

IVERMECTIN – A POTENTIAL GLOBAL SOLUTION TO THE COVID-19 PANDEMIC

Recently, a wave of negative results were published from trials on numerous COVID-19 therapies, essentially eliminating any role for remdesivir, hydroxychloroquine, lopinavir/ritonavir, interferon, convalescent plasma, tocilizumab, and mono-clonal antibody therapy.^{1–6} One year on, the only therapy considered "proven" as an effective treatment in COVID-19 are the use of corticosteroids in patients with moderate to severe illness.⁷

Since March 2020, our expert panel, the Front Line COVID-19 Critical Care Alliance (www.flccc.net) led by Professor Paul Marik, has continuously reviewed the rapidly emerging basic science, translational, and clinical data in COVID-19 with the aim of ensuring that our MATH+ Hospital Treatment protocol both continuously evolves and stays current. As of October 28th, 2020, based on the increasing and recently reported data from a number of published and unpublished trials, we have concluded that the drug Ivermectin, an anti-parasitic drug with increasingly well-known anti-viral^{8–16} and anti-inflammatory properties has demonstrated profound activity against COVID-19. Based on these data, we have devised a new prophylaxis and early treatment protocol against COVID-19 which we have named the "I-MASK+" protocol which we believe may serve as a global solution to the pandemic. The evidence base in support of this conclusion shows that Ivermectin:

- 1. Inhibits SARS-CoV-2 replication, leading to absence of nearly all viral material by 48h in infected cell cultures¹⁷
- 2. Prevents transmission and development of COVID-19 disease in household members of infected patients^{18,19}
- 3. Hastens recovery and prevents deterioration in patients with mild to moderate disease treated early after symptoms $^{20-25}$
- 4. Hastens recovery and avoidance of ICU admission and death in hospitalized patients^{25,26}
- 5. Leads to striking reductions in case-fatality rates in regions with population-wide distribution and use^{27,28}

Equally critical features of Ivermectin supporting its potential role as a global intervention are that it is FDA approved, inexpensive, easily compounded, well-tolerated, and has an excellent safety profile and long history of use.²⁹ Further, the drug has an extended duration of activity, and would require as little as one dose a week as a prophylaxis agent, and from 4-6 doses over two days as a therapeutic agent. The data suggests that as little as one or two doses a week taken by a significant proportion of citizens may lead to population-wide protection and reduced transmission in a manner that is easier to achieve, more effective, and less expensive than the still elusive and widely suspect vaccine.¹⁹

The above listed studies showing the physiologic impacts of Ivermectin therapy in COVID-19 are all referenced below. One study deserves particular attention, posted on the pre-print server Researchgate earlier this month by Dr. Juan Chamie which provides an analysis of large amounts of real-world epidemiologic data in support of Ivermectin as an effective population-wide intervention in Peru.²⁷

The study provides population mortality data among 8 regions in Peru before and after the decision of the Peruvian Ministry of Health to recommend and initiate the widespread distribution of hundreds of thousands of doses of Ivermectin for the treatment of COVID-19 patients. Figure 1 below illustrates a dramatic, temporally associated reduction in case fatality rates in patients over 60 after widespread distribution of ivermectin was initiated, a response seen in multiple regions at different times in the pandemic corresponding to the varying dates of initiation of distribution of Ivermectin. By focusing solely on patients over 60, the analyses remove the potential confounding decreases in mortality that could be caused by an increase of infections in healthier, younger people.





Figure 1 Excess of deaths/population & COVID-19 cases/population (on population older than 60)

Source: Datos Abiertos Gobierno de Perú - datosabiertos.gob.pe - Calculations: JuanJChamie@gmail.com @ijchamie

Daily Deaths

COVID-19 Cases / Population Excess of deaths / Population

Figure 2 Cases and deaths by country

Daily Deaths





In a corroboration of the data in Figure 1, our group pulled case counts and death rates from several countries including Peru from the highly cited Worldometer COVID-19 global data site.³⁰ The data from Peru in Figure 2 above reflect similar impacts, i.e. compared to the other countries which reveal a "mirrored" increase in deaths correlating with each "spike" of cases, in Peru, the large increase in case counts from early August to mid-September instead correlated with first a plateau and then a steady decrease in deaths, even beginning during the massive spike, with death rates now approaching pre-pandemic levels.

