A. The Priority Question

For people at risk of, or with Covid-19 infection (P), does ivermectin (I) compared with placebo or no ivermectin (C) improve health outcomes (O)?

Problem: Global deaths from Covid-19 reached 1,876,100 in early 2021 and the virus causes a considerable burden of morbidity. Ivermectin is a widely used anti-parasitic medication and due to its antiviral and anti-inflammatory properties it has been evaluated for the prophylaxis and treatment of Covid-19 infection

Perspective : Clinical practice recommendation – population perspective

Population: Adults at high risk of, or with, Covid-19 infection

Intervention: Ivermectin administered orally for prophylaxis or treatment of Covid-19 infection

Comparison: Placebo or no ivermectin

Setting: Low-, middle- and high-income countries

Main outcomes:

Ivermectin treatment versus control

- Death (primary outcome)
- Condition improvement, as measured by the study authors
- Condition deterioration, as measured by the study authors
- Recovery time, in days
- Length of hospital stay, in days
- Admission to hospital (for outpatient treatment)
- Admission to ICU or requiring ventilation
- Serious adverse events

Ivermectin prophylaxis versus control

- Covid-19 infection, defined as a positive Covid-19 test with or without symptoms (primary outcome)
- Serious adverse events

Background

In countries across the globe, hospitalisations and deaths from Covid-19 have increased rapidly over recent months. On the 7th January 2021, the WHO Covid-19 dashboard reported 735,944 new cases of infection and a global total of 85,929,428 confirmed cases.(1) For deaths, the total across the world was 1,876,100 on this date. These figures may be underestimates of the true burden of this disease as in many settings tests are not readily available. In the UK alone, the Office of National Statistics reported that up to the 18th Dec 2020, UK "deaths involving Covid" had been registered for 82,615 people.(2)

To date, very few treatments have been identified which have been demonstrated to reduce the burden of morbidity and mortality from Covid-19. While corticosteroids are used in those with severe illness and have been shown to reduce mortality,(3) there has been little evidence on interventions that may prevent disease, reduce hospitalisations and reduce the numbers of people progressing to critical disease and death.

Ivermectin is an anti-parasitic medication widely used in low- and middle-income countries to treat parasitic worm infections in adults and children.(4,5) Having been used for decades for this purpose, it is considered extremely safe and effective (5,6) and has an increasing list of indications due to its antiviral and anti-inflammatory properties.(6) On the WHO's *Model List of Essential Medicines* it is retained in the form of a 3 mg tablet.(7)

The dominant mechanism of action of ivermectin as an anti-viral (against a wide class of RNA viruses)(8) is believed to be the blocking of the nuclear import of viral proteins.(9) If imported into the host nucleus, these proteins play a key role in viral replication by suppressing the normal immune response to infection. However, ivermectin's anti-viral action may be multi-modal.

A recent literature review by the Front Line Covid-19 Critical Care Alliance (FLCCC) summarised findings from 27 studies on the effects of ivermectin for the prevention and treatment of Covid-19 infection. Their conclusion was that ivermectin "demonstrates a strong signal of therapeutic efficacy" and the they recommended that ivermectin be adopted globally and systematically for the prophylaxis and treatment of Covid-19.(10) The FLCCC called upon national and international health care agencies to

check and confirm their findings and conclusions. To this end, due to the urgency of the situation, the Evidence-based Medicine Consultancy Limited undertook a rapid review and meta-analysis on ivermectin for COIVD-19.(11) This DECIDE Evidence to Decision (EtD) framework presents the evidence on the effectiveness of ivermectin for preventing and treating Covid-19, as well as other considerations related to the use of ivermectin, including values and preferences, equity, resources, acceptability and feasibility.

B. Assessment of the evidence

1) Evidence of effectiveness

Evidence for this framework is derived from E-BMC Ltd's rapid review and meta-analysis.(11) The rapid review included randomized controlled trials (RCTs) and controlled observational studies (OCTs) included in the FLCCC literature review,(10) but due to their higher risk of bias, excluded case-control studies and case series.

The E-BMC review assessed the risk of study bias of all included studies using the Cochrane Handbook for Systematic Reviews of Interventions and the ROBINS-I tools for RCTs and OCTs, respectively.(12,13) Fifteen study reports were included, nine of RCTs and six of OCTs. A new RCT reported findings on the 10th January 2021, bringing the number of RCTs in the updated analysis to 10.(14) One RCT reported findings of a prophylaxis study and a treatment study within the same paper and these were regarded as separate studies. Similarly, one OCT reported findings of a pilot study and a further multi-centre study and these were treated separately.

Five of the included studies involving 2045 participants were of Covid-19 prophylaxis among health care workers and patient contacts; the remaining 13 involving 1947 participants were of Covid-19 treatment. Study sample sizes ranged from 24 to 1195 participants and studies were conducted in Argentina (2), Bangladesh (6), Egypt (3) India (2), Iran (2), Pakistan (1), Spain (1), and the USA (1) (Table 1). Sixteen studies were at low or moderate risk of bias and two studies were assessed as having a potentially high risk of bias pending further information from investigators. Eight were registered on clinical trial registries; most studies appeared to be self-funded, undertaken by clinicians working in the field, not by dedicated research teams. There were no apparent conflicts of interest.

Table 1. Included study characteristics

Study ID (refs 12-27)	Country	Design	Sample size	Ivermectin dose and frequency*	Risk of bias
Covid-19 treatment studies					
Ahmed 2020	Bangladesh	RCT	72	12mg x1 or x5 (3 arms)*	Low
Cepelowicz Rajter 2020	USA	OCT	280	0.2mg/kg x 1 or 2	Low
Chaccour 2020	Spain	RCT	24	0.4mg/kg x 1	Low
Chachar 2020	Pakistan	RCT	50	12mg at 0, 12, and 24 hours	Moderate
Chowdhury 2020	Bangladesh	RCT	116	0.2mg/kg x1*	Moderate
Elgazzar 2020a	Egypt	RCT	200	0.4mg/kg daily x4	Moderate
Mahmud 2020	Bangladesh	RCT	363	12mg x 1*	Low
Podder 2020	Bangladesh	RCT	62	0.2mg/kg x1	High
Hashim 2020	Iran	RCT	140	0.2mg/kg x 2 days* Some had a 3rd dose a week later	Moderate
Khan 2020	Bangladesh	OCT	248	12mg x 1	Moderate
Niaee 2020	Iran	RCT	180	0.2mg/kg x 1 and others (6 arms)	Low
Ravikirti 2021	India	RCT	112	12 mg x 2 days	Low
Spoorthi 2020	India	OCT	100	0.2mg/kg x 1*	Moderate
Covid-19 prophylaxis studies					
Alam 2020	Bangladesh	OCT	118	12mg tab monthly x4	Low
Carvallo 2020 pilot	Argentina	OCT	229	1 drop of 0.6mg/ml solution x 5 daily	Moderate
Carvallo 2020	Argentina	OCT	1195	12mg tab weekly	High
Elgazzar 2020b	Egypt	OCT	200	0.4mg/kg, weekly x 2	Moderate
Shouman 2020	Egypt	RCT	303	2 doses 72 hours apart -15mg tab for 60-80 kg	Moderate

OCT, observational controlled trial; RCT, randomised controlled trial
*Also administered doxycycline.
Note: 0.2 mg/kg is equivalent to giving 12 mg and 0.4 mg/kg is equivalent to giving 24 mg for a 60 kg person.

Participant characteristics

The mean age of study participants was between 30 and 40 years old for six studies, 40 and 50 years old for four studies, and 50 to 60 years old for six studies; two studies reported a median age of participants of 26 and 35 years old, respectively; one study did not report participant age.

People with co-morbidities (e.g. diabetes mellitus, hypertension, cardiovascular disease, asthma, obesity) were excluded from three studies and were included in nine studies in which they occurred at a cumulative frequency ranging from 28% to the vast majority of participants; co-morbidities were not reported in seven studies. Four studies reported the proportion of smokers, which ranged from 13% to 30%. In most studies pregnant and lactating women were excluded from participation, and several studies excluded people with chronic liver or kidney disease.

I. Effects of the ivermectin for Covid-19 treatment

Thirteen of the included studies evaluated ivermectin to treat Covid-19 in people with mild, moderate and severe disease. The most frequent dose of ivermectin was 0.2mg/kg (12 mg) as a one or two dose regimen (10 studies). Five studies used these regimen of ivermectin plus the antibiotic doxycycline, which was administered for between five and 10 days.

Outcome 1.1: Death

Moderate certainty evidence from RCTs indicates that ivermectin probably reduces deaths by an average 83% (95% CI, 67% to 92%) compared with no ivermectin treatment (6 RCTs, 1219 participants; RR 0.17, 95% 0.08 to 0.33; risk of death 1.3% versus 8.3% among participants in this analysis; evidence downgraded due to study design limitations). This is equivalent to an average 69 fewer deaths per 1000 people in hospital with Covid-19. The effect favouring ivermectin was consistent among people in hospital with mild, moderate and severe disease.

