The Efficacy of Ivermectin for the Treatment or Prophylaxis of Covid-19: A Literature Review

Rick Bradford, August 2021

Contents

1. Methodology

A convenient jumping-off point for this review is the web site c19ivermectin.com. **If reliable**, this site has done the job already. The methodology adopted in my review will therefore be to address the reliability of c19ivermectin.com by,

(i) Examining whether that site represents faithfully the findings, and limitations, of the 63 clinical trial studies it uses in its analyses (as of 27/8/21); and,

(ii) Determining whether the 63 studies in question are "almost all" the relevant studies which exist in accessible form (not just journal publications) by conducting independent searches; and,

(iii) Reviewing the conclusions of meta-analyses that I discover in the course of step (ii) or as otherwise identified.

Step (i) will be conducted by independent examination of a large sample of the source references. Should c19ivermectin.com prove to accurately represent the findings of this large sample of studies, then checking all studies will not be necessary.

A by-product of my independent examination of studies should be the identification of shortcomings that may not be apparent in a bland figure for "percent improvement", e.g., statistical significance, subjectivity, alternative outcome measures, bias by researchers, excessive dosage, adverse effects, etc.

Step (ii) will be carried out using (a) Google Scholar, and (b) ClinicalTrials.gov (the US National Library of Medicine site where workers worldwide commonly post clinical trial results, generally prior to publication). The keywords used for the searches will be specified. In step (ii), the phrase "almost all" leaves scope for c19ivermectin.com having missed a few studies (and it may be debatable in some cases whether a given study is, or is not, of a quality which justifies its inclusion). The aim of step (ii) is only to determine if c19ivermectin.com has skewed the perception of study findings by cherry picking. To rule this out it is sufficient to show that the number of studies missed out is small (though it should also be confirmed that none of the missed studies is particularly huge and authoritative, and hence would have far greater weight than the other studies).

The dosage of Ivermectin used in the studies forms part of this review, which is of relevance to safety (as well as efficacy).

Potential publication bias also needs consideration. This is an effect whereby positive results tend to be reported but negative results may not be reported. This is addressed in §3.8.

The detailed outcome of steps (i), (ii) and (ii) are given in a series of Appendices, A – E.

2. Summary Claims of c19ivermectin.com

These are the claims being made at 23rd August 2021,

- 112 studies, 70 peer reviewed, 613 scientists/authors;
- 26,422 patients involved in trials;
- 63 trials with results comparing treatment and control groups;
- 58 of the 63 trials reported positive effects;
- 31 randomised control trials (RCTs);
- 86% improvement from 14 prophylaxis trials;
- 72% improvement in 27 early treatment trials;
- 40% improvement in 22 late treatment trials;
- 58% improvement in 25 mortality trials;
- 58% improvement across the 31 RCTs.

The 63 trials with control groups are the focus of my review here.

The last para on the site includes this…

"*Vaccines and treatments are both extremely valuable and complementary. All practical, effective, and safe means should be used. Elimination of COVID-19 is a race against viral evolution. No treatment, vaccine, or intervention is 100% available and effective for all current and future variants. Denying the efficacy of any method increases the risk of COVID-19 becoming endemic; and increases mortality, morbidity, and collateral damage."*

3. Step (i): Examination of Source References

The total of 112 studies are of several types,

- The 63 original studies on people, with treatment and control groups;
- Other original studies on people;
- Meta-analyses (which provide no new data but accumulate and analyse data from other studies);
- Studies not on people, e.g., in-vitro or in-silico studies, studies on animals, and theoretical papers.

I shall concentrate here on the first category, which provide the most direct evidence. These 63 studies break down according to the timing of the treatment,

- Prior to symptoms (i.e., prevention, prophylaxis);
- Shortly after first symptoms (early treatment);
- Late treatment (when symptoms are serious / disease is progressing to later stages)

According to c19ivermectin.com these 63 studies break down as shown in Table 1.

Table 1: The 63 studies with controls (from c19ivermectin.com)

	Studies	*Prophylaxis*	*Early treatment*	*Late treatment*	*Patients*	*Authors*
All studies	63	**86%** [75-92%]	**72%** [55-82%]	**40%** [24-52%]	26,422	613
Peer-reviewed	42	**86%** [73-93%]	**75%** [61-84%]	**43%** [21-59%]	16,455	436
Randomized Controlled Trials	31	**84%** [25-96%]	**61%** [46-71%]	**30%** [2-50%]	6,561	359
Percentage improvement with ivermectin treatment						

The 63 studies may also be broken down according to the effect measure deployed. These are,

- Avoidance of a positive test result;
- Avoidance of becoming ill;
- Avoidance of being admitted to hospital;
- Recovery time criteria;
- Avoidance of the need for ventilation;
- Avoidance of death.

Different studies use different criteria of "success" depending upon the study group.

There are a great many variables which cause the trials to differ, in addition to those issues listed above. Some of these are,

- Dosage;
- Deployment of Ivermectin in conjunction with other drugs;
- Deployment of alternative drug regimes in the "control" group;
- Age, sex and ethnicity of subjects;
- Health status of subjects;
- Statistical power (number of subjects, N);
- "Blindness": possible placebo effects if subjects knew they were being treated and/or with what drug;
- "Double Blindness": possible researcher bias if researchers knew what drug subjects were being given.

I shall attempt to identify these issues in the studies I examine. Figures 1, 2 and 3 which follow are taken from c19ivermectin.com and show the percentage improvement due to the Ivermectin treatment, with error bars, for (1) prophylaxis (27 studies), (2) early treatment (14 studies), (3) late treatment (22 studies), respectively.

Figure 1: The14 Prophylaxis Studies (from c19ivermectin.com)

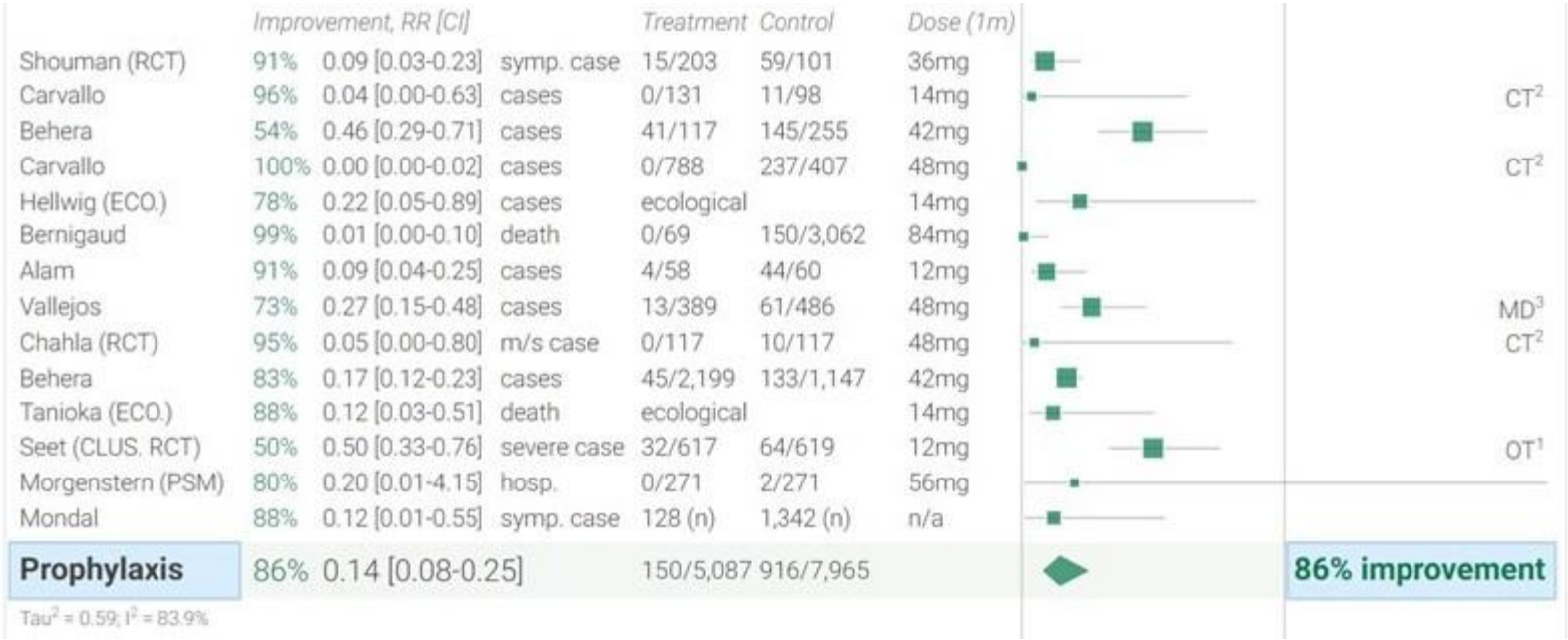


Figure 2: The 27 Early Treatment Studies (from c19ivermectin.com)

