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Strictly regular use of ivermectin as prophylaxis for COVID-19 leads to a 90% reduction in COVID-19 mortality rate, in a dose-response manner: definitive results of a prospective observational study of a strictly controlled 223,128 population from a city-wide program in Southern Brazil.

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
[7]Data Analysis, Universidad EAFIT, Cambridge, USA
[8]Front-Line Covid-19 Critical Care Alliance (FLCCC), USA
[9]Corpometria Institute, Brasilia, Brazil

***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

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Abstract

Background: Previously, we demonstrated that ivermectin use as prophylaxis for COVID-19 was associated with reductions in COVID-19 infection, hospitalization, and mortality rates, and in the risk of dying from COVID-19, irrespective of regularity and accumulated use of ivermectin, in an observational, prospectively obtained data from a strictly controlled city-wide program in a city in Southern Brazil (Itajaí, SC, Brazil) of medically-based, optional use of ivermectin as prophylaxis for COVID-19. In this study, our objective was to explore the data obtained from the program to evaluate whether the level of regularity of ivermectin use impacted in the reductions in these outcomes, aiming to determine if ivermectin showed a progressive dose- and regularity-response in terms of protection from COVID-19 and COVID-19 related outcomes.

Materials and methods: This is a prospective observational study of the program mention above, that used ivermectin at a dose of 0.2mg/kg/day for two consecutive days, every 15 days. We obtained and analyzed the data regarding the accumulated dose of ivermectin use, in addition to age and comorbidities, to analyze the patterns of reduction of COVID-19 infection, hospitalization, and mortality rates, and risk of dying from COVID-19, according to the regularity and amount of ivermectin used in a 5-month period. Following definitions of regularity, we considered as strictly regular subjects that used at least 180mg of ivermectin (180mg = 30 tablets), and as sporadic users subjects that used 60mg (= 10 tablets) or less during the 5-month period. Comparisons between subjects that did not use ivermectin and these two levels of regularity of ivermectin use were performed. Analysis of the intermediate levels of ivermectin use are present in the supplement appendix of this study. To analyze hospitalization and mortality rates, we utilized the database of COVID-19 infections of all participants, from Itajaí and outside. To analyze COVID-19 infection rate and risk of dying from COVID-19 we utilized the Itajaí city database. Propensity score matching (PSM) was employed, followed by multivariate adjusted analysis for residual differences (doubly adjusted analysis).

Results: COVID-19 infection rate within the city of Itajaí was 49% lower among strict users [283/8,325 cases; 3.40% infection rate) than in non-users [3,034/45,716 cases; 6.64% infection rate) [risk ratio (RR), 0.51; 95% confidence interval, 0.45 – 0.58; $p < 0.0001$], and 25% lower compared to sporadic users (1,542/33,971 cases; 4.54% infection rate) (RR, 0.75; 95%CI 0.66 – 0.85; $p < 0.0001$), and sporadic users had 32% lower infection rate than non-users (RR, 0.68; 95%CI, 0.64 – 0.73; $p < 0.0001$).

Of the 7,345 cases of COVID-19, 3,034 cases in non-users, 1,627 cases in sporadic users (1,542 cases from Itajaí 85 cases from outside Itajaí), and 289 in strict users (283 cases from Itajaí six cases from outside Itajaí), while the remaining cases occurred in the intermediate levels of ivermectin use. Strict users were older ($p < 0.0001$) and non-significant higher prevalence of type 2 diabetes and hypertension. Hospitalization rate was reduced by 100% in strict users, compared to non-users and to sporadic users, both before and after PSM (RR, 0.00; 95%CI, not applicable; $p < 0.0001$). After PSM, hospitalization rate was 35% lower among sporadic users than non-users (RR, 0.65; 95%CI, 0.44 – 0.70; $p = 0.03$). In propensity score matched groups ($n = 289$ in each group between non-users and strict users, and between sporadic users and strict users, and $n = 1,627$ between non-users and sporadic users), multivariate-adjusted mortality rate was 90% lower in strict users compared to non-users (RR, 0.10, 95%CI, 0.02 – 0.45; $p = 0.003$) and 79% lower than in sporadic users (RR, 0.21; RR, 0.04 – 1.00; $p = 0.05$), while sporadic users had a 37% reduction in mortality rate compared to non-users (RR, 0.63; 95%CI, 0.41 – 0.99; $p = 0.043$). Risk of dying from COVID-19 was 86% lower among strict users than non-users (RR, 0.14; 95%CI, 0.03 – 0.57; $p = 0.006$) and marginally significant, 72% lower than sporadic users (RR, 0.28; 95%CI, 0.07 – 1.18; $p = 0.083$), while sporadic 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 10-times increase in mortality risk and 7-times increased risk of dying from COVID-19, compared to strictly regular use of ivermectin in a prospectively collected, strictly controlled population. A progressive dose-response pattern was observed between level of ivermectin use and level of protection from COVID-19 related outcomes, and was consistent across different levels of ivermectin use.

Introduction

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

Based on the absence of therapeutical and preventive alternative options in 2,020, and on the extensive, well-established safety profile and known absence or risks with long-term use of ivermectin, a city-wide program in a city in Southern Brazil (Itajaí, state of Santa Catarina) offered a medically-prescribed program of ivermectin as prophylaxis for COVID-19 between July and December of 2020.

Previously, as resulted from the systematically collected data from this program, we have shown that ivermectin use as prophylaxis for COVID-19 improved COVID-19 related-outcomes, leading to a 44% reduction in infection rate, 56% reduction in hospitalization rate, and 68% reduction in mortality rates, employing propensity score matching (PSM) to balance groups [25].

These conclusions were based on an analogue analysis of intent-to-treat (ITT) analysis of randomized clinical trials (RCTs), i.e., all participants of the program were included for analysis, irrespective of regularity of ivermectin use and total amount of ivermectin used. Among participants of the program of ivermectin use as prophylaxis for COVID-19, whether regular ivermectin use would lead to more substantial reductions in COVID-19 infection rate and related outcomes is unknown.

In this study, we aimed to evaluate, among subjects that used ivermectin prophylactically for COVID-19, whether its regular use, when compared to non-regular use, impacted in the level of reduction in COVID-19 infection, hospitalization, and mortality rates.

Materials and Methods

Study population

A thorough description of the program, study population and study protocol are described elsewhere [25]. This was an observational study of a citywide program of medical-based, voluntary ivermectin as prophylaxis for COVID-19 that occurred between July 7, 2020 and December 2, 2020, in the city of Itajaí, in the state of Santa Catarina, Brazil. Data collected prospectively and systematically, as per the mandatory reporting of all events upon their occurrence.

Study design, institutional review board (IRB) approval, and data analysis occurred after completion of the program. The study 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

Optional, voluntary prophylactic use of ivermectin was offered to patients during medical visits in a provisional outpatient clinic setting in the Convention Center of Itajaí and secondary outpatient settings in 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, use of 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 prescribed optionally, whenever not contraindicated, in a dose of 0.2mg/kg/day for two consecutive days, every 15 days.

During the study, subjects who became infected with COVID-19 were diagnosed with a positive rtPCR-SARS-CoV-2 were registered and medically followed up, without use of any specific drug, except to relieve symptoms. Data on hospitalizations and deaths due to COVID-19 were also registered systematically.

For the present analysis, all subjects from the city of Itajaí were considered, including those who participated in the program and used ivermectin prophylactically and those that did not participate in the program. Subjects that had the diagnosis of COVID-19 before July 7, 2020 and below 18 years old were excluded from the both samples of ivermectin users and non-users. Registry data from all subjects included in the sample were analyzed.

Of the 223,128 subjects from the city of Itajaí, 114,568 subjects above 18 years old used ivermectin prophylactically through the citywide program, among which 113,844 subjects were not infected until July 7, 2020, and 45,716 subjects above 18 years old did not use ivermectin. Additionally, 8,352 subjects above 18 years old from other cities participated in the program.

While ivermectin non-users remained unchanged from the first analysis [25], ivermectin users were divided two groups: of definitely irregular users, possibly irregular users, possibly regular users, and definitively regular users. Categories were established according to the accumulated number of ivermectin tablets used regularly, uninterruptedly, of one to 10, 11 to 20, 21 to 29, and 30 or more tablets, respectively. Definitively and possibly irregular users were then grouped as 'irregular users', while possibly and definitively were grouped as 'regular users'.

Due to uncertainties regarding the exact level of regularity in the possibly regular and possibly irregular users, we focused on the analysis of definitively irregular (until 10 tablets – including participants that used 10 tablets) and definitively regular (at least 30 tablets – including participants that used 30 tablets), since these groups represent a higher certainty of irregularity and regularity, respectively. These groups were compared to non-users, *i.e.,* this study is a three-group comparison analysis.

The three two-group combinations, of ivermectin non-users and definitely regular users, non-users and definitely irregular users, and definitely irregular users and definitely regular users, were balanced and matched between them using PSM, using the following variables: age, sex, smoking, history of myocardial infarction (MI) and stroke, and presence of hypertension, type 2 diabetes (T2D), cardiovascular diseases (CVD), cancer

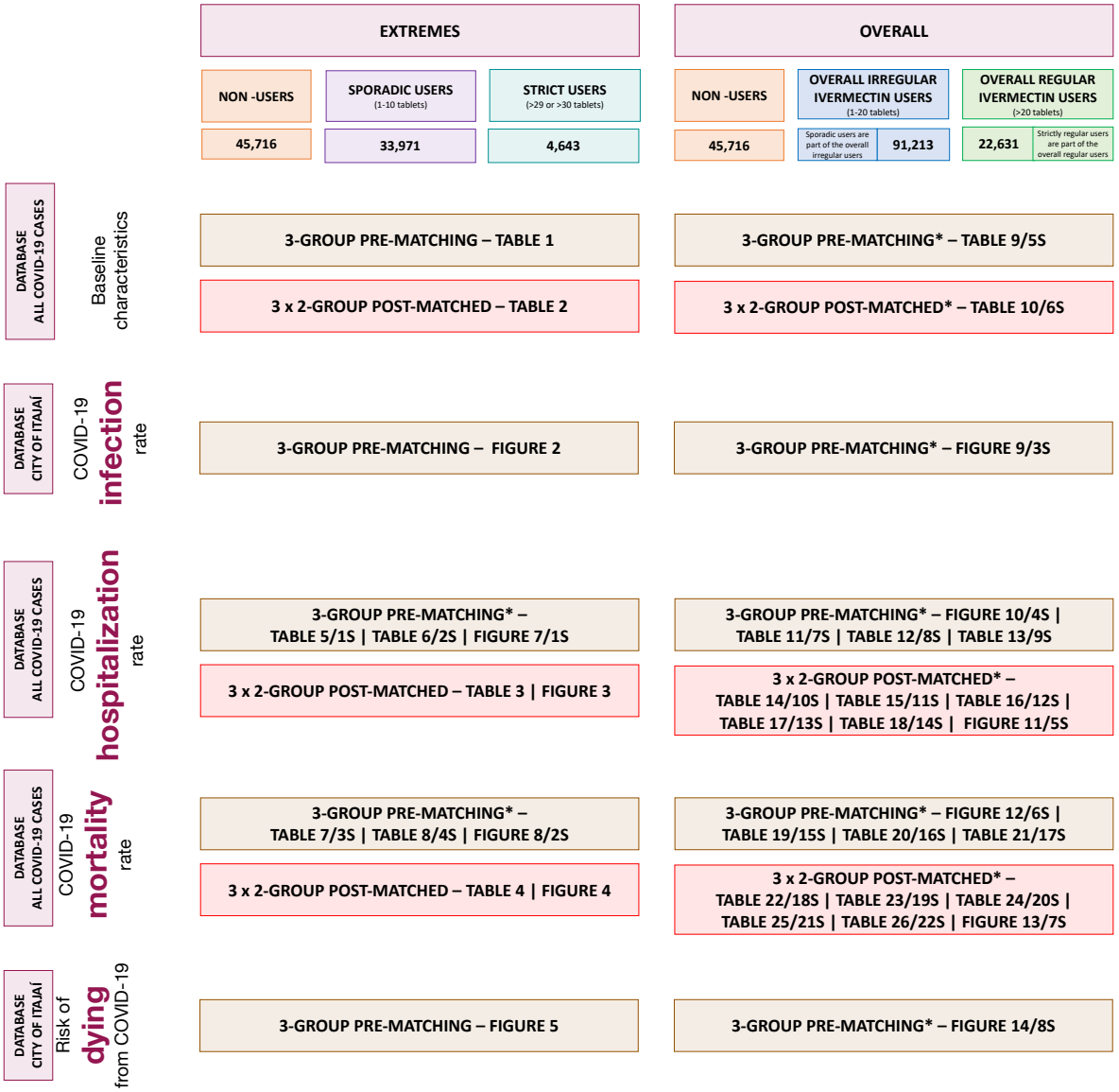
(any type), asthma, chronic obstructive pulmonary disease (COPD) and other pulmonary diseases.

