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RESEARCH ARTICLE

The Place of Ivermectin in the Management of Covid-19: State of the Evidence

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ABSTRACT

Background and aims.

The covid 19 pandemic necessitated the use of old, repurposed, and new drugs, in addition to vaccines and public health measures. There are still many controversies about the efficacy and impact of some of the medications used, which need further elucidation.

We review the pharmacological properties and the place of the repurposed drug, Ivermectin (IVM) in the prophylaxis and treatment of SARS - CoV- 2 (severe acute respiratory syndrome coronavirus 2.) infection or Covid 19 disease.

Major findings: in-vitro, in-vivo, and human studies

In vitro studies in Vero/hSlam cells caused a 99.98 % inhibition of SARS - Cov-2 (5000-fold) within 48 hours. The IC50 (half maximal inhibitory concentration) for this virucidal action was 2.8µM, which was thought unattainable in humans in-vivo. Thus, there was initial skepticism on pharmacokinetic grounds as to possible efficacy of IVM in humans with Covid 19. There are, however, a multiplicity of anti-covid 19 mechanisms, beyond mere anti-viral effects, such as blockade of ACE2 receptor viral entry, and the anti-cytokine and anti-inflammatory effects of IVM. IVM has a long half-life of 18 - 24 hours, Mean Residence Time (MRT) of 3.4 days and a preferential site of lung accumulation.

In-vivo studies in Syrian Golden hamsters confirmed the symptomatic, anti-inflammatory, anti-cytokine, histopathological and survival benefit of IVM, which was more manifest in female animals.

In a January 2023 meta-analysis of studies (s) in total number of patients (n) for various parameters (p), the reduction in risk relative to placebo or controls were as follows:

1. Overall improvement (s= 95) (n= 134,554) was 62% [95%CI 54-69].
2. Mortality (s=48) (n=120,000) there was 51% reduction [95%CI 37-62].
3. Hospitalization (s=29) (n = 44, 784), there was 34% reduction [95% CI 20-45].
4. Viral clearance (s=20) (n= 3945) there was 45% reduction [95%CI 31-55].
5. Prophylaxis (s=17) (n=19,764) showed 82% reduction [95%CI 73-88]

6 Randomised Control Trial (RCT) studies (s= 45) (n=2173) showed a 54 % mortality reduction [95% CI 39-65]

In addition, IVM has been shown in studies to cause a rapid reversal of hypoxemia (SPO2 < 94%) and a rapid increase in SPO2, an effect exhibiting a gender dichotomy. (SPO2 is the percentage of the maximum carrying capacity of the blood). This effect on SPO2 has been attributed to IVM's reversal and prevention of SARS-CoV-2 virus induced hemagglutination. The dosage used for treatment of covid 19 varied widely within studies, but doses of 200-400 µg/kg twice weekly or daily for 5 consecutive days, caused significant viral clearance and clinical improvement, with minimal safety concerns. For prophylaxis, a dose of 200µg/kg for two consecutive days every 15 days was found effective in studies.

Conclusion: This review provides powerful evidence that IVM is efficacious singly or as a part of a regimen for covid 19. IVM could potentially be combined with newer oral anti-covid 19 agents, such as Paxlovid, for effective and life-saving regimen in patients infected with covid-19. The anti-viral properties of these drugs can synergize with the anti-inflammatory and anti-cytokine properties of Ivermectin. Ivermectin is also useful prophylactically, especially where vaccines are unavailable or undesirable.

Brief Description of the SARS-Cov2 epidemic

The Covid 19 Pandemic commenced in Wuhan, China around December 2019, when the first cases of unexplained pneumonia were seen[1]. It is thought that the epidemic commenced in a wet market in the city, but controversy persists as to the role of a research laboratory funded by the FDA in Wuhan, with some people suggesting that the virus is an experimental 'leak' from this research facility[2]. As of today, according to the WHO, over 752.5 million people have been affected worldwide, while over 6.8 million have unfortunately perished. The bulk of the epidemic has occurred in India, Europe, North and South America and China, while for reasons not clearly elucidated, Africa has been relatively spared of this disease where less than 6.5 million cases have been recorded, with 175,000 deaths.[3]

The virus continues to evolve and several variants have been documented[4]. The variants of concern are, in order of emergence, Alpha, Beta, Delta and Omicron, not counting sub-variants.

About 13.1 billion doses of Covid 19 vaccines have been administered worldwide and this is said to have mitigated mortality and hospitalisations. On the 16th of January 2023, only 750,000 cases were reported worldwide. There was a recent surge in China with 40 million cases reported in December 2022 after the sudden relaxation of the lockdown, but numbers have dropped to about 40,000 daily[3].

The Discovery of Ivermectin.

Ivermectin is a product of a soil dwelling bacteria called *Streptomyces Avermictilis*. It was initially extracted from soil samples collected near a golf club in Japan in 1975. Ivermectin is an anti-parasitic drug developed during the 1970s as a partnership between the Kitasato Institute in Japan and Merck & Co. The project was led by Satoshi Omura and William Campbell on each side respectively. Satoshi Omura cultured the bacteria, which produce substances that inhibit the growth of other microorganisms. In 1978, Omura succeeded in culturing a strain from which William Campbell purified a substance, avermectin, which in a chemically modified form, ivermectin, proved effective against river blindness and elephantiasis. For their efforts, they won the Nobel prize in 2015 "for their discoveries concerning a novel therapy against infections caused by roundworm parasites."[5] IVM has been used safely in 3.7 billion doses worldwide since 1987[6].

Chemical structure of Ivermectin (IVM): IVM is a macrocyclic lactone. A lactone is an organic compound containing an ester group —OCO— as part of a ring.

Macrocyclic lactones specifically describe chemicals derived from soil microorganisms belonging to the genus streptomyces. The chemical name is $C_{48}H_{74}O_{14}$ Ivermectin B1a 70288-86-7, Dihydroavermectin B1a 22,23-Dihydroavermectin B1a

Previous Medicinal uses of Ivermectin:

Ivermectin was discvovered to have antiparasitic properties in animals (especially for the treatment of Dog heartworm and other ascarid parasites)[7], and later in man. It has been used to treat over 165 million Africans for onchocerciasis and is the main drug used by the African Program for Onchocerciasis Control (APOC)[8]. In addition, it is has demonstrated efficacy against loiasis, scabies, head lice[9] and malaria[10]. It is a safe drug with few side effects even in high doses. Before the advent of Covid 19, it was found to have antiviral properties blocking importation of alpha particles and viral entry in Dengue fever virus[11].

