest, Southeast, and, more evidently, the North. AZI consumption increased notably right after the first flag (EW 16/2020). There was also a significant upward trend in AZI usage between EW 17 to 20/2020 and 22 to 28/2020 in the Southeast and Northeast, respectively. At the beginning of 2021, AZI consumption sharply increased in the North, coinciding with an increased trend in cases and the launch of the 'TrateCov' app in EW 3/2021 (Flag2). The Southern region had the highest total consumption of AZI during the pandemic, although the inflection points differed from those of COVID-19 incidence. The increase in AZI consumption in the South at EW 09/2021 coincided with the COVID-19 cases until EW 24/2021.

Regarding CQ/HCQ utilization, a pronounced upward trend occurred in the initial phase of the pandemic across all regions. However, during the second peak of incidence, the CQ/HCQ usage remained low and stable, except in the South and Midwest. The South experienced its more relevant upward CQ/HCQ consumption trend in 2021 (EW 6/2021). In the Midwest, there was another increasing trend at the end of 2020, between EW 45 and 50. Changes in CQ/HCQ use trends did not seem relevant in the Northeast and particularly in the Southeast.

The IVM consumption was highest in the North and Midwest, increasing drastically from EW 18/2020 and 24/2020, respectively, coinciding with a significant increase in the incidence of COVID-19 and with Flag 1. Similarly, the subsequent decline in consumption converged with a reduction in incidence. We observed increased IVM consumption across all regions as the COVID-19 incidence built up, particularly in the North, South, and Midwest, especially during the second wave.

The initial shift in trend, marked by a significant increase in IVM use, was observed in the North and Northeast during epidemiological weeks 15 and 17/2020, respectively, followed shortly after in the Midwest (EW 24/2020). After decreasing COVID-19 incidence around EW 28/2020, a decline in the consumption of IVM was also observed. However, this trend shifted during the second wave of cases, reaching more pronounced consumption levels in the North, South, and Midwest. The models

Table 2 Correlation between the new COVID-19 cases and the consumption of azithromycin, chloroquine/ hydroxychloroquine, and ivermectin by joint point regression. Brazil, January 2019 to December 2021

Variables	Baseline			Trend 2			Trend 3			Trend 4			Trend 5			Trend 6		
	Period	Trend	p-value	Period	Trend	p-value	Period	Trend	p-value	Period	Trend	p-value	Period	Trend	p-value	Period	Trend	p-value
Brazil																		
New COVID-19 cases	2020/1–16	0.0026	0.868	2020/16–31	0.0991	**0.000***	2020/31–42	-0.1832	**0.000***	2020/42-2021/14	0.1488	**0.000***	2021/14–52	-0.1312	**0.000***			
AzIthromycin	2020/1–30	0.0077	**0.000***	2020/30–42	-0.0193	**0.003***	2020/42-2021/10	0.0226	**0.001***	2021/10–44	-0.0191	**0.000***	2021/44–52	0.0157	0.115			
Chloroquine/ Hydroxychloroquine	2020/1–19	0.0000	0.856	2020/19–30	0.0002	**0.000***	2020/30–39	-0.0004	**0.000***	2020/39-2021/11	0.0002	**0.000***	2021/11–37	-0.0001	**0.000***	2021/37–52	0.0000	**0.041***
Ivermectin	2020/1–23	0.0019	0.162	2020/23–28	0.0463	**0.013***	2020/28–43	-0.0611	**0.001***	2020/43-2021/11	0.0315	**0.000***	2021/11–15	-0.0732	**0.013***	2021/15–52	0.0470	0.106
North																		
New COVID-19 cases	2020/1–18	0.0102	0.235	2020/18–22	0.4371	**0.001***	2020/22–52	-0.4895	**0.000***	2020/52-2021/3	0.4740	**0.000***	2021/3–38	-0.4936	**0.000***	2021/38–52	0.0732	**0.000***
Azithromycin	2020/1–17	0.0054	**0.050***	2020/17–20	0.0760	0.124	2020/20–52	-0.0882	0.074	2020/52-2021/2	0.1284	**0.010***	2021/2–40	-0.1343	**0.007***	2021/40–52	0.0243	**0.000***
Chloroquine/ Hydroxychloroquine	2020/1–18	0.0000	0.725	2020/18–29	0.0013	**0.000***	2020/29–41	-0.0024	**0.000***	2020/41-2021/19	0.0012	**0.000***	2021/19–52	-0.0001	**0.007***			
Ivermectin	2020/1–15	-0.0019	0.715	2020/15–28	0.0332	**0.000***	2020/28–52	-0.0460	**0.000***	2020/52-2021/2	0.3971	**0.001***	2021/2–17	-0.4369	**0.000***	2021/17–52	0.0415	**0.000***
Northeast																		
New COVID-19 cases	2020/1–17	0.0040	0.401	2020/17–28	0.0979	**0.000***	2020/28–44	-0.1504	**0.000***	2020/44-2021/23	0.0858	**0.000***	2021/23–32	-0.1793	**0.000***	2021/32–52	0.1340	**0.000***
Azithromycin	2020/1–12	0.0092	**0.002***	2020/12–17	-0.0378	**0.002***	2020/17–20	0.1392	**0.000***	2020/20–37	-0.1271	**0.000***	2020/37-2021/15	0.0178	**0.000***	2021/15–52	-0.0028	**0.001***
Chloroquine/ Hydroxychloroquine	2020/1–18	0.0000	0.950	2020/18–21	0.0004	0.082	2020/21–25	-0.0006	**0.034***	2020/25–28	0.0007	**0.013***	2021/28–36	-0.0008	**0.002***	2020/36-2021/52	0.0003	**0.000***
Ivermectin	2020/1–17	0.0000	0.994	2020/17–28	0.0084	**0.000***	2020/28–40	-0.0133	**0.000***	2020/40-2021/12	0.0064	**0.000***	2021/12–52	-0.0032	**0.000***			
Southeast																		
New COVID-19 cases	2020/1–17	0.0025	0.644	2020/17–32	0.0471	**0.000***	2020/32–42	-0.0767	**0.000***	2020/42-2021/23	0.0553	**0.000***	2021/23–36	-0.1064	**0.000***	2021/36–52	0.0538	**0.000***
Azithromycin	2020/1–22	-0.0007	0.665	2020/22–28	0.0329	**0.016***	2020/28–35	-0.0585	**0.001***	2020/35-2021/23	0.0304	**0.003***	2021/23–36	-0.0176	**0.000***	2021/36–52	0.0159	**0.000***

