Ibuprofen for COVID-19: real-time meta analysis of 13 studies

Abstract

Meta analysis using the most serious outcome reported shows 0% [-9-9%] lower risk, without reaching statistical significance.

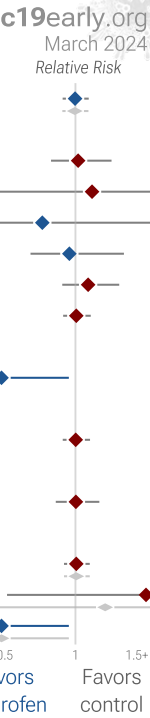4 studies from 4 independent teams in 4 countries show statistically significant improvements.

Concerns have been raised over potential harm with the use of ibuprofen for COVID-19 [Day] due to the suppression of beneficial immune and inflammatory responses during early infection, ACE2 upregulation, and delaying further care. There is limited clinical data currently, especially with regard to acute usage at onset of infection, however current results suggest harm with early treatment and benefit with late treatment.

No treatment or intervention is 100% effective. All practical, effective, and safe means should be used based on risk/benefit analysis. Multiple treatments are typically used in combination, and other treatments are significantly more effective.
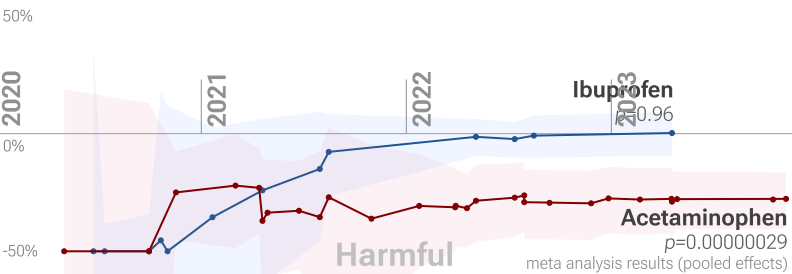
All data to reproduce this paper and sources are in the appendix.

Ibuprofen for COVID-19

c19early.org
March 2024
Relative Risk

Improvement, Studies, Patients

	Improvement	Studies	Patients
All studies	0%	13	54,707
Mortality	-2%	8	50,525
Ventilation	-12%	1	403
ICU admission	23%	2	583
Hospitalization	4%	3	577
Progression	-9%	3	4,160
Cases	-1%	2	0
RCTs	52%	1	180
Peer-reviewed	-0%	12	43,233
Symptomatic	-0%	12	54,707
Prophylaxis	-1%	10	53,727
Early	-52%	2	800
Late	52%	1	180

0   0.5   1   1.5+

after exclusions

Favors ibuprofen   Favors control

Evolution of COVID-19 clinical evidence

100%

Effective

50%

0%

-50%

2020   2021   2022   2023

Ibuprofen
p=0.96

Acetaminophen
p=0.00000029

Harmful

meta analysis results (pooled effects)
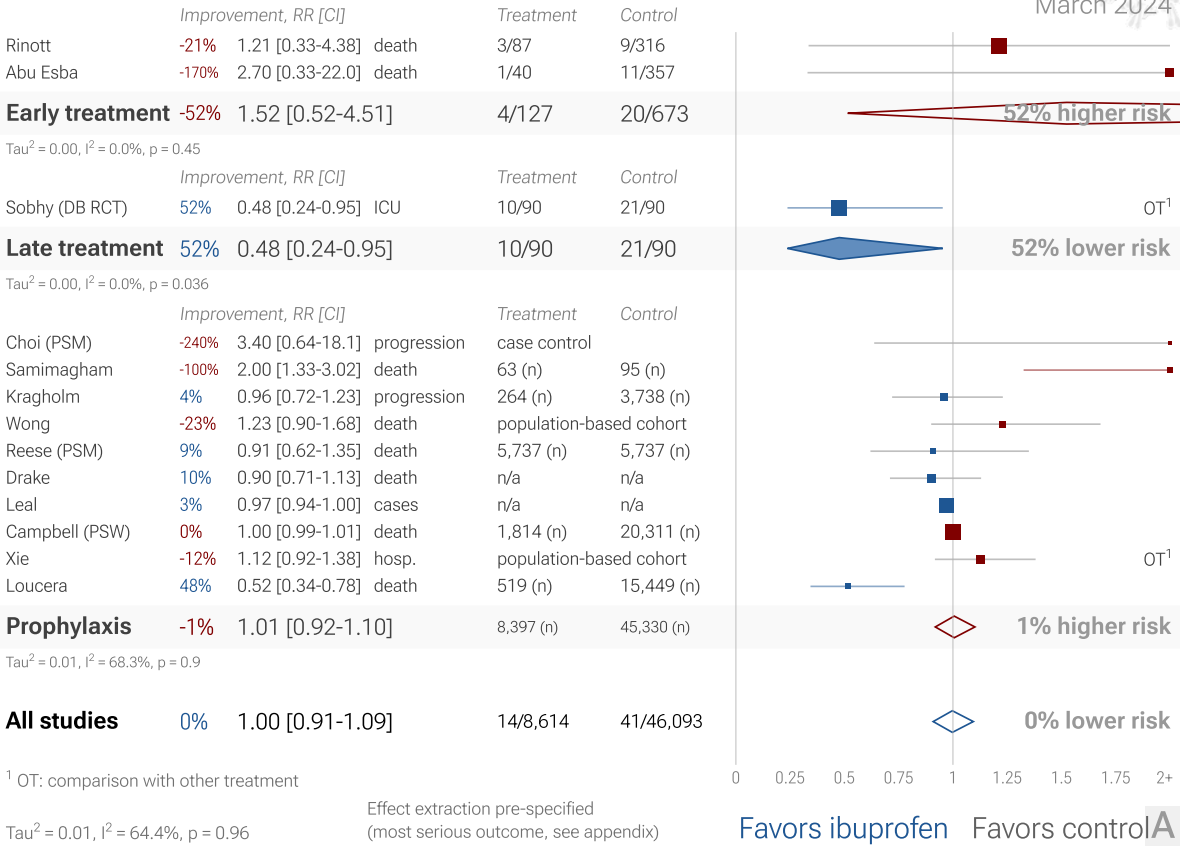
c19early.org
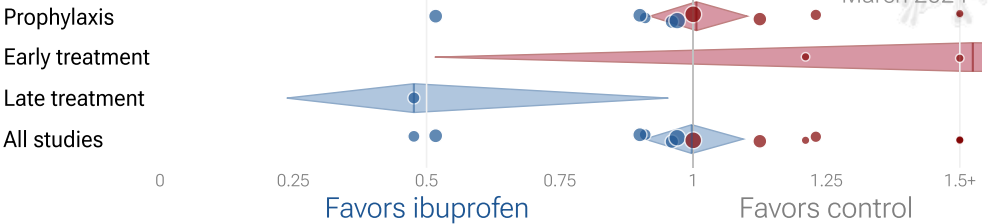March 2024

HIGHLIGHTS

We show traditional outcome specific analyses and combined evidence from all studies, incorporating treatment delay, a primary confounding factor in COVID-19 studies.

Real-time updates and corrections, transparent analysis with all results in the same format, consistent protocol for 66 treatments.

13 ibuprofen COVID-19 studies

	Improvement, RR [CI]			Treatment	Control	
Rinott	-21%	1.21 [0.33-4.38]	death	3/87	9/316	
Abu Esba	-170%	2.70 [0.33-22.0]	death	1/40	11/357	
Early treatment	**-52%**	**1.52 [0.52-4.51]**		**4/127**	**20/673**	**52% higher risk**

Tau² = 0.00, I² = 0.0%, p = 0.45

	Improvement, RR [CI]			Treatment	Control	
Sobhy (DB RCT)	52%	0.48 [0.24-0.95]	ICU	10/90	21/90	OT[1]
Late treatment	**52%**	**0.48 [0.24-0.95]**		**10/90**	**21/90**	**52% lower risk**

Tau² = 0.00, I² = 0.0%, p = 0.036

	Improvement, RR [CI]			Treatment	Control	
Choi (PSM)	-240%	3.40 [0.64-18.1]	progression	case control		
Samimagham	-100%	2.00 [1.33-3.02]	death	63 (n)	95 (n)	
Kragholm	4%	0.96 [0.72-1.23]	progression	264 (n)	3,738 (n)	
Wong	-23%	1.23 [0.90-1.68]	death	population-based cohort		
Reese (PSM)	9%	0.91 [0.62-1.35]	death	5,737 (n)	5,737 (n)	
Drake	10%	0.90 [0.71-1.13]	death	n/a	n/a	
Leal	3%	0.97 [0.94-1.00]	cases	n/a	n/a	
Campbell (PSW)	0%	1.00 [0.99-1.01]	death	1,814 (n)	20,311 (n)	
Xie	-12%	1.12 [0.92-1.38]	hosp.	population-based cohort		OT[1]
Loucera	48%	0.52 [0.34-0.78]	death	519 (n)	15,449 (n)	
Prophylaxis	**-1%**	**1.01 [0.92-1.10]**		**8,397 (n)**	**45,330 (n)**	**1% higher risk**

Tau² = 0.01, I² = 68.3%, p = 0.9

All studies	**0%**	**1.00 [0.91-1.09]**		**14/8,614**	**41/46,093**	**0% lower risk**

[1] OT: comparison with other treatment

Tau² = 0.01, I² = 64.4%, p = 0.96

Effect extraction pre-specified
(most serious outcome, see appendix)

Favors ibuprofen   Favors control   A

0   0.25   0.5   0.75   1   1.25   1.5   1.75   2+

Efficacy in COVID-19 ibuprofen studies (pooled effects)

Prophylaxis
Early treatment
Late treatment
All studies

0   0.25   0.5   0.75   1   1.25   1.5+

Favors ibuprofen   Favors control   B

Efficacy in COVID-19 studies (pooled effects)

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Regdanvimab
Ivermectin
Diet
PVP-I
Quercetin
Melatonin
Vitamin D
Metformin
Zinc
HCQ
Vitamin C
Molnupiravir — mutagenic/teratogenic
Paxlovid — independent trials refused
Remdesivir — worse w/longer follow-up
Ibuprofen
Conv. Plasma
Cannabidiol
Acetaminophen

0   0.25   0.5   0.75   1   1.25   1.5+

Lower risk   Increased risk

C

Timeline of COVID-19 ibuprofen studies (pooled effects)

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Favors ibuprofen / Favors control

100%
50%
0%
-50%
-100%

2020   2021   2022   2023

D

Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix. **B. Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis. **C. Results within the context of multiple COVID-19 treatments.** 0.6% of 6,686 proposed treatments show efficacy *c19early.org*. **D. Timeline of results in ibuprofen 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 issues *Scardua-Silva, Yang*, cardiovascular complications *Eberhardt*, 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 *Note A, Malone, Murigneux, Lv, Lui*, providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 6,000 compounds may reduce COVID-19 risk *c19early.org (B)*, either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

Analysis. We analyze all significant controlled studies of ibuprofen 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, studies within each treatment stage, individual outcomes, peer-reviewed studies, Randomized Controlled Trials (RCTs), and higher quality studies.

