ResearchGate

See discussions, stats, and author profiles for this publication at: https://www.researchgate.net/publication/358386329

Regular use of ivermectin as prophylaxis for COVID-19 led up to 92% reduction in COVID-19 mortality rate in a dose-response manner: results of a prospective observational study of...

Preprint · July 2022

CITATIONS
0

READS
139,745

9 authors, including:

Lucy Kerr
Instituto Kerr
25 PUBLICATIONS **114** CITATIONS

SEE PROFILE

Fernando Baldi
São Paulo State University
456 PUBLICATIONS **5,069** CITATIONS

SEE PROFILE

Raysildo Barbosa Lôbo
Center for Genetic Engineering and Biotechnology
198 PUBLICATIONS **1,257** CITATIONS

SEE PROFILE

Juan Chamie
Universidad EAFIT
23 PUBLICATIONS **39** CITATIONS

SEE PROFILE

Some of the authors of this publication are also working on these related projects:

Project Real World Evidence (RWE). Ivermectin and COVID-19 View project

Project TRANSCRIPTOME STUDY OF MUSCLE TISSUE IN NELLORE CATTLE DIVERGENT FOR BEEF QUALITY View project

All content following this page was uploaded by Cadegiani Flávio on 11 July 2022.

The user has requested enhancement of the downloaded file.

Regular use of ivermectin as prophylaxis for COVID-19 led up to 92% reduction in COVID-19 mortality rate in a dose-response manner: results of a prospective observational study of a strictly controlled population of 88,012 subjects among 223,128 participants.

Lucy Kerr, MD, ARDMS[1], Fernando Baldi, PhD[2], Raysildo Barbosa Lôbo, PhD[3], Washington Luiz Olivato Assagra[4], Fernando Carlos Proença[5], Jennifer A. Hibberd, DDS, DPD, MRCDC[6*], Juan J Chamie-Quintero[7], Pierre Kory, MD, MPA[8], Flavio A. Cadegiani, MD, MSc, PhD[8,9]

[1]Instituto Kerr, São Paulo, Brazil
[2]Department of Animal Sciences, State University of São Paulo, São Paulo, Brazil
[3]Department of Genetics, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil.
[4]Centro Técnico de Avaliação Genômica C.T.A.G, Ribeirão Preto, Brazil
[5]Itajaí City Hall, Itajaí, Brazil
[6]University of Toronto, Toronto, Canada, World Council for Health, Canadian Covid Care Alliance,
[7]Data Analysis, Universidad EAFIT, Cambridge, USA
[8]Front-Line Covid-19 Critical Care Alliance (FLCCC), USA
[9]Corpometria Institute, Brasilia, Brazil

***Corresponding author:**
Jennifer A. Hibberd, DDS, DPD, MRCDC
Faculty of Dentistry, University of Toronto, Toronto, Ontario M5G 1X3 Canada
drjenniferhibberd@gmail.com

Keywords: COVID-19, SARS-CoV-2, rtPCR-SARS-CoV-2, ivermectin (IVM), prophylaxis, prevention, coronavirus

Note: Terms & Dosages of Ivermectin
IVM = 6mg/tablet
Daily dosage = 0.2mg/kg/day = 1 tablet/30kg body weight
Non-users, regular users, irregular users

Abstract

Background: We have previously demonstrated that ivermectin used as prophylaxis for COVID-19, irrespective of the regularity or the level of monitoring, in a strictly controlled city-wide program in Southern Brazil (Itajaí, SC, Brazil), was associated with reductions in COVID-19 infection, hospitalization, and mortality rates. In this study, our objective was to determine if the regular use of ivermectin showed an impact on the level of protection from COVID-19 and related outcomes, reinforcing the efficacy of ivermectin through the demonstration of a dose-response effect.

Materials and methods: This exploratory analysis of a prospective observational study involved a program that used ivermectin at a dose of 0.2mg/kg/day for two consecutive days, every 15 days. Data was gathered over a 150-day period. Regularity definitions were as follows: regular users had 180mg or more of ivermectin; irregular users had up to 60mg, in total, throughout the period of the program. Comparisons were made between non-users (subjects who did not use ivermectin), regular and irregular users from the city of Itajaí after multivariate adjustments. The full city database was used to calculate and compare COVID-19 infection and risk of dying from COVID-19. The COVID-19 database was used, propensity score matching (PSM) was evened for intervals of age and comorbidities for hospitalization and mortality rates, and then adjusted for remaining variables (doubly adjusted). Risk of dying from COVID-19 was determined by the number of COVID-19 deaths in a certain population exposed to COVID-19.

Results: Among 223,128 subjects analyzed from the city of Itajaí, 159,560 had 18 years old or up and were not infected by COVID-19 until July 7, 2020, from which 45,716 (28.7%) did not use and 113,844 (71.3%) used ivermectin. Among ivermectin users, 33,971 (29.8% of users) used irregularly (up to 60mg) and 8,325 (7.3%) used regularly (more than 180mg). The remaining 71,548 participants (62.9%) used intermediate dioses (between 60mg and 180mg) and were not included for analysis. A total of COVID-19 infection rate was 49% lower for regular users (3.40% rate) than non-users (6.64% rate) [risk rate (RR), 0.51; 95% confidence interval (95%CI), 0.45–0.58; p<0.0001], and 25% lower than irregular users (4.54% rate) (RR, 0.75; 95%CI, 0.66–0.85; p<0.0001]. The infection rate was 32% lower for irregular users than non-users (RR, 0.68; 95%CI, 0.64–0.73; p<0.0001). Among COVID-19 participants, regular users were older and had higher a prevalence of type 2 diabetes and hypertension than irregular and non-users. After PSM,

the matched analysis contained 283 subjects in each group of non-users and regular users, and between regular users and irregular users, and 1,542 subjects between non-users and irregular users. Hospitalization rate was reduced by 100% in regular users compared to both irregular users and non-users (p<0.0001 for both), and by 29% among irregular users compared to non-users (RR, 0.781; 95%CI, 0.49–1.05; p=0.099). Mortality rate was 92% lower in regular users than non-users (RR, 0.08; 95%CI, 0.02–0.35; p=0.0008) and 84% lower than irregular users (RR, 0.16; 95%CI, 0.04–0.71; p=0.016), while irregular users had a 37% lower mortality rate reduction than non-users (RR, 06.7; 95%CI, 0.40–0.99; p=0.049). Risk of dying from COVID-19 was 86% lower among regular users than non-users (RR, 0.14; 95%CI, 0.03–0.57; p=0.006), and 72% lower than irregular users (RR, 0.28; 95%CI, 0.07–1.18; p=0.083), while irregular users had a 51% reduction compared to non-users (RR, 0.49; 95%CI, 0.32–0.76; p=0.001).

Conclusion: Non-use of ivermectin was associated with a 12.5-fold increase in mortality rate and seven-fold increased risk of dying from COVID-19 compared to the regular use of ivermectin in a PSM comparison of a strictly controlled population. This dose-response efficacy reinforces the prophylactic effects of ivermectin against COVID-19.

Introduction

Ivermectin has been proposed as a potential prophylaxis and therapy for COVID-19 due to its previously reported anti-viral [1-4], metabolic [5-10] and anti-inflammatory [11-19] actions, with strong plausibility [20,21] and positive *in-vitro*, *in-vivo* and epidemiological findings [22-24] in preliminary studies.

Between July and December 2020, a city-wide program in Itajaí, in the state of Santa Catarina, Southern Brazil, offered a voluntary, medically prescribed program of ivermectin as prophylaxis for COVID-19. This was based on the extensive, well established safety profile and known absence of risks with long term use of ivermectin, and the lack of therapeutic and preventive alternative options in 2020.

The systematically collected data within this program, demonstrated that ivermectin used as prophylaxis for COVID-19 improved COVID-19 related-outcomes. The use of ivermectin led to a 44% reduction in infection rate; 56% reduction in hospitalization rate, and a 68% reduction in mortality rates by using propensity score matching (PSM) to balance the study groups [25].

These conclusions were based on an analogue evaluation of the intent-to-treat (ITT) analysis of randomized clinical trials (RCTs). All participants of the program were included for analysis, irrespective of regularity or total amount of ivermectin taken. Among participants of the ivermectin use (regular and irregular) as prophylaxis for the COVID-19 program, it was unknown if regular ivermectin use would lead to a more substantial reduction in COVID-19 infection rate and related outcomes than irregular use.

In this study, an evaluation was done with participants that used ivermectin prophylactically for COVID-19, to determine if regular use compared to irregular use impacted the degree of reduction in COVID-19 infection, hospitalization, and mortality rates. Regular and irregular ivermectin users were also compared to non-users, to evaluate evidence of a dose-response pattern of efficacy.

Materials and Methods

Study population

A thorough description of the program, study population and protocol were described elsewhere [25]. This was a medically based, observational and prospective study that involved voluntary use of ivermectin as prophylaxis for COVID-19. in the city of Itajaí, Santa Catarina, Brazil. It was a citywide program conducted between July 7 and December 2, 2020. Data was collected prospectively and systematically, as were the mandatory reporting of all events.

The study design, institutional review board (IRB) approval, and data analysis were done upon completion of the program. The study of the COVID-19 cases reported in the city of Itajaí (n = 9,956, including cases that occurred before July 7, 2020, as a

comparison) was approved by the National Research Ethics Council (CONEP) [approval number, 4.821.082, protocol (CAAE) number, 47124221.2.0000.5485].

Study procedures and data collection

Voluntary prophylactic use of ivermectin was offered as an option to patients during medical visits in a provisional outpatient clinic at the Convention Center and in secondary outpatient clinics at local health centers in the city of Itajaí, as part of the Universal Health System (SUS). During medical visits, patient data, including medical history; comorbidities, previous diseases, medications, and physical signs (body weight, height, body mass index, systolic and diastolic blood pressure, and heart rate), were recorded in the SUS-based system. Ivermectin was then optionally prescribed in a dose of 0.2mg/kg/day for two consecutive days, every 15 days to participants who presented without symptoms of Covid-19 or any contradictions.

During the study, subjects who became infected with COVID-19 and diagnosed with a positive rtPCR-SARS-CoV-2 were documented and medically followed up. Data on hospitalizations and deaths due to COVID-19 were also systematically registered.

In this analysis, all residents from the city of Itajaí were considered. This included participants in the program that used and did not use ivermectin prophylactically. Registry data was analyzed for all participants included in the sample. Subjects with a positive diagnosis of COVID-19 before July 7, 2020, when the program was initiated, and those below 18 years old were excluded from the analysis.

The 223,128 residents from Itajaí included 114,568 participants, 18 years of age and above who used ivermectin prophylactically and 45,716 who did not use ivermectin, throughout the citywide program. Among these participants, 113,844 were not infected prior to July 7, 2020. This program also included. 8,352 subjects, 18 years of age and above, from other cities that participated in the program, although not included in the present analysis.

While ivermectin non-users remained unchanged from the first analysis [25], ivermectin users were divided according to the accumulated dose of ivermectin taken. The analysis focused on data for participants that used up to 60mg (10 tablets) of ivermectin and those that used more than 180mg (more than 30 tablets). Grouping the users in this manner represented a higher certainty of regularity and irregularity, respectively. These groups were compared to non-users, *i.e.,* a three-group comparison analysis.

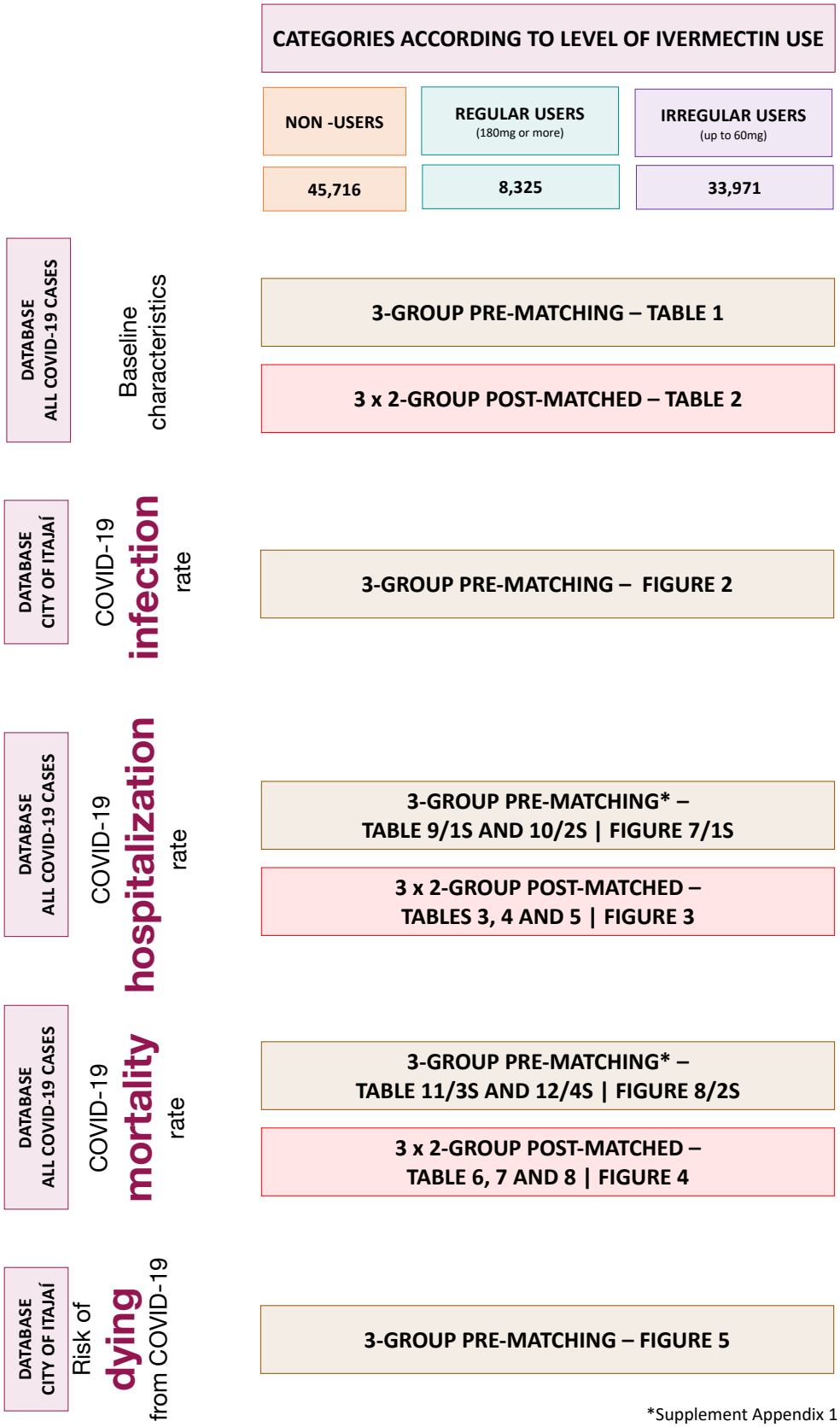
The three, two-group matching of ivermectin (1) non-users and regular users, (2) non-users and irregular users, and (3) regular users and irregular users, were balanced and matched using PSM with the following variables: age, sex, history of smoking, myocardial infarction (MI), stroke, hypertension, type 2 diabetes (T2D), cardiovascular diseases (CVD), cancer (any type), asthma, chronic obstructive pulmonary disease (COPD) and other pulmonary diseases.

