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Ivermectin Prophylaxis Used for COVID-19 Reduces COVID-19 Infection and Mortality Rates: A City-Wide, Prospective Observational Study of 223,128 Subjects Using Propensity Score Matching.

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Acromyums: COPD = Chronic Obstructive Pulmonary Disease; CVD = cardiovascular disease; MI = Myocardial infarction; T2D = Type 2 Diabetes

Abstract

Background: Ivermectin has demonstrated different mechanisms of action that potentially protect from both COVID-19 infection and COVID-19-related comorbidities. Based on the studies suggesting efficacy in prophylaxis combined with the known safety profile of ivermectin, a citywide prevention program using ivermectin for COVID-19 was implemented in Itajai, a Southern city in Brazil in the state of Santa Catarina. The objective of this study was to evaluate the impact of regular ivermectin use on subsequent COVID-19 infection and mortality rates.

Materials and methods: We analyzed data from a prospective, observational study of the citywide COVID-19 prevention with ivermectin program which occurred between July 2020 to December of 2020 in Itajaí, Brazil. Study design, institutional review board approval, and analysis of registry data occurred after completion of the program. The program consisted of inviting the entire population of Itajaí to a medical visit in order to enroll in the program and to compile baseline, personal, demographic and medical information. In the absence of contraindications, ivermectin was offered as an optional treatment to be taken 2 consecutive days every 15 days at a dose of 0.2mg/kg/day. In cases where a participating citizen of Itajai became ill with COVID-19, they were recommended to not use ivermectin or any other medication in early outpatient treatment. Clinical outcomes of infection, hospitalization, and death were automatically reported and entered into the registry in real time. Study analysis consisted of comparing ivermectin users with non-users using cohorts of infected patients propensity score matched (PSM) by age, sex, and comorbidities. COVID-19 infection and mortality rates were analyzed with and without use of propensity score matching.

Results: Of the 223,128 citizens of Itajaí considered for the study, a total of **159,561** subjects were included in the analysis; **113,845** (**71.3**%) regular ivermectin users and **45,716** (**23.3**%) non-users. **Of these, 4,311 ivermectin users were infected, among which 4,197 from the city of Itajaí (3.7% infection rate) and 3,034 non-users (from Itajaí) were infected (6.6% infection rate), a 44% reduction in COVID-19 infection rate (Risk ratio (RR), 0.56; 95% confidence interval (95%CI), 0.53 – 0.58; p < 0.0001).** Using PSM, two cohorts of 3,034 subjects suffering COVID-19 infection were compared. The regular use of ivermectin led to a 68% reduction in COVID-19 mortality [25 (0.8%) versus 79 (2.6%) among ivermectin non-users; risk ratio (RR), 0.32; 95% confidence interval (CI), 0.20 – 0.49; p < 0.0001]. When adjusted for residual variables,

reduction in mortality rate was 70% (RR, 0.30; 95%CI 0.19 – 0.46; p < 0.0001). There was a 56% reduction in hospitalization rate (44 versus 99 hospitalizations among ivermectin users and non-users, respectively; RR, 0.44; 95%CI, 0.31 – 0.63; p < 0.0001). After adjustment for residual variables, reduction in hospitalization rate was 67% (RR, 0.33; 95%CI 023 – 0.66; p < 0.0001).

Conclusion: In this large, propensity score matched study, regular use of ivermectin as a prophylactic agent was associated with significantly reduced COVID-19 infection, hospitalization, and mortality rates.

Introduction

Ivermectin has been demonstrated to have not only extensive anti-parasitic actions[1,2], but alsoanti-viral, anti-bacterial, and anti-protozoan properties. Ivermectin has been long proposed for use as a repurposed antiviral agent[4-6]. Indeed, antiviral effects of ivermectin have been reported against both RNA and DNA types of viruses, including HIV-1, Yellow fever (YFV), Japanese encephalitis, tick-borne encephalitis, West Nile, Zika (ZKV), Dengue fever, Chikungunya (CHIKV), Venezuelan equine encephalitis and the Pseudorabies virus[3,5,7], as well as functioning in regulation of proteins involved in antiviral responses[8].

Additional actions of ivermectin described include agonism activity to the X-LBD binding receptor (FXR), with multiple potential metabolic benefits[9,10]; neuronal regeneration[11,12], prevention of muscle hypoxia[13], anti-inflammatory activity to Interferon (INF)[14], nuclear factor-κB (NF-κB), lipopolysaccharide (LPS)[15] and JAK-STAT pathway, PAI-1[16,17]; generation of P21 activated Kinase 1 (PAK-1)[18,19]; reduction of Interleukin-6 (IL-6) levels[15]; allosteric modulation of P2X4 receptor[20]; inhibition of high mobility group box 1 (HMGB1)[21,22]; suppression of mucus hypersecretion, diminished recruitment of immune cells and production of cytokines in the lung[23]. ivermectin is also described to induce Th1-type immune response against protozoans[24], and anti-coagulant action through binding to the S protein of some viruses[25].

The hypothesis that ivermectin could be protective against COVID-19 is substantiated by its multi-pathway, anti-inflammatory effects[15,26] and multi-antiviral mechanisms. COVID-19 pathogenesis is largely understood as an inflammation-mediated hemagglutinating infection disrupting pulmonary, vascular and endothelial systems, leading to a multi-systemic disease. *In vitro* and *in-silico*, ivermectin has demonstrated anti-SARS-CoV-2 activity through more than 20 direct and indirect mechanisms[2,27,28].

Ivermectin has demonstrated preliminary protective effects against SARS-CoV-2 infection in terms of reducing times to clinical recovery, rates of disease progression and mortality[2,29,30]. However, more robust studies with larger sample sizes are still

recommended to confirm the possible beneficial effects ivermectin confers in COVID-19.

Since the onset of the COVID-19 pandemic, the use of inexpensive options based on a consistently beneficial signal of efficacy, a well-established safety profile, favourable cost-effectiveness, ivermectin is a highly attractive intervention for the patient centred medicine practiced by frontline clinicians, with use aligning strongly with the bioethical principles for medical practice outlined in Article 36 of the Helsinki declaration[31].

However, despite this favorable risk/benefit profile and absense of therapeutic alternatives, ivermectin has yet to be approved for prophylaxis and treatment of COVID-19 by agencies throughout the world, including FDA (Food & Drug Administration; United States of America), EUA (European Medicines Agency; Europe) and ANVISA (Agência Nacional de Vigilância Sanitária – Brazilian Health Regulatory Agency; Brazil).

