Ivermectin in COVID-19 patients

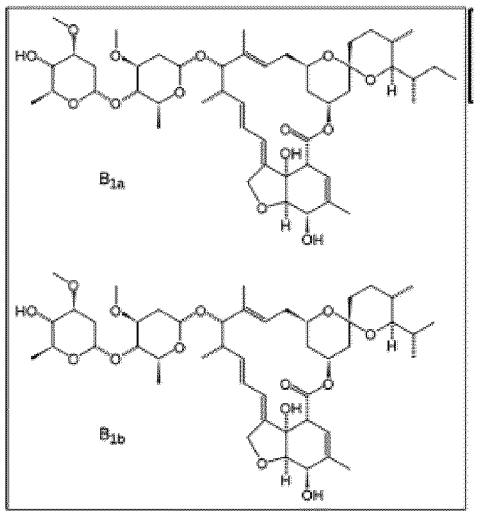
EMA review – Date 8 March 2021

Information	Details
Total number of studies with breakdown:	Total: RCT: 22 (20 treatment, 2 prophylaxis) Observational: 10 Non-clinical: 8 Clinical pharmacology: 2
EMA contact points	[redacted]

1. Summary of benefits and risks based on current evidence

Introduction

Ivermectin is a semisynthetic macrocyclic lactone first derived from a fermentation broth of the soil bacteria *Streptomyces avermitilis*. It has a broad antiparasitic activity, was discovered in 1975 (for which William Campbell and Satoshi Omura received the Nobel Prize for Medicine in 2015) and came into use in 1981; it is on the WHO list of essential medicines.



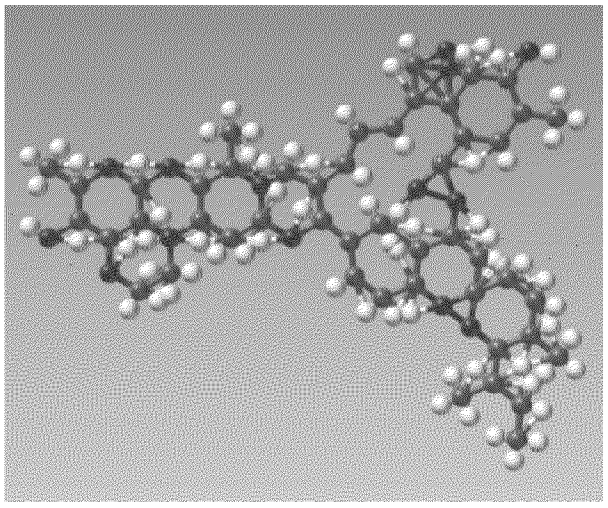


Figure 1. *The ivermectin molecule. PubChem CID: 6321424.*

Figure The chemical structure of ivermectin represented by two constituent 22,23-dihydroavermectin B_{1a} and 22,23-dihydroavermectin B_{1b} enantiomers

Its activity is mainly antihelmintic, but it is also active against other parasites: it is used to treat onchocerciasis, strongyloidosis, enterobiasis, scabies and even malaria, as well as parasites such as human lice, Loa loa, Trichuris trichura. It is also used as a topical treatment for papulopustular rosacea in adults. As an antiparasitic, it causes stimulation of GABA-gated-Cl− channels, leading to hyperpolarization and consequently blocking neurotransmission in neurons and myocytes, resulting in paralysis and death of the infesting organism. (Geary et al, 2005)

IVM is approved in humans for some of the above mentioned indications, in the United States (Stromectol USPI), as well as in some EU Member States (e.g. France, the Netherlands). It is also approved as topical treatment for rosacea in the UK (Soolantra PI) and for head lice. Of note, it has recently received an EUA in Slovakia for prevention and treatment of SARS-CoV-2 infection.

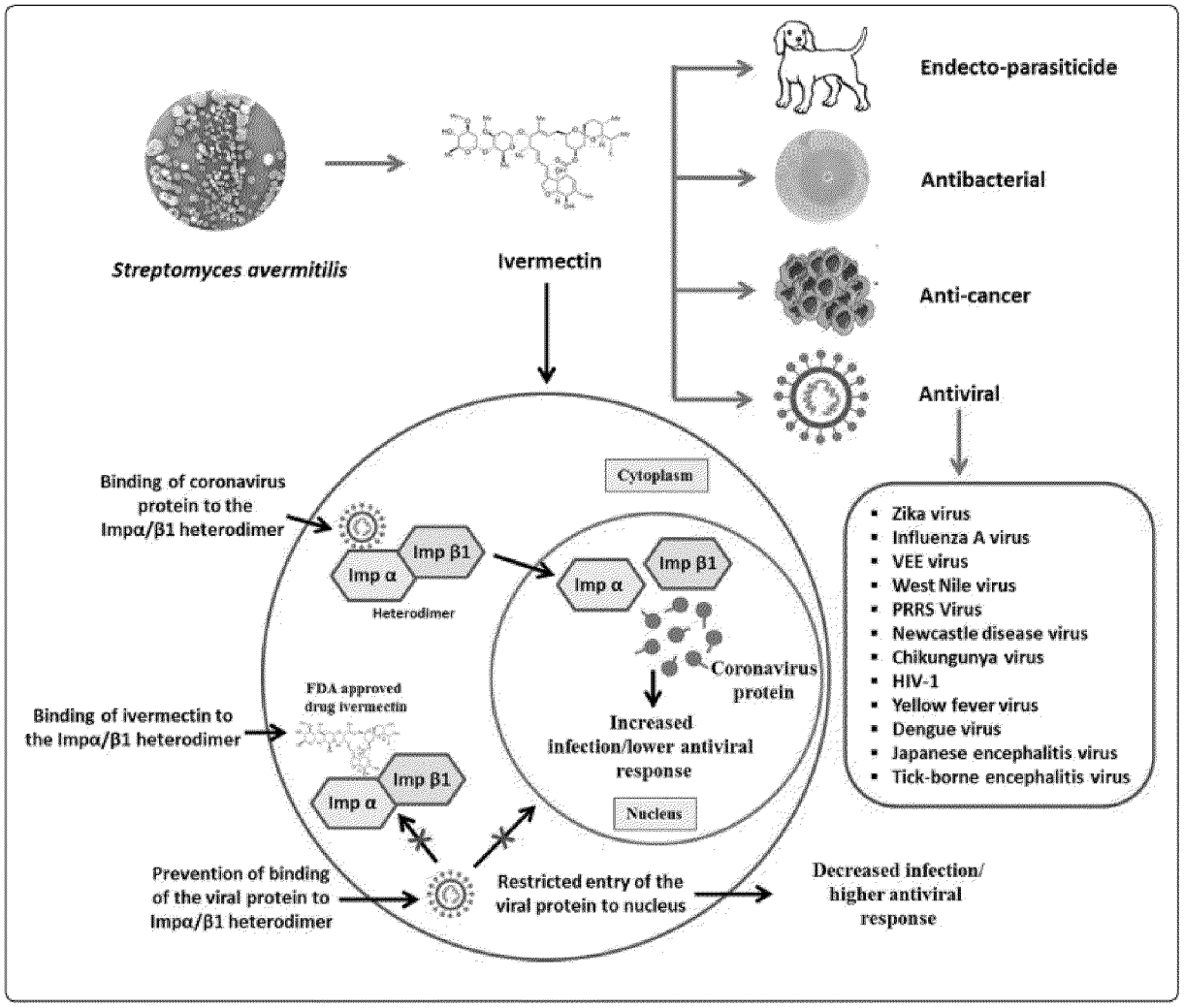
Approved dosage regimens vary from single oral yearly dose (e.g., 150 or 200 µg/kg, respectively) to treat onchocerciasis and strongyloidiasis, once-yearly dose (300–400 µg/kg) or alternatively bi-yearly dosing (150–200 µg/kg) to treat lymphatic filariasis.

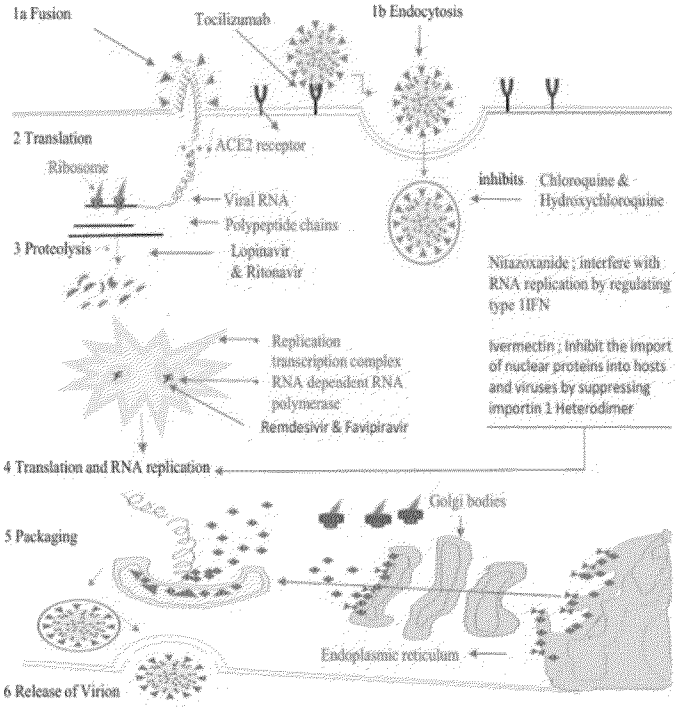
IVM is also approved for veterinary use, both in the US and in the EU. Of note, due to increased off-label use of the veterinary approved ivermectin in the US, in April 2020 the FDA published a letter to stakeholders advising them not to use veterinary approved IVM for human use.

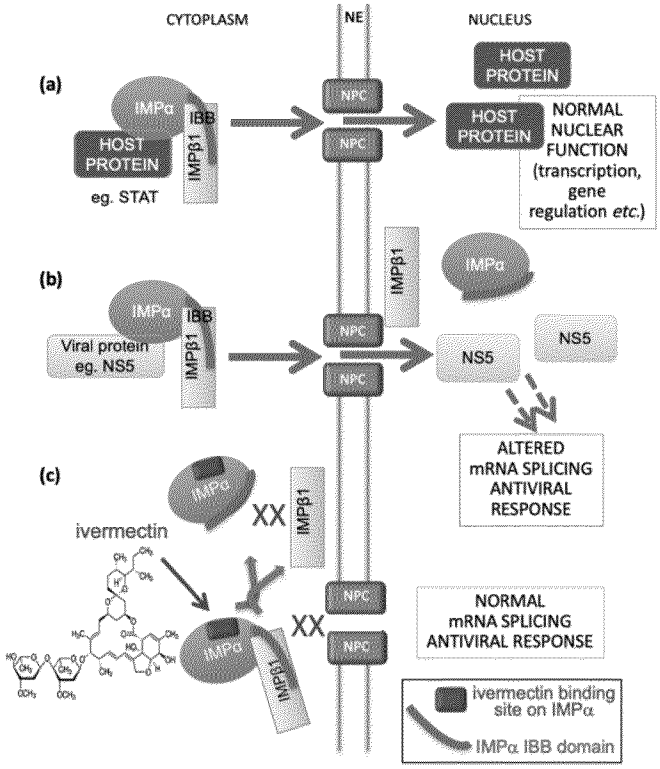
Ivermectin exhibits **broad antiviral activity** *in vitro*, against a large number of viruses (flaviviruses such as Dengue and Zika viruses, Venezuelan equine encephalitis virus, Newcastle disease virus and even HIV-1 and influenza) (Wagstaff et al,2012, Lundberg et al, 2013, Tay et al, 2013, Gotz et al, 2016, Yang et al, 2020) , including SARS-CoV-2 (Caly et al, 2020).

Compound	Documented Action on IMPα	Antiviral Against	Inhibitory Concentration (Assay)/Fold reduction
Ivermectin	• Inhibits interaction in vitro of IMPα with HIV-IN [34], DENV2 NS5 (1 µM) [7,11], T-ag [31], Hendra V (15 µM) [13], IMPβ1 (7 µM) [11] • Inhibits interaction of IMPα with T-ag and NS5 in a cell context as visualised by quantitative BiFc [11] • Inhibits CoIP from cell lysates of IMPα with T-ag, Adenovirus E1A [20] • Inhibits nuclear accumulation in a cellular context of IMPα/β1- but not β1-recognised viral proteins such as T-ag [7,16], DENV2 NS5 [7], VEEV Capsid [16], adenovirus E1A [20], PSV UL42 [18] as well as host cargoes (see [15,30]) • Reduces nuclear localisation in infected cells of VEEV Capsid [9] and adenovirus E1A [20]	Coronavirus SARS-CoV-2 HIV-1 (VSV-G-pseudotyped NL4-3.Luc.R-E-HIV) Influenza VLPs (avian influenza A/MxA escape mutants) Flavivirus: YFV (17D) DENV1 (EDEN-1) DENV2 (NGC) DENV2 (EDEN-2) DENV3 (EDEN-3) DENV4 (EDEN-4) WNV (NY99) WNV (MRM61C) ZIKV (Asian/Cook Islands/2014) Alphavirus: Chikungunya virus (CHIKV-Rluc) Sindbis (HR) Semliki forest virus VEEV (TC83) Hendra (Hendra virus/Australia/Horse/1994) DNA viruses Adenovirus (HAdV-C5) Adenovirus (HAdV-B3) BK polyomavirus (BKPyV) Pseudorabies	EC_{50} = 2.2/2.8 µM (qPCR/released/cell-associated virus) [17] 5000-fold 50 µM > 2-fold (luciferase) [7] 10 µM total inhibition (luciferase) [10] EC_{50} = 5/0.5 nM (CPE/qPCR) [12] 3 µM > 50,000-fold (pfu) [15] EC_{50} = 2.3/3 µM (CFI, 2 hosts) [8] EC_{50} = 0.7 µM (qPCR) [12] EC_{50} = 0.4/0.6 µM (pfu/qPCR) [11] 50 µM total inhibition (pfu) [7] EC_{50} = 2.1/1.7 µM (CFI, 2 hosts) [8] EC_{50} = 1.7 µM (CFI) [8] EC_{50} = 1.9 µM (CFI) [8] EC_{50} = 4 µM (qPCR) [12] EC_{50} = 1/0.5 µM (pfu/qPCR) [11] EC_{50} = 1.3/1.6 µM (pfu/qPCR) [11] EC_{50} = 1.9/0.6 µM (luciferase, 2 hosts) 3 µM > 5000-fold (pfu) [15] 3 µM > 1000-fold (pfu) [15] 3 µM > 200-fold (pfu) [15] 1 µM c. 20-fold (pfu) [9] est. EC_{50} = 2 µM (TCID/luciferase) [13] EC_{50} = c. 2.5 µM; 10 µM 20-fold (qPCR) [20] 10 µM c. 8-fold (qPCR) [20] Est. EC_{50} 1.5 µM (PFU/CPE/qPCR) [19] Est. EC_{50} c. 0.8 µM 1000-fold [18]

It is postulated that this broad antiviral activity may be due to its capacity of inhibiting the import of host and viral proteins into the nucleus, by inhibiting importins (the formation of the importin-α (IMPα) and IMPβ1 subunits as well as causes the dissociation of the formed IMPα/β1 heterodimer), and to the fact that many RNA viruses rely on IMPα/β1 during infection.

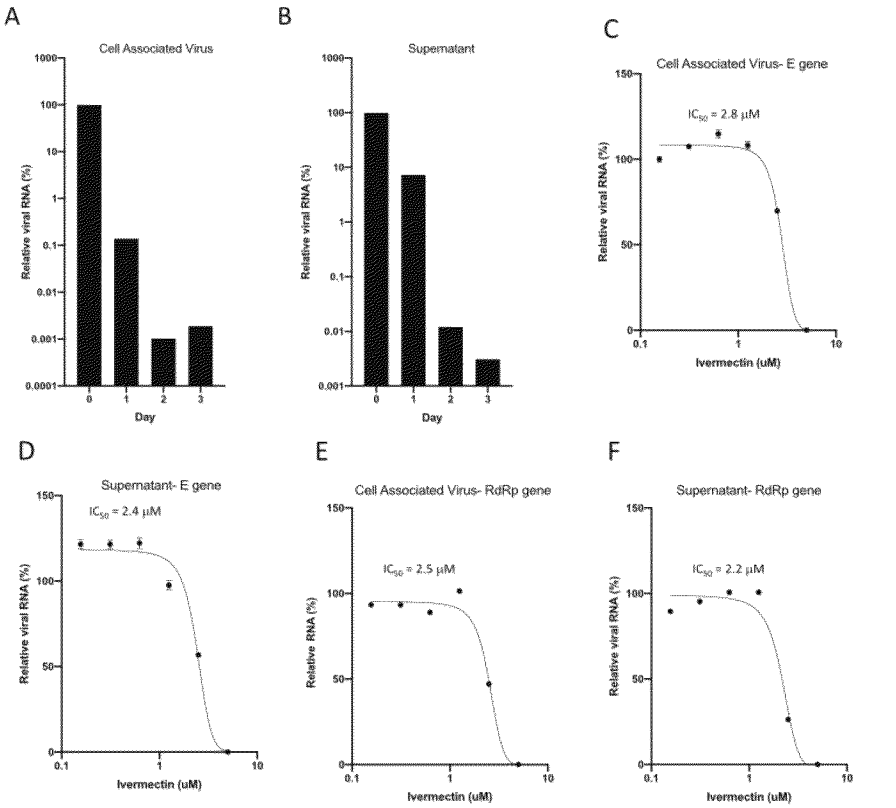

Endecto-parasiticide
Antibacterial
Anti-cancer
Antiviral
Streptomyces avermitilis
Ivermectin
Cytoplasm
Binding of coronavirus protein to the Impα/β1 heterodimer
Imp β1
Imp α
Heterodimer
Coronavirus protein
Increased infection/lower antiviral response
Nucleus
FDA approved drug ivermectin
Binding of ivermectin to the Impα/β1 heterodimer
Prevention of binding of the viral protein to Impα/β1 heterodimer
Restricted entry of the viral protein to nucleus
Decreased infection/ higher antiviral response
Zika virus
Influenza A virus
VEE virus
West Nile virus
PRRS Virus
Newcastle disease virus
Chikungunya virus
HIV-1
Yellow fever virus
Dengue virus
Japanese encephalitis virus
Tick-borne encephalitis virus


1a Fusion
Tocilizumab
1b Endocytosis
2 Translation
ACE2 receptor
Ribosome
Viral RNA
Polypeptide chains
3 Proteolysis
Lopinavir & Ritonavir
inhibits Chloroquine & Hydroxychloroquine
Nitazoxanide ; interfere with RNA replication by regulating type I IFN
Replication transcription complex
RNA dependent RNA polymerase
Remdesivir & Favipiravir
Ivermectin ; Inhibit the import of nuclear proteins into hosts and viruses by suppressing importin 1 Heterodimer
4 Translation and RNA replication
Golgi bodies
5 Packaging
Endoplasmic reticulum
6 Release of Virion



The mechanism of action is not fully elucidated, but IVM seems to prevent the nuclear localization signal (NLS) recognition (Azam et al, 2020). A molecular modelling study has claimed the inhibition of the coupling of the SARS-CoV-2S-protein with the human ACE2 receptor through the binding of ivermectin in the RBD region (de Oliveira et al, 2020).