In vitro/in silico effects of Ivermectin for SARS-Cov2

With the advent of the Covid 19 pandemic, in-vitro studies on the possible efficacy of ivermectin against Covid 19 was carried out by Caly et al in Australia[12]. They discovered that ivermectin reduces SARS- Cov2 viral load in culture by 5000 times after 48hrs of incubation when a certain concentration of Ivermectin is used. Their paper described the *in-vitro* antiviral activity of ivermectin in a model of Vero/hSLAM cells infected with a SARS-CoV-2 isolate (Australia/VIC01/2020) using continuous exposure of the cells to ivermectin at 5 µmol/L. They found time-dependent decrease of cell associated and supernatant viral RNA. Also, serial dilutions of ivermectin caused concentration-

dependent antiviral effects with virtually total eradication at 5 μmol/L and half-maximal inhibition at approximately 2.5 μmol/L. The question was whether the drug could be safely used In-vivo to treat cases of Covid-19. It was suggested that the concentration of ivermectin would be too high for human consumption[13].

Nonetheless, several invitro/in silico studies described other effects of ivermectin relevant to the management of Covid 19. These are summarised as follows:

1. IVM binds to the spike protein of the virus and binds to the ACE2 receptor of the host cell[14]
2. IVM binds to the IMPα component of the IMP α/β1 heterodimer and thereby blocks the nuclear transport of viral proteins.[15]
3. IVM prevents viral protein assembly in vitro[16]
4. It selectively accumulates in the lungs over 10 times higher than predicted.[16]
5. IVM promotes the expression of several IFN-related genes (i.e. Interferon-related genes), such as IFIT1, IFIT2, IF144, ISG20, IRF9, and OASL[17]
6. IVM inhibits lipopolysaccharide (LPS)-induced production of inflammatory cytokines by blocking the NF-κB pathway and improving LPS-induced survival in mice[18].
7. IVM acts on the JAK-STAT pathway, PAI-1 and COVID-19 sequalae. It inhibits STAT-3 and 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.[19]
8. IVM blocks activation of the NF-kappa B pathway and inhibition of toll-like receptor 4 (TLR4) signaling. [20]
9. IVM suppresses immune cell recruitment, cytokine production, IgE, and IgG1 production and mucus hypersecretion by goblet cells.[21]
10. Ivermectin has been shown to increase prothrombin time by disrupting vitamin K–dependent clotting factors II, V, VII, and X.[22,23,24]

As Wagstaff et al suggested[25], the broad-spectrum activity of ivermectin is because it acts, among its several other mechanisms, as a host-directed agent (HDA).

Ivermectin in in-vivo experimental animal (golden hamster) models.

Syrian golden hamsters are often used for the study of infectious disease to foster better understanding of disease progression and to develop prophylactic and therapeutic treatment options, particularly since they closely reflect disease progression in humans. Studies on the effect of ivermectin on clinical and immunological outcomes were carried out by Dias de Melo et al.[26] The authors report that at a dose of 400 μg/kg, Covid-19 infected hamsters retained their sense of smell relative to controls. It will be recalled that anosmia is a common feature of Covid 19 in humans. Supporting the in-vitro concept, they also noted a reduced type I/III interferon stimulation and a modulation in several intracellular signalling pathways, such as a reduction of the *Il-6/Il-10* ratio. There was also a promotion of M2 polarization of myeloid cells recruited to the lung. Treated females exhibited the best outcome, similar to observations in humans. In addition, the authors noted protection against the histopathological effects of covid 19. However, they failed to detect a significant effect on viral load by IVM. This study thus provides evidence of the efficacy of IVM in covid 19 in a vertebrate animal other than humans, and replicates the gender dichotomy seen in clinical use in human therapeutics. The beneficial effects reported, despite absence of significant viral load suppression by IVM in this study, suggests the primacy of the anti- cytokine and anti-inflammatory effects of IVM in this animal model.

The pharmacokinetics of Ivermectin:

Ivermectin is orally absorbed with higher absorption as a solution than tablets. It has a high volume of distribution Vd of about 3.1-3.5 L/Kg or about 210L in a 70 kg man. Ivermectin has 99% hepatic metabolism via CYP3A4. Only 1% is excreted in the urine unchanged. The half-life ($t_{1/2}$) is 18 - 24 hours. The Mean Residence Time (MRT) is 3.4 days[27]. In view of the preceding considerations, subsequent in-vivo studies have employed various dosing regimes, and it is as yet unclear if a consensus has emerged. A randomized, controlled, observer blinded study, of the pharmacokinetics (PK) and anti- SARS-CoV-2 pharmacodynamics of high dose Ivermectin (600μg/kg /day) for 5 days was undertaken in Argentina[28].

There was a trend to a higher viral clearance under IVM compared to the Standard-Of-Care control group. A significant IVM plasma concentration dependent effect on nasopharyngeal viral clearance (log 10 copies/reaction) was noted. Whereby Covid 19 patients with higher median IVM concentrations (> 160 ng/ml) had a higher viral clearance (72%, IQR 59 -77), than low (< 160ng /ml) (i.e. 42%, IQR 31 – 73) p = 0.004.

Faster viral load decay was also noted at a rate of 0.6/day for the IVM > 160 ng/ml group,

compared to 0.15/day at IVM < 160 ng/ml , p = 0.01.

There is also a strong correlation between the viral load decay rate/day (virucidal rate) and plasma IVM concentration (r = 0.47, p = 0.002). Thus there was a concentration- dependent anti- SARS - CoV - 2 activity of IVM, which is consistent with clinical dose - dependent effects reported by other workers. The study also reported a wide variation in plasma concentration of IVM attained. (45 - 400 ng/ml) with a weight based dosing regime of 600 µg/kg/day. This variability was attributed both to concurrent food (which increased plasma IVM) and also to the induction of GIT efflux P-glycoprotein , which pumps out IVM from entry into blood stream.

Thus, it is possible to speculate that bioavalability differences, differences in plasma concentration attained, and under-dosing may contribute to the variable efficacy of IVM in some Covid 19 studies that have failed to show effect.