The ability to prescribe ivermectin or any other off-label drug for COVID-19 has long been at the discretion of frontline physicians once all risks, uncertainties, potential benefits, and patients' rights are exposed, and informed consent has been obtained. Of particular note, in Brazil, this follows the medical autonomy to determine the best therapeutic strategies for individuals, as per the Medical Code of Ethics of the Brazilian Board of Medical Doctors; the Federal Council of Medicine – Conselho Federal de Medicina (CFM), that determines the obligations and rights of medical doctors in Brazil[32].

Since vaccines for COVID-19 were not available in Brazil until 2,021, and the lack of prophylactic alternatives in the absence of vaccines, Itajai, a city in the Southern Brazilian state of Santa Catarina, initiated a population wide government program for COVID-19 prophylaxis. The medical-focused decision parameters established are based on the distribution of ivermectin to whole populations in different countries. To ensure the safety of the population, a well-controlled computer program was developed to compile and maintain all relevant demographic and clinical data. The

use of ivermectin was optional and based on patients' preferences given its benefits as a preventative agent was unproven.

This study's objective is to assess the impact on important clincal outcomes when ivermectin is used as prophylaxis for COVID-19. The prophylaxis program occurred in addition to the standard non-pharmacological strategies of masking and social distancing, as part of a citywide program conducted in outpatient settings.

Material and Methods

Study population

This was a prospective, observational study. Although study design, IRB approval, and data analysis occurred after completion of the voluntary prophylaxis program, all data were collected prospectively in real-time with mandated reporting to the registry of all events as they occurred during the citywide governmental COVID-19 prevention with ivermectin program, from July 2020 to December 2020, developed in the city of Itajaí, in the state of Santa Catarina, Brazil. Demographic and clinical data was reported from medical records of patients followed in a large outpatient setting; a provisional outpatient clinic set in the Convention Center of Itajaí, and several secondary outpatient settings, as part of the Universal Health System (SUS).

The objective was to determine the number of patients affected by COVID-19 (positivity rate of rtPCR-SARS-CoV-2), risk of death due to COVID-19 (whether infected or not), and COVID-19 mortality rate (risk of death from COVID-19) of those who used and did not use ivermectin prophylactically for COVID-19. This data was analyzed stratified by age, sex, presence of comorbidities, and correlated demographic characteristics.

The present retrospective analysis of the prospectively collected data was approved by the CONEP - National Research Ethics Council (CONEP) under the number 4.821.082 with the project number CAAE: 47124221.2.0000.5485. Although study design, IRB approval, and data analysis occurred after completion of the voluntary

prophylaxis program, all data were collected prospectively in real-time with mandated reporting to the registry of all events as they occurred during the citywide governmental COVID-19 prevention with ivermectin program, from **July 7, 2020 to December 2, 2020**, developed in the city of Itajaí, in the state of Santa Catarina, Brazil.

Study procedures and data collection

Optional, voluntary prophylactic use of ivermectin was offered to patients during regular medical visits between July 7, 2020 and December 31, 2020 in 35 different sites, including 34 local SUS health centres and a large temporary patient setting. Doctors working in these sites were free to prescribe ivermectin prophylactically. Subjects that did not use ivermectin either refused or their primary care physicians opted not to offer ivermectin.

The program was conducted in all 35 sites, 24/7, with the initial enrollment in the program occurring during a two-week time frame, due to the large number of subjects to evaluate in the entire population of Itajaí. In order to avoid underreported data, strict procedure sequencing was followed: 1. Registration and recording of patient data, documented by assistants; 2. Weighing subjects (Subject weight was essential to calculate the appropriate dose of ivermectin); 3. Brief medical evaluation of past medical history, comorbidities, use of medications and contraindications to drugs; 4. Medical prescription of prophylactic doses of ivermectin, according to medical judgment and following a subject's informed consent related to potential benefits, risks, and side effects. **Regarding drug interactions with ivermectin, use of warfarin was a contra-indication for prophylaxis with ivermectin due to drug interactions. Subjects under chronic use of glucocorticoids, protease inhibitors and anti-epileptics were recommended to schedule regular medical visits every six to eight weeks. Subjects were recommended to inform medical doctors about the use of ivermectin, in case one or more of the following medications were prescribed: warfarin, azithromycin, dexamethasone, prednisone or prednisolone (Hydrocortisone or cortisone are not commercially available in regular pharmacies in Brazil).**

All details of this citywide program and campaign had been previously agreed upon between the city local department of the National Healthcare System (SUS), city mayor, and local public prosecutors.

The following data were analyzed, adjusted as confounding factors, and used as variables for balancing and matching groups for the employment of propensity score matching (PSM) in the present study: age, sex, past medical history, previous diseases; myocardial infarction (MI), stroke: existing comorbidities; type 2 diabetes (T2D), asthma, chronic obstructive pulmonary disease (COPD), hypertension, dyslipidemia, cardiovascular diseases (CVD), cancer (any type), and other pulmonary diseases: habits (past or current smoking). Additional data analyzed included self-reported comorbidities and medications used.

Patients who presented signs or the diagnosis of COVID-19 before July 7, 2020, were excluded from the sample. Other exclusion criteria were contraindications to ivermectin and subjects below 18 years of age. The dose and frequency of ivermectin treatment was 0.2mg/kg/day; *i.e.,* giving one 6mg-tablet for every 30kg. for 2 consecutive days every 15 days.

During the study, subjects who became infected with COVID-19 were diagnosed with a positive rtPCR-SARS-CoV-2 and then underwent a specific medical visit to assess COVID-19 clinical manifestations and severity. All subjects were recommended not to use ivermectin, nitazoxanide, hydroxychloroquine, spironolactone or any other drug claimed to be effective against COVID-19. The city did not provide or support any specific pharmacological outpatient treatment for subjects infected with COVID-19.

They were questioned for the presence of common COVID-19 symptoms. These included chills, high-grade fever, cough, myalgia, fatigue, anosmia, ageusia, sore throat, headache, nasal congestion, sneeze, runny nose, hemoptysis, nauseas, vomiting, abdominal pain, diarrhea, cutaneous rash, arthralgia, chest pain, eye pain and pinkeye, and presence of alert signs, including shortness of breath, signs of hypoxia, signs of coagulation abnormalities and an altered level of consciousness. Systolic and diastolic blood pressure, heart rate, respiratory rate, oxygen saturation, and axillar temperature were measured. The same signs and symptoms, and vital signs were collected at each

following medical visit during COVID-19. Individual data was compiled and reviewed by the researchers.