Ivermectin reduced the SARS-CoV-2 VL by 5000-fold in Vero hSLAM cells submerged with a single dose of ivermectin for period of 48 hour, however increase in exposure period up to 72 hour did not show any effect in the reduction of the viral load (Choudhary and Sharma, 2020). Caly et al. reported that ivermectin inhibited SARS-CoV-2 in vitro for up to 48 h using ivermectin at 5μM. The concentration resulting in 50% inhibition (IC50, 2 μM) was >35x higher than the maximum plasma concentration (Cmax) after oral administration of the approved dose of ivermectin when given fasted.

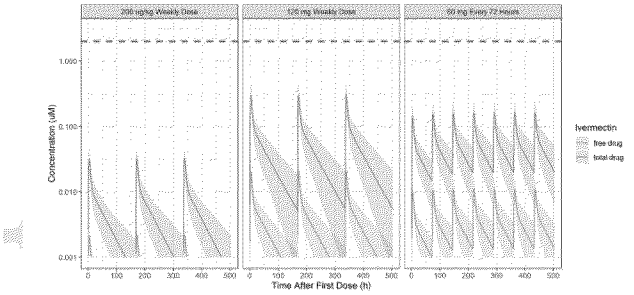


Schmith et al showed however that ***the likelihood of a successful clinical trial using the approved dose of ivermectin is low*** by conducting simulations using an available popPK model to predict total and unbound plasma concentration-time profiles after a single and repeat fasted administration of the approved dose of ivermectin (200 µg/kg), 60 mg, and 120 mg. Plasma ivermectin concentrations of total and unbound concentrations **do not reach the IC50**, even for a dose level 10x higher than the approved dose. Even with the high lung/plasma ratio, ***ivermectin is unlikely to reach the IC50 in lungs after single oral administration of the approved dose*** (predicted lung: 0.0873 µM) or at doses 10x higher that the approved dose administered orally (predicted lung: 0.820 µM).

Table 1 **Predicted Maximum Total Plasma Concentrations and Lung Concentrations After Various Doses of Ivermectin Administered Fasted**

Treatment		Predicted Total Cmax (μM) Median [2.5th, 97.5th Percentiles]	
		Plasma	Lung[b]
Single Dose	200 μg/kg Single Dose (Labelled Dose)	0.0327 [0.0228, 0.0429]	0.0873 [0.0609, 0.115]
	120 mg Single Dose[a]	0.307 [0.204, 0.449]	0.820 [0.545, 1.20]
Repeated Dose (3 Weeks)	200 μg/kg Weekly	0.0334 [0.0230, 0.0439]	
	60 mg Every 72 hours[a]	0.169 [0.113, 0.248]	
	120 mg Weekly	0.313 [0.207, 0.462]	

[a]Each Administered to 12 subjects (Guzzo et al., 2002)
[b]Calculated based on reported lung:plasma ratio of 2.67 in cattle (Lifschitz et al., 2000).
CI = Confidence Interval



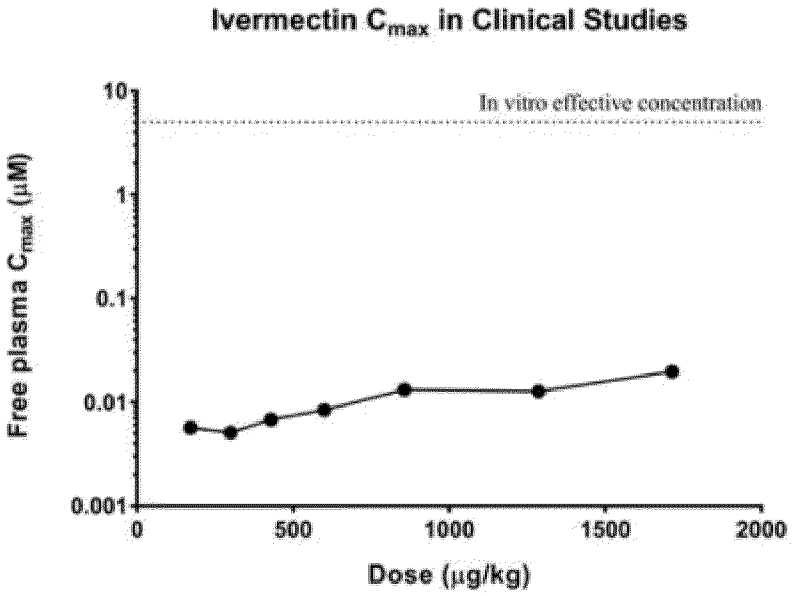


FIGURE 1 Expected free plasma concentrations of ivermectin based on 93% binding to plasma proteins and previously published total plasma concentrations.[3–5] When necessary, an estimated body weight of 70 kg was used for calculations. Note that none of the doses reached the 5μM concentration required for the antiviral effect of ivermectin (dotted line)

While no comprehensive evaluation of the target plasma and lung concentrations of ivermectin following approved dosing in humans was conducted, other published simulation work (based on different assumptions) derived lung Cmax/EC50 as an indicator of potential human efficacy and

indicated that ***ivermectin was predicted to achieve lung concentrations over 10-fold higher than its reported EC50*** (Arshad et al, 2020).

Despite the above, effective drug concentrations are unlikely to be achieved by orally administering the currently approved doses.

In addition to its in vitro antiviral effect, IVM possesses an ***in vitro anti-inflammatory effect***, that might have some clinical usefulness (DiNicolantonio et al, 2020). The anti-inflammatory and immunomodulatory properties of IVM have been known before the COVID pandemic and have been shown both in vitro and in animal models; they underpin the IVM topical use for the treatment of inflammatory lesions in rosacea. The anti-inflammatory effect of ivermectin were explained as inhibition of cytokine production by lipopolysaccharide challenged macrophages, blockade of activation of NF-kappaB and the stress-activated MAP kinases JNK and p38, and inhibition of toll-like receptor 4 (TLR4) signalling. It is possible therefore that IVM exerts an anti-inflammatory action in SARS-CoV-2 associated respiratory illness. However, data generated in animal models and clinical studies are needed to understand whether such a mechanism effectively gets translated *in vivo*.

Some *in silico* models have raised the possibility of ***additional mechanisms*** of IVM (e.g. blockade of a high affinity docking site on the human ACE-2 receptor).

There are currently 73 clinical trials worldwide testing the clinical benefit of ivermectin to treat or prevent SARS-CoV-2: 41 are actively recruiting patients, 32 are not recruiting patients at the time of this review. Most of the ongoing trials are small, but there are a handful of trials that may issue interpretable results (e.g. NCT04446104, NCT04527211, NCT04529525) allowing us to conclude on the efficacy of ivermectin in the treatment and prevention of COVID.

14 studies have been completed, among them the recently published Lopez-Medina et. al that **does not support the use of ivermectin for treatment of mild COVID-19**, although it acknowledges that larger trials may be needed to confirm these results.

The medicine has been and is widely used in the COVID setting in South America, where based on reviews looking at essentially the same evidence as this report, some countries even provided recommendations for use. Proposed dose is generally 0.2 mg/kg for 4–5 days.

PK: The peak plasma concentration of IVM is achieved within 4 h–5 h after oral ingestion and is about 93% bound to plasma proteins. The half-life is18 hours following oral administration. The drug is metabolised by hepatic microsomal enzymes CYP3A4. Ivermectin is both a substrate and a potent inducer of the P-gp. P-gp inhibitors can increase ivermectin plasma levels. IVM displays great PK variability after oral administration. Ivermectin is generally given on an empty stomach, but administration with food increases its bioavailability.

Benefits

Based on the evidence reviewed in this report, it currently seems **unlikely** for ivermectin to play an important role in the treatment or prevention of COVID. It is acknowledged nevertheless that reviewed clinical studies have important limitations (most small in size with generally unsatisfactory quality and fraught with many important uncertainties, see further below), therefore **the putative benefits of using ivermectin cannot be completely ruled out** and **well designed and conducted RCTs are needed** to draw definitive conclusions.

Several randomised and observational studies have been reviewed. Results were rather heterogenous, with some studies showing no benefit and other studies reporting putative benefits (shorter time to resolution of clinical manifestations, shorter time to viral clearance, lower mortality etc). Most studies reviewed had important limitations (small sample size, many open label, unblinded, disease severity unclear, various dosage regimens and even pharmaceutical forms, concomitant medications etc).

Known risks and precautions of use

IVM has a rather well characterised **wide** safety margin (several phase I studies showing safety at doses up to 10x higher than the usual 200 mcg/kg dose). Guzzo et al. showed that higher doses of ivermectin 120 mg (up to 2,000 µg/kg) taken once or at 180 mg (up to 3,000 µg/kg) taken in split doses over 1 week were well-tolerated and safe.

IVM is generally well tolerated when administered at the approved dosage, with mild and self-limited hepatic injury if rarely happening. An analysis of the first 11 years of mass global ivermectin (Mectizan) administration indicating a cumulative incidence of one serious adverse side effect case per million. No resistance in humans has yet been confirmed.

Acute or chronic liver dysfunction are not linked with ivermectin. Other adverse effect includes fever, pruritus, arthralgia, postural hypertension, tachycardia, oedema, lymphadenopathy, sore throat, cough and headache. Ototoxic effects associated with ivermectin use (manifesting as vestibulopathy) have also been reported. There have been rare reports of increased INR when ivermectin has been co-prescribed with warfarin. IVM should be avoided in pregnancy and children below 5 years of age or weighing less than 15 kg.

Based on this weight of evidence ***ivermectin may seem a safe medicine*** when used at the doses previously approved for other indications (and potentially even at higher doses). It should be however noted that ivermectin is a host-directed substance whose antiviral activity is exerted by inhibiting IMPs and therefore may impact other important cell activities. ***Toxicity of using much higher than approved doses cannot be totally excluded***. IVM may penetrate the blood-brain barrier and affect GABA-ergic transmission at large doses; human overdose has been associated with several adverse effects, including depression, ataxia, psychosis, confusion, and seizure.

2. Summary of triaged studies

2.1. Clinical trials in the treatment setting

2.1.1. Clinical trial description

1. Karamat **Hussain** Shah **Bukhari** et al. **Efficacy of Ivermectin in COVID-19 Patients with Mild to Moderate Disease** medRxiv preprint doi: https://doi.org/10.1101/2021.02.02.21250840 15/02/2021

A randomised open label clinical trial at Lahore Military Hospital. Hundred patients were randomised, 1:1. Patients, suffering mild or moderate (chest imaging abnormalities, no supplementary oxygen need) agreed hospitalisation for 14 days and received either SOC (Vit D3, Vit C , paracetamol) [group A] or SOC + ***once only*** administration of ***12 mg IVM*** (at randomisation) [group B]. Attrition rate during the 14 -day period was 5 versus 9 subjects, for groups A and B respectively. Eighty-six patients with reverse transcriptase-polymerase chain reaction (RTPCR) proven SARS-CoV-2 infection completed the trial protocol (outcome "per protocol" analysis). Following baseline, PCR was repeated at 72 hours, 7th day, and at 14th day of admission for both the groups and the point at which the PCR became negative was noted. Complete blood counts, liver function tests and renal function tests were done at recruitment, 7th day, and 14th day. The primary outcome was the viral clearance, measured as days to achieve PCR negativity. The secondary outcome was the development of any adverse side effects pertinent to ivermectin or derangement in baseline laboratory parameters.

Results: In group A, 36 (80%) participants were males, and 9 (20%) were females, whereas in group B, 37 (90.2%) were males and 4 (9.8%) were females. Mean age was 39.0 ± 12.6 and 42.2 ± 12.0 years for groups A and B, respectively (p= 0.394). There was early viral clearance in group B as

compared to group A (p=0.001). No adverse reaction or derangements in laboratory parameters was noted in the intervention arm during the trial period.

The authors concluded that in the intervention arm, early viral clearance was observed and no side effects were documented.

2. Mohan et al.: Ivermectin in mild and moderate COVID-19 (RIVETCOV): a randomized, placebo-controlled trial DOI: https://doi.org/10.21203/rs.3.rs-191648/v1

Exploratory single centre (AIIMS, India) randomized placebo-controlled trial of ***a single oral*** administration of Ivermectin elixir at two different dosage strengths (***12 mg*** and ***24 mg***) in patients with mild and moderate COVID-19. Double-blind conduct.

(Ivermectin concocted in 40% alcohol elixir, compounded by local pharmacist, with aim to increase bioavailability; 2 dose levels: 12 mg and 24 mg)

Non severe patients (at room air, SpO2 > 90%) were randomized to elixir formulation of Ivermectin in 24 mg, 12 mg or placebo in 1:1:1 ratio. The co-primary outcomes were conversion of RT-PCR to negative result and the decline of viral load at day 5 of enrolment and were assessed in patients with positive RT-PCR at enrolment (modified intention-to-treat population). Safety outcomes included total and serious adverse events and were assessed in all patients who received the trial drug (intention-to-treat population).

Results: Among 157 patients randomized, 125 patients were included in mITT analysis. Forty patients each were assigned to IVM 24 mg and 12 mg, and 45 patients to placebo. The RT-PCR negativity at day 5 was higher in the two IVM arms but failed to attain statistical significance (Ivermectin 24 mg, 47.5%; 12 mg, 35.0%; and placebo, 31.1%; p= 0.30). The decline of viral load at day 5 was similar in the three arms. No serious adverse events were encountered

Authors conclude that for a single oral administration of Ivermectin elixir at two different dosage strengths (12 mg and 24 mg) in patients with mild and moderate COVID-19, *"a trend"* towards higher negativity of RT-PCR at day 5 was observed with the use of Ivermectin 24 mg, while the decline in viral load was similar in all three arms. There were no safety concerns with the use of Ivermectin at either dose. **Larger studies** employing **different dosing** regimens of Ivermectin are **required** to further elucidate its potential role in treatment of COVID-19.

3. Ravikirti et al. Ivermectin as a potential treatment for mild to moderate COVID-19 – A double blind randomized placebo-controlled trial medRxiv preprint doi: https://doi.org/10.1101/2021.01.05.21249310

Parallel, double blind, randomised, single centre, placebo-controlled trial. Intervention with ***IMV 12 mg on day 1 and day 2*** of admission or placebo; 1:1

Adult patients (> 18 years) admitted with mild to moderate COVID 19 disease (on the basis of a positive RTPCR or Rapid Antigen Test report) at AIIMS, Patna, India with mild or moderate disease as defined by the ministry of health and family welfare guidelines (saturation > 90% on room air, respiratory rate < 30 and no features of shock). Randomisation by permuted blocks with varying length.

The following outcomes were measured:

Primary outcome: A negative RT-PCR report on day 6.

Secondary outcomes:

1. Whether or not symptomatic on day 6

2. Discharge by day 10

3. Admission to ICU

4. Need for invasive mechanical ventilation

Sample calculation: Assuming an improvement of 30% in 10-day recovery in patients receiving the intervention (50%) compared to the standard of care (20%) with 5% absolute precision and 80% power the total sample size was calculated to be 90

Results: A total of 115 patients were enrolled for the study of which 112 were included in the final Analysis (80% mild disease). Of them, 55 were randomised to the intervention arm while 57 were randomised to the placebo arm. There was **no** significant difference in the baseline characteristics of the two arms. There was **no** significant difference in the primary outcome, i.e. negative RT-PCR status on day 6 between the two groups. Similarly, there was **no** significant difference between the two groups in most of the secondary outcome measures, viz. symptom status on day 6, discharge status on day 10, admission to ICU, and need for invasive mechanical ventilation. However, while there was no in-hospital mortality in the intervention arm, there were 4 deaths in the placebo arm. As a result, all patients in the intervention arm (n=56) were successfully discharged as compared to 93.1% (n=54/58) in the placebo arm (RR 1.1, 95% CI 1.0 to 1.2, p=0.019).

Authors conclude that there was **no difference** in the primary outcome i.e. negative RT-PCR status on day 6 of admission with the use of ivermectin.

4. Ahmed et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. Int J Infect Dis. 2020; 103:214-6. (Bangladesh)

A randomized, double-blind, placebo-controlled trial conducted to determine the rapidity of viral clearance and safety of ivermectin among adult SARS-CoV-2 patients.

The trial included **72** hospitalized patients in Dhaka, Bangladesh, who were assigned to **one of three groups**: oral ivermectin alone (**12 mg once daily for 5 days**), oral ivermectin in combination with doxycycline (**12 mg ivermectin single dose and 200 mg doxycycline on day 1, followed by 100 mg every 12 h for the next 4 days**), and a placebo control group. 24 patients were included per study arm.

Patients included, ranged in age 18–65 years; admitted to hospital within the last 7 days; presence of a fever, cough, and/or sore throat; diagnosed positive for SARS-CoV-2 by real-time reverse transcription PCR (rRT-PCR).

The primary endpoints were the time required for virological clearance (a negative rRT-PCR result on nasopharyngeal swab), and remission of fever and cough within 7 days. Secondary outcomes included failure to maintain an SpO2 >93% despite oxygenation and days on oxygen support, the duration of hospitalisation, and all-cause mortality. Drug safety outcomes recorded were adverse events that occurred during treatment and post treatment, and the discontinuation of the study drug during the trial.

The duration of illness before assessment was an average of 3.83 days. The mean age was 42 Y, and 52% were women.

The mean duration of hospitalization after treatment was 9.7 days (95% confidence interval (CI) 8.1–11.0 days) in the placebo group, 10.1 days (95% CI 8.5–11.8 days) in the ivermectin + doxycycline

group, and 9.6 days (95% CI 7.7–11.7 days) in the ivermectin alone group (p = 0.93). None of the patients enrolled required oxygen. Clinical symptoms of fever, cough, and sore throat were comparable among the three groups. Virological clearance was earlier in the 5-day ivermectin treatment arm when compared to the placebo group (9.7 days vs 12.7 days; p = 0.02), but this was not the case for the ivermectin + doxycycline arm (11.5 days; p = 0.27). There were no severe adverse drug events recorded in the study. A 5-day course of ivermectin was found to be safe and effective in treating adult patients with mild COVID-19. Larger trials will be needed to confirm these preliminary findings.

5. Babalola et al. Ivermectin shows clinical benefits in mild to moderate COVID19: A randomised controlled double blind dose response study in Lagos. medRxiv preprint doi: https://doi.org/10.1101/2021.01.05.21249131

Proof of concept (PoC) randomized, double blind controlled, dose response, parallel group study of IV

efficacy in RT - PCR proven COVID 19 positive patients. Patients were randomized to 3 treatment groups. (A) IV 6mg regime, (B)IV 12 mg regime (C, control) Lopinavir/Ritonavir. All groups plus standard of Care.

All were either asymptomatic or had mild/moderate symptoms. Excluded were COVID pneumonia or requiring ventilator therapy, renal failure, thromboembolic complications, or unconscious by reduced Glasgow Coma Scale.

62 patients randomized to the 3 treatments, which was given bi-weekly (every 84 hour) for 2 weeks. COVID 19 PCR testing was undertaken at baseline (pre-treatment time 0 hour) and after dosing at 0 hours, 84 hours, 168 hours (7 days), 232 hours (1.5 week) and 336 hours (14 days).

Main outcome: time to PCR negativity. Changes in clinical and laboratory parameters at baseline and at seven days were recorded for the three arms.

Results:

Mean duration of illness at study entry was not stated.