Table 2 (continued)

Variables	Baseline			Trend 2			Trend 3			Trend 4			Trend 5			Trend 6		
	Period	Trend	p-value	Period	Trend	p-value	Period	Trend	p-value	Period	Trend	p-value	Period	Trend	p-value	Period	Trend	p-value
Chloroquine/ Hydroxychloroquine	2020/1-2021/12	0.0000	**0.000***	2021/12–42	0.0000	**0.000***	2021/42–52	0.0000	0.220									
Ivermectin	2020/1–23	0.0006	0.586	2020/23–27	0.0365	0.121	2020/27–40	-0.0477	**0.045***	2020/40-2021/12	0.0180	**0.000***	2021/12–52	-0.0130	**0.000***			
South																		
New COVID-19 cases	2020/1–12	-0.0021	0.942	2020/12-2021/24	0.0432	0.132	2021/24–30	-0.3238	**0.001***	2021/30–52	0.2514	**0.009***						
Azithromycin	2020/1-2021/6	0.0092	**0.000***	2021/6–9	0.3240	0.131	2021/9–13	-0.6013	**0.013***	2021/13–20	0.2900	**0.011***	2021/20–52	-0.0408	**0.000***			
Chloroquine/ Hydroxychloroquine	2020/1–36	0.0000	0.290	2020/36–49	0.0002	**0.000***	2020/49-2021/6	-0.0003	**0.001***	2021/6–9	0.0017	**0.050***	2021/9–12	-0.0029	**0.016***	2021/12–52	0.0012	0.141
Ivermectin	2020/1–45	0.0090	**0.000***	2020/45–49	0.1035	0.186	2020/49-2021/6	-0.1401	0.079	2021/6–10	0.3978	**0.000***	2021/10–14	-0.7480	**0.000***	2021/14–52	0.3636	**0.000**
Midwest																		
New COVID-19 cases	2020/1–21	0.0032	0.659	2020/21–33	0.0978	**0.000***	2020/33–45	-0.1617	**0.000***	2020/45-2021/21	0.0973	**0.000***	2021/21–52	-0.0850	**0.000***			
Azithromycin	2020/1–24	-0.0005	0.820	2020/24–27	0.1315	0.170	2020/27–45	-0.1451	0.130	2020/45-2021/12	0.0333	**0.000***	2021/12–41	-0.0370	**0.000***	2021/41–52	0.0257	**0.000***
Chloroquine/ Hydroxychloroquine	2020/1–24	0.0000	0.770	2020/24–32	0.0012	**0.001***	2020/32–45	-0.0016	**0.000***	2020/45–50	0.0017	**0.035***	2020/50-2021/52	-0.0015	0.063			
Ivermectin	2020/1–24	0.0026	0.564	2020/24–28	0.2438	**0.018***	2020/28–45	-0.2863	**0.006***	2020/45-2021/10	0.0698	**0.000***	2021/10–52	-0.0538	**0.000***			