Outcome 1.2 Improvement in clinical condition

Moderate certainty evidence suggests that ivermectin probably increases the likelihood of people with mild to moderate Covid-19 improving by about 34% (22% to 48%) compared with those receiving no ivermectin treatment (5 studies, 743 participants; RR 1.34, 95% CI 1.22 to 1.48; evidence downgraded for study design limitations). This is equivalent to an average 185 more people experiencing improvement in their clinical condition per 1000 compared with those not receiving ivermectin.

For those with severe Covid-19 infection, low certainty evidence suggests that ivermectin may increase the chance of improvement by a greater extent than for mild to moderate infections (1 study, 200 participants, RR 1.88, 95% CI 1.54 to 2.30; evidence downgraded because of study design limitations and because it was derived from a single small study).

Outcome 1.3 Deterioration in clinical condition

Moderate certainty evidence suggests that ivermectin may reduce the risk of a person's condition deteriorating by about 78% (95% CI 50% to 90%) compared with no ivermectin treatment (5 studies, 1175 participants; RR 0.22, 95% CI 0.10 to 0.50; evidence downgraded due to study design limitations and inconsistency). This is equivalent to an average 147 fewer people experiencing deterioration in their clinical condition per 1000 compared with those not receiving ivermectin.

Outcome 1.4 Recovery time (clinical), as measured by study authors

Two studies evaluated ivermectin as an outpatient treatment for Covid-19 infection, and low certainty evidence suggests that ivermectin may reduce recovery time compared with no ivermectin treatment by about a day for outpatients (2 studies, 176 participants; MD -1.06 fewer days, 95% CI -1.63 to -0.49; evidence downgraded for imprecision and study design limitations). A similar effect was estimated for mild to moderate hospital inpatients.

In one study that evaluated Covid-19 illness among inpatients with mild to critical Covid-19, low certainty suggests that ivermectin may reduce recovery time by an

average of about 7 days (MD 7.29 fewer days, 95% CI 9.31 to 5.27; downgraded for study limitations and imprecision).

Outcome 1.5 Recovery time to a negative PCR test

Evidence for this outcome was graded as very low certainty.

Outcome 1.6 Length of hospital stay

Low certainty evidence suggests that ivermectin may reduce the length of hospital stay by about a day in people with mild to moderate Covid-19 infection (2 studies, 172 participants; MD -1.03 fewer days, 95% CI -1.82 to -0.23; downgraded for study design limitations and imprecision). The direction of effect for this outcome was consistent in an RCT and in two of three observational studies where data were not reported in a way that allowed them to be included in the meta-analysis.(11)

Outcome 1.7 Admission to ICU or requiring ventilation

Moderate certainty evidence suggests that ivermectin probably reduces the number of people with Covid-19 infections who require management and ventilation in ICU (360 participants; RR 0.15, 95% CI 0.03 to 0.63; evidence downgraded due to design limitations). This is equivalent to an average of 72 fewer per 1000 people hospitalised.

Outcome 1.8 Severe adverse events

Although three studies reported this outcome the number of adverse events was very low and overall findings were of very low certainty.

II. Effects of the ivermectin for Covid-19 prophylaxis

Five of the included studies involving 2045 participants were of Covid-19 prophylaxis among health care workers and Covid-19 contacts.

Outcome 2.1 Covid-19 infection

Moderate certainty evidence suggests that ivermectin prophylaxis among health care workers and Covid-19 contacts probably reduces the risk of Covid-19 infection by

about 88% (4 studies, 851 participants; RR 0.12, 95% CI 0.08 to 0.18; 4.3% vs 34.5% contracted Covid-19). The certainty of this evidence was downgraded to moderate due to study design limitations.

Additional considerations

- A sensitivity analysis was conducted which, in addition to RCT data, included findings from controlled observational studies (OCTs). Including 9 studies and 1847 participants, these findings were consistent with the main RCT analysis and suggested a probable reduction in deaths of approximately 70% on average (RR 0.30, 95% CI 0.17 to 0.55; risk of death was 3.7% vs 9.7%).
- A personal communication was received from Dr Dave Chesler, a geriatrician in Central Virginia, USA, on the 10th January 2021. He reported on his observations of treating over 200 elderly and high-risk Covid-19 patients, at six assisted living and nursing homes. The clinical observations were included in correspondence with Tess Lawrie upon having read her January 3rd report on Ivermectin for the prevention and treatment of Covid-19,(11) and had previously been sent to the US National Institute of Health (NIH). These clinical observations are valuable as evidence gathered by expert clinicians of what works and what doesn't work. Early on in the pandemic, based on evidence from an in-vitro study of Ivermectin from Monash University, and his extensive experience of using Ivermectin to successfully combat scabies among residents and staff, the clinician started treating elderly residents in the facilities under his care as they tested positive for Covid-19, with a combination of Vitamins (C, D3, Zinc), Ivermectin (12mg on Day 1 and Day 8), Zithromycin and Lovinox. At some point he switched to Doxycycline. Over the Spring and Summer, he treated over 200 elderly residents. Of those who tested positive, a small number died, most of them of other causes, but no survivors experienced respiratory failure, and none needed to be put on a respirator. Many did require low flow O2 to keep sats above 92 % . Except for facility 1, at the other facilities residents were tested weekly. Take-away points:
  - *At six facilities housing a total of 444 high-risk elderly residents, 223 tested positive for Covid-19, and 37 died.*
  - *Residents were tested for Covid-19 on a weekly basis.*
  - *Residents who tested positive were treated with a combination of Vitamins C and D3, Zinc, Ivermectin (12 mg/day 1 and day 8), and Zithromycin and Lovinox (later Doxycyline). In some cases, the treatment was used as prevention.*
  - *The majority of deaths that did occur were among very old residents, those in hospice, and those with pre-existing conditions such as diabetes.*
  - *No residents experienced respiratory failure or needed respirator support*.

- There is also non-trial evidence from South American countries that suggests that ivermectin reduces Covid-19 transmission. In Peru, Brazil and Paraguay, health authorities instituted ivermectin distribution campaigns in a bid to reduce infection rates. Comparisons of groups in cities where ivermectin was distributed with neighbouring cities where ivermectin was not provided, showed a decline in new cases in the intervention areas.(15)
- In early August the largest state by population in India, Uttar Pradesh, announced that they would switch from hydroxychloroquine to ivermectin in their treatment guidelines and have reported relatively low proportions of deaths for the population size (>200 million). Ivermectin kiosks were set up in the city of Lucknow.
- Testimony to the notion that ivermectin has been found to be a useful therapy in India, in early October the state of Goa's Health Minister Vishwajit Rane issued a free home isolation kit available at all Urban and Primary Health Centres for any Covid-19 positive person in the State who opts for Home Isolation. In addition to ivermectin (12 mg tabs x10), the kit contains Pulse Oximeter, Digital Thermometer, Paracetamol tablets (x15), Vitamin C tablets (x30), Multivitamin tablets with Zinc (x30), Vitamin D3 tablets (2 packs), Doxycycline 100mg tablets (x10), Three-ply face masks (x5), N-95 Masks (x2), Sanitizer (100ml), Alcohol based Wipes (1 box with 20 plies) and Gloves (2 pairs).

Summary of effects

Ivermectin substantially reduces the risk of a person dying from Covid-19 by probably somewhere in the region of 67% to 92% according to RCT data. The evidence also suggests that ivermectin reduces the severity of the illness. When ivermectin is used as prophylaxis among health care workers and contacts, ivermectin reduces Covid-19 infections.

Desirable effects

How substantial are the desirable anticipated effects of ivermectin compared with no ivermectin?

Judgement					
☐ Don't know	☐ Varies	☐ Trivial	☐ Small	☐ Moderate	☐ Large

Rationale for judgement:

Undesirable effects

How substantial are the undesirable anticipated effects of ivermectin compared with no ivermectin?

Judgement					
☐ Don't know	☐ Varies	☐ Large	☐ Moderate	☐ Small	☐ Trivial

Rationale for judgement:

Certainty of the evidence

What is the overall certainty of the evidence of effects of ivermectin?

Judgement				
☐ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Rationale for judgement:

Values and preferences

Is there important uncertainty about, or variability in, how much people value the main outcomes associated with ivermectin?

- Mortality is considered a critical outcome by all, the public, patients (34) as well as healthcare professionals.(35)
- Mortality, respiratory failure, multiple organ failure, shortness of breath, and recovery are critically important outcomes to be consistently reported in coronavirus disease 2019 trials.(36)

- The COS-Covid includes one outcome for the mild type (time to 2019-nCoV PCR negativity), four outcomes for the ordinary type (length of hospital stay, composite events, score of clinical symptoms, and time to 2019-nCoV RT-PCR negativity), five outcomes for the severe type (composite events, length of hospital stay, arterial oxygen partial pressure (PaO2)/fraction of inspired oxygen (FiO2), duration of mechanical ventilation, and time to 2019-nCoV RT-PCR negativity), one outcome for critical type (all-cause mortality), and one outcome for rehabilitation period (pulmonary function) Importance of outcomes from clinicians' perspective.(37)

Judgement			
☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Rationale for judgement:

Balance of effects

Does the balance between desirable and undesirable effects favour ivermectin or no ivermectin?

