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1 **Ivermectin Prophylaxis Used for COVID-19 Reduces COVID-19 Infection and**  
2 **Mortality Rates: A City-Wide, Prospective Observational Study of 220,517**  
3 **Subjects Using Propensity Score Matching.**

4  
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28  
29 **Key-words:** COVID-19, SARS-CoV-2, ivermectin, prophylaxis, prevention,  
30 coronavirus

31  
32 **Acromyums:** COPD = Chronic Obstructive Pulmonary Disease; CVD = cardiovascular  
33 disease; MI = Myocardial infarction; T2D = Type 2 Diabetes

41 **Abstract**

42

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

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

65 **Results:** A total of 220,517 subjects were included in the analysis; 133,051 (60.3%)  
66 regular ivermectin users and 87,466 (39.7%) non-users. Using PSM, two cohorts of 3,034  
67 subjects suffering COVID-19 infection were compared. The regular use of ivermectin led  
68 to a 68% reduction in COVID-19 mortality [25 (0.8%) versus 79 (2.6%) among  
69 ivermectin non-users; risk ratio (RR), 0.32; 95% confidence interval (CI), 0.20 – 0.49;  $p$   
70  $< 0.0001$ ]. When adjusted for residual variables, reduction in mortality rate was 70% (RR,  
71 0.30; 95%CI 0.19 – 0.46;  $p < 0.0001$ ). There was a 56% reduction in hospitalization rate  
72 (44 versus 99 hospitalizations among ivermectin users and non-users, respectively; RR,  
73 0.44; 95%CI, 0.31 – 0.63;  $p < 0.0001$ ). After adjustment for residual variables, reduction  
74 in hospitalization rate was 67% (RR, 0.33; 95%CI 0.23 – 0.66;  $p < 0.0001$ ).

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

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109 **Introduction**

110

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

119

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

130

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

137

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

141 recommended to confirm the possible beneficial effects ivermectin confers in COVID-  
142 19.

143

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

150

151 However, despite this favorable risk/benefit profile and absence of therapeutic  
152 alternatives, ivermectin has yet to be approved for prophylaxis and treatment of COVID-  
153 19 by agencies throughout the world, including FDA (Food & Drug Administration;  
154 United States of America), EMA (European Medicines Agency; Europe) and ANVISA  
155 (Agência Nacional de Vigilância Sanitária – Brazilian Health Regulatory Agency;  
156 Brazil).

157

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

166

167 Itajaí, a city in the Southern Brazilian state of Santa Catarina, initiated a population  
168 wide government program for COVID-19 prophylaxis. The medical-focused decision  
169 parameters established are based on the distribution of ivermectin to whole populations  
170 in different countries. To ensure the safety of the population, a well-controlled computer  
171 program was developed to compile and maintain all relevant demographic and clinical  
172 data. The use of ivermectin was optional and based on patients' preferences given its  
173 benefits as a preventative agent was unproven.

174

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

## 181 **Material and Methods**

### 183 *Study population*

184  
185 This was a prospective, observational study. Although study design, IRB approval, and  
186 data analysis occurred after completion of the voluntary prophylaxis program, all data  
187 were collected prospectively in real-time with mandated reporting to the registry of all  
188 events as they occurred during the citywide governmental COVID-19 prevention with  
189 ivermectin program, from July 2020 to December 2020, developed in the city of Itajaí, in  
190 the state of Santa Catarina, Brazil. Demographic and clinical data was reported from  
191 medical records of patients followed in a large outpatient setting; a provisional outpatient  
192 clinic set in the Convention Center of Itajaí, and several secondary outpatient settings, as  
193 part of the Universal Health System (SUS).

194  
195 The objective was to determine the number of patients affected by COVID-19  
196 (positivity rate of rtPCR-SARS-CoV-2), risk of death due to COVID-19 (whether  
197 infected or not), and COVID-19 mortality rate (risk of death from COVID-19) of those  
198 who used and did not use ivermectin prophylactically for COVID-19. This data was  
199 analyzed stratified by age, sex, presence of comorbidities, and correlated demographic  
200 characteristics.

