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

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Background: After COVID-19 emerged on U.S shores, providers began reviewing the emerging basic science, translational, and clinical data to identify potentially effective treatment options. In addition, a multitude of both novel and repurposed therapeutic agents were used empirically and studied within clinical trials.

Areas of Uncertainty: The majority of trialed agents have failed to provide reproducible, definitive proof of efficacy in reducing the mortality of COVID-19 with the exception of corticosteroids in moderate to severe disease. Recently, evidence has emerged that the oral antiparasitic agent ivermectin exhibits numerous antiviral and anti-inflammatory mechanisms with trial results reporting significant outcome benefits. Given some have not passed peer review, several expert groups including Unitaid/World Health Organization have undertaken a systematic global effort to contact all active trial investigators to rapidly gather the data needed to grade and perform meta-analyses.

Data Sources: Data were sourced from published peer-reviewed studies, manuscripts posted to preprint servers, expert meta-analyses, and numerous epidemiological analyses of regions with ivermectin distribution campaigns.

Therapeutic Advances: A large majority of randomized and observational controlled trials of ivermectin are reporting repeated, large magnitude improvements in clinical outcomes. Numerous prophylaxis trials demonstrate that regular ivermectin use leads to large reductions in transmission. Multiple, large "natural experiments" occurred in regions that initiated "ivermectin distribution" campaigns followed by tight, reproducible, temporally associated decreases in case counts and case fatality rates compared with nearby regions without such campaigns.

Conclusions: Meta-analyses based on 18 randomized controlled treatment trials of ivermectin in COVID-19 have found large, statistically significant reductions in mortality, time to clinical recovery, and time to viral clearance. Furthermore, results from numerous controlled prophylaxis trials report significantly

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Off-Label Use: This manuscript includes discussion of off-label use in COVID-19 of the FDA-approved medication ivermectin.

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reduced risks of contracting COVID-19 with the regular use of ivermectin. Finally, the many examples of ivermectin distribution campaigns leading to rapid population-wide decreases in morbidity and mortality indicate that an oral agent effective in all phases of COVID-19 has been identified.

Keywords: ivermectin, COVID-19, infectious disease, pulmonary infection, respiratory failure

INTRODUCTION

In early 2020, on the onset of the spreading pandemic, many providers and institutions began to continuously review the rapidly emerging basic science, translational, and clinical data to identify potentially effective treatment options for COVID-19. Although there is now a small and increasing number of therapeutics showing some efficacy in important clinical outcomes, chief of which are corticosteroids in moderate to severe illness, the world continues to suffer from a worsening crisis with the potential of again overwhelming hospitals and intensive care units (ICU). As of February 21, 2020, the number of deaths attributed to COVID-19 in the United States reached 510,248 with more than 9.3 million active cases, the highest number to date. In addition, multiple European countries have imposed new rounds of restrictions and lockdowns.

Further compounding these alarming developments was a wave of recently published results from therapeutic randomized controlled trials conducted on medicines believed effective for COVID-19 that found a lack of impact on mortality in hospitalized patients with the use of remdesivir, hydroxychloroquine, lopinavir/ritonavir, interferon, convalescent plasma, and monoclonal antibody therapy.[1–4] 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.[5,6] Similarly, most concerning is the fact that no agent has yet proven effective in outpatients to prevent disease progression to prevent hospitalization.

More recently, trial results of ivermectin, a widely used antiparasitic medicine with known antiviral and anti-inflammatory properties, have been showing benefits in multiple important clinical and virologic outcomes, including mortality. 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 preprint servers, a now standard practice for both rapid dissemination and adoption of new therapeutics throughout the pandemic. 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* bacterium from the soil near a golf course along the southeast 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 *S. avermitilis* for the compounds' ability to clear mice of worms.[7] 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 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.[7] Although it was used to treat a variety of internal nematode infections, it was most known as the essential mainstay of 2 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 Mectizan Donation Program that then provided more than 570 million treatments in its first 20 years alone.[8] Ivermectin's 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 World Health Organization's (WHO) "List of Essential Medicines." Furthermore, it has also been used to successfully overcome several other human diseases and new uses for it are continually being found.[7]

Preclinical studies of Ivermectin's activity against SARS-CoV-2

Since 2012, a growing number of cellular studies have demonstrated that ivermectin has antiviral properties against an increasing number of RNA viruses, including influenza, *Zika*, HIV, *Dengue*, and most importantly, SARS-CoV-2.[9–17] 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[18] first reported that ivermectin significantly inhibits SARS-CoV-2 replication in a cell culture model, observing the near absence of all viral material 48 hours after exposure to ivermectin. However, some questioned whether this observation is generalizable clinically given the inability to achieve similar tissue concentrations used in their experimental model using standard or even massive doses of ivermectin.[19,20] It should be noted that the concentrations required for an 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. Furthermore, prolonged durations of exposure to a drug likely would require a fraction of the dosing in short-term cell model exposure. Furthermore, multiple coexisting 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 6 molecular modeling studies.[21–26] In 4 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 4 of these studies.[27] 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.[21,22,26–28] Ivermectin has also been shown to bind to or interfere with multiple essential structural and nonstructural proteins required by the virus to replicate.[26,29] Finally, ivermectin also binds to the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), thereby inhibiting viral replication.[30]

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 μg/kg of ivermectin versus 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 killed to obtain tissues for examination and viral load assessment. The 20 nonivermectin-treated infected mice all showed severe hepatocellular necrosis surrounded by a severe lymphoplasmacytic inflammatory infiltration associated with a high hepatic viral load (52,158), whereas in the ivermectin-treated mice a much lower viral load was measured (23,192; $P < 0.05$), 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 et al[32] 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 0.4 mg/kg on day 1. 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%, $P = 0.03$), 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 turbinates 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 the optimal dose and frequency required.

