Dr. Wheeler

I am a pediatrician and thus I will start with how we use medications in children.

Hypocrisy of Medicine Today:

1. Most drugs prescribed for children have not been tested in children.

2. Historically, only about 20 percent of drugs are approved by the FDA for pediatric use and yet we use them all the time on our sick children.

3. We even have drugs that were once FDA approved medications and now are taken off the market.

> For example, FDA appoved Zantac in 1983 (Glaxo Holdings Ltd, a company that is now part of GlaxoSmithKline PLC). According to https://www.arnolditkin.com/blog/product-liability/history-of-zantac-ranitidine-/ Zantac had become the world's best-selling drug by 1988.
>
> After 33 years of using Zantac (April 2020), FDA released an official request for all Zantac and ranitidine products to stop being sold in the United States

4. There are many classes of drugs that have very common off-label uses (meaning not FDA approved for that specific illness)

> According to https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3538391/
>
> "Radley et al1 reported in 2006 that in a group of commonly used medications, 21% of prescriptions were for an off-label use."
>
> "78.9% of children discharged from pediatric hospitals were taking at least 1 off-label medication"
>
> "In an intensive care unit, Lat et al13 reported that 36.2% of medication orders were for an off-label use"
>
> "In a headache specialty practice, Loder and Biondi14 reported that off-label use accounted for 47% of prescriptions written"

Drug repurposing, redirecting meaning "off-label uses" is defined as the identification of novel usages for existing drugs.

> Please refer to pdf (examples of off-label use drugs)
> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3538391/

How to we come up with this idea for a novel usage of a drug?

1. Well, physicians are given the freedom to make a clinical decision for their patient based on their knowledge base.
2. Physicians understand the how the drug works for a certain disease process... meaning that they understand the mechanism of action for that medication, how the medication interacts at a cellular level, how it is metabolized in the body and how it is eliminated
3. For example, one may ask how does an anti seizure medication be useful for a migraine or nerve pain?
4. The class of drugs known as statins was FDA approved for reducing cholesterol levels. But physicians who take care of patients were able to use their knowledge base, do clinical trials and use statins in diabetic patients to help decrease their risk of heart attacks. This was not an FDA approved drug for the treatment of diabetes or heart attacks. This was an off-label use of this drug
5. Because this empirical reasoning process was not hindered by a narrative, statins are now considered a standard treatment to prevent heart attacks in people with diabetes.
6. This is how science and progress works.
7. Medicine is practiced because decision standards are to be challenged, reevaluation and reaffirmed.
8. If we continue to quench any scientific reasoning that goes against the narrative, we have lost the scientific progress in medicine.

Unfortunately, this scientific discord where physicians are allowed to challenge one another has been politicized as misinformation.

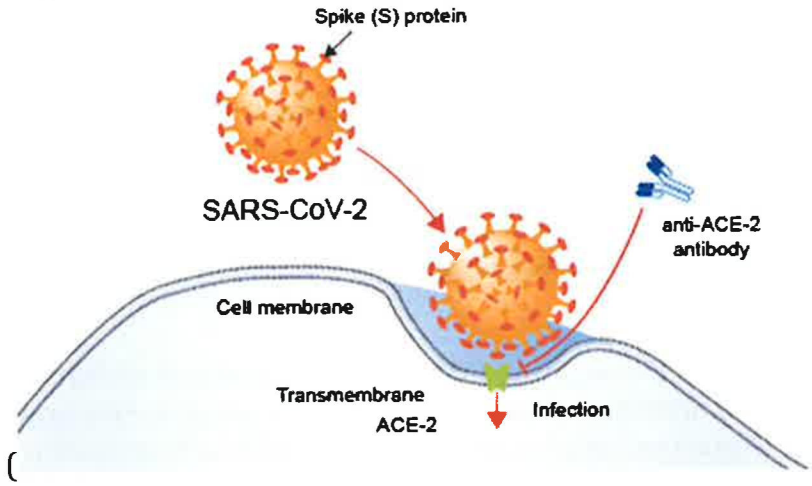
Since the elephant in the room is Ivermectin in our current polarized society, let's address it together. Let's put our own personal biases (as we all have one) aside and try to understand this Nobel Prize winning medication.

Many studies have shown that Ivermectin has anti-viral and anti-inflammatory properties against COVID-19

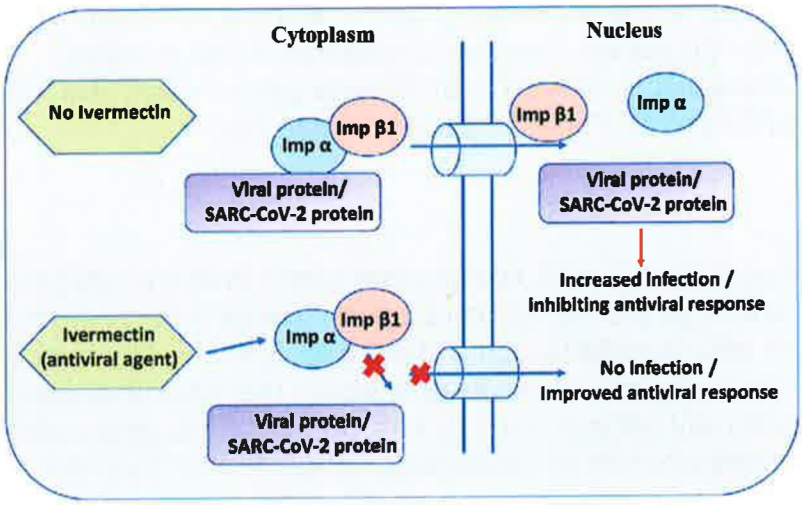
Let's talk about the anti-viral activity:

A study published in https://pubmed.ncbi.nlm.nih.gov/32871846/) says that "Ivermectin shows broad-spectrum anti-viral activity *in vitro*"

1. Ivermectin can prevent the virus from entering the cell. It can bind to the SARS-CoV-2 and prevent the virus from entering the cell. (Ivermectin is docked in the region of leucine 91 of the spike and histidine 378 of the SARS Cov2-ACE2 receptor complex, between the SARS-Cov2 protein and the ACE2 protein.)



2. Ivermectin can prevent SAR2-CoV-2 from entering the nucleus of the host cell by blocking it's transport though the ionopores of the nuclear membrane in vivo study. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8203399/ and https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7652439/)



https://www.researchgate.net/profile/Swapnil_Tiwari4/publication/342086153/figure/fig5/AS:964207566655505@1606896406829/Proposed-antiviral-mechanism-of-action-of-ivermectin-against-severe-acute-respiratory.png

3. The above are just 2 mechanisms of action. Ivermectin has also been shown to halt SARS-2_CoV-2 replication

Let's talk about the anti-inflammatory activity:

4. Ivermectin inhibits STAT-3 (the central hub of the "cytokine storm" that is responsible for inflammation and alveolar damage.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8203399/pdf/41429_2021_Article_430.pdf

The above study details many more mechanisms of actions of Ivermectin against SARS-2-CoV2.

Thus, this study published on May 20, 2021 on the NIH website (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8203399/pdf/41429_2021_Article_430.pdf) states

"considering the urgency of the ongoing COVID-19 pandemic, simultaneous detection of various new mutant strains and future potential re-emergence of novel coronaviruses, repurposing of approved drugs such as Ivermectin could be worthy of attention."

This is science!

I want to also give you specific example of what happened to a patient in the ICU at St. Luke's Hospital. That actually died. This patient was intubated for weeks and the hospital protocols were not working. A physician was willing to give Ivermectin but decided against it because "it was not in the protocol" and not FDA approved for SARS2-CoV-2. However, the patient was given another medication called Pulmazyme, a medication that is used in Cystic Fibrosis patients, that also is NOT FDA approved for SARS2-CoV-2. This is hypocrisy in medicine!

Is this compassion?

It is not science to quench the scientific thought that varies from one established narrative. We must unite and proclaim science again. Science is the bedrock of varied thought, where ideas are challenged and progress is made. Physicians must have the freedom to make the best decisions possible for that individual patient unhindered by protocols and policies made by non-clinicians. We must unite and reestablish TRUST in medicine where the physician-patient covenant is the foundation.

TABLE

Examples of Common Off-label Uses of Drugs

Category and drug	Off-label use(s)[a]
Allergy	
Diphenhydramine	Chemotherapy-related emesis, insomnia[16]
Anesthesiology	
Propofol	Intracranial hypertension
Dexamethasone, propofol	Postoperative nausea
Meperidine	Postanesthetic shivering
Cardiology	
Amiodarone	Supraventricular tachycardia[16]
Aspirin	Antithrombosis in atrial fibrillation, Kawaskai disease[16]
Atorvastatin, simvastatin	Extended-interval dosing for hyperlipidemia[16]
Indomethacin	Pharmacologic closure of patent ductus arteriosus[18]
Dermatology	
Azathioprine	Atopic dermatitis, pemphigus; psoriasis[19]
Biologic agents (eg, etanercept, infliximab, intravenous immunoglobulin, rituximab)	Alopecia areata, atopic dermatitis, Behçet disease, dermatomyositis, hidradenitis suppurativa, pemphigoid, pityriasis, vasculitis[20]
Gastroenterology	
Erythromycin	Gastroparesis[21]
Omeprazole	Reflux-related laryngitis[16]
Hematology/oncology	
Alendronate	Hypercalcemia of malignancy[16]
Dabigatran	Venous thromboembolism prophylaxis after orthopedic surgery[22]
Doxorubicin	Refractory multiple myeloma[16]
Furosemide (nebulized)	Dyspnea[16]
Rituximab	Idiopathic thrombocytopenic purpura, Waldenström macroglobulinemia[16]
Infectious disease	
Linezolid	Infective endocarditis[16]
Sulfamethoxazole-trimethoprim	Sinusitis[16]
Nephrology	
Acetylcysteine	Prevention of contrast nephrotoxicity[16]
Albuterol	Hyperkalemia[16]
Erythropoietin	Anemia of chronic disease[16]

Neurology	
Atenolol, metoprolol, propranolol	Migraine prophylaxis[10]
Isoflurane	Seizure, status epilepticus
Donepezil	Frontotemporal dementia[23]
Gabapentin	Bipolar disorder, diabetes, fibromyalgia, neuropathic pain symptoms, headache, hiccups, hot flashes, restless leg syndrome[24]
Lidocaine	Postherpetic neuralgia[24]
Tricyclic antidepressants	Bulemia, insomnia, irritable bowel syndrome, neuropathic pain symptoms[15,16,24]
Obstetrics	
Magnesium sulfate	Premature labor[16]
Volatile anesthetics (eg, enflurane, isoflurane, halothane)	Intraoperative uterine contraction
Pediatrics	
Amoxicillin (high dose)	Otitis media in children[16]
Atenolol	Hypertension in children[16]
Intranasal desmopressin	Nocturnal enuresis[25]
Pediatrics (continued)	
Morphine	Pain in children[11]
Sildenafil	Pulmonary hypertension in children[16]
Pulmonary	
Volatile anesthetics (eg, enflurane, isoflurane, halothane)	Status asthmaticus[26]
Psychiatry	
Atypical antipsychotics (eg, risperidone, olanzapine, quetiapine)	Anxiety, dementia, eating disorders, obsessive-compulsive disorder, personality disorders, posttraumatic stress disorder, substance abuse[27]
β-Blockers	Social phobia, public speaking[28]
Citalopram	Alcoholism, fibromyalgia, irritable bowel syndrome, obsessive-compulsive disorder, pathologic gambling, stuttering[16]
Fluoxetine	Borderline personality disorder, diabetic neuropathy, fibromyalgia, hot flashes, premature ejaculation[24]
Trazodone	Insomnia in elderly patients[16]
Urology	
Sildenafil	Sexual dysfunction symptoms in women[29]

*This table is not comprehensive and is not intended as an endorsement of these off-label drug uses.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3538391/

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JARA Japan Antibiotics Research Association
The Society for Actinomycetes Japan

REVIEW ARTICLE

The mechanisms of action of Ivermectin against SARS-CoV-2: An evidence-based clinical review article

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Abstract
Considering the urgency of the ongoing COVID-19 pandemic, detection of various new mutant strains and future potential re-emergence of novel coronaviruses, repurposing of approved drugs such as Ivermectin could be worthy of attention. This evidence-based review article aims to discuss the mechanism of action of ivermectin against SARS-CoV-2 and summarizing the available literature over the years. A schematic of the key cellular and biomolecular interactions between Ivermectin, host cell, and SARS-CoV-2 in COVID-19 pathogenesis and prevention of complications have been proposed.