201  
202 The present retrospective analysis was approved by the CONEP - National  
203 Research Ethics Council (CONEP) under the number 4.821.082 with the project number  
204 CAAE: 47124221.2.0000.5485.

### 206 *Study procedures and data collection*

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

214

215 The program was conducted in all 35 sites, 24/7, with the initial enrollment in the  
216 program occurring during a two-week time frame, due to the large number of subjects to  
217 evaluate in the entire population of Itajaí. In order to avoid underreported data, strict  
218 procedure sequencing was followed: 1. Registration and recording of patient data,  
219 documented by assistants; 2. Weighing subjects (Subject weight was essential to calculate  
220 the appropriate dose of ivermectin); 3. Brief medical evaluation of past medical history,  
221 comorbidities, use of medications and contraindications to drugs; 4. Medical prescription  
222 of prophylactic doses of ivermectin, according to medical judgment and following a  
223 subject's informed consent related to potential benefits, risks, and side effects. All details  
224 of this citywide program and campaign had been previously agreed upon between the city  
225 local department of the National Healthcare System (SUS), city mayor, and local public  
226 prosecutors.

227

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

236

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



242

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

249

250           They were questioned for the presence of common COVID-19 symptoms. These  
251 included chills, high-grade fever, cough, myalgia, fatigue, anosmia, ageusia, sore throat,  
252 headache, nasal congestion, sneeze, runny nose, hemoptysis, nauseas, vomiting,  
253 abdominal pain, diarrhea, cutaneous rash, arthralgia, chest pain, eye pain and pinkeye,  
254 and presence of alert signs, including shortness of breath, signs of hypoxia, signs of  
255 coagulation abnormalities and an altered level of consciousness. Systolic and diastolic  
256 blood pressure, heart rate, respiratory rate, oxygen saturation, and axillar temperature  
257 were measured. The same signs and symptoms, and vital signs were collected at each  
258 following medical visit during COVID-19. Individual data was compiled and reviewed  
259 by the researchers.

260

261           Registry data of all patient records from the city of Itajaí between July 7, 2020 and  
262 December 31, 2020, including those who used ivermectin and did not use ivermectin were  
263 reviewed. Subjects who tested positive for COVID-19 during the study were considered  
264 for this analysis, whether they used ivermectin or not. Of the infected subjects, two groups  
265 were considered: subjects who used ivermectin prophylactically (treated group) and  
266 subjects who did not use ivermectin prophylactically (untreated group). Any missing data  
267 from patients were actively searched by the investigators, via phone or in person. Since  
268 this is a citywide program, all recorded data must have matched the exact number of  
269 COVID-19 cases and deaths of the city. This strict interval avoids differences in terms of  
270 periods of exposure.

271

272           Due to the uncertainty of reinfection with COVID-19, subjects with a history of  
273 previous COVID-19 did not participate in the program although they were still permitted  
274 to use ivermectin prophylactically. Limiting parameters of the government system  
275 allowed the recording of a first episode of COVID-19 infection only.

276

277           Finally, city-wide COVID-19 hospitalization and mortality rates of Itajaí were  
278 compared between the period before the program (before July 7, 2020) and during the  
279 program between July 7, 2020 and December 31, 2020) aiming to evaluate whether a  
280 program of prophylaxis with ivermectin for COVID-19 would cause a positive impact in  
281 the overall numbers of the city, despite only partial adoption. Chances of dying from  
282 COVID-19 in the overall population, according to use or non-use of ivermectin  
283 (irrespective of COVID-19 infection) were only calculated prior to matching. Conversely,  
284 mortality rate, i.e., among those who were infected by the SARS-CoV-2, was calculated  
285 for both pre and post-matched cohorts. Analysis of hospitalization and mortality rates  
286 before matching, mortality rate in subpopulations among ivermectin users, among  
287 ivermectin non-users, and mortality rate ratios between iveremctin users and non-users in  
288 subpopulations, before and after propensity score matching, and STROBE checklist are  
289 presented in the **Supplement Appendix 1**.

