Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19

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Abstract

In March 2020, the Front Line COVID-19 Critical Care Alliance (FLCCC) was created and led by Professor Paul E. Marik to continuously review the rapidly emerging basic science, translational, and clinical data to develop a treatment protocol for COVID-19. The FLCCC then recently discovered that ivermectin, an anti-parasitic medicine, has highly potent anti-viral and anti-inflammatory properties against COVID-19. They then identified repeated, consistent, large magnitude improvements in clinical outcomes in multiple, large, randomized and observational controlled trials in both prophylaxis and treatment of COVID-19. Further, data showing impacts on population wide health outcomes have resulted from multiple, large "natural experiments" that occurred when various

city mayors and regional health ministries within South American countries initiated "ivermectin distribution" campaigns to their citizen populations in the hopes the drug would prove effective. The tight, reproducible, temporally associated decreases in case counts and case fatality rates in each of those regions compared to nearby regions without such campaigns, suggest that ivermectin may prove to be a global solution to the pandemic. This was further evidenced by the recent incorporation of ivermectin as a prophylaxis and treatment agent for COVID-19 in the national treatment guidelines of Belize, Macedonia, and the state of Uttar Pradesh in Northern India, populated by 210 million people. To our knowledge, the current review is the earliest to compile sufficient clinical data to demonstrate the strong signal of therapeutic efficacy as it is based on numerous clinical trials in multiple disease phases. One limitation is that half the controlled trials have been published in peer-reviewed publications, with the remainder taken from manuscripts uploaded to medicine pre-print servers. Although it is now standard practice for trials data from pre-print servers to immediately influence therapeutic practices during the pandemic, given the controversial therapeutics adopted as a result of this practice, the FLCCC argues that it is imperative that our major national and international health care agencies devote the necessary resources to more quickly validate these studies and confirm the major, positive epidemiological impacts that have been recorded when ivermectin is widely distributed among populations with a high incidence of COVID-19 infections.

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.[1] 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 based on the core therapeutic interventions of methylprednisolone, ascorbic acid, thiamine and heparin (MATH+), with the "+" referring to multiple, optional adjunctive treatments. The MATH+ protocol was based on the collective expertise of the group in both the research and treatment of multiple other severe infections causing lung injury.

Two manuscripts reviewing different aspects of both the scientific rationale and evolving published clinical evidence in support of the MATH+ protocol were published in major medical journals at two different time points in the pandemic (Kory et al., 2020;Marik et al., 2020). The most recent paper reported a 6.1% hospital mortality rate in COVID-19 patients measured in the two U.S hospitals that systematically adopted the MATH+ protocol (Kory et al., 2020). This was a markedly decreased mortality rate compared to the 23.0% hospital mortality rate calculated from a review of 45 studies including over 230,000 patients (unpublished data; available on request).

Although the adoption of MATH+ has been considerable, it largely occurred only after the treatment efficacy of the majority of the protocol components (corticosteroids, ascorbic acid, heparin, statins, Vitamin D, melatonin) were either validated in subsequent randomized controlled trials or more strongly supported with large observational data sets in COVID-19 (Entrenas Castillo et al., 2020;Horby et al., 2020;Jehi et al., 2020;Nadkarni et al., 2020;Rodriguez-Nava et al., 2020;Zhang et al., 2020a;Zhang et al., 2020b). 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 December 31st, 2020, the number of deaths attributed to COVID-19 in the United States reached 351,695 with over 7.9 million active

[1] https://www.flccc.net

cases, the highest number to date.[2] Multiple European countries have now begun to impose new rounds of restrictions and lockdowns.[3]

Further compounding these alarming developments was a wave of recently published results from therapeutic trials done on medicines thought effective for COVID-19 which found a lack of impact on mortality with use of remdesivir, hydroxychloroquine, lopinavir/ritonavir, interferon, convalescent plasma, tocilizumab, and mono-clonal antibody therapy (Agarwal et al., 2020;Consortium, 2020;Hermine et al., 2020;Salvarani et al., 2020).[4] One year into the pandemic, the only therapy considered "proven" as a life-saving treatment in COVID-19 is the use of corticosteroids in patients with moderate to severe illness (Horby et al., 2020). Similarly, most concerning is the fact that little has proven effective to prevent disease progression to prevent hospitalization.

Fortunately, 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 growing numbers of the studies supporting this conclusion have passed through peer review, approximately half of the remaining trials data are from manuscripts uploaded to medical pre-print servers, a now standard practice for both rapid dissemination and adoption of new therapeutics throughout the pandemic. 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 (Mastrangelo et al., 2012;Wagstaff et al., 2012;Tay et al., 2013;Götz et al., 2016;Varghese et al., 2016;Atkinson et al., 2018;Lv et al., 2018;King et al., 2020;Yang et al., 2020).
2) Ivermectin inhibits SARS-CoV-2 replication and binding to host tissue via several observed and proposed mechanisms (Caly et al., 2020a).
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 (Zhang et al., 2008;Ci et al., 2009;Zhang et al., 2009).
4) Ivermectin significantly diminishes viral load and protects against organ damage in multiple animal models when infected with SARS-CoV-2 or similar coronaviruses (Arevalo et al., 2020;de Melo et al., 2020).
5) Ivermectin prevents transmission and development of COVID-19 disease in those exposed to infected patients (Behera et al., 2020;Bernigaud et al., 2020;Carvallo et al., 2020b;Elgazzar et al., 2020;Hellwig and Maia, 2020;Shouman, 2020).
6) Ivermectin hastens recovery and prevents deterioration in patients with mild to moderate disease treated early after symptoms (Carvallo et al., 2020a;Elgazzar et al., 2020;Gorial et al., 2020;Khan et al., 2020;Mahmud, 2020;Morgenstern et al., 2020;Robin et al., 2020).
7) Ivermectin hastens recovery and avoidance of ICU admission and death in hospitalized patients (Elgazzar et al., 2020;Hashim et al., 2020;Khan et al., 2020;Niaee et al., 2020;Portmann-Baracco et al., 2020;Rajter et al., 2020;Spoorthi V, 2020).

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[2] https://www.worldometers.info/coronavirus/country/us/

[3] https://www.npr.org/sections/coronavirus-live-updates/2020/12/15/946644132/some-european-countries-batten-down-for-the-holidays-with-new-coronavirus-lockdo

[4] https://www.lilly.com/news/stories/statement-activ3-clinical-trial-nih-covid19

8) Ivermectin reduces mortality in critically ill patients with COVID-19 (Elgazzar et al., 2020;Hashim et al., 2020;Rajter et al., 2020).
9) Ivermectin leads to striking reductions in case-fatality rates in regions with widespread use (Chamie, 2020).[5]
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 (Kircik et al., 2016).
11) The World Health Organization has long included ivermectin on its "List of Essential Medicines".[6]

Following is a comprehensive review of the available efficacy data as of December 12, 2020, taken from *in vitro*, animal, clinical, and real-world studies all showing the above impacts of ivermectin in COVID-19.

History of ivermectin

In 1975, Professor Satoshi Omura at the Kitsato institute in Japan isolated an unusual *Streptomyces* bacteria from the soil near a golf course along the south east coast of Honshu, Japan. Omura, along with William Campbell, found that the bacterial culture could cure mice infected with the roundworm *Heligmosomoides polygyrus*. Campbell isolated the active compounds from the bacterial culture, naming them "avermectins" and the bacterium *Streptomyces avermitilis* for the compounds' ability to clear mice of worms (Crump and Omura, 2011). Despite decades of searching around the world, the Japanese microorganism remains the only source of avermectin ever found. Ivermectin, a derivative of avermectin, then proved revolutionary. Originally introduced as a veterinary drug, it soon after made historic impacts in human health, improving the nutrition, general health and well-being of billions of people worldwide ever since it was first used to treat Onchocerciasis (river blindness) in humans in 1988. It proved ideal in many ways, given that it was highly effective, broad-spectrum, safe, well tolerated and could be easily administered (Crump and Omura, 2011). Although it was used to treat a variety of internal nematode infections, it was most known as the essential mainstay of two global disease elimination campaigns that has nearly eliminated the world of two of its most disfiguring and devastating diseases. The unprecedented partnership between Merck & Co. Inc., and the Kitasato Institute combined with the aid of international health care organizations has been recognized by many experts as one of the greatest medical accomplishments of the 20th century. One example was the decision by Merck & Co to donate ivermectin doses to support the Meztican Donation Program which then provided over 570 million treatments in its first 20 years alone (Tambo et al.). Ivermectins' impacts in controlling Onchocerciasis and Lymphatic filariasis, diseases which blighted the lives of billions of the poor and disadvantaged throughout the tropics, is why its discoverers were awarded the Nobel Prize in Medicine in 2015 and the reason for its inclusion on the WHO's "List of Essential Medicines." Further, it has also been used to successfully overcome several other human diseases and new uses for it are continually being found (Crump and Omura, 2011).