The analysis of hospitalization and mortality rates considered all participants, from Itajaí and outside, once upon the report of the diagnosis of COVID-19, follow-up of all cases, including mandatory reports of the COVID-19 related outcomes, was performed, irrespective of the city of origin, i.e., hospitalization and mortality rate was calculated over the reported cases only. To analyze these rates, we used the propensity score matched groups, followed by multivariate adjusted analysis of the residual differences (doubly adjusted model).

The analysis of infection rates considered the cases among inhabitants of the city of Itajaí only, since the precision of the registry of the reports could only be guaranteed for inhabitants of the city. Correspondingly, the analysis of the chances of dying from COVID-19, i.e., among ivermectin non-users and among ivermectin users, what was the resulting number of deaths due to COVID-19, irrespective of the number of cases reported, was based on the registry data of the city of Itajaí. Hence, the database used for the calculation of the risk of dying from COVID-19 was of participants from the city of Itajaí only.

In **Supplement Appendix 1**, we provide the comparisons of the overall groups of irregular and regular users. In **Figure 1**, we illustrate the locations of each analysis performed in this study. **Dataset**s are publicly available at https://osf.io/uxhaf/.

Figure 1. Illustrative guide for this study.



*Supplement Appendix 1

Statistical analysis

Risk of hospitalization and death were calculated for all three groups before matching and for the resulting groups after each of the three two-group matghing. Comparisons between groups for hospitalization and mortality rates were calculated using Chi-Square before adjusting for variables and after multivariate adjustments, employing a generalized linear mixed model, assuming the binomial distribution for the residues and including the

fixed classificatory effects of each of the variables. While there were no missing data, as per the system, illogical data were corrected individually after searching for the accurate data. Statistical Analysis Software (SAS/STAT) (SAS Institute Inc., Care, North Carolina, USA) was used for the present study.

Results

Of the 159,560 subjects above 18 years old from the city of Itajaí that were not infected until July 7, 2020, 45,716 (28.7%) did not use and 113,844 (71.3%) used ivermectin prophylactically. Of the 113,844 participants, 91,212 used ivermectin irregularly (80.1% of the participants), from which 33,970 used sporadically (29.8% of the participants). Conversely, 22,631 subjects used ivermectin regularly (19.9% of the participants), from which 4,643 used strictly regularly (4.1% of the participants).

Before matching, a total of 7,345 subjects that were infected by COVID-19 between July 7, 2020 and December 12, 2020, included. Of these, 3,034 did not use ivermectin prophylactically (41.3%), 3,392 used ivermectin irregularly (46.2%) (from which 1,627 used sporadically), and 919 used ivermectin regularly (12.5%), among which 289 used strictly regularly. A summary of the findings is present in **Figure 1**, which includes COVID-19 infection, hospitalization and mortality rates, and chances of dying from COVID-19, across different levels of ivermectin use, including ivermectin non-users, sporadic (definitively irregular) users, overall irregular users (that contains sporadic users within the group), overall regular users (that contains strictly regular users within the group), and strictly (definitively) regular users. Comparisons between overall regular ivermectin users, overall irregular ivermectin users, and non-users are present in **Supplement Appendix 1**. Comparisons between ivermectin non-users, sporadic (definitively irregular) users, and strictly regular (definitively regular) users are described below.

Baseline characteristics

Table 1 describes the baseline characteristics of the groups of ivermectin non-users (n = 3,034), ivermectin sporadic users (n = 1,627), and ivermectin strictly regular users (n = 289), before matching groups. Age was significantly different across groups of levels of ivermectin use $p < 0.0001$). Ivermectin strictly regular users had a higher percentage of subjects above 50 years old (39.8%) than sporadic users (29.2%) and non-users (20.0%), while there were fewer subjects below 30 years old among strictly regular users (13.8%) than among sporadic users (25.6%) and non-users (27.8%).

All other baseline characteristics were numerical but not statistically different. There were slightly more males among strictly regular users (50.2%) than sporadic users (44.6%) and non-users (46.5%) ($p = 0.17$). The percentage of subjects with type 2 diabetes was numerically higher among strictly regular users (3.1%) than sporadic users (2.6%) and non-users (2.1%) ($p = 0.35$). Hypertension was more prevalent in strictly regular users (8.0%) than sporadic users (6.1%) and non-users (5.5%) ($p = 0.18$).

Table 1. Pre-matching baseline characteristics of ivermectin non-users, sporadic users, and strictly regular users.

Characteristic	**NON-USERS (n = 3,034)**	**SPORADIC USERS (n = 1,627)**	**STRICTLY REGULAR USERS (n = 289)**	p-value
Age				
Mean (SD)	39.8 ± 14.2	41.0 ± 14.4	46.9 ± 14.2	
Age				< 0.0001
< 30 y/o	844 (27.8%)	416 (25.6%)	40 (13.8%)	
30-50 y/o	1,582 (52.2%)	817 (50.2%)	134 (46.4%)	
> 50 y/o	608 (20.0%)	394 (29.2%)	115 (39.8%)	
Sex				0.17
Female	1,624 (53.5%)	901 (55.4%)	144 (49.8%)	
Male	1,410 (46.5%)	726 (44.6%)	145 (50.2%)	
Race				0.089
Afro-Brazilian	100 (3.3%)	43 (2.6%)	4 (1.4%)	

Mixed	682 (22.5%)	392 (24.1%)	61 (21.1%)	
Caucasian	2,192 (72.5%)	1,159 (71.2%)	224 (77.5%)	
Asian-Brazilian	60 (51.7%)	33 (2.0%)	0 (0.0%)	
Type 2 diabetes				0.35
Yes	63 (2.1%)	42 (2.6%)	9 (3.1%)	
No	2,971 (97.9%)	1,585 (97.4%)	280 (96.9%)	
Hypertension				0.18
Yes	166 (5.5%)	100 (6.1%)	23 (8.0%)	
No	2,868 (94.5%)	1,527 (93.9%)	266 (92.0%)	
Asthma				0.35
Yes	6 (0.2%)	7 (0.4%)	0 (0.0%)	
No	3,028 (99.8%)	1,620 (99.6%)	289 (100.0%)	
COPD				0.68
Yes	6 (0.2%)	2 (0.1%)	1 (0.3%)	
No	3,028 (99.8%)	1,625 (99.9%)	288 (99.7%)	
Other respiratory diseases				0.79
Yes	5 (0.2%)	3 (0.2%)	1 (0.3%)	
No	3,029 (99.8%)	1,624 (99.8%)	288 (99.7%)	
Cardiovascular diseases				0.15
Yes	15 (0.5%)	16 (1.0%)	2 (0.7%)	
No	3,019 (99.5%)	1,611 (99.0%)	287 (99.3%)	
Cancer				0.72
Yes	12 (0.4%)	6 (0.4%)	2 (0.7%)	
No	3,022 (99.6%)	1,621 (99.6%)	287 (99.3%)	
Smoking				0.78
Yes	47 (1.5%)	24 (1.5%)	3 (1.0%)	
No	2,987 (98.5%)	1,603 (98.5%)	286 (99.0%)	
History of stroke				0.66
Yes	10 (0.3%)	3 (0.2%)	1 (0.3%)	
No	3,024 (99.7%)	1,624 (99.8%)	288 (99.7%)	
History of MI				0.66
Yes	4 (0.1%)	3 (0.2%)	0 (0.0%)	
No	3,030 (99,9%)	1,624 (99.8%)	289 (100.0%)	

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

Table 2 describes the baseline characteristics of ivermectin non-user and strictly regular user matched groups, ivermectin non-user and ivermectin sporadic matched groups, and ivermectin sporadic and ivermectin strictly regular user matched groups. After balancing and matching between each of the three combinations of two groups

(non-users and strictly regular users, non-users and sporadic users, and sporadic and strictly regular users), there were 289 subjects in each group (n = 578) between non-users and strictly regular users and between sporadic and strictly regular users, and 1,627 in each group (n = 3,254) between non-users and sporadic users, with similar baseline characteristics.

Table 2. Baseline characteristics of the prophylactic study after propensity score matching (post-matching) between non-users and strictly regular users, non-users and sporadic users, and sporadic users and strictly regular users.