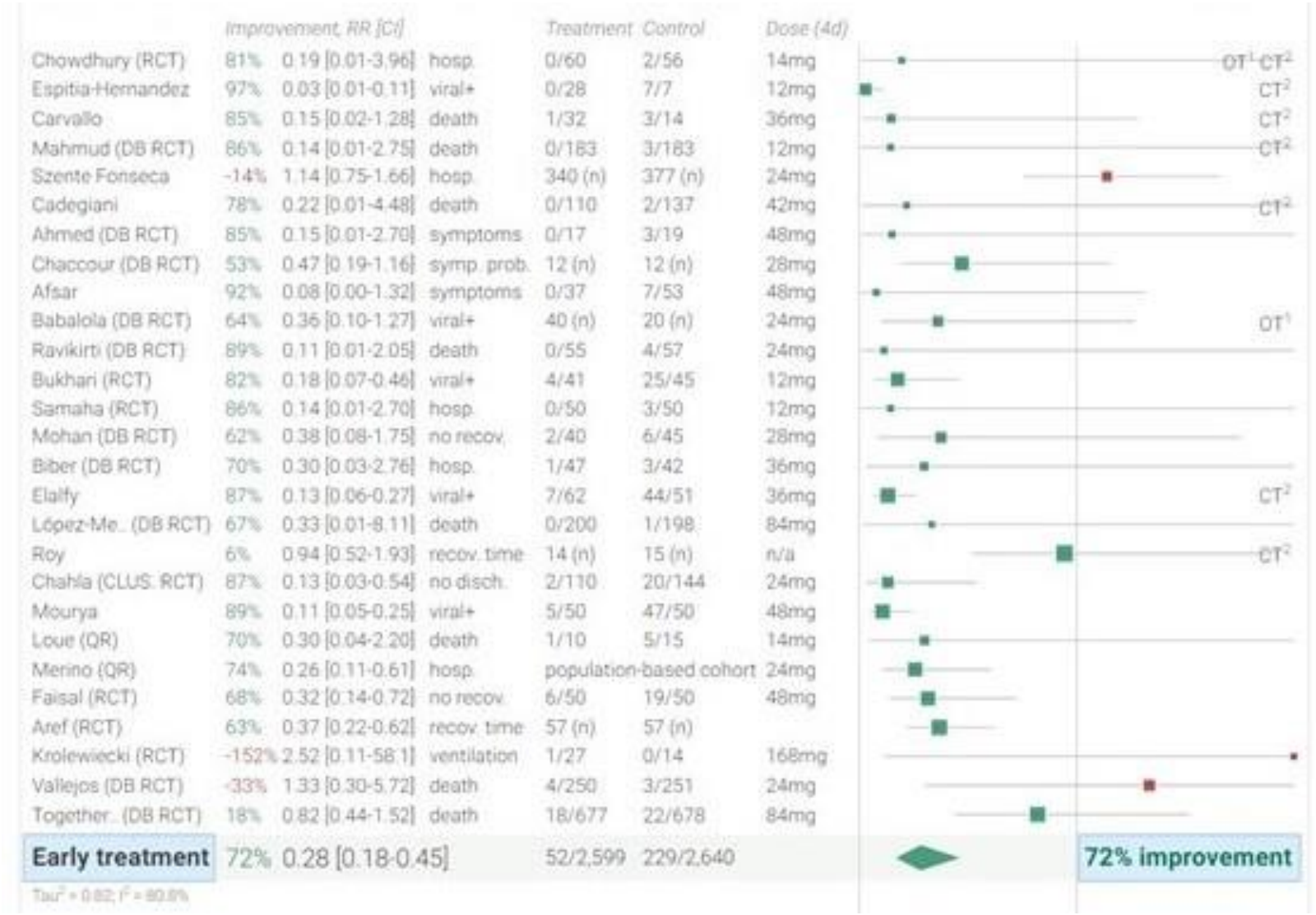
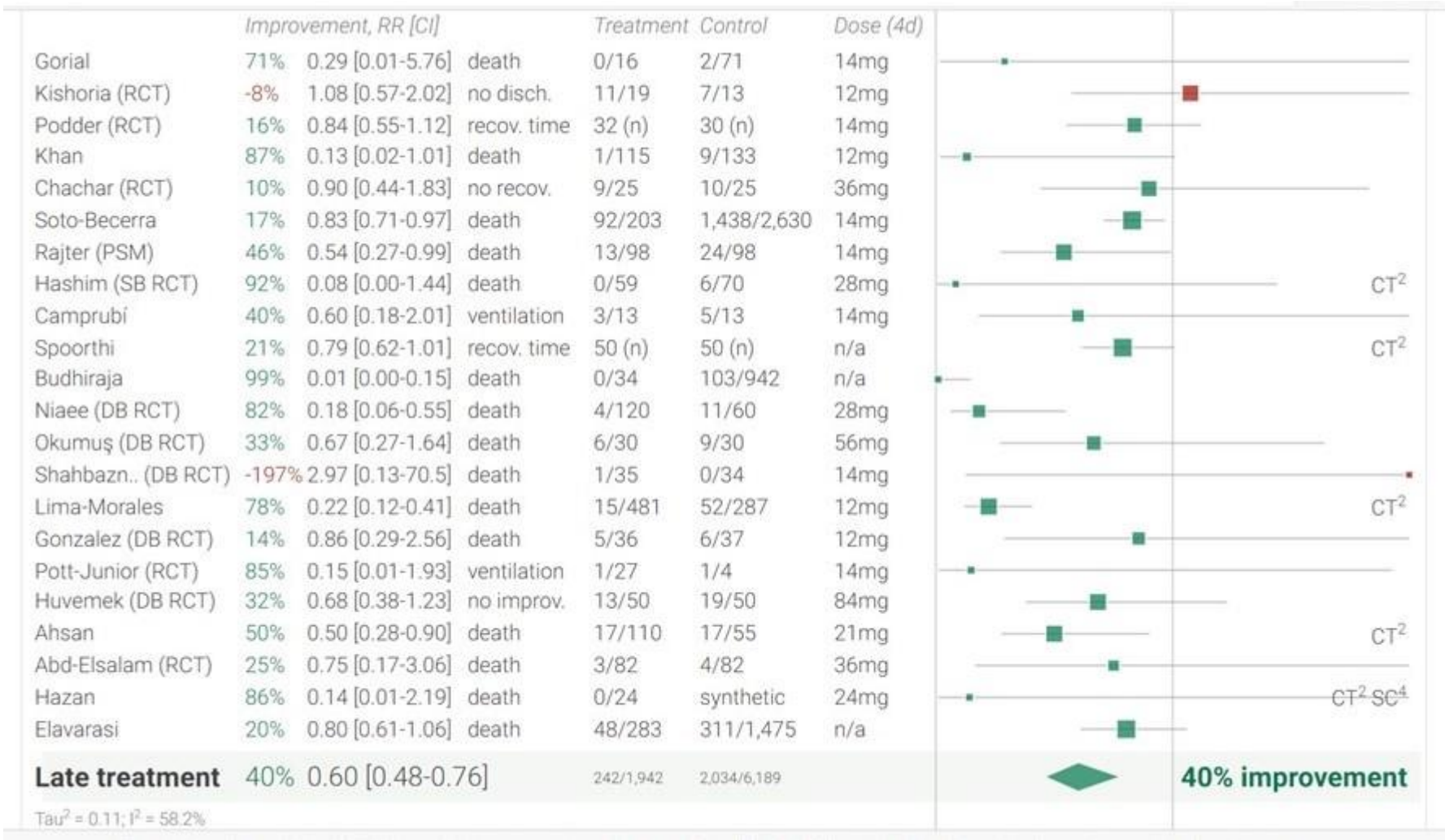


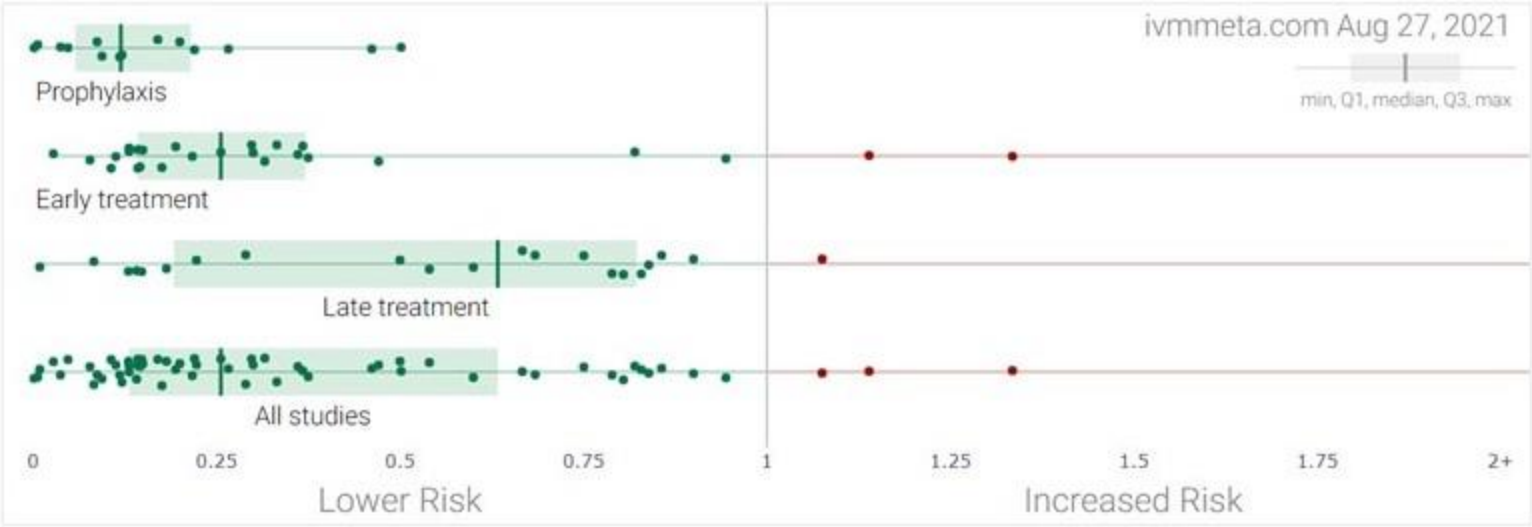
Figure 3: The 22 Late Treatment Studies (from c19ivermectin.com)