Preclinical 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,[33–35] the most likely pathophysiologic mechanism is that identified by Li et al[36] where they showed that the nonviable RNA fragments of SARS-CoV-2 lead to a high mortality and morbidity in COVID-19 through the provocation of an overwhelming and injurious inflammatory response. Based on these insights and the clinical benefits of ivermectin in the late phase of disease to be reviewed below, it seems 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.[37–39]

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

Data are also now available showing large and statistically significant decreases in the transmission of COVID-19 among human subjects based on data from 3 randomized controlled trials (RCTs) and 5 observational controlled trials (OCTs) with 4 of the 8 (2 of them RCTs) published in peer-reviewed journals.[40–46]

Elgazzar and colleagues[45] at Benha University in Egypt randomized 200 health care and household contacts of patients with COVID-19 where the intervention group consisted of 100 patients given a high dose of 0.4 mg/kg on day 1 and a second dose on day 7 in addition to wearing personal protective equipment, whereas the control group of 100 contacts wore personal protective equipment alone. They reported a large and statistically significant reduction in contacts testing positive by Reverse Transcriptase Polymerase Chain Reaction (PCR) when treated with ivermectin versus controls, 2% versus 10%, $P < 0.05$.

Shouman conducted an RCT at Zagazig University in Egypt, including 340 (228 treated and 112 control) family members of patients positive for SARS-CoV-2 through PCR.[44] Ivermectin (approximately 0.25 mg/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% versus 58.4%, $P < 0.001$.

Recently, Alam et al from Bangladesh performed a prospective observational study of 118 patients who were evenly split into those who 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 difference between the 2 groups was so large (6.7% vs. 73.3%, $P < 0.001$) and similar to the other prophylaxis trial results that confounders alone are unlikely to explain such a result.[47] 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.[40] Of the 229 study subjects, 131 were treated with 0.2 mg of ivermectin drops taken by mouth 5 times per day. After 28 days, none of those receiving ivermectin in the prophylaxis group had tested positive for SARS-COV-2 versus 11.2% of patients in the control arm ($P < 0.001$). In a much larger follow-up prospective, observational controlled trial by the same group that included 1195 health care workers, they found that over a 3-month period there were no infections recorded among the 788 workers who took weekly ivermectin prophylaxis, whereas 58% of the 407 controls had become ill with COVID-19. This study demonstrates that remarkable protection against transmission can be achieved among high-risk health care workers by taking 12 mg once weekly.[40] 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 versus 21.4% of controls, $P < .0001$.[46]

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 12 mg once monthly for a similar 4-month period and also reported a large and statistically significant decrease in infections compared with controls, 6.9% versus 73.3%, $P < 0.05$.[47] Then, in a large retrospective observational case–control study from India, Behera et al[41] reported that among 186 case–control pairs (n = 372) of health care workers, they identified 169 participants who had taken some form of prophylaxis, with 115 participants that had taken ivermectin. After matched pair analysis, they reported that in the workers who had taken 2 dose ivermectin prophylaxis, the odds ratio for contracting COVID-19 was markedly decreased (0.27, 95% confidence interval (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 0.3 mg/kg doses of ivermectin 72 hours apart and repeat the dose monthly.

Data that further illuminates the potential protective role of ivermectin against COVID-19 come 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,[41] they found that during the period surrounding this event, 7 of the 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.

Further evidence supporting the efficacy of ivermectin as a prophylaxis agent was published recently in the *International Journal of Antimicrobial 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

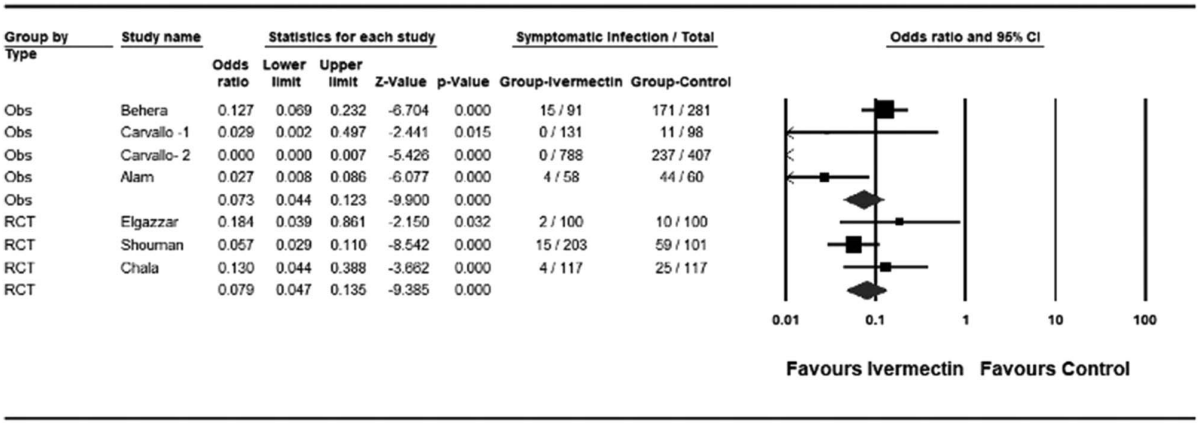

FIGURE 1. Meta-analysis of ivermectin prophylaxis trials in COVID-19. OBS, observational study; RCT, randomized controlled trial. Symbols: Squares: Indicate treatment effect of an individual study. Large diamond: Reflect summary of study design immediately above. Size of each symbol correlates with the size of the confidence interval around the point estimate of treatment effect with larger sizes indicating a more precise confidence interval.

aggregation site used by among others, the Johns Hopkins University.[42] 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, $P < 0.001$.

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

Further data supporting a role of ivermectin in decreasing transmission rates can be found from South American countries where, in retrospect, large "natural experiments" seem 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.[48] 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. The distribution campaign of Itajai began in mid-July, in Natal they began on June 30th, and in Macapa, the capital city of Amapa and others nearby, they incorporated ivermectin into their treatment protocols in late May after they were particularly hard hit in April. The data in Table 1 were obtained from the official Brazilian government site and the national press consortium and show large decreases in case counts in the 3 cities soon after distribution began compared with their neighboring cities without such campaigns.

The decreases in case counts among the 3 Brazilian cities given in Table 1 were also associated with reduced mortality rates as summarized in Table 2.

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

Currently, 7 trials that include a total of more than 3000 patients with mild outpatient illness have been completed, a set composed of 7 RCTs and 4 case series.[49–60]

Table 1. Comparison of case count decreases among Brazilian cities with and without ivermectin distribution campaigns.

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%

Bolded cities distributed ivermectin, neighboring regional city below did not.

Table 2. Change in death rates among neighboring regions in Brazil.

Region	State	% Change in average deaths/week compared with 2 weeks before
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%

Bolded regions contained a major city that distributed ivermectin to its citizens, the other regions did not.

