Ivermectin prophylaxis used for COVID-19 reduces COVID-19 infection and mortality rates: A 220,517-subject, populational-level retrospective citywide.

Preprint · December 2021

CITATIONS
0

READS
57,353

11 authors, including:

Cadegiani Flávio
Applied Biology
113 PUBLICATIONS **714** CITATIONS
SEE PROFILE

Fernando Baldi
São Paulo State University
305 PUBLICATIONS **2,466** CITATIONS
SEE PROFILE

Raysildo Barbosa Lôbo
Center for Genetic Engineering and Biotechnology
179 PUBLICATIONS **1,174** CITATIONS
SEE PROFILE

Juan Chamie
Universidad EAFIT
4 PUBLICATIONS **10** CITATIONS
SEE PROFILE

Ivermectin prophylaxis used for COVID-19 reduces COVID-19 infection and mortality rates: A 220,517-subject, populational-level retrospective citywide observational study.

Lucy Kerr, MD, ARDMS[1], Flavio A. Cadegiani, MD, MSc, PhD[2], Fernando Baldi, PhD[3], Raysildo Barbosa Lôbo, PhD[4], Washington Luiz Olivato Assagra[5], Fernando Carlos Proença[6], Jennifer A. Hibberd, DDS, DPD, MRCDC[7], Juan J Chamie-Quintero[8]

[1]Instituto Kerr de Ensino e Pesquisa, São Paulo, Brazil
[2]Corpometria Institute, Brasilia, Brazil
[3]Department of. Veterinary Medicine, State University of São Paulo, São Paulo, Brazil
[4]Department of Genetics, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil.
[5]Centro Técnico de Avaliação Genômica C.T.A.G, Ribeirão Preto, Brazil
[6]Itajaí City Hall, Itajaí, Brazil
[7]University of Toronto, Toronto, Canada
[8]Data Analysis, Universidad EAFIT, Cambridge, USA

***Corresponding author:**
Flávio A. Cadegiani, MD, MSc, PhD
Corpometria Institute
SGAS 915 Centro Clínico Advance, Rooms 260/262/264, Brasília, DF, Brazil
f.cadegiani@gmail.com, flavio.cadegiani@unifesp.br, flavio@flccc.net
+55 61 981.395.395

Abstract

Background: Ivermectin has demonstrated different mechanisms of actions that could potentially protect from both COVID-19 infection and COVID-19-related comorbidities. Based on the existing literature and safety profile of ivermectin, a citywide program of prophylactic use of ivermectin for COVID-19 was implemented in Itajai, a Southern city in Brazil in the state of Santa Catarina. The objective of this analysis is to evaluate the effects of the use of ivermectin for prevention of COVID-19 infection, risk of dying and mortality, compared to non-users.

Materials and methods: This is a retrospective analysis of registry data from the medical based citywide COVID-19 prevention with ivermectin program, between July 2020 to December of 2020. The whole population of Itajaí was invited for a medical visit to

compile demographic and medical parameters. In the absence of contraindications, ivermectin was offered as an optional treatment for 2 days every 15 days at a dose of 0.2mg/kg/day. Patients' preferences and medical autonomy were preserved. Ivermectin users were compared with the comorbidity-matched population of non-users for COVID-19 by age, sex, COVID-19 infection rate, and COVID-19 mortality rate. Results in terms of mortality were adjusted for all relevant variables and Propensity Score Matching (PSM) was calculated.

Results: A total of 220,517 subjects were included in the analysis; 133,051 (60.3%) ivermectin users and 87,466 (39.7%) non-users. COVID-19 infection occurred in 4,311 (3.2%) treated subjects, and 3,034 (3.5%) non-treated subjects. This evidence showed a 7% reduction in COVID-19 infection rate with use of ivermectin: COVID-19 infection rate ratio (Risk ratio (RR) of 0.93; 95% confidence interval (CI), 0.89 – 0.98; p = 0.003). A total of 62 deaths (1.4% mortality rate) occurred among users and 79 deaths (2.6% mortality rate) among non-users, showing a 48% reduction in mortality rate (RR, 0,52; 95%CI, 0.37 – 0.72; p = 0.0001). Risk of dying from COVID-19 among ivermectin users was 45% lower than non-users (RR, 0.55; 95%CI, 0.40 – 0.77; p = 0.0004).

Conclusion: Prophylactic use of ivermectin showed significantly reduced COVID-19 infection rate, mortality rate and chance of dying from COVID-19 on a calculated population-level analysis, which controlled for all relevant confounding variables.

Key - words: COVID-19, SARS-CoV-2, ivermectin, prophylaxis, prevention, coronavirus

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

Introduction

Ivermectin, has been demonstrated to have not only extensive anti-parasitic actions[1,2], but also has been described to present direct activity in humans[3], against viruses, bacteria, and protozoa. It has been proposed that ivermectin could be repurposed as an antiviral and antimicrobial 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 effect[15,26] and multi-antiviral effect. COVID-19 pathogenesis is largely explained to be an inflammation-mediated heamaglutinating infection, disrupting pulmonary, vascular and endothelial systems, leading to a multi-systemic disease. In vitro, ivermectin has demonstrated an 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 relative to speed of clinical recovery, rate of disease progression and mortality rate[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 this COVID-19 pandemic, the use of inexpensive options based on the convincingly beneficial existing evidence, well-established safety profile and favourable cost-effectiveness, ivermectin was not only highly attractive for patient centred medicine, practiced by frontline clinicians, it aligned with strict bioethical principles for medical practice and the Helsinki declaration.