Introduction

A relatively recent surge in zoonotic diseases has been noted over the past few decades. Several reasons could be responsible for this "spill-over" of disease-causing agents from animals to humans. These include an exponential rise in the global population causing man to encroach new ecological habitats in search of space, food, and resources as well as improved opportunities for rampant wildlife trade causing inter-species pathogen jumps. The 1980s was known for HIV/AIDS crisis that originated from the great apes, while the Avian flu pandemic in 2004-07 came from the birds. The pigs lead to the Swine flu pandemic in 2009 and bats were the original hosts of Ebola, Severe Acute Respiratory Syndrome (SARS), Middle Eastern respiratory syndrome (MERS), and probably Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) outbreak as well.

COVID-19 has already caused millions of deaths worldwide and has paralyzed not only the world's health-care system but also the political and economic relations between countries [1]. The fact that the SARS-CoV-2 virus has been thought to have originated from wildlife and may have "jumped" into humans, not only highlights future risks from animal-borne diseases but also provides an important clue to its resolution. In such a scenario, where this "jump" has been made from animal to human, it seems only logical to review a drug that has worked efficiently against a disease-causing agent and is available in a form that is safe for human consumption since the early 1980 s.

Ivermectin belongs to a group of avermectins (AVM), which is a group of 16 membered macrocyclic lactone compounds discovered at the Japanese Kitasato institute in 1967 during actinomycetes cultures with the fungus *Streptomyces avermitilis* [2]. This drug radically lowered the incidence of river blindness and lymphatic filariasis and was discovered and developed by William C. Campbell and Satoshi Ōmura for which they received the Nobel Prize in Physiology or Medicine in 2015 [3, 4]. Ivermectin is enlisted in the World Health Organization's Model List of Essential Medicines [5].

Drug repurposing, drug redirecting, or drug reprofiling is defined as the identification of novel usages for existing drugs. The development risks, costs as well as safety-related failure, are reduced with this approach since these drugs have a well-established formulation development, in vitro and in vivo screening, as well as pharmacokinetic and pharmacodynamic profiles. Moreover, the first clinical trial phases of many such drugs have been completed and can be bypassed to reduce several years of development. Therefore, drug repurposing has the potential to reduce the time frame for the whole process by up to 3–12 years and carries great potential [6].

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Table 1 All 55 ivermectin COVID-19 trials (As per data available on 16 May 2021) divided based on stage of treatment (Early Vs Late) and the type of study

Study	Study Type
EARLY TREATMENT	
Random effects meta-analysis with pooled effects showed 79% improvement for early treatment RR 0.21 and CI [0.11-0.37]	
Double-Blind Randomized controlled trial	Mahmud et al.*, Ahmed et al.*, Chaccour et al.*, Babalola et al.*, Kirti et al., Mohan et al., Schwartz et al., Lopez- Medina et al.*, Chahla et al.
Single-blind Randomized controlled trial	Raad et al.
Randomized controlled trial	Bukhari et al., Chowdhury et al.*, Faisal et al.*
Retrospective quasi-randomized study	Loue et al*, Merino et al
Other studies	Espitia-Hernandez et al.*, Carvallo et al., Cadegiani et al., Afsar et al., Elalfy et al.*, Roy et al., Mourya et al.*
LATE TREATMENT	
Random effects meta-analysis with pooled effects showed 46% improvement for late treatment RR 0.54 and CI [0.40-0.72]	
Randomized controlled trial	Kishoria et al.*, Podder et al.*, Chachar et al.*, Elgazzar et al.. Pott-Junior et al.*
Double-Blind Randomized controlled trial	Niaee et al.,Okumus et al.*, Shahbazn et al.*, Gonzalez et al.*. Huvemek et al.
Single-Blind Randomized controlled trial	Hashim et al.
Other studies	Gorial et al., Khan et al., Soto-Becerra et al, Rajter et al.*, Camprubi et al.*, Spoorthi et al*, Budhiraja et al., Lima Morales et al.*

The 29 peer-reviewed trials have been marked with an asterisk as a superscript. (*) (source: https://ivmmeta.com/)

Although several drugs received Emergency Use Authorization for COVID-19 treatment with unsatisfactory supportive data, Ivermectin, on the other hand, has been sidelined irrespective of sufficient convincing data supporting its use. Nevertheless, many countries adopted ivermectin as one of the first-line treatment options for COVID-19.

With the ongoing vaccine roll-out programs in full swing across the globe, the longevity of the immunity offered by these vaccines or their role in offering protection against new mutant strains is still a matter of debate. The adoption of Ivermectin as a "safety bridge" by some sections of the population that are still waiting for their turn for vaccination could be considered as a "logical" option.

Several doctor-initiated clinical trial protocols that aimed to evaluate outcomes, such as reduction in mortality figures, shortened length of intensive care unit stay and/or hospital stay and elimination of the virus with ivermectin use have been registered at the US ClinicalTrials.gov [7]. Real-time data is also available with a meta-analysis of 55 studies to date. As per data available on 16 May 2021, 100% of 36 early treatment and prophylaxis studies report positive effects (96% of all 55 studies). Of these, 26 studies show statistically significant improvements in isolation. Random effects meta-analysis with pooled effects using the most serious outcome reported 79% and 85% improvement for early treatment and prophylaxis respectively (RR 0.21 [0.11–0.37] and 0.15 [0.09–0.25]). The results were similar after exclusion based sensitivity analysis: 81% and 87% (RR 0.19 [0.14–0.26] and 0.13 [0.07–0.25]), and after restriction to 29 peer-reviewed studies: 82% and 88% (RR 0.18 [0.11–0.31] and 0.12 [0.05–0.30]). Statistically significant improvements were seen for mortality, ventilation, hospitalization, cases, and viral clearance. 100% of the 17 Randomized Controlled Trials (RCTs) for early treatment and prophylaxis report positive effects, with an estimated improvement of 73% and 83% respectively (RR 0.27 [0.18–0.41] and 0.17 [0.05–0.61]), and 93% of all 28 RCTs. These studies are tabulated in Table 1. The probability that an ineffective treatment generated results as positive for the 55 studies to date is estimated to be 1 in 23 trillion ($p = 0.000000000000043$). The consistency of positive results across a wide variety of cases has been remarkable. It is extremely unlikely that the observed results could have occurred by chance [8].

However, a controlled outpatient trial by López-Medina et al. demonstrated that, in mild COVID-19, Ivermectin showed no improvement [9]. Misinterpretation of results were noted due to possible gaps in regards to the study quality (study design, the methodology adopted, statistical analysis, and hence the conclusion).

Ivermectin has rapid oral absorption, high liposolubility, is widely distributed in the body, metabolized in the liver (cytochrome P450 system) and excreted almost exclusively in feces [4]. Following a standard oral dose in healthy humans, it reaches peak plasma levels at 3.4 to 5 h; and plasma half-life has been reported to be 12 to 66 h [10]. Despite its widespread use, there are relatively few studies

Table 2 A list of studies demonstrating the role of Ivermectin (IVM) on SARS-CoV-2

MAIN ROLE OF IVERMECTIN AGAINST SARS-COV-2	STUDY AUTHORS	STUDY YEAR	REFERENCES
A. DIRECT ACTION ON SARS-COV-2			
Level 1: Action on SARS-CoV-2 cell entry			
IVM docks in the region of leucine 91 of the spike protein and histidine 378 of the ACE2 receptor	Leher et al.	2020	[22]
IVM has the highest binding affinity to the predicted active site of the S glycoprotein; Considerable binding affinity to the predicted active site of the SARS-CoV-2 RdRp protein; Highest binding affinity to the predicted active site of nsp14; highest binding affinity to the active site of the TMPRSS2 protein	Eweas et al.	2021	[23]
IVM utilizes viral spike protein, main protease, replicase, and human TMPRSS2 receptors as the most possible targets for executing its antiviral efficiency by disrupting binding	Choudhury et al.	2021	[24]
Level 2: Action on Importin (IMP) superfamily			
in presence of a viral infection, IVM targets the IMPα component of the IMP α/β1 heterodimer and binds to it, preventing interaction with IMP β1, subsequently blocking the nuclear transport of viral proteins.	Yang, S.N.Y et al.	2020	[26]
Level 3: Action as an Ionophore			
Two ivermectin molecules, reacting with each other in a "head-tail" mode, can create a complex suitable to be considered as ionophore. These ionophores allow neutralizing the virus at an early stage of the infection before it can adhere to the host cells and enter it.	Rizzo E et al.	2020	[28]
B. ACTION ON HOST TARGETS FOR VIRAL REPLICATION			
Level 4: Action as an antiviral			
IVM has antiviral properties against other viruses including the RNA viruses such as Zika Virus (ZKV), Dengue virus, yellow fever virus (YFV), and West Nile virus (WNV), Hendra virus (HEV), Newcastle virus, Venezuelan equine encephalitis virus (VEEV), Chikungunya virus (CHIKV), Semliki Forest virus (SFV), and Sindbis virus (SINV), Avian influenza A virus, Porcine Reproductive and Respiratory Syndrome virus (PRRSV), Human immunodeficiency virus type 1 as well as DNA viruses such as Equine herpesvirus type 1 (EHV-1) and Pseudorabies virus (PRV).	Heidary, F et al.	2020	[29]
Level 5: Action on viral replication and assembly			
In Vero/hSLAM cells infected with the SARS-CoV-2 virus when "exposed" to 5 μM IVM showed a 5000-fold reduction in viral RNA at 48 h when compared to the control group	Caly L et al.	2020	[30]
utilizing modeling approach, predicted lung accumulation of Ivermectin over 10 times higher than EC 50	Arshad et al	2020	[31]
best binding interaction between IVM and RNA-dependent RNA polymerase (RdRp)	Swargiary et al.*	2020	[33]
highly efficient binding of IVM to nsp14	Ma et al.	2015	[35]
highly efficient binding of IVM to the viral N phosphoprotein and M protein	Eweas et al.	2021	[23]
Level 6: Action on post-translational processing of viral polyproteins			
IVM binds to both proteins, Mpro, and to a lesser extent to PLpro of SARS-CoV-2	Eweas et al.	2021	[23]
Level 7: Action on Karyopherin (KPNA/KPNB) receptors			
IVM inhibits the KPNA/KPNB1- mediated nuclear import of viral proteins	Caly L et al.	2020	[30]
C. ACTION ON HOST TARGETS FOR INFLAMMATION			
Level 8: Action on Interferon (INF) levels			
IVM promotes the expression of several IFN-related genes, such as IFIT1, IFIT2, IF144, ISG20, IRF9, and OASL	Seth C	2016	[40]
Level 9: Action on Toll- like-Receptors (TLRs)			
IVM blocks activation of NF-kappa B pathway and inhibition of toll-like receptor 4 (TLR4) signaling	Zhang X et al.	2008	[42]
Level 10: Action on Nuclear Factor-κB (NF-κB) pathway			
IVM at its very low dose, which did not induce cytotoxicity, drastically reversed the resistance of tumor cells to the chemotherapeutic drugs both in vitro and in vivo by inhibition of the transcriptional factor NF-κB.	Jiang L et al.	2019	[44]

