Review of the Emerging Evidence Supporting the Use of Ivermectin in the Prophylaxis and Treatment of COVID-19

Front Line COVID-19 Critical Care Alliance

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Abstract

In March 2020, an expert panel called the Front Line COVID-19 Critical Care Alliance (FLCCC) was created and led by Professor Paul E. Marik with the goal of continuously reviewing the rapidly emerging basic science, translational, and clinical data in order to gain insight into and to develop a treatment protocol for, COVID-19. At the same time, many centers and groups employed a multitude of novel therapeutic agents empirically and within clinical trials, often during inappropriate time points during this now well-described multi-phase disease. Either as a result of these frequent trial design failures or due to the lack of their insufficient anti-viral or anti-inflammatory properties, nearly all trialed agents have proven ineffective in treating COVID-19 as of November 11, 2020. Based on a recent series of negative published therapeutic trial results, in particular the SOLIDARITY trial, virtually eliminates any treatment role for remdesivir, hydroxychloroquine, lopinavir/ritonavir, interferon, convalescent plasma, tocilizumab, and mono-clonal antibody therapy. Despite this growing list of failed therapeutics in COVID-19, the FLCCC recently discovered that ivermectin, an anti-parasitic medicine, has highly potent real-world, anti-viral, and anti-inflammatory properties against SARS-CoV-2 and COVID-19. This conclusion is based on the increasing numbers of study results reporting effectiveness, not only within in-vitro and animal models, but also in numerous randomized and observational controlled clinical trials. Repeated, large magnitude improvements in clinical outcomes have now been recorded when ivermectin is used not only as a prophylactic agent but also in mild, moderate, and even severe disease states. The review that follows of the existing evidence for ivermectin relies on "emerging" data in that, although compelling, only a minority of studies have been published in peer-reviewed publications with the majority of results compiled from manuscripts uploaded to medicine pre-print servers or posted on clinicaltrials.gov.

Introduction

In March 2020, an expert panel called the Front Line COVID-19 Critical Care Alliance (FLCCC) was created and led by Professor Paul E. Marik. The group of expert critical care physicians and thought leaders immediately began continuously reviewing the rapidly emerging basic science, translational, and clinical data in COVID-19 which then led to the early creation of a treatment protocol for hospitalized patients called MATH+, based on the collective expertise of the group in both the research and treatment of multiple other severe infections causing lung injury.[1]

Two manuscripts reviewing the scientific rationale and evolving published clinical evidence base in support of the MATH+ protocol passed peer review and have been accepted for publication in major medical journals at two different time points in the pandemic.[2] The most recent paper, currently in production, reports a 6.1% hospital mortality rate in COVID-19 patients measured in the two U.S hospitals that systematically adopted the MATH+ protocol, a markedly decreased mortality rate compared to the 23.9% hospital mortality rate calculated from a review of 39 studies including over 165,000 patients (unpublished data; available on request). For a review of the therapeutic interventions comprising the current MATH+ protocol, see Table 1 below.

Table 1. MATH+ Hospital Treatment Protocol for COVID-19

MATH+ Hospital Treatment Protocol for COVID-19 (www.flccc.net)

Medication	Indication/Initiation	Recommended dosing	Titration/Duration
Methylprednisolone	A. *Mild hypoxemia: requires O_2 via NC to maintain saturation > 92%*	40 mg IV bolus then 20 mg IV twice daily	A1. Once off O_2, then taper with 20 mg daily x 3 days then 10 mg daily x 3 days, monitor CRP response. A2. If FiO_2, or CRP increase move to B.
	B. *Moderate–severe hypoxemia (High Flow O_2, NIPPV, IMV)*	COVID-19 Respiratory Failure protocol (see Figure 2) Preferred: 80 mg IV bolus, followed by 80 mg / 240 ml normal saline IV infusion at 10 ml/hr Alternate: 40 mg IV twice daily	B1. Once off IMV, NPPV, or High flow O_2, decrease to 20 mg twice daily. Once off O_2, then taper with 20 mg/day for 3 days then 10 mg/day for 3 days. B2. If no improvement in oxygenation in 2–4 days, double dose to 160 mg/daily. B3. If no improvement and increase in CRP/Ferritin, move to "Pulse Dose" below.
	C. *Refractory Illness/ Cytokine Storm*	"Pulse" dose with 125 mg IV every 6–8 hours	Continue for 3 days then decrease to 80 mg IV/daily dose above (B). If still no response or CRP/Ferritin high/rising, consider "Salvage Therapy" below
Ascorbic Acid	*O_2 < 4 L on hospital ward*	500–1000 mg oral every 6 hours	Until discharge
	O_2 > 4 L or in ICU	1.5–3 g intravenously every 6 hours	Sooner of 7 days or discharge from ICU, then switch to oral dose above
Thiamine	*ICU patients*	200 mg IV twice daily	Sooner of 7 days or discharge from ICU
Heparin (LMWH)	*Hospital ward patients on ≤ 4 L O_2*	0.5 mg/kg twice daily Monitor anti-Xa, target 0.2–0.5 IU/ml	Until discharge then start DOAC at half dose for 4 weeks
	ICU patients or > 4 L O_2	1 mg/kg twice daily Monitor anti-Xa levels, target 0.6–1.1 IU/ml	Later of: discharge from ICU or off oxygen, then decrease to hospital ward dosing above
Ivermectin *(should be considered a core medication)*	*Upon admission to hospital and/or ICU*	0.2 mg/kg – days 1 and 3	Repeat – days 6 and 8 if not recovered
Vitamin D	*Hospital ward patients on ≤ 4 L O_2*	Calcifediol preferred: 0.532 mg PO day 1, then 0.266 mg PO day 3 and 7 and weekly thereafter Cholecalciferol: 10,000 IU/day PO or 60,000 IU day 1, 30,000 IU days 3 and 7 and then weekly	Until discharge from ICU
	ICU patients or on > 4 L O_2	Cholecalciferol 480,000 IU (30 ml) PO on admission, then check Vitamin D level on day 5, if < 20 ng/ml, 90,000 PO IU/day for 5 days	Until discharge from ICU
Atorvastatin	*ICU Patients*	80 mg PO daily	Until discharge
Melatonin	*Hospitalized patients*	6–12 mg PO at night	Until discharge
Zinc	*Hospitalized patients*	75–100 mg PO daily	Until discharge
Famotidine	*Hospitalized Patients*	40–80 PO mg twice daily	Until discharge
Therapeutic Plasma Exchange	*Patients refractory to pulse dose steroids*	5 sessions, every other day	Completion of 5 exchanges