In-vivo anti SARS Cov-2 effects of ivermectin

A real time meta-analysis of ivermectin for covid 19 is regularly published and updated. For this paper we will rely on data published in January 2023[29]. The meta-analysis is based on 95 studies in which ivermectin used singly or in combination is compared with placebo or active drug. A summary of this metanalysis is shown below:

Table 1: Meta-analysis of selected outcomes with the use of Ivermectin for Covid 19. (Based on ivmmeta.com, published January 2023[29])

Criteria of studies	Number of studies	Number of patients	% Relative improvement Over placebo or other Rx	95% Confidence interval	Number of studies suggesting lack of efficacy
ALL comparative studies	95	134,554	62%	54-69%	15
Early treatment	37	57,715	62%	51-70%	8
Late treatment	41	57,075	42%	27-64%	8
Mortality	48	120,000	51%	37-62%	9
Need for mechanical ventilation	18	33,157	29%	13-42%	1
Need for ICU admission	12	23,897	41%	16-58%	1
Hospitalization	29	44,784	34%	20-45%	1
Recovery	34	7,623	42%	31-52%	1
Viral clearance	29	3,945	45%	31-55%	5
RCT only	45	2,173	54%	39-65%	7
Prophylaxis	17	19,764	82%	73-88%	0
After exclusions of studies with possible significant Bias	63	118,191	67%	60-73%	7

A total of 95 studies are captured in this meta-analysis comparing the effect of ivermectin with active or inactive placebo. The meta-analysis covered 134,554 patients. There was an overall 62% relative improvement with ivermectin (95% CI 54-69%). However, fifteen studies failed to demonstrate improvement with ivermectin. It is clear that early treatment with ivermectin is advantageous over late treatment (relative improvement 62% vs 42%). An analysis of 48 studies that reported on mortality demonstrated an improvement of 51%. There was a 29% improvement on the need for mechanical ventilation, and 41% on the need for Intensive Care Unit admission. There was also a 34% advantage on the need for hospitalization, and a 42% improved recovery rate. Twenty-four studies demonstrated improved viral clearance rates with ivermectin, while five did not. When the analysis is limited to Forty-five of these studies which were Randomised Controlled Trials, an overall improvement of 54% was demonstrable. Seven of these studies, however, did not show an advantage.

The most powerful and consistent effect of ivermectin appeared to be in the use of ivermectin as prophylaxis. Seventeen studies involving 181,191 patients showed an 82% improvement in protection against disease. Significantly, none of the studies showed a lack of prophylactic efficacy. The dose and frequency of prophylaxis recommended by the various studies however varied from as little as 12mg to as much as 203mg. The largest prophylactic studies have been carried out by Behera et al[30,31], and Kerr et al[32]. In the second Behera study, two doses of oral ivermectin (300 µg/kg/dose 72 hours apart) was given as chemoprophylaxis among Health Care Workers (All India Institute of Medical Sciences (AIIMS) Bhubaneswar). 2,385 were given ivermectin, while 1,147 were not. The use of ivermectin reduced the risk of COVID-19 infection by 83% in the following month. The authors concluded that safe, effective, and low-cost chemoprophylaxis has relevance in the containment of the pandemic alongside vaccine.

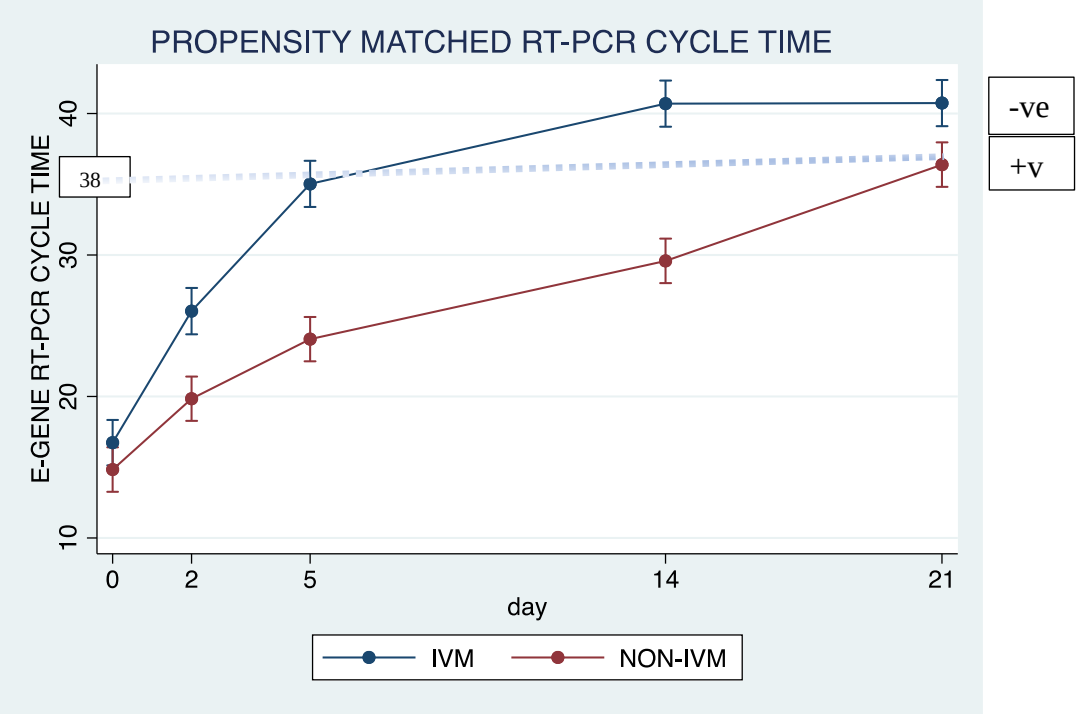
Kerr et al[32] analysed 159,561 subjects of Itajai, Brazil who participated in a comparative prophylactic trial of Ivermectin. There was an infection rate of 3.7% in regular ivermectin users compared with 6.6% in non-ivermectin regular users. There was a 56% reduction in hospitalization rate among ivermectin users. There was also a reduction in mortality rate of 70% (RR, 0.30; 95% CI, 0.19-0.46; $p < 0.0001$). They had offered ivermectin prophylaxis as an optional treatment to be taken for two consecutive days every 15 days at a dose of 0.2 mg/kg/day. It is instructive that at such a low dose and with a frequency of twice a month only, a 70% reduction in mortality was attained. In a study by Alam et al[33] on exposed hospital workers, only 6% of the hospital workers on ivermectin 12mg per month were positive at the end of 4 months, versus 73% in the untreated arm.

An ecological study by Hellwig et al[34] suggests that countries who routinely use ivermectin as prophylaxis for parasitic diseases, especially African countries, tended to have a lower incidence of Covid 19. Chemoprophylaxis with Ivermectin thus appears to have relevance in the containment of the pandemic.

In-vivo antiviral properties of Ivermectin

Commenting further on the antiviral properties of Ivermectin, Thairu et al[35] demonstrated that Rt PCR neutralization of the Nuclear (N-Gene) and Envelope (E-gene) occurred faster in the Ivermectin treated group, Likelihood ratio 64.2, P<0.0001. (Figure 1). Where a Cycle threshold (Ct) of 38 is selected as the cutoff point for 'negativity', then 33% of patients in the ivermectin treated group (IVM) were negative by day 5 compared with 0 % in the non-ivermectin treated group.

