The BIRD Recommendation on the Use of Ivermectin for Covid-19

B/RD

British
Ivermectin
Recommendation
Development

Proceedings and conclusions of the British Ivermectin Recommendation Development meeting held on the 20th February 2021 in Bath, United Kingdom.

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The BIRD Ethos

The ethos of the BIRD process is that of scientific rigour and transparency in the spirit of international collaboration towards a common goal – that of saving lives.

"Research is essential in the context of public health emergencies. The primary purpose of such research is to advance public health, prevent illness and save lives. Every researcher that engages in generation of information related to a public health emergency or acute public health event with the potential to progress to an emergency has the fundamental moral obligation to share preliminary results once they are adequately quality controlled for release. The onus is on the researcher, and the funder supporting the work, to disseminate information through pre-publication mechanisms, unless publication can occur immediately using post-publication peer review processes."

World Health Organization statement on 'Global norms for sharing data and results during public health emergencies', after the Ebola emergency (2015)

Executive summary

Introduction

A global health emergency that causes significant mortality and morbidity with serious economic and societal consequences is of the highest priority. Global deaths from covid-19 have reached 2.4 million. No specific treatments are recommended for routine use in all covid-19 infections, and while the population of developed countries will eventually be given the choice of having a vaccine, this choice may not be afforded to people in low- and middle-income countries (LMICs) for a long time.

The antiparasitic medicine ivermectin, which is widely available in LMICs, has been tested in numerous clinical trials of prevention and treatment of covid-19 with promising results. A large body of evidence on ivermectin use in covid-19 had thus accumulated, which required urgent review by health professionals and other stakeholders to determine whether it could inform clinical practice in the UK and elsewhere. More specifically, answers were needed to the following priority questions: (i) For people with covid-19 infection, does ivermectin compared with placebo or no ivermectin improve health outcomes?, and (ii) for people at higher risk of covid-19 infection, does ivermectin compared with placebo or no ivermectin improve health outcomes?

On the 20th of February 2021, the British Ivermectin Recommendation Development (BIRD) meeting was convened in Bath, United Kingdom, to evaluate the evidence on ivermectin use for the prevention and treatment of covid-19. Evidence to address the priority questions was evaluated by a panel of clinical experts and other stakeholders in the form of a DECIDE evidence-to-decision framework, the gold standard tool for developing clinical practice guidelines.

Target audience

The recommendation in this document are aimed at informing national- and local-level health policies and clinical protocols on covid-19 prevention and treatment. As such, the target audience includes national and local policymakers, health care professionals, implementers, patients and the public.

Recommendation development methods

This recommendation on ivermectin for covid-19 was developed using the standard procedures for guideline development as described in the *World Health Organization Handbook for Guideline Development* (2014). Briefly, these procedures include: (i) Identification of priority questions and outcomes; (ii) Evidence retrieval and synthesis; (iii) Assessment of the evidence; (iv) Formulation of the recommendation; and (v) Planning for implementation, dissemination, impact evaluation and updating. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for quantitative evidence was applied, to ensure the quality of the scientific evidence that forms the basis of the recommendation. An up-to-date systematic review and meta-analysis were conducted to prepare the evidence underpinning each of the priority questions.

The BIRD panel of international experts and stakeholders convened to review and make judgements on the evidence and other relevant considerations for each of the following criteria: intervention effects, values, resources, equity, acceptability, and feasibility. The intervention effect criterion refers to the benefits and harms associated with ivermectin for covid-19. The values criterion refers to the importance that those affected by covid-19 assign to the outcomes associated with ivermectin. The resources criterion refers to the resource implications (costs and cost-effectiveness) of ivermectin implementation. The equity criterion considers the health equity implications associated with ivermectin. How acceptable ivermectin would be to relevant stakeholders, including health care workers and patients, and how feasible it would be to implement were also judged by the panel.

Using an electronic survey link, the panel made judgements on these different decision-making criteria which were recorded in a summary table. The summary of the panel judgements then informed the formulation of the draft recommendation, which was guided by the BIRD Steering Group. Possible recommendations included:

- A recommendation in favour of the use of ivermectin for covid-19
- A recommendation not in favour of the use of ivermectin for covid-19
- A recommendation in favour of the use of ivermectin in certain contexts, such as a research context or specific populations or settings.

For the purpose of transparency, the meeting was recorded and live-streamed. The public was invited to participate through a survey link on a streaming channel. With

this online survey they were able to make judgements on the evidence as part of a public participation and involvement initiative (PPI).

The BIRD recommendation

The British Ivermectin Recommendation Development panel recommends ivermectin for the prevention and treatment of covid-19 to reduce morbidity and mortality associated with covid-19 infection and to prevent covid-19 infection among those at higher risk.

To ensure that the recommendation is understood and applied in practice, the contributing experts provided additional remarks where necessary. Whilst the panel agreed that ivermectin should be immediately rolled out, they suggested that further randomized trials of ivermectin for covid-19 within individual country settings would be of value to investigate optimal dosage (dose, duration) and combination treatments according to covid-19 severity and risk factors. The overwhelming majority of the panel agreed that placebo control trials are unlikely to be ethical unless conducted among individuals who are uncertain whether or not to use ivermectin. The panel noted that Ivermectin for human use is given orally. Prevention and treatment protocols can be derived from the clinical trials and numerous protocols already developed by expert clinicians in the field. Many of the expert protocols for the treatment and prevention of covid-19 also include vitamin D3, vitamin C and zinc. The panel also suggested that the public would benefit from general advice on how to keep healthy and to boost immunity.

Implementation considerations

The BIRD panel also considered how to implement the recommendation. They agreed that policymakers will need to address with urgency the authorization, manufacture/import, and distribution of ivermectin to guarantee supply. The panel also indicated the need to raise awareness among frontline workers and the public about the benefits of ivermectin.

Additional considerations by the panel included the postal distribution of covid-19 home kits that include ivermectin and possibly also nutritional supplements, such as zinc and vitamins, to reduce the pressure on health services. For pregnant and lactating women, the panel noted some uncertainty with regard to the safety of

ivermectin and suggested that pregnant and lactating women should be encouraged to consult their health care practitioners before using ivermectin. This caution also applies to parents and carers, as ivermectin may not be suitable for young children under five. Finally, for prophylaxis during foreign travel, the panel considered that pre-travel advisory clinics could control the dispensing of the medication depending on individual risk factors and covid-19 prevalence in the area of travel.

Dissemination of the recommendation

The Steering Group undertook to communicate and disseminate the recommendation to policy makers, decision makers, regulatory bodies, and implementers as soon as possible in the interest of expediting implementation. These bodies include the World Health Organization, the United States National Institutes of Health, Public Health England, among others.

GRADE DECIDE Evidence-to-decision framework

A. The priority questions

1. For people with covid-19 infection, does ivermectin compared with placebo or no ivermectin improve health outcomes?
2. For people at higher risk of covid-19 infection, does ivermectin compared with placebo or no ivermectin improve health outcomes?

Priority of the problem:

A global health emergency that causes significant mortality and morbidity with serious economic and societal consequences is of the highest priority. Global deaths from covid-19 have reached 2.4 million. No specific treatments are recommended for routine use in all covid-19 infections.

Perspective: Clinical practice recommendation – population perspective

Population: For question 1: People with covid-19 infection

For question 2: People without infection at higher risk of contracting covid-19

Intervention: Ivermectin administered orally for prevention or treatment of covid-19 infection

Comparison: Placebo or no ivermectin (with or without co-interventions)

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

Main outcomes:

Comparison 1: Ivermectin treatment versus control

- **Death (primary outcome)**
- Admission to ICU
- Mechanical ventilation
- Recovery time to negative PCR, in days
- Clinical recovery time, in days
- Length of hospital stay, in days
- Improvement

- Deterioration
- Admission to hospital (for outpatient treatment)
- Duration of mechanical ventilation
- Serious adverse events

Comparison 2: Ivermectin prevention versus control

- **Covid-19 infection (primary outcome)**
- Death due to any cause
- Serious adverse events

Background

In countries across the globe, hospitalisations and deaths from covid-19 have increased rapidly over recent months with total deaths now exceeding 2.4 million people (1). 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, 'deaths involving covid-19' have exceeded 120,000 (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 infections in adults and children (4,5). Having been used for decades for this purpose, it is considered safe and effective (5,6) and has an increasing list of indications due to its antiviral and anti-inflammatory properties (6). It is included in the World Health Organization's *Model List of Essential Medicines* (7).

The dominant mechanism of action of ivermectin as an anti-viral agent 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. Ivermectin has also been shown to have a variety of anti-inflammatory effects (10).

Ivermectin's utility has expanded considerably over the last decade and since April 2020 a large and growing database of observational and randomised studies of ivermectin use against covid-19 has been accumulating. A recent review by the Front Line Covid-19 Critical Care Alliance (FLCCC) summarised findings from 27 randomised controlled trials (RCTs) and observational studies on ivermectin for prevention and treatment of covid-19 infection. Their conclusion was that ivermectin "demonstrates a strong signal of therapeutic efficacy"; the FLCCC has therefore recommended the global adoption of ivermectin use against covid-19 (11). Another review commissioned by WHO has reported that ivermectin reduces deaths by 75% but that more evidence is needed (12).

New trials on ivermectin have reported data since these reviews; therefore, an up-to-date systematic review and meta-analysis has been conducted using Cochrane systematic review methodology (13). This systematic review was more comprehensive and interpreted findings in light of risk of bias in individual trials and the certainty of the evidence for each of the outcomes in the review. This Evidence to Decision (EtD) framework presents this latest evidence from this review on the effectiveness and safety of ivermectin for preventing and treating covid-19, as well as other considerations related to the use of ivermectin, including people's values and preferences, equity implications, resources, acceptability and feasibility considerations.

The evidence on the effects of ivermectin in this EtD framework is based on evidence from a systematic review that included RCTs, which offer the highest level of evidence in a review (14). The use of evidence in the form of systematic reviews is now considered to be an international standard for guideline development (15). Guidelines are systematically developed recommendations to assist practitioner and patient decisions about treatments for clinical conditions. Many guideline developers, such as the WHO and NICE, recommend the use of these research syntheses to underpin guideline recommendations (16, 17). Guideline development in response to a health and social care emergency requires an acceleration of the process while maintaining transparency of decision-making and reporting. This is one of the core principles underpinning the development of all NICE guidance and standards. It ensures that users can make judgements on the credibility and applicability of the guideline recommendations (17). Full inclusion criteria and details of methodology of the systematic review that underpins this evidence to decision framework is given in Annex 5.

B. Assessment of the evidence

1) Effects

The evidence on health effects is derived from a systematic review and meta-analysis that originally included 18 RCTs (15 RCTs and 3 quasi-RCTs)(13). This is a rapidly evolving research field and, since the original review, 3 additional studies have reported results, bringing the total number of studies contributing data to updated analyses as at 18 February 2021 to 21 (18 RCTs and 3 quasi-RCTs). The review was conducted using Cochrane review methodology (14). The overall risk of bias in trials was judged as low in 10 trials, moderate or unclear in 5 trials and high in 6 trials. Table 1 summarises the characteristics of these included studies.

Three trials involving 738 participants evaluated covid-19 prevention and 18 trials involving 2003 participants evaluated covid-19 treatment. No trials were conducted among people with long-covid-19. Trial size ranged from 24 to 363 participants. Among the trials of ivermectin for covid-19 treatment, most looked at mild to moderate covid-19; however, four trials included patients with severe covid-19.

Most studies were registered on clinical trial registries, appeared to be self-funded and had been undertaken by clinicians working in the field. There were no obvious conflicts of interest.

Summary of review findings – Forest plots can be found in Annex 1

A. Evidence on ivermectin use for the treatment of covid-19 infection compared with no ivermectin use

Outcome	No. of participants (studies)	Risk ratio or Mean diff (95% confidence interval)	Assumed risk without IVM	Corresponding risk with IVM	Certainty of evidence***	Number needed to treat (NNT) to prevent 1 event	Interpretation of evidence
Death due to any cause*	1892 (13)	RR 0.32 (0.14 to 0.73)	91 deaths per 1000 (all inpatients, including severe covid)*	62 fewer deaths per 1000 (from 25 fewer to 78 fewer)	Low to moderate	NNT (all severity of illness): 16 (13 to 41)	IVM may have a significant effect on reducing deaths
Admission to ICU	279 (2)	RR 1.22 (0.75 to 2.00)	Evidence on admission to ICU was very low certainty.		Very low	–	–
Need for mechanical ventilation	431 (3)	0.65 (0.14 to 3.10)	There was no clear difference between study groups for this outcome		Low	–	IVM may make little or no difference to need for mechanical ventilation

Recovery time in days (negative PCR)	375 (4)	MD -3.20 days (-5.99 to -0.40)	Evidence on relative recovery time to negative PCR (in days) is very low certainty.		Very low	–	–
Recovery time in days (clinical)	176 (2)	MD -3.98 (-10.06 to 2.10)	Evidence on relative clinical recovery time (in days) is very low certainty.		Very low	–	–
Length of hospital stay	72 (2)	MD 0.13 days (-2.04 to 2.30)	Evidence on length of hospital stay is very low certainty.		Very Low	–	–
Improvement	681 (4)	RR 1.34 (1.22 to 1.48) mild/mod RR1.88 (1.54 to 2.30) severe	543 improved per 1000 (with mild/moderate covid) Not calculated	185 more per 1000 (from 119 more to 260 more) Not calculated	Low	–	IVM may lead to relatively more patients improving in a given time frame
Deterioration	1041 (5)	RR 0.26 (0.11 to 0.61)	189 per 1000 (any disease severity)	140 fewer per 1000 (from 74 fewer to 169 fewer)	Low	_	IVM may lead to fewer patients deteriorating in a given time frame

Admission to hospital	194 (2)	RR 0.16 (0.02 to 1.32)	Evidence on admission to hospital is very low certainty	Very low	–	–
Duration of mechanical ventilation	_	_	_	Not estimable	_	_
Severe adverse events (SAEs)	880 (8)	RR 3.23 (0.55 to 18.87)	5/547 (<1%) had an SAE in the IVM group and 0/427 (0%) in control**	Low	–	There may be little or no difference between IVM or no IVM on SAEs

GRADE Working Group grades of evidence
Very low certainty: We are very uncertain about the estimate.
Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.

* Control group rate across all included studies

**The five SAEs occurred in 3 trials – two patients had esophagitis (this is a known side effect of doxycycline, which was co-administered with ivermectin in this trial); one patient had hyponatraemia (this trial used high-dose ivermectin for 5 days); and two patients in a study from Turkey had serious "delirium-like behaviour", which the authors attributed to a possible genetic mutation.

*** See Section D. Evidence Profile, for grade details.

B. Evidence on ivermectin use for preventing covid-19 infection among people at high risk compared with no ivermectin use

Outcome	No. of participants (studies)	RR (95% CI)	Assumed risk without ivermectin	Corresponding risk with ivermectin	Certainty of evidence**	Number needed to treat (NNT) to prevent 1 event	Interpretation of evidence
Covid-19 infection	738 (3)	RR 0.14 (0.09 to 0.21)	296 infections per 1000*	254 fewer infections per 1000 (234 to 269)	Low	NNT: 4 (4 to 4)	IVM may have a significant effect on reducing covid-19 infection
Severe adverse events	538 (2)	–	No severe adverse events recorded.				

GRADE Working Group grades of evidence
Very low certainty: We are very uncertain about the estimate.
Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.

*Control group rate across all included studies

** See Section D. Evidence Profile, for grade details

Summary of effects

The evidence from meta-analyses show that ivermectin treatment may reduce the risk of death among people with covid-19 by an average of 68% (27% to 86%). Analysis also suggests that, in contexts where the death rate among hospitalized patients is high (around 9.1%), the number needed to treat (NNT) to prevent one death may be around 16 patients (95% CI 13 to 41). The evidence also suggests that it may lead to fewer patients deteriorating if they receive ivermectin compared with them not getting ivermectin. Severe adverse events were infrequent suggesting there may be little or no difference in these events with ivermectin use.

With regard to prophylaxis among those with high exposure, the evidence shows that prevention with ivermectin may reduce the risk of getting infected with covid-19 infection by an average of 86% (79% to 91%). The NNT to prevent one covid-19 infection among those with high exposure may be around 4 (95% CI 4 to 4). No severe adverse events occurred in the two studies reporting this outcome.

Desirable effects

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

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

Undesirable effects

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

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

Certainty of the evidence

Judgement: What is the overall certainty of the evidence on the health outcomes associated with ivermectin?

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

BALANCE OF EFFECTS

Judgement: 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

Additional considerations on effects
1. Findings from controlled observational studies are consistent with the RCT evidence demonstrating significant reductions in mortality and morbidity associated with covid-19 (11).[1]

[1]Due to time and resource constraints, we have not expanded on these in this EtD framework.

2. Ivermectin has a well-established safety profile with billions of doses of ivermectin having been used worldwide for parasitic indications (5,6,39,40). Various WHO documents on parasitic infections refer to ivermectin's long safety record (40, 41), noting it to have a wide therapeutic window, which minimizes the risk of adverse events (41). In addition, a systematic review of adverse events associated with ivermectin use suggests that it is safe even at higher than usual doses (39). The low risk of serious adverse events is evident on the World Health Organization and Uppsala University VigiAccess database for pharmacovigilance (42) (updated 1 March 2021), which shows that 16 deaths and 4673 adverse events have been reported for ivermectin since 1992. Putting this in context, 417 deaths and 5489 adverse events had been registered for remdesivir, and 1585 deaths and 177052 adverse events had been registered for covid-19 vaccines by same date with less than a year of use and far fewer doses administered.

Data retrieved from VigiAccess (01.03.2021)			
Medicine[2]	**Year reporting started**	**Deaths[3]**	**Adverse events[4]**
Ivermectin	1992	16	4673
Remdesivir	2020	417	5489

[2] It is not possible to compare different drugs based on this information and conclude that one drug is safer than another. VigiBase reports refer to a suspected causal relationship between a drug and an event, not a confirmed relation. Spontaneous reporting is influenced by many factors and only a small percentage of the occurring adverse drug reactions are notified.

[3] These are unadjusted estimates, therefore do not take into account patient characteristics, indications for treatment, number of patients treated, etc.

[4] VigiAccess is a user-friendly interface that allows us to search VigiBase® and retrieve statistical data on medicines and vaccines side effects (suspected adverse reactions) reported to the WHO Programme for International Drug Monitoring (WHO PIDM).

COVID-19 vaccines	2020	1585	177052

3. The Peruvian government approved ivermectin for use for covid-19 in May 2020 (43). After implementation, death rates in eight states reduced from between 64% to 91% over a two-month period (44). In a further analysis of Peruvian data from 24 states with early ivermectin deployment, excess deaths dropped 59% at 30 or more days and 75% at 45 or more days (44). Overall, between July 31st and November 30th 2020, deaths dropped from 646 to 50 per day. When government policy changed limiting ivermectin use, after a new president took office in November 2020, excess deaths rose from 50 on November 30th to 578 on January 31st 2021. It is possible that this might be due to better compliance with lockdowns, PPE, or other factors. (see Annex 2 for Peru graphs).
4. Uttar Pradesh, the largest state by population in India, started using ivermectin for coivd-19 in early August 2020. Ivermectin kiosks were set up and treatment kits of ivermectin, doxycycline and zinc were disseminated. Deaths declined soon after and have since been extremely low for the population size (>210 million)(45). For example, no deaths due to covid-19 were reported in this state on the 9th Feb 2021. (see Annex 2 for Uttar Pradesh graphs and other regional case studies).
5. Slovakia, Honduras, Bolivia, Panama and Zimbabwe are among several countries that have incorporated the use of ivermectin into their treatment protocols (46-49).
6. Covid-19 death rates between countries where the African Programme for Onchocerciasis Control (APOC) has been implemented and those of non-APOC countries has been compared (50). Among APOC countries with a community-directed treatment with ivermectin strategy, they report a 28% lower mortality (RR= 0.72, 95% CI: 0.67-0.78) and an 8% lower rate of covid-19 infection (RR= 0.92, 95% CI: 0.91-0.93) compared with non-APOC countries. The authors suggest that substantial community use of ivermectin in APOC countries may have inadvertently had a preventive effect against covid-19.

7. A French study has reported serendipitous control of covid-19 by prophylactic treatment of residents and staff at a nursing home where the index case was hospitalised for scabies and treated with ivermectin (51). In addition, a US geriatrician has reported on his observations of treating over 200 high-risk, elderly residents at six assisted living and nursing homes (52). 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 successfully to combat scabies among residents and staff, the clinician started treating residents in the facilities under his care as they tested positive for covid-19 with ivermectin (12mg on Day 1 and Day 8), a combination of vitamins (C, D3, zinc), and an antibiotic (usually doxycycline). He later started using the cocktail for prevention too, when someone in a nursing home tested positive, to prevent infection among others. At six facilities housing a total of 444 high-risk elderly residents, 223 tested positive for covid-19 and 37 died. He reports that the majority of deaths that occurred 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.
8. There is currently no specific treatment on offer for long-covid-19 patients. Emerging evidence suggests that ivermectin may be effective in ameliorating symptoms in this vulnerable group of long-term sufferers, possibly at different dose regimen than for acute covid-19 (53). In a prospective observational study from Peru, 33 long-covid sufferers who were between 4 and 12 weeks from the onset of symptoms were given ivermectin (0.2mg or 0.4mg/kg/day) for between 2 to 4 days depending on symptom severity (53). Additional doses were also given depending on clinical improvement. Total improvement (without any symptoms) was observed in 29 out of the 33 patients after 2 daily doses and total clinical resolution of symptoms was observed among 31 patients.
9. Several prominent clinical covid-19 experts are strongly recommending ivermectin for use in prompt, early initiation therapy for covid-9 infection. (11,54-56) (See protocols table in Annex 3).

VALUES AND PREFERENCES

Is there important uncertainty about, or variability in, how much health professionals and the public value the health outcomes associated with ivermectin?

Treatment outcomes included in this review and meta-analysis were derived from the core outcome set for covid-19 (COS-covid) for hospitalised patients, therefore are important outcomes from a clinician's perspective.(56) Mortality is considered a critical outcome by all, the public and patients (57), as well as healthcare professionals.

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

2) RESOURCES

How large are the resource requirements (costs) associated with ivermectin use for covid-19?

Research evidence

The resources required to manage people with covid-19 in hospital are substantial; it has been estimated that between 5-10% of those with a coronavirus infection will require hospitalisation and 25% of hospitalisations require intensive care (58). A global systematic review of hospitalisations due to covid-19 identified median lengths of hospitalisation ranging from 5 to 29 days, and median stays in an ICU ranging between 5 and 19 days (59). Few published studies have explored the costs associated with covid-19 hospitalisations; however, recently published economic evaluations of treatments for covid-19 infections have reported the cost of one day in ICU to range from USD 1,128 in South Africa (60) to £4520 in the UK (61), and ventilation in a non-ICU setting in the UK has been reported to cost £1356 (61). A further economic evaluation based on US data estimated an average hospital admission cost for

moderate covid-19 infection of USD 7,207 and USD a cost of 33,247 for a severe covid-19 infection admission (62).