Pre-Clinical Studies of Ivermectin's activity against SARS-CoV-2

[5] https://trialsitenews.com/an-old-drug-tackles-new-tricks-ivermectin-treatment-in-three-brazilian-towns/
[6] https://www.who.int/publications/i/item/WHOMVPEMPIAU201907

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 (Mastrangelo et al., 2012;Wagstaff et al., 2012;Tay et al., 2013;Götz et al., 2016;Varghese et al., 2016;Atkinson et al., 2018;Lv et al., 2018;King et al., 2020;Yang et al., 2020). 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. 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 (Caly et al., 2020b). However, some questioned whether this observation is generalizable clinically given the inability to achieve similar tissue concentrations employed in their experimental model using standard or even massive doses of ivermectin (Bray et al., 2020;Schmith et al., 2020). It should be noted that the concentrations required for effect in cell culture models bear little resemblance to human physiology given the absence of an active immune system working synergistically with a therapeutic agent such as ivermectin. Further, prolonged durations of exposure to a drug likely would require a fraction of the dosing in short term cell model exposure. Further, multiple co-existing or alternate mechanisms of action likely explain the clinical effects observed, such as the competitive binding of ivermectin with the host receptor-binding region of SARS-CoV-2 spike protein, as proposed in six molecular modeling studies (Dayer, 2020;Hussien and Abdelaziz, 2020;Lehrer and Rheinstein, 2020;Maurya, 2020;Nallusamy et al., 2020;Suravajhala et al., 2020). In four of the studies, ivermectin was identified as having the highest or among the highest of binding affinities to spike protein S1 binding domains of SARS-CoV-2 among hundreds of molecules collectively examined, with ivermectin not being the particular focus of study in four of these studies (Scheim, 2020). This is the same mechanism by which viral antibodies, in particular, those generated by the Pfizer and Moderna vaccines, contain the SARS-CoV-2 virus. The high binding activity of ivermectin to the SARS-CoV-2 spike protein could limit binding to either the ACE-2 receptor or sialic acid receptors, respectively either preventing cellular entry of the virus or preventing hemagglutination, a recently proposed pathologic mechanism in COVID-19 (Dasgupta J, 2020;Dayer, 2020;Lehrer and Rheinstein, 2020;Maurya, 2020;Scheim, 2020). 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 (Lehrer and Rheinstein, 2020;Sen Gupta et al., 2020). Finally, ivermectin also binds to the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), thereby inhibiting viral replication (Swargiary, 2020).

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 (Arevalo et al., 2020). 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.

Dias De Melo and colleagues recently posted the results of a study they did with golden hamsters that were intranasally inoculated with SARS-CoV-2 virus, and at the time of the infection, the animals also received a single subcutaneous injection of ivermectin at a dose of 0.4mg/kg on day 1 (de Melo et al., 2020). Control animals received only the physiologic solution. They found the following among the ivermectin treated hamsters; a dramatic reduction in anosmia (33.3% vs 83.3%, p=.03) which was also sex-dependent in that the male hamsters exhibited a reduction in clinical score

while the treated female hamsters failed to show any sign of anosmia. They also found significant reductions in cytokine concentrations in the nasal turbinate's and lungs of the treated animals despite the lack of apparent differences in viral titers.

Despite these mounting insights into the existing and potential mechanisms of action of ivermectin both as a prophylactic and treatment agent, it must be emphasized that significant research gaps remain and that many further *in vitro* and animal studies should be undertaken to better define not only these mechanisms but also to further support ivermectin's role as a prophylactic agent, especially in terms of the optimal dose and frequency required.

Pre-Clinical studies of ivermectin's anti-inflammatory properties

Given that little viral replication occurs 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 (Perera et al., 2020;Polak et al., 2020;Young et al., 2020), the most likely pathophysiologic mechanism is that identified by Li et al. where they showed that the non-viable RNA fragments of SARS-CoV-2 leads to a high mortality and morbidity in COVID-19 via the provocation of an overwhelming and injurious inflammatory response (Li et al., 2013). Based on these insights and the clinical benefits of ivermectin in late phase disease to be reviewed below, 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 (Zhang et al., 2008;Ci et al., 2009;Zhang et al., 2009).

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 three randomized controlled trials (RCT) and five observational controlled trials (OCT) with four of the eight (two of them RCT's) published in peer-reviewed journals (Behera et al., 2020;Bernigaud et al., 2020;Carvallo et al., 2020b;Chala, 2020;Elgazzar et al., 2020;Hellwig and Maia, 2020;Shouman, 2020).

Elgazzar and colleagues at Benha University in Egypt randomized 200 health care and households contacts of COVID-19 patients where the intervention group consisted of 100 patients given a high dose of 0.4mg/kg on day 1 and a second dose on day 7 in addition to wearing personal protective equipment (PPE), while the control group of 100 contacts wore PPE only (Elgazzar et al., 2020). They reported a large and statistically significant reduction in contacts testing positive by RT-PCR when treated with ivermectin vs. controls, 2% vs 10%, $p<.05$.

Shouman conducted an RCT at Zagazig University in Egypt, including 340 (228 treated, 112 control) family members of patients positive for SARS-CoV-2 via PCR (Shouman, 2020). 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%, $p<.001$.

Recently Alam et al from Bangladesh performed a prospective observational study of 118 patients that were evenly split into those that volunteered for either the treatment or control arms, described as a persuasive approach. Although this method, along with the study being unblinded likely led to confounders, the differences between the two groups were so large (6.7% vs. 73.3%, $p<.001$) and similar to the other prophylaxis trial results that confounders alone are unlikely to explain

such a result (Alam et al., 2020). Carvallo et al also performed a prospective observational trial where they gave healthy volunteers ivermectin and carrageenan daily for 28 days and matched them to similarly healthy controls who did not take the medicines (Carvallo et al., 2020b). Of the 229 study subjects, 131 were treated 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 ($p<.001$). In a much larger follow-up observational controlled trial by the same group that included 1,195 health care workers, they found that over a 3-month period, there were no infections recorded among the 788 workers that took weekly ivermectin prophylaxis while 58% of the 407 controls had become ill with COVID-19. This study demonstrates that protection against transmission can be achieved among high-risk health care workers by taking 12mg once weekly (Carvallo et al., 2020b). The Carvallo IVERCAR protocol was also separately tested in a prospective RCT by the Health Ministry of Tucuman, Argentina where they found that among 234 health care workers, the intervention group that took 12 mg once weekly, only 3.4% contracted COVID-19 vs. 21.4% of controls, $p<.0001$(Chala, 2020).

The need for weekly dosing in the Carvallo study over a 4 month period may not have been necessary given that, in a recent RCT from Dhaka, Bangladesh, the intervention group (n=58) took 12mg only once monthly for a similar 4 month period and also reported a large and statistically significant decrease in infections compared to controls, 6.9% vs. 73.3%, $p<.05$ (Alam et al., 2020). Then, in a large retrospective observational case-control study from India, Behera 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 (Behera et al., 2020). 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 instituted a prophylaxis protocol for their health care workers where they now take two 0.3mg/kg doses of ivermectin 72 hours apart and repeat the dose monthly.

Data which further illuminates the protective role of ivermectin against COVID-19 comes from a study of nursing home residents in France which reported that in a facility that suffered a scabies outbreak where all 69 residents and 52 staff were treated with ivermectin (Behera et al., 2020), they found that during the time period surrounding this event, 7/69 residents fell ill with COVID-19 (10.1%). In this group with an average age of 90 years, only one resident required oxygen support and no resident died. In a matched control group of residents from surrounding facilities, they found 22.6% of residents fell ill and 4.9% died.

Likely the most definitive evidence supporting the efficacy of ivermectin as a prophylaxis agent was published recently in the International Journal of Anti-Microbial agents where a group of researchers analyzed data using the prophylactic chemotherapy databank administered by the WHO along with case counts obtained by Worldometers, a public data aggregation site used by among others, the Johns Hopkins University (Hellwig and Maia, 2020). When they compared the data from countries with active ivermectin mass drug administration programs for the prevention of parasite infections, they discovered that the COVID-19 case counts were significantly lower in the countries with recently active programs, to a high degree of statistical significance, $p<.001$.

Figure 1 below presents a meta-analysis performed by the study authors of the controlled ivermectin prophylaxis trials in COVID-19.