	Improvement, RR [CI]			Treatment	Control	Dose (4d)
Gorial	71%	0.29 [0.01-5.76]	death	0/16	2/71	14mg
Kishoria (RCT)	-8%	1.08 [0.57-2.02]	no disch.	11/19	7/13	12mg
Podder (RCT)	16%	0.84 [0.55-1.12]	recov. time	32 (n)	30 (n)	14mg
Khan	87%	0.13 [0.02-1.01]	death	1/115	9/133	12mg
Chachar (RCT)	10%	0.90 [0.44-1.83]	no recov.	9/25	10/25	36mg
Soto-Becerra	17%	0.83 [0.71-0.97]	death	92/203	1,438/2,630	14mg
Rajter (PSM)	46%	0.54 [0.27-0.99]	death	13/98	24/98	14mg
Hashim (SB RCT)	92%	0.08 [0.00-1.44]	death	0/59	6/70	28mg
Camprubí	40%	0.60 [0.18-2.01]	ventilation	3/13	5/13	14mg
Spoorthi	21%	0.79 [0.62-1.01]	recov. time	50 (n)	50 (n)	n/a
Budhiraja	99%	0.01 [0.00-0.15]	death	0/34	103/942	n/a
Niaee (DB RCT)	82%	0.18 [0.06-0.55]	death	4/120	11/60	28mg
Okumuş (DB RCT)	33%	0.67 [0.27-1.64]	death	6/30	9/30	56mg
Shahbazn.. (DB RCT)	-197%	2.97 [0.13-70.5]	death	1/35	0/34	14mg
Lima-Morales	78%	0.22 [0.12-0.41]	death	15/481	52/287	12mg
Gonzalez (DB RCT)	14%	0.86 [0.29-2.56]	death	5/36	6/37	12mg
Pott-Junior (RCT)	85%	0.15 [0.01-1.93]	ventilation	1/27	1/4	14mg
Huvemek (DB RCT)	32%	0.68 [0.38-1.23]	no improv.	13/50	19/50	84mg
Ahsan	50%	0.50 [0.28-0.90]	death	17/110	17/55	21mg
Abd-Elsalam (RCT)	25%	0.75 [0.17-3.06]	death	3/82	4/82	36mg
Hazan	86%	0.14 [0.01-2.19]	death	0/24	synthetic	24mg
Elavarasi	20%	0.80 [0.61-1.06]	death	48/283	311/1,475	n/a
Late treatment	40%	0.60 [0.48-0.76]		242/1,942	2,034/6,189	

$Tau^2 = 0.11; I^2 = 58.2\%$

Figure 4: All 63 Studies' Central Estimates (from c19ivermectin.com)



Summary of claims of c19ivermectin.com

[1] 13 of the 14 prophylaxis studies are consistent with Ivermectin usage resulting in improved outcomes at the 95%Cl level, and all 14 do so at the central estimate level.

[2] 24 of the 27 early treatment studies show improved outcomes with Ivermectin usage at the central estimate level, though only 8 do so at the 95%CL level.

[3] 20 of the 22 late treatment studies show improved outcomes with Ivermectin usage at the central estimate level, though only 8 do so at the 95%CL level

[4] Limited positive results at the 95%CL level is due to virtually all trials being small. The reason for this is discussed below.

I have independently examined 20 of the 63 study reports, as follows,

- 9 of the early treatment studies (see Appendix A for details)
- 5 of the prophylaxis studies (see Appendix B for details)
- 6 of the late treatment studies (see Appendix C for details)

Some relevant points to bear in mind are as follows…

3.1 Ivermectin Dosage

Some pundits claim that excessively large doses of Ivermectin are required for anti-viral usage. To gauge the dosage deployed in the studies note that in established usage, normal Ivermectin dosage is 0.2 mg/kg, or (using 3mg tablets) 12 mg for light adults (8 stone to 10st 4lb) or 15 mg for medium-light adults (10st 5lb to 12st 6lb) or 18 mg for medium-heavy adults (12st 6lb to 14st 2lb), these as one-off doses: see Ivermectin Tablets - FDA prescribing information, side effects and uses (drugs.com). However, these relate to treatment for parasitic conditions.

The simplified dosages stated in c19ivermectin.com (as shown in Figures 1, 2, 3) are the total dose in the first four days for treatment, or the monthly dose for prophylaxis, for a 70kg person (medium-light in my designation). Most of these exceed the single dose for a parasitic condition but this does not imply overdosage as the total dose is spread over several days or weeks. Moreover, note that some treatments involved dosing beyond 4 days, so the total dose in these cases would be higher than shown Figures 1, 2, 3.

Guidance on Covid-19 treatment with Ivermectin has been published by the FLCCC (Front Line COVID-19 Critical Care Alliance). They advise as follows,

3.1.1 Prevention Protocol

Chronic Prevention: 0.2 mg/kg twice per week for as long as disease risk is elevated. This is a weekly dose of 30 mg for a medium-light adult or 36 mg for a medium-heavy adult. Monthly doses under this regime are thus around 120 – 144 mg.

Post-Exposure Prevention: 0.4 mg/kg – one dose followed by a second dose 48 hours later. For medium adults this would be 60 to 72 mg in two days.

3.1.2 Early Outpatient Protocol

0.4 – 0.6 mg/kg per day for 5 days. This would be a total dose over 5 days of 150 to 270 mg for a medium adult.

The dosages in Figures 1, 2, 3 are quite low in comparison with the above protocols, all but three studies being well within the smallest of the above ranges (and none exceeding all of them).

3.2 Note on Confidence Intervals

Confidence intervals on Risk Ratio (see §3.3) were evaluated from p values using Altman & Bland, where "estimate" relates to log(Risk Ratio) and log is natural. A methodology for the reverse process, generating a p value from a stated confidence interval, is given here.

3.3 Note on the calculation of Risk Ratio and Improvement

For a group with N_A members, of whom D_A have adverse outcomes the risk is $r_A = D_A/N_A$. If Group A receive the Ivermectin treatment and Group B is the control group whose risk, defined in the same manner, is $r_B = D_B/N_B$, then the Risk Ratio (RR) is $RR = r_A/r_B$. Risk Ratio less than 1 indicates improved outcomes associated with the Ivermectin regime.

Improvement is defined as $1 - RR$ expressed in percent.

If $D_A = 0$, as is common (i.e., none of the treated group have the adverse outcome in question) then the above definitions would lead, misleadingly, to a risk of zero and an improvement of 100%. In this case I use a pragmatic approach of gauging improvement by setting $D_A = 0.5$ and increasing the number of adverse outcomes for the control group by 0.5 also for parity, i.e., $D_B \to D_B + 0.5$. c19ivermectin.com used a rather different procedure in such cases, but the results seemed to be similar.

3.4 Note on Effect Measure

As noted previously, the outcome, or effect, measure varies. It may be avoidance of becoming infected (prophylaxis), in which case trials started by confirming an initial negative test. Where subjects were already ill, effect measures might be death or viral clearance as measured by PCR tests or avoidance of the need for hospitalisation or ventilation. Recovery time (recovery speed) was used as the measure in some cases. There is good reason to consider quick clearance of the virus to be far preferable in the case of Covid-19, and not only because it reduces patient suffering time. This is because a prolonged "first stage" leads to a greater possibility of disease escalation into the more intractable later stages. To quote Bukhari, early viral clearance is "of importance because high viral load and prolonged viremia can potentially trigger the immune dysregulation phase leading to more severe disease, and the requirement of treatment escalation".

3.5 Note on Multi-Drug Trials

It was sometimes the case that Ivermectin was deployed in combination with other drugs. This has been noted in the Appendices when it applies. However, Ivermectin is the common factor between all the treatment groups. (And, in some cases, the "control" groups might involve the same drugs that have been used in conjunction with Ivermectin in other trials – so the superior performance of Ivermectin follows from those. Some studies used multivariate regression to disaggregate the effects of different factors – and hence controlled for age, sex, ethnicity and comorbidities as well as various drug combinations).

3.6 Note on Control Treatment

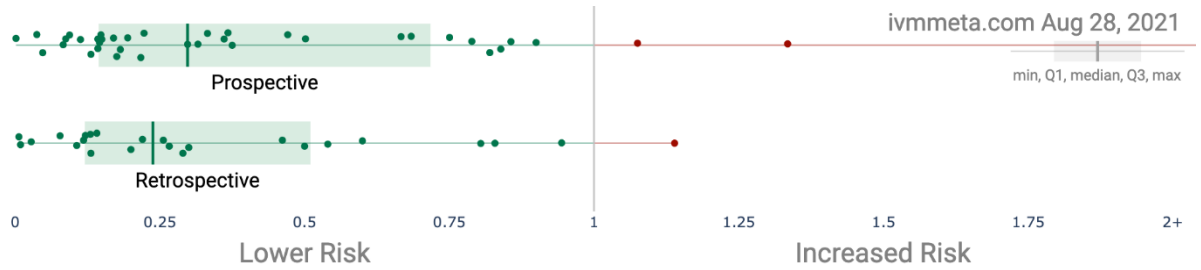
The Control group was sometimes being treated with an alternative drug regime. Sometimes the Control group received only paracetamol and vitamins, but frequently they received other drugs thought to be potentially efficacious against Covid-19 (typically hydroxychloroquine, HCQ, or azithromycin, AZM, perhaps both). The Treatment group would receive Ivermectin but may also receive these other drugs, or possibly not. Virtually every possible permutation was used in different trials. The important point to note is that HCQ and AZM are also believed to have some efficacy against Covid-19. So where these were given to the Control

group, the improvement due to Ivermectin derived from the study is over and above any benefit due to these other drugs compared to no drug usage.

3.8 Publication Bias

I simply reproduce the argument from c19ivermectin.com relating to publication bias:-

Publishing is often biased towards positive results, which we would need to adjust for when analyzing the percentage of positive results. For ivermectin, there is currently not enough data to evaluate publication bias with high confidence. One method to evaluate bias is to compare prospective vs. retrospective studies. Prospective studies are likely to be published regardless of the result, while retrospective studies are more likely to exhibit bias. For example, researchers may perform preliminary analysis with minimal effort and the results may influence their decision to continue. Retrospective studies also provide more opportunities for the specifics of data extraction and adjustments to influence results. The Figure below shows a scatter plot of results for prospective and retrospective studies. The median effect size for prospective studies is 70% improvement, compared to 76% for retrospective studies, showing no significant difference. Bryant also perform a funnel plot analysis, which they found did not suggest evidence of publication bias.



3.9 Conclusion from Step (i)

c19ivermectin.com faithfully represents the outcomes of the 20 studies I examined. In Appendices A, B, C I note some minor points for a few papers, but nothing of serious import. My overall impression is that c19ivermectin.com are to be congratulated on doing a thorough job.

Subject to Step (ii) being satisfactory, the outcomes summarised in Figures 1, 2 and 3 appear to be a reliable indication of the efficacy of Ivermectin against Covid-19.

4. Step (ii): Independent Searches for Relevant Studies

I have carried out an independent search for relevant studies, i.e., trials which produce data on the efficacy of Ivermectin against Covid-19 compared with control groups. The purpose is to examine whether by c19ivermectin.com might be guilty of cherry-picking. I have not attempted to independently locate all 63 studies used by c19ivermectin.com. It suffices to confirm the adequacy of my searches by finding a reasonable number of them, and, in so doing, whether a large number of additional studies come to light (especially if their findings are adverse). The details of my searches are in Appendix D. In summary,

[1] I looked at the Abstract of 70 hits via Google Scholar using keywords “Ivermectin + Covid” or “Ivermectin + SARS”. This revealed 20 of the 63 studies used by c19ivermectin.com. In addition, I found two other studies, but both seem to have been

excluded with good reason. I found no studies in these 70 hits which should have been included but were not.