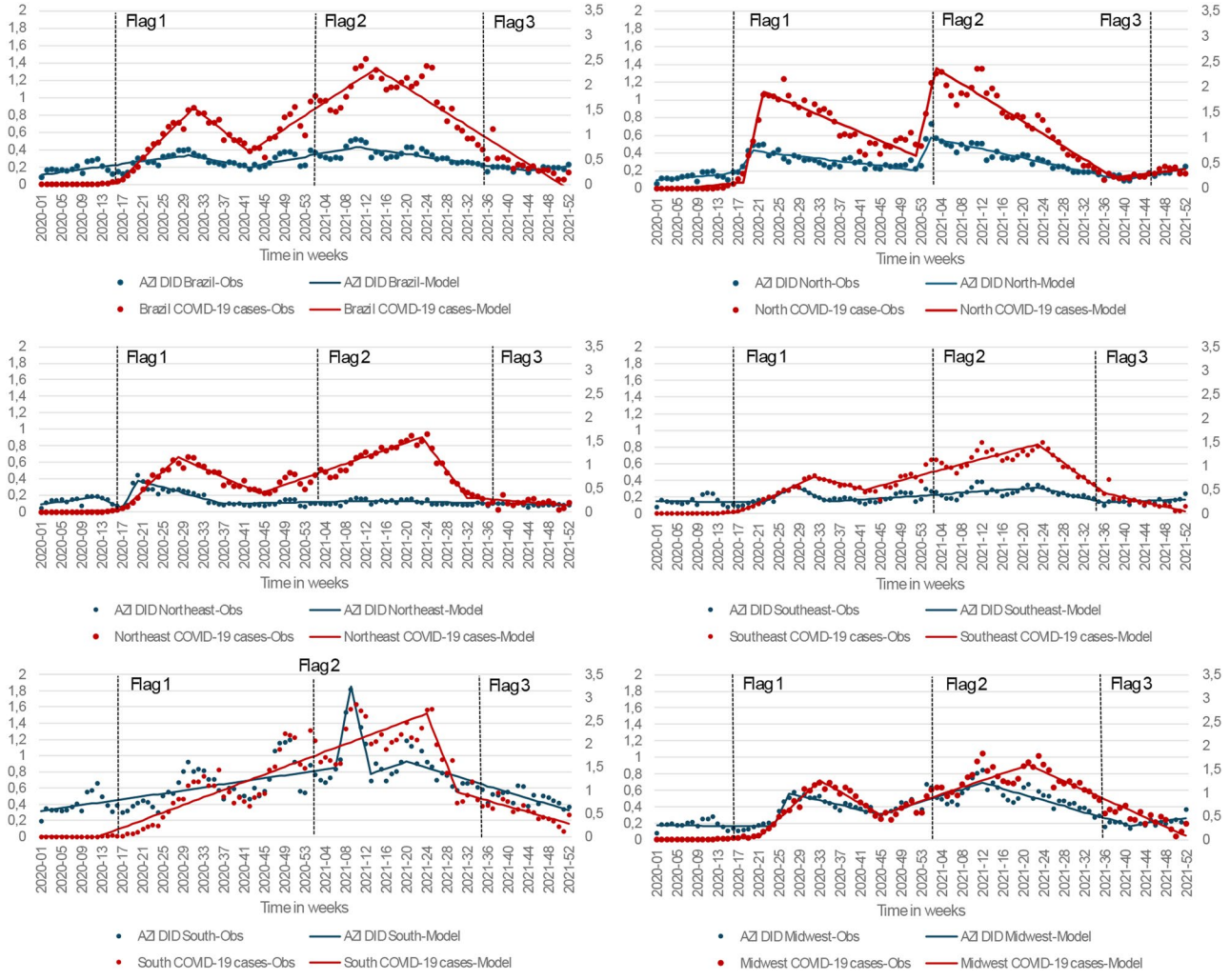

Fig. 1 Azithromycin and new COVID-19 cases in Brazil and its geographical regions. Brazil, 2020 to 2021. Flag 1: Technical report of the Brazilian Federal Board of Medicine (FBM-Br) advocating using chloroquine and hydroxychloroquine in patients diagnosed with COVID-19. Flag 2: The Minister of Health launched the 'TrateCov' app in person in Manaus, and the COVID-19 vaccination has begun. Flag 3: Over 60% of COVID-19 vaccination coverage for the first dose

did not point out relevant upward trends in IVM usage in the Northeast and Southeast.

In early 2021, the consumption of the three drugs showed a downward trend despite the incidence of COVID-19. When vaccination reached 60% coverage (Flag 3), consumption levels were already lower and close to pre-pandemic levels. By the end of this year, following a new increase in the rate of new cases, there was a discreet but significant increase in the consumption of AZI in the North, Southeast, and Midwest, such as IVM in the North and South.

Discussion

Our study provides significant evidence of the relationship between COVID-19 cases, key political events, and AZI, CQ/HCQ, and IVM consumption in the SUS during the pandemic in Brazil.

We found a 62.8% increase in the dispensing of AZI, 504.6% of CQ/HCQ, and 525.7% IVM compared to the pre-pandemic level at SUS public pharmacies. AZI consumption increased at the two points in time of highest COVID-19 incidence rates in the period analyzed. This antibiotic was widely used in patients diagnosed with the disease, due to its immunomodulatory and anti-inflammatory effects and the possibility of bacterial secondary or co-infections of these patients. However, its use was not associated with improved clinical outcomes [29].

The peak in CQ/HCQ consumption occurred during the first wave of the pandemic. At this moment the FBM-Br's technical report was published, followed by MoH's guideline, recommending the use of this medicine to treat COVID patients. A similar pattern was observed in the U.S [30], where the then President also advocated using CQ/CHQ, attempting to offer a simplistic solution