Because accuracy of the reports was guaranteed for Itajaí residents only, all calculations and rates were based on the participants from the city. The database used for the calculation of COVID-19 infection rate and for risk of dying from COVID-19 was the entire city of Itajaí, and then calculated among ivermectin regular, users irregular users and non-users of participants from Itajaí. Analyses were performed before and after adjustment for multiple variables.

Hospitalization and mortality rates were analyzed for all participants reported with a positive COVID-19 diagnosis from Itajaí. Reports of all COVID-19 deaths were mandatory, while hospitalization rates were based on the data from the local public hospital only, which may justify potential discrepancies between hospitalization and mortality rates. We calculated hospitalization and hospitalization rates before matching and after propensity score matching (PSM) groups, followed by multivariate adjusted analysis of the residual differences (doubly adjusted model).

In **Supplement Appendix 1,** pre-matched comparisons of hospitalization and mortality rates are provided. **Figure 1** illustrates locations of each analysis performed in this study. **Datasets** are publicly available at https://osf.io/uxhaf/.

Figure 1. Illustrative Study Guide


DATABASE
ALL COVID-19 CASES
Baseline characteristics
DATABASE
CITY OF ITAJAÍ
COVID-19 infection rate
DATABASE
ALL COVID-19 CASES
COVID-19 hospitalization rate
DATABASE
ALL COVID-19 CASES
COVID-19 mortality rate
DATABASE
CITY OF ITAJAÍ
Risk of dying from COVID-19
CATEGORIES ACCORDING TO LEVEL OF IVERMECTIN USE
NON -USERS
45,716
REGULAR USERS
(180mg or more)
8,325
IRREGULAR USERS
(up to 60mg)
33,971
3-GROUP PRE-MATCHING – TABLE 1
3 x 2-GROUP POST-MATCHED – TABLE 2
3-GROUP PRE-MATCHING – FIGURE 2
3-GROUP PRE-MATCHING* –
TABLE 9/1S AND 10/2S | FIGURE 7/1S
3 x 2-GROUP POST-MATCHED –
TABLES 3, 4 AND 5 | FIGURE 3
3-GROUP PRE-MATCHING* –
TABLE 11/3S AND 12/4S | FIGURE 8/2S
3 x 2-GROUP POST-MATCHED –
TABLE 6, 7 AND 8 | FIGURE 4
3-GROUP PRE-MATCHING – FIGURE 5
*Supplement Appendix 1

Statistical analysis

Risk of hospitalizations and deaths were calculated for all three groups before matching and for each of the three, two-group combinations that were propensity score matched. Comparisons between groups for hospitalization and mortality rates were calculated using Chi-Square before adjusting for variables and after multivariate adjustments. The generalized linear mixed model was employed, assuming the binomial distribution for the residues and included the fixed classificatory effects for each of the variables. While there were no missing data, as per the system, illogical data was corrected individually, although some may remain due to the exceptional amount of data gathered. Statistical Analysis Software (SAS/STAT) (SAS Institute Inc., Care, North Carolina, USA) was used for the present study.

Results

There were 159,560 participants 18 years of age and above not infected with COVID-19 prior to July 7, 2020, from the city of Itajaí, Brazil. Among them, 45,716 (28.7%) did not use ivermectin and 113,844 (71.3%) used ivermectin prophylactically. Of the 113,844 participants, 8,325 (7.3%) subjects used ivermectin regularly and 33,971 (29.8%) used ivermectin irregularly. In total, 88,012 subjects were included in the present analysis, The 71,548 (62.8%) remaining participants used intermediate doses between 60mg and 180mg and were not included in this analysis.

Before matching, a total of 7,228 subjects from the city of Itajaí were infected with COVID-19 between July 7 and December 2, 2020. Of these, 3,034 (42.0%) did not use ivermectin prophylactically, 283 (3.9%) used ivermectin regularly, 1,542 (21.3%) used ivermectin irregularly and 2,369 (32.8%) used intermediate doses of ivermectin. Comparisons between ivermectin non-users, regular users and irregular users are described in Table 1.

Baseline characteristics

Table 1 describes the baseline characteristics of the groups of ivermectin non-users (n = 3,034), regular users (n = 283), and irregular users (n = 1,542), before matching groups. Age was significantly different across groups for levels of ivermectin use ($p < 0.0001$). Ivermectin regular users had a higher percentage of subjects above 50 years old (39.9%) than irregular users (24.0%) and non-users (20.0%). There were fewer subjects below 30 years old among regular users (13.8%) than among irregular users (25.7%) and non-users (27.8%). All other baseline characteristics were numerical but not statistically different. There were slightly more males among regular users (50.2%) than irregular users (44.7%) and non-users (46.5%) ($p = 0.19$). The percentage of participants with type 2 diabetes was numerically higher among regular users (3.2%) than irregular users (2.6%) and non-users (2.1%) ($p = 0.33$). Hypertension was more prevalent in regular users (8.1%) than irregular users (6.2%) and non-users (5.5%) ($p = 0.15$).

Table 1. Pre-matched baseline characteristics of ivermectin non-users, regular users and irregular users

Characteristic	Non-users (n = 3,034)	Regular users (n = 283)	Irregular users (n = 1,542)	P-value (between the three groups)
Age				
Mean (SD)	39.8 ± 14.2	47.0 ± 14.2	41.0 ± 14.5	
Age				< 0.0001
< 30 yo	844 (27.8%)	39 (13.8%)	397 (25.7%)	
30-50 yo	1,582 (52.2%)	131 (46.3%)	775 (50.3%)	
> 50 yo	608 (20.0%)	113 (39.9%)	370 (24.0%)	
Sex				0.19
Female	1,624 (53.5%)	141 (49.8%)	853 (55.3%)	
Male	1,410 (46.5%)	142 (50.2%)	689 (44.7%)	
Race				0.055
Afro-Brazilian	100 (3.3%)	4 (1.4%)	37 (2.4%)	
Mixed	682 (22.5%)	58 (20.5%)	373 (24.2%)	
Caucasian	2,192 (72.5%)	221 (78.1%)	1,102 (71.5%)	
Asian-Brazilian	60 (51.7%)	0 (0.0%)	30 (1.9%)	
Type 2 diabetes				0.33
Yes	63 (2.1%)	9 (3.2%)	40 (2.6%)	
No	2,971 (97.9%)	274 (96.8%)	1,502 (97.4%)	
Hypertension				0.15
Yes	166 (5.5%)	23 (8.1%)	96 (6.2%)	
No	2,868 (94.5%)	260 (91.9%)	1,446 (93.8%)	
Asthma				0.47
Yes	6 (0.2%)	0 (0.0%)	6 (0.4%)	
No	3,028 (99.8%)	283 (100.0%)	1,536 (99.6%)	
COPD				0.42

Characteristic		Non-users (n = 3,034)	Regular users (n = 283)	Irregular users (n = 1,542)	P-value (between the three groups)
	Yes	6 (0.2%)	1 (0.4%)	1 (0.1%)	
	No	3,028 (99.8%)	282 (99.6%)	1,541 (99.9%)	
Other respiratory diseases					0.78
	Yes	5 (0.2%)	1 (0.4%)	3 (0.2%)	
	No	3,029 (99.8%)	282 (99.6%)	1,539 (99.8%)	
Cardiovascular diseases					0.11
	Yes	15 (0.5%)	2 (0.7%)	16 (1.0%)	
	No	3,019 (99.5%)	281 (99.3%)	1,526 (99.0%)	
Cancer					0.73
	Yes	12 (0.4%)	2 (0.7%)	6 (0.4%)	
	No	3,022 (99.6%)	281 (99.3%)	1,536 (99.6%)	
History of Smoking					0.81
	Yes	47 (1.5%)	3 (1.1%)	23 (1.5%)	
	No	2,987 (98.5%)	280 (98.9%)	1,519 (98.5%)	
History of stroke					0.71
	Yes	10 (0.3%)	1 (0.4%)	3 (0.2%)	
	No	3,024 (99.7%)	282 (99.6%)	1,539 (99.8%)	
History of MI					0.64
	Yes	4 (0.1%)	0 (0.0%)	3 (0.2%)	
	No	3,030 (99,9%)	283 (100.0%)	1,539 (99.8%)	

MI = myocardial infarction; COPD = chronic obstructive pulmonary disease; yo = years old; SD = standard deviation.

Table 2 describes the baseline characteristics of ivermectin non-users paired with regular users and non-users paired with irregular users. After balancing and matching between each of the three combinations of two groups (non-users and regular users, non-users and irregular users and regular and irregular users), there were 283 subjects in each group (n = 566) between non-users and regular users and between irregular and regular users, and 1,542 (n = 3,084) between non-user and irregular users, with similar baseline characteristics.

Table 2. Baseline characteristics of the prophylactic study, after propensity score matching between non-users and regular users, non-users and irregular users, and irregular users and regular users.

	NON-USERS PAIRED WITH REGULAR IVERMECTIN USERS		NON-USERS PAIRED WITH IRREGULAR IVERMECTIN USERS		REGULAR USERS PAIRED WITH IRREGULAR IVERMECTIN USERS	
Variable	Non-users (n = 283)	Regular users (n = 283)	Non-users (n = 1,542)	Irregular users (n = 1,542)	Regular users (n = 283)	Irregular users (n = 283)
Age						
Mean (SD)	41.6 ± 14.8	47.0 ± 14.2	40.3 ± 14.4	41.0 ± 14.5	47.0 ± 14.2	43.8 ± 16.0
Age						
< 30 yo	63 (22.3%)	39 (13.8%)	410 (26.6%)	397 (25.7%)	39 (13.8%)	60 (21.2%)
30-50 yo	152 (53.7%)	131 (46.3%)	808 (52.4%)	775 (50.3%)	131 (46.3%)	132 (46.4%)
> 50 yo	68 (24.0%)	113 (39.9%)	324 (21.0%)	370 (24.0%)	113 (39.9%)	91 (32.2%)
Sex						
Female	156 (55.1%)	141 (49.8%)	846 (54.9%)	853 (55.3%)	141 (49.8%)	155 (54.8%)
Male	127 (44.9%)	142 (50.2%)	696 (45.1%)	689 (44.7%)	142 (50.2%)	128 (45.2%)
Race						
Afro-Brazilian	9 (3.2%)	4 (1.4%)	45 (2.9%)	37 (2.4%)	4 (1.4%)	5 (1.8%)
Mixed	58 (20.5%)	58 (20.5%)	351 (22.8%)	373 (24.2%)	58 (20.5%)	68 (24.0%)
Caucasian	213 (75.3%)	221 (78.1%)	1,114 (72.2%)	1,102 (71.5%)	221 (78.1%)	209 (73.9%)
Asian-Brazilian	3 (1.1%)	0 (0.0%)	32 (2.1%)	30 (2.0%)	0	1 (0.3%)
Type 2 diabetes						
Yes	10 (3.5%)	9 (3.2%)	37 (2.4%)	40 (2.6%)	9 (3.2%)	10 (3.5%)
No	273 (96.5%)	274 (96.8%)	1,505 (97.6%)	1,502 (97.4%)	274 (96.8%)	273 (96.5%)
Hypertension						
Yes	21 (7.4%)	23 (8.1%)	86 (5.6%)	96 (6.2%)	23 (8.1%)	20 (7.1%)
No	262 (92.6%)	260 (91.9%)	1,456 (94.4%)	1,446 (93.8%)	260 (91.9%)	263 (92.9%)
Asthma						
Yes	0	0	6 (0.4%)	6 (0.4%)	0	0
No	283 (100.0%)	283 (100.0%)	1,536 (99.6%)	1,536 (99.6%)	283 (100.0%)	283 (100.0%)
COPD						
Yes	0 (0.0%)	1 (0.3%)	1 (0.1%)	1 (0.1%)	1 (0.3%)	0
No	283 (100.0%)	282 (99.7%)	1,541 (99.9%)	1,541 (99.9%)	282 (99.7%)	283 (100.0%)
Other respiratory diseases						
Yes	1 (0.3%)	1 (0.3%)	3 (0.2%)	3 (0.2%)	1 (0.3%)	0
No	282 (99.7%)	282 (99.7%)	1,539 (99.8%)	1,539 (99.8%)	282 (99.7%)	283 (100.0%)
Cardiovascular diseases						
Yes	1 (0.3%)	2 (0.7%)	9 (0.6%)	16 (1.0%)	2 (0.7%)	5 (1.8%)
No	282 (99.7%)	281 (99.3%)	1,533 (99.4%)	1,526 (99.0%)	281 (99.3%)	278 (98.2%)
Cancer						
Yes	2 (0.7%)	2 (0.7%)	6 (0.4%)	6 (0.4%)	2 (0.7%)	2 (0.7%)
No	281 (99.3%)	281 (99.3%)	1,536 (99.6%)	1,536 (99.6%)	281 (99.3%)	281 (99.3%)
History of Smoking						
Yes	2 (0.7%)	3 (1.1%)	21 (1.4%)	23 (1.5%)	3 (1.1%)	1 (0.3%)
No	281 (99.3%)	286 (98.1%)	1,521 (98.6%)	1,519 (98.5%)	280 (98.9%)	282 (99.7%)
History of stroke						

	NON-USERS PAIRED WITH REGULAR IVERMECTIN USERS		NON-USERS PAIRED WITH IRREGULAR IVERMECTIN USERS		REGULAR USERS PAIRED WITH IRREGULAR IVERMECTIN USERS	
Yes	1 (0.3%)	1 (0.3%)	2 (0.1%)	3 (0.2%)	1 (0.3%)	1 (0.3%)
No	282 (99.7%)	282 (99.7%)	1,540 (99.9%)	1,539 (99.8%)	282 (99.7%)	282 (99.7%)
History of MI						
Yes	0	0	1 (0.1%)	3 (0.2%)	0	0
No	283 (100.0%)	283 (100.0%)	1,541 (99.9%)	1,539 (99.8%)	283 (100.0%)	283 (100.0%)

MI = myocardial infarction; COPD = chronic obstructive pulmonary disease; yo = years old; SD = standard deviation.