Legend: CRP = C-Reactive Protein, DOAC = direct oral anti-coagulant, ICU = Intensive Care Unit, IMV = Invasive Mechanical Ventilation, IU = International units, IV = intravenous, NIPPV = Non-Invasive Positive Pressure Ventilation, O_2 = oxygen, PO (per os) = oral administration

Although the adoption of MATH+ has been considerable, it largely occurred only after the RECOVERY and other trials were published which supported one of the main components (corticosteroids) of the combination therapy approach created at the onset of the pandemic.[3-8] Despite the plethora of supportive evidence, the MATH+ protocol for hospitalized patients has not yet become widespread. Further, the world is in a worsening crisis with the potential of again overwhelming hospitals and ICU's. As of November 10th, 2020, the number of deaths attributed to COVID-19 in the United States reached 245,799 with over 3.7 million active cases, the highest number to date.[9] Multiple European countries have now begun to impose new rounds of restrictions and lockdowns.[10]

Further compounding these alarming developments was a wave of recently published negative results from therapeutic trials done on medicines thought effective for COVID-19, that now virtually eliminate any treatment role for remdesivir, hydroxychloroquine, lopinavir/ritonavir, interferon, convalescent plasma, tocilizumab, and mono-clonal antibody therapy.[11-16] One year into the pandemic, the only therapy considered "proven" as an effective treatment in COVID-19 is the use of corticosteroids in patients with moderate to severe illness.[17] Similarly most concerning is the fact that little has proven effective to prevent disease progression to prevent hospitalization.

Despite this growing list of failed therapeutics in COVID-19, it now appears that ivermectin, a widely used anti-parasitic medicine with known anti-viral and anti-inflammatory properties is proving a highly potent and multi-phase effective treatment against COVID-19. Although much of the trials data supporting this conclusion is available on medical pre-print servers or posted on clinicaltrials.gov, most have not yet undergone peer-review. Despite this limitation, the FLCCC expert panel, in their prolonged and continued commitment to reviewing the emerging medical evidence base, and considering the impact of the recent surge, has now reached a consensus in recommending that ivermectin for both prophylaxis and treatment of COVID-19 should be systematically and globally adopted.

The FLCCC recommendation is based on the following set of conclusions derived from the existing data, which will be comprehensively reviewed below:

1) Since 2012, multiple in-vitro studies have demonstrated that Ivermectin inhibits the replication of many viruses, including influenza, Zika, Dengue and others[18-26]
2) Ivermectin inhibits SARS-CoV-2 replication, leading to absence of nearly all viral material by 48h in infected cell cultures[27]
3) Ivermectin has potent anti-inflammatory properties with in-vitro data demonstrating profound inhibition of both cytokine production and transcription of nuclear factor-κB (NF-κB), the most potent mediator of inflammation[28-30]
4) Ivermectin significantly diminishes viral load and protects against organ damage when administered to mice upon infection with a virus similar to SARS-CoV-2[31]
5) Ivermectin prevents transmission and development of COVID-19 disease in those exposed to infected patients[32-34]
6) Ivermectin hastens recovery and prevents deterioration in patients with mild to moderate disease treated early after symptoms[35-40]

7) Ivermectin hastens recovery and avoidance of ICU admission and death in hospitalized patients[40,41]
8) Ivermectin reduces mortality in critically ill patients with COVID-19[41,42]
9) Ivermectin leads to striking reductions in case-fatality rates in regions with widespread use[43-45]
10) The safety, availability, and cost of ivermectin is nearly unparalleled given its near nil drug interactions along with only mild and rare side effects observed in almost 40 years of use and billions of doses administered[46]
11) The World Health Organization has long included ivermectin on its "List of Essential Medicines"[47]

Following is a comprehensive review of the available efficacy data as of November 8, 2020, taken from in-vitro, animal, clinical, and real-world studies all showing the above impacts of ivermectin in COVID-19.

In-vitro and animal studies of ivermectin activity against SARS-CoV-2

Since 2012, a growing number of cellular studies have demonstrated that ivermectin has anti-viral properties against an increasing number of RNA viruses, including influenza, Zika, HIV, Dengue, and most importantly, SARS-CoV-2. [18-26] Caly et al first reported that ivermectin significantly inhibits SARS-CoV-2 replication in a cell culture model, observing the near absence of all viral material 48h after exposure to Ivermectin.[27] Insights into the mechanisms of action by which ivermectin both interferes with the entrance and replication of SARS-CoV-2 within human cells are mounting. Researchers report high binding activity to the SARS-CoV-2 spike protein thereby limiting binding to the ACE-2 receptor and preventing cellular entry of the virus.[48] Ivermectin has also been shown to bind to or interfere with multiple essential structural and non-structural proteins required by the virus in order to replicate.[48,49] Finally, ivermectin also binds to the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), thereby inhibiting viral replication.[50]

Arevalo et al investigated in a murine model infected with a type 2 family RNA coronavirus similar to SARS-CoV-2, (mouse hepatitis virus), the response to 500 mcg/kg of ivermectin vs. placebo.[31] The study included 40 infected mice, with 20 treated with ivermectin, 20 with phosphate buffered saline, and then 16 uninfected control mice that were also given phosphate buffered saline. At day 5, all the mice were euthanized to obtain tissues for examination and viral load assessment. The 20 non-ivermectin treated infected mice all showed severe hepatocellular necrosis surrounded by a severe lymphoplasmacytic inflammatory infiltration associated with a high hepatic viral load (52,158 AU), while in the ivermectin treated mice a much lower viral load was measured (23,192 AU; $p<0.05$), with only few livers in the ivermectin treated mice showing histopathological damage such that the differences between the livers from the uninfected control mice were not statistically significant.