Effective prevention of covid-19 could yield significant reductions in hospitalisation-related resources and, if all strategies are equally effective, the one that can be delivered to the largest numbers with the lowest associated costs will be the most cost-effective option. Treatment that minimises the severity of covid-19 infection and reduces hospitalisation length of stay (in particular admission to ICU) would also have potential to reduce hospital resources substantially. As the review evidence on effects of ivermectin suggests that fewer covid-19 patients may deteriorate and that more patients are likely to improve in a given time frame this has the potential to lead to reductions in hospital resource use.

Main resource requirements

No studies examining the resources required for the use of ivermectin for treatment or prophylaxis of covid-19 were identified. However, in many countries (particularly LMICs) ivermectin is readily available and affordable (5,40). The direct cost of ivermectin to either individuals or healthcare purchasing bodies will vary across countries, however, a pack of 100 12mg tablets of ivermectin in 2018 was estimated at approximately $2.90, with a unit price of 0.029 per tablet by an Expert Committee on scabies (40).

In some countries (e.g. the UK and South Africa), oral ivermectin is not currently licensed or registered for human use, therefore, there is no available data on the cost of ivermectin on which to pass judgement of the resources required for its provision. Ivermectin, is however, a generic drug and can be manufactured widely.

Resources required for the administration and monitoring of ivermectin use in hospitalised patients with covid-19 could be expected to be similar to, or less than, comparable oral treatments such as dexamethasone, which is also a generic drug that has been re-purposed to treat covid-19. Economic evaluations of dexamethasone for treating covid-19 have assumed a regimen of one-dose daily for up to 10 days (59,61). Comparatively, the studies of ivermectin reported above in Table 1 propose regimens of one-dose daily for up to five days for inpatients. The resources required for prophylactic use of ivermectin in the community would be lower again, with Table 1 recommending doses ranging from a single dose to three doses, without any associated inpatient administration or monitoring costs.

Excluding non-healthcare technology strategies for the prevention of covid-19 (such as social distancing, national lockdowns, promoting hand washing and wearing of masks etc), resources required for the prevention of covid-19 are substantial. For example, the most prominent healthcare-technology prevention strategy currently is mass vaccination. The UK National Audit Office recently reported total expected investment of £11.7 billion to "purchase and manufacture COVID-19 vaccines for the UK, deploy them in England and support global efforts to find vaccines" (63). Furthermore, purchase of sufficient supplies of vaccinations in LMICs, and even upper-middle income countries such as South Africa, will be slower than in high-income countries (64). The resources required for the use of ivermectin prophylactically would likely be lower than that of vaccination on a per-dose basis as vaccination programmes are associated with administration costs of skilled vaccinators and vaccination centres. Comparably, oral ivermectin would not be subject to these costs as the medication can be taken unsupervised in one's own home. However, doses of ivermectin for prophylaxis would be required more frequently than vaccination, which is expected to provide protection after one or two doses (65), as ivermectin would be required at regular intervals prophylactically or following each potential exposure to a coronavirus infection.

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

Judgement: What is the certainty of the evidence on costs?

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

COST-EFFECTIVENESS

How cost-effective is ivermectin compared with no ivermectin?

There is no existing evidence of the cost-effectiveness of ivermectin for either treatment or prophylaxis of covid-19 compared to alternative courses of action. However, a systematic review of economic evaluations of antiviral treatments in pandemics and outbreaks of respiratory diseases, similar to covid-19, has shown that antiviral treatments are likely to be cost-effective either as standalone treatments or as part of a multifaceted treatment approach (66). Economic evaluations of ivermectin for treatment and prophylaxis of covid-19 are needed to examine whether it is cost-effective against alternative treatments and preventive programmes, such as vaccination.

Judgement: 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

3) EQUITY

What would be the impact of ivermectin on equity?

Research evidence

No specific research studies were identified in related to the equity implications of ivermectin for covid-19.

Additional considerations
1. Covid-19 is a disease that is proving to disproportionately affect disadvantaged communities, both in low- and high-income settings. Cheap and effective treatments for covid-19, therefore, have the potential to improve health equity. 2. Black and Minority Ethnic (BAME) population groups are more exposed to Covid-19 due to occupation and living conditions and are thus at higher risk than the general population for being infected and experiencing worse associated health outcomes compared with other ethnic groups (68, 69). 3. BAME groups are also accessing vaccines in lower numbers than other ethnic groups in certain countries (70). Ivermectin may more effectively reach traditionally 'hard-to-reach' groups because it is cheap, easy to distribute and administer, and has a good safety record. 4. Some countries, such as India, are awaiting further safety data on the covid-19 vaccines (71); it would therefore improve health equality to offer people in these countries a re-purposed medicine such as ivermectin that has a good chance of reducing deaths and infection rates among those at risk. 5. Disadvantaged people and those living in LMICs are likely to have lower access to covid-19 vaccinations than those living in high-income countries, as the roll-out of the vaccines is expected to take much longer in LMICs. 6. Health care and other frontline workers are great risk of covid-19 infection. The evidence shows that ivermectin may reduce their occupational risk, thereby improving health equity for this occupationally vulnerable group. 7. The UK Office of National Statistics reports that covid-19 disproportionally affects people with disabilities – 'in England, the risk of death involving the coronavirus (COVID-19) was 3.1 times greater for more-disabled men and 1.9 times greater for less-disabled men, compared with non-disabled men; among women, the risk of death was 3.5 times greater for more-disabled women and 2.0 times greater for less-disabled women, compared with non-disabled women' (67). 8. Ivermectin is affordable, and can be distributed by various means, e.g. post, and self-administered. It can therefore effectively reach traditionally

'hard-to-reach' and vulnerable populations such as undocumented migrants, homeless, 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.

9. Ivermectin has for the past 30+ years has been used extensively, safely and successfully for the control and eradication of common and disabling tropical diseases affecting a majority of populations in LMICs. The mass drug administration (MDA) of ivermectin in these settings has also brought significant non-target benefits, e.g. health and socioeconomic prospects, of all communities where MDA has been carried out (72).
10. 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 (73). Having an alternative preventive measure against covid-19 will buy time and increase equity through increased access to health care for when vaccination is not widely available or not an option.
11. There are some early indications that vaccination may not be suitable for all elderly people, who are an at-risk group for poor health outcomes associated with covid-19 infection (74). Having an alternative or additional preventive measure with a known safety profile in this age group could be welcomed by care takers and nursing home residents and could, therefore, improve health equity for this vulnerable group.
12. Recognition of the contributions made by clinician-researchers' in LMICs to covid-19 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 journals in high-income countries to be more receptive and supportive of clinician-researchers in LMICs (for example, by providing assistance with medical writing and paper submission) and may reduce publication bias against research originating from LMICs.
13. Health care waiting lists for people suffering from non-covid-19 health issues are increasing exponentially and in England, for example, it is estimated that numbers could reach 10 million by April 2021, which

represents 185 of the population (76). Any intervention that will reduce waiting times and facilitate increased access to hospital treatment will improve equity.

Judgement: What would be the impact of ivermectin on equity?

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

4) ACCEPTABILITY

Would ivermectin be acceptable to health professionals, patients, families and other stakeholders?

Research evidence

No specific research studies were identified on the acceptability of ivermectin for covid-19.

Additional considerations
1. Several of the previous additional consideration bullet points of this document indicate that this would be an acceptable intervention, such as its widespread use in many countries for parasitic indications, its growing use for covid-19, its potential to reduce the health, social and economic impact of covid-19 and lockdowns and its long safety record.

2. Ivermectin is already on the WHO Essential Medicine List (7) and has a long track record of clinical safety (40,41). This is supported by the adverse events registrations on the Vigiaccess database (42) described above, and findings of a recent systematic review of adverse events confirming that ivermectin is safe, even at higher than usual doses (39). As it has been used for covid-19 in several countries and states for some months, any increase in deaths would have been demonstrated on the Vigiaccess database by now, as has been shown with Remdesivir and covid-19 vaccines. This further suggests that ivermectin would be acceptable.
3. The evidence shows that ivermectin may reduce covid-19 deaths, as well as the severity of illness, therefore, it is likely to be very acceptable to people with any stage of covid-19 infection.
4. For prevention of at-risk people, such as health workers and family 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 (40), which suggests that people would find this acceptable.
5. Logic suggests that any intervention that reduces the demand for hospital beds would be very acceptable to policymakers and health care workers.
6. Similarly, logic suggests that any intervention that reduces the risk of getting covid-19 infection without serious side effects would be acceptable to most stakeholders.
7. Logic also suggests that individuals suffering with long-covid would be interested in trying a re-purposed, widely used and inexpensive medicine such as ivermectin, with its long safety record, when there is nothing else on offer, if there is the remotest chance that it may ameliorate symptoms.

8. Finally, Emergency Use Authorisation (EUA) has been acceptable for covid-19 vaccines and other novel treatments. The Emergency use authorisation for covid-19 vaccines is based on "the totality of scientific evidence available that the product may be effective to prevent covid-19 during the covid-19 pandemic and that the known and potential benefits outweigh the known and potential risks." The terminology "may prevent" is consistent with low certainty evidence. In addition, the options that have already been given EUA, such as covid-19 vaccines and remdesivir, have less safety data than ivermectin – therefore an EUA for ivermectin is likely to be at least as acceptable to stakeholders as these options.

Judgement: Would ivermectin be acceptable to health professionals, patients, families and other stakeholders?

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

5) FEASIBILITY

Would ivermectin be feasible to implement?

Research evidence

No specific research studies were identified on the feasibility of ivermectin for covid-19.

Additional considerations
1. 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 (5). 2. From the demand side, if ivermectin is free and available, it is extremely feasible in all countries. As it is a relatively inexpensive medicine, many

people, particularly in higher income countries, may even be prepared to pay for ivermectin themselves.

3. 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.
4. Ivermectin is unlicensed in some countries, including the UK, and the implications of this are uncertain. However, as ivermectin is a generic medicine, there are many manufacturers worldwide. In addition, during the current emergency situation it would be expected that governments' have measures in place to expedite approval and implementation of re-purposed medicines that reduce deaths associated with covid-19.
5. For immediate supplies in those countries without a manufacturer of ivermectin, importation would be required and ways of facilitating this without delays may need additional consideration.

Judgement: Would ivermectin be feasible to implement?

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

Summary of BIRD panel 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

*Majority judgements – see Annex 7 for judgement graphs.

C. Conclusions

Recommendation

The British Ivermectin Recommendation Development Panel recommends ivermectin for the prevention and treatment of covid-19 to reduce morbidity and mortality associated with covid-19 infection and to prevent covid-19 infection among those at higher risk.

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

Remarks

- Whilst the panel agreed that ivermectin should be immediately rolled out, they suggested that further randomized trials of ivermectin for covid-19 within individual country settings would be of value to investigate optimal dosage (dose, duration) and combination treatments according to covid-19 severity and risk factors.
- The overwhelming majority of the panel agreed that placebo control trials are unlikely to be ethical unless conducted among individuals who are uncertain whether or not to use ivermectin.
- Ivermectin for human use is given orally. Prevention and treatment protocols can be derived from the clinical trials and numerous protocols already developed by expert physicians in the field. Suggested protocols include:
    - For covid-19 prevention among frontline workers: 12mg every 4 to 6 weeks. (Alam/India protocol)

  - For covid-19 prevention among case contacts: 12mg on day 1 and day 3 or 4 post-exposure. (MATH+ and Shouman protocols)
  - For covid-19 prophylaxis among elderly nursing home residents: 12mg on day 1 and day 8 after identification of an index case. (Chesler protocol)
  - For covid-19 treatment of asymptomatic and mild covid-19 (early outpatient treatment): 0.2mg/kg (~12mg tablet for a 60kg person) on day 1 and day 2. Days 3 to 5 the same, if not recovered. (MATH+ protocol) Some protocols use 0.4mg/kg instead of 0.2mg/kg.
  - No RCT evidence was found on ivermectin for the treatment of people with long-covid and it is possible that different dosing regimen may be required. Therefore, determining the appropriate dosing regimen for long-covid sufferers represents an important research gap. In the meantime, a published regimen for long covid-19 gives an ivermectin dose of 0.2mg/kg or 0.4mg/kg, depending on symptom severity, for 2 to 4 days. (Aguirre-Chang protocol)
- Many of the expert protocols for the treatment and prevention of covid-19 also include vitamin D3, vitamin C and Zinc. (refer to Annex 4)
- The public would benefit from general advice on how to keep healthy and to boost immunity, such as taking daily exercise; avoidance of alcohol and sugar; daily vitamin and mineral supplements during the pandemic (in particular, vitamin D, vitamin C and zinc); getting as much sunshine on the skin as possible; and spending time in nature.
- Courtesy of Professor Satoshi Omura and colleagues at Kitasano University, a list of international suppliers can be found in Annex 8. This list is not comprehensive.

Implementation considerations

1. Policymakers will need to expedite ivermectin authorisation. Those countries without ivermectin manufacturers will need to look at how to establish a guaranteed supply of the medicine and how to distribute it in the most efficient way, e.g. based on prioritisation according to high risk groups or areas.
2. Media coverage and campaigns may be the most effect way to raise public awareness and to counter-act the extensive misinformation that has been disseminated about this effective and safe medicine.
3. Policymakers may wish to ensure that frontline workers are informed of the benefits of ivermectin prevention as soon as possible and, after allocating doses to hospitals for covid-19 treatment, may wish to prioritise supplies of ivermectin for this at-risk group.
4. Policymakers in some countries may wish to make ivermectin a medically dispensed medicine rather than an over the counter medicine and a registry could be kept, to accumulate country-specific evidence on its uptake, use and safety.
5. Policymakers may wish to consider providing their populations with a covid-19 home kit for each family member, consisting of a blister pack of a dose of ivermectin, plus 7 days of zinc, vitamin D3 and vitamin C for use in the event of exposure to, or contact with, a person with covid-19 infection. This should be possible at relatively low cost. Guidance on the appropriate ivermectin dose according to weight, and for children over five, could also be provided with the kit.
6. The covid-19 home kit could be delivered by post in many countries, thereby, reducing the risk of those with covid-19 infection infecting others. This would alleviate the need for people to visit a doctor for the medication and would reduce the pressure on health services.
7. Pregnant and lactating women would need to be made aware that they must consult their general practitioners if they are exposed to someone with covid-19 or if they develop symptoms, as ivermectin may not be suitable for use.
8. Parents and carers would need to be made aware that ivermectin may not be suitable for young children under five; they would need to consult their general practitioners for advice should their young child develop symptoms.
9. For prophylaxis during foreign travel, the prescribing process could be within the remit of pre-travel advisory clinics run by general practitioners. Pre-travel advisory clinics could control the dispensing of the medication depending on individual risk factors and covid-prevalence in the area of travel.

Research gaps

1. In people with covid-19 infection, what are the optimal ivermectin dose regimens to reduce the risk of having long covid-19 and other longer-term sequelae?
2. In people with covid-19 infection, does ivermectin in combination with doxycycline or other medicines, such as hydroxychloroquine, compared with ivermectin alone lead to improved health outcomes?
3. For people with long-covid, what are the effects of different ivermectin regimen (with or without other medications) on health outcomes?
4. What is the best dose and frequency to be used for routine prophylaxis among different at-risk groups?

D. Evidence Profile

Author(s): Andrew Bryant, Theresa A Lawrie, Therese Dowswell, Edmund Fordham, Sarah Hill, Scott Mitchell, Tony Tham
Date: 2021-02-13
Question: Should Ivermectin vs control be used for the treatment of covid-19 infection?
Settings:
Bibliography: Bryant A, Lawrie TA, Dowswell T, Fordham E, Hill S, Mitchell S, Tham T. Ivermectin for prevention and treatment of covid-19 infection. (updated analyses of a submitted review)

Quality assessment							No of patients		Effect		Certainty	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ivermectin	Control	Relative (95% CI)	Absolute		
Death from any cause (subgrouped by disease severity												
13	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	25/989 (2.5%)	82/903 (9.1%)	RR 0.32 (0.14 to 0.73)	62 fewer per 1000 (from 25 fewer to 78 fewer)	⊕⊕OO LOW	CRITICAL
Death (sensitivity analysis excluding Fonseca 2021)												
12	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/937 (1.4%)	57/788 (7.2%)	RR 0.25 (0.13 to 0.48)	54 fewer per 1000 (from 38 fewer to 63 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Death (sensitivity analysis excluding studies at high ROB)												
11	randomised trials	serious[3]	serious[4]	no serious indirectness	no serious imprecision	none	19/894 (2.1%)	67/803 (8.3%)	RR 0.28 (0.09 to 0.88)	60 fewer per 1000 (from 10 fewer to 76 fewer)	⊕⊕OO LOW	CRITICAL
Death (sensitivity analysis excluding studies with active controls)												

9	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/575 (1.2%)	22/508 (4.3%)	RR 0.45 (0.21 to 0.98)	24 fewer per 1000 (from 1 fewer to 34 fewer)	⊕⊕OO LOW	CRITICAL
Recovery time to -ve PCR test (Better indicated by lower values)												
4	randomised trials	serious[6]	serious[7]	no serious indirectness	serious[8]	none	207	168	-	MD 3.2 lower (5.99 to 0.4 lower)	⊕OOO VERY LOW	IMPORTANT
Recovery time (clinical) - Outpatient treatment (Better indicated by lower values)												
2	randomised trials	very serious[9]	no serious inconsistency	no serious indirectness	serious[10]	none	92	84	-	MD 1.06 lower (1.63 to 0.49 lower)	⊕OOO VERY LOW	IMPORTANT
Recovery time (clinical) - Inpatient (mild to moderate) (Better indicated by lower values)												
1	randomised trials	very serious[9]	no serious inconsistency	no serious indirectness	serious[11]	none	48	48	-	MD 7.32 lower (9.25 to 5.39 lower)	⊕OOO VERY LOW	IMPORTANT
Recovery time (clinical) - Inpatient (severe) (Better indicated by lower values)												
1	randomised trials	very serious[9]	no serious inconsistency	no serious indirectness	serious[11]	none	11	22	-	MD 3.98 lower (10.06 lower to 2.1 higher)	⊕OOO VERY LOW	IMPORTANT
Admission to ICU												
2	randomised trials	no serious risk of bias[12]	no serious inconsistency	serious[13]	serious[14]	none	20/107 (18.7%)	31/172 (18%)	RR 1.22 (0.75 to 2)	40 more per 1000 (from 45 fewer to 180 more)	⊕OOO VERY LOW	CRITICAL
Mechanical ventilation												

3	randomised trials	no serious risk of bias[12]	no serious inconsistency	serious[13]	serious[14]	none	13/207 (6.3%)	29/224 (12.9%)	RR 0.65 (0.14 to 3.1)	45 fewer per 1000 (from 111 fewer to 272 more)	⊕⊕OO LOW	CRITICAL
Length of hospital stay - Mild to moderate covid-19 (Better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[15]	none	45	23	-	MD 0.13 higher (2.04 lower to 2.3 higher)	⊕OOO VERY LOW	IMPORTANT
Improvement - Mild to moderate covid-19												
4	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	other	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)	⊕⊕OO LOW	IMPORTANT
Improvement - Severe covid-19												
1	randomised trials	Very serious[16]	no serious inconsistency	no serious indirectness	no serious imprecision	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	no serious risk of bias[12]	serious[17]	no serious indirectness	no serious imprecision	none	27/534 (5.1%)	96/507 (18.9%)	RR 0.26 (0.11 to 0.61)	140 fewer per 1000 (from 74 fewer to 169 fewer)	⊕⊕OO LOW	IMPORTANT
Admission to hospital												
2	randomised trials	serious[16]	no serious inconsistency	no serious indirectness	very serious[18]	none	0/99 (0%)	5/95 (6%)	RR 0.16 (0.02 to 1.32)	-	⊕OOO VERY LOW	IMPORTANT
Serious adverse events												

9	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[19]	none	5/547 (1%)	0/427 (0%)	RR 3.23 (0.55 to 18.87)	-	⊕⊕OO LOW	CRITICAL

[1] Most of the studies contributing data had design limitations or serious design limitations

[2] Statistical heterogeneity (I2) = 61%. There was considerable variation in the size of treatment effect

[3] Most of the studies contributing data had design limitations

[4] High statistical heterogeneity (I2 = 69%)

[5] Most of the data (80%) were from studies with very serious design limitations

[6] Studies contributing data had design limitations (approximately half had serious design limitations (49.4%)

[7] There was serious statistical heterogeneity (i2 =90%)

[8] Total sample size less than 400 participants

[9] Data from studies with serious design limitations

[10] Total sample size >200

[11] Data from single study with small sample size (<100)

[12] Not downgraded for study design. Most of the data was from a study with lower risk of bias

[13] The study contributing most of the weight had an active control group

[14] Wide 95% CI crossing the line of no effect

[15] Wide 95% CI crossing the line of no effect and low sample size

[16] Single study with design limitations

[17] High statistical heterogeneity (i2 = 63%)

[18] Wide 95% CI crossing line of no effect and low event rate

[19] Wide 95% CI crossing line of no effect (not downgraded for low events - sample size 974 - but only 5 events

Author(s): Andrew Bryant, Theresa A Lawrie, Therese Dowswell, Edmund Fordham, Sarah Hill, Scott Mitchell, Tony Tham

Date: 2021-02-13

Question: Should Ivermectin vs control be used for the prevention of covid-19 infection?

Settings:

Bibliography: Bryant A , Lawrie TA, Dowswell T, Fordham E, Hill S, Mitchell S, Tham T. Ivermectin for prevention and treatment of covid-19 infection. (updated analyses of a submitted review)

Quality assessment							No of patients		Effect		Certainty	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ivermectin	Control	Relative (95% CI)	Absolute		
covid-19 infection												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	21/420 (5%)	94/318 (29.6%)	RR 0.14 (0.09 to 0.21)	254 fewer per 1000 (from 234 fewer to 269 fewer)	⨁⨁⨁◯ LOW	IMPORTANT
Serious adverse events												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/320 (0%)	0/218 (0%)	not pooled	No estimable data	⨁◯◯◯ VERY LOW	CRITICAL

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.
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. Accessed 28 December 2020.
5. 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.
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. Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen. J. Antibiot (Tokyo) 2020; 73, 593-602
9. Caly L, Druce L, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res. 178, 104787.
10. DiNicolantonio JJ, Barroso J, McCarty, M. Ivermectin may be a clinically useful anti-inflammatory agent for late-stage covid-19. Open Heart 2020;7:e001350.
11. 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.
12. Andrew Hill, Ahmed Abdulamir, Sabeena Ahmed, Asma Asghar, Olufemi Emmanuel Babalola, Rabia Basri, et al. Meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection, 19 January 2021, PREPRINT (Version 1). Research Square January 19, 2021. https://www.researchsquare.com/article/rs-148845/v1.
13. Bryant A, Lawrie TA, Dowswell T, Fordham E, Tham T, Hill S, Mitchell S. Ivermectin for prevention and treatment of covid-19 infection: a systematic review and meta-analysis (submitted 5-2-2021).