Figure 1. Change in E-gene Rt-PCR cycle threshold (Ct) over time. Note that by day 5, most patients on IVM group (Ivermectin) are already in the 35-40 Ct bracket as opposed to the non-IVM group. Likelihood Ratio 64.2, P<0.0001. n=61 IVM, n=26 NIVM (Federal Capital Territory, Abuja).



Effect of mass distribution of Ivermectin in cities and states.

Pierre Kory et al[36] looked at municipalities in Peru, Paraguay and Mexico where mass distribution of Ivermectin had occurred, mostly using Ivermectin as part of 'test and treat' kits. They reported on the effect of this intervention. In all cases, there was an immediate reduction in reported incidence and mortality.

The graphs below show the experience in some municipalities in Paraguay.

Figure 2. Effect of Ivermectin distribution on the incidence and mortality of Covid 19 in selected municipalities in Paraguay. Note the clear temporal relationship between ivermectin intervention and change in incidence/mortality parameters. Reproduced with permission

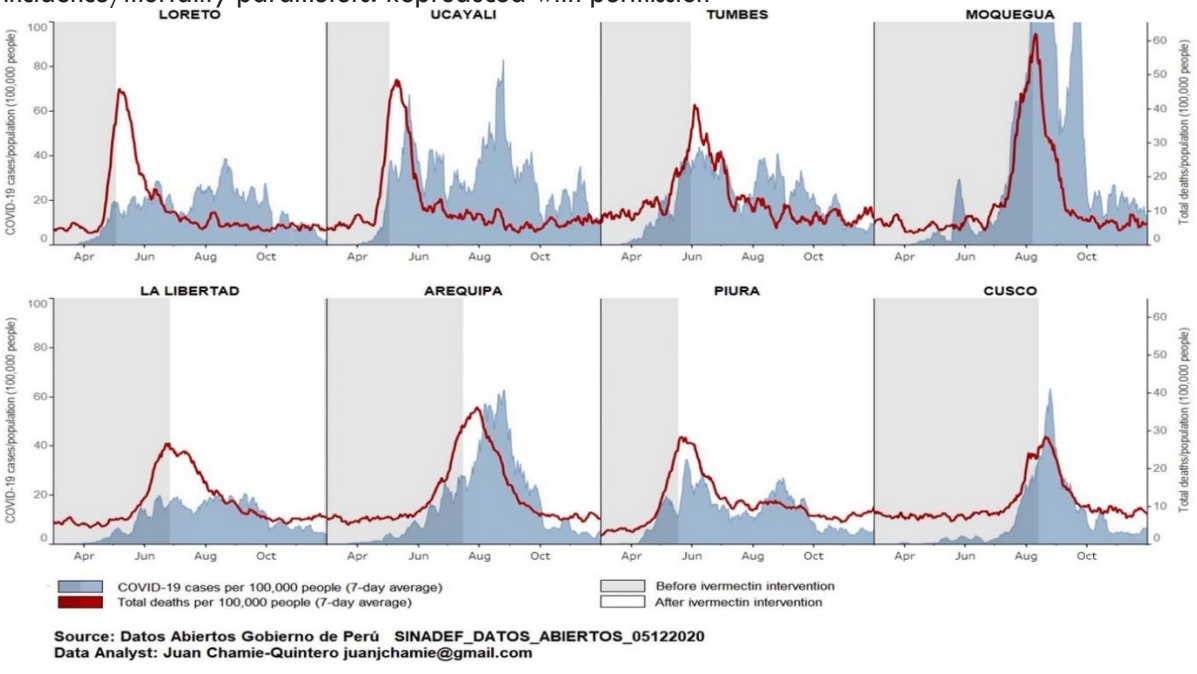
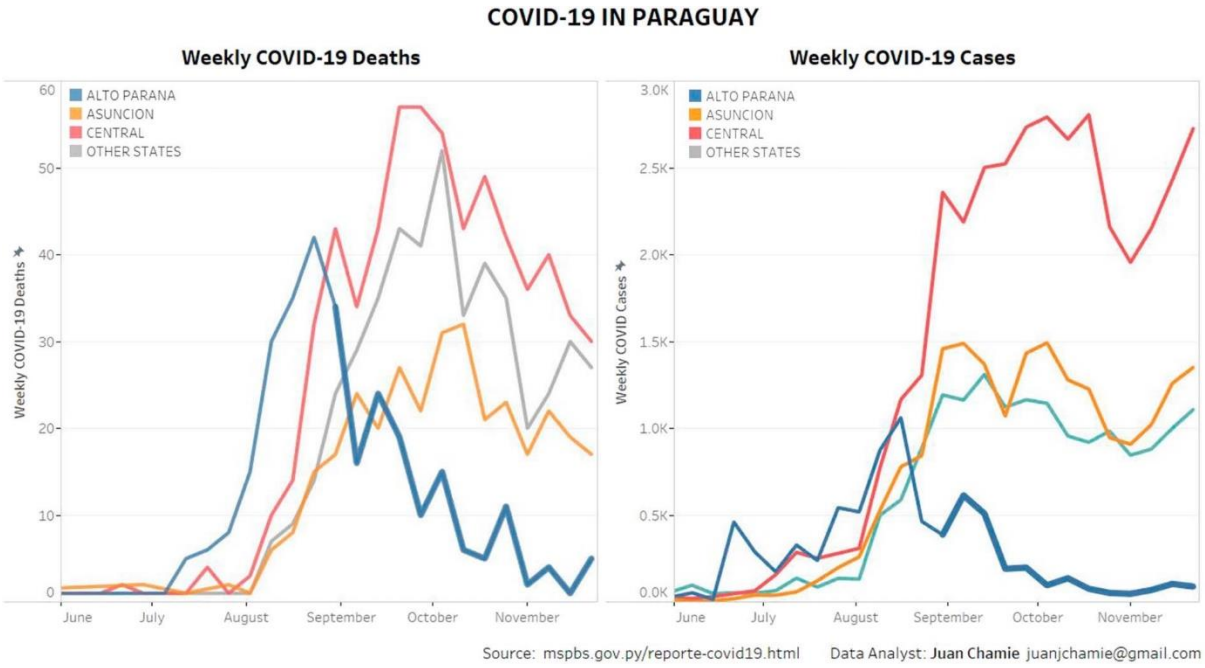


Figure 3: Comparative analysis of trends in covid 19 mortality and incidence in selected states in Paraguay. Ivermectin was introduced in Alto Parana state in late August 2021, (thick blue line) but not in the other states. (Reproduced with permission.)