In a similar "natural experiment" in Brazil, several large cities made the decision to widely distribute "home treatment kits" containing Ivermectin to its citizens, the city of Itajai offered ivermectin to the entire population (approx. 200,000) and some 120,000 accepted. In May the large city of Macapa opted to treat patients with Ivermectin and Azithromycin, targeting those at risk or who had contact with a possible carrier. The city of Natal with a population of 1 million had recommended Ivermectin for COVID-19 treatment and also for prophylaxis of health staff; after initial legal resistance, 1 million doses were distributed.²⁸

The data is for September 14 from the official Brazilian government site (https://covid.saude.gov.br/) and the national press consortium, the table shows data mid-September compared to mid-August (most Ivermectin was administered during July). The bolded regions below all had a major city with Ivermectin distribution, the other nearby regions did not.

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

Table 1 Change in death rates among neighboring regions in Brazil

(bolded regions contained a major city that distributed Ivermectin to its citizens, the unbolded regions did not)

Beyond the death rate reductions found above, case counts also were reduced in the cities compared to neighboring ones without Ivermectin distribution as below:

Table 2 Case count decreases in Brazilian cities with ivermectin distribution programs

(bolded cities distributed ivermectin, neighboring cities in same region without distribution programs listed below)

REGION	CONFIRMED NEW CASES/MONTH	JUNE	JULY	AUGUST	POPULATION 2020 (1000)	% august vs. june/july
South	Itajaí	2123	2854	998	223	40%
	Chapecó	1760	1754	1405	224	80%
North	Macapá	7966	2481	2370	503	45%
	Ananindeua	1520	1521	1014	535	67%
North East	Natal	9009	7554	1590	890	19%
	João Pessoa	9437	7963	5384	817	62%



The country of Haiti presents another interesting case in that it has a national program to prevent lymphatic filariasis in which it distributes ivermectin to 1.2 million people a year. In Figure 3, case counts and death rates in Haiti (middle section) is compared to its neighbor the Dominican Republic as well as the United States.

From the CDC website about this program: "CDC and partners have been supporting Haiti to eliminate LF and, over the past year, have dramatically increased the number of people in the capital of Port-au-Prince who have received treatment, reaching an additional 600,000 people and achieving mass drug administration targets of 65% for the first time in more than five years. CDC experts worked on community-level planning to improve local engagement and drug distribution, as well as real-time tracking to confirm drugs were reaching those in need."



Figure 3 COVID-19 cases and deaths (per million habitants) in the Dominican Republic, Haiti and the USA

Similar population-wide decreases are also seen in Figure 4 below using data from Paraguay which demonstrate that after the government of the state of Alta Parana launched its ivermectin distribution "de-worming" program in early September (apparently a guise to avoid reprimand from the National Ministry of Health which was against using Ivermectin to treat coronavirus), they distributed 30,000 boxes of Ivermectin in early September. By October 15th, the governor declared there were very few cases left in the state.

The numerous randomized and observational trials cited above can also be looked at using meta-analysis. Using this technique, a consistent, reproducible, and summary mortality benefit is found among both the randomized and observational trials, wherein both sets of trials reach a high degree of statistical significance in favor of Ivermectin treatment as seen in Figure 5.







Figure 5 Meta-analysis of Ivermectin clinical studies

Group by	Study name	Statistics for each study				<u>/</u>	
RCT-Obs		Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
OBS	Rajter	0.524	0.287	0.958	-2.099	0.036	
OBS	Khan	0.121	0.015	0.969	-1.990	0.047	
OBS	Gorial	0.842	0.039	18.393	-0.109	0.913	
OBS		0.477	0.270	0.844	-2.546	0.011	
RCT	Mahmud	0.138	0.007	2.694	-1.306	0.192	(
RCT	Hashim	0.314	0.061	1.611	-1.389	0.165	
RCT		0.259	0.062	1.087	-1.846	0.065	
Overall		0.439	0.259	0.745	-3.047	0.002	
							0.01

Odds ratio and 95% CI



Favours Ivermectin Favours Control

In conclusion, based on the in-vitro, animal, clinical, and real-world epidemiologic evidence to date, we find that Ivermectin, due to its highly potent anti-viral and anti-inflammatory activity, should be considered a highly effective global solution to the COVID-19 pandemic, not only by drastically reducing transmission rates via its prophylaxis capability but



also as a therapeutic intervention which can reduce both the morbidity and mortality among mild, moderate, and even severe disease phases.