Treatment timing. 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.
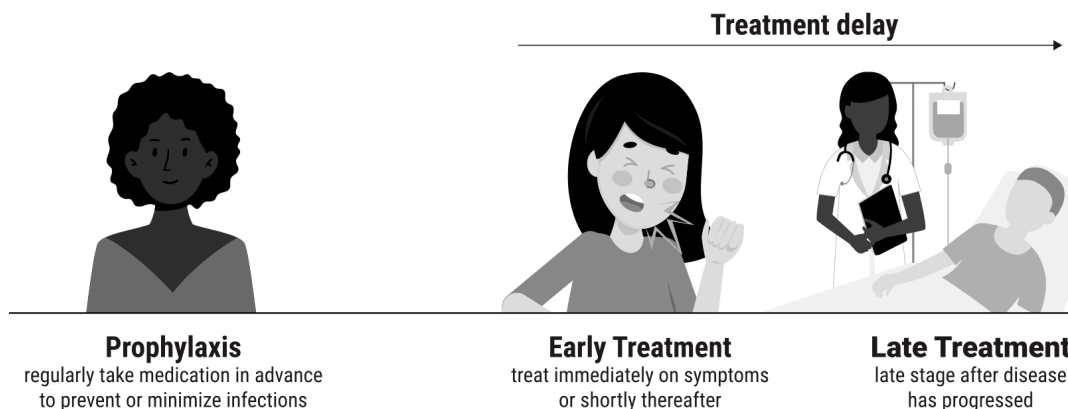
Figure 2. Treatment stages.

Potential Harm of NSAIDs

Stuart et al. performed a retrospective study of 142,925 outpatients in the UK showing significantly higher risk of hospitalization or death with prescription of NSAIDs for respiratory tract infections, OR 3.19 [2.42-4.23]. Practice-level analysis also found a 0.32 percentage point increase in hospitalizations/deaths for every 1 percentage point increase in NSAID prescribing, which increases confidence in an assocation rather than confounding by indication.

NSAIDs may be harmful due to suppression of inflammatory and immune responses needed to clear infections. They inhibit cyclooxygenase enzymes and production of prostaglandins involved in inflammation. This anti-inflammatory effect could hamper the body's ability to fight the infection. NSAIDs may mask symptoms of worsening infection. By reducing pain, fever, and inflammation, they could provide symptomatic relief while the infection progresses unchecked, delaying further medical care. NSAIDs may increase risks of certain complications, for example some evidence links NSAIDs to a higher risk of cardiovascular events.

For COVID-19, the potential harm or benefit may depend strongly on the timing of use, and any direct antiviral effects of the specific NSAID. For example, anti-inflammatory effects may be detrimental at the early stage of COVID-19 infection, but may be helpful in later stages depending on severity.

While there is very limited evidence to date, notably current results for ibuprofen suggest harm with early treatment and benefit with late treatment.

Beneficial Effects of Fever

Fever is an important component of the acute response to coronavirus infection [Wrotek]. Viral particle sensing occurs via pattern recognition receptors like toll-like receptors, triggering release of endogenous pyrogens such as interleukin-1. These cytokines induce thermoregulatory centers in the hypothalamus to elevate core temperature setpoints above normal homeostasis. The resulting fever promotes improved immune system function and creates a suboptimal internal environment that impairs SARS-CoV-2 enzyme function and replication. *In vitro* studies

demonstrate reduced viral output at sustained febrile temperatures of 38-39°C compared to basal 37°C conditions. Fever also correlates clinically with heightened interferon-γ, interleukin-6, lymphocyte activation, and antibody production critical for viral clearance.

Downing et al. induced hyperthermia (fever-like temperatures) in human volunteers by immersing them in warm water baths. They found that lymphocytes isolated from individuals with core body temperatures elevated to 39°C produced up to 10 times more interferon-γ, as shown in Figure 3. They also found an increase in suppressor/cytotoxic T cells and natural killer cells. The threshold of 39°C suggests relevance to fever, and the results suggest fever may play a role in boosting antiviral and immunoregulatory activities.
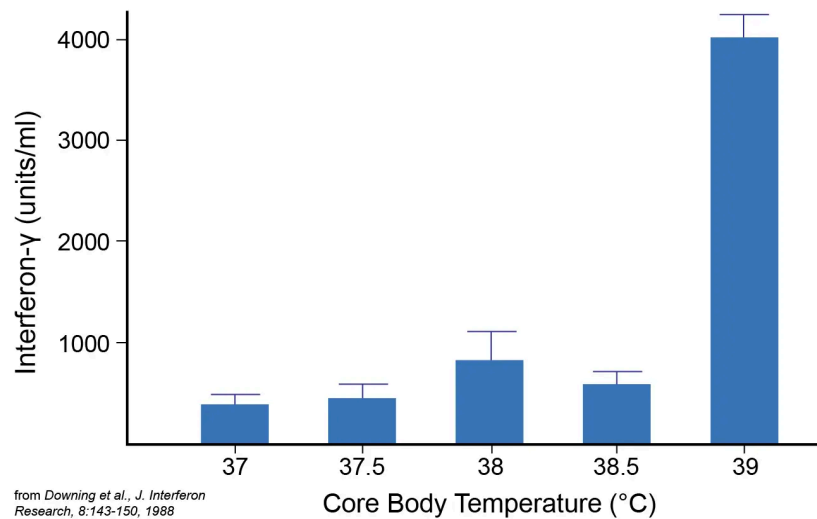

from *Downing et al., J. Interferon Research, 8:143-150, 1988*

Figure 3. 10 fold increase in interferon-γ production when core body temperature reached 39°C, from *Downing et al.*

Herder et al. perform *in vitro* analysis with a 3D respiratory epithelial model using cells from human donors. Authors showed that elevated temperature (39-40°C) restricts SARS-CoV-2 infection and replication independently of interferon-mediated antiviral defenses. Authors found SARS-CoV-2 can still enter respiratory cells at 40°C but viral transcription and replication are inhibited, limiting infectious virus production. This temperature-dependent restriction correlates with altered host gene expression related to antiviral immunity and epigenetic regulation. The results suggest that febrile temperature ranges may confer protection to respiratory tissues by restricting SARS-CoV-2 propagation.

Dominguez-Nicolas et al. induced localized hyperthermia using LF-ThMS applied to the dorsal thorax (up to 44°C externally), resulting in significantly increased peripheral oxygen saturation (SpO_2) levels in COVID-19 patients, as shown in Figure 4.
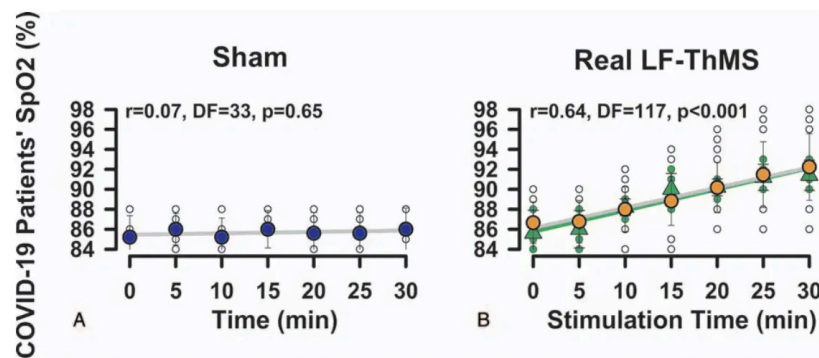
Figure 4. Rapidly increasing SpO$_2$ in COVID-19 patients with localized thoracic hyperthermia, from *Dominguez-Nicolas et al.*

Ramirez et al. compared COVID-19 mortality in Finland and Estonia, where sauna is part of the culture and is typically practiced at least once a week, with the rest of Europe. Authors found significantly lower mortality with sauna culture, and suggest this may be due to the beneficial effects of hydrothermotherapy.

Ruble compared army hospital vs. sanitarium treatment of the 1918 Spanish influenza, showing lower progression to pneumonia and lower mortality with sanitarium treatment, which involves hydrothermotherapy, sunlight, and fresh air.

In summary, fever is a key component of the acute phase response to infection. Fever enhances immune cell performance, induces cellular stress on pathogens, and may act synergistically with other stressors like iron deprivation. While results show beneficial effects of fever, we note that it is not universally beneficial, for example extreme and prolonged cases may be harmful.

Fever may also reduce transmissibility. Fever helps clear infection faster by enhancing immune responses and applying cellular stress to pathogens. Faster clearance gives the pathogen less time to amplify within the host to reach contagious levels. Fever may also apply evolutionary pressure resulting in sacrificing replicative fitness at normal temperatures, minimizing infection in other hosts. Further, fever promotes reduced activity, minimizing the opportunity for transmission.

The beneficial effects of fever suggest potential harm from fever-reducing medications in terms of an increased risk of poor outcomes and increased transmission. However, these may be offset by other effects of specific medications, including anticoagulant, anti-inflammatory, or antiviral effects. Notably, studies for COVID-19 show significantly increased risk with acetaminophen *c19early.org (C)*.

Results

Table 1 summarizes the results for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, after exclusions, and for specific outcomes. Table 2 shows results by treatment stage. Figure 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, ICU admission, hospitalization, progression, recovery, cases, peer reviewed studies, and non-symptomatic vs. symptomatic results.

	Improvement	Studies	Patients	Authors
All studies	**0%** [-9-9%]	13	54,707	485
After exclusions	**0%** [-9-9%]	12	54,310	479
Peer-reviewed studies	**-0%** [-10-9%]	12	43,233	462
Randomized Controlled Trials	**52%** [5-76%] *	1	180	6
Mortality	**-2%** [-26-17%]	8	50,525	444
ICU admission	**23%** [-118-73%]	2	583	11
Hospitalization	**4%** [-34-32%]	3	577	21
Cases	**-1%** [-11-9%]	2	0	14

Table 1. **Random effects meta-analysis for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, after exclusions, and for specific outcomes.** Results show the percentage improvement with treatment and the 95% confidence interval. * $p<0.05$.

	Early treatment	Late treatment	Prophylaxis
All studies	**-52%** [-351-48%]	**52%** [5-76%] *	**-1%** [-10-8%]
After exclusions	**-21%** [-338-67%]	**52%** [5-76%] *	**-1%** [-10-8%]
Peer-reviewed studies	**-52%** [-351-48%]	**52%** [5-76%] *	**-1%** [-11-8%]
Randomized Controlled Trials		**52%** [5-76%] *	
Mortality	**-52%** [-351-48%]		**-0%** [-25-19%]
ICU admission	**-40%** [-281-49%]	**52%** [5-76%] *	
Hospitalization	**-18%** [-136-41%]	**26%** [6-42%] *	**-12%** [-38-8%]
Cases			**-1%** [-11-9%]

Table 2. **Random effects meta-analysis results by treatment stage.** Results show the percentage improvement with treatment, the 95% confidence interval, and the number of studies for the stage. * $p<0.05$.

