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ARTICLE

Sales of "COVID kit" drugs and adverse drug reactions reported by the Brazilian Health Regulatory Agency

Vendas de "kit-COVID" e reações adversas a esses medicamentos relatadas pela Agência Nacional de Vigilância Sanitária

Ventas de medicamentos del "kit-COVID" y reacciones adversas a los medicamentos notificadas por la Agencia Nacional de Vigilancia Sanitaria

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Abstract

Off-label use of azithromycin, hydroxychloroquine, and ivermectin (the "COVID kit") has been suggested for COVID-19 treatment in Brazil without clinical or scientific evidence of efficacy. These drugs have known adverse drug reactions (ADR). This study aimed to analyze if the sales of drugs in the "COVID kit" are correlated to the reported number of ADR after the COVID-19 pandemic began. Data was obtained from the Brazilian Health Regulatory Agency (Anvisa) website on reported sales and ADRs for azithromycin, hydroxychloroquine, and ivermectin for all Brazilian states. The period from March 2019 to February 2020 (before the pandemic) was compared to that from March 2020 to February 2021 (during the pandemic). Trend adjustment was performed for time series data and cross-correlation analysis to investigate correlation between sales and ADR within the same month (lag 0) and in the following months (lag 1 and lag 2). Spearman's correlation coefficient was used to assess the magnitude of the correlations. After the pandemic onset, sales of all investigated drugs increased significantly (69.75% for azithromycin, 10,856,481.39% for hydroxychloroquine, and 12,291,129.32% for ivermectin). ADR levels of all medications but azithromycin were zero before the pandemic, but increased after its onset. Cross-correlation analysis was significant in lag 1 for all drugs nationwide. Spearman's correlation was moderate for azithromycin and hydroxychloroquine but absent for ivermectin. Data must be interpreted cautiously since no active search for ADR was performed. Our results show that the increased and indiscriminate use of "COVID kit" during the pandemic correlates to an increased occurrence of ADRs.

COVID-19; Drug-Related Side Effects and Adverse Reactions; Azithromycin; Hydroxychloroquine; Ivermectin

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Introduction

During the COVID-19 pandemic, a set of drugs including azithromycin, hydroxychloroquine, and ivermectin was proposed as prophylactic or early treatment for COVID-19 in Brazil and other countries [1,2,3,4,5]. As of April 2020, increasing evidence showed that these medicines were inefficient against the disease [6,7,8]. Some groups, however, continued to advocate the off-label use of such drugs. Off-label administration is acceptable if no standard therapy is available for a serious condition and if its potential benefit is evidenced [9,10].

Potential adverse drug reactions (ADR) may occur even for recommended drugs. The World Health Organization (WHO) defines ADR as *"a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function"* [11] (p. 40). In turn, Edwards & Aronson [12] (p. 1255) define it as *"an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product"*.

The Brazilian Health Regulatory Agency (Anvisa) has a national surveillance program on ADR. The agency reports on and discloses pharmacovigilance data on their website, an important resource to record the safety of medicines and the late ADRs that often escape clinical research [13]. The website also presents data on release of controlled medicines, such as the ones used for the early treatment of COVID-19.

Melo et al. [14] described the ADRs reported for patients with COVID-19 during the first half of 2020. On average, 1.6 ADRs were reported per patient, and the drugs frequently associated with were those included in the "COVID kit". The authors also found that pharmacists notified the most ADRs whereas physicians notified the least, raising discussion on underreporting and the importance of training health professionals in pharmacovigilance. Also, Melo et al. [15] stress that notifications reported in the VigiMed system do not discriminate whether the drug was used by medical indication or self-medication.

This study aimed to analyze if the sales of azithromycin, hydroxychloroquine, and ivermectin increased after the onset of the COVID-19 pandemic and if this is correlated with increased reports of ADR.

Methodology

Data were obtained from the Anvisa website both for sales [16] and for reported ADR [17]. Drugs included in the search were azithromycin, hydroxychloroquine, and ivermectin. Sales history was selected considering both manipulated and industrialized drugs, and the number of sales was converted to grams if presented in another measurement. Chloroquine was not included since it lacked available industrialized sales data. The monthly history was obtained from March 2019 to February 2021 to analyze the 12 months before and after the onset of the COVID-19 pandemic (Brazil's first case of COVID-19 was diagnosed on February 26, 2020, and WHO declared the pandemic on March 11, 2020).