Figure 1. Meta-analysis of ivermectin prophylaxis trials in COVID-19

Group by Type	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Symptomatic Infection / Total: Group-Ivermectin	Group-Control
Obs	Behera	0.127	0.069	0.232	-6.704	0.000	15 / 91	171 / 281
Obs	Carvallo -1	0.029	0.002	0.497	-2.441	0.015	0 / 131	11 / 98
Obs	Carvallo- 2	0.000	0.000	0.007	-5.426	0.000	0 / 788	237 / 407
Obs	Alam	0.027	0.008	0.086	-6.077	0.000	4 / 58	44 / 60
Obs		0.073	0.044	0.123	-9.900	0.000		
RCT	Elgazzar	0.184	0.039	0.861	-2.150	0.032	2 / 100	10 / 100
RCT	Shouman	0.057	0.029	0.110	-8.542	0.000	15 / 203	59 / 101
RCT	Chala	0.130	0.044	0.388	-3.662	0.000	4 / 117	25 / 117
RCT		0.079	0.047	0.135	-9.385	0.000		

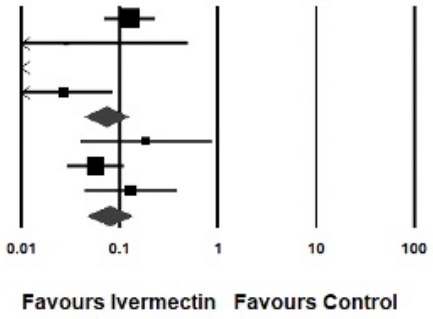


Figure 1 legend: OBS: Observational study, RCT: Randomized Controlled Trial Symbols: Squares: indicate treatment effect of an individual study. Large diamond: reflect summary of study design immediately above. Small diamond: sum effect of all trial designs. Size of each symbol correlates with the size of the confidence interval around the point estimate of treatment effect with larger sizes indicating a more precise confidence interval.

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 (Chamie, 2020). In one such example from Brazil, the cities of Itajai, Macapa, and Natal distributed massive amounts of ivermectin doses to their city's population, where, in the case of Natal, 1 million doses were distributed.[7] The distribution campaign of Itajai began in mid-July, and in Natal they began on June 30th , and in Macapa, the capital city of Amapa and others nearby incorporated ivermectin into their treatment protocols in late May after they were particularly hard hit in April. The data in Table 1 below was obtained from the official Brazilian government site and the national press consortium and show large decreases in case counts in the three cities soon after distribution began compared to their neighboring cities without such campaigns.

The decreases in case counts among the three Brazilian cities shown in Table 1 was also associated with reduced mortality rates as seen in Table 2 below.

[7] https://trialsitenews.com/an-old-drug-tackles-new-tricks-ivermectin-treatment-in-three-brazilian-towns/

Table 1. Comparison of case count decreases among Brazilian cities with and without ivermectin distribution campaigns (bolded cities distributed ivermectin, neighboring regional city below did not)

REGION	NEW CASES	JUNE	JULY	AUGUST	POPULATION 2020 (1000)	% DECLINE IN NEW CASES BETWEEN JUNE AND AUGUST 2020
South	**Itajaí**	**2123**	**2854**	**998**	**223**	**– 53 %**
	Chapecó	1760	1754	1405	224	– 20 %
North	**Macapá**	**7966**	**2481**	**2370**	**503**	**– 70 %**
	Ananindeua	1520	1521	1014	535	– 30 %
North East	**Natal**	**9009**	**7554**	**1590**	**890**	**– 82 %**
	João Pessoa	9437	7963	5384	817	– 43 %

Table 2. 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
South	**Santa Catarina**	**– 36 %**
	PARANÁ	– 3 %
	Rio Grande do Sul	– 5 %
North	**Amapá**	**– 75 %**
	AMAZONAS	– 42 %
	Pará	+ 13 %
North East	**Rio Grande do Norte**	**– 65 %**
	CEARÁ	+ 62 %
	Paraíba	– 30 %

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

Currently, seven trials which include a total of over 3,000 patients with mild outpatient illness have been completed, a set comprised of 7 RCT's and four case series (Babalola et al.;Cadegiani et al., 2020;Carvallo et al., 2020a;Chaccour et al., 2020;Chowdhury et al., 2020;Espitia-Hernandez et al., 2020;Gorial et al., 2020;Hashim et al., 2020;Khan et al., 2020;Mahmud, 2020;Podder et al., 2020;Ravikirti et al., 2021).

The largest, a double blinded RCT by Mahmud et al. was conducted in Dhaka, Bangladesh and targeted 400 patients with 363 patients completing the study (Mahmud, 2020). 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 (*58-61*). 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<.02). Given that mildly ill outpatients mainly comprised the study cohort, only two deaths were observed (both in the control group).

Ravikirti performed a double-blind RCT of 115 patients, ang although the primary outcome of PCR positivity on Day 6 was no different, the secondary outcome of mortality was 0%vs. 6.9%, p=.019 (Ravikirti et al., 2021). Babalola in Nigeria also performed a double blind-RCT of 62 patients, and, in contrast to Ravikirti, they found a significant difference in viral clearance between both the low and high dose treatment groups and controls in a dose dependent fashion, p=.006 (Babalola et al.).

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 (Hashim et al., 2020). 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).

Chaccour et al conducted a small, double-blinded RCT in Spain where they randomized 24 patients to ivermectin vs placebo and although they found no difference in PCR positivity at day 7, they did find statistically significant decreases in viral loads, patient days of anosmia (76 vs 158, p<.05), and patient days with cough (68 vs 98, p<.05) (Chaccour et al., 2020).

Another RCT of ivermectin treatment in 116 outpatients was performed by Chowdhury et al. in Bangladesh where 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 (Chowdhury et al., 2020). 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) (Podder et al., 2020).

A medical group 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 (Morgenstern et al., 2020).

In another case series of 100 patients 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 (Robin et al., 2020).

A case series from Argentina reported on a combination protocol which used ivermectin, aspirin, dexamethasone and enoxaparin. In the 135 mild illness patients, all survived (Carvallo et al.,

2020a). Similarly, a case series from Mexico of 28 consecutively treated patients with ivermectin, all were reported to have recovered with an average time to full recovery of only 3.6 days (Espitia-Hernandez et al., 2020).

Clinical studies of the efficacy of ivermectin in hospitalized patients

Studies of ivermectin amongst more severely ill hospitalized patients include 6 RCT's, 5 OCTs, and a database analysis study (Ahmed et al., 2020;Budhiraja et al., 2020;Chachar et al., 2020;Elgazzar et al., 2020;Gorial et al., 2020;Hashim et al., 2020;Khan et al., 2020;Niaee et al., 2020;Portmann-Baracco et al., 2020;Rajter et al., 2020;Soto-Becerra et al., 2020;Spoorthi V, 2020).

The largest RCT in hospitalized patients was performed concurrent with the prophylaxis study reviewed above by Elgazzar et al (Elgazzar et al., 2020). 400 patients were randomized amongst 4 treatment groups of 100 patients each. Groups 1 and 2 included mild/moderate illness patients only, with Group 1 treated with one dose 0.4mg/kg ivermectin plus standard of care (SOC) and Group 2 received hydroxychloroquine (HCQ) 400mg twice on day 1 then 200mg twice daily for 5 days plus standard of care. There was a statistically significant lower rate of progression in the ivermectin treated group (1% vs. 22%, p<.001) with no deaths and 4 deaths respectively. Groups 3 and 4 all included only severely ill patients, with group 3 again treated with single dose of 0.4mg/kg plus SOC while Group 4 received HCQ plus SOC. In this severely ill subgroup, the differences in outcomes were even larger, with lower rates of progression 4% vs. 30%, and mortality 2% vs 20% (p<.001).

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 (*45*). 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.

A recent RCT from Iran found a dramatic reduction in mortality with ivermectin use (Niaee et al., 2020). Among multiple ivermectin treatment arms (different ivermectin dosing strategies were used in the intervention arms), the average mortality was reported as 3.3% while the average mortality within the standard care and placebo arms was 18.8%, with an OR of 0.18 (95% CI 0.06-0.55, p<.05).

Spoorthi and Sasanak performed a prospective RCT of 100 hospitalized patients whereby they treated 50 with ivermectin and doxycycline while the 50 controls were given a placebo consisting of Vitamin B6 (Spoorthi V, 2020). Although no deaths were reported in either group, the ivermectin treatment group had a shorter hospital LOS 3.7 days vs 4.7 days, p=.03, and a shorter time to complete resolution of symptoms, 6.7 days vs 7.9 days, p=.01.