Patient groups seemed comparable. Comorbidities were few: diabetes mellitus (DM) (n= 2) and hypertension (n=9).

The time (mean +/-SD) to negativity (days) in the treatments were for 6mg; 6+/-2.95, for 12 mg; 4.65+/- 3.19, and for the controls 9.15+/- 7.26, p =0.02. When both Ivermectin groups were combined (with a new mean 5.34 +/- 0.07 days n=41) the mean difference SEM from placebo control, of - 3.81 +/- 1.34 days was stated as statistically significant p = 0.0066.

There was no difference in clinical symptom resolution or evolution of clinical parameters.

6. Chaccour C et al.
The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with mild COVID-19: a pilot, double-blind, placebo controlled, randomized clinical trial

https://doi.org/10.21203/rs.3.rs-116547/v1 (Spain)

Pilot, randomized, double-blind, placebo-controlled trial to determine the efficacy of a single

dose of ivermectin to reduce the proportion of PCR positives, viral load at day 7 post treatment.

Consecutive patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

infection and mild COVID-19 (no pneumonia) and no risk factors for complicated disease attending the

emergency room of the Clínica Universidad de Navarra. Patients were randomized 1:1 to receive ivermectin, 400 mcg/kg, single dose (n = 12) or placebo (n = 12).

The primary outcome measure was the proportion of patients with detectable SARS-CoV-2 RNA by PCR from nasopharyngeal swab at day 7 post-treatment. The primary outcome was supported by determination of the viral load and infectivity of each sample. The differences between ivermectin and placebo were calculated using Fisher's exact test and presented as a relative risk ratio.

All patients recruited completed the trial (median age, 26 [range, 18-54] years; 12 [50%] women; 100% had symptoms at recruitment, 70% reported headache, 62% reported fever, 50% reported general malaise and 25% reported cough). At day 7, there was no difference in the proportion of PCR positive patients (RR 0.92, 95% CI: 0.77-1.09, p = 1.0). The ivermectin group had lower median viral loads at days 4 and 7 post treatment as well as lower median IgG titers at day 21 post treatment. Hyposmia/anosmia (76 vs 158 patient-days) and cough (68 vs 97 patient-days) were less frequent in the ivermectin group.

Conclusion: Among patients with **mild** COVID-19 and **no risk factors** for severe disease receiving a single 400 mcg/kg dose of ivermectin within 48 hours of fever or cough onset there was **no** difference in the proportion of PCR positives. There was however a marked reduction of anosmia/hyposmia, a reduction of cough and a tendency to lower viral loads and lower IgG titers which warrants assessment in larger trials.

7. Niaee S et al. Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: A randomized multi-center clinical trial
https://doi.org/10.21203/rs.3.rs-109670/v1 preprint (Iran)

A randomized, double-blind, placebo-controlled, multicentre, phase 2 study. Patients who met the following criteria were admitted: a) Age >18 years; b) signed the informed consent; c) clinical symptoms of suggestive of COVID-19 pneumonia: cough (with or without sputum), fever, pleuritic chest pain or dyspnoea; d) mild to severe COVID-19 disease confirmed by chest computed tomography (CT) scan findings compatible with COVID-19 or positive real-time RT-PCR.

The primary endpoint of this trial was clinical recovery within 45 days of enrolment. Clinical recovery was defined as normal fever, respiratory rate, and oxygen saturation (>94) without oxygen therapy sustained for 24h. The patients would be discharged if this trend continued.

Using a two-sided test level of 0.05 and a desired statistical power of 90% and under the assumption that each treatment arm would yield a 75 % success rate, the number of patients in the study was obtained equal to 163 patients

30 patients per study arm were enrolled; 6 arms:

- common regimen (standard) S

- placebo + standard (P)

- Arm 1: single dose 200 mcg/kg (added to standard)

- Arm 2: 3 tablets: 200 mcg/kg at day 1, 3 and 5 added to standard

- Arm 3: single dose 400 mcg/kg (added to standard)

- Arm 4: 3 tablets: 400 mcg/kg at day 1, 3 and 5 added to standard

Randomisation was stratified per disease severity: mild, moderate, severe.

Results: Average age of the participants was 56 years (45-67) and 50% were women. Groups were comparable at baseline.

Results showed significant changes between day zero and day five of admission (Δ 0/5) in terms of lab parameters Δ platelets PLT5/0, Δ sedimentation rate ESR5/0, Δ C- reactive protein CRP5/0, duration of low O2 saturation, and duration of hospitalization (CI = 95%).

Mortality rate in patients receiving ivermectin treatment to 0 (0/30), 10 (3/27), 0 (0/30) and 3.3% (1/29) for arms 1- 4 respectively, compared to the standard and placebo plus standard arms which was 16.7% (6/24) (S) and 20% (5/25) (P) respectively.

Mean duration of hospitalisation, 6, 8, 5, 7 vs 7 and 8 days respectively and reported as significant different for group (1-4) vs group (S+P).

The authors conclude that IVM as an adjunct reduced the rate of mortality, low O2 duration, and duration of hospitalization in adult COVID 19 patients. The improvement of other clinical parameters showed that the ivermectin, with a wide margin of safety, had a high therapeutic effect on COVID-19.

8. Elgazzar et al. Efficacy and Safety of Ivermectin for Treatment and prophylaxis of COVID-19 Pandemic

DOI: https://doi.org/10.21203/rs.3.rs-100956/v3

Double blind randomised study aims to evaluate IVM plus standard care in the treatment of mild/moderate and severely ill cases with COVID 19 infection, as well as prophylaxis of health care and/ or household contacts.

600 subjects; 400 symptomatic confirmed COVID-19 patients and 200 health care and household contacts distributed over 6 groups;

Group I: 100 patients with **mild/moderate** COVID-19 infection received a **4-days course** of IVM plus standard of care;

Group II: 100 patients with **mild/moderate** COVID-19 infection received **hydroxychloroquine plus standard care**;

Group III: 100 patients with **severe** COVID-19 infection received **IVM plus standard care**;

Group IV: 100 patients with Severe COVID-19 infection received **hydroxychloroquine plus standard of care.**

Group V: personal protective measures (**PPM) plus Ivermectin** o.4mg / kg on empty stomach to be repeated after one week,

Group VI: **PPM only**. Both groups V&VI were followed for two weeks.

At least one positive rt-PCR result from nasopharyngeal/oropharyngeal swab.

Categorised:

Mild = symptomatic and normal chest imaging

Moderate= Patients have symptoms such as fever, respiratory tract symptoms, gastrointestinal symptoms, etc. and pneumonia manifestations can be seen in chest imaging.

Severe fulfilling any of the following criteria:

a. Respiratory rate more than 30/min.
b. Blood oxygen saturation of less than 93%.
c. PaO2/FiO2 ratio of less than 200
d. Lung infiltrates >50% of the lung fields or rapid progression within 24-48 hours.
e. Patients need respiratory support e.g. high flow oxygen non-invasive or invasive mechanical

The primary endpoint stated as: clinical, laboratory investigations improvement and/or 2 consecutive negative PCR tests taken at least 48 hours apart.

Secondary endpoint: Patients presenting with adverse events requiring stoppage of treatment and management of any side effects accordingly.

Patients were followed up daily clinically and by laboratory assessment for two weeks but radiological assessment after two weeks or until one of the endpoints is reached. Follow up the duration of treatment, swab conversion, hospital stay, the clinical and radiological improvement was recorded.

Results reported as significant improvement in groups received Ivermectin plus standard care & (groups I & III), (99% & 94% respectively) compared to those received Hydroxychloroquine plus standard care only (Group III&IV), (74% & 50% respectively), (p-value <0.001). The mortality rates significantly reduced in Ivermectin treated patients groups I& III (0.0% & 2%, respectively) versus Hydroxychloroquine treated groups II & IV (4% & 20%, respectively). Significant improvement in biochemical / BC parameters in treated groups.

IVM reported as very effective in preventing corona virus infection in health care or household contacts of COVID 19 patients group V (2%) compared to non IVM group VI (10%).

Authors concluded that addition of Ivermectin to standard care is very effective drug for treatment of COVID-19 patients with significant reduction in mortality, recovery time and

hospital stay days compared to Hydroxychloroquine plus standard treatment only. Early use of Ivermectin is very useful for controlling COVID 19 infections; improving cytokines storm and prophylaxis of frontline health care as well as household contacts.

9. Krolewiecki et al. Antiviral effect of high-dose ivermectin in adults with COVID-19: a pilot randomised, controlled, open label, multicentre trial. (Argentina) preprint

A pilot, randomized, controlled, outcome-assessor blinded clinical trial with the goal of evaluating the antiviral activity of high dose IVM in COVID-19 patients. Eligible patients were adults (aged 18 to 69 years) with mild or moderate RT-PCR confirmed SARS CoV-2 infection within 5 days of symptoms onset. 45 patients were randomized in a 2:1 ratio to standard of care plus oral IVM at 0·6 mg/kg/day for 5 days versus standard of care.

The primary endpoint was viral load reduction in respiratory secretions between baseline and at day 5. Viral load in respiratory secretions was measured through quantitative RT-PCR. Concentrations of IVM in plasma were measured on multiple treatment days.

45 randomized patients (30 in the IVM group and 15 controls). There was no difference in viral load reduction between groups but a significant difference in reduction was found in patients with higher median plasma IVM levels (72% IQR 59 – 77) versus untreated controls (42% IQR 31 – 73) (p=0·004). The mean ivermectin plasma concentration levels also showed a positive correlation with viral decay rate (r:0·47, p=0·02). Adverse events were reported in 5 (33%) patients in the controls

and 13 (43%) in the IVM treated group, without a relationship between IVM plasma levels and adverse events.

10. Carvallo et al. Safety and efficacy of combined use of ivermectin, dexamethasone, enoxaparin and aspirin against COVID-19. https://doi.org/10.1101/2020.09.10.20191619 doi: medRxiv preprint

Single-centre, prospective clinical trial run at Eurnekian Hospital in the Province of Buenos Aires, Argentina. Comparison versus external group.

All medications on licensed dosage, except ivermectin (0.6 mg/kg).

Male and female persons not less than 5 years old, with a positive rt-PCR diagnosis of COVID-19 performed on nasal swab specimens. Categorised, mild to severe:

- mild = mild symptoms; no clinical pneumonia (outpatients)

- moderate: 3 severe symptoms or 2 severe and 2 mild; clinical pneumonia

- severe: 4 severe symptoms or 3 severe and not less than 2 mild. Clinical signs of bilateral pneumonia.

Symptoms classified:

mild: Fever not above 38.5 °C; Isolated diarrheal episodes; Hyposmia or Hypogeusia; Mild desaturation (93 – 96 %); Dyspnoea without matter; Polymyoarthralgias, Persistent headache; Abdominal pain

severe: Fever above 38.5 °C; Diarrhoea (more than 3 daily depositions); Flictenular conjunctivitis; Strong desaturation (92% or less); Tachypnoea

Treatment according to disease severity classification, with use of aspirin 250 mg /d at least for 30 days in mild, moderate categories; dexamethasone 4mg /d in moderate and severe; enoxaparin 100 IU/kg in severe stage; for IVM: 24mg, 36 mg and 48 mg at Day 0 and 7 for mild, moderate and severe groups respectively.

Outcome parameters:

The primary outcomes were:
- Percentage of patients progressing from mild to moderate or severe stages of disease
- Mortality rate by day 30

Statistics: Descriptive

The outcomes of the study were compared with data from the literature and, in the case of moderate to severe cases, with a group of patients admitted to the hospital in the same period of time who did not join the study protocol and received other treatments.

Results:

All the135 patients who joined the study at a mild stage of COVID-19 did not worsen illness and had no need of hospitalization of any kind.

Regarding the remaining 32 patients, only one of them died. This patient had been included already at a severe stage of disease. The remaining 31 patients did not worsen during treatment.

Overall mortality rate of patients treated according to IDEA protocol was 0.59 %. As a comparison, estimated overall mortality rate in Argentina is approximately 2.1 %.

For patients needing hospitalization, only 1 patient out of 32 receiving IDEA treatment died (3.1 %), A group of 12 patients were hospitalized in Eurnekian hospital in the same period but did not receive IDEA treatment. Three of them died, thus presenting a mortality rate of 25 %,

Conclusions:

Authors conclude that IDEA protocol may be of use to help stop COVID-19 progression and reduce hospitalization and mortality.

Based on the outcomes of this study, a possible preventive strategy for COVID-19 in communities of high viral circulation is postulated.

11. Chachar et al. Effectiveness of IVM in COVID-19 patients. Int J Sciences 2000; 9 (Sep 20). Doi: https://doi.org/10.18483/ijSci.2378

Single centre, randomised, open label trial in Fatima Memorial Hospital (Lahore), including 50 patients, 62% male; all with mild symptoms; co-morbidities were evenly distributed with 20(40%) patients suffering diabetes mellitus, 11(22%) in intervention group and 9(18%) in control group.

Intervention: IVM at admission after 12 and after 24 hours; each time 12 mg dose.

Outcome: Day 7 on follow up in terms of improvement of symptoms like (Fever, Cough, sore throat, headache, shortness of breath, lethargia and fever.

Treatment was well tolerated. For both groups, comparable proportions in both groups were asymptomatic at Day 7 (16/25 vs 15/25).

12. Elalfy et al Effect of a combination of Nitazoxanide, Ribavirin and Ivermectin plus zinc supplement (MANS.NRIZ study) on the clearance of mild COVID-19.
https://doi.org/10.1002/jmv.26880

Non-randomized controlled trial included 62 patients on triple combination treatment versus 51 age- and sex-matched patients on routine supportive treatment.

Case confirmation by positive RT-PCR of nasopharyngeal swab. 130 enrolled; 61 intervention; 69 control

Results: Trial results showed that the clearance rates were 0% and 58.1% at 7th day and 13.7% and 73.1% at the 15th day in supportive treatment and combined antiviral groups, respectively. The cumulative clearance rates at 15th day are 13.7 and 88.7% in supportive treatment and combined antiviral groups, respectively.

Authors conclude combined use of Nitazoxanide, Ribavirin, and Ivermectin plus zinc supplement effectively clear the SARS-COV2 from nasopharynx in shorter time than the symptomatic therapy.

13. Espitia-Hernandez et al *Biomedical Research 2020; 31 (5): 129-133*

This was a proof-of-concept study for the evaluation of clinical efficacy of Ivermectin, Azithromycin and Cholecalciferol combination in the treatment of new coronavirus (COVID-19).

35 adult patients who were tested positive for SARS-CoV-2 infection by RT PCR were included. Patients were voluntarily allocated into 2 groups at a 4:1 ratio; 1)

Combination group (n=28): Ivermectin (6 mg once daily in day 0,1,7 and 8) plus Azithromycin (500 mg once daily for 4 days) plus Cholecalciferol (4000 UI twice daily for 30 days) plus standard treatment and 2) Control group (n=7): Standard treatment (self-isolation, proper nutrition, oral hydration and acetaminophen). Subjects enrolled in this study were treated as outpatients

The primary end point was the efficacy of the combination therapy. A negative PCR was counted as treatment success. Secondary end points included the duration from the first-day drug intake to the alleviation of clinically significant symptoms of COVID-19, temperature and ventilatory responsiveness.

An overall mean of 45 ± 10 years of age. Obesity (34%) was the most frequent comorbidity.

Significant reduction in the duration of symptoms was found in the combination group as compared with control group (3 ± 1.3 vs. 10 ± 4.8), respectively

Transient and mild adverse reactions like diarrhoea and nausea were reported in 3 (10.7%) patients in the combination group.

All patients in the combination group achieved a negative PCR on day 10, whereas the control group remained positive.

14. Gonzales et al. Efficacy and safety of Ivermectin and Hydroxychloroquine in patients with severe COVID-19. A randomized controlled trial doi: https://doi.org/10.1101/2021.02.18.21252037

Randomized double-blind 3-arm controlled trial in patients with pneumonia secondary to SARS-CoV-2 infection and in need of hospitalization. The study was conducted at the Hospital Centenario Miguel Hidalgo in the state of Aguascalientes (Mexico), a tertiary care institution for the population lacking social security. Group 1 received hydroxychloroquine, Group 2 ivermectin (12 mg or 18 mg according to patient weight) and Group 3 placebo. The primary outcome was established as the duration of hospitalization until discharge due to patient improvement, the total duration of hospitalization, and the safety outcomes were either respiratory deterioration or death.

Patients were classified as high- or low-risk for the development of QT interval prolongation due to hydroxychloroquine, according to their electrocardiogram. Patients with high risk were randomized to ivermectin or placebo, while those with low risk were randomized to ivermectin, hydroxychloroquine, or placebo. The dose of ivermectin was 12 mg in patients weighing less than 80 kg and 18 mg in those above 80 kg. During the last week of June and based on the RECOVERY trial, administration of dexamethasone was initiated in patients requiring oxygen therapy.

One hundred and six (106) patients with an average age of 53 yrs. (±16.9) were included, with a greater proportion of males (n=66, 62.2 %). Ninety percent (90 %) of patients were discharged due to improvement (n=96). The average duration of hospitalization was 6 days (IQR, 3 – 10). No difference in hospitalization duration was found between the treatment groups (HQ: 7 vs Ivermectin: 6 vs Placebo: 5, p =0.43) nor in respiratory deterioration or death (HQ: 18 % vs Ivermectin: 22.2 % vs Placebo: 24.3 %, p =0.83).

15. Chowdhury et al. A Randomized Trial of Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin therapy on COVID19 patients. doi: https://doi.org/10.21203/rs.3.rs-38896/v1

Patients with mild to moderate COVID-19 disease, tested positive by RT PCR for SARS-CoV-2 infection at Chakoria Upazilla Health Complex, Cox's Bazar, Bangladesh, were included in this study. Patients

were randomized to Ivermectin 200µgm/kg single dose + Doxycycline 100 mg BID for 10days in group A, and Hydroxychloroquine 400 mg 1st day, then200mg BID for 9days + Azithromycin 500 mg daily for 5 days in group B. PCR for SARS-CoV-2 was repeated in all symptomatic patients on the second day onward without symptoms, or, for those who were asymptomatic (throughout the process), on the 5th day after taking medication and repeated every two days onward if the result was positive. Time to negative PCR and time to full symptomatic recovery was measured for each group.

All subjects in the Ivermectin-Doxycycline group (group A) reached a negative PCR for SARS-CoV-2, at a mean of 8.93days, and all reached symptomatic recovery, at a mean of 5.93days, with 55.10% symptom-free by the 5th day. In the Hydroxychloroquine-Azithromcyin group (group B), 96.36% reached a negative PCR at a mean of 6.99days and were symptoms-free at 9.33days. Group A patients had symptoms that could have been caused by the medication in 31.67% of patients, including lethargy in 14(23.3%), nausea in 11(18.3%), and occasional vertigo in 7(11.66%) of patients. In Group B, 46.43% had symptoms that could have been caused by the medication, including 13(23.21%) mild blurring of vision and headache; 22(39.2%) increased lethargy and dizziness, 10(17.85%) occasional palpitation, and 9(16.07%) nausea and vomiting.