In India in 2021, certain states adopted the inclusion of Ivermectin in the test and treat series, while others did not. New Delhi was one of such states that adopted Ivermectin as part of the treatment kit. Figure 4 is a reproduction of the reduction in incidence of Covid 19 between the 1st of May and the 28th of May.

Figure 4: Change in incidence of Covid 19 after introduction of Ivermectin in New Delhi, May 2021 (After Justus R. Hope, in 'The Desert Herald'.)[37] (Reproduced with permission)

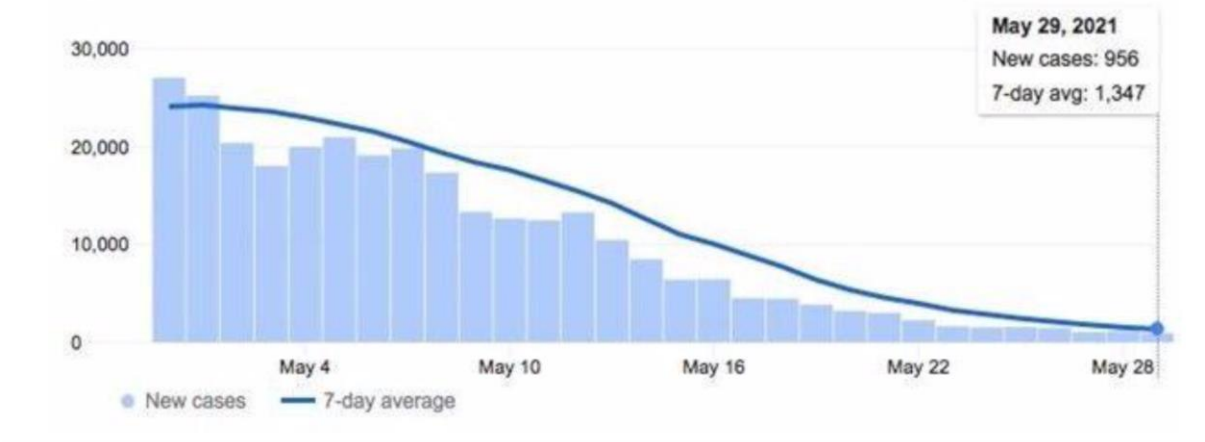


Table 2: Reduction in incidence of Covid 19 in Ivermectin adapting selected states in India (May 2021) (After Justus Hope[37])

Delhi :	⁻ 97%	[28,395 to 956]
Uttar Pradesh:	⁻ 95%	[37,944 to 2,014]
Goa:	⁻ 85%	[4195 to 645]
Karnataka:	⁻ 60%	[50,112 to 20,378]
Uttarakhand:	⁻ 87%	[9,642 to 1,226]

Table 3: Increase in incidence of Covid 19 in States that opted not to adapt Ivermectin in the same period (May 2021) (After Justus Hope[37])

Tamil Nadu	173%	[10,986 to 30,016]
Odisha	50%	[4,761 to 7,148]
Assam	240%	[1,651 to 5,613]
Arunachal Pradesh	656%	[61 to 461]
Tripura	828%	[92 to 854]

All these findings support anecdoctal evidence from prisons and nursing homes where ivermectin has been used in the treatment of other conditions like scabies, to the effect that the use of Ivermectin is associated with significant reduction in the incidence of Covid-19.

Ivermectin and changes in arterial oxygen.

Ivermectin has been associated with increase in SpO2 in covid 19 patients. This phenomenon was first published by Babalola et al[38] who noticed that patients on IVM therapy tended to have superior SpO2 outcomes than patients on Lopinavir/Ritonavir therapy. While there was an overall average decrease in SpO2 levels in the Lopinavir/Ritonavir arm of -1.44%, there was an average increase in the ivermectin arm of +0.125%, a net difference of 1.565% (P=0.0975). In a later study[39] Ivermectin based therapy (IVM) was compared with Non-ivermectin based therapy (NIVM) with regards to changes in oxygen saturation on treatment. The IVM group demonstrated earlier and greater increase in SPO_2 (p=0.000) which paralleled greater and faster virological clearance (p=0.000) on Repeat measures Analysis of Variance RMANOVA. Also, increase in SPO2 on IVM was magnified in Males (Figure 5). Similar findings of rapid rise in SPO2 on Ivermectin was reported by Stone et al[40]. In 34 patients treated in Zimbabwe, the authors noted a mean increase in SpO2 as a percentage of full normalization to SpO2 = 97% of 55.1% at +12 h and 62.3% at +24 h after the first IVM dose (paired*t*-test,$p<$ 0.0000001). In California[41], 19 severe COVID-19 patients treated with IVM were analysed. The mean (±SD) SpO2 values rose from 86.7% ± 4.5% pre-treatment to 93.3% ± 2.6% at +24 h after the first IVM dose while the percentage

of normalization to SpO2 = 97%, at 24 h was 65.2% ± 17.5%p< 0.0000001. On the other hand, Osman, et al.[42] and Annunziata, et al.[43] have documented changes in SpO_2in non-ivermectin treated COVID-19 patients. These two studies show unequivocally that there is an initial dip in SpO_2towards day 8 before a recovery towards day 14. This corroborates studies in which SpO_2increases from day 1 and is at normal levels by day 7 in ivermectin-treated patients, while SpO2 levels dip initially in Non Ivermectin treated patients and only begin to recover by day 5 (Babalola et al[39]).

Figure 5. Change in SPO2 over time in room air for Ivermectin IVM and Non-Ivermectin NIVM based treatment after propensity matching of baseline to SPO2 less than 94%, (95% CI Bars shown). RMANOVA allowing for time*treatment interaction LR=40.12, P<0.0001.