	NON-USERS PAIRED WITH STRICTLY REGULAR IVERMECTIN USERS		**NON-USERS PAIRED WITH SPORADIC IVERMECTIN USERS**		**SPORADIC IVERMECTIN USERS PAIRED WITH STRICTLY REGULAR IVERMECTIN USERS**	
Variable	Non-users (n = 289)	Strictly regular users (n = 289)	Non-users (n = 1,627)	Sporadic users (n = 1,627)	Sporadic users (n = 289)	Strictly regular users (n = 289)
Age						
Mean (SD)	41.4 ± 14.0	46.9 ± 14.2	40.1 ± 14.7	41.0 ± 14.4	42.5 ± 15.3	46.9 ± 14.2
Age						
< 30 y/o	65 (22.5%)	40 (13.8%)	455 (28.0%)	416 (25.6%)	70 (24.2%)	40 (13.8%)
30-50 y/o	162 (56.1%)	134 (46.4%)	831 (51.1%)	817 (50.2%)	137 (47.4%)	134 (46.4%)
> 50 y/o	62 (21.5%)	115 (39.8%)	341 (20.9%)	394 (24.2%)	82 (28.4%)	115 (39.8%)
Sex						
Female	160 (55.4%)	144 (49.8%)	891 (54.8%)	901 (55.4%)	160 (54.3%)	144 (49.8%)
Male	129 (44.6%)	145 (50.2%)	736 (45.2%)	726 (44.6%)	132 (45.7%)	145 (50.2%)
Race						
Afro-Brazilian	11 (3.8%)	4 (1.4%)	49 (3.0%)	43 (2.6%)	26 (2.8%)	26 (2.8%)
Mixed	57 (19.7%)	61 (21.1%)	362 (22.3%)	392 (24.1%)	220 (23.9%)	175 (19.0%)
Caucasian	219 (75.8%)	224 (77.5%)	1,186 (72.9%)	1,159 (71.2%)	664 (72.3%)	711 (77.4%)
Asian-Brazilian	2 (0.7%)	0 (0.0%)	30 (1.8%)	33 (2.0%)	9 (1.%)	7 (0.8%)
Type 2 diabetes						
Yes	7 (2.4%)	9 (3.1%)	44 (2.7%)	42 (2.6%)	6 (2.1%)	9 (3.1%)
No	282 (97.6%)	280 (96.9%)	1,583 (97.3%)	1,585 (97.4%)	283 (97.9%)	280 (96.9%)
Hypertension						
Yes	16 (5.5%)	23 (8.0%)	99 (6.1%)	100 (6.2%)	15 (5.2%)	23 (8.0%)
No	273 (94.5%)	266 (92.0%)	1,528 (93.9%)	1,527 (93.8%)	274 (94.8%)	266 (92.0%)
Asthma						
Yes	0	0	5 (0.3%)	7 (0.4%)	0	0

No	289 (100.0%)	289 (100.0%)	1,622 (99.7%)	1,620 (99.6%)	289 (100.0%)	289 (100.0%)
COPD						
Yes	2 (0.7%)	1 (0.4%)	4 (0.2%)	2 (0.1%)	0	1 (0.3%)
No	287 (99.3%)	288 (99.6%)	1,623 (99.8%)	1,625 (99.9%)	289 (100.0%)	288 (99.7%)
Other respiratory diseases						
Yes	1 (0.4%)	1 (0.4%)	3 (0.2%)	3 (0.2%)	0	1 (0.3%)
No	288 (99.6%)	288 (99.6%)	1,624 (99.8%)	1,624 (99.8%)	289 (100.0%)	288 (99.7%)
Cardiovascular diseases						
Yes	2 (0.7%)	2 (0.7%)	13 (0.8%)	16 (1.0%)	2 (0.7%)	2 (0.7%)
No	287 (99.3%)	287 (99.3%)	1,614 (99.2%)	1,611 (99.0%)	287 (99.3%)	287 (99.3%)
Cancer						
Yes	2 (0.7%)	2 (0.7%)	8 (0.5%)	6 (0.4%)	1 (0.3%)	2 (0.7%)
No	287 (99.3%)	287 (99.3%)	1,619 (99.5%)	1,621 (99.6%)	288 (99.7%)	287 (99.3%)
Smoking						
Yes	1 (0.4%)	3 (1.0%)	29 (1.8%)	24 (1.5%)	2 (0.7%)	3 (1.0%)
No	288 (99.6%)	286 (99.0%)	1,598 (99.2%)	1,603 (98.5%)	287 (99.3%)	286 (99.0%)
History of stroke						
Yes	1 (0.4%)	1 (0.4%)	4 (0.3%)	3 (0.2%)	0	1 (0.3%)
No	288 (99.6%)	288 (99.6%)	1,623 (99.7%)	1,624 (99.8%)	289 (100.0%)	288 (99.7%)
History of MI						
Yes	1 (0.4%)	0 (0.0%)	3 (0.2%)	3 (0.2%)	0	0
No	288 (99.6%)	289 (100.0%)	1,624 (99.8%)	1,624 (99.8%)	289 (100.0%)	289 (100.0%)

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

Infection rates

Figure 2. Impact of use of ivermectin use on infection rates during the full period in the first half, and in the second half of the program in sporadic users, strictly regular users, and non-users.

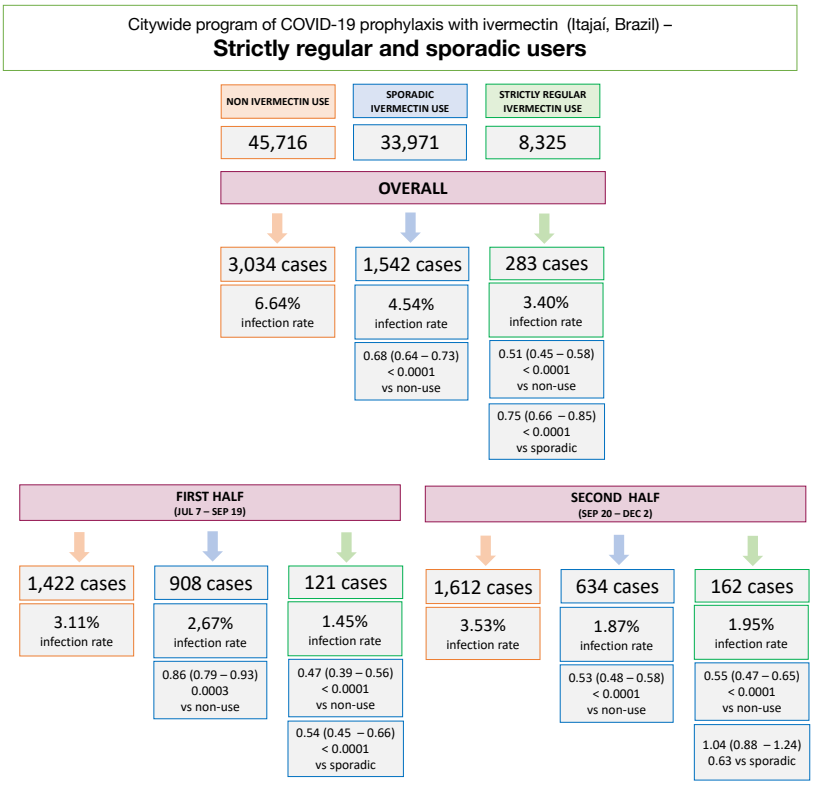


Figure 2 illustrates infection rates in ivermectin non-users, sporadic users, and strict users, during the overall period, in the first half period, and in the second half of the period of the program . During the period of the program, infection rate among ivermectin non-users was 6.64% (3,034/45,716 infections). Sporadic ivermectin users had a 32% lower infection rate than non-users [1,542/33,971 cases; 4.54% infection rate; risk ratio (RR) versus non-users, 0.68; 95% confidence interval (95%CI), 0.64 – 0.73); $p < 0.0001$]. Ivermectin strictly regular users had a reduction of 49% in infection rate compared to non-users (283/8,325 cases; 3.40% infection rate; RR versus non-users, 0.51; 95%CI 0.45 – 0.58; $p < 0.0001$). Ivermectin strict users had a non-significant 25% lower infection rate than sporadic 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, 2020 and September 19, 2020, infection rate was 3.11% among ivermectin non-users (1,422 cases), 2.67% among ivermectin sporadic users (908 cases), a 14% reduction compared to non-users (RR, 0.86; 95%CI 0.79 – 0.93; $p = 0.0003$), and 1.45% among ivermectin strictly regular users (121 cases), a 53% reduction compared to non-users (RR, 0.47; 95%CI 0.39 – 0.56; $p < 0.0001$). Strict users had 46% lower infection rate than sporadic users (RR, 0.54; 95%CI, 0.45 – 0.66; $p < 0.0001$).

In the second half of the program, between September 20, 2020 and December 2, 2020, infection rate was 3.53% among ivermectin non-users (1,612 cases), 1.87% among ivermectin sporadic users (634 cases), a 47% reduction in infection rate compared to non-users (RR, 0.53; 95%CI 0.48 – 0.58; $p < 0.0001$), and 1.95% among ivermectin strictly regular users (162 cases), a 45% reduction in infection rate compared to non-users (RR, 0.55; 95%CI 0.47 – 0.65; $p < 0.0001$). Strict users had similar infection rate than sporadic users during the second half of the period of the program (RR, 1.04; 95%CI, 0.88 – 1.24; $p = 0.63$).

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

Hospitalization rates before matching are described in **Supplement Appendix 1** (**Tables 5/1S** and **6/2S**, and **Figure 6/1S**). **Table 3** describes the hospitalization rates and unadjusted and multivariate-adjusted values for each of the three two-group comparisons after balancing and matching. **Figure 3** illustrates the differences in hospitalization rates in overall and in major subpopulations between matched groups. Balanced and matched groups of non-users and strictly regular users showed 14 hospitalizations among non-users (4.8% hospitalization rate) and zero hospitalizations among strictly 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 sporadic and strictly regular users (289 subjects in each group), there were eight hospitalizations among sporadic users (2.8% hospitalization rate) and zero hospitalizations among strictly regular users (0.0% hospitalization rate), a 100% reduction after adjustment for variables (RR, 0.00; 95% CI, n/a, $p < 0.0001$). Between non- and sporadic users ($n = 1,627$ in each group), there were 63 hospitalizations among non-users (3.9% hospitalization rate) and 41 hospitalizations among sporadic ivermectin users (2.5% hospitalization rate), a 35% reduction (RR, 0.65; 95%CI, 0.44 – 0.96; $p = 0.03$). Precise comparisons between subpopulations of strictly regular users and non-users and between strictly regular users and sporadic users were precluded due to lack of hospitalizations between strictly regular users, as observed in **Table 3**.

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

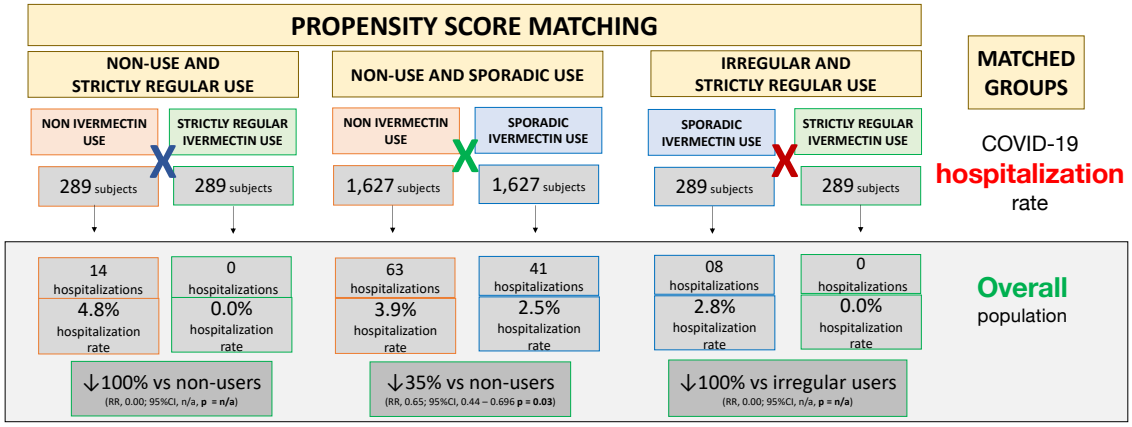


Table 3. Hospitalization rates in two-group matched groups of non-users and regular ivermectin users, non-users and irregular ivermectin users, and irregular and regular ivermectin users.