Impact of ivermectin on infection rates in non-users, regular, irregular users

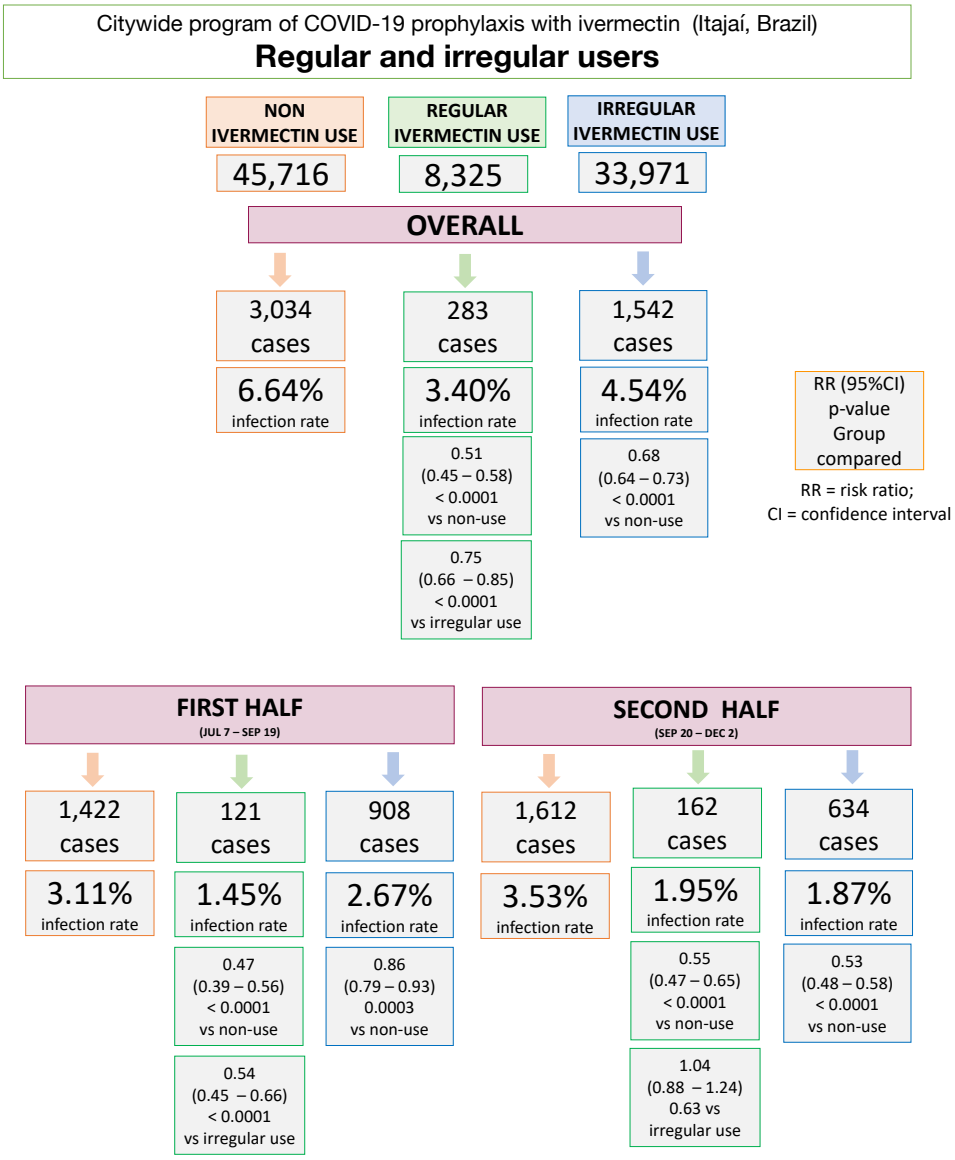
Figure 2 illustrates infection rates for ivermectin non-users, regular users and irregular users, during the overall, first and second half of the program. In the program, infection rate among ivermectin non-users was 6.64% (3,034/45,716 infections). Ivermectin regular users had a reduction of 49% in infection rate compared to non-users (283/8,325 cases; 3.40% infection rate; RR 0.51; 95%CI 0.45 – 0.58; $p < 0.0001$). Irregular ivermectin users had a 32% lower infection rate than non-users [1,542/33,971; 4.54% infection rate; risk ratio (RR) 0.68; 95% confidence interval (95%CI), 0.64 – 0.73); $p < 0.0001$]. Ivermectin regular users had a 25% lower infection rate than irregular users (RR versus sporadic users, 0.75; 95%CI 0.66 – 0.85; $p < 0.0001$).

In the first half of the program, between July 7 and September 19, 2020, infection rate was 3.11% (1,422 cases) among ivermectin non-users and 1.45% (121 cases) among ivermectin regular users; a 53% reduction compared to non-users (RR, 0.47; 95%CI 0.39 – 0.56; $p < 0.0001$). Infection rate was 2.67% (908 cases) among ivermectin irregular users, showing a 14% reduction compared to non-users (RR, 0.86; 95%CI 0.79 – 0.93; $p = 0.0003$). Regular users had 46% lower infection rate than irregular users (RR, 0.54; 95%CI, 0.45 – 0.66; $p < 0.0001$).

In the second half of the program, between September 20 and December 2, 2020, infection rate was 3.53% (1,612 cases) among ivermectin non-users, 1.95% (162 cases) among ivermectin regular users; a 45% reduction compared to non-users (RR, 0.55; 95%CI 0.47 – 0.65; $p < 0.0001$). Infection rate was 1.87% among ivermectin irregular users (634 cases), showing a 47% reduction in infection rate compared to non-users (RR,

0.53; 95%CI 0.48 – 0.58; p < 0.0001). Regular users had similar infection rate to irregular users during the second half of the program (RR, 1.04; 95%CI, 0.88 – 1.24; p = 0.63).

Figure 2. Impact of ivermectin use on infection rates during the overall, first half and second half of the program in non-users, regular users and irregular users.



Hospitalization rates for ivermectin non-users, regular users and irregular users

Supplement Appendix 1 (**Tables 9/1S and 10/2S,** and **Figure 7/1S**) show hospitalization rates before matching. **Tables 3, 4 and 5** shows hospitalization rates and unadjusted and multivariate-adjusted values for each of the three, two-group comparisons after balancing and matching.

Figure 3 illustrates differences in hospitalization rates in the overall population between matched groups. Balanced and matched groups of non-users and regular users (283 subjects in each group) showed 13 hospitalizations among non-users (4.6% hospitalization rate) and ***zero hospitalizations among regular users*** (0.0% hospitalization rate), a 100% reduction after adjustment for variables [RR, 0.00; 95%CI, not applicable (n/a); $p < 0.0001$]. Between non-users and irregular users (n = 1,542 in each group), there were 47 hospitalizations among non-users (3.0% hospitalization rate) and 38 hospitalizations among irregular ivermectin users (2.5% hospitalization rate), a 29% marginally significant reduction (RR, 0.71; 95%CI, 0.49 – 1.05; $p = 0.099$). Between regular and irregular users (n = 283 in each group), there were 10 hospitalizations among irregular users (3.5% hospitalization rate) and ***zero hospitalizations among regular users*** (0.0% hospitalization rate); a 100% reduction after adjustment for variables (RR, 0.00; 95% CI, n/a, $p < 0.0001$). Precise comparisons between subpopulations of regular users and non-users and between regular users and irregular users were precluded due to lack of hospitalizations among regular users, as observed in **Figure 3**.

Figure 3. Hospitalization rates for overall population in post-matched groups.

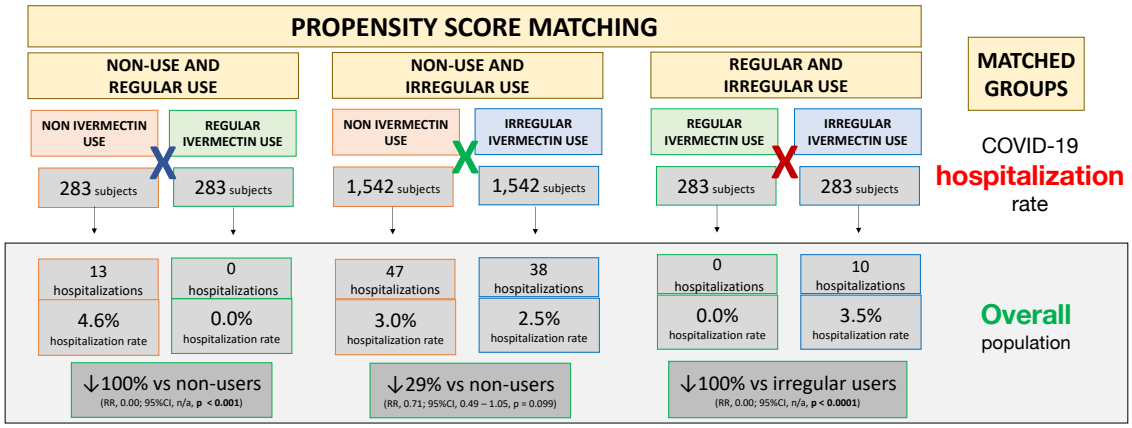


Table 3. Hospitalization rates in the three, two-group comparisons after balancing & matching the groups of non-users and regular ivermectin users.

PROPENSITY SCORE MATCHED NON-USERS AND REGULAR USERS	Ivermectin non-users (n = 283)	Regular ivermectin users (n = 283)	Unadjusted hospital risk ratio (95%CI) and p-value [p]	Multivariate adjusted hospital risk ratio (95%CI) and p-value [p]
Overall	13/283 (4.6%)	0/283 (0.0%)	**0.04 (0.002 – 0.60) [0.02]**	**0.00 (n/a) [<0.0001]**
Age				
< 30 y/o	0/63 (0.0%)	0/39 (0.0%)	1.61 (0.03 – 82.7) [0.81]	1.00 (n/a) [1.00]
30-50 y/o	3/152 (2.0%)	0/131 (0.0%)	0.16 (0.01 – 3.17) [0.23]	n/a
> 50 y/o	10/68 (14.7%)	0/113 (0.0%)	**0.02 (0.001 – 0.43) [0.011]**	**n/a (n/a) [<0.001]**
Sex				
Female	7/156 (4.5%)	0/141 (0.0%)	0.07 (0.004 – 1.24) [0.07]	**n/a (n/a) [<0.001]**
Male	6/127 (4.7%)	0/142 (0.0%)	0.07 (0.004 – 1.18) [0.064]	**n/a (n/a) [<0.001]**
Race				
Afro-Brazilian	0/9 (0.0%)	0/4 (0.0%)	2/11 (0.04 – 124.5) [0.72]	1.00 (n/a) [1.00]
Mixed	3/58 (5.2%)	0/58 (0.0%)	0.14 (0.01 – 2.7) [0.19]	n/a
Caucasian	10/213 (4.7%)	0/221 (0.0%)	0.14 (0.01 – 2.68) [0.19]	**n/a (n/a) [< 0.001]**