16. Hashim et al. Controlled randomized clinical trial on using Ivermectin with Doxycycline for treating COVID-19 patients in Baghdad, Iraq. Doi: https://doi.org/10.1101/2020.10.26.20219345

Randomized controlled study in 70 COVID-19 patients (48 mild-moderate, 11 severe, 11 critical) treated with Ivermectin + Doxycycline + standard therapy vs. 20 patients treated with standard therapy alone. The time to recovery, the progression of the disease, and the mortality rate were the outcome-assessing parameters. Patients were recruited in 2 hospitals in Baghdad city from July 1st to September 30th.

Among all patients and among severe patients, 3/70 (4.28%) and 1/11 (9%), respectively progressed to a more advanced stage of the disease in the Ivermectin-Doxycycline group versus 7/70 (10%) and 7/22 (31.81%), respectively in the control group (P>0.05). The mortality rate was 0/48 (0%), 0/11 (0%), and 2/11 (18.2%) in mild-moderate, severe, and critical COVID-19 patients, respectively in Ivermectin-Doxycycline group versus 0/48 (0%), and 6/22 (27.27%) in mild-moderate and severe COVID-19 patients, respectively in standard therapy group (p=0.052). Moreover, the mean time to recovery was 6.34, 20.27, and 24.13 days in mild-moderate, severe, and critical COVID-19 patients, respectively in Ivermectin-Doxycycline group versus 13.66 and 24.25 days in mild-moderate and severe COVID-19 patients, respectively in standard therapy group (P<0.01).

Conclusions: Ivermectin with doxycycline reduced the time to recovery and the percentage of patients who progress to more advanced stage of disease; in addition, Ivermectin with doxycycline reduced mortality rate in severe patients from 22.72% to 0%; however, 18.2% of critically ill patients died with Ivermectin and doxycycline therapy. Taken together, the earlier administered Ivermectin with doxycycline, the higher rate of successful therapy.

17. Podder et al. Outcome of ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomised controlled study.

An open-label randomised controlled study that was conducted at a sub-district (Upazila) health complex from 1st May 2020 to the end of July 2020. Consecutive RT-PCR positive eligible COVID-19 patients were randomised into control and intervention arm (ivermectin 200 micrograms/kg single dose was administered orally in addition to usual care). Repeat RT-PCR was done on day ten since the

first positive result. The primary endpoint was the time required for the resolution of symptoms from the onset of the symptoms and following enrolment in the study.

Results: 82 patients with mild to moderate COVID-19 disease were randomized. Out of these, 62 were included in the final analysis (30 patients in the control arm vs. 32 patients in the ivermectin arm). Total recovery time from the onset of symptoms to complete resolution of symptoms of the patients in the intervention arm was 10.09 ± 3.236 days, compared to 11.50 ± 5.32 days in the control arm (95% CI -0.860, 3.627, p >. 05) and was not significantly different. The mean recovery time after enrolment in the intervention arm was 5.31 ± 2.48 days, which also did not differ significantly from the control arm of 6.33 ± 4.23 days (95% CI – 0.766, 2.808, p> 0.05). Results of negative repeat RT-PCR were not significantly different between control and intervention arms (control 90% vs intervention 95%, p>.05).

Conclusion: Ivermectin had no beneficial effect on the disease course over usual care in mild to moderate COVID-19 cases.

18. Spoorthi et al. Utility of Ivermectin and Doxycycline combination for the treatment of SARS- CoV-2.

A total of 122 patients admitted in a tertiary care centre, who tested positive for SARS-CoV2 using RT-PCR and with mild to moderate symptoms were included in the study and a total sample size of 100 patients was obtained after exclusion. 50 patients of the treatment group were treated with Ivermectin-Doxycycline combination and compared to 50 patients treated with placebos (Vitamin B6).

Results: A significant reduction was observed in mean duration of hospitalization (3.70 ± 2.27 days vs. 4.69 ± 2.3 days), and in complete resolution of symptoms stay (6.67 ± 2.01 days vs 4.69 ± 2.3 days). In a subset of 10 patients RT-PCR for COVID was tested on day 10 after the symptom onset and no statistically significant difference was found. There was no significant difference in the side effect profile of either groups.

Conclusion: The authors conclude that the study supports the benefits of utilization of combination of Doxycycline and Ivermectin in mild to moderate COVID-19 infection in terms of early recovery based on the time for symptom resolution and the mean duration of hospital stay.

19. Okumus et al. Evaluation of the Effectiveness and Safety of Adding Ivermectin to Treatment in Severe COVID-19 Patients doi: https://doi.org/10.21203/rs.3.rs-224203/v1

Prospective multicentre randomized controlled "Ph 3" trial in patients with severe COVID19 pneumonia. Study group treated with 200 mcg/kg/day for five days added to reference treatment hydroxychloroquine + favipiravir + azithromycin vs. control group with reference treatment (3 drugs without ivermectin). 66 patients (36 study vs. 30 control group). Patients with mutations affecting ivermectin metabolism were excluded from study group.

No statistically significant difference in improvement rate after 5 days of treatment (primary endpoint) and 5 days after follow-up (secondary endpoint) found: study group [14/30 (46.7%)] compared to the control group [11/30 (36.7%)] with p-value = 0.43 and study group [22/30 (73.3%)] compared to the control group [16/30 (53.3%)] with p-value = 0.10 (Chi-Squared test).

Study reports statistically significant change in SOFA score for study group (p=0.009) and no stat. sign change for control group (p=0.88). Study reports statistically significant difference in PCR test negativity at "end of follow-up period" between study group and control group (14 (87.5%) patients in the study group and 3 (37.5%); p=0.01).

20. Lopez-Medina et al. Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19 JAMA March 4, 2021. doi:10.1001/jama.2021.3071

Double-blind, randomized trial conducted at a single site in Cali, Colombia.

Potential study participants were identified by simple random sampling from the state's health department electronic database of patients with symptomatic, laboratory-confirmed COVID-19 during the study period. A total of 476 adult patients with mild disease and symptoms for 7 days or fewer (at home or hospitalized) were enrolled between July 15 and November 30, 2020 and followed up through December 21, 2020.

Patients were randomized to receive ivermectin, 300 μg/kg of body weight per day for 5 days (n = 200) or placebo (n = 200).

Primary outcome was time to resolution of symptoms within a 21-day follow-up period. Solicited adverse events and serious adverse events were also collected.

Among 400 patients who were randomized in the primary analysis population (median age, 37 years [interquartile range {IQR}, 29-48]; 231 women [58%]), 398 (99.5%) completed the trial. The median time to resolution of symptoms was 10 days (IQR, 9-13) in the ivermectin group compared with 12 days (IQR, 9-13) in the placebo group (hazard ratio for resolution of symptoms, 1.07 [95% CI, 0.87 to 1.32]; $P = .53$ by log-rank test). By day 21, 82% in the ivermectin group and 79% in the placebo group had resolved symptoms. The most common solicited adverse event was headache, reported by 104 patients (52%) given ivermectin and 111 (56%) who received placebo. The most common serious adverse event was multiorgan failure, occurring in 4 patients (2 in each group).

Conclusion:

Among adults with mild COVID-19, a 5-day course of ivermectin, compared with placebo, did not significantly improve the time to resolution of symptoms. The findings do not support the use of ivermectin for treatment of mild COVID-19, although larger trials may be needed to understand the effects of ivermectin on other clinically relevant outcomes.

2.1.2. Tabular summary of clinical trials

Clinical Trial	Population	Endpoint	Strengths and limitations	Conclusion
Ahmed et al. (2021)	2 patients with mild COVID-19 who were symptomatic and tested positive by rRT-PCR for COVID-19; admitted to hospital within last 7 days; Avg. age of 42 years; 46% male	Primary Endpoint: Time until RT-PCR negativity (viral clearance); Remission of fever at 7 days post-treatment (yes/no); Remission of cough at 7 days post-treatment (yes/no) Secondary Endpoints: Failure to maintain SpO2 >93% despite oxygenation (yes/no); Days on oxygen support; Duration of hospitalization; All-cause mortality	Strengths: Randomized, double-blind, multicentre. Time until clearance reported with KM-curve including number at risk. Limitations: Limited to viral endpoints. Short communication with limited information about data and methods. Small treatment groups (24 per arm). Discrepancy in outcome between active arms, ivermectin arm and ivermectin + doxycycline, which is not well explained (interaction between both interventions?). Unclear why only 72 out of 113 who consented were enrolled. No baseline information per treatment arm reported, especially no information on time since symptom onset. No section on statistical methods. Different HRs are reported for 7 and 14 days but without information about time-varying treatment effect. Some endpoints are described without showing results, other results are reported without specifying as endpoint. No multiplicity adjustment.	Statistically significant difference found for time until negative PCR-test between ivermectin and placebo arm. No statistically significant difference found for remission of fever or cough. Results must be interpreted with caution due to limitations. Especially due to uncertainty about pre-definition of endpoints, multiple primary endpoints with lack of T1E control and missing information on patient characteristics and disease onset.
Babalola et al. (2021)	62 patients with mild or moderate COVID-19 who were asymptomatic or had mild/moderate symptoms and tested positive by PCR-test; Avg. age of 44.1 years; 69% male	Primary Endpoint: Days until RT-PCR negativity (measured at 5 times post-treatment) Secondary Endpoints: -	Strengths: Randomized, double-blind; most statistical methods described. Limitations: Preprint. Proof of concept study with small groups (21 vs. 21 vs. 20) that is exploratory. It is unclear how blinding was achieved. No information on time since symptom onset reported. "Mild" and "moderate" disease not well described, but 5 patients in 12 mg group received intranasal oxygen and 2 in control group. No real placebo, but comparison versus Kaletra. Relatively young population with few co-morbidities. ANOVA analysis potentially heavily influenced by 1-2 patients from Kaletra arm, unequal variance between groups. No sensitivity analysis. Multiple analyses for primary endpoint and it's unclear if there was any censoring. Primary analysis not well pre-defined (ANOVA, Cox model, Regression analysis, Repeated	Statistically significant difference found for time until negative PCR-test between any ivermectin and Kaletra arm. The results must be interpreted with caution due to the uncertainties around blinding and the pre-definition of the primary analysis.

			measures ANOVA – which is not really suitable for a binary outcome). No multiplicity adjustment.	
Carvallo et al. (2020)	167 patients with rt-PCR confirmed mild to severe COVID-19 infection; Avg. age of 55.7 years; 51.5% male	Primary Endpoints: Progression from mild to moderate/severe disease (yes/no); Mortality by day 30 (yes/no) Secondary Endpoints: Safety outcomes	Strengths: Medium sample size Limitations: Preprint. Uncontrolled single centre study; only referring to contemporary group of patients from own hospital and literature review. Treatment appeared safe; one patient had gastric ulcer (bleeding?) assumed to be associated with dexamethasone. Basic descriptive statistics like standard deviation missing.	This is an uncontrolled trial with a focus on description and a brief comparison against selected data from the literature. For this reason, no sensible conclusions on efficacy can be reached from the data.
Chaccour et al. (2020)	24 patients with PCR confirmed COVID-19; symptomatic; Median age of 26; 50% male	Primary Endpoint: Detectable SARS-CoV-2 RNA by PCR-test at day 7 post-treatment Secondary Endpoints: Viral load at days 4, 7, 14, 21 post-treatment; Proportion of patients with symptoms at 4, 7, 14, 21 days post-treatment; Proportion progressing to severe disease or death; Proportion with seroconversion at day 21 post-treatment; Drug-related adverse events	Strengths: Randomized and double-blind with detailed description. Placebo-controlled. Statistical methods reported. Differentiation between pre-specified and post-hoc analyses. Limitations: Preprint. Very small study, pilot (2x12 patients). Very young population. Logistic regression results not reported as OR. Relevance of primary EP with trial objective. Per protocol analysis planned for primary EP. Only moderate description of secondary EPs. SAP and protocol did not specify outcomes with patient-days.	No statistically significant difference at day 7 post-treatment for PCR positivity (gene N and gene E) between ivermectin and placebo arm was found.
Chachar et al. (2020)	50 patients with PCR-confirmed mild COVID-19 infection; Avg. age of 41.8 years; 62% male	Primary Endpoint: Relief of symptoms by day 7 post-treatment (yes/no) Secondary Endpoints: Safety outcomes	Strengths: Randomized Limitations: Single centre, open label, small groups (2x25). Authors mix up terminology with that of case-control study. Wording indicates lack of proper understanding about statistical testing. Statistical test used not specified and only p-value reported (most likely one-sided p-value from Fisher's exact test).	No statistically significant difference for relief of symptoms by day 7 post-treatment was found between the ivermectin and the comparator arm (only symptomatic treatment).
Chowdhury et al. (2020)	116 patients with PCR-confirmed mild or moderate	Primary endpoints: Negative PCR-test at some point during follow-up of the study;	Strengths: Consort flow diagram and checklist; subset of raw patient data included as supplementary file. Limitations:	No statistically significant difference for time until negative PCR-test between ivermectin + doxycycline

	COVID-19 infection; asymptomatic or symptomatic; no severe comorbidities; Avg. age of 33.9 years	Days until negative PCR-test; Days until symptom relief <u>Secondary Endpoints</u> Safety outcomes	Preprint. No isolated treatment and no real comparator (Ivermectin + Doxycyline vs. HCQ + BID + Azithromycin). Unblinded. Very young population. Description of statistical methods insufficient and not all statistical methods are suitable. No differentiation between primary and secondary endpoints. Binary endpoint of negative PCR-test during study not well defined. Time until negative PCR-test was not handled as time-to-event endpoint and 2 patients without negative test seem to be excluded from this comparison (exclusion is conservative and favours comparator). Predictable randomization by odd/even registration number with high risk for selection bias. Some secondary subgroup analyses; unknown if pre-defined. No adjustment for multiplicity.	and HCQ + BI + Azithromycin comparator was found. The results must be interpreted with caution due to uncertainties about the statistical methods, the unblinded trial design, and the predictable randomization sequence.
Elalfy et al. (2021)	113 patients with PCR-confirmed mild or early moderate COVID-19 infection; asymptomatic or symptomatic; no comorbidities; Avg. age of 37.7; 46% male	<u>Primary Endpoint:</u> Viral clearance at day 7 and day 15 (yes/no) <u>Secondary Endpoints:</u> Side effects	<u>Strengths:</u> Statistics described <u>Limitations:</u> Non-randomised design with self-allocation; no blinding. PP analysis. Primary endpoint not well defined. Relatively young population. Large baseline differences for clinical symptoms between the two groups (in favour of ivermectin). Extreme discrepancies to information on clinicaltrials.gov (e.g. randomization, single-blind, interim analyses, duration of trial, primary endpoint). Very little information on matching method provided (high risk for selection bias of comparator group). Statistics reported not always correct. No adjustment for multiplicity.	Statistically significant difference found at days 7 and 15 post-treatment with regard to the proportion of patients with negative PCR-test between the combined ivermectin and the supportive treatment arm. Due to the trial's limitations, especially with regard to the non-randomised design and baseline difference (high risk for selection bias), no robust conclusions can be drawn on efficacy.
Elgazzar et al. (2020)	400 patients with mild/moderate or severe COVID-19 infection; symptomatic; Avg. age of 57 years; 70% male	<u>Primary Endpoint:</u> Composite endpoint based on improvement or 2 consecutive negative PCR tests described but not reported; Days until PCR-test negativity reported <u>Secondary Endpoints:</u> Prognosis of patients (improvement/progression/ death);	<u>Strengths:</u> Multicentre, randomized, double-blind controlled trial. Large sample size. <u>Limitations:</u> Preprint. Design is unclear, but cannot be randomized between 6 groups, only 1 vs 2, 3 vs. 4, 5 vs. 6 would have been possible. No real comparator (comparison against HCQ). Unclear how blinding was achieved. No patient flow (CONSORT) provided. Patient characteristics not tabulated (only lab values). Baseline comparison of lab values between 6 groups via ANOVA not informative as these are different patient	Statistically significant difference found for time until PCR-test negativity in patients with mild to moderate or severe COVID-19. Despite the large sample size and the large differences reported, no robust conclusions on the efficacy of ivermectin treatment can be drawn from this study due to major uncertainties around the

		Time until recovery and hospital stay; Side effects	populations. Comparison of prognosis and recovery time between groups 1-4 isn't informative either as different patient populations are being compared. Primary endpoint not well described (clinical, laboratory investigations improvement and/or 2 consecutive negative PCR tests taken at least 48 hours apart; as a composite). Other endpoints reported in the results. No details on sample size calculation or assumptions provided. Methods sections mentions some statistical tests without a clear concept, Statistical plan is obscure. No sensitivity analyses reported. No adjustment for multiplicity.	study design, the comparator, and the uncertainties around the pre-definition of the primary endpoint.
Espitia-Hernandez et al. (2020)	35 patients with mild or moderate PCR-confirmed COVID-19 infection; Symptomatic; No severe comorbidities; Avg. age of 45.1 years; 45.7% male	<u>Primary Endpoint:</u> Negative PCR test at day 10 post-treatment (yes/no) <u>Secondary Endpoints:</u> Days post-treatment until symptom relief; Temperature; Ventilatory responsiveness; Side effects.	<u>Strengths:</u> Flow chart shown. <u>Limitations:</u> Non-randomised allocation with no clear description of the selection mechanism. Proof of concept study with very small numbers. Combination therapy of ivermectin + azithromycin + cholecalciferol. Not all statistical results are sufficiently reported (neither effect estimate with confidence interval or p-value). Primary endpoint not well defined (Efficacy of the combination therapy). Only descriptive results reported for the suspected primary endpoint (PCR-test at day 10 post-treatment), however, inferential results reported for secondary endpoints. Results are reported for progression of symptoms in the control group although this is not defined as endpoint and the authors conclude that the combination treatment was effective in reducing clinical progression of COVID-19.	Statistically significant difference found for the secondary endpoint of days until symptom relief. It was reported that on day 10 post-treatment all 28 patients from the combination group tested negative, whereas all patients from the control group tested positive for COVID-19. As the non-randomised allocation mechanism of control and combination arm patients is not well described, there is a large risk for selection bias which prevents drawing conclusions on efficacy from this study.
Gonzales et al. (2021)	106 patients with COVID-19 induced pneumonia and hospitalization criteria; Avg. age of 53 years; 62.2% male	<u>Primary Endpoint:</u> Duration of hospitalization until discharge due to patient improvement <u>Secondary Endpoints:</u> Respiratory deterioration (yes/no); Death (yes/no);	<u>Strengths:</u> Randomized, double-blind. Statistics described. Baseline characteristics well described <u>Limitations:</u> Preprint. Randomisation method not described. Trial is underpowered based on sample-size estimation (47 per arm), however, description of sample size estimation is not clear. Primary endpoint and primary analysis population are not well described (unclear if patients without discharge due to improvement were excluded). Uncommon wording was	No statistically significant differences in primary or secondary endpoints were found between the treatment groups. The descriptive results did not indicate a trend towards better outcomes in the ivermectin treated arm.