The largest, a double-blinded RCT by Mahmud[49] was conducted in Dhaka, Bangladesh, and targeted 400 patients with 363 patients completing the study. 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 versus hospitalized patients treated, important clinical outcomes were profoundly affected, with increased rates of early improvement (60.7% vs. 44.4% $P < 0.03$) and decreased rates of clinical deterioration (8.7% vs. 17.8%, $P < 0.02$). Given that mildly ill outpatients mainly comprised the study cohort, only 2 deaths were observed (both in the control group).

Ravikirti performed a double-blinded RCT of 115 patients, and although the primary outcome of PCR positivity on day 6 was no different, the secondary outcome of mortality was 0% versus 6.9%, $P = .019$.[60] Babalola in Nigeria also performed a double-blinded RCT of 62 patients, and in contrast to Ravikirti, they found a significant difference in viral clearance between both the low-dose and high-dose treatment groups and controls in a dose dependent fashion, $P = .006$.[59]

Another RCT by Hashim et al[53] in Baghdad, Iraq, included 140 patients equally divided; the control group received standard care, and the treated group included a combination of both outpatient and hospitalized patients. 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 with the 48 patients treated with standard of care alone. The standard of care in this trial included medicines such as dexamethasone 6 mg/d or methylprednisolone 40 mg twice per day if needed, vitamin C 1000 mg twice/day, zinc 75–125 mg/d, vitamin D3 5000 IU/day, azithromycin 250 mg/d for 5 days, and acetaminophen 500 mg 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, $P < 0.0001$).

Chaccour et al conducted a small, double-blinded RCT in Spain where they randomized 24 patients to ivermectin versus 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, $P < 0.05$), and patient days with cough (68 vs. 98, $P < 0.05$).[57]

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.[54] 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, $P = 0.07$). 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, $P > 0.05$, 95% CI, 0.86–3.67).[55]

A medical group in the Dominican Republic reported a case series of 2688 consecutive symptomatic outpatients seeking treatment in the emergency department, most whom were diagnosed using a clinical algorithm. The patients were treated with a high-dose ivermectin of 0.4 mg/kg for one dose along with 5 days of azithromycin. Remarkably, only 16 of the 2688 patients (0.59%) required subsequent hospitalization with only a single death recorded.[61]

In another case series of 100 patients in Bangladesh, all treated with a combination of 0.2 mg/kg ivermectin and doxycycline, they found that no patient required hospitalization nor died, and all patients' symptoms improved within 72 hours.[62]

A case series from Argentina reported on a combination protocol that used ivermectin, aspirin, dexamethasone, and enoxaparin. In the 135 mild illness patients, all survived.[50] 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.[58]

Clinical studies of the efficacy of ivermectin in hospitalized patients

Studies of ivermectin among more severely ill hospitalized patients include 6 RCTs, 5 OCTs, and a database analysis study.[45,51–53,63–70]

The largest RCT in hospitalized patients was performed concurrent with the prophylaxis study reviewed above by Elgazzar et al.[45] Four hundred patients were randomized among 4 treatment groups of 100 patients each. Groups 1 and 2 included mild/moderate illness patients alone, with group 1 treated with one dose 0.4 mg/kg ivermectin plus standard of care (SOC) and group 2 received hydroxychloroquine 400 mg twice on day 1 then 200 mg 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%, $P < 0.001$), with no deaths and 4 deaths, respectively. Groups 3 and 4 included only severely ill patients, with group 3 again treated with a single dose of 0.4 mg/kg plus SOC, whereas group 4 received hydroxychloroquine plus SOC. In this severely ill subgroup, the differences in outcomes were even larger, with lower rates of progression 4% versus 30% and mortality 2% versus 20% ($P < 0.001$).

The one largely outpatient RCT conducted 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, whereas in the standard of care group, only severely ill patients (n = 22) were included because of 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 among the severely ill groups that reached a borderline statistical significance (0% vs. 27.3%, $P = 0.052$). Another important finding was the relatively 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.[65] Among multiple ivermectin treatment arms (different ivermectin dosing strategies were used in the intervention arms), the average mortality was reported as 3.3%, whereas the average mortality within the standard care and placebo arms was 18.8%, with an odds ratio (OR) of 0.18 (95% CI 0.06–0.55, $P < 0.05$).

Spoorthi[64] and Sasanak performed a prospective trial of 100 hospitalized patients whereby they treated 50 with ivermectin and doxycycline, whereas the 50 controls were given a placebo consisting of vitamin B6. Although no deaths were reported in either group, the ivermectin treatment group had a statistically significant shorter hospital length of stay (LOS) 3.7 days versus 4.7 days, $P = 0.03$, and shorter time to complete resolution of symptoms, 6.7 days versus 7.9 days, $P = 0.01$.

The largest OCT (n = 280) in hospitalized patients was conducted 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 using a propensity-matched design on 280 consecutive treated patients and compared those treated with ivermectin to those without. One hundred seventy-three patients were treated with ivermectin (160 received a single dose and 13 received a second dose at day 7) while 107 were not.[63] In both unmatched and propensity-matched cohort comparisons, similar, large, and statistically significant lower mortality was found among ivermectin-treated patients (15.0% vs. 25.2%, $P = 0.03$). Furthermore, in the subgroup of patients with severe pulmonary involvement, mortality was profoundly reduced when treated with ivermectin (38.8% vs. 80.7%, $P = 0.001$).

Another large OCT in Bangladesh compared 115 patients treated with ivermectin to a standard care cohort consisting of 133 patients.[51] Despite a significantly higher proportion of patients in the ivermectin group being men (ie, 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%, $P < 0.05$). The largest OCT is a study from Brazil, published as a letter to the editor and included almost 1500 patients.[66] Although the primary data were not provided, they reported that in 704 hospitalized patients treated with a single dose of 0.15 mg/kg ivermectin, compared with 704 controls, overall mortality was reduced (1.4% vs. 8.5%, HR 0.2, 95% CI 0.12–0.37, $P < 0.0001$). 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 with 71