HOSPITALIZATION RATES												
	NON-USERS AND STRICTLY REGULAR USERS				NON-USERS AND SPORADIC USERS				SPORADIC AND STRICTLY REGULAR USERS			
	PROPENSITY SCORE MATCHED GROUPS		NON-USERS VERSUS STRICTLY REGULAR USERS		PROPENSITY SCORE MATCHED GROUPS		PROPENSITY SCORE MATCHED GROUPS		NON-USERS VERSUS STRICTLY REGULAR USERS		PROPENSITY SCORE MATCHED GROUPS	
Population	**Ivermectin non-users (n = 289)**	**Strictly regular ivermectin users (n = 289)**	Unadjusted hospital risk ratio (95%CI) and p-value [p]	Multivariate adjusted hospital risk ratio (95%CI) and p-value [p]	**Ivermectin non-users (n = 1,627)**	**Sporadic ivermectin users (n = 1,627)**	Unadjusted hospital risk ratio (95%CI) and p-value [p]	Multivariate adjusted hospital risk ratio (95%CI) and p-value [p]	**Sporadic ivermectin users (n = 289)**	**Strictly regular ivermectin users (n = 289)**	Unadjusted hospital risk ratio (95%CI) and p-value [p]	Multivariate adjusted mortality risk ratio (95%CI) and p-value [p]
Overall	14/289 (4.8%)	0/289 (0.0%)	0.03 (0.002 – 0.58) [0.019]	0.00 (n/a) [< 0.0001]	63/1,627 (3.9%)	41/1,627 (2.5%)	0.65 (0.44 – 0.96) [0.03]	0.65 (0.44 – 0.96) [0.03]	8/289 (2.8%)	0/289 (0.0%)	0.06 (0.003 – 1.01) [0.051]	0.00 (n/a) [< 0.0001]
Age												
< 30 y/o	0/65 (0.0%)	0/40 (0.0%)	1.61 (0.03 – 79.6) [0.81]	1.00 (n/a) [1.00]	0/455 (0.0%)	1/416 (2.4%)	3.28 (0.13 – 80.3) [0.47]	> 1000 (>1000) [< 0.001]	0/70 (0.0%)	0/40 (0.0%)	1.73 (0.04 – 65.6) [0.78]	1.00 (n/a) [1.00]
30-50 y/o	4/162 (2.5%)	0/134 (0.0%)	0.13 (0.01 – 2.47) [0.18]	0.00 (n/a) [0.99]	17/831 (2.0%)	7/817 (0.9%)	0.42 (0.17 – 1.00) [0.051]	0.42 (0.18 – 1.01) [0.053]	1/137 (0.7%)	0/134 (0.0%)	0.34 (0.01 – 8.29) [0.51]	n/a
> 50 y/o	10/62 (16.1%)	0/115 (0.0%)	0.03 (0.002 – 0.43) [0.011]	0.00 (0.00 – 0.00) [< 0.001]	46/341 (13.5%)	33/394 (8.4%)	0.62 (0.41 – 0.95) [0.027]	0.59 (0.38 – 0.92) 0.019]	7/82 (8.6%)	0/115 (0.0%)	0.05 (0.003 – 0.82) [0.036]	n/a
Sex												

Female	6/160 (3.8%)	0/144 (0.0%)	0.09 (0.005 – 1.50) [0.093]	0.00 (0.00 – 0.00) [< 0.001]	29/891 (3.3%)	19/901 (2.1%)	0.65 (0.37 – 1.15) [0.14]	0.60 (0.35 – 1.05) [0.074]	6/157 (3.8%)	0/144 (0.0%)	0.08 (0.005 – 1.47) [0.09]	n/a
Male	8/129 (6.2%)	0/145 (0.0%)	0.05 (0.003 – 0.90) [0.042]	0.00 (0.00 – 0.00) [< 0.001]	34/736 (4.6%)	22/726 (3.0%)	0.66 (0.39 – 1.11) [0.12]	0.54 (0.32 – 0.91) [0.021]	2/132 (1.5%)	0/145 (0.0%)	0.18 (0.009 – 3.76) [0.27]	n/a
Race												
Afro-Brazilian	1/11 (9.1%)	0/4 (0.0%)	0.80 (0.04 – 16.5) [0.089]	n/a	2/49 (4.1%)	0/43 (0.0%)	0.23 (0.01 – 4.61) [0.33]	0.00 (0.00 – 0.00) [< 0.0001]	0/4 (0.0%)	0/4 (0.0%)	1.00 (0.02 – 41.2) [1.00]	1.00 (n/a) [1.00]
Mixed	1/57 (1.8%)	0/61 (0.0%)	0.31 (0.01 – 7.50) [0.47]	n/a	14/362 (3.9%)	11/392 (2.8%)	0.73 (0.33 – 1.58) [0.42]	0.68 (0.32 – 1.44) [0.31]	2/76 (2.6%)	0/61 (0.0%)	0.25 (0.01 – 5.08) [0.37]	n/a
Caucasian	12/219 (5.5%)	0/224 (0.0%)	0.04 (0.002 – 0.66) [0.024]	n/a	47/1,186 (4.0%)	29/1,159 (2.5%)	0.63 (0.40 – 0.99) [0.048]	0.54 (0.34 – 0.85) [0.007]	6/205 (2.9%)	0/224 (0.0%)	0.07 (0.004 – 1.24) [0.007]	n/a
Asian-Brazilian	0/2 (0.0%)	0/0	3.00 (0.12 – 73.6) [0.50]	n/a	0/30 (0.0%)	1/33 (3.3%)	2.74 (0.12 – 64.7) [0.53]	n/a [0.99]	0/4 (0.0%)	0/0	5.00 (0.19 – 132.8) [0.34]	n/a
Type 2 diabetes												
Yes	5/7 (71.4%)	0/9 (0.0%)	0.07 (0.005 – 1.13) [0.061]	0.00 (0.00 – 0.00) [< 0.001]	10/44 (22.7%)	3/42 (7.1%)	0.31 (0.099 – 1.06) [0.063]	0.49 (0.14 – 1.63) [0.24]	0/6 (0.0%)	0/9 (0.0%)	0.70 (0.02 – 31.3) [0.85]	1.00 (n/a) [1.00]
No	9/282 (3.2%)	0/280 (0.0%)	0.05 (0.003 – 0.91) [0.043]	0.00 (0.00 – 0.00) [< 0.001]	53/1,583 (3.3%)	38/1,585 (2.4%)	0.72 (0.48 – 1.08) [0.11]	0.58 (0.39 – 0.87) [0.008]	8/283 (2.8%)	0/280 (0.0%)	0.06 (0.003 – 1.03) [0.052]	n/a]
Hypertension												
Yes	5/16 (31.3%)	0/23 (0.0%)	0.06 (0.004 – 1.09) [0.057]	0.06 (0.002 – 2.26) [0.13]	18/99 (18.2%)	10/100 (10.0%)	0.55 (0.27 – 1.13) [0.10]	0.43 (0.20 – 0.94) [0.034]	0/15 (0.0%)	0/23 (0.0%)	0.67 (0.01 – 31.9) [0.84]	1.00 (n/a) [1.00]
No	9/273 (3.3%)	0/266 (0.0%)	0.05 (0.003 – 0.92) [0.044]	0.34 (0.078 – 1.50) [0.16]	45/1,528 (2.9%)	31/1,527 (2.0%)	0.69 (0.44 – 1.08) [0.11]	0.63 (0.40 – 0.97) 0.037]	8/274 (2.9%)	0/266 (0.0%)	0.07 (0.004 – 1.23) [0.069]	n/a
Asthma												
Yes	0/0	0/0	n/a	n/a [1.00]	0/5 (0.0%)	1/7 (14.3%)	2.25 (0.11 – 46.1) [0.60]	141.5 (n/a) [0.62]	0/0	0/0	n/a	n/a
No	14/289 (4.8%)	0/289 (0.0%)	0.03 (0.002 – 0.58) [0.019]	0.00 (0.00 – 0.00) [< 0.001]	63/1,622 (3.9%)	40/1,620 (2.5%)	0.64 (0.43 – 0.94) [0.022]	0.56 (0.38 – 0.82) [0.003]	8/289 (2.8%)	0/289 (0.0%)	0.06 (0.003 – 1.01) [0.051]	n/a
COPD												
Yes	1/2 (50.0%)	0/1 (0.0%)	0.50 (0.04 – 7.10) [0.61]	0.00 (0.00 – 0.00) [< 0.001]	0/4 (0.0%)	1/2 (50.0%)	5.00 (0.29 – 87.5) [0.27]	773.5 (n/a) [0.70]	0/0	0/1 (0.0%)	0.50 (0.02 – 11.1) [0.66]	n/a [1.00]
No	13/287 (4.5%)	0/288 (0.0%)	0.04 (0.002 – 0.62) [0.022]	0.00 (0.00 – 0.00) [< 0.001]	63/1,622 (3.9%)	40/1,625 (2.5%)	0.63 (0.43 – 0.94) [0.022]	0.55 (0.37 – 0.81) [0.002]	8/289 (2.8%)	0/288 (0.0%)	0.06 (0.003 – 1.02) [0.051]	n/a
Other respiratory diseases												
Yes	1/1 (100.0%)	0/1 (0.0%)	0.33 (0.03 – 4.19) [0.39]	0.00 (n/a) [< 0.001]	0/3 (0.0%)	0/3 (0.0%)	1.00 (0.03 – 39.1) [1.00]	0.16 (0.11 – 0.23) [< 0.0001]	0/0	0/1 (0.0%)	0.50 (0.02 – 11.1) [0.66]	n/a [1.00]
No	13/288 (4.5%)	0/288 (0.0%)	0.04 (0.002 – 0.62) [0.022]	0.00 (0.00 – 0.00) [< 0.001]	63/1,624 (3.9%)	41/1,624 (2.5%)	0.65 (0.44 – 0.96) [0.03]	0.57 (0.39 – 0.83) [0.004]	8/289 (2.8%)	0/288 (0.0%)	0.06 (0.003 – 1.02) [0.051]	n/a
Cardiovascular diseases												
Yes	1/2 (50.0%)	0/2 (0.0%)	0.33 (0.02 – 5.33) [0.44]	0.00 (n/a) [< 0.001]	3/13 (23.1%)	1/16 (6.3%)	0.27 (0.03 – 2.31) [0.23]	0.07 (0.003 – 1.60) [0.097]	0/2 (0.0%)	0/2 (0.0%)	1.00 (0.03 – 35.8) [1.00]	1.00 (n/a) [1.00]
No	13/287 (4.5%)	0/287 (0.0%)	0.04 (0.002 – 0.62) [0.022]	0.00 (0.00 – 0.00) [< 0.001]	60/1,614 (3.7%)	40/1,611 (2.5%)	0.63 (0.42 – 0.93) [0.021]	0.60 (0.41 – 0.88) [0.009]	8/287 (2.8%)	0/287 (0.0%)	0.06 (0.003 – 1.01) [0.051]	n/a
Cancer												
Yes	0/2 (0.0%)	0/2 (0.0%)	1.00 (0.03 – 35.8) [1.00]	n/a [1.00]	1/8 (12.5%)	0/6 (0.0%)	0.43 (0.02 – 9.00) [0.59]	0.00 (n/a) [0.98]	0/1 (0.0%)	0/2 (0.0%)	0.67 (0.02 – 21.8) [0.82]	n/a [1.00]