		Time until respiratory deterioration or death (time-to-event)	noted (e.g. "abnormal distribution"). Mix-up of average and median was noted. No multiplicity adjustment.	
Hashim et al. (2020)	140 patients with mild-moderate, severe, or critical PCR-confirmed COVID-19 infection; inpatients and outpatients; Avg. age of 48.7 years; 52% male	Primary Endpoint: Time to recovery (if any) Secondary Endpoints: Progression of disease after at least 3 days of therapy (yes/no). All-cause mortality (yes/no).	Strengths: Median post-infection day before start of therapy reported. Results reported by severity of COVID-19 disease. Limitations: Preprint. No proper randomization (recruited at odd/even date, risk for selection bias). It is stated that patients from the combination and the control arm were age- and sex-matched, however, it is unclear how this was achieved by the design. No blinding. Combination therapy of Ivermectin + Doxycycline. Patient characteristics not tabulated. No patient flow (CONSORT) provided. Statistical description insufficient (e.g. incorrect wording, no description of software used, not all statistical tests specified). Time until recovery reported as mean ± SD without specifying strategy for patients that never recovered (e.g. died). Cut-off date for disease progression and mortality not specified. No multiplicity adjustment.	Statistically significant differences reported between combination treatment vs. standard of care for time to recovery. No statistically significant differences found for the progression of disease or mortality although descriptive results favour the combination arm. However, due to the unblinded nature of the study, serious concerns about selection bias, and uncertainties regarding the statistical methods, no robust conclusions can be drawn for efficacy.
Hussain et al. (2021)	86 patients with mild to moderate PCR-confirmed COVID-19 infection; Avg. age of 40.5 years; 85% male	Primary Endpoint: Days until RT-PCR negativity measured at fixed days (unclear if as continuous or time-to-event endpoint) Secondary Endpoints: Side effects	Strengths: Randomized. Flowchart shown. Limitations: Preprint. Open label. PP analysis of 86 from 100 randomized subjects with more patients dropping out in the ivermectin arm. Large proportion of patients were male (85%). Duration of illness prior to admission was not reported (potential imbalance). Qualitative expression on viral load only (+ or -). Statistical methods not described. Only p-values were reported, no effect estimates or confidence intervals.	Statistically significant difference reported for the time until viral clearance between the ivermectin and the control arm. However, due to the uncertainties regarding the definition of the primary endpoint, the statistical test used, the open-label design, and the PP analysis population, no robust conclusions on efficacy can be drawn.
Krolewiecki et al. (2020)	45 patients with mild to moderate PCR-confirmed COVID-19 infection;	Primary Endpoint: Viral load reduction in respiratory secretions at day-5 (continuous) Secondary Endpoints:	Strengths: Assessor blinded randomised design, multicentre. Stratified randomisation (by centre) with variable block length. Incorporation of quantitative viral load determinations and measurements of ivermectin plasma levels. Flowchart shown.	No statistically significant difference found for viral load on day 5 post-treatment between the ivermectin and the control group. Significant difference found in subgroup based on

	Avg. age of 40.9 years; 55.6% male	Clinical evolution at day 7 post-treatment; Correlation between IVM plasma concentrations and viral load (Spearman); Safety outcomes	Limitations: Preprint. Small sample size; pilot; hypothesis generating only. Sample size based on standardized effect size and the consideration that 9% of a full-scale clinical trial is sufficient. No clear analysis plan for primary analysis outlined, lots of tests mentioned. ITT principle not followed, efficacy analysis on 32 instead of 45 patients. It is stated that the trial is listed on clinicaltrials.gov but the trial cannot be found under the number provided. Analyses in subgroups not pre-defined and without multiplicity control.	median plasma concentration of ivermectin. This analysis is post-hoc without T1E control and consequently no robust conclusions can be drawn for efficacy.
Lopez-Medina et al. (2021)	398 patients with mild symptomatic laboratory-confirmed COVID-19; onset of illness within 7 days or less; Median age of 37 years; 42% male	Primary Endpoint: Time to complete resolution of symptoms within 21-day follow-up period (8-category ordinal scale used; time-to-event) Secondary Endpoints: Time until worsening in 2 or more points in the 8-category ordinal scale with 21 days (time-to-event); Adverse events	Strengths: Double-blind randomised controlled trial. Permuted block randomisation. Large sample size. Peer-reviewed publication. Methods well-described including definition of primary and secondary outcomes. Trial protocol provided as supplement. Statistical methods well described including sample size estimation and designating which analyses were post hoc. Informative results (e.g. KM-curves, HRs with confidence intervals) and sensitivity analyses reported. Flowchart shown. Patient adherence checked. Protocol amendment explained and implemented after approval from DSMB. Results reported based on ITT principle. Limitations: Single centre. Relatively young population. Error in medication labelling during first month of the trial which resulted in all patients receiving ivermectin. Patients were replaced following DSMB recommendation but included in a sensitivity analysis.	No statistically significant difference was found between the ivermectin and the placebo arm with regard to the time until complete resolution of symptoms within 21 days. Overall, the trial seems to be well designed with transparent and comprehensive reporting of results.
Mohan et al. (2021)	125 patients with mild or moderate PCR-test confirmed COVID-19; symptomatic or asymptomatic; Avg. age of 35.3 years; 88.8% male	Primary Endpoint: RT-PCR negativity on day 5 after intervention (yes/no); Viral load on day 5 after intervention (continuous) Secondary Endpoints: Qualitative and quantitative results of RT-PCR on day 3 and 7 after intervention; Time to clinical resolution; Clinical worsening (yes/no); Clinical WHO scale status of the subject on day 14;	Strengths: Exploratory randomized double-blind placebo-controlled study with randomisation stratified by disease severity. Statistical methods were well described. Median duration and IQR of symptom onset at time of enrolment reported. Efficacy analysis based on mITT population (excluding patients with negative PCR-test at baseline). Limitations: Late presentation: median duration of symptoms = 5 days (antiviral effect likely highest at start when high titres). Young population (avg. age of 35 years), predominantly male patients (88.8%) and few co-morbidities limits generalisability of results. It is not explained why patients	No statistically significant difference found in the proportion of patients who became PCR negative on day 5 post-treatment between the 24mg ivermectin, the 12mg ivermectin and the placebo arm. There were no statistically significant differences in the viral load on day 5 post-treatment between the three treatment arms.

		Hospital-free days at day 28	were first randomised (ITT) and then tested for COVID-19 using a PCR-test which was an essential inclusion criterion for the primary endpoint (mITT). Unclear if primary endpoint of PCR-test negativity on day 5 post-treatment was pre-specified and results on day 3 and day 7 are less convincing. It is not described how blinding was achieved. Non-commercial formulation. Not all subgroup analyses appear to be pre-specified. No multiplicity adjustment.	
Niaee et al. (2020)	180 patients with mild to severe PCR-test or CT confirmed COVID-19; Avg. age of 56 years; 50% male	Primary Endpoint: Clinical recovery within 45 days of enrolment (no single result reported can unambiguously be attributed to this endpoint) Secondary Endpoints: Radiographic findings; Hospitalization time; Mortality (yes/no); Several clinical parameters	Strengths: Randomised, double-blind, placebo-controlled, multicentre trial. Flowchart shown. Limitations: Preprint. Small numbers per treatment arm (30 each). Categorization as mild, moderate, or severe COVID-19 was not defined in the paper. Results from table 1 indicate that it was mostly based on CT findings. Authors describe that randomisation was stratified by severity of disease, but it is unclear if this was implemented as there are non-substantial baseline differences with regard to disease characteristics between the 6 groups (e.g. 47% vs. 97% PCR positive). Overall, PCR recorded as negative in 29% at baseline. Sample size calculation based on equivalence test, but equivalence margins were unclear and not justified. Analysis not based on ITT principle, term of FAS not used correctly. The different endpoints were not well defined in the paper (especially the primary endpoint). The criteria for discharge were changed over the course of the trial. Some results are reported as aggregated comparison of all ivermectin arms (1, 2, 3, 4) vs. a combined comparator of HCQ and placebo other results are reported as comparison between the 6 groups. Generic statistical methods section with many statistical tests listed. Statistical comparisons and tests used often unclear or seem to have been misunderstood. It is not described how blinding was achieved. No adjustment for multiplicity. No sensitivity analyses.	Statistically significant difference observed between the 6 groups (4 ivermectin, 2 control) with regard to the proportion of patients who died within 45 days post-treatment, the duration of low oxygen saturation and the duration of hospital stay. No statistically significant difference found with regard to the recovery of tachypnoea or fever. Due to the trial's limitations, especially regarding not well-defined endpoints and statistical methods as well as lack of multiplicity control, no robust conclusions regarding efficacy can be drawn.
Okumus et al. (2021)	60 patients who were hospitalized with severe pneumonia and PCR-test	Primary Endpoint: Composite binary endpoint "clinical response/ improvement" after 5-day treatment (extubation in mechanically ventilated	Strengths: Multicentre, randomised, controlled trial; statistical methods described. Limitations:	No statistically significant difference found for composite primary endpoint of clinical improvement at the end of five-day treatment between the

	confirmed severe COVID-19 disease; Avg. age of 62 years; 67% male	patients, respiratory rate < 26, SpO2 level >90%, PaO2/FiO2 > 300 in patients receiving oxygen, presence of at least 2 of the 2-point SOFA reduction criteria); Side effects Secondary Endpoints: "Clinical response/ improvement" after 5-day follow-up period (yes/no); Mortality (yes/no); Change in SOFA score; PCR test negativity at end of FU period (10 days)	Preprint. The trial is described as single-blind, but it is very uncertain whether patients were truly blinded as only the study group was tested for mutations. Also, registration on clinicaltrials.gov specifies the trial as open label. No proper randomization (odd/even recruitment number) with high risk for selection bias. Patients with mutations were excluded post-randomisation only from the study group which distorts comparability between the study groups. Small sample size (30 vs. 30). Patients in the study group were slightly younger than in the control group (mean age of 58 vs. 66 years). Primary and secondary endpoints not well defined. Mortality reported as binary outcome although follow-up time per patient seems to differ (no info about censoring, only overall average FU duration). Information on some outcomes missing (e.g. only p-values for SOFA). Some tables appear incomplete due to preprint format. No adjustment for multiplicity.	ivermectin group and the control group.
Podder et al. (2020)	62 patients with mild to moderate PCR-test confirmed COVID-19 infection; symptomatic; Avg. age of 39 years; 71% male	Primary Endpoint: Total recovery time from the onset of symptoms to complete resolution of symptoms Secondary Endpoints: Recovery time after enrolment to complete resolution of symptoms; Negative RT-PCR test 10 days after the first positive test result (yes/no)	Strengths: Recovery time from onset of symptoms and from enrolment reported. Confidence intervals reported for main outcomes. Limitations: Single-centre, open-label, controlled study. No proper randomization (alternating odd/even registration number) with high risk for selection bias. Relatively young study population. 82 patients randomized, only 62 included in analysis (due to exclusion criteria but unclear when these were defined). Some data was excluded with providing detailed reasons (e.g. "Irrelevant and inconsistent data were discarded" and in Tables 3-4 it is only stated that some parameters were excluded from the analysis). No adjustment for multiplicity.	No statistically significant difference was found for the time from onset of symptoms to complete resolution between the ivermectin arm and standard of care.
Ravikirti et al. (2021)	112 patients with mild to moderate COVID-19 infection; symptomatic; Avg. age of 52.5 years; 72.3% male	Primary Endpoint: RT-PCR negativity on day 6 after intervention (yes/no) Secondary Endpoints: Symptoms on day 6 post-treatment(yes/no); Discharged on day 10 post-treatment; Admission to ICU;	Strengths: Double-blind, placebo controlled with description how blinding was achieved. Reporting follows CONSORT flow chart. Limitations: Preprint. Conclusive repeat PCR could not be obtained in 32% of patients (due to death, discharge, lost sample). PP analysis (patient from placebo group who received ivermectin was excluded from analysis post-randomisation, however, only 3 out of 115 patients were excluded). Sample	No statistically significant difference was found with regard to the proportion of patients with a negative PCR-test on day 6 after intervention between the ivermectin and the placebo arm.

		Need for invasive mechanical ventilation; In-hospital mortality	size calculation based on improvement rate 10 days post-treatment different to the primary endpoint reported and more patients were enrolled than estimated. The text includes some rounding and wording errors (e.g. alpha=0.95 and probably not rate ratio but relative risk). Authors state that they used Fisher's exact test, but p-values reported come from Chi-square test. No multiplicity adjustment.	
Spoorthi et al. (2020)	122 patients with mild to moderate PCR-test confirmed COVID-19; symptomatic; Avg. age of 49.9 years; 54% male	Primary Endpoint: Duration of hospital stay; duration until complete resolution of symptoms Secondary Endpoints: Side effects	Strengths: Statistical methods were described. Limitations: This was an open-label, non-randomised trial and no information was provided on how patients were assigned to treatments (high risk for selection bias). Ivermectin was given in combination with Doxycycline. The primary endpoint was not well-defined, and it is unclear if the endpoints were defined in advance. No multiplicity adjustment.	Statistically significant difference was found with regard to the expected duration of hospitalization and the duration until complete resolution of symptoms between the combination and the placebo arm. Due to the trial's limitations, especially the open-label non-randomised design, no robust conclusions can be drawn with regard to efficacy.

2.1.3. Systematic reviews and Meta-Analyses

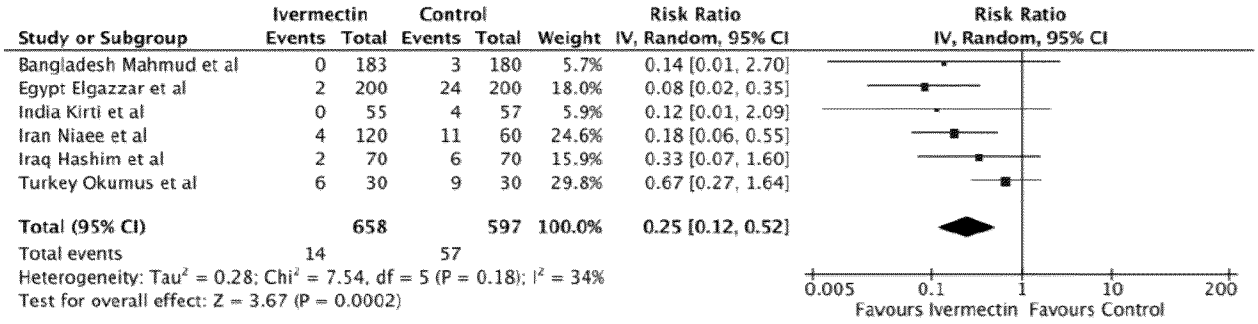
1. Hill A. on behalf of International Ivermectin project Team. Preprint

A systematic search of PUBMED, EMBASE, MedRxiv and trial registries. Meta-analysis excluded prevention studies and non-randomized or case-controlled studies. Review identified and included 18RCTs. Data were combined from 2282 patients into a systematic review and meta-analysis.

Results: Ivermectin was associated with reduced inflammatory markers (C-Reactive Protein, d-dimer and ferritin) and faster viral clearance by PCR. Viral clearance was treatment dose-and duration-dependent. Ivermectin showed significantly shorter duration of hospitalization compared to control. In six RCTs of moderate or severe infection, there was a75% reduction in mortality (Relative Risk=0.25[95%CI0.12-0.52]; p=0.0002);14/650(2.1%) deaths on ivermectin;57/597(9.5%) deaths in controls) with favourable clinical recovery and reduced hospitalization.

Discussion: Many studies that were included were not yet published or peer-reviewed and meta-analyses are prone to confounding issues. Furthermore, there was a wide variation in standards of care across trials, and ivermectin dose and duration of treatment was heterogeneous.

Ivermectin should be validated in larger, appropriately controlled randomized trials before the results are sufficient for review by regulatory authorities



Strengths & Limitations:

The risk-ratio for mortality with ivermectin was 0.25 (95% confidence interval 0.12, 0.52).

MA is limited to RCTs but also includes unpublished trials that are provided as pre-print and have yet to be published in peer-reviewed journals.

There is some heterogeneity present. How is survival defined? Consistent across trials? How are clinical and methodological diversity/heterogeneity addressed?

Inclusion of trials with limited evidence level does not increase credibility of the MA (see strengths and limitations of Elgazzar et al., Niaee et al., Hashim et al., and Okumus et al.).

Outcomes for other endpoints (time to viral clearance, time to clinical recovery, duration of hospitalization) also favoured treatment over controls.

Some studies also included inflammatory markers such as D-dimer and IL-6, with favourable outcomes seen in these endpoints as well.

The paper appropriately cites the limitations of the meta-analysis, which include the incompleteness of the data, that some of the studies were open label, and the difference between studies in dosing regimens and endpoints. Also — critically important — publication bias may play a role.

2. Kim et al. Comparative efficacy and safety of pharmacological interventions for the treatment of COVID-19: A systematic review and network meta-analysis doi: https://doi.org/10.1371/journal.pmed.1003501

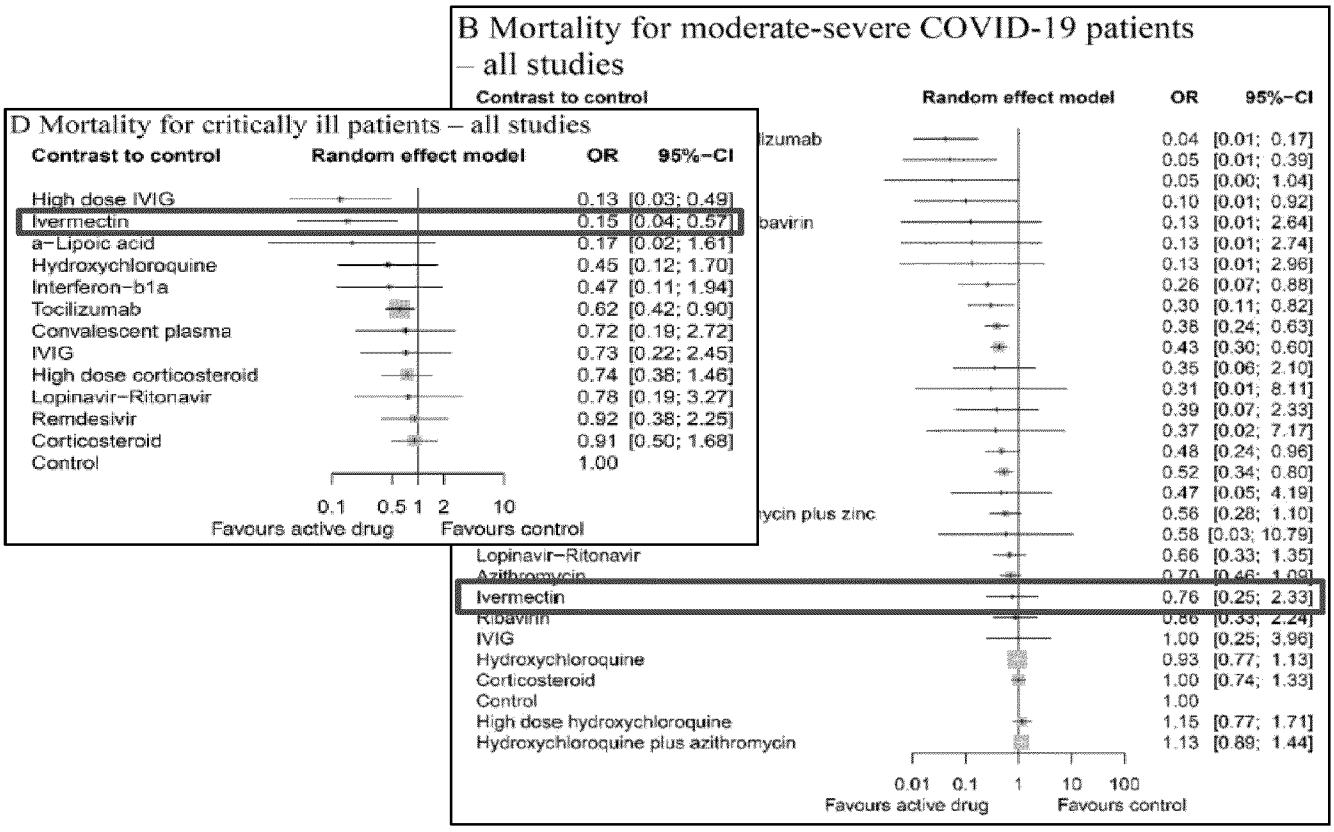
Systematic review and network meta-analysis. Based on 72 published and 38 unpublished studies (40 RCTs and 70 observational studies).