14. 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.
15. WHO. *Who Handbook for Guideline development*. 2nd edition. Geneva, Switzerland: In, 2014. https://www.who.int/publications/guidelines/handbook_2nd_ed.pdf
16. Lunny C, Ramasubbu C, Gerrish S, *et al*. Impact and use of reviews and 'overviews of reviews' to inform clinical practice guideline recommendations: protocol for a methods study. *BMJ Open* 2020;10e031442. Doi: 10.1136/bmjopen-2019-031442
17. NICE. Developing NICE guidelines: the manual. Process and methods [PMG20]Published date: 31 October 2014 Last updated: 15 October 2020
18. 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 29 Dec. 2020)
19. Babalola OE, Bode CO, Ajayi AA, Alakaloko FM, Akase IE, Otrofanowei E, et al. Ivermectin shows clinical benefits in mild to moderate covid19: A randomised controlled double blind dose response study in Lagos. medRxiv January 6, 2021. (Accessed January 25 2021). [DOI: https://doi.org/10.1101/2021.01.05.21249131]
20. Chaccour C, Casellas A, Matteo A, Pineda I, Fernandez-Montero A, Castillo P, et al. The effect of early treatment with ivermectin on viralload, symptoms and humoral response in patientswith mild covid-19: a pilot, double-blind, placebo-controlled, randomized clinical trial. Research Square December 7 2020 (Accessed January 25 2021). [DOI: 10.21203/rs.3.rs-116547/v1]
21. 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)
22. 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.)
23. 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)
24. Fonseca AJ. The effect of chloroquine, hydroxychloroquine OR ivermectin in patients with severe manifestations of coronavirus. Registro Brasileiro de Ensaios Clinicos 2020. [Other: https://ensaiosclinicos.gov.br/rg/RBR-8h7q82/]

25. 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)
26. Krolewiecki A, Lifschitz A, Moragas M, Travacio M, Valentini R, Alonso D. Antiviral effect of high-dose ivermectin in adults with covid-19: a pilot randomised,controlled, open label, multicentre trial. ResearchGate November 2020. (Accessed January 25 2021). [Other: https://www.researchgate.net/publication/345953065_Antiviral_effect_of_high-dose_ivermectin_in_adults_with_COVID-19_a_pilot_randomised_controlled_open_label_multicentre_trial_Summary_Background]
27. 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)
28. Mohan A. Randomised Controlled Trial of Ivermectin in hospitalised patients with covid19. Clinical Trials Registry -India http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=44196.
29. 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.)
30. Okumus N. Ivermectin for Severe covid-19 Management. https://clinicaltrials.gov/ct2/show/NCT04646109 2020.
31. Petkov S. Multicenter, randomized, double-blind, placebo-controlled study investigating efficacy, safety and tolerability of ivermectin HUVE-19 in patients with proven SARS-CoV-2 infection (covid-19) and manifested clinical symptoms. EU Clinical Trials Register https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-002091-12/BG.
32. 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)
33. Raad H. In vivo use of ivermectin (IVR) for treatment for corona virus infected patients (covid-19): a randomized controlled trial. Chinese Clinical Trial Registry http://www.chictr.org.cn/showproj.aspx?proj=54707.

34. Ravikirti et al. Ivermectin as a potential treatment for mild to moderate covid-19 – A double blind randomized placebo-controlled trial. 2021. (Preprint server)
35. Rezai M. Effectiveness of Ivermectin in the Treatment of Coronavirus Infection in Patients admitted to Educational Hospitals of Mazandaran in 2020. Iranian Registry of Clinical Trials https://en.irct.ir/trial/49174.
36. Schwartz E. Ivermectin vs. Placebo for the Treatment of Patients With Mild to Moderate COVID-19. https://clinicaltrials.gov/ct2/show/NCT04429711.
37. Chala RE. NCT04701710. Prophylaxis Covid-19 in Healthcare Agents by Intensive Treatment With Ivermectin and Iota-carrageenan (Ivercar-Tuc). https://clinicaltrials.gov/ct2/show/NCT04701710
38. 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)
39. Navarro M, Camprubí D, Requena-Méndez A, Buonfrate D, Giorli G, Kamgno J et al. Safety of high-dose ivermectin: a systematic review and meta-analysis. Journal of Antimicrobial Chemotherapy 2020;75(4):827-834. [DOI: 10.1093/jac/dkz524. PMID: 31960060]
40. World health Organization Expert Committee on the selection and use of essential medicines. Application for inclusion of ivermectin on the WHO Model List of Essential Medicines (EML) and Model List of Essential Medicines for Children (EMLc) for the indication of Scabies. World Health Organization; Geneva, Switzerland 2018;https://www.who.int/selection_medicines/committees/expert/22/applications/s6.6_ivermectin.pdf((accessed 28/12/2021)). [Other:]
41. WHO informal consultation on a framework for scabies control. Meeting report. WHO Regional Office for the Western Pacific. Manila 19021 February 2019. ISBN 978-92-4-000806-9.
42. World Health Organization and the Uppsala Monitoring Centre. VigiAccess. http://www.vigiaccess.org (accessed 12 February 2021).
43. Chamie J. Real-World Evidence: The Case of Peru. Causality between Ivermectin and COVID-19 Infection Fatality Rate. https://www.researchgate.net/publication/344469305 2020;Accessed 1 February 2021.
44. 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).
45. Trialsitenews. Northern Indian State of Uttar Pradesh Drops Hydroxychloroquine & Replaces with Ivermectin for COVID-19 Patients. https://trialsitenews.com/northern-indian-state-of-uttar-pradesh-drops-hydroxychloroquine-replaces-with-ivermectin-for-covid-19-patients/(Accessed 12/02/2021).
46. Trialsitenews. https://trialsitenews.com/slovakia-becomes-the-first-eu-nation-to-formally-approve-ivermectin-for-both-prophylaxis-and-treatment-for-covid-19-patients/ (accessed 12 February 2021).
47. Despacho de Communicaciones y estrategia Presidential. Honduras https://covid19honduras.org/ article title (accessed 14/2/2021)

48. Bolivian Ministry of Health. [Ministry of health authorises the use of ivermectin to control covid-19] https://www.minsalud.gob.bo/4157-ministerio-de-salud-autoriza-uso-de-ivermectina-contra-el-covid-19-bajo-protocolo
49. Repubic of Panama, Ministry of Social Security. 'Pharmaceutacol protocol will be applied to patients testing positive for covid-19 recovering at home.' www.css.gob.pa/web/13-agosto-2020ab.html 13th August 2020 (Accessed on February 18th 2021)
50. Guerrero, R, Bravo, LE, Munoz, E, et al. COVID-19: The Ivermectin African Enigma. Colombia Medica (2020). DOI: 10.25100/cm.v51i4.4613
51. Bernigaud C, Guillemot D, Ahmed-Belkacem A, Grimaldi-Bensouda L, Lespine A, Berry F, et al. Oral ivermectin for a scabies outbreak in a long-term–care facility: Potential value in preventing COVID-19 and associated mortality? British Journal of Dermatology (in press);https://doi.org/10.1111/bjd.19821.
52. Chesler DL. Letter to Dr Bray at the National Institutes of Health. Personal communication.
53. Aquirre-Chang G, Castillo Saavedra E, Yui Cerna M, Trujillo Figueredo A, Cordova Masias J. Post-acute or prolonged covid-19: treatment with ivermectin for patients wih persistent or post-acute symptoms. Researchgate. English translation. https://www.researchgate.net/publication/344318845.
54. McCullough PA, Alexander PE, Armstrong R, Arvinte C, Bain AF, Bartlett RP, et al. Multifaceted highly targeted sequential multidrug treatment of early ambulatory high-risk SARS-CoV-2 infection (COVID-19). Reviews in Cardiovascular Medicine 2020; 21(4):517-530.
55. Frontline Covid-19 Critical Care Alliance. MATH+ Protocol. https://covid19criticalcare.com/math-hospital-treatment/pdf-translations/ (accessed 16-02-2021).
56. COMET. The meta-COS for research in covid-19 hospitalised patients. https://www.comet-initiative.org/assets/downloads/covid-19%20meta%20COS_Table%201_29th%20October%202020.pdf (accessed 12/01/2021)
57. Harvey D, Kueper M. Improving patient experience during covid-19 pandemic: one family's reflections. J. Hosp. Med. 2020 December;15(12):760-762.
58. Salzberger B, Buder F, Lampl B, et al. Epidemiology of SARS-CoV-2. Infection (2020). https://doi.org/10.1007/s15010-020-01531-3.
59. 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.

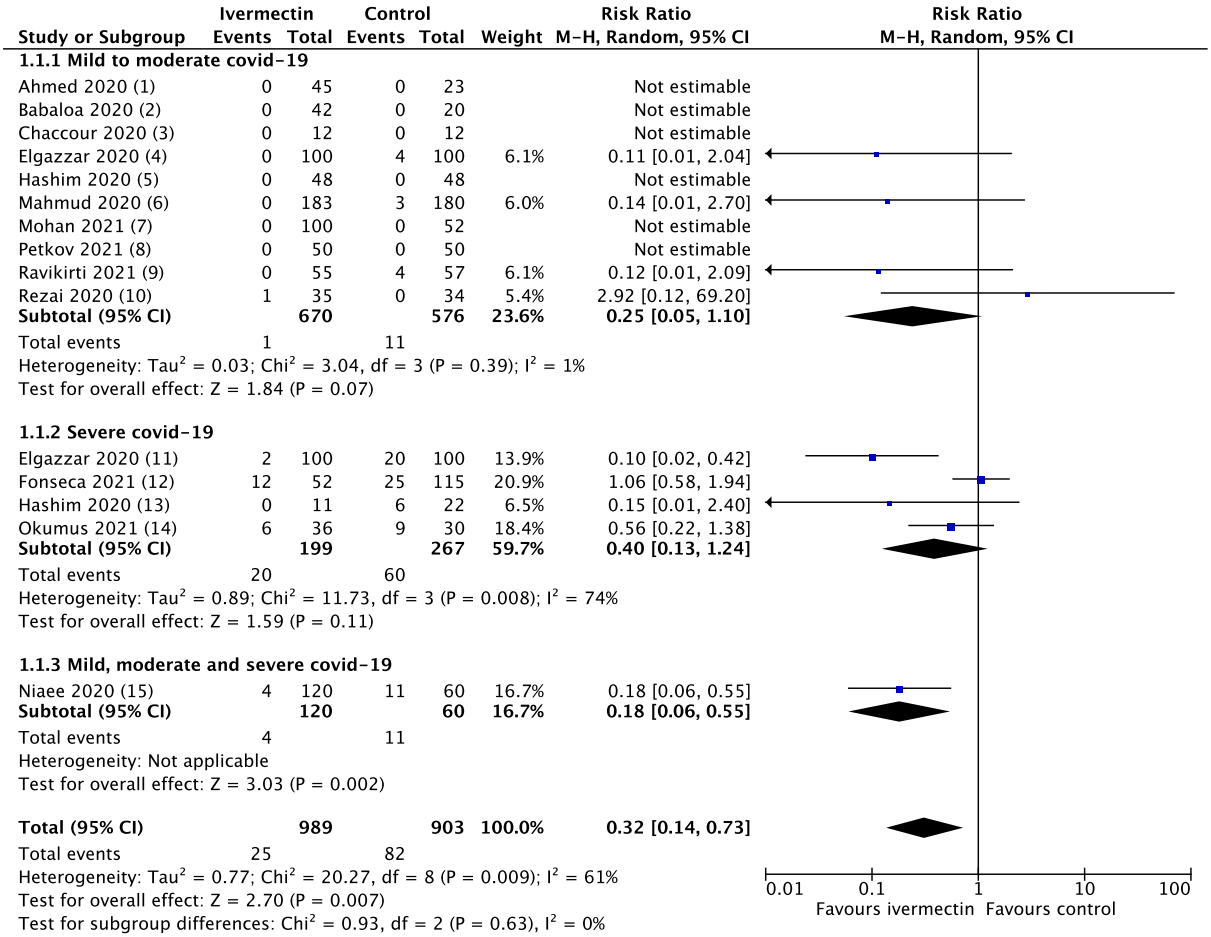
60. Jo Y, Jamieson L, Edoka I, Log L, Silal S, Pulliam JRC, Moultrie H, et al. Cost-effectiveness of remdesivir and dexamethasone for COVID-19 treatment in South Africa. 2020. medRxiv preprint doi: https://doi.org/10.1101/2020.09.24.20200196.
61. Águas R, Mahdi A, Shretta R, Horby P, Landray M, White L, the CoMo Consortium. Analysis: The potential health and economic impact of dexamethasone treatment for patients with COVID-19.
medRxiv 2020.07.29.20164269; doi:https://doi.org/10.1101/2020.07.29.20164269
62. Congly SE, Varughese RA, Brown EC, Clement FM, Saxinger L. Treatment of moderate to severe respiratory COVID-19--A cost-utility analysis.
medRxiv 2020.09.21.20199182; doi:https://doi.org/10.1101/2020.09.21.20199182
63. National Audit Office. The Comptroller and the Auditor General. Investigation into preparations for potential COVID-19 vaccines. HC 1071, Session 2019-2021. 16 December 2020. https://www.nao.org.uk/wp-content/uploads/2020/12/Investigation-into-preparations-for-potential-COVID-19-vaccines.pdf
64. Dyer Owen. Covid-19: Countries are learning what others paid for vaccines BMJ 2021; 372 :n281
65. Iacobucci G, Mahase E. Covid-19 vaccination: What's the evidence for extending the dosing interval? BMJ 2021; 372 :n18.
66. Dawoud DM, Soliman KY. Cost-Effectiveness of Antiviral Treatments for Pandemics and Outbreaks of Respiratory Illnesses, Including COVID-19: A Systematic Review of Published Economic Evaluations. Value Health. 2020;23(11):1409-1422. doi:10.1016/j.jval.2020.07.002
67. Ons.gov.uk. 2021. *Updated estimates of coronavirus (COVID-19) related deaths by disability status, England - Office for National Statistics*. [online] Available at: <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/articles/coronaviruscovid19relateddeathsbydisabilitystatusenglandandwales/24januaryto20november2020> [Accessed 18 February 2021].
68. Public Health England. Beyond the data: Understanding the impact of covid-19 on BAME groups. Public Health England(Accessed January 26 2021). [Other: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/892376/COVID_stakeholder_engagement_synthesis_beyond_the_data.pdf?fbclid=IwAR0w2j456Fg7z3EjoLDe131AAOiJVmDd9TKzfd8xhWzspYitP4oJKDWNRpk]
69. Webb Hooper M, Nápoles AM, Pérez-Stable EJ. COVID-19 and Racial/Ethnic Disparities. JAMA.2020;323(24):2466–2467. doi:10.1001/jama.2020.8598 (Accessed 17 February 2021)
70. Royal Society for Public Health. New poll finds BAME groups less likely to want covid vaccine. 16 December 2020. https://www.rsph.org.uk/about-us/news/new-poll-

finds-bame-groups-less-likely-to-want-covid-vaccine.html (Accessed 17 February 2021)

71. Trialsitenews. Pfizer bails out of India after country demands safety testing for covid vaccine. 10 February 2021. https://www.lifesitenews.com/news/pfizer-bails-out-of-india-after-country-demands-safety-testing-for-covid-vaccine/ (accessed 14 February 2021).
72. Ōmura S, Crump A. Ivermectin and malaria control. Malar J 2017. 16; 172.
73. Molyneux DH. Combating the “other diseases” of MDG 6: changing the paradigm to achieve equity and poverty reduction? Transactions of The Royal Society of Tropical Medicine and Hygiene 2008; 102(6):509–519.
74. 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.
75. https://committees.parliament.uk/publications/3965/documents/39887/default/ (accessed 12/01/2021)
76. Review Manager 5 (RevMan 5) [Computer program]. Version 5.4. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2020.
77. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557-60.
78. The GRADE Working Group. GRADE [website] 2020 [Available from: www.gradeworkinggroup.org.

ANNEX 1. FOREST PLOTS

Forest plot: Death due to any cause (main analysis)

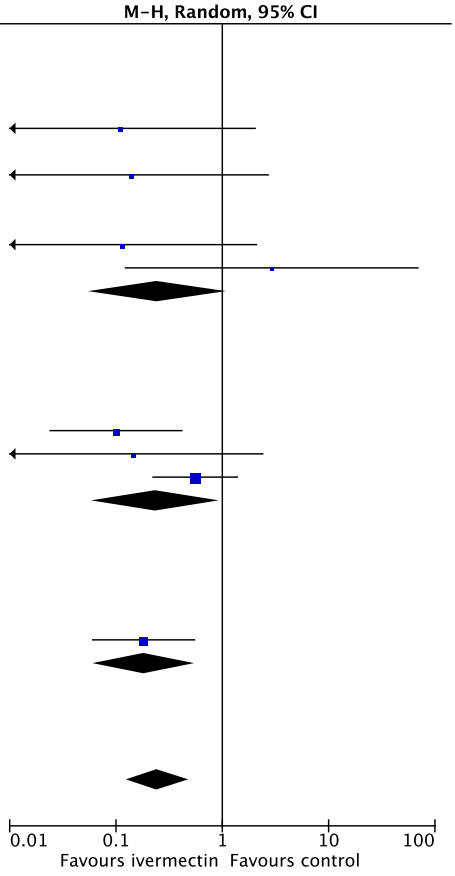


Footnotes

(1) IVM 12mg x 5 days (24 pts) or IVM 12 mg + doxy x 5 days (24 pts)
(2) IVM 6mg-12mg every 84 hrs for 2 wks; vs lopinavir/ritonavir
(3) IVM 0.4mg/kg single dose
(4) IVM up to 24 mg daily for 4 days vs HCQ
(5) IVM 0.2mg/kg x 2-3 days + Doxy 100 mg BID x 10 days
(6) IVM 6mg once + Doxy 100 mg x 5 days
(7) IVM 12mg or 24 mg single dose
(8) IVM 0.4mg/kg x 3 days
(9) IVM 12 mg x 2 days
(10) IVM 0.2mg/kg single dose
(11) IVM up to 24 mg daily for 4 days vs HCQ
(12) IVM 14 mg x 3 days vs HCQ x 5 days or CQ x 5 days
(13) IVM 0.2mg/kg x 2-3 days + Doxy 100 mg BID x 10 days
(14) IVM 0.2mg/kg x 5 days (both arms received HCQ, favipiravir, azithromycin)
(15) IVM 0.2mg/kg to 400 µgm/kg (1 to 3 doses) vs HCQ

Forest plot: Death due to any cause (excluding Fonseca)

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)	0	45	0	23		Not estimable
Babaloa 2020 (2)	0	42	0	20		Not estimable
Chaccour 2020 (3)	0	12	0	12		Not estimable
Elgazzar 2020 (4)	0	100	4	100	5.0%	0.11 [0.01, 2.04]
Hashim 2020 (5)	0	48	0	48		Not estimable
Mahmud 2020 (6)	0	183	3	180	4.9%	0.14 [0.01, 2.70]
Mohan 2021 (7)	0	100	0	52		Not estimable
Petkov 2021 (8)	0	50	0	50		Not estimable
Ravikirti 2021 (9)	0	55	4	57	5.1%	0.12 [0.01, 2.09]
Rezai 2020 (10)	1	35	0	34	4.3%	2.92 [0.12, 69.20]
Subtotal (95% CI)		**670**		**576**	**19.3%**	**0.25 [0.05, 1.10]**
Total events	1		11			
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 3.04$, df = 3 (P = 0.39); $I^2 = 1\%$						
Test for overall effect: Z = 1.84 (P = 0.07)						
1.2.2 Severe covid-19						
Elgazzar 2020 (11)	2	100	20	100	17.4%	0.10 [0.02, 0.42]
Hashim 2020 (12)	0	11	6	22	5.5%	0.15 [0.01, 2.40]
Okumus 2021 (13)	6	36	9	30	32.3%	0.56 [0.22, 1.38]
Subtotal (95% CI)		**147**		**152**	**55.2%**	**0.24 [0.06, 0.95]**
Total events	8		35			
Heterogeneity: $Tau^2 = 0.84$; $Chi^2 = 4.87$, df = 2 (P = 0.09); $I^2 = 59\%$						
Test for overall effect: Z = 2.04 (P = 0.04)						
1.2.3 Mild, moderate and severe covid-19						
Niaee 2020 (14)	4	120	11	60	25.5%	0.18 [0.06, 0.55]
Subtotal (95% CI)		**120**		**60**	**25.5%**	**0.18 [0.06, 0.55]**
Total events	4		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.03 (P = 0.002)						
Total (95% CI)		**937**		**788**	**100.0%**	**0.25 [0.13, 0.48]**
Total events	13		57			
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 8.33$, df = 7 (P = 0.30); $I^2 = 16\%$						
Test for overall effect: Z = 4.07 (P < 0.0001)						
Test for subgroup differences: $Chi^2 = 0.14$, df = 2 (P = 0.93), $I^2 = 0\%$						

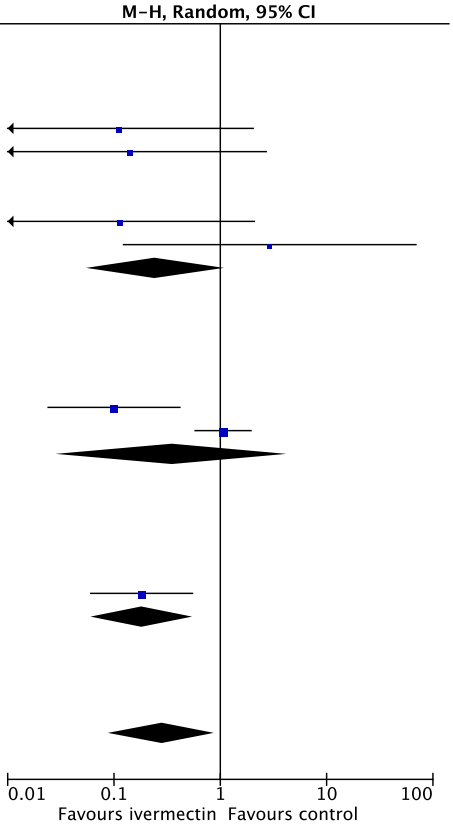


Footnotes

(1) IVM 12mg x 5 days (24 pts) or IVM 12 mg + doxy x 5 days (24 pts)
(2) IVM 6mg-12mg every 84 hrs for 2 wks; vs lopinavir/ritonavir
(3) IVM 0.4mg/kg single dose
(4) IVM up to 24 mg daily for 4 days vs HCQ
(5) IVM 0.2mg/kg x 2-3 days + Doxy 100 mg BID x 10 days
(6) IVM 6mg once + Doxy 100 mg x 5 days
(7) IVM 12mg or 24 mg single dose
(8) IVM 0.4mg/kg x 3 days
(9) IVM 12 mg x 2 days
(10) IVM 0.2mg/kg single dose
(11) IVM up to 24 mg daily for 4 days vs HCQ
(12) IVM 0.2mg/kg x 2-3 days + Doxy 100 mg BID x 10 days
(13) IVM 0.2mg/kg x 5 days (both arms received HCQ, favipiravir, azithromycin)
(14) IVM 0.2mg/kg to 400 µgm/kg (1 to 3 doses) vs HCQ

