Increase in veterinary prescriptions of azithromycin during the COVID-19 pandemic in Brazil

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Abstract

Introduction:

With the advent of the pandemic in 2020 and the lack of perspectives for the treatment of COVID-19, numerous therapeutic proposals have emerged for the disease, including hydroxychloroquine and azithromycin. Therefore, some studies have shown that in many countries, the demand for azithromycin has increased during the pandemic. In Brazil, antibiotics can only be purchased with a medical, dental, or veterinary prescription. This study aimed to determine whether the number of prescriptions made by veterinarians (which could be used by humans) has increased during the pandemic. Data on the purchase of antibiotics made under veterinary prescriptions in Brazilian pharmacies between 2014 and 2021 were collected. To assess the changes in monthly trends in the use of the selected antibiotics, we applied the Joinpoint regression.

Results

The most prescribed antibiotic in all years was cephalexin (35%), followed by amoxicillin (24%). During the pandemic, the sales of azithromycin substantially increased. Regression analysis showed that since 2014, azithromycin prescriptions grew by an average of 0.67% per month. At the beginning of the pandemic, the monthly growth rate became 12.64%. When comparing azithromycin sales during the pandemic with the historical average (2014–2019), the increase was 41%.

Conclusions

During the pandemic, there was no animal health situation in Brazil that required the use of this antibiotic. Veterinary prescriptions may have been an instrument for human access to azithromycin for the treatment of COVID-19. Stricter enforcement policies are needed to address this problem to avoid antimicrobial resistance.

Introduction

On December 12, 2019, the Municipal Health Commission of Wuhan, China, declared that 27 people had been infected by a new type of coronavirus (SARS-CoV-2), which causes severe acute respiratory syndrome (Cheng and Shan 2020). The main symptoms of the disease include fever, cough, and fatigue, in addition to changes in smell and taste, which could worsen viral pneumonia, the main cause of death associated with COVID-19 (Adil, Rahman et al. 2021). This new variant of the virus spread to all continents, leading the World Health Organization to declare a worldwide pandemic on March 11, 2020 (Cucinotta and Vanelli 2020).

The initial recommendations of the health authorities of all countries were social isolation, use of masks, and in some situations, the lockdown of entire cities and regions (Adil, Rahman et al. 2021). The scenario at the beginning of the pandemic brought fear, uncertainty, and insecurity to not only all populations, but also to the medical and scientific community owing to mortality rates of approximately 3%, uncertainty about the pathogenesis of the disease, and lack of treatments and vaccines. (Mallah, Ghorab et al. 2021).

The high number of deaths and the uncertainty about therapeutic approaches have led to numerous proposals for drug repositioning, with the aim of combating the new disease (Ghazy, Almaghraby et al. 2020, Budhathoki, Shrestha et al. 2021, Diaz-Arocutipa, Brañez-Condorena et al. 2021, Kumar, Jain et al. 2021). Among the numerous treatment proposals, an association between hydroxychloroquine and azithromycin has emerged as a therapeutic option, with a large number of articles and meta-analyses evaluating this proposal (Ghazy, Almaghraby et al. 2020, Siemieniuk, Bartoszko et al. 2020, Kim, Hwang et al. 2021, Million, Roussel et al. 2021). The anti-inflammatory and immunomodulatory activities of macrolides inspired the search for new treatments, and the hope that their activity could improve the clinical condition of patients affected by COVID-19 (Zarogoulidis, Papanas et al. 2012).

In view of this possibility, there was a rush to pharmacies in the search for these drugs. Brazilian data from companies linked to the online sale of medicines showed that the demand for hydroxychloroquine has increased by approximately 17,000% in the second half of March 2020, when compared to the first week of that month (Riviera 2020). Similarly, the search for azithromycin occurred simultaneously in multiple countries. In Croatia, the demand for azithromycin in pharmacies increased by 1.94-fold during the pandemic, that is almost double the historically recorded demand. (Bogdanić, Močibob et al. 2022). Other countries have also shown an increase in azithromycin consumption at the same levels (Grau, Hernández et al. 2021).