Exposure prophylaxis studies of ivermectin's ability to prevent transmission of COVID-19

Data is also now available showing large and statistically significant decreases in the transmission of COVID-19 among human subjects based on data from two randomized controlled trials (RCT) and one retrospective observational study (OCT); however, none of the studies have been peer-reviewed yet.[32-34] The two RCT's have submitted data to clinicaltrials.gov, which then performed a quality control review and posted the results.[32,33] The OCT was posted on the pre-print server medRxiv on November 3, 2020.[34]

The largest RCT, conducted in Egypt by Shouman et al. at Zagazig University, included 340 (228 treated, 112 control) family members of patients positive for SARS-CoV-2 via PCR.[33] Ivermectin, (approximately 0.25mg/kg) was administered twice, on the day of the positive test and 72 hours later. After a two-week follow up, a large and statistically significant decrease in COVID-19 symptoms among household members treated with ivermectin was found, 7.4% vs. 58.4%, p<.001. Similarly, in another RCT conducted by Carvallo et al. in Argentina involving 229 healthy citizens, 131 were randomized to treatment with 0.2mg of ivermectin drops taken by mouth five times per day. After 28 days, none of those receiving ivermectin prophylaxis group had tested positive for SARS-COV-2 versus 11.2% of patients in the control arm (p<.001).[51] More recently, in a large retrospective observational case-control study from India, Behara et al. reported that among 186 case-control pairs (n=372) of health care workers, they identified 169 participants that had taken some form of prophylaxis, with 115 that had taken ivermectin prophylaxis (n=38 of the COVID-19 cases and n=77 of the controls). After matched pair analysis, they reported that in the workers who had taken two dose ivermectin prophylaxis, the odds ratio for contracting COVID-19 was markedly decreased (0.27, 95% CI, 0.15–0.51). Notably, one dose prophylaxis was not found to be protective in this study. Based on both their study finding and the Egyptian prophylaxis study, the All India Institute of Medical Sciences included a consensus statement in the manuscript recommending health care workers take two 0.3mg/kg doses of ivermectin 72 hours apart and to repeat monthly.

Further data supporting a role for ivermectin in decreasing transmission rates can be found from South American countries where, in retrospect, large "natural experiments" appear to have occurred. For instance, beginning as early as May, various regional health ministries and governmental authorities within Peru, Brazil, and Paraguay initiated "ivermectin distribution" campaigns to their citizen populations. In one such example from Brazil, the cities of Itajai, Macapa, and Natal distributed massive amounts of ivermectin doses to the city's population, where, in the case of Natal, 1 million doses were distributed.[44] The data in Table 2 below was compiled on September 14, 2020 and was obtained from the official Brazilian government site (https://covid.saude.gov.br) and the national press consortium by an engineer named Alan Cannel whose findings were published on the website TrialSiteNews and are thus not peer-reviewed.

Table 2. Case count decreases in Brazilian cities with ivermectin distribution programs
(bolded cities distributed ivermectin, neighboring city listed below did not)

Region	Confirmed new cases/month	June	July	August	Population 2020 (1000)	% August vs. June/July
South	**Itajaí**	**2123**	**2854**	**998**	**223**	**40%**
	Chapecó	1760	1754	1405	224	80%
North	**Macapá**	**7966**	**2481**	**2370**	**503**	**45%**
	Ananindeua	1520	1521	1014	535	67%
North East	**Natal**	**9009**	**7554**	**1590**	**890**	**19%**
	João Pessoa	9437	7963	5384	817	62%

Similar examples of temporally associated declines in case counts and death rates in regions that undertook ivermectin distribution campaigns are rapidly emerging and will be discussed in more depth below.

Clinical studies on the efficacy of ivermectin in treating mildly ill outpatients

Currently, six studies which include a total of over 3,000 patients with mild outpatient illness have been completed, a set comprised of 4 RCT's and three case series.[36-39,42,52,53] Of the RCTs, the smallest one by Podder et al. was peer-reviewed and published, two RCTs have been posted on pre-print servers, and the largest RCT passed quality control review and the data is now available on clinicaltrials.gov.

The largest RCT by Mahmud et al. was conducted in Dhaka, Bangladesh and targeted 400 patients with 363 patients completing the study.[37] In this study, as in many other of the clinical studies to be reviewed, either a tetracycline (doxycycline) or macrolide antibiotic (azithromycin) was included as part of the treatment. The importance of including antibiotics such as doxycycline or azithromycin is unclear, however, both tetracycline and macrolide antibiotics have recognized anti-inflammatory, immunomodulatory, and even antiviral effects.[54-57] Although the posted data from this study does not specify the amount of mildly ill outpatients vs. hospitalized patients treated, important clinical outcomes were profoundly impacted, with increased rates of early improvement (60.7% vs. 44.4% $p<.03$) and decreased rates of clinical deterioration (8.7% vs 17.8%, $p<.013$). Given that mildly ill outpatients mainly comprised the study cohort, only two deaths were observed (both in the control group).

Another RCT by Hashim et al. in Baghdad, Iraq included 140 patients equally divided; the control group received standard care, the treated group included a combination of both outpatient and hospitalized patients.[42] In the 96 patients with mild-to-moderate outpatient illness, they treated 48 patients with a combination of ivermectin/doxycycline and standard of care and compared outcomes to the 48 patients treated with standard of care alone. The standard of care in this trial included many

elements of the MATH+ protocol, such as dexamethasone 6mg/day or methylprednisolone 40mg twice per day if needed, Vitamin C 1000mg twice/day, Zinc 75–125mg/day, Vitamin D3 5000 IU/day, azithromycin 250mg/day for 5 days, and acetaminophen 500mg as needed. Although no patients in either group progressed or died, the time to recovery was significantly shorter in the ivermectin treated group (6.3 days vs 13.7 days, p<.0001).

Another RCT of ivermectin treatment in 116 outpatients was recently posted on the pre-print server Research Square by Chowdhury et al. in Bangladesh.[53] In this trial they compared a group of 60 patients treated with the combination of ivermectin/doxycycline to a group of 60 patients treated with hydroxychloroquine/doxycycline with a primary outcome of time to negative PCR. Although they found no difference in this outcome, in the treatment group, the time to symptomatic recovery approached statistical significance (5.9 days vs. 7.0 days, p=.07). In another smaller RCT of 62 patients by Podder et al., they also found a shorter time to symptomatic recovery that approached statistical significance (10.1 days vs 11.5 days, p>.05, 95% CI, 0.86−3.67).[53]

Morgenstern et al. in the Dominican Republic reported a case series of 2,688 consecutive symptomatic outpatients seeking treatment in the emergency room, the majority of whom were diagnosed using a clinical algorithm. The patients were treated with high dose ivermectin of 0.4mg/kg for one dose along with five days of azithromycin. Only 16 of the 2,688 patients (0.59%) required subsequent hospitalization with one death recorded.[40]