[2] I looked at all hits from *ClinicalTrials.gov* which met criteria for being completed trials with results on Covid19 and Ivermectin. Of the 11 hits, 9 were used by c19ivermectin.com. The reasons for excluding the other two are not entirely clear, though one appears to be a null result for both treatment and control arms (so no numerical measure of efficacy) whilst the other appears supportive of the efficacy of a multi-drug treatment of which Ivermectin was one.

Overall I did not find evidence to concern me that cherry-picking was an issue, quite the opposite.

5. Step (iii): Review of Meta-Analyses

c19ivermectin.com identifies six meta-analyses and summarises their results in terms of mortality improvement as in Figure 5. The seventh in Figure 5, named ivnmeta, is c19ivermectin.com itself. All seven are (easily) significant at the 95% confidence level. This is the effect of pooling many small studies. This confirms that the failure of many of the individual, small, studies to obtain the 95%CL is likely just due to their smallness (low statistical power).

The key findings from these studies are summarised in Appendix E (E.8 to E.13).

Figure 5:

As a by-product of my searches for studies in Step (ii), I found 7 further meta-analyses in addition to those of Figure 5. The key findings from these 7 meta-analyses are given in Appendix E. Two were uncertain or considered there was no clear beneficial effect associated with the use of Ivermectin. Five were supportive of a benefit of Ivermectin, two rather weakly so, and three more strongly. The two meta-analyses most strongly supportive of Ivermectin deployed the largest number of studies in their analysis.

However, six of the seven meta-analyses listed in Figure 5 are strongly supportive of the benefits of Ivermectin. The exception is that of the World Health Organisation (WHO). Overall, therefore, nine meta-analyses are strongly supportive, two mildly supportive and three not supportive.

The WHO meta-analysis, reported in March 2021 was performed as part of the WHO's role to advise on drug usage. Their recommendation on Ivermectin was "not to use Ivermectin except in the context of a clinical trial". This is despite their meta-analysis showing a statistically significant benefit on mortality (as shown in Figure 5), namely an Odds Ratio of 0.19 (CI 95% 0.09 - 0.36). The emphasis placed by the WHO on the potential for Ivermectin to be harmful, and its lack of efficacy in respect of viral clearance and speed of recovery, stands starkly at odds with what I have myself read in the 30 or so reports I reviewed. My strong impression was that Ivermectin was particularly free of adverse effects and was also efficacious in viral clearance and improving recovery times.

Whilst the WHO's concern over the low confidence that can be gained singly from individual studies is true, their overall position seems strange. c19ivermectin.com includes Tables contrasting the number of studies/subjects used to approve other drugs for use with the current status of studies on Ivermectin in the context of Covid-19, reproduced as Figure 6.

It is worth pointing out that some meta-analyses may be making a logical error. Commonly the authors use criteria to reject studies which are based upon the study in isolation. But this fails to appreciate that the overall picture – including and especially statistical significance – may emerge only in aggregate when all studies are compiled together. This phenomenon is particularly acute in the present situation as Ivermectin has not been subject to a large scale, authoritative study, funded commensurately by a national or international body or by Big Pharma with commercial investment in mind. Instead, we have only small, locally funded studies, from single institutes or hospitals – though there are a great many of them. In this situation the key is NOT to reject studies lest the baby is thrown out with the bathwater.

This situation is well put by the Japanese meta-analysis of Morimasa Yagisawa, et al (March 2021), who opine, "Unlike clinical trials conducted by pharmaceutical companies, lack of funds and human resources are the main factors behind the delay in the progress of such clinical trials."

6. Final Word

I leave the final word to c19ivermectin.com which states,

"*the evidence base is much larger and has much lower conflict of interest than typically used to approve drugs*".

See over…

Figure 6: Drug Approval Comparison Tables from c19ivermectin.com

Indication	*Studies*	*Patients*	*Status*
Strongyloidiasis *[Kory (B)]*	5	591	Approved
Scabies *[Kory (B)]*	10	852	Approved
COVID-19	63	26,398	Pending
COVID-19 RCTs	31	6,561	

Table 3. *WHO ivermectin approval status.*

Medication	*Studies*	*Patients*	*Improvement*	*Status*
Budesonide (UK)	1	1,779	17%	Approved
Remdesivir (USA)	1	1,063	31%	Approved
Casiri/imdevimab (USA)	1	799	66%	Approved
Ivermectin evidence	63	26,398	68% [60-75%]	Pending

Table 4. *Evidence base used for other COVID-19 approvals compared with the ivermectin evidence base.*

	Ibuprofen	*Ivermectin (for scabies)*	*Ivermectin (for COVID-19)*
Lives saved	0	0	>500,000
Deaths per year	~450	<1	<1
CDC recommended	Yes	Yes	No
Based on	0 RCTs	10 RCTs 852 patients	31 RCTs 6,561 patients

Table 5. *Comparison of CDC recommendations [Kory (B)].*

Appendix A: Summary of Checks of Early Treatment Studies

Study: Chowdhury, February 2021 (RCT)

Improvement quoted	Correct (81%)
Error bars (graphic)	Correct (not statistically significant so error bar includes "no improvement")
Other results	-
Criterion	Stated as "hospitalisation" but actually recovery to negative PCR
Treatment numbers	Correct
Combined with?	Doxycycline
Control numbers	Correct
Control treatment	HCQ-Azithromycin
Ivermectin Dosage	Correct (0.2 mg/kg single dose)
Placebo possible?	No – randomised blind
Double-blind?	Not clear
Country	Bangladesh
Age	34 +/- 14 (sd), 8 - 80
Comorbidity	Low – comorbidity patients excluded
Sex	90m / 26f
Conclusions of paper	"The Ivermectin-Doxycycline combination therapy has better symptomatic relief, shortened recovery duration, fewer adverse effects, and superior patient compliance compared to the Hydroxychloroquine-Azithromycin combination. Based on this study's outcomes, the Ivermectin-Doxycycline combination is a superior choice for treating patients with mild to moderate COVID-19 disease."
Comments	The improvement is wrt an alternative drug treatment and so may under-estimate the improvement wrt no treatment
Conclusion of Review	c19ivermectin.com represents the paper faithfully

Study: Faisal et al (RCT)

Improvement quoted	Correct, 68%
Error bars (graphic)	Correct (using p = 0.005, 95%CL improvement = 29% - 85%
Other results	Improvement related to recovery by day 10 was 75%.
Criterion	Speed of recovery, recovery at 8th day (NB: all recovered, in both groups).
Treatment numbers	Correct
Combined with?	AZM (500mg once a day for 5 days)
Control numbers	Correct
Control treatment	AZM (500mg once a day for 5 days)
Ivermectin Dosage	Correct (12mg once a day for 5 days)
Placebo possible?	No – randomised blind
Double-blind?	unclear
Country	Pakistan
Age	46 +/- 3
Comorbidity	Low – comorbidity patients excluded
Sex	80m / 20f
Conclusions of paper	Combination of ivermectin and azithromycin was more effective in making patients symptom free than azithromycin alone.
Comments	The improvement is wrt an alternative drug treatment and so may under-estimate the improvement wrt no treatment
Conclusion of Review	c19ivermectin.com represents the paper faithfully

Study: Bukhari (RCT)

Improvement quoted	Correct, 82% based on RR at day 7
Error bars (graphic)	Correct, based on p=0.001 (95%CL improvement 50% to 94%)
Other results	17 oo 41 treated negative PCR in 3 days, cf. 2 oo 45 untreated
Criterion	Time to negative PCR
Treatment numbers	41
Combined with?	No other drugs, just standard care
Control numbers	45
Control treatment	“Standard Care” (paracetamol & vitamins only)
Ivermectin Dosage	Correct, Single dose of 12 mg
Placebo possible?	Yes, patients in treatment arm were informed about Ivermectin
Double-blind?	No
Country	Pakistan
Age	42 +/- 13 (15 – 65)
Comorbidity	Low – comorbidity patients, or those in more severe stages of Covid, were excluded
Sex	85%m / 15%f
Conclusions of paper	In the intervention arm, early viral clearance was observed in patients without experiencing any side effects.
Comments	The potential for placebo effect is not significant because the effect measure was a negative PCR test
Conclusion of Review	c19ivermectin.com represents the paper faithfully

Study: Mourya

Improvement quoted	Correct, 89%
Error bars (graphic)	I get a slight difference: RR range 0.03 to 0.40, so the improvement range is 60% to 97% (cf web site's 75% to 95%: good enough)
Other results	-
Criterion	Negative PCR after 7 days treatment
Treatment numbers	Correct
Combined with?	Same as Control treatment, HCQ + AZM
Control numbers	Correct
Control treatment	Correct: HCQ 400 mg twice daily + AZM 500 mg once per day, for 7 days
Ivermectin Dosage	12 mg per day for 7 days
Placebo possible?	Patients knew what treatment they were getting (not RCT)
Double-blind?	no
Country	India
Age	38 +/- 12 (20 – 60)
Comorbidity	excluded
Sex	68m / 32f
Conclusions of paper	The treatment with HCQ, azithromycin, and ivermectin had a better success rate compared to HCQ and azithromycin. Based on the results, ivermectin could be the potential therapeutic agents for the COVID-19 disease.
Comments	Use of PCR suggests placebo effect not possible
Conclusion of Review	c19ivermectin.com represents the paper faithfully

Study: Chahla (Cluster RCT)