PROPENSITY SCORE MATCHED NON-USERS AND REGULAR USERS	Ivermectin non-users (n = 283)	Regular ivermectin users (n = 283)	Unadjusted hospital risk ratio (95%CI) and p-value [p]	Multivariate adjusted hospital risk ratio (95%CI) and p-value [p]
Asian-Brazilian	0/3 (0.0%)	0/0	n/a	n/a
Type 2 diabetes				
Yes	3/10 (30.0%)	0/9 (0.0%)	0.11 (0.005 – 2.54) [0.17]	n/a
No	10/273 (3.7%)	0/274 (0.0%)	**0.05 (0.003 – 0.78) [0.033]**	n/a
Hypertension				
Yes	5/21 (23.8%)	0/23 (0.0%)	0.06 (0.003 – 1.24) [0.069]	n/a
No	8/262 (3.1%)	0/260 (0.0%)	**0.06 (0.003 – 1.00) [0.05]**	n/a
Asthma				
Yes	0/0	0/0	n/a	n/a
No	13/283 (4.6%)	0/283 (0.0%)	**0.04 (0.002 – 0.60) [0.02]**	**0.00 (0.00 – 0.00) [< 0.001]**
COPD			n/a	
Yes	0/0	0/1 (0.0%)	0.50 (0.04 – 7.10) [0.61]	n/a
No	13/283 (4.6%)	0/282 (0.0%)	**0.04 (0.002 – 0.60) [0.021]**	**0.00 (0.00 – 0.00) [< 0.001]**
Other respiratory diseases				
Yes	0/1 (0.0%)	0/1 (0.0%)	1.00 (0.01 – 92.4) [1.00]	n/a
No	13/282 (4.6%)	0/282 (0.0%)	**0.04 (0.002 – 0.60) [0.021]**	**0.00 (0.00 – 0.00) [< 0.001]**
Cardiovascular diseases				
Yes	0/1 (0.0%)	0/2 (0.0%)	0.33 (0.02 – 5.33) [0.44]	1.00 (n/a) [1.00]
No	13/282 (4.6%)	0/281 (0.0%)	**0.04 (0.002 – 0.60) [0.021]**	**0.00 (0.00 – 0.00) [< 0.001]**
Cancer				
Yes	1/2 (50.0%)	0/2 (0.0%)	0.20 (0.01 – 8.83) [0.40]	n/a
No	12/281 (4.3%)	0/281 (0.0%)	**0.04 (0.002 – 0.65) [0.024]**	**0.00 (0.00 – 0.00) [< 0.001]**
History of Smoking				
Yes	0/2 (0.0%)	0/3 (0.0%)	0.71 (0.01 – 49.7) [0.88]	1.00 (n/a) [1.00]
No	13/281 (4.6%)	0/280 (0.0%)	**0.04 (0.002 – 0.60) [0.021]**	**0.00 (0.00 – 0.00) [< 0.001]**
History of stroke				
Yes	0/1 (0.0%)	0/1 (0.0%)	1.00 (0.01 – 92.4) [1.00]	n/a
No	13/282 (4.6%)	0/282 (0.0%)	**0.04 (0.002 – 0.60) [0.021]**	**0.00 (0.00 – 0.00) [<0.001]**
History of MI				
Yes	0/0	0/0	n/a	n/a
No	13/283 (4.6%)	0/283 (0.0%)	**0.04 (0.002 – 0.60) [0.02]**	**0.00 (0.00 – 0.00) [<0.001]**

MI = myocardial infarction; COPD = chronic obstructive pulmonary disease; y/o = years old; CI = confidence interval; n/a = not applicable; (in bold = statistically significant differences)

Table 4. Hospitalization rates in the three, two-group comparisons after balancing & matching the groups of non-users and irregular ivermectin users.

PROPENSITY SCORE MATCHED NON-USERS AND IRREGULAR USERS	Ivermectin non-users (n = 1,542)	Irregular ivermectin users (n = 1,542)	Unadjusted hospital risk ratio (95%CI) and p-value [p]	Multivariate adjusted hospital risk ratio (95%CI) and p-value [p]
Overall	47/1,542 (3.0%)	38/1,542 (2.5%)	0.80 (0.52 – 1.24) [0.32]	0.71 (0.49 – 1.05) [0.099]
Age				
< 30 y/o	0/410 (0.0%)	1/397 (0.3%)	3.11 (0.13 – 76.5) [0.49]	n/a [0.98]
30-50 y/o	4/808 (0.5%)	7/775 (0.9%)	1.83 (0.53 – 6.28) [0.34]	1.82 (0.54 – 6.21) [0.34]
> 50 y/o	43/324 (13.3%)	30/370 (8.1%)	0.58 (0.35 – 0.94) [0.028]	0.61 (0.39 – 0.95) [0.029]
Sex				
Female	24/846 (2.8%)	17/853 (2.0%)	0.70 (0.37 – 1.31) [0.26]	0.69 (0.38 – 1.26) [0.23]
Male	23/696 (3.3%)	21/689 (3.0%)	0.92 (0.50 – 1.68) [0.79]	0.71 (0.40 – 1.24) [0.22]
Race				
Afro-Brazilian	2/45 (4.4%)	0/37 (0.0%)	0.23 (0.01 – 4.99) [0.35]	n/a [0.98]
Mixed	9/351 (2.6%)	11/373 (3.0%)	1.15 (0.47 – 2.82) [0.75]	1.02 (0.44 – 2.34) [0.97]
Caucasian	36/1,114 (3.2%)	26/1,102 (2.4%)	0.73 (0.44 – 1.21) [0.22]	0.65 (0.40 – 1.05) [0.078]
Asian-Brazilian	0/32 (0.0%)	1/30 (3.3%)	3.31 (0.13 – 84.3) [0.47]	n/a [0.98]
Type 2 diabetes				
Yes	6/37 (16.2%)	3/40 (7.5%)	0.42 (0.097 – 1.81) [0.24]	0.51 (0.14 – 1.85) [0.31]
No	41/1,505 (2.7%)	35/1,502 (2.3%)	0.85 (0.54 – 1.35) [0.49]	0.75 (0.49 – 1.15) [0.19]
Hypertension				
Yes	13/86 (15.1%)	9/96 (9.4%)	0.58 (0.24 – 1.44) [0.24]	0.59 (0.27 – 1.31) [0.20]
No	34/1,456 (2.3%)	29/1,446 (2.0%)	0.86 (0.52 – 1.41) [0.54]	0.75 (0.47 – 1.23) [0.26]
Asthma				
Yes	0/6 (0.0%)	1/6 (16.7%)	3.55 (0.12 – 105.8) [0.47]	n/a [0.58]
No	47/1,536 (3.1%)	37/1,536 (2.4%)	0.78 (0.51 – 1.21) [0.27]	0.70 (0.46 – 1.05) [0.087]
COPD				
Yes	0/1 (0.0%)	0/1 (0.0%)	1.00 (0.01 – 92.4) [1.00]	1.00 (n/a) [1.00]
No	47/1,541 (3.0%)	38/1,541 (2.5%)	0.80 (0.52 – 1.24) [0.32]	0.71 (0.48 – 1.07) [0.11]
Other respiratory diseases				
Yes	1/3 (33.3%)	0/3 (0.0%)	0.24 (0.01 – 8.62) [0.43]	0.74 (0.00 – 1,830.4) [0.59]
No	46/1,539 (3.0%)	38/1,539 (2.5%)	0.82 (0.53 – 1.27) [0.38]	0.74 (0.49 – 1.12) [0.15]
Cardiovascular diseases				
Yes	1/9 (11.1%)	1/16 (6.3%)	0.53 (0.03 – 9.71) [0.67]	n/a [0.99]
No	46/1,533 (3.0%)	37/1,526 (2.4%)	0.80 (0.52 – 1.25) [0.33]	0.70 (0.46 – 1.06) [0.09]
Cancer				
Yes	1/6 (16.7%)	0/6 (0.0%)	0.28 (0.01 – 8.42) [0.47]	n/a [0.98]
No	46/1,536 (3.0%)	38/1,536 (2.5%)	0.82 (0.53 – 1.27) [0.38]	0.74 (0.49 – 1.11) [0.14]
History of Smoking				
Yes	0/21 (0.0%)	0/23 (0.0%)	0.91 (0.02 – 48.2) [0.96]	0.97 (n/a) [1.00]
No	47/1,521 (3.1%)	38/1,519 (2.5%)	0.80 (0.52 – 1.24) [0.33]	0.71 (0.48 – 1.07) [0.10]
History of stroke				

PROPENSITY SCORE MATCHED NON-USERS AND IRREGULAR USERS	Ivermectin non-users (n = 1,542)	Irregular ivermectin users (n = 1,542)	Unadjusted hospital risk ratio (95%CI) and p-value [p]	Multivariate adjusted hospital risk ratio (95%CI) and p-value [p]
Yes	0/2 (0.0%)	0/3 (0.0%)	0.71 (0.01 – 49.7) [0.88]	n/a [1.00]
No	47/1,540 (3.1%)	38/1,539 (2.5%)	0.80 (0.52 – 1.24) [0.32]	0.72 (0.48 – 1.08) [0.11]
History of MI				
Yes	0/1 (0.0%)	1/3 (33.3%)	1.80 (0.04 – 79.4) [0.76]	n/a [0.99]
No	47/1,541 (3.0%)	37/1,539 (2.4%)	0.78 (0.51 – 1.21) [0.27]	0.70 (0.46 – 1.07) [0.09]

MI = myocardial infarction; COPD = chronic obstructive pulmonary disease; y/o = years old; CI = confidence interval; n/a = not applicable; (in bold = statistically significant differences)

Table 5. Hospitalization rates in the three, two-group comparisons after balancing & matching the groups of regular and irregular ivermectin users.

PROPENSITY SCORE MATCHED REGULAR USERS AND IRREGULAR USERS	Regular ivermectin users (n = 283)	Irregular ivermectin users (n = 283)	Unadjusted hospital risk ratio (95%CI) and p-value [p]	Multivariate adjusted hospital risk ratio (95%CI) and p-value [p]
Overall	0/283 (0.0%)	10/283 (3.5%)	**0.05 (0.003 – 0.79) [0.034]**	**0.00 (n/a) [< 0.0001]**
Age				
< 30 y/o	0/39 (0.0%)	0/60 (0.0%)	1.53 (0.03 – 78.8) [0.83]	1.00 (n/a) [1.00]
30-50 y/o	0/131 (0.0%)	3/132 (2.3%)	0.14 (0.01 – 2.75) [0.20]	n/a
> 50 y/o	0/113 (0.0%)	7/91 (7.7%)	**0.05 (0.003 – 0.88) [0.041]**	**n/a (n/a) [< 0.0001]**
Sex				
Female	0/141 (0.0%)	2/155 (1.3%)	0.22 (0.01 – 4.56) [0.33]	**n/a (n/a) [< 0.0001]**
Male	0/142 (0.0%)	8/128 (6.3%)	**0.05 (0.003 – 0.87) [0.04]**	**n/a (n/a) [< 0.0001]**
Race				
Afro-Brazilian	0/4 (0.0%)	0/5 (0.0%)	1.22 (0.02 – 74.3) [0.92]	1.00 (n/a) [1.00]
Mixed	0/58 (0.0%)	3/68 (4.4%)	0.16 (0.01 – 3.16) [0.23]	n/a
Caucasian	2/221 (0.0%)	7/209 (3.3%)	0.26 (0.05 – 1.28) [0.099]	**n/a (n/a) [< 0.0001]**
Asian-Brazilian	0/0	0/1 (0.0%)	3.00 (0.02 – 473.1) [0.67]	n/a
Type 2 diabetes				
Yes	0/9 (0.0%)	1/10 (10.0%)	0.33 (0.01 – 9.26) [0.52]	n/a
No	0/274 (0.0%)	9/273 (3.3%)	**0.05 (0.003 – 0.88) [0.04]**	**0.00 (n/a) [< 0.0001]**
Hypertension				
Yes	0/23 (0.0%)	1/20 (5.0%)	0.28 (0.01 – 7.18) [0.44]	n/a
No	0/260 (0.0%)	9/263 (3.4%)	**0.05 (0.003 – 0.89) [0.041]**	**n/a (n/a) [< 0.0001]**
Asthma				
Yes	0/0	0/0	n/a	n/a
No	0/283 (0.0%)	10/283 (3.5%)	**0.05 (0.003 – 0.79) [0.034]**	**0.00 (n/a) [< 0.0001]**
COPD				
Yes	0/1	0/0	0.33 (0.002 – 52.6)	n/a

PROPENSITY SCORE MATCHED REGULAR USERS AND IRREGULAR USERS	Regular ivermectin users (n = 283)	Irregular ivermectin users (n = 283)	Unadjusted hospital risk ratio (95%CI) and p-value [p]	Multivariate adjusted hospital risk ratio (95%CI) and p-value [p]
	(0.0%)		[0.67]	
No	0/282 (0.0%)	10/283 (3.5%)	**0.05 (0.003 – 0.79) [0.034]**	**0.00 (n/a) [< 0.0001]**
Other respiratory diseases				
Yes	0/1 (0.0%)	0/0	0.33 (0.002 – 52.6) [0.67]	n/a
No	0/282 (0.0%)	10/283 (3.5%)	**0.05 (0.003 – 0.79) [0.034]**	**0.00 (n/a) [< 0.0001]**
Cardiovascular diseases				
Yes	0/2 (0.0%)	0/5 (0.0%)	2.20 (0.03 – 146.0) [0.71]	1.00 (n/a) [1.00]
No	0/281 (0.0%)	10/278 (3.6%)	**0.05 (0.003 – 0.78) [0.033]**	**0.00 (n/a) [< 0.0001]**
Cancer				
Yes	0/2 (0.0%)	0/2 (0.0%)	1.00 (0.01 – 73.3) [1.00]	1.00 (n/a) [1.00]
No	0/281 (0.0%)	10/281 (3.6%)	**0.05 (0.003 – 0.79) [0.034]**	**0.00 (n/a) [< 0.0001]**
History of Smoking				
Yes	0/3 (0.0%)	0/1 (0.0%)	0.43 (0.01 – 33.6) [0.70]	1.00 (n/a) [1.00]
No	0/280 (0.0%)	10/282 (3.5%)	**0.05 (0.003 – 0.79) [0.034]**	**0.00 (n/a) [< 0.0001]**
History of stroke				
Yes	0/1 (0.0%)	0/1 (0.0%)	1.00 (0.01 – 92.4) [1.00]	n/a
No	0/282 (0.0%)	10/282 (3.5%)	**0.05 (0.003 – 0.79) [0.034]**	**0.00 (n/a) [< 0.0001]**
History of MI				
Yes	0/0	0/0	n/a	n/a
No	0/283 (0.0%)	10/283 (3.5%)	**0.05 (0.003 – 0.79) [0.034]**	**0.00 (n/a) [< 0.0001]**

MI = myocardial infarction; COPD = chronic obstructive pulmonary disease; y/o = years old; CI = confidence interval; n/a = not applicable; (in bold = statistically significant differences)

Mortality rates among ivermectin non-users, regular users and irregular users

Supplement Appendix 1 - Tables 11/3S and 12/4S, and Figure 18/2S show mortality rates in ivermectin non-users, regular, and irregular users before matching is described**. Table 6, 7 and 8** and **Figure 4 show** mortality rates for each of the three combinations of post-matched groups of ivermectin non-users and regular users, non-users and irregular users, and regular and irregular users, are described.