In another case series of 100 patients by Mushed et al. in Bangladesh, all treated with a combination of 0.2mg/kg ivermectin and doxycycline, they found that no patient required hospitalization nor died, and all patients symptoms improved within 72 hours.[35]

Finally, in a case series from Argentina by Carvallo et al., they reported on a combination protocol called IDEA which used ivermectin, aspirin, dexamethasone and enoxaparin. In the 135 mild illness patients, all survived.[36]

Clinical studies of the efficacy of ivermectin in hospitalized patients

Studies of ivermectin amongst more severely ill hospitalized patients include 3 OCTs, one RCT, a database analysis study and one case series.[38,39,41,42,58] Two of the OCTs were published in major medical journals, with one RCT and one OCT and the database analysis posted on pre-print servers. The one largely outpatient RCT done by Hashim reviewed above also included 22 hospitalized patients in each group. In the ivermectin/doxycycline treated group, there were 11 severely ill patients and 11 critically ill patients while in the standard care group, only severely ill patients (n=22) were included due to their ethical concerns of including critically ill patients in the control group.[42] This decision led to a marked imbalance in the severity of illness between these hospitalized patient groups. However, despite the mismatched severity of illness between groups and the small number of patients included, beneficial differences in outcomes were seen, but not all reached statistical significance. For instance, there was a large reduction in the rate of progression of illness (9% vs. 31.8%, p=0.15) and, most importantly, there was a large difference in mortality amongst the severely ill groups which reached a borderline statistical significance, (0% vs 27.3%, p=.052). Another important

finding was the surprisingly low mortality rate of 18% found among the subset of critically ill patients, all of whom were treated with ivermectin.

The largest OCT in hospitalized patients was done by Rajter et al. at Broward Health Hospitals in Florida and which was recently published in the major medical journal *Chest*.[41] They performed a retrospective OCT on 280 consecutive treated patients and compared those treated with ivermectin to those without. 173 patients were treated with ivermectin (almost all with a single dose) while 107 were not. In both unmatched and propensity matched cohort comparisons, similar, large, and statistically significant lower mortality was found amongst ivermectin treated patients (15.0% vs. 25.2%, p=.03). Further, in the subgroup of patients with severe pulmonary involvement, mortality was profoundly reduced when treated with ivermectin (38.8% vs. 80.7%, p=.001).

Another large OCT by Khan et al. in Bangladesh compared 115 pts treated with ivermectin to a standard care cohort consisting of 133 patients.[38] Despite a significantly higher proportion of patients in the ivermectin group being male (i.e. with well-described, lower survival rates in COVID), the groups were otherwise well matched, yet the mortality decrease was statistically significant (0.9% vs. 6.8%, p<.05).[59-61] Another OCT from Brazil was published in the form of a brief letter to the editor by Portman-Baracco et al. Although the primary data was not provided, they reported that in 704 hospitalized patients treated with a single dose of 0.15mg/kg ivermectin compared to 704 controls, overall mortality was reduced (1.4% vs. 8.5%, HR 0.2, 95% CI 0.12-0.37, p<.0001). Similarly, in the patients on mechanical ventilation, mortality was also reduced (1.3% vs. 7.3%).[62] A small study by Gorial et al. from Baghdad, Iraq recently posted on the pre-print server *medRxiv*, compared 16 ivermectin treated patients to 71 controls. This study also reported a significant reduction in length of hospital stay (7 days vs. 13 days, p<.001) in the ivermectin group.[39] The case series by Carvallo using the IDEA protocol, which included ivermectin, reported a 3.1% mortality rate amongst the 32 hospitalized patients treated.[36]

One retrospective analysis of a database of hospitalized patients compared responses in patients receiving ivermectin, azithromycin, hydroxychloroquine or combinations of these medicines. In this study, no benefit for ivermectin was found, however the treatment groups in this analysis all included a number of patients who died on day 2, while in the control groups no early deaths occurred, thus the comparison appears limited.[63]

Anti-inflammatory properties of ivermectin supporting efficacy in late phase disease

The evidence for the anti-viral activity of ivermectin from the in-vitro and animal studies is consistent with and supportive of the efficacy demonstrated in the above prophylactic and early treatment trials; however, the large, beneficial impacts reviewed in the preceding section on hospitalized and ICU patient populations suggest that the potent anti-inflammatory properties of ivermectin also play a major role. This assumption is based on the fact that little viral replication is occurring in the later phases of COVID-19, nor can virus be cultured, and only in a minority of autopsies can viral

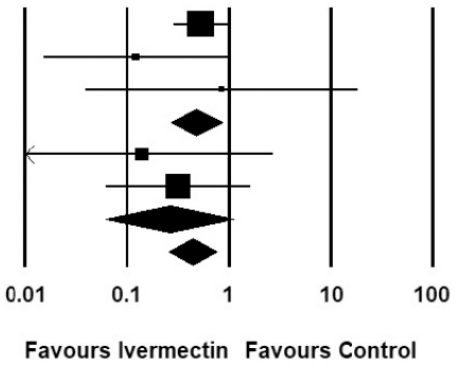
cytopathic changes be found.[64,65,66] Given the general lack of viral presence or cytopathic activity late in the disease course, this supports the finding by Li et al. that it is the non-viable RNA fragments of SARS-CoV-2 that lead to the high mortality and morbidity in COVID-19 via the provocation of an overwhelming and injurious inflammatory response.[67] Based on these insights, it appears that the increasingly well described in-vitro properties of ivermectin as an inhibitor of inflammation are far more clinically potent than previously recognized. The growing list of studies demonstrating the anti-inflammatory properties of ivermectin include its ability to; inhibit cytokine production after lipopolysaccharide exposure, downregulate transcription of NF-kB, and limit the production of both nitric oxide and prostaglandin E_2.[28-30]

Summary of the clinical evidence base for ivermectin against COVID-19

The below meta-analysis includes the mortality data from the OCTs and RCTs separately (Figure 1). The consistent and reproducible signals leading to an overall statistically significant mortality benefit from within both study designs is remarkable, especially given that in several of the studies treatment was initiated late in the disease course.