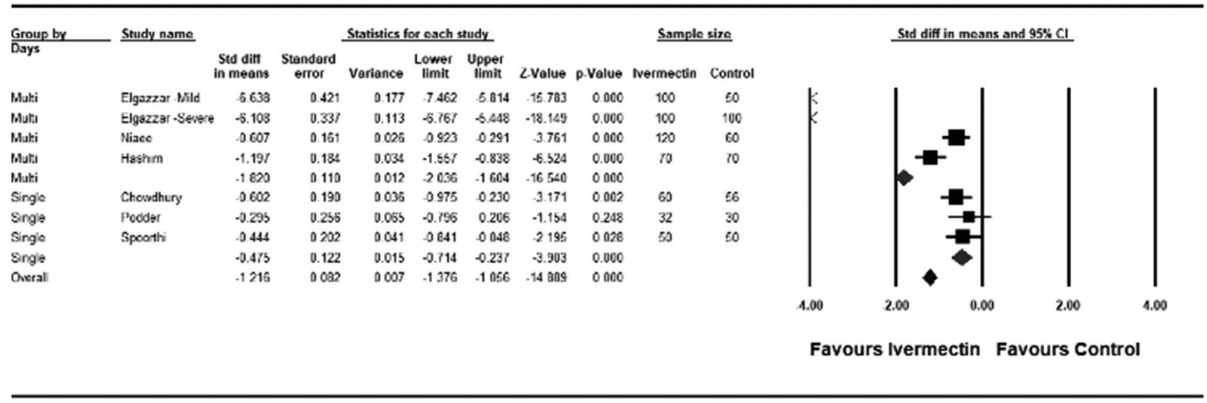

FIGURE 2. Meta-analysis of the outcome of time to clinical recovery from controlled trials of ivermectin treatment in COVID-19. OBS, observational study; RCT, randomized controlled trial. Symbols: Squares: Indicate treatment effect of an individual study. Large diamond: Reflect summary of study design 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.

controls.[52] This study also reported a significant reduction in length of hospital stay (7.6 days vs. 13.2 days, $P < 0.001$) 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, whereas in more than 900 patients treated with other agents, there was an overall mortality of 11.1%.[70]

Meta-analyses of the above controlled treatment trials were performed by the study authors focused on the 2 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 are remarkable, especially given that in several of the studies treatment was initiated late in the disease course.

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

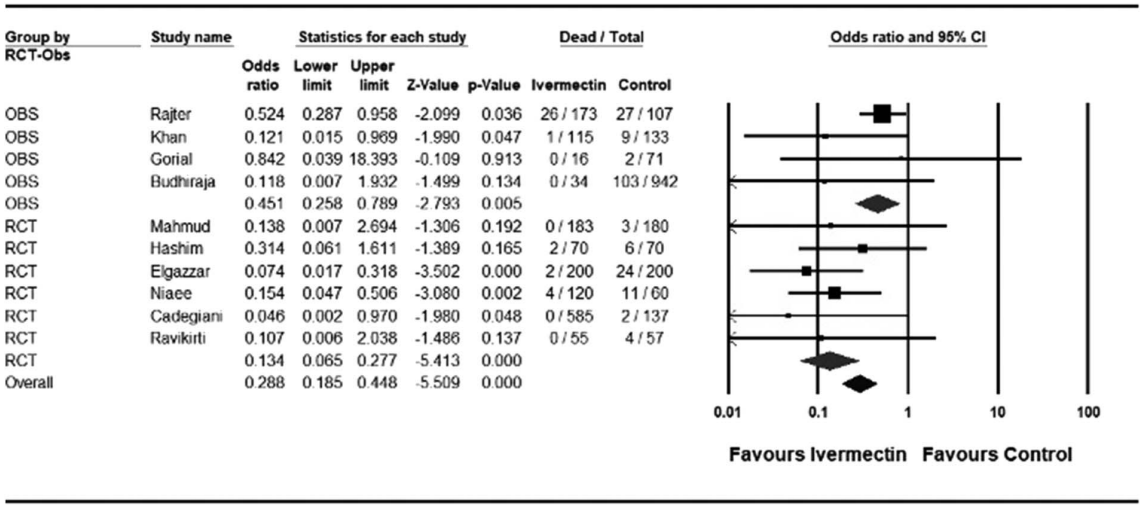

FIGURE 3. Meta-analysis of the outcome of mortality from controlled trials of ivermectin treatment in COVID-19. OBS, observational study; RCT, randomized controlled trial. Symbols: Squares: Indicate treatment effect of an individual study. Large diamond: Reflect summary of study design immediately above. 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.

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
Prophylaxis trials					
Shouman W, Egypt *www.clinicaltrials.gov* NCT04422561	RCT N = 340	Household members of pts with +COVID-19 PCR test	40–60 kg: 15 mg, 60–80 kg: 18 mg, and > 80 kg: 24 mg	Two doses, 72 hours apart	7.4% versus 58.4% developed COVID-19 symptoms, $P < 0.001$
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	0.4 mg/kg	Two doses, day 1 and day 7	2% versus 10% tested positive for COVID-19 $P < 0.05$
Chala R, Argentina NCT04701710 *Clinicaltrials.gov*	RCT N = 234	Health care workers	12 mg	Every 7 d	3.4% versus 21.4%, $P = 0.0001$.
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 test	0.2 mg drops	1 drop 5 times a d x 28 d	0.0% versus 11.2% contracted COVID-19 $P < 0.001$
Alam MT, Bangladesh *European J Med Hlth Sciences* 10.24018/ejmed.2020.2.6.599	OCT N = 118	Health care workers	12 mg	Monthly	6.9% versus 73.3%, $P < 0.05$
Carvallo H, Argentina *Journal of Biochemical Research and Investigation* doi.org/10.31546/2633–8653.1007	OCT N = 1195	Health care workers	12 mg	Once weekly for up to 10 wk	0.0% of the 788 workers taking ivermectin versus 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 Venereologi* 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% versus 22.6% residents contracted COVID-19 0.0% versus 4.9% mortality
Hellwig M, USA *J Antimicrobial Agents* doi.org/10.1016/j.ijantimicag.2020.106,248	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 $P < 0.001$