No	14/287 4.9%)	0/287 (0.0%)	0.03 (0.002 – 0.58) [0.019]	0.00 (0.00 – 0.00) [< 0.001]	62/1,619 (3.8%)	41/1,621 (2.5%)	0.66 (0.45 – 0.97) [0.036]	0.57 (0.39 – 0.84) [0.005]	8/288 (2.8%)	0/287 (0.0%)		n/a
Smoking												
Yes	0/1 (0.0%)	0/3 (0.0%)	0.50 (0.01 – 17.1) [0.70]	n/a [1.00]	1/29 (3.4%)	0/24 (0.0%)	0.40 (0.02 – 9.39) [0.57]	0.00 (n/a) [0.98]	0/2 (0.0%)	0/3 (0.0%)	0.75 (0.02 – 28.1) [0.88]	1.00 (n/a) [1.00]
No	14/288 4.9%)	0/286 (0.0%)	0.03 (0.002 – 0.58) [0.019]	0.00 (0.00 – 0.00) [< 0.001]	62/1,598 (3.9%)	41/1,603 (2.6%)	0.65 (0.43 – 0.97) [0.036]	0.58 (0.39 – 0.84) [0.005]	8/287 (2.8%)	0/286 (0.0%)	0.06 (0.003 – 1.02) [0.051]	n/a
History of stroke												
Yes	1/1 (100.0%)	0/1 (0.0%)	0.33 (0.03 – 4.19) [0.39]	0.01 (0.001 – 0.05) [< 0.0001]	1/4 (25.0%)	0/3 (0.0%)	0.42 (0.02 – 7.71) [0.56]	0.00 (n/a) [0.98]	0/0	0/1 (0.0%)	0.50 (0.02 – 11.1) [0.66]	n/a [1.00]
No	13/288 (4.5%)	0/288 (0.0%)	0.04 (0.002 – 0.62) [0.022]	0.08 (0.01 – 0.47) [0.005]	62/1,623 (3.8%)	41/1,624 (2.5%)	0.66 (0.45 – 0.97) [0.037]	0.58 (0.39 – 0.85) [0.005]	8/289 (2.8%)	0/288 (0.0%)	0.06 (0.003 – 1.02) [0.051]	n/a
History of MI												
Yes	1/1 (100.0%)	0/0	0.67 (0.08 – 5.54) [0.71]	0.00 (n/a) [< 0.001]	1/3 (33.3%)	1/3 (33.3%)	1.00 (0.10 – 9.61) [1.00]	0.07 (0.002 – 3.56) [0.19]	0/0	0/0	n/a	n/a
No	13/288 (4.5%)	0/289 (0.0%)	0.04 (0.002 – 0.62) [0.022]	0.00 (0.00 – 0.00) [< 0.001]	62/1,624 (3.8%)	40/1,624 (2.5%)	0.65 (0.44 – 0.95) [0.028]	0.59 (0.40 – 0.87) [0.007]	8/289 (2.8%)	0/289 (0.0%)	0.06 (0.003 – 1.01) [0.051]	n/a

MI = myocardial infarction; COPD = chronic obstructive pulmonary disease; y/o = years old; CI = confidence interval; n/a = not applicable

Mortality rates among ivermectin strictly regular users, sporadic users, and non-users

Mortality rates in ivermectin non-, sporadic, and strictly regular users before matching are described in **Supplement Appendix 1** (**Tables 7/3S** and **8/4S**, and Figure **7/2S**). In **Table 4** and **Figure 4** mortality rates between each of the three combinations of post-matched groups, of ivermectin non-users and strictly regular users, of sporadic and strictly regular users, and of non-users and sporadic users, are described.

Between matched groups of non-users and strictly regular users (n=289 in each group), mortality rate was 3.8% among non-users (11 deaths) and 0.7% (two deaths) among strictly regular users, a 90% reduction in mortality rate (RR, 0.10; 95%CI 0.02 – 0.45; p = 0.003). Compared to non-users, reductions in mortality rate among strictly regular users were 100% among females (six deaths among 160 non-users and zero deaths among 144 strictly regular users; RR, 0.00; 95%CI n/a; p < 0.0001), 81% among males (five deaths among 129 non-users and two deaths among strict users; RR, 0.19; 95%CI 0.04 – 0.94; p = 0.043), 89% reduction among subjects above 50 years old (10 deaths

among 62 non-users and two deaths among 115 strict users; RR, 0.11; 95%CI 0.02 – 0.48; p = 0.004), 86% reduction among subjects with type 2 diabetes (six deaths among seven non-users and one death among nine strict users; RR, 0.14; 95%CI 0.02 – 0.93; p = 0.042), and 88% among subjects with hypertension (five deaths among 16 non-users and one death among 23 strict users; RR 0.12; 95%CI 0.02 – 0.88; p = 0.037). Reductions were also significant in lower-risk populations (below 50 years old and/or without comorbidities).

When groups of strict users and sporadic users are matched (289 subjects in each group), there were 2.4% and 0.7% mortality rate among sporadic and among strict users (seven deaths and two deaths, respectively), a multivariate-adjusted 79% reduction in mortality rate (RR, 0.21; 95%CI 0.04 – 1.00; p = 0.05). Mortality rate was 1.9% among non-user females (4/157 deaths) and 0.0% among strict user females (out of 144 females). There were three deaths among 132 non-user males (2.3% mortality rate) and two deaths among strict user males (1.4% mortality rate), a non-significant reduction of 67% in mortality rate (RR, 0.33; 95%CI, 0.05 – 1.95; p = 0.22). Reduction in mortality rate was 80% when above 50 years old (six deaths among 82 non-users and two deaths among 115 strict users; RR, 0.20; 95%CI 0.04 – 1.01; p = 0.052), while was not determined for subjects with type 2 diabetes or with hypertension, since there was only one death among strict users and no deaths among non-users in these two subpopulations.

Between matched groups of non-users and sporadic users (n=1,627 in each group), there were 43 deaths among non-users (2.6% mortality rate) and 31 deaths among sporadic users (1.9% mortality rate), a 37% reduction in mortality rate (RR compared to non-users, 0.63; 95%CI, 0.41 – 0.99; p = 0.043). Reductions in mortality rate occurred among females (39%; 25 deaths among 891 female non-users and 16 deaths among female sporadic users; RR, 0.61; 95%CI, 0.33 – 1.11; p = 0.11), males (31%; 18 deaths among 736 male non-users and 15 deaths among 726 male sporadic users; RR, 0.69; 95%CI, 0.35 – 1.33; p = 0.27), subjects above 50 y/o (34%; 39 deaths among 341 non-users and 29 deaths among sporadic users; RR, 0.66; 95%CI, 0.41 – 1.04; p = 0.074), subjects with type 2 diabetes (49%; 10 deaths among 44 non-users and three deaths among 42 sporadic users; RR, 0.51; 95%CI, 0.15 – 1.72; p = 0.28), and subjects with hypertension (60%; 18 deaths among 99 non-users and eight deaths among 100 sporadic

users; RR, 0.40; 95%CI, 0.18 – 0.90; p = 0.027). In subpopulations without comorbidities reductions in mortality rates were between 35% and 40%.

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

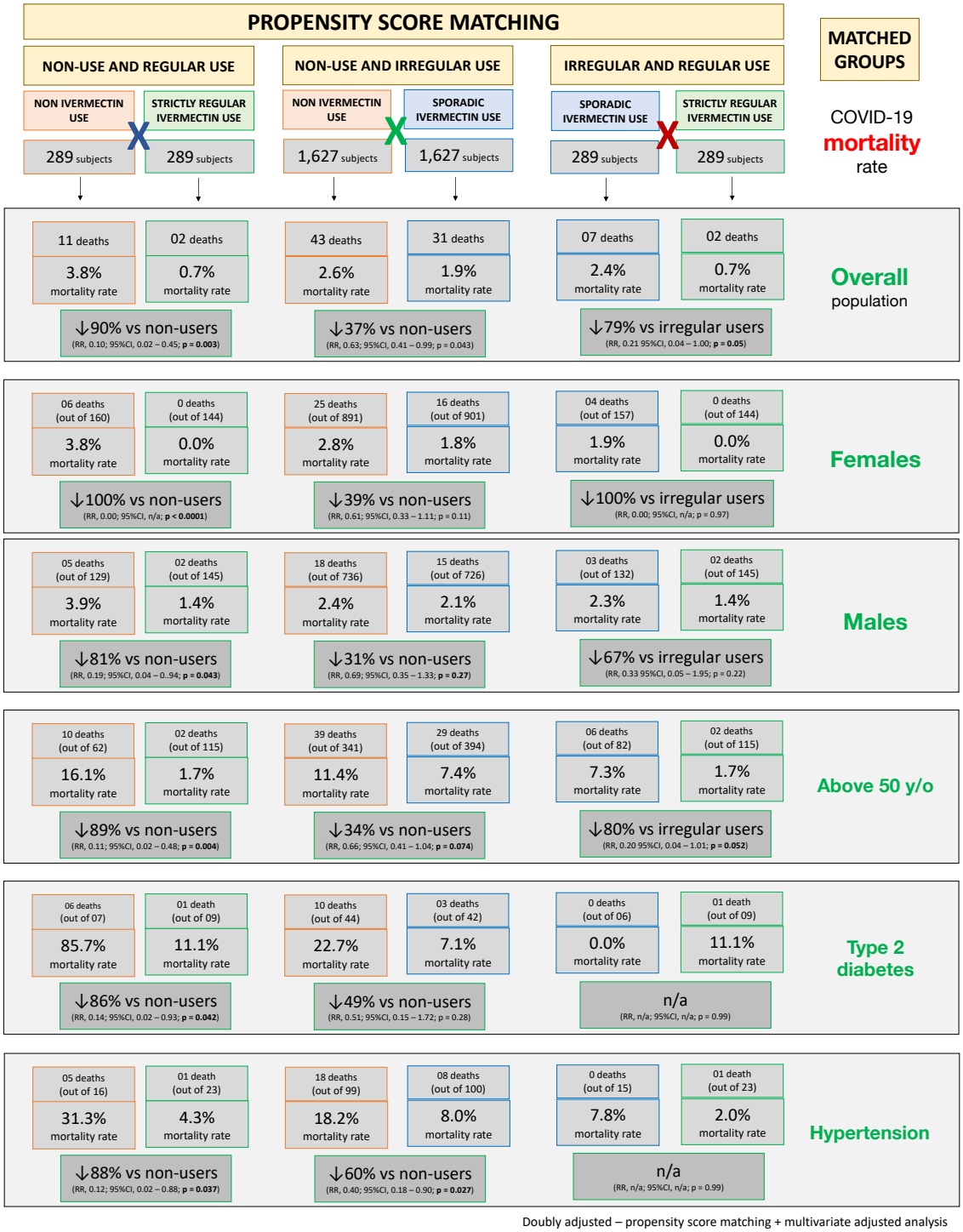


Table 4. Mortality rates in two-group matched groups of non-users and regular ivermectin users, non-users and irregular ivermectin users, and irregular and regular ivermectin users.