13 ibuprofen COVID-19 studies

	Improvement, RR [CI]			Treatment	Control		
Rinott	-21%	1.21 [0.33-4.38]	death	3/87	9/316		
Abu Esba	-170%	2.70 [0.33-22.0]	death	1/40	11/357		
Early treatment	**-52%**	**1.52 [0.52-4.51]**		**4/127**	**20/673**		52% higher risk

Tau² = 0.00, I² = 0.0%, p = 0.45

	Improvement, RR [CI]			Treatment	Control		
Sobhy (DB RCT)	52%	0.48 [0.24-0.95]	ICU	10/90	21/90		OT[1]
Late treatment	**52%**	**0.48 [0.24-0.95]**		**10/90**	**21/90**		52% lower risk

Tau² = 0.00, I² = 0.0%, p = 0.036

	Improvement, RR [CI]			Treatment	Control		
Choi (PSM)	-240%	3.40 [0.64-18.1]	progression	case control			
Samimagham	-100%	2.00 [1.33-3.02]	death	63 (n)	95 (n)		
Kragholm	4%	0.96 [0.72-1.23]	progression	264 (n)	3,738 (n)		
Wong	-23%	1.23 [0.90-1.68]	death	population-based cohort			
Reese (PSM)	9%	0.91 [0.62-1.35]	death	5,737 (n)	5,737 (n)		
Drake	10%	0.90 [0.71-1.13]	death	n/a	n/a		
Leal	3%	0.97 [0.94-1.00]	cases	n/a	n/a		
Campbell (PSW)	0%	1.00 [0.99-1.01]	death	1,814 (n)	20,311 (n)		
Xie	-12%	1.12 [0.92-1.38]	hosp.	population-based cohort			OT[1]
Loucera	48%	0.52 [0.34-0.78]	death	519 (n)	15,449 (n)		
Prophylaxis	**-1%**	**1.01 [0.92-1.10]**		**8,397 (n)**	**45,330 (n)**		1% higher risk

Tau² = 0.01, I² = 68.3%, p = 0.9

All studies	**0%**	**1.00 [0.91-1.09]**		**14/8,614**	**41/46,093**		0% lower risk

[1] OT: comparison with other treatment

Tau² = 0.01, I² = 64.4%, p = 0.96

Effect extraction pre-specified
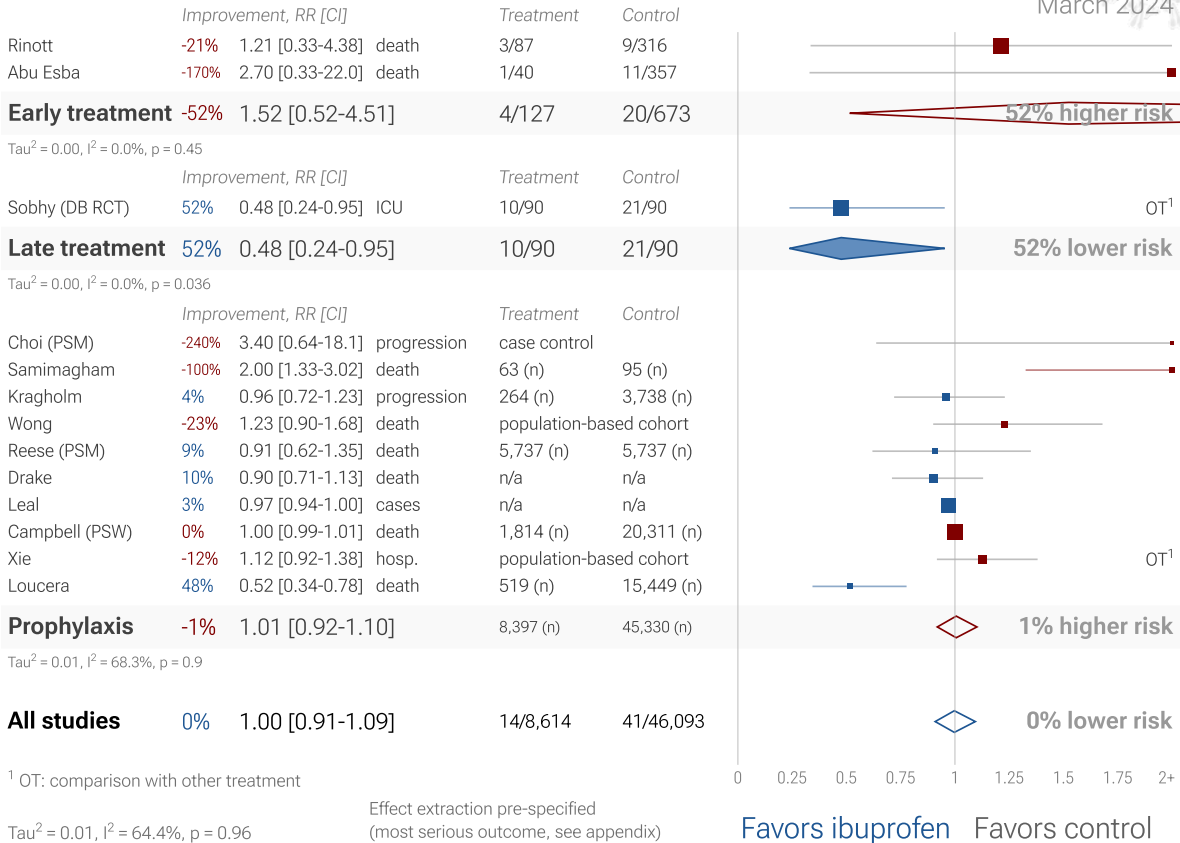(most serious outcome, see appendix)

Favors ibuprofen   Favors control

Figure 5. Random effects meta-analysis for all studies with pooled effects. This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.
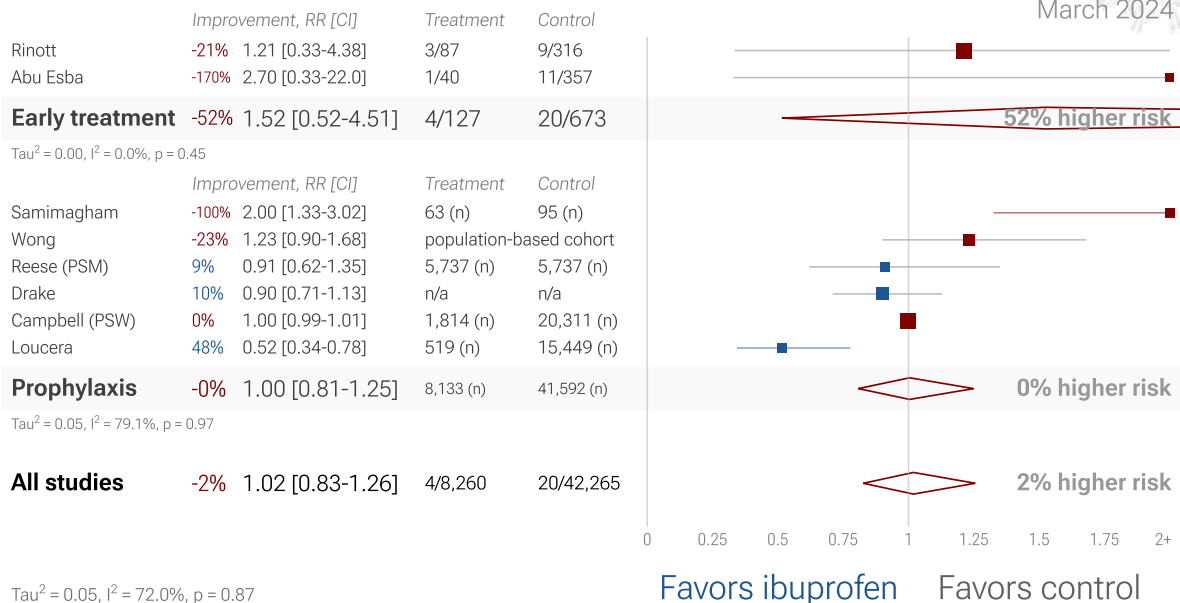
8 ibuprofen COVID-19 mortality results

	Improvement, RR [CI]		Treatment	Control		
Rinott	-21%	1.21 [0.33-4.38]	3/87	9/316		
Abu Esba	-170%	2.70 [0.33-22.0]	1/40	11/357		
Early treatment	-52%	1.52 [0.52-4.51]	4/127	20/673		52% higher risk

Tau² = 0.00, I² = 0.0%, p = 0.45

	Improvement, RR [CI]		Treatment	Control		
Samimagham	-100%	2.00 [1.33-3.02]	63 (n)	95 (n)		
Wong	-23%	1.23 [0.90-1.68]	population-based cohort			
Reese (PSM)	9%	0.91 [0.62-1.35]	5,737 (n)	5,737 (n)		
Drake	10%	0.90 [0.71-1.13]	n/a	n/a		
Campbell (PSW)	0%	1.00 [0.99-1.01]	1,814 (n)	20,311 (n)		
Loucera	48%	0.52 [0.34-0.78]	519 (n)	15,449 (n)		
Prophylaxis	-0%	1.00 [0.81-1.25]	8,133 (n)	41,592 (n)		0% higher risk

Tau² = 0.05, I² = 79.1%, p = 0.97

All studies	-2%	1.02 [0.83-1.26]	4/8,260	20/42,265		2% higher risk

Tau² = 0.05, I² = 72.0%, p = 0.87

Favors ibuprofen   Favors control

Figure 6. Random effects meta-analysis for mortality results.

1 ibuprofen COVID-19 mechanical ventilation result

	Improvement, RR [CI]		Treatment	Control
Rinott	-12%	1.12 [0.37-3.34]	4/87	13/316
Early treatment	-12%	1.12 [0.37-3.34]	4/87	13/316

Tau² = 0.00, I² = 0.0%, p = 0.85

All studies	-12%	1.12 [0.37-3.34]	4/87	13/316

12% higher risk

12% higher risk

Tau² = 0.00, I² = 0.0%, p = 0.85

Favors ibuprofen   Favors control
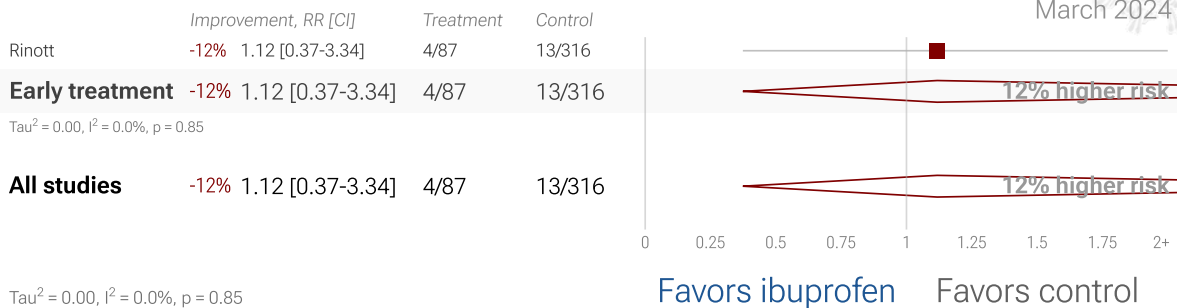
Figure 7. Random effects meta-analysis for ventilation.