Ivermectin use is 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 should be at the discretion of the frontline physician, once informed consent has been provided. 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.

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, since there was no indisputable evidence for its routine use.

This study's objective is to present the data related to patients' clinical outcomes using ivermectin as a prophylaxis for COVID-19, collected retrospectively, in addition to the standard non-pharmacological strategies of masking and social distancing, as part of a citywide program conducted in outpatient settings. The aim is to evaluate if ivermectin exerted a protective effect relative to COVID-19 infection, risk of dying and COVID-19 mortality rate.

Material and Methods

Study population

This is a retrospective observational study based on the analysis of registry data from the medical based 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 collected 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 according to age intervals, sex, and presence of comorbidities, as per the stratification of the population according to age, sex, race, comorbidities, and correlated demographic characteristics with the acceptance rate of ivermectin.

The present retrospective analysis 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.

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, within 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. Weighting 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 ivermectin, a prophylactic dose, according to medical judgment and following a subject's informed consent related to potential benefits, risks, and side effects. All details of this citywide program and campaign had been previously accorded between the city local healthcare system, connected to the National Healthcare System (SUS), city mayor, and local public prosecutors.

The following data was collected, registered digitally, analyzed, and adjusted as confounding factors 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 collected included self-reported presence of other comorbidities and medications that were used regularly.

Patients who presented signs of Covid-19 upon the first visit to the program were excluded from the sample and received a different therapy regimen. Other exclusion riteria 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 days every 15 days.

During the study, subjects who got infected with COVID-19 that was diagnosed with a positive rtPCR-SARS-CoV-2, underwent a specific medical visit to assess COVID-19 clinical manifestations and severity. 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 31, 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, notwithstanding, 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. Of significance, we now know that an individual experiencing the COVID-19 infection reduces their chance of having a reinfection. To include participants that had COVID-19 and used ivermectin, would falsely increase the efficacy of ivermectin.

Finally, COVID-19 hospitalization and mortality rates of the city of Itajaí were compared between the period before the program (before July 7, 2020) and during the program between July 7, 2020 and December 31, 2020) aiming to evaluate whether a citywide program of prophylaxis with ivermectin for COVID-19 would cause a positive impact in the overall numbers of the city, even being only partially adopted.

Statistical analysis

In this outpatient study of those who tested positive for SARS-CoV-2, mortality rate was evaluated according to each parameter adjusted against other variables (multivariate regression analysis), 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. 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. Parameters were also balanced and Propensity Score Matching (PSM) was calculated for mortality risk between ivermectin and non-vermectin users, and also for the other characteristics. COVID-19 infection rate and risk of dying were also calculated matching for variables. The statistical approach for missing data depended on the percentage of missing data for each parameter. However, due to the system limitations, it was necessary to fill all parameters in order to be formally included in the program. Missing data was unlikely to be present.

Results

In Itajai, a Southern city of Brazil in the state of Santa Catarina, between July 2020 to December 2020, a citywide study was conducted involving 220,517 people. A total of 133,051 of these people (60.3% of the population) received ivermectin before being infected by COVID-19. A total of 87,466 people (39.7 %) did not receive or did not want to receive the ivermectin during the program, including its use for prophylactic, outpatient, inpatient therapeutical purposes, or after having COVID-19.

Of the 133,051 treated subjects, 4,311 had a positive rtPCR-SARS-CoV-2 (3.2% infection rate), while 3,034 of the 87,466 untreated subjects had positive rtPCR-SARS-CoV-2 (3.5% infection rate), showing a significant reduction of 7% in infection rate ratio (Risk ratio (RR), 0.93; 95% confidence interval (95%CI), 0.89-0.98; p = 0.003).

Baseline characteristics of the 9,956 subjects included in the above analysis are described in **Table 1**. 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 had a higher percentage of caucasians ($p = 0.004$), than non-users.

Of the 7,345 subjects with COVID-19, there were 232 hospitalizations (3.16% hospitalization rate). Of the 4,311 ivermectin users, there were 105 hospitalizations (2.43% hospitalization rate), while among the 3,034 ivermectin non-users, there were 127 hospitalizations (4.18% hospitalization rate), with a reduction in hospitalization rate due to COVID-19 of 42% (RR, 0.58; 95%CI, 0.45-0.75; $p < 0.0001$).

Among the 7,345 subjects from both groups with COVID-19, there were 141 deaths (1.9% mortality rate). Among the 4,311 ivermectin users, there were 62 deaths (1.4% mortality rate), while among the 3,034 subjects that did not use ivermectin prophylactically, there were 79 deaths (2.6% mortality rate), with a reduction in mortality rate of 45% (RR, 0.55; 95%CI, 0.40-0.77; $p = 0.0004$) (**Table 2**).

When the overall population is accounted for, the risk of dying from COVID-19 was 0.09% among ivermectin non- users and 0.05% among ivermectin users, with a reduction of 48% of the chances of dying from COVID-19 (RR, 0.52; 95%CI, 0.37 – 0.72; $p = 0.0001$) (**Table 2**). **Figure 1** summarizes the main findings.

Table 1. Baseline Characteristics of Subjects Enrolled in Study.

