Adintrevimab for COVID-19: real-time meta analysis of 2 studies
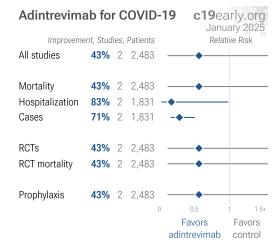
Abstract

Significantly lower risk is seen for hospitalization and cases. 2 studies (both from the same team) show significant benefit.
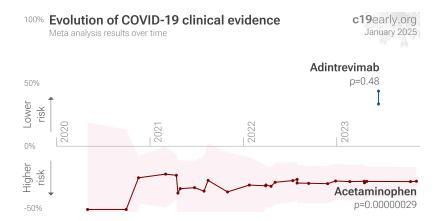
Meta analysis using the most serious outcome reported shows 43% [-169-88%] lower risk, without reaching statistical significance. Currently all studies are RCTs.

Currently there is limited data, with only 4 control events for the most serious outcome in trials to date. All studies to date are from the same group.

mAb use may create new variants that spread globally [1,2], and may be associated with prolonged viral loads, clinical deterioration, and immune escape [2-5].
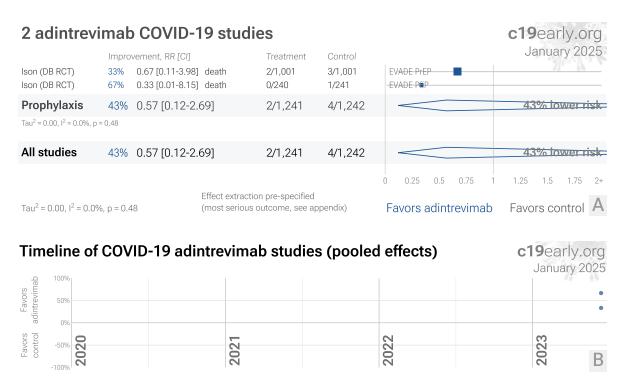
No treatment is 100% effective. Protocols combine safe and effective options with individual risk/benefit analysis and monitoring. All data and sources to reproduce this analysis are in the appendix.

Adintrevimab for COVID-19 — c19early.org — January 2025 — Relative Risk

	Improvement, Studies, Patients		
All studies	43%	2	2,483
Mortality	43%	2	2,483
Hospitalization	83%	2	1,831
Cases	71%	2	1,831
RCTs	43%	2	2,483
RCT mortality	43%	2	2,483
Prophylaxis	43%	2	2,483

Favors adintrevimab — Favors control

Evolution of COVID-19 clinical evidence
Meta analysis results over time

c19early.org
January 2025

Adintrevimab
p=0.48

Acetaminophen
p=0.00000029

ADINTREVIMAB FOR COVID-19 — HIGHLIGHTS

Adintrevimab reduces risk with low confidence for hospitalization and cases.

Real-time updates and corrections with a consistent protocol for 112 treatments. Outcome specific analysis and combined evidence from all studies including treatment delay, a primary confounding factor.

2 adintrevimab COVID-19 studies

	Improvement, RR [CI]		Treatment	Control	
Ison (DB RCT)	33%	0.67 [0.11-3.98] death	2/1,001	3/1,001	EVADE PrEP
Ison (DB RCT)	67%	0.33 [0.01-8.15] death	0/240	1/241	EVADE PEP
Prophylaxis	**43%**	**0.57 [0.12-2.69]**	**2/1,241**	**4/1,242**	43% lower risk
Tau² = 0.00, I² = 0.0%, p = 0.48					
All studies	**43%**	**0.57 [0.12-2.69]**	**2/1,241**	**4/1,242**	43% lower risk

Tau² = 0.00, I² = 0.0%, p = 0.48   Effect extraction pre-specified (most serious outcome, see appendix)

Favors adintrevimab   Favors control   **A**

Timeline of COVID-19 adintrevimab studies (pooled effects)

Figure 1. **A.** **Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in adintrevimab studies.**

Introduction

Immediate treatment recommended

SARS-CoV-2 infection primarily begins in the upper respiratory tract and may progress to the lower respiratory tract, other tissues, and the nervous and cardiovascular systems, which may lead to cytokine storm, pneumonia, ARDS, neurological injury[6-18] and cognitive deficits[9,14], cardiovascular complications[19-22], organ failure, and death. Minimizing replication as early as possible is recommended.

Many treatments are expected to modulate infection

SARS-CoV-2 infection and replication involves the complex interplay of 50+ host and viral proteins and other factors[A,23-29], providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 8,000 compounds may reduce COVID-19 risk[30], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

Monoclonal antibodies

Adintrevimab is a monoclonal antibody (mAb). mAbs are laboratory-engineered proteins designed to mimic the immune system's ability to fight pathogens. In the context of COVID-19, mAbs typically target specific regions of the SARS-CoV-2 spike protein, inhibiting viral entry into human cells and neutralizing the virus. These antibodies are derived from the B cells of recovered patients or immunized animals and are produced in large quantities using recombinant DNA technology and cell culture methods.

Analysis

We analyze all significant controlled studies of adintrevimab for COVID-19. Search methods, inclusion criteria, effect extraction criteria (more serious outcomes have priority), all individual study data, PRISMA answers, and statistical methods are detailed in Appendix 1. We present random effects meta-analysis results for all studies, individual outcomes, and Randomized Controlled Trials (RCTs).

Figure 2 shows stages of possible treatment for COVID-19. **Prophylaxis** refers to regularly taking medication before becoming sick, in order to prevent or minimize infection. **Early Treatment** refers to treatment immediately or soon after symptoms appear, while **Late Treatment** refers to more delayed treatment.
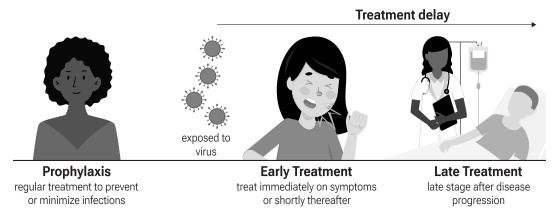

Figure 2. Treatment stages.