The largest OCT (n=280) in hospitalized patients was done by Rajter et al. at Broward Health Hospitals in Florida and was recently published in the major medical journal *Chest* (*43*). They performed a retrospective OCT with a propensity matched design on 280 consecutive treated patients and compared those treated with ivermectin to those without. 173 patients were treated with ivermectin (160 received a single dose, 13 received a 2nd dose at day 7) while 107 were not (Rajter et

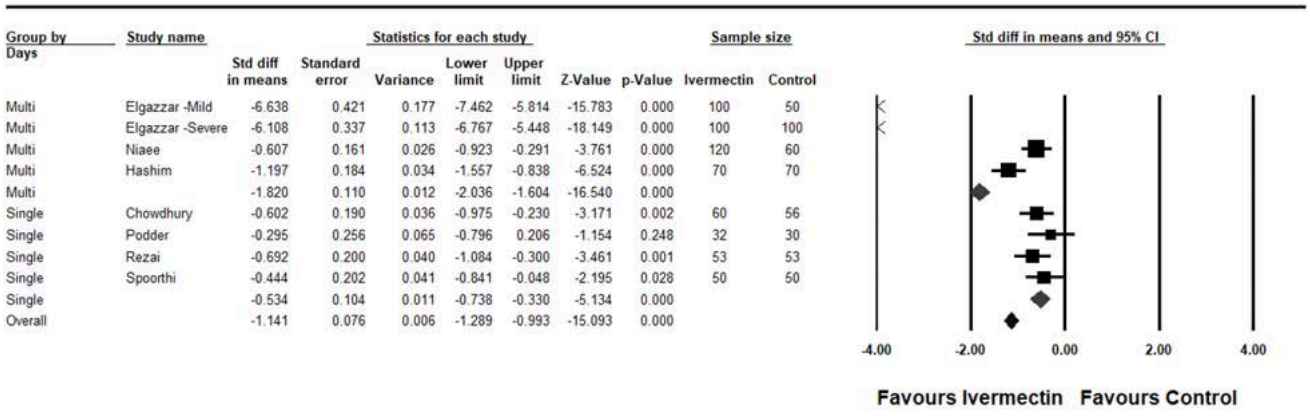
al., 2020). In both unmatched and propensity matched cohort comparisons, similar, large, and statistically significant lower mortality was found amongst ivermectin treated patients (15.0% vs. 25.2%, p =.03). Further, in the subgroup of patients with severe pulmonary involvement, mortality was profoundly reduced when treated with ivermectin (38.8% vs. 80.7%, p=.001).

Another large OCT in Bangladesh compared 115 pts treated with ivermectin to a standard care cohort consisting of 133 patients (Khan et al., 2020). 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). The largest OCT is a study from Brazil which included almost 1,500 patients (Portmann-Baracco et al., 2020). 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%). A small study from Baghdad, Iraq compared 16 ivermectin treated patients to 71 controls (Gorial et al., 2020). This study also reported a significant reduction in length of hospital stay (7.6 days vs. 13.2 days, p<.001) in the ivermectin group. In a study reporting on the first 1000 patients treated in a hospital in India, they found that in the 34 patients treated with ivermectin alone, all recovered and were discharged, while in the over 900 patients treated with other agents, there was an overall mortality of 11.1% (Budhiraja et al., 2020).

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 (Soto-Becerra et al., 2020).

Meta-analyses of the above controlled treatment trials were performed by the study authors focused on the two important clinical outcomes: time to clinical recovery and mortality (Figures 2 and 3). The consistent and reproducible signals leading to large overall statistically significant benefits from within both study designs is remarkable, especially given that in several of the studies treatment was initiated late in the disease course.

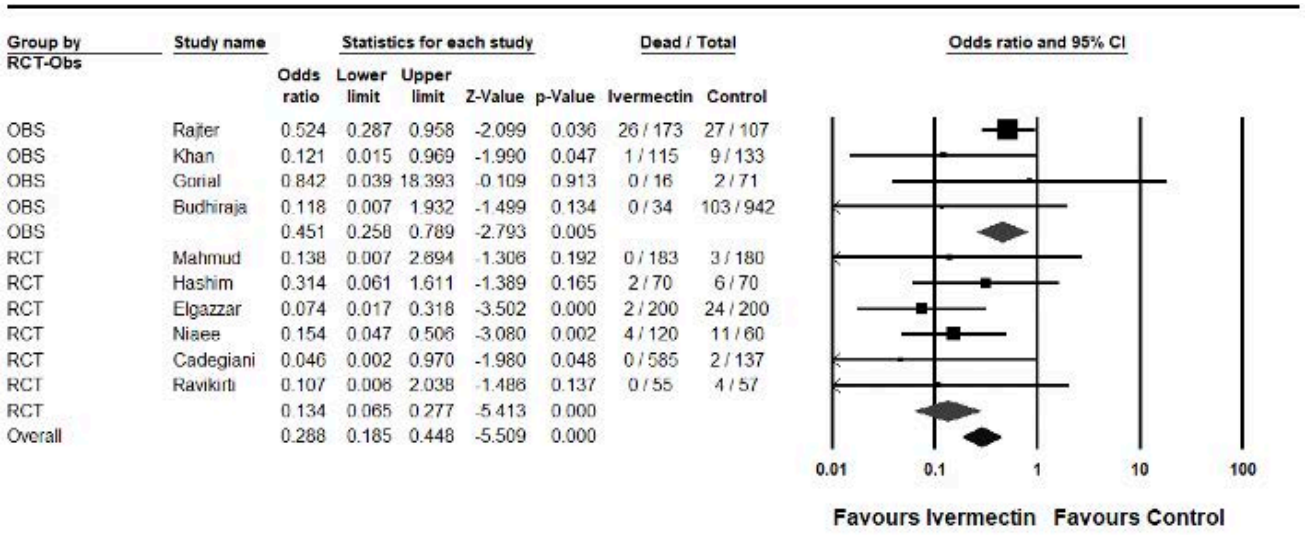
Figure 2. Meta-analysis of the outcome of time to clinical recovery from randomized controlled trials of ivermectin treatment in COVID-19



Group by Days	Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Ivermectin	Control
Multi	Elgazzar -Mild	-6.638	0.421	0.177	-7.462	-5.814	-15.783	0.000	100	50
Multi	Elgazzar -Severe	-6.108	0.337	0.113	-6.767	-5.448	-18.149	0.000	100	100
Multi	Niaee	-0.607	0.161	0.026	-0.923	-0.291	-3.761	0.000	120	60
Multi	Hashim	-1.197	0.184	0.034	-1.557	-0.838	-6.524	0.000	70	70
Multi		-1.820	0.110	0.012	-2.036	-1.604	-16.540	0.000		
Single	Chowdhury	-0.602	0.190	0.036	-0.975	-0.230	-3.171	0.002	60	56
Single	Podder	-0.295	0.256	0.065	-0.796	0.206	-1.154	0.248	32	30
Single	Rezai	-0.692	0.200	0.040	-1.084	-0.300	-3.461	0.001	53	53
Single	Spoorthi	-0.444	0.202	0.041	-0.841	-0.048	-2.195	0.028	50	50
Single		-0.534	0.104	0.011	-0.738	-0.330	-5.134	0.000		
Overall		-1.141	0.076	0.006	-1.289	-0.993	-15.093	0.000		

Figure 2 legend: Multi: multiple day dosing regimen. Single: single dose regimen Symbols: Squares: indicate treatment effect of an individual study. Large diamond: reflect summary of study design immediately above. Small diamond: sum effect of all trial designs. Size of each symbol correlates with the size of the confidence interval around the point estimate of treatment effect with larger sizes indicating a more precise confidence interval.

Figure 3. Meta-analysis of the outcome of mortality from controlled trials of ivermectin treatment in COVID-19



Group by RCT-Obs	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Dead / Total Ivermectin	Dead / Total Control
OBS	Rajter	0.524	0.287	0.958	-2.099	0.036	26 / 173	27 / 107
OBS	Khan	0.121	0.015	0.969	-1.990	0.047	1 / 115	9 / 133
OBS	Gorial	0.842	0.039	18.393	-0.109	0.913	0 / 16	2 / 71
OBS	Budhiraja	0.118	0.007	1.932	-1.499	0.134	0 / 34	103 / 942
OBS		0.451	0.258	0.789	-2.793	0.005		
RCT	Mahmud	0.138	0.007	2.694	-1.306	0.192	0 / 183	3 / 180
RCT	Hashim	0.314	0.061	1.611	-1.389	0.165	2 / 70	6 / 70
RCT	Elgazzar	0.074	0.017	0.318	-3.502	0.000	2 / 200	24 / 200
RCT	Niaee	0.154	0.047	0.506	-3.080	0.002	4 / 120	11 / 60
RCT	Cadegiani	0.046	0.002	0.970	-1.980	0.048	0 / 585	2 / 137
RCT	Ravikirti	0.107	0.006	2.038	-1.486	0.137	0 / 55	4 / 57
RCT		0.134	0.065	0.277	-5.413	0.000		
Overall		0.288	0.185	0.448	-5.509	0.000		

Figure 3 legend: OBS: Observational study, RCT: Randomized Controlled Trial. Symbols: Squares: indicate treatment effect of an individual study. Large diamond: reflect summary of study design immediately above. Small diamond: sum effect of all trial designs. Size of each symbol correlates with the size of the confidence interval around the point estimate of treatment effect with larger sizes indicating a more precise confidence interval.