The Front Line COVID-19 Critical Care Alliance

Pierre Kory, MPA, MD, Associate Professor of Medicine, Aurora St. Luke's Medical Center
G. Umberto Meduri MD, Professor of Medicine, University of Tennessee
Jose Iglesias, DO, Associate Professor of Medicine, Hackensack School of Medicine, Seton Hall
Joseph Varon, MD, Professor of Medicine, University of Texas Health Science Center
Keith Berkowitz, MD, Center for Balanced Health, New York
Howard Kornfeld, MD, Medical Director, Recovery Without Walls
Eivind Vinjevoll, MD Critical Care and Emergency Department Chief, Volda, Norway
Scott Mitchell, MRCS, Associate Specialist, Princess Elizabeth Hospital, Guernsey
Fred Wagshul, MD, Lung Center of America, Dayton, Ohio
Paul E. Marik, MD, Professor of Medicine, Eastern Virginia Medical School

I-MASK+ and MATH+

In March, 2020, the Front Line COVID-19 Critical Care Alliance developed the **MATH+ Hospital Treatment Protocol for COVID-19**, for use in the hospitalized patient, with an emphasis on early initiation — you will find our "Scientific Review of COVID-19 and MATH+", a detailed explanation of the efficacy of the protocol, as well as the MATH+ protocol itself (in several languages) on www.flccc.net/math-hospital-treatment

In October, 2020, the FLCCC Alliance developed the **I-MASK+ Prophylaxis & Early Outpatient Treatment Protocol for COVID-19**, centered around the use of Ivermectin — the I-MASK+ protocol can be downloaded from www.flccc.net/ flccc-ivermectin-protocol

References

- 1. Hermine O, Mariette X, Tharaux PL, et al. Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. *JAMA Intern Med.* 2020.
- 2. Salvarani C, Dolci G, Massari M, et al. Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial. *JAMA Intern Med.* 2020.
- **3.** Pan H, Peto R, Karim QA, et al. Repurposed antiviral drugs for COVID-19 interim WHO SOLIDARITY trial results. medRxiv 2020:2020.10.15.20209817. doi: 10.1101/2020.10.15.20209817
- 4. Agarwal A, Mukherjee A, Kumar G, et al. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). *BMJ*. 2020;371:m3939.
- 5. Lilly. Lilly Statement Regarding NIH's ACTIV-3 Clinical Trial. 2020; https://www.lilly.com/news/stories/statement-activ3clinical-trial-nih-covid19.
- 6. Rosas I, Bräu N, Waters M, et al. Tocilizumab in Hospitalized Patients With COVID-19 Pneumonia. *medRxiv*. 2020.
- 7. World Health Organization. Corticosteroids for COVID-19. 2020. https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1