Variant Dependence

Extensive mutations in SARS-CoV-2 have resulted in variants that evade neutralizing antibodies from monoclonal antibody treatments[31,32], resulting in efficacy that is highly variant dependent. Table 1 shows efficacy by variant for several monoclonal antibodies. This table covers earlier SARS-CoV-2 variants and has not been updated for more recent variants and more recent monoclonal antibodies.
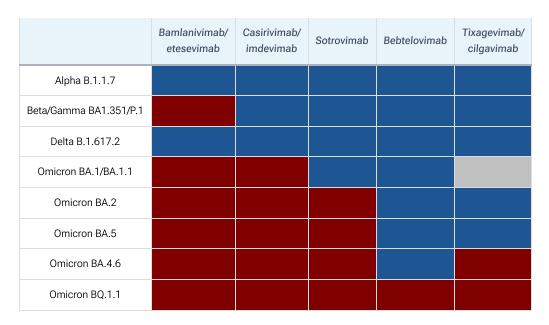
	Bamlanivimab/ etesevimab	Casirivimab/ imdevimab	Sotrovimab	Bebtelovimab	Tixagevimab/ cilgavimab
Alpha B.1.1.7	■	■	■	■	■
Beta/Gamma BA1.351/P.1	■	■	■	■	■
Delta B.1.617.2	■	■	■	■	■
Omicron BA.1/BA.1.1	■	■	■	■	■
Omicron BA.2	■	■	■	■	■
Omicron BA.5	■	■	■	■	■
Omicron BA.4.6	■	■	■	■	■
Omicron BQ.1.1	■	■	■	■	■

Table 1. Predicted efficacy by variant from *Davis et al.* (not updated for more recent variants). ■: likely effective ■: likely ineffective ■: unknown. Submit updates.

Results

Table 2 summarizes the results for all studies, for Randomized Controlled Trials, and for specific outcomes. Figure 3, 4, 5, and 6 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, hospitalization, and cases.

	Improvement	Studies	Patients	Authors
All studies	**43%** [-169-88%]	2	2,483	30
Randomized Controlled Trials	**43%** [-169-88%]	2	2,483	30
Mortality	**43%** [-169-88%]	2	2,483	30
Hospitalization	**83%** [2-97%] *	2	1,831	30
Cases	**71%** [49-84%] ****	2	1,831	30
RCT mortality	**43%** [-169-88%]	2	2,483	30

Table 2. Random effects meta-analysis for all studies, for Randomized Controlled Trials, and for specific outcomes. Results show the percentage improvement with treatment and the 95% confidence interval. * $p<0.05$ **** $p<0.0001$.

Figure 3. Random effects meta-analysis for all studies. This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.
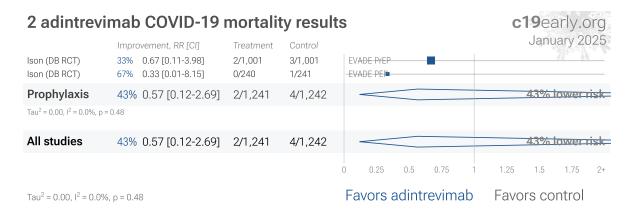

Figure 4. Random effects meta-analysis for mortality results.

2 adintrevimab COVID-19 hospitalization results

	Improvement, RR [CI]		Treatment	Control		
Ison (DB RCT)	84%	0.16 [0.02-1.34] hosp.	1/752	6/728	EVADE PrEP	
Ison (DB RCT)	80%	0.20 [0.01-4.15] hosp.	0/175	2/176	EVADE PEP	
Prophylaxis	**83%**	**0.17 [0.03-0.98]**	**1/927**	**8/904**		**83% lower risk**
Tau^2 = 0.00, I^2 = 0.0%, p = 0.047						
All studies	**83%**	**0.17 [0.03-0.98]**	**1/927**	**8/904**		**83% lower risk**

0   0.25   0.5   0.75   1   1.25   1.5   1.75   2+

Tau^2 = 0.00, I^2 = 0.0%, p = 0.047

Favors adintrevimab   Favors control

Figure 5. Random effects meta-analysis for hospitalization.

2 adintrevimab COVID-19 case results

	Improvement, RR [CI]		Treatment	Control		
Ison (DB RCT)	70%	0.30 [0.16-0.56] symp. case	12/752	39/728	EVADE PEP	
Ison (DB RCT)	75%	0.25 [0.07-0.88] symp. case	3/175	12/176	EVADE PEP	
Prophylaxis	**71%**	**0.29 [0.16-0.51]**	**15/927**	**51/904**		**71% lower risk**
Tau^2 = 0.00, I^2 = 0.0%, p < 0.0001						
All studies	**71%**	**0.29 [0.16-0.51]**	**15/927**	**51/904**		**71% lower risk**

0   0.25   0.5   0.75   1   1.25   1.5   1.75   2+

Tau^2 = 0.00, I^2 = 0.0%, p < 0.0001

Favors adintrevimab   Favors control

Figure 6. Random effects meta-analysis for cases.

Randomized Controlled Trials (RCTs)

Currently all studies are RCTs.

Heterogeneity

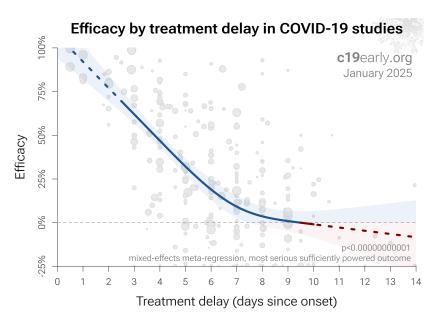Heterogeneity in COVID-19 studies arises from many factors including:

Treatment delay

The time between infection or the onset of symptoms and treatment may critically affect how well a treatment works. For example an antiviral may be very effective when used early but may not be effective in late stage disease, and may even be harmful. Oseltamivir, for example, is generally only considered effective for influenza when used within 0-36 or 0-48 hours [34,35]. Baloxavir marboxil studies for influenza also show that treatment delay is critical — *Ikematsu et al.* report an 86% reduction in cases for post-exposure prophylaxis, *Hayden et al.* show a 33 hour reduction in the time to alleviation of symptoms for treatment within 24 hours and a reduction of 13 hours for treatment within 24-48 hours, and *Kumar et al.* report only 2.5 hours improvement for inpatient treatment.

Treatment delay	Result
Post-exposure prophylaxis	**86% fewer cases** [36]
<24 hours	**-33 hours symptoms** [37]
24-48 hours	**-13 hours symptoms** [37]
Inpatients	**-2.5 hours to improvement** [38]

Table 3. Studies of baloxavir marboxil for influenza show that early treatment is more effective.