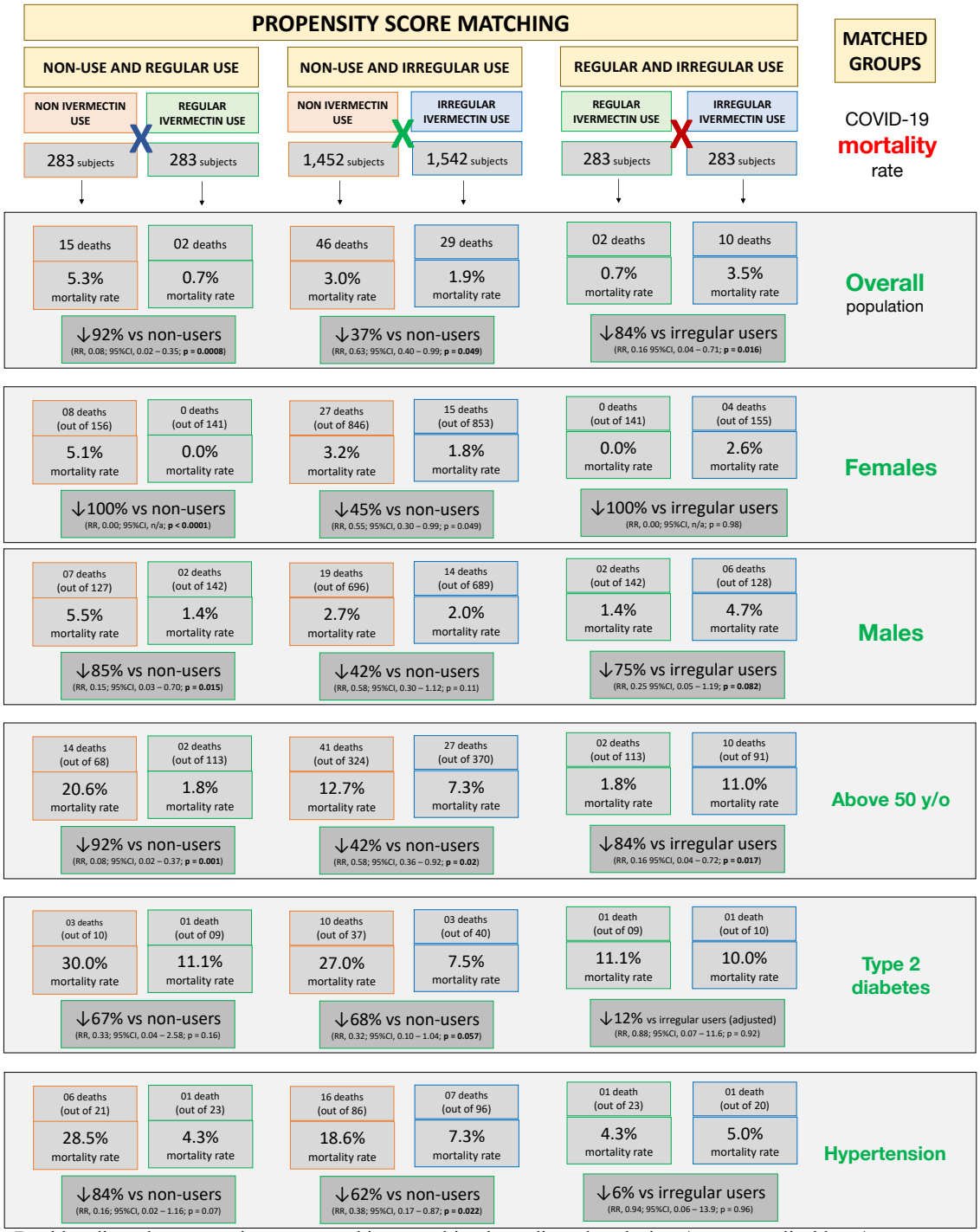
Between matched groups of non-users and regular users (n=283 in each group), mortality rate was 5.3% (15 deaths) among non-users and 0.7% (2 deaths) among regular users; a 92% reduction in mortality rate (RR, 0.08; 95%CI 0.02 – 0.35; p = 0.00083). Compared to non-users, *reductions in mortality rate among regular users were 100% among females* (8 deaths among 156 non-users and zero deaths among 141 regular users; RR, 0.00; 95%CI n/a; p < 0.0001), 85% among males (7 deaths among 127 non-users and 2 deaths among 142 regular users; RR, 0.15; 95%CI 0.03 – 0.70; p = 0.015) with 92% for subjects above 50 years of age (14 deaths among 68 non-users and 2 deaths among 113 regular users; RR, 0.08; 95%CI 0.02 – 0.37; p = 0.001). *There* was statistically a non-significant 67% reduction for type 2 diabetes (3 deaths among 10 non-users and 1 death among 9 regular users; RR, 0.33; 95%CI 0.04 – 2.58; p = 0.16), and 84% among subjects with hypertension (6 deaths among 21 non-users and 1 death among 23 regular users; RR 0.16; 95%CI 0.02 – 1.16; p = 0.07).

Between matched groups of non-users and irregular users (n=1,542 in each group), there was a 3.0% mortality rate (46 deaths) among non-users and a 1.9% mortality rate (29 deaths) among irregular users, showing a 37% reduction in mortality rate (RR compared to non-users, 0.63; 95%CI, 0.40 – 0.99; p = 0.049). A 45% reduction in mortality rate occurred among females; 3.2% for non-users (27 death among 846) and 1.8% for irregular users (15 deaths among 853) (RR, 0.55; 95%CI, 0.30 – 0.99; p = 0.049), and 42% reduction occurred for males; 2.7% of non-users (19 deaths among 696) and 2.0% of irregular users (14 deaths among 689) (RR, 0.58; 95%CI, 0.30 – 1.12; p = 0.11). Mortality rate for subjects above 50 years old was 12.7% for 324 non-users (41 deaths) and 7.3% for 370 regular users (27 deaths); a 42% reduction in mortality rate (RR, 0.58; 95%CI, 0.36 – 0.92; p = 0.02). Participants with type 2 diabetes had 27.0% mortality rate for 37 non-users (10 deaths) and 7.5% for 40 irregular users (3 deaths); a 68% reduction in mortality rate among participants with type 2 diabetes (RR, 0.32; 95%CI, 0.10 – 1.04; p = 0.057). Those with hypertension had a 62% reduction in mortality rate; 18.6% of 86 non-users (16 deaths) and 7.3% of 96 irregular users (7 deaths) (RR, 0.38; 95%CI, 0.17 – 0.87; p = 0.022). In sub-populations without comorbidities, reductions in mortality rates were between 40% and 45%.

When groups of regular users and irregular users are matched (283 subjects in each group), there was a 0.7% and 3.5% (2 deaths and 10 deaths) mortality rate among

regular and irregular users, reflecting a multivariate-adjusted 84% reduction in mortality rate (RR, 0.16; 95%CI 0.04 – 0.71; p = 0.016). The small number of events between these two groups precludes from more statistically significant differenfes, despite large effect size and differences, in particular in subproups with fewer subjects. Mortality rate was 2.6% (4 deaths out of 155) among non-user females and 0.0% (out of 141 females) among regular user females. There was a 4.7% mortality rate (6 deaths) among 128 non-user males and a 1.4% mortality rate (2 deaths) among 142 regular user males, showing a reduction of 75% (RR, 0.25; 95%CI, 0.05 – 1.19; p = 0.082) in mortality rate. Reduction in mortality rate was 84% for those over 50 years of age; 11.0% for non-users (10 deaths among 91) and 1.8% for regular users (2 deaths among 113) (RR, 0.16; 95%CI 0.04 – 0.72; p = 0.017). Among participants with type 2 diabetes, mortality rate was 10.0% (1 death) among 10 irregular users and 11.1% (1 death) among 9 regular users, statistically similar between groups (RR, 0.88; 95%CI, 0.07 – 11.6; p = 0.92). Subjects with hypertension had 5.0% mortality rate (1 death) among 20 irregular users and 4.3% mortality rate (1 death) among 23 regular users, similar between groups (RR, 0.94; 95%CI, 0.06 – 13.9; p = 0.96).

Figure 4. Mortality rates in post-matched, overall population and subpopulation groups.



Doubly adjusted = propensity score matching + multivariate adjusted analysis; n/a = not applicable; y/o = years old; RR = risk ratio; CI = confidence interval

Table 6. Mortality rates in the three ivermectin two-group matches of non-users and regular users.

PROPENSITY SCORE MATCHED NON-USERS AND REGULAR USERS	Ivermectin non-users (n = 283)	Regular ivermectin users (n = 283)	Unadjusted mortality risk ratio (95%CI) and p-value [p]	Multivariate adjusted mortality risk ratio (95%CI) and p-value [p]
Overall	15/283 (5.3%)	2/283 (0.7%)	**0.13 (0.03 – 0.56) [0.006]**	**0.08 (0.02 – 0.35) [0.0008]**
Age				
< 30 y/o	0/63 (0.0%)	0/39 (0.0%)	1.61 (0.03 – 82.7) [0.81]	n/a [1.00]
30-50 y/o	1/152 (0.7%)	0/131 (0.0%)	0.38 (0.02 – 9.51) [0.56]	n/a [0.98]
> 50 y/o	14/68 (20.6%)	2/113 (1.8%)	**0.07 (0.02 – 0.32) [0.0006]**	**0.08 (0.02 – 0.37) [0.001]**
Sex				
Female	8/156 (5.1%)	0/141 (0.0%)	0.06 (0.004 – 1.08) [0.056]	**0.00 (0.00 – 0.00) [<0.0001]**
Male	7/127 (5.5%)	2/142 (1.4%)	0.24 (0.05 – 1.20) [0.083]	**0.15 (0.03 – 0.70) [0.015]**
Race				
Afro-Brazilian	1/9 (11.1%)	0/4 (0.0%)	0.63 (0.02 – 18.8) [0.79]	n/a
Mixed	1/58 (1.7%)	0/58 (0.0%)	0.33 (0.01 – 8.21) [0.50]	n/a
Caucasian	13/213 (6.1%)	2/221 (0.9%)	**0.15 (0.03 – 0.66) [0.012]**	n/a
Asian-Brazilian	0/3 (0.0%)	0/0	7.00 (0.05 – 953.3) [0.44]	n/a
Type 2 diabetes				
Yes	3/10 (30.0%)	1/9 (11.1%)	0.29 (0.02 – 3.48) [0.33]	0.33 (0.04 – 2.58) [0.16]
No	12/273 (4.4%)	1/274 (0.4%)	**0.08 (0.01 – 0.62) [0.015]**	**0.05 (0.01 – 0.37) [0.004]**
Hypertension				
Yes	6/21 (28.5%)	1/23 (4.3%)	0.11 (0.01 – 1.04) [0.054]	0.16 (0.02 – 1.16) [0.07]
No	9/262 (3.4%)	1/260 (0.4%)	**0.11 (0.01 – 0.86) [0.036]**	**0.06 (0.01 – 0.49) [0.009]**
Asthma				
Yes	0/0	0/0	n/a	n/a
No	15/283 (5.3%)	2/283 (0.7%)	**0.13 (0.03 – 0.56) [0.006]**	n/a
COPD				
Yes	0/0	0/1 (0.0%)	0.33 (0.002 – 52.6) [0.67]	n/a
No	15/283 (5.3%)	2/282 (0.7%)	**0.13 (0.03 – 0.56) [0.007]**	n/a
Other respiratory diseases				
Yes	0/1 (0.0%)	0/1 (0.0%)	1.00 (0.01 – 92.4) [1.00]	n/a
No	15/282 (5.3%)	2/282 (0.7%)	**0.13 (0.03 – 0.56) [0.006]**	n/a
Cardiovascular diseases				
Yes	0/1 (0.0%)	0/2 (0.0%)	0.60 (0.007 – 49.5) [0.82]	n/a
No	15/282 (5.3%)	2/281 (0.7%)	**0.13 (0.03 – 0.56) [0.007]**	n/a
Cancer				
Yes	1/2 (50.0%)	0/2 (0.0%)	0.20 (0.005 – 8.83) [0.40]	n/a
No	14/281 (5.0%)	2/281 (0.7%)	**0.14 (0.03 – 0.61) [0.009]**	**0.09 (0.02 – 0.37) [0.001]**
Hiofstory of Smoking				
Yes	0/2 (0.0%)	0/3 (0.0%)	0.71 (0.01 – 49.7) [0.88]	n/a [1.00]
No	15/281 (5.3%)	2/280 (0.7%)	**0.13 (0.03 – 0.56) [0.007]**	**0.08 (0.02 – 0.36) [0.0008]**
History of stroke				

PROPENSITY SCORE MATCHED NON-USERS AND REGULAR USERS	Ivermectin non-users (n = 283)	Regular ivermectin users (n = 283)	Unadjusted mortality risk ratio (95%CI) and p-value [p]	Multivariate adjusted mortality risk ratio (95%CI) and p-value [p]
Yes	1/1 (100.0%)	0/1 (0.0%)	0.11 (0.001 – 10.3) [0.34]	0.01 (0.001 – 0.02) [<0.0001]
No	14/282 (5.0%)	2/282 (0.7%)	**0.14 (0.03 – 0.61) [0.009]**	**0.10 (0.02 – 0.40) [0.001]**
History of MI				
Yes	0/0	0/0	n/a	n/a
No	15/283 (5.3%)	2/283 (0.7%)	0.13 (0.03 – 0.56) [0.007]	n/a

MI = myocardial infarction; COPD = chronic obstructive pulmonary disease; y/o = years old; CI = confidence interval; n/a = not applicable; (in bold = statistically significant differences)

Table 7. Mortality rates in the three ivermectin two-group matches of non-users and irregular users.