Since 2013, Brazilian pharmacies and drugstores have been required to record all the following data on the sales of antibiotics: the prescriber category (dentist, doctor, or veterinarian) and patient data. Thus, since 2013, there has been no possibility of purchasing an antibiotic in a pharmacy in Brazil without presenting a prescription from a valid pres

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Therefore, this study analyzed whether the number of azithromycin prescriptions made by veterinarians has changed during the pandemic, similar to other countries.

Materials And Methods

Study design

This was an interrupted time series study (2014–2021) that analyzed the consumption trends of the most prescribed oral antibiotics by veterinarians in Brazil (outcome of interest) during the COVID-19 pandemic (exposure of interest) and sold in pharmacies and drugstores in Brazil.

Setting and study size

Since 2013, all pharmacies and drugstores in Brazil are required to register in the National System of Controlled Products Management (SNGPC), the amount of antibiotics sold, the professional registration number of the prescriber, and the data of the patient who will use the antibiotic (ANVISA 2011). Sales data for the most prescribed oral antibiotics by veterinarians and sold in pharmacies and drugstores were collected between January 2014 and July 2021.

Data sources, measurement, and variables

Data were collected in CSV format at the SNGPC, taken to a data server, and then the following variables were extracted: name and amount of the active ingredient and veterinarian prescriber. All prescriptions containing at least one antibacterial agent under special control were considered for data collection (ANVISA 2011).

Studies on drug consumption are typically conducted on DDD/1000 inhabitants. In this case, there is no reference for calculating the DDDs because they are prescribed for animals. Thus, the number of commercial units sold in pharmacies and drugstores under veterinary prescriptions was used in the calculation.

Statistical methods

To assess the changes in monthly trends in the use of the antibiotics studied, we applied joinpoint regression, a statistical method used to identify the best-fitting points in case of the presence of a statistically significant change in the trend,

assessing changes in time series data (Institute 2021). The Joinpoint Regression Program was used (version 4.9.0.0. March 2021; Statistical Research and Applications Branch, National Cancer Institute).

Results

Table 1 shows the most prescribed oral antibiotics by veterinarians, sold in pharmacies in Brazil between January 2014 and July 2021. Cephalexin accounted for more than 35% of all prescriptions, followed by amoxicillin (24%). The amoxicillin data contemplated its use alone or in association with beta-lactamase inhibitors.

Table 1
Most prescribed oral antibiotics by veterinarians in Brazil and sold in pharmacies and drugstores (January 2014 to July 2021) in commercial units and percentage.

Antibiotics	Units sold	%
Cefalexin	3,782,411	35.27
Amoxicillin	2,607,055	24.31
Metronidazole	1,513,699	14.12
Doxycycline	977,267	9.11
Sulfamethoxazole trimethoprim	628,924	5.86
Ciprofloxacin	622,555	5.81
Azithromycin	591,590	5.52
Total	**10,723,501**	**100,00**

Table 2 shows the average monthly sales, from 2014 to 2021, of oral antibiotics prescribed by veterinarians, and the increase in percentage, comparing the monthly averages sold in 2021 with 2014. An increase in the sales of all antimicrobials during the study period was noted. In 2014, there was an average sale of 100,000 commercial units of all antibiotics, which, in just seven years, reached more than 169,000 units, an average increase of 68.9%. Azithromycin and metronidazole showed the highest percentage of increase. Brazil is currently the third country in terms of the total population of pets, according to information from the Brazilian Association of the Pet Products Industry (2022). Moreover, data from the Federal Council of Veterinary Medicine show that, from 2017 to 2020, the number of veterinarians in Brazil jumped from 111,000 to more than 145,000, a 30% increase in the number of professionals in just 3 years (FVMC 2020).

For azithromycin, the numbers show the monthly average of 4,449 commercial units sold in 2014. This number reaches 10,484 units in 2020 and 13,921 units in 2021, with an increase of approximately 212% between 2014 and 2021.

Table 2
Monthly average of commercial units of antibiotics sold under veterinary prescription and percentage of increase between 2014 and 2021.