Registry data of all patient records from the city of Itajaí between July 7, 2020 and December **2,** 2020, including those who used ivermectin and did not use ivermectin were reviewed. Subjects who tested positive for COVID-19 during the study were considered for this analysis, whether they used ivermectin or not. Of the infected subjects, two groups were considered: subjects who used ivermectin prophylactically (treated group) and subjects who did not use ivermectin prophylactically (untreated group). Any missing data from patients were actively searched by the investigators, via phone or in person. Since this is a citywide program, all recorded data must have matched the exact number of COVID-19 cases and deaths of the city. This strict interval avoids differences in terms of periods of exposure.

Due to the uncertainty of reinfection with COVID-19, subjects with a history of previous COVID-19 did not participate in the program although they were still permitted to use ivermectin prophylactically. Limiting parameters of the government system allowed the recording of a first episode of COVID-19 infection only. **Subjects below 18 years old and subjects with diagnosis of COVID-19 before July 7, 2020 were excluded from all datasets and analysis.**

From the registry of the city population (223,128 inhabitants), subjects below 18 years old (61,583 subjects) were removed. Of the 161,545 subjects above 18 y/o from the city of Itajaí, we removed the 1,984 COVID-19 cases that occurred before July 7, 2020, among subjects above 18 y/o, remaining 159,561 subjects. Subjects above 18 y/o were considered those who were born before June 30, 2002.

A total of 147,223 subjects participated in the program of ivermectin prophylaxis used for COVID-19. Of these, 24,304 subjects were below 18 y/o. Of the 122,919 ivermectin users above 18 y/o, 8,346 were from other cities, and 728 had COVID-19 before July 7, 2020, although they used ivermectin afterwards. In total, 113,845 subjects that participated in the program remained in the dataset. The 45,716 non-participants, remaining subjects among the 159,561 subjects were considered as the ivermectin non-users.

Finally, city-wide COVID-19 hospitalization and mortality rates of Itajaí were compared between the period before the program (before July 7, 2020) and during the program between July 7, 2020 and December **2**, 2020) aiming to evaluate whether a program of prophylaxis with ivermectin for COVID-19 would cause a positive impact in the overall numbers of the city, despite only partial adoption. Chances of dying from COVID-19 in the overall population, according to use or non-use of ivermectin (irrespective of COVID-19 infection) were only calculated prior to matching. Conversely, mortality rate, i.e., among those who were infected by the SARS-CoV-2, was calculated for both pre and post-matched cohorts. Analysis of hospitalization and mortality rates before matching, mortality rate in subpopulations among ivermectin users, among ivermectin non-users, and mortality rate ratios between iveremctin users and non-users in subpopulations, before and after propensity score matching, and STROBE checklist are presented in the **Supplement Appendix 1**.

Statistical analysis

The full underlying data for the present analysis was analyzed by two independent statisticians, and discrepancies evalauted by a third statistics expert. In this outpatient study of those who tested positive for SARS-CoV-2, mortality rate was evaluated according to each parameter, that adjusted against other variables (for multivariate regression analysis) and used for balancing and matching groups, including age intervals, sex, history of smoking, prophylactic ivermectin use, T2D, asthma, COPD, cardiovascular diseases and other pulmonary diseases, hypertension, current cancer (any type), history of stroke and/or MI. Groups, baseline characteristics, and mortality rates were presented before matching and after matching.

Before matching, a generalized linear mixed model was employed, assuming the binomial distribution for the residues and including the fixed classificatory effects of each of these parameters. Age intervals were adjusted for the evaluation of ivermectin prophylactic use as an independent predictor of death from COVID-19. Unadjusted and multivariate Poisson- adjusted probabilities to survive from COVID-19 (p-value), according to each parameter were provided.

PSM was performed for mortality risk between ivermectin and non-vermectin users. COVID-19 infection rate and risk of dying were also calculated matching for variables. After PSM, a second adjustment ('double adjustment') with multivariate linear regression was performed for residual variables[33,34].

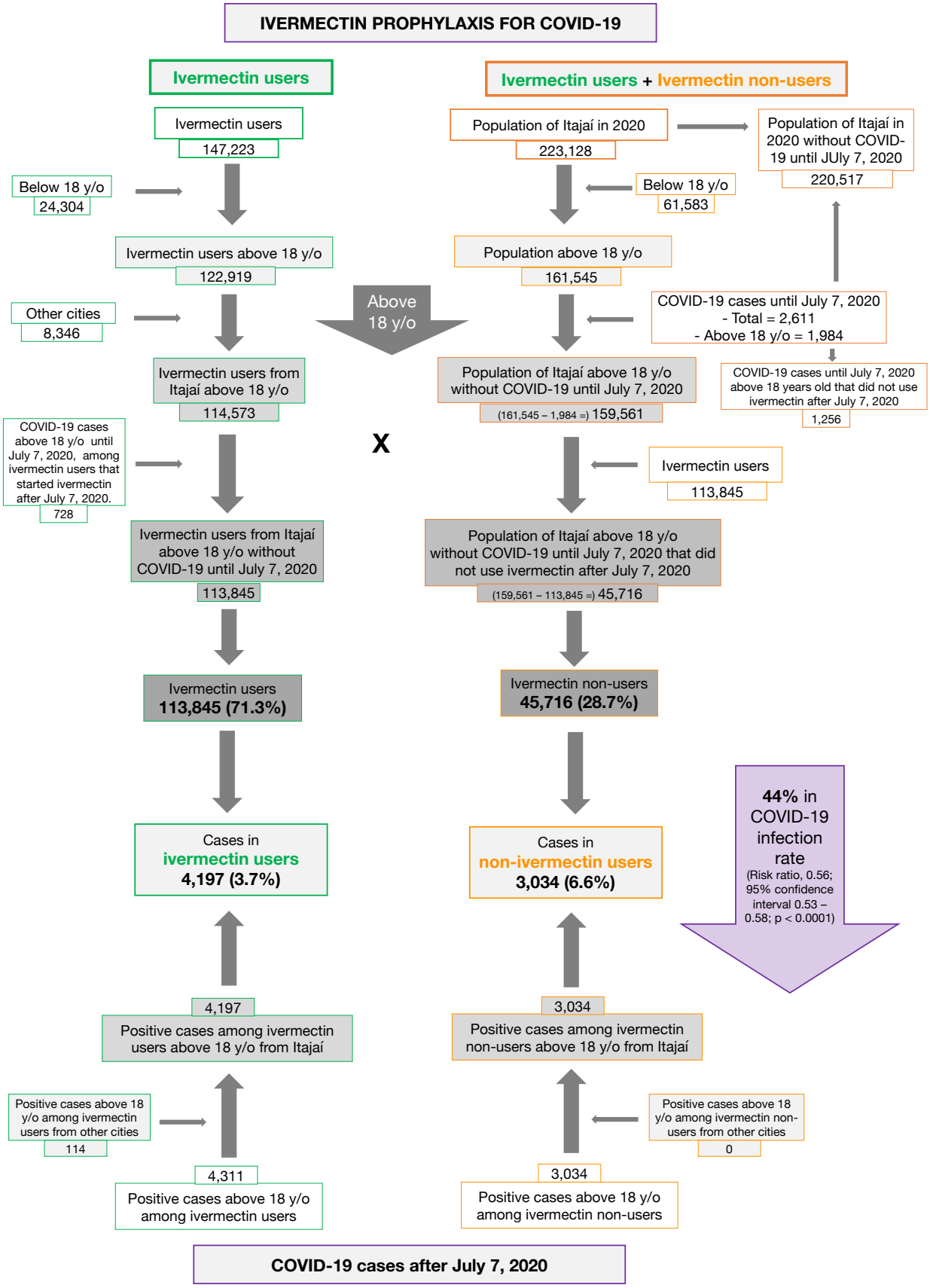
The statistical approach for missing data depended on the percentage of missing data for each parameter. However, due to the registry system design mandating that all data variables be filled to be formally included in the registry, only erroneously entered (illogical) data were found. In such instances, medical record review was performed to obtain the accurate data.