Figure 7 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 112 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

Figure 7. Early treatment is more effective. Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 112 treatments.

Patient demographics

Details of the patient population including age and comorbidities may critically affect how well a treatment works. For example, many COVID-19 studies with relatively young low-comorbidity patients show all patients recovering quickly with or without treatment. In such cases, there is little room for an effective treatment to improve results, for example as in *López-Medina et al.*

SARS-CoV-2 variants

Efficacy may depend critically on the distribution of SARS-CoV-2 variants encountered by patients. Risk varies significantly across variants [40], for example the Gamma variant shows significantly different characteristics [41-44]. Different mechanisms of action may be more or less effective depending on variants, for example the degree to which TMPRSS2 contributes to viral entry can differ across variants [45,46].

Treatment regimen

Effectiveness may depend strongly on the dosage and treatment regimen.

Medication quality

The quality of medications may vary significantly between manufacturers and production batches, which may significantly affect efficacy and safety. *Williams et al.* analyze ivermectin from 11 different sources, showing highly variable antiparasitic efficacy across different manufacturers. *Xu et al.* analyze a treatment from two different manufacturers, showing 9 different impurities, with significantly different concentrations for each manufacturer.

Other treatments

The use of other treatments may significantly affect outcomes, including supplements, other medications, or other interventions such as prone positioning. Treatments may be synergistic[49-60], therefore efficacy may depend strongly on combined treatments.

Effect measured

Across all studies there is a strong association between different outcomes, for example improved recovery is strongly associated with lower mortality. However, efficacy may differ depending on the effect measured, for example a treatment may be more effective against secondary complications and have minimal effect on viral clearance.

Meta analysis

The distribution of studies will alter the outcome of a meta analysis. Consider a simplified example where everything is equal except for the treatment delay, and effectiveness decreases to zero or below with increasing delay. If there are many studies using very late treatment, the outcome may be negative, even though early treatment is very effective. All meta analyses combine heterogeneous studies, varying in population, variants, and potentially all factors above, and therefore may obscure efficacy by including studies where treatment is less effective. Generally, we expect the estimated effect size from meta analysis to be less than that for the optimal case. Looking at all studies is valuable for providing an overview of all research, important to avoid cherry-picking, and informative when a positive result is found despite combining less-optimal situations. However, the resulting estimate does not apply to specific cases such as early treatment in high-risk populations. While we present results for all studies, we also present treatment time and individual outcome analyses, which may be more informative for specific use cases.

Pooled Effects

Combining studies is required

For COVID-19, delay in clinical results translates into additional death and morbidity, as well as additional economic and societal damage. Combining the results of studies reporting different outcomes is required. There may be no mortality in a trial with low-risk patients, however a reduction in severity or improved viral clearance may translate into lower mortality in a high-risk population. Different studies may report lower severity, improved recovery, and lower mortality, and the significance may be very high when combining the results. "*The studies reported different outcomes*" is not a good reason for disregarding results. Pooling the results of studies reporting different outcomes allows us to use more of the available information. Logically we should, and do, use additional information when evaluating treatments—for example dose-response and treatment delay-response relationships provide additional evidence of efficacy that is considered when reviewing the evidence for a treatment.

Specific outcome and pooled analyses

We present both specific outcome and pooled analyses. In order to combine the results of studies reporting different outcomes we use the most serious outcome reported in each study, based on the thesis that improvement in the most serious outcome provides comparable measures of efficacy for a treatment. A critical advantage of this

approach is simplicity and transparency. There are many other ways to combine evidence for different outcomes, along with additional evidence such as dose-response relationships, however these increase complexity.
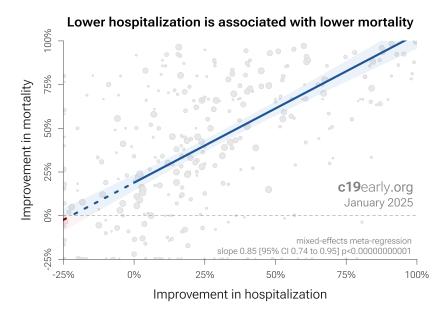
Ethical and practical issues limit high-risk trials

Trials with high-risk patients may be restricted due to ethics for treatments that are known or expected to be effective, and they increase difficulty for recruiting. Using less severe outcomes as a proxy for more serious outcomes allows faster and safer collection of evidence.
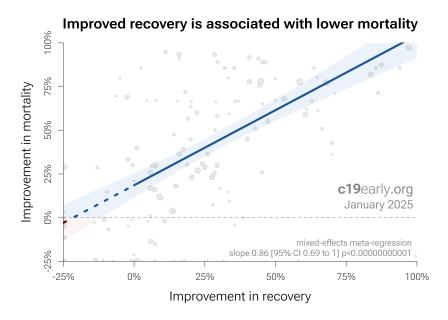
Validating pooled outcome analysis for COVID-19

For many COVID-19 treatments, a reduction in mortality logically follows from a reduction in hospitalization, which follows from a reduction in symptomatic cases, which follows from a reduction in PCR positivity. We can directly test this for COVID-19.
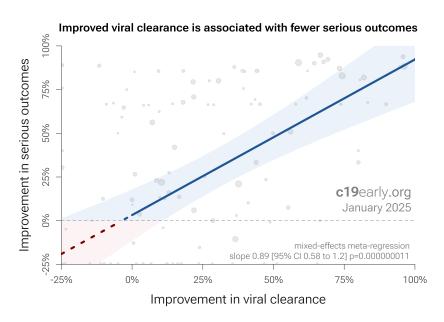
Analysis of the the association between different outcomes across studies from all 112 treatments we cover confirms the validity of pooled outcome analysis for COVID-19. Figure 8 shows that lower hospitalization is very strongly associated with lower mortality (*p < 0.000000000001*). Similarly, Figure 9 shows that improved recovery is very strongly associated with lower mortality (*p < 0.000000000001*). Considering the extremes, *Singh et al.* show an association between viral clearance and hospitalization or death, with *p = 0.003* after excluding one large outlier from a mutagenic treatment, and based on 44 RCTs including 52,384 patients. Figure 10 shows that improved viral clearance is strongly associated with fewer serious outcomes. The association is very similar to *Singh et al.*, with higher confidence due to the larger number of studies. As with *Singh et al.*, the confidence increases when excluding the outlier treatment, from *p = 0.00000032* to *p = 0.000000011*.