Forest plot: Death due to any cause (excluding high ROB trials)

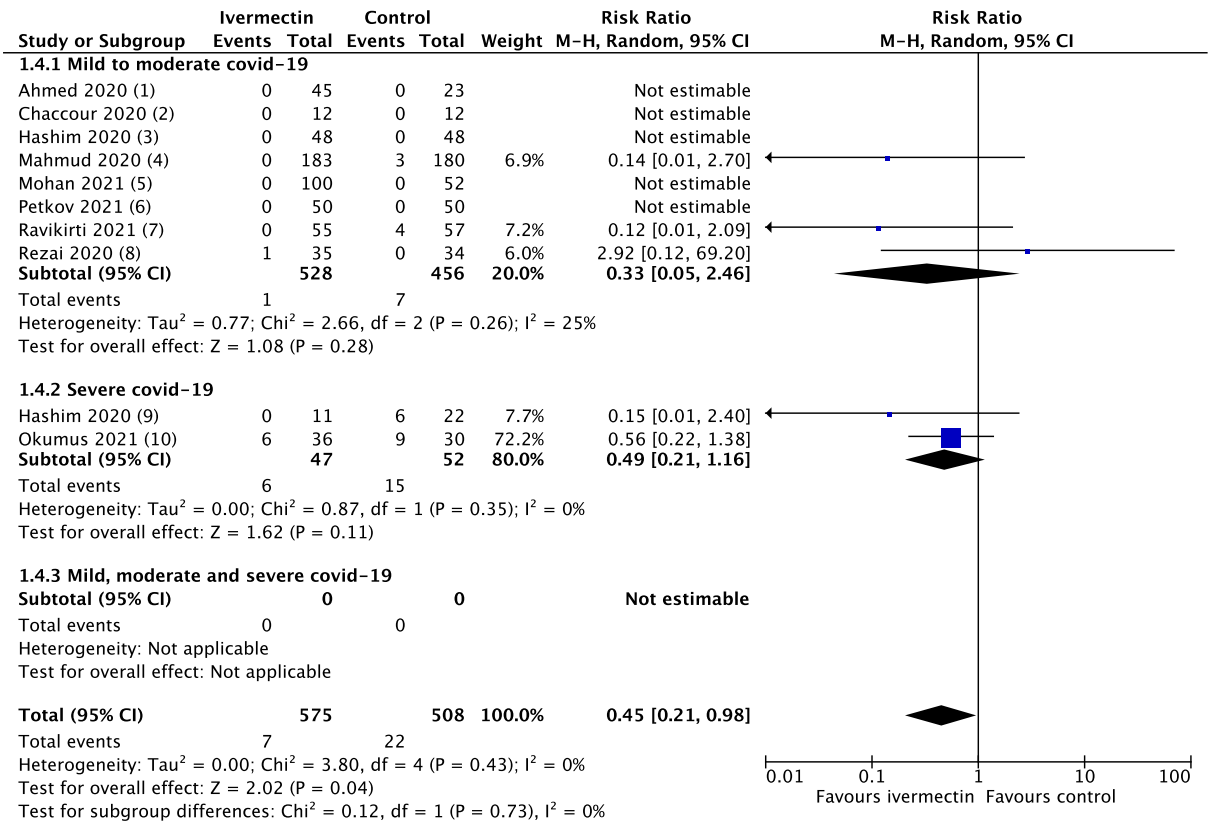
Study or Subgroup	Ivermectin Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Mild to moderate covid-19						
Ahmed 2020 (1)	0	45	0	23		Not estimable
Babaloa 2020 (2)	0	42	0	20		Not estimable
Chaccour 2020 (3)	0	12	0	12		Not estimable
Elgazzar 2020 (4)	0	100	4	100	9.6%	0.11 [0.01, 2.04]
Mahmud 2020 (5)	0	183	3	180	9.4%	0.14 [0.01, 2.70]
Mohan 2021 (6)	0	100	0	52		Not estimable
Petkov 2021 (7)	0	50	0	50		Not estimable
Ravikirti 2021 (8)	0	55	4	57	9.7%	0.12 [0.01, 2.09]
Rezai 2020 (9)	1	35	0	34	8.6%	2.92 [0.12, 69.20]
Subtotal (95% CI)		**622**		**528**	**37.3%**	**0.25 [0.05, 1.10]**
Total events	1		11			
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 3.04$, df = 3 (P = 0.39); $I^2 = 1\%$						
Test for overall effect: Z = 1.84 (P = 0.07)						
1.3.2 Severe covid-19						
Elgazzar 2020 (10)	2	100	20	100	18.3%	0.10 [0.02, 0.42]
Fonseca 2021 (11)	12	52	25	115	23.8%	1.06 [0.58, 1.94]
Subtotal (95% CI)		**152**		**215**	**42.0%**	**0.35 [0.03, 4.29]**
Total events	14		45			
Heterogeneity: $Tau^2 = 2.96$; $Chi^2 = 10.45$, df = 1 (P = 0.001); $I^2 = 90\%$						
Test for overall effect: Z = 0.82 (P = 0.41)						
1.3.3 Mild, moderate and severe covid-19						
Niaee 2020 (12)	4	120	11	60	20.6%	0.18 [0.06, 0.55]
Subtotal (95% CI)		**120**		**60**	**20.6%**	**0.18 [0.06, 0.55]**
Total events	4		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.03 (P = 0.002)						
Total (95% CI)		**894**		**803**	**100.0%**	**0.28 [0.09, 0.88]**
Total events	19		67			
Heterogeneity: $Tau^2 = 1.33$; $Chi^2 = 19.44$, df = 6 (P = 0.003); $I^2 = 69\%$						
Test for overall effect: Z = 2.18 (P = 0.03)						
Test for subgroup differences: $Chi^2 = 0.27$, df = 2 (P = 0.87), $I^2 = 0\%$						



Footnotes

(1) IVM 12mg x 5 days (24 pts) or IVM 12 mg + doxy x 5 days (24 pts)
(2) IVM 6mg-12mg every 84 hrs for 2 wks; vs lopinavir/ritonavir
(3) IVM 0.4mg/kg single dose
(4) IVM up to 24 mg daily for 4 days vs HCQ
(5) IVM 6mg once + Doxy 100 mg x 5 days
(6) IVM 12mg or 24 mg single dose
(7) IVM 0.4mg/kg x 3 days
(8) IVM 12 mg x 2 days
(9) IVM 0.2mg/kg single dose
(10) IVM up to 24 mg daily for 4 days vs HCQ
(11) IVM 14 mg x 3 days vs HCQ x 5 days or CQ x 5 days
(12) IVM 0.2mg/kg to 400 µgm/kg (1 to 3 doses) vs HCQ

Forest plot: Death due to any cause (excluding trials with active controls)



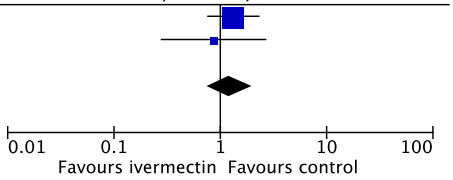
Footnotes

(1) IVM 12mg x 5 days (24 pts) or IVM 12 mg + doxy x 5 days (24 pts)
(2) IVM 0.4mg/kg single dose
(3) IVM 0.2mg/kg x 2-3 days + Doxy 100 mg BID x 10 days
(4) IVM 6mg once + Doxy 100 mg x 5 days
(5) IVM 12mg or 24 mg single dose
(6) IVM 0.4mg/kg x 3 days
(7) IVM 12 mg x 2 days
(8) IVM 0.2mg/kg single dose
(9) IVM 0.2mg/kg x 2-3 days + Doxy 100 mg BID x 10 days
(10) IVM 0.2mg/kg x 5 days (both arms received HCQ, favipiravir, azithromycin)

Forest plot: Admission to ICU

Study or Subgroup	Ivermectin Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Fonseca 2021 (1)	15	52	25	115	80.8%	1.33 [0.77, 2.30]
Ravikirti 2021 (2)	5	55	6	57	19.2%	0.86 [0.28, 2.67]
Total (95% CI)		**107**		**172**	**100.0%**	**1.22 [0.75, 2.00]**
Total events	20		31			

Heterogeneity: Tau² = 0.00; Chi² = 0.46, df = 1 (P = 0.50); I² = 0%
Test for overall effect: Z = 0.79 (P = 0.43)

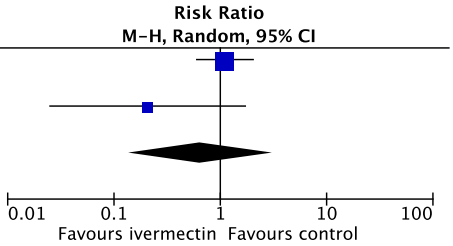


Footnotes
(1) IVM 14 mg x 3 days vs HCQ x 5 days or CQ x 5 days
(2) IVM 12 mg x 2 days; data for "invasive ventilation"

Forest plot: Need for mechanical ventilation

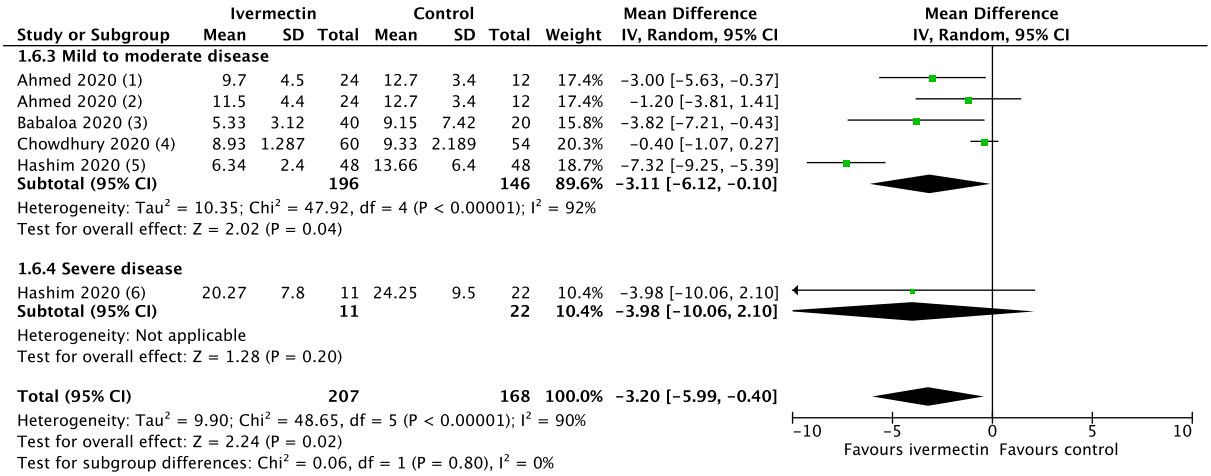
Study or Subgroup	Ivermectin Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Fonseca 2021 (1)	12	52	24	115	68.2%	1.11 [0.60, 2.04]
Mohan 2021 (2)	0	100	0	52		Not estimable
Ravikirti 2021 (3)	1	55	5	57	31.8%	0.21 [0.03, 1.72]
Total (95% CI)		**207**		**224**	**100.0%**	**0.65 [0.14, 3.10]**
Total events	13		29			

Heterogeneity: Tau² = 0.84; Chi² = 2.32, df = 1 (P = 0.13); I² = 57%
Test for overall effect: Z = 0.54 (P = 0.59)



Footnotes
(1) IVM 14 mg x 3 days vs HCQ x 5 days or CQ x 5 days
(2) IVm 12mg or 24mg
(3) IVM 12 mg x 2 days; data for "invasive ventilation"

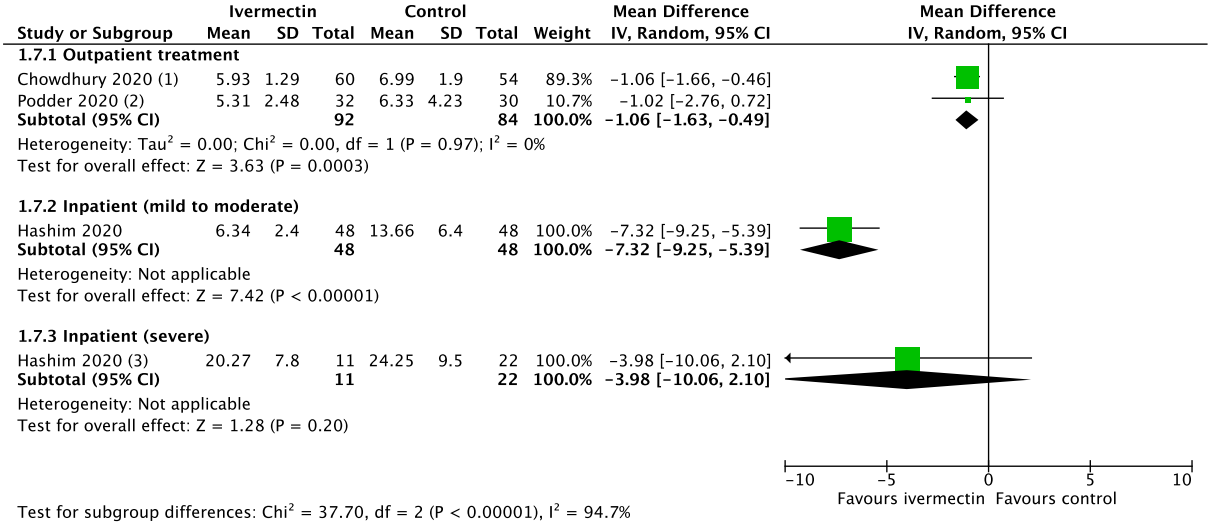
Forest plot: Recovery time to -ve PCR



Footnotes

(1) IVM 12 mg daily x 5 days
(2) IVM 12mg + doxy 200 mg stat then 100 mg BD x 4 days
(3) IVM 6mg-12mg every 84 hrs for 2 wks; vs lopinavir/ritonavir
(4) IVM 200 mcg/kg single dose + doxy 100 mg x 10 days vs HCQ and azithromycin
(5) IVM 0.2mg/kg x 2 + Doxy 100 mg BID x 10 days
(6) IVM 0.2mg/kg x 2 + Doxy 100 mg BID x 10 days

Forest plot: Recovery time (clinical)



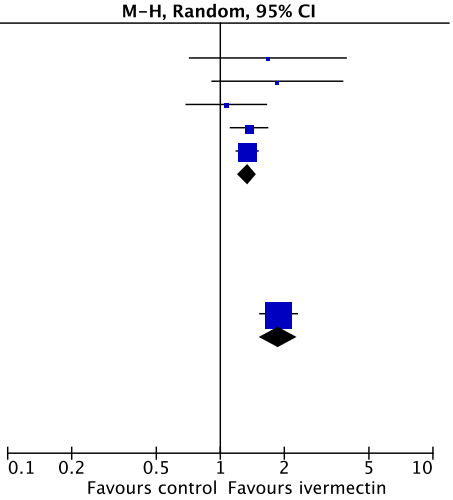
Test for subgroup differences: Chi² = 37.70, df = 2 (P < 0.00001), I² = 94.7%

Footnotes

(1) IVM 200 mcg/kg single dose + doxy 100 mg x 10 days vs HCQ and azithromycin
(2) IVM 200 mcg/kg single dose
(3) IVM 200µgm/kg x 2 + Doxy 100 mg BID x 10 days

Forest plot: Improvement

Study or Subgroup	Ivermectin Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.11.1 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]
Chachar 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: Tau² = 0.00; Chi² = 2.22, df = 4 (P = 0.70); I² = 0%						
Test for overall effect: Z = 5.91 (P < 0.00001)						
1.11.2 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)						



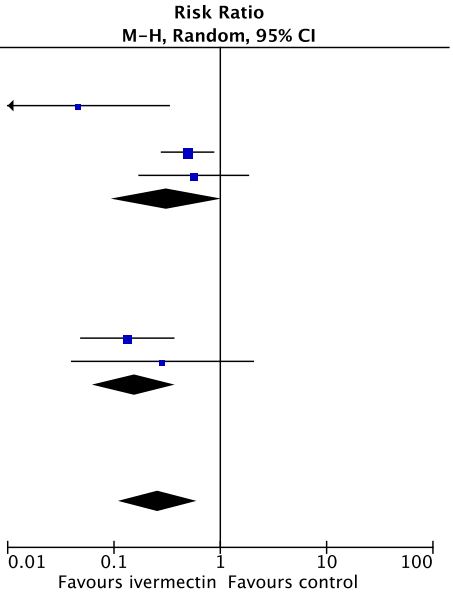
Test for subgroup differences: Chi² = 8.70, df = 1 (P = 0.003), I² = 88.5%

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: Deterioration

Study or Subgroup	Ivermectin Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 Mild to moderate covid-19						
Chaccour 2020 (1)	0	12	0	12		Not estimable
Elgazzar 2020 (2)	1	100	22	100	12.3%	0.05 [0.01, 0.33]
Hashim 2020 (3)	0	48	0	48		Not estimable
Mahmud 2020 (4)	16	183	32	180	30.5%	0.49 [0.28, 0.86]
Mohan 2021 (5)	5	80	5	45	21.1%	0.56 [0.17, 1.84]
Subtotal (95% CI)		**423**		**385**	**63.9%**	**0.31 [0.10, 1.02]**
Total events	22		59			
Heterogeneity: Tau² = 0.72; Chi² = 6.35, df = 2 (P = 0.04); I² = 69%						
Test for overall effect: Z = 1.92 (P = 0.05)						
1.12.2 Severe covid-19						
Elgazzar 2020	4	100	30	100	23.7%	0.13 [0.05, 0.36]
Hashim 2020	1	11	7	22	12.4%	0.29 [0.04, 2.04]
Subtotal (95% CI)		**111**		**122**	**36.1%**	**0.16 [0.06, 0.38]**
Total events	5		37			
Heterogeneity: Tau² = 0.00; Chi² = 0.46, df = 1 (P = 0.50); I² = 0%						
Test for overall effect: Z = 4.06 (P < 0.0001)						
Total (95% CI)		**534**		**507**	**100.0%**	**0.26 [0.11, 0.61]**
Total events	27		96			
Heterogeneity: Tau² = 0.55; Chi² = 10.79, df = 4 (P = 0.03); I² = 63%						
Test for overall effect: Z = 3.07 (P = 0.002)						
Test for subgroup differences: Chi² = 0.84, df = 1 (P = 0.36), I² = 0%						



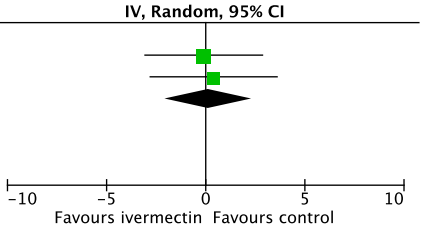
Footnotes

(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 12mg or 24mg

Forest plot: Length of hospital stay

Study or Subgroup	Favours ivermectin Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.10.1 Mild to moderate covid-19								
Ahmed 2020 (1)	9.6	3.2	23	9.7	4.7	12	53.8%	-0.10 [-3.06, 2.86]
Ahmed 2020 (2)	10.1	3.8	22	9.7	4.7	11	46.2%	0.40 [-2.80, 3.60]
Subtotal (95% CI)			**45**			**23**	**100.0%**	**0.13 [-2.04, 2.30]**

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.12 (P = 0.91)



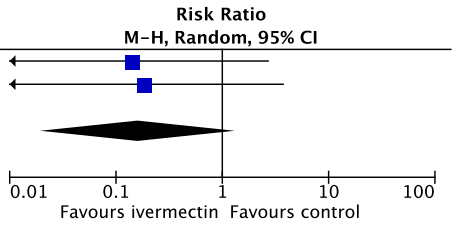
Test for subgroup differences: Not applicable

Footnotes
(1) IVM 12 mg daily x 5 days
(2) IVM 12mg + doxy 200 mg stat then 100 mg BD x 4 days

Forest plot: Admission to hospital

Study or Subgroup	Ivermectin Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Raad 2021 (1)	0	50	3	50	51.2%	0.14 [0.01, 2.70]
Schwartz 2021 (2)	0	49	2	45	48.8%	0.18 [0.01, 3.73]
Total (95% CI)		**99**		**95**	**100.0%**	**0.16 [0.02, 1.32]**
Total events	0		5			

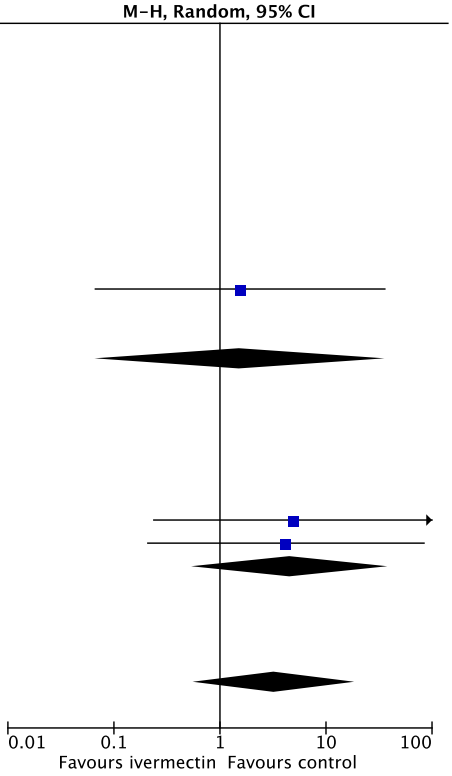
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 1.70 (P = 0.09)



Footnotes
(1) IVM 0.2mg/kg single dose
(2) IVM 12 or 15mg x 3days

Forest plot. Severe adverse events

Study or Subgroup	Ivermectin Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.14.1 Single dose						
Chaccour 2020 (1)	0	12	0	12		Not estimable
Mohan 2021 (2)	0	100	0	52		Not estimable
Subtotal (95% CI)		**112**		**64**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.14.2 IVM multi-dose						
Ahmed 2020 (3)	0	23	0	11		Not estimable
Babaloa 2020 (4)	0	42	0	20		Not estimable
Krolewiecki 2020 (5)	1	30	0	15	31.5%	1.55 [0.07, 35.89]
Petkov 2021 (6)	0	50	0	50		Not estimable
Schwartz 2021 (7)	0	49	0	45		Not estimable
Subtotal (95% CI)		**194**		**141**	**31.5%**	**1.55 [0.07, 35.89]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.79)						
1.14.3 IVM plus other drugs						
Ahmed 2020 (8)	0	22	0	12		Not estimable
Mahmud 2020 (9)	2	183	0	180	33.9%	4.92 [0.24, 101.74]
Okumus 2021 (10)	2	36	0	30	34.6%	4.19 [0.21, 84.03]
Subtotal (95% CI)		**241**		**222**	**68.5%**	**4.54 [0.54, 38.21]**
Total events	4		0			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.01$, df = 1 (P = 0.94); $I^2 = 0\%$						
Test for overall effect: Z = 1.39 (P = 0.16)						
Total (95% CI)		**547**		**427**	**100.0%**	**3.23 [0.55, 18.87]**
Total events	5		0			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.32$, df = 2 (P = 0.85); $I^2 = 0\%$						
Test for overall effect: Z = 1.30 (P = 0.19)						
Test for subgroup differences: $Chi^2 = 0.31$, df = 1 (P = 0.58), $I^2 = 0\%$						