2 ibuprofen COVID-19 ICU results

	Improvement, RR [CI]		Treatment	Control
Rinott	-40%	1.40 [0.51-3.81]	5/87	13/316
Early treatment	-40%	1.40 [0.51-3.81]	5/87	13/316

40% higher risk

Tau² = 0.00, I² = 0.0%, p = 0.52

	Improvement, RR [CI]		Treatment	Control
Sobhy (DB RCT)	52%	0.48 [0.24-0.95]	10/90	21/90
Late treatment	52%	0.48 [0.24-0.95]	10/90	21/90

OT¹

52% lower risk

Tau² = 0.00, I² = 0.0%, p = 0.036

All studies	23%	0.77 [0.27-2.18]	15/177	34/406

23% lower risk

¹ OT: comparison with other treatment

Tau² = 0.39, I² = 66.5%, p = 0.63

Favors ibuprofen   Favors control

Figure 8. Random effects meta-analysis for ICU admission.

3 ibuprofen COVID-19 hospitalization results

	Improvement, RR [CI]		Treatment	Control
Abu Esba	-18%	1.18 [0.59-2.36] hosp.	40 (n)	357 (n)
Early treatment	-18%	1.18 [0.59-2.36]	40 (n)	357 (n)

18% higher risk

Tau² = 0.00, I² = 0.0%, p = 0.64

	Improvement, RR [CI]		Treatment	Control
Sobhy (DB RCT)	26%	0.74 [0.58-0.94] hosp. time	90 (n)	90 (n)
Late treatment	26%	0.74 [0.58-0.94]	90 (n)	90 (n)

OT¹

26% lower risk

Tau² = 0.00, I² = 0.0%, p = 0.013

	Improvement, RR [CI]		Treatment	Control
Xie	-12%	1.12 [0.92-1.38] hosp.	population-based cohort	
Prophylaxis	-12%	1.12 [0.92-1.38]		

OT¹

12% higher risk

Tau² = 0.00, I² = 0.0%, p = 0.26

All studies	4%	0.96 [0.68-1.34]	130 (n)	447 (n)

4% lower risk

¹ OT: comparison with other treatment

Tau² = 0.06, I² = 72.6%, p = 0.81

Favors ibuprofen   Favors control

Figure 9. Random effects meta-analysis for hospitalization.

3 ibuprofen COVID-19 progression results

	Improvement, RR [CI]		Treatment	Control
Choi (PSM)	-240%	3.40 [0.64-18.1]	case control	
Samimagham	-13%	1.13 [1.02-1.25]	60/63	80/95
Kragholm	4%	0.96 [0.72-1.23]	264 (n)	3,738 (n)
Prophylaxis	-9%	1.09 [0.91-1.31]	60/327	80/3,833

Tau² = 0.01, I² = 32.7%, p = 0.37

All studies	-9%	1.09 [0.91-1.31]	60/327	80/3,833

9% higher risk

9% higher risk

Tau² = 0.01, I² = 32.7%, p = 0.37

Favors ibuprofen   Favors control
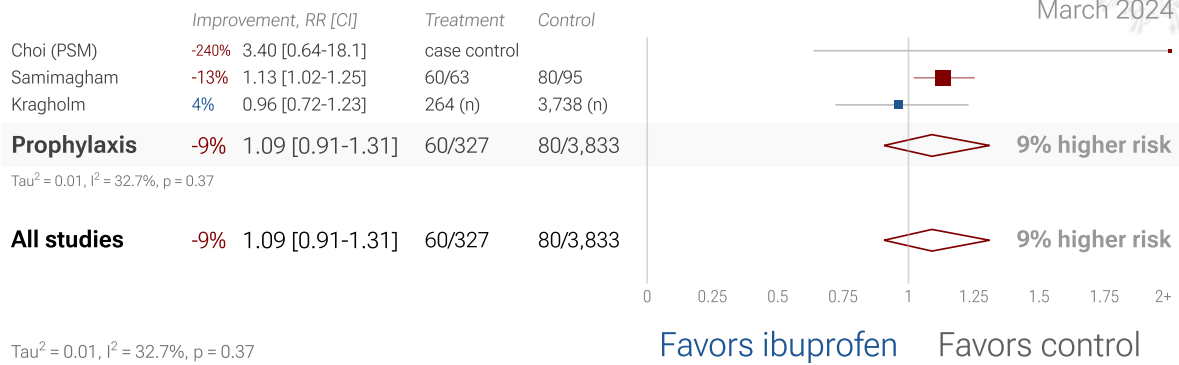
Figure 10. Random effects meta-analysis for progression.

1 ibuprofen COVID-19 recovery result

	Improvement, RR [CI]		Treatment	Control
Sobhy (DB RCT)	25%	0.75 [0.17-3.26] no recov.	3/90	4/90
Late treatment	25%	0.75 [0.17-3.26]	3/90	4/90

OT[1]

25% lower risk

Tau² = 0.00, I² = 0.0%, p = 0.71

All studies	25%	0.75 [0.17-3.26]	3/90	4/90

25% lower risk

[1] OT: comparison with other treatment

Tau² = 0.00, I² = 0.0%, p = 0.71

Favors ibuprofen   Favors control
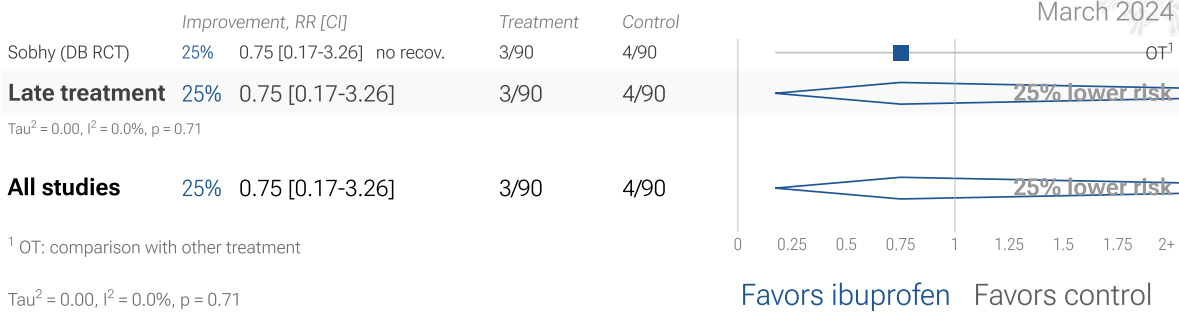
Figure 11. Random effects meta-analysis for recovery.

2 ibuprofen COVID-19 case results

	Improvement, RR [CI]		Treatment	Control
Leal	3%	0.97 [0.94-1.00] cases	n/a	n/a
Xie	-8%	1.08 [0.95-1.22] cases	population-based cohort	
Prophylaxis	-1%	1.01 [0.91-1.11]		

OT[1]

1% higher risk

Tau² = 0.00, I² = 55.0%, p = 0.91

All studies	-1%	1.01 [0.91-1.11]	

1% higher risk

[1] OT: comparison with other treatment

Tau² = 0.00, I² = 55.0%, p = 0.91

Favors ibuprofen   Favors control

Figure 12. Random effects meta-analysis for cases.

12 ibuprofen COVID-19 peer reviewed studies

	Improvement, RR [CI]			Treatment	Control
Rinott	-21%	1.21 [0.33-4.38]	death	3/87	9/316
Abu Esba	-170%	2.70 [0.33-22.0]	death	1/40	11/357
Early treatment	**-52%**	**1.52 [0.52-4.51]**		**4/127**	**20/673**

Tau² = 0.00, I² = 0.0%, p = 0.45

	Improvement, RR [CI]			Treatment	Control
Sobhy (DB RCT)	52%	0.48 [0.24-0.95]	ICU	10/90	21/90
Late treatment	**52%**	**0.48 [0.24-0.95]**		**10/90**	**21/90**

Tau² = 0.00, I² = 0.0%, p = 0.036

	Improvement, RR [CI]			Treatment	Control
Choi (PSM)	-240%	3.40 [0.64-18.1]	progression	case control	
Samimagham	-100%	2.00 [1.33-3.02]	death	63 (n)	95 (n)
Kragholm	4%	0.96 [0.72-1.23]	progression	264 (n)	3,738 (n)
Wong	-23%	1.23 [0.90-1.68]	death	population-based cohort	
Drake	10%	0.90 [0.71-1.13]	death	n/a	n/a
Leal	3%	0.97 [0.94-1.00]	cases	n/a	n/a
Campbell (PSW)	0%	1.00 [0.99-1.01]	death	1,814 (n)	20,311 (n)
Xie	-12%	1.12 [0.92-1.38]	hosp.	population-based cohort	
Loucera	48%	0.52 [0.34-0.78]	death	519 (n)	15,449 (n)
Prophylaxis	**-1%**	**1.01 [0.92-1.11]**		**2,660 (n)**	**39,593 (n)**

Tau² = 0.01, I² = 71.6%, p = 0.83

All studies	**-0%**	**1.00 [0.91-1.10]**		**14/2,877**	**41/40,356**

[1] OT: comparison with other treatment

Tau² = 0.01, I² = 67.2%, p = 0.97

Effect extraction pre-specified
(most serious outcome, see appendix)

Figure 13. Random effects meta-analysis for peer reviewed studies. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding no significant evidence that preprint results are inconsistent with peer-reviewed studies. They also show extremely long peer-review delays, with a median of 6 months to journal publication. A six month delay was equivalent to around 1.5 million deaths during the first two years of the pandemic. Authors recommend using preprint evidence, with appropriate checks for potential falsified data, which provides higher certainty much earlier. *Davidson et al.* also showed no important difference between meta analysis results of preprints and peer-reviewed publications for COVID-19, based on 37 meta analyses including 114 trials.

14 ibuprofen COVID-19 symptomatic vs. case outcomes

	Improvement, RR [CI]			Treatment	Control	
Choi (PSM)	-240%	3.40 [0.64-18.1]	progression	case control		
Samimagham	-100%	2.00 [1.33-3.02]	death	63 (n)	95 (n)	
Rinott	-21%	1.21 [0.33-4.38]	death	3/87	9/316	
Kragholm	4%	0.96 [0.72-1.23]	progression	264 (n)	3,738 (n)	
Abu Esba	-170%	2.70 [0.33-22.0]	death	1/40	11/357	
Wong	-23%	1.23 [0.90-1.68]	death	population-based cohort		
Reese (PSM)	9%	0.91 [0.62-1.35]	death	5,737 (n)	5,737 (n)	
Drake	10%	0.90 [0.71-1.13]	death	n/a	n/a	
Campbell (PSW)	0%	1.00 [0.99-1.01]	death	1,814 (n)	20,311 (n)	
Xie	-12%	1.12 [0.92-1.38]	hosp.	population-based cohort		OT[1]
Loucera	48%	0.52 [0.34-0.78]	death	519 (n)	15,449 (n)	
Sobhy (DB RCT)	52%	0.48 [0.24-0.95]	ICU	10/90	21/90	OT[1]
Symptomatic	**-0%**	**1.00 [0.86-1.17]**		14/8,614	41/46,093	**0% higher risk**

Tau^2 = 0.03, I^2 = 66.4%, p = 0.97

	Improvement, RR [CI]			Treatment	Control	
Leal	3%	0.97 [0.94-1.00]	cases	n/a	n/a	
Xie	-8%	1.08 [0.95-1.22]	cases	population-based cohort		OT[1]
Cases	**-1%**	**1.01 [0.91-1.11]**				**1% higher risk**

Tau^2 = 0.00, I^2 = 55.0%, p = 0.91

All studies	**-1%**	**1.01 [0.93-1.09]**		14/8,614	41/46,093	**1% higher risk**

[1] OT: comparison with other treatment

Tau^2 = 0.01, I^2 = 63.1%, p = 0.85

Effect extraction pre-specified
(most serious outcome, see appendix)

0   0.25   0.5   0.75   1   1.25   1.5   1.75   2+

Favors ibuprofen   Favors control

Figure 14. Random effects meta-analysis for non-symptomatic vs. symptomatic results. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details.