290

291

292           *Statistical analysis*

293

294 In this outpatient study of those who tested positive for SARS-CoV-2, mortality rate was  
295 evaluated according to each parameter, that adjusted against other variables (for  
296 multivariate regression analysis) and used for balancing and matching groups, including  
297 age intervals, sex, history of smoking, prophylactic ivermectin use, T2D, asthma, COPD,  
298 cardiovascular diseases and other pulmonary diseases, hypertension, current cancer (any  
299 type), history of stroke and/or MI. Groups, baseline characteristics, and mortality rates  
300 were presented before matching and after matching.

301

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

308

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

313  
314 The statistical approach for missing data depended on the percentage of missing  
315 data for each parameter. However, due to the registry system design mandating that all  
316 data variables be filled to be formally included in the registry, only erroneously entered  
317 (illogical) data were found. In such instances, medical record review was performed to  
318 obtain the accurate data.

319  
320 The program used for the analysis was the Statistical Analysis Software  
321 (SAS/STAT) (SAS Institute Inc., Care, North Carolina, USA).

## 322 323 324 **Results**

325  
326 A total of 133,051 citizens of Itajai (60.3% of the population) received ivermectin before  
327 being infected by COVID-19. A total of 87,466 citizens (39.7 %) did not receive or did  
328 not want to receive ivermectin during the program, including as a prophylactic or as  
329 treatment after having COVID-19.

330  
331 Of the 133,051 prophylaxed subjects, 4,311 had a positive rtPCR-SARS-CoV-2  
332 (3.2% infection rate), while 3,034 of the 87,466 untreated subjects had positive rtPCR-  
333 SARS-CoV-2 (3.5% infection rate), a relative reduction of 7% in infection rate ratio (Risk  
334 ratio (RR), 0.93; 95% confidence interval (95%CI), 0.89-0.98;  $p = 0.003$ ). After PSM,  
335 two cohorts of 3,034 subjects were created.

336  
337 Baseline characteristics of the 7,345 subjects included prior to PSM and the  
338 baseline characteristics of the 6,068 subjects in the matched groups are shown in Table  
339 1. Prior to PSM, ivermectin users had a higher percentage of subjects over 50 years old  
340 ( $p < 0.0001$ ), higher prevalence of T2D ( $p = 0.0004$ ), hypertension ( $p < 0.0001$ ), CVD ( $p$   
341  $= 0.03$ ), and a higher percentage of caucasians ( $p = 0.004$ ), than non-users. After PSM,  
342 all baseline parameters were similar between groups.