Judgement						
☐ Don't know	☐ Varies	☐ Favours no ivermectin	☐ Probably favours no ivermectin	☐ Does not favour ivermectin or no ivermectin	☐ Probably favours ivermectin	☐ Favours ivermectin

Rationale for judgement:

2) Resources

How large are the resource requirements (costs) associated with ivermectin?

Research evidence

The current UK reference costs for treating non-elective respiratory failure are between £4,800 (multiple organs, DZ27M) and £2,265 (single organ DZ27R). This will likely involve an ICU bed. For people that are hospitalised but without intensive support this will be lower.(38)

A 2007 paper reported costs for an ICU stay of £7,010 per QALY – this would be in the region of £9,800 per QALY by 2019 prices. As such, whilst ICU may be a cost effective intervention, it is undoubtedly an expensive intervention.(39) A daily bed day cost for an ICU admission would be in the region of £1169 (2007 prices; £1364 less the average bed day cost of £195) (2007) the equivalent of approximately £1634 now (2019 prices, using the Bank of England inflation calculator).(40)

Another research paper (41) shows that the median length of stay for a Covid-19 patient is 14 days (IQR 10–19 days) for China and 5 days (IQR 3–9 days) outside China. This pattern was followed for ICU length of stay, with a median of 8 days (IQR 5–13 days) for China and 7 days (IQR 4–11 days) outside China.(41)

Thus, effective prevention of Covid-19 could yield large cost savings in terms of hospitalisation and, if all the strategies are equally effective, the one that can be delivered to the largest numbers at the smallest cost will be the most cost effective option.

Main resource requirements

Additional considerations
• The cost of Covid-19 vaccines in the UK are projected to be £28 for the Moderna vaccine, £15 for the Pfizer vaccine and £6 for the Oxford Astra Zeneca Vaccine (£3 X 2 doses required).(42) The vaccine costs above are only the price charged by pharma to the NHS, they do not include any additional costs for administration and transportation. Ivermectin at a cost of around £1.50 a pack containing five 12 mg doses (£0.30 per dose) is very inexpensive by comparison. Ivermectin show

effectiveness comparable to the vaccines and because it can be self-administered as a drug blister pack, it has few other costs, aside from postage costs.

- Ivermectin is already on the WHO Essential Medicine List (7) and is available commercially at reasonably affordable local prices in most parts of the world. According to a WHO document, the direct cost of a pack of 100 12mg tablets of ivermectin is approximately $2.90 with a unit price of 0.029 per tablet. These costs are subject to variations in different countries.(43)

Resources required

How costly are the resources required for ivermectin compared with no ivermectin?

Judgement						
☐ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Rationale for judgement:

Certainty of evidence on required resources

What is the certainty of the evidence on costs?

Judgement				
☐ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Rationale for judgement:

Cost-effectiveness

How cost-effective is ivermectin compared with no ivermectin?

Judgement						
☐ Don't know	☐ Varies	☐ Favours no ivermectin	☐ Probably favours no ivermectin	☐ Does not favour ivermectin or no ivermectin	☐ Probably favours ivermectin	☐ Favours ivermectin

Rationale for judgement:

3) Equity

What would be the impact of ivermectin on health equity?

Research evidence

None.

Additional considerations
• As a relatively cheap treatment, ivermectin has the potential to benefit the worst affected by the disease in the UK.(44) • Health care and other frontline workers are receiving an unequal exposure to the SARS-cov2 virus and are at higher risk than the general population for Covid-19 infection; the evidence shows that ivermectin would reduce their occupational risk significantly. • Ivermectin can be distributed by post and self-administered, it can therefore reach the most vulnerable populations, such as the elderly living alone or in care homes, those lacking transport to reach health facilities, and those who lack access to adequate health care for other reasons. • Black, Asian, and Minority Ethnic (BAME) frontline workers have higher Covid-19 infection rates and worse associated health outcomes compared with other ethnic groups.(Public Health England, 2Beyond the data. Understanding the impact of Covid-19 on BAME groups, 2020).() • A recent review and meta-analysis of 35 studies has shown that the majority of children exhibit needle fear. Among adolescents, prevalence estimates for needle fear ranged from 20-50% and, in young adults, 20-30%. Avoidance of influenza vaccination because of needle fear occurred in 16% of adults, 27% of hospital employees, 18% of workers at long-term care facilities, and 8% of healthcare workers at hospitals.(45) Having an alternative preventive measure against Covid will increase equity through increased access to health care for when vaccination is not an option. • The drug is contraindicated for children under 5 years of age, pregnant and breastfeeding women,(46) as well as those currently on Acenocoumarol, Levamisole or Warfarin.(47) • The grateful acknowledgement by the British government, scientists and the public of the contributions made by clinician-researchers' in low- and middle-income countries (LMICs) to Covid research, as well as of the people who took part in this valuable research, will help to improve research equity. The case of ivermectin may encourage high impact factor, high-income country journals to be more receptive and supportive of clinician-researchers in LMICs (for example, by providing assistance with medical writing and paper submission) and reduce publication bias against research originating from LMICs.

Judgement						
☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☐ Increased

Rationale for judgement:

4) Acceptability

Would ivermectin be acceptable to key stakeholders?

Research evidence

No specific research identified on the acceptability of ivermectin.

Additional considerations
• Several of the additional consideration bullet points in the evidence of effectiveness section of this document indicate that this is a highly acceptable intervention. For example, the personal communication of Dr Chesler, who had previously used ivermectin for scabies among elderly care home residents in Virginia, USA, and other examples from countries that have already rolled out ivermectin. • Ivermectin is already on the WHO Essential Medicine List (7) and has a long track record of clinical safety. • Ivermectin reduces deaths, therefore is likely to be very acceptable to people with Covid infection. • For prophylaxis of at-risk people like health workers and contacts, a weekly dose of 12 mg (one tab) for a 60 kg adult has been used. This is a similar dose to treating scabies and lice, which suggests that people would find this acceptable.

Judgement					
☐ Don't know	☐ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Rationale for judgement:

5) Feasibility

Would ivermectin be feasible to implement?

Research evidence

Additional considerations
• The drug has proven record on safety in human use, with the total doses distributed in the last 30 years apparently equalling one-third of the present world population. (48) • From the demand side, if ivermectin is free and available, it is extremely feasible. However, on the supply side there may be several considerations to take into account, such as changes in regulatory norms and policies (e.g. tariffs, labelling, imports, government oversight, etc.), how sustainable the production is (local or imported), and how to guarantee product availability. • Ivermectin is unlicensed in the UK according to the British National Formulary and the implications of this are uncertain. However, as ivermectin is a generic medicine, manufacturing of ivermectin at low cost may be possible within the UK (time frame unknown). • For immediate supplies, importation would probably be required.

Judgement					
Don't know	☐ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Rationale for judgement:

Summary of GDG judgements on ivermectin (✓)

Desirable effects	- Don't know	- Varies		- Trivial	- Small	- Moderate	- Large
Undesirable effects	Don't know	- Varies		- Large	- Moderate	- Small	- Trivial
Certainty of the evidence on effects	- No included studies			- Very low	- Low	- Moderate	- High
Values				- Important uncertainty or variability	- Possibly important uncertainty or variability	- Probably no important uncertainty or variability	- No important uncertainty or variability
Balance of effects	- Don't know	- Varies	- Favours no ivermectin	- Probably favours no ivermectin	- Does not favour ivermectin or no ivermectin	- Probably favours ivermectin	- Favours Ivermectin
Resources required	- Don't know	- Varies	- Large costs	- Moderate costs	- Negligible costs or savings	- Moderate savings	- Large savings
Certainty of evidence of required resources	- No included studies			- Very low	Low	- Moderate	- High
Cost-effectiveness	- Don't know	- Varies	- Favours no ivermectin	- Probably favours no ivermectin	- Does not favour ivermectin or no ivermectin	- Probably favours ivermectin	- Favours ivermectin
Equity	- Don't know	- Varies	- Reduced	- Probably reduced	- Probably no impact	- Probably increased	- Increased
Acceptability	- Don't know	- Varies		- No	- Probably No	- Probably Yes	- Yes
Feasibility	- Don't know	- Varies		- No	- Probably No	- Probably Yes	- Yes

C. Conclusions

Draft recommendation/s

Judgement		
We do not recommend the intervention ☐	We recommend considering the intervention only ☐ in specific contexts ☐ with targeted monitoring and evaluation ☐ in the context of rigorous research	We recommend the intervention ☐

Remarks

To be drafted.