The program used for the analysis was the Statistical Analysis Software (SAS/STAT) (SAS Institute Inc., Care, North Carolina, USA).

For transparency reasons, two datasets will be made public upon peer-reviewed publication, of the 7,345 COVID-19 cases and of the 113,845 participating subjects considered for the present analysis.

Results

Figure 1. Underlying data for the study on ivermectin prophylaxis used for COVID-19.


IVERMECTIN PROPHYLAXIS FOR COVID-19
Ivermectin users
Ivermectin users + Ivermectin non-users
Ivermectin users
147,223
Below 18 y/o
24,304
Ivermectin users above 18 y/o
122,919
Other cities
8,346
Ivermectin users from Itajaí above 18 y/o
114,573
COVID-19 cases above 18 y/o until July 7, 2020, among ivermectin users that started ivermectin after July 7, 2020.
728
Ivermectin users from Itajaí above 18 y/o without COVID-19 until July 7, 2020
113,845
Ivermectin users
113,845 (71.3%)
Cases in
ivermectin users
4,197 (3.7%)
4,197
Positive cases among ivermectin users above 18 y/o from Itajaí
Positive cases above 18 y/o among ivermectin users from other cities
114
4,311
Positive cases above 18 y/o among ivermectin users
Above 18 y/o
X
Population of Itajaí in 2020
223,128
Population of Itajaí in 2020 without COVID-19 until JUly 7, 2020
220,517
Below 18 y/o
61,583
Population above 18 y/o
161,545
COVID-19 cases until July 7, 2020
- Total = 2,611
- Above 18 y/o = 1,984
COVID-19 cases until July 7, 2020 above 18 years old that did not use ivermectin after July 7, 2020
1,256
Population of Itajaí above 18 y/o without COVID-19 until July 7, 2020
(161,545 – 1,984 =) 159,561
Ivermectin users
113,845
Population of Itajaí above 18 y/o without COVID-19 until July 7, 2020 that did not use ivermectin after July 7, 2020
(159,561 – 113,845 =) 45,716
Ivermectin non-users
45,716 (28.7%)
Cases in
non-ivermectin users
3,034 (6.6%)
44% in COVID-19 infection rate
(Risk ratio, 0.56; 95% confidence interval 0.53 – 0.58; p < 0.0001)
3,034
Positive cases among ivermectin non-users above 18 y/o from Itajaí
Positive cases above 18 y/o among ivermectin non-users from other cities
0
3,034
Positive cases above 18 y/o among ivermectin non-users
COVID-19 cases after July 7, 2020

A detailed description of the data considered for the present analysis is illustrated in Figure 1. Of the 220,517 citizens of Itajaí without COVID-19 until July 7, 2020, 159,561 were above 18 years old. Of the 159,561 citizens above 18 y/o without COVID-19 until July 7, 2020, 113,845 (**71.3**% of the population above 18 years old) received ivermec tin before being infected by COVID-19. A total of **45,716** citizens (**28.7**%) did not receive or did not want to receive ivermectin during the program, including as a prophylactic or as treatment after having COVID-19.

Of the **113,845** prophylaxed subjects **from the city of Itajaí, 4,197** had a positive rtPCR-SARS-CoV-2 (**3.7**% infection rate), while 3,034 of the **37,027** untreated subjects had positive rtPCR-SARS-CoV-2 (**6.6**% infection rate), a **44% reduction in COVID-19 infection rate (Risk ratio (RR), 0.56; 95% confidence interval (95%CI), 0.53 - 0.58; p < 0.0001). An addition of 114 subjects that used ivermectin and were infected were originally from other cities but were registered as part of the program, in a total of 4,311 positive cases among ivermectin users. For the present analysis, the 4,311 positive cases among subjects that used ivermectin and 3,034 cases among subjects that did not use ivermectin were considered.** After PSM, two cohorts of 3,034 subjects were created.

Baseline characteristics of the 7,345 subjects included prior to PSM and the baseline characteristics of the 6,068 subjects in the matched groups are shown in Table 1. Prior to PSM, ivermectin users had a higher percentage of subjects over 50 years old ($p < 0.0001$), higher prevalence of T2D ($p = 0.0004$), hypertension ($p < 0.0001$), CVD ($p = 0.03$), and a higher percentage of caucasians ($p = 0.004$), than non-users. After PSM, all baseline parameters were similar between groups. **Figure 2 summarizes the main findings of this study.**

Table 1. Baseline characteristics of subjects enrolled in study before matching and after propensity score matched.