Antibiotics	2014	2015	2016	2017	2018	2019	2020	2021	Increase (%) 2021/2014
Azithromycin	4,449	5,016	5,768	6,298	6,607	7,007	10,484	13,921	212.93
Metronidazole	12,615	14,014	16,223	18,202	17,566	18,372	24,284	29,967	137.56
Amoxicillin	20,087	22,694	26,269	30,486	34,065	36,642	40,253	46,021	129.11
Ciprofloxacin	5,412	6,246	6,715	7,316	8,029	8,481	9,388	9,780	80.71
SXT*	6,906	6,837	7,296	7,826	7,987	8,010	8,981	9,385	35.88
Doxycycline	9,340	10,151	11,144	12,393	13,427	14,391	13,149	11,629	24.50
Cefalexin	41,729	46,143	47,008	48,066	47,900	48,062	49,367	49,123	17.72
Total	100,538	111,101	120,423	130,587	135,581	140,965	155,906	169,826	68.92%

*SXT = Sulfamethoxazole trimethoprim

Figure 1 shows the monthly evolution of sales of commercial azithromycin units prescribed by veterinarians in Brazilian pharmacies. In addition to the ever-increasing number of veterinarians and attendances, the number of prescriptions has remarkably increased since March 2020. Sales of azithromycin increased from 6,038 units in February 2020 to 10,149 units in the following month (an increase of approximately 68% in just 1 month). With a relapse in the pandemic in Brazil, the same phenomenon was repeated between the months of October and December 2020, with sales rising from 8,275 units in October to 16,852 units, making an increase of more than 100% in just 60 days.

The joinpoint regression model evaluates the monthly trends in azithromycin sales, marking points (joinpoint) where there are trend changes on this curve, showing the monthly percentage change and its statistical significance. The regression analysis showed that the sale of azithromycin grew by 0.67% per month since May 2014. This growth trend remained stable until March 2020 (beginning of the pandemic), when it started to grow 12.64% per month, in a statistically significant manner until at least June of the same year (Fig. 2).

Table 3 shows the percentage share of sales for each antibiotic in veterinary prescriptions from 2014 to 2021. Sales of azithromycin between 2014 and 2019 represented, on average, 4.6% of the sales of all prescribed antibiotics by veterinarians. In 2020 and 2021, sales represented 6.72% and 8.2%, respectively.

Table 3
Sales share (%) of oral antibiotics prescribed by veterinarians in Brazilian pharmacies between 2014 and 2021.

Antibiotics/year	2014	2015	2016	2017	2018	2019	2020	2021
Azithromycin	4.43	4.51	4.79	4.82	4.87	4.97	6.72	8.20
Metronidazole	12.55	12.61	13.47	13.94	12.96	13.03	15.58	17.65
Amoxicillin	19.98	20.43	21.81	23.35	25.13	25.99	25.82	27.10
Ciprofloxacin	5.38	5.62	5.58	5.60	5.92	6.02	6.02	5.76
SXT*	6.87	6.15	6.06	5.99	5.89	5.68	5.76	5.53
Doxycycline	9.29	9.14	9.25	9.49	9.90	10.21	8.43	6.85
Cefalexin	41.51	41.53	39.04	36.81	35.33	34.09	31.66	28.93
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

*SXT = Sulfamethoxazole trimethoprim

Discussion

Between January 2014 and July 2021, cephalexin represented more than a third of all the units sold in veterinary prescriptions, followed by amoxicillin. Furthermore, the sales of all antimicrobials have remarkably increased during this period, especially azithromycin (212.9%) and metronidazole (137.6%).

The average monthly sales of commercial units of azithromycin in pharmacies in Brazil, prescribed by veterinarians, increased from March 2020. This was when the first cases of COVID-19 appeared in Brazil and the search for treatments that could treat or lessen the effects of the new disease was sought after, which included the use of azithromycin. Regression analysis showed that the sale of azithromycin grew by 0.67% per month since May 2014. This growth trend remained stable until March 2020, when it began to grow at 12.64% per month.

Another fact that draws attention to the rapid growth in the sales of azithromycin in the treatment of animals is the share of this drug in the total number of antibiotics sold in veterinary medicine during the study period. The sales of azithromycin between 2014 and 2019 represented, on average, 4.6% of the sales of all antibiotics prescribed by veterinarians, this percentage being 6.72% and 8.2%, in the years 2020 and 2021, respectively.