Draft implementation considerations

To be drafted.

Research Gaps

To be drafted.

The Evidence-Based Medicine Consultancy Ltd

D. Evidence Profile

Author(s): Theresa A Lawrie
Date: 2021-01-11
Question: Ivermectin vs control for Covid-19 treatment for prevention and treatment of Covid-19 infection TREATMENT
Settings: Argentina Bangladesh, Egypt, India, Iran, Pakistan, Spain, USA
Source: Lawrie TA. Ivermectin for prevention and treatment of Covid-19 infection. RevMan data analysis file.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ivermectin	Control for Covid-19 treatment	Relative (95% CI)	Absolute		
Death (RCTs)												
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/640 (1.3%)	48/579 (8.3%)	RR 0.17 (0.08 to 0.33)	69 fewer per 1000 (from 56 fewer to 76 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Improvement - Mild to moderate Covid-19												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	257/353 (72.8%)	178/328 (54.3%)	RR 1.34 (1.22 to 1.48)	185 more per 1000 (from 119 more to 260 more)	⊕⊕⊕O MODERATE	IMPORTANT
Improvement - Severe Covid-19												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	94/100 (94%)	50/100 (50%)	RR 1.88 (1.54 to 2.3)	440 more per 1000 (from 270 more to 650 more)	⊕⊕OO LOW	IMPORTANT
Deterioration												
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	27/580 (4.7%)	112/595 (18.8%)	RR 0.22 (0.1 to 0.5)	147 fewer per 1000 (from 94 fewer to 169 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
Recovery time (as reported by study authors) - Outpatient treatment (Better indicated by lower values)												

2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	92	84	-	MD 1.06 lower (1.63 to 0.49 lower)	⊕⊕OO LOW	IMPORTANT
Recovery time (as reported by study authors) - Inpatient (mild to moderate) (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	50	50	-	MD 0.99 lower (1.89 to 0.09 lower)	⊕⊕OO LOW	IMPORTANT
Recovery time (as reported by study authors) - Inpatient (all, mild to critical) (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	70	70	-	MD 7.29 lower (9.31 to 5.27 lower)	⊕⊕OO LOW	IMPORTANT
Recovery time to -ve PCR test - Outpatient treatment (Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4,5]	none	108	78	-	MD 1.12 lower (2.58 lower to 0.35 higher)	⊕OOO VERY LOW	IMPORTANT
Length of hospital stay - Mild to moderate Covid-19 (Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	98	74	-	MD 1.03 lower (1.82 to 0.23 lower)	⊕⊕OO LOW	IMPORTANT
Admission to ICU												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/170 (1.2%)	16/190 (8.4%)	RR 0.15 (0.03 to 0.63)	72 fewer per 1000 (from 31 fewer to 82 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Serious adverse events												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[7]	none	2/434 (0.46%)	0/305 (0%)	RR 4.92 (0.24 to 101.74)	-	⊕OOO VERY LOW	IMPORTANT
Death (All studies)												
9	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	36/978 (3.7%)	84/869 (9.7%)	RR 0.3 (0.17 to 0.55)	68 fewer per 1000 (from 43 fewer to 80 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Death (subgrouped by study design)												
9	randomised trials	serious[1]	no serious inconsistency[8]	no serious indirectness	no serious imprecision	none	36/978 (3.7%)	84/869 (9.7%)	RR 0.26 (0.12 to 0.56)	72 fewer per 1000 (from 43 fewer to 85 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Death (subgrouped by study design) - RCTs												
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/640 (1.3%)	48/579 (8.3%)	RR 0.16 (0.08 to 0.33)	70 fewer per 1000 (from 56 fewer to 76 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Death (subgrouped by study design) - OCTs												

3	observational studies[9]	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	28/338 (8.3%)	36/290 (12.4%)	RR 0.51 (0.16 to 1.64)	61 fewer per 1000 (from 104 fewer to 79 more)		CRITICAL

[1] Studies contributing data had design limitations
[2] Evidence from a single study with a small sample size
[3] Most of the evidence from a B study 10.7% from a C study
[4] Sample size less than 400 (WHO SOP downgrades for small sample size)
[5] Wide 95% CI crossing the line of no effect
[6] Low sample size and most of the evidence from a single study
[7] Low event rate and wide CI crossing the line of no effect
[8] Not downgraded for heterogeneity (I2 51%)
[9] Controlled observational studies

Author(s): Theresa A Lawrie
Date: 2021-01-11
Question: Ivermectin vs control for Covid-19 prophylaxis for prevention and treatment of Covid-19 infection PROPHYLAXIS
Settings: Argentina, Egypt
Source: Lawrie TA. Ivermectin for prevention and treatment of Covid-19 infection. RevMan data analysis file.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ivermectin**	**Control for Covid-19 prophylaxis**	**Relative (95% CI)**	**Absolute**		
Covid-19 infection												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	21/492 (4.3%)	124/359 (34.5%)	RR 0.12 (0.08 to 0.18)	304 fewer per 1000 (from 283 fewer to 318 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
Covid-19 infection (with Carvallo multi data)												
4	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	21/1280 (1.6%)	361/766 (47.1%)	RR 0.05 (0.01 to 0.29)	448 fewer per 1000 (from 335 fewer to 467 fewer)	⊕⊕OO LOW	IMPORTANT

[1] Studies contributing data had design limitations
[2] Inconsistency in size of effect between studies

E. References

1. WHO (2021) WHO Coronavirus Disease (Covid-19) Dashboard. www.covid19.who.int (downloaded 7th January 2021)

2. Office for National Statistics (2021) Coronavirus (Covid-19) Latest Data and Analysis on coronavirus (Covid-19) in the UK and its effect on the economy and society. www.ons.gov.uk (downloaded 3rd January 2021)

3. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalised patients with Covid-19 - preliminary report. NEJM. 2020 Jul 17;NEJMoa2021436. doi: 10.1056/NEJMoa2021436

4. Conterno LO, Turchi MD, Corrêa I, Monteiro de Barros Almeida RA. Anthelmintic drugs for treating ascariasis. Cochrane Database of Systematic Reviews 2020, Issue 4. Art. No.: CD010599. DOI: 10.1002/14651858.CD010599.pub2. Accessed 28 December 2020.

5. Barrow NJ, Campos RK, Powell ST, et al. A screen of FDA-approved drugs for inhibitors of Zika virus infection. Cell Host & Microbe. 2016;20(2):259-270.

6. Kircik, LH, Del Rosso, JQ, Layton AM, Schauber J. Over 25 Years of Clinical Experience With Ivermectin: An Overview of Safety for an Increasing Number of Indications. J Drugs Derm 2016; 15:325-332.

7. World Health Organization. 21st Model List of Essential Medicines. Geneva, Switzerland. 2019. https://www.who.int/publications/i/item/WHOMVPEMPIAU2019.06. Accessed 29 December 2020.

8. Heidary, H. & Gharebaghi, R. (2020) *J. Antibiotics* **73,** 593-602

9. Caly, L. *et al.* (2020) *Antiviral Res.* **178,** 104787

10. Kory P, Meduri GU, Iglesias J, et al. Review of the emerging evidence demonstrating the efficacy of ivermectin in the prophylaxis and treatment of Covid-19. 18 Dec 2020.https://covid19criticalcare.com/wp-content/uploads/2020/11/FLCCC-Ivermectin-in-the-prophylaxis-and-treatment-of-Covid-19.pdf.

11. Lawrie, TA. Ivermectin reduces the risk of death from Covid-19 – a rapid review and meta-analysis in support of the recommendation of the Front Line Covid-19 Critical Care Alliance. Available at www.e-bmc.co.uk (accessed 12-01-2021).