Table 2 (continued)

MAIN ROLE OF IVERMECTIN AGAINST SARS-COV-2	STUDY AUTHORS	STUDY YEAR	REFERENCES
IVM inhibits lipopolysaccharide (LPS)-induced production of inflammatory cytokines by blocking the NF-κB pathway and improving LPS-induced survival in mice.	Zhang X et al.	2008	[42]
Level 11: Action on the JAK-STAT pathway, PAI-1 and COVID-19 sequalae			
IVM inhibits STAT-3, SARS-CoV-2-mediated inhibition of IFN and STAT 1, with the subsequent shift to a STAT 3- dominant signaling network that could result in almost all of the clinical features of COVID-19; STAT-3 acts as a "central hub" that mediates the detrimental COVID-19 cascade	Matsuyama, T.,	2020	[39]
STAT-3 induces a C-reactive protein that upregulates PAI-1 levels. Ivermectin inhibits STAT-3.	Matsuyama, T.,	2020	[39]
The PD-L1 receptors present on the endothelial cells are activated by STAT-3 causing T cell lymphopenia. IVM inhibits STAT-3 through direct inhibition	Matsuyama, T.,	2020	[39]
Level 12: Action on P21 activated Kinase 1 (PAK-1)			
IVM suppresses the Akt/mTOR signaling and promotes ubiquitin-mediated degradation of PAK-1 hence compromising STAT-3 activity and decreasing IL-6 production.	Dou Q et al.	2016	[54]
Level 13: Action on Interleukin-6 (IL-6) levels			
IVM suppressed IL-6 and TNFα production	Zhang X et al.	2008	[42]
IVM "dramatically reduced" IL-6/IL-10 ratio modulating infection outcomes.	G D de Melo et al. *	2020	[55]
Level 14: Action on allosteric modulation of P2X4 receptor			
Positive allosteric modulation of $P2X_4$ by IVM enhances ATP-mediated secretion of CXCL5	Layhadi JA et al.	2018	[58]
Level 15: Action on high mobility group box 1 (HMGB1)			
Ivermectin inhibits HMGB1	Juarez M et al.	2018	[60]
Level 16: Action as an immunomodulator on Lung tissue and olfaction			
No olfactory deficit was observed in IVM-treated females; IVM dramatically reduced the IL-6/IL-10 ratio in lung	G D de Melo et al. *	2020	[55]
Level 17: Action as an anti-inflammatory			
anti-inflammatory action of IVM was explained as inhibition of cytokine production by lipopolysaccharide challenged macrophages, blockade of activation of NF-kB, and the stress-activated MAP kinases JNK and p38, and inhibition of TLR4 signaling.	Zhang X et al., Ci X et al., Yan S et al.	2008 2009 2011	[42, 62, 63]
Immune cell recruitment, cytokine production in bronchoalveolar lavage fluid, IgE, and IgG1 secretion in serum as well as hyper-secretion of mucus by goblet cells was reduced significantly by IVM	Yan S et al.	2011	[63]
D. ACTION ON OTHER HOST TARGETS			
Level 18: Action on Plasmin and Annexin A2			
Annexin acts as a co-receptor for the conversion of plasminogen to plasmin in the presence of t-PA. increased levels of plasmin leads to direct activation of STAT-3.	Kamber Zaidi et al.	2020	[64]
IVM directly inhibits STAT-3 and could play a role in the inhibition of COVID-19 complications.	Matsuyama et al.	2020	[39]
Level 19: Action on CD147 on the RBC			
The SARS-CoV-2 does not internalize into the red blood cells but such attachments can lead to clumping. IVM binds to the S protein of the SARS-CoV-2 virus making it unavailable to bind with CD147.	David E.Scheim et al.	2020	[65]
Level 20: Action on mitochondrial ATP under hypoxia on cardiac function			
IVM increased mitochondrial ATP production by inducing Cox6a2 expression and maintains mitochondrial ATP under hypoxic conditions. This prevents pathological hypertrophy and improves cardiac function.	Nagai H et al.	2017	[67]

*available as preprint; Clinical trials of IVM on COVID-19 available on https://clinicaltrials.gov[7]; Ivermectin for COVID-19: real-time meta-analysis available on https://ivmmeta.com [8]

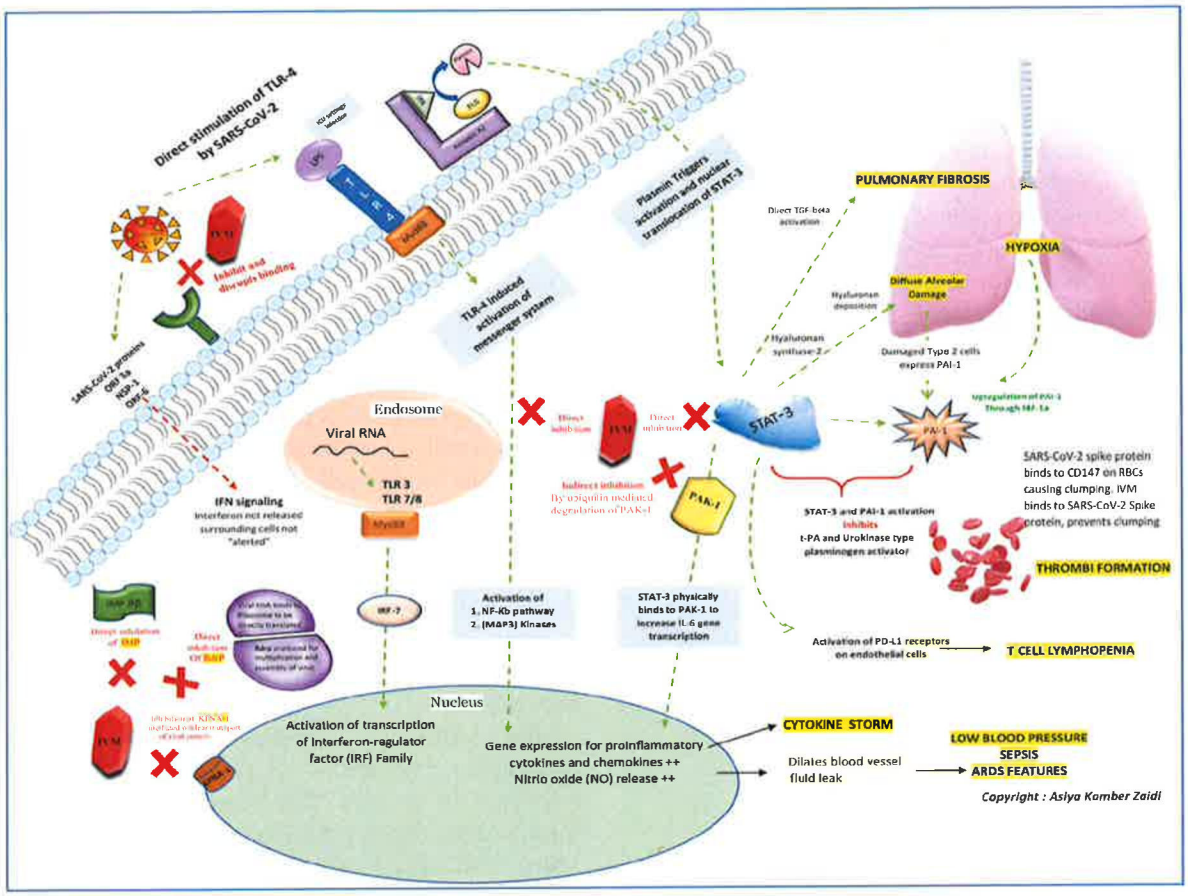

Fig. 1 A schematic of the key cellular and biomolecular interactions between Ivermectin, host cell, and SARS-CoV-2 in COVID-19 pathogenesis and prevention of complications. Ivermectin; IVM (red block) inhibits and disrupts binding of the SARS-CoV-2 S protein at the ACE-2 receptors (green). The green dotted lines depict activation pathways and the red dotted lines depict the inhibition pathways. The TLR-4 receptors are directly activated by SARS-CoV-2 and also by LPS mediated activation (seen during ICU settings) causing activation of NF-Kb pathway and MAP3 Kinases leading to increased intranuclear gene expression for proinflammatory cytokines and chemokines (responsible for cytokine storm) and NO release (responsible for blood vessel dilatation, fluid leak, low blood pressure, ARDS and sepsis). The NF-Kb and STAT-3 pathway activation is central to the pathogenesis and sequelae of COVID-19. STAT-3 physically binds to PAK-1 and increases IL-6 transcription. The annexin A2 at the cell surface converts plasminogen; PLG to plasmin under the presence of t-PA. Plasmin triggers activation and nuclear translocation of STAT-3. An upregulation of STAT-3 stimulates hyaluronan synthase-2 in the lung cells causing hyaluronan deposition leading to diffuse alveolar damage and hypoxia. STAT-3 also directly activates TGF-beta initiating pulmonary fibrosis; a typical characteristic of SARS-COV-2 lung pathology. The damaged type 2 cells express PAI-1 and an already hypoxic state also causes an upregulation of PAI (through Hypoxic inducible factor-1) along with direct stimulation by STAT-3. Simultaneous STAT-3 and PAI-1 activation inhibits t-PA and urokinase-type plasminogen activator leading to thrombi formation. Also, the SARS-CoV-2 spike protein binds to the CD147 on red blood cells and causes clumping. *IVM in turn, binds to SARS-CoV-2 Spike protein and hence prevents clumping*. T cell lymphopenia in COVID-19 can also be attributed to the direct activation of PD-L1 receptors on endothelial cells by STAT-3. *IVM directly inhibits the NF-kb pathway, STAT-3, and indirectly inhibits PAK-1 by increasing its ubiquitin-mediated degradation*. The natural antiviral response of a cell is through interferon regulatory genes and viral RNA mediated activation of TLR-3 and TLR7/8- Myd88 activation of transcription of interferon-regulator (IRF) family. For a virus to establish an infection, this antiviral response needs to be inhibited by blocking interferon production. The proteins such as importin and KPNA mediate nuclear transport of viral protein and subsequent IFN signaling. The SARS-CoV-2 proteins (ORF-3a, NSP-1, and ORF-6) directly block IFN signaling causing the surrounding cells to become unsuspecting victims of the infection. *IVM inhibits both importin a-b (green) as well as the KPNA-1 receptors (brown) causing natural antiviral IFN release. IVM also inhibits viral RdrP, responsible for viral replication. IVM* Ivermectin, *ACE-2* angiotensin-converting-enzyme 2, *LPS* Lipopolysaccharide, *TLR* Toll-like receptor, *t-PA* tissue-like plasminogen activator, *PLG* Plasminogen, *IMPab* Importin alpha-beta, *Rdrp* RNA dependant RNA polymerase, *KPNA-1* Karyopherin Subunit Alpha 1, *NF-kB* nuclear factor kappa-light-chain-enhancer of activated B cells, *Map3Kinases* Mitogen-activated Kinases, *PAK-1* P21 Activated Kinase 1, *STAT-3* Signal transducer and activator of transcription 3, *PAI-1* Plasminogen activator inhibitor-1, *HIF-1* Hypoxia-Inducible Factor