Clinical trials–Outpatients

Prophylaxis Trials Author, Country, source	Study design, size	Study subjects	Ivermectin dose	Dose frequency	% Ivermectin versus % Controls Clinical outcomes reported
Mahmud R, Bangladesh *www.clinicaltrials.gov* NCT0452383	DB-RCT N = 363	Outpatients and hospitalized	12 mg + doxycycline	Once, within 3 days of PCR+ test	Early improvement 60.7% versus 44.4%, $P < 0.03$, deterioration 8.7% versus 17.8%, $P < 0.02$
Chowdhury A, Bangladesh *Research Square* doi.org/10.21203/rs.3.rs-38896/v1	RCT N = 116	Outpatients	0.2 mg//kg + doxycycline	Once	Recovery time 5.9 versus 9.3 days ($P = 0.07$)
Ravikirti, India *medRxiv* doi.org/10.1101/2021.01.05.21249310	DB-RCT N = 115	Mild–moderate illness	12 mg	Daily for 2 d	No diff in day 6 PCR + 0% versus 6.9% mortality, $P = 0.019$
Babalola OE, Nigeria medRxiv doi.org/10.1101/2021.01.05.21249131	DB-RCT N = 62	Mild–moderate illness	6 mg and 12 mg	Every 48 hours × 2 wk	Time to viral clearance: 4.6 days high dose versus 6.0 days low dose versus 9.1 days control ($P = 0.006$)
Podder CS, Bangladesh *IMC J Med Sci 2020;14(2)*	RCT N = 62	Outpatients	0.2 mg/kg	Once	Recovery time 10.1 versus 11.5 days (NS), average time 5.3 versus 6.3 (NS)
Chaccour C. Spain *Research Square* doi.org/10.21203/rs.3.rs-116547/v1	DB-RCT N = 24	Outpatients	0.4 mg/kg	Once	No diff in PCR+ day 7, lower viral load d 4 and 7, ($P < 0.05$), 76 versus 158 pts. d of anosmia ($P < 0.05$), 68 versus 98 pts. d of cough ($P < 0.05$)
Morgenstern J, Dominican Republic *medRxiv* doi.org/10.1101/2020.10.29.20222505	Case series N = 3099	Outpatients and hospitalized	Outpatients: 0.4 mg/kg hospital patients: 0.3 mg/kg	Outpatients: 0.3 mg/kg × 1 dose Inpatients: 0.3 mg/kg, days 1,2,6, and 7	Mortality = 0.03% in 2688 outpatients, 1% in 300 non-ICU hospital patients, and 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	24 mg = mild, 36 mg = moderate, and 48 mg = severe	Days 0 and 7	All 135 with mild illness survived, 1/32 (3.1% of hospitalized) patients died
Alam A, Banglades *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 h

(*Continued on next page*)

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

Clinical trials–Outpatients					% Ivermectin versus % Controls
Prophylaxis Trials Author, Country, source	Study design, size	Study subjects	Ivermectin dose	Dose frequency	Clinical outcomes reported
Espatia-Hernandez G, Mexico *Biomedical Research* www.biomedres.info/biomedi..-proof-of-concept-study-14435.html	Case series N = 28	Outpatients	6 mg	Days 1,2, 7, and 8	All pts recovered average recovery time 3.6 d

Clinical trials–Hospitalized patients					% Ivermectin versus % Controls
Prophylaxis Trials 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	Daily for 4 days	Moderately ill: worsened 1% versus 22%, $P<0.001$. Severely ill: worsened 4% versus 30% mortality 2% versus 20% both with $P < 0.001$
Niaee S. M, Research Square doi.org/10.21203/rs.3.rs-109670/v1	DB-RCT N = 180	Hospitalized patients	0.2, 0.3, and 0.4 mg/kg (3 dosing strategies)	Once versus Days 1,3,5	Mortality 3.3% versus 18.3%. OR 0.18, (0.06–0.55, $P < 0.05$)
Hashim H, Iraq medRxiv doi.org/10.1101/2020.10.26.20219345	SB-RCT N=140	2/3 outpatients and 1/3 hospital pts	0.2 mg/kg + doxycycline	Daily for 2–3 d	Recovery time 6.3 versus 13.6 days ($P<0.001$), 0% versus 27.3% mortality in severely ill ($P = 0.052$)
Spoorthi S, India AIAM, 2020; 7(10):177-182	PCT N = 100	Hospitalized patients	0.2 mg/kg+ doxycycline	Once	Shorter hospital LOS, 3.7 versus 4.7 days, $P = 0.03$, faster resolution of symptoms, 6.7 versus 7.9 days, $P = 0.01$
Ahmed S. Dhaka, Bangladesh International journal of Infectious disease doi.org/10.1016/j.ijid.2020.11.191	DB-RCT N = 72	Hospitalized patients	12 mg	Daily for 5 d	Faster viral clearance 9.7 versus 12.7 days, $P = 0.02$
Chachar AZK, Pakistan Int J Sciences doi.org/10.18483/ijSci.2378	DB-RCT N = 50	Hospitalized patients-mild	12 mg	Two doses day 1 and one dose day 2	64% versus 60% asymptomatic by day 7
Portman-Baracco A, Brazil	OCT		0.15 mg/kg	Once	

(*Continued on next page*)

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

Clinical trials–Hospitalized patients					% Ivermectin versus % Controls
Prophylaxis Trials Author, Country, source	Study design, size	Study subjects	Ivermectin dose	Dose frequency	Clinical outcomes reported
Arch Bronconeumol. 2020 doi.org/10.1016/j.arbres.2020.06.011	N = 1408	Hospitalized patients			Overall mortality 1.4% versus 8.5%, HR 0.2, 95% CI 0.12–0.37, $P < 0.0001$
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% versus 25.2%, $P = 0.03$, severe illness mortality 38.8% versus 80.7%, $P = 0.001$
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% versus 6.8%, $P < 0.05$, LOS 9 versus 15 days, $P < 0.001$
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 versus 13.2 days, $P < 0.001$, 0/15 versus 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

DB-RCT, double-blinded randomized controlled trial; HCQ, hydroxychloroquine; IVM, ivermectin; LOS, length of stay; NS, nonstatistically significant, $P > .05$; OCT, observational controlled trial; OL, open label; PCR, polymerase chain reaction; RCT, randomized controlled trial; SB-RCT, single blinded 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 that many have termed the condition as "Long COVID" and patients as "long haulers," estimated to occur in approximately 10%–30% of cases.[71–73] Generally considered as a postviral 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 is 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 their experience with ivermectin in such patients.[74] They treated 33 patients who were between 4 and 12 weeks from the onset of symptoms with escalating doses of ivermectin; 0.2 mg/kg for 2 days if mild and 0.4 mg/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 2 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.[48] 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,[48] a data analyst and member of the FLCCC Alliance, recently posted an article based on 2 critical sets of data that he compiled and compared; first, he identified the timing and magnitude of each region's ivermectin interventions through a review of official communications, press releases, and the Peruvian Situation Room database 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.[48] It should be noted that he restricted his analyses to only those citizens older than 60 years 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 excess 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.