The history was assessed by cross-correlation analysis to investigate correlation between sales and ADR within the same month (lag 0) and in the following month (lag 1) or two months (lag 2) after sales. The necessary adjustments for time series data were performed. Spearman's correlation coefficient was used to assess the magnitude of the correlations. Such analyses were conducted for the whole country's total data and by regions for each drug. Statistical significance was considered as $p < 0.05$.
This research did not receive or use any funding.

Results

In the pre-pandemic period (from March 2019 to February 2020), azithromycin was the most sold drug nationwide. As a broad-spectrum antibiotic, it was mostly sold in the South and Southeast regions, which present more cases of respiratory infections [18]. After the pandemic onset, sales of azithromycin grew 60.18% in these regions and 69.75% nationwide (Table 1). On the other hand, before the pandemic, only the Northeast and Southeast regions of Brazil reported hydroxychloroquine sales. These sales increased nationwide from 72g to 7,816,738.60g (or 7.8 ton) in the next 12 months after the onset (10,856,481.39% increase). Sales of ivermectin, an antiparasitic drug, rose from 1.22g to 150,444.65g (12,291,129.32% increase).

Reported ADRs also increased. Before the pandemic, ADR levels were zero to must drugs but azithromycin, which went from 16 to 80 reported ADRs after the pandemic onset (Table 1). In the next 12 months, 150 ADRs of hydroxychloroquine and six ADRs of ivermectin were reported. Figure 1 shows the behavior of sales and reported ADRs in Brazil over the studies period.

The cross-correlation analysis showed that increased azithromycin sales were significantly correlated with increased ADR notifications in the following month both nationwide (correlation of 0.522, in lag 1) and in the Central-West Region (correlation of 0.517, in lag 1). Higher hydroxychloroquine sales were significantly correlated with increased ADRs within the same month for Brazil (correlation of 0.498, in lag 0) and regions South (correlation of 0.490, in lag 0) and Southeast (correlation of 0.562, in lag 0). Ivermectin sales also exploded, and the cross-correlation analysis with related ADR showed significant coefficients for a late correlation in Brazil (correlation of 0.681, in lag 2) and in the Central-