Figure 8. Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.

Figure 9. Improved recovery is associated with lower mortality, supporting pooled outcome analysis.

Figure 8. Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.

Pooled outcomes identify efficacy 5 months faster (7 months for RCTs)

Currently, 48 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 89% of these have been confirmed with one or more specific outcomes, with a mean delay of 4.8 months. When restricting to RCTs only, 56% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 6.5 months. Figure 11 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.
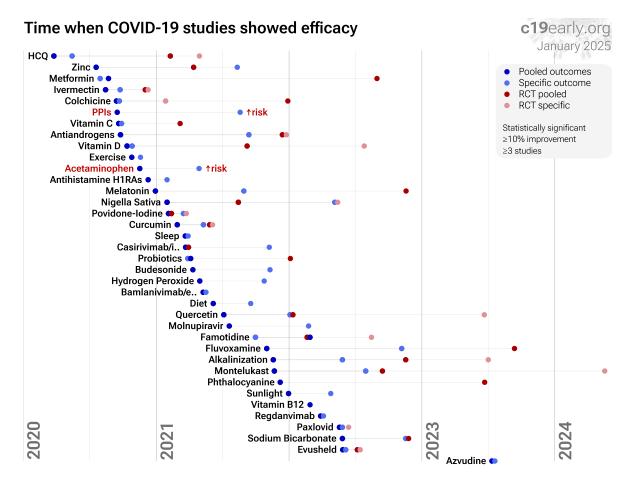
Figure 11. The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies. Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

Limitations

Pooled analysis could hide efficacy, for example a treatment that is beneficial for late stage patients but has no effect on viral clearance may show no efficacy if most studies only examine viral clearance. In practice, it is rare for a non-antiviral treatment to report viral clearance and to not report clinical outcomes; and in practice other sources of heterogeneity such as difference in treatment delay is more likely to hide efficacy.

Summary

Analysis validates the use of pooled effects and shows significantly faster detection of efficacy on average. However, as with all meta analyses, it is important to review the different studies included. We also present individual outcome analyses, which may be more informative for specific use cases.

Discussion

Publication bias

Publishing is often biased towards positive results. Trials with patented drugs may have a financial conflict of interest that results in positive studies being more likely to be published, or bias towards more positive results. For example with molnupiravir, trials with negative results remain unpublished to date (CTRI/2021/05/033864 and CTRI/2021/08/0354242). For adintrevimab, there is currently not enough data to evaluate publication bias with high confidence.

Limitations

Summary statistics from meta analysis necessarily lose information. As with all meta analyses, studies are heterogeneous, with differences in treatment delay, treatment regimen, patient demographics, variants, conflicts of interest, standard of care, and other factors. We provide analyses for specific outcomes and by treatment delay, and we aim to identify key characteristics in the forest plots and summaries. Results should be viewed in the context of study characteristics.

Some analyses classify treatment based on early or late administration, as done here, while others distinguish between mild, moderate, and severe cases. Viral load does not indicate degree of symptoms — for example patients may have a high viral load while being asymptomatic. With regard to treatments that have antiviral properties, timing of treatment is critical — late administration may be less helpful regardless of severity.

Details of treatment delay per patient is often not available. For example, a study may treat 90% of patients relatively early, but the events driving the outcome may come from 10% of patients treated very late. Our 5 day cutoff for early treatment may be too conservative, 5 days may be too late in many cases.

Comparison across treatments is confounded by differences in the studies performed, for example dose, variants, and conflicts of interest. Trials with conflicts of interest may use designs better suited to the preferred outcome.

In some cases, the most serious outcome has very few events, resulting in lower confidence results being used in pooled analysis, however the method is simpler and more transparent. This is less critical as the number of studies increases. Restriction to outcomes with sufficient power may be beneficial in pooled analysis and improve accuracy when there are few studies, however we maintain our pre-specified method to avoid any retrospective changes.

Studies show that combinations of treatments can be highly synergistic and may result in many times greater efficacy than individual treatments alone[49-60]. Therefore standard of care may be critical and benefits may diminish or disappear if standard of care does not include certain treatments.

This real-time analysis is constantly updated based on submissions. Accuracy benefits from widespread review and submission of updates and corrections from reviewers. Less popular treatments may receive fewer reviews.

No treatment or intervention is 100% available and effective for all current and future variants. Efficacy may vary significantly with different variants and within different populations. All treatments have potential side effects. Propensity to experience side effects may be predicted in advance by qualified physicians. We do not provide medical advice. Before taking any medication, consult a qualified physician who can compare all options, provide personalized advice, and provide details of risks and benefits based on individual medical history and situations.

Reviews

Focosi (B) et al. present a review covering adintrevimab for COVID-19.

Other studies

Additional preclinical or review papers suggesting potential benefits of adintrevimab for COVID-19 include[64,65]. We have not reviewed these studies in detail.

Perspective

Results compared with other treatments

SARS-CoV-2 infection and replication involves a complex interplay of 50+ host and viral proteins and other factors[23-29], providing many therapeutic targets. Over 8,000 compounds have been predicted to reduce COVID-19 risk[30], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Figure 12 shows an overview of the results for adintrevimab in the context of multiple COVID-19 treatments, and Figure 13 shows a plot of efficacy vs. cost for COVID-19 treatments.

Efficacy in COVID-19 studies (pooled effects)

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January 2025

Regdanvimab
Ivermectin
PVP-I
Diet
Alkalinization
Adintrevimab
Melatonin
Vitamin D
Metformin
HCQ
Zinc
Vitamin C
Paxlovid — independent trials refused
Molnupiravir — mutagenic/teratogenic
Remdesivir — worse w/longer followup
Conv. Plasma
Cannabidiol
Acetaminophen
PPIs

0   0.25   0.5   0.75   1   1.25   1.5+

Lower risk   Increased risk

Figure 12. Scatter plot showing results within the context of multiple COVID-19 treatments. Diamonds shows the results of random effects meta-analysis. 0.5% of 8,000+ proposed treatments show efficacy [66].