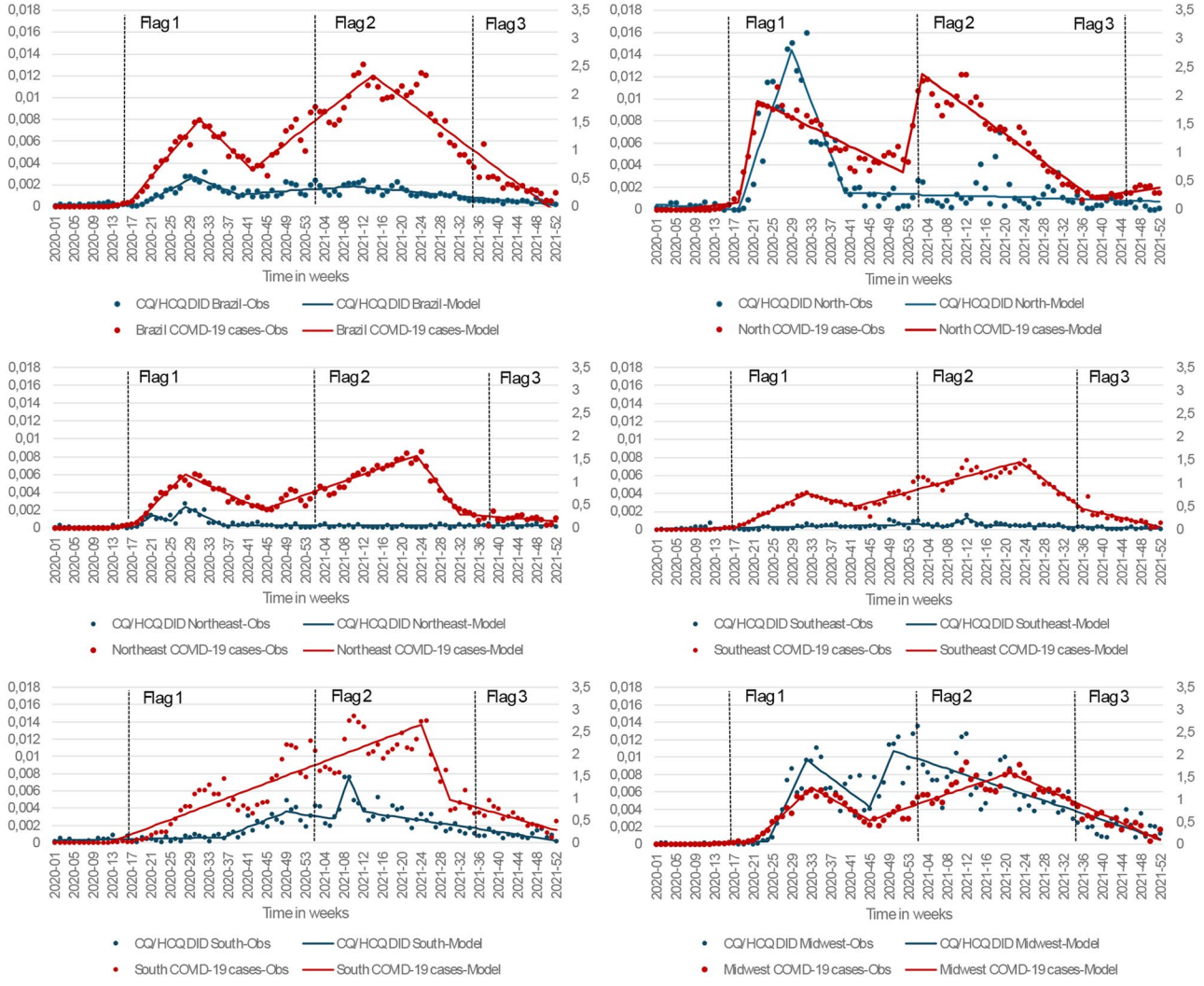

Fig. 2 Chloroquine/Hydroxychloroquine and new COVID-19 cases in Brazil and its geographical regions. Brazil, 2020 to 2021. Flag 1: Technical report of the FBM-Br advocating using chloroquine and hydroxychloroquine in patients diagnosed with COVID-19. Flag 2: The Minister of Health launched the 'TrateCov' app in person in Manaus, and the COVID-19 vaccination has begun. Flag 3: Over 60% of COVID-19 vaccination coverage for the first dose

to a complex problem, thereby politicizing the pandemic [5].

On the other hand, the increase in national IVM consumption was more pronounced during the second wave. In at least 8 countries in Latin America, including Brazil, governments distributed IVM in an attempt to reduce hospitalizations, despite the lack of good scientific evidence supporting its efficacy [9]. In the U.S. there was also a significant rise in the outpatient use of ivermectin, reaching a 989% rise in January 2021 [31].

During the COVID-19 pandemic, leadership in power downplayed the severity of the crisis and rejected scientific evidence, discredited democratic institutions, using denialist rhetoric, and shifting responsibility for deaths and economic crises onto external entities, such as subnational governments and international organizations. The rejection of scientific advice politically undermines the legitimacy of scientific expertise and its institutions, further reducing public trust in these authorities [32, 33].

Changes in consumption were not limited to public facilities. In the private sector sales of IVM and CQ/HCQ experienced a dramatic surge, skyrocketing by over 10 million percent, as their sales were negligible before this pandemic [34]. AZI sales also experienced a significant increase, reaching almost 70% [34].

Despite the significant rise in the use of these medicines throughout the pandemic, there was no corresponding decrease in the COVID-19 incidence in Brazil. The cases continued to grow regardless of the use of these medicines. These trends were more clearly observed in the Northern, Southern, and Midwest regions. A significant reduction in AZI, CQ/HCQ, and IVM usage was observed nationwide only after the advancement of vaccination coverage.