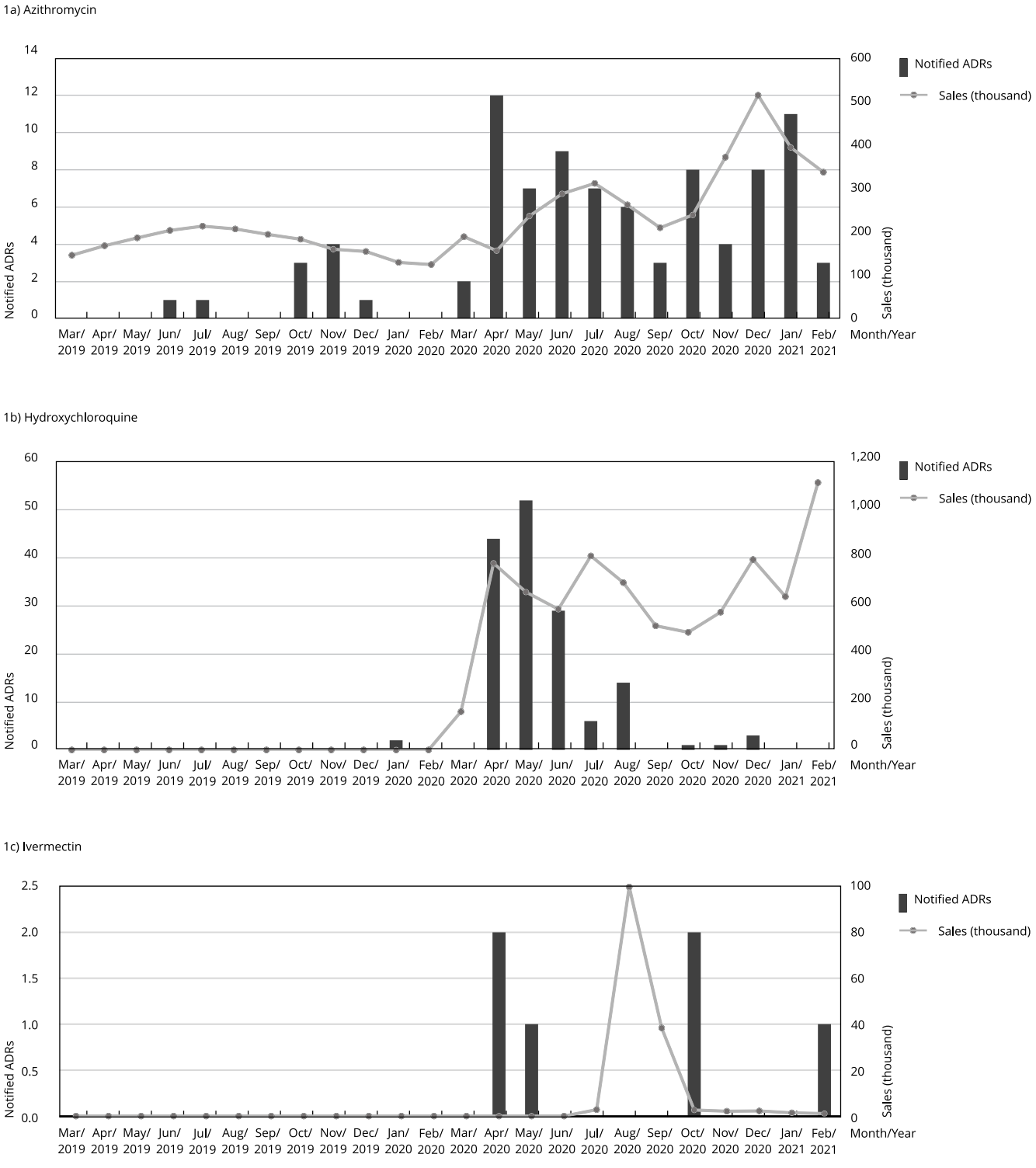
Table 1

Total number of reported sales (in grams) and reported adverse drug reactions (ADRs) of azithromycin, hydroxychloroquine, and ivermectin in the 12 months pre- and post-onset of the COVID-19 pandemic for each region of Brazil.

Drug/Region	Sales (in grams)		Reported ADRs	
	Pre-pandemic	Post-pandemic	Pre-pandemic	Post-pandemic
Azithromycin				
Central-West	104,721.70	222,787.94	8	17
North	88,407.55	247,782.60	0	0
Northeast	392,584.56	665,555.63	3	12
South	544,913.43	837,195.62	1	4
Southeast	936,880.93	1,536,323.91	4	47
Total	2,067,508.16	3,509,645.70	16	80
Hydroxychloroquine				
Central-West	0.00	528,661.30	0	3
North	0.00	312,067.07	0	0
Northeast	48.00	1,715,558.08	0	30
South	0.00	2,006,754.80	0	17
Southeast	24.00	3,253,697.35	0	100
Total	72.00	7,816,738.60	0	150
Ivermectin				
Central-West	0.22	3,369.76	0	1
North	0.20	12,198.79	0	0
Northeast	0.26	99,751.36	0	2
South	0.02	7,961.08	0	1
Southeast	0.52	27,163.65	0	2
Total	1.22	150,444.65	0	6

Figure 1

Monthly sales and reported adverse drug reactions (ADRs) in Brazil (all regions considered) between pre- and post-pandemic onset for azithromycin, hydroxychloroquine, and ivermectin.



West Region (correlation of 0.942, in lag 2) but an early correlation in the Southeast (correlation of 0.820, in lag 1). Figure 2 shows the observed cross-correlation analysis for the country.

Similarly, in Spearman's correlation analysis (Table 2) azithromycin and hydroxychloroquine were moderately correlated to ADRs (according to Devore [19]) during and one month after sales nationwide. By region, however, only hydroxychloroquine showed moderate levels of correlation in the South, Southeast, and Northeast regions. Ivermectin was not correlated to ADRs in any scenario.

Discussion and conclusion

ADRs are a major concern for all used drugs. However, they are underreported even in intra-hospital scenarios [20]. In this study, we used a public database on drug dispensing and ADRs. Despite obvious limitations, we can assume that information for drug dispensing is more accurate due to legal constraints. Since 2008, Brazil has an online database, the National System for Management of Controlled Substances (SNGPC; http://sngpc.anvisa.gov.br/), which registers the sales of pharmacies [16,21].