12. Ravikirti et al. Ivermectin as a potential treatment for mild to moderate Covid-19 – A double blind randomized placebo-controlled trial. 2021. (Preprint server)

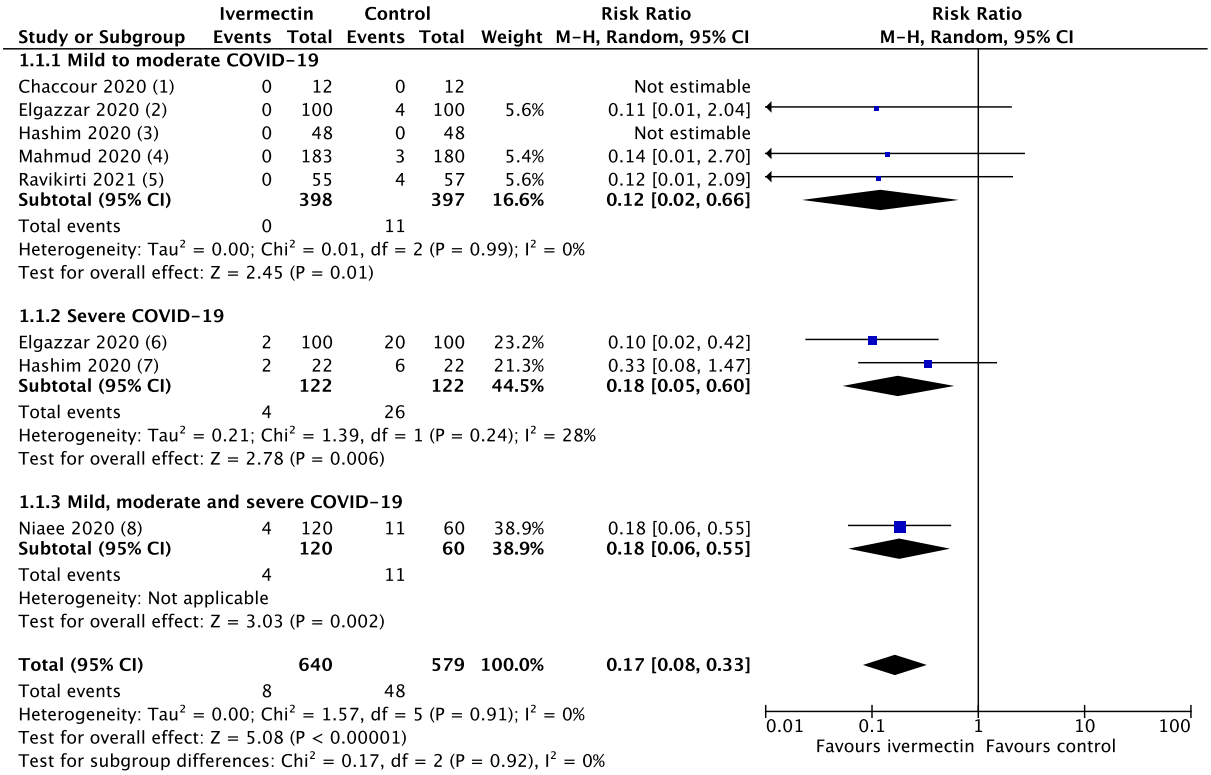
13. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 6.0 [updated July 2019]. Cochrane, 2019. Available from www.training.cochrane.org/handbook.
14. Sterne JA, Hernán MA, Reeves BS, Savović J, Berkman ND, Viswanathan V, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919.
15. Chamie-Quintero J, Hibberd J, Scheim DE. Covid-19 case fatalities and total deaths with and without ivermectin treatment in different states in Peru. Open Science Foundation. https:osf.io.ydc2p/ (accessed 12/01/2021).
16. Review Manager 5 (RevMan 5) [Computer program]. Version 5.4. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2020.
17. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557-60.
18. The GRADE Working Group. GRADE [website] 2020 [Available from: www.gradeworkinggroup.org.
19. Alam MT, Murshed R, Gomes PF, Masud ZM, Saber S, Chaklader MA, Khanam F, Hossain M, Momen ABIM, Yasmin N, Alam RF, Sultana A, Robin RC. Ivermectin as Pre-exposure Prophylaxis for Covid-19 among Healthcare Providers in a Selected Tertiary Hospital in Dhaka – An Observational Study. EJMED [Internet]. 15Dec.2020 Available from: https://ejmed.org/index.php/ejmed/article/view/599. (Accessed 29Dec.2020)
20. Carvallo HE, Hircsh R, Alkis P and Contreras V. Study of the Efficacy and Safety of Topical Ivermectin + IotaCarrageenan in the Prophylaxis against Covid-19 in Health Personnel. J. Biomed. Res. [Internet] 19oct.2020. ISSN:2633-8653. ClinicalTrials.gov registration number: NCT04425850. (Accessed 29Dec.2020)
21. Elgazzar A, Eltaweel A, Youssef SA, Hany B, Hafez M and Moussa H. Efficacy and Safety of ivermectin for Treatment and prophylaxis of Covid-19 Pandemic. Res. Square [Internet] 28Dec.2020. Available from: https://www.researchsquare.com/article/rs-100956/v3 (Accessed 29 Dec.2020)
22. Shouman W. Use of Ivermectin as a Prophylactic Option in Asymptomatic Family Close Contact for Patient with Covid-19. Clinical Trials.gov [Internet] 2020 Jun registration number NCT04422561. (Accessed 29Dec.2020)
23. Mahmud R. Clinical Trial of Ivermectin Plus Doxycycline for the Treatment of Confirmed Covid-19 Infection. ClinicalTrials.gov [Internet] 2020 Oct registration number: NCT04523831. (Accessed 20Dec.2020)
24. Chowdhury, ATMM, Shahbaz, M, Karim, MR, Islam, J, Guo, D, and He, SA Randomized Trial of Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin therapy on Covid19 patients.

Res. Square [Internet] 14Jul.2020. Available from: https://www.researchsquare.com/article/rs-38896/v1. (Accessed 29 Dec.2020.)

25. Podder CS, Chowdhury N, Mohim IS and Haque W. (2020). Outcome of ivermectin treated mild to moderate Covid-19 cases: a single-centre, open-label, randomised controlled study. IMC Journal of Medical Science. 14. Available from: https://www.researchgate.net/publication/344240147_Outcome_of_ivermectin_treated_mild_to_moderate_Covid-19_cases_a_single-centre_open-label_randomised_controlled_study. (accessed 30Dec.2020)
26. Niaee MS, Gheibi N, Namdar P, Allami A, Zolghadr L, Javadi A, et al. Ivermectin as an adjunct treatment for hospitalized adult Covid-19 patients: A randomized multi-centre clinical trial. Res. Square [Internet] 24Nov.2020. Available from: https://www.researchsquare.com/article/rs-109670/v1 (Accessed 29Dec.2020.)
27. Hashim HA, Maulood MF, Rasheed AM, Fatak DF, Kabah KK, Abdulami AS, et al. Controlled randomized clinical trial on using Ivermectin with Doxycycline for treating Covid-19 patients in Baghdad, Iraq. medRxiv [Internet] 2020.10.26.20219345. Available from: https://doi.org/10.1101/2020.10.26.20219345 (Accessed 29Dec.2020)
28. Ahmed S, Karim MM, Ross AG, Hossain MS, Clemens JD, Sumiya MK, et al. A five day course of ivermectin for the treatment of Covid-19 may reduce the duration of illness. Int. J. Infect. Disease [Internet] 2Dec.2020. Available from: https://www.ijidonline.com/article/S1201-9712(20)32506-6/fulltext (Accessed 29Dec.2020)
29. Chachar AZK, Khan KA, Asif M, Tanveer K, Khaqan A and Basri R. Effectiveness of Ivermectin in SARS-CoV-2/Covid-19 Patients, Int. J. Sciences [Internet] Nov.2020:31-35 Available from: https://www.ijsciences.com/pub/article/2378 (Accessed 29Dec.2020)
30. Cepelowicz Rajter J, Sherman MS, Fatteh N, Vogel F, Sacks J and Rajter JJ. Use of Ivermectin Is Associated With Lower Mortality in Hospitalized Patients With Coronavirus Disease 2019. J. Chest [Internet] 27Oct.2020. Available from: https://journal.chestnet.org/action/showPdf?pii=S0012-3692%2820%2934898-4 . (Accessed 29Dec.2020)
31. Khan SI, Khan SI, Debnath CR, Nath PN, Al Mahtab M, Nabeka H, et al. [Ivermectin Treatment May Improve the Prognosis of Patients With Covid-19.] Archivos de Bronconeumología, 2020. Volume 56, Issue 12, Pages 828-830,ISSN 0300-2896.Spain. Available from: https://doi.org/10.1016/j.arbres.2020.08.007.
32. Gorial FI, Mashhadani S, Sayaly HM, Dakhil BD, AlMashhadani MM, Aljabory AM, et al. Effectiveness of Ivermectin as add-on Therapy in Covid-19 Management (Pilot Trial).MedRxiv. 2020.07.07.20145979; Available from: https://doi.org/10.1101/2020.07.07.20145979 (Accessed 29Dec.2020).
33. Spoorthi V, Sasank S. Utility of ivermectin and doxycycline combination for the treatment of SARS-CoV-2. International Archives of Integrated Medicine. [Internet] 2020:7(10). Available from: https://www.iaimjournal.com/volume-7-issue-10-october-2020/