Efficacy vs. cost for COVID-19 treatments

c19early.org
January 2025

Legend:
- Lifestyle / free
- No prescription
- Prescription required
- High-cost

Ivermectin
Thermotherapy
50% Diet
pH+   PVP-I
NaHCO₃   Melatonin
Fluvox.   Curcumin   Quercetin
Exercise   Vitamin D H1RAs N. Sativa   Tixagevimab/c..   Regdanvimab $2,100
Sunlight   Nitric Oxide Metformin H. Peroxide
                        Azvudine   Vitamin A   Bamlanivimab/e..   Ensovibep >$2,000
Sleep   HCQ   Probiotics Antiandro..   Casirivimab/i.. $2,100
           Budesonide NAC   Zinc   Bebtelovimab
25%   Colchicine   Sotrovimab $2,100
           Vitamin C   Amubarvimab/r..   Vilobelimab $6,350

Lower risk   Favipiravir   Famotidine   Acebilustat >$2,000
                                                        Paxlovid   Sarilumab >$2,000
           Aspirin   Remdesivir $3,120
                                                                           Conv. Plasma $5,000
0%   Ibuprofen   Molnupiravir   Sargramostim >$2,000
                                                  mutagenic/teratogenic   Plitidepsin >$2,000
Higher risk Vitamin B9   Trimodulin >$2,000
             Cannabidiol   Lufotrelvir >$2,000
             Losartan   BMS mAbs -36% >$2,000
                                                                           Olokizumab -50% >$2,000
           Acetaminophen -28%   Glenzocimab -60% >$2,000
-25+%   PPIs -46%   Donidalorsen -151% >$2,000

$0 $1,000 $2,000+

Treatment cost (US$)

COVID-19 involves the interplay of 50+ host/viral proteins/factors, modulated by many treatments. 0.5% of 8,000+ proposed treatments show efficacy with ≥3 studies. Protocols combine treatments, none are 100% effective. **c19**early analyzes over 5,200 studies for 112 treatments.
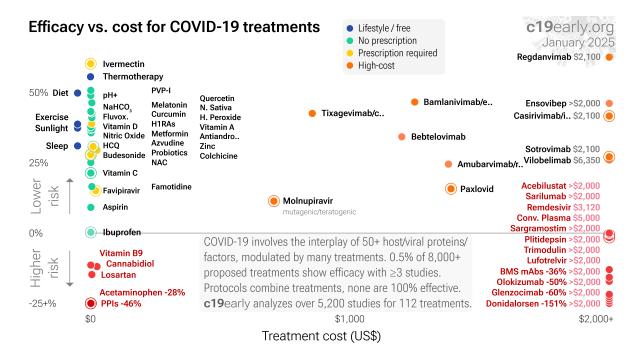
Figure 13. Efficacy vs. cost for COVID-19 treatments.
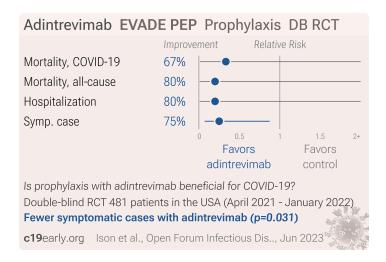
Conclusion

Significantly lower risk is seen for hospitalization and cases. 2 studies (both from the same team) show significant benefit. Meta analysis using the most serious outcome reported shows 43% [-169-88%] lower risk, without reaching statistical significance. Currently all studies are RCTs.

Currently there is limited data, with only 4 control events for the most serious outcome in trials to date. All studies to date are from the same group.

mAb use may create new variants that spread globally [1,2], and may be associated with prolonged viral loads, clinical deterioration, and immune escape [2-5].

Study Notes

Ison

Adintrevimab EVADE PEP Prophylaxis DB RCT

	Improvement	Relative Risk
Mortality, COVID-19	67%	
Mortality, all-cause	80%	
Hospitalization	80%	
Symp. case	75%	

Favors adintrevimab — Favors control

Is prophylaxis with adintrevimab beneficial for COVID-19?
Double-blind RCT 481 patients in the USA (April 2021 - January 2022)
Fewer symptomatic cases with adintrevimab (p=0.031)
c19early.org   Ison et al., Open Forum Infectious Dis.., Jun 2023

PEP RCT 351 patients, showing lower COVID-19 cases with adintrevimab. The PrEP trial is listed separately [63].

Ison

Adintrevimab EVADE PrEP Prophylaxis DB RCT

	Improvement	Relative Risk
Mortality, COVID-19	33%	
Mortality, all-cause	50%	
Mortality	84%	
Hospitalization	84%	
Symp. case	70%	

Favors adintrevimab — Favors control

Is prophylaxis with adintrevimab beneficial for COVID-19?
Double-blind RCT 2,002 patients in the USA (April 2021 - January 2022)
Fewer symptomatic cases with adintrevimab (p=0.000083)
c19early.org   Ison et al., Open Forum Infectious Dis.., Jun 2023

PrEP RCT 1480 patients, showing lower COVID-19 cases with adintrevimab. The PEP trial is listed separately [62].

Appendix 1. Methods and Data

We perform ongoing searches of PubMed, medRxiv, Europe PMC, ClinicalTrials.gov, The Cochrane Library, Google Scholar, Research Square, ScienceDirect, Oxford University Press, the reference lists of other studies and meta-analyses, and submissions to the site c19early.org. Search terms are adintrevimab and COVID-19 or SARS-CoV-2. Automated searches are performed twice daily, with all matches reviewed for inclusion. All studies regarding the use of adintrevimab for COVID-19 that report a comparison with a control group are included in the main analysis. This is a living analysis and is updated regularly.

We extracted effect sizes and associated data from all studies. If studies report multiple kinds of effects then the most serious outcome is used in pooled analysis, while other outcomes are included in the outcome specific analyses. For example, if effects for mortality and cases are both reported, the effect for mortality is used, this may be different to the effect that a study focused on. If symptomatic results are reported at multiple times, we used the latest time, for example if mortality results are provided at 14 days and 28 days, the results at 28 days have preference. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms are not used, the next most serious outcome with one or more events is used. For example, in low-risk populations with no mortality, a reduction in mortality with treatment is not possible, however a reduction in hospitalization, for example, is still valuable. Clinical outcomes are considered more important than viral test status. When basically all patients recover in both treatment and control groups, preference for viral clearance and recovery is given to results mid-recovery where available. After most or all patients have recovered there is little or no room for an effective treatment to do better, however faster recovery is valuable. If only individual symptom data is available, the most serious symptom has priority, for example difficulty breathing or low SpO_2 is more important than cough. When results provide an odds ratio, we compute the relative risk when possible, or convert to a relative risk according to[67]. Reported confidence intervals and *p*-values were used when available, using adjusted values when provided. If multiple types of adjustments are reported propensity score matching and multivariable regression has preference over propensity score matching or weighting, which has preference over multivariable regression. Adjusted results have preference over unadjusted results for a more serious outcome when the adjustments significantly alter results. When needed, conversion between reported *p*-values and confidence intervals followed *Altman, Altman (B)*, and Fisher's exact test was used to calculate *p*-values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1[70]. Results are expressed with RR < 1.0 favoring treatment, and using the risk of a negative outcome when applicable (for example, the risk of death rather than the risk of survival). If studies only report relative continuous values such as relative times, the ratio of the time for the treatment group versus the time for the control group is used. Calculations are done in Python (3.13.1) with scipy (1.14.1), pythonmeta (1.26), numpy (1.26.4), statsmodels (0.14.4), and plotly (5.24.1).