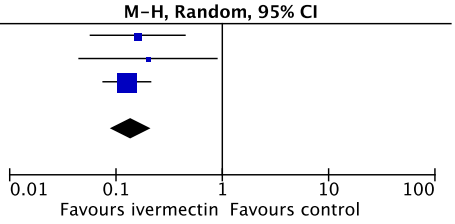
Footnotes

(1) IVM 0.4mg/kg single dose
(2) IVM 12mg or 24mg
(3) IVM 12 mg x 5 days
(4) IVM 6mg-12mg every 84 hrs for 2 wks
(5) IVM 0.6mg/kg x 5 days
(6) 0.4mg/kg x 3 days
(7) IVM 12 or 15mg x 3 days
(8) IVM 12mg + doxy x 5 days
(9) IVM 6mg once + Doxy 100 mg x 5 days
(10) IVM 0.2mg/kg x 5 days (both arms received HCQ, favipiravir, azithromycin)

Forest plot. covid-19 infection

Study or Subgroup	Ivermectin Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Chala 2021 (1)	4	117	25	117	18.4%	0.16 [0.06, 0.45]
Elgazzar 2020 (2)	2	100	10	100	8.7%	0.20 [0.04, 0.89]
Shouman 2020 (3)	15	203	59	101	73.0%	0.13 [0.08, 0.21]
Total (95% CI)		**420**		**318**	**100.0%**	**0.14 [0.09, 0.21]**
Total events	21		94			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.44$, df = 2 (P = 0.80); $I^2 = 0\%$
Test for overall effect: Z = 8.86 (P < 0.00001)

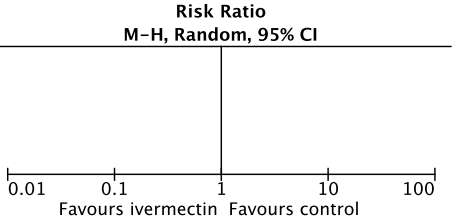


Footnotes
(1) IVM 12 mg weekly + Iota-Carrageenan 6 sprays/day
(2) IVM up to 24mg weekly depending on weight x 2 doses
(3) IVM up to 24 mg depending on weight, given in 2 doses 72 hours apart

Forest plot. Severe adverse events (prophylaxis)

Study or Subgroup	Ivermectin Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Chala 2021 (1)	0	117	0	117		Not estimable
Shouman 2020 (2)	0	203	0	101		Not estimable
Total (95% CI)		**320**		**218**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable



Footnotes
(1) 12 mg (drops) and Iota-carrageena 6 sprays daily
(2) IVM up to 24 mg depending on weight, given in 2 doses 72 hours apart

ANNEX 2. CHARACTERISTICS OF INCLUDED STUDIES

Study ID (refs 18-38)	Country	Design	Funding	Participants	Sample size	Ivermectin dose and frequency*	Comparator	Origin of data	Overall risk of bias
Covid-19 treatment studies									
Ahmed 2020 (18)	Bangladesh	Double-blind	BPL(Pharma); Bangladesh, Canada, Sweden, and UK govt	Mild to moderate covid (inpatients)	72	12mg x 1 day or x 5 days (3 study arms)*	Placebo	Published in PR journal; emailed/responded with data	LOW
Babalola 2020 (19)	Nigeria	Double blind	Self-funded	Asymptomatic, mild or moderate covid (45 inpatients and 17 outpatients)	62	6 mg every 84 hrs x 2 wks (arm 1) or 12 mg every 84 hrs x 2 wks (arm 2)	Ritonavir/lopinavir	MedRxiv pre-print: emailed/responded with data. Accepted for publication.	LOW
Chaccour 2020 (20)	Spain	Double blind	Idapharma, ISGlobal and the University of Navarra	Mild covid (outpatients)	24	0.4mg/kg x 1 dose	Placebo	Published in PR journal	LOW

Chachar 2020 (21)	Pakistan	Open label	Self-funded	Mild covid (outpatients)	50	12mg at 0, 12, and 24 hours (3 doses)	SOC	Published in PR journal	MODERATE
Chowdhury 2020 (22)	Bangladesh	Quasi-RCT	None reported	Outpatients with a +ve PCR (approx. 78% symptomatic)	116	0.2mg/kg x1 dose*	HCQ 400 mg 1st day then 200mg BID x 9 days + AZM 500 mg daily x 5 days	Research Square pre-print	HIGH
Elgazzar 2020 (23)	Egypt	Open label RCT	None reported	Mild to severe covid (inpatients)	200	0.4mg/kg daily x 4 days	HCQ 400 mg BID x 1 day then 200 mg BID x 9 days	Research Square pre-print: emailed/responded with data	MODERATE
Fonseca 2021 (24)	Brazil	Double blind	Institution-funded	Moderate to severe (inpatients)	167	14mg daily x 3 days (plus placebos x 2 additional days)	HCQ - 400mg BID on day 0 then daily x 4 days ; CQ -450mg BID day 0 then daily x 4 days	Pre-publication data/ manuscript in progress was obtained via email	LOW
Hashim 2020 (25)	Iran	Quasi-RCT	None reported	Mild to critical (inpatients)	140	0.2mg/kg x 2 days* Some had a 3rd dose a week later	SOC	MedRxiv pre-print	HIGH

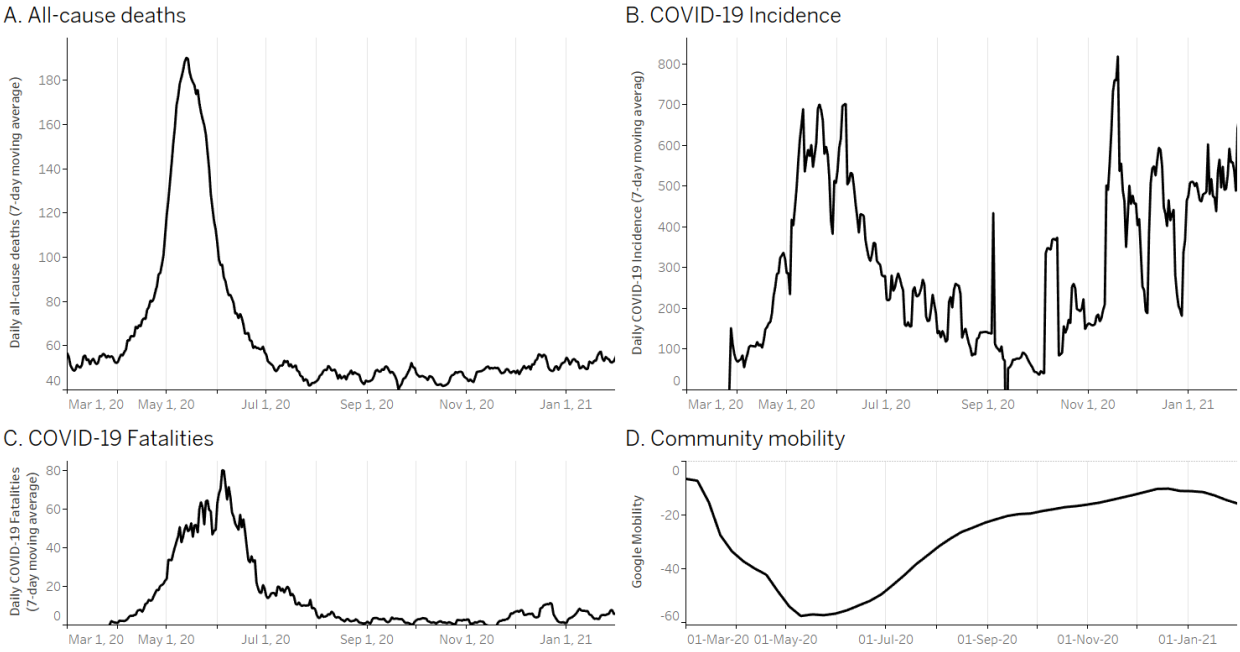
Krolewiecki 2020 (26)	Argentina	Open label	None reported	Mild to moderate (inpatients)	45	0.6mg/kg/day x 5 days	Placebo	SSRN pre-print	LOW
Mahmud 2020 (27)	Bangladesh	Double blind	None reported	Mild to moderate covid (inpatients)	363	12mg x 1 dose*	Placebo + SOC	Data published on clinical trial registry and clarification obtained via email	LOW
Mohan 2021 (28)	India	Double blind	Institution funded	Mild to moderate	152	12 mg or 24 mg elixir x 1 dose	Placebo	MedRxiv pre-print Research Square pre-print	LOW
Niaee 2020 (29)	Iran	Double blind	Institution-funded	Mild to severe covid	180	0.2mg/kg x 1 and 3 other dosing options) ~ 14 mg tablet**	HCQ 200mg/kg BID or placebo (?duration)	Research Square pre-print	LOW
Okumus 2021 (30)	Turkey	Quasi-RCT	None reported	Severe covid	66	0.2mg/kg x 5 days	SOC	Pre-publication data/manuscript in progress obtained via email	HIGH
Petkov 2021 (31)	Bulgaria	Double blind	Pharma funded	Mild to moderate covid	100	0.4mg/kg x 3 days	Placebo	Pre-publication data obtained from another source	UNCLEAR
Podder 2020 (32)	Bangladesh	Open label	Self-funded	Mild to moderate (outpatients)	62	0.2mg/kg x 1 dose	SOC	Published in PR journal	HIGH

Raad 2021 (33)	Lebanon	Double blind	Self-funded	Asymptomatic outpatients	100	9 mg PO if 45kg to 64kg, 12mg PO if 65kg to 84kg and 0.15mg/kg if body weight ≥ 85 Kg	Placebo	Pre-publication data/manuscript in progress obtained via email	UNCLEAR
Ravikirti 2021 (34)	India	Double blind	Self-funded	Mild to moderate covid (inpatients)	112	12mg x 2 days + SOC	Placebo + SOC	Published in PR journal	LOW
Rezai 2021 (35)	Iran	Double blind	None reported	Mild to moderate covid (inpatients)	60	0.2mg/kg x 1 dose	SOC	Pre-publication data obtained from another source	UNCLEAR
Schwartz 2021 (36)	Israel	Double blind	None reported	Mild to moderate (outpatients)	94	IVM 0.15 to 0.3mg/kg x 3 days	Placebo	Pre-publication data obtained from another source	UNCLEAR
Covid-19 prevention studies									
Chala 2021 (37)	Argentina	Open label	None reported	Health care workers	234	12 mg (in drops) weekly + lota-carrageenan	SOC	Pre-publication data/manuscript in progress obtained via email	HIGH

						6 sprays daily x 4 wks			
Elgazzar 2020 (23)	Egypt	Open label	Self-funded	Health care and family contacts	200	0.4mg/kg, weekly x 2 weeks	SOC	Research Square pre-print: emailed/responded with data	MODERATE
Shouman 2020 (38)	Egypt	Open label	Self-funded	Family contacts	304	2 doses (15mg – 24 mg depending on weight) on day 1 and day 3	SOC	Published in PR journal	HIGH

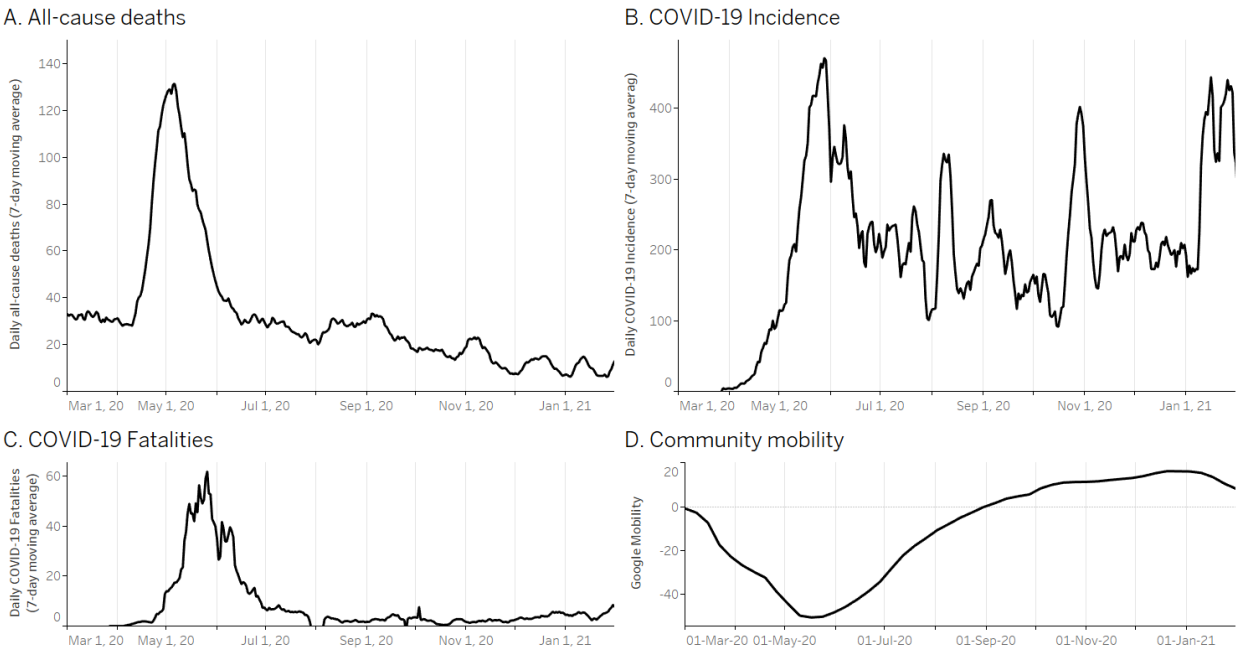
ANNEX 3. REAL WORLD EVIDENCE

Fortaleza (Brazil)



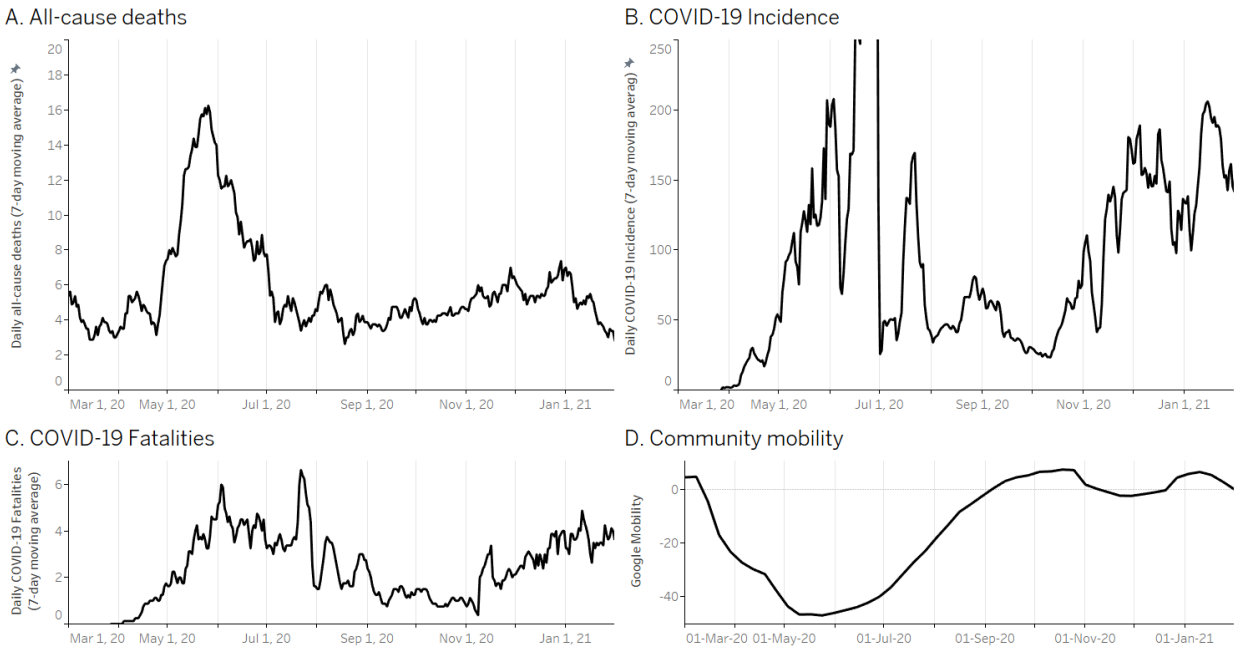
May 5 2020. Pharmacies reported increases in IVM demand.
https://www.vitamedic.ind.br/2020/05/05/ivermectina/
May 15 2020. Regional Health care institution included IVM in the treatment protocol.
https://www.focus.jor.br/covid-19-unimed-fortaleza-adota-protocolo-para-uso-da-cloroquina-no-tratamento-de-pacientes/

Belém (Brazil)



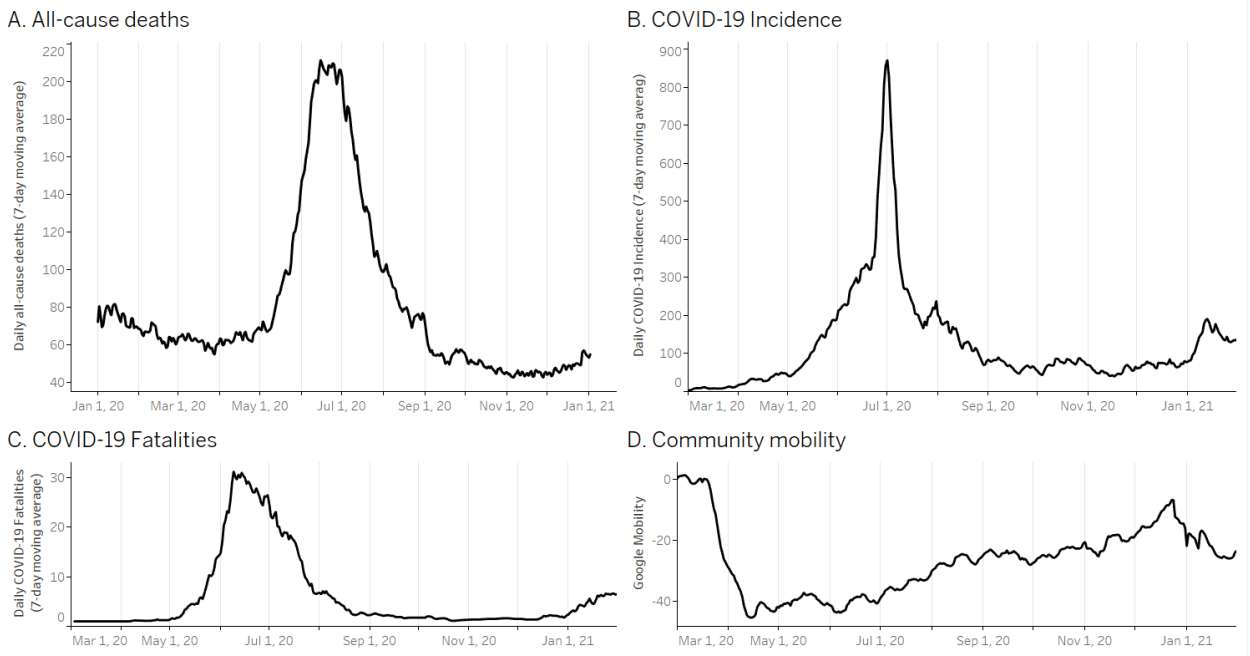
May 3 2020. Pharmacies increased process and reported increases in IVM demand.
https://www.oliberal.com/belem/remedios-contra-covid-19-tem-acesso-dificil-e-variacao-de-precos-1.263563
May 12 2020. Regional Health care institution included IVM in the treatment protocol.
https://revistaforum.com.br/coronavirus/unimed-belem-monta-drive-thru-de-cloroquina/

Macapá (Brazil)



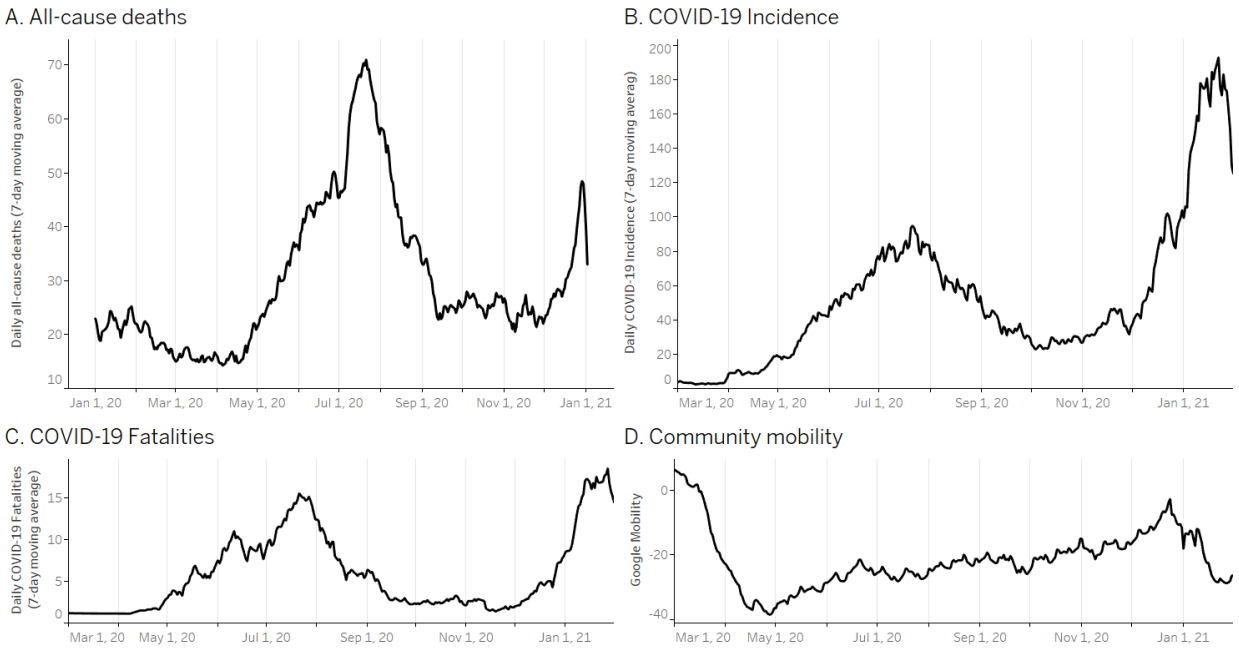
May 14 2020. Regional Government included IVM in the treatment protocol. https://bambamnoticias.com.br/prefeitura-de-macapa-flagra-pacientes-com-muitas-receitas-nas-farmacias-das-ubss

Chiapas (México)