Improvement quoted	Correct, 89%
Error bars (graphic)	Correct (improvement range 48% - 97%)
Other results	The treatment with ivermectin could significantly prevent the evolution to serious stages since the treatment group did not present any patient with referral to critical hospitalization.
Criterion	Outpatient discharge after 28 days
Treatment numbers	Correct
Combined with?	None other than standard care
Control numbers	Correct
Control treatment	Standard care only
Ivermectin Dosage	Correct: 24 mg weekly for 4 weeks
Placebo possible?	Yes. Quote "Staff of each assistance center knew what intervention was being implemented as well as patients. Data processing group was blind to analyze the database."
Double-blind?	no
Country	Argentina
Age	19/40/53 (treatment group); 29/36/48 (control group)
Comorbidity	Yes, a range of comorbidities
Sex	121m / 133f (more women in control group)
Conclusions of paper	Treatment with ivermectin in a population of outpatients with COVID-19 mild disease managed to significantly reduce the number of symptoms when clinical evaluation was performed from 5th to 9th days….Participants received ivermectin had a greater chance of medical release vs. control group (highly significant: $p = 0.0007$).
Comments	All comorbidities, percentage of male patients, and age were higher in the ivermectin group, favoring the control group. So the improvement claimed is an under-estimate.
Conclusion of Review	c19ivermectin.com represents the paper faithfully

Study: Espitia-Hernandez

Improvement quoted	Correct, improvement 98%
Error bars (graphic)	Good enough (I get a slight more generous range 76% - 99% improvement)
Other results	All treated patients were PCR- at day 10 while all control patients remained PCR+. The mean duration of symptoms was 3 days in the treatment group and 10 days in the control group.
Criterion	Negative PCR
Treatment numbers	Correct
Combined with?	Azithromycin 500 mg once daily for 4 days & Cholecalciferol 4000 UI twice daily for 30 days
Control numbers	Correct
Control treatment	Standard care only
Ivermectin Dosage	Correct: 6 mg once daily in day 0,1,7 and 8
Placebo possible?	yes
Double-blind?	no
Country	Mexico
Age	45 +/- 10
Comorbidity	Yes, range of comorbidities
Sex	16m / 19f
Conclusions of paper	A combined therapy with Ivermectin-Azithromycin-Cholecalciferol given for 7 days was effective to reduce symptomatology duration and clinical progression of COVID-19.
Comments	Use of PCR eliminate placebo effect
Conclusion of Review	c19ivermectin.com represents the paper faithfully

Study: Elalfy

Improvement quoted	Correct, 87%
Error bars (graphic)	I get a slightly broader range of improvement: 56% - 96% (cf, the site's claim of 73% - 94%). It'll do.
Other results	-
Criterion	Viral clearance by day 15
Treatment numbers	Correct
Combined with?	Nitazoxanide (500mg), ribavirin (3 x 400mg), Zinc
Control numbers	Correct
Control treatment	Supportive treatment only, sometimes ad hoc AZM
Ivermectin Dosage	Mostly correct (36 mg) but heavier people would have had 48 mg in four days. Actual dose regime is 18mg or 24mg every 3 days for 2 weeks.
Placebo possible?	Not randomised, possible
Double-blind?	no
Country	Egypt
Age	38 +/- 12
Comorbidity	Not specified as excluded
Sex	52m / 61f
Conclusions of paper	The combined use of nitazoxanide, ribavirin, and ivermectin plus zinc supplement effectively cleared the SARS-COV-2 from the nasopharynx in a shorter time than symptomatic therapy.
Comments	-
Conclusion of Review	c19ivermectin.com represents the paper faithfully other than the above minor difference on the lower bound improvement (which might be my error)

Study: Aref

Improvement quoted	Correct using the c19ivermectin.com criterion (below), i.e., 63%. Using proportion with two consecutive negative PCR tests I get 79% (and this figure is also quoted on the site's details page).
Error bars (graphic)	Using proportion with two consecutive negative PCR tests (p = 0.004) I get an improvement range of 39% - 92% compared with the duration of fever data which gives 38% - 789% - Correct
Other results	3 patients in the treated group progressed to the more severe stage of Covid, compared to 14 in the Control group
Criterion	c19ivermectin.com uses relative duration of fever (rather arbitrarily?). As an alternative I use proportion with two consecutive negative PCR tests.
Treatment numbers	c19ivermectin.com does not give risk figures for relative duration of fever. For proportion with two consecutive negative PCR test the risk is 3/57
Combined with?	Same drugs as Control
Control numbers	c19ivermectin.com does not give risk figures for relative duration of fever. For proportion with two consecutive negative PCR test the risk is 14/57
Control treatment	HCQ 500mg twice daily; AZM 1g, then 500mg daily for 3 days
Ivermectin Dosage	ivermectin nasal spray twice daily + same drugs as Control. This method of delivery makes dosage in mg unclear & is not stated in the paper
Placebo possible?	Not randomised or blind
Double-blind?	no
Country	Egypt
Age	45 +/- 19
Comorbidity	Co-morbidities were present in 47 patients (41.2%)
Sex	82m / 32f (same sex ratio in Control and Treated groups)
Conclusions of paper	Local use of ivermectin mucoadhesive nanosuspension nasal spray is safe and effective in treatment of patients with mild COVID-19 with rapid viral clearance and short ening the anosmia duration
Comments	PCR probably proof against placebo effect, though possibly not fever criterion(?). Improvement is wrt Control treatment with HCQ+AZM.
Conclusion of Review	c19ivermectin.com represents the paper faithfully

Study: Merino

Improvement quoted	Correct in that model 7 gives 74.4%. However there are six other models which produce improvement estimates between 30 % & 76%
Error bars (graphic)	Correct (model 7 range of improvement 42% - 88%)
Other results	-
Criterion	Risk of hospitalisation (model 7 used). Each of 7 models used multivariate regression controlling for effects of age, sex and comorbidities as well as use, or not, of the "medical kit"
Treatment numbers	Percentages used – absolute numbers extremely large (tens of thousands)
Combined with?	No other drugs (except paracetamol)
Control numbers	See above
Control treatment	Standard care only, no drugs
Ivermectin Dosage	Correct (24mg over two days)
Placebo possible?	Yes (patients knew if they were given a kit or not)
Double-blind?	no
Country	Mexico
Age	Large numbers at all ages 0 – 70+, but age is controlled for in regression analyses
Comorbidity	Yes, but similar between control and treated group
Sex	47% male
Conclusions of paper	We found a significant reduction in hospitalizations among patients who received the ivermectin-based medical kit; the range of the effect is 52%- 76% depending on model specification.
Comments	233,338 patients in study – huge number. 311 hospitalised with ivermectin kit; 1,884 hospitalised without.
Conclusion of Review	c19ivermectin.com represents the paper faithfully

Appendix B: Summary of Checks of Prophylaxis Studies

Study: Carvallo**1** (RCT though c19ivermectin.com does not record it as such)

Improvement quoted	Correct, 96%
Error bars (graphic)	Using p=0.001 I get 75% - 99%. Site's quoted range seems overly conservative (37% to near 100%)
Other results	-
Criterion	Number testing positive after 28 days
Treatment numbers	Correct
Combined with?	Iota carrageenan nasal spray and Ivermectin oral drops (used as buccal drops),5 times per day
Control numbers	Correct
Control treatment	Standard prophylactic measures and PPE only
Ivermectin Dosage	I was unable to confirm the dosage (site states 14mg, at 1mg per day for first 14 days)
Placebo possible?	Randomised, probably blind to patient
Double-blind?	Don't think so
Country	Argentina
Age	25 – 60, mean 40
Comorbidity	None – health workers
Sex	87m / 142f (low number of men in Control)
Conclusions of paper	None given
Comments	Trial on health personnel; all PCR negative initially
Conclusion of Review	c19ivermectin.com represents the paper faithfully except minor difference on lower bound improvement where the site seems overly conservative

Study: Carvallo2 This is a large study for which Carvallo1 was the pilot.

Improvement quoted	Correct, 100%
Error bars (graphic)	Correct, very tight 94% - 100% improvement
Other results	Health care workers in hospitals (4 centres). Total subjects 1,195. Very emphatic results 0 oo 788 treated cf 237 oo 407 tested positive. Latter very high infection rate was despite claimed adherence to "standard PPE".
Criterion	Positive test
Treatment numbers	Correct
Combined with?	Carrageenan 4 times per day*
Control numbers	Correct
Control treatment	None, just PPE
Ivermectin Dosage	12 mg weekly (hence site correct, 48mg total)
Placebo possible?	Not really, criterion is test
Double-blind?	no
Country	Argentina
Age	Not stated
Comorbidity	No – healthcare workers
Sex	Not stated
Conclusions of paper	By using ivermectin in oral solution and carrageenan in nasal spray form, we are providing an inexpensive, safe and effective means to protect people from contagion and serious forms of the disease
Comments	*The authors later reported that carrageenan is not necessary in this protocol (see (2) Interview With Dr. Hector Carvallo: Pioneer In Ivermectin, Iota Carrageenan, Bromhexine And COVID-19 - YouTube)
Conclusion of Review	c19ivermectin.com represents the paper faithfully

Study: Alam

Improvement quoted	Correct, 91% improvement
Error bars (graphic)	I was not able to confirm the p value used by site, but assuming p=0.001 then improvement range is 62% - 98% - close enough
Other results	-
Criterion	Clinical symptoms
Treatment numbers	Correct
Combined with?	-
Control numbers	Correct
Control treatment	none
Ivermectin Dosage	Correct, 12mg monthly for 4 months
Placebo possible?	Yes, as effect criterion was experience of symptoms
Double-blind?	no
Country	Bangladesh
Age	25 – 60, mean 37
Comorbidity	Yes for ~32%
Sex	42m / 76f
Conclusions of paper	Ivermectin, an FDA-approved, safe, cheap and widely available drug, should be subjected to large-scale trials all over the world to ascertain its effectiveness as pre-exposure prophylaxis for COVID-19. It is a worthy approach to expand the use of this drug for pre-exposure prophylaxis of COVID-19
Comments	Health workers exposed to infected patients
Conclusion of Review	c19ivermectin.com represents the paper faithfully subject to above unknowns

Study: Seet (RCT)