Randomized Controlled Trials (RCTs)

Figure 15 shows a forest plot for random effects meta-analysis of all Randomized Controlled Trials. RCT results are included in Table 1 and Table 2. Currently there is only one RCT.

RCTs have many potential biases. Bias in clinical research may be defined as something that tends to make conclusions differ systematically from the truth. RCTs help to make study groups more similar and can provide a higher level of evidence, however they are subject to many biases *Jadad*, and analysis of double-blind RCTs has identified extreme levels of bias *Gøtzsche*. For COVID-19, the overhead may delay treatment, dramatically compromising efficacy; they may encourage monotherapy for simplicity at the cost of efficacy which may rely on combined or synergistic effects; the participants that sign up may not reflect real world usage or the population that benefits most in terms of age, comorbidities, severity of illness, or other factors; standard of care may be compromised and unable to evolve quickly based on emerging research for new diseases; errors may be made in randomization and medication delivery; and investigators may have hidden agendas or vested interests influencing design, operation, analysis, and the potential for fraud. All of these biases have been observed with COVID-19 RCTs. There is no guarantee that a specific RCT provides a higher level of evidence.

Conflicts of interest for COVID-19 RCTs. RCTs are expensive and many RCTs are funded by pharmaceutical companies or interests closely aligned with pharmaceutical companies. For COVID-19, this creates an incentive to show efficacy for patented commercial products, and an incentive to show a lack of efficacy for inexpensive treatments. The bias is expected to be significant, for example *Als-Nielsen et al.* analyzed 370 RCTs from Cochrane reviews, showing that trials funded by for-profit organizations were 5 times more likely to recommend the experimental drug compared with those funded by nonprofit organizations. For COVID-19, some major philanthropic organizations are largely funded by investments with extreme conflicts of interest for and against specific COVID-19 interventions.

RCTs for novel acute diseases requiring rapid treatment. High quality RCTs for novel acute diseases are more challenging, with increased ethical issues due to the urgency of treatment, increased risk due to enrollment delays, and more difficult design with a rapidly evolving evidence base. For COVID-19, the most common site of initial infection is the upper respiratory tract. Immediate treatment is likely to be most successful and may prevent or slow progression to other parts of the body. For a non-prophylaxis RCT, it makes sense to provide treatment in advance and instruct patients to use it immediately on symptoms, just as some governments have done by providing medication kits in advance. Unfortunately, no RCTs have been done in this way. Every treatment RCT to date involves delayed treatment. Among the 66 treatments we have analyzed, 63% of RCTs involve very late treatment 5+ days after onset. No non-prophylaxis COVID-19 RCTs match the potential real-world use of early treatments (they may more accurately represent results for treatments that require visiting a medical facility, e.g., those requiring intravenous administration).

Non-RCT studies have been shown to be reliable. Evidence shows that non-RCT trials can also provide reliable results. *Concato et al.* found that well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment compared to RCTs. *Anglemyer et al.* summarized reviews comparing RCTs to observational studies and found little evidence for significant differences in effect estimates. *Lee et al.* showed that only 14% of the guidelines of the Infectious Diseases Society of America were based on RCTs. Evaluation of studies relies on an understanding of the study and potential biases. Limitations in an RCT can outweigh the benefits, for example excessive dosages, excessive treatment delays, or Internet survey bias could have a greater effect on results. Ethical issues may also prevent running RCTs for known effective treatments. For more on issues with RCTs see *Deaton, Nichol*.

Using all studies identifies efficacy 5.7+ months faster for COVID-19. Currently, 44 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. Of the 44 treatments with statistically significant efficacy/harm, 28 have been confirmed in RCTs, with a mean delay of 5.7 months. When considering only low cost treatments, 23 have been confirmed with a delay of 6.9 months. For the 16 unconfirmed treatments, 3 have zero RCTs to date. The point estimates for the remaining 13 are all consistent with the overall results (benefit or harm), with 10 showing >20%. The only treatments showing >10% efficacy for all studies, but <10% for RCTs are sotrovimab and aspirin.

Summary. We need to evaluate each trial on its own merits. RCTs for a given medication and disease may be more reliable, however they may also be less reliable. For off-patent medications, very high conflict of interest trials may be more likely to be RCTs, and more likely to be large trials that dominate meta analyses.

1 ibuprofen COVID-19 Randomized Controlled Trials

c19early.org
March 2024

	Improvement, RR [CI]			Treatment	Control		
Sobhy (DB RCT)	52%	0.48 [0.24-0.95]	ICU	10/90	21/90		OT[1]
Late treatment	52%	0.48 [0.24-0.95]		10/90	21/90		**52% lower risk**
Tau² = 0.00, I² = 0.0%, p = 0.036							
All studies	52%	0.48 [0.24-0.95]		10/90	21/90		**52% lower risk**

[1] OT: comparison with other treatment

Tau² = 0.00, I² = 0.0%, p = 0.036

Effect extraction pre-specified
(most serious outcome, see appendix)

0   0.25   0.5   0.75   1   1.25   1.5   1.75   2+

Favors ibuprofen   Favors control

Figure 15. Random effects meta-analysis for all Randomized Controlled Trials. This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

Exclusions

To avoid bias in the selection of studies, we analyze all non-retracted studies. Here we show the results after excluding studies with major issues likely to alter results, non-standard studies, and studies where very minimal detail is currently available. Our bias evaluation is based on analysis of each study and identifying when there is a significant chance that limitations will substantially change the outcome of the study. We believe this can be more valuable than checklist-based approaches such as Cochrane GRADE, which may underemphasize serious issues not captured in the checklists, overemphasize issues unlikely to alter outcomes in specific cases (for example, lack of blinding for an objective mortality outcome, or certain specifics of randomization with a very large effect size), and can be easily influenced by potential bias.

The studies excluded are as below. Figure 16 shows a forest plot for random effects meta-analysis of all studies after exclusions.

Abu Esba, substantial unadjusted confounding by indication likely.

12 ibuprofen COVID-19 studies after exclusions

c19early.org
March 2024

	Improvement, RR [CI]			Treatment	Control	
Rinott	-21%	1.21 [0.33-4.38]	death	3/87	9/316	
Early treatment	**-21%**	1.21 [0.33-4.38]		**3/87**	**9/316**	**21% higher risk**

Tau^2 = 0.00, I^2 = 0.0%, p = 0.78

	Improvement, RR [CI]			Treatment	Control	
Sobhy (DB RCT)	52%	0.48 [0.24-0.95]	ICU	10/90	21/90	OT[1]
Late treatment	**52%**	0.48 [0.24-0.95]		**10/90**	**21/90**	**52% lower risk**

Tau^2 = 0.00, I^2 = 0.0%, p = 0.036

	Improvement, RR [CI]			Treatment	Control	
Choi (PSM)	-240%	3.40 [0.64-18.1]	progression	case control		
Samimagham	-100%	2.00 [1.33-3.02]	death	63 (n)	95 (n)	
Kragholm	4%	0.96 [0.72-1.23]	progression	264 (n)	3,738 (n)	
Wong	-23%	1.23 [0.90-1.68]	death	population-based cohort		
Reese (PSM)	9%	0.91 [0.62-1.35]	death	5,737 (n)	5,737 (n)	
Drake	10%	0.90 [0.71-1.13]	death	n/a	n/a	
Leal	3%	0.97 [0.94-1.00]	cases	n/a	n/a	
Campbell (PSW)	0%	1.00 [0.99-1.01]	death	1,814 (n)	20,311 (n)	
Xie	-12%	1.12 [0.92-1.38]	hosp.	population-based cohort		OT[1]
Loucera	48%	0.52 [0.34-0.78]	death	519 (n)	15,449 (n)	
Prophylaxis	**-1%**	1.01 [0.92-1.10]		8,397 (n)	45,330 (n)	**1% higher risk**

Tau^2 = 0.01, I^2 = 68.3%, p = 0.9

				Treatment	Control	
All studies	**0%**	1.00 [0.91-1.09]		**13/8,574**	**30/45,736**	**0% lower risk**

[1] OT: comparison with other treatment

Tau^2 = 0.01, I^2 = 66.5%, p = 0.93

Effect extraction pre-specified
(most serious outcome, see appendix)

Favors ibuprofen   Favors control

Figure 16. Random effects meta-analysis for all studies after exclusions. This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

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 [McLean, Treanor]. Baloxavir studies for influenza also show that treatment delay is critical — *Ikematsu* report an 86% reduction in cases for post-exposure prophylaxis, *Hayden* 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* report only 2.5 hours improvement for inpatient treatment.

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

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

Figure 17 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 66 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.
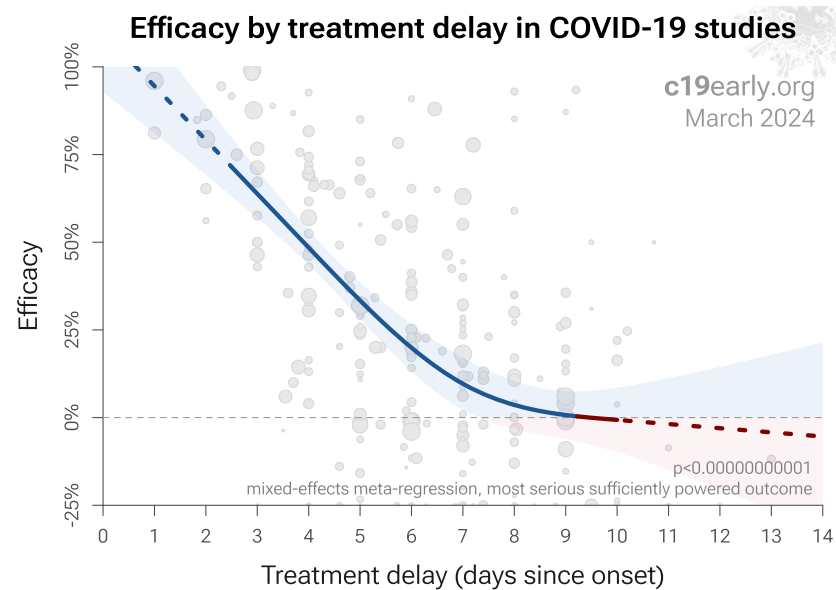
Figure 17. Early treatment is more effective. Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 66 treatments.

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 (as in *López-Medina*).

Effect measured. Efficacy may differ significantly depending on the effect measured, for example a treatment may be very effective at reducing mortality, but less effective at minimizing cases or hospitalization. Or a treatment may have no effect on viral clearance while still being effective at reducing mortality.