Among all drugs considered in this study, azithromycin and hydroxychloroquine are evidently associated with ADRs related to prolonged QT interval [22,23,24]. The literature shows that hydroxychloroquine is also related to neurotoxicity and retinopathy [25]. ADRs like gastrointestinal distress, confusion, ataxia, hypotension and seizures have been reported after high dosage exposure to ivermectin [26]. In all cases, ADRs depend on dose and duration of exposure to the drug.

Drug label information for azithromycin suggests taking daily doses of 1,500mg for three days. Though hydroxychloroquine dosing depends on indication, the maximum initial dose is 1,600mg followed by daily doses of 400mg. Most common indications, however, recommend initial doses of up to 800mg followed by daily doses of up to 400mg. For ivermectin, the drug label recommends a single daily dose of up to 200mcg/kg a day according to the cause of the disease.

The Brazilian Commission for the Incorporation of Technologies in the Unified Health System (CONITEC) prepared a document called *Brazilian Guidelines for Outpatient Drug Treatment of Patients with COVID-19* [27], published in November 2021. The document does not recommend using medicines from the "COVID kit" (azithromycin, chloroquine, hydroxychloroquine, and ivermectin) in infected patients since randomized clinical trials and other national and international guidelines showed no evidence of efficacy of these drugs for the outpatient treatment of patients with COVID-19.

The recommended dose of these medicines for treating COVID-19 is difficult to find, especially considering the increasing evidence on their inefficacy. Some documents from municipalities or private health companies can be found in Portuguese [28,29]. They suggest 500mg of azithromycin per day for five days or, if symptoms persist, for ten days, along with simultaneous use of 400mg hydroxychloroquine every 12 hours for the first day and then 400mg/day for up to ten days. For ivermectin, the documents suggested daily doses of 6mg for four days then about 250mcg/kg per day.

Exposing patients to these risks with no confirmed benefits of the drugs contradicts the risk-benefit assumptions adopted in clinical practice. ADRs can threaten life and challenge the health system. Mota et al. [13] showed that 9.2% of ADRs motivated or prolonged hospitalization and 4.7% threatened life. In Brazil, the estimated prevalence of suspected notified ADRs is 6.6% [30]. We emphasize that both manufacturers and regulatory agencies have condemned the use of such medicines for COVID-19 treatment [31,32,33]. Merck-Sharp-Dohme, for example, stated that they do not believe that the data available support the safety and efficacy of ivermectin beyond the doses and populations indicated in the regulatory agency-approved prescribing information [34].

ADR underreporting is a worldwide problem which limits our results. Several studies [35,36,37,38] indicate that underreporting is caused by the lack of knowledge about the process of notifying or identifying ADRs, insecurity, busy work routine, lack of interest, lack of incentive, guilt for having possibly harmed the patient, or the feeling that only safe drugs are allowed on the market. Many of these reasons overlap with the "seven deadly sins" list created by William Inman in the 1980s. According to the studies, continuous educational interventions and measures could mitigate several of these motivations and encourage health professionals to notify cases. Having a good notification instrument (easy to access, simple to fill out, anonymous, with little bureaucracy) also eliminates other possible obstacles [38].

Figure 2

Cross-correlation between sales and notified adverse drug reactions (ADRs) in Brazil.