Improvement quoted	Correct (improvement 50%)
Error bars (graphic)	Correct (improvement range 20% - 69%).
Other results	See below
Criterion	For trial main results (essentially for HCQ):- Positive serologic test for SARS-CoV-2 antibody on day 42, or a positive PCR test for SARS-CoV-2 at any time up to day 42. But for Ivermectin c19ivermectin.com has used the occurrence of acute respiratory symptoms over 42 days. This is important because, based on infection evidence, there was no indication of Ivermectin efficacy.
Treatment numbers	Correct
Combined with?	See below
Control numbers	Correct
Control treatment	See below
Ivermectin Dosage	Five different treatments in 40 groups:- HCQ, 400mg, then 200mg daily for 42 days; OR, Ivermectin, 12mg ONCE only; (hence Correct); povidone-iodine throat spray (3 times/day, 270 mg/day); OR, oral zinc (80 mg/day) + vitamin C (500 mg/day); OR, oral vitamin C, 500 mg/day. Ivermectin dose was very low for a 42 day prophylaxis, so not clear if the is a meaningful test for Ivermectin. The trials was primarily of HCQ. (It's presence in body would be virtually nil over most of the 42 day period).
Placebo possible?	Probably not – patients unlikely to know which treatment they were receiving and in any case HCQ was probably being promoted as the "treatment under examination". Random on dormitory basis.
Double-blind?	no
Country	Singapore
Age	Mean 33
Comorbidity	Very low
Sex	100% male
Conclusions of paper	Conclusions relate to HCQ which was the main drug of study. "significant absolute risk reductions (%, 98.75% confidence interval) were observed for oral hydroxychloroquine (21%, 2–42%) and povidone-iodine throat spray (24%, 7–39%). No statistically significant differences were observed with oral zinc/vitamin C combination (23%, –5 to +41%) and ivermectin (5%, –10 to +22%)."
Comments	Migrant workers in quarantine, all negative at start
Conclusion of Review	c19ivermectin.com numerical results are correct assuming effect is based on acute respiratory symptoms, but infection data would not be supportive of an effect. However, one modest dose could not be expected to provide prophylaxis over 42 days, so the test is actually meaningless for Ivermectin – and it is remarkable that using acute symptoms showed a benefit. Overall I think its inclusion is fair game game.

Study: Shouman (RCT)

Improvement quoted	Almost – I make it 87% (cf quoted 91%, and paper itself quotes 92.6%). Good enough.
Error bars (graphic)	I get a somewhat broader 95%CL improvement range (57% - 96%), cf. the site's 77% - 97%.
Other results	-
Criterion	Development of symptoms (fever and respiratory symptoms) over two week period
Treatment numbers	Correct
Combined with?	none
Control numbers	Correct
Control treatment	none
Ivermectin Dosage	Correct: Typically 2 x 18mg
Placebo possible?	Yes "open label" trial, but randomised
Double-blind?	no
Country	Egypt
Age	40 +/- 15
Comorbidity	Yes in approx. 25% of both groups
Sex	51%m / 49%f
Conclusions of paper	Ivermectin is suggested to be a promising, effective and safe chemoprophylactic drug in management of COVID-19
Comments	-
Conclusion of Review	c19ivermectin.com represents the paper faithfully

Appendix C: Summary of Checks of Late Treatment Studies

Study: Hashim (RCT)

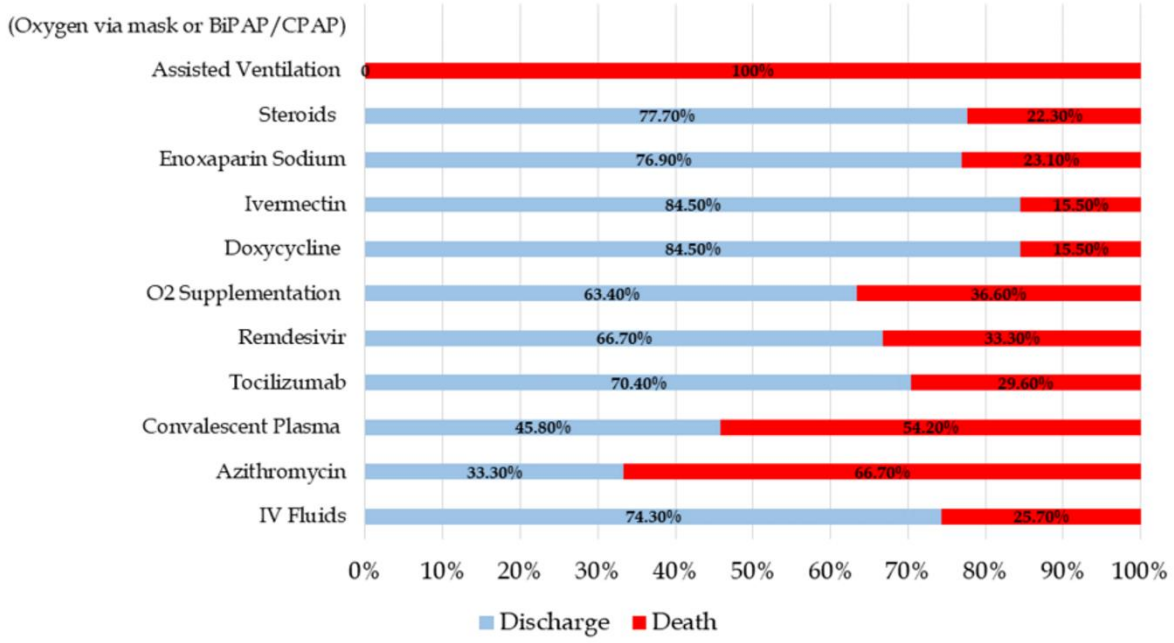
Improvement quoted	Correct (improvement 91%)
Error bars (graphic)	Correct: improvement range from no improvement to 99%
Other results	9 of 11 patients classed as critical (and not counted in the trial results) survived on the Ivermectin+doxycycline regime.
Criterion	Death
Treatment numbers	Correct
Combined with?	100 mg doxycycline twice per day for 5-10 days plus standard therapy as per Control
Control numbers	Correct
Control treatment	AZM, Zinc, dexamethasone, vitamins
Ivermectin Dosage	Correct: 0.2mg/kg per day for 2 or 3 days
Placebo possible?	Unlikely, randomised
Double-blind?	Don't know
Country	Iraq
Age	49 +/- 9 (16 – 86)
Comorbidity	Unknown, but likely in the older patients
Sex	52%m / 48%f
Conclusions of paper	Ivermectin with doxycycline reduced the time to recovery, reduced the percentage of patients progressing to more advanced stage of disease, and reduced mortality rate in severe patients from 22.72% to 0%.
Comments	-
Conclusion of Review	c19ivermectin.com represents the paper faithfully

Study: Lima-Morales

Improvement quoted	Correct (I get improvement 83%)
Error bars (graphic)	Correct (get improvement range 51% - 94%)
Other results	Improved recovery time and avoidance of hospitalisation also
Criterion	Death
Treatment numbers	Correct
Combined with?	Azithromycin (500mg /dy for 4 days) , Montelukast (60mg then 10mg per day), and Acetylsalicylic acid
Control numbers	Correct
Control treatment	Various treatments
Ivermectin Dosage	Correct 12mg single dose
Placebo possible?	no
Double-blind?	no
Country	Mexico
Age	18 – 80; mean 41 (treatment), 46 (control)
Comorbidity	39% in treatment group; 46% in Control group
Sex	47.5%m (treatment); 57.8%m (control)
Conclusions of paper	TNR4 therapy (the combined drug treatment used) improved recovery and prevented the risk of hospitalization and death among ambulatory COVID-19 cases.
Comments	Slight concern that greater proportion of males and comorbidities, and older people, in Control group may bias the results. However this concern is allayed because details in the paper show that far larger proportions (>=3.5 times) of control patients died in each sub-class defined by (a) males, (b)age, (c)comorbidities.
Conclusion of Review	c19ivermectin.com represents the paper faithfully. However, as regards Ivermectin efficacy it should be noted that this is a combined drug treatment.

Study: Ahsan

Improvement quoted	Correct (improvement 50%)
Error bars (graphic)	Correct if p = 0.03, which I failed to confirm (improvement range is then 6% to 73%)
Other results	All patients who received assisted ventilation died
Criterion	Death
Treatment numbers	Correct
Combined with?	Various other drugs were combined with Ivermectin, and it seems that different patients got different combinations
Control numbers	Correct
Control treatment	A wide range of other drugs were used in unspecified combinations which varied between patients
Ivermectin Dosage	Correct: 0.15 – 0.2 mg/dy for 2 days
Placebo possible?	no
Double-blind?	no
Country	Pakistan
Age	56 +/- 16
Comorbidity	Yes, common
Sex	55%m
Conclusions of paper	Best summarised by graphic below
Comments	If my understanding is correct, patients received a variety of combinations of several drugs. Treatment outcomes were best when ivermection or doxycycline were one of the drugs used (see graph from paper below). The "treatment" group is therefore all those patients who had Ivermectin among their drugs; whereas the "control" group consists of all patients who did not get Ivermectin, but other drugs.
Conclusion of Review	c19ivermectin.com represents the paper faithfully



Study: Pott-Junior (RCT)

Improvement quoted	Correct (improvement 85%)
Error bars (graphic)	Correct (very wide range easily encompassing zero effect)
Other results	
Criterion	Requirement for ventilation (however the paper uses a criterion of two negative tests within 7 days of start of treatment)
Treatment numbers	Correct
Combined with?	none
Control numbers	Correct
Control treatment	"standard of care" only
Ivermectin Dosage	0.1, 0.2 or 0.4 mg/kg (three dosages investigated)
Placebo possible?	Yes, randomised but open-label
Double-blind?	No, but "we tried to minimize bias by blinding investigators and patients to the viral load results during the study dosing period."
Country	Brazil
Age	Treatment 49 +/- 15 (21 – 92); ontrol 55 +/1 10
Comorbidity	median Charlson Comorbidity Index was 1
Sex	45%m / 55%f (Control was all women)
Conclusions of paper	Ivermectin is safe in patients with SARS-CoV-2, reducing symptomatology and the SARS-CoV-2 viral load.
Comments	-
Conclusion of Review	c19ivermectin.com represents the paper faithfully as regards the stated ventilation criterion, but not the negative test criterion for which the statistical power was too small to indicate an improvement, though the authors clearly thought there was a more rapid decrease in viral load and improvement in symptomology. Overall OK.