Figure 5 from the same study presents data on the case fatality rates in patients older than 60 years, again among the 8 states in Peru. Note the dramatically decreased case fatality rates among older patients diagnosed with COVID-19 after ivermectin became widely distributed in those areas, a result which cannot be explained by changes in mask-wearing or lock-downs.

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 period. Figure 6 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.

Another 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 "deworming" 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 the use of ivermectin to treat COVID-19 in Paraguay. 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.

The evidence base for ivermectin against COVID-19

To date, the efficacy of ivermectin in COVID-19 has been supported by the following:

1. Since 2012, multiple in vitro studies have demonstrated that Ivermectin inhibits the replication of many viruses, including influenza, *Zika, Dengue*, and others.[9–17]
2. Ivermectin inhibits SARS-CoV-2 replication and binding to host tissue through several observed and proposed mechanisms.[18]
3. Ivermectin has potent anti-inflammatory properties with in vitro data demonstrating profound

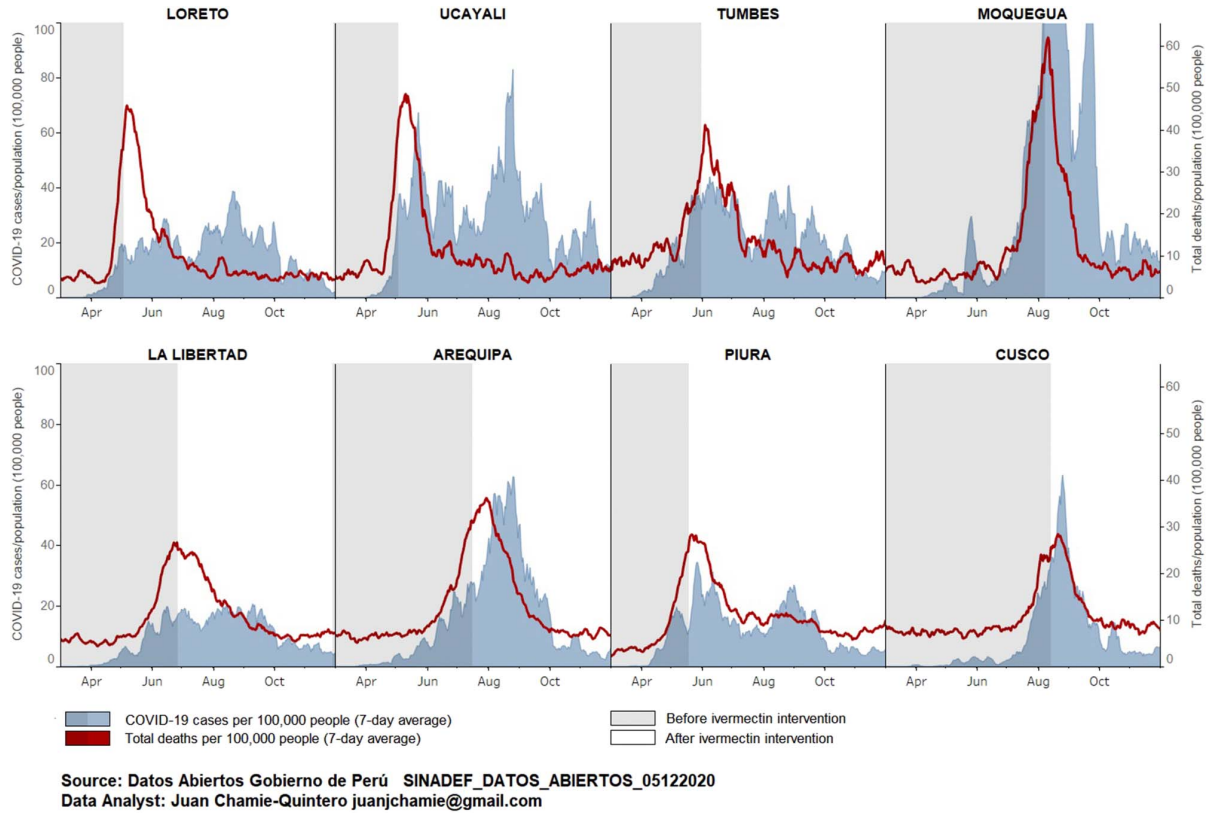

FIGURE 4. Decrease in total case incidences and total deaths/population of COVID-19 in the over 60 population among 8 Peruvian states after deploying mass ivermectin distribution campaigns.

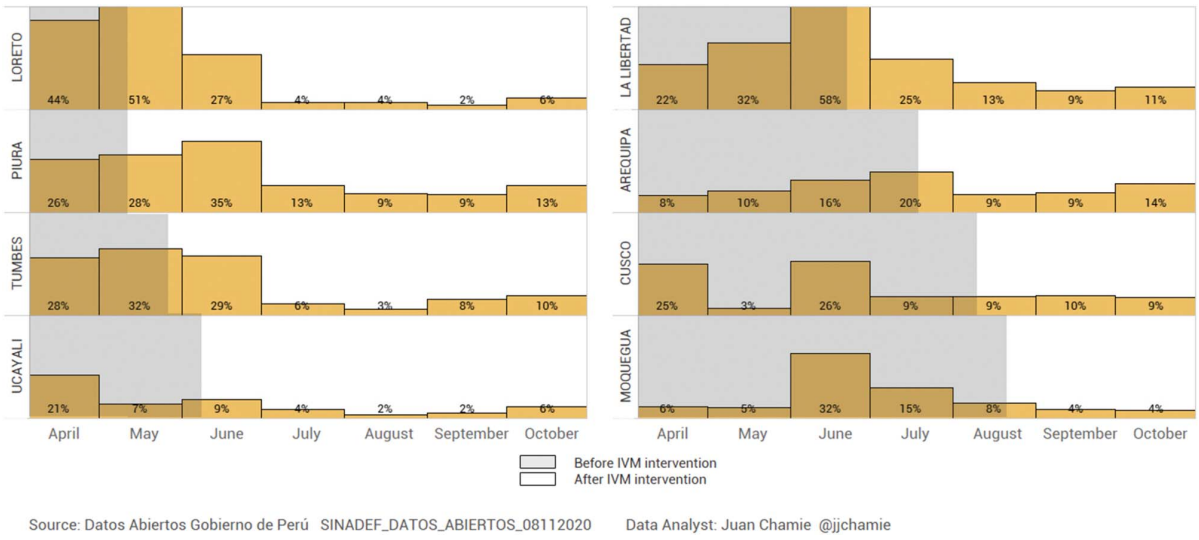

FIGURE 5. Daily total deaths, case fatalities, and case incidence for COVID-19 in populations of patients aged 60 and older for 8 states in Peru deploying early mass ivermectin treatments versus the state of Lima, including the capital city, where ivermectin treatment was applied months later.