FLCCC A L L I A N C E

- 8. Atkinson SC, Audsley MD, Lieu KG, et al. Recognition by host nuclear transport proteins drives disorder-to-order transition in Hendra virus V. *Scientific Reports*. 2018;8(1):358.
- 9. Yang SNY, Atkinson SC, Wang C, et al. The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β 1 heterodimer. *Antiviral Research*. 2020;177:104760.
- 10. Götz V, Magar L, Dornfeld D, et al. Influenza A viruses escape from MxA restriction at the expense of efficient nuclear vRNP import. *Scientific Reports*. 2016;6(1):23138.
- 11. Lv C, Liu W, Wang B, et al. Ivermectin inhibits DNA polymerase UL42 of pseudorabies virus entrance into the nucleus and proliferation of the virus in vitro and vivo. *Antiviral Research*. 2018;159:55-62.
- 12. Mastrangelo E, Pezzullo M, De Burghgraeve T, et al. Ivermectin is a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity: new prospects for an old drug. *Journal of Antimicrobial Chemotherapy*. 2012;67(8):1884-1894.
- 13. Tay MYF, Fraser JE, Chan WKK, et al. Nuclear localization of dengue virus (DENV) 1–4 non-structural protein 5; protection against all 4 DENV serotypes by the inhibitor Ivermectin. *Antiviral Research*. 2013;99(3):301-306.
- 14. Varghese FS, Kaukinen P, Gläsker S, et al. Discovery of berberine, abamectin and ivermectin as antivirals against chikungunya and other alphaviruses. *Antiviral Research*. 2016;126:117-124.
- 15. Wagstaff Kylie M, Sivakumaran H, Heaton Steven M, Harrich D, Jans David A. Ivermectin is a specific inhibitor of importin α/β -mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. *Biochemical Journal*. 2012;443(3):851-856.
- King CR, Tessier TM, Dodge MJ, Weinberg JB, Mymryk JS. Inhibition of Human Adenovirus Replication by the Importin α/β1 Nuclear Import Inhibitor Ivermectin. *Journal of Virology*. 2020;94.
- 17. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res.* 2020;178:104787.
- 18. H C. Usefulness of Topical Ivermectin adn Carrageenan to Prevent Contagion of COVID-19 (IVERCAR). *Clinical Trials.gov* 2020; https://clinicaltrials.gov/ct2/show/NCT04425850.
- 19. Shouman W. Use of Ivermectin as a Prophylactic Option in Asymptomatic Family Close Contact for Patient with COVID-19. *Clincal Trials.gov.* 2020.
- 20. Robin RC, Alam RF, Saber S, Bhiuyan E, Murshed R, Alam MT. A Case Series of 100 COVID-19 Positive Patients Treated with Combination of Ivermectin and Doxycycline. *Journal of Bangladesh College of Physicians and Surgeons*. 2020:10-15.
- 21. Carvallo HE, Hirsch RR, Farinella ME. Safety and Efficacy of the Combined use of Ivermectin, dexamethasone, exoxaparin, and aspirin. medxriv. 2020.
- 22. Reaz Mahmud. Clinical Trial of Ivermectin Plus doxycycline for the treatment of COVId-19 Infection. *ClinicalTrials.Gov.* 2020.
- 23. Khan MSI, Khan MSI, Debnath CR, et al. Ivermectin Treatment May Improve the Prognosis of Patients With COVID-19. *Archivos de Bronconeumología*. 2020.
- 24. Gorial FI, Mashhadani S, Sayaly HM, et al. Effectiveness of Ivermectin as add-on Therapy in COVID-19 Management (Pilot Trial). *medRxiv*. 2020.
- 25. Hashim HA, Maulood MF, Rasheed AM, Fatak DF, Kabah KK, Abdulamir AS. Controlled randomized clinical trial on using Ivermectin with Doxycycline for treating COVID-19 patients in Baghdad, Iraq. *medRxiv*. 2020.
- 26. Rajter JC, Sherman MS, Fatteh N, Vogel F, Sacks J, Rajter JJ. Use of Ivermectin is Associated with Lower Mortality in Hospitalized Patients with COVID-19 (ICON study). *Chest.* 2020.
- 27. Chamie J. Real-World Evidence: The Case of Peru. Causality between Ivermectin and COVID-19 Infection Fatality Rate. 2020.
- 28. Connel A. An Old Drug Tackles New Tricks: Ivermectin Treatment in Three Brazilain Towns. 2020; https://www.trialsite-news.com/an-old-drug-tackles-new-tricks-ivermectin-treatment-in-three-brazilian-towns/.
- 29. Kircik LH et al. Over 25 years of Clinical Experience with Ivermectin: An overview of safety for an increasing number of indications. *J Drugs Dermatology*. 2016; Mar;15(3):325-32.
- 30. Worldometer. Coronavirus Update Live. 2020; https://www.worldometers.info/coronavirus/#countries.

7/7