Variable	Overall (n = 7345)	Ivermectin users (n = 4311)	Non-ivermectin users (n = 3034)	*p-value*
Age				
Median ± SD	42.0 ± 14.7	43.5 ± 14.9	39.8 ± 14.2	*< 0.0001*
< 30 y/o	1730 (23.6%)	886 (20.5%) 51.2%	844 (27.8%) 48.8%	*< 0.0001*
30-50 y/o	3703 (50.4%)	2121 (49.2%) 57.3%	1582 (52.1%) 42.7%	*< 0.0001*
> 50 y/o	1912 (26.0%)	1304 (30.3%) 68.2%	608 (20.0%) 31.8%	*< 0.0001*
Sex				*0.31*
Female	3983 (54.2%)	2359 (54.7%)	1624 (53.5%)	

Male	3362 (45.8%)	1952 (45.3%)	1410 (46.5%)	
Race				
Caucasians	5437 (74.0%)	3245 (75.3%)	2192 (72.2%)	*0.004*
Afro-Brazilians	209 (2.8%)	109 (2.5%)	100 (3.3%)	*0.052*
Mixed	1583 (22.6%)	901 (20.9%)	682 (22.5%)	*0.10*
Asian-Brazilians	116 (1.6%)	56 (1.3%)	60 (2.0%)	*0.023*
Type 2 diabetes				*0.0004*
Yes	214 (2.9%)	151 (3.5%)	63 (2.1%)	
No	7131 (97.1%)	4160 (96.5%)	2971 (97.9%)	
Asthma				*0.067*
Yes	26 (0.3%)	20 (0.5%)	6 (0.2%)	
No	7319 (99.7%)	4291 (99.5%)	3028 (99.8%)	
COPD				*0.72*
Yes	13 (0.2%)	7 (0.2%)	6 (0.2%)	
No	7332 (99.8%)	4304 (99.8%)	3028 (99.8%)	
Hypertension				*< 0.0001*
Yes	528 (7.2%)	362 (8.4%)	166 (5.5%)	
No	6817 (92.8%)	3949 (91.6%)	2868 (94.5%)	
CVD				*0.03*
Yes	56 (0.8%)	41 (1.0%)	15 (0.5%)	
No	7289 (99.2%)	4270 (99.0%)	3019 (99.5%)	
Other pulmonary diseases				*0.53*
Yes	15 (0.2%)	10 (0.2%)	5 (0.2%)	
No	7330 (99.8%)	4301 (99.8%)	3029 (99.8%)	
Cancer (any type)				*0.66*
Yes	32 (0.4%)	20 (0.5%)	12 (0.4%)	
No	7313 (99.6%)	4291 (99.5%)	3023 (99.6%)	
Current smoking				*0.76*
Yes	110 (1.5%)	63 (1.5%)	47 (1.5%)	
No	7235 (98.5%)	4248 (98.5%)	2987 (98.5%)	
History of MI				*0.26*
Yes	15 (0.2%)	11 (0.3%)	4 (0.1%)	
No	7330 (99.8%)	4300 (99.7%)	3030 (99.9%)	
History of stroke				*0.56*
Yes	21 (0.3%)	11 (0.3%)	10 (0.3%)	
No	7324 (99.7%)	4300 (99.7%)	3024 (99.7%)	

COPD = Chronic Obstructive Pulmonary Disease; CVD = Cardiovascular disease; MI = Myocardial infarction; SD = Standard deviation

Table 2. Infection, horpitalization, death, and mortality rate among ivermectin users and non-users.

		Overall	Ivermectin users	Non-IVM users	Relative risk ratio (95%CI) *p-value*
	Overall population (n)	220,517	133,051 (60.3%)	87,466 (39.7%)	
COVID-19 infection	Infected population (n)	7,345	4,311 (58.7%)	3,034 (41.3%)	
	Infection rate (%)	3.3%	3.2%	3.5%	0.93 (0.89-0.98) p = 0.003
COVID-19 hospitalization	Hospitalization due to COVID-19	232	105	127	
	Hospitalization rate (in case of COVID-19) (%)	3.16%	2.43%	4.18%	0.58 (0.45-0.75) p<0.0001
	Risk of hospitalization due to COVID-19	0.11%	0.08%	0.15%	0.54 (0.42-0.70) p<0.0001
COVID-19 death	COVID-19 deaths (n)	141	62	79	-
	Risk of dying from COVID-19 (%)	0.06%	0.05%	0.09%	0.52 (0.37-0.72) p = 0.0001
	Mortality rate (among infected subjects) (%)	1.9%	1.4%	2.6%	0.55 (0.40-0.77) p = 0.0004

CI = Confidence interval;

Figure 1. Summary of the findings.