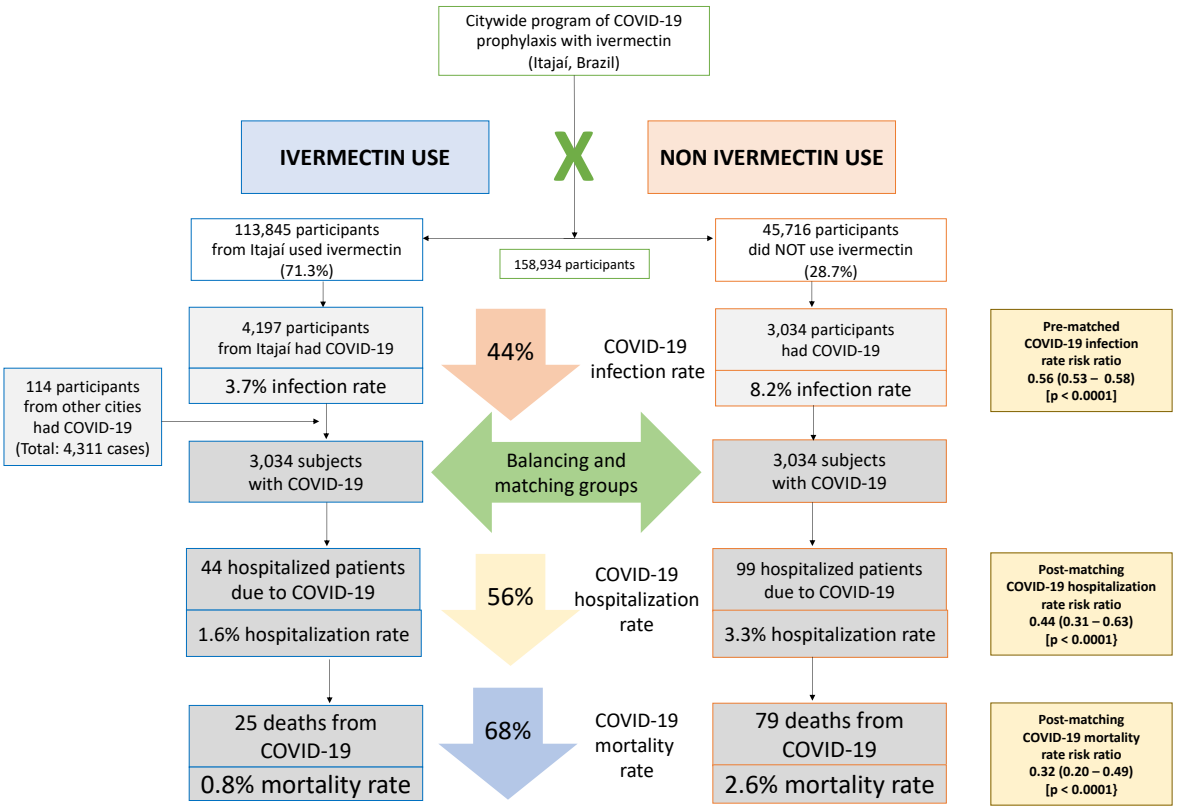
	Pre-Matching				**Propensity Score Matched**		
	Overall (n = 7,345)	**Ivermectin users (n = 4,311)**	**Non-ivermectin users**	***p-value***	**Overall (n = 6,068)**	**Ivermectin users (n = 3,034)**	**Non-ivermectin users**

			(n = 3,034)				(n = 3,034)
Age							
Mean ± SD	42.0 ± 14.7	43.5 ± 14.9	39.8 ± 14.2	***< 0.0001***	39.7 ± 14.0	3967 ± 13.8	39.8 ± 14.2
< 30 y/o	1730 (23.6%)	886 (20.5%)	844 (27.8%)		1,691 (27.9%)	844 (27.9%)	847 (27.8%)
30-50 y/o	3703 (50.4%)	2121 (49.2%)	1582 (52.2%)		3,155 (52.0%)	1,573 (51.9%)	1,582 (52.1%)
> 50 y/o	1912 (26.0%)	1304 (30.3%)	608 (20.0%)		1,222 (20,1%)	614 (20.2%)	608 (20.1%)
Sex				*0.31*			
Female	3983 (54.2%)	2359 (54.7%)	1624 (53.5%)		3,231 (53.2%)	1,607 (53.0%)	1,624 (53.5%)
Male	3362 (45.8%)	1952 (45.3%)	1410 (46.5%)		2,837 (46.8%)	1,427 (47.0%)	1,410 (46.5%)
Race							
Caucasians	5437 (74.0%)	3245 (75.3%)	2192 (72.2%)	***0.004***	4,398 (72.5%)	2,206 (72.7%)	2,192 (72.3%)
Afro-Brazilians	209 (2.8%)	109 (2.5%)	100 (3.3%)	***0.052***	193 (3.2%)	93 (3.1%)	100 (3.3%)
Mixed	1583 (22.6%)	901 (20.9%)	682 (22.5%)	*0.10*	1,364 (22.5%)	93 (3.1%)	100 (3.3%)
Asian-Brazilians	116 (1.6%)	56 (1.3%)	60 (2.0%)	***0.023***	113 (1.9%)	53 (1.8%)	60 (2.0%)
Type 2 diabetes				***0.0004***			
Yes	214 (2.9%)	151 (3.5%)	63 (2.1%)		141 (2.3%)	78 (2.6%)	63 (2.1%)
No	7131 (97.1%)	4160 (96.5%)	2971 (97.9%)		5,927 (97.7%)	2,956 (97.4%)	2,971 (97.9%)
Asthma				***0.067***			
Yes	26 (0.3%)	20 (0.5%)	6 (0.2%)		21 (0.3%)	15 (0.5%)	6 (0.2%)
No	7319 (99.7%)	4291 (99.5%)	3028 (99.8%)		6,047 (99.7%)	3,019 (99.5%)	3,028 (99.8%)
COPD				*0.72*			
Yes	13 (0.2%)	7 (0.2%)	6 (0.2%)		12 (0.2%)	6 (0.2%)	6 (0.2%)
No	7332 (99.8%)	4304 (99.8%)	3028 (99.8%)		6,056 (99.8%)	3,028 (99.8%)	3,028 (99.8%)
Hypertension				***< 0.0001***			
Yes	528 (7.2%)	362 (8.4%)	166 (5.5%)		343 (5.6%)	177 (5.8%)	166 (5.5%)
No	6817 (92.8%)	3949 (91.6%)	2868 (94.5%)		5,725 (94.4%)	2,857 (94.2%)	2,868 (94.5%)
CVD				***0.03***			
Yes	56 (0.8%)	41 (1.0%)	15 (0.5%)		32 (0.5%)	17 (0.6%)	15 (0.5%)
No	7289 (99.2%)	4270 (99.0%)	3019 (99.5%)		6,036 (99.5%)	3,017 (99.4%)	3,019 (99.5%)
Other pulmonary diseases				*0.53*			
Yes	15 (0.2%)	10 (0.2%)	5 (0.2%)		9 (0.1%)	4 (0.1%)	5 (0.1%)
No	7330 (99.8%)	4301 (99.8%)	3029 (99.8%)		6,059 (99.9%)	3,030 (99.9%)	3,029 (99.9%)
Cancer (any type)				*0.66*			