An assessment of the use of antibiotics in cats in Switzerland showed that together, azithromycin, lincosamides, amphenicols, and nitroimidazoles accounted for less than 2% of all prescriptions for cats in the country between 2016 and 2018 (Hubbuch, Schmitt et al. 2020). Similarly, another study in Switzerland evaluated the prescription profile of antibiotics intended for animals. In that study, the entire macrolide group represented only 1.5% of the prescriptions for dogs and 0.1% for cats (Regula, Torriani et al. 2009). In the present study, azithromycin represented 8.2% of the prescriptions in 2021, which is five times greater than that in the aforementioned study. (Regula, Torriani et al. 2009).

A working group formed by professors from American universities, and supported by the International Society for Companion Animal Infectious Diseases, published important guidelines on the use of antibiotics in animals. The guidelines note that, for the treatment of feline ocular chlamydiosis, azithromycin should only be used if other treatments with tetracyclines or penicillin are not effective. Likewise, the guidelines state a lack of evidence to guide the use of azithromycin in the treatment of suspected bacterial pneumonia (Lappin, Blondeau et al. 2017). Allerton et al. (2021) stated that macrolides should be of restricted use in veterinary practice and not of the first choice, and their prescription should be conditioned to the results of sensitivity or antibiogram tests (Allerton, Prior et al. 2021).

Azithromycin is an antimicrobial agent with important effect on exclusive organelles of protozoa, such as *Babesia* spp. and *Toxoplasma gondii*, which are important and common parasites in veterinary routine. The efficacy of treating babesiosis with azithromycin alone or in combination has already been demonstrated in dogs infected with different *Babesia* species (Jefferies, Ryan et al. 2007, Baneth 2018). However, the drug is not the main indication for the treatment of the disease caused by *Babesia vogeli* detected in Brazil (Checa, Montoya et al. 2017). Animals are usually asymptomatic to *T. gondii* infection, and dogs in particular, rarely suffer from toxoplasmosis as a primary disease. In these cases, they do not require treatment with antiprotozoal drugs such as azithromycin (Calero-Bernal and Gennari 2019). Therefore, the indication for the use of azithromycin in the treatment of animal diseases is limited, and there is no public knowledge of any outbreak of infectious diseases that require the use of azithromycin in animals during the pandemic which justifies the sudden and abrupt increase in the number of antibiotics sold.

The increase in azithromycin consumption during the pandemic is not an event that only occurred in the veterinary field. In the field of human medicine, other studies have also found increased consumption of antibiotics during the pandemic. In some cases, consumption has increased by up to two-fold (Castro-Lopes and Correia 2021, Grau and Hernández 2021, Sulis and Batomen 2021). Sulis and Batomen (2021) (Sulis and Batomen 2021) reported the increase in azithromycin use in India during the pandemic, jumping from 26.4 million to 49.2 million doses, an increase of 53%, justifying its use as a possible treatment for COVID-19. In March 2021, data from the American Veterinary Medical Association showed that only 115 cats and 81 dogs worldwide were infected by SARS-CoV-2 (AVMA 2022). However, Manzini et al. (2021) (Manzini, Rodrigues et al. 2021) pointed out that most domestic animals that tested positive for COVID-19, manifesting mild clinical signs or remaining asymptomatic, do not play a role in the transmission of the disease; therefore, antibiotic therapy is of questionable indication.

A point worth mentioning is the prescription of antibiotics by veterinarians, which indicates commercial preparations intended for humans. Options in the veterinary drug market are restricted and expensive compared to human drugs, whose preparations, in most of the cases, are also suitable for the treatment of pets.

The use of drugs by humans prescribed for animals is not a new problem, as well as the administration of human drugs to animals without veterinary guidance. In 2002, in the United States, 1,077 veterinarians answered a questionnaire about their perceptions of the use of medicines intended for animals but used in humans. The question was, “What percent of your clients, whose animals you treat, do you suspect misuse of veterinary medications in themselves, their children, or friends?” Responses showed that, on average, 23% could use prescription drugs in humans and 39% could be using over-the-counter veterinary medications. This study also showed that the most used classes by humans were anti-inflammatory and analgesics, followed by antibiotics (Erramouspe, Adamcik et al. 2002).