34. https://www.journalofhospitalmedicine.com/jhospmed/article/231557/hospital-medicine/improving-patient-experience-during-covid-19-pandemic-one (accessed 12/01/2021)
35. https://www.comet-initiative.org/assets/downloads/Covid-19%20meta%20COS_Table%201_29th%20October%202020.pdf (accessed 12/01/2021)
36. https://journals.lww.com/ccmjournal/Fulltext/2020/11000/Core_Outcomes_Set_for_Trials_in_People_With.10.aspx. (accessed 12/01/2021)
37. https://www.sciencedirect.com/science/article/pii/S2095809920300424?via%3Dihub (accessed 12/01/2021)
38. https://www.who.int/selection_medicines/committees/expert/22/applications/s6.6_ivermectin.pdf?ua=1 (section 11) (accessed 12/01/2021)
39. 1. https://www.england.nhs.uk/national-cost-collection/#ncc1819 last accessed 11/01/21 17:06
40. Ridley S, Moriss S. Anaesthesia, 2007, 62: 547–554
41. https://www.bankofengland.co.uk/monetary-policy/inflation/inflation-calculator
42. Rees EM, et al (2020) Covid-19 length of hospital stay: a systematic review and data synthesis. BMC Medicine (2020) 18:270 pp1-22, https://doi.org/10.1186/s12916-020-01726-3
43. https://news.sky.com/story/covid-19-vaccines-how-do-the-moderna-and-pfizer-coronavirus-jab-candidates-compare-12134062
44. https://bnfc.nice.org.uk/drug/ivermectin.html (accessed 12/01/2021)
45. McLenon J, Rogers MAM. The fear of needles: A systematic review and meta-analysis. J Adv Nurs. 2019 Jan;75(1):30-42. doi: 10.1111/jan.13818. Epub 2018 Sep 11. PMID: 30109720.
46. https://bnf.nice.org.uk/interaction/ivermectin-2.html (accessed 12/01/2021)
47. https://committees.parliament.uk/publications/3965/documents/39887/default/ (accessed 12/01/2021)
48. Banerjee K, Nandy M, Dalai CK, Ahmed SN. The Battle against COVID 19 Pandemic: What we Need to Know Before we "Test Fire" Ivermectin. Drug Res (Stuttg). 2020 Aug;70(8):337-340. doi: 10.1055/a-1185-8913. Epub 2020 Jun 19. PMID: 32559771; PMCID: PMC7417290.

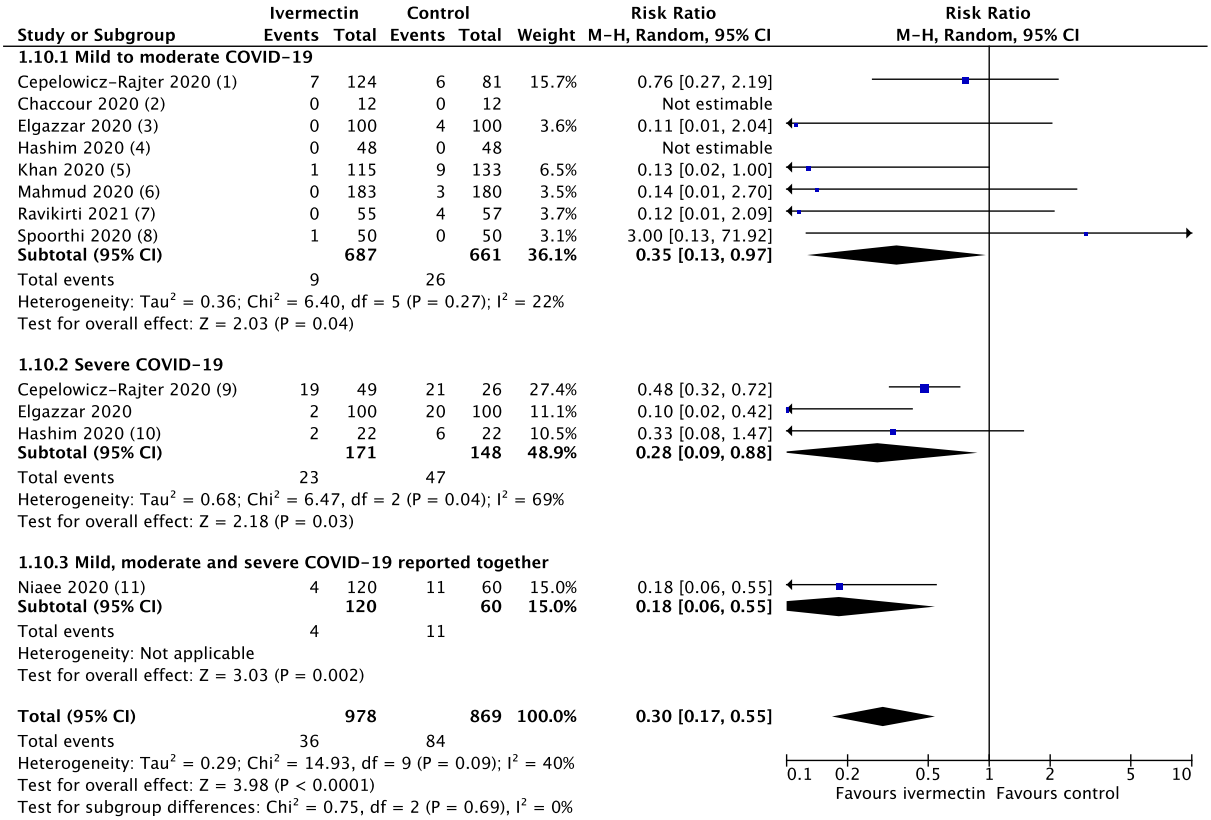
Forest plot 1.1 Deaths (RCTs only)



Footnotes

(1) IVM 0.4mg/kg single dose
(2) IVM up to 24 mg daily for 4 days. Control group received hydroxychloroquine
(3) IVM 200µgm/kg + Doxy 100 mg BID x 10 days
(4) IVM 6mg once + Doxy 100 mg x 5 days
(5) IVM 12 mg x 2 days
(6) IVM up to 24 mg daily for 4 days. Control group received hydroxychloroquine
(7) IVM 200µgm/kg x 2 + Doxy 100 mg BID x 10 days
(8) IVM 200µgm/kg to 400 µgm/kg (1 to 3 doses). Compared with hydroxychloroquine

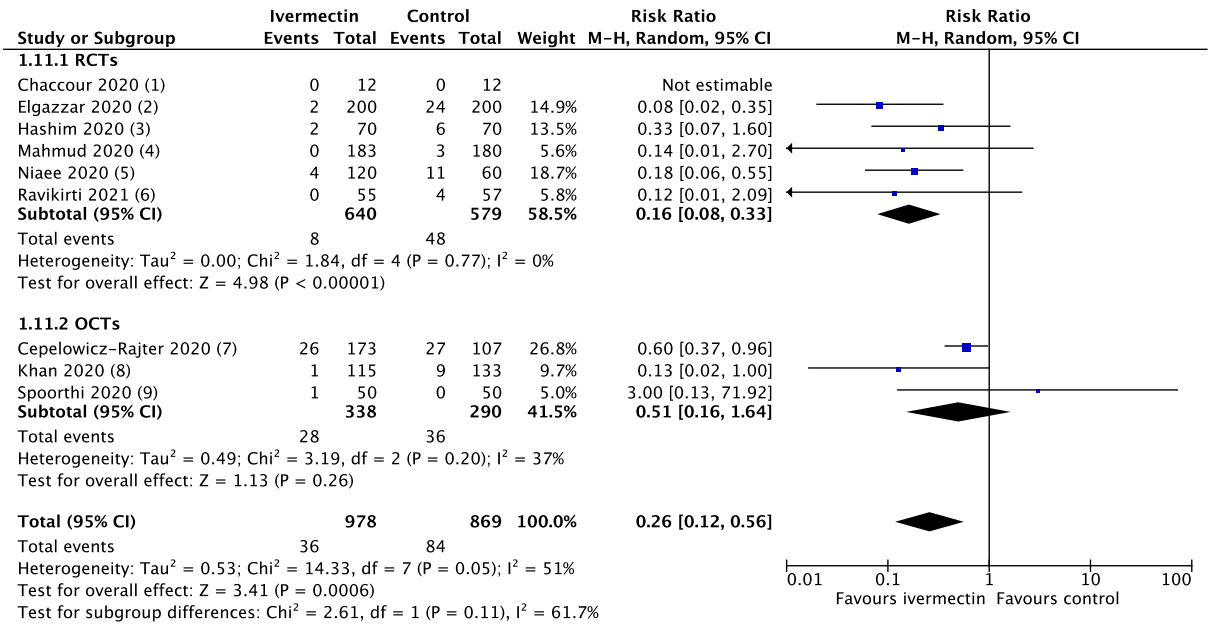
Forest plot 1.1 Deaths (RCTs and OCTs)



Footnotes

(1) IVM 0.2mg/kg one or two doses
(2) IVm 0.4mg/kg single dose
(3) IVM up to 24 mg daily for 4 days. Control group received hydroxychloroquine
(4) IVM 200µgm/kg + Doxy 100 mg BID x 10 days
(5) IVM 12 mg single dose
(6) IVM 6mg once + Doxy 100 mg x 5 days
(7) IVM 12 mg x 2 days
(8) IVM 200µgm/kg + Doxy 100 mg BID x 7 days
(9) IVM 0.2mg/kg one or two doses
(10) IVM 200µgm/kg + Doxy 100 mg BID x 10 days
(11) IVM 200µgm/kg to 400 µgm/kg (1 to 3 doses). Compared with hydroxychloroquine