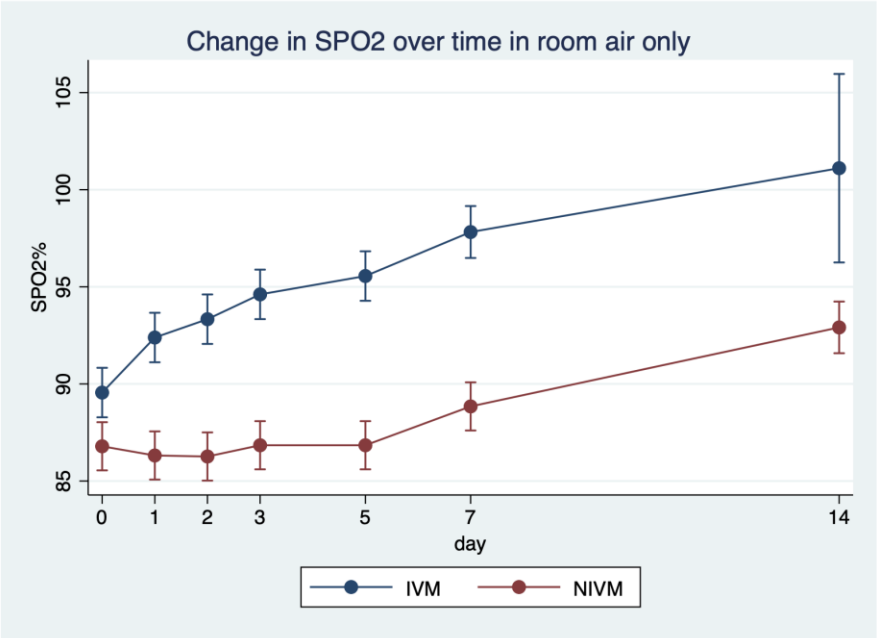
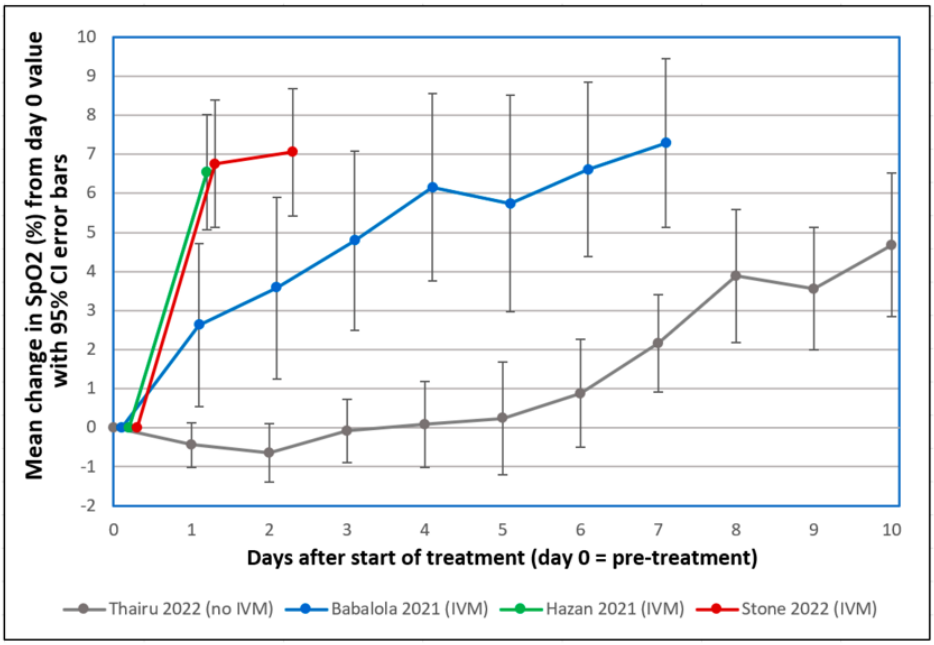


Figure 6. Mean change in SPO2 in ivermectin treated and Non-ivermectin treated patients from various studies (Stone et al[40], Hazan et al[41], Babalola et al[39], Thairu et al[35]) . (Reproduced with Permission.)



Effect of Ivermectin on hemagglutination in SARS-Cov-2.

The SARS Cov-2 virus has been known to induce hemagglutination (HA) in infected individuals through attachments of its spike proteins to glycans on the surface of red blood cells. Ivermectin is now known to block this hemagglutination by competitively binding to surface glycans on the RBC. It also reverses the binding of SARS Cov-2 to RBCs. It is hypothesized that this reversal of HA might be responsible for the sharp rise in SPO2 noticed in Covid 19 patients[44,45].

Comparison of Ivermectin with other drugs used in the treatment of Covid 19 infection.

Here we compare the pharmacology of ivermectin in the treatment of covid 19 with three other drugs namely Paxlovid, Molnupiravir, and Remdesivir. This comparison is shown in table 2. Paxlovid is a combination of Nirmatrelvir and Ritonavir, essentially a protease inhibitor. Molnupiravir is a false nucleoside, while Remdesivir acts on the RNA dependent RNA polymerase (RdRp) of the SARS-Cov-2 virus. Paxlovid has the lowest IC50 but accumulates in Renal dysfunction. Viral clearance is fastest with Paxlovid (2-4 days) and slowest with Remdesivir (16-34 days), while for ivermectin it takes an average of 4.6 days. One big advantage of ivermectin over the others is the anti-inflammatory and anti-hemagglutination properties (vide infra)[48,49], which counteract the cytokine storm and hemagglutination experienced in the disease.

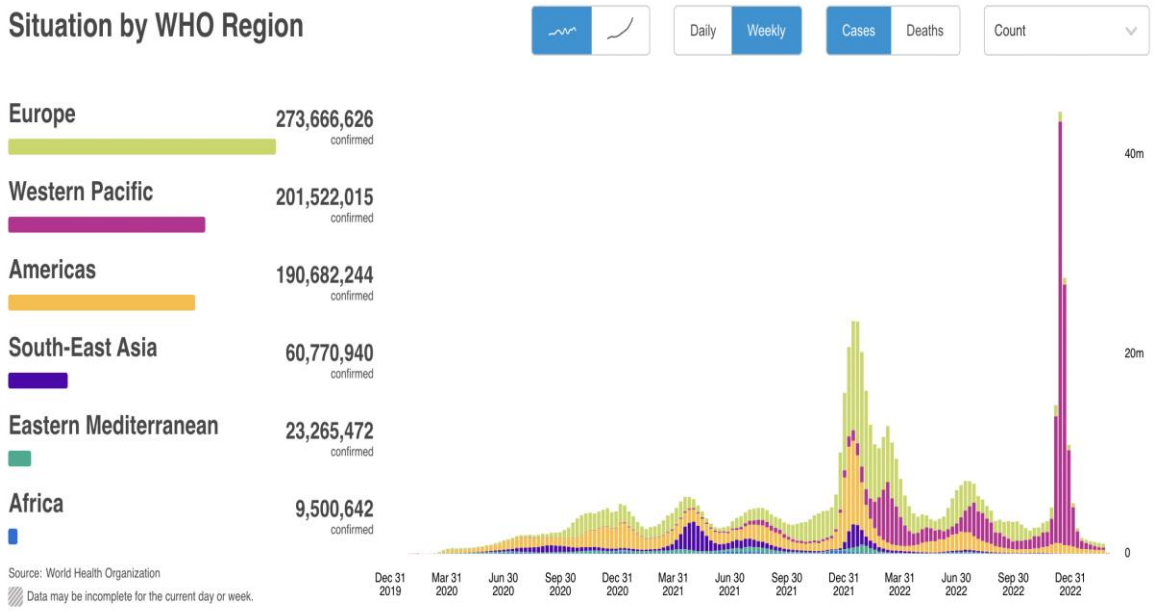
Table 2. Pharmacological comparison of four drugs used in the management of Covid 19