Includes both published and unpublished randomized controlled trials (RCTs) and confounding-adjusted observational studies which met predefined eligibility criteria. MA limited to studies investigating the effect of treatment in patients hospitalized for COVID-19. The outcomes of interest were mortality, progression to severe disease (severe pneumonia, admission to intensive care unit (ICU), and/or mechanical ventilation), viral clearance rate, QT prolongation, fatal cardiac complications, and noncardiac serious adverse events.

Ivermectin (OR 0.15, 95% CI 0.04 to 0.57, p = 0.005) was associated with reduced mortality rate in critically ill patients (ICU setting). Studies contributing to the Ivermectin comparison:

Rajter et al (2020) doi https://doi.org/10.1371/journal.pmed.1003501 - Observational retrospective study – 173 Ivermectin vs. 107 patients on usual Care; outcome: all-cause in-hospital mortality; Patients in the Ivermectin group received at least one oral dose of ivermectin at 200 micrograms/kilogram in addition to usual clinical care; all COVID.

Gorial et al (2020) doi: https://doi.org/10.1101/2020.07.07.20145979 – Pilot clinical trial – 16 Ivermectin+HCQ+ATZ vs. 71 Control (HCQ+ATZ) Patients; primary outcome: percentage cured within 23 days; secondary EP: mortality. Patients received IVM 200 Mcg single dose at the admission day as add on therapy to Iraqi; mild to moderate COVID.



Strengths & Limitations:

MA is based on both published and unpublished (not peer-reviewed) RCTs as well as confounding-adjusted observational studies. MA limited to studies investigating the effect of treatment in patients hospitalized for COVID-19.

MA covers 47 pharmacological agents as potential treatment for COVID-19 with little information per treatment. For this reason, no comprehensive information is provided for ivermectin: the only outcome considered is mortality and it is not well-described which studies contribute to which comparison.

For critically ill patients that were hospitalized in the ICU, a statistically significant favourable prognosis with ivermectin is reported. Looking at the underlying studies, the evidence seems to be based on only 1 observational study by Rajter et al. (2021) which has several limitations as discussed later in the section on observation studies. The level of evidence for this comparison was assessed as very low.

For patients who have not been admitted to the ICU, a non-significant favourable prognosis with ivermectin is reported. Looking at the underlying studies, the evidence seems to be based on the observational study by Rajter et al. (2021) and the preprint pilot trial with a synthetic control group by Gorial et al. (2020). There is some heterogeneity regarding the treatments compared as the study by Gorial et al. compared Ivermectin vs. Ivermectin + HCQ + AZT in all patients whereas only 80%-90% of the patients in the study by Rajter et al. also received HCQ + AZT. The level of evidence for this comparison was assessed as low.

The certainty of the evidence was evaluated using the GRADE framework. Supplementary analyses for heterogeneity and publication bias are provided. Sensitivity analyses are provided in a supplement based on RCT results only.

3. Kalfas et al. The therapeutic potential of IVM for COVID-19: a systematic review of mechanisms and evidence
medRxiv preprint doi: https://doi.org/10.1101/2020.11.30.20236570; posted December 4, 2020

Review of PubMed, medRxiv, ClinicalTrials.gov, Global Coronavirus COVID-19 Clinical Trial Tracker, World Health Organization International Clinical Trials Registry Platform, EU Clinical Trials Register, ANZ clinical trials registry, and references from relevant articles.

Search keywords- "COVID-19 (and synonyms) AND ivermectin"- generated 86 articles on PubMed, 48 on medRvix and 37 on clinicaltrials.gov. Twelve of these were listed as completed studies and of these, **8 were included** as investigators had released results.

Authors conclude that positive mortality benefit, reduced time to clinical recovery, reduced incidence of disease progression and decreased duration of hospital admission were reported in patients across all stages of clinical severity.

They acknowledge that notwithstanding potential, easy availability and cost advantage, *further research in dosing, routes of administration, synergistic therapies and drug interactions will help inform the safest and most efficacious approach*

Strengths & Limitations:

General overview of IVM's pharmacological activity.

Results on 8 studies cited (mix of observational data and high-level results from intervention trials)

Prominence is given on the observational study by Rajter.

Also, combination with doxycycline is discussed with cited "synergistic potential". Reference is made to publication by Hashim in this respect.

Authors discuss prophylactic use, mainly reviewing paper by Beherra.

No in depth analyses are provided.

4. Kory et al. Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19

(Front Line COVID-19 Critical Care Alliance; "FLCCC")

Review of available evidence with recommendation to systematically introduce IVM as therapy / prophylaxis.

Authors state that based on the existing and cumulative body of evidence, use of ivermectin be recommended in both prophylaxis and treatment for COVID-19. Widespread use of this safe, inexpensive intervention would lead to a drastic reduction in transmission rates and the morbidity and mortality in mild, moderate, and even severe disease phases.

Their review concludes that sufficiently clinical data has been compiled to demonstrate the strong signal of therapeutic efficacy. One limitation acknowledged 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.

The FLCCC recommendation is based on the following set of supporting evidence:

1) Since 2012, multiple *in vitro* studies have demonstrated that IVM 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) IVM inhibits SARS-CoV-2 replication and binding to host tissue via several observed and proposed mechanisms (Caly et al., 2020a).

3) IVM 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) IVM 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) IVM 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; and Maia, 2020; Shouman, 2020).

6) IVM 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) IVM 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).

8) IVM reduces mortality in critically ill patients with COVID-19 (Elgazzar et al., 2020; Hashim et al., 2020; Rajter et al., 2020).

9) IVM leads to striking reductions in case-fatality rates in regions with widespread use (Chamie, 2020).

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"

Discussion by authors:

Mild disease

Authors stress that studies including a total of over 3,000 patients with mild outpatient illness have been completed; the set comprised of RCT's and 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 trials' top line results are stated.

Hospitalised 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; Camprubi 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).

Evidence from:

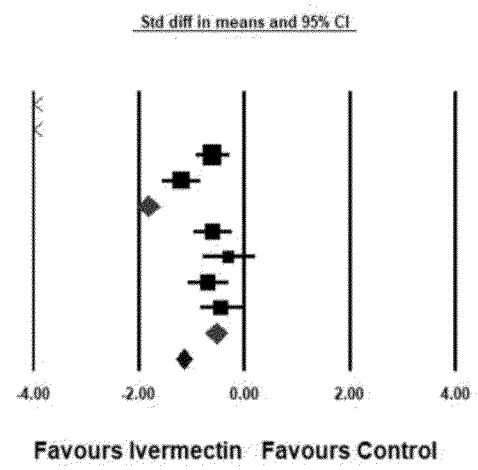
- 5 RCT's with statistically significant impacts in **time to recovery** or hospital length of stay (Elgazzar et al., 2020; Hashim et al., 2020; Mahmud, 2020; Niaee et al., 2020; Spoorthi V, 2020)
- • 1 RCT with a **"near"** statistically significant decrease in time to recovery, p=.07, N=130 (Chowdhury 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)

Meta-analyses of the controlled treatment trials were performed, focused on the two important clinical outcomes: time to clinical recovery and mortality. It is stated that 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.

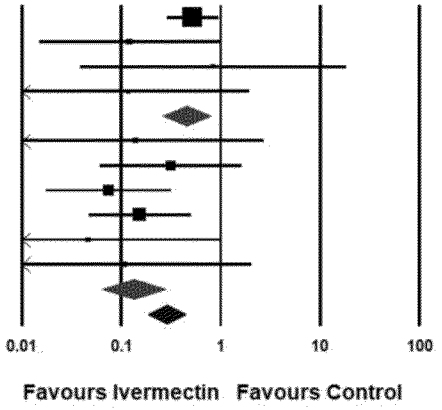
Meta-analysis of the outcome of time to clinical recovery from controlled trials of ivermectin treatment in COVID-19

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		



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

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



Prophylaxis

Data available 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

- 3 RCT's with large statistically significant reductions in transmission rates, N=774 patients (Chala, 2020; Elgazzar et al., 2020; Shouman, 2020)

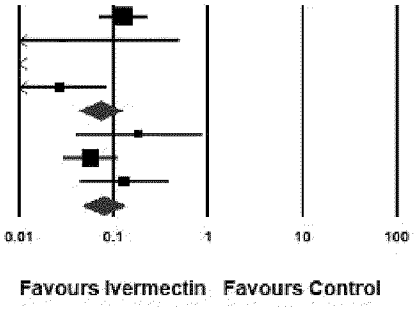
- 5 OCT's with large statistically significant reductions in transmission rates, N=2052 patients

  (Alam et al., 2020; Behera et al., 2020; Bernigaud et al., 2020; Carvallo et al., 2020b; Hellwig and Maia, 2020)

Authors present a **meta-analysis** performed by the study authors of the controlled ivermectin prophylaxis trials in COVID-19.

Meta-analysis *of* ivermectin prophylaxis trials in COVID-19

Group by Type	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Symptomatic Infection / Total Group-Ivermectin	Group-Control
Obs	Behera	0.127	0.089	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		



It is also stated that 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. It is stated that 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 worthwhile for wide implementation.

Ivermectin in post COVID-19 syndrome

Aguirre-Chang et al (Peru) reported on the experience with ivermectin in patients with long-COVID (Aguirre-Chang, 2020). Uncontrolled observations.

Case series of 33 patients who were between 4 and 12 weeks from the onset of symptoms were treated 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.

Safety

A general overview is provided, confirming good tolerance and safety profile. Neurological adverse events such as ataxia, altered consciousness, seizure, or tremor are cited as potential adverse events stated in literature (Chandler, 2018). SAEs are especially noted in Loa Loa endemic region.

Concurrent administration of anti-tuberculosis and cholera vaccines is contra-indicated, while the anticoagulant warfarin would require dose monitoring. Another special caution is that immunosuppressed or organ transplant patients who are on calcineurin inhibitors.

Authors state a longstanding safety profile, with good tolerance in the reviewed trials.

Strengths & Limitations:

This systemic review does not bring new data to light. Most of the source publications are discussed in this EMA review. Authors of FLCCC do not discuss merits and limitations of the various study designs. GRADE framework is not used.

The methodology for the meta-analyses is not provided (e.g. unclear if random or fixed effects model was used; no information about heterogeneity or software used); only a high- level outcome (as a figure) is stated. This does not support the credibility of the reported findings. The overall conclusion of the various meta-analyses is impacted by the low grade of evidence from the contributing trials.

The logic to defend effectiveness based on epidemiological data (association between introduction of IVM and drop of deaths in Peru, Paraguay, and case count decreases in Brazil regions) is without merit.

Based on the data in the systematic review, the conclusions reached by the FLCCC authors cannot be concurred with.

The authors pool data across different disease severities (e.g. mild and severe disease) and across different dosing and treatment regimens (e.g. in addition to antibiotics or without). The potential heterogeneity is not discussed. Limitations of the underlying studies (e.g. insufficient randomisation, unblinded design, methodological flaws) or the risk for publication bias are not discussed by the authors.

5. Castañeda-Sabogal et al. Outcomes of Ivermectin in the treatment of COVID-19: a systematic review and meta-analysis

medRxiv preprint doi: https://doi.org/10.1101/2021.01.26.21250420

Aim: To assess the outcomes of ivermectin in ambulatory and hospitalized patients with COVID-19.

Methods: Five databases and websites for preprints were searched until January 2021 for randomized controlled trials (RCTs) and retrospective cohorts assessing ivermectin versus control in ambulatory and hospitalized participants. The primary outcome was overall mortality. Secondary outcome was recovered patients.

Results: After the selection, twelve studies (five retrospective cohort studies, six randomized clinical trials and one case series), were included. In total, 7412 participants were reported, the mean age was 47.5 (SD 9.5) years, and 4283 (58%) were male. Ivermectin was not associated with reduced mortality (logRR: 0.89, 95% CI 0.09 to 1.70, p = 0.04, I2= 84.7%), or reduced patient recovery (logRR 5.52, 95% CI -24.36 to 35.4, p = 0.51, I2 = 92.6%). All

studies had a high risk of bias and showed a very low certainty of the evidence.

Conclusion: There is insufficient certainty and quality of evidence to recommend the use of ivermectin to prevent or treat ambulatory or hospitalized patients with COVID-19.

Strengths & Limitations:

Strength: methodology well described. Systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Certainty of evidence assessed using the GRADE methodology.

2.1.4. Cumulative review of clinical trials

Overall summary:

- Most of the clinical trials included in this review were rather exploratory than confirmatory with various limitations around the trial design, the conduct, or the analysis. Therefore, it is not possible to draw robust conclusions on the efficacy of ivermectin treatment based on the data available.
- The patient populations included in the clinical trials were heterogenous. Most trials included patients with mild to moderate COVID-19 disease whereas other trials included patients of all stages of disease. Characterisation of disease severity was most often described and sometimes based on official criteria (e.g. by WHO), however, several publications did not report how the disease severity was determined. The age of patients enrolled also varied largely between trials (median age of 26 years to average age of 62 years).
- There treatments compared were heterogeneous in terms of ivermectin dose and timing administered, pharmaceutical form used, and concomitant medications.
- The primary endpoint was often not well-defined, e.g. not well described or listing several primary endpoints or not designating which of the endpoints considered was the primary endpoint. Often it was also uncertain if primary and secondary endpoints were defined in advance. The types of endpoints reported were heterogeneous but the by far most commonly reported primary endpoint was virological (the PCR-test result on a specific day post-treatment, the time until PCR test negativity, or the continuous viral load). Other less frequently considered primary endpoints were progression from mild to moderate/severe disease, improvement of clinical symptoms, and mortality.
- Approximately half of the trials were either non-randomised or used an inappropriate randomisation technique that was very susceptible to selection bias. While approximately half of the trials were blinded, it was rarely described how blinding was achieved and the proportion of trials with successful blinding may therefore be lower.
- Usually it was unclear what statistical analyses were pre-defined and what analyses were done post-hoc and statistical testing was not adjusted for multiplicity. Often statistical methods were not well described, and the results reported were not informative (e.g. reporting only a p-value). In some cases, the results reported were erroneous (e.g. reporting a wrong p-value or describing a wrong statistical test). Compliance with GCP was explicitly mentioned in only two publications.

2.2. Clinical trials in the prophylaxis setting

2.2.1. Clinical trial description

1. **Carvallo et al.** Study of the Efficacy and Safety of Topical Ivermectin + Iota- Carrageenan in the Prophylaxis against COVID-19 in Health Personnel. Doi: https://doi.org/10.31546/2633-8653.1007

Negative CoVID-19 (PCR or rapid test) HCWs were recruited for preventive measures with active combination treatment (IVERCAR) arm (N=131) in addition to their wearing of personal protective

equipment (PPE). A cohort of healthy, Covid-19 negative HCWs using standard PPE alone was used as a comparative arm (N=98), in a prospective, not randomized trial. This group was matched for age, demographics, past medical history, work environment including hours worked and possible exposure to CoVid 19 positive patients within the hospital.

IVERCAR: 0.2mg of ivermectin drops taken by mouth five times per day in association with 1 spray of topical Carrageenan (100 ml, 0.9 g of sodium chloride and 0.17 g of carrageenan) into each nostril and four sprays of topical Carageenan into the oral cavity; total duration: 14 consecutive days.

At day 28, none of those receiving ivermectin prophylaxis group had tested positive for SARS-COV-2 versus 11.2% of patients in the control arm ($p<.001$).

Study was followed up with a larger likewise multicentre, non-randomised intervention, including 1,195 health care workers and revised schedule: Carageenan application was reduced to 4 x a day at the same total dose, and Ivermectin was administered as once per week dose of 12mg (1 month).

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.

Strengths & Limitations:

Multi-center pilot trial; Non-randomised design which was open-label (large risk for selection bias). Combined add-on prophylactic treatment of carrageenan + ivermectin vs. protective equipment only. It is possible that only patients from the treatment group had to have a negative PCR test at enrolment, whereas it is not clear if the required "COVID-19 negativity" for the control group was tested or assumed as long as the patients had no diagnosis of COVID-19.

Outcomes assessed: Appearance of symptoms related to COVID-19; Detection of COVID-19 by PCR, Reported adverse events

Study provides high level overview. No in-depth methodology, no participant flow or detailed results reported for pilot and follow-up study. Authors do not provide critical discussion nor limitations of findings.

2. Elgazzar et al. https://doi.org/10.21203/rs.3.rs-100956/v3 (preprint)

Also see earlier (table /listing): mixed study including therapeutic + prevention arms. 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 PPE, while the control group of 100 contacts wore PPE only.

Statistically significant reduction in contacts testing positive by RT-PCR when treated with ivermectin vs. controls, 2% vs 10%.

Strengths & Limitations:

Multicenter, randomized, double-blind controlled trial.

Preprint. Study design is described as double-blind, but the description of the treatment administration suggests that it cannot have been blinded for prophylaxis (group V receiving prophylactic doses of ivermectin vs. group VI adhering to personal protective measures only without placebo). The recruitment of subjects is obscure, measurements were taken on "health care and household contacts" which might introduce dependencies between the subjects, however, detailed information is missing to better understand the number of healthcare workers and the number of household members being

included. No clear inclusion criteria were reported for the part on prophylaxis. No patient flow (CONSORT) provided.

Patient characteristics not tabulated (only lab values). Baseline comparison of lab values between 6 groups via ANOVA not informative as these are different patient populations (groups I-IV were had COVID-disease and were treated with ivermectin).

No clear primary endpoint was defined for the study part on prophylaxis, however, the only endpoint reported was the number of confirmed subjects with positive PCR-test or a positive PCR-test within their household. No details on sample size calculation or assumptions provided.

2.3. Observational studies description

2.3.1. Overview

Ten observational studies were reviewed which addressed the impact of ivermectin on COVID-19. These were a mix of non-peer reviewed preprints and peer-reviewed manuscripts accepted for publication. The studies predominantly originated from middle-income countries familiar with the use of ivermectin, where it is widely used for its antiparasitic action. Most studies made use of ad hoc data collection with a lack of convincing discussion on data qualify or quality assurance procedures relating to the data/analysis.

Seven studies addressed the use of ivermectin in the treatment setting, mostly with mortality, hospitalisation or time-to-discharge as outcomes. Five of these showed a large treatment effects but had significant flaws beyond those inherent to observational research. One study, which had the most convincing methodology (Soto-Becerra et al, 2020), show no treatment effect on the primary outcome (mortality) and a harmful effect for one of the secondary outcomes.