PROPENSITY SCORE MATCHED NON-USERS AND IRREGULAR USERS	Ivermectin non-users (n = 1,542)	Irregular ivermectin users (n = 1,542)	Unadjusted mortality risk ratio (95%CI) and p-value [p]	Multivariate adjusted mortality risk ratio (95%CI) and p-value [p]
Overall	46/1,542 (3.0%)	29/1,542 (1.9%)	**0.62 (0.39 – 0.99) [0.049]**	**0.63 (0.40 – 0.99) [0.049]**
Age				
< 30 y/o	0/410 (0.0%)	0/397 (0.0%)	1.03 (0.02 – 52.2) [0.99]	1.00 (0.63 – 1.59) [1.00]
30-50 y/o	5/808 (0.6%)	2/775 (0.3%)	0.42 (0.08 – 2.15) [0.29]	0.42 (0.08 – 2.14) [0.30]
> 50 y/o	41/324 (12.7%)	27/370 (7.3%)	**0.54 (0.33 – 0.91) [0.019]**	**0.58 (0.36 – 0.92) [0.02]**
Sex				
Female	27/846 (3.2%)	15/853 (1.8%)	0.54 (0.29 – 1.03) [0.061]	**0.55 (0.30 – 0.99) [0.049]**
Male	19/696 (2.7%)	14/689 (2.0%)	0.74 (0.37 – 1.49) [0.40]	0.58 (0.30 – 1.12) [0.11]
Race				
Afro-Brazilian	2/45 (4.4%)	0/37 (0.0%)	0.23 (0.01 – 4.99) [0.35]	n/a
Mixed	7/351 (2.0%)	7/373 (1.9%)	0.94 (0.33 – 2.71) [0.91]	0.83 (0.31 – 2.26) [0.72]
Caucasian	36/1,114 (3.2%)	21/1,102 (1.9%)	**0.58 (0.34 – 1.00) [0.05]**	**0.53 (0.32 – 0.89) [0.016]**
Asian-Brazilian	1/32 (3.1%)	1/30 (3.3%)	1.07 (0.06 – 17.9) [0.96]	0.81 (0.07 – 9.99) [0.87]
Type 2 diabetes				
Yes	10/37 (27.0%)	3/40 (7.5%)	**0.22 (0.05 – 0.87) [0.031]**	0.32 (0.10 – 1.04) [0.057]
No	36/1,505 (2.4%)	26/1,502 (1.7%)	0.72 (0.43 – 1.20) [0.20]	0.64 (0.39 – 1.04) [0.069]
Hypertension				
Yes	16/86 (18.6%)	7/96 (7.3%)	**0.34 (0.13 – 0.88) [0.026]**	**0.38 (0.17 – 0.87) [0.022]**
No	30/1,456 (2.1%)	22/1,446 (1.5%)	0.73 (0.42 – 1.27) [0.26]	0.66 (0.39 – 1.12) [0.12]
Asthma				
Yes	1/6 (16.7%)	1/6 (16.7%)	1.00 (0.05 – 20.8) [1.00]	3.95 (0.02 – 789.8) [0.61]
No	45/1,536 (2.9%)	28/1,536 (1.8%)	**0.62 (0.38 – 0.99) [0.046]**	**0.56 (0.36 – 0.88) [0.011]**
COPD				
Yes	0/1 (0.0%)	0/1 (50.0%)	1.00 (0.01 – 92.4) [1.00]	1.00 (0.64 – 1.56) [1.00]
No	46/1,541 (3.0%)	29/1,541 (1.9%)	**0.62 (0.39 – 0.99) [0.049]**	**0.56 (0.36 – 0.88) [0.011]**
Other respiratory diseases				
Yes	1/3 (33.3%)	0/3 (0.0%)	0.24 (0.01 – 8.62) [0.43]	0.06 (0 – 4178.4) [0.62]

PROPENSITY SCORE MATCHED NON-USERS AND IRREGULAR USERS	Ivermectin non-users (n = 1,542)	Irregular ivermectin users (n = 1,542)	Unadjusted mortality risk ratio (95%CI) and p-value [p]	Multivariate adjusted mortality risk ratio (95%CI) and p-value [p]
No	45/1,539 (2.9%)	29/1,539 (1.9%)	0.64 (0.40 – 1.02) [0.062]	**0.58 (0.37 – 0.91) [0.017]**
Cardiovascular diseases				
Yes	1/9 (11.1%)	0/16 (0.0%)	0.17 (0.01 – 4.68) [0.30]	**0.04 (0.03 – 0.07) [<0.0001]**
No	45/1,533 (2.9%)	29/1,526 (1.9%)	0.64 (0.40 – 1.03) [0.064]	**0.57 (0.36 – 0.88) [0.012]**
Cancer				
Yes	1/6 (16.7%)	0/6 (0.0%)	0.28 (0.01 – 8.42) [0.47]	n/a
No	45/1,536 (2.9%)	29/1,536 (1.9%)	0.64 (0.40 – 1.02) [0.062]	**0.58 (0.37 – 0.90) [0.016]**
History of Smoking				
Yes	1/21 (4.8%)	0/23 (0.0%)	0.29 (0.01 – 7.54) [0.46]	**0.00 [< 0.0001]**
No	45/1,521 (3.0%)	29/1,519 (1.9%)	0.64 (0.40 – 1.02) [0.063]	**0.57 (0.37 – 0.90) [0.015]**
History of stroke				
Yes	0/2 (0.0%)	0/3 (0.0%)	0.71 (0.01 – 49.7) [0.88]	**0.40 (0.26 – 0.62) [< 0.0001]**
No	46/1,540 (3.0%)	29/1,539 (1.9%)	**0.62 (0.39 – 0.99) [0.049]**	**0.56 (0.36 – 0.88) [0.011]**
History of MI				
Yes	0/1 (0.0%)	0/3 (0.0%)	0.43 (0.01 – 33.6) [0.70]	**0.04 (0.03 – 0.07) [<0.0001]**
No	46/1,541 (3.0%)	29/1,539 (1.9%)	**0.62 (0.39 – 0.99) [0.049]**	**0.57 (0.36 – 0.88) [0.012]**

MI = myocardial infarction; COPD = chronic obstructive pulmonary disease; y/o = years old; CI = confidence interval; n/a = not applicable; (in bold = statistically significant differences)

Table 8. Mortality rates in the three ivermectin two-group matches of regular users and irregular users.

PROPENSITY SCORE MATCHED REGULAR USERS AND IRREGULAR USERS	Regular ivermectin users (n = 283)	Irregular ivermectin users (n = 283)	Unadjusted mortality risk ratio (95%CI) and p-value [p]	Multivariate adjusted mortality risk ratio (95%CI) and p-value [p]
Overall	2/283 (0.7%)	10/283 (3.5%)	**0.19 (0.04 – 0.89) [0.036]**	**0.16 (0.04 – 0.71) [0.016]**
Age				
< 30 y/o	0/39 (0.0%)	0/60 (0.0%)	1.53 (0.03 – 78.8) [0.83]	1.00 (0.22 – 4.46) [1.00]
30-50 y/o	0/131 (0.0%)	0/132 (0.0%)	1.01 (0.02 – 51.2) [1.00]	1.00 (0.22 – 4.46) [1.00]
> 50 y/o	2/113 (1.8%)	10/91 (11.0%)	**0.15 (0.03 – 0.68) [0.015]**	**0.16 (0.04 – 0.72) [0.017]**
Sex				
Female	0/141 (0.0%)	4/155 (2.6%)	0.12 (0.01 – 2.23) [0.15]	0.00 (n/a) [0.98]
Male	2/142 (1.4%)	6/128 (4.7%)	0.29 (0.06 – 1.47) [0.13]	0.25 (0.05 – 1.19) [0.082]
Race				
Afro-Brazilian	0/4 (0.0%)	0/5 (0.0%)	1.22 (0.02 – 74.7) [0.92]	n/a
Mixed	0/58 (0.0%)	3/68 (4.4%)	0.16 (0.01 – 3.16) [0.23]	n/a
Caucasian	2/221 (0.9%)	7/209 (3.3%)	0.26 (0.05 – 1.28) [0.099]	n/a
Asian-Brazilian	0/0	0/1 (0.0%)	3.00 (0.02 – 473.1) [0.67]	n/a
Type 2 diabetes				
Yes	1/9	1/10	1.13 (0.06 – 21.1)	0.88 (0.07 – 11.6)

PROPENSITY SCORE MATCHED REGULAR USERS AND IRREGULAR USERS	Regular ivermectin users (n = 283)	Irregular ivermectin users (n = 283)	Unadjusted mortality risk ratio (95%CI) and p-value [p]	Multivariate adjusted mortality risk ratio (95%CI) and p-value [p]
	(11.1%)	(10.0%)	[0.94]	[0.92]
No	1/274 (0.4%)	9/273 (3.3%)	**0.11 (0.01 – 0.85) [0.035]**	**0.09 (0.01 – 0.69) [0.021]**
Hypertension				
Yes	1/23 (4.3%)	1/20 (5.0%)	0.86 (0.05 – 14.8) [0.92]	0.94 (0.06 – 13.9) [0.96]
No	1/260 (0.4%)	9/263 (3.4%)	**0.11 (0.01 – 0.79) [0.036]**	**0.09 (0.01 – 0.67) [0.019]**
Asthma				
Yes	0/0	0/0	n/a	n/a
No	2/283 (0.7%)	10/283 (3.5%)	**0.19 (0.04 – 0.89) [0.036]**	**0.16 (0.04 – 0.71) [0.016]**
COPD				
Yes	0/1 (0.0%)	0/0	0.33 (0.002 – 52.6) [0.67]	n/a
No	2/282 (0.7%)	10/283 (3.5%)	**0.19 (0.04 – 0.90) [0.036]**	**0.16 (0.04 – 0.72) [0.017]**
Other respiratory diseases				
Yes	0/1 (0.0%)	0/0	n/a	n/a
No	2/282 (0.7%)	10/283 (3.5%)	**0.19 (0.04 – 0.90) [0.036]**	**0.16 (0.04 – 0.72) [0.017]**
Cardiovascular diseases				
Yes	0/2 (0.0%)	0/5 (0.0%)	2.20 (0.03 – 146.1) [0.71]	0.52 (0.11 – 2.30) [0.38]
No	2/281 (0.7%)	10/278 (3.6%)	**0.19 (0.04 – 0.88) [0.034]**	**0.16 (0.04 – 0.71) [0.016]**
Cancer				
Yes	0/2 (0.0%)	0/2 (0.0%)	1.00 (0.01 – 73.3) [1.00]	1.00 (0.22 – 4.46) [1.00]
No	2/281 (0.7%)	10/281 (3.6%)	**0.19 (0.04 – 0.89) [0.036]**	**0.16 (0.04 – 0.70) [0.016]**
History of Smoking				
Yes	0/3 (0.0%)	0/1 (0.0%)	0.43 (0.01 – 33.6) [0.70]	n/a
No	2/280 (0.7%)	10/282 (3.5%)	**0.20 (0.04 – 0.90) [0.036]**	**0.16 (0.03 – 0.72) [0.017]**
History of stroke				
Yes	0/1 (0.0%)	0/1 (0.0%)	1.00 (0.01 – 92.4) [1.00]	1.00 (0.22 – 4.46) [1.00]
No	2/282 (0.7%)	10/282 (3.5%)	**0.19 (0.04 – 0.89) [0.036]**	**0.16 (0.04 – 0.72) [0.017]**
History of MI				
Yes	0/0	0/0	n/a	n/a
No	2/283 (0.7%)	10/283 (3.5%)	**0.19 (0.04 – 0.89) [0.036]**	**0.16 (0.04 – 0.71) [0.016]**

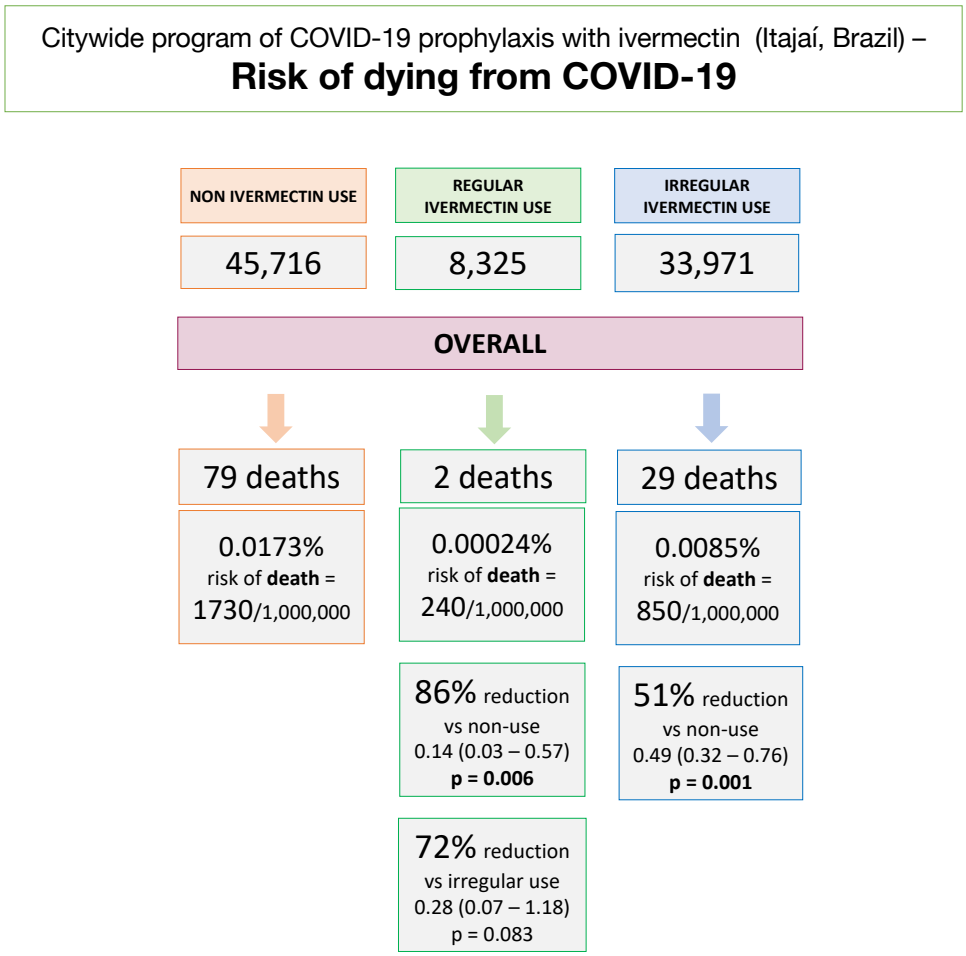
MI = myocardial infarction; COPD = chronic obstructive pulmonary disease; y/o = years old; CI = confidence interval; n/a = not applicable; (in bold = statistically significant differences)