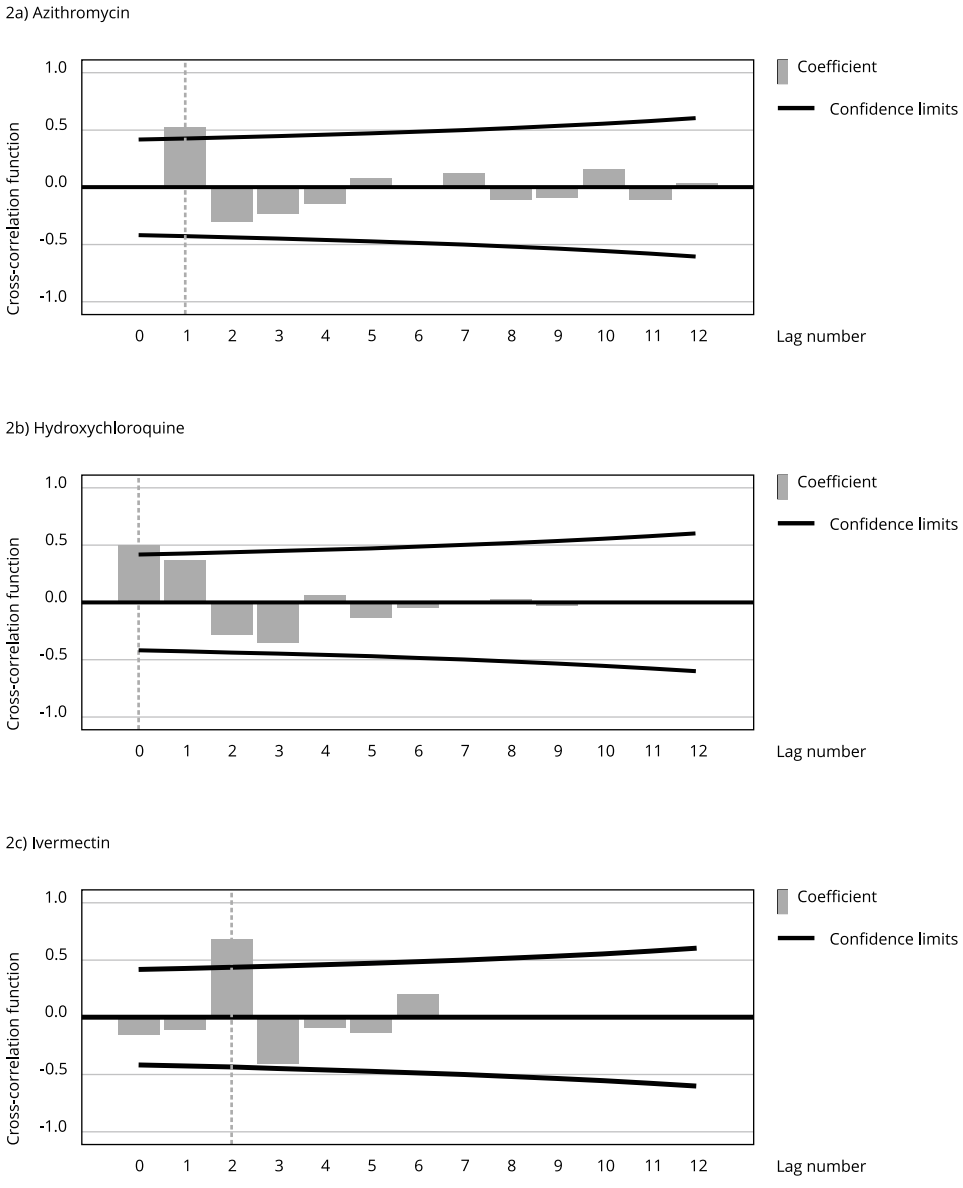


Table 2

Spearman's correlation coefficient between sales and adverse drug reactions (ADRs) in Brazil and Brazilian regions for lag 0 and lag 1.

Region	Azithromycin		Hydroxychloroquine		Ivermectin	
	Lag 0	Lag 1	Lag 0	Lag 1	Lag 0	Lag 1
Brazil	0.614 *	0.537 *	0.606 *	0.531 *	0.243	0.107
South	0.152	0.015	0.562 *	0.508 **	-0.181	-0.177
Southeast	0.344	0.311	0.555 *	0.578 *	0.263	0.374
Central-West	0.240	0.245	0.293	0.347	0.181	0.355
Northeast	0.276	0.287	0.641 *	0.593 *	-0.273	0.016

* Correlation is significant at 0.01 level (two-tailed);

** Correlation is significant at 0.05 level (two-tailed).

Another limitation of this study is the lack of an active search for ADRs to gather data closer to reality. However, this would be impractical considering the size of Brazil and the regional differences in using the "COVID kit". Moreover, in some periods, data was not up-to-date and repressed data were logged into the system at once. Monthly data should thus be interpreted cautiously. Nevertheless, the use of these medicines and of ADRs over the year-long period increased overall.

Finally, though this type of analysis does not allow making causal inferences, it analyzes the association between the rising sales of off-label drugs for COVID-19 and side effects to these drugs. In short, our results show that, despite underreporting, the increased and indiscriminate use of azithromycin, hydroxychloroquine, and ivermectin during the pandemic correlates to an increased development of ADRs.

Contributors

M. Hentschke-Lopes contributed to the data collection and analysis, writing, and review of the manuscript. M. R. Botton contributed to the data analysis, writing, and review of the manuscript. P. Borges and M. Freitas contributed to the data collection and review of the manuscript. A. C. B. Mancuso contributed to the study concepotion and design, data analysis, writing, and review of the manuscript. U. Matte contributed to the study conception and design, writing, and review of the manuscript. All the authors approved the final version of the manuscript.