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

	Pre-Matching				Propensity Score Matched		
	Overall (n = 7,345)	Ivermectin users (n = 4,311)	Non- ivermectin users (n = 3,034)	<i>p-value</i>	Overall (n = 6,068)	Ivermectin users (n = 3,034)	Non- ivermectin users (n = 3,034)
<b>Age</b>							
<b>Mean ± SD</b>	42.0 ± 14.7	43.5 ± 14.9	39.8 ± 14.2	<b>&lt; 0.0001</b>	39.7 ± 14.0	39.67 ± 13.8	39.8 ± 14.2
< 30 y/o	1730 (23.6%)	886 (20.5%)	844 (27.8%)		1,691 (27.9%)	844 (27.9%)	847 (27.8%)
30-50 y/o	3703 (50.4%)	2121 (49.2%)	1582 (52.2%)		3,155 (52.0%)	1,573 (51.9%)	1,582 (52.1%)
> 50 y/o	1912 (26.0%)	1304 (30.3%)	608 (20.0%)		1,222 (20.1%)	614 (20.2%)	608 (20.1%)
<b>Sex</b>				<i>0.31</i>			
Female	3983 (54.2%)	2359 (54.7%)	1624 (53.5%)		3,231 (53.2%)	1,607 (53.0%)	1,624 (53.5%)
Male	3362 (45.8%)	1952 (45.3%)	1410 (46.5%)		2,837 (46.8%)	1,427 (47.0%)	1,410 (46.5%)
<b>Race</b>							
Caucasians	5437 (74.0%)	3245 (75.3%)	2192 (72.2%)	<b>0.004</b>	4,398 (72.5%)	2,206 (72.7%)	2,192 (72.3%)
Afro- Brazilians	209 (2.8%)	109 (2.5%)	100 (3.3%)	<b>0.052</b>	193 (3.2%)	93 (3.1%)	100 (3.3%)
Mixed	1583 (22.6%)	901 (20.9%)	682 (22.5%)	<i>0.10</i>	1,364 (22.5%)	93 (3.1%)	100 (3.3%)
Asian- Brazilians	116 (1.6%)	56 (1.3%)	60 (2.0%)	<b>0.023</b>	113 (1.9%)	53 (1.8%)	60 (2.0%)
<b>Type 2 diabetes</b>				<b>0.0004</b>			
Yes	214 (2.9%)	151 (3.5%)	63 (2.1%)		141 (2.3%)	78 (2.6%)	63 (2.1%)
No	7131 (97.1%)	4160 (96.5%)	2971 (97.9%)		5,927 (97.7%)	2,956 (97.4%)	2,971 (97.9%)
<b>Asthma</b>				<b>0.067</b>			
Yes	26 (0.3%)	20 (0.5%)	6 (0.2%)		21 (0.3%)	15 (0.5%)	6 (0.2%)
No	7319 (99.7%)	4291 (99.5%)	3028 (99.8%)		6,047 (99.7%)	3,019 (99.5%)	3,028 (99.8%)
<b>COPD</b>				<i>0.72</i>			
Yes	13 (0.2%)	7 (0.2%)	6 (0.2%)		12 (0.2%)	6 (0.2%)	6 (0.2%)
No	7332 (99.8%)	4304 (99.8%)	3028 (99.8%)		6,056 (99.8%)	3,028 (99.8%)	3,028 (99.8%)
<b>Hypertension</b>				<b>&lt; 0.0001</b>			
Yes	528 (7.2%)	362 (8.4%)	166 (5.5%)		343 (5.6%)	177 (5.8%)	166 (5.5%)
No	6817 (92.8%)	3949 (91.6%)	2868 (94.5%)		5,725 (94.4%)	2,857 (94.2%)	2,868 (94.5%)
<b>CVD</b>				<b>0.03</b>			
Yes	56 (0.8%)	41	15		32	17	15

		(1.0%)	(0.5%)		(0.5%)	(0.6%)	(0.5%)
No	7289 (99.2%)	4270 (99.0%)	3019 (99.5%)		6,036 (99.5%)	3,017 (99.4%)	3,019 (99.5%)
<b>Other pulmonary diseases</b>				0.53			
Yes	15 (0.2%)	10 (0.2%)	5 (0.2%)		9 (0.1%)	4 (0.1%)	5 (0.1%)
No	7330 (99.8%)	4301 (99.8%)	3029 (99.8%)		6,059 (99.9%)	3,030 (99.9%)	3,029 (99.9%)
<b>Cancer (any type)</b>				0.66			
Yes	32 (0.4%)	20 (0.5%)	12 (0.4%)		22 (0.4%)	10 (0.3%)	12 (0.4%)
No	7313 (99.6%)	4291 (99.5%)	3023 (99.6%)		6,046 (99.6%)	3,024 (99.7%)	3,022 (99.6%)
<b>Current smoking</b>				0.76			
Yes	110 (1.5%)	63 (1.5%)	47 (1.5%)		95 (1.6%)	48 (1.6%)	47 (1.6%)
No	7235 (98.5%)	4248 (98.5%)	2987 (98.5%)		5,973 (98.4%)	2,986 (98.4%)	2,987 (98.4%)
<b>History of MI</b>				0.26			
Yes	15 (0.2%)	11 (0.3%)	4 (0.1%)		8 (0.1%)	4 (0.1%)	4 (0.1%)
No	7330 (99.8%)	4300 (99.7%)	3030 (99.9%)		6,060 (99.9%)	3,030 (99.9%)	3,030 (99.9%)
<b>History of stroke</b>				0.56			
Yes	21 (0.3%)	11 (0.3%)	10 (0.3%)		21 (0.4%)	11 (0.4%)	10 (0.3%)
No	7324 (99.7%)	4300 (99.7%)	3024 (99.7%)		6,047 (99.6%)	3,023 (99.6%)	3,024 (99.7%)

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

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348

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

351

352 As described in **Table 2**, after employing PSM, of the 6,068 subjects (3,034 in each  
353 group), there were 44 hospitalizations among ivermectin users (1.6% hospitalization rate)  
354 and 99 hospitalizations (3.3% hospitalization rate) among ivermectin non-users, a 56%  
355 reduction in hospitalization rate (RR, 0.44; 95%CI, 0.31 – 0.63). When adjustment for  
356 variables was employed, reduction in hospitalization rate was 67% (RR, 0.33; 95%CI 0.23  
357 – 0.66;  $p < 0.0001$ ).