Variants. There are many different variants of SARS-CoV-2 and efficacy may depend critically on the distribution of variants encountered by the patients in a study. For example, the Gamma variant shows significantly different characteristics *Faria, Karita, Nonaka, Zavascki*. Different mechanisms of action may be more or less effective depending on variants, for example the viral entry process for the omicron variant has moved towards TMPRSS2-independent fusion, suggesting that TMPRSS2 inhibitors may be less effective *Peacock, Willett*.

Regimen. Effectiveness may depend strongly on the dosage and treatment regimen.

Other treatments. The use of other treatments may significantly affect outcomes, including anything from supplements, other medications, or other kinds of treatment such as prone positioning.

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

Pooled outcome analysis. We present both pooled analyses and specific outcome analyses. Notably, pooled analysis often results in earlier detection of efficacy as shown in Figure 18. For many COVID-19 treatments, a reduction in mortality logically follows from a reduction in hospitalization, which follows from a reduction in symptomatic cases, etc. An antiviral tested with a low-risk population may report zero mortality in both arms, however a reduction in severity and improved viral clearance may translate into lower mortality among a high-risk population, and including these results in pooled analysis allows faster detection of efficacy. Trials with high-risk patients may also be restricted due to ethical concerns for treatments that are known or expected to be effective.

Pooled analysis enables using more of the available information. While there is much more information available, for example dose-response relationships, the advantage of the method used here is simplicity and transparency. Note that pooled analysis could hide efficacy, for example a treatment that is beneficial for late stage patients but has no effect on viral replication or early stage disease could show no efficacy in pooled analysis if most studies only examine viral clearance. While we present pooled results, we also present individual outcome analyses, which may be more informative for specific use cases.

Pooled outcomes identify efficacy faster. Currently, 44 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 88% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 3.6 months. When restricting to RCTs only, 50% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 6.1 months.
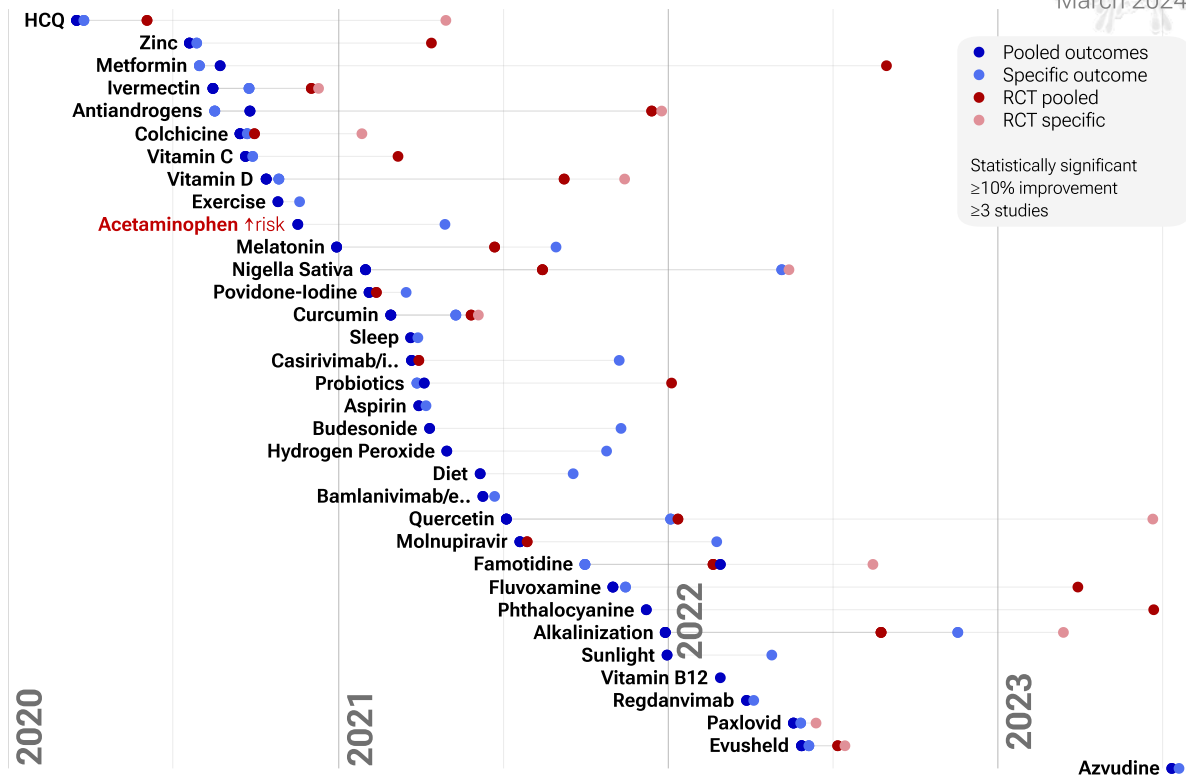
Figure 18. The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies. Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

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. This may have a greater effect than pooling different outcomes such as mortality and hospitalization. For example a treatment may have 50% efficacy for mortality but only 40% for hospitalization when used within 48 hours. However efficacy could be 0% when used late.

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.

Discussion

Publication bias. Publishing is often biased towards positive results, however evidence suggests that there may be a negative bias for inexpensive treatments for COVID-19. Both negative and positive results are very important for COVID-19, media in many countries prioritizes negative results for inexpensive treatments (inverting the typical

incentive for scientists that value media recognition), and there are many reports of difficulty publishing positive results *Boulware, Meeus, Meneguesso*. For ibuprofen, there is currently not enough data to evaluate publication bias with high confidence.

Funnel plot analysis. Funnel plots have traditionally been used for analyzing publication bias. This is invalid for COVID-19 acute treatment trials — the underlying assumptions are invalid, which we can demonstrate with a simple example. Consider a set of hypothetical perfect trials with no bias. Figure 19 plot A shows a funnel plot for a simulation of 80 perfect trials, with random group sizes, and each patient's outcome randomly sampled (10% control event probability, and a 30% effect size for treatment). Analysis shows no asymmetry (p > 0.05). In plot B, we add a single typical variation in COVID-19 treatment trials — treatment delay. Consider that efficacy varies from 90% for treatment within 24 hours, reducing to 10% when treatment is delayed 3 days. In plot B, each trial's treatment delay is randomly selected. Analysis now shows highly significant asymmetry, *p* < 0.0001, with six variants of Egger's test all showing p < 0.05 *Egger, Harbord, Macaskill, Moreno, Peters, Rothstein, Rücker, Stanley*. Note that these tests fail even though treatment delay is uniformly distributed. In reality treatment delay is more complex — each trial has a different distribution of delays across patients, and the distribution across trials may be biased (e.g., late treatment trials may be more common). Similarly, many other variations in trials may produce asymmetry, including dose, administration, duration of treatment, differences in SOC, comorbidities, age, variants, and bias in design, implementation, analysis, and reporting.
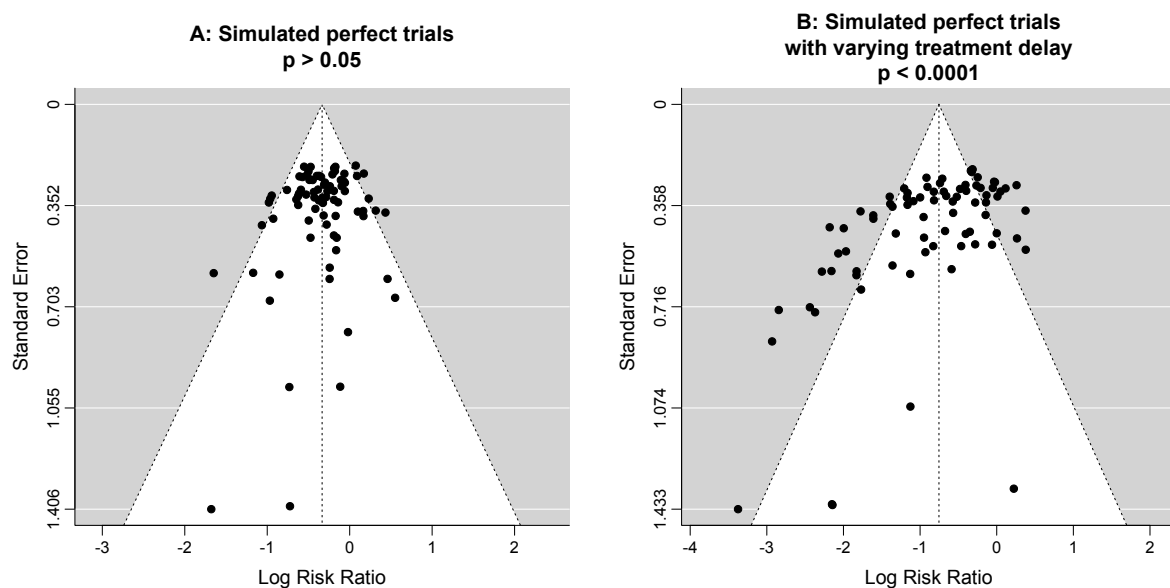
Figure 19. Example funnel plot analysis for simulated perfect trials.

Conflicts of interest. Pharmaceutical drug trials often have conflicts of interest whereby sponsors or trial staff have a financial interest in the outcome being positive. Ibuprofen for COVID-19 lacks this because it is off-patent, has multiple manufacturers, and is very low cost. In contrast, most COVID-19 ibuprofen trials have been run by physicians on the front lines with the primary goal of finding the best methods to save human lives and minimize the collateral damage caused by COVID-19. While pharmaceutical companies are careful to run trials under optimal conditions (for example, restricting patients to those most likely to benefit, only including patients that can be treated soon after onset when necessary, and ensuring accurate dosing), not all ibuprofen trials represent the optimal conditions for efficacy.

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 by 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 affiliated with special interests 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 *Alsaidi, Andreani, De Forni, Fiaschi, Jeffreys, Jitobaom, Jitobaom (B), Ostrov, Said, Thairu, Wan*. 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, vaccine, 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.

Notes. 2 of the 13 studies compare against other treatments, which may reduce the effect seen.

Reviews. Multiple reviews cover ibuprofen for COVID-19, presenting additional background on mechanisms and related results, including *Day, Moshawih*.

Conclusion

Meta analysis using the most serious outcome reported shows 0% [-9-9%] lower risk, without reaching statistical significance. 4 studies from 4 independent teams in 4 countries show statistically significant improvements.

Concerns have been raised over potential harm with the use of ibuprofen for COVID-19 *Day* due to the suppression of beneficial immune and inflammatory responses during early infection, ACE2 upregulation, and delaying further care. There is limited clinical data currently, especially with regard to acute usage at onset of infection, however current results suggest harm with early treatment and benefit with late treatment.

Study Notes

Abu Esba

Ibuprofen *Abu Esba et al.* EARLY TREATMENT

	Improvement	Relative Risk
Mortality	-170%	
Mortality (b)	37%	
Oxygen therapy	-45%	
Hospitalization	-18%	
Severe case	-85%	

0   0.5   1   1.5   2+
Favors ibuprofen   Favors control

Is early treatment with ibuprofen beneficial for COVID-19?
Prospective study of 397 patients in Saudi Arabia (Apr - Jun 2020)
Higher mortality *(p=0.35)* and severe cases *(p=0.42)*, not sig.

c19early.org   Abu Esba et al., Infectious Diseases a.., Nov 2020

Abu Esba: Prospective study of 503 COVID-19 cases in Saudi Arabia, 40 using ibuprofen during infection, and 357 not using NSAIDs, showing no significant differences in outcomes. Results are subject to confounding by indication.