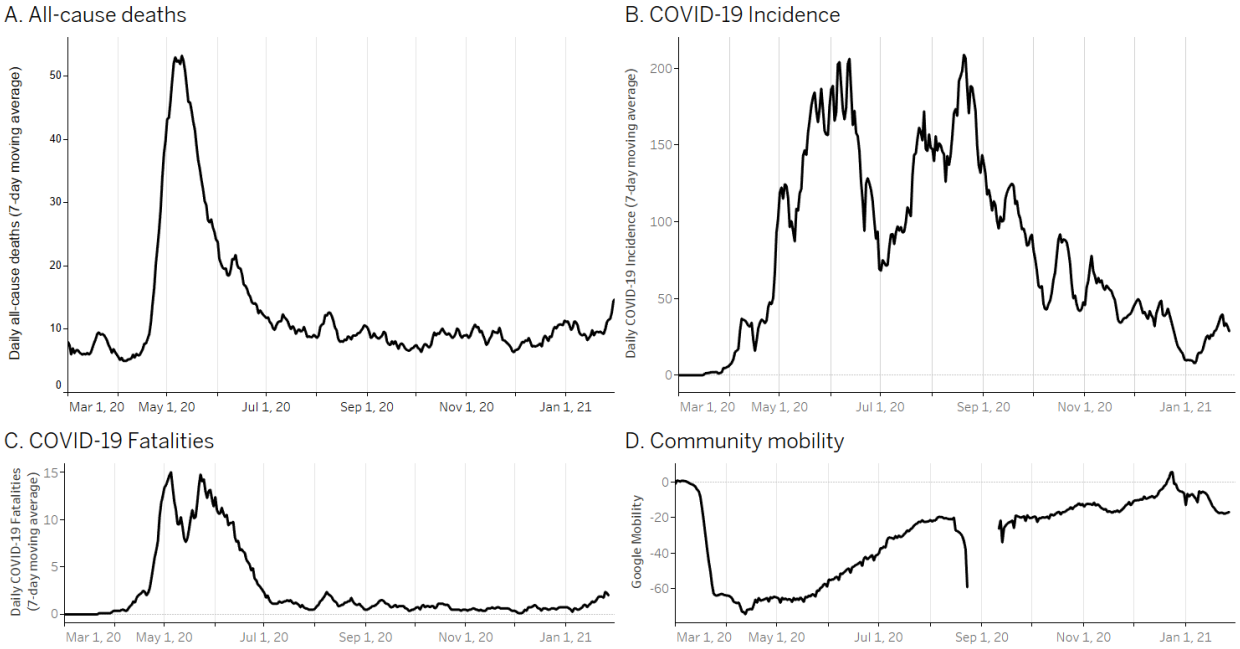
Jun 17 2020. MDs prescribe IVM as a COVID treatment
https://aquinoticias.mx/kit-covid-19-tiene-costo-aproximado-de-600-pesos-pero-esta-agotado/
Jul 2 2020. Local Government started campaign detecting patients and early treating with IVM
https://www.sie7edechiapas.com/post/repartir%C3%A1n-10-mil-kits-con-ivermectina-para-combatir-covid-19-en-tuxtla

Tlaxcala (México)



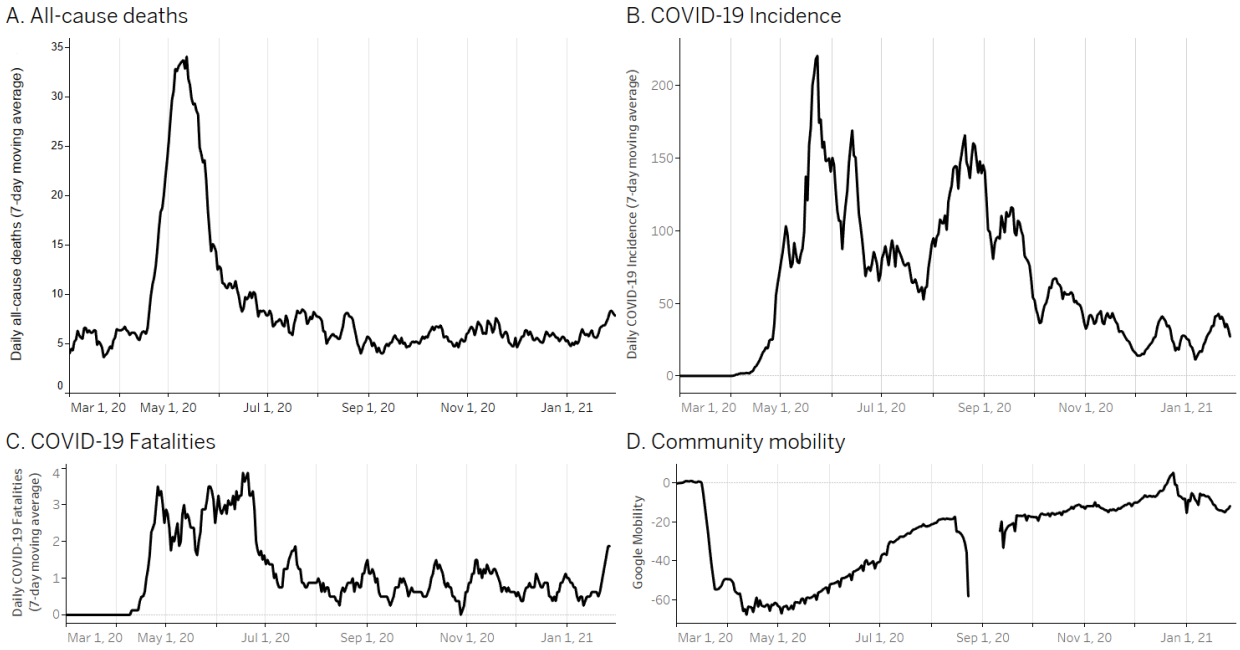
July 7 2020 Local government embraced IVM as their official COVID treatment
https://gentetlx.com.mx/2020/07/07/tlaxcala-pionero-en-la-utilizacion-de-medicamento-efectivo-contra-el-covid-19/

Loreto (Peru)



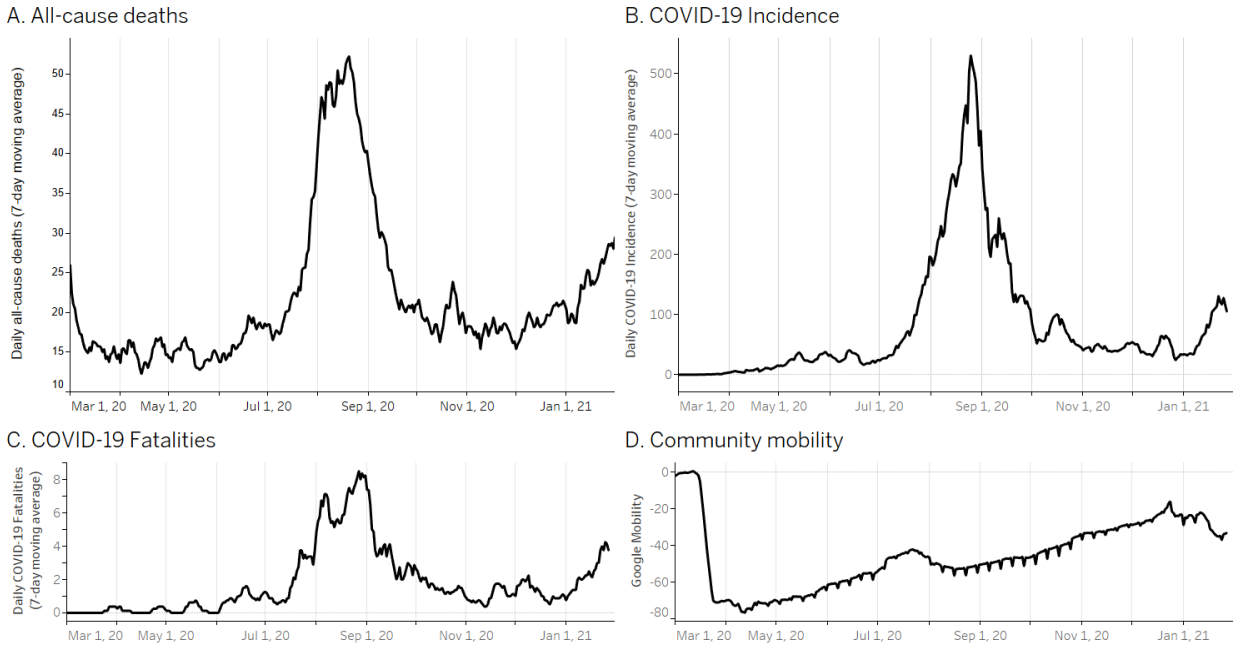
IVM treatments started in late April
Source: Sharp reductions in COVID-19 case fatalities and excess deaths in Peru in close time conjunction, state-by-state, with ivermectin treatments

Ucayali (Peru)



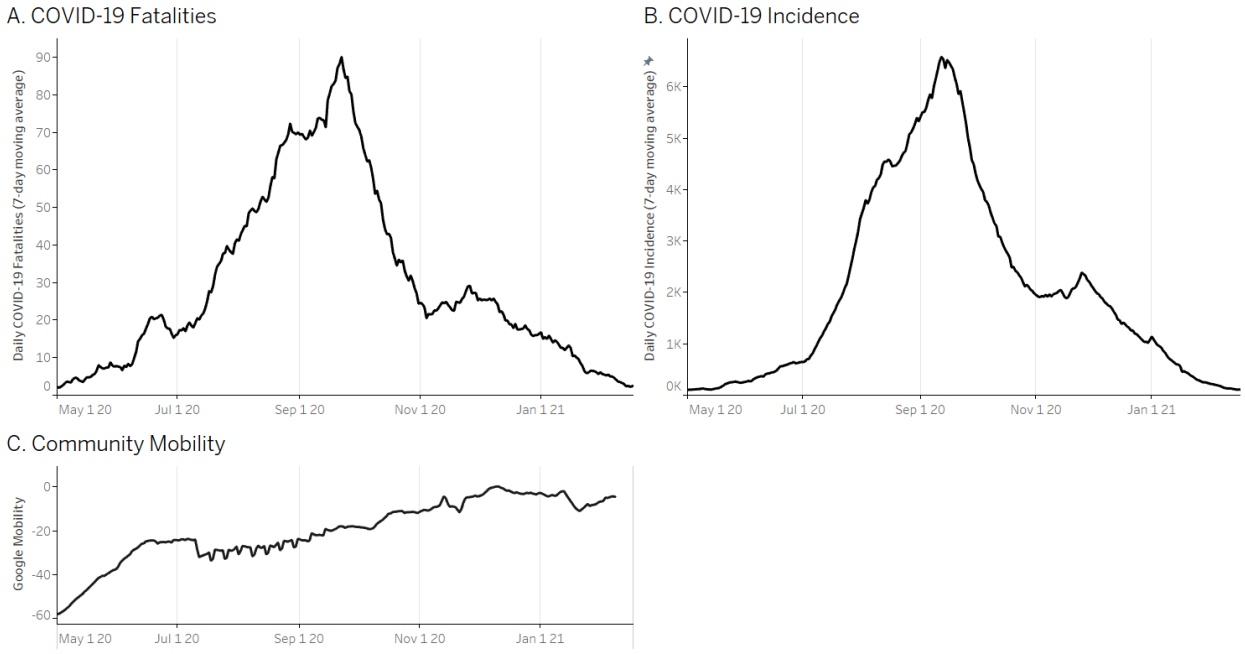
IVM treatments started in early May
Source: Sharp reductions in COVID-19 case fatalities and excess deaths in Peru in close time conjunction, state-by-state, with ivermectin treatments

Cusco (Perú)



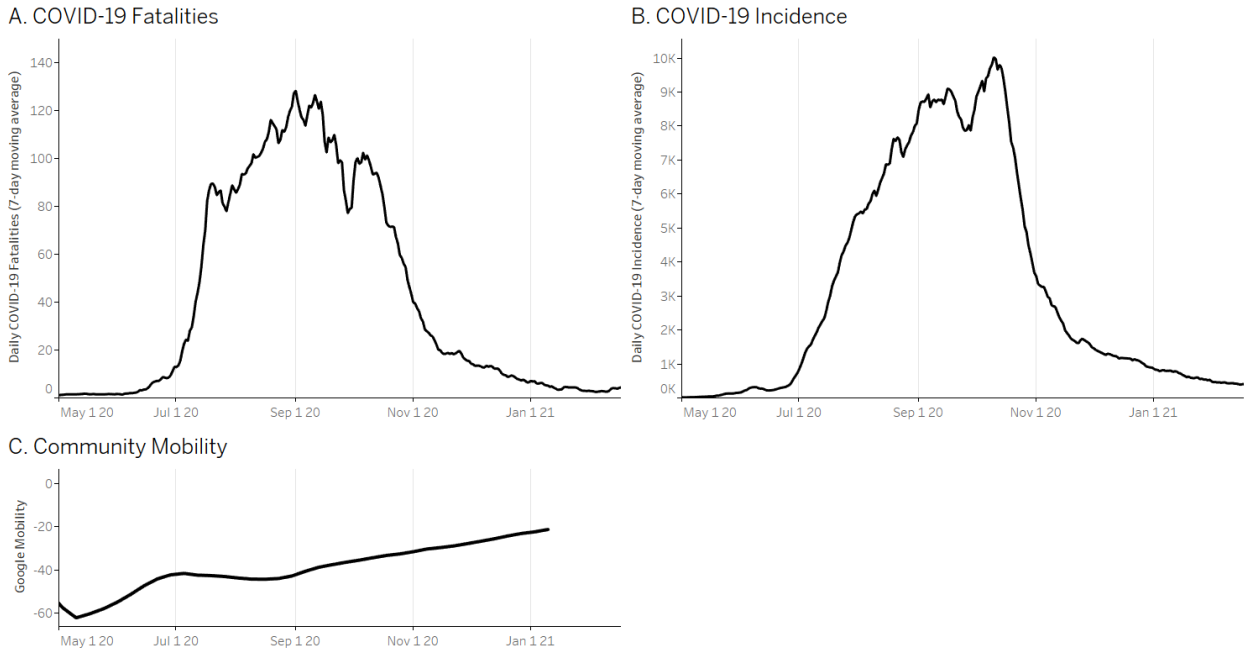
IVM treatments started in early mid August
Source: Sharp reductions in COVID-19 case fatalities and excess deaths in Peru in close time conjunction, state-by-state, with ivermectin treatments

Uttar Pradesh (India)



Aug 8, 2020. Uttar Pradesh embraces IVM as their treatment protocol
https://www.indiatvnews.com/fyi/ivermectin-new-drug-to-treat-covid-19-coronavirus-to-be-used-in-uttar-pradesh-640473
Aug 22, 2020. The government assure IVM supply after a temporary shortage.
https://timesofindia.indiatimes.com/city/lucknow/ivermectin-back-in-stores-but-could-cost-rs-2-rs-90-per-tablet/articleshow/77684406.cms

Karnakata (India)



Sep 19,2020. Doctors in Karnataka embraces IVM
https://www.newindianexpress.com/states/karnataka/2020/sep/19/hcq-no-longer-a-magic-pill-doctors-move-to-new-drugs-2198937.html
Sep 20, 2020. Regional Health Authority
https://www.business-standard.com/article/news-ani/health-ministry-plans-to-introduce-mass-drug-administration-programme-in-yadgir-district-karnataka-119092000834_1.html

Sources:
Peru:
Data SINADEF – MINSA, https://cloud.minsa.gob.pe/s/NctBnHXDnocgWAg/download
Centro Nacional de Epidemiologia, prevención y Control de Enfermedades – MINSA
https://www.datosabiertos.gob.pe/group/datos-abiertos-de-covid-19

Brazil:
Portal de Transparência do Registro Civil, https://transparencia.registrocivil.org.br
Marcelo Oliveira: https://github.com/capyvara
Painel de casos de doença pelo coronavírus 2019 (COVID-19) no Brasil pelo Ministério da Saúde
https://covid.saude.gov.br/
México:
Datos Abiertos Dirección General de Epidemiología https://www.gob.mx/salud/documentos/datos-abiertos-152127
Bases de datos del boletín estadístico sobre el exceso de mortalidad en México
https://www.datos.gob.mx/busca/dataset/bases-de-datos-del-boletin-estadistico-sobre-el-exceso-de-mortalidad-en-mexico
India:
COVID-19 India Org Data Operations Group
https://api.covid19india.org/
Google mobility:
https://www.google.com/covid19/mobility/

ANNEX 4. IVERMECTIN PROPHYLAXIS AND TREATMENT PROTOCOLS IN USE

Source	Prophylaxis (PrEP and PEP) healthcare workers (PrEP); contacts of confirmed cases (PEP) ***ivermectin***	*adjuncts*	Early outpatient treatment and /or "mild"case treatment ***ivermectin***	*adjuncts*
Marik *et al.* "I-MASK" & "MATH+" protocols EVMS	**Day 1: 200 µg/kg** **Day 3: 200 µg/kg** (PEP: per exposure) (PrEP: **200 µg/kg** fortnightly)	Vit D3: ≤ 3000 IU qd Vit C: 1 g bid Zn: 50 mg qd Quercetin: 250 mg qd Melatonin: 6 mg qhs	**Day 1: 200 µg/kg** **Day 2: 200 µg/kg** **Days 3 -5: same** (if not recovered)	Vit D3: 4000 IU qd Vit C: 2 g bid or tds Zn: 100 mg qd Quercetin: 250 mg bid Melatonin: 10 mg qhs Aspirin: 325 mg qd
Borody CDD	**Day 1: 12 mg** (PrEP: Fortnightly)	Doxycycline: 100 mg qd (4 days) Zn: unspecified	**Day 1: 12 mg** **Day 4: 12 mg** **Day 8: 12 mg**	Doxycycline: 100 mg qd (10 days) Zn: unspecified
McCullough *et al.* Baylor U., Dallas	No prophylaxis recommendations		**200-600 µg/kg** **Days 1, 3, 5** or: qd 2-5 Days Plus: hydroxychloroquine or: favipiravir (dual antiviral policy)	Doxycycline: 100 mg bid or: Azithromycin 250 mg bid Vit D3: 5000 IU qd Vit C: 3 g qd Zn: 50 mg qd Quercetin: 500 mg bid
Chesler Nursing Homes, Virginia	**Day 1: 12 mg** **Day 8: 12 mg** PEP: Immediate on first confirmed case	Doxycycline: 100 mg qd (10 days) Vit D3: unspecified Vit C: unspecified Zn: unspecified	**Day 1: 12 mg** **Day 8: 12 mg**	Doxycycline: 100 mg qd (10 days) Vit D3: unspecified Vit C: unspecified Zn: unspecified Dexamethasone: prn Enoxaparin: prn
Fareed Brawley Medical Center California	**Day 1: 200 µg/kg** **Day 3: 200 µg/kg**	Vit D3: 4000 IU qd Zn: 25 mg qd	**Day 1: 200 µg/kg** **Day 3: 200 µg/kg**	Doxycycline: 100 mg qd (5 days)

	Weekly: **50 µg/kg** or: Monthly: **200 µg/kg** (PrEP and PEP)	Vit C: unspecified Multivitamins: unspecified Quercetin: unspecified	**Day 5: 200 µg/kg**	Vit D3: 4000 IU qd Zn: 25 mg qd Vit C: unspecified Multivitamins: unspecified Quercetin: unspecified
Source	*Prophylaxis (PrEP and PEP)* *healthcare workers* (PrEP)*; contacts of confirmed cases* (PEP) ***ivermectin***	*adjuncts*	*Early outpatient treatment* *and /or "mild"case treatment* ***ivermectin***	*adjuncts*
Shouman Zagazig U, Egypt	**Day 1: 15 mg, 18 mg, 24 mg** **Day 4: same** 15mg: 40-60 kg BW 18 mg: 60-80 kg BW 24 mg: > 80 kg	Hygiene measures	Not a treatment trial	
Chala *et al.* Tucuman, Argentina	**Day 1: 12 mg oral solution** **repeat weekly** PrEP of healthcare workers	Iota-carageenan topical spray (daily)	Not a treatment trial	
Carvallo *et al.* Buenos Aires, Argentina	**Day 1: 12 mg tablet** **repeat weekly** PrEP of healthcare workers	Iota-carageenan topical spray (daily)	Not a treatment trial	
Elgazzar *et al.* U. Benha, Egypt	**Day 1: 400 µg/kg** **repeat weekly** PrEP health care workers; PEP contacts conf. cases	Hygiene measures	**Day 1: 400 µg/kg** **Days 2, 3, 4: same**	Azithromycin 500 mg qd (6 days) Vit C: 1 g qd Zn: 50 mg qd Lactoferrin: 100 mg bid Acetylcysteine: 200 mg tds
Alam Bangladesh Medical College Hospital	**Day 1: 12 mg** **repeat monthly** PrEP healthcare workers	None specified	Not a treatment trial	
Behera *et al.* All India Institute of Medical Sciences	**Day 1: 300 µg/kg** **Day 4: 300 µg/kg** **Repeat monthly** PrEP healthcare workers	None specified	Not a treatment trial	

ANNEX 5. OUTLINE OF THE BRITISH IVERMECTIN RECOMMENDATION DEVELOPMENT (BIRD) PROCESS

INTRODUCTION

A large body of evidence had accumulated on a drug called ivermectin for the prevention and treatment of covid-19 that required urgent review by health professionals and other stakeholders to determine whether it could inform clinical practice in the UK and elsewhere.

TARGET AUDIENCE

National and local policymakers, health care professionals, implementers, patients and the public.

RECOMMENDATION DEVELOPMENT METHODS

The recommendation on ivermectin for covid-19 was developed using the standard procedures for guideline development as described in the *World Health Organization Handbook for Guideline Development*. Briefly, these procedures include:

1. Identification of priority questions and outcomes;
2. Evidence retrieval and synthesis;
3. Assessment of the evidence;
4. Formulation of the recommendations; and
5. Planning for implementation, dissemination, impact evaluation and updating.

GROUPS INVOLVED IN THE PROCESS

1. The Steering Group

The role of the BIRD Steering Group was to co-ordinate the BIRD meeting, draft the recommendation for the stakeholder panel to review, assist in preparation of the finalized recommendations document, and manage its publication and dissemination. The members of the BIRD Steering Group are listed below (in alphabetical order):

Mr. Andrew Bryant (Statistician, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne)
Dr. Ketan Gajjar (Consultant Gynae-Oncologist, Obstetrics and Gynaecology, Nottingham City Hospital, Nottingham)
Dr. Tess Lawrie (Director of the Evidence-based Medicine Consultancy Ltd, Bath)
Dr. Claire Mock-Muñoz de Luna (Public Health Researcher, Evidence-based Medicine Consultancy Ltd, Bath)
Dr. Tina Peers (Consultant in Contraception and Reproductive Healthcare, Surrey)
Dr. Tony Tham (Consultant Gastroenterology, Ulster Hospital, Belfast)

2. The Recommendation Development Panel (RDP)

This international panel comprised invited health care professionals as well as patient and public representatives. All attendees were required to submit a declaration of interest before the meeting.

3. Technical Working Group (TWG)

The Technical Working Group comprised systematic reviewers and guidelines methodologists from the independent Evidence-Based Medicine Consultancy Ltd, Bath, and the University of Newcastle, Newcastle upon Tyne. The TWG also included a health economist and a data analyst, who produced real-world evidence graphs.