Forest plots are computed using PythonMeta[71] with the DerSimonian and Laird random effects model (the fixed effect assumption is not plausible in this case) and inverse variance weighting. Results are presented with 95% confidence intervals. Heterogeneity among studies was assessed using the I^2 statistic. Mixed-effects meta-regression results are computed with R (4.4.0) using the metafor (4.6-0) and rms (6.8-0) packages, and using the most serious sufficiently powered outcome. For all statistical tests, a *p*-value less than 0.05 was considered statistically significant. Grobid 0.8.0 is used to parse PDF documents.

We have classified studies as early treatment if most patients are not already at a severe stage at the time of treatment (for example based on oxygen status or lung involvement), and treatment started within 5 days of the onset of symptoms. If studies contain a mix of early treatment and late treatment patients, we consider the treatment time of patients contributing most to the events (for example, consider a study where most patients are treated early but late treatment patients are included, and all mortality events were observed with late treatment patients). We note that a shorter time may be preferable. Antivirals are typically only considered effective when used within a shorter timeframe, for example 0-36 or 0-48 hours for oseltamivir, with longer delays not being effective[34,35].

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A summary of study results is below. Please submit updates and corrections at https://c19early.org/admeta.html.

Prophylaxis

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. For pooled analyses, the first (most serious) outcome is used, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

Ison, 6/13/2023, Double Blind Randomized Controlled Trial, placebo-controlled, USA, peer-reviewed, 15 authors, study period 27 April, 2021 - 11 January, 2022, trial NCT04859517 (history) (EVADE PEP).	risk of death, 66.6% lower, RR 0.33, *p* = 1.00, treatment 0 of 240 (0.0%), control 1 of 241 (0.4%), NNT 241, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), COVID-19, 6 months, supplementary table 6.
	risk of death, 80.0% lower, RR 0.20, *p* = 0.50, treatment 0 of 240 (0.0%), control 2 of 241 (0.8%), NNT 120, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), all-cause, 6 months, supplementary table 6.
	risk of hospitalization, 80.0% lower, RR 0.20, *p* = 0.50, treatment 0 of 175 (0.0%), control 2 of 176 (1.1%), NNT 88, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 28.
	risk of symptomatic case, 74.9% lower, RR 0.25, *p* = 0.03, treatment 3 of 175 (1.7%), control 12 of 176 (6.8%), NNT 20, day 28.
Ison (B), 6/13/2023, Double Blind Randomized Controlled Trial, placebo-controlled, USA, peer-reviewed, 15 authors, study period 27 April, 2021 - 11 January, 2022, trial NCT04859517 (history) (EVADE PrEP).	risk of death, 33.3% lower, RR 0.67, *p* = 1.00, treatment 2 of 1,001 (0.2%), control 3 of 1,001 (0.3%), NNT 1001, COVID-19, 6 months, supplementary table 6.
	risk of death, 50.0% lower, RR 0.50, *p* = 0.51, treatment 3 of 1,001 (0.3%), control 6 of 1,001 (0.6%), NNT 334, all-cause, 6 months, supplementary table 6.
	risk of death, 83.9% lower, RR 0.16, *p* = 0.07, treatment 1 of 752 (0.1%), control 6 of 728 (0.8%), NNT 145, 3 months.
	risk of hospitalization, 83.9% lower, RR 0.16, *p* = 0.07, treatment 1 of 752 (0.1%), control 6 of 728 (0.8%), NNT 145, 3 months.
	risk of symptomatic case, 70.2% lower, RR 0.30, *p* < 0.001, treatment 12 of 752 (1.6%), control 39 of 728 (5.4%), NNT 27, 3 months.

Supplementary Data

Supplementary Data

Footnotes

a. Viral infection and replication involves attachment, entry, uncoating and release, genome replication and transcription, translation and protein processing, assembly and budding, and release. Each step can be disrupted by therapeutics.

References

1. **Focosi** et al., *Analysis of SARS-CoV-2 mutations associated with resistance to therapeutic monoclonal antibodies that emerge after treatment*, Drug Resistance Updates, doi:10.1016/j.drup.2023.100991.

2. **Leducq** et al., *Spike protein genetic evolution in patients at high-risk of severe COVID-19 treated by monoclonal antibodies*, The Journal of Infectious Diseases, doi:10.1093/infdis/jiad523.

3. **Choudhary** et al., *Emergence of SARS-CoV-2 Resistance with Monoclonal Antibody Therapy*, medRxiv, doi:10.1101/2021.09.03.21263105.

4. **Günther** et al., *Variant-specific humoral immune response to SARS-CoV-2 escape mutants arising in clinically severe, prolonged infection*, medRxiv, doi:10.1101/2024.01.06.24300890.

5. **Casadevall** et al., *Single monoclonal antibodies should not be used for COVID-19 therapy: a call for antiviral stewardship*, Clinical Infectious Diseases, doi:10.1093/cid/ciae408.

6. **Rong** et al., *Persistence of spike protein at the skull-meninges-brain axis may contribute to the neurological sequelae of COVID-19*, Cell Host & Microbe, doi:10.1016/j.chom.2024.11.007.

7. **Yang** et al., *SARS-CoV-2 infection causes dopaminergic neuron senescence*, Cell Stem Cell, doi:10.1016/j.stem.2023.12.012.

8. **Scardua-Silva** et al., *Microstructural brain abnormalities, fatigue, and cognitive dysfunction after mild COVID-19*, Scientific Reports, doi:10.1038/s41598-024-52005-7.