Campbell

Ibuprofen for COVID-19 *Campbell et al.* Prophylaxis

	Improvement	Relative Risk
Mortality, day 60	0%	
Mortality, day 30	1%	

0   0.5   1   1.5   2+
Favors ibuprofen   Favors control

Is prophylaxis with ibuprofen beneficial for COVID-19?
Retrospective 22,125 patients in the USA (March - December 2020)
No significant difference in mortality

c19early.org   Campbell et al., PLOS ONE, May 2022
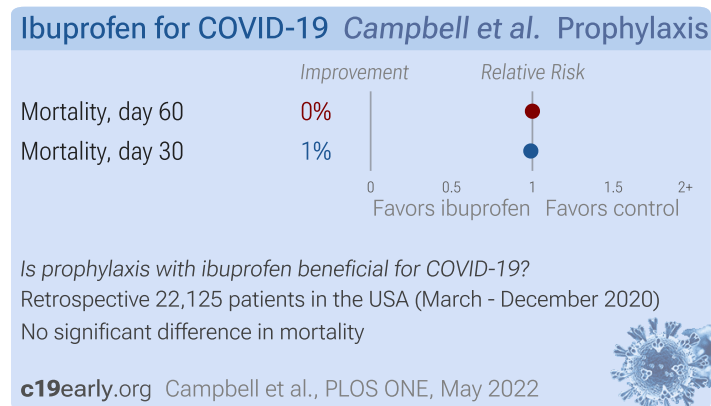
Campbell: Retrospective 28,856 COVID-19 patients in the USA, showing no significant difference in mortality for chronic ibuprofen use vs. sporadic NSAID use. Since ibuprofen is available OTC and authors only tracked prescriptions, many patients classified as sporadic users may have been chronic users.

Choi

Ibuprofen for COVID-19 *Choi et al.* Prophylaxis

	Improvement	Relative Risk
Progression	-240%	

0   0.5   1   1.5   2+
Favors ibuprofen   Favors control

Is prophylaxis with ibuprofen beneficial for COVID-19?
PSM retrospective 72 patients in South Korea (Mar - Mar 2020)
Higher progression with ibuprofen *(not stat. sig., p=0.26)*

c19early.org   Choi et al., J. Clinical Medicine, Jun 2020
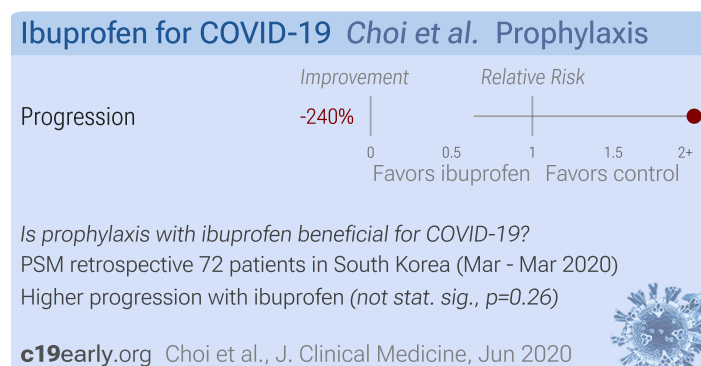
Choi: Retrospective 293 patients in South Korea, showing higher risk of progression with ibuprofen use, without statistical significance.

Drake

Ibuprofen for COVID-19 *Drake et al.* **Prophylaxis**

	Improvement	Relative Risk
Mortality	10%	

0   0.5   1   1.5   2+
Favors ibuprofen   Favors control

Is prophylaxis with ibuprofen beneficial for COVID-19?
Prospective study in the United Kingdom (January - August 2020)
No significant difference in mortality

c19early.org   Drake et al., The Lancet Rheumatology, Jul 2021
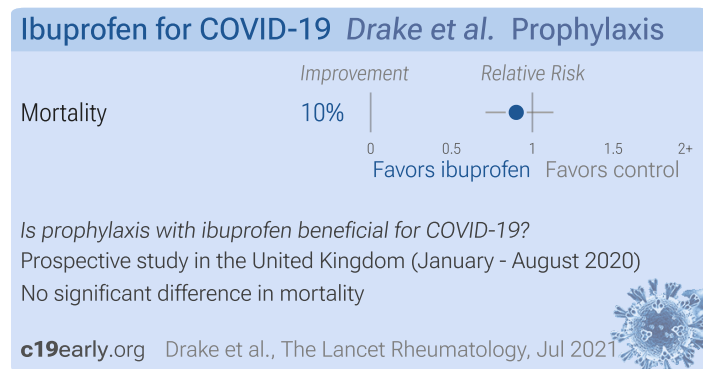
Drake: Prospective study of 78,674 COVID-19 patients, showing no significant difference in mortality with ibuprofen use.

Kragholm

Ibuprofen for COVID-19 *Kragholm et al.* **Prophylaxis**

	Improvement	Relative Risk
Progression	4%	

0   0.5   1   1.5   2+
Favors ibuprofen   Favors control

Is prophylaxis with ibuprofen beneficial for COVID-19?
Retrospective 4,002 patients in Denmark (January - April 2020)
No significant difference in progression

c19early.org   Kragholm et al., Clinical and Translat.., Oct 2020
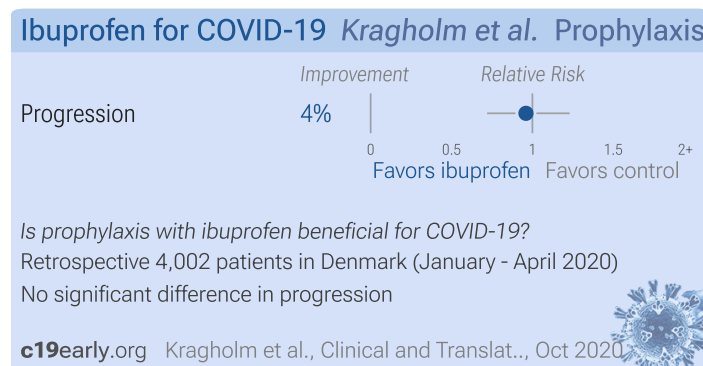
Kragholm: Retrospective 4,002 COVID-19 patients in Denmark, 264 with ibuprofen prescriptions, showing no significant difference for COVID-19 severity.

Leal

Ibuprofen for COVID-19 *Leal et al.* **Prophylaxis**

	Improvement	Relative Risk
Case	3%	

0   0.5   1   1.5   2+
Favors ibuprofen   Favors control

Does ibuprofen reduce COVID-19 infections?
Retrospective study in the United Kingdom (March 2020 - February 2021)
No significant difference in cases

c19early.org Leal et al., COVID, August 2021
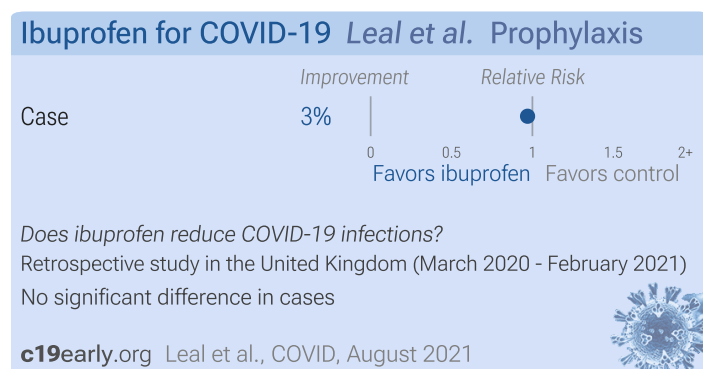
Leal: UK Biobank retrospective showing no significant difference in cases with ibuprofen use.

Loucera
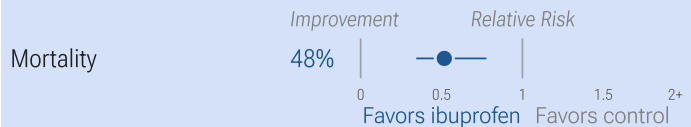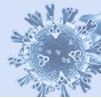
Loucera: Retrospective 15,968 COVID-19 hospitalized patients in Spain, showing lower mortality with existing use of several medications including metformin, HCQ, azithromycin, aspirin, vitamin D, vitamin C, and budesonide. Since only hospitalized patients are included, results do not reflect different probabilities of hospitalization across treatments.

Reese
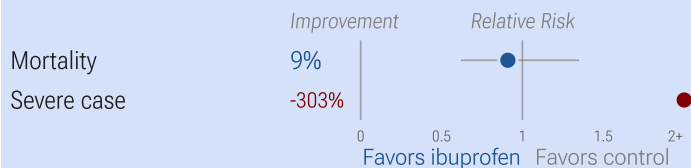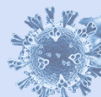
Reese: N3C retrospective 250,533 patients showing higher COVID-19 severity with ibuprofen use. Note that results for individual treatments are not included in the journal version or v2 of this preprint.

Rinott
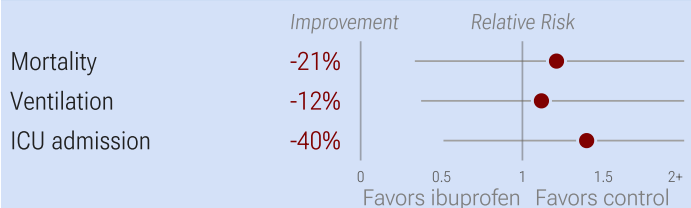
Rinott: Retrospective 403 COVID-19 cases in Israel, showing no significant difference in outcomes with ibuprofen use. Patients were asked about ibuprofen use starting a week before diagnosis of COVID-19 - treatment time may have been early, late, or prophylactic.

Samimagham

Ibuprofen for COVID-19 *Samimagham et al.* Prophylaxis

	Improvement	Relative Risk
Mortality	-100%	
Severe case	-428%	
Progression	-13%	

0   0.5   1   1.5   2+
Favors ibuprofen   Favors control
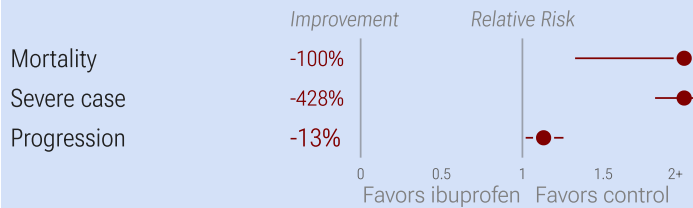
Is prophylaxis with ibuprofen beneficial for COVID-19?
Retrospective 158 patients in Iran
Higher mortality (p=0.001) and severe cases (p=0.00069)

c19early.org   Samimagham et al., Archives of Clinica.., Jul 2020

Samimagham: Retrospective 158 COVID-19 patients in Iran, showing higher risk of mortality with ibuprofen use.