Additional informations

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Resumo

No Brasil, o uso off label de azitromicina, hidroxicloroquina e ivermectina (o "kit-COVID") foi sugerido para tratar COVID-19 sem que tivéssemos evidências clínicas ou científicas de sua eficácia. Estas drogas têm causado reações adversas (RA) em quem as tomam. Este estudo almejou analisar se a venda dos medicamentos que compõem o "kit-COVID" correlaciona-se com o número relatado de RAs após o início da pandemia da COVID-19. Os dados sobre vendas e RA associados a azitromicina, hidroxicloroquina e ivermectina foram obtidos no site *da Agência Nacional de Vigilância Sanitária (Anvisa) para todos os estados brasileiros. Comparamos o período entre março de 2019 e fevereiro de 2020 (antes da pandemia) ao de março de 2020 a fevereiro de 2021 (durante a pandemia). Ajustamos tendências para os dados de séries temporais e as análises de correlação cruzada para investigar a correlação entre vendas e RA em um mesmo mês* (lag *0) e nos seguintes* (lag *1 e 2). O coeficiente de correlação de Spearman foi utilizado para avaliar a magnitude das correlações. Após o início da pandemia, as vendas de todos os medicamentos investigados aumentaram significativamente (69,75% para azitromicina, 10.856.481,39% para hidroxicloroquina e 12.291.129,32% para ivermectina). Os níveis de RAs de todos os medicamentos (com exceção de azitromicina) eram zero antes da pandemia mas aumentaram após seu início. A análise de correlação cruzada foi significativa no* lag *1 para todas as drogas em todo o país. A correlação de Spearman foi moderada para azitromicina e hidroxicloroquina, mas ausente para ivermectina. Os dados devem ser interpretados com cautela, uma vez que não realizamos uma busca ativa por RA. Nossos resultados mostram que o uso aumentado e indiscriminado do "kit-COVID" durante a pandemia se correlaciona com uma ocorrência aumentada de RAs.*

COVID-19; Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos; Azitromicina; Hidroxicloroquina; Ivermectina

Resumen

Se ha sugerido el uso fuera de lo establecido de azitromicina, hidroxicloroquina e ivermectina (el "kit-COVID") para el tratamiento de la COVID-19 en Brasil sin evidencia clínica o científica de su eficacia. Estos medicamentos tienen reacciones adversas (RAM) conocidas. Este estudio pretendía analizar si las ventas de medicamentos del "kit-COVID" están correlacionadas con el número de reacciones adversas notificadas tras el inicio de la pandemia de COVID-19. Los datos se obtuvieron del sitio web *de la Agencia Nacional de Vigilancia Sanitaria (Anvisa) sobre las ventas y las RAM notificadas para la azitromicina, la hidroxicloroquina y la ivermectina para todos los estados brasileños. Se comparó el periodo de marzo de 2019 a febrero de 2020 (antes de la pandemia) con el de marzo de 2020 a febrero de 2021 (durante la pandemia). Se realizó un ajuste de tendencia para los datos de las series de tiempo y un análisis de correlación cruzada para investigar la correlación entre las ventas y la RAM dentro del mismo mes* (lag *0) y en los meses siguientes* (lag *1 y* lag *2). Se utilizó el coeficiente de correlación de Spearman para evaluar la magnitud de las correlaciones. Tras el inicio de la pandemia, las ventas de todos los medicamentos investigados aumentaron significativamente (69,75% para la azitromicina, 10.856.481,39% para la hidroxicloroquina y 12.291.129,32% para la ivermectina). Los niveles de RAM de todos los medicamentos, excepto la azitromicina, eran nulos antes de la pandemia, pero aumentaron tras su inicio. El análisis de correlación cruzada fue significativo en el* lag *1 para todos los medicamentos a nivel nacional. La correlación de Spearman fue moderada para la azitromicina y la hidroxicloroquina, pero no para la ivermectina. Los datos deben interpretarse con cautela, ya que no se realizó una búsqueda activa de RAM. Nuestros resultados muestran que el uso creciente e indiscriminado del "kit-COVID" durante la pandemia se correlaciona con una mayor aparición de las RAM.*

COVID-19; Efectos Colaterales y Reacciones Adversas Relacionados con Medicamentos; Azitromicina; Hidroxicloroquina; Ivermectina

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