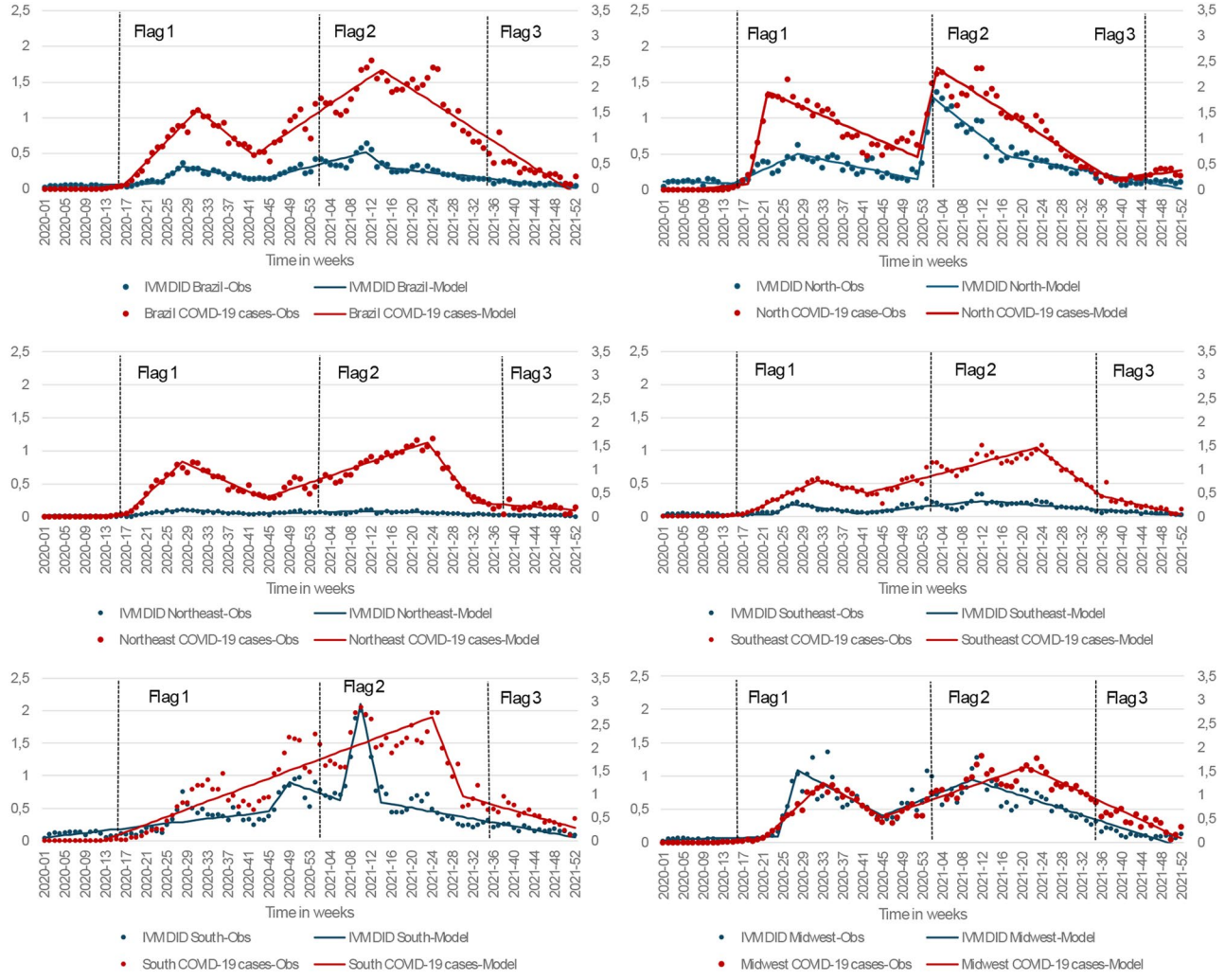

Fig. 3 Ivermectin and new COVID-19 cases in Brazil and its geographical regions. Brazil, 2020 to 2021. Flag 1: Technical report of the FBM-Br advocating using chloroquine and hydroxychloroquine in patients diagnosed with COVID-19. Flag 2: The Minister of Health launched the 'TrateCov' app in person in Manaus, and the COVID-19 vaccination has begun. Flag 3: Over 60% of COVID-19 vaccination coverage for the first dose

The increases in consumption in men were exceptionally high compared to women. This might be related to the higher incidence of COVID-19 in males [35] and political alignment [36]. Our findings indicate that consumption trends are associated with the region's political affiliations. Areas with a higher concentration of voters leaning towards the right spectrum [37], such as the Northern, Southern, and Midwest regions, exhibited the most significant shifts in consumption trends of AZI, CQ/HCQ, and IVM, strongly aligned with the epidemiological landscape of COVID-19.

The federal government made successive efforts to promote using these three medicines for early COVID-19 treatment. The then-president heavily used his social media to disseminate misinformation regarding COVID-19. He downplayed the disease's lethality, referring to it as a "little flu" nationally at the onset of the pandemic, opposed key containment measures, and promoted treatments with medicines not recommended outside clinical trials [7]. In addition, evidence suggests that he sabotaged vaccination, delaying their purchase and fostering public mistrust in the efficacy and safety of vaccines [38].

The results provide a detailed analysis of the association between the COVID-19 case incidence and the consumption of AZI, CQ/HCQ, and IVM. For instance, in periods of increased incidence, consumption showed an upward trend and decreased when the transmission was more controlled. This is clear in the case of Manaus, located in the Amazon region (North), the first large city severely affected by the coronavirus in April and May 2020. This period was characterized by hospital overcrowding, the collapse of the city's funeral system, and the use of mass graves, coinciding with the sharp increase in AZI, CQ/HCQ, and IVM consumption [39].

At the end of 2020, following the emergence of the new P1 (gamma) variant in Manaus, the federal government intensified its promotion of the Covid Kit [7] and pressured the Amazonas state government to avoid implementing stricter lockdown measures despite a surge in cases [40]. There are indications that the federal government aimed to position Manaus as a successful model for early treatment [40]. However, the outcomes were catastrophic: the city experienced the most severe pandemic scenario in Brazil, recording the highest mortality rate during this period. The healthcare system ultimately collapsed, leading to a critical shortage of oxygen cylinders in hospitals, which resulted in patient deaths from asphyxiation [39, 40].

Given this context, it was expected that the North region would experience a more significant increase [35] in the consumption of Covid Kit medications in early 2021, as observed in this study. The Midwest and South regions also experienced significant changes in consumption trends, which can be linked to the greater political alignment of the population from these regions [37].

The introduction of treatment guidelines or apps to guide prescription was associated with changes in consumption. In early January 2021 (EW 02/2021), the minister of Health personally visited Manaus, the capital of Amazonas State, to launch the TrateCov app. This app aimed to facilitate the diagnosis and to propose treatment with drugs such as AZI and IVM from Covid Kit [16]. As launched in Manaus, the app seemed to impact increasing the consumption of AZI and IVM only in the North region, despite becoming accessible all over the country. The fact that the app was disabled within 15 days due to many controversies, such as suggesting treatment for anyone with few symptoms and the same dose for different groups (e.g., children, pregnant women, and the elderly) [16] may explain why consumption trends did not seem to have been affected by the app release in other regions.

The study results suggest that the use of AZI, CQ/HCQ, and IVM did not prevent the transmission of the infection, which is aligned with many studies' evidence regarding the inefficacy of these to improve COVID-19 patient outcomes [29, 41, 42]. In contrast, the false sense of security decreases adherence to containment measures, such use of masks and social distancing. Lalwani et al. [35] found that risky behavior during the pandemic was more prevalent among users of the Covid Kit. Besides, the use of these medicines was associated with an increased development of adverse drug reactions [34]. A recent study estimated that, during the pandemic's first wave,17,000 COVID-19 inpatient deaths were related to the use of HCQ [43].

The absence of national unity and integrated policies compelled states and municipalities in Brazil to develop their own strategies based on political alignment and financial capacity. This fragmentation resulted in significant asymmetries in pandemic mitigation measures across the country. Such disparities are particularly concerning given Brazil's vast size and the existing regional inequities [44].

An intense decentralization of pandemic management measures occurred in the second wave, marked by the health ministers' increased deference to the President [37]. This may explain the significant difference in AZI, CQ/HCQ, and IVM consumption across regions in 2021.