Yes	32 (0.4%)	20 (0.5%)	12 (0.4%)		22 (0.4%)	10 (0.3%)	12 (0.4%)
No	7313 (99.6%)	4291 (99.5%)	3023 (99.6%)		6,046 (99.6%)	3,024 (99.7%)	3,022 (99.6%)
Current smoking				*0.76*			
Yes	110 (1.5%)	63 (1.5%)	47 (1.5%)		95 (1.6%)	48 (1.6%)	47 (1.6%)
No	7235 (98.5%)	4248 (98.5%)	2987 (98.5%)		5,973 (98.4%)	2,986 (98.4%)	2,987 (98.4%)
History of MI				*0.26*			
Yes	15 (0.2%)	11 (0.3%)	4 (0.1%)		8 (0.1%)	4 (0.1%)	4 (0.1%)
No	7330 (99.8%)	4300 (99.7%)	3030 (99.9%)		6,060 (99.9%)	3,030 (99.9%)	3,030 (99.9%)
History of stroke				*0.56*			
Yes	21 (0.3%)	11 (0.3%)	10 (0.3%)		21 (0.4%)	11 (0.4%)	10 (0.3%)
No	7324 (99.7%)	4300 (99.7%)	3024 (99.7%)		6,047 (99.6%)	3,023 (99.6%)	3,024 (99.7%)

COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; MI = myocardial infarction; SD = standard deviation

Figure 2. Summary of the findings.



Hospitalization and mortality rates in ivermectin users and ivermectin non-users in propensity score matched analysis

As described in **Table 2**, after employing PSM, of the 6,068 subjects (3,034 in each group), there were 44 hospitalizations among ivermectin users (1.6% hospitalization rate) and 99 hospitalizations (3.3% hospitalization rate) among ivermectin non-users, a 56% reduction in hospitalization rate (RR, 0.44; 95%CI, 0.31 – 0.63). When adjustment for variables was employed, reduction in hospitalization rate was 67% (RR, 0.33; 95%CI 023 – 0.66; $p < 0.0001$).

There were 25 deaths among ivermectin users (0.8% mortality rate) and 79 deaths among non-ivermectin users (2.6% mortality rate), a 68% reduction in mortality rate (RR, 0.32; 95%CI 0.20 – 0.49). When PSM was adjusted, reduction in mortality rate was 70% (RR, 0.30; 95%CI 0.19 – 0.46; $p < 0.0001$).

Table 2. Propensity socre matched hospitalization and mortality rate among ivermectin users and non-users.

		Overall	IVM users	Non-IVM users	PSM mortality risk ratio (95%CI) and p-value [p]	Adjusted PSM mortality risk ratio (95%CI) and p-value [p]
COVID-19 infection	Infected population (n)	6,068	3,034	3,034	-	-
COVID-19 hospitalization	Hospitalization due to COVID-19	143	44	99	-	-
	Hospitalization rate* (in case of COVID-19) (%)	2.3%	1.6%	3.3%	**0.44 (0.31 – 0.63) [< 0.0001]**	**0.33 (0.23 – 0.46) [<0.0001]**
COVID-19 death	COVID-19 deaths (n)**	104	25	79	-	-
	Mortality rate (among infected subjects) (%)	1.7%	0.8%	2.6%	**0.32 (0.20 – 0.49) [< 0.0001]**	**0.30 (0.19 – 0.46) [< 0.0001]**

IVM = ivermectin; PSM = propensity score matching; CI = confidence interval; *Only subjects hospitalized in public hospitals; **All deaths, including from public and private hospitals, and in-home.

Determinants of COIVD-19 mortality through propensity score matched analysis

Table 3 describes resulting risk factors for COVID-19 death amongst the overall population through PSM analysis. Risk factors for mortality in COVID-19 included aging ($p < 0.0001$), male sex ($p = 0.015$), T2D ($p < 0.0001$), hypertension ($p < 0.0001$), asthma ($p = 0.011$), COPD ($p < 0.0001$), other pulmonary diseases ($p = 0.048$), history of MI ($p = 0.034$) and history of stroke ($p < 0.0001$). To detect independent risk factors, post-PSM adjustment for variables showed that ivermectin ($p < 0.0001$; 70% reduction in mortality risk) and female sex ($p = 0.022$; 38% reduction in mortality risk) were protectors, whereas T2D ($p = 0.041$; 79% increase in mortality risk), hypertension ($p = 0.008$; 98% increase in mortality risk), and, marginally, other pulmonary diseases ($p = 0.061$; 468% increase in mortality risk) and history of stroke ($p = 0.054$; 97% increase in mortality risk) were identified as independent risk factors.

Table 3. Propensity score matched COVID-19 mortality rate according to each characteristic, in overall population, ivermectin users, and non-users.