CONDUCT OF THE MEETING

For the purpose of transparency, the meeting was recorded and live-streamed. The public were invited to participate through a survey link on the streaming channel. With this online survey they were able to make judgements on the evidence – these data will be analysed and included in the final recommendation document.

The meeting was chaired by Professor Jim Neilson, Emeritus Professor of Obstetrics and Gynaecology at the University of Liverpool. Dr. Tess Lawrie presented the evidence and other relevant considerations on ivermectin for covid-19 infection in the form of a DECIDE evidence to decision (EtD) framework. The panel considered evidence and other relevant considerations for each of the following criteria:

- Effects: What are the benefits and harms associated with ivermectin for covid-19?
- Values: What importance do those affected assign to the outcomes associated with ivermectin?
- Resources: What are the resource implications of ivermectin implementation?
- Equity: What are the equity implications associated with ivermectin for covid-19?
- Acceptability: Will ivermectin be acceptable to key stakeholders, e.g. patients, their families and health care professionals?
- Feasibility: Will ivermectin be feasible to implement in terms of resource availability, infrastructure and training?

Using an electronic survey link, the panel made judgements on these different decision-making criteria, which were recorded in a summary table. Twelve judgements were made during the course of the BIRD proceedings. Statistician, Mr. Andrew Bryant presented a summary of the panel judgements. This summary informed the formulation of the draft recommendation.

FORMULATING THE RECOMMENDATION

Any of the following recommendations could have been made:

- A recommendation in favour of the use of ivermectin for covid-19
- A recommendation not in favour of the use of ivermectin for covid-19

- A recommendation in favour of the use of ivermectin in certain contexts, such as a research context or specific populations or settings.

After the recommendation was made, a 30-minute panel discussion followed during which implementation and research gaps were considered.

Declarations of interest (DOI)

In line with the *WHO handbook for guideline development*, all those invited were asked to declare in writing any competing interests (academic, financial or other) they may have at the time of the invitation to participate in the BIRD meeting. They were asked to sign a DOI form and return it prior to the meeting for review by the Steering Group. If an individual was considered to have a substantial conflict of interest, for example, research grants or other financial interests from private industry, the Steering Group reserved the right to withdraw the invitation. No invitations were withdrawn.

Document preparation, review and dissemination

Following the BIRD meeting, the Steering Group prepared a draft of the recommendation/s document with revisions to accurately reflect the deliberations and decisions of the panel. The draft recommendation document was sent electronically to the panel members for approval and suggestions. The document was also sent to 12 external health professionals to review. The revised final version of the document has been made freely available to all stakeholders. The Steering Group undertook to communicate and disseminate the recommendation as soon as possible in the interest of expediting implementation.

ANNEX 5. IVERMECTIN FOR PREVENTION AND TREATMENT OF COVID-19: SYSTEMATIC REVIEW METHODOLOGY

Objectives

To assess the effectiveness of ivermectin treatment among people with covid-19 infection (to address priority question 1) and as a prophylaxis among people at higher risk of covid-19 infection (to address priority question 2).

Safety will also be assessed in included randomised controlled trials (RCTs). However, since it is one of the World Health Organisation's *Essential Medicines* (WHO 2019) and is considered safe for use in humans (Banerjee 2020; Navarro 2020; WHO 2018), no assessment will be made beyond included RCTS.

Methods

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

TYPES OF STUDIES

Prespecified eligibility criteria is as follows:

Study design

- Randomised controlled trials (RCTs)
- Quasi-RCTs
- Cluster-RCTs

Minimum study duration

Any time frame.

TYPES OF PARTICIPANTS

- For research question 1: People with mild, moderate, severe or critical covid-19 infection.
- For research question 2: People at higher risk of covid-19 infection, such as frontline workers and covid-19 contacts.

Special populations of interest are healthcare and other frontline workers, the elderly, and those with pre-existing health conditions.

TYPES OF INTERVENTIONS

Intervention

- Oral ivermectin, administered as a minimum single dose of 6 mg.
    - Studies assessing ivermectin in combination with doxycycline or other medicines or supplements will be included.
    - Studies comparing different formulations, doses, and schedules of ivermectin will also be included.

Comparator(s)

- No ivermectin
    - placebo, or
    - another active treatment

TYPES OF OUTCOME MEASURES

PRIMARY OUTCOMES

For Question 1: Ivermectin treatment vs control/comparator:

- Death from any cause

For Question 2: Ivermectin prophylaxis vs control:

- covid-19 infection

SECONDARY OUTCOMES

For Question 1: Ivermectin treatment vs control/comparator:

- Time to PCR negativity, in days
- Time to clinical recovery, in days
- Admission to ICU
- Requiring mechanical ventilation
- Length of hospital stay, in days
- Admission to hospital
- Duration of mechanical ventilation
- Serious adverse events
- Improvement, as measured by investigators

- Deterioration, as measured by investigators

For Question 2: Ivermectin prophylaxis vs control:

- Admission to hospital
- Death from any cause
- Serious adverse events

Studies will be included in the review irrespective of whether they measured outcome data that are reported in a way that allows us to include them in meta-analysis. We will also include studies that are otherwise eligible but may not necessarily report on the review's outcomes; these studies will be summarised in Characteristics of included studies tables. This will be done in case we miss any outcomes that are pertinent as new outcomes of importance may emerge given the changing nature of the pandemic. We will note any such analyses as post hoc and interpret accordingly.

We will also produce a brief economic commentary (BEC) to summarise the available economic evidence relating to: 1) ivermectin as treatment and 2) ivermectin as prophylaxis for covid-19 infection.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

ELECTRONIC SEARCHES

An information specialist, (JP) designed all of the searches and will conduct them. These were informed and verified by a content expert (TL) and were independently peer reviewed by (ANS). The Medline search strategy is presented in Appendix 1. The search strategies in other electronic databases will be adapted accordingly. The following electronic databases will be searched:

- Medline from 1946 (for completeness but nothing should appear until 2019 in theory)
- Embase from 1980
- CENTRAL (latest issue)
- Cochrane covid-19 Study Register
- Chinese databases

We will perform a supplementary search to identify economic evaluation studies. The search will be conducted in Medline and Embase and limited to published studies from November 2019 to capture studies conducted since the initial outbreak of SARS-CoV-2. The search strategies that will be used to identify economic evidence can be viewed in Appendix 2. Following current guidance (Aluko 2020), the reference lists of the studies included in the main review will also be examined for any relevant economic data.

SEARCHING OTHER RESOURCES

We will search www.controlled-trials.com/rct, www.clinicaltrials.gov and www.cancer.gov/clinicaltrials for ongoing trials.

We will search the reference list of included studies, and of two other 2021 literature reviews that we are aware of on ivermectin (Kory 2021; Hill 2021). We have made initial contacts to experts in the field (Drs. Andrew Hill, Pierre Kory and Paul Marik) for information on new and emerging trial data but will follow these contacts up during the review process. This is a rapidly expanding evidence base so the number of trials are increasing quickly; as such, we will check for updates on ongoing trials regularly and perform hand searches as necessary.

DATA COLLECTION AND ANALYSIS

SELECTION OF STUDIES

Screening

All titles and abstracts retrieved by electronic searching will be downloaded to Endnote and duplicates will be removed. Two review authors (AB, TL, TD) with expertise in systematic reviewing will screen all titles and abstracts for eligibility. Full texts will also be reviewed by two reviewers (AB, TL, TD). Discrepancies will be resolved by consensus. Reasons for exclusion will be recorded for all studies excluded after full text review.

Inclusion of non-English language studies

Where possible, we will translate any reports of RCTs published in other languages than English.

DATA EXTRACTION AND MANAGEMENT

We will abstract data using a pilot form which will be trialled by two reviewers (TL, TD, AB or GG) to record the following:

- Study design (including methods, location, sites, funding, study author declaration of interests, inclusion/exclusion criteria)
- Setting: hospital inpatient, outpatient
- Participant characteristics: disease severity, age, gender, co-morbidities, smoking, occupational risk
- Intervention characteristics: dose and frequency of ivermectin
- Comparator characteristics: dose and frequency of comparator
- Risk of bias items (see below)
- Length of follow-up
- Outcomes (as above) including numbers in each arm, definitions, unit of measurements, etc.

Data on outcomes will be extracted as below:

- For dichotomous outcomes (i.e. death from any cause, SAEs, etc), we will extract the number of participants in each treatment arm and the number of participants assessed at endpoint, in order to estimate a risk ratio.
- For continuous outcomes (i.e. length of hospital stay), we will extract the final value and standard deviation of the outcome of interest and the number of participants assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference between treatment arms and its standard error.

If possible, we will extract data relevant to an intention-to-treat analysis, in which participants are analysed in groups to which they are assigned.

We will use Microsoft Excel to collate the data. If there is a conflict between data reported across multiple sources for a single study (e.g. between a published article and a trial registry record), we will email the authors for clarification. Differences between reviewers will be resolved by discussion.

Assessment of risk of bias in included studies

An assessment of risk of bias in each included RCT will be conducted by two reviewers (TL, TD, AB or GG) using the Cochrane risk of bias tool (Higgins 2019). Discrepancies will be resolved by discussion and, if necessary, involving a third reviewer. The risk of bias includes assessment of:

- sequence generation
- allocation concealment
- blinding (Assessment of blinding will be relevant to participants, health care personnel and outcome assessors)
- incomplete outcome data: We will record the proportion of participants whose outcomes were not reported at the end of the trial and will note whether loss to follow-up is not reported. We will code a satisfactory level of loss to follow-up for each outcome as:
    - Yes, if fewer than 20% of participants are lost to follow-up and reasons for loss to follow-up are similar in both treatment arms
    - No, if more than 20% of patients are lost to follow-up or reasons for loss to follow-up is different between treatment arms
    - Unclear if loss to follow-up is not reported
- selective reporting of outcomes
- other possible sources of bias

We will pay close scrutiny to unpublished reports and those of unpublished works and preprints that have not undergone formal peer review. If we can retrieve adequate information we will reach consensus in

either making an appropriate risk of bias judgement in each domain for that trial or exclude is sufficient doubt as to whether it is truly an RCT.

Results will be presented in both a risk of bias graph and a risk of bias summary. Results of meta-analyses will be interpreted in light of the findings with respect to risk of bias.

Measures of treatment effect

We will use the following measures of the effect of treatment:

- For dichotomous outcomes (e.g. death from any cause, SAEs), we will use the risk ratio
- For continuous outcomes, we will use the mean difference (MD) or standardised mean difference (SMD) as appropriate. Continuous outcome data for length of hospital stay and time to recovery will be standardised to the same unit of measurement (i.e. days) so the need to use SMD is unlikely.

Unit of analysis issues

We will consider interventions that comprised multiple doses of ivermectin as a single intervention and subgroup when necessary. None of our outcomes should be time-dependent (e.g. measured at a particular time point since these are relatively short term outcomes given nature of the virus and intention of the interventions).

We will also include cluster randomised controlled trials (cluster-RCTs). If the analysis accounts for the cluster design then a direct estimate of the desired treatment effect will be extracted e.g. RR plus 95% CI. If the analysis does not account for the cluster design, we will extract the number of clusters randomised to each intervention, the average cluster size in each intervention group and the outcome data, ignoring the cluster design, for all participants in each group. We will then use an external estimate of the intracluster coefficient (ICC) to estimate a design effect to inflate the variance of the effect estimate (Higgins 2019). It will then enter the data into RevMan 5.4 and combine the cluster randomised trials with individually randomised trials in the same meta-analysis.

Dealing with missing data

We will not impute missing data for any of the outcomes.

Contacting study authors

Authors of trials will be contacted for missing outcome data and for clarification on study methods, if possible, and for trial status for ongoing trials. We are aware that many studies will be in preprint form or not in peer review journals yet, so we will request full and transparent information on trial conduct including risk of bias confirmation as well as details on participants populations, interventions and

outcomes if necessary. We will follow Cochrane guidelines and recommendations on the need to include these data from unpublished studies to attempt to reduce publication bias and selective reporting of outcomes (Higgins 2019).

Assessment of heterogeneity

We will assess heterogeneity between studies by visual inspection of forest plots, by estimation of the I^2 statistic (I^2 ≥60% was considered substantial heterogeneity) (Higgins 2003), by a formal statistical test to indicate statistically significant heterogeneity (Deeks 2001) and, if possible, by subgroup analyses (see below). If there is evidence of substantial heterogeneity, the possible reasons for this will be investigated and reported.

Assessment of reporting biases

Funnel plots corresponding to meta-analysis of the primary outcome will be examined to assess the potential for small study effects if more than 10 trials are included in the analysis. If there is evidence of small-study effects, publication bias will be considered as only one of a number of possible explanations. If these plots suggest that treatment effects may not be sampled from a symmetric distribution, as assumed by the random effects model, sensitivity analyses will be performed using fixed effects models (Higgins 2019).

Data synthesis

If sufficient clinically similar trials are available, we will pool their results in meta-analyses. We will use forest plots to display the results of the data syntheses.

- For dichotomous outcomes, the risk ratios will be pooled.
- For continuous outcomes, the MD or standardised mean difference (if appropriate) will be pooled

Trials with multiple treatment groups are discussed above, but in the unlikely event the 'shared' comparison group was divided into the number of treatment groups and comparisons made between each treatment group, the split comparison group were treated as independent comparisons.

We will meta-analyse data using the random effects model (DerSimonian 1986). Results will use Mantel-Haentzel method for weighting.

Where interventions differed to any degree or there was other substantial heterogeneity the results were reported in a narrative.

Subgroup analysis and investigation of heterogeneity

Where possible, we will perform subgroup analyses grouping trials by:

- Disease severity, namely mild, moderate, severe and any disease
- Inpatients vs outpatients
- Single dose vs multiple doses

Sensitivity analysis

We will perform sensitivity analysis by excluding trials which do not confirm adequate methods of randomisation for treatment assignment and allocation concealment. We will also perform sensitivity analysis for other aspects that may put a trial at high risk of bias and trials creating unexplained heterogeneity as outlined above in Assessment of heterogeneity and trials identified in subgroup analysis.

GRADE and Summary of findings

All outcomes will be assessed independently by two review authors (TD and AB) using the GRADE approach (Schünemann 2019; GRADE 2020), which ranks the quality of the evidence. Results will be presented in a summary of findings table for treatment and prophylaxis outcomes (Appendix 4). Any differences will be resolved by discussion with the wider group. We will use Cochrane Effective Practice and Organisation of Care guidance to interpret the evidence (EPOC 2015).

Brief economic commentary

We will develop a brief economic commentary (BEC) based on current methods guidance (Aluko 2020). The (BEC) will summarise the availability and core findings of full economic evaluations (cost-utility analyses, cost-effectiveness analyses and cost-benefit analyses) of ivermectin compared to alternatives regimens for 1) treatment and 2) prophylaxis of SARS-CoV-2. Findings from studies conducted in all settings globally will be considered.

ANNEX 6. BRITISH IVERMECTIN RECOMMENDATION DEVELOPMENT PARTICIPANTS

BIRD STEERING GROUP (ENGLAND, UK)

Theresa Lawrie
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ANNEX 7. DECLARATION OF INTERESTS OF PARTICIPANTS

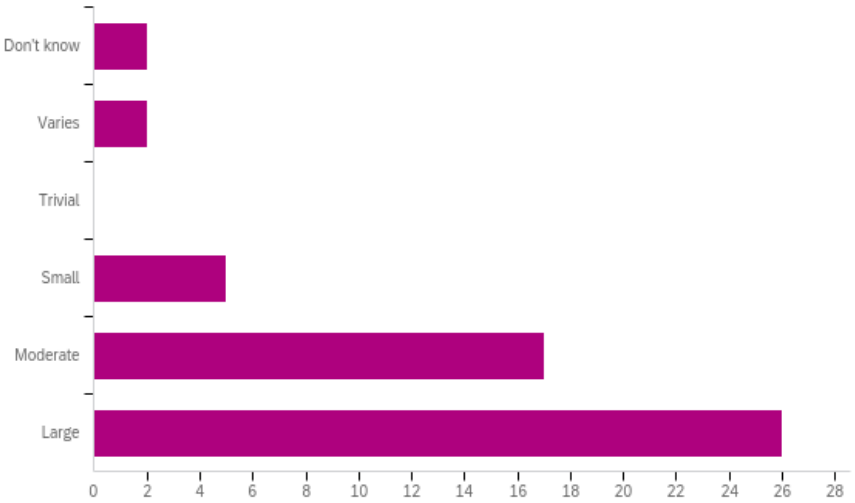
Name (with title)	Disclosure of interest	Conflict of interest and management
Prof. Jose Luis Abreu Quinter	None declared	None declared
Dr. Gustavo Aguirre-Chang	None declared	None declared
Prof. Olufemi Babalola	None declared	Not applicable
Prof. Ira Bernstein	None declared	Not applicable
Mr. Mark Bradley	None declared	Not applicable
Dr. Tau Braun	Has a research company involved in non-medical and non-pharmaceutical solutions and strategies to covid amongst other diseases	Not considered serious enough to preclude participation
Prof. Hector Eduardo Carvallo	None declared	Not applicable
Dr. David Chesler	None declared	Not applicable
Ms. Emma-May Chitty	None declared	Not applicable
Dr. Christine Clark	None declared	Not applicable
Mr. Ian Clayton	None declared	Not applicable
Mr. Roger Felber	None declared	Not applicable
Mr. Kenneth Finlayson	None declared	Not applicable
Dr. Yasmin George	None declared	Not applicable
Dr. Marie Gerval	None declared	Not applicable
Dr. Martin Gill	None declared	Not applicable
Ms. Sharon Gray	None declared	Not applicable
Mrs. Jane Green	None declared	Not applicable
Dr. Rebecca Hall	None declared	Not applicable
Mrs. Sally Harrison	None declared	Not applicable

Dr. Jennifer Hibberd	None declared	Not applicable
Dr. Vicky Hildreth	None declared	Not applicable
Dr. Shaun Hiu	None declared	Not applicable
Dr. Wendy Hoy	None declared	Not applicable
Dr. Christopher Hughes	None declared	Not applicable
Ms. Juliet Johnson	None declared	Not applicable
Dr. Rosemond Jones	None declared	Not applicable
Dr. Denise Kelly	None declared	Not applicable
Prof. Pierre Kory	None declared	Not applicable
Dr. Allan Landrito	None declared	Not applicable
Dr. Michael McConville	None declared	Not applicable
Dr. Abbi Lulsegged	None declared	Not applicable
Dr. Shashikanth Manikappa	None declared	Not applicable
Mr. Gavin McKinley	None declared	Not applicable
Mr. Gez Medinger	None declared	Not applicable
Dr. Eunice Minford	None declared	Not applicable
Prof. Biswa Mohan Padhy	None declared	Not applicable
Mr. Antoine Guérin de Montgareuil	None declared	Not applicable
Emeritus Prof. Jim Neilson	None declared	Not applicable
Dr. Arabella Onslow	None declared	Not applicable
Ms. Jessica Peers	None declared	Not applicable
Ms. Agnes Pinnel	None declared	Not applicable
Ms. Linda Rae	None declared	Not applicable
Prof. Linda Rapson	None declared	Not applicable
Dr. Jill Rasmussen	None declared	Not applicable
Ms. Margarita Reygan	None declared	Not applicable

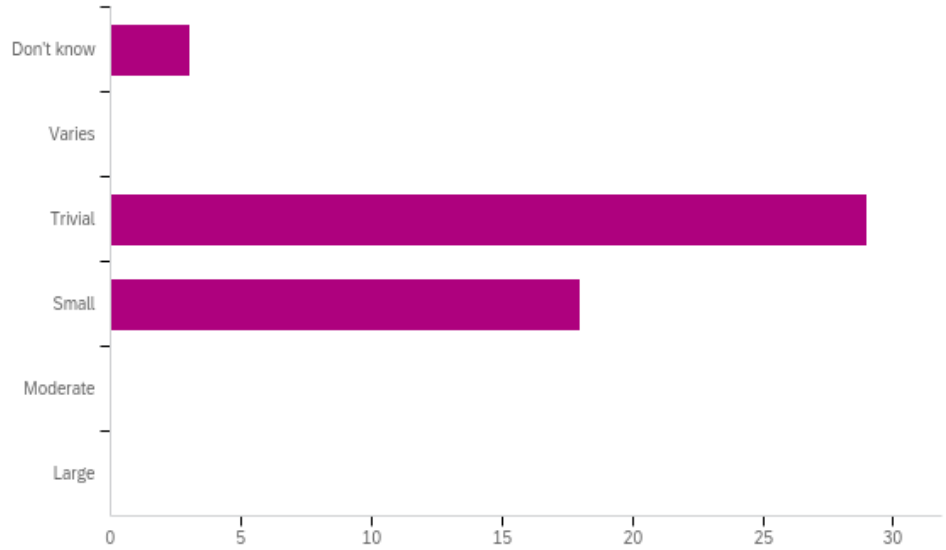
Dr. Jon Rogers	None declared	Not applicable
Mr. David Rose	None declared	Not applicable
Mr. Jon Spiteri	None declared	Not applicable
Mr. Chris Street	None declared	Not applicable
Emeritus Prof. Geoffrey Taylor	A colleague of Prof Borody who promotes an ivermectin treatment pack	Not considered serious enough to preclude participation
Dr. Robert Taylor	None declared	Not applicable
Ms. Seema Taylor	None declared	Not applicable
Prof. Hannah Vowles	None declared	Not applicable
Dr. Deborah Waller	None declared	Not applicable
Dr. Marc Wathelet	Reviewer for EU Covid-related research proposals	Not considered serious enough to preclude participation
Dr. Robert Watkins	None declared	Not applicable
Prof. Morimasa Yagisawa	None declared	Not applicable
Dr. Michael Yeadon	None declared	Not applicable

ANNEX 8. SUMMARY OF BIRD RECOMMENDATION DEVELOPMENT PANEL JUDGEMENTS

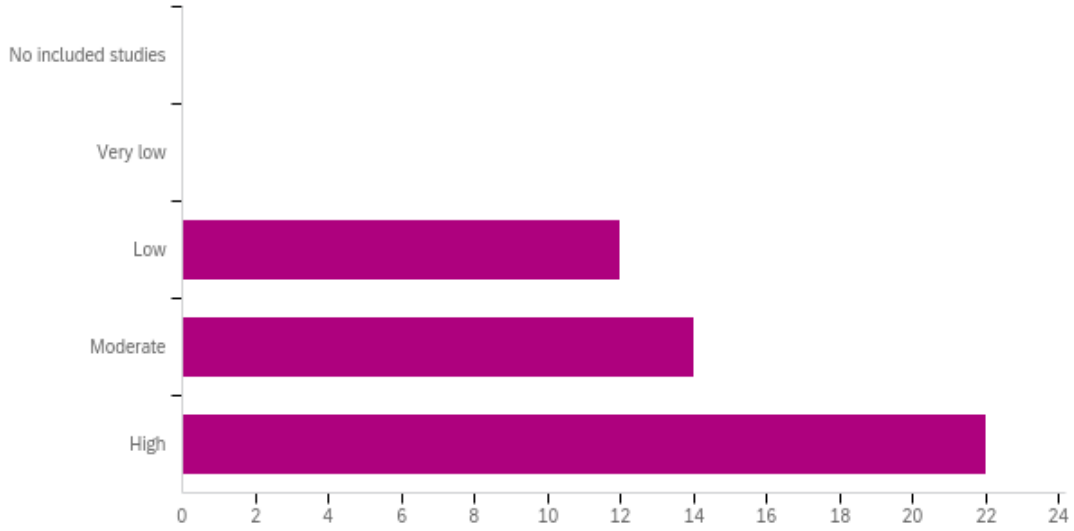
Q1 - How substantial are the desirable anticipated effects of ivermectin compared with no ivermectin?