358

359 There were 25 deaths among ivermectin users (0.8% mortality rate) and 79 deaths  
360 among non-ivermectin users (2.6% mortality rate), a 68% reduction in mortality rate (RR,

361 0.32; 95%CI 0.20 – 0.49). When PSM was adjusted, reduction in mortality rate was 70%  
 362 (RR, 0.30; 95%CI 0.19 – 0.46; p < 0.0001).

363

364 **Table 2a.** Propensity score matched hospitalization and mortality rate among ivermectin users  
 365 and non-users.

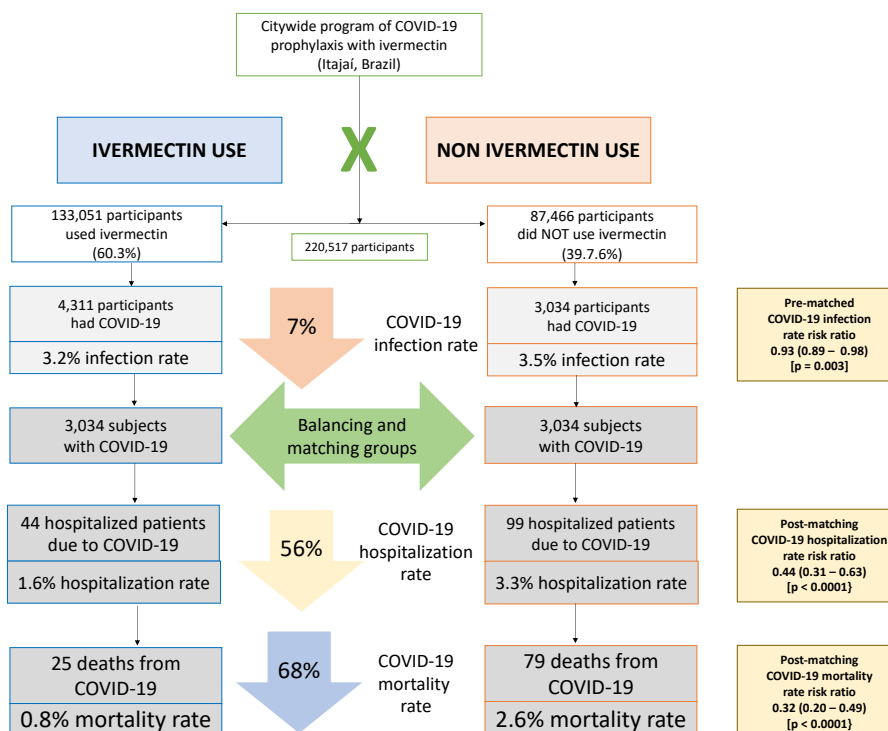
		Overall	IVM users	Non-IVM users	PSM mortality risk ratio (95%CI) and p-value [p]	Adjusted PSM mortality risk ratio (95%CI) and p-value [p]
<b>COVID-19 infection</b>	Infected population (n)	6,068	3,034	3,034	-	-
<b>COVID-19 hospitalization</b>	Hospitalization due to COVID-19	143	44	99	-	-
	Hospitalization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

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

368

369 **Figure 1.** Summary of the findings.