Xavier et al. [37] suggested that the pandemic's impact on Brazil's municipalities varied according to pre-existing social and political conditions. Municipalities with a high Human Development Index (HDI), lower income inequality, and well-structured healthcare services may have exhibited high mortality rates due to their political stance affecting individual risk behavior and counteracted favorable pandemic responses.

Conversely, areas with fewer financial resources and more precarious health services, such as the Northeast, were able to achieve better outcomes in managing the pandemic. The nine region states joined forces through the Northeast Sustainable Development Interstate Consortium (Northeast Consortium), created in 2019, to define joint actions and facilitate the purchase of medical equipment and necessary supplies [45]. Additionally, a Scientific Committee was created to guide actions based on scientific evidence. This may explain the less significant changes in the consumption of AZI, CQ/HCQ, and IVM in the region, even during high COVID-19 incidence periods in the second wave.

The rise in the consumption of AZI, CQ/HCQ, and IVM, led to a poor management of scarce resources, especially considering the public production of medicines. As an example, CQ/HCQ had its production increased 12 times in 2020, much higher than the increase in consumption [46].

After the onset of vaccination in EW 3/2021 (almost the same period as Flag 2), the incidence of COVID-19 began to decrease, along with a decline in medicine consumption trends. The reason for the decline was possibly the rapid increase of the vaccine update, which resulted in a 76% vaccination rate, at least with the first dose, by December 2021 [17].

Limitations

First, BNAFAR's coverage of SUS pharmacies is limited, especially in the Northeast and Northern regions, where we have an underrepresentation of PHC facilities. However, we analyzed consumption patterns within the same facilities over the study period. This minimizes potential biases and provides valuable results about significant

changes in the consumption behavior of medicines of interest during the pandemic.

Second, some Brazilian municipalities carried out a mass distribution of the Covid Kit. It is possible that the dispensing of these medicines was not recorded in the database and, therefore, the consumption results may be underestimated. Third, the consumption from SUS outpatient health facilities does not necessarily reflect the whole country. Private pharmacies sold 52 million Covid Kit tablets during the pandemic with or without medical prescription [47]. Patients can only access medicines at SUS pharmacies with a prescription. Therefore, the medicine consumption reported here reflects the physician's prescription patterns within SUS.

Despite most of the Brazilian population being dependent on SUS services, significant regional differences exist. North and Northeast have the highest percentage of SUS dependence (almost 90%) [48]. However, being disadvantaged in terms of financial resources, these regions may have experienced shortages of these medicines, potentially resulting in data loss due to suppressed demand. Another limitation was that the joinpoint model could not appropriately capture the trend variations in COVID-19 incidence and DID consumption in the Southern region. This was due to the significant instability of the trend over time.

Conclusion

This study revealed significant changes in AZI, CQ/HCQ, and IVM consumption during the COVID-19 pandemic in Brazil, particularly in the North, Midwest, and South regions, where medicine consumption mainly coincided with the trends of COVID-19 incidence and key political events. The increased use of these medicines did not lead to a decline in COVID-19 incidence. Both, incidence and medicine use decreased as vaccination coverage expanded nationwide.

Political endorsement of therapies has shown to be a crucial determinant of medication use and must be carefully and adequately employed. Also, it should be studied more systematically to understand better drivers of inappropriate consumption, population harm, waste of limited resources, and an increased risk of antimicrobial resistance. This research suggests that COVID-19 treatment recommendations, heavily influenced by a political party ideology and lack of scientific backing, likely contributed to increased AZI, CQ/HCQ, and IVM consumption in Brazil's National Health System.

Future policies should focus on developing and implementing evidence-based guidelines, particularly in response to political influences that may skew public health decisions, followed by close monitoring compliance. Robust communication strategies that clearly convey the risks associated with unproven treatments must be prioritized. Furthermore, future studies should investigate the long-term impact of political determinants on prescription practices and public health outcomes, including antimicrobial resistance and adverse health effects. Research should explore the effectiveness of educational interventions aimed at both healthcare providers and the public to mitigate the misuse of medications in future health crises.

Abbreviations

ANVISA	Brazilian National Health Surveillance Agency
AZI	Azithromycin
BNAFAR	National Database of Actions and Services of Pharmaceutical Services in SUS
COVID-19	The coronavirus disease 2019
CQ/HCQ	Chloroquine/hydroxychloroquine
DDD	Defined Daily Dose
DID	Defined Daily Dose per 1,000 inhabitants per day
EW	Epidemiological Week
FBM-Br	Brazilian Federal Board of Medicine
HDI	Human Development Index
ITS	Interrupted Time Series
IVM	Ivermectin
MoH	Ministry of Health
PHC	Primary Health Care
RENAME	National Essential Medicines List
SUS	Unified Health System
WHO	World Health Organization

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Author contributions

All authors were involved in the study's conception and design. MCC and VLL acquired the data. Data analysis and interpretation were performed by DCP, ICME, MCC, MRC, and VJW. MCC wrote the first draft of the manuscript, with contributions to critical revisions from DCP, ICME, MRC, VJW, and VLL. All authors reviewed and approved the final version of the manuscript.

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Data availability

The original data is available, at no cost, upon request to the Brazilian Ministry of Health through the Brazilian Law on Access to Information (Law No 12,527/2011). The incidence cases of COVID-19 in Brazil are publicly available at 'Coronavirus Brazil Panel'. The data generated by this analysis is available upon request to the corresponding author.