The exaggerated and extensive use of certain antibiotics, such as azithromycin, will, as is already known, exert great selective pressure on the local microbiome, favoring the emergence of multi-resistant microbial specimens such as non-typhoidal *Salmonella* strains (Hooda, Tanmoy et al. 2020) and *Enterobacteriaceae* (Babu, Kumar et al. 2016). This excessive and unnecessary use must be discouraged to fight and prevent the emergence of antibiotic-resistant bacteria.

Conclusions

Drug prescriptions for humans are exclusively the responsibility of doctors and dentists, while veterinary prescriptions are for the treatment of animals. Disrespecting this determination and distributing antimicrobials without control represent a risk to public health, spreading resistance genes, and thus, shortening the time in which azithromycin can still be clinically effective in the treatment of respiratory infections in humans.

During the study period, the sale of all antimicrobials, especially azithromycin, has substantially increased during the COVID-19 pandemic. Such findings imply the need for even greater rigor in the sale of antimicrobials in Brazil, in addition to measures to inspect and monitor the use of antimicrobials in animals to avoid the worsening of antimicrobial resistance.

Declarations

Disclosure of potential conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics approval and consent to participate

This study did not require ethical approval. The study used data from drugs prescribed to animals, using the Brazilian government's public database.

Authors' contributions

FSDF, CCB, IPA-Jr, conceived the study, designed, collect and analyzed the data, BGBS, ACHN performed the literature search. SBF, MTS, LCL wrote the manuscript, and all authors revised and approved the final manuscript.

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Availability of data

Data are available at: https://dados.gov.br/dataset/venda-de-medicamentos-controlados-e-antimicrobianos-medicamentos-industrializados

Consent to participate

Not applicable

Consent for publication

Not applicable

Conflicts of interest/Competing interests

There is no conflict of interest of all authors to be declared.

Authors' Contributions

All authors participated in data extraction, data analysis, paper writing and conclusions.