HOSPITAL RATES	NON-USERS AND STRICTLY REGULAR USERS			NON-USERS AND SPORADIC USERS			SPORADIC AND STRICTLY REGULAR USERS		
	PROPENSITY SCORE MATCHED GROUPS		NON-USERS VERSUS STRICTLY REGULAR USERS	PROPENSITY SCORE MATCHED GROUPS		NON-USERS VERSUS SPORADIC USERS	PROPENSITY SCORE MATCHED GROUPS		SPORADIC VERSUS STRICTLY REGULAR USERS
Population	**Ivermectin non-users (n = 289)**	**Strictly regular ivermectin users (n = 289)**	Multivariate adjusted hospital risk ratio (95%CI) and p-value [p]	**Ivermectin non-users (n = 1,627)**	**Sporadic ivermectin users (n = 1,627)**	Multivariate adjusted hospital risk ratio (95%CI) and p-value [p]	**Sporadic ivermectin users (n = 289)**	**Strictly regular ivermectin users (n = 289)**	Multivariate adjusted mortality risk ratio (95%CI) and p-value [p]
Overall	11/289 (3.8%)	2/289 (0.7%)	0.10 (0.02 – 0.45) [0.003]	43/1,627 (2.6%)	31/1,627 (1.9%)	0.63 (0.41 – 0.99) [0.043]	7/289 (2.4%)	2/289 (0.7%)	0.21 (0.04 – 1.00) [0.05]
Age									
< 30 y/o	0/65 1.7(0.0%)	0/40 (0.0%)	n/a [1.00]	0/455 (0.0%)	0/416 (0.0%)	1.20 (0.75 – 1.90) [0.45]	0/70 (0.0%)	0/40 (0.0%)	1.07 (n/a) [1.00]
30-50 y/o	1/162 (0.6%)	0/134 (0.0%)	0.00 (n/a) [0.97]	4/831 (0.5%)	2/817 (0.2%)	0.51 (0.09 – 2.79) [0.44]	1/137 (0.7%)	0/134 (0.0%)	0.00 (n/a) [0.97]
> 50 y/o	10/62 (16.1%)	2/115 (1.7%)	0.11 (0.02 – 0.48) [0.004]	39/341 (11.4%)	29/394 (7.4%)	0.66 (0.41 – 1.04) [0.074]	6/82 (7.3%)	2/115 (1.7%)	0.20 (0.04 – 1.01) [0.052]
Sex									
Female	6/160 (3.8%)	0/144 (0.0%)	0.00 (0.00 – 0.00) [< 0.0001]	25/891 (2.8%)	16/901 (1.8%)	0.61 (0.33 – 1.11) [0.11]	4/157 (1.9%)	0/144 (0.0%)	0.00 (n/a) [0.97]
Male	5/129 (3.9%)	2/145 (1.4%)	0.19 (0.04 – 0.94) [0.043]	18/736 (2.4%)	15/726 (2.1%)	0.69 (0.35 – 1.33) [0.27]	3/132 (2.3%)	2/145 (1.4%)	0.33 (0.05 – 1.95) [0.22]
Race									
Afro-Brazilian	1/11 (9.1%)	0/4 (0.0%)	n/a	2/49 (4.1%)	0/43 (0.0%)	n/a [0.98]	0/4 (0.0%)	0/4 (0.0%)	n/a
Mixed	0/57 (0.0%)	0/61 (0.0%)	n/a	9/362 (2.5%)	7/392 (1.8%)	0.68 (0.26 – 1.73) [0.41]	2/76 (2.6%)	0/61 (0.0%)	n/a
Caucasian	10/219 (4.6%)	2/224 (0.9%)	n/a	32/1,176 (2.7%)	23/1,159 (2.0%)	0.64 (0.38 – 1.08) [0.095]	5/205 (2.4%)	2/224 (0.9%)	n/a
Asian-Brazilian	0/2 (0.0%)	0/0	n/a	0/30 (0.0%)	1/32 (3.1%)	n/a [0.99]	0/4 (0.0%)	0/0	n/a
Type 2 diabetes									
Yes	6/7 (85.7%)	1/9 (11.1%)	0.14 (0.02 – 0.93) [0.042]	10/44 (22.7%)	3/42 (7.1%)	0.51 (0.15 – 1.72) [0.28]	0/6 (0.0%)	1/9 (11.1%)	n/a [0.99]
No	5/282 (1.8%)	1/280 (0.4%)	0.12 (0.01 – 0.98) [0.048]	33/1,583 (2.1%)	28/1,585 (1.8%)	0.67 (0.41 – 1.09) [0.11]	7/283 (2.5%)	1/280 (0.4%)	0.10 (0.01 – 0.82) [0.032]
Hypertension									
Yes	5/16 (31.3%)	1/23 (4.3%)	0.12 (0.02 – 0.88) [0.037]	18/99 (18.2%)	8/100 (8.0%)	0.40 (0.18 – 0.90) [0.027]	0/15 (0.0%)	1/23 (4.3%)	n/a [0.99]
No	6/273 (22.0%)	1/266 (0.4%)	0.10 (0.01 – 0.78) [0.029]	25/1,528 (1.6%)	23/1,527 (1.5%)	0.82 (0.47 – 1.41) [0.47]	7/274 (2.6%)	1/266 (0.4%)	0.10 (0.01 – 0.77) [0.028]
Asthma									
Yes	0/0	0/0	n/a	1/5 (20.0%)	1/7 (14.3%)	2.75 (0.03 – 273.1) [0.67]	0/0	0/0	n/a
No	11/289 (3.8%)	2/289 (0.7%)	n/a	42/1,622 (2.6%)	30/1,620 (1.8%)	0.63 (0.40 – 0.99) [0.043]	7/289 (2.4%)	2/289 (0.7%)	n/a
COPD									

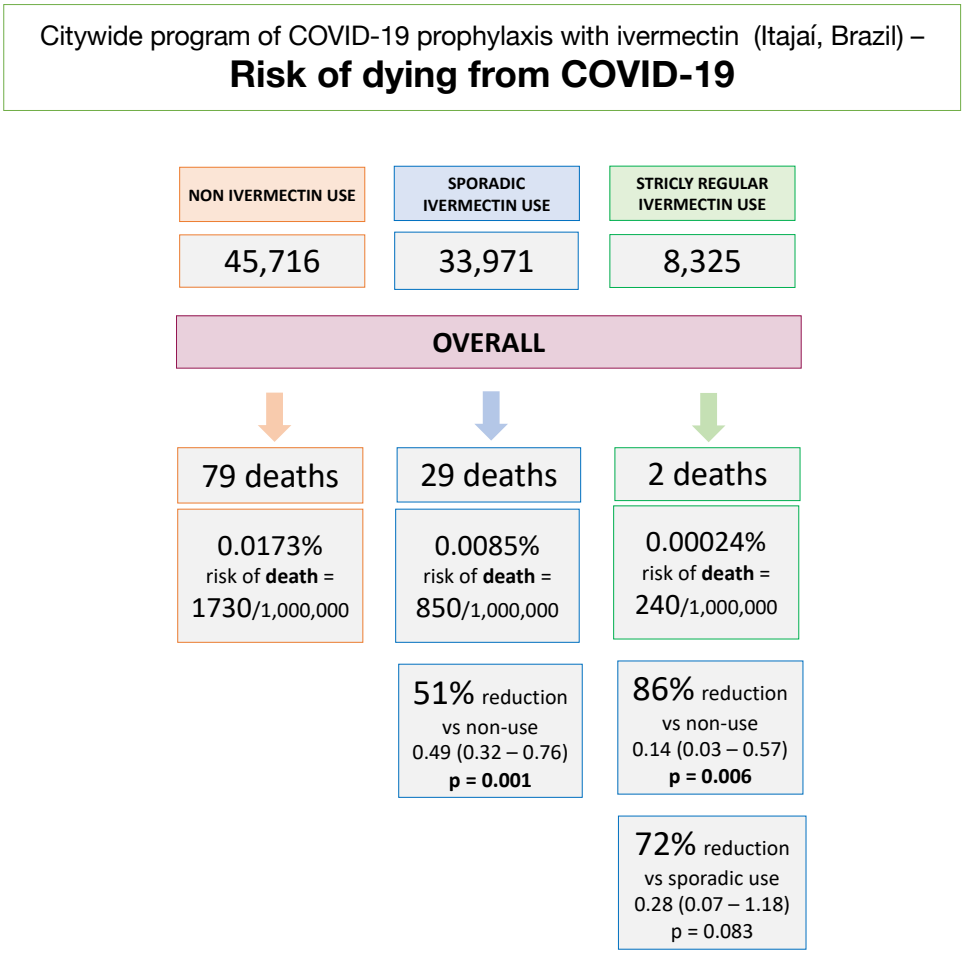
Yes	1/2 (50.0%)	0/1 (0.0%)	0.00 (n/a) [1.00]	0/4 (0.0%)	1/2 (50.0%)	2644.9 (n/a) [0.81]	0/0	0/1 (0.0%)	0.18 (0.04 – 0.89) [0.035]
No	10/287 (3.5%)	2/288 (0.7%)	0.11 (0.02 – 0.49) [0.004]	43/1,623 (2.6%)	30/1,625 (1.8%)	0.62 (0.40 – 0.97) [0.035]	7/289 (2.4%)	2/288 (0.7%)	n/a
Other respiratory diseases									
Yes	0/1 (0.0%)	0/1 (0.0%)	n/a [1.00]	0/3 (0.0%)	0/3 (0.0%)	0.07 (0.04 – 0.10) [< 0.0001]	0/0	0/1 (0.0%)	n/a
No	11/288 (3.8%)	2/288 (0.7%)	0.10 (0.02 – 0.46) [0.003]	43/1,624 (2.6%)	31/1,624 (1.9%)	0.46 (0.41 – 1.01) [0.053]	7/289 (2.4%)	2/288 (0.7%)	n/a
Cardiovascular diseases									
Yes	1/2 (50.0%)	0/2 (0.0%)	0.00 (n/a) [0.99]	1/13 (7.7%)	0/16 (0.0%)	0.00 (n/a) [0.99]	0/2 (0.0%)	0/2 (0.0%)	1.64 (n/a) [1.00]
No	10/287 (3.5%)	2/287 (0.7%)	0.11 (0.03 – 0.50) [0.004]	42/1,604 (2.6%)	31/1,611 (1.9%)	0.66 (0.42 – 1.03) [0.067]	7/287 (2.4%)	2/287 (0.7%)	0.18 (0.04 – 0.89) [0.035]
Cancer									
Yes	0/2 (0.0%)	0/2 (0.0%)	n/a [1.00]	1/8 (12.5%)	0/6 (0.0%)	0.00 (n/a) [< 0.0001]	0/1 (0.0%)	0/2 (0.0%)	n/a [1.00]
No	11/287 (3.8%)	2/287 (0.7%)	0.10 (0.02 – 0.47) [0.003]	42/1,619 (2.6%)	31/1,621 (1.9%)	0.65 (0.42 – 1.92) [0.064]	7/288 (2.4%)	2/287 (0.7%)	0.18 (0.04 – 0.89) [0.035]
Smoking									
Yes	0/1 (0.0%)	0/3 (0.0%)	n/a [1.00]	1/29 (3.4%)	0/24 (0.0%)	n/a [0.99]	0/2 (0.0%)	0/3 (0.0%)	1.18 (n/a) [0.98]
No	11/288 (3.8%)	2/286 (0.7%)	0.10 (0.02 – 0.45) [0.003]	42/1,598 (2.6%)	31/1,603 (1.9%)	0.66 (0.42 – 1.03) [0.068]	7/287 (2.4%)	2/286 (0.7%)	0.65 (0.42 – 1.02) [0.061]
History of stroke									
Yes	1/1 (100.0%)	0/1 (0.0%)	0.01 (0.002 – 0.03) [< 0.0001]	1/3 (33.3%)	0/3 (0.0%)	0.00 (n/a) [< 0.0001]	0/0	0/1 (0.0%)	0.18 (0.04 – 0.89) [0.035]
No	10/288 (3.5%)	2/288 (0.7%)	0.13 (0.03 – 0.56) [0.006]	42/1,624 (2.6%)	31/1,624 (1.9%)	0.66 (0.42 – 1.04) [0.071]	7/289 (2.4%)	2/288 (0.7%)	n/a [1.00]
History of MI									
Yes	1/1 (100.0%)	0/0 (0.0%)	n/a	0/3 (0.0%)	0/3 (0.0%)	0.15 (0.10 – 0.23) [< 0.0001]	0/0	0/0	n/a
No	10/288 (3.5%)	2/289 (0.7%)	n/a	43/1,624 (2.6%)	31/1,624 (1.9%)	0.64 (0.41 – 1.01) [0.053]	7/289 (2.4%)	2/289 (0.7%)	n/a