	Propensity Score Matched Groups			
Variable	**Overall (n = 6,068)**	**Death (%)**	**Unadjusted COVID-19 mortality risk ratio and p-value [p]**	**Multivariate adjusted COVID-19 mortality risk ratio and p-value [p]**
Ivermectin use - n (%)			**0.32 (0.20 – 0.49) [< 0.0001]**	**0.30 (0.19 – 0.46) [< 0.0001]**
Yes	3,034	25 (0.8%)		
No	3,034	79 (2.6%)		
Age - n (%)			**[< 0.0001]**	**[< 0.0001]**
< 30 y/o	1,691	1 (0.1%)		
30-50 y/o	3,155	12 (0.4%)		
> 50 y/o	1,222	91 (7.4%)		
Sex- n (%)			**0.62**	**0.64**

			(0.42 – 0.91) **[0.015]**	**(0.44 – 0.93)** **[0.022]**
Female	3,231	43 (1.3%)		
Male	2,837	61 (2.2%)		
Race - n (%)			[0.24]	[0.44]
Caucasians	4,398	79 (1.8%)		
Afro-Brazilians	193	6 (3.1%)		
Mixed	1.364	17 (1.3%)		
Asian-Brazilians	113	2 (1.9%)		
Type 2 diabetes - n (%)			**10.0** **(6.32-15.8)** **[< 0.0001]**	**1.79** **(1.03 – 3.12)** **[0.041]**
Yes	141	20 (14.2%)		
No	5,927	84 (1.4%)		
Hypertension - n (%)			**8.83** **(5.99 – 13.0)** **[< 0.0001]**	**1.98** **(1.19 – 3.30)** **[0.008]**
Yes	343	36 (10.5%)		
No	5,725	68 (1.2%)		
Asthma - n (%)			**5.64** **(1.49 – 21.4)** **[0.011]**	1.74 (0.52 – 5.81) [0.36]
Yes	21	2 (9.5%)		
No	6,047	102 (1.7%)		
COPD - n (%)			**15.0** **(5.52 – 40.7)** **[< 0.0001]**	1.71 (0.68 –4.31) [0.25]
Yes	12	3 (25.0%)		
No	6,056	101 (1.7%)		
Cardiovascular diseases - n (%)			**7.54** **(2.96 – 19.3)** **[< 0.0001]**	1.22 (0.44 – 3.37) [0.70]
Yes	32	4 (12.5%)		
No	6,036	100 (1.7%)		
Other pulmonary diseases - n (%)			**6.54** **(1.02 – 41.9)** **[0.048]**	5.68 (0.92 – 35.0) [0.061]
Yes	9	1 (11.1%)		
No	6,059	103 (1.7%)		
Cancer (any type) - n (%)			2.67 (0.39 – 18.3) [0.32]	1.97 (0.30 – 12.9) [0.48]
Yes	22	1 (4.6%)		

No	6,046	103 (1.7%)		
Current smoking - n (%)			1.23 (0.31 – 4.92) [0.77]	0.36 (0.08 – 1.70) [0.20]
Yes	95	2 (2.1%)		
No	5,973	102 (1.7%)		
History of MI - n (%)			**7.35 (1.16 – 46.5) [0.034]**	1.91 (0.17 – 21.6) [0.60]
Yes	8	1 (12.5%)		
No	6,060	103 (1.7%)		
History of stroke - n (%)			**17.6 (8.72 – 35.7) [< 0.0001]**	**1.97 (0.99 – 3.92) [0.054]**
Yes	21	6 (28.6%)		
No	6,047	98 (1.6%)		

COPD = Chronic obstructive pulmonary disease; CVD = cardiovascular disease; MI = myocardiac infarction

In a comparison of city-wide COVID-19 hospitalization rates prior to and during the program, COVID-19 mortality decreased from 6.8% before the program with prophylactic use of ivermectin, to 1.8% after its beginning (RR, 0.27; 95%CO, 0.21 – 0.33; $p < 0.0001$), and in COVID-19 mortality rate, from 3.4% to 1.4% (RR, 0.41; 95%CI 0.31 – 0.55; $p < 0.0001$). (**Table 4**).

Table 4. Hospitalization and mortality rates registered in the city of Itajaí, Brazil, before verus after the beginning of the citywide program with ivermectin use as prophylaxis for COVID-19, independent of the ivermectin use status.

	Overall	**Until July 30th**	**After July 30th**	**Relative risk ratio (95%CI)**	*p-value*
Infected COVID-19 population (n)	9956	2663	7293	-	-
Infected non-hospitalized COVID-19 population (n)	9641	2481	7160	-	-
Hospitalized COVID-19 population (n)	315	182	133	-	-
COVID-19 hospitalization rate COVID-19 (%)	3.2%	6.8%	1.8%	0.27 (0.21 – 0.33)	*<0.0001*
Overall number of COVID-19 deaths	192	90	102	-	-
Overall mortality rate (%)	1.9%	3.4%	1.4%	0.41 (0.31 – 0.55)	*<0.0001*

Discussion

This prospective, citywide COVID-19 ivermectin prophylaxis program resulted in significant reductions of COVID-19 infections, hospitalizations, and deaths. The ivermectin non-users were two times more likely to die from COVID-19 than ivermectin users in the overall population analysis. **Since groups were compared for the exposure during the same period, in a parallel manner, changes in transmission rates would affect ivermectin users and non-users equally.**

The city of Itajai, in the state of Santa Catarina, Brazil, started a citywide program of prophylaxis with ivermectin in July 2020 as part of several initiatives to reduce the burden

of COVID-19. ivermectin was used, based on the existing literature at that time and on the virtual absence of risks. The National Health System (Sistema Único de Saúde – SUS) that functions as a full healthcare support to the entire population allowed the city to establish a non-restricted population program. This program included a support structure consisting of a large outpatient clinic located at the Convention Center of Itajaí. This outpatient clinic became the main locale of assistance for COVID-19 patients, supported by multiple public facilities where general practitioners regularly saw patients.

The use of ivermectin was optional unless contraindicated, and given upon medical discretion. A structured medical-based program with a medical visit and evaluation of basic demographic characteristics and comorbidities offered ivermectin as an optional prophylaxis to those who agreed to participate in this preventive treatment program. Health status was assessed and data was enterered prospectively throughout the period of the program, in a fully digitzed system provided by the national health system (SUS). Since the system existed prior to the pandemic, a significant number of the population were already registered with their health information, including past and current diseases, use of medications and other characteristics. The adaptations made to the SUS for the pandemic preparedness, prior to the initiation of this ivermectin outpatient program, allowed a structured, well-organized collection of the data that monitored any missing values, reinforcing the reliability of the results.

An important conservative bias was present. Major risk factors for severe COVID-19 and mortality due to COVID-19, including aging, diabetes, and hypertension, were more present among ivermectin users, which may have underestimated the benefits measured Ivermectin was demonstrated to be particularly effective in subjects above 49 years old in terms of reduction of absolute risk, which corresponds to the group at the highest risk for COVID-19. This allows the understanding that prophylactic use of ivermectin can be particularly impactful in older subjects. In addition, ivermectin seemed to reduce the exceeding risk of hypertension, T2D, and other diseases.