Forest plot 1.1 Deaths (subgrouped according to study design – RCT or OCT)

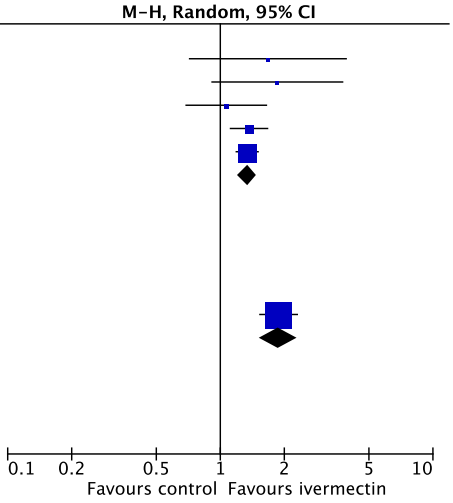


Footnotes

(1) IVm 0.4mg/kg single dose
(2) IVM up to 24 mg daily for 4 days. Control group received hydroxychloroquine
(3) IVM 200µgm/kg + Doxy 100 mg BID x 10 days
(4) IVM 6mg once + Doxy 100 mg x 5 days
(5) IVM 200µgm/kg to 400 µgm/kg (1 to 3 doses). Compared with hydroxychloroquine
(6) IVM 12 mg x 2 days
(7) IVM 0.2mg/kg one or two doses
(8) IVM 12 mg single dose
(9) IVM 200µgm/kg + Doxy 100 mg BID x 7 days

Forest plot 1.2 Improvement

Study or Subgroup	Ivermectin Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Mild to moderate COVID-19						
Ahmed 2020 (1)	14	23	4	11	1.3%	1.67 [0.72, 3.91]
Ahmed 2020 (2)	17	22	5	12	1.9%	1.85 [0.91, 3.76]
Chaccar 2020 (3)	16	25	15	25	5.0%	1.07 [0.69, 1.65]
Mahmud 2020 (4)	111	183	80	180	23.5%	1.36 [1.12, 1.67]
Elgazzar 2020 (5)	99	100	74	100	68.2%	1.34 [1.19, 1.51]
Subtotal (95% CI)		**353**		**328**	**100.0%**	**1.34 [1.22, 1.48]**
Total events	257		178			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.22$, df = 4 (P = 0.70); $I^2 = 0\%$						
Test for overall effect: Z = 5.91 (P < 0.00001)						
1.2.2 Severe COVID-19						
Elgazzar 2020 (6)	94	100	50	100	100.0%	1.88 [1.54, 2.30]
Subtotal (95% CI)		**100**		**100**	**100.0%**	**1.88 [1.54, 2.30]**
Total events	94		50			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.12 (P < 0.00001)						

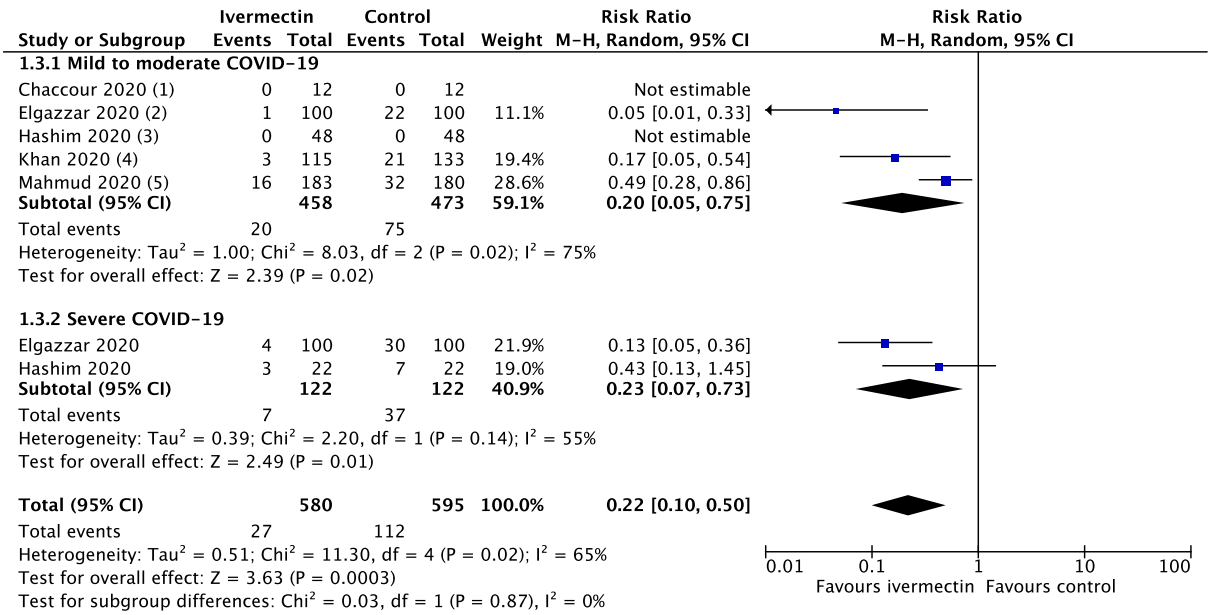


Test for subgroup differences: $Chi^2 = 8.70$, df = 1 (P = 0.003), $I^2 = 88.5\%$

Footnotes

(1) IVM 12mg daily x 5 days
(2) IVM 12mg s+ doxy 200mg stat then 100 mg BD x 4 days
(3) IVM 12 mg at 0, 12, and 24 hours
(4) IVM 6mg once + Doxy 100 mg x 5 days
(5) IVM up to 24 mg daily for 4 days. Control group received hydroxychloroquine
(6) IVM up to 24 mg daily for 4 days. Control group received hydroxychloroquine

Forest plot 1.3 Deterioration



Footnotes

(1) IVM 0.4mg/kg single dose

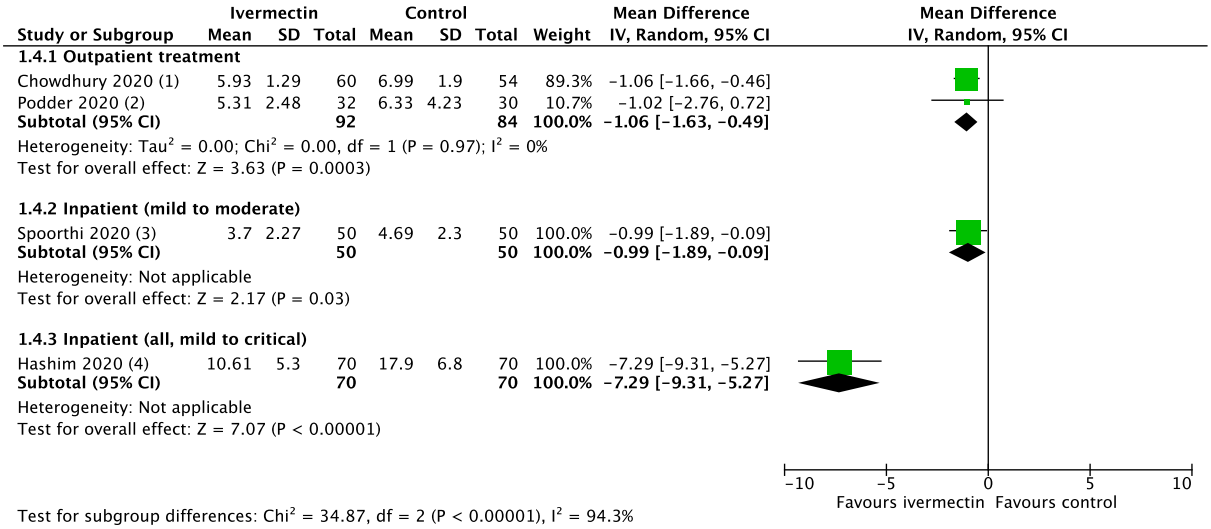
(2) IVM up to 24 mg daily for 4 days. Control group received hydroxychloroquine

(3) IVM 200µgm/kg + Doxy 100 mg BID x 10 days

(4) IVM 12 mg single dose

(5) IVM 6mg once + Doxy 100 mg x 5 days

Forest plot 1.4 Recovery time (clinical)