Sobhy

Ibuprofen *Sobhy et al.* LATE TREATMENT DB RCT

	Improvement	Relative Risk
ICU admission	52%	
Oxygen therapy	52%	
Hospitalization time	26%	
Recovery, dyspnea	25%	
Recovery, fever	43%	
Recovery, lymphopenia	48%	
Recovery, cough	41%	

0   0.5   1   1.5   2+
Favors ibuprofen   Favors acetaminophen
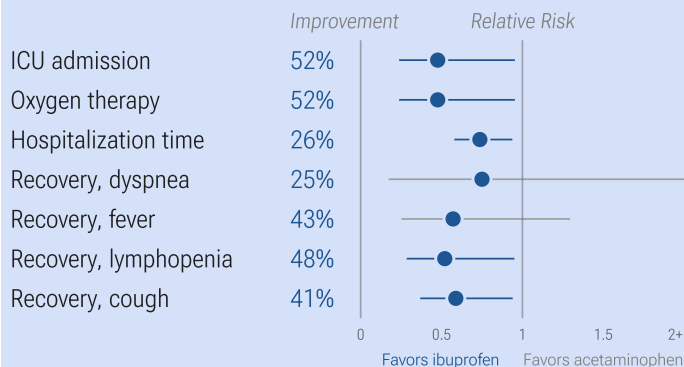
*Is **late** treatment with ibuprofen beneficial for COVID-19?*
Double-blind RCT 180 patients in Egypt (January - May 2022)
Trial compares with acetaminophen, results vs. placebo may differ
Lower ICU admission (p=0.047) and lower oxygen therapy (p=0.047)

c19early.org   Sobhy et al., The Open Anesthesia J., Apr 2023

Sobhy: RCT 180 moderate hospitalized COVID-19 patients in Egypt, showing lower ICU admission and shorter hospitalization with ibuprofen compared with acetaminophen.

Wong

Ibuprofen for COVID-19 *Wong et al.* Prophylaxis

	Improvement	Relative Risk
Mortality	-23%	
Mortality (b)	17%	

0   0.5   1   1.5   2+
Favors ibuprofen   Favors control
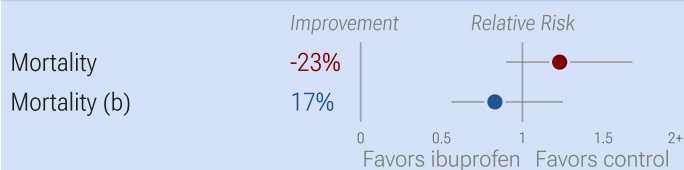
Is prophylaxis with ibuprofen beneficial for COVID-19?
Retrospective 1,977,972 patients in the United Kingdom (Mar - Jun 2020)
Higher mortality with ibuprofen *(not stat. sig., p=0.19)*

c19early.org   Wong et al., Annals of the Rheumatic D.., Jan 2021

Wong: Retrospective 2,463,707 people in the UK, showing no significant difference in COVID-19 mortality with NSAID use. Current NSAID users were defined as those ever prescribed an NSAID in the 4 months prior to study start, and non-users were those with no record of NSAID prescription in the same time period.

Xie

Ibuprofen for COVID-19 *Xie et al.* Prophylaxis

	Improvement	Relative Risk
Hospitalization	-12%	
Case	-8%	

0   0.5   1   1.5   2+
Favors ibuprofen   Favors other NSAIDs

Is prophylaxis with ibuprofen beneficial for COVID-19?
Retrospective 1,697,522 patients in the USA (Feb - Oct 2020)
Study compares with other NSAIDs, results vs. placebo may differ
No significant difference in outcomes seen

c19early.org Xie et al., Drugs, July 2022

Xie: PSM retrospective 1,697,522 osteoarthritis or back pain patients in the US, showing no significant differences in COVID-19 cases and hospitalization for ibuprofen vs. other NSAIDs.

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 ibuprofen 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 ibuprofen for COVID-19 that report a comparison with a control group are included in the main analysis. Sensitivity analysis is performed, excluding studies with major issues, epidemiological studies, and studies with minimal available information. 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 [Zhang]. 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 [Sweeting]. 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 (3.12.2) with scipy (1.12.0), pythonmeta (1.26), numpy (1.26.4), statsmodels (0.14.1), and plotly (5.19.0).

Forest plots are computed using PythonMeta *Deng* 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 (4.1.2) using the metafor (3.0-2) and rms (6.2-0) 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 *McLean, Treanor*.

We received no funding, this research is done in our spare time. We have no affiliations with any pharmaceutical companies or political parties.

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

Early treatment

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.

Abu Esba, 11/2/2020, prospective, Saudi Arabia, peer-reviewed, 6 authors, study period 12 April, 2020 - 1 June, 2020, excluded in exclusion analyses: substantial unadjusted confounding by indication likely.	risk of death, 169.5% higher, RR 2.70, *p* = 0.35, treatment 1 of 40 (2.5%), control 11 of 357 (3.1%), adjusted per study, multivariable.
	risk of death, 36.8% lower, HR 0.63, *p* = 0.68, treatment 40, control 357, Cox proportional hazards.
	risk of oxygen therapy, 44.8% higher, RR 1.45, *p* = 0.64, treatment 40, control 357, adjusted per study, multivariable.
	risk of hospitalization, 18.2% higher, RR 1.18, *p* = 0.64, treatment 40, control 357, adjusted per study, multivariable.
	risk of severe case, 84.8% higher, RR 1.85, *p* = 0.42, treatment 40, control 357, adjusted per study, multivariable.
Rinott, 9/30/2020, retrospective, Israel, peer-reviewed, median age 45.0, 5 authors, study period 15 March, 2020 - 15 April, 2020.	risk of death, 21.1% higher, RR 1.21, *p* = 0.73, treatment 3 of 87 (3.4%), control 9 of 316 (2.8%).
	risk of mechanical ventilation, 11.8% higher, RR 1.12, *p* = 0.77, treatment 4 of 87 (4.6%), control 13 of 316 (4.1%).
	risk of ICU admission, 39.7% higher, RR 1.40, *p* = 0.56, treatment 5 of 87 (5.7%), control 13 of 316 (4.1%).

Late treatment

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.

Sobhy, 4/19/2023, Double Blind Randomized Controlled Trial, Egypt, peer-reviewed, 6 authors, study period January 2022 - May 2022, this trial compares with another treatment - results may be better when compared to placebo, trial PACTR202202880140319.	risk of ICU admission, 52.4% lower, RR 0.48, *p* = 0.047, treatment 10 of 90 (11.1%), control 21 of 90 (23.3%), NNT 8.2.
	risk of oxygen therapy, 52.4% lower, RR 0.48, *p* = 0.047, treatment 10 of 90 (11.1%), control 21 of 90 (23.3%), NNT 8.2.
	hospitalization time, 26.3% lower, relative time 0.74, *p* = 0.01, treatment 90, control 90.
	risk of no recovery, 25.0% lower, RR 0.75, *p* = 1.00, treatment 3 of 90 (3.3%), control 4 of 90 (4.4%), NNT 90, day 4, dyspnea.
	risk of no recovery, 42.9% lower, RR 0.57, *p* = 0.25, treatment 8 of 90 (8.9%), control 14 of 90 (15.6%), NNT 15, day 4, fever.
	risk of no recovery, 48.0% lower, RR 0.52, *p* = 0.04, treatment 13 of 90 (14.4%), control 25 of 90 (27.8%), NNT 7.5, day 4, lymphopenia.
	risk of no recovery, 41.2% lower, RR 0.59, *p* = 0.03, treatment 20 of 90 (22.2%), control 34 of 90 (37.8%), NNT 6.4, day 4, cough.

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.

Campbell, 5/5/2022, retrospective, USA, peer-reviewed, 4 authors, study period 2 March, 2020 - 14 December, 2020.	risk of death, no change, OR 1.00, *p* = 0.54, treatment 1,814, control 20,311, adjusted per study, propensity score weighting, multivariable, day 60, RR approximated with OR.
	risk of death, 1.0% lower, OR 0.99, *p* = 0.23, treatment 1,814, control 20,311, adjusted per study, propensity score weighting, multivariable, day 30, RR approximated with OR.
Choi, 6/23/2020, retrospective, South Korea, peer-reviewed, median age 29.0, 8 authors, study period 5 March, 2020 - 18 March, 2020.	risk of progression, 240.0% higher, OR 3.40, *p* = 0.26, treatment 6 of 36 (16.7%) cases, 2 of 36 (5.6%) controls, case control OR, propensity score matching.
Drake, 7/31/2021, prospective, United Kingdom, peer-reviewed, 362 authors, study period 17 January, 2020 - 10 August, 2020.	risk of death, 10.0% lower, OR 0.90, *p* = 0.36, adjusted per study, multivariable, RR approximated with OR.
Kragholm, 10/21/2020, retrospective, Denmark, peer-reviewed, 13 authors, study period 1 January, 2020 - 30 April, 2020.	risk of progression, 4.0% lower, RR 0.96, *p* = 0.78, treatment 264, control 3,738.

Leal, 8/16/2021, retrospective, United Kingdom, peer-reviewed, 5 authors, study period 16 March, 2020 - 1 February, 2021.	risk of case, 3.0% lower, OR 0.97, *p* = 0.29, RR approximated with OR.
Loucera, 8/16/2022, retrospective, Spain, peer-reviewed, 8 authors, study period January 2020 - November 2020.	risk of death, 48.3% lower, HR 0.52, *p* = 0.002, treatment 519, control 15,449, Cox proportional hazards, day 30.
Reese, 4/20/2021, retrospective, USA, preprint, 23 authors.	risk of death, 9.0% lower, HR 0.91, *p* = 0.65, treatment 5,737, control 5,737, propensity score matching, Cox proportional hazards, Table S56.
	risk of severe case, 303.0% higher, OR 4.03, *p* < 0.001, treatment 5,737, control 5,737, propensity score matching, Table S48, RR approximated with OR.
Samimagham, 7/13/2020, retrospective, Iran, peer-reviewed, 4 authors.	risk of death, 100% higher, OR 2.00, *p* < 0.001, treatment 63, control 95, adjusted per study, multivariable, RR approximated with OR.
	risk of severe case, 427.8% higher, RR 5.28, *p* < 0.001, treatment 14 of 63 (22.2%), control 4 of 95 (4.2%).
	risk of progression, 13.1% higher, RR 1.13, *p* = 0.04, treatment 60 of 63 (95.2%), control 80 of 95 (84.2%), moderate or severe.
Wong, 1/21/2021, retrospective, United Kingdom, peer-reviewed, median age 53.0, 32 authors, study period 1 March, 2020 - 14 June, 2020.	risk of death, 23.0% higher, HR 1.23, *p* = 0.19, adjusted per study, general population, multivariable.
	risk of death, 17.0% lower, HR 0.83, *p* = 0.37, adjusted per study, rheumatoid arthritis/osteoarthritis patients, multivariable.
Xie, 7/13/2022, retrospective, USA, peer-reviewed, 9 authors, study period 1 February, 2020 - 31 October, 2020, this trial compares with another treatment - results may be better when compared to placebo.	risk of hospitalization, 12.5% higher, HR 1.12, *p* = 0.26, Open Claims, PharMetrics Plus, both periods combined.
	risk of case, 7.6% higher, HR 1.08, *p* = 0.25, Open Claims, PharMetrics Plus, both periods combined.

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.

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