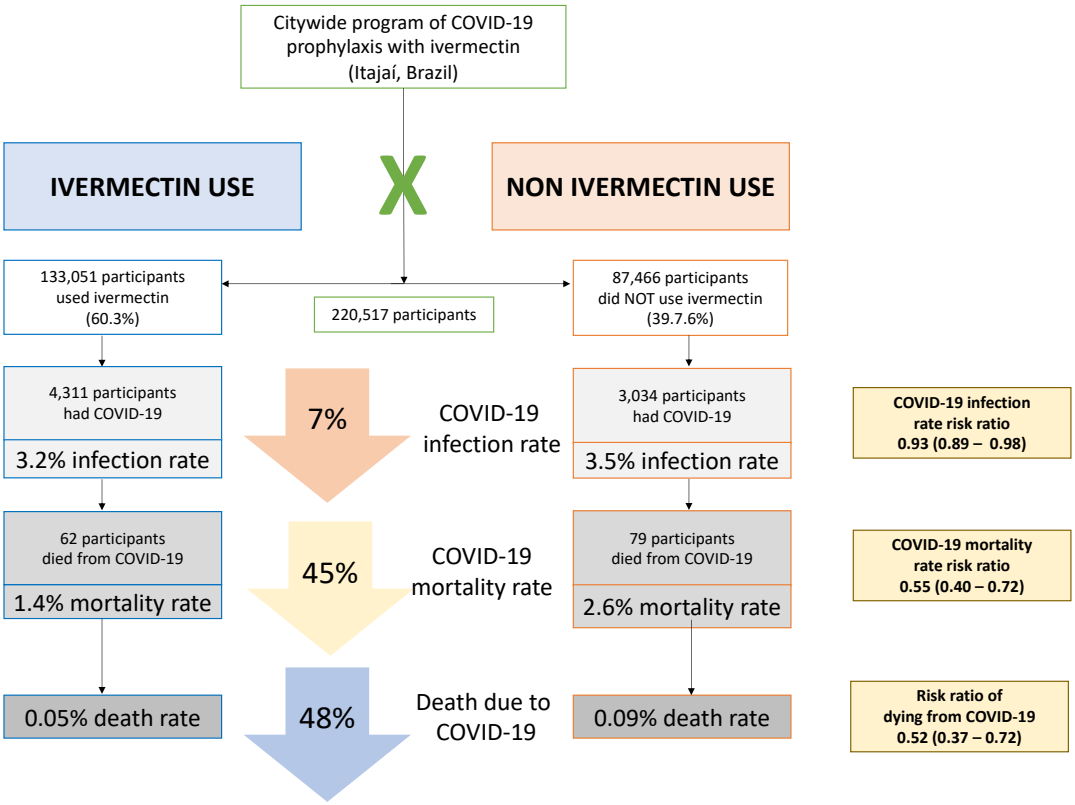

Table 3 describes the death rate according to each characteristic in the overall population, ivermectin users, and non-ivermectin users, with the unadjusted and adjusted p-values in multivariate regression analysis (adjustment for multiple confounders) provided for each characteristic. Unadjusted risk factors for COVID-19 among all participants included ivermectin non-users ($p = 0.0004$), age ($p < 0.0001$), sex ($p = 0.014$), T2D ($p < 0.0001$), hypertension ($p < 0.0001$), asthma ($p = 0.041$), COPD ($p < 0.0001$), cancer (overall) ($p = 0.004$), CVD ($p < 0.0001$), pulmonary diseases other than asthma and COPD ($p = 0.003$), and history of stroke ($p < 0.0001$).

After adjustment for all variables, ivermectin non-users ($p < 0.0001$), age ($p < 0.0001$), sex ($p = 0.002$), race ($p = 0.052$), T2D ($p = 0.008$) and pulmonary diseases other than asthma and COPD ($p = 0.024$) were demonstrated to be risk factors. After balancing and employing PSM, non-ivermectin users ($p = 0.001$), aging ($p < 0.0001$), race ($p < 0.0001$) and history of stroke ($p=0.058$) remained as independent risk factors of dying from COVID-19.

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

Variable	Overall (n = 7,345)	Death (%)	COVID-19 Death risk ratio	*Unadjusted p-value*	*Adjusted p-value*	*Propensity Score Matching p-value*
Ivermectin use - n (%)			0.55 (0.40-0.77)	*0.0004*	*< 0.0001*	*0.001*
Yes	4311	62 (1.4%)		-		
No	3034	79 (2.6%)		-		
Age - n (%)			-	*<0.0001*	*<0.0001*	*< 0.0001*
< 30 y/o	2336	0 (0.0%)				
30-50 y/o	4915	22 (0.45%)				
> 50 y/o	2705	170 (6.28%)				
Sex - n (%)			0.66 (0.48 – 0.92)	*0.014*	*0.002*	*0.34*
Female	3983	62 (1.6%)				
Male	3362	79 (2.4%)				
Race - n (%)			-	*0.20*	*0.052*	*< 0.0001*
Caucasians	5437	110 (2.0%)				
Afro-Brazilians	209	7 (3.3%)				
Mixed	1583	22 (1.4%)				
Asian-Brazilians	114	2 (1.7%)				
Type 2 diabetes - n (%)			5.38 (3.59 – 8.06)	*< 0.0001*	*0.008*	*0.35*
Yes	214	27 (12.6%)				
No	7131	114 (1.6%)				
Hypertension - n (%)			6.57 (4.91 – 8.81)	*< 0.0001*	*0.79*	*0.45*
Yes	528	47 (8.9%)				
No	6817	94 (1.4%)				
Asthma - n (%)			4.05 (1.06 – 15.5)	*0.041*	*0.27*	*0.097*
Yes	26	2 (7.7%)				
No	7319	139 (1.9%)				
COPD - n (%)			12.3 (4.48 – 33.5)	*< 0.0001*	*0.11*	*0.30*
Yes	13	3 (23.1%)				
No	7332	138 (1.9%)				
Cardiovascular diseases			6.46 (4.60 – 9.06)	*< 0.0001*	*0.52*	*0.48*

- n (%)						
Yes	56	5 (8.9%)				
No	7289	136 (1.9%)				
Other pulmonary diseases - n (%)			7.03 (1.91 – 25.8)	*0.003*	*0.024*	*0.78*
Yes	15	2 (13.3%)				
No	7330	139 (1.9%)				
Cancer (any type) - n (%)			4.97 (1.67 – 14.8)	*0.004*	*0.65*	*0.59*
Yes	32	3 (9.4%)				
No	7313	138 (1.9%)				
Current smoking - n (%)			1.43 (0.46 – 4.42)	*0.53*	*0.74*	*0.28*
Yes	110	3 (2.7%)				
No	7235	138 (1.9%)				
Hystory of MI - n (%)			3.49 (0.52 – 23.4)	*0.20*	*0.91*	*0.51*
Yes	15	1 (6.7%)				
No	7330	140 (1.9%)				
Hystory of stroke - n (%)			15.5 (6.58 – 27.1)	*< 0.0001*	*0.13*	*0.058*
Yes	21	6 (28.6%)				
No	7324	135 (1.8%)				

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

Table 4 depicts the differences in death rate, according to each characteristic, among ivermectin users and non-users with unadjusted and multi-variable adjusted p-values. **Table 4** also shows the differences in death rates between ivermectin users and non-users according to each demographic and medical characteristic, expressed in death risk-rate ratio**. Figure 2** illustrates COVID-19 death rates in subpopulations.