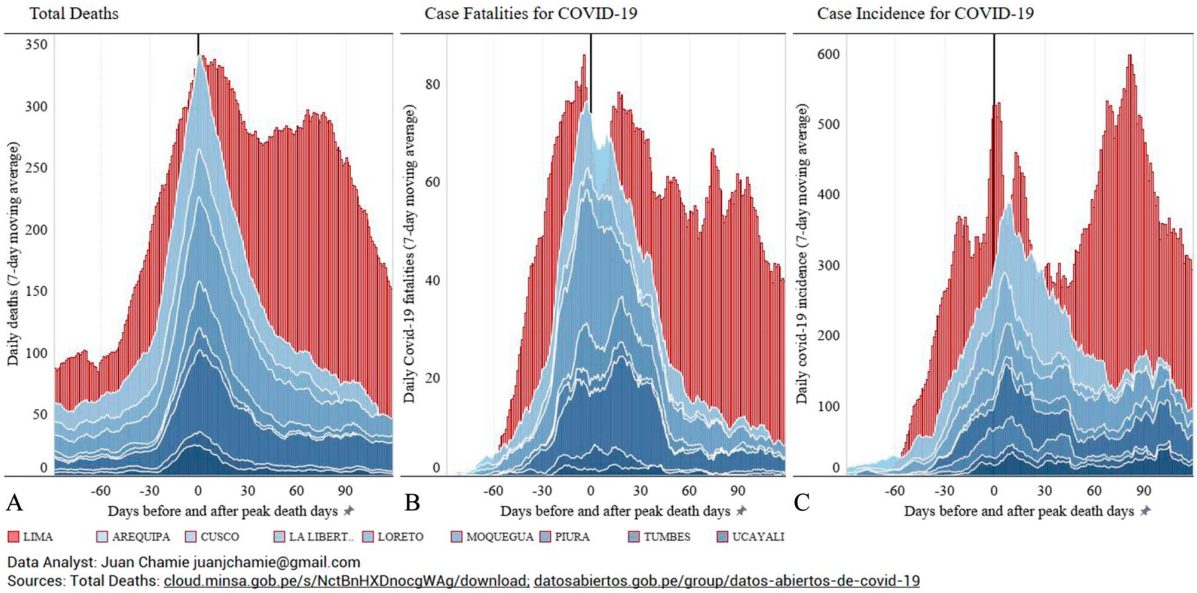

FIGURE 6. Covid-19 case fatalities and total deaths with and without mass ivermectin in different states of Peru.

inhibition of both cytokine production and transcription of nuclear factor-κB (NF-κB), the most potent mediator of inflammation.[37–39]

4. Ivermectin significantly diminishes viral load and protects against organ damage in multiple animal models when infected with SARS-CoV-2 or similar coronaviruses.[31,32]
5. Ivermectin prevents transmission and development of COVID-19 disease in those exposed to infected patients.[40–45]

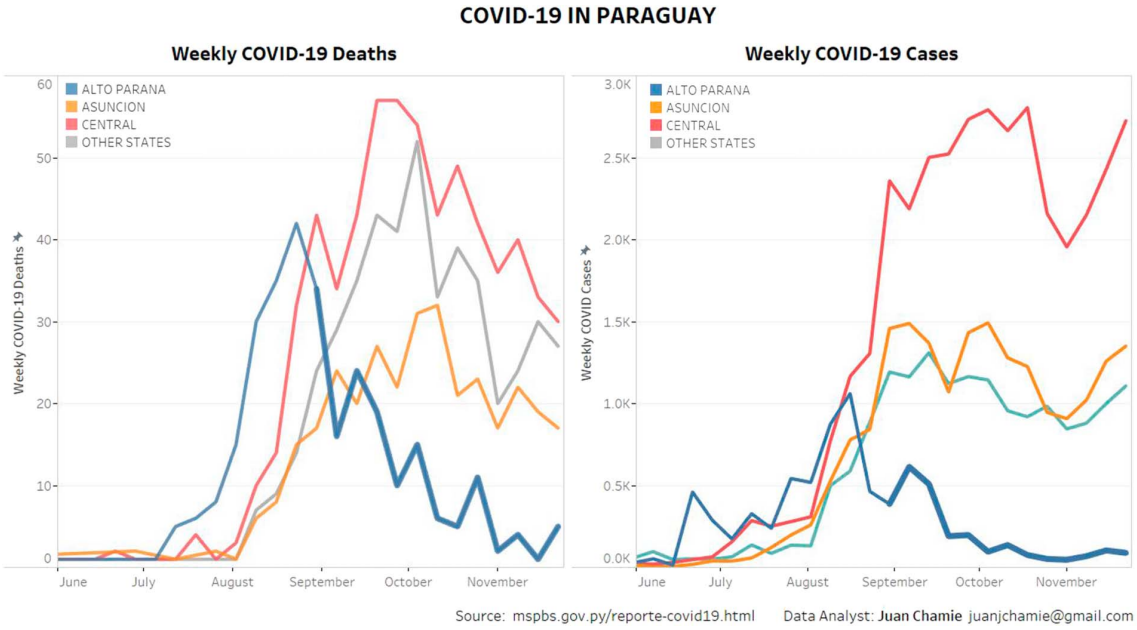

FIGURE 7. Paraguay – COVID-19 case counts and deaths in Alto Parana (bolded blue line) after ivermectin distribution began compared to other regions.

6. Ivermectin hastens recovery and prevents deterioration in patients with mild to moderate disease treated early after symptoms.[45,49–52,61,62]
7. Ivermectin hastens recovery and avoidance of ICU admission and death in hospitalized patients.[45,51,53,63–66]
8. Ivermectin reduces mortality in critically ill patients with COVID-19.[45,53,63]
9. Ivermectin leads to temporally associated reductions in case fatality rates in regions after ivermectin distribution campaigns.[48]
10. The safety, availability, and cost of ivermectin are nearly unparalleled given its low incidence of important drug interactions along with only mild and rare side effects observed in almost 40 years of use and billions of doses administered.[75]
11. The World Health Organization has long included ivermectin on its "List of Essential Medicines."