Details of the prophylaxis, early, and late treatment trials of ivermectin in COVID-19 can be found in Table 3 below.

Table 3. Clinical studies assessing the efficacy of ivermectin in the prophylaxis and treatment of COVID-19

Prophylaxis Trials					
AUTHOR, COUNTRY, SOURCE	**STUDY DESIGN, SIZE**	**STUDY SUBJECTS**	**IVERMECTIN DOSE**	**DOSE FREQUENCY**	**CLINICAL OUTCOMES REPORTED**
Shouman W, Egypt *www.clinicaltrials.gov* NCT04422561	RCT N=340	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
Elgazzar A, Egypt ResearchSquare doi.org/10.21203/rs.3.rs-100956/v1	RCT N=200	Health care and Household contacts of pts with +COVID-19 PCR test	0.4mg/kg	Two doses, Day 1 and Day 7	2% vs. 10% tested positive for COVID-19 p<.05
Chala R. Argentina NCT04701710 *Clinicaltrials.gov*	RCT N=234	Health Care Workers	12mg	Every 7 days	3.4% vs. 21.4%, p=.0001.
Carvallo H, Argentina *Journal of Biochemical Research and Investigation* doi.org/10.31546/2633-8653.1007	OCT N=229	Healthy patients negative for COVID-19 PCR	0.2mg drops	1 drop five times a day x 28 days	0.0% vs. 11.2% contracted COVID-19 p<.001
Alam MT. Bangladesh *European J Med Hlth Sciences* 10.24018/ejmed.2020.2.6.599	OCT N=118	Health Care Workers	12mg	Monthly	6.9% vs. 73.3%, p<.05
Carvallo H. Argentina *Journal of Biochemical Research and Investigation* doi.org/10.31546/2633-8653.1007	OCT N=1,195	Health Care Workers	12 mg	Once weekly for up to ten weeks	0.0% of the 788 workers taking ivermectin vs. 58% of the 407 controls contracted COVID-19.
Behera P, India *medRxiv* doi.org/10.1101/2020.10.29.20222661	OCT N=186 case control pairs	Health Care Workers	0.3 mg/kg	Day 1 and Day 4	2 doses reduced odds of contracting COVID-19 (OR 0.27 95% CI 0.16–0.53)
Bernigaud C. France *Annales de Dermatologie et de Venereologie* doi.org/10.1016/j.annder.2020.09.231	OCT N=69 case control pairs	Nursing Home Residents	0.2 mg/kg	Once	10.1% vs. 22.6% residents contracted COVID-19 0.0% vs 4.9% mortality
Hellwig M. USA *J Antimicrobial Agents* doi.org/10.1016/j.ijantimicag.2020.106248	OCT N=52 countries	Countries with and without IVM prophylaxis programs	Unknown	Variable	Significantly lower-case incidence of COVID-19 in African countries with IVM prophylaxis programs p<.001
Clinical Trials – Outpatients					% Ivermectin vs. % Controls
AUTHOR, COUNTRY, SOURCE	**STUDY DESIGN, SIZE**	**STUDY SUBJECTS**	**IVERMECTIN DOSE**	**DOSE FREQUENCY**	**CLINICAL OUTCOMES REPORTED**
Mahmud R, Bangladesh *www.clinicaltrials.gov* NCT0452383	DB-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
Chowdhury A, Bangladesh *Research Square*	DB-RCT N=116	Outpatients	0.2 mg//kg + doxycycline	Once	Recovery time 5.9 vs 9.3 days (p=.07)

doi.org/10.21203/rs.3.rs-38896/v1					
Ravikirti, India *medRxiv* doi.org/10.1101/2021.01.05.21249310	DB-RCT N=115	Mild-moderate illness	12mg	Daily for 2 days	No diff in day 6 PCR+ 0% vs 6.9% mortality, p=.019
Babalola OE, Nigeria medRxiv doi.org/10.1101/2021.01.05.21249131	DB-RCT N=62	Mild-moderate illness	6mg and 12 mg	Every 48h x 2 weeks	Time to viral clearance: 4.6 days high dose vs 6.0 days low dose vs 9.1 days control (p=.006)
Podder CS, Bangladesh *IMC J Med Sci 2020;14(2)*	RCT N=62	Outpatients	0.2 mg/kg	Once	Recovery time 10.1 vs 11.5 days (NS), average time 5.3 vs 6.3 (NS)
Chaccour C. Spain *Research Square* doi.org/10.21203/rs.3.rs-116547/v1	RCT N=24	Outpatients	0.4mg/kg	Once	No diff in PCR+ Day 7, lower viral load days 4 and 7, (p<.05), 76 vs 158 pt. days of anosmia (p<.05), 68 vs 98 pt. days of cough (p<.05)
Morgenstern J, Dominican Republic *medRxiv* 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
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
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	0.2 mg/kg/kg + doxycycline	Once	All improved within 72 hours
Espatia-Hernandez G, Mexico *Biomedical Research* www.biomedres.info/biomedi..-proof-of-concept-study-14435.html	Case Series N=28	Outpatients	6mg	Days 1,2, 7, 8	All pts recovered Average recovery time 3.6 days
Clinical Trials – Hospitalized Patients					% Ivermectin vs. % Controls
AUTHOR, COUNTRY, SOURCE	**STUDY DESIGN, SIZE**	**STUDY SUBJECTS**	**IVERMECTIN DOSE**	**DOSE FREQUENCY**	**CLINICAL OUTCOMES REPORTED**
Elgazzar A, Egypt *ResearchSquare* doi.org/10.21203/rs.3.rs-100956/v1	OL-RCT N=400	Hospitalized Patients	0.4 mg/kg	Once	Moderately Ill: worsened 1% vs 22%, p<.001. Severely ill: worsened 4% vs 30% mortality 2% vs 20% both with p<.001
Niaee S. M. *Research Square* doi.org/10.21203/rs.3.rs-109670/v1	DB-RCT N=180	Hospitalized Patients	0.2, 0.3, 0.4 mg/kg (3 dosing strategies)	Once vs. Days 1,3,5	Mortality 3.3% vs. 18.3%. OR 0.18, (.06-0.55, p<.05)
Hashim H, Iraq *medRxiv* doi.org/10.1101/2020.10.26.20219345	SB-RCT N=140	2/3 outpatients, 1/3 hospital pts	0.2 mg/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)
Spoorthi S, India *AIAM, 2020; 7(10):177-182*	RCT N=100	Hospitalized Patients	0.2mg/kg+ Doxycycline	Once	Shorter Hospital LOS, 3.7 vs. 4.7 days,

					p=.03, faster resolution of symptoms, 6.7 vs 7.9 days, p=.01
Ahmed S. Dhaka, Bangladesh *International Journal of Infectious Disease* doi.org/10.1016/j.ijid.2020.11.191	DB-RCT N=72	Hospitalized Patients	12mg	Daily for 5 days	Faster viral clearance 9.7 vs 12.7 days, p=.02
Chachar AZK, Pakistan *Int J Sciences* doi.org/10.18483/ijSci.2378	DB-RCT N=50	Hospitalized Patients-Mild	12mg	Two doses Day 1, one dose Day 2	64% vs 60% asymptomatic by Day 7
Portman-Baracco A, Brazil *Arch Bronconeumol. 2020* doi.org/10.1016/j.arbres.2020.06.011	OCT N=1408	Hospitalized patients	0.15 mg/kg	Once	Overall mortality 1.4% vs. 8.5%, HR 0.2, 95% CI 0.12-0.37, p<.0001
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
Rajter JC, Florida *Chest 2020* doi.org/10.1016/j.chest.2020.10.009	OCT N=280	Hospitalized patients	0.2 mg/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	Hospitalized patients	12 mg	Once on admission	Mortality 0.9% vs. 6.8%, p<.05, LOS 9 vs. 15 days, p<.001
Gorial FI, Iraq *medRxiv* doi.org/10.1101/2020.07.07.20145979	OCT N=87	Hospitalized patients	0.2 mg/kg + HCQ and azithromycin	Once on admission	LOS 7.6 vs. 13.2 days, p<.001, 0/15 vs. 2/71 died
Budiraja S. India *medRxiv* doi.org/10.1101/2020.11.16.20232223	OCT N=1000 IVM=34	Hospitalized Patients	n/a	n/a	100% IVM pts recovered 11.1% mortality in non-IVM treated pts

Legend: DB-RCT = double-blind randomized controlled trial, HCQ = hydroxychloroquine, IVM = ivermectin, LOS = Length of stay, NS = non-statistically significant, p>.05, OCT = observational controlled trial, OL = open label, PCR – polymerase chain reaction, RCT = randomized controlled trial, SB-RCT =single blind, randomized controlled trial