Risk of dying from COVID-19 between ivermectin non-users, regular users, irregular users

Considering the population and participants of Itajaí, as well as inhabitants of Itajaí, who did not use ivermectin prophylactically, the unadjusted risk of dying from COVID-19 was 1,730 in every 1,000,000 subjects among non-users, 240 among regular users and 850 among irregular users. Compared to non-users, the risk of dying from COVID-19

was 86% lower in regular users (RR, 0.14; 95%CI, 0.03 – 0.57; p = 0.006) and 51% lower in irregular users (RR, 0.49; 95%CI, 0.32 – 0.76; p = 0.001). The risk of dying from COVID-19 was 72% lower in regular users than irregular users, (RR, 0.28; 95%CI, 0.07 – 1.18; p = 0.089). Figure 5 illustrates the risk of dying from COVID-19 in each population.

Figure 5. Risk of dying from COVID-19 among ivermectin non-users, regular users, and irregular users.



Discussion

The program in Itajaí, Brazil: Ivermectin prophylaxis for COVID-19

The present study provides in depth results on the prospective study of ivermectin as prophylaxis for COVID-19, in Itajaí, located in Southern Brazil. Particularities of Itajaí, included its dynamic population due to the presence of an overwhelmingly large port compared to the size of the city. This explained why the city was one of the first in the state to reach 1,000 cases in 2020 [26]. In the past, the city experienced some of the highest rates of HIV infections in Brazil [27], partially substantiated by being a port city, an 'independent' predictor of higher prevalence of HIV infection [28].

The decision to adopt a prophylaxis program with ivermectin in Itajaí was based on: (1) the fact that case numbers rose rapidly and at a higher speed than in other cities; (2) the inability to isolate port workers in the absence of pharmacological or non-pharmacological therapies for COVID-19; (3) Because, it had already been proven to be a potent antiviral for over 20 viruses studied independently and peer-reviewed, including the first SARS-CoV epidemic; before the COVID-19 pandemic,; (4) the extensive safety profile and favorable cost-effectiveness of ivermectin. Hence, the program of Itajaí strictly followed all bioethical principles using ivermectin as prophylaxis for COVID-19. The ivermectin was offered optionally, as a prophylaxis for COVID-19, following medical screening by medical doctors.

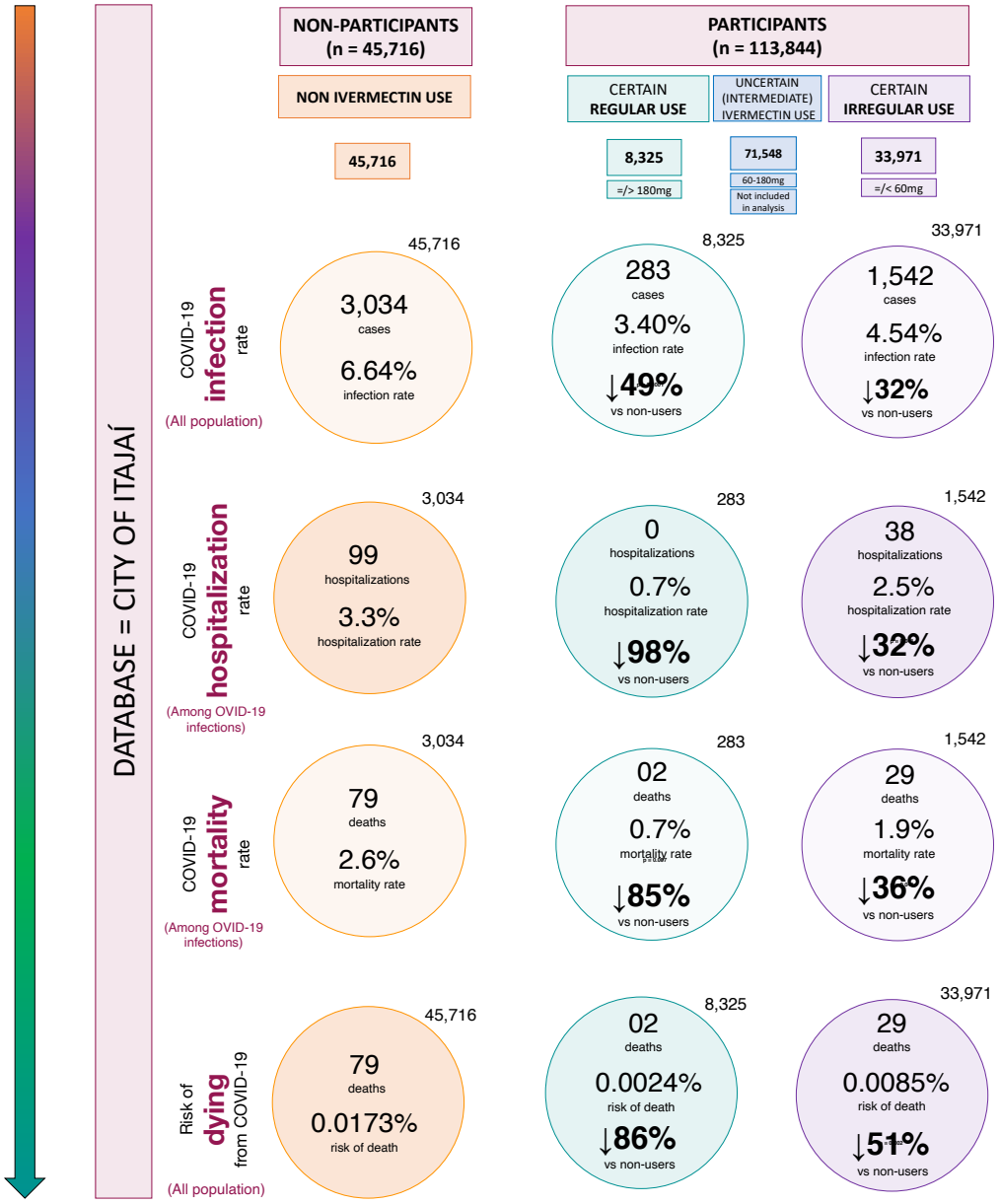
Ivermectin as a defense against all major COVID-19 outcomes: does it depend on the regularity of ivermectin use?

In our first paper [25], ivermectin was shown to be associated with significant reductions in infection rate (44%), hospitalization rate (56%), and mortality rate (68%), when compared to subjects that did not use ivermectin prophylactically and irrespective of the regularity of ivermectin use.

This study paper analyzes the impact of the regular use of ivermectin on COVID-19 infection. This impact included non-users, regular and irregular ivermectin users; results are presented. These groups were estimated from the matched population in the

city of Itajaí, with an impressive 100% of the population of Itajaí being digitalized, in the government data system. Their COVID-19 cases, hospitalizations in public hospitals and all deaths due to COVID-19 were strictly followed and recorded. Figure 6 summarizes an overall view of the findings of this study.

Figure 6. COVID-19 infection, hospitalization, mortality rates and risk of dying from COVID-19, across different patterns of ivermectin use.



All analysis were before matching groups. Analyses of COVID-19 infection rate and risk of dying from COVID-1 were not adjusted. Analyses of COVID-19 hospitalization and mortality rates were based multivariate

This reduction of COVID-19 infection had a significant effect on the reduction of transmission and perpetuation of the pandemic in Itajaí. Also, the reduction of the related hospitalizations and mortality is indisputably meaningful. They reduced not only costs and pressure on the health system but saved many lives.

Ivermectin regular users were older (average age = 47 y/o) compared to irregular users (average age = 41 y/o). The non-users (average age = 39.8 y/o) had approximately 20% to 50% higher prevalence of type 2 diabetes and hypertension. If ivermectin did not work, one would expect higher hospitalizations and mortality rate in the group of regular users, which did not happen, as seen in the pre-matched analysis, in Supplement Appendix 1.

Notably, there were no hospitalizations for any of the 289 regular users. After observing matching between groups, reduction in hospitalization rate was 100% in regular users compared to non-users and irregular users. Analysis of sub-populations in these two comparisons were unfeasible due to the lack of hospitalizations for the regular users. Statistically significant reductions were observed in hospitalization rate for irregular users, when compared to non-users (35% reduction; $p = 0.03$), which was more relevant in high-risk populations. This included subjects 50 years of age and above (reduction of 38%; $p = 0.027$) and those with comorbidities. A 69% reduction was seen among subjects with type 2 diabetes ($p = 0.063$); 45% among subjects with hypertension ($p = 0.10$) and 73% among subjects with cardiovascular diseases ($p = 0.23$), with reductions similar between males and females. This means that even with uncontrolled, irregular use of ivermectin, there is a significant reduction in the number of hospitalizations in COVID-19 infected participants.

The regularity of ivermectin intake demonstrated a progressive impact on the reduction of mortality rate, which was more clearly observed after matching groups. The regular users showed a 90% mortality rate reduction compared to non-users ($p = 0.003$) and 79% reduction compared to irregular users ($p = 0.05$). Irregular users had a reduction of 37% compared to non-users ($p = 0.63$). Reductions among regular users were similar (between 86% and 89%) across different high-risk populations (50 years old and above with comorbidities). High-risk populations of irregular users had reductions in mortality rate between 34% and 60% compared to non-users. The most profoundly significant

results were for women who used ivermectin regularly, with no deaths among all 144 participants.

Risk of dying from COVID-19, when considering the whole population, was notably lower among regular users, compared to both non-users (86% reduction) and irregular users (72% reduction). This risk was also lower among irregular users compared to non-users (51% reduction). Since baseline characteristics were not present for non-user, non-infected subjects, there were no adjustments to be done for variables relative to their chances of dying from COVID-19.

In common, all outcomes related to COVID-19 infection demonstrated a dose related response-effect, with greater reductions in all outcomes with the higher ivermectin intake. This strong correlation reinforces the causal relationship between ivermectin intake and protection from COVID-19. Also, although regular users still had COVID-19 cases (with a lower infection rate than non-users), these cases tended to be milder, compared to non-users or irregular users, as observed in the significant absence of hospitalizations and deaths.

Mechanistically, the accumulated dose of ivermectin, consequently obtained with the regular use of ivermectin, had strong impacts on COVID-19 related outcomes, *i.e.,* once infected, higher amounts of ivermectin administered related to a better prognosis. Of note, the strict control of which days ivermectin was used did not affect the results.

Although a demonstrative dose-response was observed consistently across the groups (non-users, regular, and irregular users) unexpectedly, the risk of COVID-19 infection was not largely influenced by the regularity of ivermectin use (Figure 2) The possible long-term actions of ivermectin, that go beyond its serum or cytoplasmatic concentration, may explain the progressive protection with higher regularity of ivermectin use.

Our results demonstrated protection against Covid-19 when regularly used for a 2 day, every 15 days regimen. This prophylactic treatment regimen respected the already, extensively known safety profile of ivermectin, since notably, it did not surpass the usual doses for scabies.

Noteworthy aspects of the study

Regularity is defined as something happening repeatedly in a fixed pattern. As such, this study determined the criteria for regularity to be more than 30 tablets of ivermectin over five months, with a continuous supply of ivermectin, determined by the number of tablets prescribed and taken every other week over 12 weeks.

To determine different outcomes, it was critical that a correct baseline population was established for each outcome. Because there were more than 8,000 subjects from outside the city of Itajaí that participated in the study, infection rate could not be calculated based on the participating subjects because COVID-19 cases from other cities were underreported in Itajaí among ivermectin non-users. In fact, the "infection rate" of overall participants, 1.40%, among subjects from other cities (177 cases out of 8,352 subjects), was much lower than the infection rates within the city of Itajaí This clearly demonstrated underreporting. Calculations were based on participants from Itajaí only, for which COVID-19 cases were strictly controlled. Correspondingly, the risk of dying from COVID-19 aims to evaluate the risk of an undesired outcome irrespective of how many cases occurred, unlike mortality rate that included the full population.

The use of ivermectin was able to reduce COVID-19 infection significantly. A small portion of regular users were sufficient to positively affect the city's numbers related to COVID-19. Unfortunately, because most of the population failed to continue in a program of prophylactic ivermectin use, the rise in cases after July 7, 2020 in the state of Santa Catarina, led to a skewed perception to potentially discredit the efficacy of ivermectin. However, misleading this perception, a committed program of ivermectin could have led to a huge positive health impact across the whole state.