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)

1. All 8 available controlled trial results show statistically significant reductions in transmission.
2. Three RCTs with large statistically significant reductions in transmission rates, N = 774 patients.[44–46]
3. Five OCTs with large statistically significant reductions in transmission rates, N = 2052 patients.[40–43,47]

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

1. Five RCTs with statistically significant impacts in time to recovery or hospital length of stay.[45,49,53,64,65]
2. One RCT with a near statistically significant decrease in time to recovery, $P = 0.07$, N = 130.[54]
3. One RCT with a large, statistically significant reduction in the rate of deterioration or hospitalization, N = 363.[49]
4. Two RCTs with a statistically significant decrease in viral load, days of anosmia, and cough, N = 85.[57,60]
5. Three RCTs with large, statistically significant reductions in mortality (N = 695).[45,60,65]
6. One RCT with a near statistically significant reduction in mortality, $P = 0.052$ (N = 140).[53]
7. Three OCTs with large, statistically significant reductions in mortality (N = 1688).[51,63,66]

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.[75] In a study that combined results from trials including more than 50,000 patients, serious events occurred in less than 1% and largely associated with administration in Loa loa.[76] Furthermore, according to the pharmaceutical reference standard *Lexicomp*, the only medications contraindicated for use with ivermectin are the concurrent administration of antituberculosis 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 that 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 because of decreased levels may be a concern.[77]

Concerns of safety in the setting of liver disease are unfounded given that, to the best of our knowledge, only 2 cases of liver injury have ever been reported in association with ivermectin, with both cases rapidly resolved without need for treatment.[78,79] Furthermore, 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 among almost 4 billion doses with serious neurological adverse events, such as ataxia, altered consciousness, seizure, or tremor.[80] Potential explanations included the effects of concomitantly administered drugs that 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 exceedingly rare. Finally, ivermectin has been used safely in pregnant women, children, and infants.

DISCUSSION

Currently, as of December 14, 2020, there is accumulating evidence that demonstrates both the safety and efficacy of ivermectin in the prevention and treatment of COVID-19. Large-scale epidemiologic analyses validate the findings of in vitro, animal, prophylaxis, and clinical studies. Epidemiologic data from regions of the world with widespread ivermectin use have demonstrated a temporally associated reduction in case counts, hospitalizations, and fatality rates.

In the context of ivermectin's long-standing safety record, low cost, and wide availability along with the

consistent, reproducible, large magnitude of findings on transmission rates, need for hospitalization, and mortality, widespread deployment in both prevention and treatment has been proposed. Although a subset of trials are of an observational design, it must be recognized that in the case of ivermectin (1) half of the trials used a randomized controlled trial design (12 of the 24 reviewed above) and (2) observational and randomized trial designs reach equivalent conclusions on average as reported in a large Cochrane review of the topic from 2014.[81] In particular, OCTs that use propensity-matching techniques (as in the Rajter study from Florida) find near identical conclusions to later-conducted RCTs in many different disease states, including coronary syndromes, critical illness, and surgery.[82–84] 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 aligns in both direction and magnitude of benefit. Such a consistency of benefit among numerous trials of varying sizes designs from multiple different countries and centers around the world is unique and provides strong, additional support.

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 commensurate 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 Institutes of Health. Their most recent recommendation on the use of ivermectin in patients with COVID-19 was last updated on February 11, 2021, where they found that "there was insufficient evidence to recommend for or against ivermectin in COVID-19." For a more definitive recommendation to be issued by major leading public health agencies (PHA), it is apparent that even more data on both the quality and quantity of trials are needed, even during a global health care emergency, and in consideration of a safe, oral, low-cost, widely available and deployable intervention such as ivermectin.

Fortunately, large teams sponsored by 2 different organizations have embarked on this effort. One team, sponsored by the Unitaid/WHO's ACT Accelerator Program and led by the University of Liverpool Senior Research Fellow Dr. Andrew Hill, is performing a systematic review and meta-analysis focused solely on ivermectin treatment RCTs in COVID-19. Although a preliminary meta-analysis of 17 RCTs was posted to a preprint server in February, it is expected that by March 19, 2021, results from approximately 27–29 RCTs including almost 4500 patients will be presented to the WHO Guidelines Committee and that the epidemiologic studies reviewed above by Chamie et al were already presented to the committee in early March (personal communication with Dr. Andrew Hill). It is important to note that on February 5, the WHO Guidelines Committee announced that they had begun a review of the accumulating ivermectin data and expected to arrive at their own formal treatment recommendation within 4–6 weeks. If the above benefits in clinical outcomes continue to be reported in the remaining trials, it is hoped that this almost doubling of the current supportive evidence base would merit a recommendation for use by the WHO, NIH, and other PHA's would be forthcoming.

Because of the urgency of the pandemic, and in response to the surprising persistent inaction by the leading PHA's, the British Ivermectin Recommendation Development Panel was recently coordinated by the Evidence-Based Medicine Consultancy Ltd to more rapidly formulate an ivermectin treatment guideline using the standard guideline development process followed by the WHO. Made up of long-time research consultants to numerous national and international public health organizations including the WHO, they convened both a steering committee and a technical working group that then performed a systematic review and meta-analysis. On February 12, 2021, a meeting was held that included an international consortium of 75 practitioners, researchers, specialists, and patient representatives representing 16 countries and most regions of the world. This Recommendation Development Panel was presented the results of the meta-analysis of 18 treatment RCTs and 3 prophylaxis RCTs including more than 2500 patients along with a summary of the observational trials and the epidemiologic analyses related to regional ivermectin use. After a discussion period, a vote was held on multiple aspects of the data on ivermectin, according to standard WHO guideline development processes. The Panel *found the certainty of evidence for ivermectin's effects on survival to be strong and they recommended unconditional adoption for use in the prophylaxis and treatment of COVID-19.*

In summary, based on the totality of the trials and epidemiologic evidence presented in this review along with the preliminary findings of the Unitaid/WHO meta-analysis of treatment RCTs and the guideline recommendation from the international BIRD conference, ivermectin should be globally and systematically deployed in the prevention and treatment of COVID-19.

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