Ivermectin in post-COVID-19 syndrome

Increasing reports of persistent, vexing, and even disabling symptoms after recovery from acute COVID-19 have been reported and which many have termed the condition as “long Covid” and patients as “long haulers”, estimated to occur in approximately 10% of cases (Callard and Perego, 2020;Rubin, 2020;Siegelman, 2020). Generally considered as a post-viral syndrome consisting of a chronic and sometimes disabling constellation of symptoms which include, in order, fatigue, shortness of breath, joint pains and chest pain. Many patients describe their most disabling symptom as impaired memory and concentration, often with extreme fatigue, described as “brain fog”, and are highly suggestive of the condition myalgic encephalomyelitis/chronic fatigue syndrome, a condition well-reported to begin after viral infections, in particular with Epstein-Barr virus. Although no specific treatments have been identified for long COVID, a recent manuscript by Aguirre-Chang et al from the National University of San Marcos in Peru reported on the experience with ivermectin in such patients (Aguirre-Chang, 2020). They treated 33 patients who were between 4 and 12 weeks

from the onset of symptoms with escalating doses of ivermectin; 0.2mg/kg for 2 days if mild, 0.4mg/kg for 2 days if moderate, with doses extended if symptoms persisted. They found that in 87.9% of the patients, resolution of all symptoms was observed after two doses with an additional 7% reporting complete resolution after additional doses. Their experience suggests the need for controlled studies to better test efficacy in this vexing syndrome.

Epidemiological data showing impacts of widespread ivermectin use on population case counts and case fatality rates

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 (Chamie, 2020).[8] 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. Juan Chamie, a data analyst and member of the FLCCC Alliance recently posted a paper based on two critical sets of data that he compiled and compared; first he identified the timing and magnitude of each region's 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, he extracted data on the total all-cause deaths from the region along with COVID-19 case counts in selected age groups over time from the registry of the National Computer System of Deaths (SINADEF), and from the National Institute of Statistics and Informatics (Chamie, 2020). It should be noted that he restricted his analyses to only those citizens over 60 years old in order to avoid the confounding of rises in the numbers of infected younger patients. With these data, he was then able to compare the timing of major decreases in this age group of both total COVID-19 cases and total deaths per 1000,000 people among 8 states in Peru with the initiation dates of their respective ivermectin distribution campaigns as shown in Figure 4 below.

[8] https://trialsitenews.com/trialsite-news-original-documentary-in-peru-about-ivermectin-and-covid-19/

Figure 4. Decrease in total case incidences and total deaths/population of COVID-19 in the over 60 population among 8 Peruvian states after deploying mass ivermectin distribution campaigns

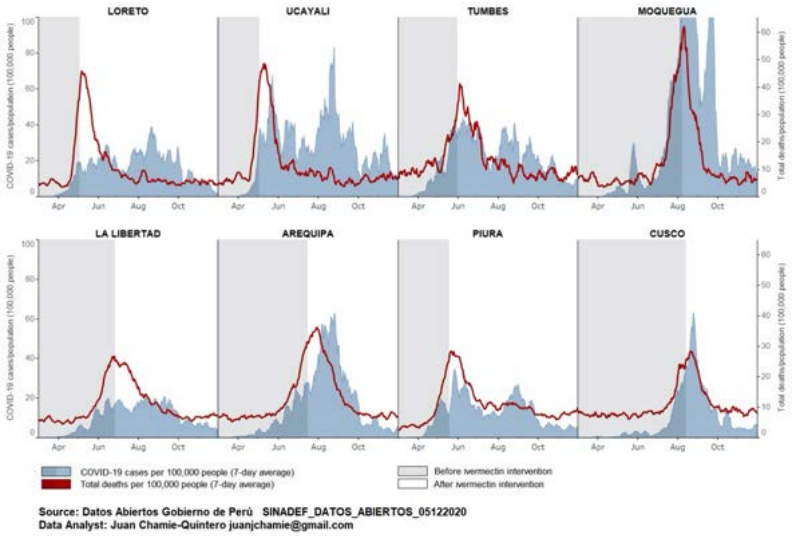
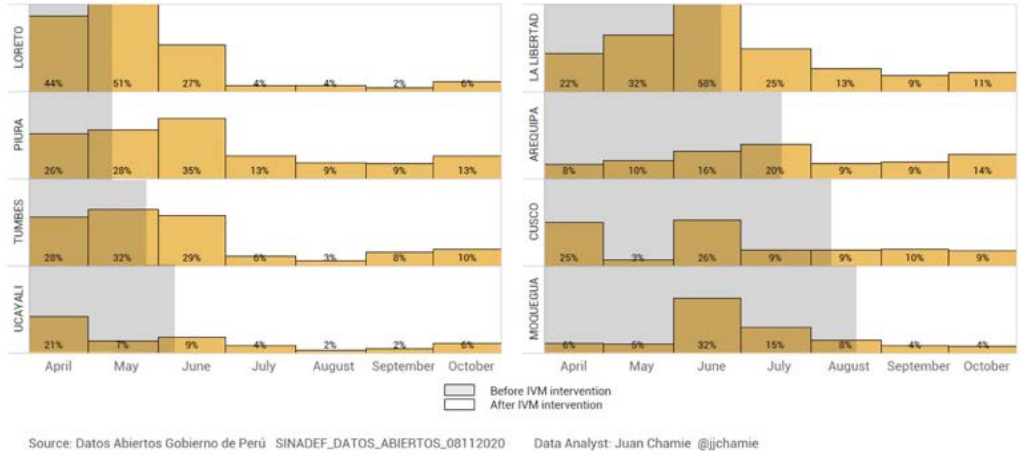


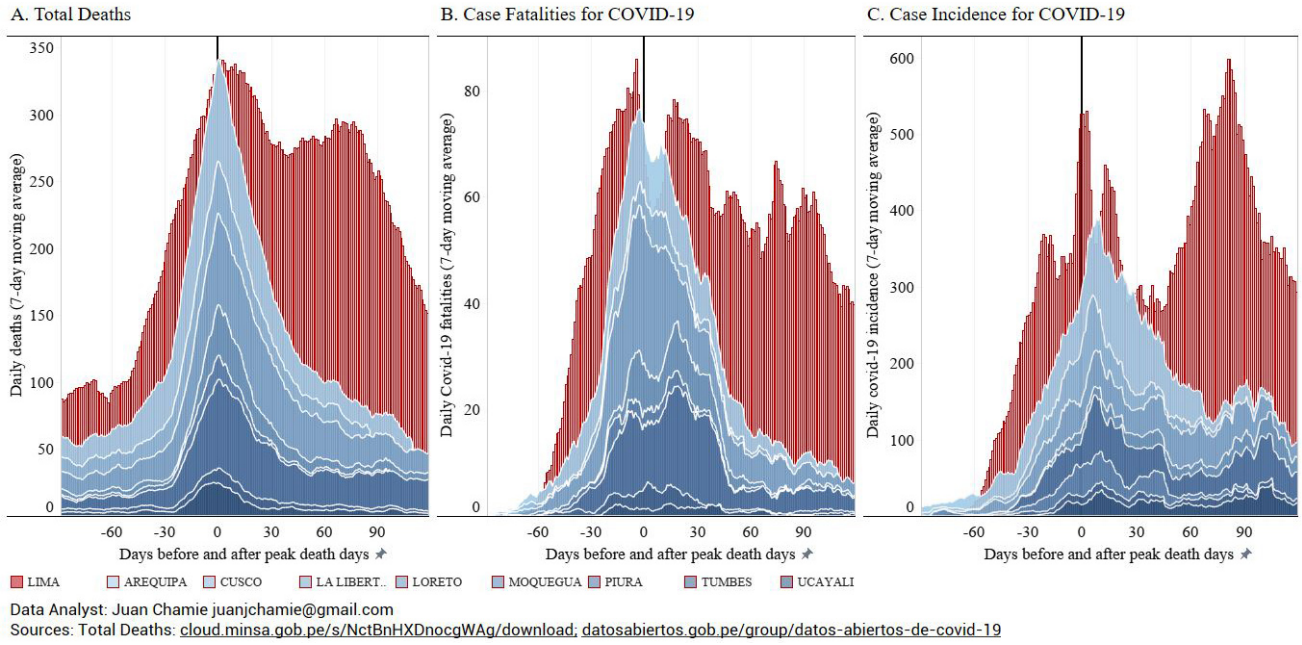
Figure 5 below from the same study presents data on the case fatality rates in patients over 60, again among the 8 states in Peru. Note the dramatically decreased case fatality rates among older patients with COVID-19 after ivermectin became widely distributed in those areas.

Figure 5. Monthly reported case fatality rates among patients over 60 in eight Peruvian states after deploying mass ivermectin treatment.