Unadjusted values showed that risk factors for both ivermectin users and non-users were aging ($p < 0.0001$ for both), T2D ($p<0.0001$ for both), hypertension ($p<0.0001$ for both), CVD ($p = 0.003$ and $p = 0.012$, respectively), COPD ($p < 0.0001$ and $p = 0.042$, respectively), other pulmonary diseases ($p = 0.041$ and $p = 0.009$, respectively), and history of stroke ($p = 0.0001$ and $p < 0.0001$, respectively). Male sex and cancer were risk

factors for ivermectin users (p = 0.044 and p = 0.22, respectively). History of MI was a risk factor for ivermectin non-users (p = 0.009)

After adjustment for variables, remaining independent risk factors include aging for both ivermectin users (p < 0.0001) and non-users (p < 0.0001), male sex for non-users (p = 0.012) and T2D for ivermectin non-users (p = 0.024).

Death rates between ivermectin users were statistically lower than non-users among the following groups: between 31 and 49 years old (RR, 0.15; 95%CI, 0.03 – 0.68; p = 0.014), above 50 years old (RR, 0.41; 95%CI, 0.30 – 0.57; p < 0.0001), male sex (RR, 0.60; 95%CI, 0.39 – 0.94; p = 0.024), female sex (RR, 0.50; 95%CI, 0.30 – 0.82; p = 0.006), caucasians (RR, 0.52; 95%CI, 0.36 – 0.76; p = 0.0007), subjects with T2D (RR, 0.29; 95%CI, 0.14 – 0.58; p = 0.0006), with hypertension (RR, 0.33; 95%CI, 0.19 – 0.57; p = 0.0001), and subjects without hypertension, T2D, COPD, asthma, other pulmonary diseases, CVD, history of MI, history of stroke, and non-smokers (RR, 0.54 to 0.61; 95%CI, 0.19 to 0.91; p = 0.0003 to 0.017).

Relative reduction of death risk rate with ivermectin use was more substantial in those with major common comorbidities, including T2D (71% reduction among subjects with T2D versus 42% reduction among subjects without T2D), hypertension (67% reduction in COVID-19 death rate among subjects with hypertension, versus 39% reduction among subjects without hypertension), asthma (70% reduction in COVID-19 death rate among subjects with asthma versus 45% among subjects without asthma), and history of MI (86% reduction in COVID-19 death rate among subjects with history of MI versus 44% among subjects without history of MI). Reduction of death risk was higher in females (50%) than in males (40%), in caucasians (48%) than in mixed race subjects (37%) and afro-Brazilians (31%), and between 30 and 50 y/o (85%) than above 50 y/o (59%). However, the absolute risk reduction was higher among those above 50 y/o (6.6 points percent – p.p.) than those between 30 and 50 y/o (0.5p.p.) and below 30 y/o (0.1p.p.).

Table 4. COVID-19 mortality rate according to each characteristic in ivermectin users and ivermectin non-users, according to each characteristic, and mortality rate between ivermectin users versus non-users in each group.

	Ivermectin users				Non-Ivermectin users				Users versus non-users
Variable	**N (n = 4311)**	Death among Ivermectin users (%)	*Risk ratio (95%CI) and unadjusted p-value*	*Adjusted p-value*	**N (n = 3034)**	Death (%) among non-Ivermectin users	*Risk ratio (95%CI) and unadjusted p-value*	*Adjusted p-value*	COVID-19 Death risk ratio comparing Ivermectin users versus non-users
Age			-	*<0.0001*			-	*<0.0001*	
< 30 y/o	886	0 (0.0%)			844	1 (0.1%)			0.32 (0.01 – 7.78) p = 0.48
31-49 y/o	2119	2 (0.1%)			1572	10 (0.6%)			0.15 (0.03 – 0.68) p = 0.014
> 50 y/o	1304	60 (4.6%)			608	68 (11.2%)			0.41 (0.30 – 0.57) p < 0.0001
Sex			*p = 0.044*	*0.14*			*p = 0.15*	*0.012*	
Female	2359	26 (1.1%)			1624	36 (2.2%)			0.50 (0.30 – 0.82) p = 0.006
Male	1952	36 (1.8%)			1410	43 (3.1%)			0.60 (0.39 – 0.94)\ p = 0.024
Race			-	*0.079*			-	*0.74*	
Caucasians	3245	48 (1.5%)			2192	62 (2.8%)			0.52 (0.36 – 0.76) p = 0.0007
Afro-Brazilians	109	3 (2.7%)			100	4 (4.0%)			0.69 (0.16 – 3.00) p = 0.62
Mixed	901	10 (1.1%)			682	12 (1.8%)			0.63 (0.27 – 1.45) p = 0.28
Asian-Brazilians	56	1 (1.8%)			60	1 (1.7%)			1.07 (0.07 – 16.7) p = 0.96
Type 2 diabetes			*5.94 (3.16 – 11.2) p < 0.0001*	*0.089*			*12.0 (7.35 – 19.5) p < 0.0001*	*0.024*	
Yes	151	11 (7.3%)			63	16 (25.4%)			0.29 (0.14 – 0.58) p = 0.0006
No	4160	51 (1.2%)			2971	63 (2.0%)			0.58 (0.40 – 0.83) p = 0.003
Hypertension			*4.82 (2.84 – 8.18) p < 0.0001*	*0.97*			*8.95 (5.79 – 13.8) p < 0.0001*	*0.29*	
Yes	362	19 (5.2%)			166	28 (16.9%)			0.33 (0.19 – 0.57) p = 0.0001
No	3949	43 (1.1%)			2868	51 (1.8%)			0.61 (0.40 – 0.91) p = 0.017
Cardiovascular diseases			*5.30 (1.73 – 16.2) p = 0.003*	*0.40*			*5.40 (1.46 – 20.0) p = 0.012*	*0.87*	
Yes	41	3 (7.3%)			15	2 (13.3%)			0.55 (0.10 – 2.97) p = 0.49
No	4270	59 (1.4%)			3019	77 (2.6%)			0.56 (0.40 – 0.78)