Declarations

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of the Sergio Arouca National School of Public Health/ Oswaldo Cruz Foundation (Technical Opinion No. 5.710.204) to access the database containing individually traceable but anonymized patient information.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054–62.
2. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res. 2020;178:104787.
3. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. J Infect. 2020;81(2):266–75.
4. Furlan L, Caramelli B. The regrettable story of the Covid Kit and the early treatment of Covid-19 in Brazil. Lancet Reg Health - Americas. 2021;4:100089.
5. Casarões G, Magalhães D. The hydroxychloroquine alliance: how far-right leaders and alt-science preachers came together to promote a miracle drug. Rev Adm Pública. 2021;55:197–214.
6. Niburski K, Niburski O. Impact of Trump's Promotion of Unproven COVID-19 treatments on Social Media and subsequent internet trends: Observational Study. J Med Internet Res. 2020;22(11):e20044.
7. Ventura D, de FL, Reis RR. An unprecedented attack on human rights in Brazil: the timeline of the federal government's strategy to spread Covid-19. Offprint. Translation by Luis Misiara, revision by Jameson Martins. Bulletin Rights in the Pandemic n. 10. São Paulo, Brazil: CEPEDISA/USP and Conectas Human Rights; 2021.
8. Stanford V, Gresh L, Toledo J, Méndez J, Aldighieri S, Reveiz L. Evidence in decision-making in the context of COVID-19 in Latin America. Lancet Reg Health Am. 2022;14:100322.
9. Requejo Domínguez JA, Mino-León D, Wirtz VJ. Quality of clinical evidence and political justifications of ivermectin mass distribution of COVID-19 kits in eight latin American countries. BMJ Glob Health. 2023;8(5):e010962.
10. Silva NBLD, Rocha RPDS, Andrade ACDS, Terças-Trettel ACP, Muraro AP. Prevalence of Ivermectin use to prevent COVID-19 during the pandemic in Mato Grosso: cross-sectional home-based study. Rev bras Epidemiol. 2023;26:e230026.
11. Shalders A. Tratamento precoce': governo bolsonaro gasta quase R$ 90 milhões em remédios ineficazes, mas ainda não pagou butantan por vacinas. BBC NEWS Brasil. 2021. file:///C:/Users/Michele/Zotero/storage/65AMKR2X/brasil-55747043.html. Accessed July 2023.
12. Federal Council of Medicine (CFM). CFM Consultation Process No. 8/2020. CFM Opinion No. 4/2020. CFM. 2020. https://cremers.org.br/wp-content/uploads/2020/06/16.04.2020-Parecer-CFM-4-2020-Tratamento-de-Pacientes-Portadores-de-Covid-19-com-Cloroquina-e-Hidroxicloroquina.pdf. Accessed July 2023.
13. Brazil. Ministry of Health. Executive Secretary. Informative Note No 9/2020-Se/Gab/Se/Ms. Orientações para Manuseio Medicamentoso Precoce de Pacientes com Diagnóstico da Covid-19. 2022. https://static.poder360.com.br/2021/05/Nota-informativa-Orienta-es-para-manuseio-medicamentoso-precoce-de-pacientes-com-diagn-stico-da-COVID-19.pdf. Accessed December 2023.
14. Evans PBRAZIL. An Unfolding Tragedy. Center for Latin American & Caribbean Studies. 2018. https://clacs.berkeley.edu/brazil-unfolding-tragedy. Accessed October 2024.
15. Ricard J, Medeiros J. Using misinformation as a political weapon: COVID-19 and Bolsonaro in Brazil. HKS Misinfo Review. 2020. https://misinforeview.hks.harvard.edu/article/using-misinformation-as-a-political-weapon-covid-19-and-bolsonaro-in-brazil/. Accessed October 2024.
16. Pagliari C, Klafke GF, Camelo AP, Da Silveira VD, Evans J. The Covid-19 app that lasted two weeks: how technology may embody controversial public policies for health care and why we should worry about it. Oxf Open Digit Health. 2023;1:oqad004.
17. Oswaldo Cruz Foundation (Fiocruz). Institute of Communication and Scientific Information Technology in Health. MonitoraCovid-19. 2023. https://bigdata-covid19.icict.fiocruz.br/. Accessed December 2023.
18. Brazil. Ministry of Health. Decree No. 271, February 27, 2013. http://bvsms.saude.gov.br/bvs/saudelegis/gm/2013/prt0271_27_02_2013.html. Accessed June 2023.
19. Brazil, Ministry of Health. Secretariat of Science, Technology, Innovation, and Strategic Health Inputs. Department of Pharmaceutical Assistance and Strategic Inputs. Bnafar Base Nacional de Dados de Ações e Serviços da Assistência Farmacêutica do Sistema Único de Saúde: manual do usuário. Brasília: Ministry of Health; 2021. http://bvsms.saude.gov.br/bvs/publicacoes/base_dados_assistencia_farmaceutica_manual.pdf. Accessed February 2023.
20. Brazil. Ministry of Health. Decree No. 1.737, June 14, 2018. 2018. https://bvsms.saude.gov.br/bvs/saudelegis/gm/2018/prt1737_18_06_2018.html. Accessed January 2024.
21. Brazil. Ministry of Health. Qualifar-SUS. gov.br: Serviços e informações do Brasil. 2023 https://www.gov.br/saude/pt-br/composicao/sectics/daf/cbaf/qualifar-sus/qualifar-sus. Accessed January 2024.
22. Brazil. Ministry of Health. Programa Nacional de Melhoria do Acesso e da Qualidade da Atenção Básica (PMAQ). Ministry of Health. 2017 https://www.gov.br/saude/pt-br/composicao/saps/pmaq/pmaq. Accessed March 2024.
23. World Health Organization. GLASS methodology for surveillance of national antimicrobial consumption. Geneva: WHO. 2020. https://apps.who.int/iris/handle/10665/336215. Accessed February 2024.
24. Brazil. Ministry of Health. Datasus. Painel Coronavírus. Coronavírus Brasil. 2023. https://covid.saude.gov.br/. Accessed December 2023.
25. Qiu D, Katanoda K, Marugame T, Sobue T. A joinpoint regression analysis of long-term trends in cancer mortality in Japan (1958–2004). Int J Cancer. 2009;124(2):443–8.
26. Colonna M. Analyse descriptive de la tendance évolutive d'observations épidémiologiques avec le logiciel Joinpoint: un outil simple, en apparence. Rev Épidémiol Santé Publique. 2011;59(2):123–33.
27. Box GEP, Jenkins GM, Reinsel GC, Ljung GM. Time series analysis: forecasting and control. Fifth edition. Hoboken, New Jersey: Wiley; 1976.
28. Kim MS, An MH, Kim WJ, Hwang TH. Comparative efficacy and safety of pharmacological interventions for the treatment of COVID-19: a systematic review and network meta-analysis. PLoS Med. 2020;17(12):e1003501.
29. Mangkuliguna G, Glenardi, Natalia PLA. Efficacy and safety of azithromycin for the treatment of COVID-19: a systematic review and Meta-analysis. Tuberc Respir Dis (Seoul). 2021;84(4):299–316.
30. Harrigan JJ, Hubbard RA, Thomas S, Riello RJ, Bange E, Mamtani M, et al. Association between US Administration Endorsement of Hydroxychloroquine for COVID-19 and Outpatient Prescribing. J Gen Intern Med. 2020;35(9):2826–8.
31. Lind JN, Lovegrove MC, Geller AI, Uyeki TM, Datta SD, Budnitz DS. Increase in Outpatient Ivermectin dispensing in the US during the COVID-19 pandemic: a cross-sectional analysis. J Gen Intern Med. 2021;36(9):2909–11.
32. Putzel J. The populist right challenge to neoliberalism: social policy between a rock and a hard place. Dev Change. 2020;51(2):418–41.
33. da Fonseca EM, Nattrass N, Lazaro LLB, Bastos FI. Political discourse, denialism and leadership failure in Brazil's response to COVID-19. Glob Public Health. 2021;16(8–9):1251–66.
34. Hentschke-Lopes M, Botton MR, Borges P, Freitas M, Mancuso ACB, Matte U. Sales of COVID kit drugs and adverse drug reactions reported by the Brazilian Health Regulatory Agency. Cad Saúde Pública. 2022;38(7):e00001022.
35. Lalwani P, Salgado BB, Filho IVP, da Silva DSS, de Morais TB do, Jordão N et al. MF,. SARS-CoV-2 seroprevalence and associated factors in Manaus,