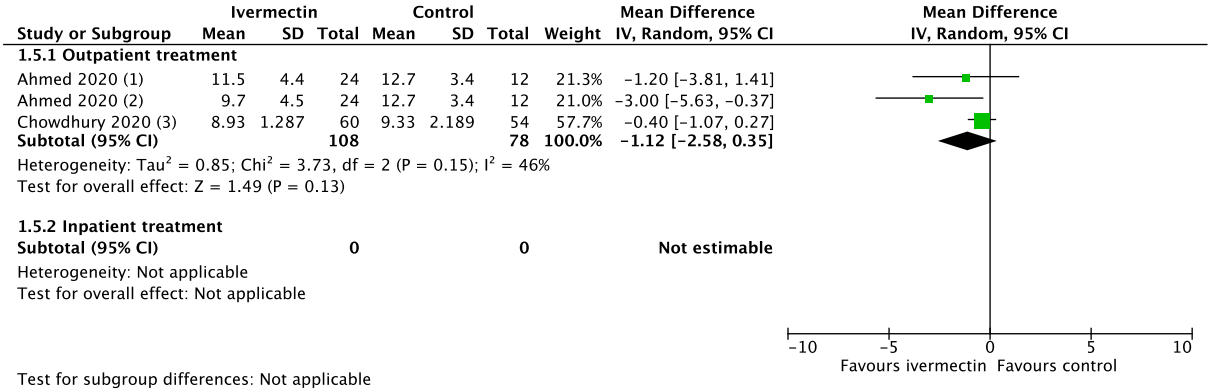


Test for subgroup differences: Chi² = 34.87, df = 2 (P < 0.00001), I² = 94.3%

Footnotes

(1) IVM 200 mcg/kg single dose + doxy 100 mg x 5 days
(2) IVM 200 mcg/kg single dose
(3) IVM 200µgm/kg + Doxy 100 mg BID x 7 days
(4) IVM 200µgm/kg x 2 + Doxy 100 mg BID x 10 days

Forest plot 1.5 Recovery time to -ve PCR



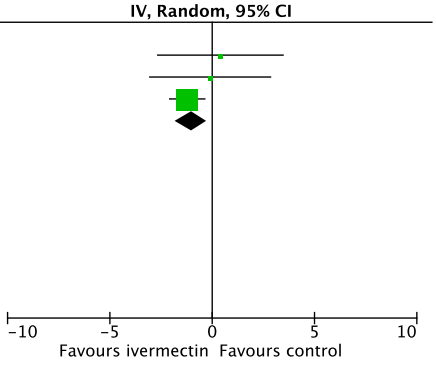
Test for subgroup differences: Not applicable

Footnotes

(1) IVM 12mg + doxy 200 mg stat then 100 mg BD x 4 days
(2) IVM 12 mg daily x 5 days
(3) IVM 200 mcg/kg single dose + doxy 100 mg x 5 days

Forest plot 1.6 Length of hospital stay

Study or Subgroup	Ivermectin Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.6.1 Mild to moderate COVID-19								
Ahmed 2020 (1)	10.1	3.8	24	9.7	4.7	12	6.7%	0.40 [-2.66, 3.46]
Ahmed 2020 (2)	9.6	3.2	24	9.7	4.7	12	7.3%	-0.10 [-3.05, 2.85]
Spoorthi 2020 (3)	6.67	2.01	50	7.89	2.35	50	86.0%	-1.22 [-2.08, -0.36]
Subtotal (95% CI)			**98**			**74**	**100.0%**	**-1.03 [-1.82, -0.23]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.41$, df = 2 (P = 0.49); $I^2 = 0\%$								
Test for overall effect: Z = 2.54 (P = 0.01)								
1.6.2 Severe COVID-19								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Test for subgroup differences: Not applicable

Footnotes

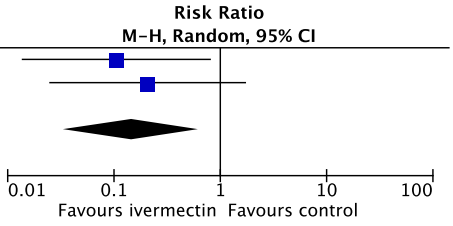
(1) IVM 12mg + doxy 200 mg stat then 100 mg BD x 4 days

(2) IVM 12 mg daily x 5 days

(3) IVM 200µgm/kg + Doxy 100 mg BID x 7 days

Forest plot 1.7 Admission to ICU or ventilation

Study or Subgroup	Ivermectin Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Khan 2020 (1)	1	115	11	133	52.0%	0.11 [0.01, 0.80]
Ravikirti 2021 (2)	1	55	5	57	48.0%	0.21 [0.03, 1.72]
Total (95% CI)		**170**		**190**	**100.0%**	**0.15 [0.03, 0.63]**
Total events	2		16			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.21$, df = 1 (P = 0.65); $I^2 = 0\%$						
Test for overall effect: Z = 2.58 (P = 0.010)						



Footnotes

(1) IVM 12mg single dose; data for "intensive care management"

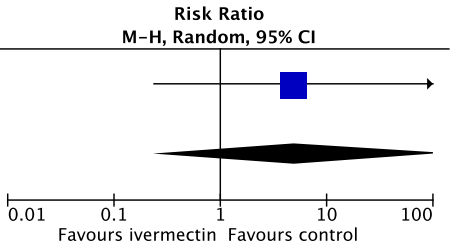
(2) IVM 12 mg x 2 days; data for "invasive ventilation"

Forest plot 1.8 Admission to hospital – no data

Forest plot 1.9 Serious adverse events

Study or Subgroup	Ivermectin Events	Ivermectin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Ahmed 2020 (1)	0	48	0	24		Not estimable
Mahmud 2020 (2)	2	183	0	180	100.0%	4.92 [0.24, 101.74]
Shouman 2020 (3)	0	203	0	101		Not estimable
Total (95% CI)		**434**		**305**	**100.0%**	**4.92 [0.24, 101.74]**
Total events	2		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.03 (P = 0.30)

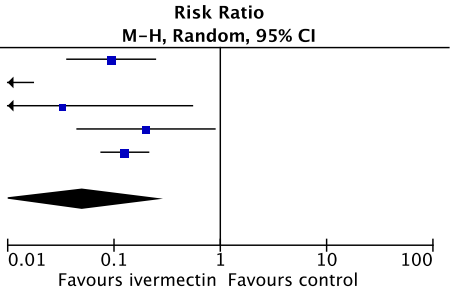


Footnotes
(1) IVM 12 mg (24 pts) and IVM 12mg + doxy (24 pts)
(2) IVM 6mg once + Doxy 100 mg x 5 days
(3) IVM up to 24 mg depending on weight, given in 2 doses 72 hours apart

Forest plot 2.1 Covid-19 infection (all data)

Study or Subgroup	Ivermectin Events	Ivermectin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Alam 2020 (1)	4	58	44	60	23.4%	0.09 [0.04, 0.25]
Carvallo 2020a (2)	0	788	237	407	15.4%	0.00 [0.00, 0.02]
Carvallo 2020a (3)	0	131	11	98	15.2%	0.03 [0.00, 0.55]
Elgazzar 2020 (4)	2	100	10	100	21.3%	0.20 [0.04, 0.89]
Shouman 2020 (5)	15	203	59	101	24.7%	0.13 [0.08, 0.21]
Total (95% CI)		**1280**		**766**	**100.0%**	**0.05 [0.01, 0.29]**
Total events	21		361			

Heterogeneity: $Tau^2 = 3.13$; $Chi^2 = 37.16$, df = 4 (P < 0.00001); $I^2 = 89\%$
Test for overall effect: Z = 3.35 (P = 0.0008)

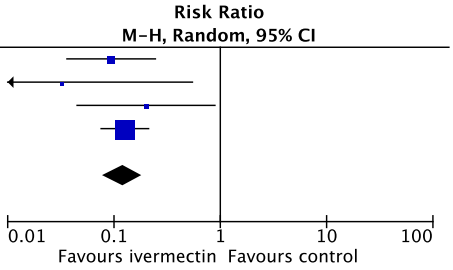


Footnotes
(1) IVM 12 mg weekly x 4 doses
(2) IVM 12 mg weekly + carageenan oro-nasal spray
(3) IVM drops daily + carageenan oro-nasal spray x 14 days
(4) IVM up to 24mg weekly depending on weight x 2 doses
(5) IVM up to 24 mg depending on weight, given in 2 doses 72 hours apart

Forest plot 2.2 Covid-19 infection (sensitivity analysis, excluding Carvallo multi-data)

Study or Subgroup	Ivermectin Events	Ivermectin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Alam 2020 (1)	4	58	44	60	20.0%	0.09 [0.04, 0.25]
Carvallo 2020a (2)	0	131	11	98	2.3%	0.03 [0.00, 0.55]
Elgazzar 2020 (3)	2	100	10	100	8.2%	0.20 [0.04, 0.89]
Shouman 2020 (4)	15	203	59	101	69.5%	0.13 [0.08, 0.21]
Total (95% CI)		**492**		**359**	**100.0%**	**0.12 [0.08, 0.18]**
Total events	21		124			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.63$, df = 3 (P = 0.65); $I^2 = 0\%$
Test for overall effect: Z = 9.70 (P < 0.00001)



Footnotes
(1) IVM 12 mg weekly x 4 doses
(2) IVM drops daily + carageenan oro-nasal spray x 14 days
(3) IVM up to 24mg weekly depending on weight x 2 doses
(4) IVM up to 24 mg depending on weight, given in 2 doses 72 hours apart