370



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373

374 **Table 3** describes resulting risk factors for COVID-19 death amongst the overall  
 375 population through PSM analysis. Risk factors for mortality in COVID-19 included aging  
 376 ( $p < 0.0001$ ), male sex ( $p = 0.015$ ), T2D ( $p < 0.0001$ ), hypertension ( $p < 0.0001$ ), asthma  
 377 ( $p = 0.011$ ), COPD ( $p < 0.0001$ ), other pulmonary diseases ( $p = 0.048$ ), history of MI ( $p$   
 378  $= 0.034$ ) and history of stroke ( $p < 0.0001$ ). To detect independent risk factors, post-PSM  
 379 adjustment for variables showed that ivermectin ( $p < 0.0001$ ; 70% reduction in mortality  
 380 risk) and female sex ( $p = 0.022$ ; 38% reduction in mortality risk) were protectors, whereas  
 381 T2D ( $p = 0.041$ ; 79% increase in mortality risk), hypertension ( $p = 0.008$ ; 98% increase  
 382 in mortality risk), and, marginally, other pulmonary diseases ( $p = 0.061$ ; 468% increase  
 383 in mortality risk) and history of stroke ( $p = 0.054$ ; 97% increase in mortality risk) were  
 384 identified as independent risk factors.

385

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

<b>Propensity Score Matched Groups</b>				
<b>Variable</b>	<b>Overall (n = 6,068)</b>	<b>Death (%)</b>	<b>Unadjusted COVID-19 mortality risk ratio and p-value [p]</b>	<b>Multivariate adjusted COVID-19 mortality risk ratio and p-value [p]</b>
<b>Ivermectin use - n (%)</b>			<b>0.32 (0.20 – 0.49) [&lt; 0.0001]</b>	<b>0.30 (0.19 – 0.46) [&lt; 0.0001]</b>
Yes	3,034	25 (0.8%)		
No	3,034	79 (2.6%)		
<b>Age - n (%)</b>			<b>[&lt; 0.0001]</b>	<b>[&lt; 0.0001]</b>
< 30 y/o	1,691	1 (0.1%)		
30-50 y/o	3,155	12 (0.4%)		
> 50 y/o	1,222	91 (7.4%)		
<b>Sex- n (%)</b>			<b>0.62 (0.42 – 0.91) [0.015]</b>	<b>0.64 (0.44 – 0.93) [0.022]</b>
Female	3,231	43 (1.3%)		
Male	2,837	61 (2.2%)		
<b>Race - n (%)</b>			<b>[0.24]</b>	<b>[0.44]</b>
Caucasians	4,398	79 (1.8%)		
Afro-Brazilians	193	6 (3.1%)		
Mixed	1,364	17 (1.3%)		

Asian-Brazilians	113	2 (1.9%)		
<b>Type 2 diabetes - n (%)</b>			<b>10.0 (6.32-15.8) [&lt; 0.0001]</b>	<b>1.79 (1.03 – 3.12) [0.041]</b>
Yes	141	20 (14.2%)		
No	5,927	84 (1.4%)		
<b>Hypertension - n (%)</b>			<b>8.83 (5.99 – 13.0) [&lt; 0.0001]</b>	<b>1.98 (1.19 – 3.30) [0.008]</b>
Yes	343	36 (10.5%)		
No	5,725	68 (1.2%)		
<b>Asthma - n (%)</b>			<b>5.64 (1.49 – 21.4) [0.011]</b>	<b>1.74 (0.52 – 5.81) [0.36]</b>
Yes	21	2 (9.5%)		
No	6,047	102 (1.7%)		
<b>COPD - n (%)</b>			<b>15.0 (5.52 – 40.7) [&lt; 0.0001]</b>	<b>1.71 (0.68 – 4.31) [0.25]</b>
Yes	12	3 (25.0%)		
No	6,056	101 (1.7%)		
<b>Cardiovascular diseases - n (%)</b>			<b>7.54 (2.96 – 19.3) [&lt; 0.0001]</b>	<b>1.22 (0.44 – 3.37) [0.70]</b>
Yes	32	4 (12.5%)		
No	6,036	100 (1.7%)		
<b>Other pulmonary diseases - n (%)</b>			<b>6.54 (1.02 – 41.9) [0.048]</b>	<b>5.68 (0.92 – 35.0) [0.061]</b>
Yes	9	1 (11.1%)		
No	6,059	103 (1.7%)		
<b>Cancer (any type) - n (%)</b>			<b>2.67 (0.39 – 18.3) [0.32]</b>	<b>1.97 (0.30 – 12.9) [0.48]</b>
Yes	22	1 (4.6%)		
No	6,046	103 (1.7%)		
<b>Current smoking - n (%)</b>			<b>1.23 (0.31 – 4.92) [0.77]</b>	<b>0.36 (0.08 – 1.70) [0.20]</b>
Yes	95	2 (2.1%)		
No	5,973	102 (1.7%)		
<b>History of MI - n (%)</b>			<b>7.35 (1.16 – 46.5) [0.034]</b>	<b>1.91 (0.17 – 21.6) [0.60]</b>
Yes	8	1 (12.5%)		
No	6,060	103 (1.7%)		
<b>History of stroke - n (%)</b>			<b>17.6 (8.72 – 35.7)</b>	<b>1.97 (0.99 – 3.92)</b>