In an even more telling example, Chamie compared the case counts and fatality rates of the 8 states above with the city of Lima, where ivermectin was not distributed nor widely used in treatment during the same time period. Figure 6 below compares the lack of significant or sustained reductions in case counts or fatalities in Lima with the dramatic reductions in both outcomes among the 8 states with widespread ivermectin distribution.

Figure 6. Covid-19 case fatalities and total deaths with and without mass ivermectin in different states of Peru

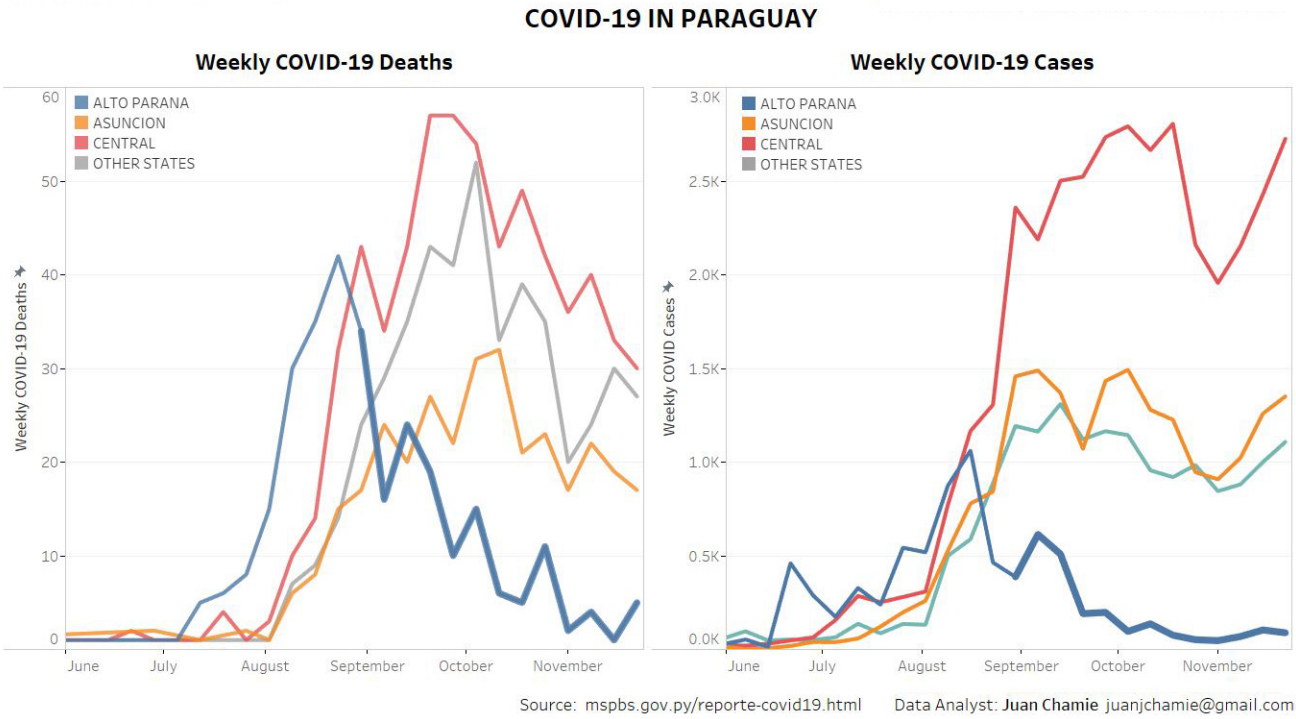


Legend: Daily total deaths, case fatalities and case incidence for COVID-19 in populations of patients age 60 and above for eight states in Peru deploying early mass ivermectin treatments vs. the state of Lima, including the capital city, where ivermectin treatment was applied months later.

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.[9] 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 7 below.[10]

[9] https://public.tableau.com/profile/jchamie#!/vizhome/COVID-19PARAGUAY/Paraguay
[10] https://public.tableau.com/profile/jchamie#!/vizhome/COVID-19PARAGUAY/Paraguay

Figure 7. Paraguay – COVID-19 case counts and deaths in Alto Parana (bolded blue line) after ivermectin distribution began compared to other regions.



The clinical evidence base for ivermectin against COVID-19

A summary of the statistically significant results from the above controlled trials are as follows:

Controlled trials in the prophylaxis of COVID-19 (8 studies)

- All 8 available controlled trial results show statistically significant reductions in transmission
- 3 RCT's with large statistically significant reductions in transmission rates, N=774 patients (Chala, 2020;Elgazzar et al., 2020;Shouman, 2020)
- 5 OCT's with large statistically significant reductions in transmission rates, N=2052 patients (Alam et al., 2020;Behera et al., 2020;Bernigaud et al., 2020;Carvallo et al., 2020b;Hellwig and Maia, 2020)

Controlled trials in the treatment of COVID-19 (19 studies)

- 5 RCT's with statistically significant impacts in time to recovery or hospital length of stay (Elgazzar et al., 2020;Hashim et al., 2020;Mahmud, 2020;Niaee et al., 2020;Spoorthi V, 2020)
- 1 RCT with a near statistically significant decrease in time to recovery, p=.07, N=130 (Chowdhury et al., 2020)
- 1 RCT with a large, statistically significant reduction in the rate of deterioration or hospitalization, N=363 (Mahmud, 2020)
- 2 RCT's with a statistically significant decrease in viral load, days of anosmia and cough, N=85 (Chaccour et al., 2020;Ravikirti et al., 2021)

- 3 RCT's with large, statistically significant reductions in mortality (N=695) (Elgazzar et al., 2020;Niaee et al., 2020;Ravikirti et al., 2021)
- 1 RCT with a near statistically significant reduction in mortality, p=0.052 (N=140) (Hashim et al., 2020)
- 3 OCT's with large, statistically significant reductions in mortality (N=1,688) (Khan et al., 2020;Portmann-Baracco et al., 2020;Rajter et al., 2020)

Safety of Ivermectin

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 (Kircik et al., 2016). 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 (Gardon et al., 1997). Further, according to the pharmaceutical reference standard *Lexicomp*, the only medications contraindicated for use with ivermectin are the concurrent administration of anti-tuberculosis and cholera vaccines while the anticoagulant warfarin would require dose monitoring. Another special caution is that immunosuppressed or organ transplant patients who are on calcineurin inhibitors such as tacrolimus or cyclosporine or the immunosuppressant sirolimus should have close monitoring of drug levels when on ivermectin given that interactions exist which can affect these levels. A longer list of drug interactions can be found on the *drugs.com* database, with nearly all interactions leading to a possibility of either increased or decreased blood levels of ivermectin. Given studies showing tolerance and lack of adverse effects in human subjects given escalating high doses of ivermectin, toxicity is unlikely although a reduced efficacy due to decreased levels may be a concern (Guzzo et al., 2002)..

Concerns of safety in the setting of liver disease are unfounded given that, to our knowledge, only two cases of liver injury have ever been reported in association with ivermectin, with both cases rapidly resolved without need for treatment. (Sparsa et al., 2006;Veit et al., 2006). Further, no dose adjustments are required in patients with liver disease. Some have described ivermectin as potentially neurotoxic, yet one study performed a search of a global pharmaceutical database and found only 28 cases of serious neurological adverse events such as ataxia, altered consciousness, seizure, or tremor (Chandler, 2018). Potential explanations included the effects of concomitantly administered drugs which increase absorption past the blood brain barrier or polymorphisms in the mdr-1 gene. However, the total number of reported cases suggests that such events are rare. Finally, ivermectin has been used safely in pregnant women, children, and infants.

Discussion

Currently, as of December 14, 2020, the accumulating evidence demonstrating the safety and efficacy of ivermectin in COVID-19 strongly supports its immediate use on a risk/benefit calculation in the context of a pandemic. Large-scale epidemiologic analyses validate the findings of *in vitro*, animal, prophylaxis, and clinical studies. Regions of the world with widespread ivermectin use have demonstrated a sizable reduction in case counts, hospitalizations, and fatality rates. This approach should be urgently considered in the presence of an escalating COVID-19 pandemic and as a bridge to vaccination. A recent systematic review of eight RCTs by Australian researchers, published as a pre-print, similarly concluded that ivermectin treatment led to a reduction in mortality, time to clinical recovery, the incidence of disease progression, and duration of hospital admission in patients across all stages of clinical severity (Kalfas et al., 2020). Our current review includes a total of 6,612

patients from 27 controlled studies [16 of them were RCTs, 5 double blinded, one single blinded, (n= 2,503)]; 11 published in peer-reviewed journals including 3,900 patients.