Study: Budhiraja

Improvement quoted	Correct. Improvement 99% as listed.
Error bars (graphic)	Suspect, assuming p=0.04 I get RR range ~0 to 0.81, so improvement range 19% to ~100% (cf. site's 85% - 100%). I think the lower bound improvement should be far smaller.
Other results	Of the 103 deaths that occurred in the sample of 976 patients in the study, 69 had received HCQ, or HCQ+AZM; 57 steroids; 22 Tocilizumab. 34 patients received Ivermectin and none died
Criterion	Death
Treatment numbers	Correct
Combined with?	none
Control numbers	Correct
Control treatment	See above (various drug treatments, mostly HCQ+AZM)
Ivermectin Dosage	The paper does not state the dosage (c19ivermectin.com has "n/a")
Placebo possible?	Not really the patients were all given drugs of some sort
Double-blind?	no
Country	India
Age	Median 48 (25% over 60)
Comorbidity	High, 47%
Sex	67%m / 33%f (general hospital admission ratio)
Conclusions of paper	Male patients above the age of 60 and with co-morbidities faced the highest rates of mortality.
Comments	The paper was not primarily concerned with Ivermectin but with reporting correlates of mortality (specifically age, being male and need for ventilation)
Conclusion of Review	c19ivermectin.com represents the paper faithfully except I get afar smaller lower bound improvement. However, significance at 95%CL still applies, and I am not certain that my assumed p=0.04 is correct anyway.

Study: Hazan

Improvement quoted	Correct (improvement 86%)
Error bars (graphic)	Perhaps overly pessimistic? I get an RR range of 0.02 to 0.92 using p=0.04 (improvement range 8% to 98%), and so >95% confidence of a beneficial effect (unlike the site that fails to confirm this at 95%CL).
Other results	Using hospitalisation as the criterion actually implies a greater improvement (mean 93%), range 66% - 99%, so easily significant at >95%CL
Criterion	Death
Treatment numbers	Correct (0/24)
Combined with?	Doxycycline (100mg twice daily for 10 days), zinc, and Vitamins D and C.
Control numbers	Correct (45,369/313,805) "Control" was actually drawn from a public database, not part of the study. The selected 'control' subjects closely matched the subjects in the study, all of whom had some underlying condition and a large majority were over 50 years of age.
Control treatment	Various in public
Ivermectin Dosage	Correct. 12mg on days 1, 4 and 8 only; two patients got 36mg on day 1 due to urgency
Placebo possible?	Open label: subjects were drawn from those rejected from a double-blind RCT due to being too sick for a placebo controlled trial.
Double-blind?	no
Country	USA
Age	Mean 66 (43 – 94)
Comorbidity	46%
Sex	63%m
Conclusions of paper	Triple combination therapy is safe and effective even in moderate-severe patients with hypoxia treated in the outpatient setting. This study builds on an extensive literature, to provide a practical inexpensive, safe, readily available and highly effective triple therapy aiming to prevent resistance and one that can confidently be used as a routine treatment for outpatient COVID-19.
Comments	subjects with high risk features, hypoxia and untreated moderate-severe symptoms averaging 9 days
Conclusion of Review	c19ivermectin.com represents the paper faithfully

Study: Khan

Improvement quoted	Correct, improvement 87%
Error bars (graphic)	Correct. Improvement range 0 to 98% (i.e., JUST significant at 95%CL)
Other results	-
Criterion	Death
Treatment numbers	Correct
Combined with?	None, only standard care
Control numbers	Correct
Control treatment	Antihistamine or antipyretic drugs only (“standard care”)
Ivermectin Dosage	Correct: one 12mg dose
Placebo possible?	Given death as the criterion, probably not
Double-blind?	no
Country	Bangladesh
Age	34 (30 – 42) much the same in treatment & control groups
Comorbidity	Yes, but <17% for any specific condition
Sex	Treatment 70%m (control 52%m) – this is a bias
Conclusions of paper	In addition to rapid SARS-CoV-2 clearance, ivermectin seems to control the course of the disease in patients with COVID-19… given the urgent need to manage the COVID-19 patients with a safe, cheap and widely available drug, the present findings suggest that ivermectin can be considered as a first-line treatment for containing SARS-CoV-2 to prevent severe irreversible respiratory complications and community transmission.
Comments	-
Conclusion of Review	c19ivermectin.com represents the paper faithfully

Appendix D: Independent Search Results

I concentrate on reports of clinical trials which produce data on the efficacy of Ivermectin against Covid-19 compared with control groups. Many papers revealed by searches are just opinion or theoretical arguments, or commentaries on other reports, including meta-analyses, or studies on animals, or studies *in vitro*, or are merely advising on required research. But here I seek only original trials with outcome data compared to controls.

However, meta-analyses or other sources reporting their own searches are useful as a further means of potentially identifying relevant studies missed by c19ivermectin.com. These reports are listed separately at the end (§D.5).

Like Step (i), it is not necessary to independently find via searches all 63 studies analysed by c19ivermectin.com. It is only necessary to find a substantial fraction of them whilst not finding any additional relevant studies (or, more precisely, without finding too many such additional studies to raise a question about the thoroughness or impartiality of the review of c19ivermectin.com).

I noted as a by-product of these searches that there were many papers which, though they did not report clinical comparison studies, were calling for large-scale controlled trials to be carried out. There has clearly been a massive worldwide consensus that this should be done since early in the pandemic. It would appear that the reason for there being no very large, authoritative, study has been lack of funding. Instead what we have got is a large number of small studies funded locally 'on the cheap'.

The other thing I noticed was the huge number of downloads these studies have received. I am used to looking at academic publications and a hundred or two hundred downloads over many years is their common fate. These studies were getting thousands of downloads per month.

Relevant studies found are listed below. Relevant studies which were NOT used by c19ivermectin.com are highlighted in yellow, with a commentary. All others are in the c19ivermectin.com database.

D.1 Summary of Findings

[1] I looked at the Abstract of 70 hits via Google Scholar which revealed 20 of the 63 studies used by c19ivermectin.com. In addition I found two other studies, but both seem to have been excluded with good reason. I found no studies which should have been included but were not.

[2] I looked at all hits from *ClinicalTrials.gov* which met criteria for being completed trials with results on Covid19 and Ivermectin. Of the 11 hits, 9 are used by c19ivermectin.com. The reasons for excluding the other two are not entirely clear, though one appears to be a null result for both treatment and control arms (so no numerical measure of efficacy) whilst the other appears supportive of the efficacy of a multi-drug treatment of which Ivermectin was one.

D.2 Google Scholar, Keywords: Ivermectin + Covid (first 50 hits examined)

Juliana Cepelowicz Rajter, Michael S. Sherman, et al

Eduardo López-Medina, Pío López, Isabel C. Hurtado, et al

Henrique Pott-Junior, Mônica Maria Bastos Paoliellob, et al

Daniel Camprubí,Alex Almuedo-Riera,Helena Martí-Soler, et al

Md. Saiful Islam Khan, Sakirul Islam Khan, Chitto Ranjan Debnath, et al

Ahmed Elgazzar, Basma Hany, Shaimaa Abo Youssef, et al. This paper is mentioned in c19ivermectin.com as having been retracted, and so was removed from their database. The paper was supportive of Ivermectin efficacy so its exclusion is certainly not to bolster a case for Ivermectin but in the interests of accuracy (assuming that it has indeed been retracted, which I failed to confirm).

Faiq Gorial, Sabeeh Mashhadani, Hend Sayaly, et al

Morteza Shakhsi Niaee, Peyman Namdar, et al

Sabeena Ahmed, Mohammad Mahbubul Karim, et al

Hashim A., Hashim, Mohammed, F. Maulood, et al

Ravikirti, Ranjini Roy, Chandrima Pattadar, Rishav Raj, et al

Nurullah Okumuş, Neşe Demirtürk, et al

Chinmay Saha Podder , Nandini Chowdhury , et al

Alam, Murshed, Bhiuyan, et al. This paper was not used by c19ivermectin.com probably because it has no control and no means of quantifying improvement. A later study from this same Bangladeshi group, with control, ***was*** used by c19ivermectin.com. The paper reports positive results using a combination of Ivermectin and Doxycycline.

Carlos Chaccour, Aina Casellas, Andrés Blanco-Di Matteo, et al

Jose Lenin Beltran Gonzalez, Mario González Gámez, et al

Shoumann, Waheed, et al

Aijaz Zeeshan Khan Chachar, Khurshid Ahmad Khan, et al

Guadalupe Espitia-Hernandez, Levy Munguia, et al

D.3 Google Scholar, Keywords: Ivermectin + SARS (first 20 hits examined)

Omitting hits which duplicate studies listed above.

Priyamadhaba Behera, Binod Kumar Patro, et al

Veerapaneni Spoorthi and Surapaneni Sasank

Juliana Cepelowicz Rajter, Michael S. Sherman, et al

D.4 US National Library of Medicine, *ClinicalTrials.gov*

Site: Home - ClinicalTrials.gov. I confine my list to hits marked by *ClinicalTrials.gov* as "Completed" and "Has Results" for search terms Covid19 and Ivermectin. This resulted in…

Clinical Trial of Ivermectin Plus Doxycycline for the Treatment of Confirmed Covid-19 Infection - Full Text View - ClinicalTrials.gov: This is same as Mahmud in c19ivermectin.com

Ivermectin for Severe COVID-19 Management - Full Text View - ClinicalTrials.gov. This is the same as Okumus in c19ivermectin.com

Ivermectin Effect on SARS-CoV-2 Replication in Patients With COVID-19 - Full Text View - ClinicalTrials.gov. This is the same as Krolewiecki in c19ivermectin.com

USEFULNESS of Topic Ivermectin and Carrageenan to Prevent Contagion of Covid 19 - Full Text View - ClinicalTrials.gov. This is the same as Carvallo1 in c19ivermectin.com.

Effectiveness of Ivermectin as add-on Therapy in COVID-19 Management - Full Text View - ClinicalTrials.gov. This is the same as Gorial in c19ivermectin.com.

Efficacy and Safety of Ivermectin for Treatment and Prophylaxis of COVID-19 Pandemic - Full Text View - ClinicalTrials.gov. This is the is the same as Elgazzar discussed above.

Sars-CoV-2/COVID-19 Ivermectin Navarra-ISGlobal Trial - Full Text View - ClinicalTrials.gov. This is the same as Chaccour in c19ivermectin.com.