Figure 1. Meta-analysis of ivermectin clinical studies

Group by RCT-Obs	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
OBS	Rajter	0.524	0.287	0.958	-2.099	0.036
OBS	Khan	0.121	0.015	0.969	-1.990	0.047
OBS	Gorial	0.842	0.039	18.393	-0.109	0.913
OBS		0.477	0.270	0.844	-2.546	0.011
RCT	Mahmud	0.138	0.007	2.694	-1.306	0.192
RCT	Hashim	0.314	0.061	1.611	-1.389	0.165
RCT		0.259	0.062	1.087	-1.846	0.065
Overall		0.439	0.259	0.745	-3.047	0.002



A detailed summary of each trial which comprised the previously reviewed clinical evidence base can be found in Table 3 below:

Table 3. Clinical studies on ivermectin efficacy in COVID-19

AUTHOR, COUNTRY, SOURCE	STUDY DESIGN, SIZE	STUDY SUBJECTS	IVERMECTIN DOSE	DOSE FREQUENCY	CLINICAL OUTCOMES REPORTED
Prophylaxis Trials					% Ivermectin vs. % Controls
Shouman W, Egypt *www.clinicaltrials.gov* NCT0442256	RCT N=304	Household members of pts with +COVID-19 PCR test	40–60kg: 15mg 60–80kg: 18mg > 80kg: 24mg	Two doses, 72 hours apart	7.4% vs. 58.4% developed COVID-19 symptoms, p<.001
Carvallo H, Argentina *www.clinicaltrials.gov* NCT04425850	RCT N=229	Healthy patients negative for COVID-19 PCR	200 mcg drops	1 drop five times a day x 28 days	0.0% vs. 11.2% contracted COVID-19 p<.001
Behera P, India *medRxiv* doi.org/10.1101/2020.10.29.20222661	OCT N=186 case control pairs	Health Care Workers	300 mcg/kg	Day 1 and Day 4	2 doses reduced odds of contracting COVID-19 (OR 0.27 95% CI 0.16–0.53)
Clinical Trials – Hospitalized Patients					
Rajter JC, Florida *Chest 2020* doi.org/10.1016/j.chest.2020.10.009	OCT N=280	All hospitalized patients	200 mcg/kg + azithromycin	Day 1 and Day 7 if needed	Overall mortality 15.0% vs. 25.2%, p=.03, Severe illness mortality 38.8 vs. 80.7%, p=.001)
Khan X, Bangladesh *Arch Bronconeumol. 2020* doi.org/10.1016/j.arbres.2020.08.007	OCT N=248	All hospitalized patients	12 mg	Once on admission	Mortality 0.9% vs. 6.8%, p<.05, LOS 9 vs. 15 days, p<.001
Goria FI, Iraq *medRxiv* doi.org/10.1101/2020.07.07.20145979	OCT N=87	All Hospitalized patients	200 mcg/kg + HCQ and azithromycin	Once on admission	LOS 7.6 vs. 13.2, p<.001, 0/15 vs. 2/71 died
Soto-Beccerra P, Peru *medRxiv* doi.org/10.1101/2020.10.06.20208066	OCT N=5683, IVM, N=563	Hospitalized patients, database analysis	Unknown dose <48hrs after admission	Unknown	No benefits found
Hashim H, Iraq *medRxiv* doi.org/10.1101/2020.10.26.20219345	RCT N=140	2/3 outpatients, 1/3 hospital pts	200mcg/kg + doxycycline	Daily for 2–3 days	Recovery time 6.3 vs 13.6 days (p<.001), 0% vs 27.3% mortality in severely ill (p=.052)
Portman-Baracco A, Brazil *Arch Bronconeumol. 2020* Doi.org/10.1016/j.arbres.2020.06.011	OCT N=1408	All Hospitalized patients	150mcg/kg	Once	Overall mortality 1.4% vs. 8.5%, HR 0.2, 95% CI 0.11-0.37, p<.0001
Clinical Trials – Outpatients					
Carvallo H, Argentina *medRxiv* doi.org/10.1101/2020.09.10.20191619	Case Series N= 167	Outpatients and hospitalized	24mg=mild, 36mg=moderate, 48mg=severe	Days 0 and 7	All 135 with mild illness survived, 1/32 (3.1% of hospitalized patients died
Mahmud R, Bangladesh *www.clinicaltrials.gov* NCT0452383	RCT N=363	Outpatients and hospitalized	12mg + doxycycline	Once, within 3 days of PCR+ test	Early improvement 60.7% vs. 44.4%, p<.03, deterioration 8.7% vs 17.8%, p<.02
Podder CS, Bangladesh *IMC J Med Sci 2020;14(2)*	RCT, N=62	Outpatients	200mcg/kg	Once	Recovery time 10.1 vs 11.5 days (NS), average time 5.3 vs 6.3 (NS)
Alam A, Bangladesh, *J of Bangladesh College Phys and Surg*, 2020;38:10-15 doi.org/10.3329/jbcps.v38i0.47512	Case series N=100	Outpatients	200mcg/kg + doxycycline	Once	All improved within 72 hours
Chowdhury A, Bangladesh *Research Square* doi:10.21203/rs.3.rs-38896/v1	RCT N=116	Outpatients	200mcg/kg + doxycycline	Once	Recovery time 5.93 vs 9.33 days (p=.071)
Morgenstern J, Dominican Republic *medRxiv* doi: https://doi.org/10.1101/2020.10.29.20222505	Case Series N=3,099	Outpatients and hospitalized	Outpatients: 0.4mg/kg Hospital Patients: 0.3mg/kg	Outpatients:0.3mg/kg x 1 dose Inpatients: 0.3mg/kg, Days 1,2,6,7	Mortality = 0.03% in 2688 outpatients, 1% in 300 non-ICU hospital patients, 30.6% in 111 ICU patients

Epidemiological data showing impacts of widespread ivermectin use on population mortality

Similar to the individual cities in Brazil that measured large decreases in case counts soon after distributing ivermectin in comparison to neighboring cities without such campaigns, in Peru, the government approved the use of ivermectin by decree on May 8, 2020, solely based on the in-vitro study by Caly et al. from Australia.[43,68] Soon after, multiple state health ministries initiated ivermectin distribution campaigns in an effort to decrease what was at that time some of the highest COVID-19 morbidity and mortality rates in the world. In a recent paper posted to the preprint server Research Square by a data analyst named Juan Chamie, two critical sets of data were compiled and compared; first he reviewed the reports on the timing and magnitude of each regions ivermectin interventions via a review of official communications, press releases, and the Peruvian Situation Room database in order to confirm the dates of effective delivery, and second, data on the mortality and fatality in selected age groups over time was compiled from the registry of the National Computer System of Deaths (SINADEF), and from the National Institute of Statistics and Informatics.[43] With these data, he was then able to compare the timing of major decreases in both excess deaths and case fatality rates among 8 states in Peru with the initiation dates of their respective ivermectin distribution campaigns as shown in Figure 2 below. Excess deaths were calculated by comparison to death rates at the same time in the 3 years prior to the COVID-19 pandemic. The analysis was restricted solely to patients over 60 in order to remove any confounding due to increases in infections amongst healthier younger, adults.