Three studies addressed the use of ivermectin in the prophylaxis setting. Two cohort studies implied large beneficial treatment effects but had methodological flaws. The other study was ecological: although interesting, it cannot seriously be considered evidence of prophylactic efficacy.

2.3.2. Study description

Cohort studies in treatment setting

1. Khan et al, 2020. Ivermectin Treatment May Improve the Prognosis of Patients With COVID-19

Research letter published in *Arch Bronconeumol.* https://doi.org/10.1016/j.arbres.2020.08.007

Summary

A cohort study from Bangladesh where the authors describe their experience of using of ivermectin to treat 115 hospitalised COVID-19 patients compared with 133 receiving standard care. Consecutive cases were used from April-June 2020 and a variety of outcomes were considered: time to negative SARS-CoV-2 test, disease progression, duration of hospital stay & mortality. Ivermectin was used as a single dose of 12mg. Unadjusted analyses show a range of benefits associated with treatment: improved treatment progression, reduced time to clearance of virus, reduced death. No harmful effects of the treatment were reported.

This study does not provide convincing evidence that ivermectin is an effective treatment for COVID-19.

Strengths

All cases were PCR confirmed.

Treatment well described (12mg within 24 hours of admission – although route not specified)

Weaknesses

As a research letter, methodological details are lacking.

There is no attempt to calculate an effect size.

There are several issues which might account for some or all of the treatment effect observed:

The mechanisms underlying treatment allocation are not clear and are not discussed. Factors like physician discretion, ability to pay, and other treatments given whilst in hospital are either not addressed or are inadequately described: such factors could be important confounders.

It is not clear whether the treated and comparator patients were selected equally across the time periods of the study.

There is no attempt to undertake a multivariate analysis that could adjust for differences in baseline characteristics and (at least in part) adjust for confounding.

The population is much younger than observed elsewhere (median age 35 years with 75% of the cohort were under 43 years). The validity to the European population is therefore questionable, particularly as regards harmful effects.

The severity of symptoms on admission are not well described.

It is not clear how the data used in the analysis were collected or if any quality control procedures were applied.

2. Rajter et al 2021 Use of Ivermectin Is Associated with Lower Mortality in Hospitalized Patients with Coronavirus Disease 2019 The Ivermectin in COVID Nineteen Study

A treatment-focused original Research publication appearing in *Chest*.
https://doi.org/10.1016/j.chest.2020.10.009

Summary

A cohort study from Florida comparing a variety of outcomes in patients hospitalised with COVID-19 (primary outcome: in-hospital mortality; also: extubation rates, length of hospital stay and subgroup analyses in patients with severe pulmonary involvement). The results report on 173 ivermectin exposed and 107 comparator patients. Ivermectin was used as a single dose of 200mcg/kg. The author's present a variety of analyses which showed a large reduction in mortality (e.g. a propensity-score matched OR 0.47, an logistic regression adjusted OR 0.27). The propensity-score matched analysis found an 11.2% reduction in events with NNT 8.9. However, the benefit seems largely to be confined to the minority of patients with severe pulmonary severity. No statistically significance difference was seen for extubation rates (an underpowered analysis) or duration of stay.

Quite apart from the usual caveats relating to such observational studies, this study should be interpreted with caution as there are several areas of uncertainly that could be the source of significant bias.

Strengths

Well-presented and well written manuscript.

Laboratory confirmed entry criteria.

Weaknesses

Time from admission to initiation of therapy is not adequately described. Data on baseline characteristics were collected at different times for exposed and unexposed patients. There could be a source of immortal time. Although the author address this in their discussion, this should have been better addressed in the results.

Patients received a varied of other treatments for COVID: corticosteroids, hydroxychloroquine, azithromycin.

There is no description of the basis on which treatment was allocated (e.g. physician discretion, patient choice, availability of treatment, etc). As a potential source of significant bias, this needs to be better understood in order to assess whether the adjustments for confounding are adequate.

The choice of analysis is unusual (binary logistic regression): a survival analysis considering time-to-event with ivermectin modelled as a time-dependent variable would have been more informative.

The external validity of the propensity score matched analysis is undermined by the including only 98 of 173 ivermectin exposed patients.

As acknowledged by the authors, the non-ivermectin exposed comparator cohort disproportionately came from the first weeks of the study, so there is the risk of a timing bias.

There are some unexpected findings in the multivariate analysis: non-white ethnic groups, the existence of co-morbid pulmonary disease and increasing BMI all associated with better outcomes. Use of corticosteroids was associated with worse outcomes (although it is not clear when they were used).

3. Patel et al, 2020. Ivermectin in COVID-19 Related Critical Illness. WITHDRAWN

A treatment-focused preprint manuscript that originally appeared on the SSRN website. In common with other manuscripts published by MR Mehra, this was subsequently withdrawn following concerns relating to the provenance of the underlying data.

Summary

A withdrawn study in which the use of ivermectin was associated with a large reduction in mortality in COVID-19 patients on mechanical ventilation.

Strengths

None apparent.

Weaknesses

Withdrawn publication.

Discredited source data.

Inadequate description of methods.

4. Lima-Morales, 2021. Effectiveness of a multidrug therapy consisting of ivermectin, azithromycin, montelukast and acetylsalicylic acid to prevent hospitalization and death among ambulatory COVID-19 cases in Tlaxcala, Mexico.

A treatment-focused pre-proof peer-reviewed manuscript accepted for publication the *International Journal of Infectious Diseases*

https://doi.org/10.1016/j.ijid.2021.02.014

Summary

A study from Tlaxcala, Mexico from May to September 2020 which describes the use of ivermectin as part of a multidrug COVID-19 treatment (Ivermectin, Azithromycin, Montelukast and Aspirin). Ambulatory patients (481 exposed, 287 unexposed) were followed up for 14 days during which time improvements with exposure were seen for both hospitalisation (75% reduced risk) and death (81% reduced risk). The ivermectin component of the regimen was a single dose of 12mg. A number of methodological concerns mean this study should be interpreted with caution.

Strengths

Follow-up of laboratory confirmed COVID-19 cases.

Reporting of undesirable effects of treatment, although these could not be attributed to any one of the four medicines used.

Weaknesses

Ivermectin used as part of a four-drug treatment regimen (so hard to attribute any effect to ivermectin along).

The results rely on rather crude analyses of unadjusted odds ratio stratified by broad categories such as "with comorbidities", "health workers". There is no attempt to present adjusted relative risk associate with the therapy, despite there being baseline differences between the exposed and unexposed cohorts which would be expected to bias the results in favour of treatment.

Very limited duration of follow-up (14 days maximum).

The factors influencing treatment allocation are a concern. Patients were excluded from receiving treatment if they had been offered another treatment, had self-medicated for cold and flu symptoms, or were asymptomatic. This is a significant potential source of bias that is not addressed by the study design.

It is not clear when follow-up started in the analysis. There is potential for this this to be different between the treated and comparator cohorts: again, this could be the source of (immortal time) bias which could account for the treatment effect seen. Related to this, nine patients were excluded who died on the day or the day following initiation of treatment started. The rationale for this is not clear; however, it is a potential source of bias and suggests an uneven approach to follow-up.

5. Gorial et al, 2020. Effectiveness of Ivermectin as add-on Therapy in COVID-19 Management (Pilot Trial).

A treatment-focused non-peer-reviewed preprint manuscript available from medRxiv.org

https://doi.org/10.1101/2020.07.07.20145979

Summary

A study from Baghdad, Iraq from April to May 2020 which aimed to assess the effectiveness of ivermectin (IVM) as add-on therapy to hydroxychloroquine (HCQ) and azithromycin (AZT) in treatment of hospitalised adult patients with mild to moderate COVID-19. Ivermectin was used as a single dose of 200mcg/kg. 16 patients were treated with ivermectin in addition to hydroxychloroquine and azithromycin and were compared with 71 match historic "controls" treated with just hydroxychloroquine and azithromycin. The primary outcome was proportion of cured patients within 23 days. The secondary outcome was time from admission to "cure" (free of symptoms with a negative PCR). There was no apparent difference in survival (100% survival vs 97.2% survival in the ivermectin and comparator groups respectively). In a univariate analysis, the mean length of hospital stay was significantly lower in the ivermectin cohort. The small size, short duration of follow-up, lack of

adjustment for baseline difference and use of non-concurrent control means this study should be interpreted with caution.

Strengths

The intervention is clearly described.

Weaknesses

Small sample size.

Short duration of follow-up (23 days).

No adjusted analysis, despite some difference in baseline characteristics.

Use of non-concurrent comparators could bias results with different survival/duration of stays arising from different stages in the epidemic.

6. Soto-Becerra et al, 2020. Real-world effectiveness of hydroxychloroquine, azithromycin, and ivermectin among hospitalized COVID-19 patients: results of a target trial emulation using observational data from a nationwide healthcare system in Peru.

A treatment-focused non-peer-reviewed preprint publication from medRxiv.org

https://doi.org/10.1101/2020.10.06.20208066

Summary

A Peruvian study from April to July 2020 in which with ivermectin – alone and in combination with azithromycin – were two of five treatments in non-severely ill hospitalised COVID-19 patients compared with standard of care alone. The dosages of ivermectin used are not mentioned. Outcomes considered were all-cause death, all-cause death and/or ICU transfer, all-cause deaths and/or oxygen use. 203 patients were treated with ivermectin alone and were found to be at increased risk of all-cause deaths and/or ICU transfer. No significant effect was found for other outcomes. Not significant effects were found for 358 patients receiving ivermectin with azithromycin. This would seem to be a well-conducted and appropriately analysed study.

Strengths

A retrospective cohort emulating a target trial, using nationwide data of hospital data from the Peruvian Social Health Insurance.

An inverse probability of treatment weighting analyses was used with propensity scores estimated using machine learning boosting models and weighted hazard ratios calculated using Cox regression

Large study size (5683 patients in total)

Weaknesses

Follow-up started on the data of admission but ascertain of exposure was made in the first 48 hours of admission. This implies the risk of immortal time bias (although no such effect is implied in the results). The authors addressed this by randomly assigning patients who suffered events between 24 and 48 hours to the control and treatment groups. This seems a strange approach and it is not quite clear why forcing misclassification was preferred to other approaches, for example by modelling treatment as a time-dependent variable or by following patients up from 48 hours post admission.

The details of the exposure are not well described with no mention of dosing used.

Descriptive study in treatment setting

7. Camprubí et al, 2020. Lack of efficacy of standard doses of ivermectin in severe COVID-19 patients

A treatment-focused peer-reviewed publication appearing in PLOS ONE.
https://doi.org/10.1371/journal.pone.0242184

Summary

A retrospective study comparing a case-series of 13 hospitalised COVID-19 patients treated with ivermectin with selected comparators, all occurring in Barcelona during March 2020. Ivermectin exposed patients (a single dose of 200mcg/kg) all originated from countries where *Strongyloides stercoralis* in endemic and were receiving immunosuppressive drugs (corticosteroids and/or tocilizumab). The rationale for using ivermectin was in line with consensus guidelines on the pre-emptive use of ivermectin to treat patients at risk of *Strongyloides stercoralis*, including those from endemic areas. It was not intended as a treatment for COVID.

Strengths

The case series is well described.

Weaknesses

All patient received concomitant treatments for COVID-19, so it is hard to know which medicines might be having an effect.

The small sample size means all statistical comparison tends towards non-significance.

There is no attempt to provide an effect size. Similarly, there is no attempt to adjust for confounding.

Not all COVID-19 cases were PCR confirmed.

The sample size was inadequate for testing the authors stated hypothesis that standard doses of ivermectin were not an effective treatment for patients with SARS-CoV-2 pneumonia.

Cohort studies in prophylaxis setting

8. Beherra et al, 2020 Prophylactic role of ivermectin in SARS-CoV-2 infection among healthcare workers

A prophylaxis-focused non-peer-reviewed preprint publication from ResearchSquare.
https://doi.org/10.21203/rs.3.rs-208785/v1

Summary

This prospective study described the use of ivermectin as a prophylaxis in healthcare workers at a hospital in the Indian state of Odisha. Ivermectin was offered to all staff at the hospital based on a local policy advocating its use as prophylaxis when taken as two oral doses at 300µg/kg at a gap of 72 hours. The author reported a large effect size suggesting a protective effect of patients, but only where subjects took both doses of ivermectin.

For the reasons listed below, this study should be interpreted cautiously. The authors finding – that ivermectin given as chemoprophylaxis reduces the risk of COVID-19 infection – is not supported by the results.

Strengths

A large study (2,199 exposed, 1,333 unexposed) with a low loss to follow-up.

The intervention is clearly described (15-24mg depending on bodyweight).

Case of COVID during follow-up were PCR confirmed.

The is a brief description of adverse effects associated with treatment.

Weaknesses

A healthy worker effect means the external validity questionable, particularly as regards side effects.

Patients self-selected whether or not they took ivermectin. Such a decision would have likely been influenced by the individuals perceived risk, which in turn would likely influence other behaviours patterns that might increase the risk of COVID infection.

There is a lack of methodological detail regarding the statistical analysis. In particular, it is not clear when follow-up started for the non-exposed comparator cohort and there are scant details of the multivariate model used to develop the "adjusted relative risk". There is risk of immortal time bias.

The large protective effect was found only in patients receiving two doses. Patients receiving one dose received no benefit. In the analysis, the single dose patients were added to the unexposed comparator cohort: it would have been mode appropriate to include then in the treated cohort (akin to an intention to treat analysis).

9. Alam et al, 2020. Ivermectin as Pre-exposure Prophylaxis for COVID-19 among Healthcare Providers in a Selected Tertiary Hospital in Dhaka An Observational Study.

A prophylaxis-focused peer-reviewed publication from the *European Journal of Medical and Health Sciences*

http://dx.doi.org/10.24018/ejmed.2020.2.6.599

Summary

An observational study at the Bangladesh Medical College Hospital from May 2020 to August 2020. 58 healthcare workers were received a prophylactic dose of ivermectin 12mg every 4 week for 4 months. These were compared against 60 unexposed comparators. 93.1% of the exposed cohort remained healthy, compared to just 27.6% of the comparator cohort. There are a number of methodological weaknesses that require this study to be interpreted extremely cautiously.

Strengths

The intervention is well described.

Weaknesses

The basis for the allocation of the prophylaxis between the cohorts is not explained or described. As a potential source of significant bias, it needs to be understood whether this was physician discretion, patient choice, relate to availability of treatment or some other means.

There is imbalance in the baseline demographic characteristics: although not statistically significant, these have to potential to bias the analysis.

There is no calculation of an effect size.

There is no attempt to adjust for confounding.

The population consisted of relatively young, healthy workers, so the external validity is poor.

The authors refer to "Ivermectin's astounding impact on preventing transmission and contraction of COVID-19 in the most vulnerable setting of a hospital among healthcare workers". This seems to be overstated.

Ecological study in prophylaxis setting

10. Hellwig & Maia, 2021. A COVID-19 prophylaxis? Lower incidence associated with prophylactic administration of ivermectin.

A prophylaxis-focused peer-reviewed publication appearing in the *International Journal of Antimicrobial Agents*. https://doi.org/10.1016/j.ijantimicag.2020.106248

Summary

As ecological study comparing COVID-19 rates between countries where ivermectin is routinely included in mass drug administration campaigns and those where it is not. Ivermectin was reported as typically being used at a dose of 150-200mcg/kg. The authors found that counties which have routine mass drug administration of prophylactic chemotherapy including ivermectin have a significantly lower incidence of COVID-19. They infer that that this can be attributed to a chemoprophylactic effect.

Although interesting, the study design is particularly prone to bias and does not provide convincing evidence that ivermectin is effective prophylaxis again infection with COVID-19.

Strengths

Interesting background reading into the widespread use of ivermectin as prophylaxis against filariasis in mass drug administration campaigns in low-income countries.

Weaknesses

As an ecological study, there are several alternative explanations which could account for the effect seen. The observed effect was predominantly driven by findings from African countries. It is notable that the countries with ivermectin included as a part of routine mass drug administration were lower-income countries where COVID-19 testing rates have been much lower. This likely accounts for some – if not all – of the effect seen.

3. Non-clinical studies

- **Ivermectin in vivo studies:**

1. Arévalo *et al.*, 2020
Ivermectin reduces coronavirus infection in vivo: a mouse experimental model
Doi: https://doi.org/10.1101/2020.11.02.363242

Objective of the study:
Test ivermectin in a mouse model of a type 2 family RNA coronavirus (similar to SARS-CoV2) the mouse hepatitis virus (MHV).

BALB/cJ female mice (6-8 weeks old) were distributed in three groups: infected with 6,000 plaque forming unit (PFU) of MHV-A59 and treated with PBS (n=20); infected with MHV-A59 and immediately treated s.c. with a single dose of 500 µg/kg ivermectin (n=20); control group not infected and treated with PBS (n=16). Animals' general health and hepatic viral load and functionality was evaluated 5 days after infection/treatment.

Results:

Viral infection induces the typical MHV disease, with severe hepatocellular necrosis and lymphoplasmacytic inflammatory infiltration associated with a high hepatic viral load. Mice treated with ivermectin showed a significantly lower hepatic viral load and a better general health status when compared with infected animals without ivermectin treatment. Particularly, ivermectin treated mice gained weight during the experimental period, presented lower incidence of hepatocellular lesions, while having heavier liver and spleen compared with the control group.

While most biochemical outcomes suggested liver damage in infected animals, serum transaminases levels were significantly lower in ivermectin treated mice. Furthermore, similar hematological profile was observed in both infected groups, regardless of ivermectin treatment. As treatment with ivermectin did not exert a significant effect in the modulation of most of the inflammatory cytokines, the authors suggest the used *in vivo* mouse model of MHV infection does not support a modulatory action of ivermectin on the immune response.

Conclusion:
Ivermectin administration seems to reduce MHV liver viral load in infected mice, enhancing general health status. The authors propose this mouse model for *in vivo* evaluation of therapies against coronavirus diseases, particularly SARS-CoV2.

2. Chaccour et al. 2020. Nebulized ivermectin for COVID-19 and other respiratory diseases, a proof of concept, dose-ranging study in rats'

DOI: 10.21203/rs.3.rs-64501/v1

Objective:

Ivermectin (IVM) is a widely used antiparasitic drug with known efficacy against several single-strain RNA viruses. Previous data (Cali et al.) showed a significant reduction of SARS-CoV-2 replication after incubating Vero cells, a cell line derived from African Green Monkey kidney epithelial cells, for 48 h with ivermectin concentrations not readily attainable in patients

Another proposed mechanism for IVM in covid19 is the increase of the airway epithelial cell expression of the angiotensin-converting enzyme II (ACE-2) viral entry receptor mediated by activation of nicotinic acetylcholine receptors (nAChR), primarily the α7 subtype. This would help explain the additional susceptibility of smokers to Covid-19. Inhibition of a7-nAChR may suppress this process, thereby reducing within-host infectivity and transmission. Krause et al. found a comparatively low a7-nAChR IC50 for ivermectin of 0.156 μM, a concentration realistically attainable even on oral drug dosing. Inhaled therapy could be used to instantaneously reach and maintain effective concentrations in lung tissue.

The authors report of a pilot rat-model evaluating the feasibility of therapeutic delivery of nebulized ivermectin to rats by using an ethanol-based formulation due to water insolubility of the compound. The main objectives were to assess the ivermectin pharmacokinetics in plasma and lung tissue as well as safety of this formulation through a comprehensive toxicology profile.