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Figures

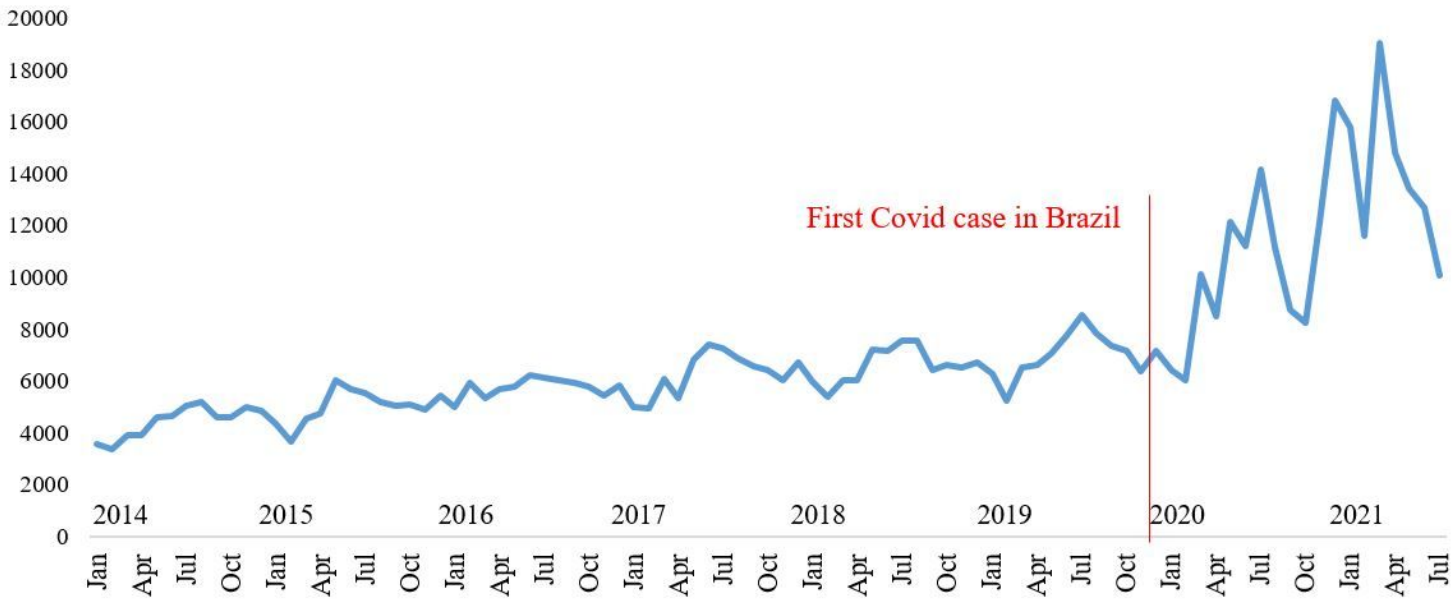

Figure 1

Number of sold units of azithromycin before and after the onset of the first case of COVID-19 in Brazil

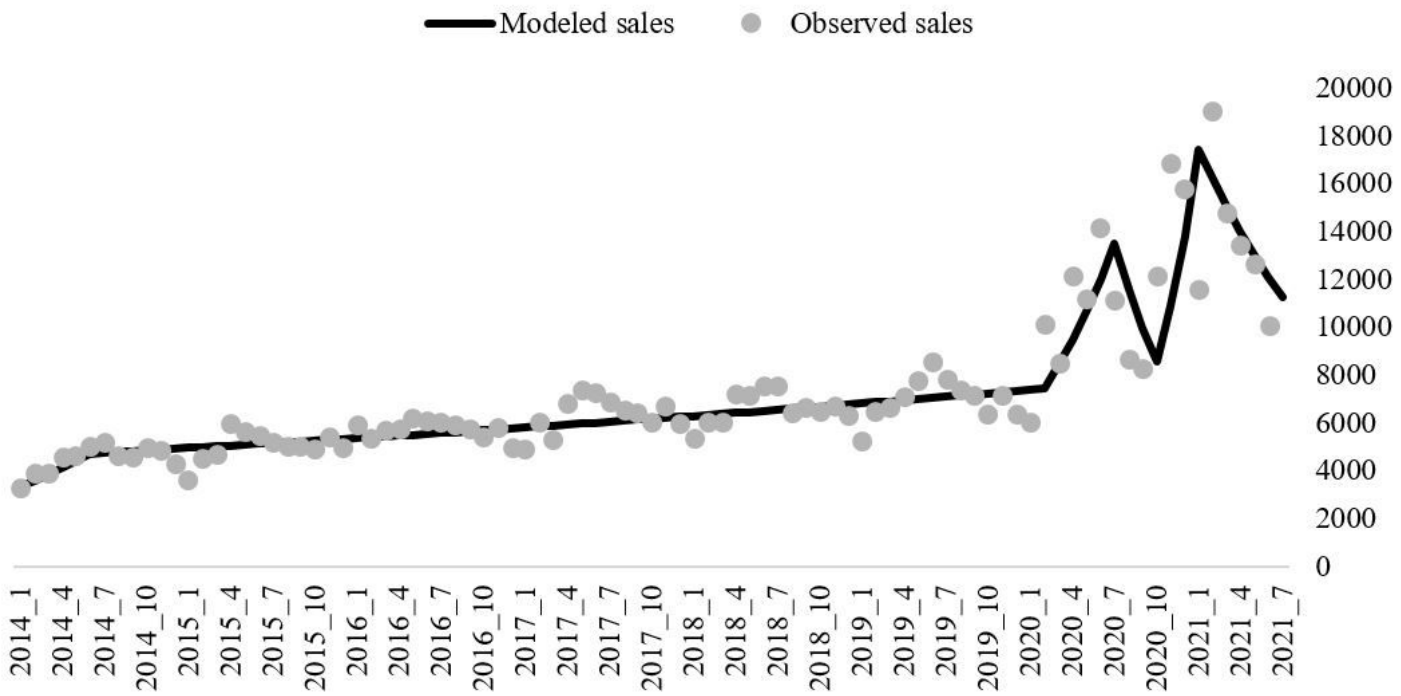

Figure 2

Monthly evolution in sales of commercial units of azithromycin prescribed by veterinarians in pharmacies in Brazil