MI = myocardial infarction; COPD = chronic obstructive pulmonary disease; y/o = years old; CI = confidence interval; n/a = not applicable

Risk of dying from COVID-19 among ivermectin strict users, sporadic users, and non-users

Considering the population and participants of Itajaí, as well as inhabitants of Itajaí that 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, 850 among sporadic users, and 240 among strict users. Compared to non-users, the risk of dying from COVID-19 was 86% lower in strict users (RR, 0.14; 95%CI, 0.03 – 0.57; p = 0.006) and 51% lower in sporadic users (RR, 0.49; 95%CI, 0.32 – 0.76; p = 0.001). Compared to sporadic users, risk of dying from COVID-19 was 72% lower in strict 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, sporadic users, and strict users.



Comparisons between overall regular users, overall irregular users, and non-users.

Comparisons between overall regular users, which encompass subjects that used more than 20 tablets within five months of program, including strict users (30 or more tablets) and possibly regular users (21 to 29 tablets), overall irregular users, which encompass subjects that used 20 or less tablets, including sporadic users (1 to 10 tablets) and possibly irregular users (11 to 20 tablets) are described in Supplement Appendix 1 for unmatched and matched baseline characteristics (**Tables 9/5S** and **10/6S**, respectively), infection rates (Figure 8/3S), hospitalization rates before matching (**Tables 11/7S**, **12/8S** and **13/9S**, and **Figure 9/4S**) and after matching (**Tables 14/10S**, **15/11S**, **16/12S**, **17/13S** and

18/14S, and **Figure 10/5S**), and mortality rates before matching (**Tables 19/15S**, **20/16S** and **21/17S**, and **Figure 11/6S**) and after matching (**Tables 22/18S**, **23/19S**, **24/20S**, **25/21S** and **26/22S**, and **Figure 12/7S**).

Discussion

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

The present study provides further results on the prospective program of ivermectin as prophylaxis for COVID-19 in the city of Itajaí, located in Southern Brazil. Particularities of the city of Itajaí, including its dynamic population due to the presence of an proportionally overwhelmingly large port (compared to the size of the city) with a dynamic population, possibly justify why the city was amongst the first cities in the state to reach 1,000 cases in 2,020 [26]. In the past, the city experimented amongst the highest rates of HIV infections in Brazil [27], not fully related to the prevalence of intravenous or nasal drug use or percentage of males that have intercourses with males. This is speculated to be related to be at least partially explained by being a port city, an 'independent' predictor of higher prevalence of HIV infection [28].

The decision of adopting a prophylaxis program with ivermectin was based on the fact that the number of cases was raising rapidly in the city of Itajaí, at a higher speed than in other cities, the absence of pharmacological or non-pharmacological therapies for COVID-19, the inability to lock port workers and the extensive safety profile and favorable cost-effectiveness of ivermectin. Hence, the program of Itajaí using ivermectin as prophylaxis for COVID-19 has strictly followed all bioethical principles when offering, optionally, through medical doctors, ivermectin as a prophylaxis for COVID-19.

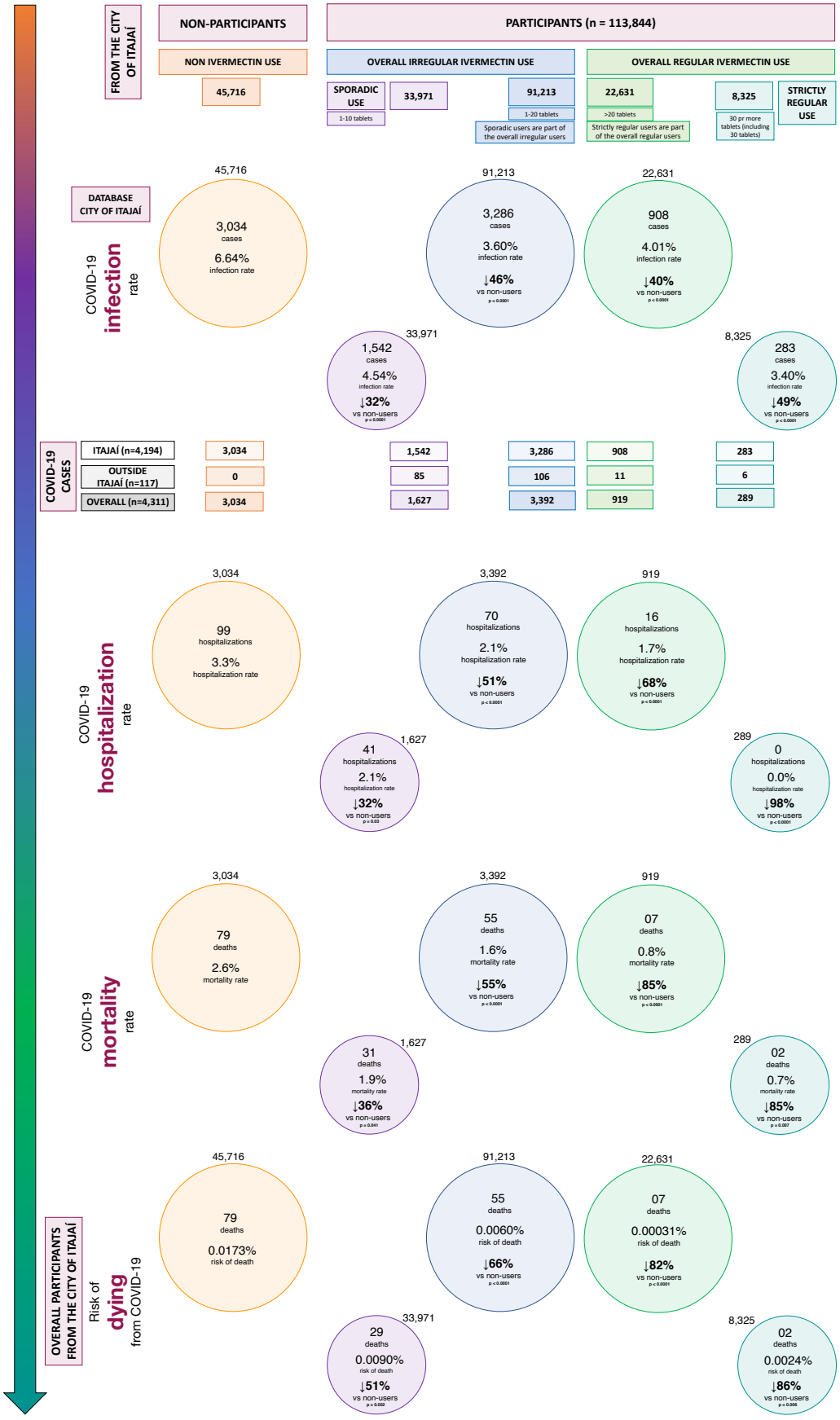
Ivermectin as a protector against all major COVID-19 outcomes: does it depend on the regularity of ivermectin use?

In our first article [25], we demonstrated that use of ivermectin, irrespective of the regularity, was associated with significant reductions of 44% in infection rate, 56% in

hospitalization rate, and 68% in mortality rate, when compared to subjects that did not use ivermectin prophylactically.

In the present study, we visited the impact of the regularity of ivermectin use in COVID-19 infection and related outcomes. In this manuscript, we analyzed users that used ivermectin sporadically, *i.e.*, no more than once, or, in some cases, twice, during a 5-month period, with subjects that used ivermectin strictly regular manner, every other week, for at least three months. We decided not to include in the manuscript subjects that used ivermectin possibly regularly (21 to 29 tablets in total) and possibly irregularly (11 to 20 tablets in total), since their patterns of use tended to be erratic, rather than definitively regular or irregular, which could preclude from more precise analysis. In the Supplement Appendix 1, we present the results of overall irregular (including both sporadic and possibly irregular) and overall regular (including strict and possibly regular) users. In both cases, groups were also compared to non-users, that were estimated from the matched population of the city of Itajaí, since 100% of the population of Itajaí is not only registered, but their COVID-19 cases, hospitalizations (in public hospitals) and all deaths due to COVID-19 are strictly followed. Figure 6 summarizes and provides an overall view of the findings of this study.

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


FROM THE CITY OF ITAJAÍ
NON-PARTICIPANTS
PARTICIPANTS (n = 113,844)
NON IVERMECTIN USE
OVERALL IRREGULAR IVERMECTIN USE
OVERALL REGULAR IVERMECTIN USE
45,716
SPORADIC USE
1-10 tablets
33,971
91,213
1-20 tablets
Sporadic users are part of the overall irregular users
22,631
>20 tablets
Strictly regular users are part of the overall regular users
8,325
30 pr more tablets (including 30 tablets)
STRICTLY REGULAR USE
DATABASE CITY OF ITAJAÍ
COVID-19 infection rate
45,716
3,034 cases
6.64% infection rate
91,213
3,286 cases
3.60% infection rate
↓46% vs non-users
22,631
908 cases
4.01% infection rate
↓40% vs non-users
33,971
1,542 cases
4.54% infection rate
↓32% vs non-users
8,325
283 cases
3.40% infection rate
↓49% vs non-users
COVID-19 CASES
ITAJAÍ (n=4,194)
OUTSIDE ITAJAÍ (n=117)
OVERALL (n=4,311)
3,034
0
3,034
1,542
85
1,627
3,286
106
3,392
908
11
919
283
6
289
COVID-19 hospitalization rate
3,034
99 hospitalizations
3.3% hospitalization rate
3,392
70 hospitalizations
2.1% hospitalization rate
↓51% vs non-users
919
16 hospitalizations
1.7% hospitalization rate
↓68% vs non-users
1,627
41 hospitalizations
2.1% hospitalization rate
↓32% vs non-users
289
0 hospitalizations
0.0% hospitalization rate
↓98% vs non-users
COVID-19 mortality rate
3,034
79 deaths
2.6% mortality rate
3,392
55 deaths
1.6% mortality rate
↓55% vs non-users
919
07 deaths
0.8% mortality rate
↓85% vs non-users
1,627
31 deaths
1.9% mortality rate
↓36% vs non-users
289
02 deaths
0.7% mortality rate
↓85% vs non-users
OVERALL PARTICIPANTS FROM THE CITY OF ITAJAÍ
Risk of dying from COVID-19
45,716
79 deaths
0.0173% risk of death
91,213
55 deaths
0.0060% risk of death
↓66% vs non-users
22,631
07 deaths
0.00031% risk of death
↓82% vs non-users
33,971
29 deaths
0.0090% risk of death
↓51% vs non-users
8,325
02 deaths
0.0024% risk of death
↓86% vs non-users

While reduction in COVID-19 infections have undisputable benefits, including reduction of transmission and perpetuation of the pandemic, reductions in hospitalization and mortality rates are at least as important since they reduce costs and pressure over the health system, and avoid the worst related outcome, respectively.