9. **Hampshire** et al., *Cognition and Memory after Covid-19 in a Large Community Sample*, New England Journal of Medicine, doi:10.1056/NEJMoa2311330.

10. **Duloquin** et al., *Is COVID-19 Infection a Multiorganic Disease? Focus on Extrapulmonary Involvement of SARS-CoV-2*, Journal of Clinical Medicine, doi:10.3390/jcm13051397.

11. **Sodagar** et al., *Pathological Features and Neuroinflammatory Mechanisms of SARS-CoV-2 in the Brain and Potential Therapeutic Approaches*, Biomolecules, doi:10.3390/biom12070971.

12. **Sagar** et al., *COVID-19-associated cerebral microbleeds in the general population*, Brain Communications, doi:10.1093/braincomms/fcae127.

13. **Verma** et al., *Persistent Neurological Deficits in Mouse PASC Reveal Antiviral Drug Limitations*, bioRxiv, doi:10.1101/2024.06.02.596989.

14. **Panagea** et al., *Neurocognitive Impairment in Long COVID: A Systematic Review*, Archives of Clinical Neuropsychology, doi:10.1093/arclin/acae042.

15. **Ariza** et al., *COVID-19: Unveiling the Neuropsychiatric Maze—From Acute to Long-Term Manifestations*, Biomedicines, doi:10.3390/biomedicines12061147.

16. **Vashisht** et al., *Neurological Complications of COVID-19: Unraveling the Pathophysiological Underpinnings and Therapeutic Implications*, Viruses, doi:10.3390/v16081183.

17. **Ahmad** et al., *Neurological Complications and Outcomes in Critically Ill Patients With COVID-19: Results From International Neurological Study Group From the COVID-19 Critical Care Consortium*, The Neurohospitalist, doi:10.1177/19418744241292487.

18. **Wang** et al., *SARS-CoV-2 membrane protein induces neurodegeneration via affecting Golgi-mitochondria interaction*, Translational Neurodegeneration, doi:10.1186/s40035-024-00458-1.

19. **Eberhardt** et al., *SARS-CoV-2 infection triggers pro-atherogenic inflammatory responses in human coronary vessels*, Nature Cardiovascular Research, doi:10.1038/s44161-023-00336-5.

20. **Van Tin** et al., *Spike Protein of SARS-CoV-2 Activates Cardiac Fibrogenesis through NLRP3 Inflammasomes and NF-κB Signaling*, Cells, doi:10.3390/cells13161331.

21. *Borka Balas* et al., *COVID-19 and Cardiac Implications—Still a Mystery in Clinical Practice*, Reviews in Cardiovascular Medicine, doi:10.31083/j.rcm2405125.

22. *AlTaweel* et al., *An In-Depth Insight into Clinical, Cellular and Molecular Factors in COVID19-Associated Cardiovascular Ailments for Identifying Novel Disease Biomarkers, Drug Targets and Clinical Management Strategies*, Archives of Microbiology & Immunology, doi:10.26502/ami.936500177.

23. *Malone* et al., *Structures and functions of coronavirus replication–transcription complexes and their relevance for SARS-CoV-2 drug design*, Nature Reviews Molecular Cell Biology, doi:10.1038/s41580-021-00432-z.

24. *Murigneux* et al., *Proteomic analysis of SARS-CoV-2 particles unveils a key role of G3BP proteins in viral assembly*, Nature Communications, doi:10.1038/s41467-024-44958-0.

25. *Lv* et al., *Host proviral and antiviral factors for SARS-CoV-2*, Virus Genes, doi:10.1007/s11262-021-01869-2.

26. *Lui* et al., *Nsp1 facilitates SARS-CoV-2 replication through calcineurin-NFAT signaling*, Virology, doi:10.1128/mbio.00392-24.

27. *Niarakis* et al., *Drug-target identification in COVID-19 disease mechanisms using computational systems biology approaches*, Frontiers in Immunology, doi:10.3389/fimmu.2023.1282859.

28. *Katiyar* et al., *SARS-CoV-2 Assembly: Gaining Infectivity and Beyond*, Viruses, doi:10.3390/v16111648.

29. *Wu* et al., *Decoding the genome of SARS-CoV-2: a pathway to drug development through translation inhibition*, RNA Biology, doi:10.1080/15476286.2024.2433830.

30. *c19early.org*, c19early.org/treatments.html.

31. *Hattab* et al., *SARS-CoV-2 journey: from alpha variant to omicron and its sub-variants*, Infection, doi:10.1007/s15010-024-02223-y.

32. *Focosi (B)*, D., *Monoclonal Antibody Therapies Against SARS-CoV-2: Promises and Realities*, Current Topics in Microbiology and Immunology, doi:10.1007/82_2024_268.

33. *Davis* et al., *The Promise and Peril of Anti-SARS-CoV-2 Monoclonal Antibodies*, Clinical Infectious Diseases, doi:10.1093/cid/ciac902.

34. *Treanor* et al., *Efficacy and Safety of the Oral Neuraminidase Inhibitor Oseltamivir in Treating Acute Influenza: A Randomized Controlled Trial*, JAMA, 2000, 283:8, 1016-1024, doi:10.1001/jama.283.8.1016.

35. *McLean* et al., *Impact of Late Oseltamivir Treatment on Influenza Symptoms in the Outpatient Setting: Results of a Randomized Trial*, Open Forum Infect. Dis. September 2015, 2:3, doi:10.1093/ofid/ofv100.

36. *Ikematsu* et al., *Baloxavir Marboxil for Prophylaxis against Influenza in Household Contacts*, New England Journal of Medicine, doi:10.1056/NEJMoa1915341.

37. *Hayden* et al., *Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents*, New England Journal of Medicine, doi:10.1056/NEJMoa1716197.

38. *Kumar* et al., *Combining baloxavir marboxil with standard-of-care neuraminidase inhibitor in patients hospitalised with severe influenza (FLAGSTONE): a randomised, parallel-group, double-blind, placebo-controlled, superiority trial*, The Lancet Infectious Diseases, doi:10.1016/S1473-3099(21)00469-2.

39. *López-Medina* et al., *Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial*, JAMA, doi:10.1001/jama.2021.3071.

40. *Korves* et al., *SARS-CoV-2 Genetic Variants and Patient Factors Associated with Hospitalization Risk*, medRxiv, doi:10.1101/2024.03.08.24303818.

41. *Faria* et al., *Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil*, Science, doi:10.1126/science.abh2644.