In accordance with the literature, subjects with higher age, diabetes and males were less likely to survive ($p < 0.05$ for all), only aging remained as an independent risk factor after PSM ($p < 0.0001$). However, prophylactic ivermectin use appears to mitigate

the additional risk of COVID-19 death due to T2D, hypertension, and cardiovascular diseases.

The narrative that using preventive & early treatment therapies will have people relax their caution of remaining socially & physically distanced to allow more COVID-19 related infections is not supported here. This study data demonstrates that the use of preventive ivermectin significantly lowers the infection rate, ands benefits outweigh the supposed increased risk of changes in social behaviours. Hence, we can speculate that the prophylactic use of ivermectin could play an important role in the reduction of the pandemic burden.

Even after adjustments to measure the most relevant variables that could influence COVID-19 related outcomes, including age, sex, comorbidities, and habits, aiming to avoid overestimation of the effects of ivermectin and to resemble a randomized clinical trial, prophylactic ivermectin proved to be protective for the overall population, with a reduction of 46% in death rate and $p < 0.0001$ after employment of PSM.

The protection provided by ivermectin when used prophylactically for COVID-19 may have reflected in the reduction in COVID-19 hospitalization and mortality rates observed in a populational level. Compared to before the beginning of the program, COVID-19 hospitalization and mortality rates were reduced by 73% and 59%, respectively ($p < 0.0001$ for both). These reductions were obtained when overall population of the city of Itajaí, as well as overall number of COVID-19 cases, hospitalizations, and deaths, were considered, irrespective of the percentage of patients using ivermectin prophylactically. **There were no changes in SARS-CoV-2 variants, infectivity and pathogenicity between before and during the program.**

When compared to all other major cities in the State of Santa Catarina, where Itajaí is located, differences in COVID-19 mortality rate between before July 7, 2020 and between July 7, 2020 and December 21, 2020, Itajaí is ranked number one, and far from the second place[35]. These results indicate that medical-based optional prescription, citywide covered ivermectin can have a positive impact in the healthcare system. **However, the present results do not provide sufficient support for the hypothesis that ivermectin could be an alternative to COVID-19 vaccines.**

Due to the large number of participants, this citywide program was unable to supervise whether ivermectin users were using ivermectin regularly, **although the accumulated number of ivermectin tablets was strictly controlled.** This occurred to be a potential another conservative bias, since the effects of ivermectin on prophylaxis could be underestimated due to adherence to the recommended frequency of ivermectin use.

While ivermectin is a multi-target drug[36], its maximum benefits occur when it's present at minimum concentration in a wide range of sites to inhibit multiple metabolic and inflammatory pathways. However, although the dose of ivermectin employed in the program was smaller than the minimum to reach the concentration required to act in these multiple sites, the reduction in infection, mortality, and death rates in the infected group that used ivermectin prophylactically was surprisingly lower. Long-term or accumulated ivermectin could also play a critical role for its long-term protection against COVID-19.

Limitations

Being a prospective observational study which allowed subjects to self select between treatment vs. non-treatment instead of relying on randomization, important confounders may have been differentially present which could otherwise explain the differnces observed. Given that the benefits measured occurred despite negative risk factors being more present in the treatment group, this suggests the benefits are likely accurate and unbiased. Further, studies relying on PSM techniques have been to shown to consistently agree with those employing randomization[37,38], again supporting the likelihood the benefits measured are accurate, The prevailing type of SARS-CoV-2 in the city was unknown due to the lack of genotyping surveillance during the period of the program. Whether the prophylaxis proposed in this program would be as effective in other SARS-CoV-2 variants is unclear. Also, there was not a strict control of whether infected subjects used any specific drug in case of COVID-19 infection, this allows the possibility that the differences may be explained by differences in the use of ivermectin or other medications as treatment.

Final discussion

In this city-wide ivermectin prophylaxis program, a large, statistically significant decrease in mortality rate was observed after the program began among the entire population of city residents. When comparing subjects that used ivermectin regularly, non-users were two times more likely to die from COVID-19 while ivermectin users were 7% less likely to be infected with SARS-CoV-2 ($p = 0.003$).

Although this study is not a randomized, double-blind, placebo-controlled clinical trial, the data was prospectively collected and resulted in a massive study sample that allowed adjustment for numerous confounding factors, thus strengthening the findings of the present study.

Due to the well-established, long-term safety profile of ivermectin, with rare adverse effects, the absence of proven therapeutic options to prevent death caused by COVID-19, and while effectiveness of vaccines in real-life all-cause mortality analyses lacks, we recommend that ivermectin could be considered as a preventive strategy, in particular for those at higher risk of complications from COVID-19 or at higher risk of contracting the illness, **not as a substitute for COVID-19 vaccines, but as an additional tool, particularly during periods of high transmition rates.**

Conclusion

In a city-wide ivermectin program with prophylactic, optional ivermectin use for COVID-19, ivermectin was associated with significantly reduced COVID-19 infection, hospitalization, and death rates from COVID-19.

Statements

Conflict of Interest

The authors declare no conflict of interest regarding the drug, ivermectin, and potential commercial benefits of the expansion of its use for COVID-19, or any other related gains. Dr Lucy Kerr received funding from Vitamedic, that manufactures ivermectin, unrelated to this study. Dr. Flavio A. Cadegiani was contracted by Vitamedic for consulting services unrelated to this study, and donated the full budget for COVID-19 patient care and research. Other authors have no conflicts of interest.

Data availability statement

Dataset is available under reasonable request by institutions and organizations.

Author contributions

Lucy Kerr designed the study. Washington Luiz Olivato Assagra and Fernando Carlos Proença developed the computer program, compiled and ran the data. Raysildo Barbosa Lôbo, Fernando Baldi, Flavio A. Cadegiani and Juan J. Chamie designed and performed the statistical analyses. Lucy Kerr, Flavio A. Cadegiani, Fernando Baldi and Pierre Kory performed the analyses and interpretation of clinical and demographic data generated by the statistical analysis. Fernando Carlos Proença was responsible for the medical surveillance, subjects follow-up and other aspects related to the program administration of the present analysis. Raysildo Barbosa Lôbo and Lucy Kerr were responsible for resources, supervision and project administration related to the analyses. Pierre Kory, Juan J Chamie and Jennifer Hibberd reviewed the data and the manuscript. All authors contributed to the writing of the original draft and final reviewed manuscript. All authors have read and approved the manuscript.

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