Ivermectin strict users were older (average age of almost 47 y/o) compared to sporadic users (average age = 41 y/o) and non-users (average age = 39.8 y/o), and had approximately 20% to 50% higher prevalence of type 2 diabetes and hypertension. In case ivermectin did not work, one would expect higher hospitalization and mortality rates in the group of strict users, which did not happen, as seen in the pre-matched analysis, in **Supplement Appendix 1**. In particular, there were no hospitalizations among all the 289 subjects of strict users. After matching between groups, reduction in hospitalization rate was, consequently, 100% in strict users, when compared to non-users and to sporadic users, since this group had no hospitalizations. Performance of analysis of subpopulations in these two comparisons was unfeasible due to the lack of hospitalizations in the group of strict users. Statistically significant reduction in hospitalization rate was also observed in sporadic users, when compared to non-users (35% reduction; $p = 0.03$), which was more relevant in high-risk populations: among subjects above 50 y/o (reduction of 38%; $p = 0.027$) and with comorbidities, of 69% reduction among subjects with type 2 diabetes ($p = 0.063$), 45% among subjects with hypertension ($p = 0.10$) and 73% among subjects with cardiovascular diseases ($p = 0.23$), while reductions were similar between males and females. This means that even uncontrolled, sporadic use of ivermectin is sufficient to reduce the number of hospitalizations in a determinant number of COVID-19 infections, reducing the risk of reach 100% occupancy during outbreaks.

Levels of regularity of ivermectin intake demonstrated a progressive impact in reduction of mortality rate, which was more clearly observed after matching groups, since strict ivermectin users had a reduction of 90% in mortality rate when compared to non-users ($p = 0.003$) and 79% when compared to sporadic users ($p = 0.05$), while sporadic users had a non-significant reduction of 37% compared to non-users ($p = 0.63$). In particular, women that used ivermectin strictly did not present any death, among 144 subjects. Reductions among strict users were similar (between 86% and 89%) across different high-risk populations (above 50 y/o, with comorbidities). High-risk populations

of sporadic users had reductions in mortality rate between 34% and 60% when compared to non-users.

Risk of dying from COVID-19, when considering all the population, irrespective of the COVID-19 infection rate, was notably lower among strict users, compared to both non-users (86% reduction) and sporadic users (72% reduction), and lower among sporadic users compared to non-users (51% reduction). For the chances of dying from COVID-19, since baseline characteristics were not present for non-user non-infected subjects, we were unable to adjust for variables. However, strict users were clearly at higher risk of dying from COVID-19 due to their higher age and prevalence of comorbidities.

In common, all outcomes related to COVID-19 infection demonstrated a dose-, regular-response effect, with increased reductions in all outcomes with the higher ivermectin intake. This strong correlation reinforces the causality relationship between ivermectin intake and protection not only from COVID-19, but, more importantly, from COVID-19 related outcomes. Also, although strict users still had COVID-19 cases (in a lower infection rate than non-users), these cases tended to be milder, compared to non-users or sporadic users, as observed in the almost 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 amount of ivermectin used is directly related to better prognosis. Of note, the strict control of which specific days ivermectin was used did not seem to affect the results, or, even better, in case this had been strictly controlled, results tended to be at least similar, if not better.

Although a significant dose-response was observed consistently across the extreme of groups (non-, sporadic, and strict users), unexpectedly, the risk of COVID-19 infection was not largely influenced by the regularity of ivermectin use. Possibly, the long-term actions of ivermectin that go beyond its serum or cytoplasmatic concentration may reflect the lack of differences and the lack of a progressive protection pattern with higher regularity of ivermectin use. Analyzing the data from overall regular and irregular

users (in **Supplement Appendix 1**), the lack of differences according to the level of ivermectin use is reinforced.

Indeed, considering the half-life of ivermectin and its metabolites, of no longer than 10 to 12 days, its use every 15 days, even for two consecutive days, may be questioned regarding whether this regimen could be considered as a regular use of ivermectin. However, morphological structural changes that have been demonstrated to be induced by exposure to ivermectin could explain the strong level of protection even when used in the 2-day every 15 days regimen. Also, the proposed prophylactic treatment regimen respects the already, extensively known safety profile of ivermectin, since it does not surpass the usual doses.

Noteworthy aspects of the study

The definition of regularity admits different concepts, but is basically something happening repeatedly in a fixed pattern. From this perspective, we were allowed to determine that 30 or more tablets of ivermectin throughout five months, showing at least 12 weeks of continuous ivermectin supply every other week, as criteria for regularity.

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, were could not calculate infection rate based on the participating subjects, since COVID-19 cases in subjects from other cities tended to be underreported in Itajaí. In fact, the "infection rate" of overall participants, of 1.40%, among subjects from other cities (177 cases our of 8,352 subjects), much lower than the infection rates within the city of Itajaí, is clearly underreported. Hence, we based the calculations on the subjects from Itajaí only, using the own population of Itajaí, for which COVID-19 cases were strictly controlled, as baseline for these calculations. Correspondingly, the risk of dying from COVID-19, unlike mortality rate, was not based on COVID-19 cases, but on the full population instead, since this outcome aims to evaluate the risk of an undesired outcome irrespective of how many cases occurred. For this, since the control of deaths was only strict within the population of Itajaí, subjects from Itajaí only were considered, also based on the population of Itajaí

for the calculation, from which the number of non-users and users (and levels or regularity of ivermectin use) could be determined.

Conversely, hospitalization rates and mortality rates were tracked from the reported COVID-19 cases, whether these cases occur within or outside Itajaí. Hence, for the evaluation of these rates, all participants were considered, irrespective of their city of origin, since they were tracked regardless.

Unfortunately, most of the population failed to continue in the program of prophylactic ivermectin use regularly. Possibly, the raise in the number of cases, which occurred after July 7, 2020, not only in the city of Itajaí, but in the whole state of Santa Catarina, may have led a perception of lack of efficacy in the use of ivermectin. However, this is a misleading perception, once the use was able to reduce COVID-19 infection significantly. A stronger engagement could have led to a greater impact in the city, even though a small portion of regular users was sufficient to affect the city's numbers related to COVID-19 positively

Unexpectedly, there was a lack of increased reductions of COVID-19 infection with higher regularity ivermectin use. We could speculate that subjects that did not obtain ivermectin from the program in a regular manner may have acquired ivermectin in pharmacies, since medical prescription was not retained by pharmacies, and then was not strictly necessary. However, during the period of the program, in particular in the first two months, Brazil experimented a temporary shortage of ivermectin due to the sudden increase in its demand, while when present in pharmacies, prices for ivermectin temporarily raised from five to times, precluding its use outside the program. Finally, 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 strictly regular users may be explained by the fact that patients either used a hospital outside the city of Itajaí or in a private hospital (deaths are mandatorily informed for both public and private hospitals, but hospitalizations are not). Another hypothesis is that these deaths occurred without hospitalization, which may be not so

unusual, depending on the characteristics and social context of these participants, or when hospitals are overwhelmingly occupied, or when patients avoid seeking for hospital assistance for a variety or reasons.

Limitations

More details regarding baseline characteristics of ivermectin non-users were not feasible to be obtained. The calculation of infection rate could have some differences in the methods regarding the exact calculations to be performed. Imprecisions and modifications between the first manuscript of the study and this study were present, although minimal, and that did not impact the fact that ivermectin use reduced COVID-19 related outcomes. In particular, hospitalization rates could be slightly underreported due unreported hospitalizations that may have occurred in a private institution, although the private system offered very few hospital beds, compared to the public health system. Unlike hospitalizations, deaths were mandatorily reported, which precluded from any imprecision in the calculations of mortality rate and risk of dying from COVID-19.

Imprecisions regarding the regularity use of ivermectin based on the total amount of ivermectin use is inherent. As the number of tablets was calculated according to body weight, higher weights would lead to higher number of tablets, which would require a lower number of weeks to fill criteria for regularity. However, most of the population used between two and three tablets daily for two days. Due to the lack of wide differences between the number of ivermectin tablets used, the frequency of its use could be determined with a reasonable level of precision.

Other limitations are also inherent to the type of study (population, observational study), even though the strict control of the outcomes among COVID-19 cases and of the number of deaths due to COVID-19 in overall population, and the fact that PSM was employed for almost all outcomes, allowed obtaining results with high level of certainty.

Final discussion

Strictly regular use of ivermectin led to a significant, substantial reduction of 100% in hospitalization rate, 90% in mortality rate, and 86% in the risk of dying from COVID-19 when compared to non-users. Sporadic use of ivermectin led to less substantial reductions of 35% in hospitalization rate, a non-significant 37% in mortality rate and 51% in the risk of dying from COVID-19. Statistically significant or marginally significant reductions in hospitalization and mortality rates and risk of dying from COVID-19 were observed in strict users when compared to sporadic users, of 100%, 79% and 72%, respectively. A dose-, regular-response pattern of ivermectin use and level of protection from COVID-19 related outcomes was identified and consistent across levels of ivermectin use for all outcomes. Conversely, reduction in COVID-19 infection rate occurred in a weak but consistent and significant dose-dependent manner, with reductions of 32% and 49% in sporadic users and strict users, respectively, when compared to non-users.

Conclusion

The non-use of ivermectin was associated with a 10-times increase in mortality risk and a 7-times increased risk of dying from COVID-19, compared to strictly regular use of ivermectin in a dose of 0.2mg/kg for two consecutive days every 15 days, in a prospectively, strictly controlled population. A progressive, dose- and regularity-response pattern for protection from COVID-19 related outcomes was observed and consistent across levels of ivermectin use and all outcomes, except for reduction in infection rate, that was significant and consistent, but irrespective of level of ivermectin use.

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, for consulting and trainingservices, unrelated this or to any other research, related or unrelated to ivermectin. Dr. Flavio A. Cadegiani was contracted by Vitamedic for

consulting services, unrelated to this or to any other study, related or not related to ivermectin, and donated the full budget for COVID-19 patient care and research. Other authors have no conflicts of interest.

Data availability statement

Dataset is available under reasonable request by institutions and organizations.

Author contributions

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

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