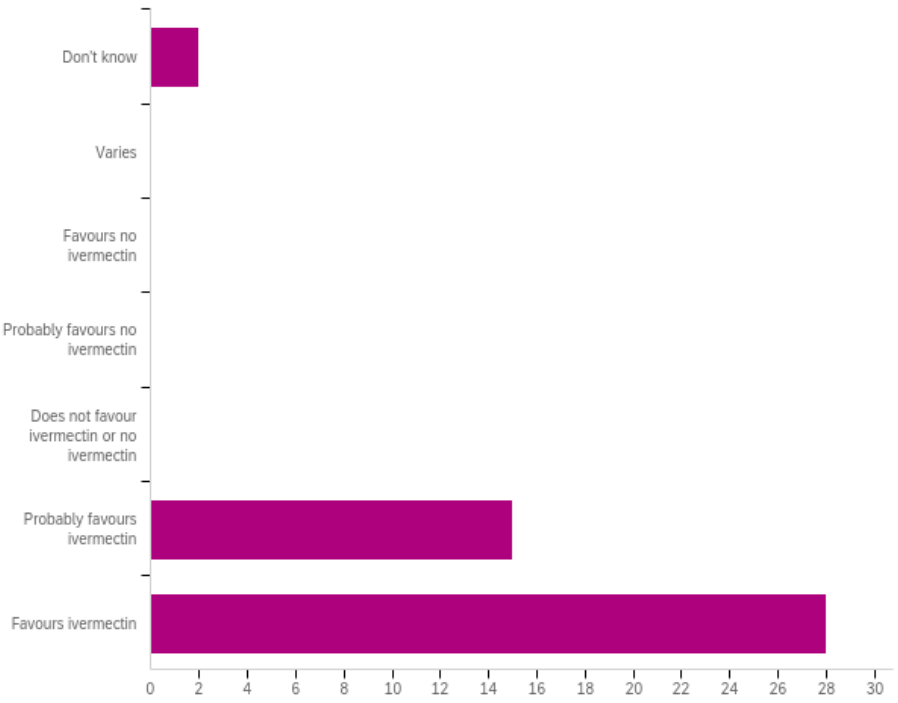
Q2 - How substantial are the undesirable anticipated effects of ivermectin compared with no ivermectin?



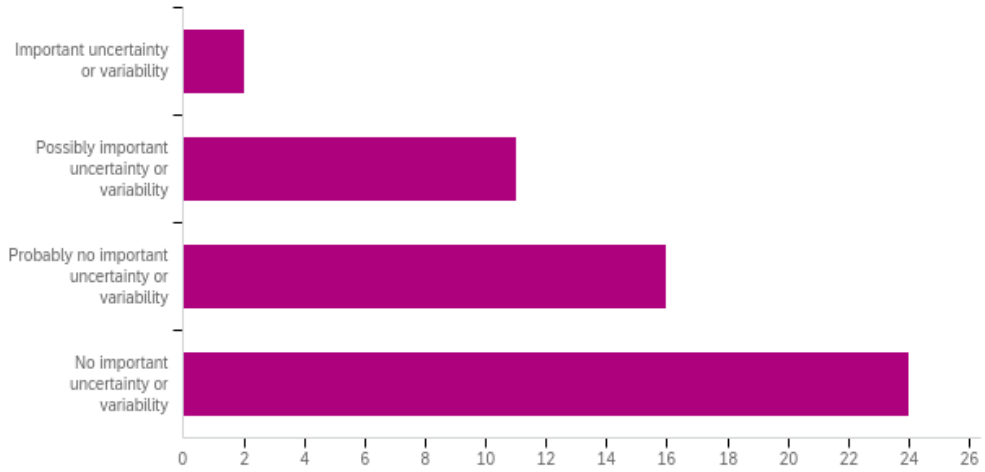
Q3 - In your view, what is the overall certainty of the evidence on the important outcomes associated with ivermectin?



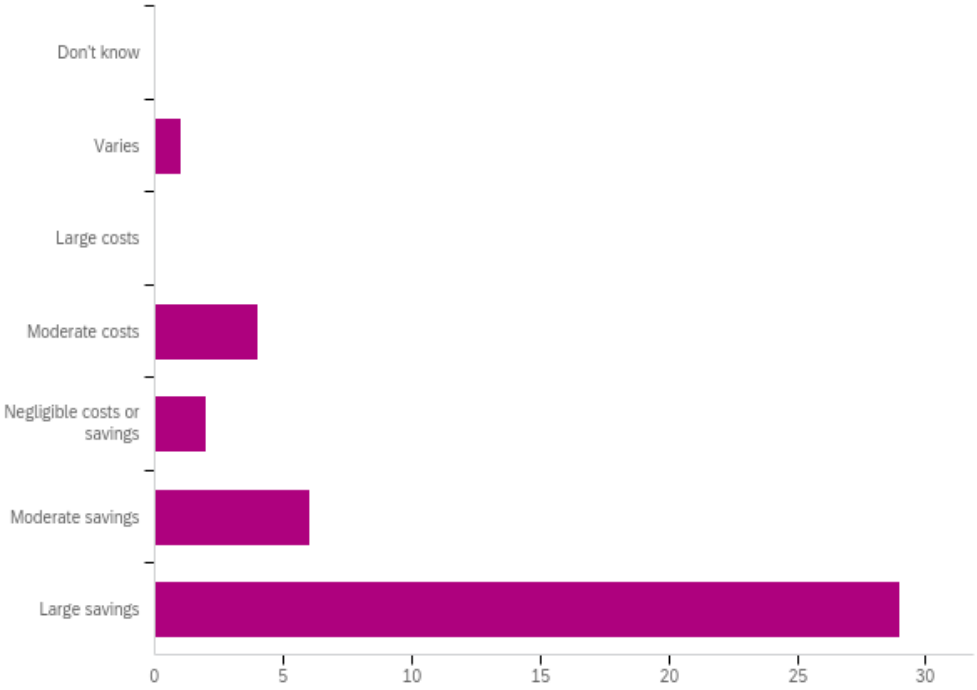
Q4 - Does the balance between desirable and undesirable effects favour ivermectin or no ivermectin?



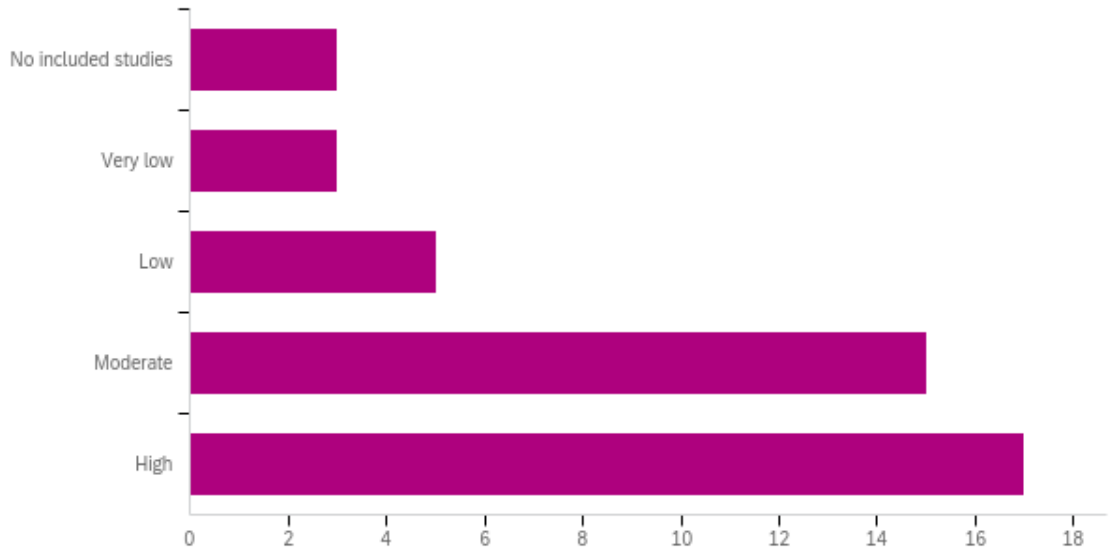
Q5 - Is there important uncertainty about, or variability in, how much people value the main outcomes associated with ivermectin?



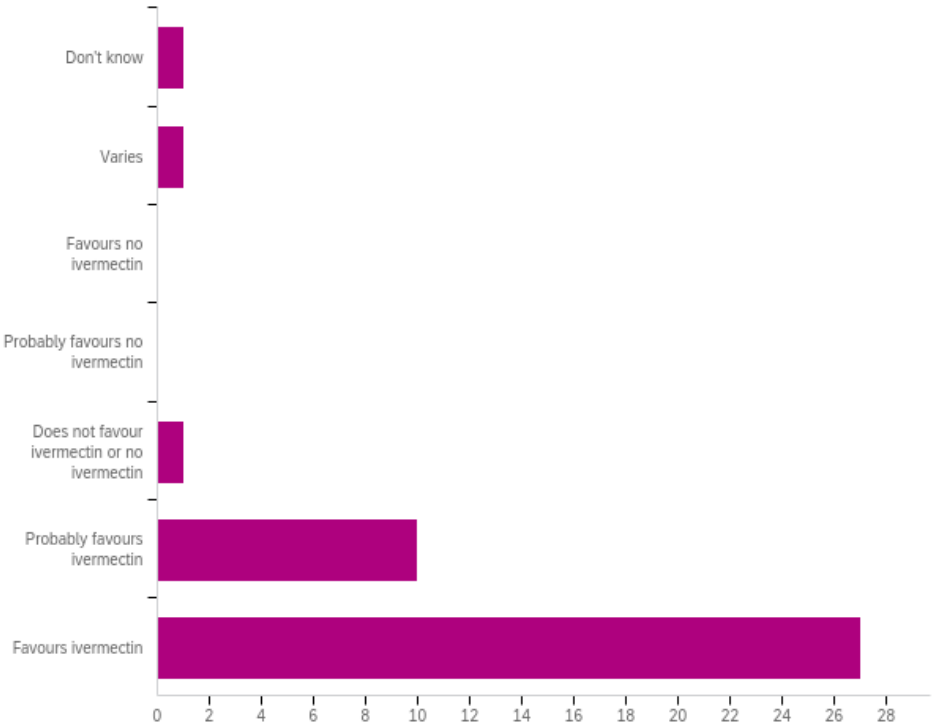
Q6 - How costly are the resources required for ivermectin compared with no ivermectin?



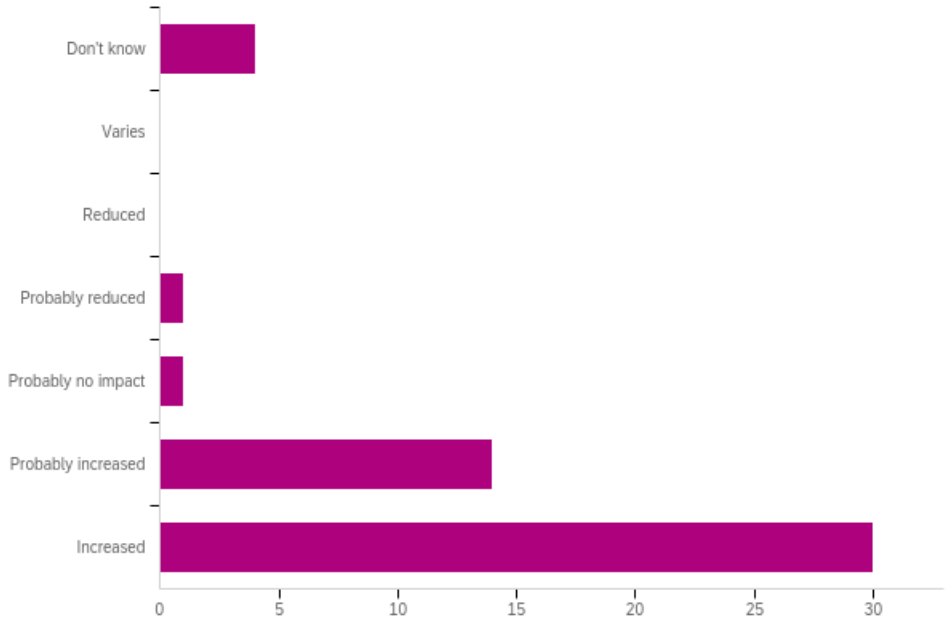
Q7 - What is the certainty of the evidence on costs?



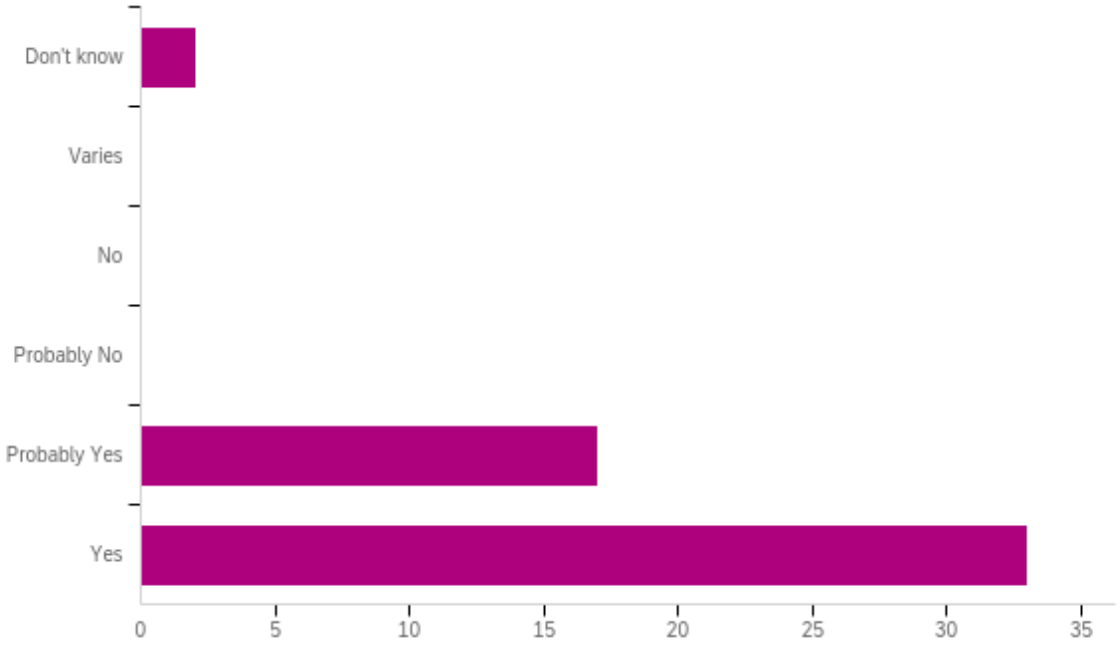
Q8 - How cost-effective is ivermectin compared with no ivermectin?



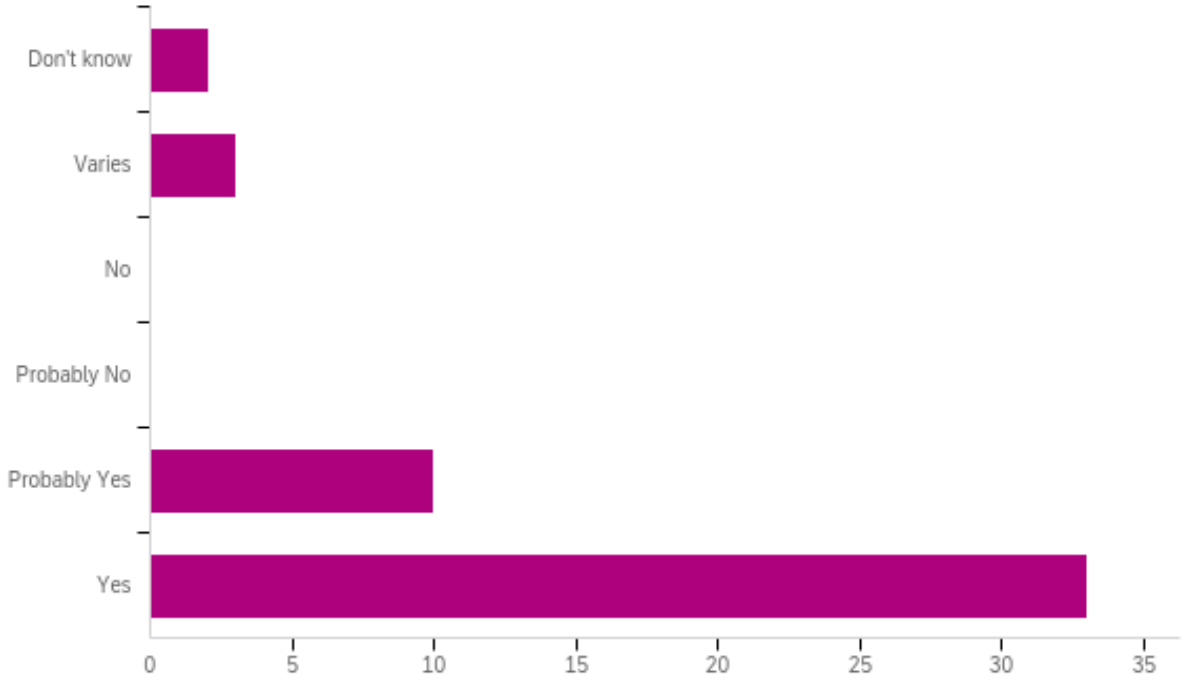
Q9 - What would be the impact of ivermectin on equity?



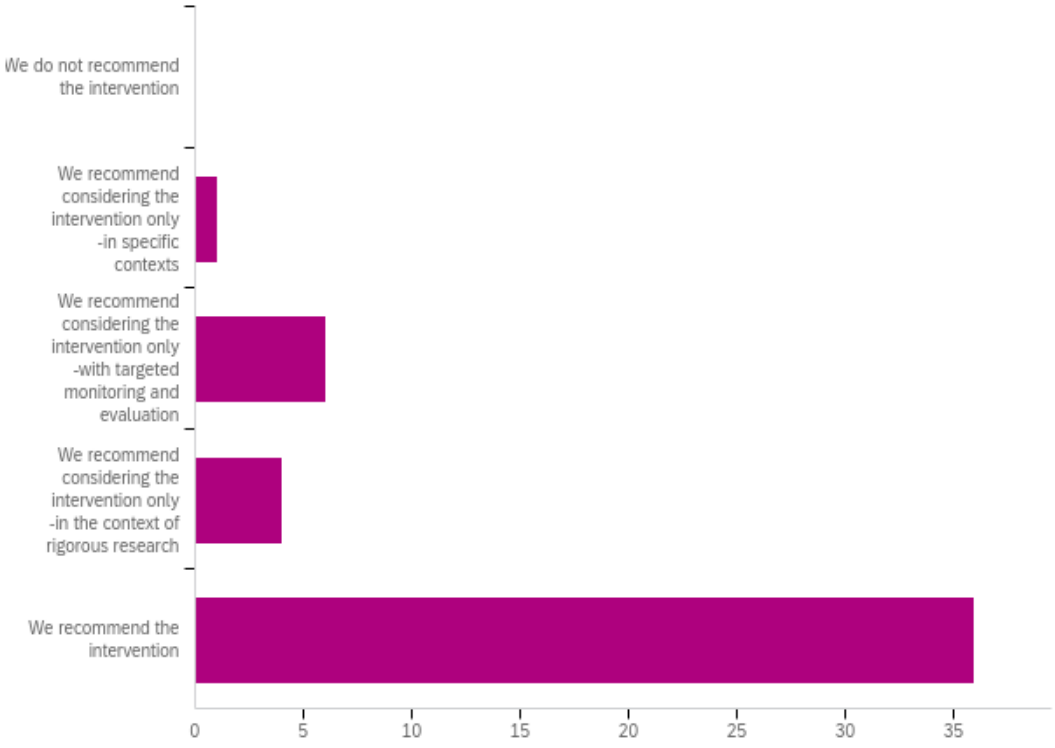
Q10 - Would ivermectin be acceptable to health professionals, patients, families and other stakeholders?



Q11 - Would ivermectin be feasible to implement?



Q12 - Based on the evidence presented, do you think ivermectin should be recommended?



ANNEX 9: IVERMECTIN API SUPPLIERS[5]

Ref Price $168/kg

China

SUZHOU RYWAY BIOTECH, Suzhou, China

RICHBERYL BIOTECH CO., LTD. OF RAOYANG COUNTY, China

Shandong Qilu King-Phar Pharmaceutical Co., Ltd., Jinan, China

ZHEJIANG APELOA KANGYU PHARMACEUTICAL CO. LTD, Hangzhou, China

Dalian Richon Chem. Co., Ltd, Dalian, China

HENGDIAN GROUP, Hangzhou, China

North China Pharmaceutical Co., Ltd., Shijiazhuang, China

Hebei Veyong Animal Pharmaceutical Co., Ltd, Shijiazhuang, China

HANGZHOU THINK CHEMICAL CO., LTD., Hangzhou, China

Zhejiang HISUN Pharmaceuticals Co., Ltd, Taizhou, China

Other than China

Jai Radhe Sales, Gujrat, India

Dr. Reddy's Laboratories, India

SAMEX OVERSEAS, Gujarat, India

Athos Chemicals, Gujarat, India

Zydus Cadila (India)

Pharmaffiliates Analytical & Synthetics Ltd., Panchkula, India

[5] List of suppliers kindly provided by Professor Satoshi Omura and colleagues of Kitasato University, Japan.

Hovione Farmaciencia, Lisboa, Portugal

Delta Synthetic Co., Ltd, New Taipei, Taiwan

Tecoland Co., Irvine CA, USA

MERCK & CO. INC., Whitehouse Station, NJ, USA

Others (API uncertain)

Galderma Laboratories LP, Fort Worth, TX, USA , SOOLANTRA

Arbor Pharmaceuticals, Atlanta, GA, USA

Licensed to Kaken Pharma.: ivermectin lotion (0.5%) for head lice;

Boehringer Ingelheim, Germany; Ivomec (veterinary)

Edenbridge Pharmaceuticals, Parsippany, NJ, USA; Generic tablets 3mg

Perrigo Company plc, Dublin, Ireland; topical cream

MedinCell S.A, Montpellier, France

Generic: Actavis, Bryant, Edenbridge, NuCare, Prasco, Taro

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* These individuals were unable to attend the BIRD meeting on the 20th of February, 2021, and sent their endorsement of the recommendation via email. We continue to accept endorsements.