			<b>[&lt; 0.0001]</b>	<b>[0.054]</b>
Yes	21	6 (28.6%)		
No	6,047	98 (1.6%)		

388 COPD = Chronic obstructive pulmonary disease; CVD = cardiovascular disease; MI = myocardial infarction;

389

390 In a comparison of city-wide COVID-19 hospitalization rates prior to and during  
 391 the program, COVID-19 mortality decreased from 6.8% before the program with  
 392 prophylactic use of ivermectin, to 1.8% after its beginning (RR, 0.27; 95%CO, 0.21 –  
 393 0.33; p < 0.0001), and in COVID-19 mortality rate, from 3.4% to 1.4% (RR, 0.41; 95%CI  
 394 0.31 – 0.55; p < 0.0001). (Table 4).

395

396 **Table 4.** Hospitalization and mortality rates registered in the city of Itajaí, Brazil, before  
 397 versus after the beginning of the citywide program with ivermectin use as prophylaxis for COVID-  
 398 19, independent of the ivermectin use status.

**Overall      Until July      After July      Relative risk ratio      p-value**  
**30th                      30th**  
**(95%CI)**

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

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## Discussion

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This prospective, citywide COVID-19 ivermectin prophylaxis program resulted in significant reductions of COVID-19 infections, hospitalizations, and deaths. The ivermectin non-users were two times more likely to die from COVID-19 than ivermectin users in the overall population analysis.

The city of Itajai, in the state of Santa Catarina, Brazil, started a citywide program of prophylaxis with ivermectin in July 2020 as part of several initiatives to reduce the burden of COVID-19. Ivermectin was used, based on the existing literature at that time and on the virtual absence of risks. The National Health System (Sistema Único de Saúde – SUS) that functions as a full healthcare support to the entire population allowed the city to establish a non-restricted population program. This program included a support structure consisting of a large outpatient clinic located at the Convention Center of Itajai. This outpatient clinic became the main locale of assistance for COVID-19 patients, supported by multiple public facilities where general practitioners regularly saw patients.

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

An important conservative bias was present. Major risk factors for severe COVID-19 and mortality due to COVID-19, including aging, diabetes, and hypertension, were

446 **more** prevalent among ivermectin users, which may have underestimated the benefits  
447 measured Ivermectin was demonstrated to be particularly effective in subjects above 49  
448 years old in terms of reduction of absolute risk, which corresponds to the group at the  
449 highest risk for COVID-19. This allows the understanding that prophylactic use of  
450 ivermectin can be particularly impactful in older subjects. In addition, ivermectin seemed  
451 to reduce the exceeding risk of hypertension, T2D, and other diseases.

452

453 In accordance with the literature, subjects with higher age, diabetes and  
454 males were less likely to survive ( $p < 0.05$  for all), only aging remained as an independent  
455 risk factor after PSM ( $p < 0.0001$ ). However, prophylactic ivermectin use appears to  
456 mitigate the additional risk of COVID-19 death due to T2D, hypertension, and  
457 cardiovascular diseases.

458

459 The narrative that using preventive & early treatment therapies will have people  
460 relax their caution of remaining socially & physically distanced to allow more COVID-  
461 19 related infections is not supported here. This study data demonstrates that the use of  
462 preventive ivermectin significantly lowers the infection rate, ands benefits outweigh the  
463 supposed increased risk of changes in social behaviours. Hence, we can speculate that the  
464 prophylactic use of ivermectin could play an important role in the reduction of the  
465 pandemic burden.