Unexpectedly, the different regularity of ivermectin use did not show significant changes in the reduction of COVID-19 infections. One could speculate that subjects that did not obtain ivermectin from the program in a regular manner may have acquired ivermectin over the counter, where it was available. However, during the first two months of the program, Brazil experienced not only a temporary shortage of ivermectin due to a sudden increase in demand, but required a medical prescription and experienced an

associated price increase by five times, precluding its use outside the program. More importantly, while infection rates did not reduce with regular use of ivermectin, compared to irregular users, hospitalization and mortality rates reduced substantially, showing a dose-effect response of ivermectin for COVID-19 related outcomes.

The apparent contradictory lack of hospitalizations while there were two deaths in the group of regular users may be explained by the fact that patients either used a private hospital outside the city of Itajaí or in an institution that was not a hospital. Deaths reports are mandatorily for public and private hospitals; however, hospitalizations are not reported. Another hypothesis is that these deaths occurred without hospitalization. Depending on the characteristics and social context of these participants, this is not unusual when hospitals get overwhelmed, or when patients avoid seeking hospital care for other reasons.

Limitations

Updated medical histories were done for ivermectin users at follow-up appointments with medical doctors from the SUS. Regarding the non-users, the participants did not have follow-ups to update their medical records. Depending on the calculation methods performed for infection rates, this could create some differences. Imprecisions and modifications evident, although minimal, between the first manuscript (25) and this study, did not impact the fact that ivermectin use reduced COVID-19 related outcomes. In addition, in the present analysis, we did not control for the COVID-19 infection dates. Of note, although there were no other hospitals in Itajaí, due to the limited capacity of the city hospital, some patients with health insurance were transferred to private hospitals outside of Itajaí, while some patients without private insurance were cared for in institutions that were not hospitals. Unlike hospitalizations, deaths were mandatorily reported, which precluded any imprecision in the calculations of mortality rate.

The number of tablets were calculated according to body weight. Most of the population used between two and three tablets daily for 2 days, every 15 days. Due to the minimal difference between the number of ivermectin tablets used, the amount used (frequency of its use) could be determined with a reasonable level of precision.

This observational study obtained results that presented a high level of certainty by employing strict control of the data outcome among COVID-19 cases and strict control of the number of deaths due to COVID-19 in the overall population. The fact that PSM was employed for outcomes in such a large population makes this data reliable, being sourced from official government data bases (Datasets: https://osf.io/uxhaf/)

Final discussion

Regular use of ivermectin led to a 100% reduction in hospitalization rate, 92% reduction in mortality rate, and 86% reduction in the risk of dying from COVID-19 when compared to non-users. Irregular use of ivermectin led to a 51% reduction in the risk of dying, 29% reduction in hospitalization rate, and a 37% reduction in mortality rate from COVID-19. Statistically significant reductions in hospitalization (100%) and mortality rates (84%), and risk of dying from COVID-19 (72%) were observed in regular users when compared to irregular users. The response pattern of ivermectin use and level of protection from COVID-19 related outcomes was identified and consistent across dose-related levels. The reduction in COVID-19 infection rate occurred in a consistent and significant dose-dependent manner, with reductions of 49% and 32% in regular users and irregular users, when compared to non-users. The most striking evidence of ivermectin effectiveness was the 100% reduction in mortality for female regular users.

The analysis of the data gathered from official government databases showed that ivermectin had an impactful reduction in the incidence of COVID-19 infection, in a dose response manner. Even for irregular users, benefits were observed.

The data conclusively shows, the risk of dying from Covid 19, was lower for all regular & irregular users of ivermectin, compared to non-users, considering the whole population.

A progressive, dose-response pattern of protection from Covid-19 related outcomes was observed and consistent across all levels of ivermectin used. Consequently, the findings in this study show how the risk of contracting Covid-19 infection was not

greatly influenced by the regularity (regular user = 3.4%, irregular user = 4.54%) of ivermectin use, making it very significant as a preventive therapy for Covid-19.

Finally, the evidence, in this study, added to the efficacy of ivermectin as prophylaxis for COVID-19. There is no equivalent on RCTs when it comes to effects of prophylaxis, since this was an observational study of a strictly controlled population with a great level of control for confounding factors at a magnitude unfeasible to be conducted in a RCT. This study demonstrated the effects of ivermectin in real life in an overwhelmingly precise manner, close to post-RCT real-life studies [29,30,31]. The evidence provided by the present study is amongst the strongest and conclusive data regarding ivermectin efficacy.

Conclusion

The regular use of ivermectin decreased hospitalization for Covid-19 by 100%, mortality by 92% and the risk of dying from Covid-19 by 86%, when compared to non-users.
Protection from COVID-19 related outcomes was observed across all levels of ivermectin use, with notable reduction for risk of death in the over 50-year-old population and those with comorbidities. The reduction in infection rate was significant, irrespective of level of ivermectin use. The results of this prospective observational study of a strictly controlled population of 223,128 participants reinforce the efficacy of ivermectin and the demonstration of a dose-response effect.

Statements

Conflict of Interest –

None of the authors have received any money from any organization that had any material, financial or intellectual property gain from ivermectin. None of the organizations that one or more authors participate, including the Front-Line COVID-19 Critical Care (FLCCC) Alliance, Canadian Covid Care Alliance (CCCA), World Council for Health(WCH), Médicos Pela Vida (Doctors for Life) and other ones, that in common believe in the hypothesis of ivermectin as a treatment for COVID-19, have obtained any financial gain from ivermectin sales, or received money from ivermectin suppliers or manufacturers. FLCCC is a medical research and education organization, educating those interested in what research has concluded as some of the potentially most effective treatment protocols for COVID-19, used by hundreds of thousands of physicians around the world. The other organizations have similar characteristics and goals.

Dr. Lucy Kerr used ivermectin for treatment and prevention of COVID-19 and has lectured in conferences, classes, interviews and live, not charging for any of these events. She provided medical services for Vitamedic, an invermectin manufacturer.

Dr. Flavio A. Cadegiani was contracted by Vitamedic, an ivermectin manufacturer, without any collaborative relationship, exclusively for consulting services, with a budget irrespective of the response to the consulting, Dr. Cadegiani has become part of the Front Line COVID-19 Critical Care (FLCCC) Alliance in August due to his contributions related to research on anti-androgen agents for COVID-19.

Dr. Pierre Kory is the President and Chief Medical Officer of the Front Line COVID-19 Critical Care Alliance (FLCCC). He receives funds that are related to FLCCC, but the FLCCC does not profit from ivermectin, mouthwash, hydroxychlooquine, methylprednisone, melatonin, quercetin, or any of the over a dozen medicines present in FLCCC protocols. In February of 2022, he opened a private tele-health fee-based practice where he and a team of nurse practitioners evaluate and treat patients with acute COVID, long haul COVID, and post-vaccination syndromes, which is unrelated to prescriptions of ivermectin and does not reflect any benefit from prescribing ivermectin.

Dr. Jennifer Hibberd is a cofounder of the Canadian Covid Care Alliance (CCCA) and World Council for Health (WCH). At no time has she received money or anything of monetary value from any of these organizations, or in participation in any activities within or related to these organizations.

Mr. Juan J Chamie-Quintero is a data analyst living in Cambridge, USA. Mr. Chamie has been supporting the Front Line COVID-19 Critical Care Alliance (FLCCC) with epidemiological analysis on Covid since 2021 with paid consulting services. None of the companies he has worked for makes material or financial gains from the promotion of ivermectin.

Data availability statement

Datasets are publicly available at https://osf.io/uxhaf/.

Author contributions

Itajaí Ivermectin Protocol

Lucy Kerr designed the protocol of the citywide program. The local government obtained authorization at all levels to employ the program within each community and engaged health centres & local hospital to follow the program as developed.

Lucy Kerr was the principal medical responsible for the program and monitored the centers, adequacy of implementation of the protocol and resulting records remotely, through local coordinators and regular meetings.

Washington Luiz Olivato Assagra and Fernando Carlos Proença developed the computer program to collect detailed data and medical information on all study participants,

Data was compiled and ran though the computer program developed by Washington Luiz Olivato Assagra, Fernando Carlos Proença and Raysildo Barbosa Lôbo.

Study

After the approval of the ethics committee for the analysis of the data from the program, the retrospective study of the prospectively collected data was performed.

Flávio A. Cadegiani organized the full data in multiple datasets, according to different characteristics, directed and coordinated of all directions and types of statistical analysis to be employed.

Flávio A. Cadegiani performed all pre-matching non-adjusted analysis and calculated all pre-matching frequencies for COVID-19 infection, hospitalization, and mortality rates, and for risk of dying from COVID-19.

Fernando Baldi performed all pre-matching multivariate adjusted analysis and respective frequencies, performed propensity score matching (PSM) for all head-to-head group comparisons for hospitalization and mortality rates, and performed all PSM adjusted analysis and respective frequencies.

Flávio A. Cadegiani interpreted all statistical analysis, analyzed the results from the statistical analysis, transmitted all results to the manuscript, and wrote the body of all the preliminary versions of the present manuscript.

Lucy Kerr and Jennifer Hibberd performed extensive reviews and editing of all versions of the manuscript, thoroughly depicting each section of the article, and contributing with further insights from the analysis.

A second independent layer of review round was independently performed by Pierre Kory and by Juan J Chamie.

Flávio A. Cadegiani performed the last review before the submission.

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 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.

References

1. Mastrangelo E, Pezzullo M, De Burghgraeve T, et al. Ivermectin is a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity: new prospects for an old drug. J Antimicrob Chemother. 2012 Aug;67(8):1884-94. doi: 10.1093/jac/dks147. Epub 2012 Apr 25. PMID: 22535622; PMCID: PMC3888155.
2. Wagstaff KM, Sivakumaran H, Heaton SM, Harrich D, Jans DA. Ivermectin is a specific inhibitor of importin α/β-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. Biochem J. 2012 May 1;443(3):851-6. doi: 10.1042/BJ20120150. PMID: 22417684; PMCID: PMC3327999.
3. 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.
4. 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.
5. Li N, Zhao L, Zhan X. Quantitative proteomics reveals a broad-spectrum antiviral property of ivermectin, benefiting for COVID-19 treatment. J Cell Physiol. 2021 Apr;236(4):2959-2975. doi: 10.1002/jcp.30055. Epub 2020 Sep 22. PMID: 32959892; PMCID: PMC7536980.
6. 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
7. Yang JS, Qi W, Farias-Pereira R, Choi S, Clark JM, Kim D, Park Y. Permethrin and ivermectin modulate lipid metabolism in steatosis-induced HepG2 hepatocyte. Food Chem Toxicol. 2019 Mar;125:595-604. doi: 10.1016/j.fct.2019.02.005. Epub 2019 Feb 6. PMID: 30738135; PMCID: PMC6527113.
8. 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
9. 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
10. 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
11. 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. doi: 10.1016/j.chom.2020.05.008. Epub 2020 May 27. PMID: 32464097; PMCID: PMC7255347.

12. 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.
13. Zaidi AK, 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
14. 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
15. Wang K, Gao W, Dou Q, et al. Ivermectin induces PAK1-mediated cytostatic autophagy in breast cancer. Autophagy. 2016 Dec;12(12):2498-2499. doi: 10.1080/15548627.2016.1231494. Dou Q, Chen HN, Wang K, et al. Ivermectin Induces Cytostatic Autophagy by Blocking the PAK1/Akt Axis in Breast Cancer. Cancer Res. 2016 Aug 1;76(15):4457-69. doi: 10.1158/0008-5472.CAN-15-2887. Epub 2016 Jun 14. PMID: 27302166.
16. 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
17. 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
18. Andersson U, Ottestad W, Tracey KJ. Extracellular HMGB1: a therapeutic target in severe pulmonary inflammation including COVID-19? Mol Med. 2020 May 7;26(1):42. doi: 10.1186/s10020-020-00172-4. PMID: 32380958; PMCID: PMC7203545.
19. Yan S, Ci X, Chen N, et al. Anti-inflammatory effects of ivermectin in mouse model of allergic asthma. Inflamm Res. 2011 Jun;60(6):589-96. doi: 10.1007/s00011-011-0307-8. Epub 2011 Jan 29. PMID: 21279416.
20. 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.
21. 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.
22. 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
23. 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.
24. 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.
25. Kerr L, Cadegiani FA, Baldi F, Lobo RB, Assagra WLO, Proença FC, Kory P, Hibberd JA, Chamie-Quintero JJ. Ivermectin Prophylaxis Used for COVID-19: A Citywide, Prospective, Observational Study of 223,128 Subjects Using

Propensity Score Matching. Cureus. 2022 Jan 15;14(1):e21272. doi: 10.7759/cureus.21272.
26. https://itajai.sc.gov.br/noticias/59/boletins-coronavirus#.Yev0oi35Q_U (Last accessed July 8, 2022)
27. https://pesquisa.bvsalud.org/portal/resource/pt/lil-528899 (Last accessed July 8, 2022)
28. https://www.itfglobal.org/sites/default/files/resources-files/HIV_AIDS_portworkers.pdf (Last accessed January 22, 2021)
29. Eichler HG, Pignatti F, Schwarzer-Daum B, Hidalgo-Simon A, Eichler I, Arlett P, Humphreys A, Vamvakas S, Brun N, Rasi G. Randomized Controlled Trials Versus Real World Evidence: Neither Magic Nor Myth. Clin Pharmacol Ther. 2021 May;109(5):1212-1218. doi: 10.1002/cpt.2083.
30. Wang SV, Schneeweiss S, Gagne JJ, Evers T, Gerlinger C, Desai R, Najafzadeh M. Using Real-World Data to Extrapolate Evidence From Randomized Controlled Trials. Clin Pharmacol Ther. 2019 May;105(5):1156-1163. doi: 10.1002/cpt.1210.
31. Franklin JM, Schneeweiss S. When and How Can Real World Data Analyses Substitute for Randomized Controlled Trials? Clin Pharmacol Ther. 2017 Dec;102(6):924-933. doi: 10.1002/cpt.857.

View publication stats