Results

The highest observed plasma concentration was 186.7 ng/mL which corresponds to 0.21 μM/L and is clearly below the IC_{50} 2 μM reported by Caly et al. Concentrations are, however, above the nicotinergic acetylcholine receptor (nAChR) IC_{50} for ivermectin as estimated by Krause et al. Lung tissue concentrations in male rats in the high-dose arm were well above this concentration after 72–168 h.

Conclusions:

By exploring this new route of administration and formulation, the authors demonstrated that IVM administered in rats attains concentrations which are higher than the nicotinergic acetylcholine receptor (nAChR) IC_{50} and that ivermectin lung delivery with nebulized formulations can maintain detectable concentrations for 7 days. However, the delivery method investigated here is not directly translatable to human clinical trials. Furthermore, Safety has to be demonstrated not only for ivermectin but also the ethanol vehicle.

This proof-of-concept study should be considered as a pilot given the reduced number of animals used and also taking into account other study design limitations. Additionally, the formulation was administered by nose and mouth exposure, hence, the lung levels achieved may not reflect those potentially achieved in a human with active inhalation.

3. De Melo et al. 2020 *Anti-COVID-19 efficacy of ivermectin in the golden hamster.*
DOI: https://doi.org/10.1101/2020.11.21.392639

Objective of the study:

The aim of this study was to investigate the effects of Ivermectine (IVM) alone on SARS-CoV-2 infection using the golden Syrian hamster as a model for COVID-19. Male and female adult golden Syrian hamsters were intranasally inoculated with $6x10^4$ PFU of SARS-CoV-2. This inoculum size was selected as it invariably causes symptomatic infection in golden Syrian hamster, with a high incidence of anosmia and high viral loads in the upper and lower respiratory tracts within four days post-infection. At the time of infection, animals received a single subcutaneous injection of IVM at the anti-parasitic 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.

A panel of selected cytokines (Il-6, Il-10, Il-b, Tnf-a and Ifn-g) and chemokines (Cxcl10 and Ccl5), already known to be affected in COVID-19 disease progression in humans and animal models, were used to assess the impact of IVM treatment on the immune response of SARS-CoV-2 infected hamsters. Two airway compartments: nasal turbinates and lungs were evaluated.

Results:

IVM-treated and infected animals exhibited a significant reduction in the severity of clinical signs and remarkably, IVM treatment reduced the olfactory deficit in infected animals: 66.7% (12/18) of the saline-treated hamsters presented with hyposmia/anosmia, whereas only 17 22.2% (4/18) of IVM-treated hamsters presented signs of olfactory dysfunction (Fisher's exact test p=0.018). 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.

Marked differences between sex groups in the nasal turbinates were observed. Female hamsters manifested a down-regulation of some mediators, such as the IL-6 and IL-10, tumor necrosis factor (Tnf-α), and the C-X-C motif chemokine ligand 10 (CXCL10). Meanwhile, males presented an increase in two pro-inflammatory mediators, interferon-gamma (IFNg) and chemokine ligand 5 (Ccl5).

In the lungs, however, the significant overexpression of Il-10 was a common feature of IVM treated males and females. This effect may be related to a modulation of the inflammatory response in the lung (down-regulation of Tnf-a and Cxcl10 in males, and of IL-6 in females) associated with the reduced clinical signs. Additionally, the Il-6/Il-10 ratio in the lung of IVM-treated hamsters was significantly lower than in non-treated animals.

The viral RNA load in the respiratory tract remained unaffected by IVM treatment in both nasal turbinates and lung samples. These were tested using both classical RT-qPCR and the highly sensitive technique of digital droplet PCR. Furthermore, IVM treatment did not influence the viral replication rate, as evaluated by the ratio between structural and non-structural gene transcription. Finally, IVM treatment did not

alter infectious viral titers in the lungs. These results differ from a previous report suggesting that IVM, albeit used at far higher concentrations, inhibits the replication of SARS-CoV-2 in vitro. Therefore, the action of IVM on COVID-19 signs in the golden hamster model does not result from its antiviral activity.

Conclusions:

IVM administered in SARS-cov2 infected hamsters reduce the severity of clinical signs and remarkably, IVM treatment reduced the olfactory deficit in infected animals. The compound seems to also have some immunomodulatory effect compatible with what had been seen in covid19 patients. The viral RNA load in the respiratory tract remained unaffected by IVM treatment in both nasal turbinates and lung samples. Furthermore, IVM treatment did not influence the viral replication rate and did not alter infectious viral titers in the lungs. These results differ from a previous report suggesting that IVM, albeit used at far higher concentrations, inhibits the replication of SARS-CoV-2 in vitro. Therefore, the action of IVM on COVID-19 signs in the golden hamster model does not result from its antiviral activity.

4. Errecalde et. al. 2021. Safety and Pharmacokinetic Assessments of a Novel Ivermectin Nasal Spray Formulation in a Pig Model

Doi: 10.1016/j.xphs.2021.01.017

Objective:

The objective for this study was to investigate the safety and pharmacokinetics of a novel Ivermectin spray formulation for intranasal administration in piglets. Based on in vitro data there are some evidence that ivermectin inhibits the replication of SARS-CoV-2 in the range of 2.5 - 5 microM, which is considerably higher than can be achieved using currently approved dosing regimens. Therefore, it is desirable to explore dosing regimens that could achieve high concentrations in tissues where the entry and initial transmission of SARS-CoV-2 occurs.

The Ivermectin concentration profiles were measured in plasma, nasopharyngeal and lung tissues after the intranasal treatment (one or two applications 12 h apart) and was also compared to exposure after oral tablet administration with a dose level approved for human use.

Study groups

Group 1. One dose 2 mg, 1 puff/nostril of N-IVM-spray (0.1 mL of 1 mg in each nostril),

Group 2 Two 2 mg each, 1 puff/nostril doses of N-IVM-spray 12 h apart,

Group 3 Oral tablets (0.2 mg/kg) animal BW ca. 10 kg

Results

The authors claim that this is the first time the overall assessment of an Ivermectin spray formulation in a pig model, measuring the Ivermectin concentrations attained in the nasopharyngeal anatomical area, is described.

Safety

Overall it was well tolerated and no macroscopic changes in tissues of application and no histopathologic changes. A mild to moderate inflammation in tonsils were observed. No blood chemistry alterations were observed. Comment; note that this study was only a single or two doses given.

Exposure

Group 1. Highest concentration was found in nasopharyngeal tissue and lowest in systemic exposure.

Group 2. An accumulation in the expected range was achieved with a 2nd dose after 12h in tissues and plasma, approx. a doubling in the timepoints compared 6 and 24 h (not optimal timepoint for all samples)

Group 3. At 6 h 8.6 ng/mL and higher than after nasal administration.

Conclusions
After single (or repeated after 12 h) nasal administration high levels in nasopharyngeal tissue and low systemic exposure was shown. It was also shown to be safe and absence of neurotoxicity, which should be noted as nasal administration has the potential to reach CNS via olfactory organ.

Comment: note that the first sampling point was as 2 h, which may be a bit late for capturing the Cmax in nasopharyngeal tissue. Although it is agreed that nasal administration may be an advantageous route for this indication the EMA reviewer do not fully understand what the novelty of the formulation is, several nasal administration studies are ongoing in clinical trials. Even if high concentrations are attained in nasopharyngeal tissue it is unclear if target attainment is sufficient.

5. Formiga et al. 2021 Ivermectin: an award-winning drug with expected antiviral activity against COVID-19

doi: 10.1016/j.jconrel.2020.10.009

Objective:

An increasing body of evidence points to the potential of the antiparasitic medicine ivermectin as an antiviral and anti-inflammatory agent.

Results
There is some in vitro data on antiviral activity of ivermectin against SARS-CoV-2, but at high drug concentrations (35-fold higher than the one approved by the FDA for treatment of parasitic diseases) which raises concerns about its efficacy in humans using the FDA approved dose in clinical trials . The inhibition of importin α/β1-mediated nuclear import of viral proteins is suggested as the probable mechanism underlying its antiviral activity.

With regard to its anti-inflammatory properties, ivermectin has been shown to mitigate skin inflammation. Ivermectin has been shown to diminish the recruitment of immune cells and cytokine production, TNF-alpha, IL-1ss and IL-6 in vivo and in vitro.

With regard to investigations into potential drug treatments against COVID-19, ivermectin has received particular attention. A number of clinical studies have been conducted in various countries.

Conclusions
Despite its promising antiviral and preliminary anti-inflammatory potential, the development of ivermectin formulations presents challenges, primarily due to its property of poor water solubility. Although patients could be treated using systemic therapy, high-dose antiviral therapy could lead to severe adverse effects.

Considering that the respiratory tract has been shown to be a primary site of infection, the delivery of ivermectin by pulmonary route would provide high drug deposition in the airways and lungs to mitigate the high viral loads seen in these sites. Novel delivery strategies are needed to optimize ivermectin bioavailability at its target sites for COVID-19, e.g. micro- and nanotechnology-based systems for the pulmonary delivery.

6. Lehrer et al. 2020. Ivermectin Docks to the SARS-CoV-2 Spike Receptor-binding Domain Attached to ACE2
Doi: 10.21873/invivo.12134

Objective of the study
An increased number of evidence suggest that SARS-CoV-2 viral spike protein binds to the membrane angiotensin-converting enzyme 2 (ACE2) to infect the host cell. Thus, a docking study was carried out to determine if ivermectin might be able to attach to the SARS-CoV-2 spike receptor-binding domain bound with ACE2 receptor.

AutoDock Vina Extended program was used to perform the docking study. The data about the drug and the molecules originated from PubChem CID and Protein Data Bank.

Main results

- Only one docking position out of ten was considered highly valid and accurate having a root-mean-square deviations of atomic positions (RSMD) equal to 0.
- Ivermectin 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.
- The binding energy of ivermectin to the spike-ACE2 complex was –18 kcal/mol and binding constant was 5.8×10–8.

Conclusions
The ivermectin docking site that was identified, between the viral spike and the ACE2 receptor, may interfere with the attachment of the spike to the human cell membrane. This observation is consistent with other studies, but clinical trials are needed to determine whether ivermectin is an effective treatment for SARS-Cov2 infection.

7. Mittal et al. 2021. Inhaled route and anti-inflammatory action of ivermectin: Do they hold promise in fighting against COVID-19?
Doi: 10.1016/j.mehy.2020.110364

Objective of the study
The authors performed a literature review to test two hypotheses related to the use and therapeutic role of ivermectin against COVID-19.

Hypothesis 1: Potential therapeutic role of inhaled ivermectin in covid-19

Background to hypothesis
Notwithstanding the fact that favourable findings support the inhibitory role of ivermectin on replication of SARS-COV-2, it is imperative to carefully consider the fundamental pharmacological principles for the possible repurposing in COVID-19.
One of the key pharmacological factors is the dose required to achieve the desirable IC50 levels in vivo. Studies show that there is negligible prospect of achieving inhibitory activity of ivermectin following oral administration despite excessive or repeated dosing.

As SARS-CoV-2 is a respiratory virus, the authors are questioning weather the inhalational route of administration of ivermectin could be more efficient order to achieve desired IC50.

Evaluation of hypothesis
Several animal studies (calves, goats, mice) suggest a possibility of sufficient accumulation of ivermectin in lung tissues at conventional doses. Moreover, another study utilizing a modelling approach predicted lung accumulation of ivermectin over 10 times higher than EC50.
There is no data on the lung tissue disposition of ivermectin in humans.

Conclusion
The authors propose to test inhaled formulation of ivermectin for potential efficacy in COVID-19. However, it is essential to test the its suitability as inhalational agent and its safety and tolerability in animals before human exposure.

Hypothesis 2: Ivermectin as anti-inflammatory agent in COVID pneumonia

Background to hypothesis
Based on the findings of a retrospective cohort study, patients having severe pulmonary disease and who were treated with Ivermectin, reported significantly higher survival benefit.
As inflammatory changes in the lungs are major hallmark of pulmonary diseases, the authors hypothesised that ivermectin may have an additional anti-inflammatory role in the setting of COVID pneumonia.

Evaluation of hypothesis
Ivermectin has demonstrated anti-inflammatory activity in few *in vitro* and animal models. The mechanism for anti-inflammatory action were explained, but it is still unknown whether such a mechanism effectively gets translated in-vivo. The anti-inflammatory dose was calculated as 18 mg (IVIVE) and 36 mg.

Conclusion
Ivermectin can be presumed to exert anti-inflammatory action in SARS-CoV-2 associated respiratory illness. However, it demands further extrapolation in preclinical animal models and clinical studies as well as additional dose finding and drug interaction studies.

➢ Ivermectin in vitro studies:

8. Caly *et al.*, 2020. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in Vitro

Doi: https://doi.org/10.1016/j.antiviral.2020.104787

Objective of the study:
Test *in vitro* the antiviral activity of ivermectin towards SARS-CoV-2.

Vero-hSLAM cells were infected with SARS-CoV-2 clinical isolate Australia/VIC01/2020 (MOI= 0.1) for 2 hours, followed by a single addition of vehicle (DMSO) or ivermectin incubated for 0–3 days.

Results:
Ivermectin treatment (5 μM) resulted in the reduction of viral RNA present in the supernatant (indicative of released virions) and cell-associated viral RNA (indicative of unreleased and unpackaged virions). Effective loss of viral RNA (99.98% reduction) occurred 48 hours after treatment.

The IC50 of ivermectin was determined to be ~2 μM and no toxicity was observed at any of the timepoints tested.

Conclusion:
Authors state that ivermectin has antiviral action against the SARS-CoV-2 *in vitro*, with a single dose able to control viral replication within 24–48 h.

Summary for the Non-clinical studies:

- Ivermectin has antiviral action against the SARS-CoV-2 *in vitro*, with a single dose able to control viral replication within 24–48 h.
- IVM administered in vivo to SARS-cov2 infected hamsters reduce the severity of clinical signs including olfactory deficit in infected animals.
- In contrast with what seen in vitro, the viral RNA load in the respiratory tract remained unaffected by IVM treatment in both nasal turbinates and lung samples. IVM treatment did not influence the viral replication rate and did not alter infectious viral titers in the lungs → the action of IVM on COVID-19 signs in the golden hamster model does not result from its antiviral activity.
- Preliminary studies where IVM is administered by inhalation show low systemic exposure and absence of (neuro)toxicity. However, even if high concentrations are attained in nasopharyngeal tissue it is unlikely that in vitro target concentration could be reached.
- Novel delivery strategies are needed to optimize ivermectin bioavailability at its target sites for COVID-19.

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- Novel delivery strategies are needed to optimize ivermectin bioavailability at its target sites for COVID-19.

4. Clinical pharmacology

1. Bray, M, et al. Ivermectin and COVID-19: A report in Antiviral Research, widespread interest, an FDA warning, two letters to the editor and the authors' responses. Antiviral Research 178; 2020: 104805. https://doi.org/10.1016/j.antiviral.2020.104805.

This is an Editorial piece summarising reaction to a paper from April 2020 where Caly et al. reported in vitro activity of ivermectin against SARS-CoV-2 following a single addition to Vero-hSLAM cells, and suggested that these data "demonstrate that ivermectin is worthy of further consideration as a possible SARS-CoV-2 antiviral (Caly et al., 2020 see Introduction above). This paper stimulated interest in repurposing ivermectin.

A. One Letter to the Editor came from a company that a is major platform developer for PBPK modelling and simulation. These are the key points:

- Ivermectin is extensively used for 5 tropical diseases at single oral doses of 150–200 μg/kg, resulting in the mean peak plasma concentrations of approximately 30–47 ng/mL.
- Certara applied a PBPK model of ivermectin using the Simcyp platform to explore the plasma and lung concentrations relative to the IC50 values against SARS-CoV-2 determined in vitro.
- Even with most generous assumptions for clinical translation, the in vitro IC50 is>9-fold and >21-fold higher than the day 3 plasma and lung tissue simulated Cmax respectively, following a high dose ivermectin regimen of 600 μg/kg dose daily for 3 days. (Smit et al., 2019 (*this was a PK/PD study of a high-dose over 3 days of ivermectin with dihydroartemisinin-piperaquine on mosquitocidal activity and QT-prolongation*))
- This dose scenario, which ignores consistent exposure, exceeds the highest regulatory approved dose of ivermectin, being a 200 μg/kg single dose for the treatment of Strongyloidiasis.

B. A second Letter to the Editor showed the *in vitro* activity for Caly et al. occurred at much higher concentrations (IC50≈2–3 μM) than the very low (nanomolar) concentrations effective against nematode species obtained after a usual dose of 200 μg/kg. This micromolar concentration is also higher than the therapeutic peak plasma concentration (about 40 nM) measured in humans treated for onchocerciasis control with a standard dose of 150 μg/kg and even after a high daily dose (600 μg/kg) where Cmax of 105–119 ng/ml (0.12–0.14 μM) has been obtained by PK/PD modeling (Smit et al., 2019).

C. The Caly et al authors responded acknowledging the concerns expressed in the letters to the Editor and although they point out that ivermectin's mechanism of action targets a host protein important in intracellular transport, and hence with potential to reduce viral load, they urge great caution in approaching its use for COVID-19.

In summary blood levels of ivermectin achieved during standard therapy are much (many-fold) lower than the concentrations reported as inhibitory for SARS-CoV-2 in cell culture (Caly et al., 2020) and if high concentrations of ivermectin could be achieved, this would likely be toxic.

2. Jermain, B., et al. Development of a Minimal Physiologically Based Pharmacokinetic Model to Simulate Lung Exposure in Humans Following Oral Administration of Ivermectin for COVID-19 Drug Repurposing. Journal of Pharmaceutical Sciences 109; 2020: 3574 – 3578. https://doi.org/10.1016/j.xphs.2020.08.024

Plasma and lung ivermectin concentrations vs. time profiles in cattle were used to determine the apparent plasma to lung tissue partition coefficient of ivermectin. This coefficient, together with a

simulated geometric mean plasma profile of ivermectin from a published PopPK model, was utilized to develop a minimal PBPK (mPBPK) model. The mPBPK model was also used to simulate human lung exposure to ivermectin after the typical single dose administered to humans (12 mg) and supratherapeutic oral doses, 30, and 120 mg. The simulated ivermectin lung exposures reached a maximum concentration of 772 ng/mL, far less than the estimated 1750 ng/mL IC50 reported for ivermectin against SARSCoV-2 in vitro.

In summary, while the authors suggest a potential mechanism of action by making the host cell environment unfavourable for SARS-CoV-2 assembly and replication after importin a/b1 heterodimer dissociation and inhibition, however, again the exposures are far less than what was needed for the documented in vitro activity. The point is made in the paper that their results and conclusions are in agreement with previous analysis regarding iveremctin's potential as a COVID-19 therapeutic agent in the Bray et al paper reviewed above and another paper 2020 (i.e. Schmith et al see Introduction above).

In summary from a Clinical Pharmacology perspective although there appears to be plausibility around potential mechanisms of action, the oral doses in human that are likely to be required for any beneficial anti-viral effects far exceed what are currently approved for use. The means a full developmental approach starting with phase I studies, or ivermectin reformulation for inhaled delivery, or in combination with other antivirals with differing mechanisms of action, are needed to assess its therapeutic potential.

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