on the pharmacokinetics of Ivermectin in humans [11]. Ivermectin binds strongly to plasma proteins in healthy subjects (93.2%) [12]. Such an "avid binding" can be beneficial when administered in countries where malnutrition and hypoalbuminemia are common, leading to an increased availability of "free fraction" of ivermectin [4].

Hypoalbuminemia is a frequent finding in patients with COVID-19 and it also appears to be linked to the severity of lung injury [13]. Therefore, Ivermectin might be useful when used in such a setting.

There is evidence supporting the use of Ivermectin in decreasing mortality figures in patients with SARS-CoV-2 infection. However, the use of ivermectin orally in an outpatient setting also requires strict and well defined guidelines to avoid any form of overdosing that could lead to toxicity. A study by Baudou, E et. al described two human ABCB1 nonsense mutations associated with a loss of function in a patient who had an adverse reaction to ivermectin after the administration of a usual dose. This finding warrants caution regarding medical prescriptions of ivermectin and other ABCB1 substrates [14].

This article aims to discuss the mechanism of action by summarizing the in vitro and in vivo evidence demonstrating the role of Ivermectin in COVID-19 as per the available literature over the years. [Table 2] A schematic of the key cellular and biomolecular interactions between Ivermectin, host cell, and SARS-CoV-2 in COVID-19 pathogenesis and prevention of complications has been proposed. [Fig. 1]

Methods

A comprehensive search of the PubMed database was conducted from January 1, 2008 up to January 30, 2021 using syntax constructed using MeSH Database as follows: (stromectol OR Ivermectin OR "dihydroavermectin") OR (22 AND 23-dihydroavermectin B) AND (antiviral OR virus OR COVID-19 OR SARS-CoV-2). All the results obtained were manually reviewed for content, relevance and included when considered appropriate. The papers cited in the references were also reviewed and included when considered appropriate. The articles were retrieved manually to exclude any duplicates.

Results

Ivermectin as an anti-helminth

Ivermectin has been approved as an anti-helminthic [15]. It is a selective positive allosteric modulator at the glutamate-gated chloride channels found in nematodes and insects and acts by binding to these channels leading to chloride ion influx causing hyperpolarization of the cell and hence, dysfunction [16]. However, at higher concentrations, Ivermectin can also bind to host GABA receptors only when the blood-brain barrier (BBB) is "leaky". This is not the case in healthy human beings with an intact BBB as the drug is "excluded" by a *p*-glycoprotein drug pump (MDR-1). Chandler et al. considered Ivermectin to be free of potential neurological adverse drug reactions, except in situations of overdose [17].

SARS-CoV-2 virus structure

SARS-CoV-2 is a sarbecovirus with structural similarity to SARS-CoV-1. Out of the four structural proteins of the SARS-CoV-2 beta coronavirus, namely: Spike (S) protein, membrane (M) protein, envelope (E) protein, and nucleocapsid (N) protein, the S protein is responsible for eliciting potent neutralizing antibody responses. The entry of SARS-CoV-2 into the host cell is mediated by the binding of the S1 subunit of its S protein (receptor binding domain) to the Angiotensin-converting enzyme 2 (ACE-2) receptors present on the host cell surface [18]. The S2 subunit is associated with a fusion protein that binds with the cell membrane after priming with Transmembrane protease, serine 2 (TMPRSS-2) and is responsible for fusion with the host cell.

The SARS-CoV-2 genome consists of ~29.8 kb nucleotides; it possesses 14 open reading frames (ORFs) encoding 27 proteins [19]. The 5′ two-thirds of the viral genome encodes the replicase gene. It contains two ORFs: ORF1a and ORF1b. ORF1a/b encodes two polyproteins by polymerase frameshifting; these are then post-translationally cleaved into 15 non-structural proteins (nsps): nsp1–10 and nsp12–16. The rest of the genome encodes for the four structural proteins [(S protein, E protein, M protein, N protein], in addition to eight accessory proteins (3a/3b, p6, 7a/7b, 8b, 9b, and ORF14) [19]. The replicase also encodes the papain-like protease (PLpro) and the serine-type protease or main protease (Mpro) [20].

In principle, a molecule can act as an anti-viral drug if it "inhibits some stage of the virus replication cycle, without being too toxic to the body's cells [21]."

The possible modes of action of anti-viral agents would include the following:

1. Inactivate extracellular virus particles.
2. Prevent viral attachment and/or entry.
3. Prevent replication of the viral genome.
4. Prevent synthesis of specific viral protein(s).
5. Prevent assembly or release of new infectious virions

The role of Ivermectin against the SARS-CoV-2 virus

The targets of activity of Ivermectin can be divided into the following four groups:

A. *Direct action on SARS-CoV-2*
   Level 1: Action on SARS-CoV-2 cell entry
   Level 2: Action on Importin (IMP) superfamily
   Level 3: Action as an Ionophore
B. *Action on host targets important for viral replication*
   Level 4: Action as an antiviral
   Level 5: Action on viral replication and assembly
   Level 6: Action on post-translational processing of viral polyproteins
   Level 7: Action on Karyopherin (KPNA/KPNB) receptors
   C. *Action on host targets important for inflammation*
      Level 8: Action on Interferon (INF) levels
      Level 9: Action on Toll- like-Receptors (TLRs)
      Level 10: Action on Nuclear Factor-κB (NF-κB) pathway
      Level 11: Action on the JAK-STAT pathway, PAI-1 and COVID-19 sequalae
      Level 12: Action on P21 activated Kinase 1 (PAK-1)
      Level 13: Action on Interleukin-6 (IL-6) levels
      Level 14: Action on allosteric modulation of P2X4 receptor
      Level 15: Action on high mobility group box 1 (HMGB1),
      Level 16: Action as an immunomodulator on Lung tissue and olfaction
      Level 17: Action as an anti-inflammatory
   D. *Action on other host targets*
      Level 18: Action on Plasmin and Annexin A2
      Level 19: Action on CD147 on the RBC
      Level 20: Action on mitochondrial ATP under hypoxia on cardiac function

The direct "antiviral targets" may be useful in the early stages while the anti-inflammatory targets might be addressed in the later stages of the disease.

Direct action of Ivermectin on SARS-CoV-2

Level 1: Action on SARS-CoV-2 cell entry

A study by Lehrer S et al observed that Ivermectin docked in the region of leucine 91 of the SARS-CoV-2 spike protein and histidine 378 of the host cell ACE-2 receptor blocking its entry into the host cell [22]. In yet another study by Eweas et al., potential repurposed drugs such as Ivermectin, chloroquine, hydroxychloroquine, remdesivir, and favipiravir were screened and molecular docking with different SARS-CoV-2 target proteins including S and M proteins, RNA-dependent RNA polymerase (RdRp), nucleoproteins, viral proteases, and nsp14, was performed. Ivermectin showed the following 5 important docking properties [23]:

1. Highest binding affinity to the predicted active site of the S glycoprotein (Mol Dock score −140.584) and protein–ligand interactions (MolDock score−139.371).
2. Considerable binding affinity to the predicted active site of the SARS-CoV-2 RdRp protein (MolDock score −149.9900) and protein–ligand interactions (MolDock score −147.608), it formed H-bonds with only two amino acids: Cys622 and Asp760.
3. Highest binding affinity (MolDock score −212.265) to the predicted active site of nsp14.
4. The highest binding affinity to the active site of the TMPRSS2 protein (MolDock score −174.971) and protein–ligand interactions (MolDock score −180.548). Moreover, it formed five H-bonds with Cys297, Glu299, Gln438, Gly462, and Gly464 amino acid residues present at the predicted active site of the TMPRSS protein
5. The free binding energy of the spike protein (open) was higher in Ivermectin (−398.536 kJ/mol) than remdesivir (−232.973 kJ/mol).

An In-silico data analysis conducted by Choudhury et al. demonstrated that Ivermectin efficiently utilizes viral spike protein, main protease, replicase, and human TMPRSS2 receptors as the most possible targets for executing its "antiviral efficiency" by disrupting binding. Since Ivermectin exploits protein targets from both, the virus and human, this could be the behind its excellent in vitro efficacy against SARS-CoV-2 [24].

The development of vaccines for SARS-CoV-2 is centered around spike protein biology (virus targeted) and the recently documented "vaccine escape strains" have been a cause of worry. In such a situation, Ivermectin, is both, virus as well as host targeted and hence could act as a potential therapeutic against these new strains that could "escape" immunity offered by the vaccine.

Level 2: Action on Importin (IMP) superfamily

Inside the cell, the nuclear transport of proteins into and out of the nucleus is signal-dependent and mediated by the Importin (IMP) superfamily of proteins that exist in α and β forms. This IMPα/β1 exists as a heterodimer with a "IBB" (IMP β-binding) site present over IMP α that binds to IMP β1 on "cargo recognition" by IMPα. The SARS-CoV-2 virus upon host cell entry tends to "load" its proteins over the host protein IMP α/β1 heterodimer (importin) to enter the nucleus through the nuclear pore complex. Once inside, the importin molecule detaches while the viral protein from the SARS-CoV-2 virus hijacks the host cell machinery and inhibits the natural cell "anti-viral" response by blocking the release of

interferon (an antiviral substance released by an infected cell to alert the surrounding cells of an ongoing viral attack). As a result, the surrounding cells become "unsuspecting victims" of the virus and the infection continues with the virus escaping recognition by the immune cells [25]. Ivermectin, in presence of a viral infection, targets the IMPα component of the IMP α/β1 heterodimer and binds to it, preventing interaction with IMP β1, subsequently blocking the nuclear transport of viral proteins. This allows the cell to carry out its normal antiviral response [26]. In such a case, it should be noted that the activity of Ivermectin here is viro-static, that is, it neutralizes the virus by competing for the same receptor.