Pre-print publications have exploded during the COVID-19 pandemic. Except for hydroxychloroquine and convalescent plasma that were widely adopted before availability of any clinical data to support, almost all subsequent therapeutics were adopted after pre-print publication and *prior to peer review*. Examples include remdesivir, corticosteroids, and monoclonal antibodies. An even more aggressive example of rapid adoption was the initiation of inoculation programs using novel mRNA vaccines prior to review of either pre-print or peer-reviewed trials data by physicians ordering the inoculations for patients.[11] In all such situations, both academia and governmental health care agencies relaxed their standard to rise to the needs dictated by the pandemic.

In the context of ivermectin's long standing safety record, low cost, and wide availability along with the consistent, reproducible, large magnitude findings on transmission rates, need for hospitalization, mortality, and population-wide control of COVID-19 case and fatality rates in areas with widespread ivermectin distribution, insisting on the remaining studies to pass peer review prior to widespread adoption appears to be imprudent and to deviate from the now established standard approach towards adoption of new therapeutics during the pandemic. In fact, insisting on such a barrier to adoption would actually violate this new standard given that 12 of the 24 controlled trials have already been published in peer reviewed journals.

In regard to concerns over the validity of observational trial findings, it must be recognized that in the case of ivermectin; 1) half of the trials employed a randomized, controlled trial design (12 of the 24 reviewed above), and 2) that observational and randomized trial designs reach equivalent conclusions on average in nearly all diseases studied, as reported in a large Cochrane review of the topic from 2014 (Anglemyer et al., 2014). In particular, OCTs that employ propensity-matching techniques (as in the Rijter study from Florida), find near identical conclusions to later-conducted RCTs in many different disease states, including coronary syndromes, critical illness, and surgery (Dahabreh et al., 2012;Lonjon et al., 2014;Kitsios et al., 2015). Similarly, as evidenced in the prophylaxis (Figure 1) and treatment trial (Figures 2 and 3) meta-analyses as well as the summary trials table (Table 3), the entirety of the benefits found in both OCT and RCT trial designs align in both direction and magnitude of benefit. Such a consistency of benefit amongst numerous trials of varying designs from multiple different countries and centers around the world is both unique in the history of evidence-based medicine and provides strong, additional support to the conclusions reached in this review. 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.*

The continued challenges faced by health care providers in deciding on appropriate therapeutic interventions in patients with COVID-19 would be greatly eased if more updated and definitive evidence-based guidance came from the leading governmental health care agencies. Currently, in the United States, the treatment guidelines for COVID-19 are issued by the National

[11] https://www.wsj.com/articles/u-k-begins-rollout-of-pfizers-covid-19-vaccine-in-a-first-for-the-west-11607419672

Institutes of Health (NIH). Unfortunately, the NIH's recommendation on the use of ivermectin in COVID-19 patients was last updated on August 27, 2020. At that time, ivermectin received a recommendation of A-III *against* use outside of a clinical trial. An A-III recommendation, per the NIH recommendation scheme, means that it was a strong opinion (A), and based on expert opinion only (III) given that presumably little clinical evidence existed at the time to otherwise inform that recommendation.

Based on the totality of the clinical and epidemiologic evidence presented in this review, and in the context of a worsening pandemic in parts of the globe where ivermectin is not widely used, the authors believe the recommendation must be immediately updated to support and guide the nation's health care providers. One aspect that the NIH expert panel may debate is on the grade of recommendation that should be assigned to ivermectin. Based on the NIH rating scheme, the strongest recommendation possible would be an A-I in support of ivermectin which requires "one or more randomized trials with clinical outcomes and/or laboratory endpoints." Given that data from 16 randomized controlled trials (RCT's) demonstrate consistent and large improvements in "clinical outcomes" such as transmission rates, hospitalization rates, and death rates, it appears that the criteria for an A-I level recommendation has been exceeded. However, although troubling to consider, if experts somehow conclude that the entirety of the available RCT data should be invalidated and dismissed given that either; they were conducted outside of US shores and not by US pharmaceutical companies or academic research centers, that some studies were small or of "low quality", or that such data from foreign countries are not generalizable to American patients, an A-II level recommendation would then have to be considered. In the context of worsening pandemic conditions, when considering a safe, low-cost, widely available early treatment option, even an A-II would result in immediate, widespread adoption by providers in the treatment of COVID-19. The criteria for an A-II requires supportive findings from "one of more well-designed non-randomized, or observational cohort studies". Fortunately, there are many such studies on ivermectin in COVID-19, with one of the largest and best designed being Dr. Rijter's study from Florida, published in the major peer-reviewed medical journal *Chest*, where they used propensity matching, a technique accorded by many to be as valid a design as RCT's. Thus, at a minimum, an A-II recommendation is met, which again would and should lead to immediate and widespread adoption in early outpatient treatment, an area that has been little investigated and is devoid of any highly effective therapies at the time of this writing. Further, it is clear that these data presented far exceed any other NIH strength or quality level such as moderate strength (B), weak strength (C) or grade III quality. To merit the issuance of these lower grades of recommendation would require both a dismissal of the near entirety of the evidence presented in this review in addition to a risk benefit calculation resulting in the belief that the risks of widespread ivermectin use would far exceed any possible benefits in the context of rising case counts, deaths, lockdowns, unemployment, evictions, and bankruptcies.

It is the authors opinion, that based on the totality of these data, the use of ivermectin as a prophylactic and early treatment option should receive an A-I level recommendation by the NIH in support of use by the nation's health care providers. When, or if, such a recommendation is issued, the Front Line COVID-19 Critical Care Alliance has developed a prophylaxis and early treatment protocol for COVID-19 (I-MASK+), centered around ivermectin combined with masking, social distancing, hand hygiene, Vitamin D, Vitamin C, quercetin, melatonin, and zinc, with all components known for either their anti-viral, anti-inflammatory, or preventive actions (Table 4). The I-MASK+ protocol suggests treatment approaches for prophylaxis of high-risk patients, post-exposure prophylaxis of household members with COVID-19, and an early treatment approach for patients ill with COVID-19.

Table 4. I-MASK+ Prophylaxis & Early Outpatient Treatment Protocol for COVID-19

Prophylaxis Protocol	
MEDICATION	RECOMMENDED DOSING
Ivermectin	*Prophylaxis for high-risk individuals*: 0.2 mg/kg per dose* — one dose today, 2nd dose in 48 hours, then one dose every 2 weeks
	*Post COVID-19 exposure prophylaxis****: 0.2 mg/kg per dose, one dose today, 2nd dose in 48 hours
Vitamin D3	1,000–3,000 IU/day
Vitamin C	1,000 mg twice daily
Quercetin	250 mg/day
Melatonin	6 mg before bedtime (causes drowsiness)
Zinc	50 mg/day of elemental zinc
Early Outpatient Treatment Protocol**	
MEDICATION	RECOMMENDED DOSING
Ivermectin	0.2 mg/kg per dose – one dose daily for minimum of 2 days, continue daily until recovered (max 5 days)
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 (causes drowsiness)
Zinc	100 mg/day elemental zinc
Aspirin	325 mg/day (unless contraindicated)

* Example for a person of 60 kg body weight: 60 kg × 0.2 mg = 12 mg (1 kg = 2.2 lbs) = 4 tablets (3mg/tablet). To convert pounds, divide weight in pounds by 11: example for a person of 165 pounds: 165 ÷ 11 = 15 mg
** The dosing may be updated as further scientific studies emerge.
*** 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

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. In the presence of a global COVID-19 surge, the widespread use of this safe, inexpensive, and effective intervention would lead to a drastic reduction in transmission rates and the morbidity and mortality in mild, moderate, and even severe disease phases. The authors are encouraged and hopeful at the prospect of the many favorable public health and societal impacts that would result once adopted for use.

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None

Contribution to the field statement

COVID-19 has caused a worldwide pandemic that has caused over 1.5 million global deaths along with continued rising case counts, lockdowns, unemployment and recessions in multiple countries. In response, the Front Line COVID-19 Critical Care Alliance (FLCCC), formed early in the pandemic, began to review the rapidly emerging basic science, translational, and clinical data to develop effective treatment protocols. The supportive evidence and rationale for their highly effective hospital treatment protocol called "MATH+" was recently published in a major medical journal. More recently, during their ongoing review of the studies on a wide range of both novel and repurposed drugs, they identified 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. This manuscript comprehensively reviews the diverse and increasing amount of available evidence from studies on ivermectin which then concludes with the FLCCC consensus recommendation that ivermectin for both the prophylaxis and treatment of COVID-19 should be systematically and globally adopted with the achievable goal of saving countless lives and reversing the rising and persistent transmission rates in many areas of the world.

Figures

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

Study conception and design: Pierre Kory, G. Umberto Meduri, Howard Kornfeld, Keith Berkowitz. Acquisition of data: Scott Mitchell, Eivind Norjevoll, Paul Marik, Fred Wagshul Analysis and interpretation of data: Paul Marik, Pierre Kory Drafting of manuscript: Pierre Kory Critical revision: Umberto Meduri, Joseph Varon.

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