Figure 2. Total Deaths/Population and Case Incidence for COVID-19/Population in population older than 60 years old for eight Peruvian states deploying mass ivermectin treatment

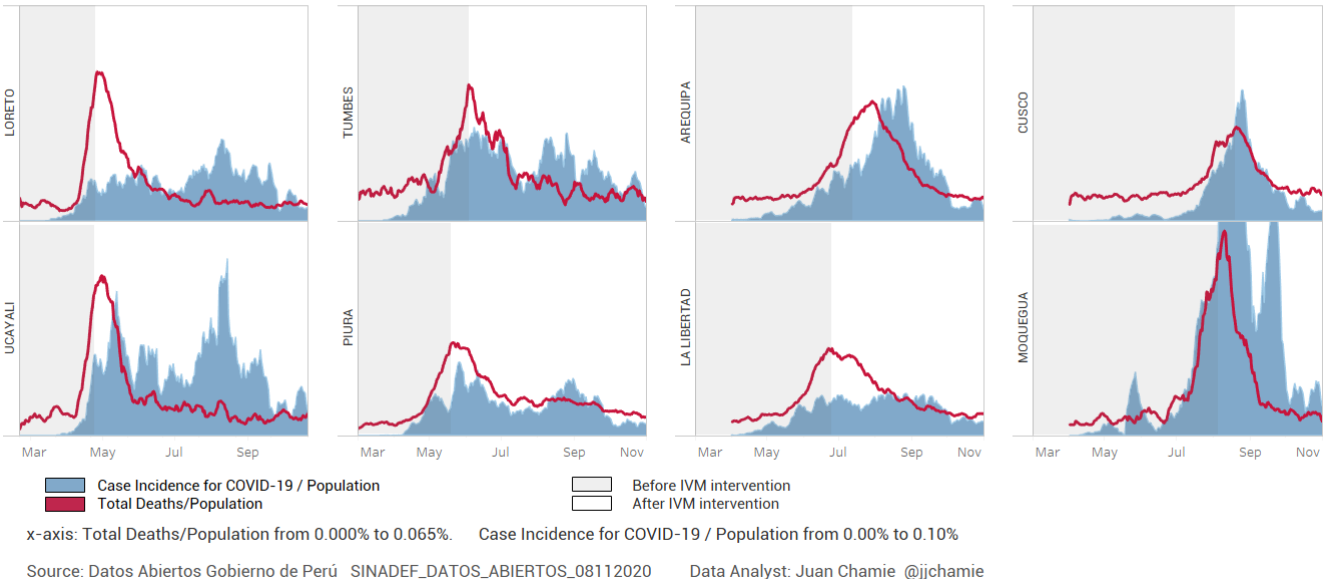
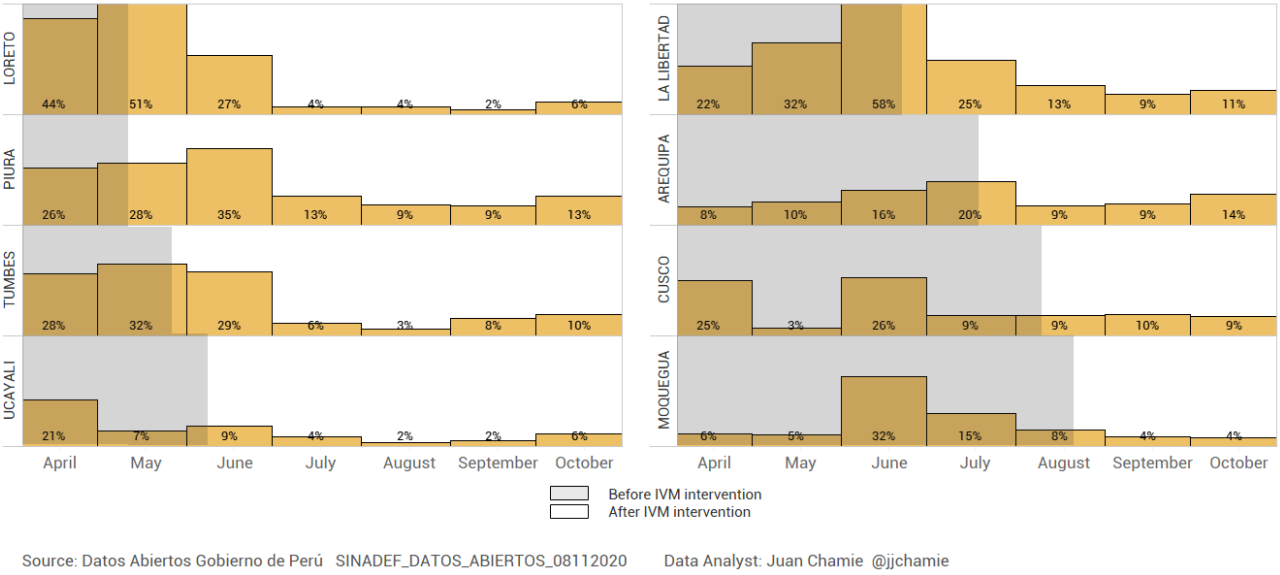


Figure 3 below from the same paper presents data on the case fatality rates in patients over 60, again among the 8 states in Peru. Note the dramatically decreased case fatality rates among older patients with COVID-19 after ivermectin became widely distributed in those areas.

Figure 3. Case Fatality Rate in population older than 60 years old for eight Peruvian states deploying mass ivermectin treatment



The reduced mortality rates achieved throughout Peru can also be seen from the analysis of the three Brazilian cities reviewed above, shown in Table 3 below.