466

467 Even after adjustments to measure the most relevant variables that could influence  
468 COVID-19 related outcomes, including age, sex, comorbidities, and habits, aiming to  
469 avoid overestimation of the effects of ivermectin and to resemble a randomized clinical  
470 trial, prophylactic ivermectin proved to be protective for the overall population, with a  
471 reduction of 48% in death rate and  $p = 0.001$  after employment of PSM.

472

473 The protection provided by ivermectin when used prophylactically for COVID-  
474 19 may have reflected in the reduction in COVID-19 hospitalization and mortality rates  
475 observed in a populational level. Compared to before the beginning of the program,  
476 COVID-19 hospitalization and mortality rates were reduced by 73% and 59%,  
477 respectively ( $p < 0.0001$  for both). These reductions were obtained when overall  
478 population of the city of Itajaí, as well as overall number of COVID-19 cases,  
479 hospitalizations, and deaths, were considered, irrespective of the percentage of patients

480 using ivermectin prophylactically. When compared to all other major cities in the State  
481 of Santa Catarina, where Itajaí is located, differences in COVID-19 mortality rate  
482 between before July 7, 2020 and between July 7, 2020 and December 21, 2020, Itajaí is  
483 ranked number one, and far from the second place<sup>35</sup>. These results indicate that medical-  
484 based optional prescription, citywide covered ivermectin can have a positive impact in  
485 the healthcare system.

486

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

492

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

500

#### 501 *Limitations*

502

503 Being a prospective observational study which allowed subjects to self select  
504 between treatment vs. non-treatment instead of relying on randomization, important  
505 confounders may have been differentially present which could otherwise explain the  
506 differences observed. Given that the benefits measured occurred despite negative risk  
507 factors being more present in the treatment group, this suggests the benefits are likely  
508 accurate and unbiased. Further, studies relying on PSM techniques have been shown  
509 to consistently agree with those employing randomization<sup>37,38</sup>, again supporting the  
510 likelihood the benefits measured are accurate, The prevailing type of SARS-CoV-2 in the  
511 city was unknown due to the lack of genotyping surveillance during the period of the  
512 program. Whether the prophylaxis proposed in this program would be as effective in other  
513 SARS-CoV-2 variants is unclear. Also, there was not a strict control of whether infected

514 subjects used any specific drug in case of COVID-19 infection, this allows the possibility  
515 that the differences may be explained by differences in the use of ivermectin or other  
516 medications as treatment.

517

### 518 *Final discussion*

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520 In this city-wide ivermectin prophylaxis program, a large, statistically significant  
521 decrease in mortality rate was observed after the program began among the entire  
522 population of city residents. When comparing subjects that used ivermectin regularly,  
523 non-users were two times more likely to die from COVID-19 while ivermectin users were  
524 7% less likely to be infected with SARS-CoV-2 ( $p = 0.003$ ).

525

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

530

531 Due to the well-established, long-term safety profile of ivermectin, with rare  
532 adverse effects, the absence of proven therapeutic options to prevent death caused by  
533 COVID-19, and lack of effectiveness of vaccines in real-life all-cause mortality analyses  
534 to date, we recommend that ivermectin be considered as a preventive strategy, in  
535 particular for those at higher risk of complications from COVID-19 or at higher risk of  
536 contracting the illness

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538

### 539 **Conclusion**

540

541 In a city-wide ivermectin program with prophylactic, optional ivermectin use for COVID-  
542 19, ivermectin was associated with significantly reduced COVID-19 infection,  
543 hospitalization, and death rates from COVID-19.

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549 **Statements**

550

551 *Conflict of Interest*

552

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

559

560 *Data availability statement*

561

562 Dataset is available under reasonable request by institutions and organizations.

563

564 *Author contributions*

565

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

578

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580

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583 obtained.

584

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586

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590 program for COVID-19 prevention with ivermectin in Itajaí, state of Santa Catarina,  
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592 participated in the program, compilation of data, or were involved in any other step that  
593 led to the present analysis.

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722 **Table list**

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735 **Figure list**

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737 Figure 1. Summary of the findings.

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