Level 3: Action as an Ionophore

Ionophores are molecules that typically have a hydrophilic pocket which constitutes a specific binding site for one or more ions (usually cations), while its external surface is hydrophobic, allowing the complex thus formed to cross the cell membranes, affecting the hydro-electrolyte balance [27]. It can be hypothesized that two ivermectin molecules, reacting with each other in a "head-tail" mode, can create a complex suitable to be considered such [28]. These ionophores allow neutralizing the virus at an early stage of the infection before it can adhere to the host cells and enter it to exploit their biochemical machinery for the production of other viral particles.

Action on host targets for viral replication

Level 4: Action as an antiviral

A systematic review article by Heidary, F. discussed the "anti-viral" properties of Ivermectin against other viruses including the RNA viruses such as Zika Virus (ZKV), Dengue virus, yellow fever virus (YFV), and West Nile virus (WNV), Hendra virus (HEV), Newcastle virus, Venezuelan equine encephalitis virus (VEEV), Chikungunya virus (CHIKV), Semliki Forest virus (SFV), and Sindbis virus (SINV), Avian influenza A virus, Porcine Reproductive and Respiratory Syndrome virus (PRRSV), Human immunodeficiency virus type 1 as well as DNA viruses such as Equine herpesvirus type 1 (EHV-1) and Pseudorabies virus (PRV) [29].

Level 5: Action on viral replication and assembly

An in-vitro study by Caly L et al. demonstrated that the Vero/hSLAM cells infected with the SARS-CoV-2 virus when "exposed" to 5 μM Ivermectin showed a 5000-fold reduction in viral RNA at 48 h when compared to the control group [30]. This study attracted opinions regarding the inability of Ivermectin to achieve the therapeutic effect of COVID-19 through routine dosage. Contrary to this, Arshad et al, by utilizing modeling approach, predicted lung accumulation of Ivermectin over 10 times higher than EC_{50}. This likelihood of attainment of higher lung tissue concentrations of Ivermectin leaves the door open for further research especially for respiratory infections [31].

An explanation for the study by Caly et al was provided in a review article: Global trends in clinical studies of ivermectin in COVID-19 by Yagisawa et al., co-authored by Prof. Satoshi Ōmura, regarding the "setting of the sensitivity for experimental systems in vitro". As per the authors, using Vero/hSLAM cells, the antiviral activity of the test drug was reliably measured and the sensitivity of the $IC_{50} = 2\,\mu M$ set by them was appropriate as neither false positives nor false negatives occurred. Therefore, the study by Caly et al. merely indicated that ivermectin was found to have anti-SARS-CoV-2 activity in vitro—no more, no less. Also, the fact that there are in vivo infection experiments that could be used to connect in vitro experiments to clinical studies [32].

Another in-silico study by Swargiary et al. demonstrated the best binding interaction of −9.7 kcal/mol between Ivermectin and RdRp suggesting inhibition of viral replication [33]. The RdRP residing in nsp12 is the centerpiece of the coronavirus replication and transcription complex and has been suggested as a promising drug target as it is a crucial enzyme in the virus life cycle both for replication of the viral genome but also for transcription of subgenomic mRNAs (sgRNAs) [34]. Ivermectin binds to the viral rdrp and disrupts it. The highly efficient binding of ivermectin to nsp14 confirms its role in inhibiting viral replication and assembly. It is well known that nsp14 is essential in transcription and replication. It acts as a proofreading exoribonuclease and plays a role in viral RNA capping by its methyltransferase activity [35]. Moreover, highly efficient binding of ivermectin to the viral N phosphoprotein and M protein is suggestive of its role in inhibiting viral replication and assembly [23].

Level 6: Action on post-translational processing of viral polyproteins

Once gaining entry into the host cell, the viral RNA is translated by the host ribosome into a large "polyprotein". Some enzymes break away through autoproteolysis from this polyprotein and further help other proteins to break off and carry out their function for replication. One such enzyme, 3 chymotrypsin-like proteases (3'cl pro/ Mpro) is responsible for working on this polyprotein causing other proteins to "librate" and carry out viral replication. Ivermectin binds to this enzyme and disrupts it. It also efficiently binds to both proteins, Mpro, and to a lesser extent to PLpro of SARS-CoV-2; therefore, it has a role in preventing the post-translational processing of viral polyproteins [23].

Level 7: Action on Karyopherin (KPNA/KPNB) receptors

Karyopherin-α1 (KPNA1) is essential for the nuclear transport of signal transducers and activators of transcription 1 (STAT1) [36], and the interaction between STAT1 and KPNA1 (STAT1/KPNA1) involves a nonclassical nuclear

localization signal (NLS). Ivermectin inhibits the KPNA/KPNB1- mediated nuclear import of viral proteins allowing the cell to carry out its normal antiviral response [30].

Action on host targets for inflammation

Level 8: Action on Interferon (INF) levels

These virus-infected cells release interferons that bind to the IFN receptors present on neighboring cells alerting them of a viral attack. The IFN-I and IFN-III receptors then further activate members of the JAK-STAT family. The virus after gaining entry into the host cell hijacks the host cell machinery and works towards antagonizing the normal interferon-mediated host cell antiviral response. SARS-CoV-2 proteins such as ORF3a, NSP1, and ORF6 inhibit IFN-I signaling [37, 38]. As a result, the cells surrounding the SARS-CoV-2 virus-infected cell "fail" to receive "critical and protective IFN signals" causing this SARS-CoV-2 virus to replicate and spread without any hindrance. This is one of the main reasons that, at this stage, COVID-19 infection is "hard to detect" clinically [39].

Ivermectin has been shown to promote the expression of several IFN-related genes, such as IFIT1, IFIT2, IF144, ISG20, IRF9, and OASL [40].

Level 9: Action on Toll- like-Receptors (TLRs)

Upon virus entry, the intracellular pattern recognition receptors (PRRs) present on the host cells are responsible for detecting the viral attack. The virus activates one such PRR named the Toll-like receptors (TLRs). These receptors are present on various immune system cells that help them locate and bind with the pathogen. The activation of TLRs, causes oligomerization, further activating downstream interferon regulatory factors (IRFs) and nuclear factor-kappa B (NF-kB) transcription factors inducing INF production [41]. Ivermectin plays a role in the blockade of activation of NF-kB pathway and inhibition of TLR4 signaling [42].

Level 10: Action on Nuclear Factor-κB (NF-κB) pathway

Activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway induces the expression of various pro-inflammatory genes, including those encoding cytokines and chemokines [43]. Jiang et al. demonstrated that Ivermectin at its very low dose, which did not induce cytotoxicity, drastically reversed the resistance of tumor cells to the chemotherapeutic drugs both in vitro and in vivo by inhibition of the transcriptional factor NF-κB [44]. Also, Zhang et al., suggested that Ivermectin inhibits lipopolysaccharide (LPS)-induced production of inflammatory cytokines by blocking the NF-κB pathway and improving LPS-induced survival in mice [42]. Therefore, using Ivermectin would be helpful in ICU settings where there are increased chances of bacterial infections (LPS mediated).

Level 11: Action on the JAK-STAT pathway, PAI-1 and COVID-19 sequalae

A strong correlation exists between SARS-CoV-2 viral load, disease severity, and progression [45]. COVID-19 not only causes flu-like symptoms such as fever, dry cough but could also lead to widespread thrombosis with micro-angiopathy in pulmonary vessels [46], raise D-dimer levels [47], cause lymphopenia [48], raise proinflammatory cytokine and chemokine production [49] as well as lead to a significant elevation of CRP levels [50]. SARS-CoV-2 has structural similarity with SARS-CoV-1. Several SARS-CoV-1 proteins antagonize the antiviral activities of IFNs and the downstream JAK (Janus kinase)-STAT signaling pathways they activate. JAK family kinases display a wide range of functions in ontogeny, immunity, chronic inflammation, fibrosis, and cancer [51].

The host proteins, such as the members of the signal transducers and activators of transcription (STATs) and NF-κB, enter the nucleus through nuclear envelope-embedded nuclear pores mediated by the IMPα/β1 heterodimer and play a role in COVID-19 pathogenesis. Frieman et al. demonstrated that accessory SARS ORF6 antagonizes STAT1 function by sequestering nuclear import factors on the rough endoplasmic reticulum/Golgi membrane [52]. A review article by Matsuyama et al, hinted at SARS-CoV-2-mediated inhibition of IFN and STAT 1, with the subsequent shift to a STAT 3 dominant signaling network that could result in almost all of the clinical features of COVID-19 [39].

Before discussing further, it is important to understand the link between STAT-3 upregulation and COVID-19 sequelae and the role of Ivermectin in inhibiting STAT-3. STAT-3 acts as a "central hub" that mediates the detrimental COVID-19 cascade. In the lungs, STAT-3 activates Hyaluronan synthase-2 leading to deposition of hyaluronan causing diffuse alveolar damage. The damaged type 2 alveolar cells express PAI-1 (plasminogen activator inhibitor-1). Additionally, hypoxia due to diffuse alveolar damage causes an upregulation of PAI-1 through HIF-1a. STAT-3 also directly activates PAI-1. The simultaneous activation of PAI-1 and STAT-3 inhibits t-PA and urokinase-type plasminogen activator leading to thrombi formation in the capillaries. PAI-1 also binds to TLR-4 receptors on macrophages further activating the NF-kB pathway.

The "cytokine storm" typical of severe COVID-19 involves STAT-3 mediated upregulation of proinflammatory cytokines, TNFα, and IL-6 in macrophages. Additionally, STAT-3 induces a C-reactive protein that upregulates PAI-1 levels. STAT-3 is directly responsible for activating IL-6 gene transcription which further leads to an increase in TGF-β causing pulmonary fibrosis. The PD-L1 receptors present on the endothelial cells are activated by

STAT-3 causing T cell lymphopenia. Ivermectin inhibits STAT-3 through direct inhibition preventing COVID-19 sequalae [39].

Level 12: Action on P21 activated Kinase 1 (PAK-1)

The p21 activated kinase 1 (PAK1) physically binds to both JAK1 and STAT3, and the resultant PAK1/STAT3 complex activates IL-6 gene transcription responsible for cytokine storm in COVID-19 [53]. Ivermectin suppresses the Akt/mTOR signaling and promotes ubiquitin-mediated degradation of PAK-1 hence compromising STAT-3 activity and decreasing IL-6 production [54].

Level 13: Action on Interleukin-6 (IL-6) levels

A study by Zhang et al. demonstrated that Ivermectin suppressed IL-6 and TNFα production, two major components of the detrimental cytokine storm induced by SARS-CoV-2 and "dramatically reduced" IL-6/IL-10 ratio modulating infection outcomes [42, 55].

Level 14: Action on allosteric modulation of P2X4 receptor

P2X receptors are the channels selective to cation, are gated by extracellular ATP [56] and mediate several functions in health and disease [57]. From the seven subunits of P2X receptors, $P2X_4$ is most sensitive to Ivermectin. Positive allosteric modulation of $P2X_4$ by Ivermectin enhances ATP-mediated secretion of CXCL5 (pro-inflammatory chemokine). CXCL5 is a chemo-attractant molecule expressed in inflammatory cells in different tissues and modulates neutrophil chemotaxis and chemokine scavenging [58].