42. *Nonaka* et al., *SARS-CoV-2 variant of concern P.1 (Gamma) infection in young and middle-aged patients admitted to the intensive care units of a single hospital in Salvador, Northeast Brazil, February 2021*, International Journal of Infectious Diseases, doi:10.1016/j.ijid.2021.08.003.

43. *Karita* et al., *Trajectory of viral load in a prospective population-based cohort with incident SARS-CoV-2 G614 infection*, medRxiv, doi:10.1101/2021.08.27.21262754.

44. *Zavascki* et al., *Advanced ventilatory support and mortality in hospitalized patients with COVID-19 caused by Gamma (P.1) variant of concern compared to other lineages: cohort study at a reference center in Brazil*, Research Square, doi:10.21203/rs.3.rs-910467/v1.

45. **Willett** et al., *The hyper-transmissible SARS-CoV-2 Omicron variant exhibits significant antigenic change, vaccine escape and a switch in cell entry mechanism*, medRxiv, doi:10.1101/2022.01.03.21268111.

46. **Peacock** et al., *The SARS-CoV-2 variant, Omicron, shows rapid replication in human primary nasal epithelial cultures and efficiently uses the endosomal route of entry*, bioRxiv, doi:10.1101/2021.12.31.474653.

47. **Williams**, T., *Not All Ivermectin Is Created Equal: Comparing The Quality of 11 Different Ivermectin Sources*, Do Your Own Research, doyourownresearch.substack.com/p/not-all-ivermectin-is-created-equal.

48. **Xu** et al., *A study of impurities in the repurposed COVID-19 drug hydroxychloroquine sulfate by UHPLC-Q/TOF-MS and LC-SPE-NMR*, Rapid Communications in Mass Spectrometry, doi:10.1002/rcm.9358.

49. **Jitobaom** et al., *Favipiravir and Ivermectin Showed in Vitro Synergistic Antiviral Activity against SARS-CoV-2*, Research Square, doi:10.21203/rs.3.rs-941811/v1.

50. **Jitobaom (B)** et al., *Synergistic anti-SARS-CoV-2 activity of repurposed anti-parasitic drug combinations*, BMC Pharmacology and Toxicology, doi:10.1186/s40360-022-00580-8.

51. **Jeffreys** et al., *Remdesivir-ivermectin combination displays synergistic interaction with improved in vitro activity against SARS-CoV-2*, International Journal of Antimicrobial Agents, doi:10.1016/j.ijantimicag.2022.106542.

52. **Ostrov** et al., *Highly Specific Sigma Receptor Ligands Exhibit Anti-Viral Properties in SARS-CoV-2 Infected Cells*, Pathogens, doi:10.3390/pathogens10111514.

53. **Alsaidi** et al., *Griffithsin and Carrageenan Combination Results in Antiviral Synergy against SARS-CoV-1 and 2 in a Pseudoviral Model*, Marine Drugs, doi:10.3390/md19080418.

54. **Andreani** et al., *In vitro testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect*, Microbial Pathogenesis, doi:10.1016/j.micpath.2020.104228.

55. **De Forni** et al., *Synergistic drug combinations designed to fully suppress SARS-CoV-2 in the lung of COVID-19 patients*, PLoS ONE, doi:10.1371/journal.pone.0276751.

56. **Wan** et al., *Synergistic inhibition effects of andrographolide and baicalin on coronavirus mechanisms by downregulation of ACE2 protein level*, Scientific Reports, doi:10.1038/s41598-024-54722-5.

57. **Said** et al., *The effect of Nigella sativa and vitamin D3 supplementation on the clinical outcome in COVID-19 patients: A randomized controlled clinical trial*, Frontiers in Pharmacology, doi:10.3389/fphar.2022.1011522.

58. **Fiaschi** et al., *In Vitro Combinatorial Activity of Direct Acting Antivirals and Monoclonal Antibodies against the Ancestral B.1 and BQ.1.1 SARS-CoV-2 Viral Variants*, Viruses, doi:10.3390/v16020168.

59. **Xing** et al., *Published anti-SARS-CoV-2 in vitro hits share common mechanisms of action that synergize with antivirals*, Briefings in Bioinformatics, doi:10.1093/bib/bbab249.

60. **Thairu** et al., *A Comparison of Ivermectin and Non Ivermectin Based Regimen for COVID-19 in Abuja: Effects on Virus Clearance, Days-to-discharge and Mortality*, Journal of Pharmaceutical Research International, doi:10.9734/jpri/2022/v34i44A36328.

61. **Singh** et al., *The relationship between viral clearance rates and disease progression in early symptomatic COVID-19: a systematic review and meta-regression analysis*, Journal of Antimicrobial Chemotherapy, doi:10.1093/jac/dkae045.

62. **Ison** et al., *Prevention of COVID-19 Following a Single Intramuscular Administration of Adintrevimab: Results From a Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Trial (EVADE)*, Open Forum Infectious Diseases, doi:10.1093/ofid/ofad314.

63. **Ison (B)** et al., *Prevention of COVID-19 Following a Single Intramuscular Administration of Adintrevimab: Results From a Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Trial (EVADE)*, Open Forum Infectious Diseases, doi:10.1093/ofid/ofad314.

64. **Rubino** et al., *591. Adintrevimab (ADI) Population Pharmacokinetics (PPK) in Phase 1 and Phase 2/3 COVID-19 Prevention and Treatment Study Participants*, Open Forum Infectious Diseases, doi:10.1093/ofid/ofac492.643.

65. **Gutlapalli** et al., *Exploring the Potential of Broadly Neutralizing Antibodies for Treating SARS-CoV-2 Variants of Global Concern in 2023: A Comprehensive Clinical Review*, Cureus, doi:10.7759/cureus.36809.

66. **c19early.org (B)**, c19early.org/timeline.html.

67. **Zhang** et al., *What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes*, JAMA, 80:19, 1690, doi:10.1001/jama.280.19.1690.

68. **Altman**, D., *How to obtain the P value from a confidence interval*, BMJ, doi:10.1136/bmj.d2304.

69. **Altman (B)** et al., *How to obtain the confidence interval from a P value*, BMJ, doi:10.1136/bmj.d2090.

70. **Sweeting** et al., *What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data*, Statistics in Medicine, doi:10.1002/sim.1761.

71. **Deng**, H., *PyMeta, Python module for meta-analysis*, www.pymeta.com/.