Prophylactic Ivermectin in COVID-19 Contacts - Study Results - ClinicalTrials.gov. This is the same as Shouman in c19ivermectin.com.

Evaluation of Prognostic Modification in COVID-19 Patients in Early Intervention Treatment - Full Text View - ClinicalTrials.gov. I could not find this one in c19ivermectin.com under author Arteaga. Possibly it was excluded on the grounds that "Evaluation of Prognostic Modification" was not a sound effect measure. The study involved multi-drug therapy of which Ivermectin was only one. However, the results appear to indicate statistically significant benefit of the treatments studied, so exclusion of this study does not bias the outcome of the analysis of c19ivermectin.com towards the positive.

Efficacy, Safety and Tolerability of Ivermectin in Subjects Infected With SARS-CoV-2 With or Without Symptoms - Study Results - ClinicalTrials.gov. I could not find this one in c19ivermectin.com. It may be because the outcome appears to have been null for both treatment and control so no quantitative conclusion was possible (not sure).

Ivermectin, Aspirin, Dexamethasone and Enoxaparin as Treatment of Covid 19 - Study Results - ClinicalTrials.gov. This is another of the Carvallo studies used in c19ivermectin.com, namely this one.

D.5 Meta-Analyses and Searches

Maria Popp, Miriam Stegemann, et al

Harpinder Kaur, Nishant Shekhar, et al

Alex Castañeda-Sabogal, et al

Chia Siang Kow, Hamid A. Merchant, et al

Biswa Mohan Padhy, et al

Andrew Hill, Ahmed Abdulamir, et al

Morimasa Yagisawa, et al

Appendix E: Key Findings of the Meta-Analyses

Here I give the main findings of 15 meta-analyses: 8 found by me (see §D.4) and 6 listed in c19ivermectin.com. I will make no commentary on them beyond suggesting the number of studies contributing to these meta-analyses needs to be compared with the 63 studies deployed by c19ivermectin.com (with appropriate attention to error bars). In some cases you can find comments by other parties on the sites linked.

E.1Maria Popp, Miriam Stegemann, et al

Maria Popp, Miriam Stegemann, et al (July 2021)

14 studies used

Based on the current very low- to low-certainty evidence, we are uncertain about the efficacy and safety of ivermectin used to treat or prevent COVID-19. The completed studies are small and few are considered high quality. Several studies are underway that may produce clearer answers in review updates. Overall, the reliable evidence available does not support the use of ivermectin for treatment or prevention of COVID-19 outside of well-designed randomized trials.

E.2 Harpinder Kaur, Nishant Shekhar, et al

Harpinder Kaur, Nishant Shekhar, et al (January 2021)

5 studies used

Keeping in view the available evidence from clinical studies ivermectin can be a potential drug as it reduced mortality and improved symptoms of patients with COVID-19. Moreover, ivermectin in combination with doxycycline seems effective. However, more RCTs and dose response studies are required to justify its use.

E.3 Alex Castañeda-Sabogal, et al

Alex Castañeda-Sabogal, et al (January 2021)

12 studies used

Ivermectin was not associated with reduced mortality or reduced patient recovery. All studies had a high risk of bias, and showed a very low certainty of the evidence. There is insufficient certainty and quality of evidence to recommend the use of ivermectin to prevent or treat ambulatory or hospitalized patients with COVID-19.

E.4 Chia Siang Kow, Hamid A. Merchant, et al

Chia Siang Kow, Hamid A. Merchant, et al (March 2021)

6 studies used

Of six trials, four had an overall high risk of bias. The estimated effect of ivermectin indicated mortality benefits (pooled odds ratio = 0.21; 95% confidence interval 0.11–0.42, n = 1255), with some evidence against the hypothesis of ‘no significant difference’ at the current sample size. We observed a preliminary beneficial effect on mortality associated with

ivermectin use in patients with COVID-19 that warrants further clinical evidence in appropriately designed large-scale randomized controlled trials.

E.5 Biswa Mohan Padhy, et al

Biswa Mohan Padhy, et al (November 2020)

4 studies used

The random effect model showed the overall pooled OR to be 0.53 (95%CI: 0.29 to0.96) for the primary outcome (all-cause mortality) which was statistically significant (P=0.04). Similarly, the random effect model revealed that adding ivermectin led to significant clinical improvement compared to usual therapy (OR=1.98, 95% CI: 1.11 to 3.53, P=0.02).

E.6 Andrew Hill, Ahmed Abdulamir, et al

Andrew Hill, Ahmed Abdulamir, et al (January 2021)

18 studies used

This meta-analysis of 18 RCTs in 2282 patients showed a 75% improvement in survival, faster time to clinical recovery and signs of a dose-dependent effect of viral clearance for patients given ivermectin versus control treatment.

E.7 Morimasa Yagisawa, et al

Morimasa Yagisawa, et al (March 2021)

42 studies used

By the 27th of February (2021), the results of 42 clinical trials, including approximately 15,000 patients (both registered and unregistered studies) have been subjected to a meta-analysis after exclusion of biasing factors. It was found that 83% showed improvements with early treatment, 51% improved during late-stage treatment, and there was an 89% prevention of onset rate noted. This confirms the usefulness of ivermectin. Since it is a meta-analysis based on 42 test results, it is estimated that the probability of this comprehensive judgment being a mistake is as low as 1 in 4 trillion.

In addition, two separate meta-analyses also showed the usefulness of ivermectin and their conclusions were presented to the WHO and the US FDA with a request for an expansion of the indication of ivermectin in the treatment of COVID-19.

In Japan, Kitasato University has been conducting a doctor-initiated phase 2 clinical trial, since September 2020. However, the progress of the study protocol enrolling a total of 240 patients (120 in the ivermectin group and 120 in the placebo group), has been slow. At this rate, there is concern that the clinical trial will be concluded after a time in which the COVID-19 pandemic converges. Unlike clinical trials conducted by pharmaceutical companies, lack of funds and human resources are the main factors behind the delay in the progress of such clinical trials.

E.8 Kory, Meduri, Varon, et al

Kory, Meduri, Varon, et al (June 2021)

27 studies used

Prophylaxis: All 8 available controlled trial results show statistically significant reductions in transmission.

Treatment: Five RCTs with statistically significant impacts in time to recovery or hospital length of stay. One RCT with a near statistically significant decrease in time to recovery. One RCT with a large, statistically significant reduction in the rate of deterioration or hospitalization. Two RCTs with a statistically significant decrease in viral load, days of anosmia, and cough. Three RCTs with large, statistically significant reductions in mortality. One RCT with a near statistically significant reduction in mortality. Three OCTs with large, statistically significant reductions in mortality.

In summary, based on the totality of the trials and epidemiologic evidence presented in this review along with the preliminary findings of the Unitaid/WHO meta-analysis of treatment RCTs and the guideline recommendation from the international BIRD conference, ivermectin should be globally and systematically deployed in the prevention and treatment of COVID-19.

E.9 Bryant, Lawrie, Dowswell, et al

Bryant, Lawrie, Dowswell, et al (July 2021)

15 studies used

Moderate-certainty evidence finds that large reductions in COVID-19 deaths are possible using ivermectin. Using ivermectin early in the clinical course may reduce numbers progressing to severe disease. The apparent safety and low cost suggest that ivermectin is likely to have a significant impact on the SARS-CoV-2 pandemic globally.

E.10 Tess Lawrie

Tess Lawrie (January 2021)

27 studies used

This was a research communication from one of the authors of E.9 presenting advanced information based on the FLCCC identified studies marked “Urgent” by the author.

I take full responsibility for the scientific integrity of this urgent evidence synthesis. The evidence derived from the studies included in the FLCCC review is sufficient to support a strong recommendation on ivermectin for the treatment of COVID-19. Due to the urgency and imperative to communicate this critical information to health professionals, and in the context of the probable effect size of ivermectin on COVID-19 deaths revealed by this meta-analysis, additional exploratory analyses (for example looking at the effect of co-administration of doxycycline) have not been conducted. Neither have I sought unpublished data from the numerous ongoing trials of ivermectin on clinical trial registries. It is my hope that both health professionals and policy makers now respond to this information with the required urgency, so that critical time in saving lives is not wasted.

E.11 Nardelli, Zangrillo, Sanchini, et al

Nardelli, Zangrillo, Sanchini, et al (May 2021)

7 studies used

In the present meta-analysis of RCTs, administration of ivermectin reduced mortality among patients hospitalized for COVID-19.

E.12 Hariyanto, Halim, Rosalind, et al

Hariyanto, Halim, Rosalind, et al (June 2021)

19 studies used

This meta-analysis showed that ivermectin was associated with reduction in severity of Covid-19, reduction of mortality, higher negative RT-PCR test results rate, shorter time to negative RT-PCR test results, higher symptoms alleviations rate, shorter time to symptoms alleviations and shorter time to hospital discharge. Our study suggests that ivermectin may offer beneficial effects towards Covid-19 outcomes.

E.13 World Health Organisation

Therapeutics and Covid-19: Living Guideline, WHO (March 2021)

16 studies used

This *WHO Therapeutics and COVID-19: Living Guideline* now includes a recommendation not to use ivermectin except in the context of a clinical trial. The guideline was initiated in response to international attention on ivermectin as a potential treatment for COVID-19. The section text provides an executive summary of the guidance.

Results from a living systematic review and network meta-analysis (NMA) that pooled data from 16 randomized controlled trials (RCTs) with 2407 participants, including both inpatients and outpatients with COVID-19, informed the recommendation on ivermectin. The effects of ivermectin on mortality, need for invasive mechanical ventilation, hospital admission, duration of hospitalization and time to viral clearance all remain very uncertain (all very low certainty evidence). The uncertainty results from important concerns related to risk of bias in the included studies, and imprecision from a very low number of events and, in some cases, wide confidence intervals (CIs) in pooled estimates. Ivermectin may increase the risk of serious adverse events (SAEs) leading to drug discontinuation (odds ratio [OR] 3.07; 95% CI: 0.77–12.09; low certainty evidence) and may have little or no impact on time to clinical improvement (mean difference 0.5 fewer days; 95% CI: 1.7 fewer days to 1.1 more days; low certainty evidence).