Level 15: Action on high mobility group box 1 (HMGB1)

The damage-associated molecular pattern high mobility group box 1 (HMGB1), is released by damaged cells acting as an agonist for the TLR4 receptor and hence mediating lung inflammation associated with COVID-19 [59]. Ivermectin inhibits HMGB1 [60].

Level 16: Action as an immunomodulator on Lung tissue and olfaction

In a study by DeMelo et al., the effects of Ivermectin were investigated on SARS-CoV-2 infection using the golden Syrian hamster as a model for COVID-19. Both, male and female adult golden Syrian hamsters were intranasally inoculated with 6×10^4 PFU of SARS-CoV-2. At the time of infection, animals received a single subcutaneous injection of Ivermectin (antiparasitic dose of 400 μg/kg) classically used in a clinical setting and were monitored over four days. Mock-infected animals received the physiological solution only. Interestingly, Ivermectin had a sex-dependent and compartmentalized immunomodulatory effect, preventing clinical deterioration and reducing the olfactory deficit in infected animals. This effect was sex-dependent: infected males presented a reduction in the clinical score whereas a complete absence of signs was noticed in the infected females. Regarding the olfactory performance, 83.3% (10/12) of the saline-treated males presented with hyposmia/anosmia, in contrast to only 33.3% (4/12) of IVM-treated males (Fisher's exact test $p = 0.036$). No olfactory deficit was observed in IVM-treated females (0/6), while 33.3% (2/6) of saline-treated females presented with hyposmia/anosmia (Fisher's exact test $p = 0.455$). Ivermectin dramatically reduced the IL-6/IL-10 ratio in lung tissue, which likely accounts for the more favorable clinical presentation in treated animals [55]. Loss of smell has been reported as one of the common symptoms in COVID-19 [61]. Interestingly, majority of patients in India regained their sense of smell after a brief anosmic period during their clinical course. Ivermectin is being used in India as one of the first-line drugs for COVID-19 treatment. It could be hypothesized that Ivermectin might have a role to play in reducing SARS-CoV-2 induced olfactory deficit.

Level 17: Action as an anti-inflammatory

The mechanism for anti-inflammatory action of Ivermectin was explained as inhibition of cytokine production by lipopolysaccharide challenged macrophages, blockade of activation of NF-kB, and the stress-activated MAP kinases JNK and p38, and inhibition of TLR4 signaling [42, 61, 62]. Moreover, Immune cell recruitment, cytokine production in bronchoalveolar lavage fluid, IgE, and IgG1 secretion in serum as well as hyper-secretion of mucus by goblet cells was reduced significantly by Ivermectin [63].

Action on other host targets

Level 18: Action on Plasmin and Annexin A2

As per study by Kamber Zaidi et al, annexin A2 may be linked to COVID-19 pathophysiology. Annexin A2 acts as a co-receptor for the conversion of plasminogen to plasmin in the presence of t-PA. Increased plasmin levels are found in co-morbid states and is also responsible for early stages of viral infection. Plasmin leads to direct activation of STAT-3 inducing detrimental COVID-19 sequelae. Ivermectin directly inhibits STAT-3 and could play a role in the inhibition of COVID-19 complications.

Level 19: Action on CD147 on the RBC

The transmembrane receptor CD147, present on the red blood cell (RBC) along with ACE-2 has been recognized as a key binding site for SARS-CoV-2 spike protein. The SARS-CoV-2 does not internalize into the RBC but such attachments can lead to clumping [65]. Ivermectin binds to the S protein of the virus making it unavailable to bind with CD147. This action might also be beneficial in advanced stages of COVID-19 presenting with clotting/thrombotic phenomena.

Level 20: Action on mitochondrial ATP under hypoxia on cardiac function

SARS-CoV-2 has been a well-known cause for acute myocardial injury and chronic damage to the cardiovascular

system in active infection as well as in long haulers [66]. Nagai et al. demonstrated that Ivermectin increased mitochondrial ATP production by inducing Cox6a2 expression and maintains mitochondrial ATP under hypoxic conditions preventing pathological hypertrophy and improving cardiac function [67].

Conclusion

Considering the urgency of the ongoing COVID-19 pandemic, simultaneous detection of various new mutant strains and future potential re-emergence of novel coronaviruses, repurposing of approved drugs such as Ivermectin could be worthy of attention.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interest.

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frontiers

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	Group-Ivermectin	Group-Control
		Statistics for each study					Symptomatic Infection / Total	
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		

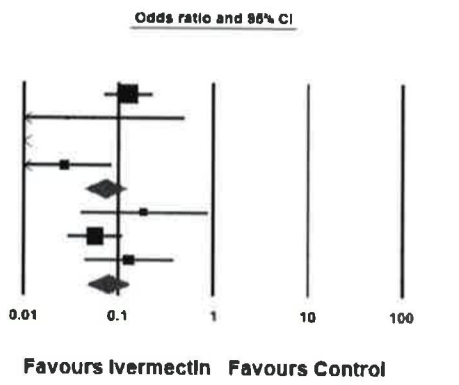


Figure 1 legend: OBS: Observational study, RCT: Randomized Controlled Trial Symbols: Squares: indicate treatment effect of an individual study. Large diamond: reflect summary of study design immediately above. Small diamond: sum effect of all trial designs. Size of each symbol correlates with the size 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

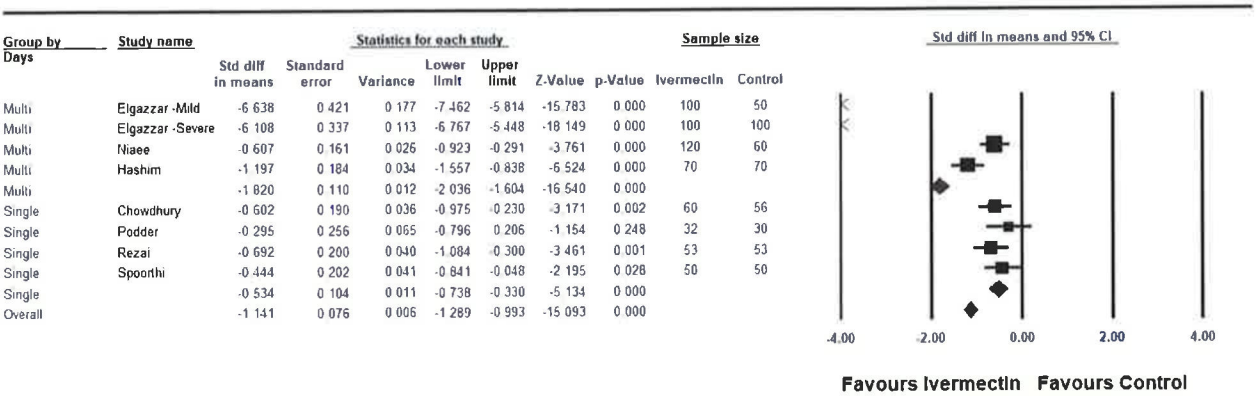
al., 2020). In both unmatched and propensity matched cohort comparisons, similar, large, and statistically significant lower mortality was found amongst ivermectin treated patients (15.0% vs. 25.2%, p =.03). Further, in the subgroup of patients with severe pulmonary involvement, mortality was profoundly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

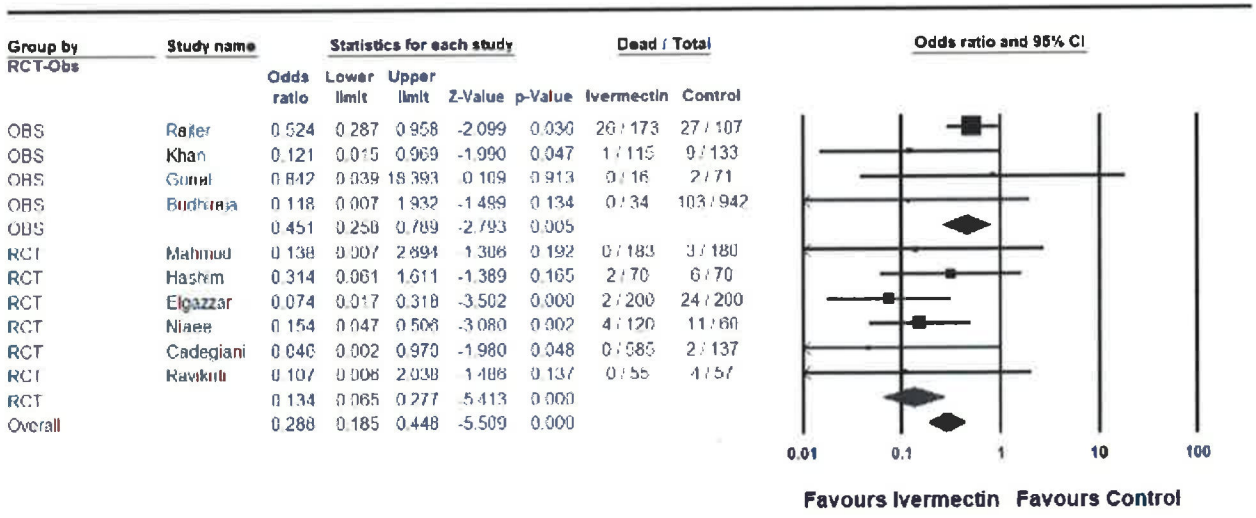
Figure 2. Meta-analysis of the outcome of time to clinical recovery from randomized controlled trials of ivermectin treatment in COVID-19



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	Gunal	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	0 040	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

AUTHOR, COUNTRY, SOURCE	STUDY DESIGN, SIZE	STUDY SUBJECTS	IVERMECTIN DOSE	DOSE FREQUENCY	CLINICAL OUTCOMES REPORTED % Ivermectin vs. % Controls
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

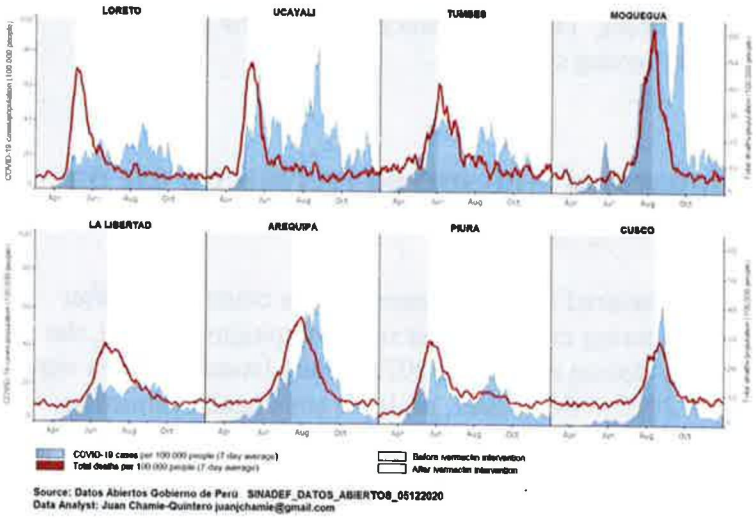
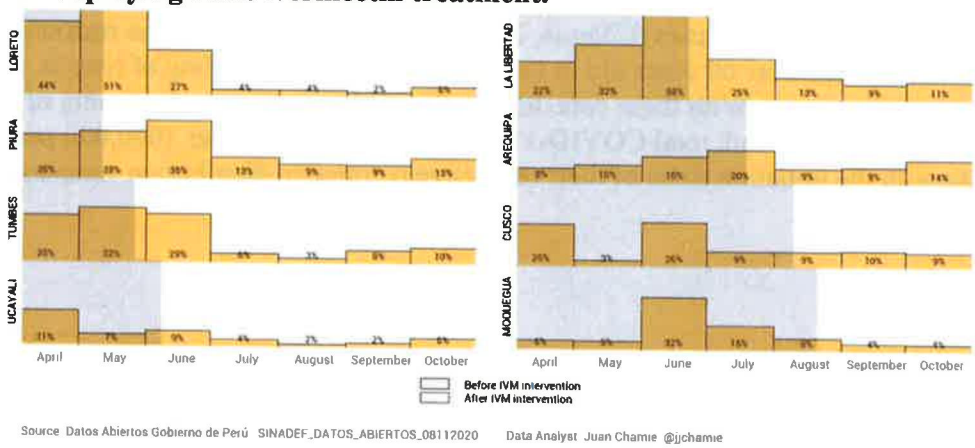