									p = 0.0007
Asthma			*3.52 (0.51 – 24.1) p = 0.20*	*0.34*			*6.47 (1.07 – 39.2) p = 0.042*	*0.59*	
Yes	20	1 (5.0%)			6	1 (16.7%)			0.30 (0.02 – 4.11) p = 0.90
No	4291	61 (1.4%)			3028	78 (2.6%)			0.55 (0.40 – 0.77) p = 0.0004
COPD			*20.5 (6.19 – 67.9) p < 0.0001*	*0.068*			*6.47 (1.07 – 39.2) p = 0.042*	*0.69*	
Yes	7	2 (28.6%)			6	1 (16.7%)			1.71 (0.20 – 14.5) p = 0.62
No	4304	60 (1.4%)			3028	78 (2.6%)			0.54 (0.39 – 0.75) p = 0.0003
Other pulmonary diseases			*7.05 (1.08 – 46.0) p = 0.041*	*0.26*			*9.70 (1.75 – 53.7) p = 0.009*	*0.16*	
Yes	10	1 (10.0%)			4	1 (20.0%)			0.40 (0.03 – 4.96) p = 0.48
No	4301	61 (1.4%)			3029	78 (2.6%)			0.55 (0.39 – 0.77) p = 0.0004
Cancer (any type)			*7.20 (1.89 – 27.5) p = 0.004*	*0.62*			*3.23 (0.49 – 21.4) p = 0.22*	*0.96*	
Yes	20	2 (10.0%)			12	1 (8.3%)			1.20 (0.12 – 11.9) p = 0.88
No	4291	60 (1.4%)			3022	78 (2.6%)			0.54 (0.39 – 0.76) p = 0.0003
Current smoking			*2.25 (0.56 – 8.99) p = 0.25*	*0.51*			*0.81 (0.12 – 5.73) p = 0.84*	*0.58*	
Yes	63	2 (3.2%)			47	1 (2.1%)			1.49 (0.14 – 16.0) p = 0.74
No	4248	60 (1.4%)			2987	78 (2.6%)			0.54 (0.39 – 0.75) p = 0.0003
Hystory of MI			*2.87 (0.19 – 43.8) p = 0.44*	-			*9.71 (1.75 – 53.8) p = 0.009*	*0.49*	
Yes	11	0 (0.0%)			4	1 (25.0%)			0.14 (0.01 – 2.87) p = 0.20
No	4300	62 (1.4%)			3030	78 (2.6%)			0.56 (0.40 – 0.78) p = 0.0006
Hystory of stroke			*13.0 (3.63 – 46.8) p = 0.0001*	*0.72*			*16.1 (7.31 – 35.6) p < 0.0001*	*0.15*	
Yes	11	2 (18.2%)			10	4 (40.0%)			0.45 (0.11 – 1.97)

									p = 0.29
No	4300	60 (1.4%)			3024	75 (2.5%)			0.56 (0.40 – 0.79) p = 0.0008

Figure 2. COVID-19 death rates in subpopulations.

A = Overall population; B = Below 30 years old (y/o); C = Between 30 and 50 y/o; D = Above 50 y/o; E = Females; F = Males; G = With type 2 diabetes; H = Without type 2 diabetes; I = With hypertension; J = Without hypertension; K = With cardiovascular diseases; L = Without cardiovascular diseases

When analyzed in populational, city level, irrespective of the the percentage of subjects that used ivermectin prophylactically, COVID-19 hospitalization rate 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 5**).

Table 5. 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 citywide COVID-19 ivermectin preventive program showed ivermectin to be effective when used prophylactically for reduction of COVID-19 and reduction of deaths from COVID-19. The ivermectin non-users were two times more likely to die from COVID-19 than ivermectin users, in the overall population analysis, without any sort of exclusion that could bias the analysis.

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 without any sort of distinction, allowed the city to establish a non-restricted population program. This program included a web of support with a large outpatient clinic set in a large facility; 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, based on the absence of contraindications, 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 monitored and data was registered, throughout the pandemic, in a fully digitalized system that belongs to the national health system (SUS). Since the system existed prior to the pandemic, a significant number of the population were already registericed 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 also prevalent among ivermectin users, which could have hampered the evaluation of its efficacy. 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. Ivermectin users had proportionally more similar outcomes between patients with and without these diseases than non-users. Ivermectin appears to not only be particularly beneficial for elders, but also for those with comorbidities.