Parameter	Paxlovid: (Nirmatrelvir/Ritonavir)	Molnupiravir	Ivermectin	Remdesivir
Mechanism of anti-SARS-Cov2 action	Nirmatrelvir is a protease inhibitor , inhibits main protein(Mpro) or 3CL protease, preventing viral replication. Ritonavir inhibits hepatic metabolism of Nirmatrelvir to increase its drug levels and CPss. (i.e. steady state plasma concentration)	False nucleoside causing viral error catastrophe, and extinction	Multiple: Inhibitionof RdRp , anti-inflammatory effects, cytokine suppression etc. Vide supra.	Acts on RdRp) of the SARS-CoV-2 virus, a protein complex responsible for mediating replication of the virus's genome.
Inhibitory concentration IC-50 (Vero-Slam cells)	0.02-0.12µm	0.3µm	2.5-2.8 µm	0.069µm (Epithelial cell culture)
Metabolic pathway	Extensive Hepatic Metabolism - CYP3A4. Accumulates in Renal dysfunction. Dose adjustment needed with other drugs in renal dysfunction.	Cellular kinases, of the kidney. Negligible hepatic metaboism	Hepatic - CYP3A5,CYP 2D6, CYP2C9	CYP450 and non-CYP enzymes such as carboxylesterases
Days for Viral clearance	2-4	9(7-9)[46]	4.6 +-3.2[38]	25 (IQR 16– 34)[47]
Anti-inflammatory activity	Nil	Nil	[47]*in vivo*and*in vitro*, reduces the production of TNF-alpha, IL-1 and IL-6, and suppressing LPS-induced NF-kB translocation. [47]Suppresses mucus hypersecretion in the respiratory tract and decreases the recruitment of immune cells and the production of cytokines and IgE/IgG1 in bronchoalveolar lavage	Nil
Reduction in length of hospitalization	51%[50]	0%[52]	34%[30]	87%[54]

Reduction in mortality	46%[51]	0%[52]	51%[29]	0%[53]
Adverse Drug Reactions (ADR); Drug-Drug-Interactions (DDI)	Allergy, skin rashes, dysphagia, hypertension. DDI via CYP3A4 induction with antiarrhythmics (amiodarone), anticoagulants (warfarin), hypolipidemics (Simvastatin, lovastatin) Immunosuppressants (cyclosporine) Anticonvulsants (carbamazepine).	Possible genotoxicity /fetotoxicity. Not used in pregnancy.	Headache, pruritus, diarrhea, blurred vision, postural hypotension and confusion skin reactions and edematous swelling	Elevated liver enzymes, acute kidney injury, raised blood creatinine levels, bradycardia, cardiac arrest, and death. Chloroquine/Hydroxychloroquine may diminish the therapeutic effect. Warfarin: Remdesivir may enhance the anticoagulant effect of Warfarin.*Risk C: Monitor therapy*

Covid 19 and the 'African Enigma'.

Figure 7. Incidence of Covid 19 cases by region. [3] (After WHO)



There was an established and sustained lower incidence of and mortality from COVID 19 in Africa, compared to the rest of the world, throughout the SARS-CoV-2 pandemic, regardless of virus variants[4] . This unexpected lower frequency of COVID 19 in a continent with poorly resourced health care infrastructure, and much lower Gross Domestic Product-Price Purchase Parity (GDP-PPP) in what are essentially Low and Middle Income Countries (LMIC) constitutes the so-called " African enigma"[55] (Figure 7).

One hypothesis proposed for this "African enigma", was the prior and extensive use of Ivermectin (which had been shown to exert SARS-CoV-2 antiviral effect in vitro)[14]. The African Program for Onchocerciasis Control (APOC) is an WHO sponsored program, involving the use of Ivermectin for the mass treatment and prophylaxis against onchocerciasis, in 19 African countries, from 1995 to 2015. Ivermectin distribution is still ongoing in some parts of the continent.

Covid 19 infections, and death rates were compared in APOC countries (n=19) and countries with no prior ivermectin mass campaign (Non-APOC countries (n=35), covering all the 54 countries of Africa. APOC countries compared to non APOC countries exhibited a -28% statistically significantly lower mortality, as well significantly reduced (-8%) infection rates.(Guerrero et al)[55].

A similar protective effect of prophylactic chemotherapy with ivermectin used for filariasis, against COVID 19 was not only replicated in another study, but also shown to be applicable to the entire world, outside Africa[34]. Thus , there appears to be not only a geographic variation in the clinical course of COVID 19, but also an association with Ivermectin use, especially in Africa. The mechanism(s) by which prolonged mass or community-based chemotherapy with Ivermectin may confer protection against subsequent SARS-CoV-2 infections as suggested above is not clear. Ivermectin is known to have a long half and residence time in the human and bovine or equine bodies. Plasma/tissue concentrations of ivermectin was not measured in these studies, so that a concentration-effect relationship against SARS-CoV-2 cannot be defined.

An interesting hypothesis was recently proposed, that if supported may explain the acute or population long-term benefits of ivermectin[56]. Bifidobacterium, a, probiotic and gut microbiota is a protective anti-inflammatory agent which suppresses TNF -alpha and pro -inflammatory cytokines IL-10 class and enhances anti imflammatory cytokines. The level of bifidobacterium is reduced in Covid 19, and more so in severe Covid 19, in obesity and covid 19 co-morbid states. Ivermectin medication and Streptomyces avermetiliis are composed of an aglycone ring and a monosaccharide. These are broken down in the gut and help to feed bifidobacterium and increase its proliferation and population and thus its anti-inflammatory and anti SARS-CoV2 as well as its cytokine-storm suppression ability[56]. Thus, Ivermectin may act as a chemotherapeutic as well as vaccine, by boosting natural immunity against SARS-COv-2.

Gender differences:
Gender differences have been reported in SARS-COV-2 infectivity and mortality with men having worse outcomes[57]. Furthermore, studies in Nigerian patients suggest that Ivermectin confers greater benefits on SPO2 increase in men than women in hypoxemic Nigerian patients[39]. Ya'qoub et al[57] have attributed these differences to a combination of factors, including hormonal differences, immune response, inflammatory markers and behavioral attitudes, among others.