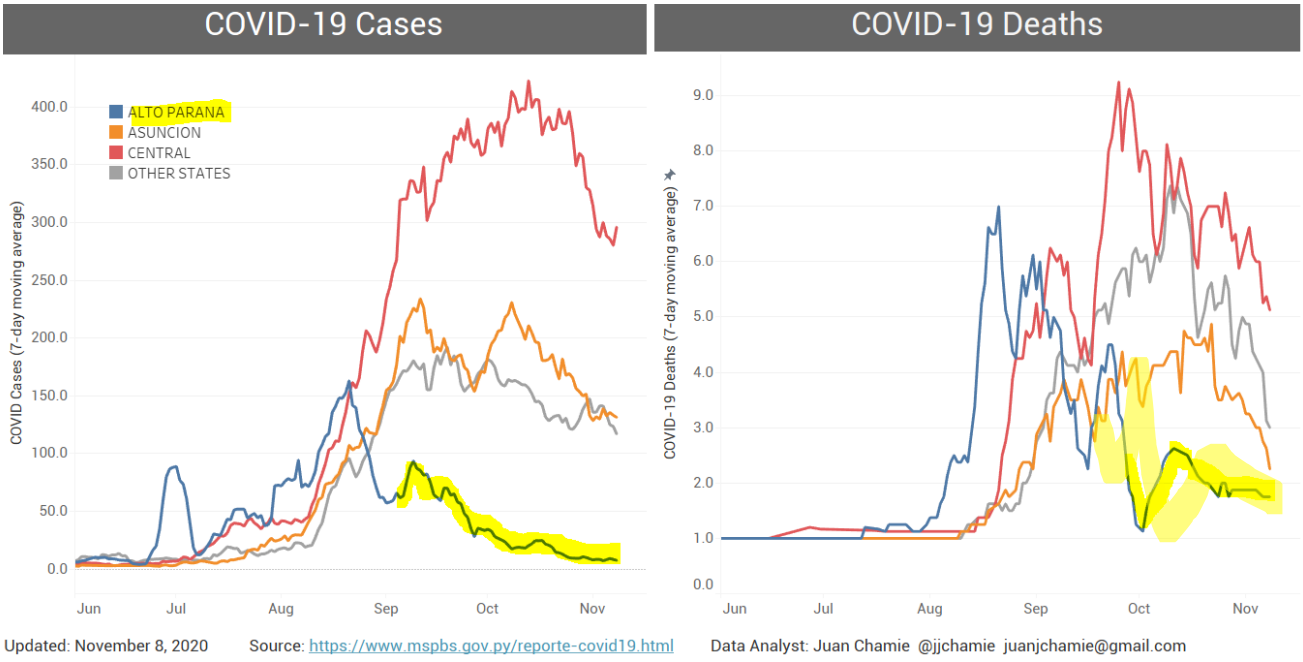
Table 4. Change in death rates among neighboring regions in Brazil
(bolded regions contained a major city that distributed Ivermectin to its citizens, the other regions did not)

REGION	STATE	% CHANGE IN AVERAGE DEATHS/ WEEK COMPARED TO 2 WEEKS PRIOR	TOTAL COVID-19 RELATED DEATHS	DEATHS/100K
South	**Santa Catarina**	**–36**	**2,529**	**35.6**
	PARANÁ	–3	3,823	35.3
	Rio Grande do Sul	–5	4,055	33.4
North	**Amapá**	**–75**	**678**	**80.2**
	AMAZONAS	–42	3,892	93.9
	Pará	13	6,344	73.7
North East	**Rio Grande do Norte**	**–65**	**2,315**	**66.0**
	CEARÁ	62	8,666	95.1
	Paraíba	–30	2,627	65.4

Another compelling example can be seen from the data compiled from Paraguay, again by Chamie, who noted that the government of the state of Alto Parana had launched an ivermectin distribution

campaign in early September. Although the campaign was officially described as a "de-worming" program, this was interpreted as a guise by the regions governor to avoid reprimand or conflict with the National Ministry of Health that recommended against use of ivermectin to treat COVID-19 in Paraguay.[69] The program began with a distribution of 30,000 boxes of ivermectin and by October 15, the governor declared that there were very few cases left in the state as can be seen in Figure 4 below.[45,70]

Figure 4. Paraguay – COVID-19 case counts and deaths in Alto Parana (blue) after Ivermectin distribution began (yellow highlight), compared to other departments[45,71]



History and safety of ivermectin

The discovery of Ivermectin in 1975 was awarded the 2015 Nobel Prize in Medicine given its global impact in reducing onchocerciasis (river blindness), lymphatic filiariasis, and scabies in endemic areas of central Africa, Latin America, India and Southeast Asia.[72] It has since been included on the WHO's "List of Essential Medicines." Beyond the massive, global reductions in morbidity and mortality achieved in many low-and middle-income populations, the knowledge base establishing its high margin of safety and low rate of adverse effects is nearly unparalleled given it is based on the experience of billions of doses dispensed. In one example, The Meztican (ivermectin) Donation Program established in 1987 to combat river blindness in over 33 countries provided more than 570 million treatments in its first 20 years alone.[72] Numerous studies report low rates of adverse events, with the majority mild, transient, and largely attributed to the body's inflammatory response to the death of the parasites and include itching, rash, swollen lymph nodes, joint paints, fever and headache.[46] In a study which combined results from trials including over 50,000 patients, serious

events occurred in less than 1% and largely associated with administration in Loa loa.[73] Further, according the pharmaceutical reference standard Lexicomp, the only medications contraindicated for use with ivermectin are the anti-tuberculosis and cholera vaccines while the anticoagulant warfarin would requires dose monitoring.

Currently, (November 8, 2020), it appears that, based on the data from the in-vitro, animal, prophylaxis, clinical, safety, and large scale epidemiologic analyses demonstrating decreases in both case counts and fatality rates in regions with widespread ivermectin use, the anti-parasitic drug ivermectin should be considered a highly effective regional and global solution to the COVID-19 pandemic. A concern with this interpretation and conclusion is that, as was detailed above, many of these trial results have not yet passed peer review and that 5 of the 9 clinical trials were conducted using an observational design. To address the former concern, it is hoped that the journals to which the study manuscripts have been submitted will undertake an expedited review due to the critical importance of those studies in providing the world the appropriate level of scientific evidence required to undertake a potentially major shift in public health policy against this pandemic.