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 48% in death rate and $p = 0.001$ 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. 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[31]. These results indicate that medical-based optional prescription, citywide covered ivermectin can have a positive impact in the healthcare system.

Due to the large number of participants, this citywide program was unable to supervise whether ivermectin users were using ivermectin regularly, in the correct dose and interval proposed. This occurred to be a potential another conservative bias, since the effects of ivermectin on prophylaxis could be underestimated due to lack of sufficient ivermectin use.

While ivermectin is a multi-target drug[32], 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 retrospective observational analysis, it is uncertain whether results would be reproducible in a randomized, placebo-controlled, double-blind clinical trial, but likely, since groups of ivermectin users and non-users had similar demographic characteristics, and rates were adjusted for the relevant confounding variables.

Final discussion

On a population-level analysis, the overall number of COVID-19 deaths shows the collective resultant of a certain intervention in large populations, in the present case, the prophylactic use of ivermectin to prevent COVID-19. Compared to 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 ($p = 0.003$). The protection provided by inveremctin was particularly effective in subjects above 30 years old, with an impactful change in a population-level analysis.

Although this study is not a randomized, double-blind, placebo-controlled clinical trial, the massive sample that was fully controlled for variables allowed us to adjust for confounding factors, which strengthens the findings of the present study and also to divide into age groups, aiming to identify whether specific populations would be more clearly benefited from prophylaxis with ivermectin. This allowed us to conclude that ivermectin has a beneficial effect in subjects above 50 years old, which corresponds to the group at greatest risk of COVID-19.

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 lack of effectiveness of vaccines in real-life analyses to date, we recommend that ivermectin be considered as a preventive strategy, in particular for those at higher risk of complications from COVID-19, and professionals above 30 y/o highly exposed to the virus, including healthcare workers, airport staff, salespeople, taxi and application car drivers and other professionals that deal directly with a large number of costumers and clients.

Conclusion

In a city-wide ivermectin program with prophylactic, optional ivermectin use for COVID-19, ivermectin demonstrated to significantly reduce COVID-19 infection rate and death rate from COVID-19, and mortality rate if infected.

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 and Fernando Baldi 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. Juan J Chamie, Jennifer Hibberd and Theresa Lawrie 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.

Funding

The city of Itajaí acquired the ivermectin, provided the medical and assistant staff and the sites where the citywide programs were conducted. No other funding sources were obtained.

Acknowledgements

We acknowledge Dr. Volnei José Morastoni, the city mayor of Itajaí, state of Santa Catarina, Brazil, for developing and enabling the citywide program of ivermectin for COVID-19 prophylaxis. We also acknowledge all the staff that worked at the citywide program for COVID-19 prevention with ivermectin in Itajaí, state of Santa Catarina, Brazil. Also, those who direct- or indirectly offered *pro bono* support for the subjects that participated in the program, compilation of data, or were involved in any other step that led to the present analysis.

References

1. Chen IS, Kubo Y. Ivermectin and its target molecules: shared and unique modulation mechanisms of ion channels and receptors by Ivermectin. J Physiol. 2018 May 15;596(10):1833-1845. doi: 10.1113/JP275236.
2. Kaur H, Shekhar N, Sharma S, Sarma P, Prakash A, Medhi B. Ivermectin as a potential drug for treatment of COVID-19: an in-sync review with clinical and computational attributes. Pharmacol Rep. 2021 Jan 3:1-14. doi: 10.1007/s43440-020-00195-y.
3. Martin RJ, Robertson AP, Choudhary S. Ivermectin: An Anthelmintic, an Insecticide, and Much More. Trends Parasitol. 2021 Jan;37(1):48-64. doi: 10.1016/j.pt.2020.10.005.
4. Mastrangelo, E. et al. (2012) Ivermectin is a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity: new prospects for an old drug. J. Antimicrob. Chemother. 67, 1884–1894.
5. Wagstaff, K.M. et al. (2012) Ivermectin is a specific inhibitor of importin α/β-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. Biochem. J. 443, 851–856
6. Crump A. Ivermectin: enigmatic multifaceted 'wonder' drug continues to surprise and exceed expectations. J Antibiot (Tokyo). 2017 May;70(5):495-505. doi: 10.1038/ja.2017.11.
7. Heidary F, Gharebaghi R. Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen. J Antibiot (Tokyo). 2020 Sep;73(9):593-602. doi: 10.1038/s41429-020-0336-z.
8. Li N, Zhao L, Zhan X. Quantitative proteomics reveals a broadspectrum antiviral property of Ivermectin, benefting for COVID19 treatment. J Cell Physiol. 2020.
9. Jin L, Feng X, Rong H. et al. The antiparasitic drug Ivermectin is a novel FXR ligand that regulates metabolism. Nat Commun 4, 1937 (2013). https://doi.org/10.1038/ncomms2924
10. Yang JS et all 2019. Permethrin and ivermectin modulate lipid metabolism in steatosis-induced HepG2 hepatocyte. Food and Chemical Toxicology. Vol 125, 2019, 595-604. https://doi.org/10.1016/j.fct.2019.02.005
11. Cairns DM, Giordano JE, Conte S, Levin M, and Kaplan DL.Ivermectin Promotes Peripheral Nerve Regeneration during Wound Healing. ACS Omega 2018 3 (10), 12392-12402. DOI: 10.1021/acsomega.8b01451
12. Zheng YY, Ma YT, Zhang JY, et al. COVID-19 and the cardiovascular system. Nat Rev Cardiol. 2020;17:259–60. https://doi.org/10.1038/s41569-020-0360-5
13. Nagai H, Satomi T, Abiru A, Miyamoto K, Nagasawa K, Maruyama M, et al. Antihypertrophic effects of small molecules that maintain mitochondrial ATP levels under hypoxia. EBioMedicine 2017;24:147–58. https://doi.org/10.1016/j.ebiom.2017.09.022
14. Park A, Iwasaki A, Type I. and type III interferons—induction, signaling, evasion, and application to combat COVID-19. Cell Host Microbe. 2020;27:870–8.
15. Zhang X, Song Y, Ci X, et al. Ivermectin inhibits LPS-induced production of inflammatory cytokines and improves LPS-induced survival in mice. Inflamm Res. 2008;57:524–9. https://doi.org/10.1007/s00011-008-8007-8.