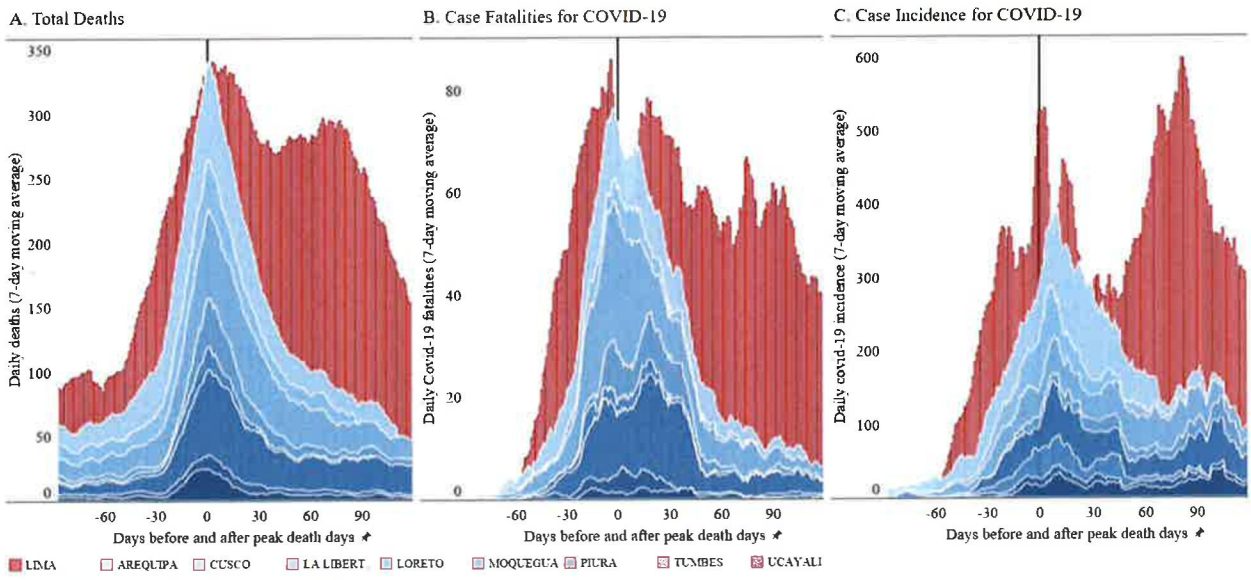
Figure 5 below from the same study presents data on the case fatality rates in patients over 60, again among the 8 states in Peru. Note the dramatically decreased case fatality rates among older patients with COVID-19 after ivermectin became widely distributed in those areas.

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

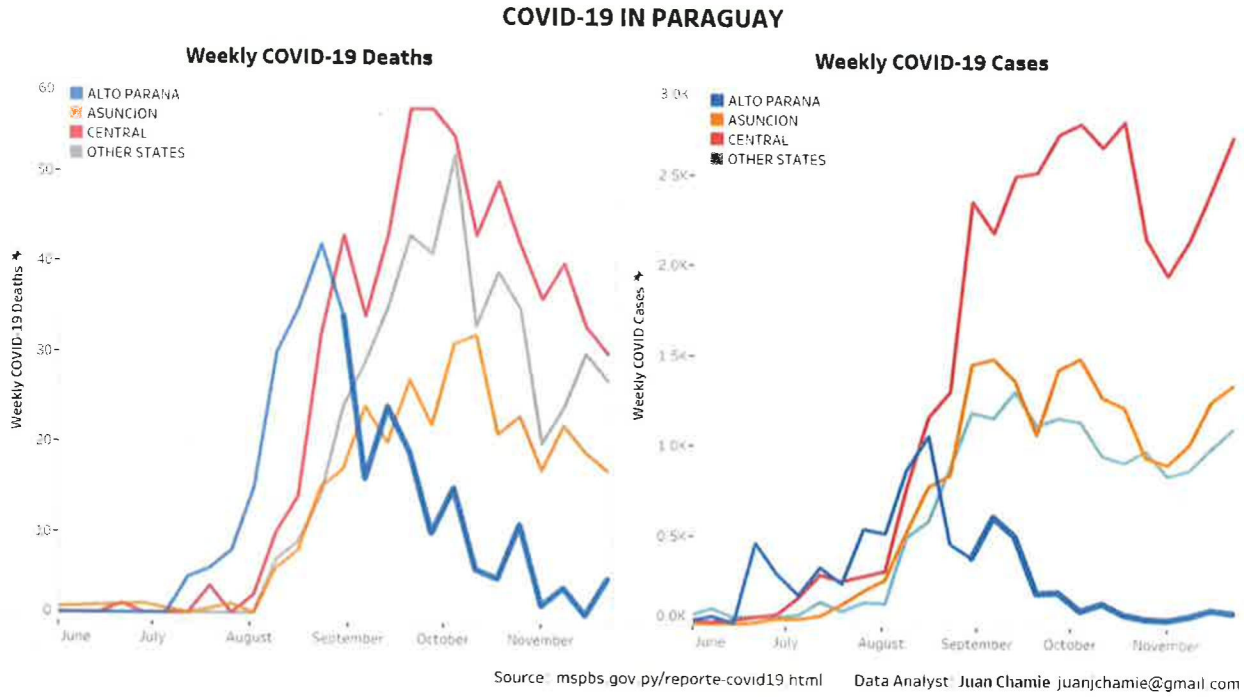


Legend: Daily total deaths, case fatalities and case incidence for COVID-19 in populations of patients age 60 and above for eight states in Peru deploying early mass ivermectin treatments vs. the state of Lima, including the capital city, where ivermectin treatment was applied months later.

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

519 patients from 27 controlled studies [16 of them were RCTs, 5 double blinded, one single blinded, (n=
520 2,503)]; 11 published in peer-reviewed journals including 3,900 patients.
521 Pre-print publications have exploded during the COVID-19 pandemic. Except for
522 hydroxychloroquine and convalescent plasma that were widely adopted before availability of any
523 clinical data to support, almost all subsequent therapeutics were adopted after pre-print publication
524 and *prior to peer review*. Examples include remdesivir, corticosteroids, and monoclonal antibodies.
525 An even more aggressive example of rapid adoption was the initiation of inoculation programs using
526 novel mRNA vaccines prior to review of either pre-print or peer-reviewed trials data by physicians
527 ordering the inoculations for patients.[11] In all such situations, both academia and governmental
528 health care agencies relaxed their standard to rise to the needs dictated by the pandemic.
529 In the context of ivermectin's long standing safety record, low cost, and wide availability
530 along with the consistent, reproducible, large magnitude findings on transmission rates, need for
531 hospitalization, mortality, and population-wide control of COVID-19 case and fatality rates in areas
532 with widespread ivermectin distribution, insisting on the remaining studies to pass peer review prior
533 to widespread adoption appears to be imprudent and to deviate from the now established standard
534 approach towards adoption of new therapeutics during the pandemic. In fact, insisting on such a
535 barrier to adoption would actually violate this new standard given that 12 of the 24 controlled trials
536 have already been published in peer reviewed journals.
537 In regard to concerns over the validity of observational trial findings, it must be recognized
538 that in the case of ivermectin; 1) half of the trials employed a randomized, controlled trial design (12
539 of the 24 reviewed above), and 2) that observational and randomized trial designs reach equivalent
540 conclusions on average in nearly all diseases studied, as reported in a large Cochrane review of the
541 topic from 2014 (Anglemyer et al., 2014). In particular, OCTs that employ propensity-matching
542 techniques (as in the Rijter study from Florida), find near identical conclusions to later-conducted
543 RCTs in many different disease states, including coronary syndromes, critical illness, and surgery
544 (Dahabreh et al., 2012;Lonjon et al., 2014;Kitsios et al., 2015). Similarly, as evidenced in the
545 prophylaxis (Figure 1) and treatment trial (Figures 2 and 3) meta-analyses as well as the summary
546 trials table (Table 3), the entirety of the benefits found in both OCT and RCT trial designs align in
547 both direction and magnitude of benefit. Such a consistency of benefit amongst numerous trials of
548 varying designs from multiple different countries and centers around the world is both unique in the
549 history of evidence-based medicine and provides strong, additional support to the conclusions
550 reached in this review. All must consider Declaration 37 of the World Medical Association's
551 "Helsinki Declaration on the Ethical Principles for Medical Research Involving Human Subjects,"
552 first established in 1964, which states:

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

560 The continued challenges faced by health care providers in deciding on appropriate
561 therapeutic interventions in patients with COVID-19 would be greatly eased if more updated and
562 definitive evidence-based guidance came from the leading governmental health care agencies.
563 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

618

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.

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PENNSYLVANIA DEPARTMENT OF HEALTH
2021-PAHAN-592-8-26-ADV
Rapid Increase in Ivermectin Prescriptions and Reports of Severe Illness Associated with Use of Products Containing Ivermectin to Prevent or Treat COVID-19

DATE:	August 26, 2021
TO:	Health Alert Network
FROM:	Alison Beam, JD, Acting Secretary of Health
SUBJECT:	**Rapid Increase in Ivermectin Prescriptions and Reports of Severe Illness Associated with Use of Products Containing Ivermectin to Prevent or Treat COVID-19**
DISTRIBUTION:	Statewide
LOCATION:	Statewide
STREET ADDRESS:	n/a
COUNTY:	n/a
MUNICIPALITY:	n/a
ZIP CODE:	n/a

This transmission is a "Health Advisory", provides important information for a specific incident or situation; may not require immediate action.