Countries and agencies where the use of Ivermectin for covid 19 has been adapted:
Based on the evidence referred to above, many countries have formally or tacitly adopted the use of ivermectin in the management of Covid-19. This rapidly growing list of national and regional health authorities include but is not limited to:
- Slovakia – National Treatment Guideline (1/26/21)
- Bulgaria – Legalized for over-the counter use (2/21)
- Czech Republic – Legalized prescribing (3/12/21)
- Peru – National Treatment Guideline (1/8/21)
- Japan – Tokyo Medical Association (2/9/21)
- Mexico – Institute of Social Security (2/3/21)
- Belize – National Treatment Guideline (12/18/20)
- South Africa – Health Products Regulatory Association (1/27/21)
- Zimbabwe – National Ministry of Health (1/28/21)
- North Macedonia – National Health Minister (1/15/21)
- Uttar Pradesh, India – Treatment Guideline (pop. 234 million -9/3/21)
- State of Bihar, India – Treatment Guideline (pop. 122 million – 8/21)
- Egypt- National Treatment Guideline (11/30/20)
- Guatemala – National Treatment Guideline (1/23/21)
- Nicaragua – National Treatment Guideline (1/25/21)
- State of Chiapas, Mexico (8/1/20)
- Jamaican Medical Association (2/26/20)
- Argentina, 1/3 of territory: States of Pampa, Jujuy, Salta, Tucuman, Misiones, Corrientes (2/26/20)
-Nigeria- Federal ministry of Health (2021)

Dose of ivermectin in the prophylaxis and therapy of different stages of Covid 19
The dose of Ivermectin used in Covid 19 has been modified and extrapolated from its posology as an antifilarial chemotherapeutic agent against ocular onchocersis (River blindness). The African Program of Onchocerciasis chemotherapeutics (APOC) utilized a dose of 0.2 - 0.4 µg/Kg body weight. Thus, for a 70 kg person this came to 1.4 - 2.8 mg dose for filaricidal activity. This dose was extrapolated for use in Covid 19 mostly based on safety considerations, but with no firm basis of efficacy before the earlier randomized controlled clinical trial.
The ideal dose of ivermecftin for human Covid 19 should produce plasma concentrations that exceeds the in vitro IC50 for SARS - CoV- 2 or the EC50 or EC 90 for the drug (Babalola et al[38,39], Ajayi[62]).
However, the multiplicity of the mechanisms of actions of ivermectin in human covid 19 (vide supra) which includes additional anti-inflammatory actions in-vivo in humans, causes an imperfect prediction or correlation to concentration that is required in human Covid 19 disease relative to in-vitro studies. Both oral tablets and elixirs of Ivermectin have been used in covid 19 clinical trials or real world. The bio-availability of elixir or syrup form of ivermectin is greater than the solid tablets forms[63]. Various doses / Regimens and drug combinations have been used in RCTs and clinical studies which show benefit in prophylactic, symptomatic, and virological treatment of covid 19 (see table 3). These have also shown benefit in intensive care and on mortality. However, as can be seen from the table, there is a wide range of doses that have been employed. For prophylaxis we would suggest the dosage regimen utilized by Kerr et al[31] (200 µg/kg/day two consecutive days every 15 days). For treatment, we would suggest the regimen enunciated by Thairu et al[35] (200 µg/kg for five days). This may be extended to 400 µg/kg/day for five days. Mohan et al[64] had used a single dose of IVM at 400 µg /kg and obtained reductions in viral load, but this did not achieve statistical significance. This treatment regimen is associated with consistent symptomatic improvement, increased SPO2, shortened Days-To-Negative, reduced Days-To-Discharge DTD and lower Mortality in our studies [35,38,39].

Table 3. Dosing regimens of Ivermectin utilized by different authors for treatment and prevention of Covid 19 with positive outcomes.

Serial	Name of author(s)	Dose of ivermectin in 4 days	Parameter measured	Improvement/ Relative Risk	RCT?
1	Ahmed S et al[55]	48mg (12mg daily for 5 days)	Symptoms	85%	Yes
2	Babalola et al[37]	24mg 12mg on days 1 and 3	Viral+	64%	Yes
3	Thairu et al[34]	56mg : 200µg/kg X 5days	Death	88%	No
4	Babalola et al[37]	24mg 12mg on days 1 and 3	ΔSPO2	41%	Yes
4	Kerr et al[31]	56mg/month two consecutive days every 15 days at a dose of 0.2 mg/kg/day.	Death	70%	No(prophylaxis)
5	Shouman et al[58]	36mg/month 0.25-0.35mg/kg/day on days 1 and 3	Symptoms and cases	91%	RCT (Prophylaxis)
6	*Espitia-Hernandez G et al*[59]	12mg in 4 days. (6 mg once daily in day 0,1,7 and 8)	Recovery time	70%	No. (comparative study)
7	Carvallo[60]	36mg in 4 days. 1 drop of IVM five times daily for 14 days.	Death	85%	No. (comparative study)

Publication Bias

It appears that the studies that report absence of evidence of ivermectin efficacy against Covid 19 have been published in high impact factor medical journals. By contrast, studies which report a treatment benefit of Ivermectin in Covid 19 are not accepted by these journals, but appear in journals of intermediate impact factors, or in national journals. Such discrepancy in publication outlet is not related to the quality of the study design or level of evidence, but may be related to intrinsic bias against Ivermectin use for covid 19, as propagated by some regulatory, professional, big pharmaceutical and media coalitions.

Overall conclusions

- Ivermectin should be considered for adoption into the uniform treatment guidelines of Covid 19.
- Ivermectin may be synergistic with other drugs such as Paxlovid especially since the more potent antiviral properties of Paxlovid may combine with the anti-inflammatory and anti-Hemagglutination properties of Ivermectin.
- Ivermectin should be used as prophylaxis alongside the rollout of vaccination programs, especially in situations where vaccination is not available or popular.
- SARS-CoV-2 infection includes several stages, where the initial stage is manifested by high viral replication followed by the second stage (occurring in the high risk groups mainly) of excessive inflammatory response causing severe disease and death. Therefore, ivermectin may have a dual role in this infection, acting as both an anti-viral and anti-inflammatory agent.
- Ivermectin is not meant to replace other Covid 19 measures such as social distancing, face masking and hygiene, or vaccinations
- It is an additional tool which should be deployed to fight pandemic or endemic SARS-CoV-2 disease.

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