Brazil: baseline results from the DETECTCoV-19 cohort study. Int J Infect Dis. 2021;110:141–50.
36. Superior Electoral Court. Electoral Statistics. Portal do TSE. 2022. https://sig.tse.jus.br/ords/dwapr/r/seai/sig-eleicao/home. Accessed January 2024.
37. Xavier DR, Silva EL e, Lara FA, Silva GRR e, Oliveira MF, Gurgel H et al. Involvement of political and socio-economic factors in the spatial and temporal dynamics of COVID-19 outcomes in Brazil: A population-based study. Lancet Reg Health Am. 2022;10:100221.
38. Henrique ALB. COVID-19 Vaccination in Brazil Is a Success, Despite the Failure of the Federal Government. O'Neill Institute. 2022. https://oneill.law.georgetown.edu/covid-19-vaccination-in-brazil-is-a-success-despite-the-failure-of-the-federal-government/. Accessed December 2023.
39. Teófilo S, Lima B. Anvisa informa à CPI que venda de 'kit covid' cresceu 166% em 2020. Correio Brasiliense. Política. 2021. https://www.correiobraziliense.com.br/politica/2021/06/4933493-anvisa-informa-a-cpi-que-venda-de----kit-covid----cresceu-166--em-2020.html. Accessed October, 2023.
40. Rede Brasil Atual - RBA. Bolsonaro usou Amazonas para. experiências de imunidade de rebanho e cloroquina, diz vice-governador. Rede Brasil Atual. 2021. https://www.redebrasilatual.com.br/saude-e-ciencia/bolsonaro-usou-amazonas-para-experiencias-de-imunidade-de-rebanho-e-cloroquina-diz-vice-governador/. Accessed October, 2023.
41. Reis G, Silva EASM, Silva DCM, Thabane L, Milagres AC, Ferreira TS, et al. Effect of early treatment with ivermectin among patients with Covid-19. N Engl J Med. 2022;386(18):1721–31.
42. Martins-Filho PR, Ferreira LC, Heimfarth L, Araújo AADS, Quintans-Júnior LJ. Efficacy and safety of hydroxychloroquine as pre-and post-exposure prophylaxis and treatment of COVID-19: a systematic review and meta-analysis of blinded, placebo-controlled, randomized clinical trials. Lancet Reg Health Am. 2021;2:100062.
43. Pradelle A, Mainbourg S, Provencher S, Massy E, Grenet G, Lega JC. Deaths induced by compassionate use of hydroxychloroquine during the first COVID-19 wave: an estimate. Biomed Pharmacother. 2024;171:116055.
44. Sott MK, Bender MS, da Silva Baum K. Covid-19 outbreak in Brazil: Health, Social, Political, and Economic implications. Int J Health Serv 2022;00207314221122658.
45. Perez OC, Santana L. Ações do Consórcio Nordeste no combate à pandemia de Covid-19. NAU Social. 31 de outubro de 2020;11(21):259–70.
46. Pitta I, Brito J. Exército multiplicou produção de cloroquina por 12 vezes em 2020. CNN Brasil. 2021. https://www.cnnbrasil.com.br/politica/exercito-multiplica-producao-de-cloroquina-por-12-vezes-em-2020/. Accessed January, 2024.
47. Muniz B, Fonseca B. Farmácias venderam mais de 52 milhões de comprimidos do kit covid na pandemia. El País Brasil. 2021. https://brasil.elpais.com/brasil/2021-04-21/farmacias-venderam-mais-de-52-milhoes-de-comprimidos-do-kit-covid-na-pandemia.html. Accessed November 2023.
48. Bigoni A, Malik AM, Tasca R, Carrera MBM, Schiesari LMC, Gambardella DD, et al. Brazil's health system functionality amidst of the COVID-19 pandemic: an analysis of resilience. Lancet Reg Health Am. 2022;10:100222.

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