In regards to the misplaced concerns over the soundness of observational trial findings, it must be recognized that observational and randomized trial designs reach equivalent conclusions on average in nearly all cases, as reported in a large Cochrane review of the topic from 2014.[74] In particular, OCTs that employ propensity-matching techniques (as in many of the above trials), find near identical conclusions to later-conducted RCTs in many different disease states, including coronary syndromes, critical illness, and surgery.[75-77]

Despite these repeated findings of equivalence between study designs, the authors recognize that, at times, there are situations where multiple OCTs may conclude a benefit of a specific intervention, while multiple, repeated RCTs do not. In such situations where the entirety of the study design conclusions conflict, it can be assumed that one of the sets of trial designs contain a systematic bias, un-identified confounder, or "fatal flaw" in execution (i.e. frequent delayed therapy in RCTs, especially in critical illness states), thus it should not be automatically assumed that such confounders or biases exist only within OCTs. Thus, expert interpretation of trial design and data in these situations must prevail. However, as evidenced in the current review, meta-analysis, and summary table, all of the various study design conclusions on ivermectin efficacy strongly align in the same direction and magnitude. Thus, in such a situation, it is imperative that health policy makers and academics avoid the non-evidence based practice of repeatedly dismissing findings from OCTs while over-emphasizing the need for placebo-controlled RCTs, given that such practices, most acutely in this pandemic, have caused harm in patient outcomes when treated with placebo. RCTs are best reserved for medicines with high risk, high cost, and/or a truly indeterminate efficacy. To study medicines that are cheap, safe, and widely available with a long track record of use and an existing favorable efficacy or benefit/ risk ratio, well-conducted OCTs, particularly those employing propensity matching, are not only scientifically valid but most consistent with widely agreed-upon ethical principles, especially in a pandemic. All must consider Declaration 37 of the World Medical Association's "Helsinki Declaration on the Ethical Principles for Medical Research Involving Human Subjects," first established in 1964, which states:

> *In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention* ***if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering.*** *This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.*

In keeping with the above principle, if a physician believes, based on the current body of evidence presented above, that it is far more likely that ivermectin will help rather than harm, it would be unethical to either withhold treatment or to treat with a placebo. However, in such cases, especially if treatment with ivermectin should become widespread, it is imperative that data on clinical outcomes and safety continue to be meticulously collected and expertly analyzed. In keeping with the robust and emerging evidence reviewed above, the Front Line COVID-19 Critical Care Alliance recently created a prophylaxis and early treatment approach for COVID-19 called "I-MASK+". This protocol includes ivermectin as a core therapy in both early treatment and prophylaxis of both high-risk patients and post-exposure to household members with COVID-19 (Tables 5 and 6). The Front Line COVID-19 Critical Care Alliance is committed to measuring outcomes in those treated with ivermectin and reviewing all emerging results from the current and any future clinical trials of ivermectin in COVID-19 (see Table 5).

In summary, based on the existing and cumulative body of evidence, we recommend the use of ivermectin in both prophylaxis and treatment for COVID-19.[75] In the presence of a global COVID-19 surge, the widespread use of this safe, inexpensive, and effective intervention could lead to a drastic reduction in transmission rates as well as the morbidity and mortality in mild, moderate, and even severe disease phases.

Table 5. I-MASK+ Prophylaxis & Early Outpatient Treatment Protocol for COVID-19

PROPHYLAXIS PROTOCOL	
MEDICATION	RECOMMENDED DOSING
Ivermectin	*Weekly Prophylaxis for high risk individuals*: 0.15–0.2 mg/kg* once weekly
	*Post COVID-19 exposure prophylaxis***: 0.2 mg/kg × 1 dose on day 1 and day 3
Vitamin D3	1,000–3,000 IU/day
Vitamin C	1,000 mg twice daily and **Quercetin** 250 mg/day
Melatonin	6 mg before bedtime (causes drowsiness)
Zinc	50 mg/day elemental zinc
Aspirin	80–100 mg/day (unless contraindicated)

Table 5. (continued)

EARLY OUTPATIENT TREATMENT PROTOCOL***	
MEDICATION	RECOMMENDED DOSING
Ivermectin	0.2 mg/kg days 1 and 4
Vitamin D3	4,000 IU/day
Vitamin C	2,000 mg 2–3 times daily and **Quercetin** 250 mg twice a day
Melatonin	10 mg before bedtime
Zinc	100 mg/day elemental zinc
Aspirin	325 mg/day (unless contraindicated)

* Example for a person of 50 kg (body weight): 50 kg × 0.15 mg = 7.5 mg (1 kg = 2.2 lbs)= 2.5 tablets (3mg/tablet). See table 6 for weight-based dose calculations
** To use if a household member is COVID-19 positive, or if you have had prolonged exposure to a COVID-19+ patient without wearing a mask
*** For late phase – hospitalized patients – see the FLCCC's "MATH+" protocol on www.flccc.net

Table 6. Suggested Ivermectin Dose by Body Weight for Prophylaxis and Treatment of COVID-19

Body weight (doses calculated per upper end of weight range)		**Weekly Prophylaxis dose*** (0.15 mg/kg) Weekly (Each tablet = 3 mg; doses rounded to nearest half tablet)		**Treatment dose*** (0.2 mg/kg) Take two doses, day 1 and day 3 (Each tablet = 3 mg; doses rounded to nearest half tablet above)	
70–90 lb	32–40 kg	6 mg	(2 tablets)	8 mg	(3 tablets=9 mg)
91–110 lb	41–50 kg	7.5 mg	(2.5 tablets)	10 mg	(3.5 tablets)
111–130 lb	51–59 kg	9 mg	(3 tablets)	12 mg	(4 tablets)
131–150 lb	60–68 kg	10 mg	(3.5 tablets)	13.5 mg	(4.5 tablets)
151–170 lb	69–77 kg	11.5 mg	(4 tablets)	15 mg	(5 tablets)
171–190 lb	78–86 kg	13 mg	(4.5 tablets)	16 mg	(5.5 tablets)
191–210 lb	87–95 kg	14.3 mg	(5 tablets)	18 mg	(6 tablets)
211–230 lb	96–104 kg	15 mg	(5 tablets)	20 mg	(7 tablets=21 mg)
231–250 lb	105–113 kg	17 mg	(5.5 tablets)	22 mg	(7.5 tablets=22.5 mg)
251–270 lb	114–122 kg	18 mg	(6 tablets)	24 mg	(8 tablets)
271–290 lb	123–131 kg	19.7 mg	(6.5 tablets)	26 mg	(9 tablets =27 mg)
291–310 lb	132–140 kg	21.1 mg	(7 tablets)	28 mg	(9.5 tablets=28.5 mg)

* "Post-exposure prophylaxis" dose = 0.2mg/kg on day 1 and day 3 (i.e. for persons with a household member that tests positive for COVID-19 or after they have had prolonged indoor exposure to a COVID-19 patient without a mask)

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