HOSPITALS: **PLEASE SHARE WITH ALL MEDICAL, PEDIATRIC, INFECTION CONTROL, NURSING AND LABORATORY STAFF IN YOUR HOSPITAL;** EMS COUNCILS: **PLEASE DISTRIBUTE AS APPROPRIATE;** FQHCs: **PLEASE DISTRIBUTE AS APPROPRIATE;** LOCAL HEALTH JURISDICTIONS: **PLEASE DISTRIBUTE AS APPROPRIATE; PROFESSIONAL ORGANIZATIONS**: PLEASE DISTRIBUTE TO YOUR MEMBERSHIP

Summary

- Ivermectin is a U.S. Food and Drug Administration (FDA)-approved prescription medication used to treat certain infections caused by internal and external parasites. When used as prescribed for approved indications, it is generally safe and well tolerated.
- During the COVID-19 pandemic, ivermectin dispensing by retail pharmacies has increased, as has use of veterinary formulations available over the counter but not intended for human use. FDA has cautioned about the potential risks of use for prevention or treatment of COVID-19.
- Ivermectin is not authorized or approved by FDA for prevention or treatment of COVID-19. The National Institutes of Health's (NIH) COVID-19 Treatment Guidelines Panel has also determined that there are currently insufficient data to recommend ivermectin for treatment of COVID-19. ClinicalTrials.gov has listings of ongoing clinical trials that might provide more information about these hypothesized uses in the future.
- Adverse effects associated with ivermectin misuse and overdose are increasing, as shown by a rise in calls to poison control centers reporting overdoses and more people experiencing adverse effects.
- Clinicians who become aware of cases similar to those described above are asked to report them to the Pennsylvania Poison Centers at 1-800-222-1222.

Please see the health advisory below on "**Rapid Increase in Ivermectin Prescriptions and Reports of Severe Illness Associated with Use of Products Containing Ivermectin to Prevent or Treat COVID-19**" provided by the Centers for Disease Control and Prevention.

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Summary
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Background
The Centers for Disease Control and Prevention (CDC) confirmed with the American Association of Poison Control Centers (AAPCC) that human exposures and adverse effects associated with ivermectin reported to poison control centers have increased in 2021 compared to the pre-pandemic baseline. These reports include increased use of veterinary products not meant for human consumption.

Ivermectin is a medication that is approved by FDA in oral formulations to treat onchocerciasis (river blindness) and intestinal strongyloidiasis. Topical formulations are used to treat head lice and rosacea. Ivermectin is also used in veterinary applications to prevent or treat internal and external parasitic infections in animals. When used in appropriate doses for approved indications, ivermectin is generally well tolerated.

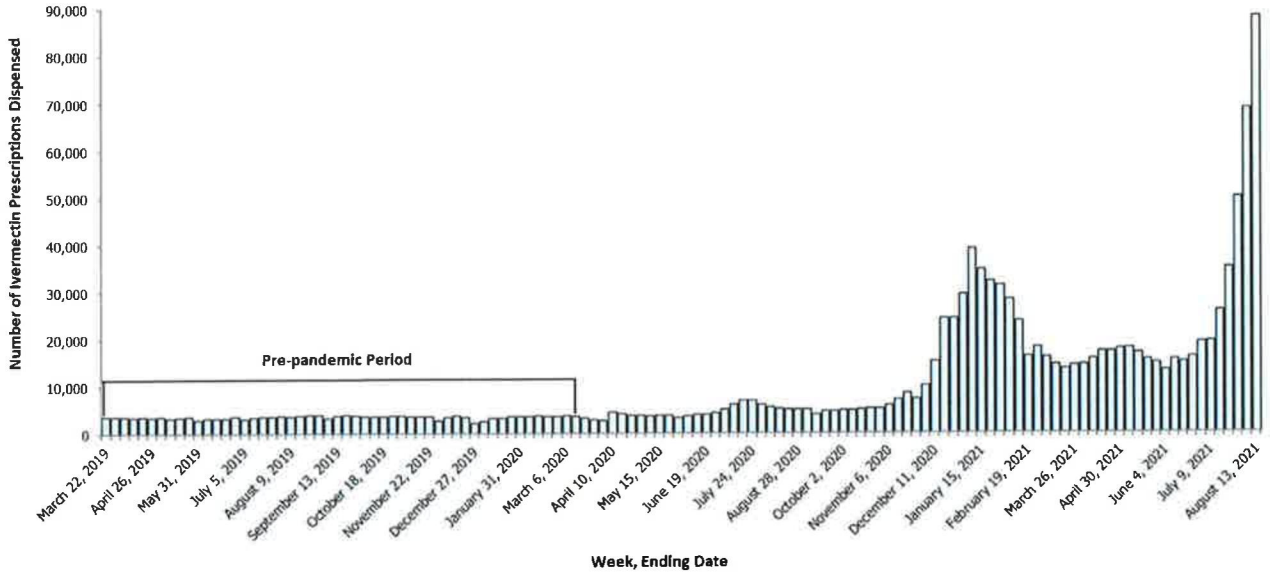
Clinical trials and observational studies to evaluate the use of ivermectin to prevent and treat COVID-19 in humans have yielded insufficient evidence for the NIH COVID-19 Treatment Guidelines Panel to recommend its use. Data from adequately sized, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin in the treatment of COVID-19.

A recent study examining trends in ivermectin dispensing from outpatient retail pharmacies in the United States during the COVID-19 pandemic showed an increase from an average of 3,600 prescriptions per week at the pre-pandemic baseline (March 16, 2019–March 13, 2020) to a peak of 39,000 prescriptions in the week ending on January 8, 2021.[1] Since early July 2021, outpatient ivermectin dispensing has again begun to rapidly increase, reaching more than 88,000 prescriptions in the week ending August 13, 2021. This represents a 24-fold increase from the pre-pandemic baseline. (**Figure**)

Figure: Estimated number of outpatient ivermectin prescriptions dispensed from retail pharmacies — United States, March 16, 2019–August 13, 2021*

*Data are from the IQVIA National Prescription Audit Weekly (NPA Weekly) database. NPA Weekly collects data from a sample of approximately 48,900 U.S. retail pharmacies, representing 92% of all retail prescription activity. Ivermectin dispensed by mail order and long-term care pharmacies, prescriptions by veterinarians, and non-oral formulations were not included.

In 2021, poison control centers across the U.S. received a three-fold increase in the number of calls for human exposures to ivermectin in January 2021 compared to the pre-pandemic baseline.



In July 2021, ivermectin calls have continued to sharply increase, to a five-fold increase from baseline. These reports are also associated with increased frequency of adverse effects and emergency department/hospital visits.

In some cases, people have ingested ivermectin-containing products purchased without a prescription, including topical formulations and veterinary products. Veterinary formulations intended for use in large animals such as horses, sheep, and cattle (e.g., "sheep drench," injection formulations, and "pour-on" products for cattle) can be highly concentrated and result in overdoses when used by humans. Animal products may also contain inactive ingredients that have not been evaluated for use in humans. People who take inappropriately high doses of ivermectin above FDA-recommended dosing may experience toxic effects.

Clinical effects of ivermectin overdose include gastrointestinal symptoms such as nausea, vomiting, and diarrhea. Overdoses are associated with hypotension and neurologic effects such as decreased consciousness, confusion, hallucinations, seizures, coma, and death. Ivermectin may potentiate the effects of other drugs that cause central nervous system depression such as benzodiazepines and barbiturates.

Examples of recent significant adverse effects reported to U.S. poison control centers include the following:

- An adult drank an injectable ivermectin formulation intended for use in cattle in an attempt to prevent COVID-19 infection. This patient presented to a hospital with confusion, drowsiness, visual hallucinations, tachypnea, and tremors. The patient recovered after being hospitalized for nine days.
- An adult patient presented with altered mental status after taking ivermectin tablets of unknown strength purchased on the internet. The patient reportedly took five tablets a day for five days to treat COVID-19. The patient was disoriented and had difficulty answering questions and following commands. Symptoms improved with discontinuation of ivermectin after hospital admission.

Recommendations for Clinicians and Public Health Practitioners

- Be aware that ivermectin is not currently authorized or approved by FDA for treatment of COVID-19. NIH has also determined that there are currently insufficient data to recommend ivermectin for treatment of COVID-19.
- Educate patients about the risks of using ivermectin without a prescription, or ingesting ivermectin formulations that are meant for external use or ivermectin-containing products formulated for veterinary use.
- Advise patients to immediately seek medical treatment if they have taken any ivermectin or ivermectin-containing products and are experiencing symptoms. Signs and symptoms of ivermectin toxicity include gastrointestinal effects (nausea, vomiting, abdominal pain, and diarrhea), headache, blurred vision,

dizziness, tachycardia, hypotension, visual hallucinations, altered mental status, confusion, loss of coordination and balance, central nervous system depression, and seizures. Ivermectin may increase sedative effects of other medications such as benzodiazepines and barbiturates. Call the poison control center hotline (1-800-222-1222) for medical management advice.

- Educate patients and the public to get vaccinated against COVID-19. COVID-19 vaccination is safe and the most effective means to prevent infection and protect against severe disease and death from SARS-CoV-2, the virus that causes COVID-19, including the Delta variant.
- Educate patients and the public to use COVID-19 prevention measures including wearing masks in indoor public places, physical distancing by staying at least six feet from other people who don't live in the same household, avoiding crowds and poorly ventilated spaces, and frequent handwashing and use of hand sanitizer that contains at least 60 percent alcohol.

Recommendations for the Public

- Be aware that currently, ivermectin has not been proven as a way to prevent or treat COVID-19.
- Do not swallow ivermectin products that should be used on skin (e.g., lotions and creams) or are not meant for human use, such as veterinary ivermectin products.
- Seek immediate medical attention or call the poison control center hotline (1-800-222-1222) for advice if you have taken ivermectin or a product that contains ivermectin and are having symptoms. Signs and symptoms include gastrointestinal effects (nausea, vomiting, abdominal pain, and diarrhea), headache, blurred vision, dizziness, fast heart rate, and low blood pressure. Other severe nervous system effects have been reported, including tremors, seizures, hallucinations, confusion, loss of coordination and balance, decreased alertness, and coma.
- Get vaccinated against COVID-19. COVID-19 vaccination is approved by FDA and is the safest and most effective way to prevent getting sick and protect against severe disease and death from SARS-CoV-2, the virus that causes COVID-19, including the Delta variant.
- Protect yourself and others from getting sick with COVID-19. In addition to vaccination, wear masks in indoor public places, practice staying at least six feet from other people who don't live in your household, avoid crowds and poorly ventilated spaces, and wash your hands often or use hand sanitizer that has at least 60 percent alcohol.

For More Information

NIH COVID-19 Treatment Ivermectin Guidelines
FDA Consumer Alert on Use of Ivermectin to Treat or Prevent COVID-19
FDA MedWatch Adverse Event Reporting program
CDC Coronavirus (COVID-19) website
U.S. Government Coronavirus (COVID-19) website
American Association of Poison Control Centers
Press Release: American College of Medical Toxicology Reports Data on Adverse Effects and Toxicity from Unapproved Use of Ivermectin for the Prevention or Treatment of COVID-19
Treatments Your Healthcare Provider Might Recommend if You Are Sick

References

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Categories of Health Alert messages:
Health Alert: conveys the highest level of importance; warrants immediate action or attention.
Health Advisory: provides important information for a specific incident or situation; may not require immediate action.
Health Update: provides updated information regarding an incident or situation; unlikely to require immediate action.

This information is current as of August 26, 2021 but may be modified in the future.