16. Zaidi, A.K., Dehgani-Mobaraki, P. The mechanisms of action of Ivermectin against SARS-CoV-2: An evidence-based clinical review article. J Antibiot (2021). https://doi.org/10.1038/s41429-021-00430-5
17. Matsuyama T, Kubli SP, Yoshinaga SK, et al. An aberrant STAT pathway is central to COVID-19. Cell Death Differ. 2020;27:3209–25. https://doi.org/10.1038/s41418-020-00633-7
18. Kim J-H, Choi HS, Kim S-L, Lee D-S. The PAK1-Stat3 signaling pathway activates IL-6 gene transcription and human breast cancer stem cell formation. Cancers 2019;11:1527.
19. Dou Q, Chen H-N, Wang K, Yuan K, Lei Y, Li K, et al. Ivermectin induces cytostatic autophagy by blocking the PAK1/Akt axis in breast cancer. Cancer Res. 2016;76:4457–69.
20. Layhadi JA, Turner J, Crossman D, Fountain SJ. ATP evokes Ca2+ responses and CXCL5 secretion via P2X4 receptor activation in human monocyte-derived macrophages. J Immunol Balt Md 1950 2018;200:1159. https://doi.org/10.4049/jimmunol.1700965
21. Juarez M, Schcolnik-Cabrera A, Dueñas-Gonzalez A. The multitargeted drug Ivermectin: from an antiparasitic agent to a repositioned cancer drug. Am J Cancer Res. 2018;8:317–31. Published 2018 Feb 1
22. Andersson U, Ottestad W, Tracey KJ. Extracellular HMGB1: a therapeutic target in severe pulmonary inflammation including COVID-19? Mol Med. 2020;26:42.
23. Yan S, Ci X, Chen N. Anti-Inflammatory effects of Ivermectin in mouse model of allergic asthma. Inflamm Res. 2011;60:589–96. athway. Fundam Clin Pharm. 2009;23:449–55.
24. Reis TAR, Oliveira-da-Silva JA, Tavares GSV, Mendonça DVC, Freitas CS *et al*. Ivermectin presents effective and selective antileishmanial activity in vitro and in vivo against Leishmania infantum and is therapeutic against visceral leishmaniasis.Exp Parasitol. 2021 Feb;221:108059. doi: 10.1016/j.exppara.2020.108059.
25. Scheim DE.Ivermectin for COVID 19 treatment Clinical response at quasi-threshold doses via hypothesized alleviation of CD147 mediated vascular occlusive (June, 2020) SS RN:https://SSRN.com/abstract=3636557.
26. Ci X, Li H, Yu Q, Zhang X, Yu L, Chen N, Song Y, Deng X. Avermectin exerts anti-inflammatory effect by downregulating the nuclear transcription factor kappa-B and mitogen-activated protein kinase activation pathway. Fundam Clin Pharmacol. 2009 Aug;23(4):449-55. doi: 10.1111/j.1472-8206.2009.00684.x.
27. Zaidi AK, Dehgani-Mobaraki P. The mechanisms of action of Ivermectin against SARS-CoV-2: An evidence-based clinical review article. J Antibiot (Tokyo). 2021 Jun 15:1-13. doi: 10.1038/s41429-021-00430-5.
28. Kalfas S, Visvanathan K, Chan K Drago J. The therapeutic potential of Ivermectin for COVID-19: a systematic review of mechanisms and evidence. doi: https://doi.org/10.1101/2020.11.30.20236570 - PREPRINT
29. Behera P, Patro BK, Singh AK, Chandanshive PD, S R R, Pradhan SK, Pentapati SSK, Batmanabane G, Mohapatra PR, Padhy BM, Bal SK, Singh SR, Mohanty RR. Role of Ivermectin in the prevention of SARS-CoV-2 infection among healthcare workers in India: A matched case-control study. PLoS One. 2021 Feb 16;16(2):e0247163. doi: 10.1371/journal.pone.0247163.

30. Hellwig MD, Maia A. A COVID-19 prophylaxis? Lower incidence associated with prophylactic administration of Ivermectin. Int J Antimicrob Agents. 2021 Jan;57(1):106248. doi: 10.1016/j.ijantimicag.2020.106248.
31. http://www.dive.sc.gov.br (Last access: December 7th, 2021)
32. Choudhury A, Das NC, Patra R, Bhattacharya M, Ghosh P, Patra BC, et al. Exploring the binding efficacy of ivermectin against the key proteins of SARS-CoV-2 pathogenesis: an in silico approach. Future Virol. 2021;10.2217/fvl-2020-0342. https://doi.org/10.2217/fvl-2020-0342.

Tables list

Figures list